UNIVERSITY OF CALIFORNIA,
IRVINE

Dual-Metal and Metaloid Reactivity with Gold(I)

DISSERTATION

Submitted in partial satisfaction of the requirements
for the degree of

Doctor of Philosophy

in Chemistry

by

Joshua John Hirner

Dissertation Committee:
Professor Suzanne A. Blum, chair
Professor Christopher D. Vanderwal
Professor David L. Van Vranken

2014

TABLE OF CONTENTS

LIST OF SCHEMES

Page

LIST OF TABLES

Page

ACKNOWLEDGEMENTS

Writing my dissertation has given me pause to reflect on my growth as a scientist and as a person. Sandwiched between re-re-formatting figures and agonizing over the perfect adjective to accurately describe just how poorly a reaction worked, these moments of introspection have been some of the most enjoyable parts of the process for me. I have been immensely fortunate to be surrounded by great people throughout my life, and I am delighted to thank them here.

First, I am grateful to all those who played a role in my development as a scientist, especially:

Mr. Matt Bueller, my high school ecology teacher, for being the first to show me that science is about developing an empirical understanding of relationships rather than rote memorization from a textbook.

Prof. Barbara Kramer, my first research advisor, for introducing me to the world of research, for nurturing my passion for science and for sharing it with others, and for helping me realize the breadth of real-world problems that can be solved by a clever chemist.

Prof. Anne Moody, my undergraduate organic chemistry professor and research advisor, for teaching me in a fun and engaging way, for her seemingly limitless kindness and patience, and for all the stickers. I still have them.

Prof. James McCormick, my physical chemistry professor, for imparting to me a persnicketiness in the conduct and communication of science that continues to be incredibly valuable. His high expectations made me challenge myself, and I am a better scientist because of it.

Dr. Harris Mason, my graduate student mentor during my summer research adventure in geochemistry, for the huge amount of his time that I doubtless consumed and for giving me a firsthand glimpse of what life in graduate school is really like.

Dr. Mike Zacuto, my mentor during my summer research experience at Merck, for starting that first conversation with me— then a complete stranger—over a funny T-shirt I was wearing, for teaching me *many* new lab techniques, for introducing me to the wonderful world of transition metal-catalyzed reactions, and for steering me towards graduate school.

Prof. Chris Vanderwal and Prof. Dave Van Vranken for a number of valuable conversations about my research and careers in science, as well as their quirky, engaging teaching styles. Additionally, I am grateful to Chris for his help and advice in his capacity as Graduate Organic Advisor and to Dave for teaching me that using tabulated bond dissociation enthalpies looks silly now that computational chemistry is ubiquitous.

Prof. Suzanne Blum for the tremendous learning experiences and support afforded to me during my time in her group. I am extremely grateful to her. Additionally, the intellectual freedom she gave me was invaluable in my development as a scientist. She appreciates a well-crafted ex-

periment like a work of art, and I am glad she instilled that value in me, too.

For better or for worse, I am not a science robot. I would be remiss if I did not also thank a number of other people for their impact on me personally. So, I owe a huge thank you to:

My parents, John & Catherine Hirner. I appreciate you for nurturing my creativity as a kid, for your continued support and encouragement, and for dealing with my nonsense, and for everything else you do. I have been incredibly lucky to have both of you in my life, and I don't say thank you often enough.

My extended family, the Hirners, Lavins, & Trippensees. Having watched me grow up from a little kid playing with frogs and dump trucks, it must be hard to take me seriously as professional. Thanks for pretending! Each of you has played an important role in my life, and I am thankful for you.

Josh Blechle, my diatomic counterpart. We had some stellar nerd adventures together, and your friendship means a lot to me. Even when I haven't spoken to you for months, each new conversation feels as natural is if we were continuing a chat from lunch.

UCI friends—especially the game night regulars, Trevor Cornell and Shawn Miller. Thank you for your friendship and all the fun memories. You really helped make my graduate experience into something more meaningful than it would have been otherwise.

Katrina Roth and Yili Shi, two former colleagues from the Blum group. Thank you both for taking me under your wings when I was first starting out at UCI. Your mentorship was very helpful to me, but it was your friendship that made coming to lab fun.

Gidget's family: Mr. & Mrs. Tay and the extended Tay, Liang, and Huang clan. Thank you all for welcoming me as a part of your family and for making me feel like I belonged. With my blood relatives 2000+ miles away, I'm very lucky to have a second family much closer.

Gidget Tay. Graduate school is an immersive experience, and it's easy to develop tunnel vision. You keep me grounded in what matters most. Thank you for your daily encouragement, and for listening when I need to talk and for understanding when I don't. You make my life pretty great.

Joshua J. Hirner
Curriculum Vitae

EDUCATION

University of California, Irvine, CA 2009–2015
Ph.D. Organic Chemistry
National Science Foundation Graduate Fellow

Truman State University, Kirksville, MO 2005–2009
B.S. in Chemistry
Magna Cum Laude

RESEARCH EXPERIENCE

Graduate-Level:

Advisor, Prof. Suzanne A. Blum
University of California–Irvine 2009–2014

Project: Development of reactions with gold and a second metal or metalloid

- Nickel-catalyzed cross-coupling of stoichiometric organogold reagents
- Gold/palladium cocatalyzed ring expansion of vinyl aziridines
- Formal boron–oxygen σ-bond activation for intramolecular addition to alkynes

Undergraduate-Level:

Advisor, Prof. Anne E. Moody
Truman State University 2007–2009

Project: Undergraduate teaching laboratory experiment development

- Environmentally-benign Diels-Alder experiment

Advisor, Dr. Michael J. Zacuto
Merck & Co. 2008

Project: Divergent functionalization of *N*-heterocyclic compounds

- Palladium-catalyzed cross-coupling reactions of chloroquinolines

Advisor, Dr. Brian L. Phillips
Stony Brook University 2007

Project: Cation exchange for lead-contaminated groundwater remediation
- Synthesis and characterization of mixed lead/calcium apatite-type minerals

Advisor, Dr. Barbara K. Kramer
Truman State University 2006–2007

Project: Use of soybeans in the remediation of lead-contaminated soils
- Localization and quantification of sequestered lead in soybean plants

PUBLICATIONS & PATENTS

7. Blum, S. A.; Hirner, J. J.; Faizi, D. J. "Organoboron Compounds and Methods of Making Organoboron Compounds." Patent pending, 17 June 2014.

6. Hirner, J. J.; Faizi, D. J.; Blum, S. A. "Alkoxyboration: Ring-Closing Addition of B–O Sigma Bonds Across Alkynes." *J. Am. Chem. Soc.* **2014**, *136*, 4740.
   » Highlighted in *Science*: "Big Break for Boron," *Science* **2014**, *344*, 10.
   » Highlighted in *Synfacts*, **2014**, *10*, 569.

5. Hirner, J. J.;* Roth, K. E.;* Shi, Y.; Blum, S. A. "Mechanistic Studies of Azaphilic versus Carbophilic Activation by Gold(I) in the Gold/Palladium Dual-Catalyzed Rearrangement of Alkenyl Vinyl Aziridines." *Organometallics* **2012**, *31*, 6843.
   (Asterisk denotes equal author contribution.)

4. Hirner, J. J.; Shi, Y.; Blum, S. A. "Organogold Reactivity with Palladium, Nickel, and Rhodium: Transmetalation, Cross-Coupling, and Dual Catalysis." *Acc. Chem. Res.* **2011**, *44*, 603.
   » A "Top 20 Most-Read" article in this journal for 12 consecutive months.

3. Hirner, J. J.; Blum, S. A. "Nickel-Catalyzed Cross-Coupling of Organogold Reagents." *Organometallics* **2011**, *30*, 1776.

2. Mason, H. E.; Hirner, J. J.; Xu, W.; Parise, J. B.; Phillips, B. L. "Solid-State NMR Spectroscopy of Pb-Rich Apatite." *Mag. Reson. Chem.* **2009**, 1062.

1. Hirner, J. J.; Zacuto, M. J. "7-Chloroquinoline: A Versatile Intermediate for the Synthesis of 7-Substituted Quinolines." *Tetrahedron Lett.* **2009**, *50*, 4989.

PRESENTATIONS

5. Hirner, J. J.; Faizi, D. J.; Blum, S. A. “Alkoxyboration: Ring-Closing Addition of B–O σ Bonds across Alkynes.” Contributed oral presentation, 247th National Meeting of the American Chemical Society. Dallas, Texas. March 2014.

4. Hirner, J. J.; Faizi, D. J.; Blum, S. A. “Alkoxyboration: Ring-Closing Addition of B–O σ Bonds across Alkynes.” Invited oral presentation, Kyoto University. Kyoto, Japan. June 2013.

3. Hirner, J. J.; Roth, K. E.; Shi, Y.; Blum, S. A. “Mechanistic Studies of Azaphilic versus Carbophilic Activation by Gold(I) in the Gold/Palladium Dual-Catalyzed Rearrangement of Alkenyl Vinyl Aziridines.” Contributed oral presentation, 245th National Meeting of the American Chemical Society. New Orleans, Louisiana. April 2013.

2. Hirner, J. J.; Blum, S. A. “Cross-Coupling with Organogold Reagents.” Contributed oral presentation, 241st National Meeting of the American Chemical Society. Anaheim, California. March 2011.

1. Hirner, J. J.; Blum, S. A. “Nickel-Catalyzed Cross-Coupling of Organogold Reagents.” Invited oral presentation, U.C. Irvine Graduate Student and Post-Doctoral Scholar Colloquium. Irvine, California. January 2011.

AWARDS

- Joan Rowland Award for a meritorious graduate career (2014)
- University of California–Irvine Regent’s Dissertation Fellowship (2014)
- National Science Foundation Graduate Research Fellowship (2010)

ABSTRACT OF THE DISSERTATION

Dual-Metal and Metaloid Reactivity with Gold(I)

by

Joshua John Hirner

Doctor of Philosophy in Chemistry

University of California, Irvine, 2014

Professor Suzanne A. Blum, Chair

Chapter 1. This chapter provides a very brief introduction to the field of homogeneous gold(I) catalysis and discusses the context of the Blum group's previous studies in this area.

Chapter 2: Organogold compounds undergo stoichiometric cross-coupling reactions with aryl and vinyl bromides in high yield under mild, nickel-catalyzed conditions. The reaction tolerates both electron-rich and electron-poor organogold complexes, and vinyl bromides undergo cross-coupling with high stereoselectivity. This novel transformation links well-established nickel catalysis with more recent developments in organogold transformations.

Chapter 3: A vinyl aziridine activation strategy cocatalyzed by Pd(0) and a Au(I) Lewis acid was developed. This rearrangement installs a C–C and a C–N bond in one synthetic step to form pyrrolizidine and indolizidine products. Two proposed mechanistic roles for the gold cocatalyst were considered: (1) carbophilic gold catalysis or (2) azaphilic gold catalysis. Mechanistic studies support an azaphilic Lewis acid activation of the aziridine over a carbophilic Lewis acid activation of the alkene.

Chapter 4: A borylation reaction cocatalyzed by Au and Rh was proposed as a means of isolating catalytic organogold intermediates as the corresponding organoboron derivatives for use in subsequent functionalization steps. Products consistent with the proposed reactivity were obtained, but control experiments indicated no role for Rh in the reaction; organogold complexes were found to undergo facile thermal reactivity with electrophilic B without Rh. Electronic effects in the chemoselective borylation of heterocyclic organogold complexes were studied, suggesting design parameters used in the development of the Au-catalyzed borylation reactions discussed in Chapters 5 and 6.

Chapter 5: For nearly 70 years, the addition of boron–X σ bonds to carbon–carbon multiple bonds has been employed in the preparation of organoboron reagents. However, the significantly higher strength of boron–oxygen bonds has thus far precluded their activation for addition, preventing a direct route to access a potentially valuable class of oxygen-containing organoboron reagents for divergent

synthesis. Herein is discussed an alkoxyboration reaction, the addition of boron–oxygen *σ* bonds to alkynes. Functionalized *O*-heterocyclic boronic acid derivatives are produced using this transformation, which is mild and exhibits broad functional group compatibility. Our results demonstrate activation of this boron–O *σ* bond using a gold catalysis strategy that is fundamentally different from that used previously for other boron addition reactions.

Chapter 6: Four additional investigations stemming from the benzofuran-forming alkoxyboration reaction (Chapter 5) are described. Discussed are electronic effects in the B/Au transmetalation reaction, progress towards an intermolecular alkoxyboration reaction, and the expansion of the alkoxyboration concept to two additional substrate classes for intramolecular B–O σ-bond activation reactivity.

Chapter 1
Brief Introduction to Gold Catalysis

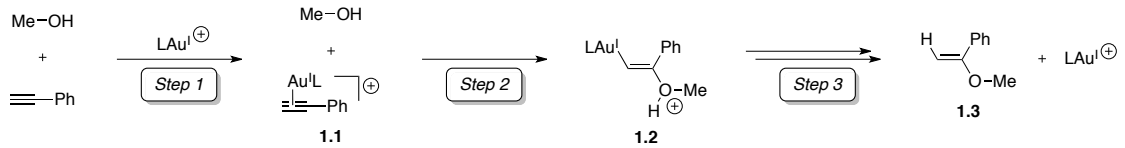
Abstract: This chapter provides a very brief introduction to the field of homogeneous gold(I) catalysis and discusses the context of the Blum group's previous studies in this area.

Historically considered an inert "noble metal,"[1–3] gold has recently become the subject of intense inquiry in the fields of homogeneous[4–10] and heterogeneous[11–13] catalysis.[14] Within the context of homogeneous catalysis, gold is most commonly used in the addition of nucleophiles to alkynes, allenes, and olefins (Scheme 1.1). Although notable exceptions exist, gold(I) *often* exhibits three key characteristics in these types of catalytic reactions:

1. *Soft Lewis acidity.* The diffuse, empty *6p* orbitals of gold(I) readily undergo productive orbital overlap with π bonds, including carbon–carbon multiple bonds.[4] The resulting π-complexes (such as **1.1**) exhibit enhanced electrophilicity at carbon versus the starting material.
2. *High redox stability.* Gold(I) is neither readily oxidized nor readily reduced.[15] Thus, unlike other late transition metals, reversible oxidation state changes are uncommon in gold catalytic cycles.[16]
3. *Catalyst turnover by protonation.* Many gold-catalyzed cycles proceed through an organogold intermediate,[17] such as **1.2**. Intermolecular pro-

ton transfer (Step 3) is typically responsible for achieving catalyst turnover.

Scheme 1.1. Representative example of a gold(I) catalyzed nucleophilic addition to a carbon–carbon multiple bond.



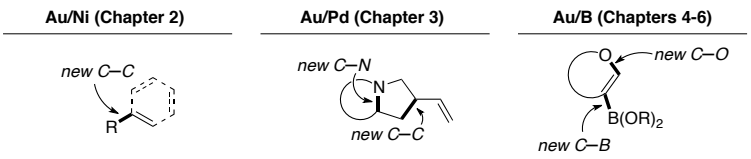
The first two characteristics, carbophilic Lewis acidity and redox stability, have been harnessed in powerful, creative ways for the synthesis of seemingly disparate architectures.[4–10] In contrast, the use of protonolysis in catalyst turnover effects a *loss* of complexity from the potentially versatile carbon–gold bond.

Previous work in the Blum group has focused on understanding the nature of the carbon–gold bond[18] and alternative functionalization methods employing a second transition metal.[19–26] The goal of these studies has been to combine pre-existing reactions uniquely accessible through gold catalysis with the carbon–carbon bond forming reactions available to other catalytic metals. The group has often used a gold-to-second-metal transmetalation step to link the two catalytic cycles.

To this end, the following chapters discuss the reactivity of gold(I) with other metals and metalloids (Scheme 1.2): a gold/nickel dual-metal cross-coupling reaction for the formation of new carbon–carbon bonds, a gold/palladium cocatalyzed reaction for the concurrent installation of new carbon–carbon and carbon–

nitrogen bonds in *N*-fused heterocycles, and a gold-catalyzed reaction for the formation of new carbon–oxygen and carbon–boron bonds in *O*-heterocycles.

Scheme 1.2. Graphical abstract for Chapters 2–6.



References

1. Hutchings, G. J.; Brust, M.; Schmidbaur, H. *Chem. Soc. Rev.* **2008**, *37*, 1759–1765.
2. Raubenheimer, H. G.; Schmidbaur, H. *J. Chem. Ed.* [Online early access]. DOI: 10.1021/ed400782p. Published Online: June 27, 2014. http://pubs.acs.org/doi/abs/10.1021/ed400782p (accessed Aug. 18, 2014).
3. Hammer, B.; Norskov, J. K. *Nature* **2002**, *376*, 238–240.
4. Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395–403.
5. Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180–3211.
6. Marion, N.; Nolan, S. P. *Chem. Soc. Rev.* **2008**, *37*, 1776–1782.
7. Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239–3265.
8. Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326–3350.
9. Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351–3378.
10. Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1194–2009.
11. Coquet, R.; Howard, K. L.; Willock, D. J. *Chem. Soc. Rev.* **2008**, *37*, 2046–

2076.

12. Zhang, Y.; Cui, X.; Shi, F.; Deng, Y. *Chem. Rev.* **2012**, *112*, 2467–2505.
13. Stratakis, M.; Garcia, H. *Chem. Rev.* **2012**, *112*, 4469–4506.
14. Over 6000 citations were found using the search keywords “gold catalyzed” in SciFinder Scholar from 2000–2014 alone. Search performed Aug. 18, 2014.
15. *CRC Handbook of Chemisty and Physics*; Weast, R. C., Astle, M. J., Eds.; CRC: Boca Raton, 1980; Vol. 60, pp D-155.
16. Zhang, G.; Peng, Y.; Cui, L.; Zhang, L. *Angew. Chem. Int. Ed.* **2009**, *48*, 3112–3115.
17. Liu, L.-P.; Hammond, G. B. *Chem. Soc. Rev.* **2012**, *41*, 3129–3139.
18. Roth, K. E.; Blum, S. A. *Organometallics*, **2010**, *29*, 1712–1716.
19. Shi, Y.; Peterson, S. M.; Haberaecker, W. W., III; Blum, S. A. *J. Am. Chem. Soc.* **2008**, *130*, 2168–2169.
20. Shi, Y.; Ramgren, S. D.; Blum, S. A. *Organometallics* **2009**, *28*, 1275–1277.
21. Shi, Y.; Roth, K. E.; Ramgren, S. D.; Blum, S. A. *J. Am. Chem. Soc.* **2009**, *131*, 18022–18023.
22. Shi, Y.; Blum, S. A. *Organometallics* **2011**, *30*, 1776–1779.
23. Hirner, J. J.; Shi, Y.; Blum, S. A. *Acc. Chem. Res.* **2011**, *44*, 603–613.
24. Roth, K. E.; Blum, S. A. *Organometallics* **2011**, *30*, 4811–4813.
25. Cornell, T. P.; Shi, Y.; Blum, S. A. *Organometallics*, **2012**, *31*, 5990–5993.
26. Al-Amin, M.; Roth, K. E.; Blum, S. A. *ACS Catal.* **2014**, *4*, 622–629.

Chapter 2
Nickel-Catalyzed Cross-Coupling Reactivity of Organogold Reagents

Abstract: Organogold compounds undergo stoichiometric cross-coupling reactions with aryl and vinyl bromides in high yield under mild, nickel-catalyzed conditions. The reaction tolerates both electron-rich and electron-poor organogold complexes, and vinyl bromides undergo cross-coupling with high stereoselectivity. This novel transformation links well-established nickel catalysis with more recent developments in organogold transformations.

Introduction

In 2009, the Blum group disclosed the first well-characterized cross-coupling reaction of stoichiometric organogold reagents.[1,2] This study lent additional mechanistic support to the group's prior development of reactions cocatalytic in both Au and Pd.[3,4] These early reports were quickly followed by related studies from the groups of Hashmi,[5,6] Sarandeses and Peréz Sestelo,[7] Sarkar,[8] and Echavarren.[9]

Like Pd, Ni is a d^{10} metal capable of catalyzing cross-coupling reactions.[10] It offers the advantages of comparatively low cost[11] and the capability of undergoing difficult C–O oxidative addition reactions not accessible with Pd.[12] However, these advantages are tempered by the accessibility of single-electron transfer pathways by Ni,[13] which could hinder reaction development and mechanism elucidation. Following the Blum group's successes with Au/Pd dual-metal reactivity,

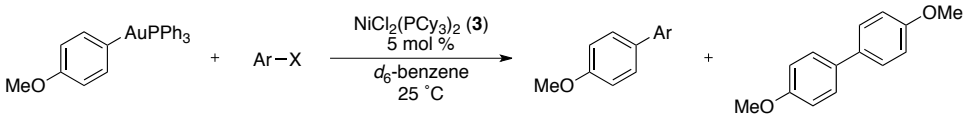
Ni catalysis represented an appealing next target for increasing the breadth of metal-catalyzed functionalization reactions available to organogold complexes—and ultimately catalytic organogold intermediates.

Results and Discussion

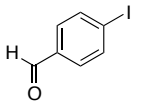
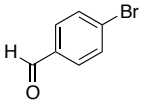
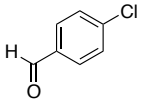
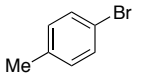
During initial experiments to establish standard reaction conditions, $NiCl_2(PCy_3)_2$ (**2.3**, Cy = cyclohexyl) was selected as an appropriate nickel pre-catalyst. Anisole-Au complex **2.1** was treated with 4-halobenzaldehydes in the presence of a catalytic quantity of **2.3** to afford high conversion to the corresponding cross-coupled biaryl product (Table 2.1). Iodotoluene and bromotoluene were found to give comparable reactivity (entries 1 and 2), and chlorotoluene afforded lower selectivity and a diminished rate of reaction (entry 3). Owing to their high availability and reactivity, bromides were selected as the oxidative addition partner of choice for further investigation.

Product selectivity was found to be highly dependent on the electronic nature of the aryl halide. Jones has demonstrated that the rate of oxidative addition by Ni is enhanced for electron-deficient substrates.[14] Electron-poor 4-bromobenzaldehyde, for which oxidative addition should be facile, afforded the desired cross-coupled product with high selectivity (entry 2). Moderately electron-rich 4-bromotoluene was anticipated to undergo oxidative addition by Ni at a retarded rate and experimentally provided homocoupling of the organogold starting material as the primary product (entry 4). Thus in this system, there are two plausible oxidation pathways for low-valent Ni: reduction of the aryl bromide through a two-electron process leading to cross-coupling, *or* reduction of the organogold

Table 2.1. Electronic effects on Ni catalyzed cross-couping reaction.



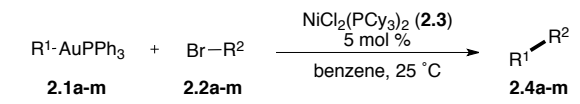
2.1a 1.1 equiv | **2.2** 1.0 equiv | **2.4a** *desired product* | **2.5a** *homocoupled product*

Entry	Ar−X	Time Temperature	Ratio by ^{1}H NMR Spectroscopy **2.4a** : **2.5a**
1		5 h 25 °C	1.0 : 0.1
2		8 h 25 °C	1.0 : 0.2
3		15 h 75 °C	1.0 : 0.5
4		20 h 25 °C	1.0 : 2.9 + unreacted starting materials

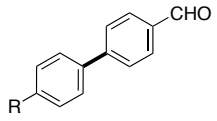
complex through a one-electron process producing homocoupled product **2.5a** and visually observable Au^0. Thus, in order to kinetically select for the desired cross-coupling pathway, electron-poor aryl halides should be employed.

The nickel-catalyzed cross-coupling reaction is tolerant of arylgold reagents ranging from electron-rich to electron poor (Table 2.2, entries **2.4a**–**d**) and a variety of electron-poor aryl- and heteroarylbromides (entries **2.4e**–**h**). Electrophilic functional groups such carbonyls and nitriles are unreacted, highlighting the low nucleophilicity of the organogold and organonickel intermediates. The scope of the transformation is not limited to arylgold reagents; isopropenyl- and alkynyl-

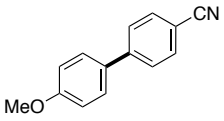
Table 2.2. Substrate scope of the Ni-catalyzed cross-coupling reaction of organogold reagents.[d]



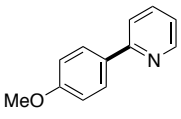
2.1a-m **2.2a-m** **2.4a-m**



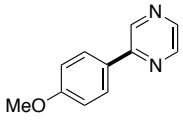
R = OMe, **2.4a**, 100%, 1 h
Me, **2.4b**, 83%, 1 h
H, **2.4c**, 96%, 1 h
CF_3, **2.4d**, 95%, 1 h



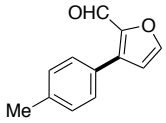
2.4e 97%, 7.5 h



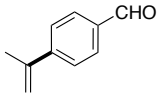
2.4f[a] 86%, 22 h



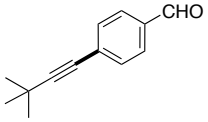
2.4g[a] 82%, 22 h



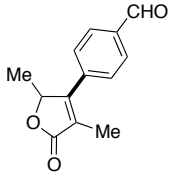
2.4h 77%, 7.5 h



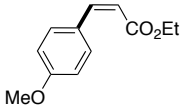
2.4i 94%, 1 h



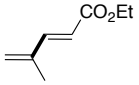
2.4j[a] 74%, 4 h



2.4k[a] 40% (75%), 4 h



2.4l[b] 87%, 1 h
Z:*E* > 95:5



2.4m[b] (89%),[c] 1 h
E:*Z* > 95:5

[a] Reaction conducted at 45 °C. [b] Starting from the *Z* bromide. [c] Not isolated due to product volatility. [d] Conditions: 1.30 equiv **2.1**, 1.00 equiv **2.2** (30 mM), and 5 mol % **2.3**. Yields are isolated yields. Values in parentheses reflect ^{1}H NMR yields of a small-scale reaction in C_6D_6 with a mesitylene internal standard.

gold reagents also proved to be suitable cross-coupling partners (entries **2.4i–j** and **2.4m**). The isopropenylgold coupling reactions demonstrate a tolerance for branching at the α carbon, while the comparatively slow formation of **2.4j** versus **2.4a**–**d** suggests that the organogold hybridization plays a role in the transmetalation rate. Consistent with this hybridization dependence, Ph_3PAuMe failed to undergo detectable cross-coupling reactivity with **2.1a** under standard reaction conditions. A similar dependence has been reported in the protodeauration of organogold compounds, the rate of which also decreases in the order of sp^2 > sp > sp^3.[15] The involvement of the π system has been postulated to be the cause of this rate dependence in protodeauration[15] and in the transmetalation of other organometallic reagents to Ni;[16] therefore, the diminished reaction rate of **2.4j** may

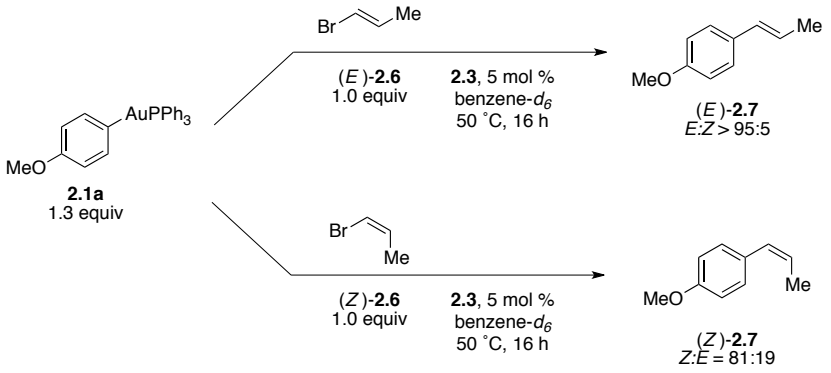
be due to a reduced kinetic accessibility of the alkynylgold π system resulting from a lower HOMO versus arylgold reagents **2.4a**–**d**.[17] This similarity to protodeauration in hybridization dependence suggests that nickel might display electrophilic character in transmetalation reactions with organogold compounds.

Organogold butenolide rearrangement substrate **2.2k** was isolated by Hammond,[18] and derivatives have been implicated as intermediates in several Au-catalyzed rearrangements.[4,19,20] When introduced to the Ni catalyst system, **2.2k** afforded cross-coupled product **2.4k** in 75% yield by ^{1}H NMR spectroscopy, demonstrating the ability to functionalize known catalytic organogold intermediates with this Ni-catalyzed cross-coupling reaction.

A stereocontrol study was conducted using 1-bromo-1-propene (**2.6**) as a model vinyl bromide. The reaction of organogold compound **2.2a** with (*E*)-**2.6** yielded exclusively the *E* cross-coupled product **2.7** (Scheme 2.1), while (*Z*)-**2.6** was converted predominately to (*Z*)-**2.7**. Control experiments to probe the origin of the incomplete stereospecificity observed with (*Z*)-**2.6** revealed that neither the product nor the starting material was subject to a Ni-catalyzed isomerization. Partial loss of stereochemical integrity could have occurred through the formation of a vinyl radical through bromine atom abstraction by low-valent Ni.[13] However, the predominance of a stereospecific cross-couping confirms that the primary pathway for oxidative addition by Ni into **2.6** does *not* generate a free organic radical,[21] which would result in a thermodynamic mixture of isomers of **2.7** regardless of the starting olefin geometry. In contrast, the reactions of ethyl (*Z*)-3-bromopropenoate yielded the cross-coupled products (*Z*)-**2.4l** and (*E*)-**2.4m** in

both high yield and stereochemical purity, but with inversion of configuration for **2.4m**. An alternative mechanism, such as Michael addition-elimination of a weakly nucleophilic Ni intermediate[22] or phosphine-catalyzed isomerization could explain the stereochemical scrambling observed to generate (*E*)-**2.4m**.

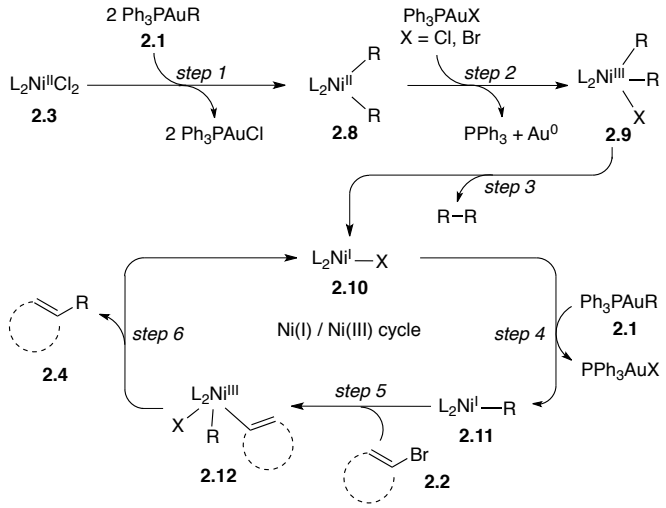
Scheme 2.1. Stereoretention in the cross-coupling reaction with vinyl bromides.



A proposed catalytic cycle for this reaction is shown in Scheme 2.2. Two successive transmetalation reactions between organogold **2.2** and Ni precatalyst **2.1** yield the diorganonickel(II) intermediate **2.8** (step 1), reductive elimination from which is kinetically disfavored;[23] therefore, single-electron oxidation by Au(I)[24] or the organobromide[23] could provide Ni(III) species **2.9**. Subsequent reductive elimination would afford the active Ni(I) catalyst **2.10** (steps 2, 3).[25] In analogy to nickel-catalyzed cross-coupling reactions with metals other than gold, transmetalation of organogold complex **2.2** to Ni(I) is expected to precede oxidative addition with organobromide **2.3**.[21,26,27] The resulting Ni(III) intermediate **2.12** would then undergo rapid reductive elimination[25] to afford the observed cross-coupled product **2.4**. Notably, once the active Ni catalyst has been generated

(steps 1–3), the absence of further homocoupling reactivity suggests that the organogold coupling partner is not reduced under these optimized reaction conditions despite the potential thermodynamic favorability[28,29] of a Au(I)/Ni(I) redox reaction to form Au(0) and Ni(II).

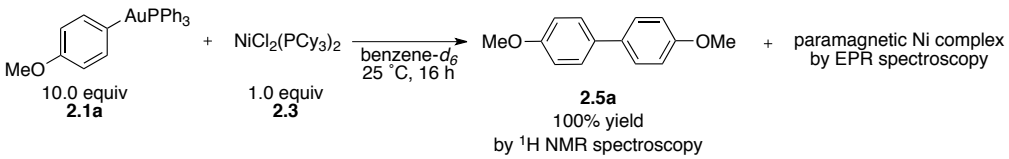
***Scheme 2.2**. Proposed Ni^{I}/Ni^{III} catalytic cycle for the Ni-catalyzed cross-coupling reaction.*



Steps 1 and 4 in the proposed mechanism invoke a transmetalation from a homogeneous organogold complex to Ni. Previously, van Koten has investigated a directed organogold-to-Ni transmetalation as a part of a study of redox-innocent arylating agents for transition metals.[30] In order to elaborate on this key transmetalation reaction within the specific context of cross-coupling reactivity, stoichiometric **2.1** was treated with an excess of **2.2a** to mimic catalytic conditions. Quantitative conversion to homocoupled product **2.5a** was observed by ^{1}H NMR spectroscopy, and a paramagnetic Ni complex was detected by EPR spec-

troscopy. This result is consistent with steps 1–3 in Scheme 2.2 showing the generation of the active Ni catalyst.

Scheme 2.3. Stoichiometric organogold homocoupling reaction.



In summary, a Ni-catalyzed cross-coupling reaction of stoichiometric organogold reagents was developed. The reaction proceeds at ambient temperatures in high yield, outcompeting potential single-electron reduction of Au(I) by low-valent Ni. The utility of this reaction in functionalizing a known catalytic organogold intermediate suggests access to unconventional cross-coupling bond disconnections. Although this stoichiometric reactivity has not yet been translated into a reaction cocatalytic in both Au and Ni, the insight gained regarding the potential for single-electron transfer reactions between Au and other transition metals has since been applied by Gagné en route to dual-metal reactivity with Au.[31]

References

1. Shi, Y.; Ramgren, S. D.; Blum, S. A. *Organometallics* **2009**, *28*, 1275–1277.
2. Jones, L. A.; Sanz, S.; Laguna, M. *Catal. Today* **2006**, *122*, 403–406.
3. Shi, Y.; Peterson, S. M.; Haberaecker, W. W., III; Blum, S. A. *J. Am. Chem. Soc.* **2008**, *130*, 2168–2169.
4. Shi, Y.; Roth, K. E.; Ramgren, S. D.; Blum, S. A. *J. Am. Chem. Soc.* **2009**, *131*, 18022–18023.

5. Hashmi, A. S. K.; Lothschütz, C.; Döpp, R.; Rudolph, M.; Ramamurthi, T. D.; Rominger, F. *Angew. Chem., Int. Ed.* **2009**, *48*, 8243–8246.
6. Hashmi, A. S. K.; Döpp, R.; Lothschütz, C.; Rudolph, M.; Riedel, D.; Rominger, F. *Adv. Synth. Catal.* **2010**, *352*, 1307–1314.
7. Peña-López, M.; Ayán-Varela, M.; Sarandeses, L. A.; Pérez Sestelo, J. *Chem.—Eur. J.* **2010**, *16*, 9905–9909.
8. Panda, B.; Sarkar, T. K. *Chem. Commun.* **2010**, *46*, 3131–3133.
9. Lauterbach, T.; Livendahl, M.; Rosellón, A.; Espinet, P.; Echavarren, A. M. *Org. Lett.* **2010**, *12*, 3006–3009.
10. For representative examples of nickel-catalyzed cross-coupling reactions that are analogous to palladium-catalyzed processes, see: (a) Indolese, A. F. *Tetrahedron Lett*. **1997**, 38, 3513–3516. (b) Percec, V.; Bae, J.-Y.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 1060–1065. (c) Adamczyk, M.; Netzel, D. A.; Watt, D. S. *J. Org. Chem.* **1984**, *49*, 4226–4237. (d) Quesnelle, C. A.; Familoni, O. B.; Snieckus, V. *Synlett* **1994**, *5*, 349–350.
11. Bulk Pd metal is approximately 1500 times more expensive than Ni based on exchange data. (a) LPPM | The London Platinum and Palladium Market | Platinum and Palladium Fixing Statistics (http://www.lppm.com/statistics.aspx). Accessed 2 July 2014. (b) London Metal Exchange: Nickel (https://www.lme.com/en-gb/metals/non-ferrous/nickel). Accessed 2 July 2014.
12. Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346–1416.
13. For a few examples of Ni-promoted radical reactions, see: (a) Vaupel, A.;

Knochel, P. *J. Org. Chem.* **1996**, *61*, 5743–5753. (b) Smith, M. B.; March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 6th ed.; Wiley: Hoboken, 2007; p 592. (c) Ozaki, S.; Horiguchi, I.; Matsushita, H.; Ohmori, H. *Tetrahedron Lett*. **1994**, *35*, 725–728.

14. Garcia, J. J.; Brunkan, N. M.; Jones, W. D. *J. Am. Chem. Soc.* **2002**, *124*, 9547–9555.
15. Roth, K. E.; Blum, S. A. *Organometallics* **2010**, *29*, 1712–1716.
16. Saito, S.; Oh-tani, S.; Miyaura, N. *J. Org. Chem.* **1997**, *62*, 8024–8030.
17. HOMOs of benzene and acetylene, see: Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: Chichester, 1976; p 22.
18. Liu, L.-P.; Zu, B.; Mashuta, M. S.; Hammond, G. B. *J. Am. Chem. Soc.* **2008**, *130*, 17642–17643.
19. Liu, L.-P.; Hammond, G. B. *Chem. Asian J.* **2009**, *4*, 1230–1236.
20. Hopkinson, M. N.; Ross, J. E.; Giuffredi, G. T.; Gee, A. D.; Gouverneur, V. *Org. Lett.* **2010**, *12*, 4904–4907.
21. Phapale, V. B.; Guisán-Ceinos, M.; Buñuel, E.; Cárdenas, D. J. *Chem.—Eur. J.* **2009**, *15*, 12681–12688.
22. Motora, M.; Ishikawa, M; Tsai, F.-Y; Takahashi, T. *Tetrahedron* **1999**, *55*, 4969–4978.
23. Morrell, D. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1975**, *97*, 7262–7270.
24. Gammons, C. H.; Yu, Y.; Williams-Jones, A. E. *Geochim. Cosmochim. Acta* **1997**, *61*, 1971–1983.
25. Kochi, J. K. *Pure Appl. Chem.* **1980**, *52*, 571–606.

26. Phapale, V. B.; Cárdenas, D. J. *Chem. Soc. Rev*. **2009**, 1598–1607.
27. Anderson, T. J.; Jones, G. D.; Vicic, D. A. *J. Am. Chem. Soc.* **2004**, *126*, 8100–8101.
28. Standard reduction potential of Au(I): *CRC Handbook of Chemisty and Physics*; Weast, R. C., Astle, M. J., Eds.; CRC: Boca Raton, 1980; Vol. 60, pp D-155.
29. The one-electron oxidation potentials of many nickel complexes have been investigated. For one example, see: Louati, A.; Huhn, M. *Inorg. Chem.* **1993**, *32*, 3601–3607.
30. Contel, M.; Stol, M.; Casado, M. A.; van Klink, G. P. M.; Ellis, D. D.; Spek, A. L.; van Koten, G. *Organometallics* **2002**, *21*, 4556–4559.
31. Weber, D.; Gagné, M. R. *Chem. Commun.* **2011**, *47*, 5172–5174.

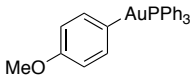
Experimental

General Considerations

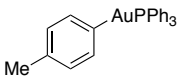
All chemicals were used as received from commercial sources unless otherwise noted. Chlorotriphenylphosphinegold(I) was purchased from Strem Chemical Co. 3-Bromo-2-formylfuran (**3h**) was obtained from Frontier Chemicals. Pre-catalyst $NiCl_2(PCy_3)_2$ (**2.3**) was prepared according to a literature procedure.[1] Benzene and tetrahydrofuran were purified by passage through an alumina column under argon pressure on a push-still solvent system. Benzene-d_6 was dried over CaH_2, degassed using three freeze-pump-thaw cycles, and vacuum transferred prior to use. All manipulations were conducted in a glovebox under nitrogen atmosphere or using standard Schlenk techniques unless otherwise specified.

Analytical and preparatory thin layer chromatography (TLC) were performed using Merck F_{250} and Analtech 1500 Å plates. Plates were visualized under UV irradiation (254 nm) and/or using a solution of phosphomolybdic acid in ethanol followed by heating. Flash chromatography of organogold compounds was conducted using Acros 50–200 μm basic aluminum oxide (activity I). All proton and carbon nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were recorded on a Bruker DRX-500 spectrometer or a Bruker DRX-500 spectrometer outfitted with a cryoprobe. All chemical shifts are reported in parts per million. ^{1}H and ^{13}C NMR spectroscopy experiments are calibrated to the residual proteosolvent resonance (δ = 7.27 ppm for $CDCl_3$ or δ = 5.32 ppm for CD_2Cl_2 in ^{1}H NMR spectroscopy experiments; δ = 77.16 ppm for $CDCl_3$ or δ = 54.00 ppm for CD_2Cl_2 in ^{13}C NMR spectroscopy experiments). For ^{31}P NMR spectroscopy experiments, spectra were obtained on a Bruker DRX-400 spectrometer, and the chemical shifts are reported relative to an external standard of 85% aq. H_3PO_4 (δ = 0.00 ppm). X-band (9.28 GHz) EPR spectra were obtained on a Bruker 300 spectrometer relative to a DPPH (2,2-diphenyl-1-picrylhydrazyl radical, g = 2.00) external standard. Low and high-resolution mass spectrometry data were obtained at the University of California, Irvine.

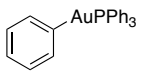
Synthetic Procedures



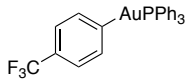
2.1a. Organogold compound **2.1a** was prepared according to a literature procedure.[2] The product was obtained as a white powder (1.03 g, 83% yield). ^{1}H NMR (CD_2Cl_2, 500 MHz): δ 3.75 (s, 3H), 6.83 (d, J = 7.4 Hz, 2H), 7.36 (m, 2H), 7.35–7.54 (m, 9H), 7.59–7.63 (m, 6H). This spectrum is in agreement with previously reported spectral data.[2]



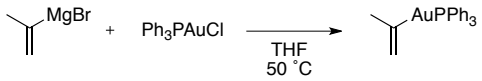
2.1b. Organogold compound **2.1b** was prepared according to a literature procedure.[2] The product was obtained as a white powder (301 mg, 55% yield). ^{1}H NMR (CD_2Cl_2, 500 MHz): δ 2.30 (s, 3H), 7.07 (d, J = 7.2 Hz, 2H), 7.38 (m, 2H), 7.47–7.54 (m, 9H), 7.60–7.64 (m, 6H). This spectrum is in agreement with previously reported spectral data.[2]



2.1c. Organogold compound **2.1c** was prepared according to a literature procedure.[2] The product was obtained as a pale purple powder (181 mg, 34% yield). ^{1}H NMR (CD_2Cl_2, 500 MHz): δ 7.03 (tt, J = 7.4 Hz, 1.4 Hz, 1H), 7.22 (t, J = 7.4 Hz, 2H), 7.47–7.55 (m, 11H), 7.59–7.64 (m, 6H). This spectrum is in agreement with previously reported spectral data.[2]



2.1d. Organogold compound 2d was prepared according to a literature procedure.[2] The product was obtained as a pale yellow powder (97 mg, 32% yield). ^{1}H NMR (CD_2Cl_2, 500 MHz): δ 7.46–7.56 (m, 11H), 7.59–7.68 (m, 8H). This spectrum is in agreement with previously reported spectral data.[2]



2.1i. Isopropenyltriphenylphosphinegold(I) was prepared in a manner adapted from the literature method used to produce **2.1a-d**. To a 50 °C solution of isopropenylmagnesium bromide in THF (0.5 M, 9 mmol, 4 equiv) in a 100-mL Schlenk flask under N_2 was added dropwise a solution of chlorotriphenylphosphinegold(I) (396 mg, 1 equiv) in dry THF (11 mL). After stirring for 30 min, the reaction was cooled to 0 °C and the excess Grignard reagent was quenched by slowly adding pieces of crushed ice. The mixture was diluted with Et_2O (100 mL) and washed with water (2 × 100 mL). The organic layer was dried over K_2CO_3 and concentrated to an oil. The oil was filtered through a plug of basic alumina (2.5 cm × 3 cm) with THF into 10 mL fractions. Fractions containing the desired product were detected by UV absorbance on TLC plates and were combined and concentrated to remove volatiles. The resulting oil was diluted in a minimum of benzene (ca. 4 mL), layered with pentanes (ca. 350 mL), and stored at 3 °C to crystallize over 3 d. The white crystalline product was collected in a fine glass frit, washed with pen-

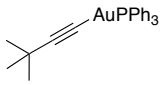
tanes (3 × 10 mL), crushed to a powder, and dried under vacuum to afford the desired product as a white powder (58 mg, 14% yield). Additional product was recovered by concentrating the filtrate in vacuo and redissolving the residue in ca. 4 mL benzene. After layering the benzene solution with 50 mL pentane and storing at 0 ˚C for 3 h, analytically pure **2.1i** was collected as a white powder by filtration through a fine glass frit for a combined yield of 188 mg (47%).

^{1}H NMR (CD_2Cl_2, 500 MHz): δ 2.09 (dt, J = 5.1, 1.4 Hz, 3H), 4.89 (m, 1H), 5.59 (m, 1H), 7.36–7.50 (m, 9H), 7.52–7.58 (m, 6H).

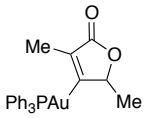
^{13}C NMR (CD_2Cl_2, 500 MHz): δ 32.1, 120.3, 129.5 (d, $J_{C\text{-}P}$ = 40.0 Hz), 131.6, 131.8 (d, $J_{C\text{-}P}$ = 190 Hz), 134.8 (d, $J_{C\text{-}P}$ = 55 Hz), 180.5 (d, $J_{C\text{-}P}$ = 113 Hz). Note: The ^{13}C signal at δ = 131.8 ppm, corresponding to the gold ipso carbon, was poorly resolved from the baseline in a standard ^{13}C NMR spectroscopy experiment after 350 scans. Its presence was confirmed through an HMBC experiment via its coupling to the methyl group protons.

^{31}P NMR (CD_2Cl_2, 400 MHz): δ = 41.2.

HRMS (ESI) found *m/z* = 523.0848. Calcd for $C_{21}H_{20}AuPNa$ ([M+Na]$^+$): 523.0866.



2.1j. Alkynyl gold compound **2.1j** was prepared according to a literature procedure.[2] The product was obtained as a white powder (58 mg, 71% yield). ^{1}H NMR (CD_2Cl_2, 500 MHz): δ 1.23 (s, 9H), 7.45 – 7.48 (m, 6 H), 7.51–7.56 (m, 9H). This spectrum is in agreement with previously reported spectral data.[2]



2.1k. Gold lactone **2.1k** was prepared according to a literature method.[3] ^{1}H NMR (CD_2Cl_2, 500 MHz): δ 1.43 (d, J = 6.9 Hz, 3H), 1.97 (t, J = 1.1 Hz, 3H), 4.99 (q, *J* = 6.6 Hz, 1H), 7.50–7.58 (m, 15H). This spectrum is in agreement with previously reported spectral data.[3]

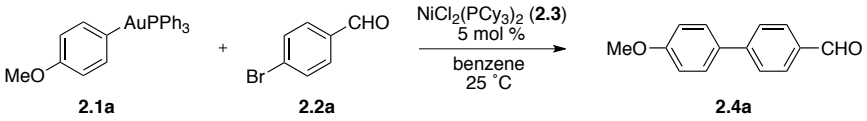
3g. 2-Bromopyrazine was prepared from 2-chloropyrazine and bromotrimethylsilane according to a literature procedure.[4] The desired product was obtained as a pale yellow oil after distillation at ca. 15 torr (631 mg, 23 % yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.37 (q, *J* = 0.2 Hz, 3.2 Hz, 1H), 8.52 (d, *J* = 2.5 Hz, 1H), 8.71 (d, *J* = 1.3 Hz, 1H). This spectrum is in agreement with previously reported spectral data.[4]

Representative small-scale cross-coupling screening procedure. In a N_2-filled glovebox, Ni catalyst **2.3** (0.6 mg, 0.0008 mmol, 0.05 equiv) was weighed into a dram vial. To it was added a solution of organohalide **2.2** (0.016 mmol, 1.0 equiv) and mesitylene (8.9 µL, 0.064 mmol, 4.0 equiv) in 0.25 mL C_6D_6. To the resulting red-purple suspension was added a solution of the organogold compound **2.1** (0.024 mmol, 1.3 equiv) in 0.25 mL C_6D_6 to afford a mixture that rapidly (ca. 2

min) became a clear solution. The solution was then transferred to a J. Young NMR tube for observation by ^{1}H NMR spectroscopy. All NMR spectra exhibited broad peaks prior to the completion of the reaction, presumably due to the presence of paramagnetic nickel complexes.

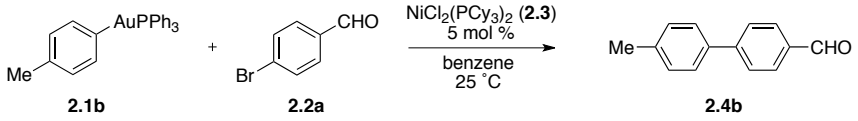
General cross-coupling procedure. In a N_2-filled glovebox, Ni catalyst 1 (3.5 mg, 0.0050 mmol, 0.050 equiv) was weighed into a 20-mL scintillation vial. To it was added a solution of halide 3 (0.100 mmol, 1.00 equiv) in 1.5 mL benzene. To the resulting red-purple suspension was pipetted a solution of organogold compund 2 (0.130 mmol, 1.30 equiv) in 1.5 mL benzene. The scintillation vial was equipped with an oven-dried stir bar and capped. The solution was stirred in the glovebox for the specified period of time. For reactions that required heating, the scintillation vial was capped, sealed with electrical tape, removed from the glovebox, and placed in a preheated oil bath. Upon completion, the reaction was exposed to air and the crude mixture was concentrated in vacuo. The resulting residue was dissolved in dichloromethane (ca. 2 mL) and loaded onto a 20 cm × 20 cm preparatory TLC plate (1500 Å or 1000 Å in thickness). The scintillation vial was rinsed with additional dichloromethane (3 × ca. 0.25 mL), and each rinsing was also loaded onto the TLC plate in order to ensure full transfer. The plate was developed as indicated, and then the product band was transferred to a 30 mL fine glass frit. Products were extracted by stirring the silica in EtOAc (3 × 25 mL), and then the silica cake was washed with additional EtOAc (2 × 25 mL) without stirring to flush any residual product-containing solvent. The resulting solution was con-

centrated and dried under high vacuum (<50 mtorr) to obtain the desired product. Most substrates required a second purification by preparatory plate TLC under identical conditions in order to fully separate tricyclohexylphosphine oxide and/or the organogold homocoupling product.



2.1a **2.2a** **2.4a**

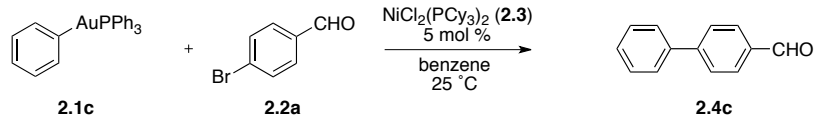
2.4a. 4-Formyl-4'-methoxybiphenyl was synthesized according to the general cross-coupling procedure. Organogold compound **2.1a** (73.6 mg) and bromide **2.2a** (18.5 mg) were employed (1.0 h, 25 ˚C). The product was isolated as a white solid (21.5 mg, quant. yield) through preparatory plate TLC developed using 2:1 hexanes:Et_2O. ^1H NMR ($CDCl_3$, 500 MHz): δ 3.88 (s, 3H), 7.02 (m, 2H), 7.61 (m, 2H), 7.73 (d, J = 8.2 Hz, 2H), 7.94 (d, J = 8.2 Hz, 2H). This spectrum is in agreement with previously reported spectral data for this compound.[5]



2.1b **2.2a** **2.4b**

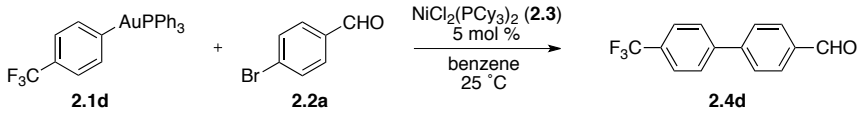
2.4b. 4-Formyl-4'-methylbiphenyl was synthesized according to the general cross-coupling procedure. Organogold compound **2.1b** (71.5 mg) and bromide **2.2b** (18.5 mg) were employed (1.0 h, 25 ˚C). The product was isolated as a white solid (17.4 mg, 83% yield) through preparatory plate TLC developed using 2:1 hexanes:Et_2O. ^1H NMR ($CDCl_3$, 500 MHz): δ 2.43 (s, 3H), 7.31 (d, J = 5.0 Hz, 2H), 7.56 (d, J = 10.0 Hz, 2H), 7.75 (d, J = 10.0 Hz, 2H), 7.95 (d, J = 5.0 Hz, 2H). This

spectrum is in agreement with previously reported spectral data for this compound.[6]



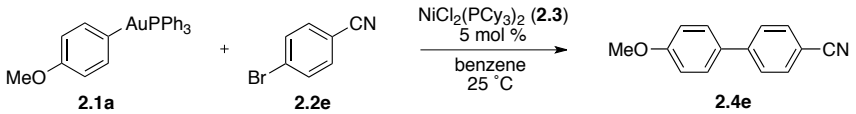
2.1c **2.2a** **2.4c**

2.4c. 4-Formylbiphenyl was synthesized according to the general cross-coupling procedure. Organogold compound **2.1c** (69.7 mg) and bromide **2.2a** (18.5 mg) were employed (1.0 h, 25 ˚C). The product was isolated as a white solid (17.5 mg, 96% yield) through preparatory plate TLC developed using 2:1 hexanes:Et_2O. ^1H NMR ($CDCl_3$, 500 MHz): 7.43 (m, 1H), 7.50 (m, 2H), 7.65 (d, *J* = 8.8 Hz, 2H), 7.77 (d, *J* = 8.2 Hz, 2H), 7.97 (d, *J* = 8.2Hz, 2H), 10.07 (s, 1H). This spectrum is in agreement with previously reported spectral data for this compound.[7]

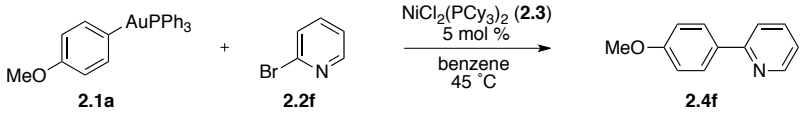


2.1d **2.2a** **2.4d**

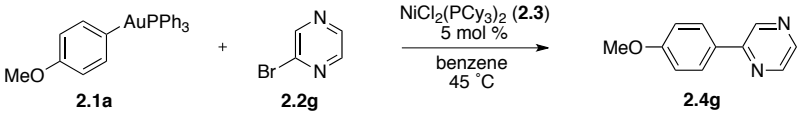
2.4d. 4-Formyl-4'-trifluoromethylbiphenyl was synthesized according to the general cross-coupling procedure. Organogold compound **2.1d** (78.5 mg) and bromide **2.1a** (18.5 mg) were employed (1.0 h, 25 ˚C). The product was isolated as a white solid (23.7 mg, 95% yield) following preparatory plate TLC developed using 2:1 hexanes:Et_2O. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.75 (s, 4H), 7.77 (d, *J* = 8.2 Hz, 2H), 8.00 (d, *J* = 8.2 Hz, 2H), 10.09 (s, 1H). This spectrum is in agreement with previously reported spectral data for this compound.[8]



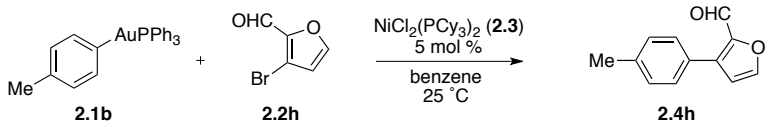
2.4e. 4-Cyano-4'-methoxybiphenyl was synthesized according to the general cross-coupling procedure. Organogold compound **2.1a** (73.6 mg) and bromide **2.2e** (18.2 mg) were employed (7.5 h, 25 °C). The product was obtained as a white solid (20.2 mg, 97% yield) following preparatory plate TLC developed using 2:1 hexanes:Et_2O. ^1H NMR ($CDCl_3$, 500 MHz): δ 3.87 (s, 3H), 7.00–7.03 (m, 2H), 7.53–7.56 (m, 2H), 7.64–7.65 (m, 2H), 7.69–7.70 (m, 2H). This spectrum is in agreement with previously reported spectral data for this compound.[9]



2.4f. 2-(4-Methoxyphenyl)pyridine was synthesized according to the general cross-coupling procedure. Organogold compound **2.1a** (73.6 mg) and bromide **2.2f** (15.8 mg) were employed (22 h, 45 °C). The product was isolated as an off-white solid (15.9 mg, 86% yield) following two TLC preparatory plates developed using 2:1 hexanes:Et_2O and 1:1 hexanes:Et_2O, respectively. ^1H NMR ($CDCl_3$, 500 MHz): δ 3.87 (s, 3H), 7.01 (d, J = 7.0 Hz, 2H), 7.17 (ddd, J = 4.9 Hz, 2.2 Hz, 1.2 Hz, 1H), 7.70 (m, 2H), 7.97 (d, J = 9.5 Hz, 2H), 8.66 (d, J = 4.0 Hz, 1H). This spectrum is in agreement with previously reported spectral data for this compound.[10]



2.4g. 2-(4-Methoxyphenyl)pyrazine was synthesized according to the general cross-coupling procedure. Organogold compound **2.1a** (73.6 mg) and bromide **2.2g** (15.9 mg) were employed (22 h, 45 ˚C). The product was isolated as white solid (15.3 mg, 82% yield) following two purifications by preparatory plate TLC. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.88, (s, 3H), 7.03 (d, J = 8.1 Hz, 2H), 7.99 (d, J = 8.1 Hz, 2H), 8.44 (s, 1H), 8.58 (s, 1H), 8.98 (s, 1H). This spectrum is in agreement with previously reported spectral data for this compound.[11]



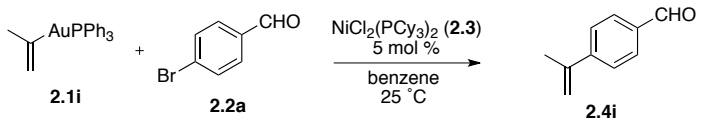
2.4h. 2-Formyl-3-(4-methylphenyl)furan was synthesized according to the general cross-coupling procedure. Organogold compound **2.1b** (71.5 mg) and bromide **2.2h** (17.5 mg) were employed (7.5 h, 25 ˚C). The initial preparatory plate TLC was developed using 2:1 hexanes:Et_2O. Two additional purifications by preparatory plate TLC were required, developed using 3:2 hexanes:Et_2O and 2:1 hexanes:Et_2O in order to achieve analytical purity. The product was isolated as a light brown oil (14.3 mg, 77% yield).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.42 (s, 3H), 6.72 (d, J = 0.9 Hz), 7.29 (d, J = 7.8 Hz), 7.47 (d, 8.0 Hz), 7.69 (d, J = 0.9 Hz).

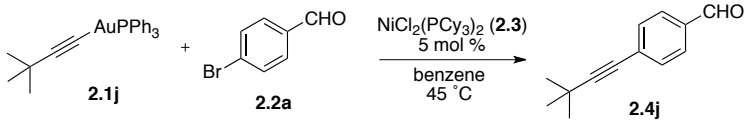
^{13}C NMR ($CDCl_3$, 500 MHz): δ 21.5, 113.8, 127.8, 129.1, 129.9, 139.2, 139.6, 147.6, 160.7, 178.1. Note: The quaternary carbon at δ = 160.7 was not

visible in a standard ^{13}C NMR spectroscopy experiment after 200 scans. It was detected through an HMBC experiment via its coupling with the neighboring aryl protons.

HRMS (ESI) found *m/z* = 209.0582. Calcd for $C_{12}H_{10}O_2Na$ ([M+Na]$^+$) 209.0578.



4i. 2-(4-Formylphenyl)propene was synthesized according to the general cross-coupling procedure. Organogold compound **2.1i** (65.0 mg) and bromide **2.2a** (18.5 mg) were employed (1.0 h, 25 ˚C). The product was obtained as a white solid following preparatory plate TLC developed using 3:1 hexanes:Et_2O. ^1H NMR ($CDCl_3$, 500 MHz): δ 2.19 (s, 3H), 5.25 (s, 1H), 5.52 (s, 1H), 7.62 (2, *J* = 8.2 Hz, 2H), 7.85 (d, *J* = 8.4 Hz, 2H), 10.00 (s, 1H). This spectrum is in agreement with previously reported spectral data for this compound.[12]

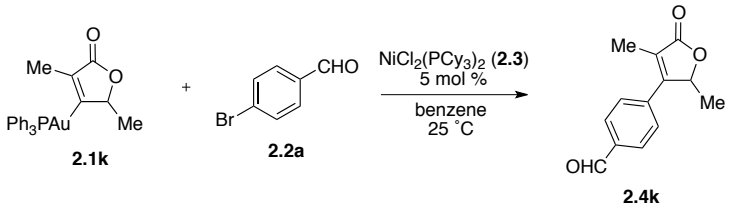


2.4j. 3,3-Dimethyl-1-(4-formylphenyl)-1-butyne was synthesized according to the general cross-coupling procedure. Organogold compound **2.1j** (66.2 mg) and bromide **2.2a** (18.5 mg) were employed (4.0 h, 45 ˚C). The product was isolated as an off-white solid (13.7 mg, 74% yield) following preparatory plate TLC developed using 2:1 hexanes:Et_2O.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.34 (s, 9H), 7.52 (d, *J* = 8.1 Hz, 2H), 7.79 (d, *J* = 8.0 Hz, 2H), 9.98 (s, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 28.4, 31.0, 78.8, 103.4, 129.6, 130.8, 132.3, 135.1, 191.8.

HRMS (ESI) found *m/z* = 209.0946. Calcd for $C_{13}H_{14}ONa$ ($[M+Na]^+$): 209.0942.

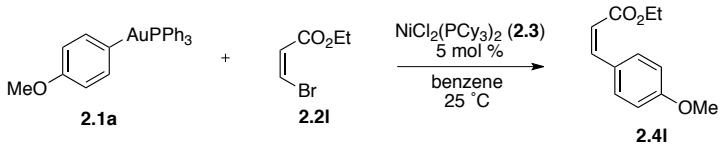


2.4k. 3,5-dimethyl-4-(4-formylphenyl)dihydrofuran-2-one was synthesized according to the general cross-coupling procedure. Organogold compound **2.1k** (74.1 mg) and bromide **2.2a** (18.5 mg) were employed (4 h, 45 °C). The product was isolated as pale yellow solid (8.6 mg, 40% yield) following three purifications by preparatory TLC developed using 3:2 hexanes:Et_2O, 1:2 hexanes:Et_2O, and 1:9 hexanes:DCM in that order.

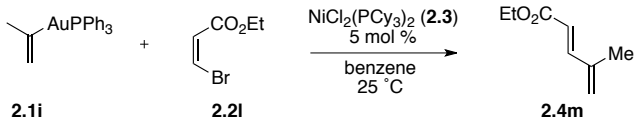
^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.39 (d, *J* = 6.8 Hz, 3H), 2.07 (d, *J* = 1.8 Hz, 3H), 5.45 (m, 1H), 7.53 (d, *J* = 8.2 Hz, 2H), 8.01 (d, *J* = 8.3 Hz, 2H), 10.08 (s, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 10.3, 19.2, 78.2, 125.7, 128.6, 130.3, 136.9, 137.4, 159.0, 173.8, 191.4.

HRMS (ESI) found *m/z* = 239.0675. Calcd for $C_{13}H_{12}O_3Na$ ($[M+Na]^+$): 239.0684.



2.4l. Ethyl (*Z*)-3-(4-methoxyphenyl)-2-propenoate was synthesized according to the general cross-coupling procedure. Organogold compound **2.1a** (73.6 mg) and bromide **2.2l** (17.9 mg) were employed (1.0 h, 25 ˚C). The product was obtained as a colorless oil (17.1 mg, 83% yield, single diastereomer) following preparatory plate TLC developed using 2:1 hexanes:Et_2O. An additional preparatory plate developed using 9:1 hexanes:Et_2O was required in order to remove trace amounts of the *E* diastereomer. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.29 (t, *J* = 7.1 Hz, 3H), 3.84 (s, 3 H), 4.21 (q, *J* = 14.3, 7.1 Hz, 2H), 5.84 (d, *J* = 12.8 Hz, 1 H), 6.85 (d, *J* = 12.8 Hz, 1H), 6.89 (m, 2H), 7.70 (d, *J* = 8.8 Hz, 2H). This spectrum is in agreement with previously reported spectral data for the *Z* isomer of this compound.[13] For reference, the E isomer is also reported in the literature.[14]



2.4m. Ethyl (*E*)-4-methylpenta-2,4-dienoate was synthesized according to the general cross-coupling procedure with modifications as described below. Organogold compound **2.1i** (65.0 mg) and bromide **2.2l** (17.9 mg) were employed (1 h, 25 ˚C). The product was not readily isolated due to its volatility. However, sufficient quantities of the clear, colorless oil were obtained for characterization (3.7 mg, 26% yield) as follows: upon completion of the 1 h reaction period, the solution

of the crude reaction was decreased in volume to ca. 0.7 mL under moderated vacuum. The solution was loaded directly onto a preparatory TLC plate using portions of DCM (3 × 0.1 mL) to ensure full transfer of the mixture. The plate was developed using 3:1 hexanes:Et_2O. The most intensely absorbing band by UV was extracted with DCM (4 × 20 mL) in a manner similar to the general procedure, and the solution was concentrated under moderated vacuum. A second preparatory TLC plate developed under identical conditions was required in order to achieve analytical purity. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.31 (t, *J* = 7.1 Hz, 3H), 1.90 (s, 3H), 4.23 (q, *J* = 7.1 Hz, 14.3 Hz), 5.35 (d, *J* = 10.3 Hz, 2H), 5.88 (d, *J* = 15.8 Hz, 2H), 7.37 (d, *J* = 15.8 Hz). This spectrum is in agreement with previously reported spectral data for this compound.[15]

Mechanistic Studies

Homocoupling of **2.1a** *to yield* **2.5a** (Scheme 2.3). In a N_2-filled glovebox, nickel complex **2.3** (2.5 mg, 0.0036 mmol, 1.0 equiv) and organogold compound **2.1a** (20.5 mg, 0.0360 mmol, 10 equiv) were weighed into separate dram vials. Mesitylene (3.0 mg, 3.5 µL, 0.025 mmol, 7.0 equiv) was added to 1 by syringe. To this mixture was added a solution of organogold compound **2.1a** in 0.5 mL C_6D_6. The reaction mixture was mixed by pipet until all solids were dissolved, and the solution was transferred to a J. Young tube for observation by ^{1}H NMR spectroscopy. This sample exhibited broad peaks by ^{1}H NMR spectroscopy both prior to and following the completion of the reaction, presumably due to the presence of paramagnetic nickel complexes. A separate sample with mesitylene omitted was

prepared in a similar manner for analysis by EPR spectroscopy after 4.5 h at 77 K. A single peak with complex nuclear coupling was observed centered at g = 2.17 at 77 K. No nuclear coupling was observed at 298 K, which is consistent with a metal-centered radical.

Stereospecific coupling of 1-bromo-1-propene (**2.6**). The light in a N_2-filled glovebox was turned off to preclude any light-induced isomerization. In the glovebox, mesitylene (8.9 µL, 7.7 mg, 0.064 mmol, 4.0 equiv) was added to (*Z*)- or (*E*)-1-bromo-1-propene, (**2.6**, 1.9 mg, 0.016 mmol, 1.0 equiv) in a dram vial. This solution was diluted in 0.15 mL C_6D_6 and was transferred to another dram vial containing $NiCl_2(PCy_3)_2$, (**2.3**, 0.6 mg, 0.0008 mmol, 0.05 equiv), using additional C_6D_6 (1 × 0.10 mL) as a rinse to ensure full transfer. To the resulting red-purple suspension was added a solution of organogold compound **2.1a** (11.9 mg, 0.0210 mmol, 1.30 equiv) in 0.25 mL C_6D_6. The reaction mixture was mixed by pipet until it became a transparent yellow solution (ca. 2 min), and the solution was then transferred to a J. Young tube and protected from light by wrapping it with aluminum foil. After being removed from the glovebox, the tube was heated in a 50 °C oil bath while still shielded from light with aluminum foil. The reaction progress was monitored periodically by ^{1}H NMR spectroscopy. Upon consumption of the organogold starting material, the reaction was exposed to air and concentrated under reduced pressure in a rotary evaporator under moderated vacuum to reduce the loss of product due to its slight volatility. The resulting residue was extracted with 3:1 hexanes:Et_2O and filtered through a silica gel plug (3 cm × 0.5

cm) using ca. 6 mL of the same solvent mixture. The solution was then concentrated under mild vacuum, and the residue was dissolved in $CDCl_3$ for ^1H NMR spectroscopic analysis. Comparison to the reported spectral data[16] for both isomers of the cross-coupled product 6 revealed that the reaction of (*Z*)-**2.6** yielded primarily (*Z*)-**2.7** and that of (*E*)-**2.6** yielded (*E*)-**2.7**.

References for Experimental Section.

1. Quasdorf, K. W.; Tian, X.; Garg, N. K. *J. Am. Chem. Soc.* **2008**, *130*, 14422–14423.
2. Roth, K. E.; Blum, S. A. *Organometallics* **2010**, *29*, 1712–1716.
3. Liu, L.-P.; Zu, B.; Mashuta, M. S.; Hammond, G. B. *J. Am. Chem. Soc.* **2008**, *130*, 17642–17643.
4. Schlosser, M.; Cottet, F. *Eur. J. Org. Chem.* **2002**, *2002*, 4181–4184.
5. Mao, J.; Guo, J.; Fang, F.; Ji, S.-J. *Tetrahedron* **2008**, *64*, 3905–3911.
6. Inada, K.; Miyaura, N. *Tetrahedron* **2000**, *56*, 8657–8660.
7. Zhou, W.-J.; Wang, K.-H.; Wang, J.-X.; Huang, D.-F. *Eur. J. Org. Chem.* **2010**, 416–419.
8. Chung, J. W.; You, Y.; Huh, H. S.; An, B.-K.; Yoon, S.-J.; Kim, S. H.; Lee, S. W.; Park, S. Y. *J. Am. Chem. Soc.* **2009**, *131*, 8163–8172.
9. Inés, B.; San Martin, R.; Moure, M. J.; Domínguez, E. *Adv. Synth. Catal.* **2009**, *351*, 2124–2134.
10. Kobayashi, O.; Uraguchi, D.; Yamakawa, T. *Org. Lett.* **2009**, *11*, 2679–2682.
11. Huh, D. H.; Ryu, H.; Kim, Y. G. *Tetrahedron* **2004**, *60*, 9857–9862.
12. Peyroux, E.; Berthiol, F.; Doucet, H.; Santelli, M. *Eur. J. Org. Chem.* **2004**,

2004, 1075–1082.

13. Kojima, S.; Takagi, R.; Akiba, K. *J. Am. Chem. Soc.* **1997**, *119*, 5970–5971.
14. Chen, Y.; Huang, L.; Ranade, M. A.; Zhang, X. P. *J. Org. Chem.* **2003**, *68*, 3714–3717.
15. Marcus, A. P. Lee, A. S.; Davis, R. L.; Tantillo, D. J.; Sarpong, R. *Angew. Chem., Int. Ed.* **2008**, *47*, 6379–6383.
16. McNulty, J.; Keskar, K. *Tetrahedron Lett.* **2008**, *49*, 7054–7057.

Chapter 3
Gold and Palladium Dual-Catalyzed Ring-Expansion of Alkenyl Vinyl Aziridines

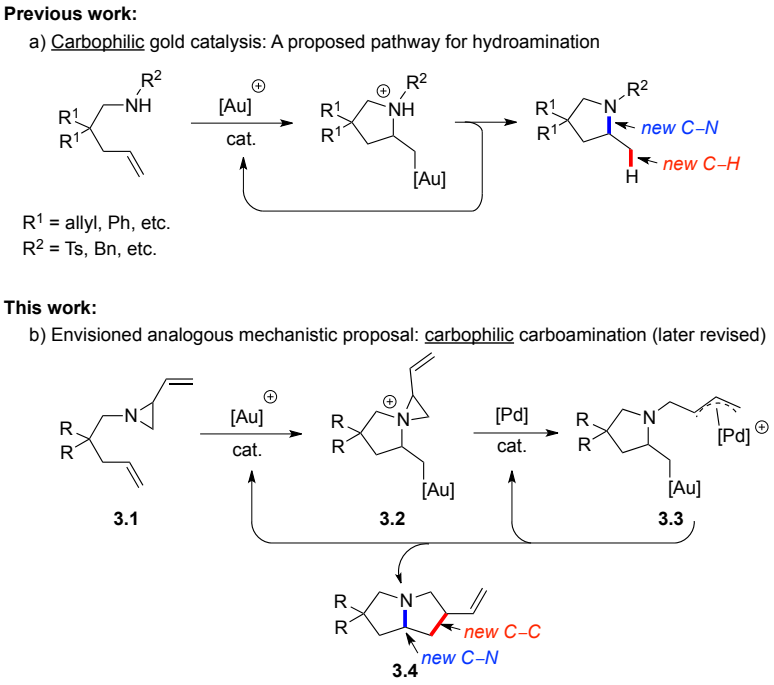
Abstract: A vinyl aziridine activation strategy cocatalyzed by Pd(0) and a Au(I) Lewis acid was developed. This rearrangement installs a C–C and a C–N bond in one synthetic step to form pyrrolizidine and indolizidine products. Two proposed mechanistic roles for the gold cocatalyst were considered: (1) carbophilic gold catalysis or (2) azaphilic gold catalysis. Mechanistic studies support an azaphilic Lewis acid activation of the aziridine over a carbophilic Lewis acid activation of the alkene.

Introduction

Following unsuccessful attempts to develop a Ni/Au dual-catalyzed reaction based upon the results disclosed in Chapter 1, attention was then turned to expanding general reaction manifold of Pd/Au dual catalysis[1,2] to include C–N bond activation. Specifically, a Pd/Au dual-catalyzed *carboamination* reaction was inspired by reports of gold-catalyzed *hydroamination* reactions of olefins,[3] which are proposed to proceed through carbophilic activation of the π system leading to alkylgold intermediates (Scheme 3.1a). This activation manifold has been supported experimentally by Toste and coworkers through the isolation of alkylgold intermediates in a gold-promoted hydroamination reaction.[4] In Au-catalyzed hy-

droamination reactions, this C–Au σ-bond is often proposed to undergo subsequent protodeauration to form a C–H bond.[5]

Scheme 3.1. (a) Previous carbophilic hydroamination work by others. (b) This work: original envisioned analogous mechanism for carbophilic carboamination.



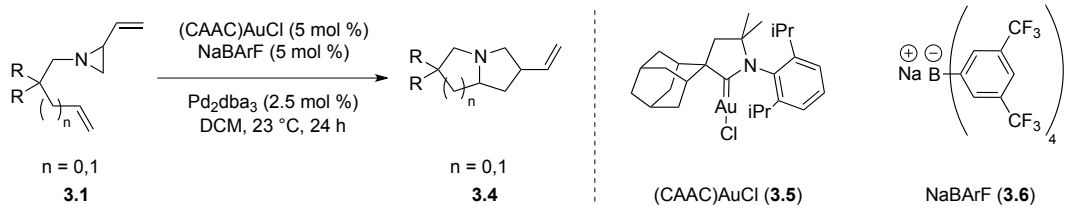
Mechanistically related to the hydroamination reaction, we envisioned a *carboamination* reaction[6] (Scheme 3.1b). It was hypothesized that vinyl aziridine **3.1** could undergo a carbophilic gold-catalyzed cyclization similar to Toste's aminoauration of olefins with ureas[4] and Bertrand's aminoauration of alkynes with tertiary amines (Scheme 3.1a).[7] The resulting vinyl aziridinium ion **3.2** would be electronically activated for oxidative addition by Pd(0) because of the enhanced leaving group ability of the ammonium as a neutral amine.[8] An intramolecular gold/palladium cross-coupling reaction would afford pyrrolizidine **3.4** and regenerate both gold and palladium catalysts.

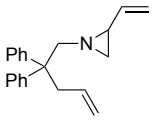
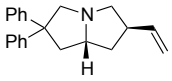
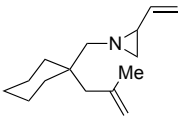
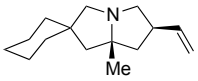
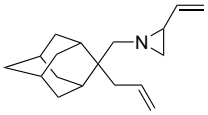
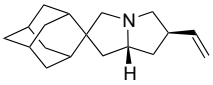
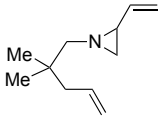
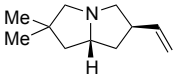
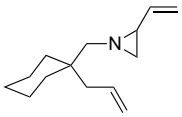
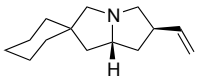
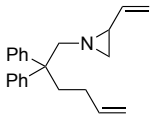
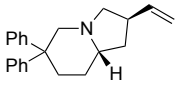
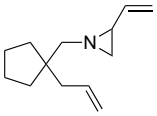
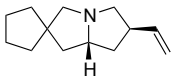
Guided by this mechanistic hypothesis, a Pd and Lewis acid cocatalyzed ring-expansion of vinyl aziridines was developed. This reaction forms pyrrolizidines and indolizidines, two classes of *N*-fused heterocycles that are of interest because they exhibit biological activity.[9-11] Subsequent mechanistic experiments revealed that the carbophilic activation pathway shown in Scheme 3.1 was *not* operative in the dual-catalyzed carboamination transformation; instead, the reaction proceeds through an uncommon azaphilic activation by Au(I).[12-14]

Results and Discussion

To probe the conceptualized carboamination reactivity, we treated *gem*-diphenyl vinyl aziridine **3.1a** with 5 mol % (CAAC)AuCl/NaBArF and 2.5 mol % Pd_2dba_3 in CD_2Cl_2 at room temperature (Table 1). This reaction afforded carboamination product pyrrolizidine **3.2a** in 76% isolated yield. This reaction tolerated adamantyl (**3.2b**, 86%), cyclohexyl (**3.2c**, 56%), and cyclopentyl (**3.2d**, 51%) substitutions. However, a *gem*-dimethyl group substitution (**3.1f**) gave no reaction, presumably due to a reduced rate of cyclization from a diminished Thorpe-Ingold effect.[15] Methyl substitution at the internal position of the tethered alkene was tolerated (**3.2e**, 67%). Increasing the olefin tether length in diphenyl vinyl aziridine **3.1g** afforded indolizidine **3.2g** in good yield (74%) with an increased diastereomeric ratio (10:1).

Table 3.1. Substrate scope of the Au/Pd dual-catalyzed ring-expansion reaction.



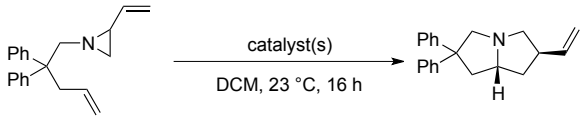
Starting material	Product	Starting material	Product
 **3.1a**	 **3.2a** 76% d.r. = 1:1	 **3.1e**	 **3.2e** 67%[b,c] d.r. = 2:1
 **3.1b**	 **3.2b** 86%[a] d.r. = 1:1	 **3.1f**	 **3.2f** no reaction[c]
 **3.1c**	 **3.2c** 56%[b] d.r. = 3:1	 **3.1g**	 **3.2g** 74%[d] d.r. = 10:1
 **3.1d**	 **3.2d** 51%[c,d] d.r. = 4:1		

[a] 15 mol % (CAAC)AuCl/NaBArF, 7.5 mol % Pd_2dba_3, 5 d. [b] 48 h.
[c] 10 mol % (CAAC)AuCl/NaBArF, 5 mol % Pd_2dba_3. [d] 40 °C.

Control experiments revealed that both Pd_2dba_3 and in situ-generated (CAAC)AuBArF were required for the observed dual-catalytic reactivity (Table 2). However, in contrast to our previous reports of Pd/Au cocatalyzed reactions,[1,2]

this reaction displayed a slow but nonzero background reaction with Pd_2dba_3 alone.

Table 3.2. Control experiments for the Au/Pd dual-catalyzed ring-expansion reaction.



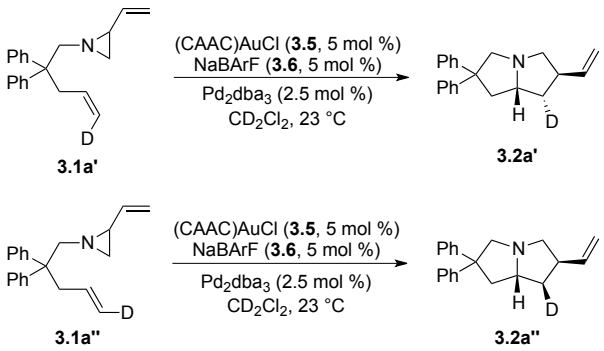
3.1a **3.4a**

Entry	*Catalyst(s)*	*Loading*	*Conversion to **3.4a***
1	(CAAC)AuCl/NaBArF (**3.5**/**3.6**)	5.0 mol % / 5.0 mol %	No reaction
2	CAAC carbene/Pd_2dba_3	10. mol % / 5.0 mol %	No reaction
3	$PdCl_2(PPh_3)_2/AgSbF_6$	10. mol % / 20. mol %	Decomposition
4	Pd_2dba_3	5.0 mol %	7 %
5	NaBArF (**3.6**)	5.0 mol %	No reaction
6	CAAC carbene	10. mol %	No reaction

[a] By ^1H NMR spectroscopy.

In order to probe the mechanism of this reaction, *Z* and *E* monodeuterated analogs of vinyl aziridine **3.1a** were subjected to the dual-catalytic rearrangement conditions (Scheme 3.2). The *Z* diastereomer (**3.1a'**) generated only the 1,2-*trans* product **3.2a'**, and the *E* diastereomer of aziridine (**3.1a"**) provided exclusively the 1,2-*cis* diastereomer **3.2a"**.

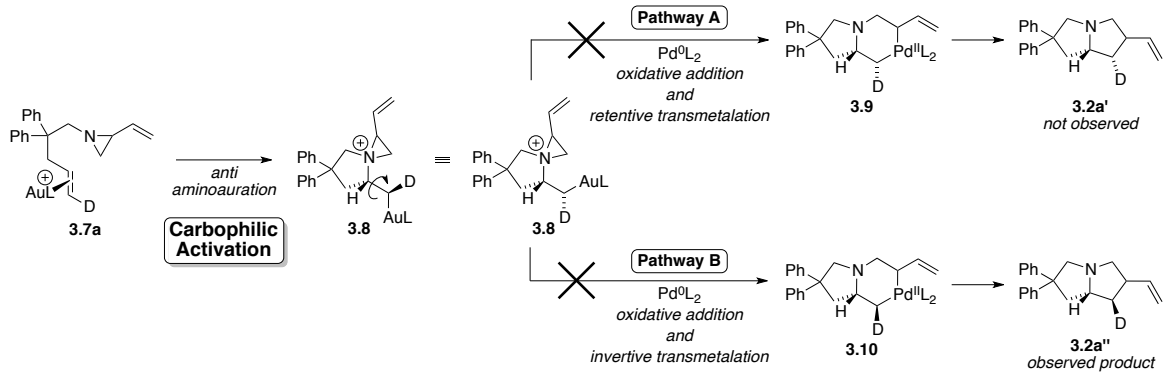
Scheme 3.2. Stereospecificity in the ring-expansion of deuterium-labelled vinyl aziridines.



This observed stereospecificity was inconsistent with a carbophilic activation mechanism (Scheme 3.1b), which would have resulted in the opposite diastereomer of each product at the deuterium-labeled carbon. In a carbophilic activation mechanism, the cationic gold catalyst could bind reversibly to the tethered olefin[16] and serve as a carbophilic Lewis acid (Scheme 3.2, complex **3.7a**). The aziridine would then be primed for an intramolecular *anti* aminoauration to provide **3.8**,[17] an elementary step well-established for other amine nucleophiles with both Au(I)[3a,4] and Au(III).[18] Pd(0) could then undergo oxidative addition into the aziridinium moiety, and alkyl Au-to-Pd alkyl transmetalation[19] with retention of configuration (Pathway A) would provide palladacycle **3.9**. A stereochemically retentive transmetalation, which is typical for Pd(II) with relatively nonpolar organometallic complexes such as trialkyl[20] or pinacol boronates[21] and alkylmercury(II) complexes,[22] is expected owing to the nonpolar nature of the C–Au bond.[23] A retentive C–C bond-forming reductive elimination[24] from Pd(II) intermediate **3.9** would have provided the expected 1,2-*cis* product **3.2a'**. Instead, 1,2-*trans* pyrrolizidine

product **3.2a''** was formed exclusively, thus eliminating Pathway A from further consideration.

Scheme 3.3. Possible mechanisms involving carbophilic activation by Au.

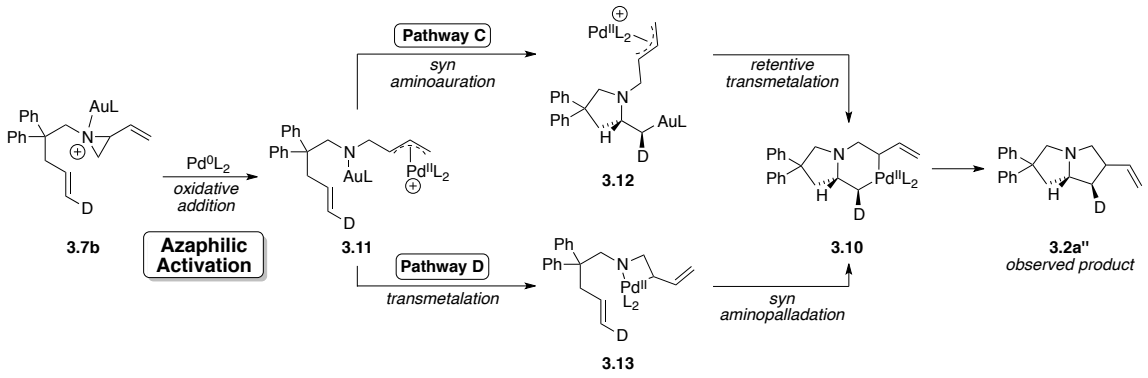


This surprising mechanistic data inspired us to consider several alternative mechanisms. First, Pd(0) could undergo oxidative addition into aziridinium complex **3.8** but instead undergo an *invertive* transmetalation reaction (Scheme 3.2, Pathway B). However, invertive transmetalation reactions generally occur only for polarized carbon–metal bonds,[25] such as alkyllithium[26] and alkyltrifluoroborate[27] compounds or in highly polar solvents, such as HMPA.[28,29] In contrast, the C–Au bond is largely nonpolar,[23] and the dichloromethane used in our reactions is a less polar solvent; an invertive transmetalation from an alkyl-Au complex would thus represent an unusual elementary step. Pathway B was therefore unlikely, but further investigation into the stereochemistry of this fundamental step was warranted (vida infra).

We considered another possible mechanism in which the cationic gold complex bound reversibly to the aziridine nitrogen as an azaphilic Lewis acid[12-14]

(Scheme 3.4, complex **3.7b**), priming the vinyl aziridine for oxidative addition by Pd(0)[30] to provide heterobimetallic amide **3.11**. Intermediate **3.11** is then poised for a *syn* aminoauration reaction (Pathway C), a selectivity postulated only infrequently.[31-34] The alkylgold fragment in **3.12** could then undergo a retentive transmetalation, which is expected based upon the polarity of the C–Au bond. Finally, retentive reductive elimination from palladacycle **3.10** would provide the observed diastereomer of pyrrolizidine product **3.2a''**. Because evidence supporting *syn* aminoauration by Au(I) is scarce in comparison to data supporting *anti* aminoauration,[3a,4] this mechanistic hypothesis remains unlikely; however, this pathway cannot be disregarded.

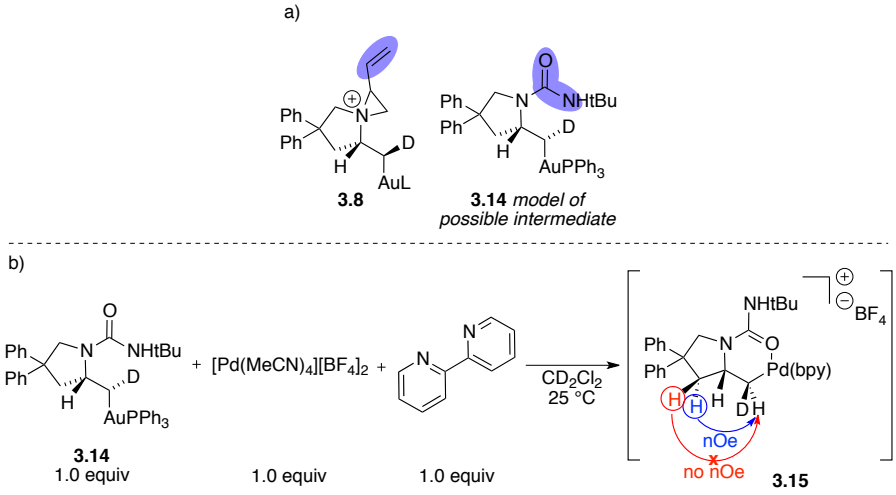
Scheme 3.4. Possible mechanisms involving azaphilic activation by Au.



An additional possible mechanism was considered in which the Pd intermediate **3.13** undergoes a *syn* aminopalladation[35,36] reaction with the tethered olefin to provide **3.10** directly (Pathway D). This mechanistic hypothesis circumvents the unlikely *syn* aminoauration step and avoids the stereochemical complexities associated with the alkyl Au-to-Pd transmetalation reaction while still

providing a plausible route to observed product **3.2a"**. Pathway D bears a mechanistic resemblance to the Pd-only-catalyzed aminoarylation reactions of olefins pioneered by Wolfe, which have been shown to proceed through *syn* aminopalladation elementary steps.[37]

Scheme 3.5. (a) A possible catalytic intermediate and an isolable model complex. (b) Stoichiometric alkyl transmetalation from Au to Pd showing retention of stereochemistry.



Attempts to characterize several of the organometallic intermediates shown in Schemes 3.3 and 3.4 were unsuccessful in differentiating between the proposed mechanisms. Attention was instead turned towards probing the stereochemical outcome of the possible Au-to-Pd alkyl transmetalation step. We prepared alkylgold complex **3.14** (Scheme 3.5), which was isolated by Toste in a gold-promoted mechanistic study of the aminoauration of olefins.[4] This isolable complex is a model for possible catalytic intermediate **3.8** (Scheme 3.3, Pathways A and B) with Pd: both complexes possess an alkylgold fragment exocyclic to a pyrrolidine core. Furthermore, both also possess a tethered Lewis basic group

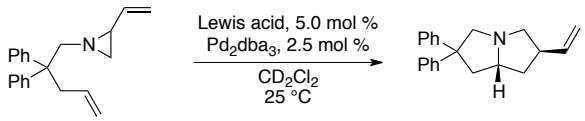
(Scheme 3.5, highlighted in blue), which could serve as a directing group for transmetalation by first binding to Pd.

Model alkylgold complex **3.14** was treated with a source of dicationic Pd and 2,2'-bipyridine. The sole pyrrolidine product was characterized spectroscopically as **3.15** via nOe experiments. Specifically, irradiating at the indicated proton in complex **3.15** resulted in an nOe enhancement at the alkyl-Pd chiral center (Scheme 3.5b). Molecular modeling on the analogous perprotiated complex with density functional theory (DFT) calculations using the PBE functional[38] confirm that the interatomic distances the ground state conformer allow for the nOe enhancements observed experimentally, thereby validating the structural assignment. This first direct observation of the stereochemical outcome of a transmetalation reaction between a chiral sp^3 organogold complex and Pd indicates complete retention of stereochemistry. Given the nOe data, the computational support of DFT calculations, and the several prior reports of retentive transmetalation with other nonpolar organometallic compounds,[20-22] mechanistic Pathway B (Scheme 3.3) was eliminated from further consideration. Consequently, both carbophilic activation mechanisms A and B were ruled out on the basis of the experimental observations.

With Pathways A and B eliminated from consideration in favor of azaphilic pathways C and D (Scheme 3.4), the nature of the active azaphilic Au(I) cocatalyst was then examined. The reaction of (CAAC)AuCl (**3.5**) with NaBArF (**3.6**) rapidly and quantitatively affords (CAAC)AuBArF and NaCl; however, it is possible that NaBArF was present in equilibrium[39] with (CAAC)AuBArF/NaCl and cocata-

lyzed the reaction. Indeed, even in the absence of Au(I), NaBArF was a competent cocatalyst with Pd(0), promoting the reaction in 87% ^{1}H NMR spectroscopic yield (Table 3.3, entry 1). This assay yield is higher than that which was obtained in the presence of (CAAC)AuBArF/NaCl (entry 2), yet rigorous removal of NaCl from (CAAC)AuBArF confirmed that (CAAC)AuBArF was also a competent cocatalyst even in the absence of Na (entry 3).[40]

Table 3.3. Investigation of the active Lewis acid cocatalst from Table 3.1.



3.1a **3.4a**

Entry	*Lewis Acid*	*^{1}H NMR Yield*[a]
1	NaBArF (**8**)	87%
2	(CAAC)AuBArF generated *in situ* from **7**+**8**, NaCl not removed	79%
3	(CAAC)AuBArF pre-formed from **7**+**8**, NaCl removed	64%
4	(NBu_4)BArF	27%
5	None	18%

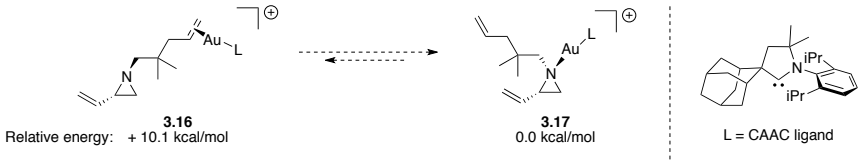
[a] Relative to mesitylene internal standard. Reaction conditions: **1a** (1.0 equiv), Pd_2dba_3 (2.5 mol%), Lewis acid (5.0 mol%), CD_2Cl_2, 25 °C, 24 h.

In order to separate the effects of the Na cation from the BArF anion, (NBu_4)BArF was examined as a cocatalyst with Pd(0) (entry 6). Its poor cocatalytic activity confirms the hypothesis that the azaphilic Lewis acid Na^+ is indeed responsible for the observed reactivity from NaBArF rather than any significant ion

exchange effects from the BArF anion itself, in contrast to that reported for a previous π-allyl palladium coupling.[41]

We suspected that the same azaphilic activation mechanism might be operative for both (CAAC)AuBArF and NaBArF. To test this hypothesis, we repeated the rearrangement of deuterium-labeled aziridine **3.1a'** (Scheme 3.2) after rigorously removing NaCl from (CAAC)AuBArF. The 1,2-*trans* product **3.2a'** was again obtained, albeit with a longer reaction time (perhaps due to catalyst loss upon filtration); the stereochemical course of the reaction is thus the same for the Au(I) Lewis acid and the mixture of Au(I) and Na, suggesting that Na and Au(I) Lewis acids operate by a similar azaphilic activation pathway. Therefore, the mechanism of this reaction represents an uncommon reaction manifold for Au(I), which is generally employed as a carbophilic Lewis acid.[42-44] We have further supported the plausibility of this Au–N binding mode in the presence of a tethered olefin by DFT calculations, which revealed that the binding of (CAAC)Au(I) cation to vinyl aziridine **3.1f** favored the *N*-bound complex over the π-complex by 10 kcal/mol (Scheme 3.6). Of course, these data do not preclude the possibility of a Curtin-Hammett-type reaction manifold in which the thermodynamically disfavored π-complex (**3.16**) is the kinetically competent intermediate; however, they do demonstrate the feasibility of Au(I) binding to the aziridine as originally established crystallographically by Nöth and coworkers,[12] and that this binding mode remains theromodynamically accessible even in the presence of a potentially competing olefin.

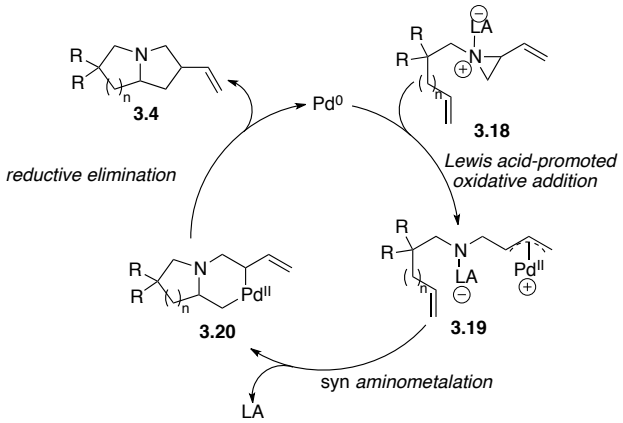
Scheme 3.6. Calculated thermodynamic favorability of azaphilic substrate binding mode.



Gas phase DFT calculations were performed at the PBE/SDD (Def2SV) level of theory.

Based on the mechanistic data and the efficacy of the NaBArF Lewis acid as a cocatalyst, we propose the catalytic cycle shown in Scheme 3.7. First, the aziridine undergoes Lewis acid-promoted oxidative addition[45–47] by Pd(0). The resulting Pd(II) intermediate **3.19** then undergoes a *syn* aminometalation.[48] The observed product **3.4** is then obtained following a reductive elimination from palladacyclic intermediate **3.20**. This catalytic cycle is generalized from mechanistic Pathways C or D from Scheme 3.4.

Scheme 3.7. General catalytic cycle for the dual-catalyzed ring-expansion reaction.



In summary, a Pd and Lewis acid dual-catalyzed ring-expansion of vinyl aziridines to pyrrolizidine and indolizidine products was developed. This reaction installs a new C−C bond and a new C−N bond in *N*-fused heterocyclic frame-

works in one synthetic step. During the course of mechanistic experiments, an alkyl Au/Pd transmetalation was found to occur with complete retention of stereochemistry. This first study of the retentive stereochemistry of transmetalation of chiral organogold(I) complexes to palladium and a successful strategy for avoiding competing redox quenching of gold(I) by palladium[49] provide insight into this subset of dual-metal catalysis. The reaction does *not* proceed through carbophilic Au(I) catalysis. Instead, an uncommon role for catalytic Au(I) as an azaphilic Lewis acid was revealed, even in the presence of a potential competing carbophilic activation pathway. These mechanistic studies lend support to previous reports that gold binding to heteroatoms may be responsible for catalytic activity in some gold-catalyzed hydroamination reactions of alkenes, rather than direct gold π-complex activation.[5a-c]

References

1. Shi, Y.; Peterson, S. M.; Haberaecker, W. W., III; Blum, S. A.; *J. Am. Chem. Soc.* **2008**, *130*, 2168–2169.
2. Shi, Y.; Roth, K. E.; Ramgren, S. D.; Blum, S. A. *J. Am. Chem. Soc.*, **2009**, *131*, 18022–18023.
3. For two noteworthy examples, see: (a) Zhang, J.; Yang, C.-G.; He, C. *J. Am. Chem. Soc.*, **2006**, *128*, 1798–1799. (b) Bender, C. F.; Widenhoefer; R. A., *Chem. Commun.* **2008**, 2741–2743.
4. LaLonde, R. L.; Brenzovich, W. E., Jr.; Benitez, D.; Tkatchouk, E.; Kelley, K.; Goddard, W. A., III; Toste, F. D. *Chem. Sci*, **2010**, *1*, 226–233.

5. The exact role of the Lewis acidic metal in metal-catalyzed hydroamination reactions is a matter of ongoing investigation. Some reports have suggested the metal is active only in forming a Brønsted acid that is responsible for protonation of the olefin. See (a) ref. 21. (b) Kanno, O.; Kuriyama, W.; Wang, Z. J.; Toste, F. D. *Angew. Chem. Int. Ed.* **2011**, *50*, 9919–9922. (c) Rosenfeld, D. C.; Shekhar, S.; Takemiya, A.; Utsunomiya, M.; Hartwig, J. F. *Org. Lett.* **2006**, *8*, 4179–4182. (d) McBee, J. L.; Bell, A. T.; Tilley, T. D. *J. Am. Chem. Soc.* **2008**, *130*, 16562–16571.
6. Wu, H.; He, Y.-P.; Gong, L.-Z.; *Adv. Synth. Catal.*, **2012**, *354*, 975–980.
7. Zeng, X.; Kinjo, R.; Donnadieu, B.; Bertrand, G. *Angew. Chem. Int. Ed.*, **2010**, *49*, 942–945.
8. Amatore, C.; Jutland, A.; Mensah, L.; Meyer, G.; Fiaud, J.-C.; Legros, J-Y. *Eur. J. Org. Chem.*, **2006**, 1185–1192.
9. Mattocks, A. R. *Nature*, **1968**, *217*, 723–728.
10. Kim, H. Y.; Stermitz, F. R.; Molyneux, R. J.; Wilson, D. W.; Taylor, D.; Coulombe, R. A., Jr., *Toxicol. Appl. Pharmacol.* **1993**, *122*, 61–69.
11. Liddell, J. R.; *Nat. Prod. Rep.* **2002**, *19*, 773–781.
12. Lorenz, I.-P.; Krinninger, C.; Wilberger, R.; Bobka, R.; Piotrowski, H.; Warchhold, M.; Nöth, H. *J. Organomet. Chem.* **2005**, *690*, 1986–1993.
13. Yamamoto, Y. *J. Org. Chem.* **2007**, *72*, 7817–7831.
14. For a proposed activation by bidentate binding of Au(I) simultaneously to an alkyne and an aziridine, see: Kern, N.; Blanc, A.; Miaskiewicz, S.; Robinette, M.; Weibel, J.-M.; Pale, P. *J. Org. Chem.* **2012**, *77*, 4323–4341.

15. Jung, M. E.; Piizi, G. *Chem. Rev.*, **2005**, ***105***, 1735–1766.

16. Shapiro, N. D.; Toste, F. D.; *Proc. Natl. Acad. Sci. USA*, **2008**, *105*, 2779–2782.

17. For selected references proposing *anti* aminoauration reactions, see: (a) Hashmi, A. S. K.; Rudolph, M.; Schymura, S.; Visus, J.; Frey, W.; *Euro. J. Org. Chem.* **2006**, 4905–4909. (b) Iglesias, A.; Muñiz, K. *Chem.—Eur. J.*, **2009**, *15*, 10563–10569. (c) Zhang, G.; Cui, L.; Wang, Y.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 1474–1475. (d) Li, H.; Song, F.; Widenhoefer, R. A. *Adv. Synth. Catal.* **2011**, *353*, 955–962. (e) de Haro, T.; Nevado, C. *Angew. Chem. Int. Ed.*, **2011**, *50*, 906–910.

18. Tkatchouk, E.; Mankad, N. P.; Benitez, D.; Goddard, W. A., III; Toste, F. D.; *J. Am. Chem. Soc.* **2011**, *133*, 14293–14300.

19. (a) Shi, Y.; Ramgren, S. D.; Blum, S. A. *Organometallics*, **2009**, *28*, 1275–1277. (b) Peña-López, M.; Ayán-Varela, M.; Sarandeses, L. A.; Pérez Sestelo, J.; *Chem.—Eur. J.*, **2010**, *16*, 9905–9909.

20. (a) Ridgway, B. H.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 458–460. (b) Taylor, B. L. H.; Jarvo, E. R. *J. Org. Chem.*, **2011**, *76*, 7573–7576.

21. Imao, D.; Glasspoole, B. W.; Laberge, V. S.; Crudden, C. M. *J. Am. Chem. Soc.* **2009**, *131*, 5024–5025.

22. Bäckvall, J.-E.; Åkermark, B. *J. Chem. Soc. Chem. Commun.* **1975**, 82–83.

23. As evidenced by its resistance to protonolysis. See: Roth, K. E.; Blum, S. A. *Organometallics* **2010**, *29*, 1712–1716.

24. Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4981–4991.

25. Alkyl Grignard reagents are thought to undergo transmetalation through a racemizing single-electron transfer pathway. See (a) Dakternieks, D.; Dunn, K.; Henry, D. J. *Organometallics* **1999**, *18*, 3342–3347. (b) Hoffmann, R. W.; Hölzer, B. *J. Am. Chem. Soc.* **2002**, *124*, 4204–4205.
26. Klein, S.; Marek, I.; Normant, J.-F. *J. Org. Chem.*, **1994**, *59*, 2925–2926.
27. Sandrock, D. L.; Jean-Gérard, L.; Chen, C.-Y.; Dreher, S. D.; Molander, G. A. *J. Am. Chem. Soc.*, **2010**, *132*, 17108–17110.
28. Benzylic siliconates are known to undergo transmetalation to Pd with either inversion or retention depending upon the solvent and temperature at which the reaction is conducted. Inversion was only observed in HMPU and is proposed to occur through an S_E2-type pathway. See: Hatanaka, Y; Hiyama, T. *J. Am. Chem. Soc.*, **1990**, *112*, 7793–7794.
29. Nonpolarized benzylic trialkylstannanes have been shown to undergo exclusively invertive benzyl transfer to Pd, but this reaction occurs in HMPA and is thought to occur thorugh an S_E2 mechanism. See: Labadie, J. W.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 669–670.
30. (a) Trost, B. M.; Fandrick, D. R. *J. Am. Chem. Soc.* **2003**, *125*, 11836–11837. (b) Trost, B. M.; Osipov, M.; Dong, G. *J. Am. Chem. Soc.* **2010**, *132*, 15800–15807.
31. Toste and coworkers originally proposed a *syn* aminoauration reaction as a part of a Au(I)/Au(III) catalytic cycle, but they have since published a revised mechanism. See ref. 18 for the revision. For the original hypothesis, see: Bernzovich, W. E., Jr.; Benitez, D.; Lackner, A. D.; Shunatona, H. P.;

Tkatchouk, E.; Goddard, W. A., III; Toste, F. D. *Angew. Chem. Int. Ed.*, **2010**, *49*, 5519–5522.

32. As a related process, we have found a single example of a hypothesized *syn* alkoxyauration with under Au(I)-catalyzed conditions. However, this reaction occurs in the presence of 0.99 equiv concentrated H_2SO_4 and is therefore not directly related to most other Au-catalyzed processes. See: Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem. Int. Ed.*, **1998**, *37*, 1415–1418.
33. Hopkinson, M. N.; Gee, A. D.; Gouverneur, V. *Chem.—Eur. J.* **2011**, *17*, 8248–8262.
34. Hesp, K. D.; Stradiotto, M. *J. Am. Chem. Soc.* **2010**, *132*, 18026–18029.
35. Hanley, P. S.; Marković, D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 6302–6303.
36. For reviews containing information regarding this elementary step and its application to the synthesis of heterocycles, see: (a) Schultz, D. M.; Wolfe, J. P. *Synthesis*, **2012**, *44*, 351–361. (b) Minatti, A.; Muñiz, K. *Chem. Soc. Rev.*, **2007**, *36*, 1142–1152.
37. (a) Bertrand, M. B.; Wolfe, J. P. *Org. Lett*. **2007**, *9*, 3073–3075. (b) Neukom, J. D.; Perch, N. S.; Wolfe, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 6276–6277. (c) Neukom, J. D.; Perch, N. S.; Wolfe, J. P. *Organometallics* **2011**, *30*, 1269–1277.
38. Perdew, J. P.; Burke, K.; Ernzerhof, M. *Phys. Rev. Lett.*, **1996**, *77*, 3865–3868.
39. Serra, D.; Moret, M.-E.; Chen, P. *J. Am. Chem. Soc.* **2011**, *133*, 8914–8926.

40. It is possible that the reduced product yield is due to the loss of a portion of the gold catalyst during filtration.
41. Evans, L. A.; Fey, N.; Harvey, J. N.; Hose, D.; Lloyd-Jones, G. C.; Murray, P.; Orpen, A. G. ; Osborne, R.; Owen-Smith, G. J. J.; Purdie, M. *J. Am. Chem. Soc.* **2008**, *130*, 14471–14473.
42. Hashmi, A. S. K. *Chem. Rev.*, **2007**, *107*, 3180–3211.
43. Li, Z.; Brouwer, C.; He, C. *Chem. Rev*., **2008**, *108*, 3239–3265.
44. Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev*., **2008**, *108*, 3351–3378.
45. Nakao, Y.; Yada, A.; Ebata, S.; Hiyama, T. *J. Am. Chem. Soc.* **2007**, *129*, 2428–2429.
46. Koester, D. C.; Kobayashi, M.; Werz, D. B.; Nakao, Y. *J. Am. Chem. Soc.* **2012**, *134*, 6544–6547.
47. Graham, T. J. A.; Shields, J. D.; Doyle, A. G. *Chem. Sci.* **2011**, *2*, 980–984.
48. These data are also consistent with a *syn* addition of the Lewis acid/amide σ-bond of **14** across the tethered olefin followed by transmetalation to the Pd π-allyl cation, but we suspect the trapping of the Pd electrophile may be a much faster pathway. For one related example of *syn* addition of Li- and Na-amides across olefins, see: Ates, A.; Quinet, C. *Eur. J. Org. Chem.* **2003**, 1623–1626.
49. Weber, D.; Gagné, M. R. *Chem. Commun.* **2011**, *47*, 5172–5174.

Experimental

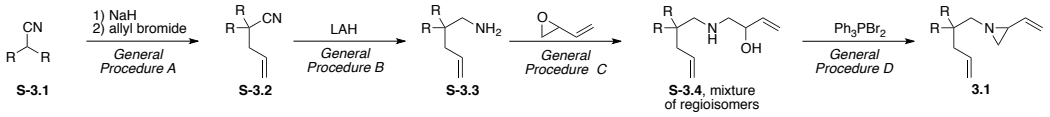
General Considerations

All chemicals were used as received from commercial sources unless otherwise noted. Acetonitrile, dichloromethane, diethyl ether, methanol, and tetrahy-

drofuran were dried by passage through an alumina column under argon pressure on a push-still solvent system. Dichloromethane-d_2 was dried over CaH_2, degassed using three freeze-pump-thaw cycles, and vacuum transferred prior to use. *N,N*-Diisopropyl ethyl amine (DIPEA) was distilled under nitrogen before use. (CAAC)AuCl[1] (**3.5**) and NaBArF[2] (**3.6**) were prepared according to literature procedures. $[Pd(MeCN)_4][BF_4]_2$ was purchased from Sigma-Aldrich. All manipulations were conducted in a glovebox under N_2 atmosphere or using standard Schlenk techniques unless otherwise specified. Analytical TLC was performed on Dynamic Absorbents 250 μm TLC plates with F-254 indicator. Plates were visualized under UV irradiation (254 nm), and/or using an aqueous solution of $KMnO_4$ or an ethanol solution of ninhydrin followed by heating. Flash chromatography was conducted using Grace Davisil 35–70 μm silica gel or Acros 50–200 μm basic aluminum oxide (activity I). All proton and carbon nuclear magnetic resonance (^1H and ^{13}C NMR) spectra were recorded on a Bruker DRX-500 spectrometer, a Bruker DRX-500 spectrometer outfitted with a cryoprobe, or a Bruker AVANCE600 spectrometer. All chemical shifts are reported in parts per million. ^1H and ^{13}C NMR spectroscopy experiments are calibrated to the residual proteosolvent resonance. Low and high-resolution mass spectrometry data were obtained at a facility operated by the University of California, Irvine.

Synthetic Procedures

All vinyl aziridines were prepared as described according to the following general procedures with exceptions as indicated.



General Procedure A: Allylation of 2,2-disubstituted nitriles. NaH (1.1 equiv) was added to a flame-dried two-neck flask under positive N_2 flow. Dimethylformamide was added to reach a final concentration of 1.0 M of **S-3.1**, and the resulting suspension was cooled to 0 °C. The nitrile (1.0 equiv) was added portionwise over ca. 10 min, and the reaction was allowed to stir for 45 min at 0 °C. Allyl bromide (1.1 equiv) was added dropwise, and then the reaction mixture was allowed to warm to 25 °C and to stir for 16 h. At this time, the reaction mixture was cooled to 0 °C and water was added slowly to quench unreacted NaH. The reaction was diluted 1:1 with Et_2O and washed with water (3 ×) and brine (1 ×). The combined aqueous layers were back-extracted with DCM (1 ×), and the combined organic layers were dried over Na_2SO_4 and then filtered. Concentration in vacuo afforded an oil that was purified by column chromatography under the indicated conditions to afford **S-3.2**.

General Procedure B: Reduction of nitriles to amines. Lithium aluminum hydride (LAH, 2.1 equiv) was added to a flame-dried two-neck flask under positive N_2 flow. Et_2O was added, and the vessel was cooled to 0 °C. Nitrile **S-3.2** was added

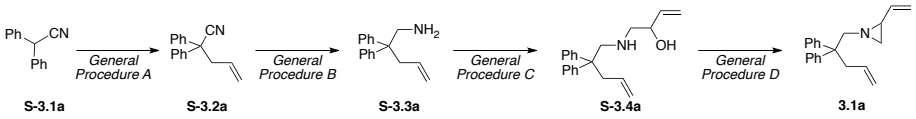
in a Et_2O solution (total reaction concentration, 0.15 M in nitrile), and then the reaction was allowed to warm to 25 °C and stir for 16 h. At this time, the reaction mixture was cooled to 0 °C and quenched by adding 20% aq. NaOH. The biphasic mixture was diluted with 1:5 with Et_2O and filtered to remove precipitated salts before discarding the aqueous layer. The organic layer was then washed with brine (3×), dried over Na_2SO_4, and then filtered. Concentration in vacuo afforded the crude amine, which was purified by column chromatography under the indicated conditions to afford **S-2.3**.

General Procedure C. Aminolysis of butadiene monoxide. Amine starting material **S-3.3** (1.0 equiv) was diluted in 2,2,2-trifluoroethanol (0.3 M in amine) in a 20 mL screw-cap scintillation vial under air. Butadiene monoxide (1.0 equiv) was added dropwise while stirring. The vial was capped and the reaction was allowed to stir for 16 h. At this time, concentration of the reaction mixture in vacuo afforded the crude α-amino alcohol **S-3.4** as a mixture of regioisomers, which in select cases was purified by column chromatography (as indicated) before use.

General Procedure D. Aziridination of α-amino alcohols. This reaction was set up in the glovebox due to moisture sensitivity. Triphenylphosphine dibromide[3] (1.1 equiv) was weighed into a screw-cap dram vial and equipped with a micro stir bar. Acetonitrile and DIPEA (2.3 equiv) were added. A solution of amino alcohol **S-3.4** (1.0 equiv) in MeCN (total reaction concentration, 0.2 M) was then added dropwise to the stirring slurry of Ph_3PBr_2 and DIPEA. CAUTION: Reaction is exo-

thermic. The vial was capped, and the reaction mixture was allowed to stir in the glovebox at 25 °C for 16 h. At this time, the crude reaction mixture was removed from the glovebox and concentrated in vacuo to ca. 1/5 of its original volume. Et_2O was added to precipitate $Ph_3P{=}O$, which was removed by filtration through a glass pipet plugged with glass fiber. This concentration/precipitation/filtration cycle was repeated two more times before purifying aziridine **3.1** by column chromatography using the indicated conditions.

Diphenyl vinyl aziridine (for pyrrolizidine product) ***3.1a****.*



*2,2-Diphenyl-4-pentenenitrile (**S-3.2a**).* Prepared from diphenylacetonitrile (5.00 g, 25.9 mmol, 1.00 equiv) according to General Procedure A. Obtained 5.66 g of **S-3.2a** which was then taken on directly to the next step without further purification. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.14 (d, J = 7.2 Hz, 2H), 5.18 (d, J = 10.5 Hz, 1H), 5.22 (d, J = 17.2 Hz, 1H), 5.78–5.76 (m, 1H), 7.29–7.32 (m, 2H), 7.35–7.41 (m, 8H). This spectrum is consistent with previously reported spectral data.[4]

Diphenyl amine ***S-3.3a****.* Prepared from **S-3.2a** (5.66 g, 24.3 mmol, 1.00 equiv) according to General Procedure B. Obtained 5.92 g (quant) of **S-3.3a** as a yellow oil which was then taken on directly to the next step without further purification. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.76 (br s, 2H), 2.94 (d, J = 7.1 Hz, 2H), 3.34 (s, 2H), 4.98 (d, J = 10.1 Hz, 1H), 5.06 (d, J = 17.0 Hz, 1H), 5.37–5.45 (m, 1H), 7.18–7.22

(m, 6H), 7.30 (m, 4H). This spectrum is consistent with previously reported spectral data.[4]

*Diphenyl amino alcohol **S-3.4a**.* Prepared from **S-3.3a** (2.00 g, 8.43 mmol, 1.00 equiv) according to General Procedure C. Obtained 671 mg (25%) as a clear, colorless oil following purification using silica gel chromatography eluting from a gradient of 7:3 hexanes:EtOAc to 10:1:0.3 hexanes:EtOAc:NEt_3.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.55 (dd, *J* = 8.9, 12.2, 1H), 2.76 (dd, *J* = 12.2, 3.6 Hz, 1H), 3.05–3.17 (m, 1H), 3.30 (d, *J* = 11.3 Hz, 1H), 3.41 (d, *J* = 11.0 Hz, 1H), 4.07–4.14 (m, 1H), 5.08 (d, *J* = 9.7 Hz, 1H), 5.15–5.22 (m, 2H), 5.35 (d, *J* = 17.2, 1H), 5.42–5.52 (m, 1H), 5.77–5.87 (m, 1H), 7.23–7.33 (m, 6H), 7.34–7.42 (m, 4H).

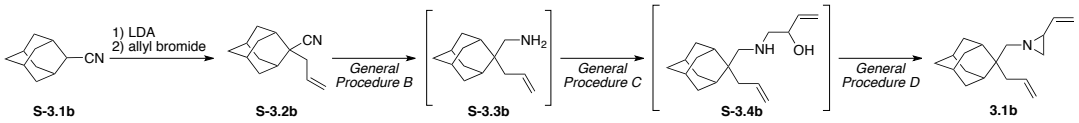
^{13}C NMR ($CDCl_3$, 125 MHz): δ 41.7, 50.1, 55.3, 55.5, 70.2, 115.6, 118.0, 126.27, 126.31, 128.02, 128.06, 128.2, 128.23, 134.7, 138.7, 146.5, 146.6.

*Diphenyl vinyl aziridine (for pyrrolizidine product) **3.1a**.* Prepared from **S-3.4a** (900. mg, 2.93 mmol, 1.00 equiv) according to General Procedure D. Obtained 576 mg (68%) as a clear, viscous oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.10 (d, *J* = 6.5 Hz, 1H), 1.46 (app s, 2H), 2.89 (d, *J* = 11.5 Hz, 1H), 3.06 (d, *J* = 11.7 Hz, 1H), 3.10–3.19 (m, 2H), 4.86–5.00 (m, 2H), 5.06 (d, *J* = 16.8 Hz, 1H), 5.27–5.48 (m, 2H), 7.14–7.21 (m, 6H), 7.23–7.27 (m, 4H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 35.6, 41.8, 50.5, 68.0, 115.4, 118.0, 125.8, 125.9, 127.8, 127.9, 128.3, 128.4, 135.0, 138.6, 147.1, 147.4.

*Adamantyl vinyl aziridine **3.1b**.*



*2-Allyladamantane-2-carbonitrile **S-3.2b**.* To a THF solution of LDA (0.29 M, 6.0 mL, 1.0 equiv) at -78 °C was added dropwise a solution of adamantane-2-carbonitrile[5] (**S-3.1b**, 215 mg, 1.34 mmol, 1.00 equiv) in 5.0 mL THF. The reaction mixture was stirred for 45 min at -78 °C, and then allyl bromide (237 μL, 2.71 mmol, 2.02 equiv) was added dropwise. The reaction mixture was warmed to 25 °C and was allowed to stir for 18 h. The reaction was then cooled to 0 °C and quenched by slowly adding 1 mL water. The biphasic mixture was diluted with 2 mL DCM, and then washed with water (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification of the mixture by column chromatography eluting from 5:95 EtOAc:hexanes afforded the desired product as a clear, colorless oil (251 mg, 93%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.66 (br d, *J* = 13.3 Hz, 2H), 1.75 (br s, 2H), 1.82–1.95 (br m, 8H), 2.27 (br d, *J* = 13.1 Hz, 2H), 2.56 (d, *J* = 7.3 Hz, 2H), 5.21 (app s, 1H), 5.24 (app d, *J* = 4.5 Hz, 1H), 5.94 (m, 1H). This spectrum is consistent with previously reported spectral data.[6]

*Adamantyl amine **S-3.3b**.* Prepared from **S-3.2b** (390 mg, 2.0 mmol, 1.0 equiv) according to General Procedure B. Obtained 330 mg (82%) crude **S-3.3b**. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.98 (br s, 2H), 1.55–1.59 (m, 2H), 1.70 (br s, 2H), 1.87 (br d, *J* = 16.0 Hz, 2H), 2.01 (br d, *J* = 11.0 Hz, 2H), 2.09 (br d, *J* = 12.5 Hz, 2H), 2.37 (d, *J* = 7.5 Hz, 2H), 2.84 (s, 2H), 5.05 (d, *J* = 10.0 Hz, 1H), 5.10 (d, *J* = 17.0 Hz, 1H), 5.77–5.85 (m, 1H). Analysis by ^{1}H NMR spectroscopy was consistent with the desired product in ca. 90 % purity, and it was used directly without further purification or characterization.

*Adamantyl amino alcohol **S-4b**.* Prepared from **S-3b** (260 mg, 1.3 mmol, 1.0 equiv) according to General Procedure C. Obtained 77 mg crude **S-4b** (22%). Analysis by ^{1}H NMR spectroscopy revealed a complex mixture of regioisomers that was used without further purification.

Adamantyl-substituted vinyl aziridine **3.*1b***. Prepared from **S-3.4b** (77 mg, 0.28 mmol, 1.0 equiv) according to General Procedure D. Obtained 43 mg (60%) following purification using silica gel chromatograpy eluting with 2:98 EtOAc:hexanes.

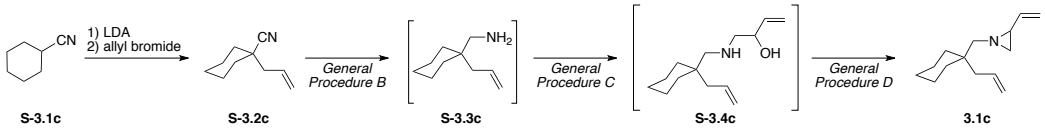
^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.49 (d, *J* = 6.5 Hz, 1H), 1.52–1.59 (m, 4H), 1.69–1.72 (m, 4H), 1.86 (br d, *J* = 12.0 Hz, 2H), 1.91 (td, *J* = 10.5, 3.5 Hz, 1H), 2.01 (br t, *J* = 8.5 Hz, 2H), 2.13 (br t, *J* = 11.5 Hz, 2H), 2.25 (d, *J* = 12.5 Hz, 1H), 2.52 (dd, *J* = 14.0, 8.0 Hz, 1H), 2.65 (dd, *J* = 14.2, 7.5 Hz, 1H), 2.71 (d, *J* = 12.5 Hz, 1H), 5.05–5.06 (m, 1H), 5.07–5.09 (m, 1H), 5.13 (d, *J* =

16.5 Hz, 1H), 5.27 (d, *J* = 17.5 Hz, 1H), 5.55 (ddd, *J* = 17.5, 10.0, 7.5 Hz, 1H), 5.83–5.88 (m, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 28.1, 32.1, 32.4, 32.7, 32.8, 33.0, 33.1, 35.1, 36.7, 39.9, 41.8, 63.0, 115.6, 116.8, 135.5, 139.2.

HRMS (ESI+): $[M+H]^+$ calcd for $C_{18}H_{27}NH$, 258.2222; found, 258.2225.

*Cyclohexyl vinyl aziridine **3.1c**.*



*1-Allylcyclohexane-1-carbonitrile **S-3.2c**.* To a THF solution of LDA (0.35 M, 11 mL, 1.0 equiv) at -78 °C was added neat cyclohexanecarbonitrile (**S-3.1c**, 590 µL, 5.0 mmol, 1.0 equiv). The reaction mixture was stirred for 2.5 h at -78 °C, and then allyl bromide (870 µL, 10. mmol, 2.0 equiv) was added dropwise. The reaction mixture was warmed to 25 °C and was allowed to stir for 15 h. The reaction was then cooled to 0 °C and quenched by slowly adding 1 mL water. The biphasic mixture was diluted with 20 mL EtOAc, and then washed with water (3 × 5 mL) and brine (1 × 5 mL). The combined aqueous layers were back-extracted with DCM (2 × 5 mL), and the combined organic layers were dried over Na_2SO_4, and then filtered. Purification by column chromatography eluting from 5:95 EtOAc:hexanes afforded the desired product as a clear, colorless oil (560 mg, 75%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.18 (ddd, *J* = 25.5, 12.5, 4.0 Hz, 1H), 1.25 (td, *J* = 22.5, 6.5 Hz, 2H), 1.63 (ddd, *J* = 26.0, 13.0, 4.0 Hz, 2H), 1.70–1.77 (m, 3H), 1.96 (d, *J* = 13.0 Hz, 2H), 2.29 (d, *J* = 7.5 Hz, 2H), 5.18 (ddd, *J* = 16.5, 3.0,

1.5 Hz, 1H), 5.20 (d, *J* = 10.0 Hz, 1H), 5.85–5.93 (m, 1H). This spectrum is consistent with previously reported spectral data.[7]

*Cyclohexyl amine **S-3.3c**.* Prepared from **S-3.2c** (560 mg, 3.8 mmol, 1.0 equiv) according to General Procedure B with the following modification: the reaction was conducted in refluxing Et_2O instead of at 25 °C. Obtained 506 mg (88%) crude **S-3.3c**. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.19 (br s, 2H), 1.23–1.33 (m, 5H), 1.43–1.47 (m, 5H), 2.07 (dt, *J* = 7.5, 1.1 Hz, 2H), 2.53 (s, 2H), 5.03–5.04 (m, 1H), 5.05–5.08 (m, 1H), 5.77–5.85 (m, 1H). Analysis by ^{1}H NMR spectroscopy was consistent with the previously reported spectral data for this compound[8] in ca. 90 % purity, and it was used directly without further purification.

*Cyclohexyl amino alcohol **S-3.4c**.* Prepared from **S-3.3c** (470 mg, 3.1 mmol, 1.0 equiv) according to General Procedure C. The amino alcohol was partially purified by three iterations of silica gel column chromatography eluting with 3:7 EtOAc:hexanes, but these attempts resulted in significant product loss. Obtained 95 mg crude **S-3.4c**. Analysis by ^{1}H NMR spectroscopy revealed a complex mixture of regioisomers that was used without further purification.

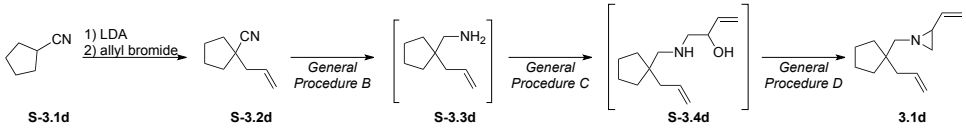
*Cyclohexyl-substituted vinyl aziridine **3.1c**.* Prepared from **S-3.4c** (88 mg, 0.39 mmol, 1.0 equiv) according to General Procedure D. Obtained 45 mg (56%) following purification by silica gel chromatography eluting from 5:95 EtOAc:hexanes.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.31–1.40 (m, 5H), 1.44–1.48 (m, 6H), 1.75 (d, *J* = 13.5 Hz, 1H), 1.81 (td, *J* = 10.5, 3.5 Hz, 1H), 1.90 (d, *J* = 12.5 Hz, 1H), 2.18–2.62 (m, 2H), 2.39 (d, *J* = 12.5 Hz, 1H), 5.03 (app s, 1H), 5.05–5.07 (m, 1H), 5.09 (dd, *J* = 10.3, 1.5 Hz, 1H), 5.28 (dd, *J* = 17.0, 1.5 Hz, 1H), 5.55 (ddd, *J* = 17.5, 10.0, 7.5 Hz, 1H), 5.79–5.88 (m, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 21.7, 26.4, 33.9, 34.0, 35.2, 37.8, 42.4, 115.9, 117.0, 135.5, 139.0.

HRMS (ESI+): $[M+H]^+$ calcd for $C_{14}H_{23}NH$, 206.1909; found, 206.1906.

*Cyclopentyl vinyl aziridine **3.1d**.*



*1-Allylcyclopentane-1-carbonitrile **S-3.2d**.* To a THF solution of LDA (0.35 M, 30 mL, 1.0 equiv) at -78 °C was added neat cyclopentanecarbonitrile (**S-3.1d**, 1.10 mL, 10.5 mmol, 1.00 equiv) dropwise. The reaction mixture was stirred for 45 min at -78 °C, and then allyl bromide (1.8 mL, 21 mmol, 2.0 equiv) was added dropwise. The reaction mixture was warmed to 25 °C and was allowed to stir for 18 h. The reaction was then cooled to 0 °C and quenched by slowly adding 20 mL water. The biphasic mixture was diluted with 10 mL EtOAc, and then washed with water (2 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification of the mixture by column chromatography eluting from 96:4 hexanes:EtOAc afforded the desired product as a yellow oil (758 mg, 53%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.64–1.87 (m, 6H), 2.07–2.13 (m, 2H),

2.34 (dt, *J* = 7.3, 1.0 Hz, 2H), 5.16–5.22 (m, 2H), 5.89 (ddt, *J* = 16.2, 10.9, 7.4 Hz, 1H). The product was used without further characterization.

Cyclopentyl(allyl) amine ***S-3.3d****.* Prepared from **S-3.2d** (758 mg, 5.60 mmol, 1.00 equiv) according to General Procedure B with the following modification: Obtained **S-3.3d** (487 mg, 63%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.13 (br s, 2H), 1.36–1.44 (m, 4H), 1.55–1.65 (m, 4H), 2.12 (dt, *J* = 7.3, 1.2 Hz, 2H), 2.52 (s, 2H), 5.02–5.09 (m, 2H), 5.81 (ddt, *J* = 17.0, 10.1, 7.4 Hz, 1H). This spectrum is consistent with previously reported spectral data.[9]

Cyclopentyl(allyl) amino alcohol ***S-3.4d***. Prepared from **S-3.3d** (487 mg, 3.50 mmol, 1.0 equiv) according to General Procedure C. The amino alcohol was partially purified by silica gel columatography eluting from 7:1 hexanes:EtOAc. Obtained crude **S-3.4d** (275 mg) as a yellow oil. Analysis by ^{1}H NMR spectroscopy revealed a mixture of regioisomers that was used without further purification.

Cyclopentyl vinyl aziridine ***3.2d***. Prepared from **S-3.4d** (275 mg, 1.32 mmol, 1.00 equiv) according to General Procedure D. Obtained a clear colorless oil (154 mg, 90%) following purification by silica gel chromatography eluting from 95:5 hexanes:Et_2O.

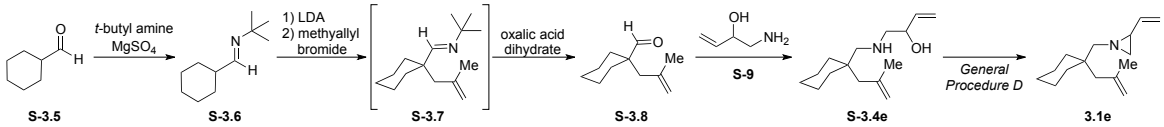
^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.39–1.53 (m, 5H), 1.55–1.61 (m, 4H), 1.66 (dd, *J* = 3.3, 1.0 Hz), 1.80–1.84 (m, 1H), 2.02 (d, *J* = 12.1 Hz), 2.15–2.23 (m, 2H),

2.29 (d, *J* = 12.1 Hz, 1H), 5.00–5.07 (m, 3H), 5.27 (dd, *J* = 17.5, 1.7 Hz, 1H), 5.49–5.56 (m, 1H), 5.82–5.87 (m, 1H).

^{13}C NMR (CD_2Cl_2, 125 MHz): δ 25.5, 25.5, 35.9, 36.1, 36.2, 42.4, 43.1, 47.8, 69.4, 115.9, 117.2, 137.2, 140.0.

HRMS (ESI+): $[M+H]^+$ calcd for $C_{13}H_{22}N$, 192.1752; found, 192.1750.

*Cyclohexyl methallyl vinyl aziridine **3.1e**.*



*Cyclohexyl tert-butyl imine **S-3.6**.* A 100-mL round-bottomed flask equipped with a condenser was charged with freshly distilled cyclohexanecarboxaldehyde (**S-3.5**, 2.39 g, 21.3 mmol, 1.00 equiv), *tert*-butylamine (2.46 mL, 23.4 mmol, 1.10 equiv), $MgSO_4$ (4.27 g, 35.6 mmol, 1.67 equiv) and dry DCM (21 mL). The solution was refluxed for 1 h under N_2. Next, the solution was cooled to 25 °C and the resulting solid suspension was filtered through a coarse glass filter frit. The filtrate was collected and concentrated in vacuo to a thick yellow oil. The crude product was purified by distillation (10 mmHg, 68 °C) to afford **S-3.6** as a clear colorless oil (2.30 g, 65%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.16 (s, 9H), 1.18–1.32 (m, 5H), 1.63–1.70 (m, 1H), 1.70–1.79 (m, 4H), 2.11–2.19 (m, 1H), 7.40 (d, *J* = 6.0 Hz, 1H). This spectrum is consistent with previously reported spectral data.[10]

*(Methallyl) cyclohexyl tert-butyl imine **S-3.7**.* To a solution of LDA (0.91 M, 8.6 mL, 1.1 equiv) in dry THF at 0 °C was added **S-3.6** (1.20 g, 7.19 mmol, 1.00

equiv) dropwise. The solution was allowed to stir for 1.5 h at 0 °C. Then, 3-bromo-2-methylpropene (0.76 mL, 7.6 mmol, 1.1 equiv) in dry THF (1.4 mL) was added dropwise at 0 °C. The solution was slowly warmed to 25 °C as the ice bath melted and the solution was allowed to stir overnight. Diethyl ether (50 mL) was added to the solution. The organic layer was extracted with water (100 mL). The aqueous layer was then extracted with Et_2O (2 × 100 mL). The organic layers were collected, dried over K_2CO_3, filtered, and concentrated in vacuo to yield a crude yellow oil. The crude product was taken directly to the next step without further purification or characterization.

2-Cyclohexyl-2-methallyl-aldehyde ***S-3.8***. A 100-mL round-bottomed flask equipped with a condenser was charged with imine **S-3.7** (1.46 g, 6.59 mmol, 1.00 equiv) in DCM (13 mL) and oxalic acid dihydrate (0.830 g, 6.59 mmol, 1.00 equiv) in water (8 mL). The solution was refluxed for 2 h. The solution was then cooled to 25 °C and the organic layer was collected. The aqueous layer was extracted with DCM (2 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to yield a crude yellow oil. The crude product was purified by distillation (10 mmHg, 85 °C) to afford **S-3.8** as a clear, colorless oil (196 mg, 18%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.24–1.40 (m, 5H), 1.45–1.62 (m, 3H), 1.65 (s, 3H), 1.86–1.90 (m, 2H), 2.22 (s, 2H), 4.67–4.69 (m, 1H), 4.82–4.85 (m, 1H), 9.53 (s, 1H). This spectrum is consistent with previously reported spectral data.[11]

Cyclohexyl methallyl amino alcohol ***S-3.4e****.* Prepared using an adapted literature procedure.[12] To a flame-dried 25-mL round-bottomed flask was added 2-cyclohexyl-2-methyallyl-aldehyde **S-3.8** (196 mg, 1.18 mmol, 1.10 equiv) and a solution of 1-amino-3-buten-2-ol[13] (93.2 mg, 1.07 mmol, 1.00 equiv) in dry MeOH (1.3 mL). The reaction mixture was allowed to stir at 25 °C for 2 h. The reaction mixture was cooled to 0 °C, and $NaBH_4$ (44.6 mg, 1.18 mmol, 1.10 equiv) was then added over 4 portions. The reaction mixture was allowed to warm back to 25 °C. After 2.5 h, 1 M HCl (50 mL) was added slowly to the solution. The aqueous layer was extracted with DCM (2 × 50 mL). The aqueous layer was then basified with 20 % aq. NaOH (50 mL) to a pH of 14. The resulting heterogeneous mixture was extracted with DCM (3 × 50 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to provide the desired crude amino alcohol as a white solid. The crude product was purified by silica gel chromatography eluting from 9:1 chloroform:MeOH to afford amino alcohol **S-3.4e** as a white solid (83 mg, 33%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.33–1.50 (m, 10H), 1.80 (d, *J* = 0.5 Hz, 3H), 2.09 (s, 2H), 2.47 (app d, *J* = 11.8 Hz, 1H), 2.52–2.60 (m, 2H), 2.75 (dd, *J* = 12.0, 3.7 Hz, 1H), 4.12–4.18 (m, 1H), 4.67–4.70 (m, 1H), 4.85–4.88 (m, 1H), 5.16 (d, *J* = 10.5 Hz, 1H), 5.34 (d, *J* = 17.3 Hz, 1H), 5.83 (ddd, *J* = 17.2, 10.6, 5.6 Hz, 1H).

^{13}C NMR ($CDCl_3$, 500 MHz): δ 21.8, 25.6, 26.3, 34.6, 34.7, 37.4, 55.4, 70.1, 114.4, 115.6, 138.7, 143.6.

HRMS (ESI+): $[M+H]^+$ calcd for $C_{15}H_{28}N$, 238.2171; found, 238.2167.

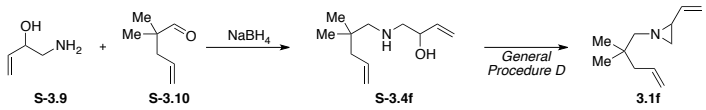
*(Methallyl) cyclohexyl vinyl aziridine **3.1e**.* Prepared from **S-3.4e** (83.0 mg, 0.350 mmol, 1.00 equiv) according to General Procedure D. The crude product was purified by silica gel chromatography eluting from 95:5 hexanes:Et_2O. The resulting product was resubjected to purification by silica gel chromatography eluting from 12:1 hexanes:EtOAc to afford **3.1e** (13 mg, 17%) as a clear, colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.33–1.50 (m, 11H), 1.73 (d, *J* = 3.2 Hz, 1H), 1.77–1.81 (m, 4H), 2.03 (d, *J* = 12.2 Hz, 1H), 2.17–2.24 (m, 2H), 2.33 (d, *J* = 12.2 Hz, 1H), 4.71 (s, 1H), 4.87 (s, 1H), 5.08 (dd, *J* = 10.5, 1.8 Hz, 1H), 5.28 (dd, *J* = 17.4, 1.7 Hz, 1H), 5.56 (ddd, *J* = 18.0, 10.2, 7.7 Hz, 1H).

^{13}C NMR ($CDCl_3$, 500 MHz): δ 21.9, 25.9, 26.4, 34.0, 34.1, 35.5, 38.5, 42.0, 77.3, 114.3, 115.6, 139.0, 143.7.

HRMS (ESI+): $[M+H]^+$ calcd for $C_{15}H_{25}N$, 220.2065; found, 220.2073.

*Dimethyl vinyl aziridine **3.1f**.*



S-3.9 S-3.10 S-3.4f 3.1f

*Dimethyl amino alcohol **S-3.4f**.* Prepared using an adapted literature procedure.[12] To an oven-dried scintillation vial was added a solution of 1-amino-3-buten-2-ol[13] (**S-3.5**, 150 mg, 1.7 mmol, 1.0 equiv) in dry MeOH (2.0 mL). 2,2-Dimethyl-4-pentenal (**S-3.6**, 290 mg, 2.6 mmol, 1.5 equiv) was then added dropwise, and the reaction mixture was allowed to stir at 25 °C for 2 h. The reaction mixture was

cooled to 0 °C, and $NaBH_4$ (96 mg, 2.6 mmol, 1.5 equiv) was then added portion-wise. The reaction mixture was allowed to warm back to 25 °C. After 3 h, the reaction was diluted with DCM (10 mL) and sat. aq. $NaHCO_3$ (3 mL) was added. The organic layer was then separated and extracted with 1 M HCl (3 × 3 mL). The combined acidic aqueous layers were washed with DCM (1 × 2 mL) and then basified with 20 % aq. NaOH (2 mL). The resulting heterogeneous mixture was extracted with DCM (2 × 5 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to provide amino alcohol **S-3.4f** (240 mg, 77%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.90 (s, 6H), 2.01 (d, *J* = 11.5 Hz, 2H), 2.37 (d, *J* = 11.5 Hz, 1H), 2.42 (d, *J* = 11.5 Hz, 1H), 2.54 (dd, *J* = 12.2, 9.0 Hz, 1H), 2.74 (dd, *J* = 12.2, 4.0 Hz, 1H), 4.10–4.13 (m, 1H), 5.01–5.03 (m, 1H), 5.15 (dt, *J* = 10.5, 1.5 Hz, 1H), 5.05 (app s, 1H), 5.33 (dt, *J* = 17.5, 1.5 Hz, 1H). No signals were observed for the amine and alcohol protons, presumably due to H/D exchange.

^{13}C NMR ($CDCl_3$, 125 MHz): δ 25.6, 34.5, 44.8, 55.5, 59.8, 70.2, 115.7, 117.2, 135.4, 138.9.

HRMS (ESI+): $[M+H]^+$ calcd for $C_{11}H_{21}NOH$, 184.1701; found, 184.1702.

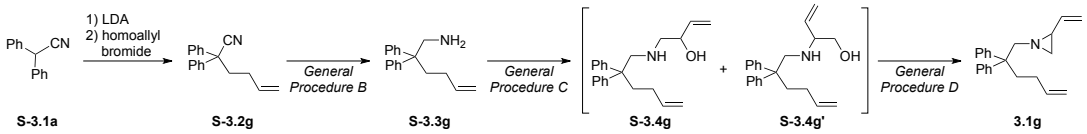
*Dimethyl vinyl aziridine **3.1f**.* Prepared from **S-3.4f** (190 mg, 1.0 mmol, 1.0 equiv) according to General Procedure D. Obtained 58 mg (35%) following purification using silica gel chromatograpy eluting with 4:96 Et_2O:hexanes.

^{1}H NMR ($CDCl_3$, 125 MHz): δ 0.94 (s, 3H), 0.95 (s, 3H), 1.43 (d, *J* = 6.5 Hz, 1H), 1.75 (d, *J* = 3.0 Hz), 1.77–1.81 (m, 1H), 1.83 (d, *J* = 12.0 Hz, 1H), 2.07 (d, *J* = 7.4 Hz, 2H), 2.37 (d, *J* = 11.9 Hz, 1H), 5.01 (d, *J* = 6.0 Hz, 1H), 5.04 (app s, 1H), 5.10 (dd, *J* = 10.3, 1.4 Hz, 1H), 5.29 (dd, *J* = 17.2, 1.3 Hz, 1H), 5.56 (ddd, *J* = 17.4, 10.0, 7.7 Hz, 1H), 5.79–5.87 (m, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 25.8, 25.8, 35.1, 35.5, 42.5, 45.3, 72.2, 116.0, 117.1, 135.6, 138.9.

HRMS (ESI+): $[M+H]^+$ calcd for $C_{11}H_{19}NH$, 166.1596; found, 166.1597.

*Diphenyl(homoallyl) vinyl aziridine **3.1g** (for indolizidine product).*



*Diphenyl(homoallyl) acetonitrile **S-3.2g**.* Prepared from diphenylacetonitrile (4.62 g, 23.9 mmol, 1.00 equiv) according to General Procedure A using homoallyl bromide instead of allyl bromide. Crude **S-3.2g** (5.90 g) was obtained as a yellow oil. The crude product (containing EtOAc and hexanes impurities) was used in the next step without purification. ^{1}H NMR ($CDCl_3$, 500 MHz): δ δ 2.17–2.21 (m, 2H), 2.46–2.49 (m, 2H), 5.01 (dd, *J* = 11.2, 1.3 Hz, 1H), 5.06 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.78–5.86 (m, 1H), 7.29–7.32 (m, 2H), 7. 36–7.41 (m, 8H). This spectrum is consistent with previously reported spectral data.[14]

*Diphenyl(homoallyl) amine **S-3.3g**.* Prepared from **S-3.2g** (5.90 g, 23.9 mmol, 1.00 equiv) according to General Procedure B. Obtained **S-3.3g** (4.30 g, 73%) as

a clear, colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.76 (br s, 2H), 1.75–1.78 (m, 2H), 2.19–2.22 (m, 2H), 3.34 (s, 1H), 4.91 (dd, *J* = 10.2, 1.3 Hz, 1H), 4.96 (dd, *J* = 17.1, 1.6 Hz, 1H), 5.75–5.80 (m, 1H), 7.19–7.32 (m, 10H). This spectrum is consistent with previously reported spectral data.[15]

*Diphenyl(homoallyl) amino alcohol **S-3.4g** and **S-3.4g'**.* Prepared from **S-3.3g** (1.89 g, 7.53 mmol, 1.00 equiv) according to General Procedure C. The amino alcohol was partially purified by silica gel column chromatography eluting from 1:1 EtOAc:hexanes, then 100% EtOAc. Obtained crude **S-3.4g** and **S-3.4g'** (1.92 g) as a yellow oil. Analysis by ^{1}H NMR spectroscopy revealed a mixture of regioisomers that was used without further purification.

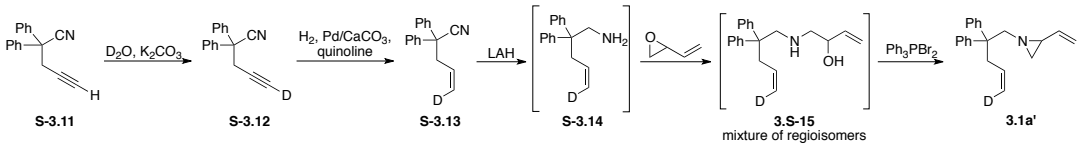
*Diphenyl(homoallyl) vinyl aziridine **3.1g**.* Prepared from **S-3.4g** and **S-3.4g'** (963 mg, 3.00 mmol) according to General Procedure D. Obtained a clear colorless oil (537 mg, 59%) following purification by silica gel chromatography eluting from 95:5 hexanes:EtOAc.

^{1}H NMR (CD_2Cl_2, 500 MHz): δ 1.16 (d, *J* = 6.3 Hz, 1H), 1.45 (d, *J* = 3.3 Hz, 1H), 1.48–1.52 (m, 1H), 1.73–1.77 (m, 2H), 2.38–2.42 (m, 2H), 2.88 (d, *J* = 11.9 Hz, 1H), 3.12 (d, *J* = 11.9 Hz, 1H), 4.89–4.97 (m, 4H), 5.28–5.35 (m, 1H), 5.78–5.83 (m, 1H), 7.14–7.18 (m, 6H), 7.23–7.26 (m, 4H).

^{13}C NMR (CD_2Cl_2, 125 MHz): δ 29.1, 35.5, 36.4, 42.2, 50.9, 68.1, 114.2, 115.6, 126.1, 126.1, 128.1, 128.1, 128.5, 128.6, 139.1, 139.6, 147.9, 148.3.

HRMS (ESI+): $[M+H]^+$ calcd for $C_{22}H_{26}N$, 304.2065; found, 304.2061.

Synthesis of deuterium-labeled vinyl aziridines.



*Deuterated alkynyl nitrile **S-3.12***. Terminal alkyne **S-3.11**[16] was deuterated using a procedure adapted from Bew[17] To a 25 mL flame-dried two-neck flask were added alkyne (780 mg, 3.4 mmol, 1.0 equiv) and anhydrous K_2CO_3 (460 mg, 3.4 mmol, 1.0 equiv) under positive N_2 flow. Dry MeCN (11 mL) was added, and the resulting heterogeneous mixture was stirred vigorously for 30 min. D_2O (3.0 mL, 150 mmol, 44 equiv) was then added, and resulting biphasic mixture was stirred vigorously for 1 h. The reaction mixture was then diluted with 30 mL dry DCM, and the two layers were quickly separated. (Note: the aqueous layer is more dense than DCM.) The organic layer was then dried over Na_2SO_4. After decanting off the drying agent, the resulting solution was concentrated in vacuo to afford a pale yellow oil. Further removal of volatiles under reduced pressure (< 10 mTorr) overnight afforded the desired product as a pale yellow solid (730 mg, 94%) with ca. 93% deuterium incorporation. This product is identical to the corresponding proteo-alkyne **S-3.11** by ^{1}H NMR spectroscopy except for a ca. 93% reduction in the terminal alkyne signal.

*(Z)-Deuterium-labeled vinyl nitrile **S-3.13***. To a warm flame-dried 50 mL round bottom flask with a stir bar under Ar atmosphere was added Lindlar's catalyst (140 mg, 37 mg per mmol alkyne). The atmosphere was purged with Ar, and then

toluene (3 mL), quinoline (1.3 g, 9.9 mmol, 2.6 equiv), and a solution of alkyne **S-12** (890 mg, 2.8 mmol, 1.0 equiv) in toluene (9 mL) were added in that order. The Ar line was replaced with a H_2 balloon, and the heterogeneous mixture was stirred vigorously. After 1.5 h, a 0.1 mL aliquot was removed by syringe, diluted with ca. 1 mL DCM, filtered through a celite pad in a pipet filter, and concentrated in vacuo. Analysis by ^{1}H NMR spectroscopy showed full consumption of the alkyne. (Note: Monitoring the reaction by TLC was unhelpful because the alkyne starting material and the desired olefin nearly overlap in all solvent systems tested.) The entire reaction mixture was then filtered through a celite pad, which was subsequently washed with 50 mL DCM. The resulting solution was concentrated in vacuo, and the crude product was purified by column chromatography eluting form 3:97 EtOAc:hexanes. After concentration of product-containing fractions in vacuo and further removal of volatiles under reduced pressure (< 10 mTorr) overnight afforded **S-3.13** as a colorless oil as an enriched mixture of olefin diastereomers (760 mg, 85%, Z:E = 2:1). Spectroscopic data were identical to the previously reported data for this compound.[18]

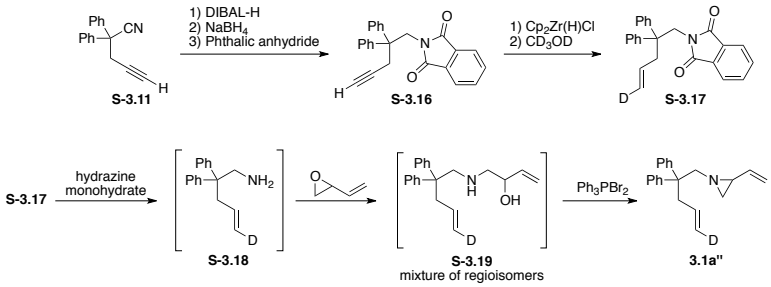
*(Z)-Deuterium-labeled vinyl amine **S-3.14***. To a flame-dried 25 mL round bottom flask was added $LiAlH_4$ (370 mg, 9.7 mmol, 3.0 equiv) and dry Et_2O (5.0 mL). The resulting suspension was cooled to 0 °C, and then nitrile **S-3.13** (760 mg, 3.2 mmol, 1.0 equiv) was added dropwise in a solution of Et_2O (5.0 mL). The reaction was allowed to warm to 25 °C and stir vigorously for 14 h under an atmosphere of static Ar. The reaction was then cooled to 0 °C and quenched by adding 3 mL of 1

M NaOH dropwise. The precipitate was removed by filtration, and the filter cake was washed with Et_2O (50 mL). The organic layer was separated, washed with brine (3 × 15 mL), and then dried over Na_2SO_4. Concentration in vacuo and further removal of volatiles under reduced pressure (< 10 mTorr) overnight afforded **S-14** as turbid, pale yellow oil (702 mg, 92%) in ca. 90% purity. No olefin isomerization was observed. The product was carried forward without further purification.

*(Z)-Deuterium-labeled vinyl amino alcohol **S-3.15**.* To a rapidly stirring suspension of amine **S-3.14** (357 mg, 1.50 mmol, 1.00 equiv) in 2,2,2-trifluoroethanol (5.5 mL) in a 15 mL round bottom flask open to air was added butadiene monoxide (120 µL, 1.50 mmol, 1.00 equiv). The flask was sealed with a septum, equipped with a vent needle, and stirred for 18 h. The resulting yellow solution was then concentrated in vacuo to a brown oil. Further removal of volatiles under reduced pressure (< 10 mTorr) afforded the desired amino alcohol **S-3.15** (quant.). Analysis by ^1H NMR spectroscopy was consistent with a mixture of regioisomers. The crude product was carried forward without further purification or characterization.

*(Z)-Deuterium-labeled vinyl aziridine **3.1a'**.* To a dry 25 mL round bottom flask was added Ph_3PBr_2 (460 mg, 1.7 mmol, 1.1 equiv) in the glovebox. The flask was sealed with a septum, removed from the glovebox, and placed under dynamic N_2. Dry MeCN (3.0 mL) and DIPEA (0.60 mL, 3.5 mmol, 2.3 equiv) were added. The reaction vessel was cooled to 0 °C in an ice/water bath, and then amino alcohol **S-3.15** (462 mg, 1.5 mmol, 1.0 equiv) was added dropwise in a solution of dry

MeCN (4.0 mL) while stirring vigorously. The ice bath was allowed to melt, slowly raising the temperature to 0 °C, and the reaction proceeded over 16 h. At this time, the crude reaction mixture was concentrated in vacuo to a volume of ca. 1 mL. Et_2O (10 mL) was added to precipitate the $Ph_3P{=}O$ coproduct, which was removed by filtration. This concentration/precipitation/filtration cycle was repeated twice more before purifying the mixture by silica gel chromatography eluting from 5:95 EtOAc:hexanes. Concentration and further removal of volatiles under reduced pressure (< 10 mTorr) provided aziridine **3.1a'** (240 mg, 55%). No olefin isomerization was observed (Z:E = 2:1). Spectroscopic characterization was identical to the protiated analog (**3.1a**) except for a diminished intensity of two olefin signals.



*Alkynyl phthalamide **S-3.16**.* Alkynyl nitrile **S-3.11**[16] (3.07 g, 13.2 mmol, 1.00 equiv) and dry Et_2O (100 mL) were added to a flame-dried 250 mL round bottom flask. The flask was cooled to -42 °C in a dry ice/acetonitrile bath. DIBAL-H (1.0 M in hexane, 20. mL, 1.5 equiv) was added slowly, and the reaction was stirred at -42 °C for 3 h. The reaction was then warmed to 0 °C and $NaBH_4$ (1.52 g, 40.2 mmol, 3.02 equiv) was added in a single portion, and then EtOH (100 mL) was added dropwise over 30 min. The reaction was then warmed to 25 °C and stirred

overnight. After that time, the reaction was cooled to 0 °C and quenched by adding water. The reaction was diluted with Et_2O, and the organic layer was separated and washed with 1 M NaOH. The organic layer was then dried over Na_2SO_4. The drying agent was removed by filtration, and concentration in vacuo afforded an oil. Analysis of the crude product by ^{1}H NMR spectroscopy indicated full conversion to the unprotected alkynyl amine. The oil was diluted in 20 mL dry toluene. Phthalic anhydride (2.3 g, 15.5 mmol, 1.2 equiv) was added, and the mixture was refluxed 3 h while distilling to remove water azeotropically. Concentration in vacuo afforded the crude solid product, which was purified by silica gel chromatography eluting from 3:7 EtOAc:hexanes. Obtained 720 mg white solid (23%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.92 (t, *J* = 2.6 Hz, 1H), 3.16 (d, *J* = 2.4 Hz, 2H), 4.58 (s, 2H), 7.22–7.29 (m, 10H), 7.66 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.72 (dd, *J* = 5.4, 3.3 Hz, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 30.3, 45.8, 51.5, 71.7, 81.5, 123.3, 127.0, 127.9, 128.6, 131.7, 134.1, 144.2, 168.3.

HRMS (ESI+): $[M+H]^+$ calcd for $C_{25}H_{19}NO_2Na$, 388.1313; found, 388.1303.

(E)-Deuterium-labeled vinyl phthalamide ***S-3.17****.* In the glovebox, alkynyl phthalamide **S-3.16** (600. mg, 1.64 mmol, 1.00 equiv) was dissolved in dry DCM (10. mL) and transferred to a scintillation vial containing Schwartz's reagent ($Cp_2Zr(H)Cl$, 593 mg, 2.30 mmol, 1.40 equiv). After stirring for 20 min at 25 °C, CD_3OD (1.2 mL) was added to deuterate the organozirconocene intermediate. After stirring for 2 h at 25 °C, the reaction mixture was concentrated in vacuo and

loaded directly onto a silica gel column in a minimum of DCM and eluted using a gradient from 3:7 EtOAc:hexanes to 1:1 EtOAc:hexanes. The product was obtained as a white solid (502 mg, 83%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.03 (d, J = 6.9 Hz, 2H), 4.48 (s, 2H), 5.11 (d, J = 17.2 Hz, 1H), 5.73 (dt, J = 17.2, 7.0 Hz, 1H), 7.21–7.29 (m, 10H), 7.66 (dd, J = 5.4, 3.1 Hz, 2H), 7.73 (dd, J = 5.6, 3.1 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 42.3, 45.2, 51.6, 118.3 (t, $J_{C\text{-}D}$ = 97.5 Hz), 123.1, 126.4, 127.7, 128.6, 131.7, 133.8, 134.0, 145.4, 168.1. These spectral data reflect a D incorporation of greater than 95%.

(E)-Deuterium-labeled vinyl amine ***S-3.18****.* In a scintillation vial, phthalamide **S-3.17** (360 mg, 0.97 mmol, 1.0 equiv) was suspended in EtOH (5 mL). Hydrazine monohydrate (49 µL, 0.97 mmol, 1.0 equiv) was added. The vial was capped and the heterogeneous reaction mixture was heated at 75 °C for 18 h. At this time, the crude reaction mixture was concentrated in vacuo and the resulting residue was extracted into DCM, which was loaded directly onto a silica gel plug. The product was eluted with 1:20 MeOH:DCM. Each fraction was spotted onto a TLC plate and checked for UV absorbance. UV-absorbing fractions were combined and concentrated in vacuo to afford a colorless oil (170 mg). Analysis by ^{1}H NMR spectroscopy was consistent with the desired amine product in ca. 70% purity, and the oil was carried forward without further purification or characterization.

*(E)-Deuterium-labeled vinyl amino alcohol **S-3.19**.* In a dram vial, crude vinyl amine **S-3.18** (170 mg, 0.71 mmol, 1.0 equiv) was diluted with MeOH (3.0 mL). Butadiene monoxide (170 µL, 2.1 mmol, 3.0 equiv) was added dropwise, the vial was capped, and the reaction was allowed to stir at 25 °C for 26 h. At this time, the reaction mixture was concentrated in vacuo and loaded onto a silica gel column in a minimum amount of DCM. The product was eluted using 1:20 MeOH:DCM. Product-containing fractions were detected as with amine **S-3.18** and were combined and concentrated in vacuo to a clear, colorless oil (110 mg). Analysis by ^{1}H NMR spectroscopy was consistent with the desired amino alcohol as a mixture of regioisomers, and the oil was carried forward without further characterization or purification.

*(E)-Deuterium-labeled vinyl aziridine **3.1a''**.* This reaction was set up in the glovebox due to moisture sensitivity. To a scintillation vial containing triphenylphosphine dibromide (180 mg, 0.43 mmol, 1.2 equiv) was added dry MeCN and DIPEA (140 µL, 0.82 mmol, 2.3 equiv). Amino alcohol **S-3.19** (110 mg, 0.36 mmol, 1.0 equiv) was added dropwise as a solution in dry MeCN (total reaction concentration, 0.20 M in amino alcohol). CAUTION: Reaction is exothermic. The vial was capped and the reaction mixture was stirred at 25 °C in the glovebox for 26 h. At this time, the reaction mixture was removed from the glovebox and concentrated in vacuo. The resulting residue was extracted into Et_2O and concentrated in vacuo again. The resulting residue was then extracted with 1:1 hexanes:Et_2O, filtered to remove much of the remaining Ph_3P=O coproduct, and con-

centrated in vacuo a final time. Purification of the resulting residue by silica gel chromatography eluting from 1:50 EtOAc:hexanes afforded the desired product as a clear, colorless oil (50. mg, 49%, Z:E = 2:1). The ^{1}H NMR spectrum was identical to the analogous per-protiated substrate (**3.1a**) except for the disappearance of one of the olefin signals. HRMS (ESI+): $[M+H]^+$ calcd for $C_{21}H_{23}DN$, 291.1971; found, 291.1973.

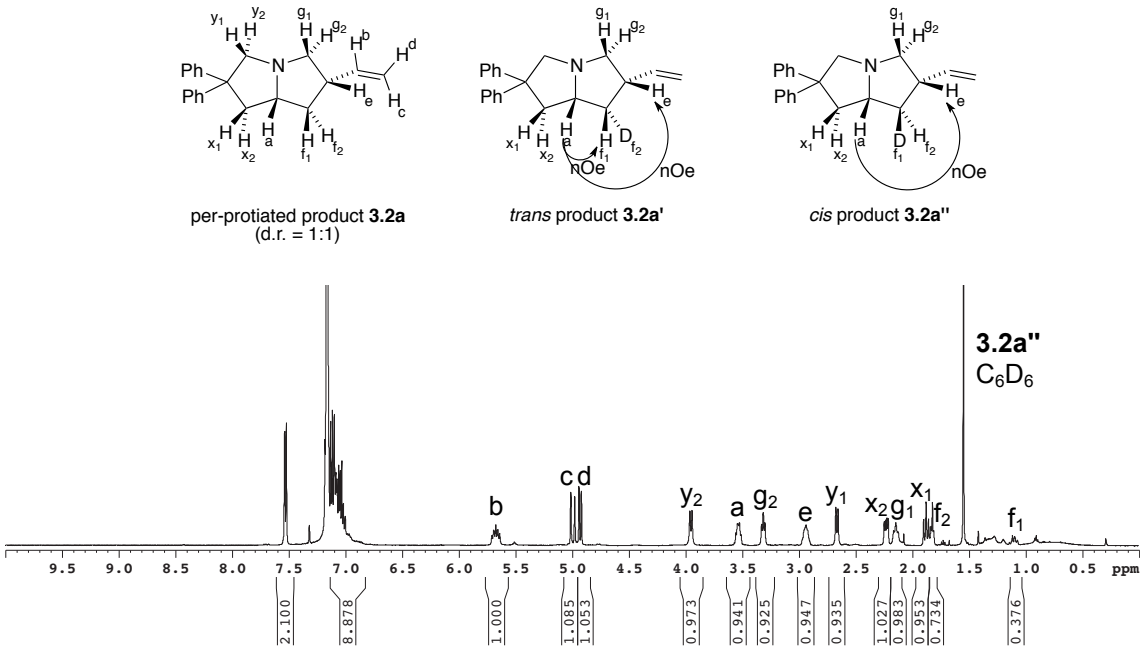
Rearrangement of deuterium-labeled vinyl aziridines.

Dual-catalyzed rearrangement of (Z)-deuterium-labeled vinyl aziridine ***3.1a'****.* In the glovebox, a solution of gold precatalyst **3.5** (6.1 mg, 0.010 mmol, 5.0 mol %) in dry DCM (0.5 mL) was added to a dram vial containing NaBArF (**3.6**, 8.9 mg, 0.010 mmol, 5.0 mol %) using 0.25 mL dry DCM as a rinse. The resulting suspension was transferred to a screw-cap dram vial containing vinyl aziridine **3.1a'** (58. mg, 0.20 mmol, 1.0 equiv) and a micro stir bar using 2 × 0.3 mL dry DCM as a rinse. Finally, Pd_2dba_3 (4.6 mg, 0.0050 mmol, 2.5 mol %) was added to the aziridine mixture in a solution with dry DCM (0.5 mL) using 04 mL dry DCM as a rinse. The vial was capped and the reaction mixture was stirred 25 °C in the glovebox for 26 h. After this time, the reaction mixture was removed from the glovebox and concentrated in vacuo to an oily brown solid, which was purified by column chromatography eluting using a gradient from 1:5:94 to 1:7:92 NH_4OH:MeOH:$CHCl_3$. Many fractions contained the two diastereomers expected based on the analogous reaction of perprotiated aziridine **3.1a** (i.e., not related to the relative stereochemistry of the deuterium), but in order to facilitate interpreta-

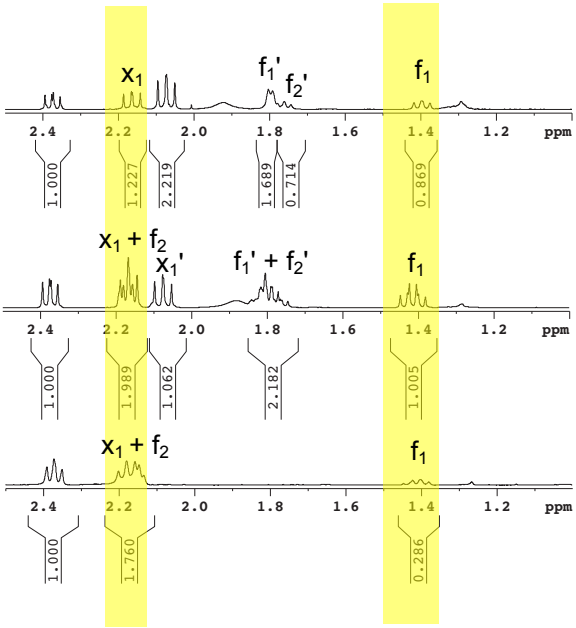
tion of spectroscopic data, only fractions containing a single diastereomer were characterized fully by nOe analysis.

*Dual-catalyzed rearrangement of (E)-deuterium-labeled vinyl aziridine **3.1a"**.* In the glovebox, a solution of gold precatalyst **3.5** (5.3 mg, 0.0086 mmol, 5.0 mol %) in dry DCM (1.5 mL, 0.11 M in aziridine) was added to a dram vial containing BArF salt **3.6** (7.6 mg, 0.0086 mmol, 5.0 mol %). The resulting suspension was transferred to a dram vial containing vinyl aziridine **3.1a"** (50. mg, 0.17 mmol, 1.0 equiv). Finally, the resulting suspension was transferred to a screw-cap dram vial containing Pd_2dba_3 (3.9 mg, 0.0043 mmol, 2.5 mol %). The vial was capped and the reaction mixture was stirred 25 °C in the glovebox for 26 h. After this time, the reaction mixture was removed from the glovebox and loaded directly onto a silica gel pipet column. The column was flushed with $CHCl_3$ to remove the yellow dba band, and then the product was eluted with 1:99 MeOH:$CHCl_3$. Fractions containing primarily diastereomers of the desired product by TLC analysis were combined and concentrated in vacuo. Following a second purification under the same conditions, the desired product was obtained as a mixture of diastereomers (20. mg, 40%).

Assignments were made for deuterated pyrrolizidines **3.2a'** and **3.2a"** on the basis of nOe analysis and by comparison to fully assigned spectral data for the analogous per-protiated pyrrolizidine **3.2a**. See the ^{1}H NMR spectra below. (Note: For samples isolated as a mixture of two diastereomers at the allylic carbon, a prime mark ['] is used to indicate peaks corresponding to the second isomer.)



The following figure is an expanded overlay of three ^{1}H NMR spectra (**3.2a'**, **3.2a**, and **3.2a''**) in $CDCl_3$. The highlighted bands show the loss of a proton signal relative to perprotiated **3.2e** corresponding to the incorporation of deuterium at that position. Top spectrum: **3.2a'** ^{1}H NMR spectrum showing the loss of proton f_2 (deuterium incorporation at this position). Middle spectrum: perprotiated **3.2a** ^{1}H NMR spectrum. Bottom spectrum: **3.2a''** ^{1}H NMR spectrum showing the reduction of proton f_1 (deuterium incorporation at this position).



Dual-catalyzed rearrangement of (Z)-deuterium-labeled vinyl aziridine ***3.1a'*** *under Na-free conditions.*

In the glovebox, gold precatalyst **3.5** (1.3 mg, 0.0022 mmol, 5.5 mol %) and BArF salt **3.6** (1.8 mg, 0.0020 mmol, 5.0 mol %) were weighed into separate dram vials. Precatalyst **3.5** was dissolved in 0.2 mL DCM and transferred to the vial containing **3.6**. The resulting suspension was taken into a syringe, which was then equipped with a Target® Luer-Lock 0.2 µm PTFE filter. The (CAAC)AuBArF/NaCl suspension was filtered into a clean dram vial, and two 0.2 mL portions of DCM were used to rinse the vials formerly containing **3.5** and **3.6** as well as the filter to ensure full transfer of the cationic gold complex. The filtrate was then concentrated under reduced pressure to a clear, colorless glassy residue, from which volatiles were further removed in vacuo for 30 min. The residue was then taken up into a syringe with 0.25 mL CD_2Cl_2, and the resulting solution was filtered through another 0.2 µm PTFE filter cartridge into a dram vial containing deute-

rium-labeled aziridine **3.1a'** (11.6 mg, 0.0400 mmol, 1.00 equiv) in order to remove residual NaCl. The resulting solution was then transferred to a screw-cap dram vial containing Pd_2dba_3 (0.9 mg, 0.001 mmol, 2.5 mol %). All vials were then rinsed with an additional 0.25 mL portion of CD_2Cl_2 to ensure full transfer. The reaction vessel was then capped, and the reaction was allowed to proceed in the glovebox at 25 °C. The crude reaction mixture was transferred to a J. Young tube for observation. After 2.5 d, the reaction had stalled at ca. 55 % conversion. The crude reaction was then concentrated in vacuo to an oily residue, which was subsequently purified by column chromatography eluting using a gradient: 0:1:99 to 4:1:95 MeOH:NH_4OH:$CHCl_3$. Analysis of the purified product by ^1H NMR spectroscopy showed stereospecific deuterium incorporation matching the analogous reaction in which NaCl had not been removed.

Computational Details and Optimized Cartesian Coordinates for **3.16** and **3.17**

Structures were first modeled using Avogadro[19] 1.1.1 and optimized using UFF molecular mechanics. Each structure was then subjected to a systematic conformational search in Spartan '08[20] of up to 10,000 conformers using molecular mechanics (MMFF). The five lowest-energy conformers were then further optimized in the gas phase in Gaussian 09[21] using density functional theory (DFT) with the PBE functional[22] and the Def2SV basis set.[23] Cationic complexes (formal charge +1) were modeled with a singlet spin state.

Olefin-bound vinyl aziridine complex **3.16**, optimized geometry.

Atom	*x (Å)*	*y (Å)*	*z (Å)*	*Atom*	*x (Å)*	*y (Å)*	*z (Å)*
Au	-0.1958	-0.3193	0.4164	H	5.5641	-2.1977	0.6224
C	1.8035	-0.1323	-0.0273	C	3.9754	-3.3505	-1.3015
N	2.3430	1.1782	-0.1462	H	3.7010	-4.1489	-2.0279
C	3.0178	-1.1542	-0.1710	H	4.8724	-2.8192	-1.6952
C	4.1538	-0.2413	-0.8500	C	3.1064	-4.7751	0.6931
C	3.8780	1.2436	-0.3619	H	5.2115	-4.6405	0.0251
H	3.8425	-0.2951	-1.9311	C	1.4868	-3.2507	-0.6150
H	5.1967	-0.5672	-0.6877	H	2.4637	-1.9580	-2.1697
C	1.5233	2.4230	-0.2780	C	2.2405	-2.6498	1.8515
C	1.2528	3.1991	0.9367	H	3.6839	-0.9645	1.9600
C	0.5933	4.4713	0.7134	C	1.8561	-3.8057	0.8308
C	0.3239	4.9922	-0.5886	H	1.2920	-4.1005	-1.3078
C	0.6066	4.1861	-1.7344	H	0.5722	-2.6236	-0.6036
C	1.1862	2.8615	-1.6351	H	3.3626	-5.2028	1.6913
C	1.4318	2.6351	2.3811	H	2.8581	-5.6111	-0.0056
C	0.0934	2.7825	3.2287	H	0.9954	-4.3795	1.2349
H	0.2046	2.1890	4.1627	H	1.3907	-1.9792	2.0820
H	-0.7998	2.4233	2.6805	H	2.5828	-3.0874	2.8198
H	-0.0639	3.8520	3.4773	C	-2.0107	0.1320	1.6728
C	2.5914	3.3528	3.2025	C	-2.5532	-0.3168	0.3919
H	1.6491	1.5524	2.2737	H	-1.9708	1.2036	1.8887
H	2.7248	2.8454	4.1740	H	-2.0571	-0.5426	2.5555
H	2.2674	4.4101	3.3522	C	-3.2758	-1.6920	0.1967
H	3.5568	3.3354	2.6582	H	-2.7952	0.4783	-0.3425
C	1.2987	1.9391	-2.8952	C	-4.0816	-1.8801	-1.1605
C	1.7817	2.7407	-4.1748	H	-4.0637	-1.7794	0.9759
H	1.8143	2.0396	-5.0274	H	-2.5360	-2.5162	0.3082
H	1.0576	3.5661	-4.3717	C	-5.1968	-0.7533	-1.2587
H	2.7912	3.1811	-4.0225	C	-4.7977	-3.2944	-1.0955
C	-0.0861	1.2195	-3.1837	H	-4.0269	-4.0930	-1.0474
H	2.0357	1.1370	-2.6425	H	-5.4176	-3.4517	-2.0039
H	-0.2942	0.4473	-2.4099	H	-5.4478	-3.3133	-0.1960
H	-0.8970	1.9760	-3.1600	C	-3.1511	-1.8285	-2.4378
H	-0.0040	0.7163	-4.1635	H	-3.7822	-1.8679	-3.3553
H	-0.1197	5.9839	-0.7102	H	-2.4517	-2.6980	-2.4435
H	0.3667	4.6073	-2.7245	H	-2.5426	-0.8934	-2.4357
H	0.3497	5.1093	1.5784	N	-6.2327	-0.8123	-0.1248
C	4.3084	2.3999	-1.3443	H	-5.7608	-0.9382	-2.1974
H	3.7553	2.4285	-2.3135	H	-4.6825	0.2542	-1.2863
H	5.3891	2.2970	-1.5279	C	-6.9659	0.5195	0.0921
H	4.0855	3.3817	-0.8493	C	-5.9585	0.0048	1.1592
C	4.6531	1.4705	1.0098	H	-4.9941	0.5066	1.2906

H	4.3456	0.6726	1.7196	H	-6.4843	-0.3561	2.0617
H	4.4434	2.4691	1.4410	C	-8.4755	0.4165	0.3088
H	5.7384	1.4034	0.8073	H	-6.6218	1.3663	-0.5312
C	2.7021	-2.3829	-1.1685	C	-9.2532	1.1026	1.2136
C	3.4453	-1.7910	1.2597	H	-8.9741	-0.2965	-0.3729
C	4.7163	-2.7516	1.0916	H	-10.3246	0.9619	1.2610
C	4.3427	-3.9583	0.1202	H	-8.7708	1.7822	1.9297
H	5.0322	-3.0959	2.0964				

N-bound vinyl aziridine complex **3.17**, optimized geometry.

Atom	*x (Å)*	*y (Å)*	*z (Å)*	*Atom*	*x (Å)*	*y (Å)*	*z (Å)*
N	2.6242	-0.2993	1.2080	C	-2.9287	3.2618	3.2941
C	3.1472	1.0605	1.7325	H	-2.2938	4.1101	3.6318
C	2.6973	0.0112	2.7691	H	-3.7663	3.6766	2.6941
H	2.5532	1.9274	1.4729	H	-3.3343	2.7082	4.1588
H	4.2407	1.2186	1.7129	C	-0.9577	1.5686	3.3762
C	3.6737	-1.2933	0.6322	H	-2.7146	1.4407	2.0475
C	3.8668	-1.3179	-0.9495	H	-0.1373	2.2994	3.5368
H	3.3683	-2.3330	0.8983	H	-1.4525	1.2852	4.3223
H	4.6275	-1.0210	1.1482	H	-0.5286	0.6405	2.9291
C	5.2230	-2.1126	-1.1919	H	0.2866	5.9164	0.4023
H	5.1637	-3.1287	-0.7389	H	-0.8932	4.8144	2.2880
H	6.0619	-1.5365	-0.7257	H	0.5032	4.7943	-1.8055
H	5.4035	-2.2058	-2.2835	C	-4.2917	2.1924	-0.1161
C	2.6826	-2.1239	-1.6222	H	-4.0633	2.4677	0.9389
H	2.6014	-3.1268	-1.1453	H	-5.3656	1.9742	-0.2227
H	2.9069	-2.2475	-2.6947	H	-4.0218	3.0907	-0.7251
H	1.7053	-1.5971	-1.5293	C	-3.7455	0.8889	-2.2407
C	3.9929	0.1485	-1.5498	H	-3.1586	0.0570	-2.6890
C	4.0424	0.2052	-3.1005	H	-3.4821	1.8508	-2.7249
H	4.9492	0.5947	-1.1937	H	-4.8238	0.7136	-2.4106
H	3.1352	0.7405	-1.1603	C	-2.3917	-2.3400	1.1626
C	4.8390	1.0292	-3.8577	C	-2.3754	-2.2190	-1.4513
H	3.4627	-0.5845	-3.6155	C	-3.5841	-3.2695	-1.4967
H	5.4955	1.7430	-3.3451	C	-3.4744	-4.2589	-0.2525
H	4.8450	0.9792	-4.9378	H	-3.5360	-3.8064	-2.4641
Au	0.5913	-0.2082	0.4521	H	-4.5646	-2.7421	-1.4404
C	-1.3810	-0.1801	-0.0439	C	-3.5918	-3.4004	1.0821
N	-1.9740	1.0211	-0.3234	H	-3.4984	-4.0453	1.9871
C	-2.4823	-1.3189	-0.0973	H	-4.5938	-2.9200	1.1169
C	-3.8461	-0.4770	-0.0409	C	-2.0825	-5.0250	-0.2935
C	-3.5084	0.9444	-0.6696	H	-4.2978	-4.9970	-0.2922
H	-4.0877	-0.3582	1.0504	C	-1.0332	-3.1897	1.1688

H	-4.6744	-0.9724	-0.5881	H	-2.4874	-1.7446	2.1036
C	-1.3198	2.3779	-0.1382	C	-1.0035	-3.0247	-1.4957
C	-0.6303	2.9721	-1.2843	H	-2.4306	-1.5485	-2.3341
C	-0.0753	4.2859	-1.0188	C	-0.9001	-3.9638	-0.2132
C	-0.1750	4.9398	0.2456	H	-1.1300	-3.9353	1.9923
C	-0.8536	4.2892	1.3212	H	-0.1330	-2.5908	1.4215
C	-1.4114	2.9578	1.2014	H	-2.0019	-5.6113	-1.2397
C	-0.4110	2.2880	-2.6713	H	-2.0138	-5.7314	0.5682
C	1.0930	2.3982	-3.1774	H	0.0657	-4.5098	-0.2365
H	1.2815	3.4785	-3.3540	H	-0.1563	-2.3178	-1.6250
H	1.1711	1.8168	-4.1169	H	-1.0246	-3.6536	-2.4134
H	1.8471	2.0055	-2.4684	C	3.7542	-0.7147	3.5926
C	-1.3211	2.9403	-3.8096	H	1.6918	0.0835	3.2148
H	-0.6775	1.2121	-2.5520	C	4.9645	-0.2093	4.0071
H	-1.2276	2.3438	-4.7375	H	3.4852	-1.7375	3.8968
H	-0.9417	3.9749	-3.9814	H	5.2400	0.8272	3.7680
H	-2.3869	2.9921	-3.5151	H	5.6468	-0.7999	4.6059
C	-2.0518	2.2481	2.4453				

References for Experimental Section.

1. Lavallo, V.; Frey, G. D.; Kousar, S.; Donnadieu, B.; Bertrand, G. *Proc. Natl. Acad. Sci. USA*, **2007**, *104*, 13569–13573.
2. Yakelis, N. A.; Bergman, R. G. *Organometallics*, **2005**, *24*, 3579–3581.
3. Schaefer, J. P.; Higgins, J. G.; Shenoy, P. K. *Org. Synth.* **1968**, *48*, 51–54.
4. Hong, S.; Tian, S.; Metz, M. V.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *48*, 14768–14783.
5. Oldenziel, O. H.; van Leusen, D.; van Leusen, A. M. *J. Org. Chem.* **1977**, *42*, 3114–3118.
6. Zoidis, G.; Kolocouris, N.; Foscolos, G. B.; Kolocouris, A.; Fytas, G.; Karayannis, P.; Padalko, E.; Neyts, J.; de Clercq, E. *Antivir. Chem. Chemother.* **2003**, *14*, 153–164.

7. Sharma, R.; Bulger, P. G., McNevin, M.; Dormer, P. G.; Ball R. G., Streckfuss, E.; Cuff, J. F.; Yin, J.; Chen, C.-Y. *Org. Lett.* **2009**, *11*, 3194–3197.
8. Bender, C. F.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2005**, *127*, 1070–1071.
9. Riegert, D.; Collin, J.; Meddour, A.; Schulz, E.; Trifonov, A. *J. Org. Chem.* **2006**, *71*, 2514–2517.
10. Fetell, A. I.; Feuer, H. *J. Org. Chem.*, **1978**, *43*, 497–501.
11. Mignami, G.. US Patent 2010/0113791, May 6, 2010.
12. Trost, B. M.; Fandrick, D. R. *J. Am. Chem. Soc.* **2003**, *125,* 11836–11837.
13. Gardrat, C.; Latxague, L.; Picard, J. P. *J. Heterocycl. Chem*. **1990**, *27*, 811–812.
14. Crimmin, M. R.; Arrowsmith, M.; Barrett, A. G. M.; Casely, I. J.; Hill, M. S.; P. Procopiou, A. *J. Am. Chem. Soc.* **2009**, *131*, 9670–9685.
15. Kondo, T.; Okada, T.; Mitsudo, T.-A. *J. Am. Chem. Soc.* **2002**, *124*, 186–187.
16. Chang, S.; Lee, M.; Jung, D. Y.; Yoo, E. J.; Cho, S. H.; Han, S. K. *J. Am. Chem. Soc.* **2006**, *128*, 12366–12367.
17. Bew, S. P.; Hiatt-Gipson, G. D.; Lovell, J. A.; Poullain, C. *Org. Lett.* **2012**, *14*, 456–459.
18. Martínez, P. H.; Hultzsch, K. C.; Hampel, F. *Chem. Commun.* **2006**, 2221–2223.
19. Hanwell, M. D.; Curtis, D. E.; Lonie, D. C.; Vandermeersch, T.; Zurek, E.; Hutchinson, G. R. *J. Cheminform.* **2012**, *4*, 17.
20. Spartan ’08; Wavefunction, Inc., Irvine CA, 2009.
21. Gaussian 09; Gaussian, Inc., Wallingford CT, 2009.

22. Perdew, J. P.; Burke, K.; Ernzerhof, M. *Phys. Rev. Lett.*, **1996**, *77*, 3865–3868.

23. Weigend, F; Ahlrichs, R. *Phys. Chem. Chem. Phys.*, **2005**, *7*, 3297–3305.

Chapter 4
Early Investigations in Dual-Catalyzed Borylation: Preface to Alkoxyboration

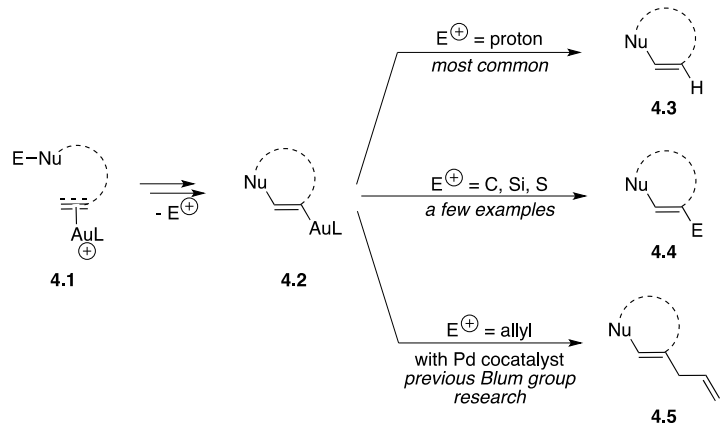
Abstract: A borylation reaction cocatalyzed by Au and Rh was proposed as a means of isolating catalytic organogold intermediates as the corresponding organoboron derivatives for use in subsequent functionalization steps. Products consistent with the proposed reactivity were obtained, but control experiments indicated no role for Rh in the reaction; organogold complexes were found to undergo facile thermal reactivity with electrophilic B without Rh. Electronic effects in the chemoselective borylation of heterocyclic organogold complexes were studied, suggesting design parameters used in the development of the Au-catalyzed borylation reactions discussed in Chapters 5 and 6.

Introduction

Because of its carbophilic Lewis acidity, Au(I) is commonly used in homogeneous catalysis to promote the attack of nucleophiles on C–C multiple bonds.[1-4] These intra- or intermolecular reactions often occur at room temperature and are general for both a wide variety of nucleophiles (e.g., amines, alcohols, carboxylates, and esters) and a diverse set of pro-electrophiles (e.g., alkynes, allenes, and olefins). The mechanism of Au(I)-catalyzed nucleophilic addition to C–C multiple bonds has been well-documented and in many cases proceeds through an organogold intermediate.[1–4] Despite the diversity of pathways through which these catalytic organogold intermediates are generated, subsequent functionalization of the C–Au bond is largely limited to protonation (**4.3**, Scheme 4.1) or

trapping with a small number of other electrophiles, such as carbocation,[5–7] silyl,[8] and sulfonyl[9] electrophiles (**4.4**). Although each of these reactions represented an important advance in the field of Au catalysis, the specialized systems they employ do not represent a general means of achieving Au catalyst turnover. An alternative method of functionalizing catalytic organogold intermediates could dramatically increase the synthetic versatility of Au-catalyzed rearrangements. Studies in the Blum group have demonstrated the interception of catalytic organogold intermediates through Pd-catalyzed cross-coupling reactivity, though this approach thus far has largely been limited to allylation (**4.5**).[10,11] We have hypothesized that this lack of generality arises from a requirement for the Pd-catalyzed steps to outcompete redox decomposition of the organogold intermediate,[12] a pathway in which the allyl group could be uniquely kinetically suitable.

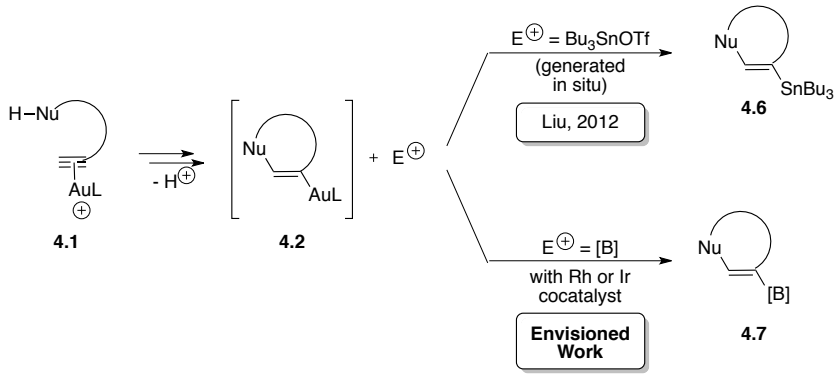
Scheme 4.1. Functionalization of catalytic organogold intermediates by electrophilic trapping.



When stoichiometric Au is employed, organogold compounds structurally similar to catalytic intermediates can be isolated and subsequently functionalized through Pd-catalyzed cross-coupling reactions,[13–15] allowing for a greater breadth

of coupling partners. However, the high cost of employing stoichiometric Au on a preparatory scale is a clear disadvantage of this method. As a conceptual alternative, we envisioned that a catalytic organogold intermediate could be trapped by a second, inexpensive stoichiometric metal, isolated and stored indefinitely, and later used in subsequent cross-coupling reactions. A previous report from the Blum group disclosed a method for preparing α-stannyl enoates using Au and Pd cocatalysis.[16] More recently, Liu demonstrated a creative approach to trap catalytic organogold intermediates in a cyclization reaction with electrophilic Sn (**4.6**, Scheme 4.2), but the resulting stannanes were sluggishly reactive in Stille cross-coupling reactions.[17] We envisioned that trapping with B (**4.7**) instead of Sn would offer the twofold advantage of (1) many available downstream functionalization reactions[18] and (2) diminished toxicity[19] of the metalated product. In this way, catalytic organogold intermediates could conceptually be isolated as their organoboron analogs for use in subsequent functionalization reactions. This reaction would thus provide a means to combine the cyclization reactivity accessible using Au catalysis with the synthetic versatility of organoboron reagents.

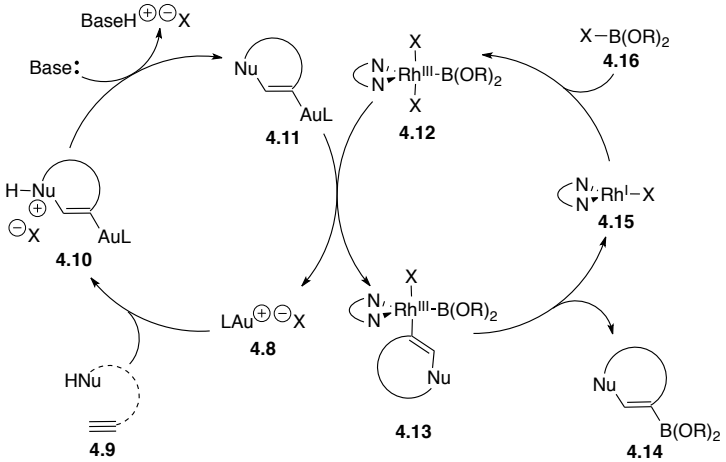
Scheme 4.2. Functionalization of catalytic organogold cyclization intermediates by metalation.



Results and Discussion

It was envisioned that a reaction cocatalyzed by Au and either Rh or Ir would allow for tandem intramolecular cyclization and borylation to furnish boronic ester products not readily available through other methods. The original mechanistic hypothesis underlying this project area is shown in Scheme 4.3. Lewis acidic Au(I) cocatalyst **4.8** was expected to promote an intramolecular nucleophilic addition to an alkyne to give vinylgold complex **4.11**, which is known to be an intermediate in many Au-catalyzed reactions.[1–4] Neutral vinylgold complex **4.11** could undergo transmetalation with Rh(III)-boryl intermediate **4.12**, an elementary step that has been studied previously in the Blum group.[20] The resulting organo-Rh(III) complex **4.13** could then undergo C–B bond-forming reductive elimination[21] to provide desired borylated product **4.14** and regenerate the active Rh(I) catalyst, **4.15**. Oxidative addition by **4.15** into haloborane **4.16**, such as *B*-chlorocatecholborane,[22] would complete the envisioned dual-catalytic cycle.

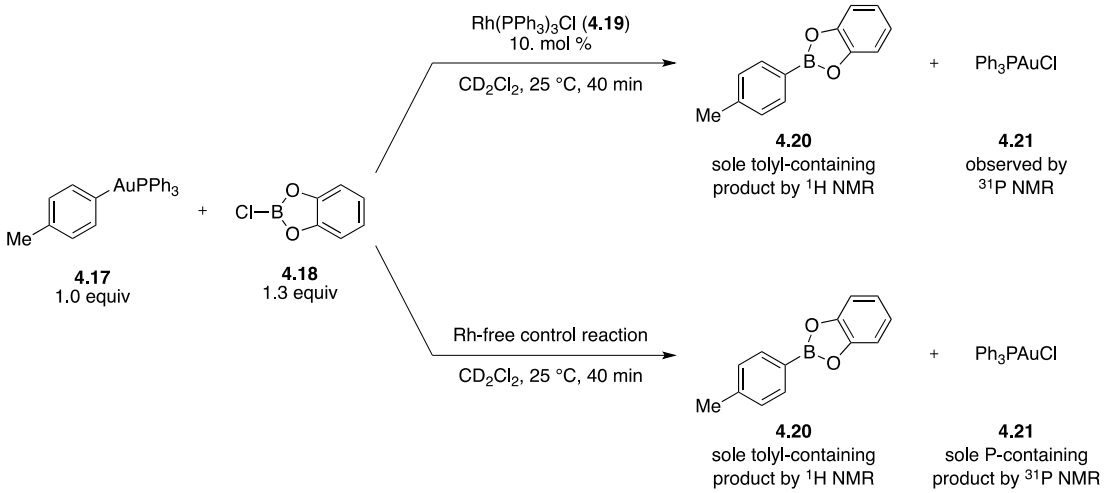
Scheme 4.3. Mechanistic hypothesis underlying early studies of Au/B dual metal reactivity.



Nu = OH or COOH; Rh ligand = 2,2'-bipyridine.

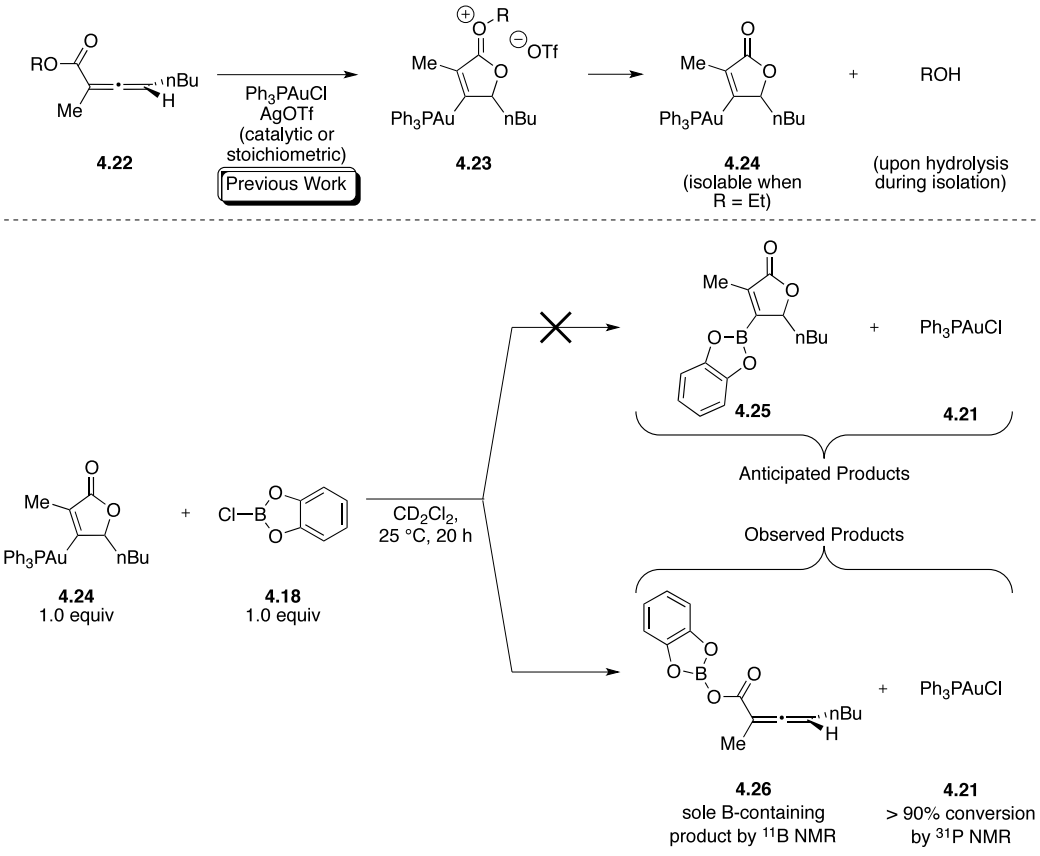
In order to simplify early investigations of the hypothesized Au/Rh dual-catalyzed borylation reaction, a pair of experiments were conducted with stoichiometric organogold complex **4.17** (Scheme 4.4). The purpose of these experiments was to study the proposed Rh catalytic cycle independent of the success or failure of Au catalyst turnover. Treatment of **4.17** and known oxidative addition partner **4.18** in the presence of Wilkinson's catalyst afforded rapid, clean conversion to the anticipated borylation product **4.20** and Au coproduct **4.21**. This result suggested a functional Rh-catalyzed borylation reaction as shown in Scheme 4.3. However, the Rh-free control experiment afforded identical borylation reactivity, thereby indicating that the observed borylation reaction is best described as a direct transmetalation from Au to B; no second metal catalyst was necessary.

Scheme 4.4. Borylation of a stoichiometric organogold complex.



Also studied was the borylation of stoichiometric organogold complex **4.24**, which Hammond demonstrated to be an intermediate in a Au-catalyzed cyclization reaction of allenoates (Scheme 4.5).[23] Treatment of isolated **4.24** with B electrophile **4.18** was expected to provide boronic ester **4.25** through a *C*-borylation pathway analogous to the one shown in Scheme 4.4. Instead, characterization data were consistent with the product of ring-opening *O*-borylation, boric ester **4.26**.

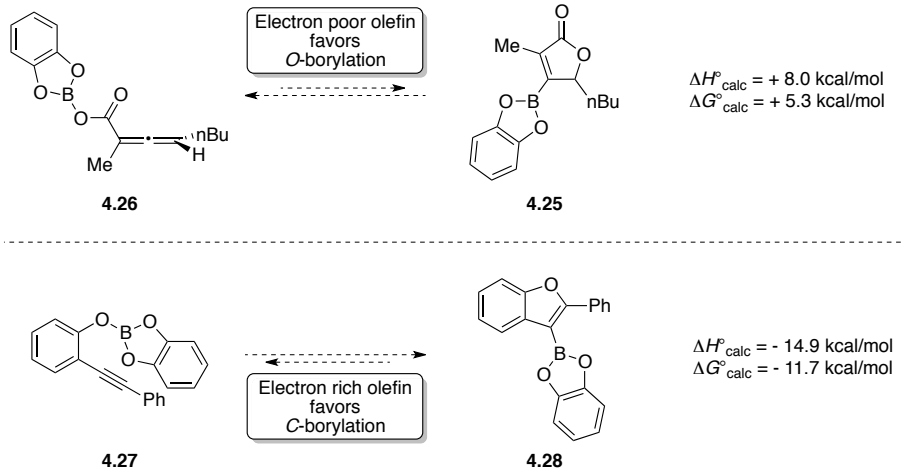
Scheme 4.5. *O*-Borylation vs. *C*-borylation in an isolable Au catalytic intermediate.



It was hypothesized that under yet-undetermined conditions (see Chapter 5), boronic ester **4.25** and boric ester **4.26** could be present in equilibrium and

thus the distribution of these two species could be subject to thermodynamic control (Scheme 4.6). Computational inquiry using density functional theory (DFT) suggested that such an equilibrium would favor undesired *O*-borylated boric ester **4.26**, presumably because the B empty p orbital in **4.25** is poorly stabilized by the electron-poor alkene. Switching to phenol-derived boric ester **4.27** reversed the calculated equilibrium to favor *C*-borylated benzofuran **4.28**. This reversal is likely due in part to better stabilization of the B empty p orbital of **4.28** afforded by the electron-rich enol ether moiety. Thus, computational studies suggested that *C*-borylation could be promoted through the formation of electron-rich vinyl boronic esters.

Scheme 4.6. Computational study of potential equilibria in *O*-borylation vs. *C*-borylation.



Gas-phase thermochemical data calculated using the B3LYP functional and 6-31G basis set at a temperature of 298.15 K and a pressure of 1.000 atm.

In light of the experimental and computational results presented in this chapter, subsequent borylation efforts were targeted towards forming electron-rich

vinylboronic esters through a reaction catalyzed only by Au and not a second transition metal. The results of these studies are described in Chapters 5 and 6.

References

1. Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180–3211.
2. Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395–403.
3. Li, Z.; Bower, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239–3265.
4. Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351–3378.
5. Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 16804–16805.
6. Nakamura, I.; Sato, T.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 4473–4475.
7. Nakamura, I.; Sato, T.; Terada, M.; Yamamoto, Y. *Org. Lett.* **2008**, *10*, 2649–2651.
8. Nakamura, I.; Sato, T.; Terada, M.; Yamamoto, Y. *Org. Lett.* **2007**, *9*, 4081–4083.
9. Nakamura, I.; Yamagishi, U.; Song, D.; Konta, S.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 2284–2287.
10. Shi, Y.; Roth, K. E.; Ramgren, S. D.; Blum, S. A. *J. Am. Chem. Soc.* **2009**, *131*, 18022–18023.
11. Al-Amin, M.; Roth, K. E.; Blum, S. A. *ACS Catal.* **2014**, *4*, 622–629.
12. Hirner, J. J.; Shi, Y.; Blum, S. A. *Acc. Chem. Res.*, **2011**, *44*, 603–613.
13. Shi, Y.; Ramgren, S. D.; Blum, S. A. *Organometallics* **2009**, *28*, 1275–1277.
14. Hashmi, A. S. K.; Döpp, R.; Lothschütz, C.; Rudolph, M.; Riedel, D.; Rominger, F. *Adv. Synth. Catal.* **2010**, *352*, 1307–1314.

15. Roth, K. E.; Blum, S. A. *Organometallics* **2011**, *30*, 4811–4813.
16. Shi, Y.; Peterson, S. M.; Haberaecker, W. W., III; Blum, S. A. *J. Am. Chem. Soc.* **2008**, *130*, 2168–2169.
17. Chen, Y.; Chen, M.; Liu, Y. *Angew. Chem. Int. Ed.* **2012**, *51*, 6181–6186.
18. Hall, D. G. *Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine, and Materials*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2011.
19. Stoner, H. B.; Barnes, J. M.; Duff, J. I. *Brit. J. Pharmacol.* **1955**, *10*, 16–25.
20. Shi, Y.; Blum, S. A. *Organometallics* **2011**, *30*, 1776–1779.
21. Chen, H.; Schlecht, S.; Semple, T. C.; Hartwig, J. F. *Science* **2000**, *287*, 1995–1997.
22. Souza, F. E. S.; Nguyen, P.; Marder, T. B.; Scott, A. J., Clegg, W. *Inorg. Chim. Acta* **2005**, *358*, 1501–1509.
23. Liu, L.-P.; Xu, B.; Mashuta, M. S.; Hammond, G. B. *J. Am. Chem. Soc.* **2008**, *130*, 17642–17643.

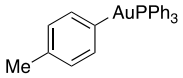
Experimental

General Considerations

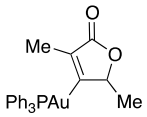
All chemicals were used as received from commercial sources unless otherwise noted. Dichloromethane-d_2 was dried over CaH_2, degassed using three freeze-pump-thaw cycles, and vacuum transferred prior to use. All manipulations were conducted in a glovebox under nitrogen atmosphere. All proton and carbon nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were recorded on a Bruker DRX-400 spectrometer, Bruker DRX-500 spectrometer outfitted with a cryoprobe, or a Bruker AVANCE-600 spectrometer. All boron nuclear magnetic

resonance (^{11}B NMR) spectra were recorded on a Bruker AVANCE-600 spectrometer. All phosphorous nuclear magnetic resonance (^{31}P NMR) spectra were recorded on a Bruker DRX-400. All chemical shifts (δ) are reported in parts per million (ppm) downfield of tetramethylsilane, and referenced to the residual protiated solvent peak (δ = 5.32 ppm for CD_2Cl_2 in ^{1}H NMR spectroscopy experiments; δ = 53.84 ppm for CD_2Cl_2 in ^{13}C NMR spectroscopy experiments). ^{11}B and ^{31}P NMR spectroscopy experiments are referenced to the absolute frequency of 0 ppm in the ^{1}H dimension according to the Xi scale. Low- and high-resolution mass spectrometry data were obtained at the University of California, Irvine.

Synthetic Procedures



4.17. Organogold compound **4.17** was prepared according to a literature procedure.[1] The product was obtained as a white powder (301 mg, 55% yield). ^{1}H NMR (CD_2Cl_2, 500 MHz): δ 7.60–7.64 (m, 6H), 7.47–7.54 (m, 9H), 7.38 (m, 2H), 7.07 (d, *J* = 7.2 Hz, 2H), 2.30 (s, 3H). This spectrum is in agreement with previously reported spectral data.



4.24. Organogold complex **4.24** was prepared according to a literature procedure.[2] ^{1}H NMR (CD_2Cl_2, 500 MHz): δ 7.50–7.58 (m, 15H), 4.99 (q, *J* = 6.6 Hz,

1H), 1.97 (t, *J* = 1.1 Hz, 3H), 1.43 (d, *J* = 6.9 Hz, 3H). This spectrum is in agreement with previously reported spectral data.

Borylation of organogold complex **4.17** (Scheme 4.4)

With catalytic Rh. In a N_2-filled glovebox, organogold complex **4.17** (14 mg, 26 μmol, 1.0 equiv) was dissolved in 300 μL CD_2Cl_2 and added to a dram vial containing Rh complex **4.19** (2.3 mg, 2.6 μmol, 10. mol %). The resulting pale yellow solution was added to a dram vial containing *B*-chlorocatecholborane (5.0 mg, 33 μmol, 1.3 equiv). The resulting solution was transferred to a J. Young NMR tube, and each vial was rinsed with an additional 200 μL CD_2Cl_2 to facilitate complete material transfer. The mixture was allowed to react for 40 min at 25 °C, after which time the following spectroscopic data were obtained for the crude mixture:

^{1}H NMR (CD_2Cl_2, 400 MHz): δ 7.97 (d, *J* = 7.7 Hz, 2H), 7.58–7.47 (m, 15H), 7.33–7.30 (m, 4H), 7.13 (dd, *J* = 2.4, 1.4 Hz, 2H), 2.43 (s, 3H), plus trace signals corresponding to unreacted **4.18** and one or two Rh-phosphine complex(es), some of which partially overlap with the peaks listed above.

^{31}P NMR (CD_2Cl_2, 162 MHz): δ 51.5 (d, *J* = 196.1 Hz, minor signal), 33.1 (s, major signal), 31.4 (dd, *J* = 143.6, 37.0 Hz, trace signal).

These spectroscopic data indicate full conversion of organogold complex **4.17** to Ph_3PAuCl (authentic sample ^{31}P NMR, δ 33.1 in CD_2Cl_2) and a single tolyl-containing product. Following spectroscopic analysis of the crude mixture, the reaction was exposed to air and concentrated in vacuo. The resulting residue was purified by sublimation at ca. 10 mTorr to afford 7.8 mg of a white solid with ^{1}H

NMR data matching previously reported spectral data for the purified borylated product **4.20**.[3]

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.00 (d, *J* = 7.9 Hz, 2H), 7.33–7.31 (m, 2H), 7.13 (dd, *J* = 5.8, 3.3 Hz, 2H), 2.44 (s, 3H), plus several other trace signals corresponding to ca. two unidentified decomposition products.

Without catalytic Rh. The Rh-free control reaction was conducted analogous to the procedure above but with rhodium complex **4.19** omitted. The mixture was allowed to react for 40 min at 25 °C, after which time the following spectroscopic data were obtained for the crude mixture.

^{1}H NMR (CD_2Cl_2, 400 MHz): δ 7.97 (d, *J* = 7.8 Hz, 2H), 7.58–7.47 (m, 15H), 7.33–7.30 (m, 4H), 7.13 (dd, *J* = 2.4, 1.4 Hz, 2H), 2.43 (s, 3H), plus trace signals corresponding to unreacted **4.18**, some of which partially overlap with the peaks listed above.

^{31}P NMR (CD_2Cl_2, 162 MHz): δ 33.1 (s). No other signals were observed.

These spectroscopic data indicate full conversion of organogold complex **4.17** to Ph_3PAuCl (authentic sample ^{31}P NMR, δ 33.1 in CD_2Cl_2) and desired borylation product **4.20**.

Borylation of organogold complex **4.24** (Scheme 4.5)

In a N_2-filled glovebox, organogold complex **4.24** (12 mg, 20. μmol, 1.0 equiv) was dissolved in 500 μL CD_2Cl_2 and added to a dram vial containing *B*-chlorocatecholborane (3.1 mg, 20. μmol, 1.0 equiv). The resulting solution was

transferred to a J. Young NMR tube and allowed to react at 25 °C. The reaction progress was monitored by ^{1}H and ^{31}P NMR spectroscopy periodically for 20 h, at which time **4.24** was ca. 90% consumed by ^{31}P NMR analysis. The following spectroscopic data were obtained for the crude mixture:

^{1}H NMR (CD_2Cl_2, 400 MHz) displayed many overlapping, broad signals, most of which were not useful in structure determination. The most diagnostic signal was observed at δ = 5.60 (br s, 3H) corresponding to the allene olefinic proton.

^{11}B NMR (CD_2Cl_2, 193 MHz): δ 22.7 (br s). No other signals were observed.

^{31}P NMR (CD_2Cl_2, 162 MHz): δ 44.1 (s, minor signal), 33.1 (s, major signal).

These spectroscopic data indicate ca. 90% conversion of organogold complex **4.24** to Ph_3PAuCl (authentic sample ^{31}P NMR, δ 33.1 in CD_2Cl_2). The observation of a vinylic proton by ^{1}H NMR and a boric ester [$B(OR)_3$] moiety by ^{11}B NMR suggested the formation of ring-opening product **4.26**. However, further analysis was precluded by the high air sensitivity of this product.

Computational Details and Cartesian Coordinates for Optimized Structures

Thermochemical data for compounds **4.25**–**4.28** were obtained for optimized geometries of the ground-state conformer for each molecule. Structures were first modeled using Avogadro[4] 1.1.1 and optimized using UFF molecular mechanics. Each structure was then subjected to a systematic conformational search in Spartan '08[5] of up to 10,000 conformers using molecular mechanics (MMFF). The five lowest-energy conformers were then further optimized in the

gas phase in Gaussian 09[6] using density functional theory (DFT) calculations with the B3LYP functional[7,8] and the 6-31G basis set.[9] Thermochemical data were calculated at the same level of theory at a temperature of 298.15 K and a pressure of 1.000 atm.

4.25, optimized Cartesian coordinates.

Atom	*x (Å)*	*y (Å)*	*z (Å)*	*Atom*	*x (Å)*	*y (Å)*	*z (Å)*
C	-0.8230	2.3695	0.0607	H	-3.7934	-2.4590	1.7608
C	-0.4531	1.0895	-0.2013	H	-2.7983	-3.5231	0.7730
C	-2.2872	2.5144	-0.1833	H	-5.7811	-2.9156	0.2606
O	-2.7793	1.2775	-0.6046	H	-5.1399	-4.4161	0.9520
C	-1.6726	0.2876	-0.6329	H	-4.7814	-3.9904	-0.7304
O	-2.9937	3.5116	-0.0601	B	0.9469	0.4849	-0.1233
C	-0.0240	3.5430	0.5193	O	2.1315	1.1447	0.2862
H	-0.4193	3.9223	1.4701	O	1.2572	-0.8540	-0.4707
H	-0.1158	4.3676	-0.1986	C	2.6453	-1.0098	-0.2743
H	1.0295	3.2909	0.6451	C	3.1745	0.1998	0.1841
C	-2.0323	-0.8963	0.2708	C	4.5207	0.3557	0.4678
H	-1.5874	-0.0452	-1.6745	C	3.4336	-2.1305	-0.4747
C	-3.2987	-1.6423	-0.1834	C	4.8030	-1.9890	-0.1917
H	-2.1624	-0.5219	1.2953	C	5.3348	-0.7728	0.2694
H	-1.1746	-1.5818	0.2798	H	6.3966	-0.7013	0.4776
C	-3.6499	-2.8274	0.7344	H	4.9187	1.2980	0.8225
H	-3.1560	-2.0096	-1.2115	H	3.0121	-3.0622	-0.8305
H	-4.1382	-0.9366	-0.2167	H	5.4621	-2.8384	-0.3330
C	-4.9096	-3.5816	0.2798				

4.26, optimized Cartesian coordinates.

Atom	*x (Å)*	*y (Å)*	*z (Å)*	*Atom*	*x (Å)*	*y (Å)*	*z (Å)*
C	-2.5941	-2.0023	0.0348	H	-2.9506	-4.1017	0.4063
C	-3.1264	-0.8884	0.5152	H	-3.3325	-3.5882	-1.2345
C	-3.6616	0.2106	0.9796	C	-1.1656	-2.0674	-0.3243
C	-4.2627	1.3243	0.1388	O	-0.4931	-0.8477	-0.1373
H	-3.6581	0.3789	2.0587	O	-0.5927	-3.0591	-0.7727
C	-3.4541	2.6419	0.2312	B	0.8519	-0.5912	-0.0985
H	-5.2897	1.5059	0.4864	O	1.3647	0.6996	-0.3608
H	-4.3285	1.0051	-0.9082	O	1.8925	-1.4694	0.2682
C	-2.0625	2.5578	-0.4202	C	3.0769	-0.7004	0.2272
H	-3.3493	2.9297	1.2884	C	2.7582	0.6081	-0.1502
H	-4.0372	3.4406	-0.2501	C	4.3751	-1.0935	0.4984
C	-1.2629	3.8645	-0.3009	C	5.3668	-0.1034	0.3777
H	-2.1809	2.2964	-1.4823	C	5.0472	1.2108	0.0003
H	-1.4916	1.7371	0.0299	C	3.7216	1.5933	-0.2737
H	-1.7794	4.6977	-0.7949	H	4.6076	-2.1109	0.7867
H	-0.2737	3.7581	-0.7595	H	6.4000	-0.3632	0.5804
H	-1.1144	4.1418	0.7508	H	5.8379	1.9483	-0.0835
C	-3.3775	-3.2825	-0.1832	H	3.4624	2.6029	-0.5667
H	-4.4231	-3.1487	0.1022				

4.27, optimized Cartesian coordinates.

Atom	*x (Å)*	*y (Å)*	*z (Å)*	*Atom*	*x (Å)*	*y (Å)*	*z (Å)*
C	-1.1274	3.0143	0.0001	H	5.6679	0.5271	0.0004
C	-0.6960	4.3452	0.0001	H	2.4225	-2.3025	-0.0004
C	-0.1800	1.9895	0.0000	H	4.0567	-4.1750	-0.0004
C	1.2075	2.2596	-0.0001	H	6.4994	-3.6989	0.0000
C	1.6105	3.6135	-0.0001	H	7.3008	-1.3430	0.0004
C	0.6715	4.6449	0.0000	B	-1.7429	0.0163	0.0000
H	1.0041	5.6774	0.0000	O	-1.8674	-1.3918	0.0001
H	-1.4311	5.1431	0.0002	O	-3.0316	0.6183	-0.0001
H	-2.1822	2.7705	0.0003	C	-3.9561	-0.4512	0.0000
H	2.6719	3.8345	-0.0002	C	-3.2513	-1.6593	0.0001
O	-0.5404	0.6377	0.0000	C	-5.3385	-0.4031	-0.0001
C	2.1644	1.2084	-0.0002	C	-6.0084	-1.6403	0.0000
C	2.9897	0.3103	0.0000	C	-5.3022	-2.8535	0.0001
C	3.9324	-0.7592	0.0000	C	-3.8959	-2.8837	0.0001
C	3.4883	-2.1013	-0.0002	H	-7.0928	-1.6540	0.0000
C	4.4104	-3.1488	-0.0002	H	-5.8506	-3.7891	0.0001
C	5.7856	-2.8813	0.0000	H	-3.3398	-3.8126	0.0002
C	6.2362	-1.5551	0.0002	H	-5.8714	0.5394	-0.0002
C	5.3217	-0.5009	0.0002				

4.28, optimized Cartesian coordinates.

Atom	*x (Å)*	*y (Å)*	*z (Å)*	*Atom*	*x (Å)*	*y (Å)*	*z (Å)*
C	-3.446	2.9971	-0.0801	H	4.1432	1.2589	-1.756
C	-4.6543	2.2934	-0.0811	H	1.7565	0.6329	-1.6722
C	-2.2791	2.2349	-0.064	H	3.4955	4.1881	1.3211
C	-2.2545	0.8446	-0.051	H	5.022	3.0356	-0.2613
C	-3.4835	0.1574	-0.0472	H	1.1067	3.5644	1.4197
C	-4.6751	0.8971	-0.0644	B	-0.3426	-0.8543	0.037
H	-5.6287	0.3732	-0.0631	O	-1.1845	-2.1479	-0.0126
H	-5.5925	2.8443	-0.0937	O	1.135	-1.2341	0.1959
H	-3.4105	4.0796	-0.0914	C	1.0761	-2.6045	0.2199
H	-3.5134	-0.9272	-0.0307	C	-0.2174	-3.1149	0.1032
O	-1.0152	2.741	-0.0573	C	-0.4592	-4.4739	0.1085
C	-0.1487	1.6779	-0.0531	C	2.1707	-3.4359	0.3465
C	-0.8781	0.5063	-0.029	C	1.9434	-4.8154	0.3537
C	1.2591	2.0384	-0.105	C	0.6388	-5.3303	0.2355
C	2.1292	1.4043	-1.0014	H	-1.4667	-4.8638	0.0177
C	1.7656	3.0493	0.7238	H	3.1723	-3.031	0.4386
C	3.1157	3.4048	0.6705	H	2.7835	-5.4998	0.4526
C	3.9722	2.7577	-0.218	H	0.4847	-6.4074	0.2439
C	3.4795	1.7592	-1.0558				

References for Experimental Section.

1. Roth, K. E.; Blum, S. A. *Organometallics* **2010**, *29*, 1712–1716.
2. Liu, L.-P.; Xu, B.; Mashuta, M. S.; Hammond, G. B. *J. Am. Chem. Soc.* **2008**, *130*, 17642–17643.
3. del Grosso, A.; Pritchard, R. G.; Muryn, C. A.; Ingleson, M. J. *Organometallics* **2010**, *29*, 241–249.
4. Hanwell, M. D.; Curtis, D. E.; Lonie, D. C.; Vandermeersch, T.; Zurek, E.; Hutchinson, G. R. *J. Cheminform.* **2012**, *4*, 17.
5. Spartan ’08; Wavefunction, Inc., Irvine CA, 2009.
6. Gaussian 09; Gaussian, Inc., Wallingford CT, 2009.
7. Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652.
8. Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.*

1994, *98*, 11623–11627.

9. Francl, M. M.; Pietro, W. J.; Hehre, W. J.; Binkley, J. S.; Gordon, M. S.; De-Frees, D. J.; Pople, J. A. *J. Chem. Phys*. **1982**, *77*, 3654–3665.

Chapter 5

Alkoxyboration: Ring-Closing Addition of B–O σ Bonds Across Alkynes

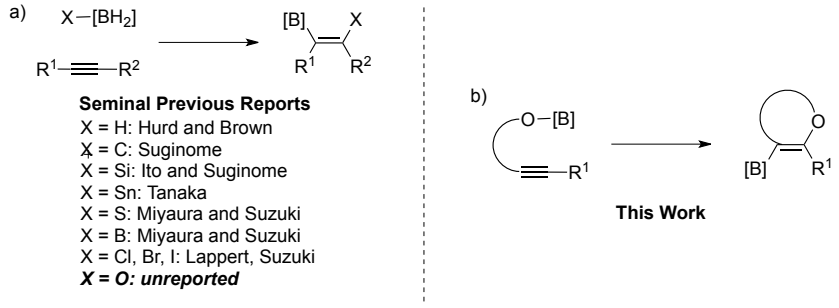
Abstract: For nearly 70 years, the addition of boron–X σ bonds to carbon–carbon multiple bonds has been employed in the preparation of organoboron reagents. However, the significantly higher strength of boron–oxygen bonds has thus far precluded their activation for addition, preventing a direct route to access a potentially valuable class of oxygen-containing organoboron reagents for divergent synthesis. Herein is discussed an alkoxyboration reaction, the addition of boron–oxygen σ bonds to alkynes. Functionalized *O*-heterocyclic boronic acid derivatives are produced using this transformation, which is mild and exhibits broad functional group compatibility. Our results demonstrate activation of this boron–O σ bond using a gold catalysis strategy that is fundamentally different from that used previously for other boron addition reactions.

Introduction

Boronic acids and their derivatives are versatile reagents in modern organic synthesis, and the hydroboration reaction is a well-established method for generating these building blocks through the addition of B–H bonds across C–C multiple bonds.[1] First described by Hurd[2] in 1948 and later developed in detail by Brown,[3] this reaction has inspired many catalyzed variants.[4,5] Recently, several compelling examples of related B–X bond addition reactivity have been reported for X = C,[6,7] Si,[5,8,9] Sn,[5,10] S,[11] B,[5,12] Cl,[13] Br,[14] and I[14] (Scheme 5.1a). Many of these transformations proceed through the oxidative addition of a catalytic transition metal such Ni(0), Pd(0), or Pt(0) into the B–X σ bond.

Despite this progress, the corresponding activation of B–O bonds and addition to C–C multiple bonds—alkoxyboration—has remained elusive.[15,16] This striking dearth of B–O bond activation reactivity may be due to the extremely high strength of the B–O bond, ~136 kcal/mol, compared to less than 105 kcal/mol for all others entries in the series.[17] This high stability may render the B–O bond unreactive towards oxidative addition, thus preventing the successful application of Ni, Pd, or Pt catalysis[6-11] in an alkoxyboration reaction. Organoboron reagents are the building blocks of choice for medicinal chemistry and drug discovery.[18] Given that ethers are found in many diverse classes of natural products[19] and in nearly 25% of the top-grossing pharmaceuticals in the United States for 2012,[20] the development of such a transformation allows for the preparation of oxygen-containing building blocks useful in drug discovery and materials science.[20,21]

Scheme 5.1. a) Previous work developing addition of B–X bonds across alkynes. b) This work demonstrating the first addition of B–O bonds across alkynes.



Results and Discussion

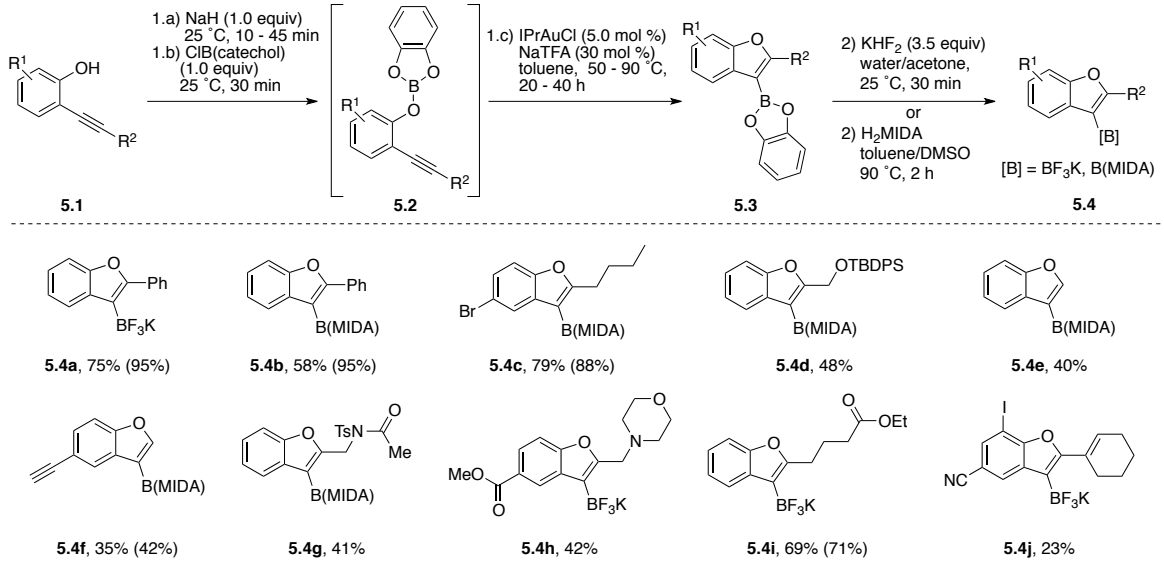
Herein is described the realization of an alkoxyboration reaction of alkynes (Scheme 5.1b), through which new *O*-heterocyclic organoboronate coupling part-

ners are available for downstream functionalization. The high functional group tolerance of this reaction enables downstream divergent synthesis of functionalized benzofurans[22]—the ability to accesses multiple benzofurans from one bench stable precursor. This work was conducted in conjunction with Blum group graduate student Darius Faizi.

We envisioned that the desired alkoxyboration reactivity could be promoted through an activation pathway employing a bifunctional Lewis acidic/Lewis basic catalyst, which could simultaneously activate both the alkyne and the B–O σ bond partners. We anticipated that this unique strategy could allow for the *anti* addition of B–O bonds across alkynes by circumventing the previous problematic strategy of oxidative cleavage of the B–O bond.

Our optimized one-pot procedure begins with 2-alkynylphenols (**5.1**), which are converted into the requisite boric ester intermediate **5.2** using the readily available reagent *B*-chlorocatecholborane (Table 5.1). Treatment of this intermediate with the commercially available Lewis acidic gold(I) precatalyst IPrAuCl and NaTFA affords alkoxyboration product **5.3** in good to excellent conversion as determined by the ERETIC method.[23] Interestingly, our examination of alternative π-Lewis acidic transition metal catalysts revealed no other active catalysts aside from Au(I).[24] For ease of isolation, the catecholboronic ester alkoxyboration product **5.3** was converted into either the organotrifluoroborate[25] or *N*-methyliminodiacetic acid (MIDA) boronate[26] derivative, **5.4**, both of which are indefinitely air stable.

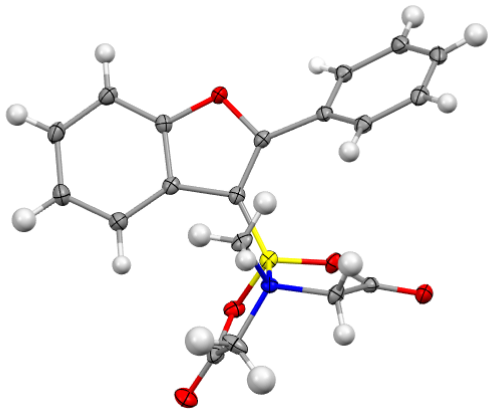
Table 5.1. Functionalized benzofuran boronic acid derivatives available through the alkoxyboration reaction.



Values represent isolated yields of organotrifluoroborate or MIDA boronate products **4**. Values in parentheses represent ^{1}H NMR yields of the corresponding catechol boronic ester **3** versus an external mesitylene standard using the ERETIC method.

Organotrifluoroborate **5.4a** is readily isolated in high yield using a chromatography-free purification, making this derivatization method particularly amenable to applying the alkoxyboration reaction on preparative scale. The corresponding MIDA derivative (**5.4b**) provides an option for purification by silica gel chromatography, but this comes at the cost of slightly diminished yield. Single-crystal X-ray diffraction analysis of **5.4b** allowed for unambiguous identification of the alkoxyboration product (Scheme 5.2).

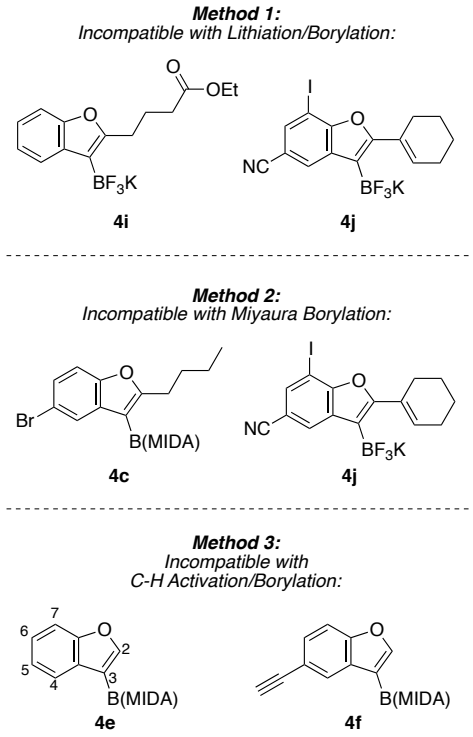
Scheme 5.2. X-ray structure of **5.4b** with the thermal ellipsoids set at the 50% probability level (B, yellow; C, gray; H, white; O, red; N, blue).



The alkoxyboration reaction is tolerant of a variety of functional groups suitable for downstream reactivity. Aryl bromide **5.4c**, silyl-protected alcohol **5.4d**, terminal alkyne **5.4f**, amide **5.4g**, esters **5.4h** and **5.4i**, and iodonitrile **5.4j** are compatible with the reaction conditions. Many of these alkoxyboration reactions proceed smoothly at 50 °C, although the reactions generating **5.4d**, **5.4g**, **5.4h**, and **5.4j** required heating to 90 °C in order to effect full conversion. We attribute the relatively slow formation of **5.4d** to the high steric encumbrance from the silyl ether at the 2-position of the benzofuran. The cyclization of substrates containing Lewis basic nitrogen atoms (forming **5.4g**, **5.4h**, and **5.4j**) was likely retarded by reversible N–B coordination that was observed by ^{11}B nuclear magnetic resonance (NMR) spectroscopy. For all substrates, the mass balance was largely attributable to protonolysis of the product C–B bond.

Notably, many of these products contain functional groups incompatible with commonly employed methods of benzofuran synthesis, including via other

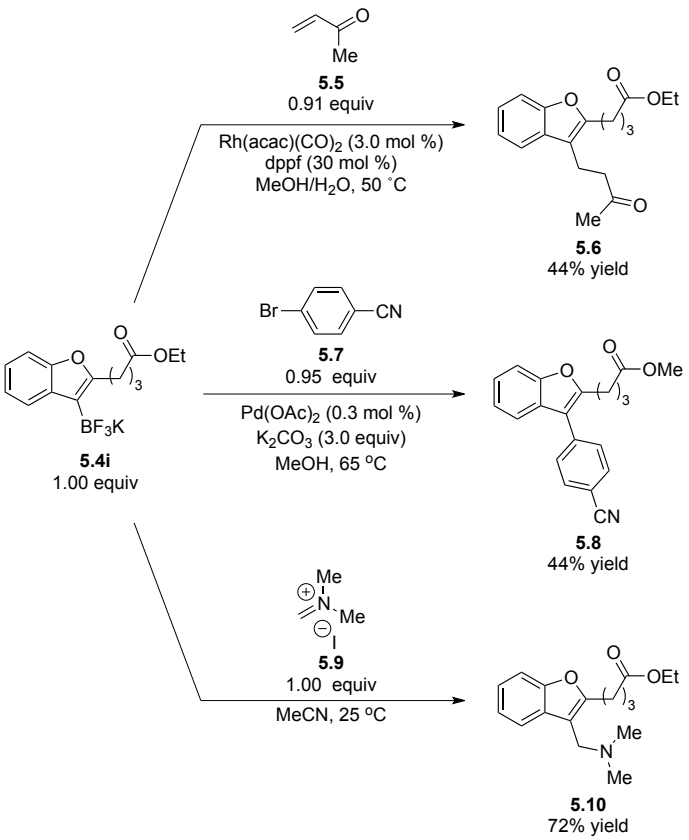
Scheme 5.3. Benzofuran boronic acid derivatives inaccessible using conventional borylation methods but newly accessible using the alkoxyboration reaction.



borylation techniques (Scheme 5.3). In one frequently used borylation technique, an aryllithium intermediate is trapped by a boron electrophile (Method 1); electrophiles such as carbonyl or nitrile groups and enolizable protons are not generally tolerated due to the highly nucleophilic and basic nature of the requisite organolithium intermediate.[27] Aryl halides may also suffer from undesired lithium/halogen exchange. The Miyaura borylation is a milder alternative that is compatible with electrophilic functional groups (Method 2), but aryl halides are borylated through this Pd(0)-catalyzed reaction[28] and are therefore not spectator functional groups under these conditions. Finally, the Ir-catalyzed C–H activation/borylation reaction[29] is an effective means of accessing arylboronic acid derivatives (Method 3),

but this reaction is regioselective for either 2- or 7-borylation; 3-borylated benzofurans such as those available through the alkoxyboration reaction cannot be synthesized regioselectively through C–H activation/borylation.[30]

Scheme 5.4. Versatility of alkoxyboration product in diversity-oriented synthesis.

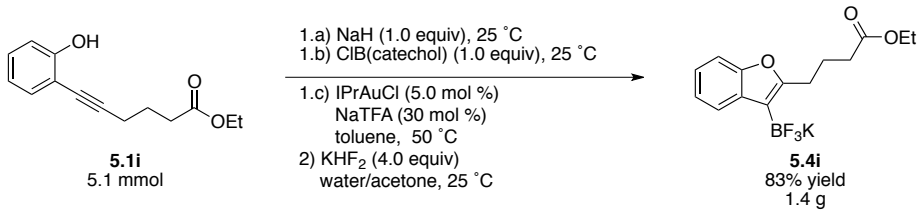


We set out to demonstrate the utility in divergent synthesis of the alkoxyboration products enabled through this synthesis in subsequent functionalization (Scheme 5.4, all yields unoptimized). Rh-catalyzed conjugate addition of **5.4i** into methyl vinyl ketone using the method developed by Batey[31] provides *β*-benzofuranyl ketone **5.6** in moderate yield. Subjection of the same benzofuran trifluoroborate to Suzuki-Miyaura coupling conditions described by Molander and

Biolatto[32] afforded afford 3-arylated benzofuran **5.8** with concomitant methanolysis of the ethyl ester. Finally, addition of **5.4i** to an iminium ion was used to prepare aminated benzofuran **5.10**. Thus, a single bench-stable alkoxyboration product can be functionalized a variety of ways, which is important in diversity oriented syntheses to develop compound catalogs for drug discovery.[18]

We next explored the scalability of the alkoxyboration reaction. Ester-containing phenol **1i** was successfully converted to more than 1 g of organotrifluoroborate **4i** on a 5 mmol scale with 2.5% gold catalyst (Scheme 5.5). Full conversion of starting material was effected even with this lower Au catalyst loading. This convenient scalability demonstrates that quantities of *O*-heterocyclic boronic acid derivatives sufficient for multistep synthesis may be prepared using the alkoxyboration method.

Scheme 5.5. Gram-scale alkoxyboration reaction.



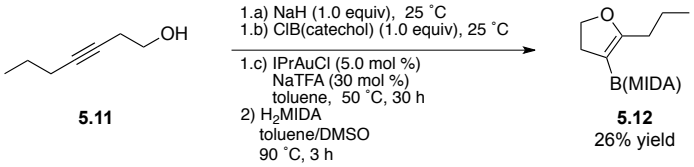
5.1i
5.1 mmol

5.4i
83% yield
1.4 g

Having demonstrated the utility of this transformation in generating members of the benzofuran class of *O*-heteroaryl boronic acid derivatives, we explored its application to the synthesis of a non-aromatic oxygen-containing heterocycle (Scheme 5.6). Simple and commercially available homopropargyl alcohol **5.11** was subjected to standard alkoxyboration reaction conditions to prepare dihydro-

furan product **5.12**. Several unidentifiable trace side products were detected in this reaction, possibly consistent with intermolecular reactivity. This substrate suggests the potential for generality in the alkoxyboration reaction: The reaction features low labor "setup cost" by employing simple, commercially available starting materials to generate highly value-added *O*-heterocyclic organoboronate compounds in one synthetic step, and the cyclization proceeds without requiring the gain of product aromaticity as a thermodynamic driving force and without the need for a fused ring system enforcing a conformational bias towards cyclization.

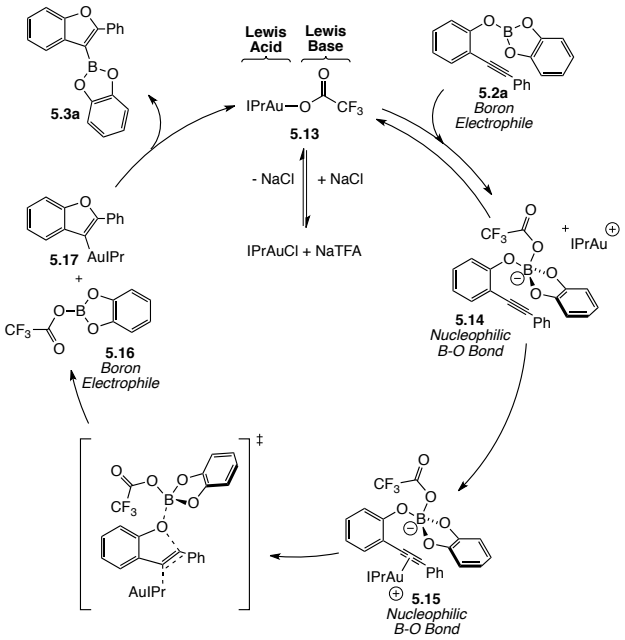
Scheme 5.6. Alkoxyboration reaction forming a simple dihydrofuran.



5.11 **5.12** 26% yield

A number of Lewis-acidic metal catalysts have been developed for the addition of oxygen-electrophile bonds across alkynes,[33] albeit not with boron. We propose the catalytic cycle shown in Scheme 5.7 featuring bifunctional Lewis acidic/Lewis basic substrate activation. The bifunctional catalyst IPrAuTFA can be generated *in situ* from IPrAuCl and NaTFA. Reaction of the Lewis basic trifluoroacetate anion with electrophilic boric ester **5.2a** gives nucleophilic borate **5.14**. The resulting Lewis acidic Au(I) cation may then bind to the alkyne (**5.15**), increasing its electrophilicity. Nucleophilic attack on the alkyne–Au π complex by the phenol B–O bond would provide neutral intermediates: boron electrophile **5.16** and organogold nucleophile **5.17**, which could recombine to regenerate **5.11** with

Scheme 5.7. Mechanistic hypothesis featuring the bifunctional Lewis acidic/Lewis basic catalyst IPrAuTFA.



concomitant formation of the observed alkoxyboration product **5.3a**. Thus, the IPrAu cation of the catalyst activates the alkyne for nucleophilic attack, and the TFA counterion allows for reversible tuning from a boron electrophile to a nucleophilic borate adduct. This reaction manifold is fundamentally unique from the metal-catalyzed addition of B–C, B–Si, B–Sn, and B–S addition reactions, which often proceed through oxidative addition of a low-valent metal catalyst into the B–X bond. We believe that the new activation strategy employed in the alkoxyboration reaction could be extended to other types of B–X bonds in order to provide additional reactivity complementary to preexisting methods. Notably, this approach also suggests a new generalizable mechanism for Au catalyst turnover by

trapping with electrophilic boron to generate other previously inaccessible organoboron building blocks.

In summary, this alkoxyboration reaction proceeds through an activation of the strong B–O *σ* bond. This fundamentally new activation is showcased in a mild, gram-scale technique for the preparation of *O*-heterocyclic boronic acid derivatives and downstream-functionalized benzofurans. The reaction provides a simple new bond disconnection for constructing these motifs with different regioselectivity and broader functional group compatibility than existing methods. This compatibility yields highly functionalized bench-stable building blocks for divergent synthesis that are not directly accessible using alternative methods. The carbophilic Lewis-acid activation mechanism for B–X bond addition suggests might see broader application in other B–X addition reactions for the synthesis of previously inaccessible organoboron building blocks. This method highlights a new strategy for turning over gold and other carbophilic metal catalysts.

References

1. Hall, D. G. Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine, and Materials, 2nd Ed.; Wiley-VCH: Weinheim, Germany, 2011.
2. Hurd, D. T. *J. Am. Chem. Soc.* **1948**, *70*, 2053–2055.
3. Brown, H. C. *Tetrahedron* **1961**, *12*, 117–138.
4. a) Männig, D.; Nöth, H. *Angew. Chem. Int. Ed.* **1985**, *24*, 878–879. b) Carrol, A.-M.; O'Sullivan, T. P.; Guiry, P. J. *Adv. Synth. Catal.* **2005**, *347*, 609–631.
5. Miyaura, N. Hydroboration, Diboration, and Stannylboration. In *Catalytic Heterofunctionalization*; Togni, A., Grützmacher, H., Eds.; Wiley-VCH: Weinheim,

2001; pp 1–46.

6. a) Suginome, M.; Yamamoto, A.; Murakami, M. *J. Am. Chem. Soc.* **2003**, *125*, 6358–6359. b) Suginome, M.; Shirakura, M.; Yamamoto, A. *J. Am. Chem. Soc.* **2009**, *128*, 14438–14439.
7. Suginome, M. *Chem. Rec.* **2010**, *10*, 348–358.
8. Suginome, M.; Nakamura, H.; Ito, Y. *Chem. Commun.* **1996**, 2777–2778.
9. Suginome, M.; Nakamura, H.; Ito, Y. *Angew. Chem. Int. Ed.* **1997**, *36*, 2516–2518.
10. Onozawa, S.; Hatanaka, Y.; Sakakura, T.; Shimada, S.; Tanaka, M. *Organometallics* **1996**, *15*, 5450–5452.
11. Ishiyama, T.; Nishijima, K.; Miyaura, N.; Suzuki, A. *J. Am. Chem. Soc.* **1993**, *115*, 7219–7225.
12. a) Ishiyama, T.; Matsuda, N.; Miyaura, N.; Suzuki, A. *J. Am. Chem. Soc.* **1993**, *115*, 11018–11019. b) Marder, T. B.; Norman, N. C. *Top. Catal.* **1998**, *5*, 63–73.
13. Lappert, M. F.; Prokai, B. *J. Orgmet. Chem.* **1964**, *1*, 384–400.
14. Hara, S.; Dojo, H.; Takinami, S.; Suzuki, A. *Tetrahedron Lett.* **1983**, *24*, 731–734.
15. Cragg, R. H.; Lappert, M. F.; Tilley, B. P. *J. Chem. Soc.* **1964**, 2108–2115.
16. Matsumi, N.; Chujo, Y. *Macromolecules* **1998**, *31*, 3802–3806.
17. Sanderson, R. T. Polar Covalence; Academic Press: Massachusetts, 1983.
18. Burke, M. D.; Berger, E. M.; Schreiber, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 14095–14104.

19. Domínguez de María, P.; van Gemert, R. W.; Straathof, A. J. J.; Hanefeld, U. *Nat. Prod. Rep.* **2010**, *27*, 370–392.
20. Drugs.com, U.S. Pharmaceutical Sales – 2012 (http://www.drugs.com/stats/top100/2012/sales).
21. Anderson, S.; Taylor, P. N.; Verschoor, G. L. B. *Chem. Eur. J.* **2004**, *10*, 518–527.
22. Joule, J. A.; Mills, K. Heterocyclic Chemistry, 5th ed.; Chichester: United Kingdom, 2010.
23. Akoka, S.; Barantin, L.; Trierweiler, M. *Anal. Chem.* **1999**, *71*, 2554–2557.
24. Full experimental details are available in the Experimental section.
25. Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275–286.
26. Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 14084–14085.
27. Nagaki, A.; Moriwaki, Y.; Yoshida, J. *Chem. Commun.* **2012**, *48*, 11211–11213.
28. Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508–7510.
29. a) Cho, J. Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E., Jr.; Smith, M. R., III. *Science*, **2002**, *295*, 305–308. b) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 390–391.
30. Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B., Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890–931.
31. Batey, R. A.; Thadani, A. N.; Smil, D. V. *Org. Lett.* **1999**, *1*, 1683–1686.
32. Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302–4314.
33. For select related examples of Lewis acid-catalyzed reactions, see: a) Naka-

mura, I; Mizushima, Y.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15022–15023. b) Fürstner, A.; Davis, P. W. *J. Am. Chem. Soc.* **2005**, *127*, 15024–15025. c) Nakamura, I.; Sato, T.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 4473–4475. d) Körner, C.; Starkov, P.; Sheppard, T. D. *J. Am. Chem. Soc.* **2010**, *132*, 5968–5969. e) Malona, J. A.; Cariou, K.; Spencer, W. T., III; Frontier, A. J. *J. Org. Chem.* **2012**, *77*, 1891–1908. f) Blanco Jaimes, M. C.; Weingand, V.; Rominger, F.; Hashmi, A. S. K. *Chem. Eur. J.* **2013**, *19*, 12504–12511. g) Marder, T. B.; Chan, D. M.-T.; Fultz, W. C.; Calabrese, J. C.; Milstein, D. *J. Chem. Soc, Chem. Commun.* **1987**, 1885–1887.

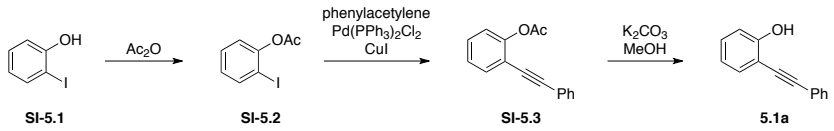
Experimental

General Considerations

All chemicals were used as received from commercial sources unless otherwise noted. Sodium trifluoroacetate was dried at 130 °C at 10 mTorr for 18 h before use. Toluene and dichloromethane were purified by passage through an alumina column under argon pressure on a push-still solvent system. Anhydrous dimethylsulfoxide was obtained by stirring over activity I alumina 18 h under N_2 atmosphere, decanting the liquid, and distilling the liquid at 10 Torr over CaH_2. Acetone was dried by distillation over anhydrous $CaSO_4$ under N_2 atmosphere. Toluene-d_8 was dried over CaH_2, degassed using three freeze-pump-thaw cycles, and vacuum transferred prior to use. All manipulations were conducted in a glovebox under nitrogen atmosphere or using standard Schlenk techniques unless otherwise specified. Analytical thin layer chromatography (TLC) was performed using Merck F_{250} plates. Plates were visualized under UV irradiation (254

nm) and/or using a basic aqueous solution of potassium permanganate. Flash chromatography was conducted using a Teledyne Isco Combiflash® Rf 200 Automated Flash Chromatography System, and Teledyne Isco Redisep® 35–70 μm silica gel. All proton and carbon nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were recorded on a Bruker DRX-400 spectrometer, Bruker DRX-500 spectrometer outfitted with a cryoprobe, or a Bruker AVANCE-600 spectrometer. All boron nuclear magnetic resonance (^{11}B NMR) spectra were recorded on a Bruker AVANCE-600 spectrometer. All fluorine nuclear magnetic resonance (^{19}F NMR) spectra were recorded on a Bruker DRX-400. All chemical shifts (δ) are reported in parts per million (ppm) downfield of tetramethylsilane, and referenced to the residual protiated solvent peak (δ = 7.26 ppm for $CDCl_3$, δ = 2.50 ppm for d_6-DMSO, or δ = 1.94 ppm for CD_3CN in ^{1}H NMR spectroscopy experiments; δ = 77.16 ppm for $CDCl_3$, δ = 39.52 ppm for d_6-DMSO, or δ = 1.34 ppm for CD_3CN in ^{13}C NMR spectroscopy experiments). ^{11}B and ^{19}F NMR spectroscopy experiments are referenced to the absolute frequency of 0 ppm in the ^{1}H dimension according to the Xi scale. Low- and high-resolution mass spectrometry data were obtained at the University of California, Irvine.

Preparation of 2-alkynyl phenol substrates **5.1a–5.1j**



SI-5.1 **SI-5.2** **SI-5.3** **5.1a**

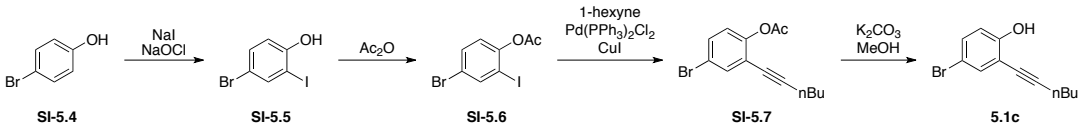
2-Iodophenyl acetate (SI-5.2). A solution of **SI-5.1** (6.72 g, 30.5 mmol, 1.00 equiv) and 4-dimethylaminopyridine (DMAP, 190 mg, 1.5 mmol, 5.0 mol %) was prepared in Et_3N (6.4 mL, 46 mmol, 1.5 equiv) and DCM (60 mL). Acetic anhydride (3.46 mL, 36.6 mmol, 1.20 equiv) was added dropwise. [Note: slight exotherm.] The reaction mixture stirred at 25 °C vented to air with a needle for 3 h. At this time, analysis by TLC (10% EtOAc/hexanes) indicated full conversion to a single new product. To the reaction mixture was added 50 mL water, and the resulting biphasic mixture was separated. The aqueous layer was extracted with DCM (3 × 25 mL), and then the combined organic layers were washed with brine (1 × 50 mL). The organic layer was then dried over Na_2SO_4, filtered, and concentrated in vacuo to a colorless oil, which solidified to a white solid upon standing. The resulting solid was crushed to a powder, and volatiles were removed at ca. 10 mTorr for 2.5 h to afford **SI-5.2** as a white powder (7.27 g, 91% yield). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.84 (dd, J = 7.9, 1.4 Hz, 1H), 7.38 (td, J = 7.2, 1.3 Hz, 1H), 7.11 (dd, J = 8.0, 1.4 Hz, 1H), 6.99 (td, J = 7.6, 1.3 Hz, 1H), 2.38 (s, 3H). This spectrum is in agreement with previously reported spectral data.[1]

2-(Phenylethynyl)phenyl acetate (SI-5.3). A 100-mL Schlenk tube was charged with Et_3N (20 mL) and sparged with N_2 for 20 min. Compound **SI-5.2** (2.62 g, 10.0

mmol, 1.00 equiv), $Pd(PPh_3)_2Cl_2$ (120 mg, 0.20 mmol, 2.0 mol %), and CuI (95 mg, 0.50 mmol, 5.0 mol %) were added under positive N_2 pressure, then neat phenylacetylene (1.20 mL, 11.0 mmol, 1.10 equiv) was added. The reaction mixture was heated at 45 °C for 19 h, at which time analysis by TLC (5% EtOAc/hexanes) indicated complete consumption of the aryl iodide. The reaction mixture was cooled to 25 °C and diluted with 75 mL Et_2O. The resulting mixture was washed with saturated aqueous NH_4Cl (4 × 25 mL) and brine (2 × 25 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to a dark brown oil. The oily residue was purified by column chromatography using an elution gradient from 5% EtOAc/hexanes to 10% EtOAc/hexanes. Volatiles were removed at ca. 10 mTorr and 25 °C for 18 h to afford **SI-5.3** as a brown oil (2.50 g, quant.). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.59 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.52–7.50 (m, 2H), 7.39–7.35 (m, 4), 7.25 (td, *J* = 7.6, 1.3 Hz, 1H), 7.14 (dd, *J* = 8.0, 1.4 Hz, 1H), 2.38 (s, 3H). This spectrum is in agreement with previously reported spectral data.[1]

2-(Phenylethynyl)phenol (5.1a). A suspension of K_2CO_3 (2.00 g, 14.5 mmol, 2.05 equiv) in MeOH (100 mL) and THF (90 mL) was cooled to 0 °C in an ice bath. A solution of **SI-5.3** (1.69 g, 7.16 mmol, 1.00 equiv) in THF (10 mL) was added dropwise over 2 min. The resulting heterogeneous mixture was stirred vigorously at 0 °C vented to air with a needle for 1.5 h, at which time analysis by TLC (20% EtOAc/hexanes) revealed complete consumption of **SI-5.3**. The cold reaction mixture was decanted into 200 mL DCM and washed with saturated aqueous

NH_4Cl (1 × 100 mL). The organic layer was then dried over Na_2SO_4, filtered, and concentrated in vacuo to a brown solid residue, which was purified by silica gel chromatography using an elution gradient from 100% hexanes to 10% EtOAc/hexanes. Removal of volatiles at ca. 10 mTorr and 50 °C for 18 h to afforded **1a** as a golden solid (970 mg, 70% yield). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.57–7.55 (m, 2H), 7.44 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.40–7.39 (m, 3H), 7.30–7.27 (m, 1H), 7.00 (dd, *J* = 8.3, 0.8 Hz, 1H), 6.93 (td, *J* = 7.5, 1.0 Hz, 1H), 5.83 (s, 1H). This spectrum is in agreement with previously reported spectral data.[2]



SI-5.4 **SI-5.5** **SI-5.6** **SI-5.7** **5.1c**

This reaction sequence was conducted by graduate student Darius Faizi.

4-Bromo-2-iodophenol (SI-5.5) was prepared according to a literature procedure[3] in 66% yield. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.78 (d, *J* = 2.3 Hz, 1H), 7.35 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 1H), 5.25 (br s, 1H). This spectrum is in agreement with previously reported spectral data.

4-Bromo-2-iodophenyl acetate (SI-5.6). A solution of **SI-5.5** (1.79 g, 6.00 mmol, 1.00 equiv) and 4-dimethylaminopyridine (DMAP, 40. mg, 0.30 mmol, 5.0 mol %) in Et_3N (1.0 mL, 7.2 mmol, 1.2 equiv) and DCM (12 mL) was cooled to 0 °C in an ice bath. Acetic anhydride (680 µL, 7.2 mmol, 1.2 equiv) was added dropwise over ca. 1 min, and then the cooling bath was removed. The reaction mixture was stirred at 25 °C while vented to air with a needle for 1 h. At this time, analysis by

TLC (10% EtOAc/hexanes) indicated full conversion to a single new product. The reaction mixture was washed with water (3 × 3 mL) and brine (3 × 3 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to a colorless oil, which solidified to a white solid upon standing. The resulting solid was crushed to a powder, and volatiles were removed at ca. 10 mTorr for 2.5 h to afford **SI-5.6** as a white powder (1.90 g, 93% yield).

TLC (10% EtOAc/hexanes): R_f = 0.52, visualized by UV absorbance and $KMnO_4$ stain.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.97 (d, *J* = 2.3 Hz, 1H), 7.49 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.98 (d, *J* = 8.6 Hz, 1H), 2.37 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): 168.5, 150.6, 141.5, 132.6, 124.5, 119.9, 91.6, 21.3.

HRMS (GC/ESI): Calculated for $C_8H_{10}BrINO_2$ ($[M+NH_4]^+$), 357.8940; found 357.8942.

4-Bromo-2-(hex-1-yn-1-yl)phenyl acetate (SI-5.7). A 100-mL Schlenk tube was charged with 25 mL THF, Et_3N (3.9 mL, 28 mmol, 4.1 equiv), and a stirbar. The combined solvents were sparged with N_2 for 25 min. Compound **SI-5.6** (2.34 g, 6.86 mmol, 1.00 equiv), $Pd(PPh_3)_2Cl_2$ (96 mg, 0.14 mmol, 2.0 mol %), and CuI (65 mg, 0.34 mmol, 5.0 mol %) were added under postive N_2 flow, followed by 1-hexyne (2.4 mL, 21 mmol, 3.0 equiv). The resulting dark brown solution was stirred at 25 °C for 15 h, at which time analysis by TLC (10% EtOAc/hexanes) suggested full consumption of the starting aryl iodide. [Note: The aryl iodide starting material overlaps the desired Sonogashira product in this solvent system, but

the reaction progress can be judged through differential staining by $KMnO_4$ solution.] The reaction mixture was diluted with 75 mL EtOAc and washed with saturated aqueous NH_4Cl (3 × 20 mL), water (1 × 20 mL), and brine (3 × 20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to a brown oil. Purification by column chromatography using an elution gradient (100% hexanes to 20% EtOAc/hexanes) followed by removal of volatiles at ca. 10 Torr for 1 h afforded **SI-5.7** as a yellow-brown oil (1.91 g, 95% yield).

TLC (10% EtOAc/hexanes): R_f = 0.52, visualized by UV absorbance and $KMnO_4$ stain.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.58 (d, *J* = 2.3 Hz, 1H), 7.40 (dd, *J* = 8.6 Hz, 2.3 Hz, 1H), 6.94 (d, *J* = 8.6 Hz, 1H), 2.43 (t, *J* = 7.0 Hz, 2H), 2.32 (s, 3H), 1.58 (m, 2H), 1.47 (app sextet, *J* = 7.3 Hz, 2H), 0.95 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.8, 150.7, 135.8, 131.7, 123.8, 120.3, 118.8, 97.2, 74.5, 30.7, 22.0, 20.9, 19.3, 13.7.

HRMS (GC/EI): Calculated for $C_{14}H_{19}BrO_2N$ ($[M+NH_4]^+$), 312.0599; found 312.0600.

4-Bromo-2-(hex-1-yn-1-yl)phenol (5.1c). A stirring suspension of K_2CO_3 (1.78 g, 12.9 mmol, 2.00 equiv) in 45 mL MeOH and 35 mL THF was cooled to 0 °C in an ice bath. To the vigorously stirring cold suspension was added solution of acetate **SI-7** (1.90 g, 6.44 mmol, 1.00 equiv) in 10 mL THF dropwise over ca. 2 min. The reaction mixture was stirred at 0 °C for 30 min, at which time analysis by TLC (10% EtOAc/hexanes) revealed full consumption of the acetate starting material.

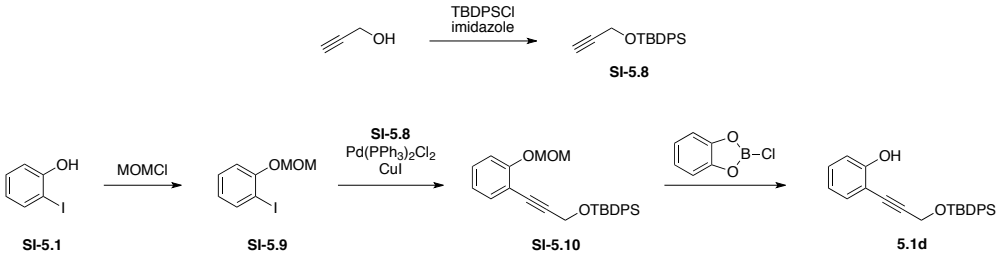
The reaction mixture was diluted with 100 mL EtOAc, then washed with saturated aqueous NH_4Cl (1 × 30 mL) and brine (3 × 10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient from 100% hexanes to 10% EtOAc/hexanes. Volatiles were removed at ca. 10 mTorr overnight with stirring to afford **5.1c** as a clear yellow oil (1.45 g, 89% yield).

TLC (10% EtOAc/hexanes): R_f = 0.40, visualized by UV absorbance.

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.41 (d, *J* = 2.4 Hz, 1H), 7.29 (dd, *J* = 8.7 Hz, 2.5 Hz, 1H), 6.82 (d, *J* = 8.7 Hz, 1H), 5.76 (s, 1H), 2.49 (t, *J* = 7.0 Hz, 2H), 1.65–1.50 (m, 2H), 1.45 – 1.52 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 155.8, 133.8, 132.6, 116.2, 112.5, 111.9, 99.5, 73.5, 30.8, 22.2, 19.4, 13.7.

HRMS (GC/CI): Calculated for $C_{12}H_{13}BrO$ (M^+), 252.0150; found 252.0148.



***tert*-Butyldiphenyl(prop-2-yn-1-yloxy)silane (SI-5.8)** was prepared according to a literature procedure[4] in 77% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.72 (d, *J* = 6.6 Hz, 4H), 7.33–7.49 (m, 6H), 4.32 (d, *J* = 2.3 Hz, 2H), 2.39 (t, *J* = 2.3 Hz, 1H), 1.07 (s, 9H). This spectrum is in agreement with previously reported spectral data.

1-Iodo-2-(methoxymethoxy)benzene (SI-5.9) was prepared according to a literature procedure[5] in 97% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.78 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.26–7.30 (m, 1H), 7.07 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.76 (td, *J* = 7.6, 1.3 Hz, 1H), 5.24 (s, 2H), 3.52 (s, 3H).This spectrum is in agreement with previously reported spectral data.

***tert*-Butyl((3-(2-(methoxymethoxy)phenyl)prop-2-yn-1-yl)oxy)diphenylsilane (SI-5.10)**. A flask was charged with compound **SI-5.9** (1.50 g, 5.67 mmol, 1.00 equiv), $(PPh_3)_2PdCl_2$ (0.20 g, 0.28 mmol, 0.050 equiv), and CuI (0.11 g, 0.57 mmol, 0.10 equiv). The flask was then evacuated and refilled with N_2 three times before Et_3N (6.3 mL, 45 mmol, 8.0 equiv) was added and stirred for 30 min. A separate flask was charged with compound **SI-5.8** (2.14 g, 7.28 mmol, 1.30 equiv), and then evacuated and refilled with N_2 three times before adding 11 mL MeCN. The resulting solution was then added dropwise over ca. 4 min to the stirring reaction mixture, which stirred for 18 h under dynamic N_2. At this time, analysis by TLC (20% EtOAc/hexanes) indicated full consumption of starting material. The reaction mixture was diluted with 50 mL EtOAc and washed with NH_4Cl (1 × 15 mL), water (1 × 10 mL), brine (1 × 10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient from 100% hexanes to 10% EtOAc/hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **SI-5.10** as a light yellow oil (2.18 g, 90% yield).

TLC (10% EtOAc/hexanes): R_f = 0.38, visualized by UV absorbance and $KMnO_4$ stain.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.76 (d, *J* = 6.7 Hz, 4H), 7.46–7.35 (m, 6H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.28–7.21 (m, 1H), 7.10 (d, *J* = 8.3 Hz, 1H), 6.95 (t, *J* = 7.5 Hz, 1H), 5.21 (s, 2H), 4.59 (s, 2H), 3.49 (s, 3H), 1.09 (s, 9H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 157.9, 135.8, 133.8, 133.4, 129.9, 129.7, 127.8, 121.9, 115.4, 113.8, 95.1, 91.7, 81.5, 56.4, 53.6, 26.9, 19.4.

HRMS (ESI+): Calculated for $C_{27}H_{30}O_3SiNa$ ($[M+Na]^+$), 453.1862; found 453.1844.

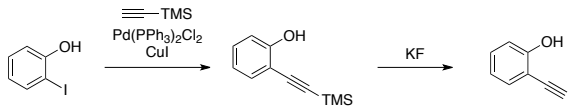
2-(3-((*tert*-Butyldiphenylsilyl)oxy)prop-1-yn-1-yl)phenol (5.1d). To a stirring solution of *B*-chlorocatecholborane (0.34 g, 2.2 mmol, 1.2 equiv) in 15 mL DCM was added **SI-10** (0.80 g, 1.9 mmol, 1.0 equiv) in 4 mL DCM. The reaction mixture was stirred for 4.5 h under dynamic N_2. At this time, analysis by TLC (10% EtOAc/hexanes) indicated full consumption of starting material. The reaction mixture was diluted with 50 mL DCM, and the organic layer was washed with NH_4Cl (1 × 10 mL), brine (1 × 10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient from 100% hexanes to 10% EtOAc/hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **5.1d** as a light yellow oil (320 mg, 45% yield).

TLC (10% EtOAc/hexanes): R_f = 0.32, visualized by UV absorbance and $KMnO_4$ stain.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.74 (d, *J* = 6.7 Hz, 4H), 7.47–7.44 (m, 2H), 7.42–7.40 (m, 4H), 7.24 (t, *J* = 7.8 Hz, 2H), 6.91 (d, *J* = 7.9 Hz, 1H), 6.84 (t, *J* = 7.5 Hz, 1H), 5.55 (s, 1H), 4.60 (s, 2H), 1.08 (s, 9H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 156.9, 135.8, 133.1, 132.0, 130.6, 130.1, 128.0, 120.3, 114.8, 109.2, 95.0, 79.3, 53.3, 26.8, 19.3.

HRMS (ESI+): Calculated for $C_{25}H_{26}O_2SiNa$ ($[M+Na]^+$), 409.1600; found 409.1584.

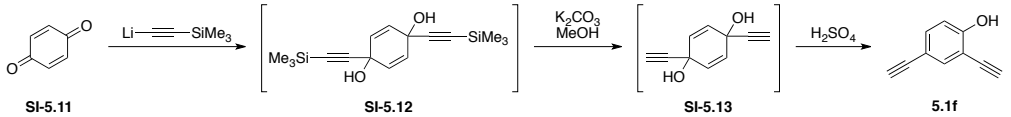


SI-5.1 **SI-5.11** **5.1e**

2-((Trimethylsilyl)ethynyl)phenol (SI-5.11) was prepared according to a literature procedure[6] in 71% yield. ^{1}H NMR ($CDCl_3$, 600MHz) δ 7.34 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.26–7.22 (m, 1H), 6.94 (d, *J* = 8.2 Hz, 1H), 6.85 (t, *J* = 6.0 Hz, 1H), 5.82 (s, 1H), 0.28 (s, 9H). This spectrum is in agreement with previously reported spectral data.

2-Ethynylphenol (5.1e) was prepared according to a literature procedure[6] in 82% yield. ^{1}H NMR ($CDCl_3$, 600MHz) δ 7.38 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.30–7.26 (dt, *J* = 7.8, 1.2 Hz, 1H), 6.96 (d, *J* = 8.2 Hz, 1H), 6.88 (dt, *J* = 7.5, 0.8 Hz, 1H), 5.77 (s,

1H), 3.47 (s, 1H). This spectrum is in agreement with previously reported spectral data.



SI-5.11 SI-5.12 SI-5.13 5.1f

1,4-Bis((trimethylsilyl)ethynyl)cyclohexa-2,5-diene-1,4-diol (SI-5.12). Anhydrous THF (60 mL) was cooled to -78 °C in a dry ice/isopropanol bath under a dynamic N_2 atmosphere. A solution of nBuLi (1.0 M in hexanes, 50. mL, 50. mmol, 2.2 equiv) was cannulated slowly into the reaction vessel. To the resulting stirring solution was then added trimethylsilyl acetylene (7.1 mL, 50. mmol, 2.2 equiv) dropwise over 30 min. After stirring an additional 30 min to affect complete deprotonation of the terminal alkyne, a solution of 1,4-benzoquinone (2.45 g, 22.7 mmol, 1.00 equiv) in 20. mL anhydrous THF was added dropwise over 30 min. During this addition, the reaction mixture turned from a clear, pale yellow solution to a dark, teal solution. The reaction mixture was stirred for 18 h as the cooling bath warmed gradually to 25 °C. After this time, the resulting red-brown semisolid reaction mixture was cooled to 0 °C, and 100 mL EtOAc was added with vigorous agitation to break up the solid aggregate. Saturated aqueous NH_4Cl (50 mL) was added to quench the reaction mixture, and then the pH was further adjusted to pH = 5 with ca. 1 mL 2 N aqueous HCl. The resulting biphasic mixture was separated, and the organic layer was extracted with EtOAc (2 × 50 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford a tan solid. Volatiles were removed at 25 °C and ca. 10 mTorr for 2 h to af-

ford crude **SI-5.12** as a tan solid (6.08 g) in 70% purity. Crude **SI-5.12** was used without further purification or characterization.

1,4-Diethynylcyclohexa-2,5-diene-1,4-diol (SI-5.13). A suspension of K_2CO_3 (5.5 g, 40. mmol, 4.0 equiv) in MeOH (50 mL) was cooled to 0 °C in an ice bath open to air. Solid **SI-12** (3.0 g, 9.9 mmol, 1.0 equiv) was added portionwise over ca. 1 min, and the resulting mixture was stirred vigorously at 0 °C for 1.5 h, at which time analysis by TLC (30% EtOAc/hexanes) indicated full consumption of **SI-5.12**. The reaction mixture was warmed to 25 °C and was decanted away from excess K_2CO_3. The resulting solution was diluted with 50 mL EtOAc and was then washed with saturated aqueous NH_4Cl (3 × 10 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo to a tan solid containing crude **SI-5.13**, which was used directly in the next step without purification or characterization.

2,4-Diethynylphenol (5.1f) was prepared using a method adapted from Ried and Schmidt.[7] Crude **SI-5.13** was dissolved in 10 mL benzene, and to the resulting solution were added H_2O (10 mL) and 1 mL 1 N aqueous H_2SO_4 (1 mmol, 10 mol %). The resulting biphasic mixture was refluxed under air with vigorous stirring for 20 min. After cooling to 25 °C, the biphasic mixture was separated, and the aqueous layer was extracted with benzene (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to a brown oil, which was purified by column chromatography using an elution gradient from 100%

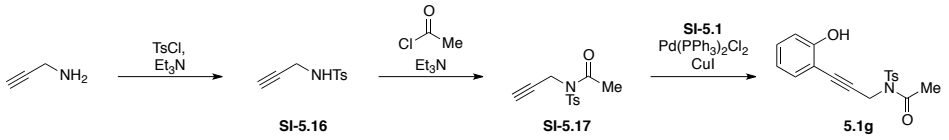
hexanes to 20%. The purified product was dried at 25 °C and ca. 10 mTorr for 18 h to afford **5.1f** as a cream-colored solid (160 mg, 12% yield over 2 steps).

TLC (20% EtOAc/hexanes): R_f = 0.43, visualized by $KMnO_4$ stain.

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.33 (d, *J* = 7.9 Hz, 1H), 7.09 (d, *J* = 1.1 Hz, 1H), 7.02 (dd, *J* = 8.0, 1.3 Hz, 1H), 5.79 (s, 1H), 3.55 (s, 1H), 3.16 (s, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 157.1, 132.0, 124.7, 124.4, 118.5, 109.2, 86.0, 82.9, 79.2, 77.8.

HRMS (GC/ESI+): Calculated for $C_{10}H_{10}NO$ ($[M+NH_4]^+$), 160.0762; found 160.0764.



This reaction sequence was conducted by graduate student Darius Faizi.

4-Ethyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (SI-5.16) was prepared according to a literature procedure[8] in 91% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.77 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 2H), 4.66 (br s, 1H), 3.83 (dd, *J* = 6.0, 2.5 Hz, 2H), 2.43 (s, 3H), 2.10 (t, *J* = 2.4 Hz, 1H). This spectrum is in agreement with previously reported spectral data.

***N*-(Prop-2-yn-1-yl)-*N*-tosylacetamide (SI-5.17)**. A flask was charged with **SI-16** (1.29 g, 6.16 mmol, 1.00 equiv), Et_3N (2.6 mL, 19 mmol, 3.0 equiv), and 13 mL DCM before it was cooled to 0 °C in an ice bath. At this time, acetyl chloride (0.88 mL, 12 mmol, 2.0 equiv) was syringed into the stirring reaction vessel over 3 min.

The ice bath was removed, and the reaction mixture was stirred for 18 h before TLC (30% EtOAc/hexanes) revealed complete consumption of starting material. The reaction was quenched with 10 mL H_2O, and the aqueous layer was extracted with DCM (2 × 10 mL). The combined organic layers were washed with brine (1 × 10 mL), and then dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient from 100% hexanes to 35% EtOAc/hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **SI-17** as a light yellow solid (1.1 g, 72% yield). ^{1}H NMR ($CDCl_3$, 600MHz) δ 7.91 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 4.67 (d, *J* = 2.3 Hz, 2H), 2.45 (s, 3H), 2.33 (s, 3H), 2.28 (t, *J* = 2.4 Hz, 1H). This spectrum is in agreement with previously reported spectral data.[9]

***N*-(3-(2-Hydroxyphenyl)prop-2-yn-1-yl)-*N*-tosylacetamide (5.1g)**. A Schlenk tube was charged with **SI-5.1** (0.71 g, 3.2 mmol, 1.0 equiv), $(PPh_3)_2PdCl_2$ (23 mg, 0.032 mmol, 1.0 mol %), CuI (13 mg, 0.064 mmol, 2.0 mol %), and a stir bar. The tube was then evacuated and refilled with N_2 three times before the addition of Et_3N (1.8 mL, 13 mmol, 4.0 equiv) and 4 mL dioxane, and then stirred for 5 min. Compound **SI-5.17** (1.05 g, 4.18 mmol, 1.30 equiv) was added over positive N_2 pressure. The Schlenk tube was heated to 45 ^{o}C under dynamic N_2. After 4 h, analysis by TLC (30% EtOAc/hexanes) revealed complete consumption of starting material. To the flask was added 10 mL water, and the aqueous phase was extracted with EtOAc (2 × 30 mL). The combined organic layers were washed

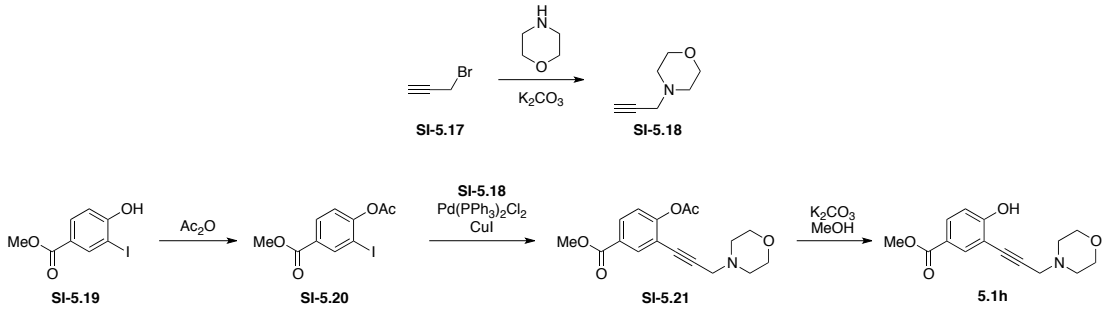
with brine (1 × 10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient from 100% hexanes to 30% EtOAc/hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **5.1g** as a light yellow solid (0.15 g, 14% yield).

TLC (30% EtOAc/hexanes) R_f = 0.31, visualized by UV absorbance.

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.88 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.23 (td, *J* = 6.7, 1.5 Hz, 2H), 6.92 (d, *J* = 8.1 Hz, 1H), 6.84 (t, *J* = 7.5 Hz, 1H), 5.92 (br. s, 1H), 4.88 (s, 2H), 2.42 (s, 3H), 2.41 (s, 3H).

^{13}C NMR (d_8-toluene, 125 MHz): δ 169.2, 158.9, 144.8, 137.1, 131.7, 131.0, 129.9, 125.4, 120.1, 115.4, 109.0, 91.9, 79.2, 36.2, 24.4, 21.0.

HRMS (ESI+): Calculated for $C_{18}H_{17}NO_4SNa$ ($[M+Na]^+$), 366.0776; found 366.0768.



4-(Prop-2-yn-1-yl)morpholine (SI-5.18) was prepared by adding propargyl bromide (80 wt % in toluene, 15 g solution, 100 mmol, 1.0 equiv) dropwise over 20 min to a stirring suspension of morpholine (22 mL, 250 mmol, 2.5 equiv) and K_2CO_3 (35 g, 250 mmol, 2.5 equiv) in THF (100 mL) at 25 °C. The resulting mix-

ture was stirred vigorously for 18 h, at which point the reaction mixture was diluted with 200 mL EtOAc. The mixture was washed with water (1 × 60 mL) and brine (3 × 20 mL), then the combined aqueous layers were back extracted with DCM (1 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to a yellow-orange oil. Purification by Kugelrohr distillation, (250 Torr, 150 °C) afforded **SI-5.18** as a clear, colorless oil (9.85 g, 79% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.74 (app t, J = 4.8 Hz, 4H), 3.29 (d, J = 2.5 Hz, 2H), 2.57 (app t, J = 4.7 Hz, 4H), 2.27 (t, J = 2.5 Hz, 1H). This spectrum is in agreement with previously reported spectral data.[10]

Methyl 4-acetoxy-3-iodobenzoate (SI-5.20). A solution of iodophenol **SI-5.19** (5.00 g, 18.0 mmol, 1.00 equiv) and 4-dimethylaminopyridine (DMAP, 110 mg, 0.90 mmol, 5.0 mol %) in Et_3N (3.0 mL, 22 mmol, 1.2 equiv) and DCM (20 mL) was cooled to 0 °C in an ice bath. Neat acetic anhydride (2.0 mL, 22 mmol, 1.2 equiv) was added dropwise over ca. 1 min, and then the cooling bath was removed. The reaction mixture was stirred at 25 °C while vented to air with a needle for 2 h. At this time, analysis by TLC (20% EtOAc/hexanes) indicated full conversion to a single new product. The reaction mixture was washed with water (1 × 40 mL), and then the aqueous layer was back extracted with DCM (3 × 15 mL). The combined organic layers were washed with brine (3 × 3 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to a colorless oil, which was purified by silica gel chromatography using an elution gradient from 100% hexanes to 10% EtOAc/hexanes. Volatiles were removed from the purified product at ca. 10 mTorr

for 2.5 h to afford **SI-5.20** as a white powder (5.41 g, 94% yield). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.52 (d, *J* = 1.8 Hz, 1H), 8.05 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 3.93 (s, 3H), 2.40 (s, 3H). This spectrum is in agreement with previously reported spectral data.[11]

Methyl 4-acetoxy-3-(3-morpholinoprop-1-yn-1-yl)benzoate (SI-5.21). A solution of **SI-5.20** (480. mg, 1.50 mmol, 1.00 equiv) in Et_3N (4 mL) was sparged with N_2 for 25 min. $PdCl_2(PPh_3)_2$ (18 mg, 0.026 mmol, 2.0 mol %) and CuI (12 mg, 0.065 mmol, 5.0 mol %) were added under positive N_2 flow, and to the resulting mixture was then added neat terminal alkyne **SI-5.18** (197 mg, 1.58 mmol, 1.05 equiv). The reaction mixture was then heated at 45 °C for 16 h. At this time, analysis by TLC (20% EtOAc/hexanes) indicated complete consumption of the starting aryl iodide. The reaction mixture was diluted with 10 mL DCM, then washed with water (1 × 15 mL) and brine (1 × 15 mL), and then the combined aqueous layers were back extracted with DCM (1 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting brown oil was purified by silica gel chromatography using an elution gradient from 100% hexanes to 100% EtOAc. Volatiles were removed from the purified product at ca. 10 mTorr for 18 h to afford **SI-5.21** as a viscous, yellow-brown oil (223 mg, 55% yield) containing trace residual EtOAc.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.17 (d, *J* = 2.5 Hz, 1H), 8.00 (dd, *J* = 10.2, 2.5 Hz, 1H), 7.18 (d, *J* = 10.1 Hz, 1H), 3.92 (s, 3H), 3.77 (app t, *J* = 5.5 Hz, 4H), 3.56 (s, 2H), 2.64 (app t, *J* = 5.5 Hz, 4H), 2.37 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.5, 165.8, 155.0, 135.0, 130.8, 128.1, 122.6, 117.6, 90.1, 80.0, 67.0, 52.5, 52.3, 48.1, 21.1.

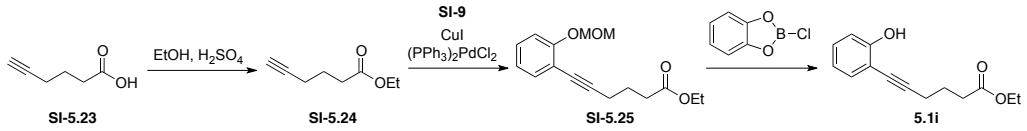
HRMS (ESI+): Calculated for $C_{17}H_{19}NO_5Na$ ($[M+Na]^+$), 340.1161; found 340.1167.

Methyl 4-hydroxy-3-(3-morpholinoprop-1-yn-1-yl)benzoate (5.1h). A solution of **SI-5.21** (1.27 g, 4.00 mmol, 1.00 equiv) in THF (30 mL) was cooled to 0 °C in an ice bath. Solid K_2CO_3 (1.1 g, 8.0 mmol, 2.0 equiv) was added followed by slow addition of MeOH (30 mL). After completion of the addition, the reaction mixture was warmed slowly to 25 °C and was stirred vigorously for 2 h. At this time, analysis by TLC (5% MeOH/$CHCl_3$) indicated complete consumption of the starting acetate. The reaction mixture was diluted with 150 mL DCM and washed with water (1 × 30 mL) and brine (1 × 30 mL). The combined aqueous layers were back-extracted with DCM (1 × 30 mL), and then the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to a pale yellow oil. The oil was purified by silica gel chromatography using an elution gradient from 100% $CHCl_3$ to 5 % MeOH/$CHCl_3$. Volatiles were removed from the purified product at ca. 10 mTorr for 18 h to afford **5.1h** as a cream-colored solid (175 mg, 16% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.07 (d, *J* = 2.1 Hz, 1H), 7.94 (d, *J* = 8.6, 2.1 Hz, 1H), 6.98 (d, *J* = 8.6 Hz, 1H), 6.27 (br s, 1H), 3.90 (s, 3H), 3.78 (app t, *J* = 4.6 Hz, 4H), 3.60 (s, 2H), 2.65 (app t, *J* = 4.5 Hz, 4H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.3, 160.5, 134.2, 132.2, 122.8, 114.9, 109.6, 92.2, 79.0, 66.9, 52.6, 52.2, 48.3.

HRMS (ESI+): Calculated for $C_{15}H_{17}NO_4Na$ ($[M+Na]^+$), 298.1055; found 298.1055.



This reaction sequence was conducted by graduate student Darius Faizi.

Ethyl hex-5-ynoate (SI-5.24) was prepared according to a literature procedure[12] in 87% yield. ^{1}H NMR ($CDCl_3$, 600MHz) δ 4.14 (q, *J* = 7.1 Hz, 2H), 2.44 (t, *J* = 7.4 Hz, 2H), 2.27 (dt, *J* = 7.0, 2.6 Hz, 2H), 1.97 (t, *J* = 2.6 Hz, 1H), 1.85 (quin, *J* = 7.2 Hz, 1H), 1.26 (t, *J* = 7.2 Hz, 3H). This spectrum is in agreement with previously reported spectral data.

Ethyl 6-(2-(methoxymethoxy)phenyl)hex-5-ynoate (SI-5.25). A flask was charged with **SI-5.9** (1.05 g, 3.98 mmol, 1.00 equiv), $(PPh_3)_2PdCl_2$ (0.14 g, 0.20 mmol, 0.050 equiv), and CuI (76 mg, 0.40 mmol, 0.10 equiv). The flask was then evacuated and refilled with N_2 three times before Et_3N (4.4 mL, 32 mmol, 8.0 equiv) and 5 mL MeCN were added, and this mixture was stirred for 30 min. Compound **SI-5.24** (0.98 g, 5.2 mmol, 1.30 equiv) was added dropwise by syringe over 2 min. The reaction mixture was stirred for 18 h under dynamic N_2. At this time, analysis by TLC (30% EtOAc/hexanes) indicated full consumption of starting material. The reaction mixture was diluted with 50 mL DCM, and the organic layer was washed with NH_4Cl (1 × 15 mL), water (1 × 10 mL), brine (1 × 10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient from 100% hexanes to 40% EtOAc/hexanes. Product-containing fractions were combined and concen-

trated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **SI-5.25** as a light yellow oil (0.97 g, 88% yield).

TLC (30% EtOAc/hexanes) R_f = 0.42, visualized by UV absorbance.

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.37 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.22 (td, *J* = 7.8, 1.2 Hz, 1H), 7.08 (d, *J* = 8.2 Hz, 1H), 6.94 (t, *J* = 7.5 Hz, 1H), 5.24 (s, 2H), 4.14 (q, *J* = 7.0 Hz, 2H), 3.52 (s, 3H), 2.59–2.48 (m, 2H), 1.95 (quin, *J* = 7.2 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.4, 157.8, 133.6, 129.1, 121.9, 115.3, 114.4, 95.1, 93.2, 77.7, 60.5, 56.4, 32.2, 24.1, 19.3, 14.4.

HRMS (ESI+): Calculated for $C_{16}H_{20}O_4Na$ ($[M+Na]^+$), 299.1259; found 299.1255.

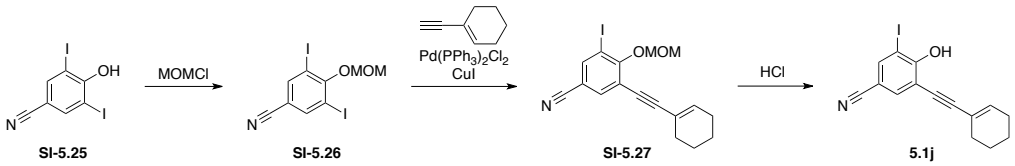
Ethyl 6-(2-hydroxyphenyl)hex-5-ynoate (5.1i). A flask was charged with **SI-5.25** (1.6 g, 5.8 mmol, 1.0 equiv), 58 mL DCM, and a stir bar. *B*-Chlorocatecholborane (1.2 g, 7.5 mmol, 1.3 equiv) was then added, and the mixture was sparged with N_2 for 10 min. The reaction mixture stirred for 18 h under dynamic N_2. At this time, analysis by TLC (20% EtOAc/hexanes) indicated complete consumption of starting material. The reaction mixture was diluted with 100 mL DCM and washed with water (3 × 30 mL) and brine (1 × 30 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient from 100% hexanes to 20% EtOAc/hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **5.1i** as a light yellow oil (1.2 g, 87% yield).

TLC (20% EtOAc/hexanes) R_f = 0.33, visualized by UV absorbance.

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.28 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.21 (t, *J* = 7.8 Hz, 1H), 6.93 (d, *J* = 8.2 Hz, 1H), 6.84 (t, *J* = 7.5 Hz, 1H), 5.99 (s, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 2.57 (t, *J* = 6.9 Hz, 2H), 2.51 (t, *J* = 7.2 Hz, 2H), 1.97 (quin, *J* = 7.0 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.5, 156.9, 131.7, 129.9, 120.3, 114.7, 110.0, 96.2, 75.9, 60.8, 33.4, 23.8, 19.2, 14.4.

HRMS (CI): Calculated for $C_{14}H_{17}O_3$ ($[M+H]^+$), 233.1178; found 233.1182.



3,5-Diiodo-4-(methoxymethoxy)benzonitrile (SI-5.26). A solution of **SI-5.25** (742 mg, 2.00 mmol, 1.00 equiv) and *N*,*N*-diisopropylethylamine (700. µL, 4.00 mmol, 2.00 equiv) in DCM (40 mL) was cooled to 0 °C under dynamic N_2 atmosphere. Chloromethyl methyl ether (210 µL, 2.8 mmol, 1.4 equiv) was then added dropwise. The reaction mixture was stirred at 0 °C for 40 min. It was then warmed gradually to 25 °C was stirred for 15 h, at which time analysis by TLC (20% EtOAc/hexanes) indicated full consumption of the phenol starting material. The reaction mixture was diluted with 20 mL EtOAc and 10 mL H_2O. The resulting biphasic mixture was stirred vigorously for 20 min to quench unreacted MOMCl, and then the phases were separated. The organic layer was washed with H_2O (2

× 10 mL) and brine (1 × 10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to a pale yellow solid (780 mg, 94% yield).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.08 (s, 2H), 5.22 (s, 2H), 3.75 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 161.1, 143.4, 115.4, 111.8, 100.9, 91.7, 59.2.

HRMS (GC/CI): Calculated for $C_9H_{11}I_2N_2O_2$ ($[M+NH_4]^+$), 432.8910; found 432.8896.

3-(Cyclohex-1-en-1-ylethynyl)-5-iodo-4-(methoxymethoxy)benzonitrile (SI-5.27). A mixture of THF (24 mL) and Et_3N (2.6 mL, 19 mmol, 5.0 equiv) was sparged with N_2 for 20 min. Solid **SI-5.26** (1.56 g, 3.76 mmol, 1.00 equiv), $Pd(PPh_3)_2Cl_2$ (66 mg, 0.094 mmol, 2.5 mol %), and CuI (36 mg, 0.19 mmol, 5.0 mol %) were added under positive N_2 pressure. To the resulting solution was added 1-ethynylcyclohexene (463 µL, 3.95 mmol, 1.05 equiv). The reaction mixture was stirred at 25 °C for 20 h, at which time analysis by TLC (10% EtOAc/hexanes) indicated complete consumption of **SI-5.26**. The reaction mixture was diluted with 100 mL EtOAc, then washed with saturated aqueous NH_4Cl (3 × 20 mL) and brine (2 × 20 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo to an orange semisolid, which was purified using three successive silica gel chromatography columns using an elution gradient from 100% hexanes to 10% EtOAc/hexanes. Volatiles were removed at 25 °C and ca. 10 mTorr for 18 h to afford **SI-5.27** as a yellow oil in 90% purity (249 mg, 17% yield).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.98 (d, *J* = 2.0 Hz, 1H), 7.66 (d, *J* = 2.0 Hz, 1H), 6.27 (m, 1H), 5.44 (s, 2H), 3.68 (s, 3H), 2.23–2.15 (m, 4H), 1.72–1.61 (m, 4H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 161.0, 141.9, 137.7, 137.6, 120.1, 118.4, 116.6, 109.3, 99.6, 98.9, 92.5, 81.0, 58.9, 28.8, 26.0, 22.2, 21.4.

HRMS (ESI+): Calculated for $C_{17}H_{16}INO_2Na$ ($[M+Na]^+$), 416.0108; found 416.0124.

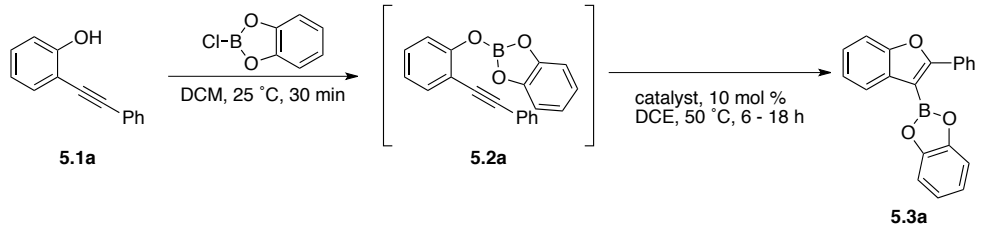
3-(Cyclohex-1-en-1-ylethynyl)-4-hydroxy-5-iodobenzonitrile (5.1j). To a solution of **SI-5.27** (91 mg, 0.23 mmol, 1.0 equiv) in 2 mL DCM at 25 °C was added $HCl{\cdot}Et_2O$ (280 µL, 1.2 equiv). The reaction mixture was stirred for 3 h, at which time analysis by TLC (10% EtOAc/hexanes) revealed complete consumption of the MOM ether starting material. The reaction mixture was diluted with 10 mL EtOAc and washed with water (3 × 2 mL) and brine (3 × 2 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to a pale yellow oil. The product was purified by silica gel chromatography using an elution gradient from 100% hexanes to 10% EtOAc/hexanes. Volatiles were removed at 25 °C and ca. 10 mTorr for 18 h to afford **5.1j** as a white solid (45 mg, 55% yield).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.92 (d, *J* = 2.3 Hz, 1H), 7.60 (d, *J* = 2.3 Hz, 1H), 6.67 (br s, 1H), 6.35–6.32 (m, 1H), 2.24–2.16 (m, 4H), 1.74–1.62 (m, 4H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.0, 142.3, 138.8, 135.3, 119.5, 117.0, 106.1, 101.1, 81.9, 78.1, 29.0, 26.0, 22.2, 21.3.

HRMS (GC/CI): Calculated for $C_{15}H_{12}INO$ (M^+), 348.9964; found 348.9967.

Screen of potential alkoxyboration catalysts



Boric ester 5.2a. A flame-dried 25-mL Schlenk tube was charged with a solution of **1a** (97.0 mg, 0.500 mmol, 1.00 equiv) in dry DCM (3 mL). To this solution was then added a solution of *B*-chlorocatecholborane (77.0 mg, 0.500 mmol, 1.00 equiv) in dry DCM (3 mL) at 25 °C. The reaction mixture was stirred for 30 min, and then the mixture was concentrated in vacuo to afford a moisture-sensitive, clear brown oil (159 mg, quant.) containing **5.2a**, which was used directly in the catalyst screen without further purification.

^{1}H NMR (d_8-toluene, 600 MHz): δ 7.38 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.23–7.21 (m, 2H), 6.98 (dd, *J* = 10.2, 1.4 Hz, 1 H), 6.92 (td, *J* = 8.7, 2.9 Hz, 1H), 6.86–6.84 (m, 3H), 6.82 (dd, *J* = 5.8, 3.4 Hz, 2H), 6.76 (td, *J* = 15.1, 9.5 Hz), 6.74 (*J* = 5.8, 3.4 Hz, 2H).

^{11}B NMR (d_8-toluene, 193 MHz): δ 23.2 (br s).

Catalyst screening reactions were set up in a N_2-filled glovebox. Catalyst (0.0040 mmol, 10. mol %) was dissolved in anhydrous 1,2-dichloroethane (400 µL) and added to a dram vial containing **5.2a** (13 mg, 0.040 mmol, 1.0 equiv). After mixing thoroughly, the reaction mixture was transferred to a J. Young NMR tube, removed from the glovebox, and heated in a preheated 50 °C oil bath. After

heating for the indicated time, the progress of the reaction was monitored by ^{1}H and ^{11}B NMR spectroscopy.

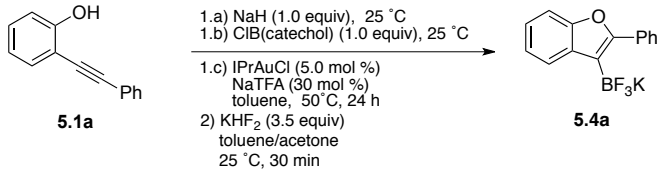
Entry	Catalyst	Product : Starting Material Ratio (**5.3a**: **5.2a**, ^{1}H NMR)
1	None	Only **5.2a**
2	$Pd(PPh_3)_2Cl_2$ + 20 mol % AgOTf	Only **5.2a**
3	PEPPSI-IPr + 20 mol % AgOTf	Only **5.2a**
4	IPrAuCl + 10 mol % AgOTf	> 95:5
5	IPrAuCl	Only **5.2a**
6	AgOTf	Only **5.2a**
7	IPrAuCl + 10 mol % AgTFA	> 95:5
8	IPrCuCl + 10 mol % AgTFA	Only **5.2a**
9	Trifluoroacetic acid	Only **5.2a**
10	$InBr_3$	Only **5.2a**

Table SI-5.1. Screen of alkoxyboration catalysts for optimal conversion to **5.3a** by ^{1}H NMR spectroscopy.

Synthesis and isolation of benzofuran alkoxyboration products **5.4a–5.4j**

Note: All alkoxyboration reactions were conducted in a N_2-filled glovebox due to the high moisture sensitivity of the boric ester intermediate **5.2**. All glass-ware and reagents must be rigorously dry for optimal yield. The reaction progress was monitored by removing a small aliquot of the reaction mixture from the glove-

box and diluting it in 1:1 EtOAc:water. This results in rapid hydrolysis of boric ester intermediate **5.2** back to the phenol starting material **5.1**. Thus, co-spotting the reaction mixture versus phenol **1** provides a convenient method for determining whether or not intermediate **5.2** has been fully consumed. The addition of PPh_3 to quench the Au catalyst.[13] between the alkoxyboration step and the formation of the organotrifluoroborate or MIDA boronate was essential.



Benzofuran trifluoroborate 5.4a. A solution of phenol **5.1a** (97.0 mg, 0.500 mmol, 1.00 equiv) in 1.0 mL toluene was added to a flame-dried 10-mL Schlenk tube. To this stirring solution was added dropwise at 25 °C a suspension of NaH (69 wt % purity, 17.4 mg, 0.500 mmol, 1.00 equiv) in 0.5 mL toluene over 2 min. A suspension of NaTFA (20. mg, 0.15 mmol, 30. mol %) in 0.5 mL toluene was added next, and the resulting suspension was stirred for 15 min to affect full deprotonation.

To the resulting stirring sodium phenoxide suspension was added at 25 °C a solution of *B*-chlorocatecholborane (77.0 mg, 0.500 mmol, 1.00 equiv) in toluene (1.0 mL), using additional toluene as a rinse to ensure full transfer (2 × 0.5 mL portions). The resulting suspension was stirred vigorously for 30 min to allow for full conversion to boric ester intermediate **5.2a**.

Next, a suspension of IPrAuCl (16 mg, 0.025 mmol, 5.0 mol %) in toluene (0.5 mL) was added to the reaction mixture at 25 °C, using additional toluene as a rinse to aid in full transfer (1 × 0.5 mL portion). The reaction mixture was then sealed with a ground glass stopper and a PTFE sealing ring and placed in a pre-heated 50 °C copper shot heating bath. The final concentration of the reaction mixture was 0.1 M in **5.1a**.

After 24 h, analysis by TLC (20% EtOAc/hexanes) indicated full consumption of boric ester intermediate **5.2a**. The reaction mixture was cooled to 25 °C, and a solution of PPh_3 (13 mg, 0.050 mmol, 10 mol %) in toluene (0.5 mL) was added. The resulting suspension was stirred for 22 h at 25 °C in order to quench IPrAuTFA before proceeding.

The quenched reaction mixture was removed from the glovebox and filtered through a fiberglass filter to remove the suspended solids. The filter was then rinsed with toluene (3 × 3 mL), and the combined filtrates were concentrated in vacuo to a pale yellow powder, which was suspended in acetone (4.5 mL) and added to a stirring solution of KHF_2 (140 mg, 1.8 mmol, 3.5 equiv) in water (1.5 mL). The resulting mixture was stirred at 25 °C for 30 min, and then concentrated in vacuo to remove the solvents. To this residue was added 2 mL Et_2O and subsequently concentrated at ca. 10 mTorr for 30 min in order to remove residual acetone. The resulting pale yellow solid residue was washed with Et_2O (4 × 2 mL) and extracted with acetone (4 × 2 mL). The combined acetone extracts were concentrated in vacuo, and the resulting residue was subjected to an additional

washing/extraction cycle to yield **5.4a** as a white powder (113 mg, 75% yield) after removing volatiles at 25 °C and ca. 10 mTorr for 18 h.

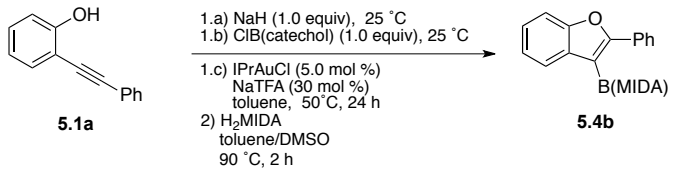
^{1}H NMR (d_6-DMSO, 600 MHz): δ 8.10 (d, *J* = 7.4 Hz, 2H), 7.88 (d, *J* = 7.7 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.26 (t, *J* = 7.3 Hz, 1H), 7.13 (td, *J* = 6.5 Hz, 1.2 Hz, 1H), 7.08 (td, *J* = 7.4, 0.9 Hz, 1H).

^{13}C NMR (d_6-DMSO, 125 MHz): δ 154.7 (q, $J_{C–F}$ = 4.6 Hz), 153.8, 135.4, 133.3, 127.9, 126.8, 126.7 (q, $J_{C–F}$ = 2.3 Hz), 124.1 (q, $J_{C–F}$ = 2.8 Hz), 122.7, 109.6. [Note: As with many organotrifluoroborates, the *ipso* carbon was not detected, presumably due to broadening through coupling to the ^{11}B nucleus. The quaternary carbon at the benzofuran 2 position was also not detected.]

^{11}B NMR (d_6-DMSO, 193 MHz): δ 3.2 (br s).

^{19}F NMR (d_6-DMSO, 376 MHz): δ -131.9 (br s).

HRMS (ESI-): Calculated for $C_{14}H_9BF_3O$ ([M-K]$^-$), 261.0701; found 261.0706.



MIDA boronate 5.4b. A solution of phenol **5.1a** (97.0 mg, 0.500 mmol, 1.00 equiv) in 1.0 mL toluene was added to a flame-dried 10-mL Schlenk tube. To this stirring solution was added dropwise at 25 °C a suspension of NaH (92 wt % purity, 13.0 mg, 0.500 mmol, 1.00 equiv) in 0.5 mL toluene over 2 min. A suspension

of NaTFA (20. mg, 0.15 mmol, 30 mol %) in 0.5 mL toluene was added next, and the resulting suspension was stirred for 15 min to affect full deprotonation.

To the resulting stirring sodium phenoxide suspension was added at 25 °C a solution of *B*-chlorocatecholborane (77.0 mg, 0.500 mmol, 1.00 equiv) in toluene (1.0 mL), using additional toluene as a rinse to ensure full transfer (2 × 0.5 mL portions). The resulting suspension was stirred vigorously for 30 min to allow for full conversion to boric ester intermediate **5.2a**.

Next, a suspension of IPrAuCl (16 mg, 0.025 mmol, 5.0 mol %) in toluene (0.5 mL) was added to the reaction mixture at 25 °C, using additional toluene as a rinse to aid in full transfer (1 × 0.5 mL portion). The reaction mixture was then sealed with a ground glass stopper and a PTFE sealing ring and placed in a preheated 50 °C copper shot heating bath. The final concentration of the reaction mixture was 0.1 M in **5.1a**.

After 24 h, analysis by TLC (20% EtOAc/hexanes) indicated full consumption of boric ester intermediate **5.2a**. The reaction mixture was cooled to 25 °C, and a solution of PPh_3 (13 mg, 0.050 mmol, 10 mol %) in toluene (0.5 mL) was added. The resulting suspension was stirred for 16 h at 25 °C in order to quench IPrAuTFA before proceeding.

Anhydrous DMSO (2.0 mL) and H_2MIDA (81 mg, 0.55 mmol, 1.1 equiv) were added to the quenched alkoxyboration reaction mixture, and the resulting suspension was stirred at 90 °C for 2h. The reaction mixture was then cooled to 25 °C and removed from the glovebox. Toluene was removed in vacuo at 25 °C and ca. 10 Torr, then DMSO was removed by Kugelrohr distillation at ca. 10

mTorr. The resulting semisolid residue was adsorbed onto Celite from a MeCN suspension and purified by silica gel chromatography using an elution gradient from 100% Et_2O to 100% MeCN. Removal of volatiles at 25 °C and ca. 10 mTorr for 18 h afforded MIDA boronate **5.4b** as a white powder (101 mg, 58% yield). Crystals suitable for X-ray diffraction analysis were prepared by slow diffusion of Et_2O into a saturated solution of **5.4b** in Et_2O/acetone at 25 °C over 3 days

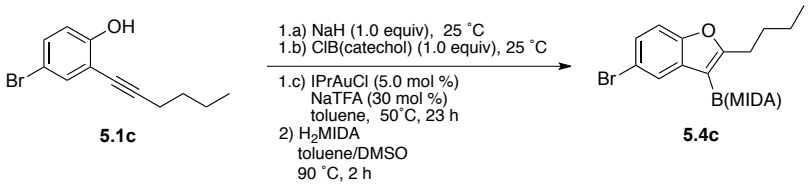
TLC (10% MeCN/ Et_2O): R_f = 0.39.

^{1}H NMR (CD_3CN, 600 MHz): δ 7.72 (dd, *J* = 7.8 Hz, 0.8 Hz, 1H), 7.67–7.65 (m, 2H), 7.55 (d, *J* = 9.7 Hz, 1H), 7.47–7.44 (m, 3H), 7.35– 7.31 (m, 1H), 7.29–7.26 (m, 1H), 3.97 (d, *J* = 17.1 Hz, 2H), 3.65 (d, *J* = 17.1 Hz, 2H), 2.56 (s, 3H).

^{13}C NMR (CD_3CN, 125 MHz): δ 169.0, 156.0, 133.6, 133.0, 130.6, 130.2, 129.3, 125.2, 123.9, 123.5, 111.8, 63.0, 48.2. [Note: no signals were observed for the quaternary C–B *ipso* carbon or the quaternary carbon at the benzofuran 2 position.]

^{11}B NMR (CD_3CN, 193 MHz): δ 11.3 (br s).

HRMS (ESI+): Calculated for $C_{17}H_{19}BBrNO_5$ ($[M+Na]^+$), 372.1023; found 372.1016.



MIDA boronate 5.4c. A solution of phenol **5.1c** (127 mg, 0.500 mmol, 1.00 equiv) in 1.0 mL toluene was added to a flame-dried 10-mL Schlenk tube. To this stirring solution was added dropwise at 25 °C a suspension of NaH (92 wt % purity, 13.0 mg, 0.500 mmol, 1.00 equiv) in 0.5 mL toluene over 2 min. A suspension of NaTFA (20. mg, 0.15 mmol, 30 mol %) in 0.5 mL toluene was added next, and the resulting suspension was stirred for 15 min to affect full deprotonation.

To the resulting stirring sodium phenoxide suspension was added at 25 °C a solution of *B*-chlorocatecholborane (77.0 mg, 0.500 mmol, 1.00 equiv) in toluene (1.0 mL), using additional toluene as a rinse to ensure full transfer (2 × 0.5 mL portions). The resulting suspension was stirred vigorously for 30 min to allow for full conversion to boric ester intermediate **5.2c**.

Next, a suspension of IPrAuCl (16 mg, 0.025 mmol, 5.0 mol %) in toluene (0.5 mL) was added to the reaction mixture at 25 °C, using additional toluene as a rinse to aid in full transfer (1 × 0.5 mL portion). The reaction mixture was then sealed with a ground glass stopper and a PTFE sealing ring and placed in a pre-heated 50 °C copper shot heating bath. The final concentration of the reaction mixture was 0.1 M in **5.1c**.

After 23 h, analysis by TLC (20% EtOAc/hexanes) indicated full consumption of boric ester intermediate **5.2c**. The reaction mixture was cooled to 25 °C, and a solution of PPh_3 (13 mg, 0.050 mmol, 10 mol %) in toluene (0.5 mL) was

added. The resulting suspension was stirred for 16 h at 25 °C in order to quench IPrAuTFA before proceeding.

Anhydrous DMSO (2.0 mL) and H_2MIDA (160 mg, 1.1 mmol, 2.2 equiv) were added to the quenched alkoxyboration reaction mixture, and the resulting suspension was stirred at 90 °C for 2h. The reaction mixture was then cooled to 25 °C and removed from the glovebox. Toluene was removed in vacuo at 25 °C and ca. 10 Torr, then DMSO was removed by Kugelrohr distillation at ca. 10 mTorr. The resulting semisolid residue was adsorbed onto Celite from a MeCN suspension and purified by silica gel chromatography using an elution gradient from 100% Et_2O to 100% MeCN. Removal of volatiles at 25 °C and ca. 10 mTorr for 18 h afforded MIDA boronate **5.4c** as a white powder (161 mg, 79% yield).

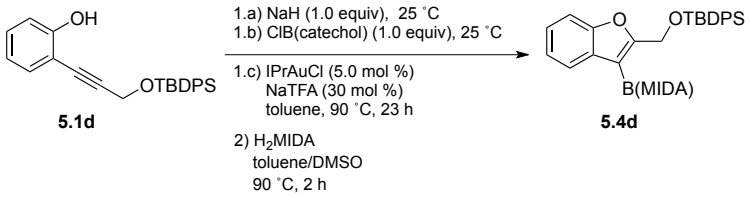
TLC (10% MeCN/ Et_2O): R_f = 0.50.

^{1}H NMR (CD_3CN, 600 MHz): δ 7.59 (dd, *J* = 1.9 Hz, 0.4 Hz, 1H), 7.37 (d, *J* = 7.4 Hz, 1H), 7.34 (dd, *J* = 8.7 Hz, 1.8 Hz, 1H), 4.12 (d, *J* = 17.2 Hz, 2H), 3.92 (d, *J* = 17.2 Hz, 2H), 2.77 (app t, *J* = 7.7 Hz, 2H), 2.66 (s, 3H), 1.70 (app quintet, *J* = 7.7 Hz, 2H), 1.38 (sextet, *J* = 7.4 Hz, 2H), 0.93 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (CD_3CN, 125 MHz): δ 169.4, 167.4, 154.6, 135.6, 126.8, 124.9, 116.1, 113.1, 63.0, 48.1, 31.6, 29.0, 23.2, 14.0. [Note: no signal was observed for the quaternary C–B *ipso* carbon.]

^{11}B NMR (CD_3CN, 193 MHz): δ 11.3 (br s).

HRMS (ESI+): Calculated for $C_{16}H_{17}BBrNO_5Na$ ($[M+Na]^+$), 430.0441; found 430.0425.



MIDA boronate 5.4d. A solution of phenol **5.1d** (85 mg, 0.22 mmol, 1.0 equiv) in 1.0 mL toluene was added to a flame-dried 10-mL Schlenk tube. To this stirring solution was added dropwise at 25 °C a suspension of NaH (92 wt % purity, 6.0 mg, 0.20 mmol, 1.0 equiv) in 0.5 mL toluene over 2 min. A suspension of NaTFA (9.0 mg, 0.070 mmol, 30 mol %) in 0.5 mL toluene was added next, and the resulting suspension was stirred for 45 min to affect full deprotonation.

To the resulting stirring sodium phenoxide suspension was added at 25 °C a solution of *B*-chlorocatecholborane (34 mg, 0.22 mmol, 1.0 equiv) in toluene (1.0 mL), using additional toluene as a rinse to ensure full transfer (2 × 0.5 mL portions). The resulting suspension was stirred vigorously for 30 min to allow for full conversion to boric ester intermediate **5.2d**.

Next, a suspension of IPrAuCl (7.0 mg, 0.010 mmol, 5.0 mol %) in toluene (0.5 mL) was added to the reaction mixture at 25 °C, using additional toluene as a rinse to aid in full transfer (1 × 0.5 mL portion). The reaction mixture was then sealed with a ground glass stopper and a PTFE sealing ring and placed in a pre-heated 50 °C copper shot heating bath. The final concentration of the reaction mixture was 0.1 M in **5.1d**.

After 23 h, analysis by TLC (20% EtOAc/hexanes) indicated full consumption of boric ester intermediate **5.2d**. The reaction mixture was cooled to 25 °C, and a solution of PPh_3 (6.0 mg, 0.020 mmol, 10 mol %) in toluene (0.5 mL) was

added. The resulting suspension was stirred for 16 h at 25 °C in order to quench IPrAuTFA before proceeding.

Anhydrous DMSO (2.0 mL) and H_2MIDA (35 mg, 0.24 mmol, 1.1 equiv) were added to the quenched alkoxyboration reaction mixture, and the resulting suspension was stirred at 90 °C for 2 h. The reaction mixture was then cooled to 25 °C and removed from the glovebox. Toluene was removed in vacuo at 25 °C and ca. 10 Torr, then DMSO was removed by Kugelrohr distillation at ca. 10 mTorr. The resulting semisolid residue was adsorbed onto Celite from a MeCN suspension and purified by silica gel chromatography using an elution gradient from 100% Et_2O to 100% MeCN. Removal of volatiles at 25 °C and ca. 10 mTorr for 18 h afforded MIDA boronate **5.4d** as a white powder (32 mg, 48% yield).

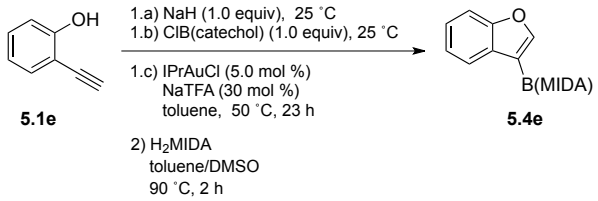
TLC (20% MeCN/Et_2O): R_f = 0.50, visualized by UV absorbance.

^{1}H NMR (CD_3CN, 600 MHz): δ 7.74 (dd, *J* = 7.8, 1.2 Hz, 4H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.51–7.46 (m, 3H), 7.46–7.40 (m, 4H), 7.32 (dt, *J* = 7.2, 1.2 Hz, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 4.87 (s, 2 H), 4.24 (d, *J* = 17.2 Hz, 2H), 3.92 (d, *J* = 17.2 Hz, 2H), 2.63 (s, 3 H), 1.02 (s, 9 H)

^{13}C NMR (CD_3CN, 125 MHz): δ 169.3, 161.7, 156.0, 136.5, 133.9, 132.7, 131.0, 128.8, 125.4, 123.8, 123.1, 111.9, 62.7, 59.6, 48.3, 27.1, 19.8. [Note: no signal was observed for the quaternary C–B *ipso* carbon.]

^{11}B NMR (CD_3CN, 193 MHz): δ 11.2.

HRMS (ESI+): Calculated for $C_{30}H_{32}O_6BNSiNa$ ($[M+Na]^+$), 564.1995; found 564.1995.



5.1e **5.4e**

MIDA boronate 5.4e. A solution of phenol **5.1e** (90. mg, 0.76 mmol, 1.0 equiv) in 1.5 mL toluene was added to a flame-dried 10-mL Schlenk tube. To this stirring solution was added dropwise at 25 °C a suspension of NaH (92 wt % purity, 20. mg, 0.76 mmol, 1.00 equiv) in 1.0 mL toluene over 2 min. A suspension of NaTFA (31 mg, 0.23 mmol, 30 mol %) in 0.5 mL toluene was added next, and the resulting suspension was stirred for 15 min to affect full deprotonation.

To the resulting stirring sodium phenoxide suspension was added at 25 °C a solution of *B*-chlorocatecholborane (120 mg, 0.76 mmol, 1.0 equiv) in toluene (1.5 mL), using additional toluene as a rinse to ensure full transfer (2 × 0.5 mL portions). The resulting suspension was stirred vigorously for 30 min to allow for full conversion to boric ester intermediate **5.2e**.

Next, a suspension of IPrAuCl (25 mg, 0.040 mmol, 5.0 mol %) in toluene (0.5 mL) was added to the reaction mixture at 25 °C, using additional toluene as a rinse to aid in full transfer (3 × 0.5 mL portion). The reaction mixture was then sealed with a ground glass stopper and a PTFE sealing ring and placed in a pre-heated 50 °C copper shot heating bath. The final concentration of the reaction mixture was 0.1 M in **5.1e**.

After 23 h, analysis by TLC (20% EtOAc/hexanes) indicated full consumption of boric ester intermediate **5.2e**. The reaction mixture was cooled to 25 °C, and a solution of PPh_3 (20. mg, 0.080 mmol, 10 mol %) in toluene (0.5 mL) was

added. The resulting suspension was stirred for 16 h at 25 °C in order to quench IPrAuTFA before proceeding.

Anhydrous DMSO (2.0 mL) and H_2MIDA (124 mg, 0.84 mmol, 1.1 equiv) were added to the quenched alkoxyboration reaction mixture, and the resulting suspension was stirred at 90 °C for 2h. The reaction mixture was then cooled to 25 °C and removed from the glovebox. Toluene was removed in vacuo at 25 °C and ca. 10 Torr, then DMSO was removed by Kugelrohr distillation at ca. 10 mTorr. The resulting semisolid residue was adsorbed onto Celite from a MeCN suspension and purified by silica gel chromatography using an elution gradient from 100% Et_2O to 100% MeCN. Removal of volatiles at 25 °C and ca. 10 mTorr for 18 h afforded MIDA boronate **5.4e** as an off-white powder (82 mg, 40% yield).

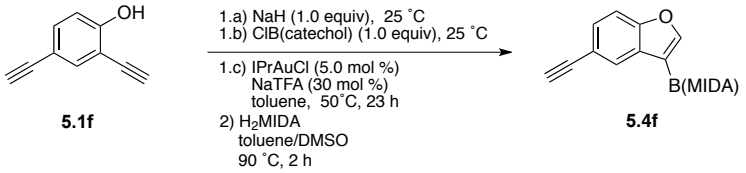
TLC (20% MeCN/Et_2O): R_f = 0.58, visualized by UV absorbance.

^{1}H NMR (CD_3CN, 600 MHz): δ 7.75 (s, 1H), 7.59 (d, *J* = 7.7 Hz, 1H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.32 (t, *J* = 8.4 Hz, 1H), 7.26 (t, *J* = 9.0 Hz, 1H), 4.12 (d, *J* = 17.2 Hz, 2H), 3.95 (d, *J* = 17.2 Hz, 2H), 2.67 (s, 3H).

^{13}C NMR (CD_3CN, 125 MHz): δ 169.3, 157.0, 151.7, 131.1, 125.2, 123.9, 122.9, 112.2, 62.6, 48.1. [Note: no signal was observed for the quaternary C–B *ipso* carbon.]

^{11}B NMR (CD_3CN, 193 MHz): δ 11.2 (br s).

HRMS (ESI+): Calculated for $C_{12}H_{12}BNO_5Na$ ($[M+Na]^+$), 296.0709; found 296.0714.



5.1f **5.4f**

MIDA boronate 5.4f. A solution of phenol **5.1f** (71.0 mg, 0.500 mmol, 1.00 equiv) in 1.0 mL toluene was added to a flame-dried 10-mL Schlenk tube. To this stirring solution was added dropwise at 25 °C a suspension of NaH (92 wt % purity, 13.0 mg, 0.500 mmol, 1.00 equiv) in 0.5 mL toluene over 2 min. A suspension of NaTFA (20. mg, 0.15 mmol, 30 mol %) in 0.5 mL toluene was added next, and the resulting suspension was stirred for 15 min to affect full deprotonation.

To the resulting stirring sodium phenoxide suspension was added at 25 °C a solution of *B*-chlorocatecholborane (77.0 mg, 0.500 mmol, 1.00 equiv) in toluene (1.0 mL), using additional toluene as a rinse to ensure full transfer (2 × 0.5 mL portions). The resulting suspension was stirred vigorously for 30 min to allow for full conversion to boric ester intermediate **5.2f**.

Next, a suspension of IPrAuCl (16 mg, 0.025 mmol, 5.0 mol %) in toluene (0.5 mL) was added to the reaction mixture at 25 °C, using additional toluene as a rinse to aid in full transfer (1 × 0.5 mL portion). The reaction mixture was then sealed with a ground glass stopper and a PTFE sealing ring and placed in a pre-heated 50 °C copper shot heating bath. The final concentration of the reaction mixture was 0.1 M in **5.1f**.

After 23 h, analysis by TLC (20% EtOAc/hexanes) indicated full cosumption of boric ester intermediate **5.2f**. The reaction mixture was cooled to 25 °C, and a solution of PPh_3 (13 mg, 0.050 mmol, 10 mol %) in toluene (0.5 mL) was

added. The resulting suspension was stirred for 16 h at 25 °C in order to quench IPrAuTFA before proceeding.

Anhydrous DMSO (2.0 mL) and H_2MIDA (160 mg, 1.1 mmol, 2.2 equiv) were added to the quenched alkoxyboration reaction mixture, and the resulting suspension was stirred at 90 °C for 2h. The reaction mixture was then cooled to 25 °C and removed from the glovebox. Toluene was removed in vacuo at 25 °C and ca. 10 Torr, then DMSO was removed by Kugelrohr distillation at ca. 10 mTorr. The resulting semisolid residue was adsorbed onto Celite from a MeCN suspension and purified by silica gel chromatography using an elution gradient from 100% Et_2O to 100% MeCN. Removal of volatiles at 25 °C and ca. 10 mTorr for 18 h afforded MIDA boronate **5.4f** as a white powder (52 mg, 35% yield).

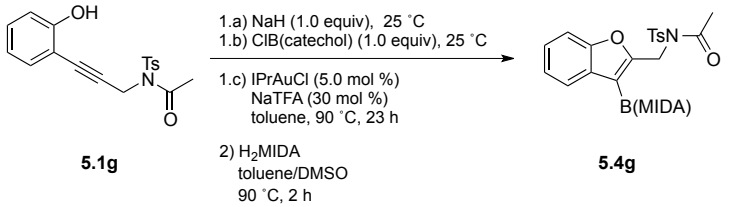
TLC (20% MeCN/ Et_2O): R_f = 0.50.

^{1}H NMR (CD_3CN, 600 MHz): δ 7.82 (s, 1H), 7.69 (s, 1H), 7.57 (d, *J* = 8.1 Hz, 1H), 7.38 (dd, *J* = 7.1, 1.3 Hz, 1H), 4.12 (d, *J* = 17.2 Hz, 2H), 3.94 (d, *J* = 17.2 Hz, 2H), 3.40 (s, 1H), 2.66 (s, 3H).

^{13}C NMR (CD_3CN, 125 MHz): δ 169.2, 156.4, 153.3, 132.1, 127.9, 123.1, 115.8, 84.4, 78.5, 62.6, 48.2. [Note: no signals were observed for the quaternary C–B *ipso* carbon and a second quaternary carbon.]

^{11}B NMR (CD_3CN, 193 MHz): δ 11.0 (br s).

HRMS (ESI+): Calculated for $C_{15}H_{12}BNO_5Na$ ($[M+Na]^+$), 320.0709; found 320.0713.



5.1g **5.4g**

MIDA boronate 5.4g. A solution of phenol **5.1g** (99 mg, 0.29 mmol, 1.0 equiv) in 0.5 mL toluene was added to a flame-dried 10-mL Schlenk tube. To this stirring solution was added dropwise at 25 °C a suspension of NaH (92 wt % purity, 8.0 mg, 0.50 mmol, 1.0 equiv) in 0.5 mL toluene over 2 min. A suspension of NaTFA (9.0 mg, 0.090 mmol, 30. mol %) in 0.5 mL toluene was added next, and the resulting suspension was stirred for 15 min to affect full deprotonation.

To the resulting stirring sodium phenoxide suspension was added at 25 °C a solution of *B*-chlorocatecholborane (45 mg, 0.29 mmol, 1.0 equiv) in toluene (0.5 mL), using additional toluene as a rinse to ensure full transfer (1 × 0.3 mL portion). The resulting suspension was stirred vigorously for 30 min to allow for full conversion to boric ester intermediate **5.2g**.

Next, a suspension of IPrAuCl (9.0 mg, 0.010 mmol, 5.0 mol %) in toluene (0.5 mL) was added to the reaction mixture at 25 °C, using additional toluene as a rinse to aid in full transfer (1 × 0.2 mL portion). The reaction mixture was then sealed with a ground glass stopper and a PTFE sealing ring and placed in a preheated 90 °C copper shot heating bath. The final concentration of the reaction mixture was 0.1 M in **5.1g**.

After 23 h, analysis by TLC (20% EtOAc/hexanes) indicated full consumption of boric ester intermediate **5.2g**. The reaction mixture was cooled to 25 °C, and a solution of PPh_3 (8.0 mg, 0.030 mmol, 10. mol %) in toluene (0.5 mL) was

added. The resulting suspension was stirred for 16 h at 25 °C in order to quench IPrAuTFA before proceeding.

Anhydrous DMSO (2.0 mL) and H_2MIDA (52 mg, 0.35 mmol, 1.1 equiv) were added to the quenched alkoxyboration reaction mixture, and the resulting suspension was stirred at 90 °C for 2h. The reaction mixture was then cooled to 25 °C and removed from the glovebox. Toluene was removed in vacuo at 25 °C and ca. 10 Torr, then DMSO was removed by Kugelrohr distillation at ca. 10 mTorr. The resulting semisolid residue was adsorbed onto Celite from a MeCN suspension and purified by silica gel chromatography using an elution gradient from 100% Et_2O to 100% MeCN. Removal of volatiles at 25 °C and ca. 10 mTorr for 18 h afforded MIDA boronate **5.4g** as a white powder (59 mg, 41% yield).

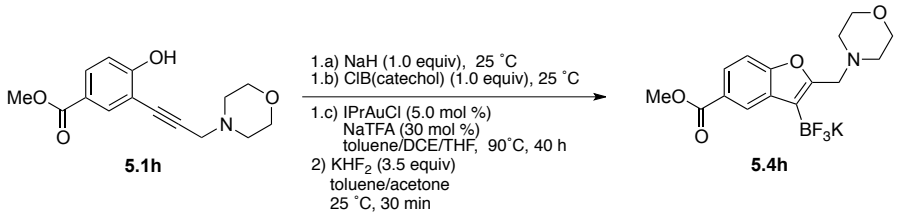
TLC (20% MeCN/Et_2O): R_f = 0.58, visualized by UV absorbance.

^{1}H NMR (CD_3CN, 600 MHz): δ 7.70 (d, *J* = 8.3 Hz, 2H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.40 (d, *J* = 7.9 Hz, 1H), 7.34–7.29 (m, 3H), 7.26 (t, *J* = 7.2 Hz, 1H), 5.28 (s, 2H), 4.19 (d, *J* = 21.0 Hz, 2H), 4.12 (d, *J* = 21.0 Hz, 2H), 2.76 (s, 3H), 2.39 (s, 3H), 2.35 (s, 3H).

^{13}C NMR (CD_3CN, 125 MHz): δ 171.7, 169.6, 158.2, 155.6, 146.4, 137.2, 132.3, 130.6, 129.0, 125.4, 124.1, 122.9, 111.9, 64.0, 49.0, 44.5, 25.0, 21.6. [Note: no signal was observed for the quaternary C–B *ipso* carbon.]

^{11}B NMR (CD_3CN, 193 MHz): δ 11.3.

HRMS (ESI+): Calculated for $C_{23}H_{23}BN_2O_8SNa$ ($[M+Na]^+$), 521.1170; found 521.1153.



Benzofuran trifluoroborate 5.4h. A solution of phenol **5.1h** (138 mg, 0.500 mmol, 1.00 equiv) in 1.0 mL toluene was added to a flame-dried 10-mL Schlenk tube. To this stirring solution was added dropwise at 25 °C a suspension of NaH (92 wt % purity, 13.0 mg, 0.500 mmol, 1.00 equiv) in 0.5 mL toluene over 2 min. A suspension of NaTFA (20. mg, 0.15 mmol, 30 mol %) in 0.5 mL toluene was added next. Due to the low solubility of **5.1h** in toluene, dry dichloroethane (0.5 mL) and dry THF (1.0 mL) were added. The resulting suspension was stirred for 15 min to affect full deprotonation.

To the resulting stirring sodium phenoxide suspension was added at 25 °C a solution of *B*-chlorocatecholborane (77.0 mg, 0.500 mmol, 1.00 equiv) in toluene (0.5 mL), using additional toluene as a rinse to ensure full transfer (1 × 0.5 mL portions). The resulting suspension was stirred vigorously for 30 min to allow for full conversion to boric ester intermediate **5.2h**.

Next, a suspension of IPrAuCl (16 mg, 0.025 mmol, 5.0 mol %) in toluene (0.5 mL) was added to the reaction mixture at 25 °C, using additional toluene as a rinse to aid in full transfer (1 × 0.5 mL portion). The reaction mixture was then sealed with a ground glass stopper and a PTFE sealing ring and placed in a pre-heated 90 °C copper shot heating bath. The final concentration of the reaction mixture was 0.08 M in **5.1h**.

After 40 h, analysis by TLC (20% EtOAc/hexanes) indicated full consumption of boric ester intermediate **5.2h**. The reaction mixture was cooled to 25 °C, and a solution of PPh_3 (13 mg, 0.050 mmol, 10 mol %) in toluene (0.5 mL) was added. The resulting suspension was stirred for 26 h at 25 °C in order to quench IPrAuTFA before proceeding.

The quenched reaction mixture was removed from the glovebox and filtered through a fiberglass filter to remove the suspended solids. The filter was then rinsed with chloroform (3 × 3 mL), and the combined filtrates were concentrated in vacuo to a pale yellow powder, which was suspended in acetone (4.5 mL) and added to a stirring solution of KHF_2 (160 mg, 2.0 mmol 4.0 equiv) in water (1.5 mL). The resulting mixture was stirred at 25 °C for 30 min, and then concentrated in vacuo to remove the solvents. To this residue was added 2 mL Et_2O and subsequently concentrated at ca. 10 mTorr for 30 min in order to remove residual acetone. The resulting pale yellow solid residue was washed with Et_2O (4 × 2 mL) and extracted with acetone (4 × 2 mL). The combined acetone extracts were concentrated in vacuo, and the resulting residue was subjected to an additional washing/extraction cycle to yield **5.4h** as a light green powder (79 mg, 42% yield) with trace residual acetone after removing volatiles at 25 °C and ca. 10 mTorr for 18 h.

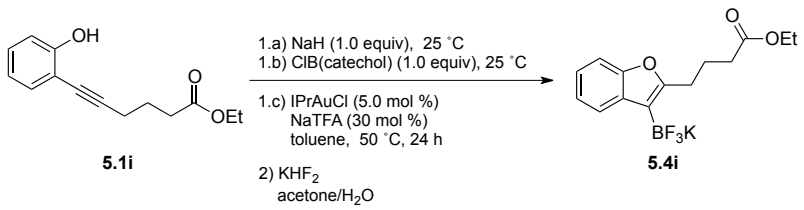
^{1}H NMR (d_6-DMSO, 600 MHz): δ 8.30 (s, 1H), 7.75 (dd, J = 9.4 Hz, 1.7 Hz, 1H), 7.44 (d, J = 8.5 Hz, 1H), 3.85, (s, 3H), 3.67 (br s, 2H), 3.54 (app t, J = 4.1 Hz, 4H), 2.44 (br s, 4H).

^{13}C NMR (d_6- DMSO, 125 MHz): δ 167.0, 157.3, 155.5 (br), 134.1, 125.2, 123.9, 122.7, 109.8, 66.2, 54.2, 53.0, 51.8. [Note: As with many organotrifluoroborates, the *ipso* carbon was not detected, presumably due to broadening through coupling to the ^{11}B nucleus.]

^{11}B NMR (d_6- DMSO, 193 MHz): δ 2.8 (br s).

^{19}F NMR (d_6-DMSO, 376 MHz): δ -133.1 (br s).

HRMS (ESI-): Calculated for $C_{15}H_{16}BF_3NO_4$ ([M-K]$^-$), 342.1127; found 342.1125.



Benzofuran trifluoroborate 5.4i. A solution of phenol **5.1i** (101 mg, 0.440 mmol, 1.00 equiv) in 0.75 mL toluene was added to a flame-dried 10-mL Schlenk tube. To this stirring solution was added dropwise at 25 °C a suspension of NaH (92 wt % purity, 11 mg, 0.44 mmol, 1.0 equiv) in 0.5 mL toluene over 2 min. A suspension of NaTFA (18 mg, 0.13 mmol, 30. mol %) in 0.5 mL toluene was added next, and the resulting suspension was stirred for 15 min to affect full deprotonation.

To the resulting stirring sodium phenoxide suspension was added at 25 °C a solution of *B*-chlorocatecholborane (67 mg, 0.44 mmol, 1.0 equiv) in toluene (0.75 mL), using additional toluene as a rinse to ensure full transfer (2 × 0.5 mL portions). The resulting suspension was stirred vigorously for 30 min to allow for full conversion to boric ester intermediate **5.2i**.

Next, a suspension of IPrAuCl (14 mg, 0.022 mmol, 5.0 mol %) in toluene (0.5 mL) was added to the reaction mixture at 25 °C, using additional toluene as a rinse to aid in full transfer (1 × 0.5 mL portion). The reaction mixture was then sealed with a ground glass stopper and a PTFE sealing ring and placed in a pre-heated 50 °C copper shot heating bath. The final concentration of the reaction mixture was 0.1 M in **5.1i**.

After 24 h, analysis by TLC (20% EtOAc/hexanes) indicated full consumption of boric ester intermediate **5.2i**. The reaction mixture was cooled to 25 °C, and a solution of PPh_3 (8.0 mg, 0.030 mmol, 10. mol %) in toluene (0.5 mL) was added. The resulting suspension stirred for 22 h at 25 °C in order to quench IPrAuTFA before proceeding.

The quenched reaction mixture was removed from the glovebox and filtered through a fiberglass filter to remove the suspended solids. The filter was then rinsed with toluene (3 × 3 mL), and the combined filtrates were concentrated in vacuo to a pale yellow powder, which was suspended in acetone (4.5 mL) and added to a stirring solution of KHF_2 (136 mg, 1.70 mmol, 3.50 equiv) in water (1.5 mL). The resulting mixture was stirred at 25 °C for 30 min, and then concentrated in vacuo to remove the solvents. To this residue was added 2 mL Et_2O and subsequently concentrated at ca. 10 mTorr for 30 min in order to remove residual acetone. The resulting pale yellow solid residue was washed with Et_2O (4 × 2 mL) and extracted with acetone (4 × 2 mL). The combined acetone extracts were concentrated in vacuo, and the resulting residue was subjected to an additional

washing/extraction cycle to yield **5.4i** as a white powder (102 mg, 69% yield) after removing volatiles at 25 °C and ca. 10 mTorr for 18 h.

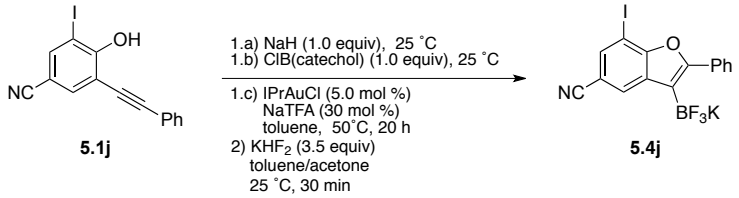
^{1}H NMR (d_6- DMSO, 600 MHz): δ 7.55 (t, *J* = 6.7 Hz, 1H), 7.27 (dd, *J* = 6.7, 1.8 Hz, 1H), 7.05–6.93 (m, 2H), 4.03 (q, *J* = 7.0 Hz, 2H), 2.77 (t, *J* = 7.3 Hz, 2H), 2.28 (t, *J* = 7.7 Hz, 2H), 1.85 (quin, *J* = 7.5 Hz, 2H), 1.16 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (d_6- DMSO, 125 MHz): δ 172.9, 157.3, 154.0, 134.6, 122.5, 121.3, 120.7, 109.2, 59.6, 33.1, 27.0, 24.0, 14.1.

^{11}B NMR (d_6- DMSO, 193 MHz): δ 2.9 (br s).

^{19}F NMR (d_6- DMSO, 377 MHz) δ -133.6 (m).

HRMS (ESI-): Calculated for $C_{14}H_{15}BF_3O_3$ ([M-K]$^-$), 299.1069; found 299.1063.



Benzofuran trifluoroborate 5.4j. A solution of phenol **5.1j** (41.4 mg, 0.119 mmol, 1.00 equiv) in 150 µL toluene was added to a flame-dried 10-mL Schlenk tube. To this stirring solution was added dropwise at 25 °C a suspension of NaH (92 wt % purity, 3.1 mg, 0.12 mmol, 1.0 equiv) in 150 µL toluene. A suspension of NaTFA (4.9. mg, 0.036 mmol, 30 mol %) in 150 µL toluene was added next. The resulting suspension was stirred for 15 min to affect full deprotonation.

To the resulting stirring sodium phenoxide suspension was added at 25 °C a solution of *B*-chlorocatecholborane (18.3 mg, 0.119 mmol, 1.00 equiv) in tolu-

ene (150 μL), using additional toluene as a rinse to ensure full transfer (1 × 150 μL portions). The resulting suspension was stirred vigorously for 30 min to allow for full conversion to boric ester intermediate **5.2j**.

Next, a suspension of IPrAuCl (16 mg, 0.025 mmol, 5.0 mol %) in toluene (150 μL) was added to the reaction mixture at 25 °C, using additional toluene as a rinse to aid in full transfer (1 × 150 μL portion). The reaction mixture was then sealed with a ground glass stopper and a PTFE sealing ring and placed in a pre-heated 90 °C copper shot heating bath. The final concentration of the reaction mixture was 0.1 M in **5.1j**.

After 20 h, analysis by TLC (10% EtOAc/hexanes) indicated full consumption of boric ester intermediate **5.2j**. The reaction mixture was cooled to 25 °C, and a solution of PPh_3 (3.1 mg, 0.012 mmol, 10 mol %) in toluene (0.5 mL) was added. The resulting suspension was stirred for 18 h at 25 °C in order to quench IPrAuTFA before proceeding.

The quenched reaction mixture was removed from the glovebox and filtered through a fiberglass filter to remove the suspended solids. The filter was then rinsed with chloroform (3 × 3 mL), and the combined filtrates were concentrated in vacuo to a pale yellow powder, which was suspended in acetone (1.0 mL) and added to a stirring solution of KHF_2 (37 mg, 0.48 mmol, 4.0 equiv) in water (300 μL). The resulting mixture was stirred at 25 °C for 30 min, and then concentrated in vacuo to remove the solvents. Residual water was removed azeotropically by adding 2 mL acetone and concentrating in vacuo again. To this residue was added 2 mL Et_2O and subsequently concentrated at ca. 10 mTorr for

30 min in order to remove residual acetone. The resulting pale yellow solid residue was washed with Et_2O (4 × 2 mL) and extracted with acetone (4 × 2 mL). The combined acetone extracts were concentrated in vacuo, and the resulting residue was subjected to an additional washing/extraction cycle to yield **5.4j** as a light green powder (12 mg, 23% yield) with trace residual acetone after removing volatiles at 25 °C and ca. 10 mTorr for 18 h.

^{1}H NMR (*d*$_6$-DMSO, 600 MHz): δ 8.07 (d, *J* = 1.4 Hz, 1H), 7.87 (d, *J* = 1.5 Hz, 1H), 7.59–7.57 (m, 1H), 2.56–2.53 (m, 2H), 2.23–2.20 (m, 2H), 1.69–1.65 (m, 2H), 1.62–1.58 (m, 2H).

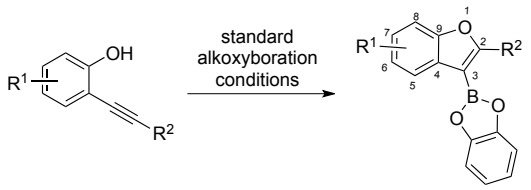
^{13}C NMR (*d*$_6$-DMSO, 125 MHz): δ. [Note: As with many organotrifluoroborates, the *ipso* carbon was not detected, presumably due to broadening through coupling to the ^{11}B nucleus. A second quaternary carbon was also not detected.]

^{11}B NMR (*d*$_6$- DMSO, 193 MHz): δ 2.8 (br s).

^{19}F NMR (*d*$_6$-DMSO, 376 MHz): δ -130.7 (br s).

HRMS (ESI-): Calculated for $C_{15}H_{11}BF_3INO$ ($[M\text{-}K]^-$), 415.9933; found 415.9916.

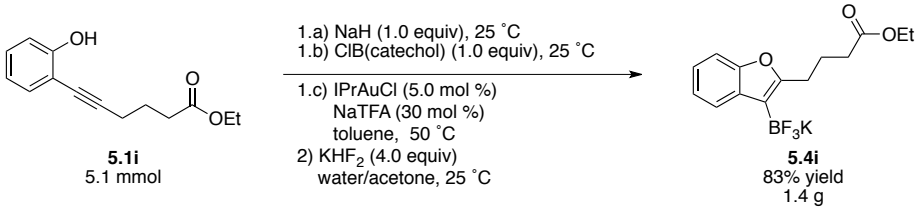
General procedure NMR conversions using ERETIC



5.1a/5.1b, 5.1c, 5.1f, 5.1i **5.2a/5.2b, 5.2c, 5.2f, 5.2i**

ERETIC experiments were conducted by Blum group graduate student Darius Faizi. A 4-mL vial was charged with a 2-substituted alkynylphenol (**5.1**, 0.05 mmol, 1 equiv), and 0.5 mL d_8-toluene. A second 4-mL vial was charged with NaH (1.3 mg, 0.050 mmol, 1.0 equiv) and NaTFA (2.7 mg, 0.020 mmol, 0.30 equiv). The solution containing the phenol was then added dropwise to the vial containing NaH and NaTFA, and swirled intermittently for 15 min. This cloudy mixture was then added dropwise to another 4-mL vial containing *B*-chlorocatecholborane (7.7 mg, 0.050 mmol, 1.0 equiv). This mixture was then swirled intermittently for 30 min before transferring into a new vial containing IPrAuCl (1.6 mg, 0.0030 mmol, 0.050 equiv). This mixture was then transferred into a J. Young NMR tube, which was sealed and removed from the glove box. This tube was then heated to 50 ^{o}C for 18-24 h. An ^{1}H NMR was taken (600 MHz, d_8-toluene), and the signals correlating to the corresponding cyclized benzofuran boronic ester (**5.3**) were compared to an external standard of mesitylene (419 mmol/L in d_8-toluene) using the ERETIC method, ensuring the acquisition parameters were identical. This general procedure was used for R^1= H, R^2=Ph (**5.3a, 5.3b**, 95%); R^1= 6-Br, R^2= Bu (**5.3c**, 88%); R^1= 6-CCH, R^2=H (**5.3f**, 42%), R^1= H, R^2= -$(CH_2)_3CO_2Et$ (**5.3i**, 71%).

Gram-scale preparation of **5.4i**



The gram-scale alkoxyboration reaction was conducted in a N_2-filled glovebox. A flame-dried 100-mL Schlenk tube with a stirbar was charged with NaH (92 wt % purity, 123 mg, 5.13 mmol, 1.00 equiv) and NaTFA (210 mg, 1.5 mmol, 30. mol %). Anhydrous toluene (12 mL) was added. To the resulting rapidly stirring suspension was added a solution of phenol **5.1i** (1.30 g, 5.13 mmol, 1.00 equiv) in toluene (2 mL) at 25 °C dropwise over 5 min. Additional toluene (3 × 2 mL) was used as a rinse to aid in complete transfer. The reaction mixture was stirred at 25 °C for 30 min to affect full deprotonation.

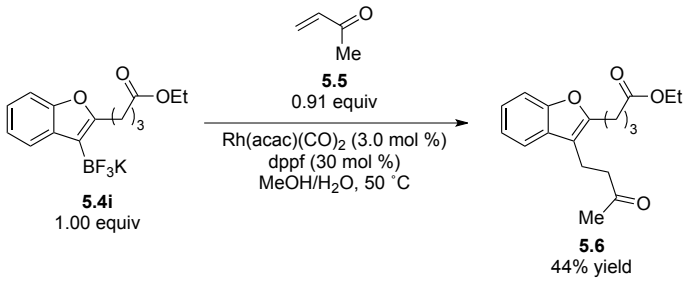
To the resulting pale yellow suspension was added a solution of *B*-chlorocatecholborane (790. mg, 5.13 mmol, 1.00 equiv) in toluene (5 mL) drop-wise over 5 min. [Note: a slight exotherm occurs.] Additional toluene (3 × 5 mL) was used as a rinse to aid in complete transfer. The reaction mixture was stirred at 25 °C for 30 min to affect full formation of boric ester intermediate **5.2i**.

A suspension of IPrAuCl (80. mg, 0.13 mmol, 2.5 mol %) in toluene (2.5 mL) was added next, using additional toluene (3 × 2.5 mL) as a rinse to ensure full transfer. The reaction vessel was then sealed with a ground glass joint and a PTFE sealing ring and placed in a preheated 60 °C copper shot heating bath. The final concentration of the reaction mixture was 0.1 M in **5.1i**.

After 22 h, analysis by TLC (10% EtOAc/hexanes) indicated complete consumption of boric ester intermediate **5.2i**. The reaction mixture was cooled to 25 °C, and then a solution of PPh_3 (67 mg, 0.26 mmol, 5.0 mol %) in 2.5 mL toluene was added to the reaction mixture. The resulting suspension was stirred for 23 h at 25 °C in order to quench IPrAuTFA before proceeding.

The suspension containing boronic ester **5.3i** was removed from the glovebox and concentrated in vacuo. The resulting solid residue was extracted with toluene (3 × 15 mL), and the combined extracts were filtered through a fiberglass filter to ensure removal of suspended solids. The filtrate was concentrated in vacuo, and the resulting residue was dissolved in acetone (45 mL) and added to a vigorously stirring solution of KHF_2 (1.6 g, 21 mmol, 4.0 equiv) in 15 mL H_2O. The reaction mixture was stirred open to air for 30 min at 25 °C before being concentrated in vacuo to remove the solvents. Residual water was removed azeotropically by adding 2 mL acetone and concentrating in vacuo again. The resulting solid residue was washed with Et_2O (15 × 30 mL) and extracted with acetone (3 × 15 mL). The combined acetone extracts were concentrated in vacuo to yield **5.4i** as a white powder (1.43 g, 83% yield) after removing volatiles at 25 °C and ca. 10 mTorr for 18 h. Spectral data were identical to those previously obtained for this compound (see page S18).

Downstream functionalization reactions to produce **5.6**, **5.8**, and **5.10**



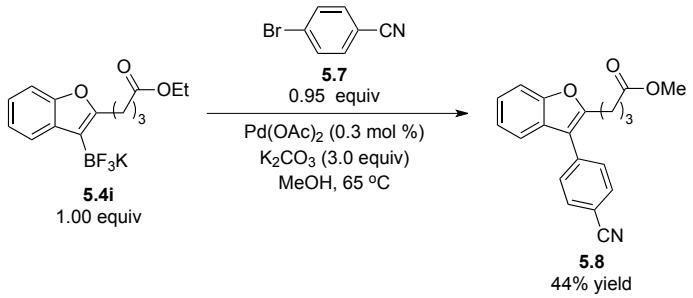
Ethyl 4-(3-(3-oxobutyl)benzofuran-2-yl)butanoate (5.6) was prepared by graduate student Darius Faizi. The Rh-catalyzed conjugate addition of **5.4i** to methyl vinyl ketone was conducted using a procedure adapted from Batey.[14] A dram vial was charged with **5.4i** (85 mg, 0.25 mmol, 1.1 equiv) and a stirbar. The vial was pumped into a N_2-filled glovebox, where $Rh(acac)(CO)_2$ (1.9 mg, 7.1 μmol, 3.0 mol %) and dppf (40. mg, 72 μmol, 30. mol %) were added. The vial was sealed with a septum cap, removed from the glovebox, and placed under dynamic N_2 atmosphere. Methanol (2.2 mL) and water (400 μL) were added, and the resulting mixture was stirred at 25 °C for 15 min to dissolve the solids. Methyl vinyl ketone (19 μL, 0.23 mmol, 1.0 equiv) was added, and the reaction mixture was heated at 50 °C for 30 h. To the resulting heterogeneous brown mixture was added 10-mL DCM, and the resulting biphasic mixture was separated. The aqueous layer was back extracted with DCM (3 × 1 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to a brown solid residue. Purification by silica gel chromatography using an elution gradient from 100% hexanes to 15% EtOAc/hexanes and removal of volatiles at 25 °C and ca. 10 mTorr for 18 h afforded **5.6** as a clear, colorless oil (33 mg, 44% yield).

TLC (15% EtOAc/hexanes): R_f = 0.29.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.43 (d, *J* = 7.2 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.23–7.18 (m, 2H), 4.11 (q, *J* = 7.0 Hz, 2H), 2.88 (t, *J* = 7.3 Hz, 2H), 2.82 (t, *J* = 7.3 Hz, 2H), 2.77 (t, *J* = 7.3 Hz, 2H), 2.36 (t, *J* = 7.4 Hz, 2H), 2.13 (s, 3H), 2.05 (quin, *J* = 7.5 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 207.9, 173.3, 154.2, 153.8, 129.1, 123.5, 122.3, 118.9, 113.8, 111.0, 60.5, 43.4, 33.6, 30.3, 25.6, 23.6, 17.6, 14.4.

HRMS (ESI+): Calculated for $C_{18}H_{22}O_4Na$ ([M+Na]$^+$), 325.1416; found 325.1420.



Methyl 4-(3-(4-cyanophenyl)benzofuran-2-yl)butanoate (5.8) was prepared by graduate student Darius Faizi. A 20-mL vial was charged with **5.4i** (99 mg, 0.29 mmol, 1.1 equiv), K_2CO_3 (116 mg, 0.837 mmol, 3.00 equiv), and $Pd(OAc)_2$ (0.2 mg, 0.001 mmol, 0.3 mol %). The vial was then evacuated and refilled with N_2 three times. To this vial was then added 0.4 mL of MeOH that had been sparged for 10 min with N_2. In a separate flask was added 4-benzonitrile (51 mg, 0.28 mmol, 1.0 equiv), which was then evacuated and refilled with N_2 three times before adding 0.4 mL MeOH that had been sparged 10 min with N_2. This solution was then syringed into the stirring reaction vial over 1 min. The vial was then equipped with an argon balloon and heated to 65 °C. The mixture stirred for 18 h

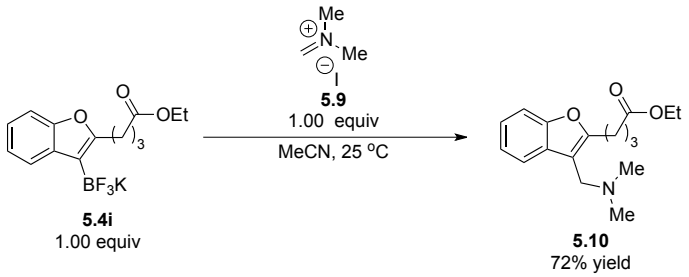
before TLC (10% EtOAc/hexanes) showed the complete consumption of starting material. The reaction mixture was diluted with 20 mL toluene, and then the organic layer was washed with H_2O (1 × 5 mL), brine (1 × 5 mL), filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient from 100% hexanes to 15% EtOAc/hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **5.8** as a white solid. (41 mg, 44% yield).

TLC (10% EtOAc/hexanes) R_f = 0.20, visualized by UV absorbance.

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.78 (d, *J* = 8.2 Hz, 2H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.50 (dd, *J* = 16.3, 7.9 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.26 (t, *J* = 7.2 Hz, 1H), 3.61 (s, 3H), 2.93 (t, *J* = 7.5 Hz, 2H), 2.38 (t, *J* = 7.3 Hz, 2H), 2.13 (quin, *J* = 7.3 Hz, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.4, 155.0, 154.3, 137.8, 132.8, 129.7, 127.8, 124.5, 123.3, 119.3, 119.0, 116.4, 111.4, 110.9, 51.8, 33.2, 26.2, 23.5.

HRMS (ESI+): Calculated for $C_{20}H_{17}NO_3Na$ ([M+Na]$^+$), 342.1106; found 342.1094.



Ethyl 4-(3-((dimethylamino)methyl)benzofuran-2-yl)butanoate (5.10). A 10-mL Schlenk tube was charged with Eschenmoser's salt (**5.9**, 74.0 mg, 0.300 mmol,

1.00 equiv) and 1.0 mL anhydrous MeCN. To the resulting suspension was added a solution of organotrifluoroborate **5.4i** (101 mg, 0.300 mmol, 1.00 equiv) in 1.3 mL dry MeCN. The reaction mixture was stirred vigorously for 30 min at 25 °C, at which time a saturated aqueous solution of $NaHCO_3$ (1 mL) was added to quench the reaction. The resulting biphasic mixture was extracted with EtOAc (3 × 3 mL), and the combined organic layers were washed with brine (3 × 3 mL), dried over Na_2SO_4, and concentrated in vacuo to an oily residue. Purification by column chromatography using an elution gradient from 1.5% Et_3N in hexanes to 40% EtOAc and 0.9% Et_3N in hexanes afforded **5.10** as a clear, pale yellow oil (63 mg, 72% yield)

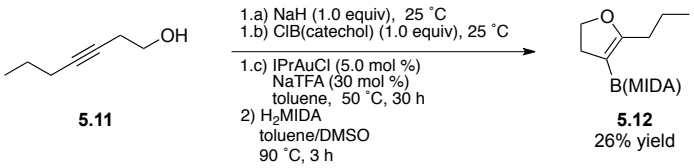
TLC (30% EtOAc + 1% Et_3N/hexanes) R_f = 0.27, visualized by UV absorbance.

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.63–7.61 (m, 1H), 7.41–7.30 (m, 1H), 7.24–7.19 (m, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.47 (s, 2H), 2.86 (t, *J* = 7.3 Hz, 2H), 2.38 (t, *J* = 7.4 Hz, 2H), 2.26 (s, 6H), 2.09 (app quin, *J* = 7.3 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.3, 155.4, 154.1, 129.7, 123.5, 122.5, 119.9, 112.6, 110.7, 60.5, 53.2, 45.6, 33.6, 25.8, 23.5, 14.4.

HRMS (ESI+): Calculated for $C_{17}H_{23}NO_3Na$ ($[M+Na]^+$), 312.1576; found 312.1570.

Synthesis of dihydrofuran product **5.12**



Prior to use, **5.11** was dried by distilling over anhydrous K_2CO_3 (15 Torr, 80 °C), and residual water was removed using activated 3Å molecular sieves. (Note: **5.11** should not be stored over sieves indefinitely; a sample stored over sieves under N_2 atmosphere at 25 °C for ca. 10 months was completely inactive under the given alkoxyboration reaction conditions despite maintaining > 95% purity by ^1H and ^{13}C NMR spectroscopy.) The alkoxyboration reaction was set up and conducted in a N_2-filled glovebox. A flame-dried 100 mL Schlenk tube with a stir-bar was charged with NaH (92 wt % purity, 26.0 mg, 1.00 mmol, 1.00 equiv) and NaTFA (41 mg, 0.30 mmol, 30 mol %). Anhydrous toluene (4 mL) was added. Compound **5.9** (103 µL, 1.00 mmol, 1.00 equiv) was added dropwise over 1 min, and then the reaction mixture was stirred at 25 °C for 40 min to affect full deprotonation.

To the resulting suspension was added a solution of *B*-chlorocatecholborane (154 mg, 1.00 mmol, 1.00 equiv) in toluene (2 mL) dropwise over 5 min. Additional toluene (2 × 1 mL) was used as a rinse to aid in complete transfer. The reaction mixture was stirred at 25 °C for 30 min to affect full formation of the boric ester intermediate.

A suspension of IPrAuCl (31 mg, 0.050 mmol, 5.0 mol %) in toluene (1 mL) was added next, using additional toluene (2 × 0.5 mL) as a rinse to ensure full

transfer. The reaction vessel was then sealed with a ground glass joint and a PTFE sealing ring and placed in a preheated 50 °C copper shot heating bath. The final concentration of the reaction mixture was 0.1 M in **5.11**.

Analysis by TLC (20% EtOAc/hexanes) at 23 h and 30 h indicated stalled, nearly complete consumption of the boric ester intermediate. The reaction mixture was cooled to 25 °C, and then a solution of PPh_3 (26 mg, 0.10 mmol, 10 mol %) in 1 mL toluene. The resulting suspension was stirred for 16 h at 25 °C in order to quench IPrAuTFA before proceeding.

To the quenched reaction mixture were added H_2MIDA (160 mg, 1.1 mmol, 1.1 equiv) and dry DMSO (4 mL), and the resulting suspension was stirred at 90 °C for 3 h. The reaction mixture was then cooled to 25 °C and removed from the glovebox. Toluene was removed in vacuo at 25 °C and ca. 10 Torr, then DMSO was removed by Kugelrohr distillation at ca. 10 mTorr. The resulting semisolid residue was adsorbed onto Celite from a MeCN suspension and purified twice by successive silica gel chromatography using an elution gradient from 100% Et_2O to 100% MeCN. Removal of volatiles at 25 °C and ca. 10 mTorr for 18 h afforded MIDA boronate **5.12** as a white powder (83 mg, 26% yield).

^{1}H NMR (CD_3CN, 600 MHz): δ 3.94 (d, *J* = 17.2 Hz, 2H), 3.84 (d, *J* = 17.2 Hz, 2H), 3.68 (t, *J* = 6.8 Hz, 2H), 2.86 (s, 3H), 2.38 (tt, *J* = 6.9, 2.3 Hz, 2H), 2.11 (tt, *J* = 6.9, 2.3 Hz, 2H), 1.46 (sextet, *J* = 7.3 Hz, 2H), 0.95 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (CD_3CN, 125 MHz): δ 168.3, 82.0, 78.3, 63.3, 63.1, 46.1, 23.2, 22.7, 21.1, 13.7.

^{11}B NMR (CD_3CN, 193 MHz): δ 8.8 (br s).

HRMS (ESI+): Calculated for $C_{12}H_{18}BNO_5Na$ ($[M+Na]^+$), 290.1178; found 290.1180.

References for Experimental Section.

1. Liu, Y.; Ma S. *Org. Lett*. **2012**, *14*, 720–723.
2. Fischer, J.; Savage, G. P.; Coster, M. J. *Org. Lett.* **2011**, *13*, 3376–3370.
3. Cowart, M.; Faghih, R.; Curtis, M. P.; Gfesser, G. A.; Bennani, Y. L.; Black, L. A.; Pan, L.; Marsh, K. C.; Sullivan, J. P.; Esbenshade, T. A.; Fox; G. B.; Hancock, A. A. *J. Med. Chem.* **2005**, *48*, 38–55.
4. Larrosa, I.; Da Silva, M. I.; Gómez, P. M.; Hannen, P.; Ko, E.; Lenger, S. R.; Linke, S. R.; White, A. J. P.; Wilton, D.; Barrett, A. G. M. *J. Am. Chem. Soc.* **2006***, 128*, 14042–14043.
5. Tsang, K. Y.; Brimble, M. A. *Tetrahedron* **2007**, *63*, 6015–6034.
6. Kawasaki, T.; Yamamoto, Y. *J. Org. Chem.* **2002**, *67*, 5138–5141.
7. Ried, W.; Schmidt, H.-J. *Chem. Ber.* **1957**, *90*, 2553–2561.
8. Achard, T.; Lepronier, A.; Gimbert, Y.; Clavier, H.; Giodano, L.; Tenaglia, A.; Buono, G. *Angew. Chem. Int. Ed.* **2011**, *50*, 3552–3556.
9. Ozaki, S.; Matsushita, H.; Ohmori, H. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2339–2344.
10. Torregrosa, J.-L.; Baboulene, M. V.; Speziale, M.; Lattes, A. *J. Orgmet. Chem.* **1983**, *244*, 311–317.
11. Rozhkov, R. V.; Larock, R. C. *J. Org. Chem.* **2010**, *75*, 4131–4134.
12. Duclos, S.; Stoeckli-Evans, H.; Ward, T. R. *Helv. Chim. Acta* **2001**, *84*, 3148–

3161.

13. Shi, Y.; Roth, K. E.; Ramgren, S. D.; Blum, S. A. *J. Am. Chem. Soc.* **2009**, *131*, 18022–18023.

14. Batey, R. A.; Thadani, A. N.; Smil, D. V. *Org. Lett.* **1999**, *1*, 1683–1686.

Chapter 6
Further Investigations of Formal B–O σ-Bond Activation by Au: Transmetalation, Intermolecular Reactivity, and Additional Intramolecular Reaction Substrate Classes

Abstract: Four additional investigations stemming from the benzofuran-forming alkoxyboration reaction (Chapter 5) are described. Discussed are electronic effects in the B/Au transmetalation reaction, progress towards an intermolecular alkoxyboration reaction, and the expansion of the alkoxyboration concept to two additional substrate classes for intramolecular B–O σ-bond activation reactivity.

Introduction

The development of the benzofuran-forming alkoxyboration reaction (Chapter 5) inspired four ongoing lines of inquiry related to the activation of B–O σ bonds through Au catalysis: (1) a fundamental study of the B/Au transmetalation step; (2) progress towards an intermolecular alkoxyboration reaction; (3) an expansion of intramolecular reactivity from alkoxyboration to *oxyboration* for the formation of isoxazole boronic acid derivatives from oximes; and (4) an applica-

tion of intramolecular oxyboration with carboxylic acids (*carboxyboration*) for the formation of lactone boronic acid derivatives.

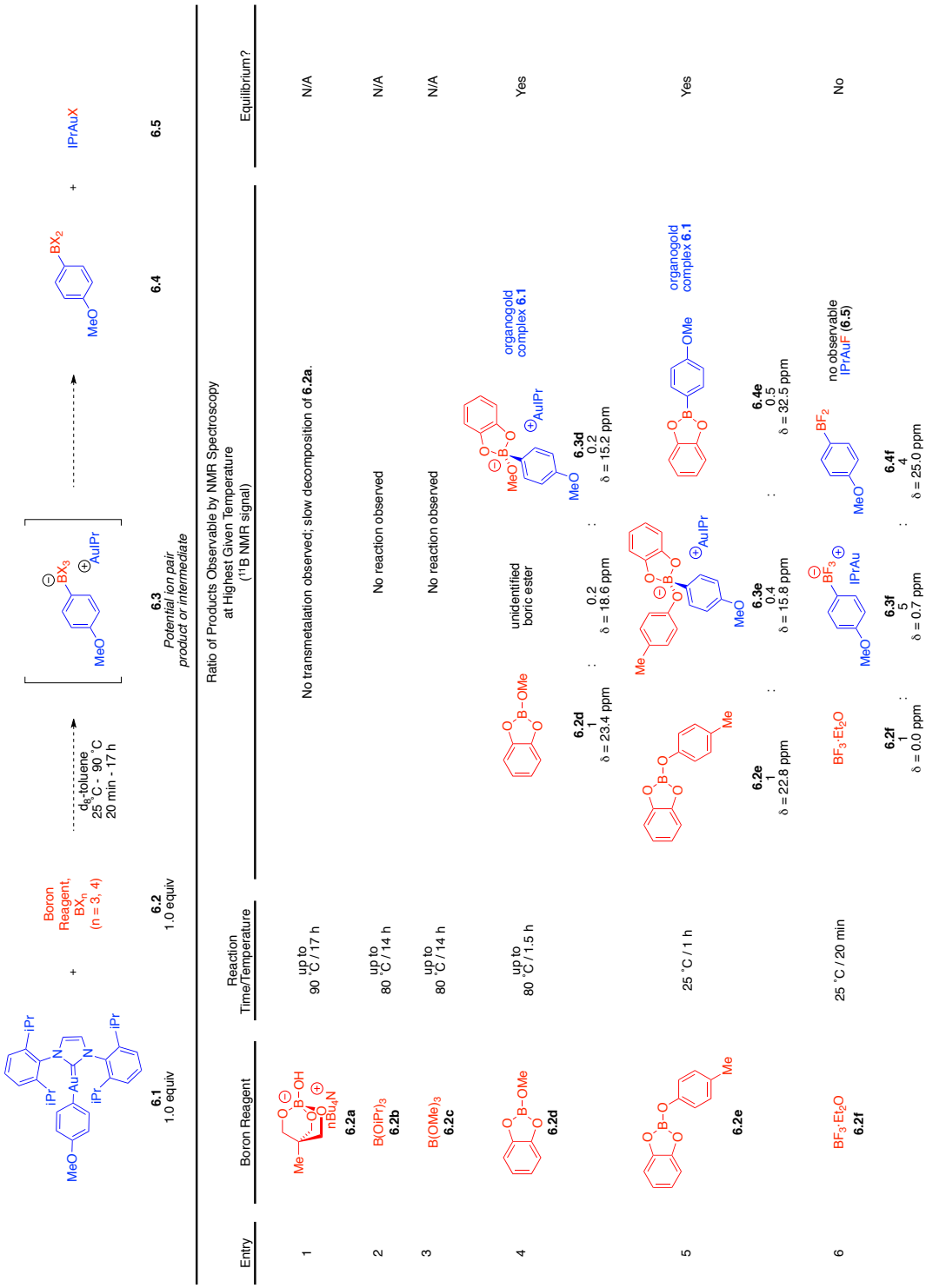
Results and Discussion

Ongoing Study 1: Studies in B/Au Transmetalation

Although the organoboron-to-gold transmetalation reaction has been studied previously,[1] the reverse reaction—an organogold-to-boron transmetalation—had not been reported prior to our hypothesis of this step in the benzofuran-forming alkoxyboration reaction (Chapter 5, Scheme 5.7). In order to better understand the mechanism of this possible key mechanistic step, the electronic factors affecting the thermodynamics and kinetics of transmetalation of an aryl group from Au to B were investigated.[1]

Arylgold complex **6.1** was treated with a range of boron reagents as shown in Table 6.1. The table is qualitatively arranged from the least electrophilic B reagent (entry 1) to the most electrophilic (entry 6).[2] Particularly useful in the analysis of the crude transmetalation reaction mixtures were diagnostic chemical shifts[3] observable by ^{11}B NMR spectroscopy: δ 33 ~ 31 ppm for boronic esters, δ 23 ~ 18 ppm for boric esters, δ 10 ~ 0 ppm for mixed borates or boronates. No detectable quantities of aryl transfer products were observed by NMR spectroscopy for borate **6.2a** or electron-rich boric esters **6.2b** and **6.2c**, even with prolonged heating (entries 1–3). Substitution of two methoxy substituents for the less electron-donating catechol ligand (**6.2d**) afforded a small amount of arylated ion pair **6.3d**, observable by ^{11}B NMR spectroscopy as a signal at δ = 15.2 ppm. Variable

Table 6.1. Electronic effects in the stoichiometric aryl transfer from Au to B.



Entry	Boron Reagent	Reaction Time/Temperature	Ratio of Products Observable by NMR Spectroscopy at Highest Given Temperature (^{11}B NMR signal)	Equilibrium?
1	**6.2a**	up to 90 °C / 17 h	No transmetalation observed; slow decomposition of **6.2a**.	N/A
2	$B(OiPr)_3$ **6.2b**	up to 80 °C / 14 h	No reaction observed	N/A
3	$B(OMe)_3$ **6.2c**	up to 80 °C / 14 h	No reaction observed	N/A
4	**6.2d**	up to 80 °C / 1.5 h	unidentified boric ester : organogold complex **6.1** (**6.3d**) 0.2 : 1 (δ = 15.2 ppm) : **6.2d** 1 : 0.2 (δ = 23.4 ppm : δ = 18.6 ppm)	Yes
5	**6.2e**	25 °C / 1 h	**6.2e** 1 (δ = 22.8 ppm) : **6.3e** 0.4 (δ = 15.8 ppm) : organogold complex **6.1** (**6.4e**) 0.5 (δ = 32.5 ppm)	Yes
6	**6.2f**	25 °C / 20 min	**6.2f** 1 (δ = 0.0 ppm) : **6.3f** 5 (δ = 0.7 ppm) : **6.4f** 4 (δ = 25.0 ppm) : no observable IPrAuF (**6.5**)	No

Ratios determined by ^{1}H, ^{11}B, and/or ^{19}F NMR spectroscopy. “Equilibrium” indicates a reversible, thermal redistribution of products was observed by variable temperature NMR.

temperature NMR data indicated a reversible, thermal dependence on the product distribution, indicating that **6.3d** was present in equilibrium with starting materials.

Similarly, the slightly more electrophilic boric ester **6.2e** afforded a greater equilibrium concentration of the ion pair **6.3e** as well as the neutral transmetalation product **6.4e**. Finally, the reaction of organogold complex **6.1** with the most electrophilic B reagent studied, $BF_3 \cdot Et_2O$ (entry 6), fully consumed **6.1** to rapidly provide a mixture of arylated ion pair **6.3f** and neutral difluoroborane **6.4f**. The resulting mixture subsequently underwent slow conversion of **6.3f** into **6.4f** through a reaction with a currently unidentified fluoride acceptor.

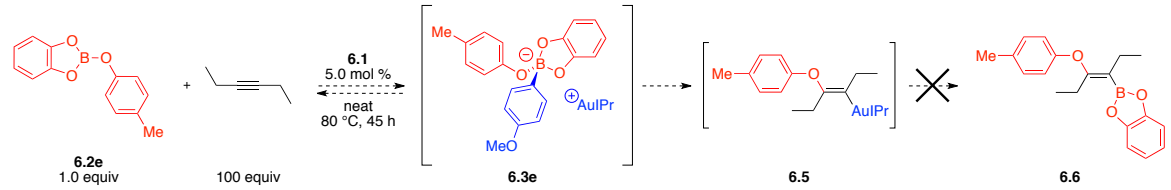
These data suggest that (1) the organogold-to-boron transmetalation is best represented as the addition of a nucleophilic C–Au σ-bond to a B electrophile, and (2) tetracoordinate anionic boron complexes may be present in equilibrium as transmetalation intermediates or off-cycle components in Au-to-B transmetalation reactions. If correct, these two conclusions lend additional understanding to the mechanism of previously studied organoboron-to-gold transmetalation reactions[1] according to the principle of microscopic reversibility.

The proposed transmetalation partner from the benzofuran-forming alkoxyboration reaction, *B*-trifluoroacetoxycatecholborane (Scheme 5.7, **5.16**), has not yet been included in this study owing to difficulties encountered in its independent synthesis. However, the electrophilicity of **5.16** likely lies between that of **6.2e** and **6.2f**; therefore **5.16** is also anticipated to undergo facile transmetalation with arylgold reagents, possibly in equilibrium.

Ongoing Study 2: Progress towards an Intermolecular Alkoxyboration Reaction

Because intermolecular reactions are generally more entropically and kinetically challenging than related intramolecular reactions, we reasoned that studies towards intermolecular reactivity could test the limits of the alkoxyboration reaction. It was envisioned that this route could be used in the synthesis of stereodefined enol ether boronic acid derivatives (such as **6.6**, Scheme 6.1), potentially valuable intermediates in the preparation of tetrasubstituted enol ethers. Thus, an intermolecular alkoxyboration could provide both interesting fundamental knowledge as well as a useful synthetic transformation.

Scheme 6.1. Attempted intermolecular alkoxyboration reaction of 3-hexyne.



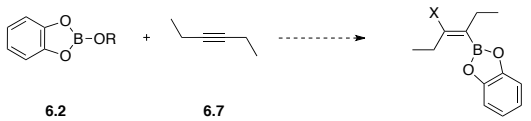
Early studies towards intermolecular alkoxyboration reactivity were inspired by results from the stoichiometric transmetalation reactions described above in Section 1. Ion pair **6.3e** was previously detected in the equilibrating transmetalation reaction between arylgold complex **6.1** and boronic ester **6.2e** (vida supra). This ion pair could potentially serve as a source of both a phenoxide nucleophile and a Lewis acidic Au cation to promote the *anti* phenoxyauration of 3-hexyne to provide **6.5**. Notably, Nolan recently disclosed a hydrophenoxylation reaction of alkynes catalyzed by Au, proposing that the transformation proceed through a similar phenoxyauration step.[4,5] Trapping of electron-rich phenoxyauration inter-

mediate **6.5** in our system with additional **6.2e** would result in the net intermolecular, *anti* addition of a B–O σ-bond across 3-hexyne to afford enol ether **6.6**.

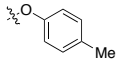
When boric ester **6.2e** was combined with a catalytic quantity of organogold complex **6.1** in neat 3-hexyne, a small amount of boronate intermediate was observable by ^{1}H and ^{11}B NMR spectroscopy (δ = 9.5 ppm, ^{11}B NMR), possibly consistent[3,6] with **6.3e**. No additional reactivity was observed upon prolonged heating. Variable temperature NMR data indicated a reversible, thermal dependence on the product distribution, suggesting that the boronate was in equilibrium with boric ester starting material **6.2e**. Generation of **6.6** from **6.3e** could plausibly face substantial kinetic or thermodynamic challenges—or both.

In order to investigate a possible thermodynamic cause for the failed reaction shown in Scheme 6.1, a series of computational experiments were conducted using density functional theory (DFT) to study the *anti* addition of catecholboric esters to 3-hexyne (Table 6.2). The data suggest that the alkoxyboration reaction is essentially neutral enthalpically for electron-rich boric esters (entries 1 and 2) and becomes more favorable for comparatively electron-poor boric esters (entries 3 and 4). This trend can readily be explained by the relative stabilization of the B empty *p* orbital through resonance;[7,8] the alkoxyboration reaction would form an electron-rich vinyl boronic acid derivative, affording an enthalpic gain associated with increased resonance stabilization of the *p* orbital when compared to electron-poor boric ester starting materials. These modest enthalpic gains are more than offset by the highly unfavorable entropic nature of an associative intermolecular

Table 6.2. Calculated thermochemical dependence of an intermolecular alkoxyboration reaction on the electronic character of the boric ester reagent.



6.2 **6.7**

Entry	OR	$\Delta H°_{calc}$ (kcal/mol)	$\Delta S°_{calc}$ (cal/[mol·K])	$\Delta G°_{calc}$ (kcal/mol)
1		- 0.5	- 43.9	+ 12.6
2		- 0.2	- 40.3	+ 11.8
3		- 5.3	- 34.6	+ 5.0
4		- 8.2	- 34.1	+ 2.0

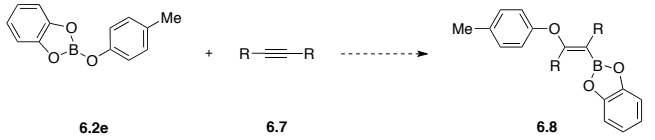
Gas phase DFT calculations were performed at the B3LYP/6-311G level of theory. Thermochemical parameters were calculated at 298.15 K and 1.000 atm.

reaction, however, and each calculated reaction was found to be thermodynamically disfavored overall. Significantly, the mechanistic hypothesis shown in Scheme 6.1 suggests that C-O bond formation could occur through Au-promoted nucleophilic addition to the alkyne in a Nolan-like[4] oxyauration step. Therefore, boric esters possessing substituents more nucleophilic at O are expected to be the more kinetically favorable alkoxyboration partners, but the desired reaction is thermodynamically disfavored for these reagents (e.g., entries 1 and 2). Conversely, boric esters with substituents less nucleophilic at O could face a greater kinetic barrier for the hypothesized oxyauration step, but the alkoxyboration reaction is more thermodynamically favorable. Thus, any potential intermolecular alkoxyboration reaction would require a careful balance of two competing parame-

ters: high substituent nucleophilicity (for kinetic competence of the reaction) and low substituent electron-donating ability (for thermodynamic viability).

Phenol-derived catechol boric esters (such as **6.2e**) were selected for additional computational investigation. We hypothesized that steric and/or electronic tuning of the internal alkyne could allow for a net exothermic alkoxyboration reaction (Table 6.3). Substitution of 3-hexyne for diphenylacetylene resulted in a substantial decrease in thermodynamic favorability (entry 2, ΔH = +9.8 kcal/mol); the optimized structure of this product indicated that steric interactions force all four olefin substituents out of conjugation with one another for R = Ph. The more electrophilic alkyne dimethyl acetylenedicarboxylate (DMAD, entry 3), was calculated to undergo a more enthalpically favorable alkoxyboration reaction than the other alkynes investigated (ΔH = -2.8 kcal/mol). Nevertheless, the free energy of the reaction remained unfavorable overall due to the large entropic component (ΔG = +10.6 kcal/mol).

Table 6.3. Calculated thermochemical dependence of an intermolecular alkoxyboration reaction on the internal alkyne employed.



6.2e **6.7** **6.8**

Entry	R	ΔH°_{calc} (kcal/mol)	ΔS°_{calc} (cal/[mol·K])	ΔG°_{calc} (kcal/mol)
1	-Et	- 0.2	- 40.3	+ 11.8
2	-Ph	+ 9.7	- 40.3	+ 21.8
3	$-CO_2Me$	- 2.8	- 45.0	+ 10.6

Gas phase DFT calculations were performed at the B3LYP/6-311G level of theory. Thermochemical parameters were calculated at 298.15 K and 1.000 atm.

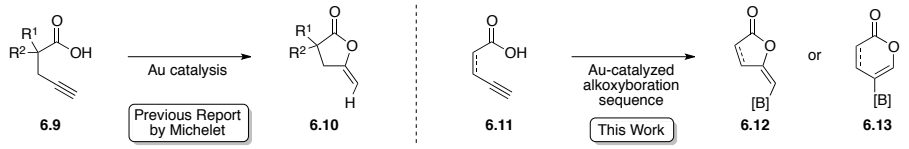
Thus, a general intermolecular alkoxyboration faces significant challenges. The potential reactions examined through DFT calculations were found to be thermodynamically disfavored; substituent manipulations affected modest variations in Δ*H*, but these variations were insufficient to overcome the uniformly large negative Δ*S*. DFT calculations suggested the *thermodynamic* unfavorability of such a reaction would be minimized with electron-poor boric esters. However, these same boric esters are inherently less nucleophilic and therefore may suffer from an increased *kinetic* challenge, which could arise from a requirement for the boron substituent to act as a nucleophile in the proposed alkyne-attack mechanism. Overall, these calculations indicate that the successful catalytic benzofuran-forming alkoxyboration reaction (Chapter 5) was enabled by a small enthalpic difference between the B–O σ bond of the starting materials and the B–C σ bond of the products, as well by as the comparatively low entropic cost of intramolecular reactivity. It is possible that an intermolecular alkyne alkoxyboration may yet be realized. Strained cyclic alkynes, for example, or other specialized systems might favor this reaction. To date, however, no such successful reactions have been found.

Ongoing Study 3: Intramolecular Alkoxyboration Reaction of Alkynyl Carboxylic Acids (Carboxyboration) to form Lactone Boronic Acid Derivatives

In light of the challenges encountered in developing an intermolecular variant of the alkoxyboration reaction, attention was turned to expanding the scope of intramolecular reactivity. Inspired by Michelet's 2006 disclosure of the Au-

catalyzed intramolecular *anti* addition of carboxylic acids to alkynes,[9] a lactone-forming borylation reaction was envisioned (Scheme 6.2). The resulting lactone boronic acid derivatives could potentially be useful intermediates in the synthesis of lactone-containing natural products, such as members of the eremophilanolide class of terpenoids.[10]

Scheme 6.2. Comparison between previously-reported Au-catalyzed lactone formation and this work for Au-catalyzed lactone-forming carboxyboration.

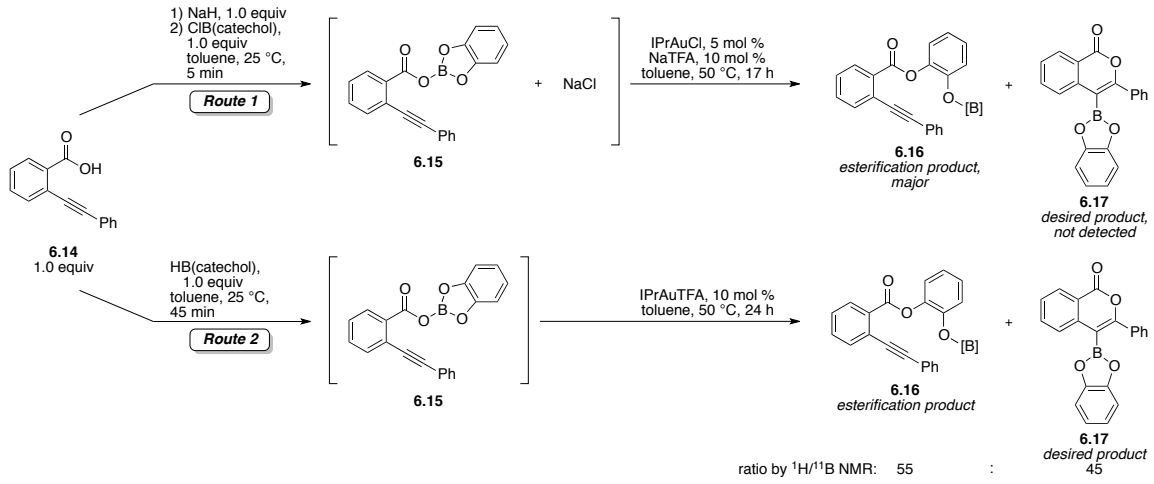


This reaction could proceed through a B–O σ-bond activation mechanism similar to the alkoxyboration reaction (Chapter 5). In order to highlight this similarity while also maintaining technical accuracy, we have termed this transformation a *carboxyboration* reaction. Significantly, the vinylboron products **6.12** and **6.13** would both be electron rich at B by resonance versus an aliphatic organoboron compound, therefore satisfying the design criteria outlined in Chapter 4 for an electron-rich vinylboron product.

Preliminary studies of the carboxyboration reaction were conducted with a 2-alkynylbenzoic acid derivatives (Scheme 6.3). Two routes to form the requisite boric ester intermediate **6.15** were investigated. The first route made use of the conditions previously established for the benzofuran-forming reaction: deprotonation by NaH followed by trapping with *B*-chlorocatecholborane (Route 1). Addition

of pre-formed IPrAuTFA and mild heating fully consumed **6.15**, but no desired carboxyboration product **6.17** was detected in the reaction mixture; esterification

Scheme 6.3. Chemoselectivity in the Au-catalyzed carboxyboration reaction of a 2-alkynyl benzoic acid derivative.



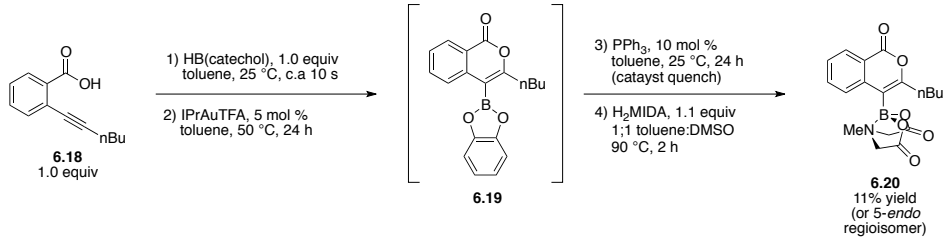
product **6.16** was instead observed as the major product. Hydrolysis of the B–O bond during silica gel chromatography allowed for unambiguous characterization of this major product via characterization of the corresponding catechol monobenzoate ester (6.16 with [B] replaced by H).

This esterification reactivity is related to a previous report by Ganem detailing the intermolecular amidation of carboxylic acids through the reaction of catecholboric ester intermediates similar to **6.15** and primary or secondary amines.[11] Reasoning that a similar esterification pathway may have been promoted in our system by the oxophilic Na(I) present in the reaction mixture, Na-free conditions were examined (Route 2). The acidity of carboxylic acid **6.14** was harnessed to develop these Na-free conditions. Specifically, the greater acidity of

6.14 than the alkynylphenols from Chapter 5 permitted deprotonation by catecholborane. Catecholborane thus served as a source of both a hydride base and a boron electrophile to furnish **6.15** without the need for exogenous base.

Treatment of intermediate **6.15**, now in the absence of NaCl, with catalytic IPrAuTFA affected full conversion to a 45:55 mixture of desired carboxyboration product **6.17** as the minor product with esterification product **6.16**. Continued heating at 50 °C resulted in slow conversion of **6.16** into additional **6.17**, stalling after 72 h at a 40:60 mixture favoring **6.17**. This kinetic profile suggests two interesting features: (1) conversion of boric ester **6.15** is kinetically controlled; and (2) the *major* mechanistic pathway to carboxyboration product **6.17** *does not* proceed through esterification product **6.16**. Selectivity for the 6-*endo* vs. 5-*exo*-regioisomer of **6.17** has not yet been determined. However, only a single regioisomer was formed under these conditions.

Scheme 6.4. Proof-of-concept isolation of a carboxyboration product.

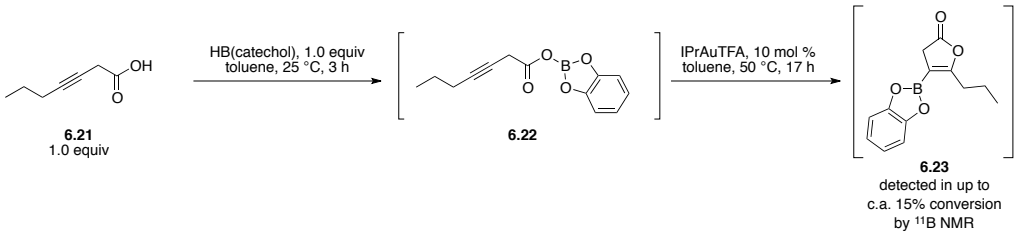


Reaction sequence performed by Kim Tu.

In order to confirm the carboxyboration reactivity detected by NMR spectroscopy, graduate student Kim Tu examined a carboxyboration reaction with the goal of derivatization and product isolation (Scheme 6.4). Use of aliphatic alkynyl

benzoic acid **6.18** afforded catecholboronic ester carboxyboration product **6.19**, which was subsequently converted into the corresponding MIDA boronate in 11% isolated yield. A higher yield could likely be realized by allowing the boric ester to preform for a greater period of time prior to the addition of IPrAuTFA. The mass balance in this reaction was largely attributed to a competitive, B-free, Au-catalyzed cyclization reaction of **6.18** that transfers proton rather than boron, similar to Michelet's B-free report.[8] As was observed with Ph-substituted derivative **6.17**, high regioselectivity was observed in the synthesis of **6.20**, but the regiochemistry of product **6.20** has not yet been unambiguously assigned. Scheme 6.4 shows the 6-*exo* regioisomer for clarity, but the 5-*endo* regioisomer is a possible alternative product.

Scheme 6.5. Carboxyboration in an acyclic alkynoic acid.



6.21
1.0 equiv

6.22

6.23
detected in up to
c.a. 15% conversion
by ^{11}B NMR

A preliminary investigation into the substrate scope of the carboxyboration reaction has commenced, and acyclic alkynoic acids (e.g., **6.21**) are an interesting, challenging substrate class owing to their lack of conformational bias towards cyclization (Scheme 6.5). The reaction of 3-heptynoic acid (**6.21**) with catecholborane provided boric ester intermediate **6.22**, and the addition of catalytic IPrAuTFA effected slow conversion to a complex mixture of products. Analysis of

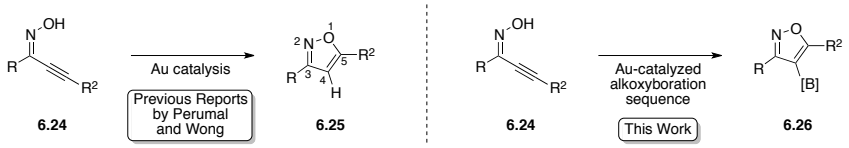
this mixture by ^{11}B NMR spectroscopy indicated the formation of a minor boronic ester product (δ = 30.0 ppm), possibly consistent with carboxyboration product **6.23**.

These preliminary results indicate that the Au-catalyzed carboxyboration reaction allows for the synthesis of lactone boronic acid derivatives. Continuing work will optimize the reaction conditions to further minimize the formation of esterification products such as **6.16** as part of the substrate scope expansion of this transformation.

Ongoing Study 4: Intramolecular Oxyboration Reaction of Alkynyl Oximes to form Isoxazole Boronic Acid Derivatives

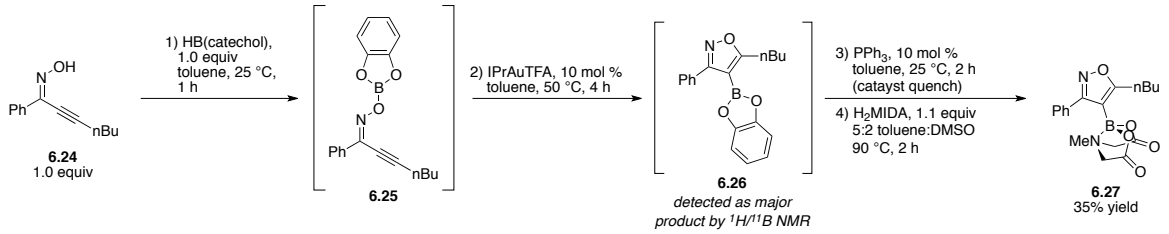
Concurrent with the investigation of the lactone-forming carboxyboration reaction, additional borylation substrate classes were also studied. Inspired by previous reports of Au-catalyzed reactions to form 4-unsubstituted isoxazoles,[12,13] an isoxazole-forming oxyboration reaction was envisioned (Scheme 6.6). As with the benzofuran-forming alkoxyboration reaction and the carboxyboration reaction, the 4-position of the isoxazole ring is electron-rich by resonance into the empty p orbital on boron in **6.26**; therefore, the this oxyboration reaction also satisfies the design requirement previously detailed in Chapter 4. We envisioned that the resulting boronic acid derivatives could be useful intermediates in the synthesis of lactone-containing pharmaceuticals, such as the COX-2 inhibitor Valdecoxib.[14]

Scheme 6.6. Comparison between previously-reported Au-catalyzed isoxazole formation and this work for Au-catalyzed isoxazole-forming alkoxyboration.



Oxime **6.24** was found to undergo facile boric ester formation when reacted with catecholborane (Scheme 6.7). Upon addition of a catalytic quantity of IPrAuTFA and mild heating, boric ester intermediate **6.25** underwent rapid, very clean conversion to borylated isoxazole **6.26**, which was converted to the corresponding MIDA boronate **6.27** under standard conditions in 35% isolated yield in one pot from **6.24**. Graduate student Kim Tu is currently conducting an optimization study and exploring the substrate scope of the isoxazole-forming alkoxyboration reaction.

Scheme 6.7. Proof-of-concept alkoxyboration reaction with an alkynyl oxime.



Conclusions

Formal activation of the B–O σ-bond for intramolecular reactivity using Au catalysis appears to be a general phenomenon extendable beyond the benzo-

furan-forming alkoxyboration reaction discussed in Chapter 5. Two additional substrate classes have already been discovered: an isoxazole-forming alkoxyboration reaction of alkynyl oximes and a lactone-forming carboxyboration reaction of alkynoic acids. The stoichiometric B/Au transmetalation study has indicated that a possible mechanistic step in these reactions, an organogold-to-boron transmetalation reaction, requires a sufficiently electrophilic B reagent and is reversible under some conditions. Further inquiry regarding the mechanism, scope, and limitations of these reactions is currently being conducted by members of the Blum group.

References

1. Stoichiometric transmetalation from an organoboron reagent to Au(I) has been reported, but not the reverse reaction prior to our report. For select examples, see: (a) Sladek, A.; Hofreiter, S.; Paul, M.; Schmidbaur, H. *J. Organomet. Chem.* **1995**, *501*, 47–51. (b) Forward, J. M.; Fackler, J. P. Jr.; Staples, R. J. *Organometallics* **1995**, *14*, 4194–4198. (c) Partyka, D. V.; Zeller, M.; Hunter, A. D.; Gray, T. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 8188–8191. (d) Partyka, D. V.; Zeller, M.; Hunter, A. D.; Gray, T. G. *Inorg. Chem.* **2012**, *51*, 8394–8401. (e) Lenker, H. K.; Gray, T. G.; Stockland, R. A. Jr. *Dalton Trans.* **2012**, *41*, 13274–13276.
2. Beckett, M. A.; Strickland, G. C.; Holland, J. R.; Varma, K. S. *Polymer* **1996**, *37*, 4629–4631.
3. Nöth, H.; Wrackmeyer, B. Nuclear Magnetic Resonance Spectroscopy of Boron Compounds. In *NMR: Basic Principles and Progress*; Diehl, P., Fluck, E.,

Kosfeld, R. Eds.; Springer-Verlag: Berlin, 1978; Vol. 14.

4. Oonishi, Y.; Gómez-Suárez, A.; Martin, A. R.; Nolan, S. P. *Angew. Chem. Int. Ed.* **2013**, *52*, 9767–9771.
5. Richard, M. E.; Fraccica, D. V.; Garcia, K. J.; Miller, E. J.; Ciccarelli, R. M.; Holahan, E. C.; Resh, V. L.; Shah, A.; Findeis, P. M.; Stockland, R. A. Jr. *Beilstein J. Org. Chem.* **2013**, *9*, 2002–2008.
6. This ^{11}B NMR signal (here in neat, protiated 3-hexyne) is suggestive of a boronate intermediate but does not match the spectral data from the stoichiometric transmetalation experiments, which were conducted at a higher concentration in d_8-toluene.
7. Good, C. D.; Ritter, D. M. *J. Am. Chem. Soc.* **1962**, *84*, 1162–1166.
8. Schulman, J. M.; Disch, R. L. *Organometallics* **1989**, *8*, 733–737.
9. Genin, E.; Toullec, P. Y.; Antoniotti, S.; Brancour, C.; Genêt, J.-P.; Michelet, V. *J. Am. Chem. Soc.* **2006**, *128*, 3112–3113.
10. a) Tori, M.; Shiotani, Y.; Tanaka, M.; Nakashima, K.; Sono, M. *Tetrahedron Lett.* **2000**, *41*, 1797–1799. b) Bardón, A.; Mitre, G. B.; Kamiya, N.; Toyota, M.; Asakawa, Y. *Phytochemistry* **2002**, *59*, 205–213.
11. Collum, D. B.; Chen, S.-C.; Ganem, B. *J. Org. Chem.* **1978**, *43*, 4393–4394.
12. Praveen, C.; Kalyanasundaram, A; Perumal, P. T. *Synlett* **2010**, *5*, 777–781.
13. Kung, K. K.-Y.; Lo, V. K.-Y.; Ko, H.-K.; Li, G.-L.; Chan, P.-Y.; Leung, K.-C.; Zhou, Z.; Wang, M.-Z.; Che, C.-M.; Wong, M.-K. *Adv. Synth. Catal.* **2013**, *355*, 2055–207.
14. Talley, J. J.; Brown, D. L.; Carter, J. S.; Graneto, M. J.; Koboldt, C. M.; Mas-

ferrer, J. L.; Perkins, W. K.; Rogers, R. S.; Shaffer, A. F.; Zhang, Y. Y.; Zweifel, B. S.; Seibert, K. *J. Med. Chem.* **2000**, *43*, 775–777.

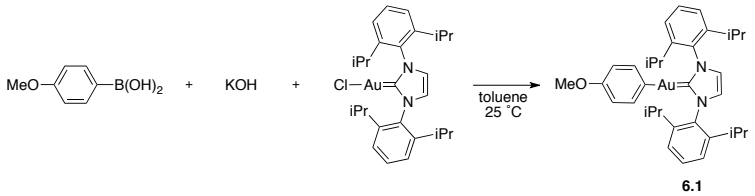
Experimental

General Considerations

All chemicals were used as received from commercial sources unless otherwise noted. Sodium trifluoroacetate was dried at 130 °C at 10 mTorr for 18 h before use. Neat catecholborane was distilled under reduced pressure and stored under N_2 atmosphere at -35 °C. Toluene was purified by passage through an alumina column under argon pressure on a push-still solvent system. Anhydrous dimethylsulfoxide was obtained by stirring over activity I alumina 18 h under N_2 atmosphere, decanting the liquid, and distilling at 10 Torr over CaH_2. Anhydrous 3-hexyne was obtained by distillation over CaH_2 under N_2 atmosphere. Toluene-d_8 was dried over CaH_2, degassed using three freeze-pump-thaw cycles, and vacuum transferred prior to use. Commercially available boric esters were distilled over Na^0 and stored under N_2 atmosphere at -35 °C. All manipulations were conducted in a glovebox under nitrogen atmosphere or using standard Schlenk techniques unless otherwise specified. Analytical thin layer chromatography (TLC) was performed using Merck F_{250} plates. Plates were visualized under UV irradiation (254 nm) and/or using a basic aqueous solution of potassium permanganate. Flash chromatography was conducted using a Teledyne Isco Combiflash® Rf 200 Automated Flash Chromatography System, and Teledyne Isco Redisep® 35–70 μm silica gel. All proton and carbon nuclear magnetic resonance (^1H and ^{13}C NMR) spectra were recorded on a Bruker DRX-400 spectrometer, Bruker DRX-

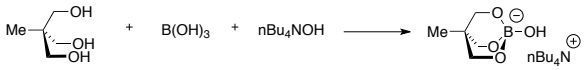
500 spectrometer outfitted with a cryoprobe, or a Bruker AVANCE-600 spectrometer. All boron nuclear magnetic resonance (^{11}B NMR) spectra were recorded on a Bruker AVANCE-600 spectrometer. All fluorine nuclear magnetic resonance (^{19}F NMR) spectra were recorded on a Bruker DRX-400. All chemical shifts (δ) are reported in parts per million (ppm) downfield of tetramethylsilane, and referenced to the residual protiated solvent peak (δ = 7.26 ppm for $CDCl_3$, δ = 2.50 ppm for d_6-DMSO, or δ = 1.94 ppm for CD_3CN in ^{1}H NMR spectroscopy experiments; δ = 77.16 ppm for $CDCl_3$, δ = 39.52 ppm for d_6-DMSO, or δ = 1.34 ppm for CD_3CN in ^{13}C NMR spectroscopy experiments). ^{11}B and ^{19}F NMR spectroscopy experiments are referenced to the absolute frequency of 0 ppm in the ^{1}H dimension according to the Xi scale. NMR spectra for new compounds and variable temperature transmetalation studies are located in Appendix A. Low- and high-resolution mass spectrometry data were obtained at the University of California, Irvine.

Synthesis of Transmetalation Partners



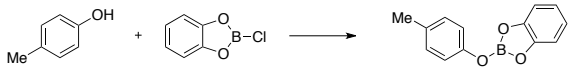
6.1

IPrAuO(4-OMePh) (6.1). Au phenoxide complex **6.1** was prepared from IPrAuCl according to a literature procedure[1] in 63% yield. ^{1}H NMR (d_8-toluene, 400 MHz) δ 7.27 (d, J = 6.5 Hz, 2H), 7.20 (t, J = 6.7 Hz, 2H), 7.09–7.05 (m, 4H), 6.73 (d, J = 6.6 Hz, 2H), 6.40 (s, 2H), 3.34 (s, 3H), 2.68 (br m, 4H), 1.46 (d, J = 5.5 Hz, 12 H), 1.11 (d, J = 5.6 Hz, 12 H).



6.2a

Tetrabutylammonium 1-hydroxy-4-methyl-2,6,7-trioxa-1-borabicyclo[2.2.2]octan-1-uide (6.2a). Triol borate **6.2a** was prepared using a procedured adapted from the synthesis of the corresponding Na salt.[2] A 20 mL vial was charged with boric acid (180 mg, 2.9 mmol, 1.0 equiv) and water (1 mL). Tetra-*n*-butylammonium hydroxide (1.7 g of 44 wt % aq solution, 2.9 mmol, 1.0 equiv) and 1,1,1-tris(hydroxymethyl)ethane (350 mg, 2.9 mmol, 1.0 equiv) were added, and the reaction mixture was heated in a preheated 100 °C oil bath for 30 min. Volatiles were removed in vacuo, and 250 the mg of resulting white powder was purified by reverse-phase silica gel chromatography eluting using a gradient from 100% water to 100% MeCN. Volatiles were removed in vacuo at 30 °C and ca. 10 mTorr overnight to afford 50 mg **6.2a** as a white powder (20% recovery). This salt exhibits a temperature- and solvent-dependent equilibrium with a dimer and higher order oligomers[3] that obfuscates analysis by NMR spectroscopy.



6.2e

2-(p-tolyloxy)benzo[*d*][1,3,2]dioxaborole (6.2e). A flame-dried 100 mL Schlenk tube with a stirbar under a dynamic N_2 atmosphere was charged with *B*-chlorocatecholborane (810 mg, 5.3 mmol, 1.0 equiv) and anhydrous DCM (7.5

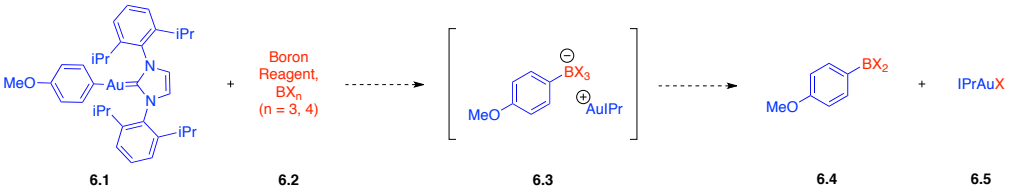
mL). The reaction vessel was equipped with a 25 °C water bath to control any potential exotherm, and a solution of *p*-cresol (570 mg, 5.3 mmol, 1.0 equiv) in anhydrous DCM (7.5 mL) was added dropwise over 5 min. The resulting solution was stirred at 25 °C for 50 min before being concentrated in vacuo using Schlenk techniques. To the resulting oily residue was added anhydrous pentane (10 mL), and the solution was again concentrated to afford a viscous, pale yellow oil that solidified upon storage at -35 °C for 18 h. Boric ester **6.2e** was obtained as a cream-colored solid in 81% yield (970 mg).

^{1}H NMR (anhydrous CD_2Cl_2, 600 MHz): δ 7.20 (br d, *J* = 8.0 Hz, 2H), 7.17 (dd, *J* = 5.7, 3.4 Hz, 2H), 7.13 (br d, *J* = 7.3 Hz, 2H), 7.08 (dd, *J* = 5.8, 3.4 Hz, 2H), 2.36 (s, 3H).

^{11}B NMR (anhydrous CD_2Cl_2, 193 MHz): δ 22.7 (br s).

^{13}C NMR (anhydrous CD_2Cl_2, 125 MHz): δ 150.6, 148.1, 134.4, 130.5, 123.0, 119.6, 112.4, 20.8.

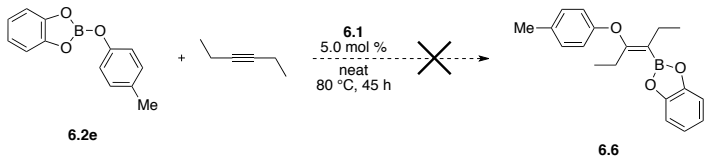
<u>General Procedure for Organogold-to-Boron Transmetalation Study</u>



All stoichiometric transmetalation reactions were set up in a N_2-filled glovebox. A solution of boric ester **6.2** (17 μmol, 1.0 equiv) in anhydrous d_8-toluene (0.5 mL) was added to a dram vial containing organogold complex **6.1** (12 mg, 17 μmol). The resulting solution was mixed well and then transferred to a

J. Young NMR tube for observation. For reactions conducted at elevated temperatures, the NMR tube was heated in a preheated oil bath as indicated. Particularly useful in the analysis of the resulting mixtures were diagnostic chemical shifts observable by ^{11}B NMR spectroscopy: δ 33 ~ 31 ppm for boronic esters such as **6.4e**, δ 23 ~ 18 ppm for boric esters such as **6.2c**, δ 10 ~ 0 ppm for mixed borates or boronates such as **6.3e** and **6.4f**.[4]

Procedure for Attempted Intermolecular Alkoxyboration



Organogold complex **6.1** (2.4 mg, 3.4 μmol, 5.0 mol %) was dissolved in 3-hexyne (0.77 mL, 560 mg, 6.8 mmol, 1$\bar{0}$0 equiv). The resulting solution was added to a dram vial containing boric ester **6.2e** (15 mg, 68 μmol, 1.0 equiv) and mixed well to afford a turbid, cream-colored suspension, which was tranferred to a J. Young NMR tube. The NMR tube was removed from the glovebox and heated in a preheated 80 °C oil bath for 45 h. The mixture was periodically monitored by deuterium-free ^{1}H and ^{11}B NMR spectroscopy, which failed to indicate any formation of **6.6**.

General Procedure for Densitiy Functional Theory (DFT) Calculations

Thermochemical data for compounds **4.24**–**4.27** were obtained for optimized geometries of each molecule. Structures were first modeled using

Avogadro[5] 1.1.1 and optimized using UFF molecular mechanics. Each structure was then further optimized in the gas phase using Gaussian 09[6] using density functional theory (DFT) calculations using the B3LYP functional[7,8] and the 6-311G basis set.[9] Thermochemical data were calculated at the same level of theory at a temperature of 298.15 K and a pressure of 1.000 atm.

Cartesian Coordinates for Optimized Structures from Tables 6.2 and 6.3

Table 6.2, 3-hexyne.

Atom	*x (Å)*	*y (Å)*	*z (Å)*	*Atom*	*x (Å)*	*y (Å)*	*z (Å)*
C	0.5655	0.2074	-0.0806	H	3.9938	-0.0401	0.1189
C	0.5655	0.2074	-0.0806	H	2.9008	-1.1863	-0.6756
C	-1.9488	-0.6823	-0.0769	C	-2.9782	0.4446	0.1223
C	1.9488	0.6824	-0.0770	H	-2.0699	-1.4315	0.7141
C	2.9782	-0.4446	0.1224	H	-2.1543	-1.2022	-1.0198
H	2.0700	1.4316	0.7139	H	-2.8149	0.9557	1.0736
H	2.1544	1.2022	-1.0199	H	-3.9938	0.0400	0.1189
H	2.8148	-0.9556	1.0737	H	-2.9009	1.1862	-0.6757

Table 6.2, entry 1, boric ester.

Atom	*x (Å)*	*y (Å)*	*z (Å)*	*Atom*	*x (Å)*	*y (Å)*	*z (Å)*
C	-2.3627	0.2713	0.0000	H	0.5698	2.9057	0.0000
C	-1.0344	-0.1048	0.0000	O	-0.4857	-1.4028	0.0000
C	-2.6266	1.6519	0.0000	O	1.2351	0.1491	0.0000
C	-1.5882	2.5925	0.0000	B	0.9130	-1.2297	0.0000
C	-0.2406	2.1924	0.0000	O	1.7958	-2.2425	0.0000
C	0.0000	0.8330	0.0000	C	3.2428	-2.0742	0.0000
H	-3.1528	-0.4643	0.0000	H	3.6697	-3.0713	0.0000
H	-3.6526	1.9923	0.0000	H	3.5615	-1.5319	0.8895
H	-1.8249	3.6473	0.0000	H	3.5615	-1.5319	-0.8895

Table 6.2, entry 1, alkoxyboration product.

Atom	*x (Å)*	*y (Å)*	*z (Å)*	*Atom*	*x (Å)*	*y (Å)*	*z (Å)*
C	-2.2617	-0.2753	-0.2754	B	0.1962	0.3395	-0.1887
C	-1.2852	0.6717	-0.2629	O	0.8277	-0.9354	-0.0984
O	-3.5787	0.2040	-0.2546	O	1.2122	1.3338	-0.2042
C	-1.6577	2.1527	-0.2775	C	2.4463	0.6681	-0.1262
C	-1.9217	2.7214	1.1324	C	2.2162	-0.7058	-0.0632
H	-0.8494	2.7200	-0.7417	C	3.7223	1.1986	-0.1099
H	-2.5506	2.2922	-0.8879	C	4.7841	0.2824	-0.0264
H	-1.0409	2.6142	1.7691	C	4.5519	-1.0986	0.0364
H	-2.7542	2.2009	1.6074	C	3.2477	-1.6213	0.0186
H	-2.1697	3.7846	1.0811	H	3.0554	-2.6828	0.0663
C	-2.0727	-1.7696	-0.2140	H	3.8865	2.2646	-0.1594
C	-2.3353	-2.3481	1.1954	H	5.7999	0.6521	-0.0104
H	-2.7291	-2.2587	-0.9392	H	5.3913	-1.7770	0.0999
H	-1.0541	-2.0075	-0.5054	C	-4.6894	-0.6172	-0.7175
H	-1.6189	-1.9393	1.9084	H	-4.5586	-0.9035	-1.7625
H	-2.2239	-3.4338	1.1866	H	-5.5617	0.0216	-0.6239
H	-3.3376	-2.1117	1.5565	H	-4.8245	-1.5068	-0.1025

Table 6.2, entry 2, boric ester.

Atom	*x (Å)*	*y (Å)*	*z (Å)*	*Atom*	*x (Å)*	*y (Å)*	*z (Å)*
C	2.4624	3.6339	0.0000	C	-1.7756	-0.7865	0.0000
C	1.6847	2.4931	0.0000	C	-3.1627	-0.8935	0.0000
C	3.8550	3.4454	0.0000	C	-0.9656	-1.9229	0.0000
C	4.4177	2.1622	0.0000	C	-1.5726	-3.1801	0.0000
C	3.6113	1.0110	0.0000	C	-2.9689	-3.3245	0.0000
C	2.2463	1.2158	0.0000	C	-3.7501	-2.1594	0.0000
H	2.0157	4.6166	0.0000	C	-3.6040	-4.6970	0.0000
H	4.5036	4.3103	0.0000	H	-4.6923	-4.6295	0.0000
H	5.4931	2.0522	0.0000	H	-3.3084	-5.2743	0.8799
H	4.0309	0.0164	0.0000	H	-3.3084	-5.2743	-0.8799
O	0.2800	2.3823	0.0000	H	-0.9455	-4.0632	0.0000
O	1.2042	0.2609	0.0000	H	0.1090	-1.8256	0.0000
B	0.0000	1.0027	0.0000	H	-4.8295	-2.2412	0.0000
O	-1.2564	0.5200	0.0000	H	-3.7585	0.0074	0.0000

Table 6.2, entry 2, alkoxyboration product.

Atom	*x (Å)*	*y (Å)*	*z (Å)*	*Atom*	*x (Å)*	*y (Å)*	*z (Å)*
C	0.6070	0.1864	0.4131	C	-3.7362	-0.9209	0.0052
C	-0.4436	0.9185	-0.0302	C	-5.4045	0.6147	-0.8646
O	1.8409	0.8733	0.5482	C	-6.3501	-0.4076	-0.6815
C	3.0589	0.3089	0.1178	C	-5.9819	-1.6579	-0.1645
C	4.1838	0.5485	0.9063	C	-4.6522	-1.9383	0.1916
C	5.4277	0.0790	0.4859	H	-4.3556	-2.8966	0.5910
C	5.5704	-0.6389	-0.7133	H	-5.6738	1.5817	-1.2621
C	4.4227	-0.8576	-1.4888	H	-7.3824	-0.2247	-0.9455
C	3.1706	-0.3856	-1.0864	H	-6.7348	-2.4230	-0.0364
H	4.0713	1.1060	1.8250	H	0.7480	2.5020	-0.8634
H	6.2998	0.2714	1.0984	C	-0.4370	3.3615	0.7236
H	4.5073	-1.3948	-2.4251	H	-0.9690	2.6186	-1.2328
H	2.2980	-0.5388	-1.7063	H	0.2953	3.1685	1.5086
C	6.9194	-1.1703	-1.1438	H	-1.4360	3.2754	1.1559
H	7.7162	-0.4540	-0.9354	H	-0.3078	4.3917	0.3834
H	6.9382	-1.3873	-2.2125	C	0.6113	-1.2284	0.9288
H	7.1699	-2.0964	-0.6177	C	0.7786	-1.2918	2.4636
C	-0.2515	2.3744	-0.4476	H	1.4262	-1.7863	0.4611
B	-1.8674	0.3712	-0.0976	H	-0.3170	-1.7149	0.6433
O	-2.3525	-0.9128	0.2698	H	1.7096	-0.8220	2.7822
O	-2.9586	1.1372	-0.5826	H	0.7907	-2.3309	2.7971
C	-4.1014	0.3221	-0.5094	H	-0.0479	-0.7841	2.9627

Table 6.2, entry 3, boric ester.

Atom	*x (Å)*	*y (Å)*	*z (Å)*	*Atom*	*x (Å)*	*y (Å)*	*z (Å)*
O	1.3447	0.4301	0.0000	H	2.8450	-3.9670	0.0000
B	0.0000	0.8333	0.0000	H	0.4989	-4.7234	0.0000
C	1.3209	-0.9814	0.0000	H	-1.3808	-3.0624	0.0000
C	-0.0057	-1.4103	0.0000	O	-0.3297	2.1622	0.0000
O	-0.8514	-0.2772	0.0000	C	-1.5792	2.8016	0.0000
C	2.3792	-1.8683	0.0000	O	-2.6315	2.1838	0.0000
C	2.0503	-3.2342	0.0000	C	-1.4295	4.2917	0.0000
C	0.7160	-3.6645	0.0000	H	-0.3862	4.5874	0.0000
C	-0.3484	-2.7474	0.0000	H	-1.9291	4.7040	0.8774
H	3.4021	-1.5234	0.0000	H	-1.9291	4.7040	-0.8774

Table 6.2, entry 3, alkoxyboration product.

Atom	*x (Å)*	*y (Å)*	*z (Å)*	*Atom*	*x (Å)*	*y (Å)*	*z (Å)*
C	-1.7058	-0.3114	0.0598	O	1.3840	-0.9465	0.0525
C	-0.7537	0.6400	-0.0417	C	2.7707	-0.7106	-0.0389
C	-1.1186	2.1212	-0.0967	C	2.9815	0.6564	-0.2096
C	-1.1748	2.7703	1.3018	C	4.2486	1.1943	-0.3310
H	-2.0836	2.2446	-0.5883	C	5.3216	0.2899	-0.2733
H	-0.3785	2.6467	-0.7017	C	5.1086	-1.0854	-0.1016
H	-1.9315	2.2871	1.9212	C	3.8134	-1.6151	0.0196
H	-1.4222	3.8315	1.2246	H	4.3981	2.2552	-0.4638
H	-0.2125	2.6886	1.8109	H	6.3318	0.6639	-0.3639
C	-1.5650	-1.8027	0.1663	O	-3.0601	0.1549	0.1984
C	-2.0311	-2.3556	1.5309	C	-4.0663	-0.2079	-0.6961
H	-0.5246	-2.0704	0.0034	O	-3.8600	-0.8634	-1.7125
H	-2.1477	-2.2626	-0.6344	C	-5.3877	0.3278	-0.2370
H	-3.0751	-2.1102	1.7301	H	-6.1543	0.0664	-0.9597
H	-1.4276	-1.9474	2.3434	H	-5.3386	1.4111	-0.1257
H	-1.9311	-3.4420	1.5471	H	-5.6441	-0.0864	0.7387
B	0.7424	0.3111	-0.0695	H	3.6356	-2.6718	0.1511
O	1.7349	1.3083	-0.2307	H	5.9573	-1.7539	-0.0621

Table 6.2, entry 4, boric ester.

Atom	*x (Å)*	*y (Å)*	*z (Å)*	*Atom*	*x (Å)*	*y (Å)*	*z (Å)*
O	-1.3755	1.0432	0.0000	H	-1.4335	5.6909	0.0000
B	-0.2262	0.2577	0.0000	H	1.0302	5.6802	0.0000
C	-0.9140	2.3824	0.0000	H	2.3023	3.5185	0.0000
C	0.4798	2.3775	0.0000	O	-0.3113	-1.1216	0.0000
O	0.9289	1.0317	0.0000	C	0.6538	-2.0812	0.0000
C	-1.6458	3.5525	0.0000	O	1.8558	-1.9072	0.0000
C	-0.9070	4.7471	0.0000	C	0.0432	-3.4842	0.0000
C	0.4954	4.7412	0.0000	F	-1.3371	-3.5017	0.0000
C	1.2233	3.5399	0.0000	F	0.4798	-4.1792	1.1234
H	-2.7250	3.5427	0.0000	F	0.4798	-4.1792	-1.1234

Table 6.2, entry 4, alkoxyboration product.

Atom	*x (Å)*	*y (Å)*	*z (Å)*	*Atom*	*x (Å)*	*y (Å)*	*z (Å)*
C	-0.8131	-0.4190	0.0526	O	2.2731	-0.9551	0.0422
C	0.0943	0.5700	-0.0359	C	3.6552	-0.6832	-0.0531
C	-0.3178	2.0388	-0.0725	C	3.8290	0.6895	-0.2169
C	-0.3293	2.6812	1.3307	C	5.0803	1.2622	-0.3408
H	-1.3070	2.1390	-0.5173	C	6.1763	0.3858	-0.2928
H	0.3811	2.5847	-0.7075	C	6.0005	-0.9959	-0.1276
H	-1.0509	2.1827	1.9790	C	4.7208	-1.5608	-0.0038
H	-0.6048	3.7353	1.2638	H	5.2013	2.3273	-0.4681
H	0.6544	2.6218	1.8001	H	7.1758	0.7865	-0.3856
C	-0.6534	-1.9058	0.1599	O	-2.2001	0.0138	0.1806
C	-1.1708	-2.4729	1.5007	C	-3.1656	-0.3799	-0.6854
H	0.3998	-2.1466	0.0417	O	-3.0337	-1.0319	-1.7087
H	-1.1855	-2.3797	-0.6686	C	-4.5110	0.1338	-0.1749
H	-2.2272	-2.2502	1.6548	F	-5.5298	-0.1889	-1.0487
H	-0.6129	-2.0563	2.3404	F	-4.5011	1.5173	-0.0213
H	-1.0492	-3.5566	1.5160	F	-4.8166	-0.4274	1.0642
B	1.6046	0.2849	-0.0693	H	4.5720	-2.6225	0.1228
O	2.5632	1.3082	-0.2290	H	6.8668	-1.6415	-0.0953

Table 6.3, entry 2, alkyne starting material (diphenylacetylene).

Atom	*x (Å)*	*y (Å)*	*z (Å)*	*Atom*	*x (Å)*	*y (Å)*	*z (Å)*
C	-0.3770	1.6064	-0.0902	H	-4.5227	0.3978	-1.7010
C	0.8362	1.5618	-0.1054	H	-2.0494	0.3049	-1.7309
C	-1.8020	1.6592	-0.0727	C	3.0213	2.2521	0.8051
C	2.2612	1.5090	-0.1231	C	4.4135	2.1970	0.7847
C	-2.4817	2.4547	0.8743	C	5.0750	1.4035	-0.1574
C	-3.8741	2.5040	0.8876	C	4.3331	0.6627	-1.0825
C	-4.6158	1.7644	-0.0386	C	2.9407	0.7121	-1.0691
C	-3.9540	0.9722	-0.9818	H	6.1559	1.3629	-0.1706
C	-2.5619	0.9172	-1.0020	H	4.8397	0.0469	-1.8139
H	-1.9074	3.0260	1.5903	H	2.5090	2.8655	1.5332
H	-4.3808	3.1187	1.6198	H	4.9823	2.7723	1.5031
H	-5.6967	1.8049	-0.0256	H	2.3662	0.1398	-1.7842

Table 6.3, entry 2, alkoxyboration product.

Atom	*x (Å)*	*y (Å)*	*z (Å)*	*Atom*	*x (Å)*	*y (Å)*	*z (Å)*
C	-0.5547	-0.1044	-0.5511	H	0.9900	-3.9993	1.4965
C	0.4066	0.8183	-0.3000	H	0.0306	-5.4421	-0.2827
O	-1.8189	0.3241	-1.0197	C	0.1621	2.2942	-0.3138
C	-3.0032	-0.0040	-0.3197	C	0.7449	3.1090	0.6779
C	-4.1762	-0.0434	-1.0732	C	-0.6134	2.9141	-1.3128
C	-5.3883	-0.3037	-0.4376	C	-0.8107	4.2954	-1.3075
C	-5.4522	-0.5333	0.9479	C	-0.2417	5.0896	-0.3083
C	-4.2569	-0.4818	1.6766	C	0.5368	4.4892	0.6839
C	-3.0327	-0.2152	1.0558	H	0.9859	5.0932	1.4617
H	-4.1247	0.1362	-2.1375	H	1.3574	2.6566	1.4443
H	-6.2979	-0.3308	-1.0250	H	-1.4089	4.7507	-2.0861
H	-4.2783	-0.6451	2.7467	H	-0.3994	6.1601	-0.3059
H	-2.1235	-0.1597	1.6364	H	-1.0609	2.3091	-2.0844
C	-6.7732	-0.8309	1.6219	B	1.8666	0.3601	-0.0709
H	-7.5285	-0.0828	1.3700	O	2.6345	-0.3947	-0.9810
H	-6.6697	-0.8440	2.7074	O	2.6723	0.6857	1.0461
H	-7.1674	-1.8045	1.3173	C	3.9407	0.1128	0.8149
C	-0.3992	-1.5750	-0.4588	C	3.9144	-0.5443	-0.4137
C	-0.9583	-2.4034	-1.4482	C	5.0717	0.1484	1.6077
C	0.2953	-2.1710	0.6082	C	6.2036	-0.5196	1.1123
C	0.4550	-3.5561	0.6673	C	6.1772	-1.1825	-0.1234
C	-0.0893	-4.3680	-0.3305	C	5.0183	-1.2062	-0.9163
C	-0.7997	-3.7867	-1.3857	H	4.9837	-1.7109	-1.8699
H	-1.2265	-4.4107	-2.1595	H	5.0788	0.6642	2.5561
H	-1.5023	-1.9532	-2.2660	H	7.1133	-0.5201	1.6964
H	0.6839	-1.5522	1.4067	H	7.0670	-1.6859	-0.4750

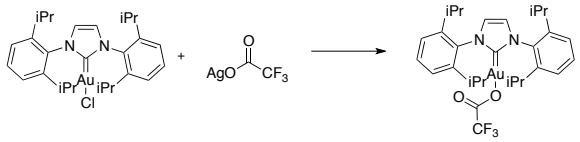
Table 6.3, entry 3, alkyne starting material (DMAD).

Atom	*x (Å)*	*y (Å)*	*z (Å)*	*Atom*	*x (Å)*	*y (Å)*	*z (Å)*
C	0.5994	0.1949	0.0682	H	-4.4751	-1.3947	1.1025
C	-0.5994	0.1955	-0.0675	H	-4.4319	-0.8995	-0.6203
C	2.0165	0.2545	0.2903	O	2.5660	0.9848	1.1191
C	-2.0166	0.2572	-0.2883	O	2.6874	-0.6054	-0.5357
O	-2.5666	0.9957	-1.1094	C	4.1550	-0.6332	-0.4030
O	-2.6869	-0.6110	0.5295	H	4.4311	-0.9064	0.6128
C	-4.1547	-0.6371	0.3980	H	4.5672	0.3438	-0.6447
H	-4.5665	0.3374	0.6504	H	4.4760	-1.3834	-1.1151

Table 6.3, entry 3, alkoxyboration product.

Atom	*x (Å)*	*y (Å)*	*z (Å)*	*Atom*	*x (Å)*	*y (Å)*	*z (Å)*
C	-0.5061	0.0190	-0.5041	O	1.2172	3.0321	-1.1431
C	0.5328	0.8670	-0.3630	O	-0.7322	2.8498	0.0458
O	-1.7162	0.4467	-1.0227	C	-0.9359	4.3013	-0.0791
C	-2.9335	0.1045	-0.3819	B	1.9778	0.3806	-0.0976
C	-4.0507	-0.0276	-1.2005	O	2.6258	-0.6521	-0.8005
C	-5.2851	-0.3119	-0.6187	O	2.8597	0.9588	0.8275
C	-5.4183	-0.4738	0.7742	C	4.0776	0.2569	0.7050
C	-4.2720	-0.3275	1.5679	C	3.9344	-0.7222	-0.2782
C	-3.0274	-0.0314	1.0033	C	5.2588	0.4374	1.3962
H	-3.9383	0.0970	-2.2652	C	6.3194	-0.4180	1.0552
H	-6.1568	-0.4145	-1.2539	C	6.1772	-1.3993	0.0624
H	-4.3498	-0.4376	2.6403	C	4.9680	-1.5684	-0.6300
H	-2.1591	0.1184	1.6326	H	4.8448	-2.3182	-1.3981
C	-6.7568	-0.8136	1.3909	H	5.3544	1.1997	2.1550
H	-7.5756	-0.3209	0.8638	H	-1.8153	-4.0787	-1.4536
H	-6.8020	-0.5080	2.4369	H	-1.3332	-3.8726	0.2621
H	-6.9495	-1.8901	1.3562	H	-0.0840	-4.0691	-0.9912
C	-0.3757	-1.4374	-0.1821	H	-1.9174	4.4777	0.3466
O	-1.0908	-2.2229	-1.0290	H	-0.8971	4.5977	-1.1250
O	0.2958	-1.8671	0.7587	H	-0.1646	4.8313	0.4777
C	-1.0741	-3.6734	-0.7749	H	7.2643	-0.3178	1.5720
C	0.3842	2.3315	-0.5563	H	7.0160	-2.0382	-0.1774

Preparation of IPrAuTFA Catalyst



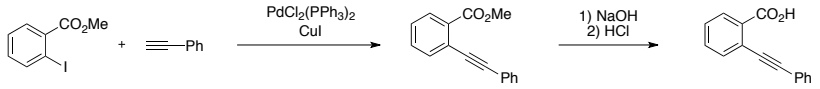
No precautions were taken to exclude air or water, but the reaction was conducted in a fume hood with the light turned off. A solution of IPrAuCl (186 mg, 300. μmol, 1.00 equiv) in DCM (3.0 mL) was added to a dram vial containing AgTFA (72.9 mg, 330. μmol, 1.10 equiv) and a stirbar. The vial was capped tightly and wrapped with aluminum foil to protect the reaction mixture from light. The reaction was stirred vigorously at 25 °C for 7 h before being filtered through a

Celite plug (ca. 0.5 mL). The Celite was rinsed with additional DCM (3 × 0.5 mL), and the resulting solution was concentrated in vacuo to a a white solid residue. The solid was crushed to a fine powder, from which volatiles were removed at 25 °C and ca. 10 mTorr overnight to afford IPrAuTFA as a white powder (213 mg, quant.).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.54 (t, *J* = 7.8 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 4H), 7.22 (s, 2H), 2.55 (sept, *J* = 6.9 Hz, 4H), 1.37 (d, *J* = 6.8 Hz, 12H), 1.24 (d, *J* = 6.9 Hz, 12H).

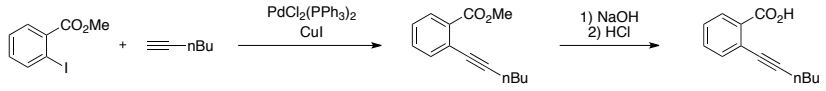
^{19}F NMR ($CDCl_3$, 376 MHz): δ -74.1 (s).

Synthesis of Alkynoic Acids for the Carboxyboration Reaction



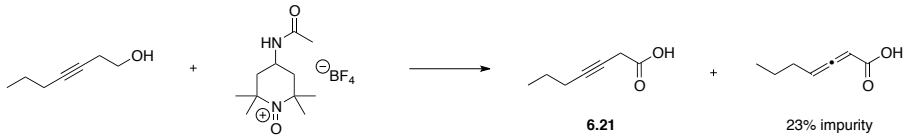
SI-6.1 6.14

2-(Phenylethynyl)benzoic acid (6.14) was prepared in two steps from methyl 2-iodobenzoate (790 mg, 3.0 mmol) using a previously published procedure.[10] ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.15 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.70 (dd, *J* = 7.8 Hz, 1.0 Hz, 1H), 7.60–7.56 (m, 3H), 7.44 (dt, *J* = 14.2, 3.8 Hz, 1H) 7.35–7.31 (m, 3H). This spectrum is in agreement with previously reported spectral data, but the carboxylic acid proton was not detected in our case.



SI-6.2 6.18

2-(Hex-1-yn-1-yl)benzoic acid (6.18) was prepared by Kim Tu in two steps from methyl 2-iodobenzoate (1.3g, 5.0 mmol) using a method adapted from the synthesis of **6.14**.[10] ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.10 (dd, *J* = 8.0, 0.5 Hz, 1H), 7.54 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.49 (td, *J* = 7.5 1.0 Hz, 1H), 7.37 (td, *J* = 8.0, 1.5 Hz, 1H), 2.51 (t, *J* = 7.0 Hz, 2H), 1.67–1.61 (m, 2H), 1.55–1.48 (m, 2H), 0.96 (t, *J* = 7.0 Hz, 3H). This spectrum is in agreement with previously reported spectral data for this compound.[11]



SI-6.4
Bobbitt's Salt

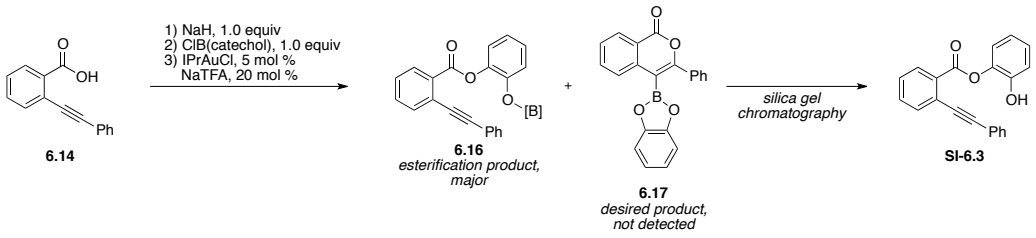
6.21 23% impurity

3-Heptynoic acid (6.21) was prepared using a method based on a published procedure for the preparation of 3-pentynoic acid.[12] A 25 mL round bottom flask was charged with Bobbitt's salt (**SI-6.4**, 1.5 g, 5.1 mmol, 2.0 equiv), water (1 mL), MeCN (9 mL), and a stir bar. 3-Heptyn-1-ol (310 µL, 290 mg, 2.5 mmol, 1.0 equiv) was added, the reaction vessel was capped loosely, and the resulting dark orange solution was stirred at 25 °C for 22 h. After this time, the resulting bright yellow solution was diluted with 20 mL water and extracted with Et_2O (4 × 10 mL). The combined organic layers were washed with 10% aq HCl (1 × 5 mL) to remove residual TEMPO derivatives and then brine (1 × 10 mL). The pale yellow organic

phase was dried over $MgSO_4$, filtered, and concentrated in vacuo to 330 mg of a yellow oil containing a 2:1 mixture of **6.21**:unreacted heptynol. This mixture was added to 10% aq NaOH (10 mL). The resulting solution was washed with Et_2O (3 × 2 mL) and then acidified to pH ≈ 1 with 2 M aq HCl. The resulting mixture was extracted with Et_2O (3 × 5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo at 30 °C and ca. 10 Torr to afford **6.21** as a pale yellow oil (50 mg, 15% yield) contaminated with 23% isomeric allenoic acid.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.37 (br s, 1H), 3.33 (t, *J* = 1.9 Hz, 2H), 2.18 (tt, *J* = 5.9, 0.9 Hz, 2H), 1.53 (app sextet, *J* = 7.3 Hz, 2H), 0.98 (t, *J* = 7.3 Hz, 3H). Allenoic acid impurity: δ 8.37 (br s, 1H), 5.68 (app q, *J* = 6.7 Hz, 1H), 5.60–5.58 (m, 1H), 2.14 (qd, *J* = 7.6, 2.9 Hz, 2H), and additional signals overlapping with **6.21**.

<u>Sodium Effect in NMR-Scale Carboxyboration Reaction with **6.14**</u>



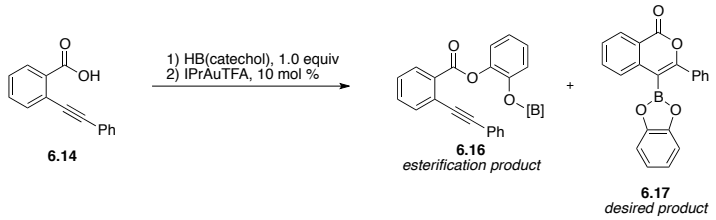
Sodium-containing reaction. In a N_2-filled glovebox, carboxylic acid **6.14** (19.4 mg, 100. μmol, 1.00 equiv) was dissolved in 0.4 mL anhydrous d_8-toluene and added to a dram vial containing NaH (2.4 mg, 0.10 mmol, 1.0 equiv). The resulting suspension was mixed by syringe for ca. 2 min until H_2 evolution was no longer observed and was subsequently transferred to a dram vial containing

B-chlorocatecholborane (15.4 mg, 100. μmol, 1.00 equiv). The resulting thick suspension was mixed by syringe for 5 min. To this was added a suspension of IPrAuCl (3.1 mg, 5.0 μmol, 5.0 mol %) and NaTFA (1.2 mg, 10. μmol, 10. mol %) in 0.4 mL anhydrous d_8-toluene. The resulting mixture was transferred to a J. Young NMR tube and heated in a preheated 50 °C oil bath for 17 h. No boronic ester was observable in the crude reaction mixture by ^{11}B NMR spectroscopy. The reaction vessel was returned to the glovebox and the catalyst was quenched by reacting with PPh_3 (2.6 mg, 10. μmol, 10. mol %) for 2 h. The quenched reaction mixture was filtered through a fiberglass filter and concentrated in vacuo, and the resulting residue was purified by silica gel chromatography eluting using a stepwise gradient from 100% hexanes to 100% EtOAc. Among the products obtained was hydrolysis product **SI-6.3**. All ^{1}H NMR signals from **SI-6.3** were observable in the crude reaction mixture prior to air exposure except the phenol OH proton.

^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.19 (d, *J* = 6.5 Hz, 1H), 7.76 (d, *J* = 6.0 Hz, 1H), 7.62 (t, *J* = 5.8 Hz, 1H), 7.54 (d, *J* = 4.6 Hz, 2H), 7.50 (t, *J* = 6.9 Hz, 1 H), 7.35–7.34 (m, 3H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.08 (dd, *J* = 6.7, 1.1 Hz, 1H), 6.98 (t, *J* = 7.6 Hz, 1H), 5.87 (br s, 1H).

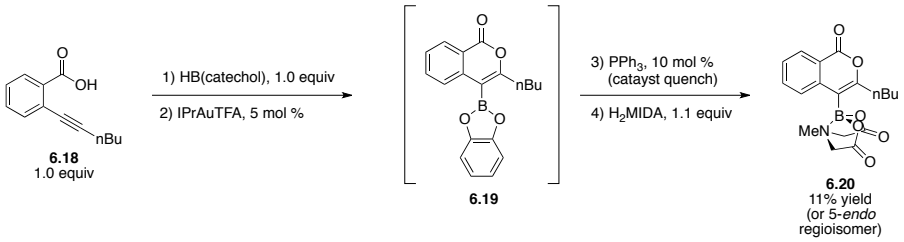
^{13}C NMR ($CDCl_3$, 125 MHz): δ 164.6, 147.1, 138.7, 134.8, 132.9, 132.0, 131.7, 131.4, 130.4, 129.1, 128.6, 128.5, 127.2, 124.2, 122.6, 120.9, 117.7, 95.5, 88.3. Note: the ^{13}C signals at 164.6, 147.1, 95.5, and 88.3 were detected indirectly using an HMBC experiment (optimized for 2 Hz coupling constants) through long-range coupling to nearby protons.

HRMS (ESI+): Calculated for $C_{21}H_{14}O_3Na$ ([M+Na]$^+$), 337.0841; found 337.0836.



Sodium-free reaction. In a N_2-filled glovebox, neat catecholborane (5.3 µL, 6.0 mg, 50. µmol, 1.0 equiv) was added to a solution of **6.14** (11 mg, 50. µmol, 1.0 equiv) in 0.5 mL anhydrous d_8-toluene. The resulting solution was mixed periodically by syringe over 45 min before being transferred to a dram vial containing IPrAuTFA (3.5 mg, 5.0 µmol, 10. mol %). After dissolving the catalyst, the reaction mixture was transferred to a J. Young NMR tube and heated in a preheated 50 °C oil bath for 24 h. After this time, analysis by ^{1}H and ^{11}B NMR spectroscopy indicated the formation of esterification product **6.16** and carboxyboration product **6.17**. Continued heating for up to 72 h resulted in slow, incomplete conversion of **6.16** into additional **6.17**.

Isolation of Carboxyboration Product **6.20**



This reaction sequence was conducted by Blum group graduate student Kim Tu in a N_2-filled glovebox. Benzoic acid derivative **6.18** (20. mg, 0.10 mmol,

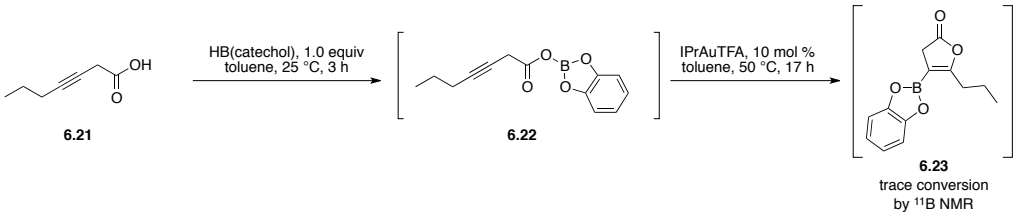
1.0 equiv) was dissolved in 0.5 mL anhydrous d_8-toluene. The resulting solution was added to a dram vial containing catecholborane (12 mg, 0.10 mmol, 1.0 equiv). After mixing thoroughly, the resulting solution was transferred to a dram vial containing IPrAuTFA (3.5 mg, 5.0 μmol, 5.0 mol %). After dissolving the catalyst, the reaction mixture was transferred to a J. Young NMR tube and heated in a preheated 50 °C oil bath for 24 h. Analysis of the mixture by ^{1}H and ^{11}B NMR spectroscopy indicated the formation of boronic ester **6.19**. The reaction vessel was returned to the glovebox and transferred to a dram vial containing PPh_3 (2.6 mg, 10. μmol, 10 mol %), and the resulting mixture was stirred at 25 °C for 24 h to quench the IPrAuTFA catalyst. After this time, to the quenched reaction mixture was added *N*-methyliminodiacetic acid (H_2MIDA, 16 mg, 0.11 mmol, 1.1 equiv) and anhydrous DMSO (0.5 mL). The vial was capped and heated in the glovebox at 90 °C to affect conversion of **6.19** into MIDA boronate derivative **6.20**. After 2 h, the reaction mixture was cooled to 25 °C, removed from the glovebox, and the solvents were removed in vacuo as described in Chapter 5. The resulting yellow semisolid was suspended in MeCN and adsorbed onto Celite for purification by silica gel chromatography eluting using a stepwise gradient from 100% Et_2O to 100% MeCN. Product-containing fractions were detected by TLC and concentrated in vacuo to afford **6.20** as a white solid (4.1 mg, 11% yield) in low purity.

^{1}H NMR (d_6-acetone, 600 MHz): δ 8.24 (d, *J* = 7.8 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.72 (t, *J* = 7.2 Hz, 1H), 7.51 (t, *J* = 7.2 Hz, 1H), 4.47 (d, *J* = 17.4 Hz, 2H), 4.34 (d, *J* = 17.4 Hz, 2H), 3.06 (s, 3H), 2.63 (t, *J* = 7.8 Hz, 2H), 1.44–1.40 (m, 2H), 1.28–1.25 (m, 2H), 0.94 (t, *J* = 7.2 Hz, 3H).

^{11}B NMR (d_6-acetone, 193 MHz): δ 12.0 (s).

^{13}C NMR (d_6-acetone, 125 MHz): δ 165.5, 162.6, 146.8, 141.5, 135.1, 130.0, 127.8, 127.6, 125.3, 121.8, 120.7, 64.1, 48.8, 35.0, 32.0, 23.3, 14.1.

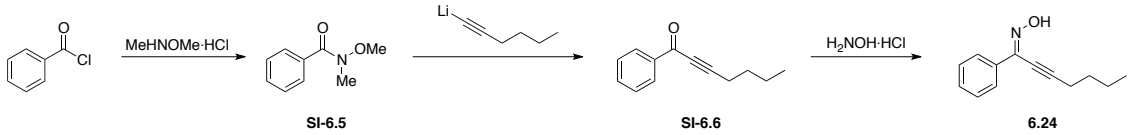
NMR-Scale Carboxyboration Reaction of **6.21**



6.21 **6.22** **6.23**
trace conversion
by ^{11}B NMR

In a N_2-filled glovebox, to a solution of **6.21** (6.3 mg, 50. μmol, 1.0 equiv) in anhydrous d_8-toluene (0.5 mL) was added neat catecholborane (5.3 μL, 6.0 mg, 50. μmol, 1.0 equiv). The resulting solution was mixed well and then transferred to a J. Young NMR tube for observation. After 3 h at 25 °C, ^{1}H and ^{11}B NMR spectra indicated full conversion to boric ester intermediate **6.22**. The reaction vessel was returned to the glovebox, and IPrAuTFA (3.5 mg, 5.0 μmol, 10. mol %) was dissolved in the reaction mixture. The J. Young tube was then removed from the glovebox and heated in a preheated 50 °C oil bath for 17 h. Analysis of the mixture by ^{1}H and ^{11}B NMR spectroscopy indicated trace conversion to a boronic ester (^{11}B NMR, δ = 30.0 ppm), possibly consistent with **6.23**.

Synthesis of Oxime **6.24**



N-Methoxy-*N*-methylbenzamide (**SI-6.5)**. This Weinreb amide was prepared using a published procedure[13] from benzoyl chloride in 78% yield (1.29 g). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.68 (app dd, *J* = 8.6, 1.5 Hz, 2H), 7.46 (tt, *J* = 7.3, 1.6 Hz, 1H), 7.42–7.39 (m, 2H), 3.56 (s, 3H), 3.37 (s, 3H). This spectrum is in agreement with previously reported spectral data.

1-Phenylhept-2-yn-1-one (SI-6.6) was prepared from **SI-6.5** using a literature procedure.[13] ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.15 (app dd, *J* = 8.6, 1.5 Hz, 2H), 7.60 (tt, *J* = 7.3, 1.6 Hz, 1H), 7.50–7.47 (m, 2H), 2.52 (t, *J* = 7.1 Hz, 2H), 1.71–1.65 (m, 2H), 1.56–1.48 (m, 2H), 0.98 (t, *J* = 7.5 Hz, 3H).

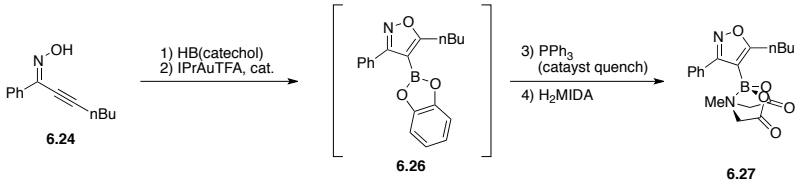
(Z)-1-Phenylhept-2-yn-1-one oxime (6.24) was prepared according to a method adapted from a published report for the synthesis of similar alkynyl oximes.[14] A 25 mL round bottom flask was charged with $H_2NOH·HCl$ (350 mg, 5.0 mmol, 2.0 equiv), Na_2SO_4 (710 mg, 5.0 mmol, 2.0 equiv), and a stir bar. The solids were suspended in MeOH (7 mL). Pyridine (0.69 mL, 670 mg, 8.5 mmol, 3.4 equiv) and then **SI-6.5** (470 mg, 2.5 mmol, 1.0 equiv) were added. The reaction vessel was loosely sealed with a septum, and the reaction mixture was stirred at 25 °C for 19 h. At this time, analysis by TLC (10% EtOAc/hexanes, visualized by UV absorbance) indicated incomplete consumption of **SI-6.5**. Additional portions of

$H_2NOH{\cdot}HCl$ (2.0 equiv), Na_2SO_4 (2.0 equiv), and pyridine (3.4 equiv) were added, and stirring was continued for an additional 24 h. Analysis by TLC still indicated incomplete consumption of **SI-6.5**. The reaction mixture was added to 15 mL water and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (1 × 5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to a yellow oil. The oil was purified by silica gel chromatography using a stepwise gradient from 5% to 15% EtOAc in hexanes to afford **6.24** as a clear, pale yellow oil (36 mg, 7% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.34 (br m, 1H), 7.86–7.82 (m, 2H), 7.40–7.37 (m, 3H), 2.59 (t, *J* = 7.1 Hz, 3H), 1.72–1.66 (m, 2H), 1.57–1.49 (m, 2H), 0.98 (t, *J* = 7.5 Hz, 3H). Irradiation of the oxime –OH proton did not produce an observable NOE enhancement at the *ortho* phenyl protons.

^{13}C NMR ($CDCl_3$, 125 MHz): δ 142.5, 133.7, 129.9, 128.5, 126.7, 105.8, 70.5, 30.4, 22.2, 19.6, 13.7.

Alkoxyboration Reaction to form Isoxazole **6.27**



6.24 **6.26** **6.27**

This reaction was set up in a N_2-filled glovebox. To a solution of oxime **6.24** (10. mg, 50. μmol, 1.0 equiv) in anhydrous d_8-toluene (0.5 mL) was added neat catecholborane (5.3 μL, 6.0 mg, 50. μmol, 1.0 equiv). The resulting solution was mixed well and transferred to a J. Young NMR tube for analysis. After 1 h at

25 °C, full conversion of **6.24** to a boric ester was observed. The reaction vessel was returned to the glovebox, and IPrAuTFA (3.5 mg, 5.0 μmol, 10. mol %) was dissolved in the reaction mixture. The resulting solution was removed from the glovebox and heated in a preheated 50 °C oil bath for 5 h, at which time analysis by ^{1}H and ^{11}B NMR spectroscopy revealed full conversion of the boric ester intermediate to a mixture containing boronic ester **6.26**. The reaction mixture was again returned to the glovebox, and it was added to a dram vial containing PPh_3 (2.6 mg, 10. μmol, 10 mol %) using an additional portion of anhydrous toluene (1 × 0.2 mL) as a rinse to aid in the transfer. The vial was capped, and the catalyst quench reaction was allowed to proceed at 25 °C for 2 h in the glovebox. After this time, the quenched reaction mixture was transferred to a dram vial containing H_2MIDA (8.1 mg, 55 μmol, 1.1 equiv) using anhydrous DMSO (1 × 0.2 mL) as a rinse to aid in the transfer. The vial was capped tightly, removed from the glovebox, and heated in a preheated 90 °C oil bath for 3 h. After this time, the reaction mixture was cooled to 25 °C and the solvents were removed in vacuo to afford a brown semisolid. Purification by silica gel chromatography using a stepwise gradient from 100% Et_2O to 50% MeCN in Et_2O afforded **6.27** was a white powder (6.2 mg, 35% yield).

TLC (10% MeCN/Et_2O): R_f = 0.41, visualized by UV absorbance and $KMnO_4$ stain.

^{1}H NMR (CD_3CN, 600 MHz): δ 7.48–7.46 (m, 3H), 7.44–7.41 (m, 2H), 3.84 (d, *J* =17.1 Hz, 2H), 3.35 (d, *J* = 17.1 Hz, 2H), 2.90 (t, *J* = 7.8 Hz, 2H), 2.47 (s, 3H), 1.73–1.68 (m, 2H), 1.44–1.38 (m, 2H), 0.97 (t, *J* = 7.5 Hz, 3H).

^{11}B NMR (CD_3CN, 193 MHz): δ 10.6 (br s).

^{13}C NMR (CD_3CN, 125 MHz): δ 179.7, 168.5, 167.5, 132.3, 130.3, 130.1, 129.5, 62.9, 48.4, 31.4, 27.7, 23.2, 14.0. Note: the aryl ^{13}C signal at 179.7 was detected indirectly by an HMBC experiment (optimized for 10 Hz coupling constants) showing coupling to the allylic and homoallylic protons. One ^{13}C signal was not detected, probably the boronate *ipso* carbon due to low sample concentration and poor signal response.

HRMS (ESI+): Calculated for $C_{18}H_{21}BN_2O_5Na$ ($[M+Na]^+$), 379.1445; found 379.1454.

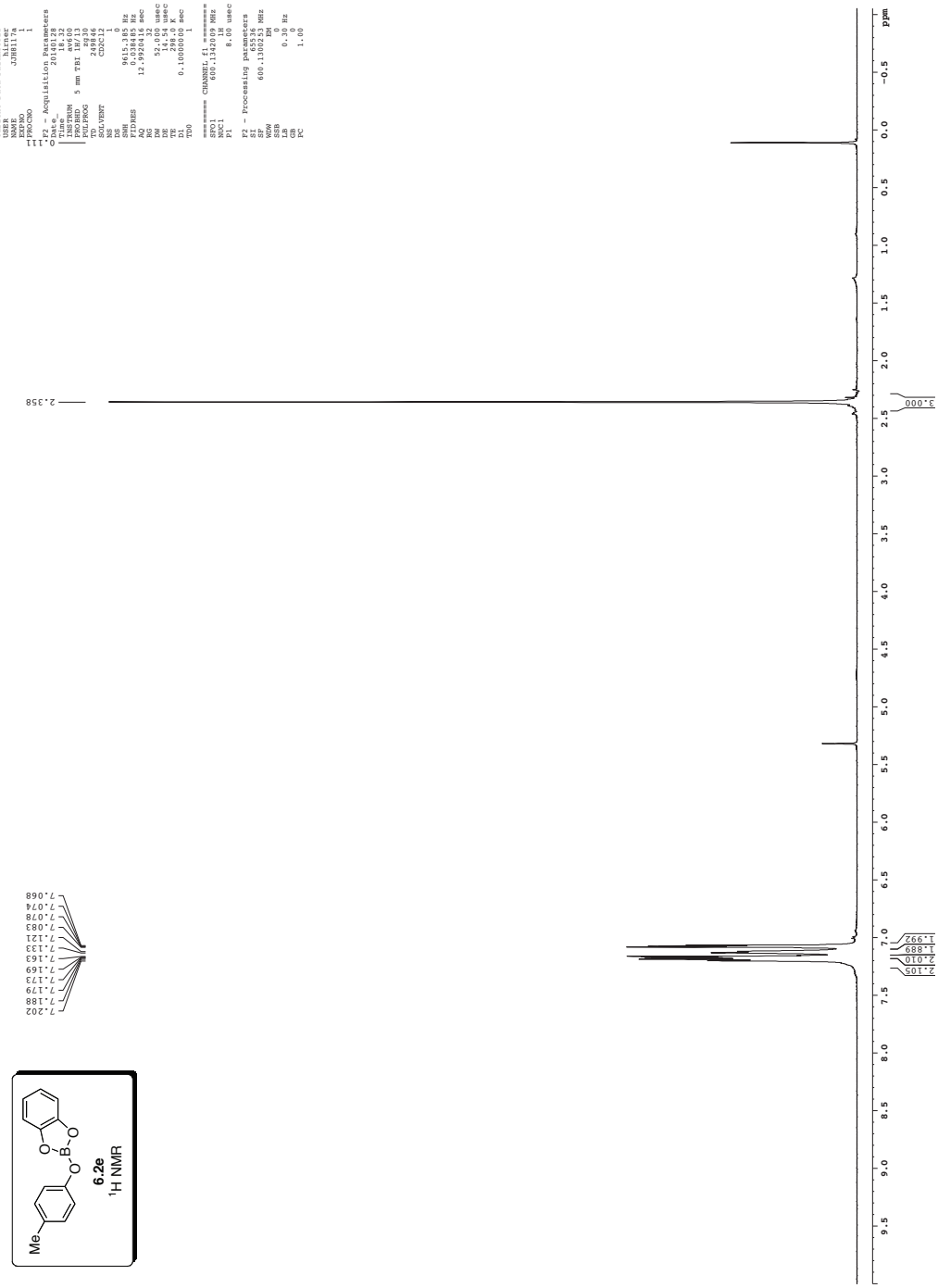
References for Experimental Section.

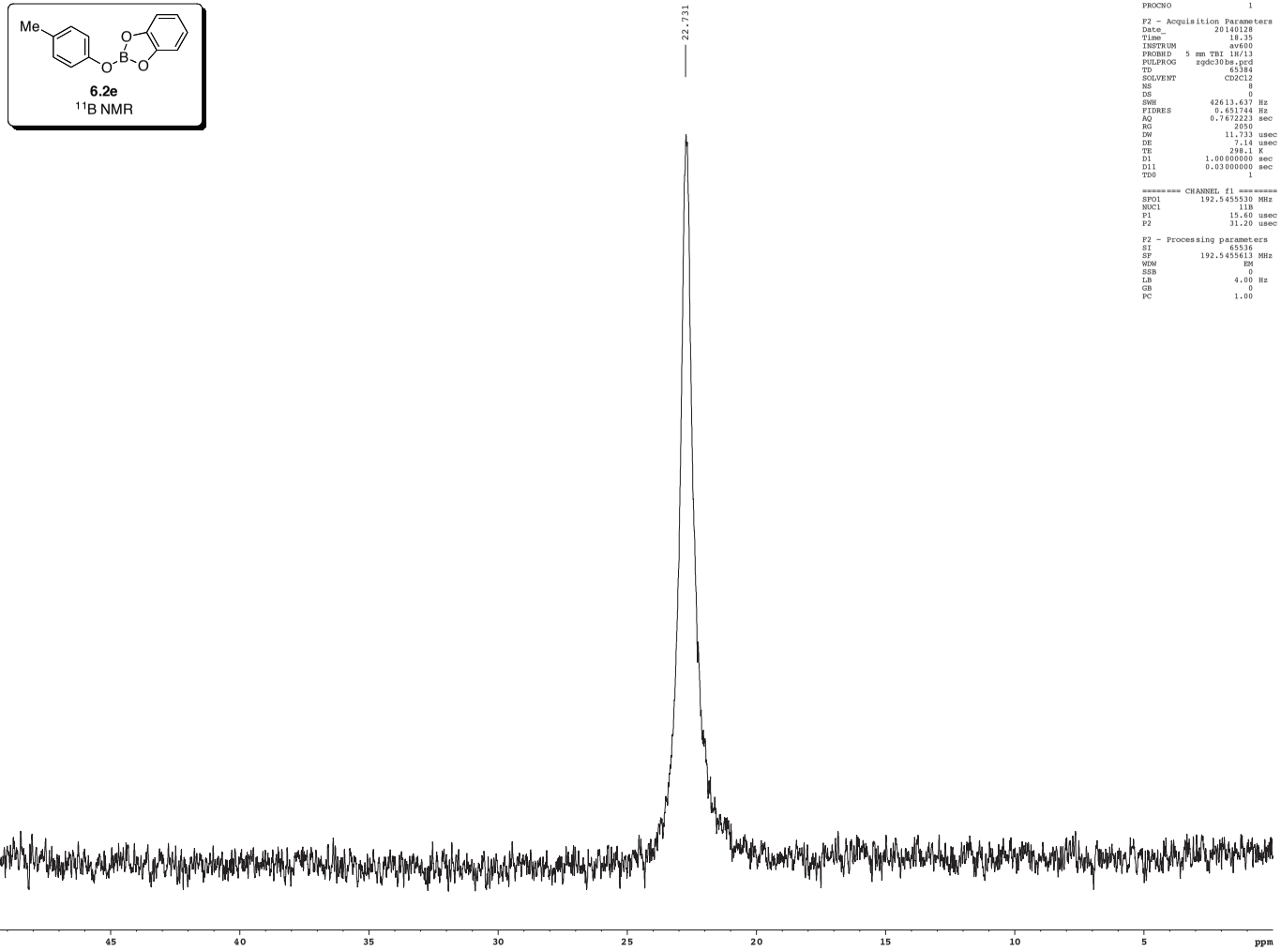
1. Dupuy, S.; Crawford, L.; Bühl, M.; Slawin, A. M. Z.; Nolan, S. P. *Adv. Synth. Catal.* **2012**, *354*, 2380–2386.
2. Taylor, M. J.; Grigg, J. A.; Rickard, C. E. F. *Polyhedron* **1992**, *11*, 889–892.
3. Taylor, M. J.; Grigg, J. A.; Laban, I. H.; *Polyhedron* **1996**, *15*, 3261–3270.
4. Nöth, H.; Wrackmeyer, B. Nuclear Magnetic Resonance Spectroscopy of Boron Compounds. In *NMR: Basic Principles and Progress*; Diehl, P., Fluck, E., Kosfeld, R. Eds.; Springer-Verlag: Berlin, 1978; Vol. 14.
5. Hanwell, M. D.; Curtis, D. E.; Lonie, D. C.; Vandermeersch, T.; Zurek, E.; Hutchinson, G. R. *J. Cheminform.* **2012**, *4*, 17.
6. Gaussian 09; Gaussian, Inc., Wallingford CT, 2009.
7. Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652.
8. Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623–11627.

9. Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. *J. Chem. Phys*. **1980**, *72*, 650–654.
10. Park, J. H.; Bhilare, S. V.; Youn, S. W. *Org. Lett.* **2011**, *13*, 2228–2231.
11. Li, Y.; Yang, X.; Liu, Y.; Zhu, C.; Yang, Y.; Yu, B. *Chem.—Eur. J.* **2010**, *16*, 1871–1882.
12. Qiu, J. C.; Pradhan, P. P.; Blanck, N. B.; Bobbitt, J. M.; Bailey, W. F. *Org. Lett.* **2012**, *14*, 350–353.
13. Jackson, M. M.; Leverett, C.; Toczko, J. F.; Roberts, J. C. *J. Org. Chem.* **2002**, *67*, 5032–5035.
14. Kung, K. K.-Y.; Lo, V. K.-Y.; Ko, H.-K.; Li, G.-L.; Chan, P.-Y.; Leung, K.-C.; Zhou, Z.; Wang, M.-Z.; Che, C.-M.; Wong, M.-K. *Adv. Synth. Catal.* **2013**, *355*, 2055–2070.

Appendix A: NMR Spectra

This appendix contains previously unpublished NMR spectra for compounds from Chapter 6.


Current Data Parameters
NAME hltner
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140128
Time 18.52
INSTRUM av600
PROBHD 5 mm TBI 1H/13
PULPROG zg30
TD 249846
SOLVENT CDCl3
NS 1
DS 0
SWH 9615.385 Hz
FIDRES 0.038485 Hz
AQ 12.992046 sec
RG 32
DW 52.000 usec
DE 14.94 usec
TE 298.0 K
D1 0.10000000 sec
TD0 1
CHANNEL f1
SFO1 600.1342009 MHz
NUC1 1H
P1 8.00 usec
F2 - Processing parameters
SI 65536
SF 600.1300253 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
2.358
7.202
7.188
7.179
7.173
7.169
7.163
7.153
7.121
7.083
7.078
7.074
7.068
3.000
1.992
1.089
2.010
2.105
ppm
Me
6.2e
1H NMR


Me
O
O
B
O
6.2e
11B NMR
22.731
Current Data Parameters
USER hirner
NAME JJH8117a
EXPNO 11
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140128
Time 18.35
INSTRUM av600
PROBHD 5 mm TBI 1H/13
PULPROG zgdc30bs.prd
TD 65384
SOLVENT CD2Cl2
NS 8
DS 0
SWH 42613.637 Hz
FIDRES 0.651744 Hz
AQ 0.7672223 sec
RG 2050
DW 11.733 usec
DE 7.14 usec
TE 298.1 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 192.5455530 MHz
NUC1 11B
P1 15.60 usec
P2 31.20 usec
F2 - Processing parameters
SI 65536
SF 192.5455613 MHz
WDW EM
SSB 0
LB 4.00 Hz
GB 0
PC 1.00
45
40
35
30
25
20
15
10
5
ppm

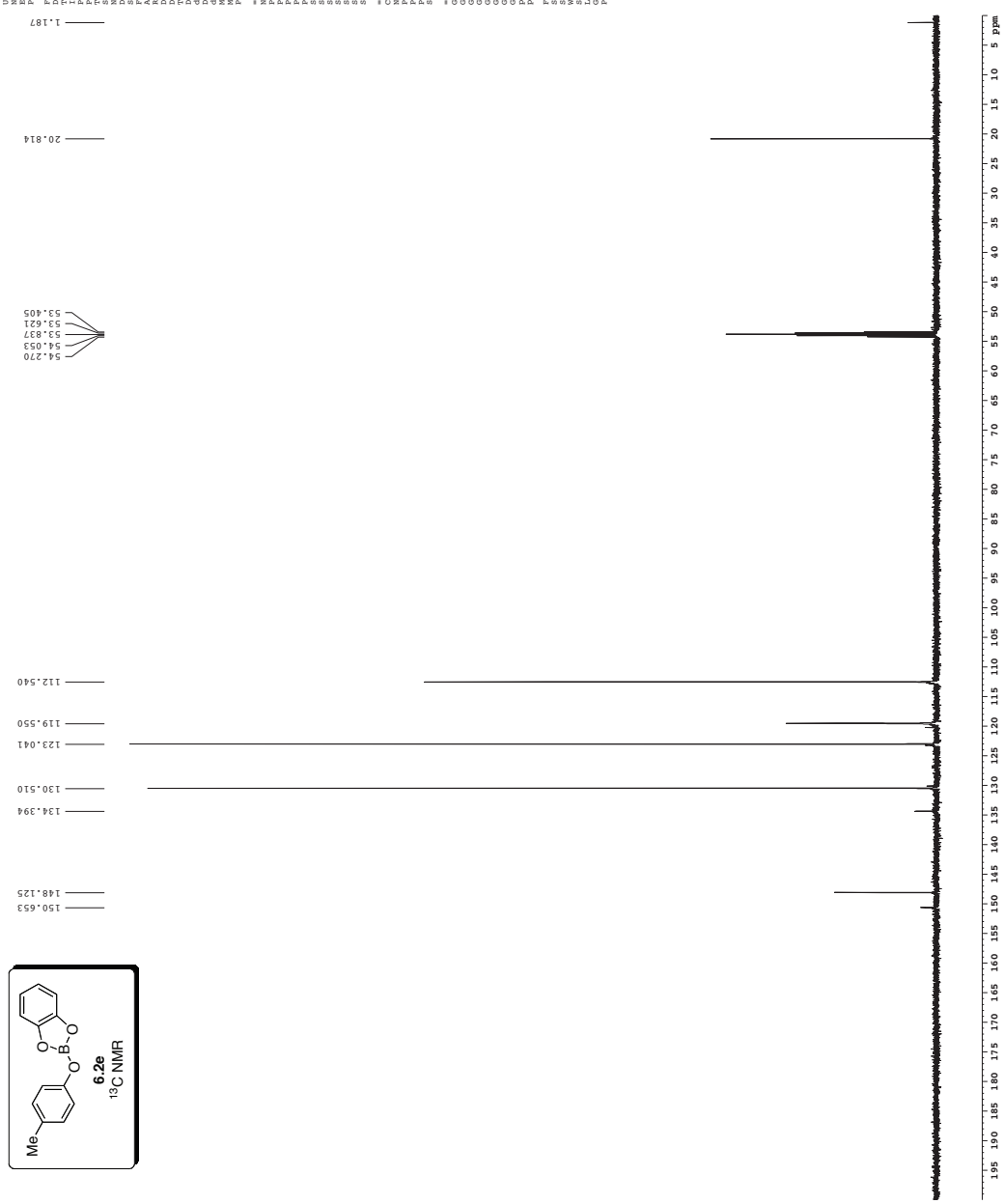
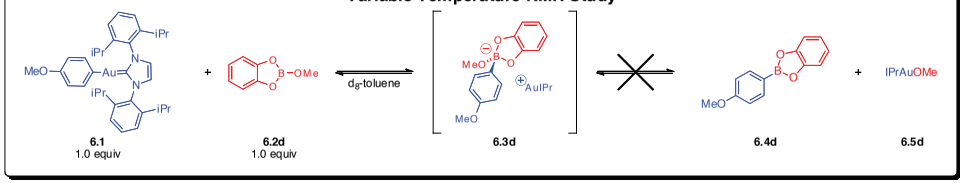
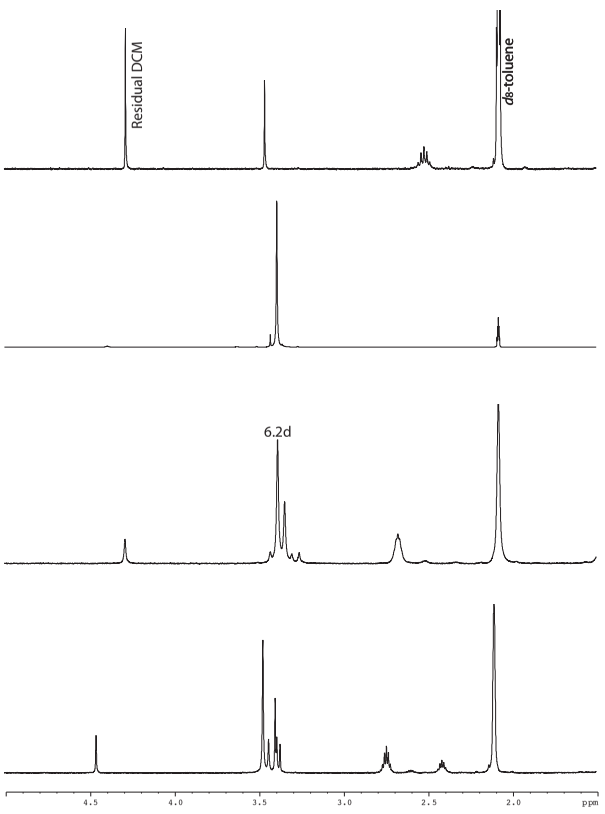

Me
6.2e
13C NMR

Table 6.1, Entry 4
Variable Temperature NMR Study

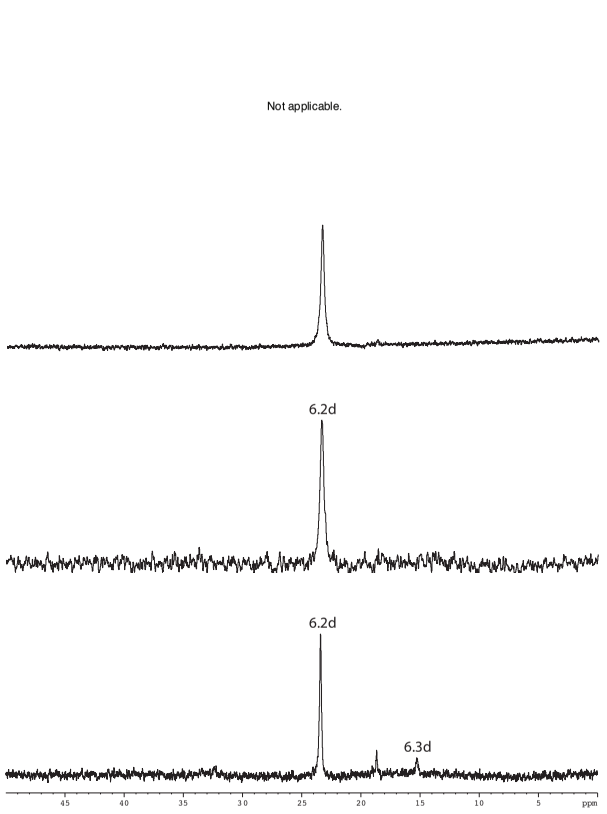


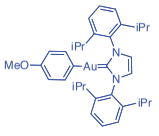
6.1 1.0 equiv + **6.2d** 1.0 equiv → **6.3d** → **6.4d** + **6.5d**

^{1}H NMR Spectra

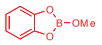


^{11}B NMR Spectra





6.1 25 °C



6.2d 25 °C

Reaction Mixture 25 °C

Reaction Mixture 80 °C

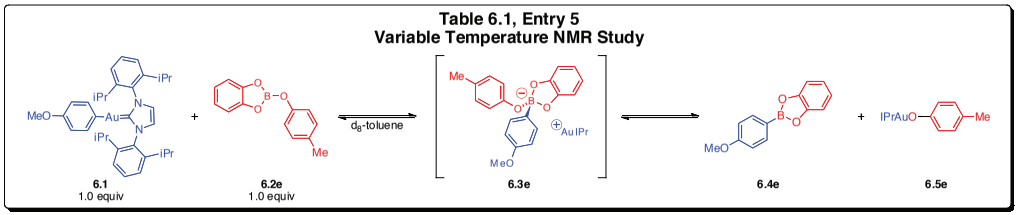


Table 6.1, Entry 5
Variable Temperature NMR Study
6.1
1.0 equiv
6.2e
1.0 equiv
d8-toluene
6.3e
6.4e
6.5e

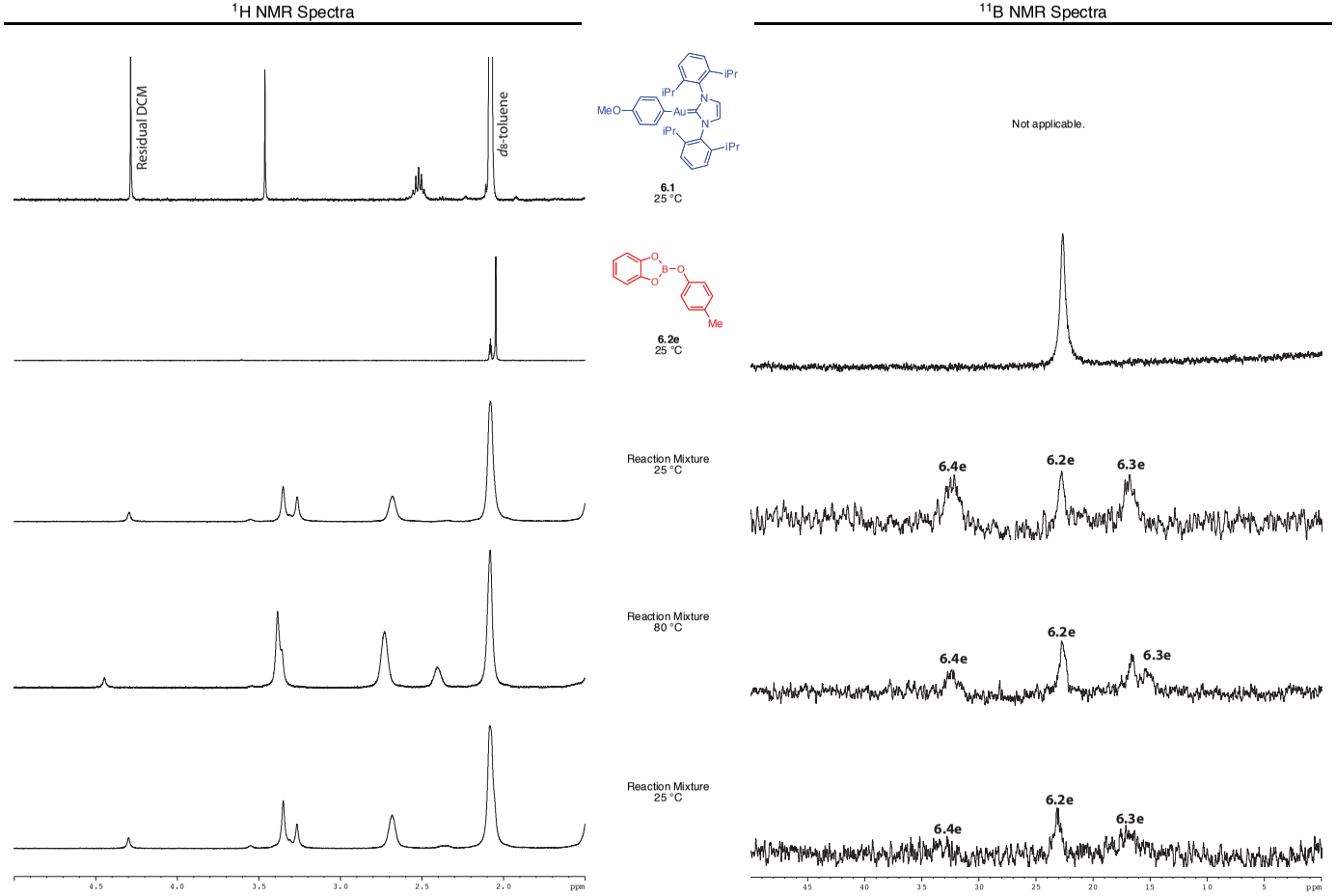
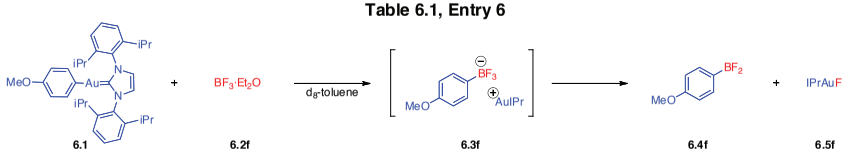
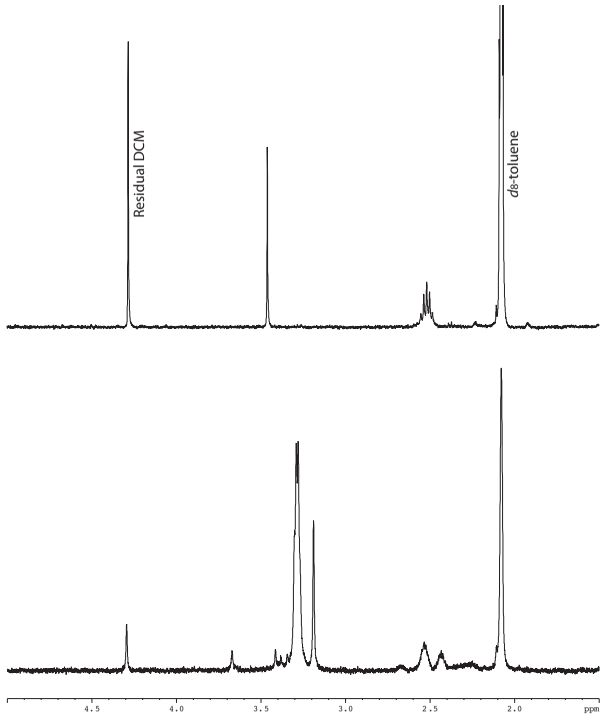

1H NMR Spectra
11B NMR Spectra
Residual DCM
d8-toluene
6.1
25 °C
Not applicable.
6.2e
25 °C
Reaction Mixture
25 °C
6.4e
6.2e
6.3e
Reaction Mixture
80 °C
Reaction Mixture
25 °C
ppm

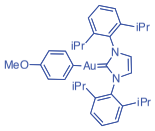
Table 6.1, Entry 6



6.1 1.0 equiv + **6.2f** 1.0 equiv → **6.3f** → **6.4f** + **6.5f** *not detected by ^{19}F NMR*

^{1}H NMR Spectra



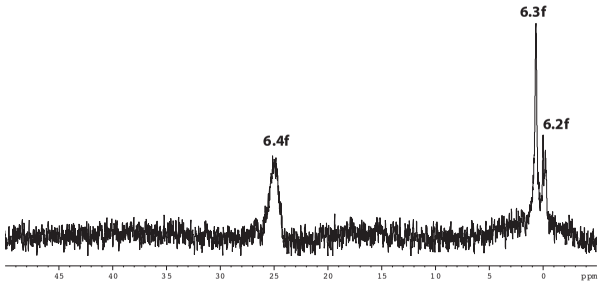


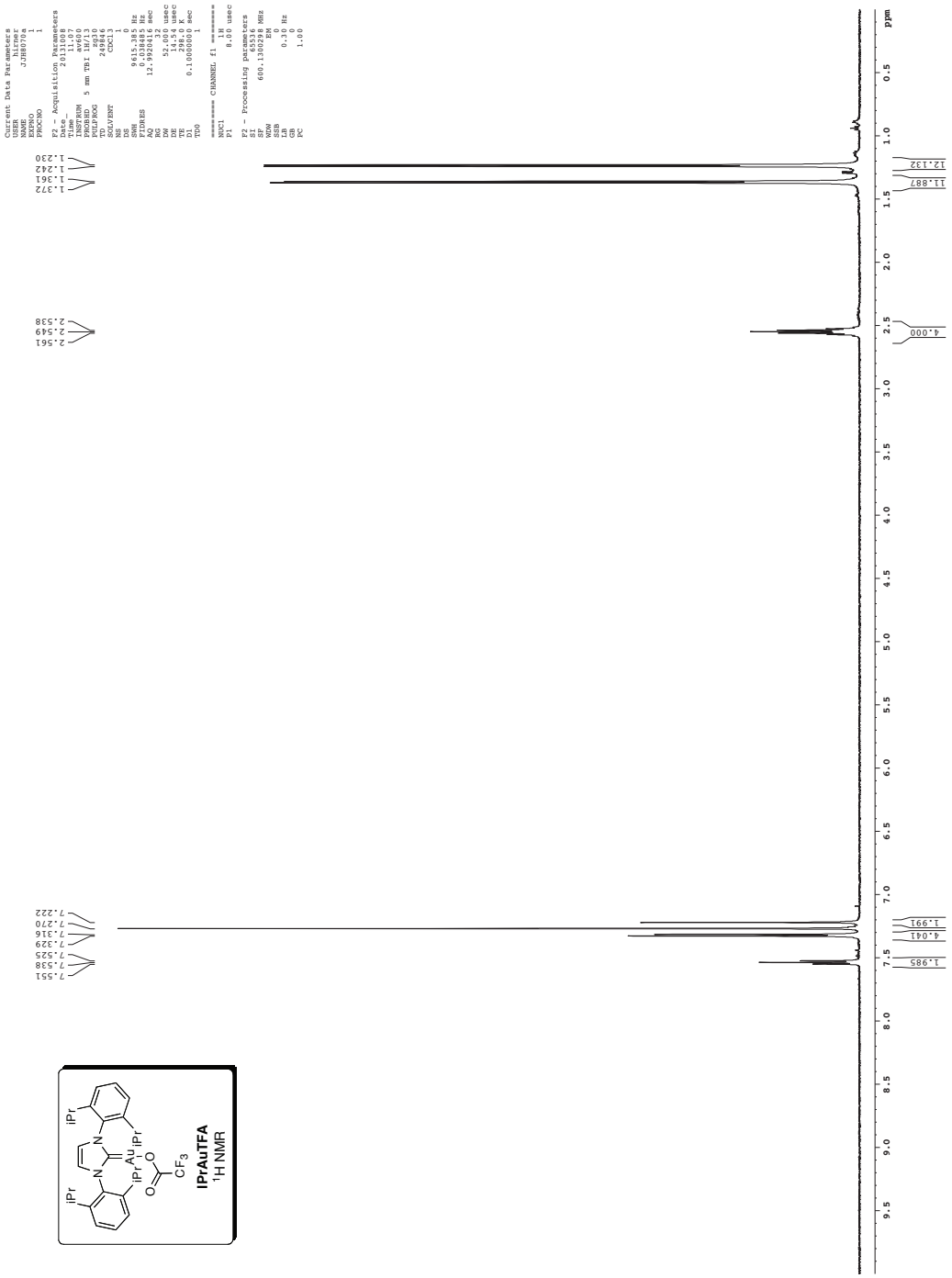
6.1
25 °C

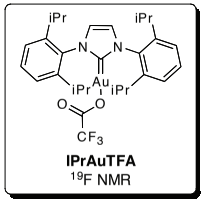
Reaction Mixture
25 °C, t = 20 min

^{11}B NMR Spectra

Not applicable.

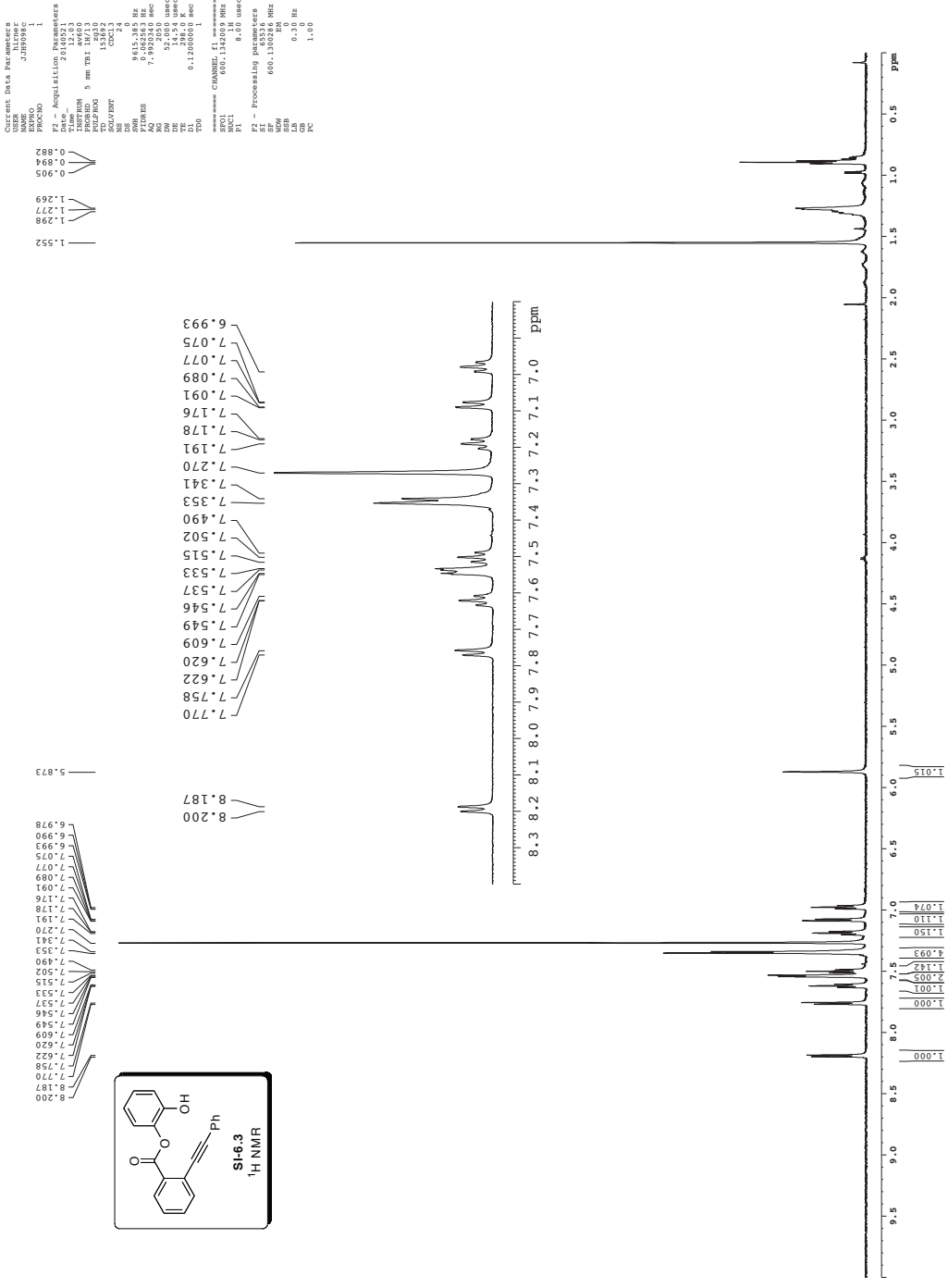


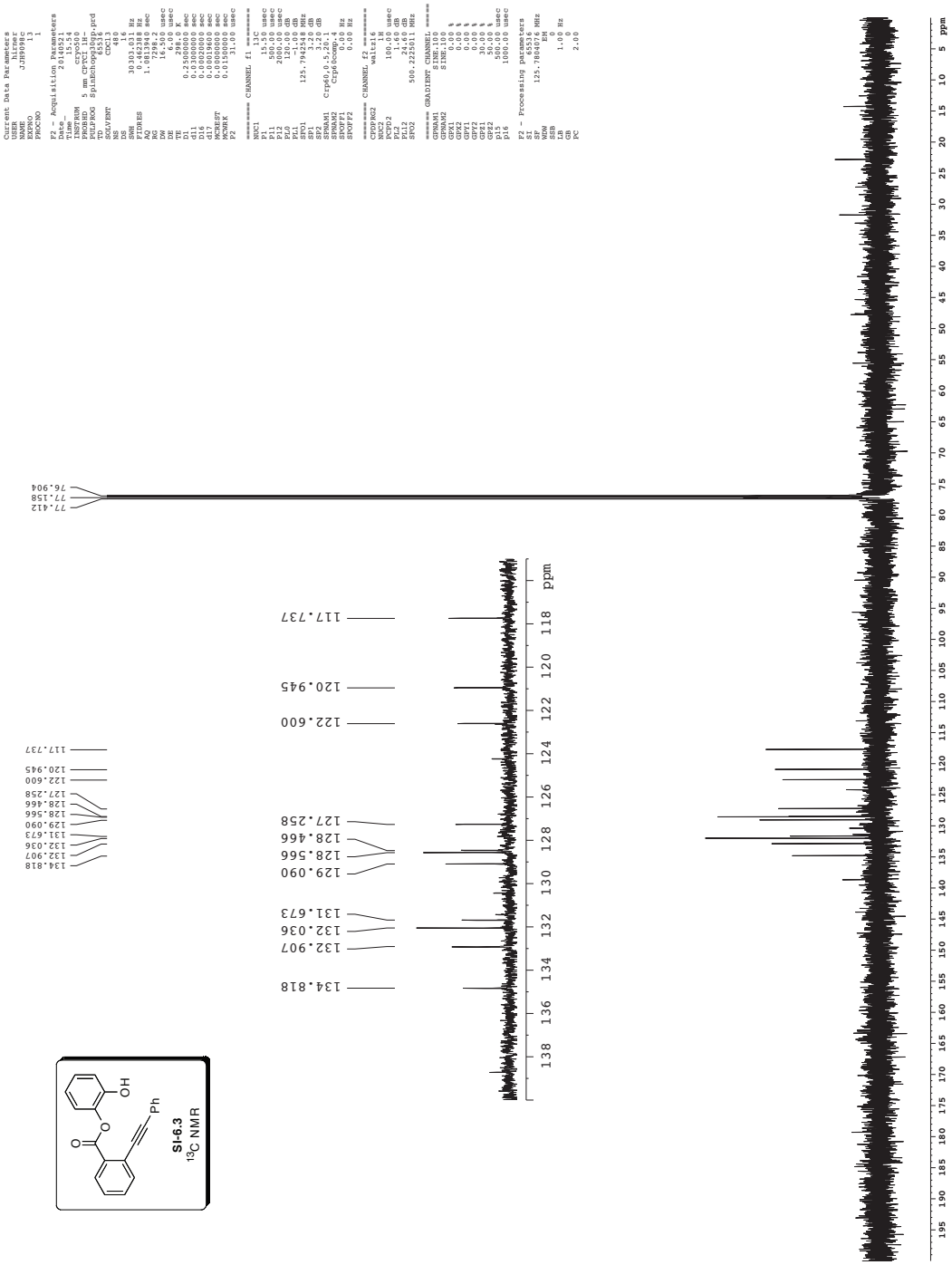

IPrAuTFA
1H NMR
ppm

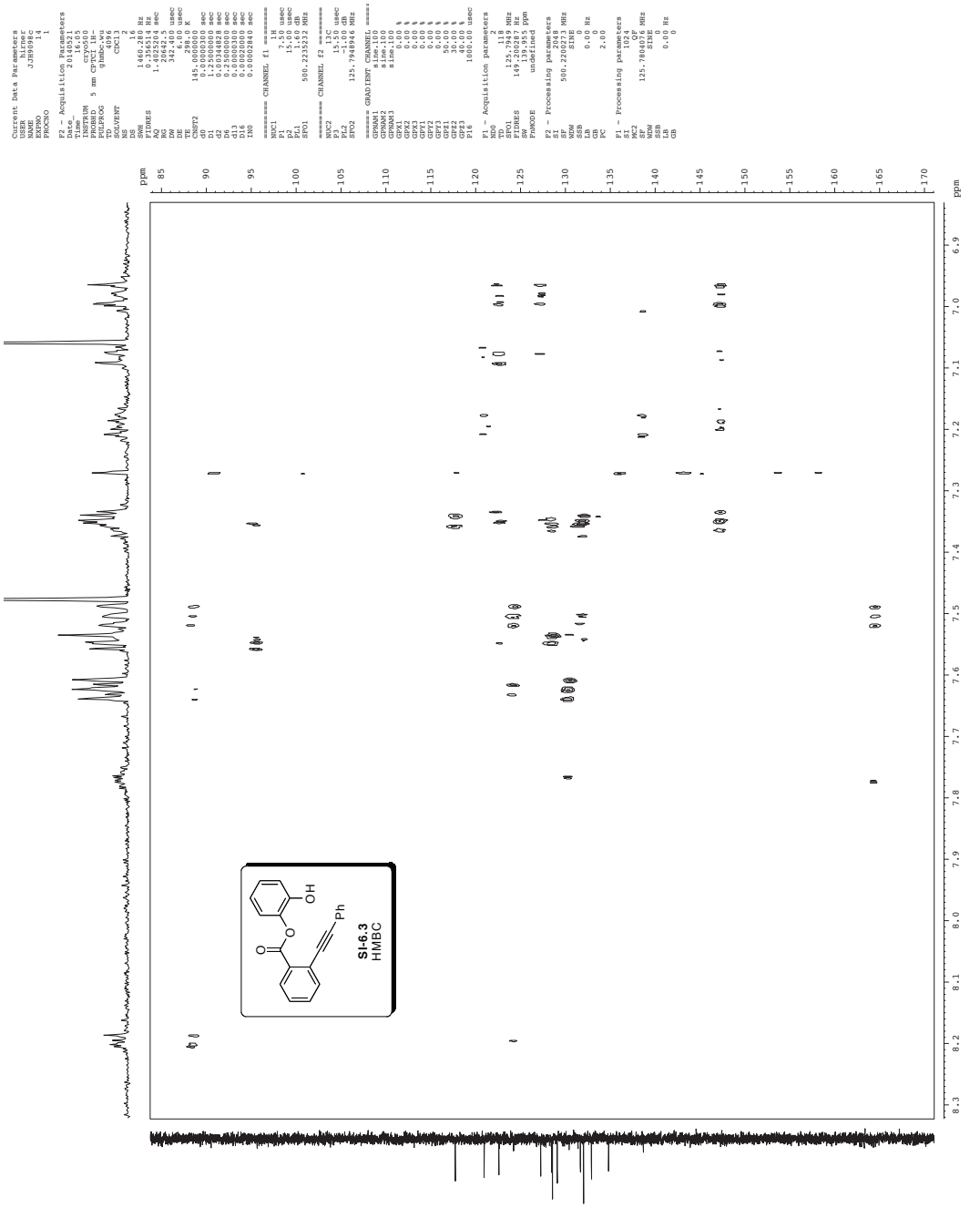


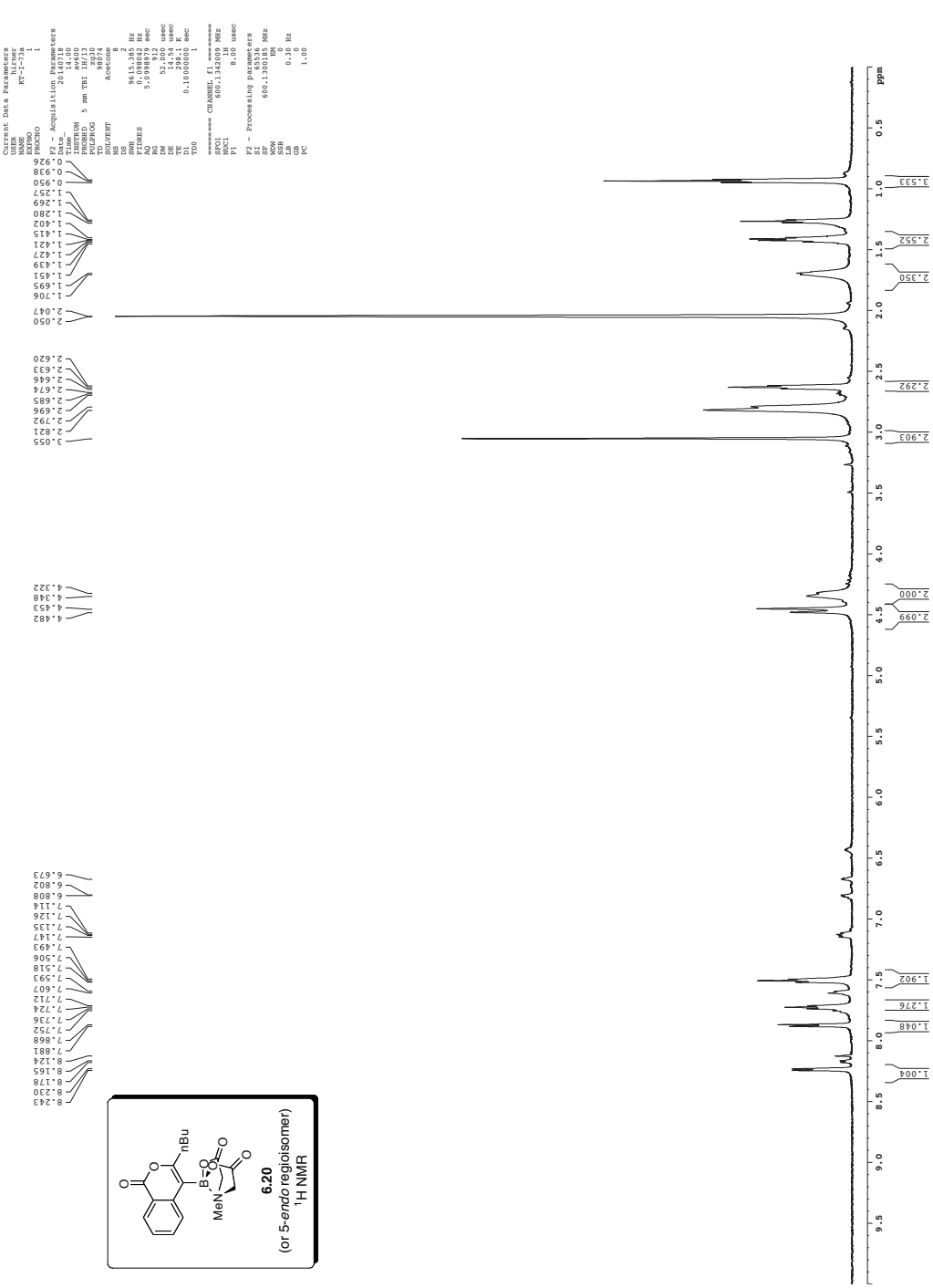
IPrAuTFA
^{19}F NMR

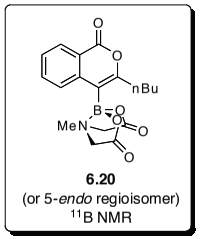

```
Current Data Parameters
USER                hlrner
NAME              JJH8070a
EXPNO                   19
PROCNO                   1

F2 - Acquisition Parameters
Date_            20131008
Time                12.27
INSTRUM          drx400
PROBHD   5 mm QNP H/F/P
PULPROG          zgflqn30
TD                  65536
SOLVENT             CDCl3
NS                     40
DS                      2
SWH              75187.969 Hz
FIDRES           1.147277 Hz
AQ               0.4358644 sec
RG                 1625.5
DW                  6.650 usec
DE                  9.46 usec
TE                298.1 K
D1           2.00000000 sec

======== CHANNEL f1 ========
NUC1                  19F
P1                  22.50 usec
PL1                 -6.00 dB
SFO1         376.4646491 MHz

F2 - Processing parameters
SI                  65536
SF           376.4983827 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   2.00
```


SI-6.3
1H NMR
OH
O
O
Ph


SI-6.3
13C NMR
OH
Ph
O
O
77.412
77.158
76.904
117.737
120.945
122.600
127.258
128.466
128.566
129.090
131.673
132.036
132.907
134.818
ppm


SI-6.3
HMBC
OH
O
O
Ph

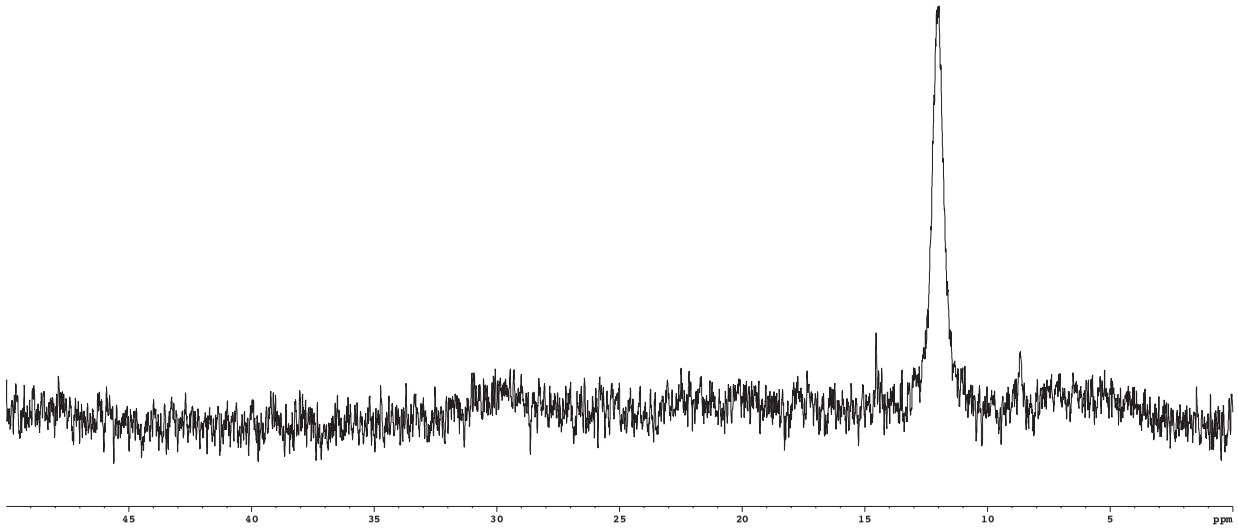

6.20
(or 5-endo regioisomer)
1H NMR

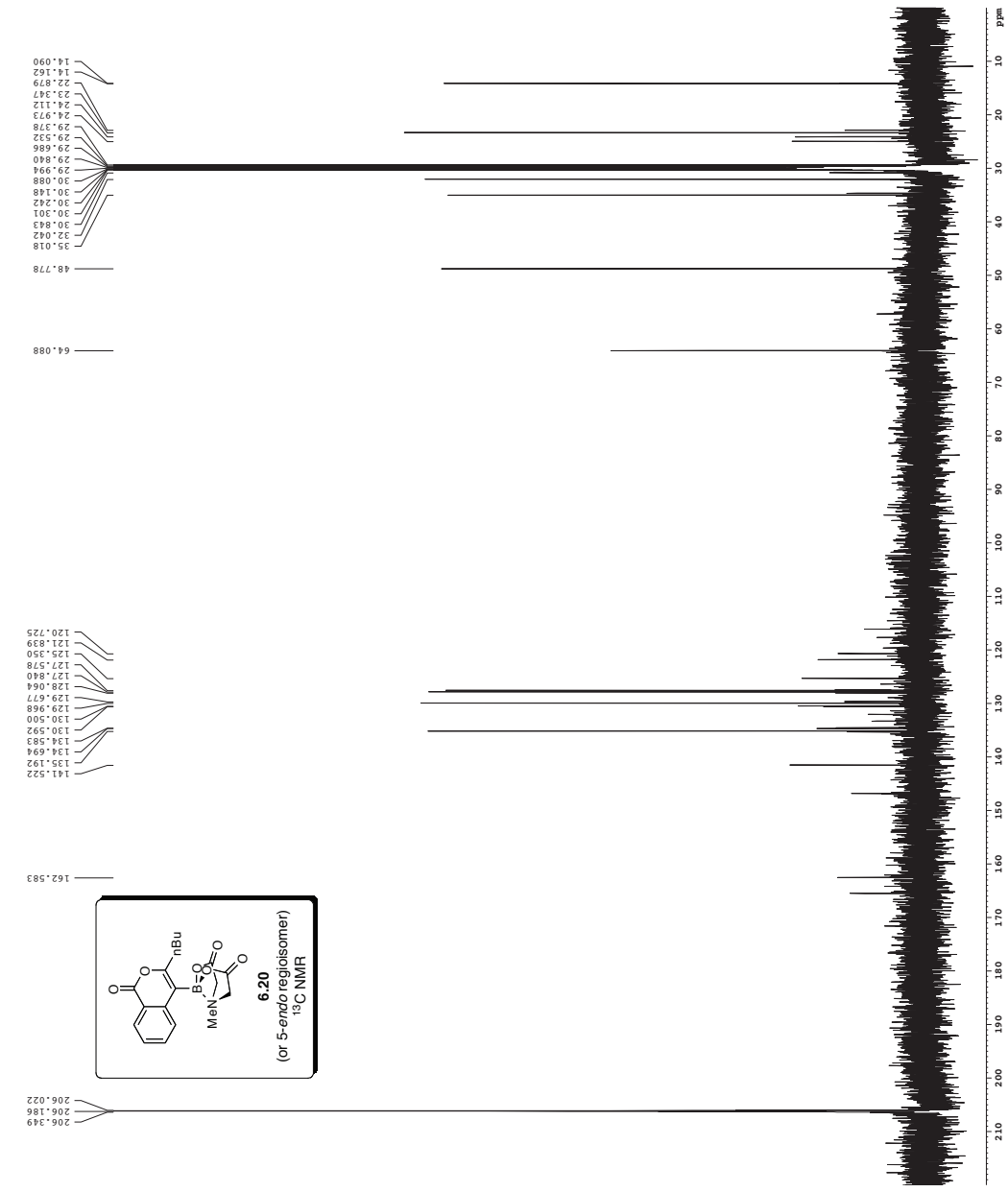


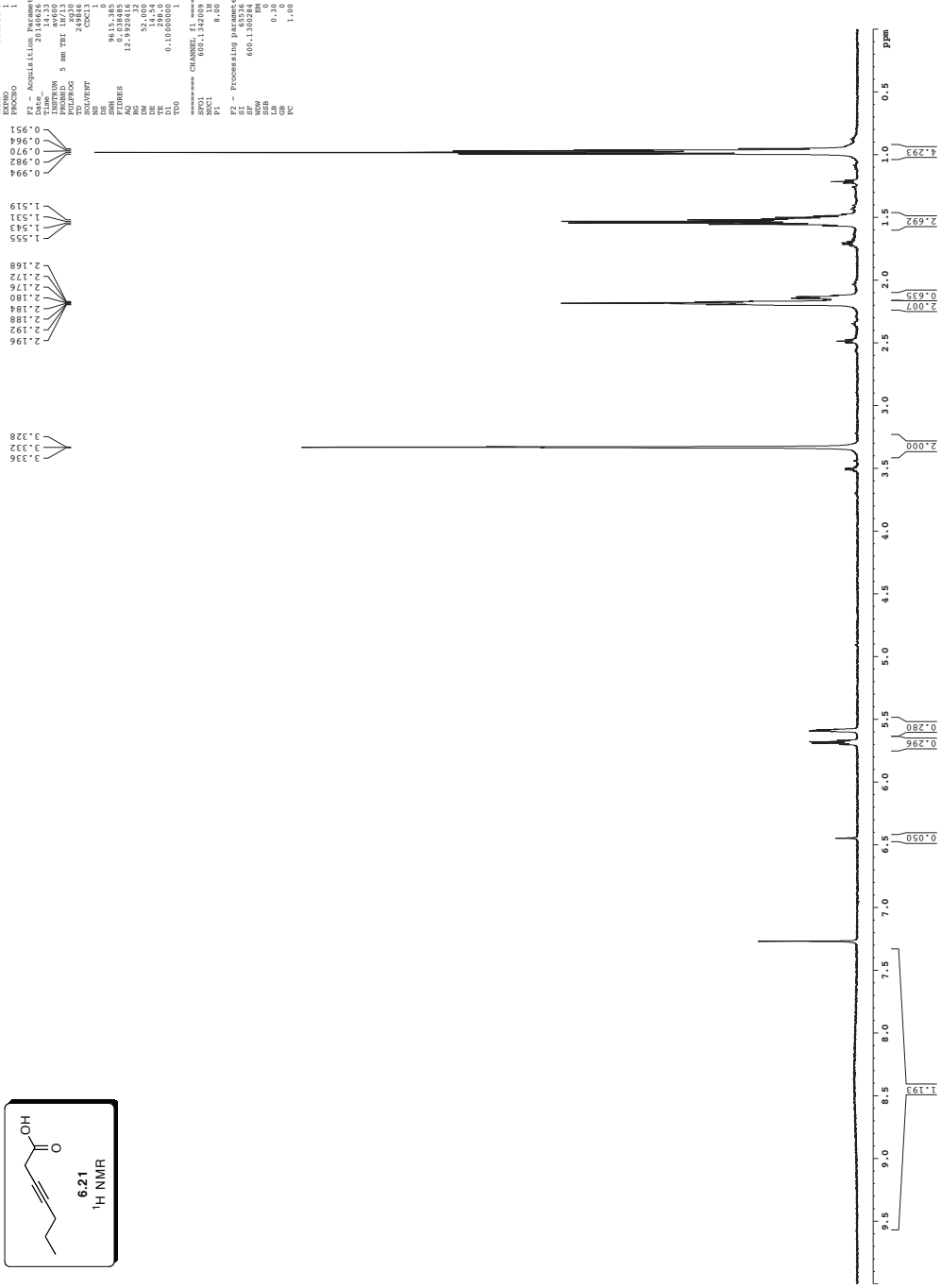
6.20
(or 5-*endo* regioisomer)
^{11}B NMR

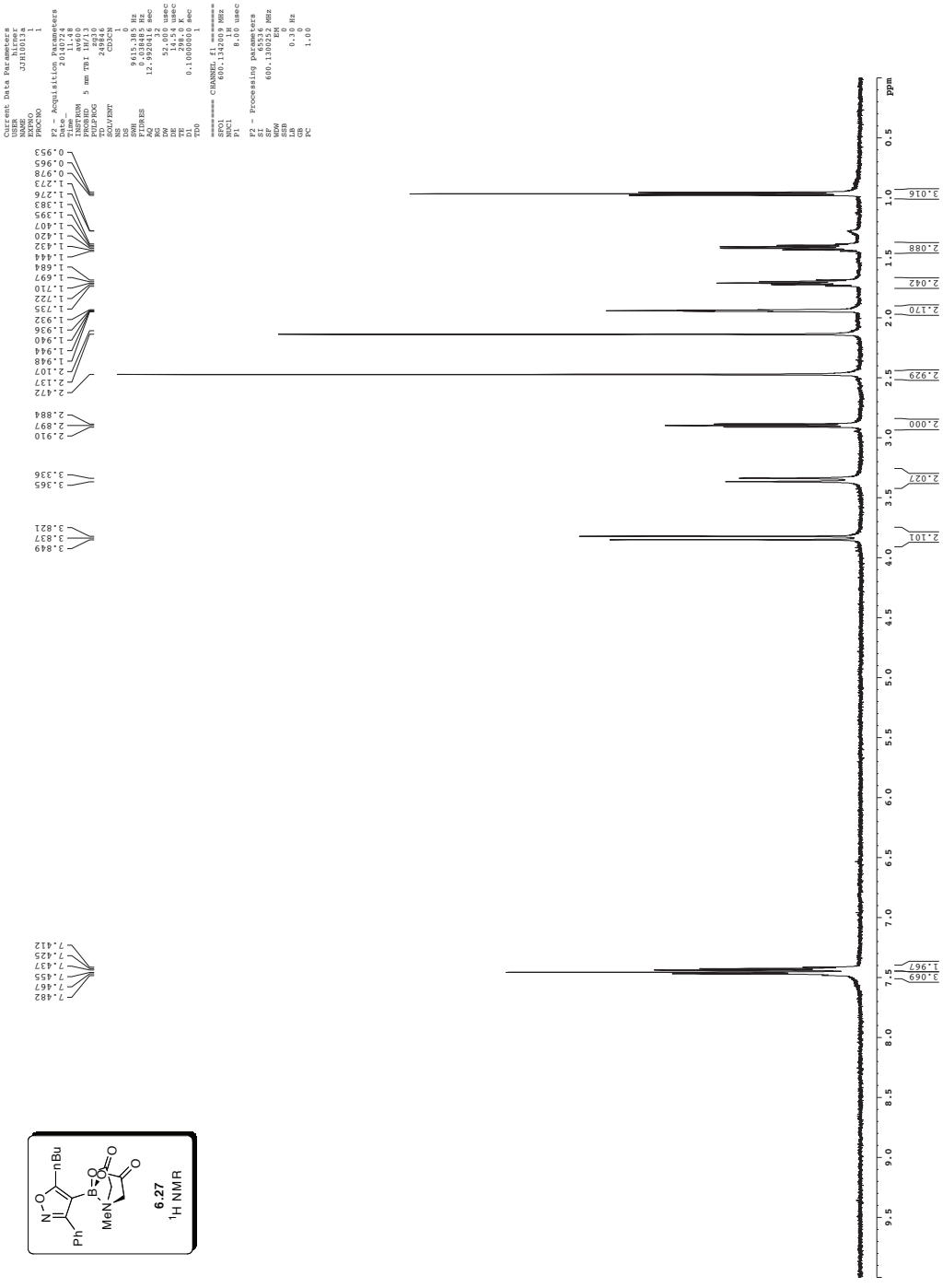
11.975

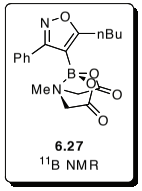
```
Current Data Parameters
USER                hirner
NAME              KT-I-73a
EXPNO                   11
PROCNO                   1

F2 - Acquisition Parameters
Date_             20140718
Time                 14.08
INSTRUM              av600
PROBHD    5 mm TBI 1H/13
PULPROG    zgdc30bs.prd
TD                   65536
SOLVENT            Acetone
NS                       239
DS                         4
SWH              42613.637 Hz
FIDRES            0.650232 Hz
AQ               0.7690057 sec
RG                       362
DW                 11.733 usec
DE                    7.14 usec
TE                  298.1 K
D1              1.00000000 sec
D11             0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
SFO1          192.5455530 MHz
NUC1                   11B
P1                   15.60 usec
P2                   31.20 usec

F2 - Processing parameters
SI                   65536
SF            192.5455591 MHz
WDW                     EM
SSB                      0
LB                    4.00 Hz
GB                       0
PC                    1.00
```




206.349
206.186
206.022
162.583
141.522
135.192
134.694
134.583
130.592
130.500
129.968
129.677
128.064
127.840
127.578
125.350
121.839
120.725
64.088
48.778
35.018
32.042
30.843
30.301
30.242
30.088
30.148
29.994
29.840
29.686
29.532
29.378
24.973
24.112
23.347
22.879
14.162
14.090
nBu
Me
N
B
O
O
O
O
O
O
6.20
(or 5-endo regioisomer)
13C NMR
ppm


OH
O
6.21
1H NMR

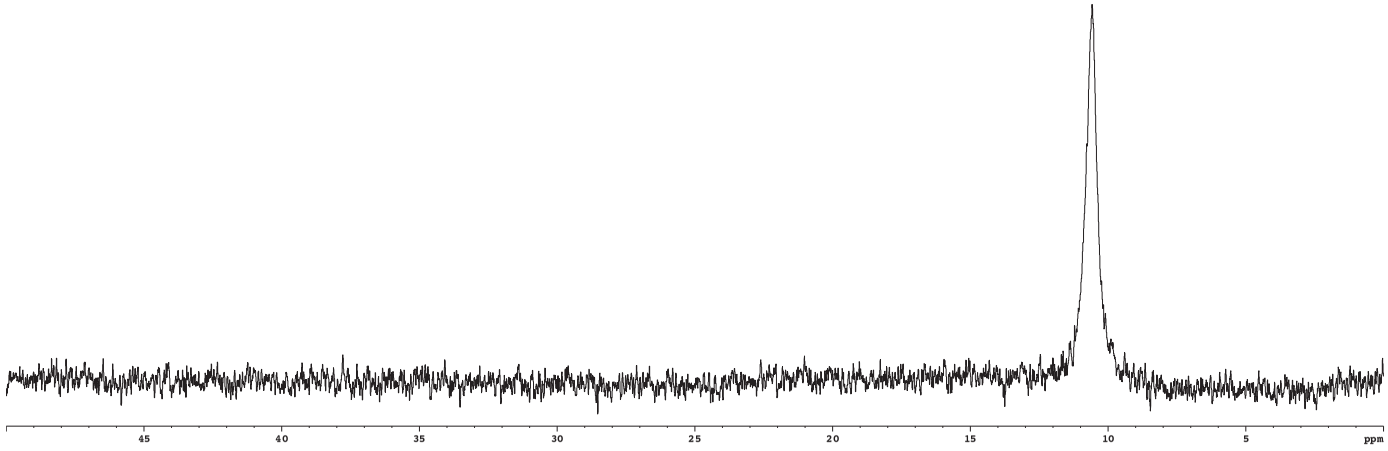

6.27
^{1}H NMR

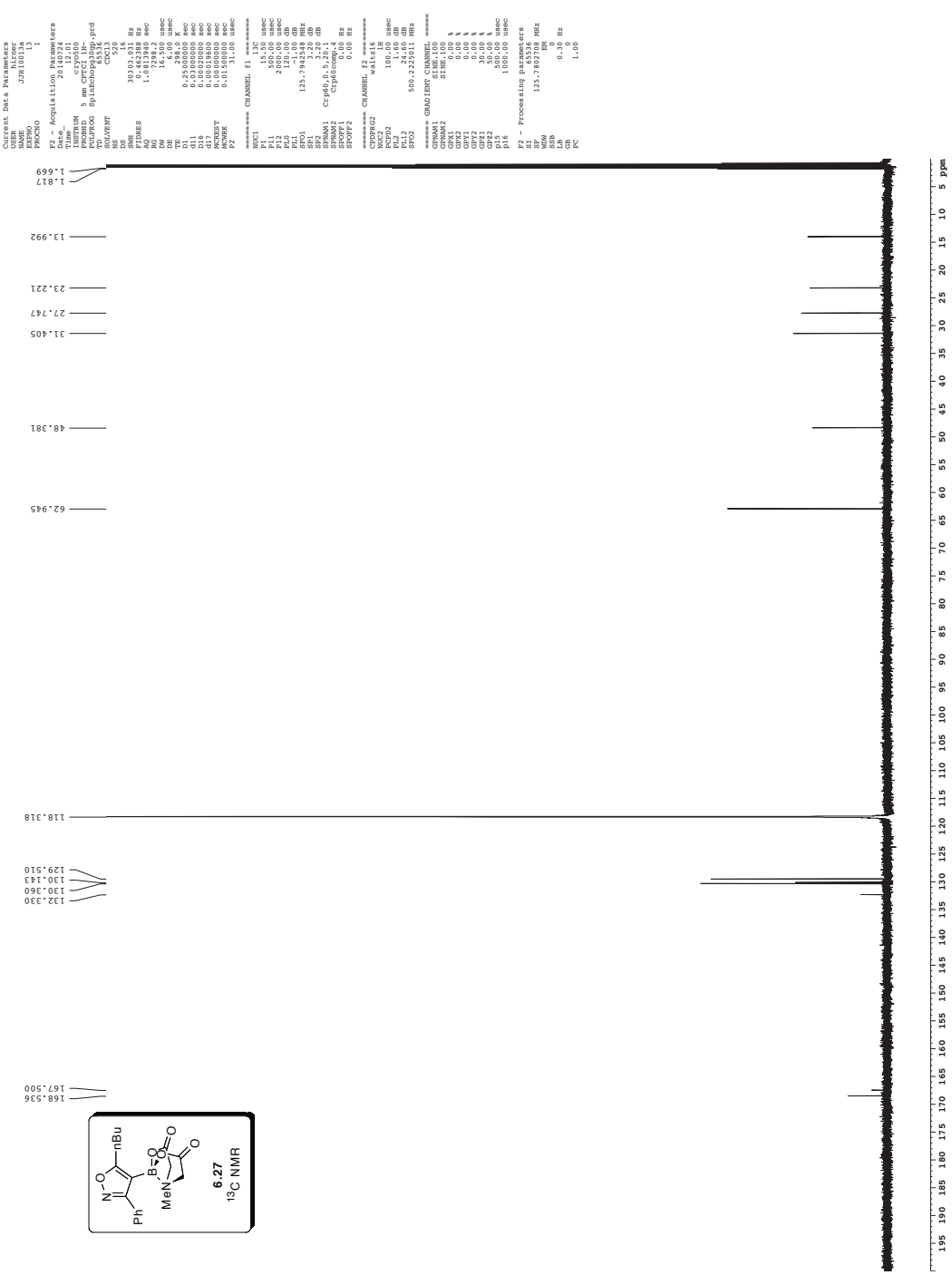


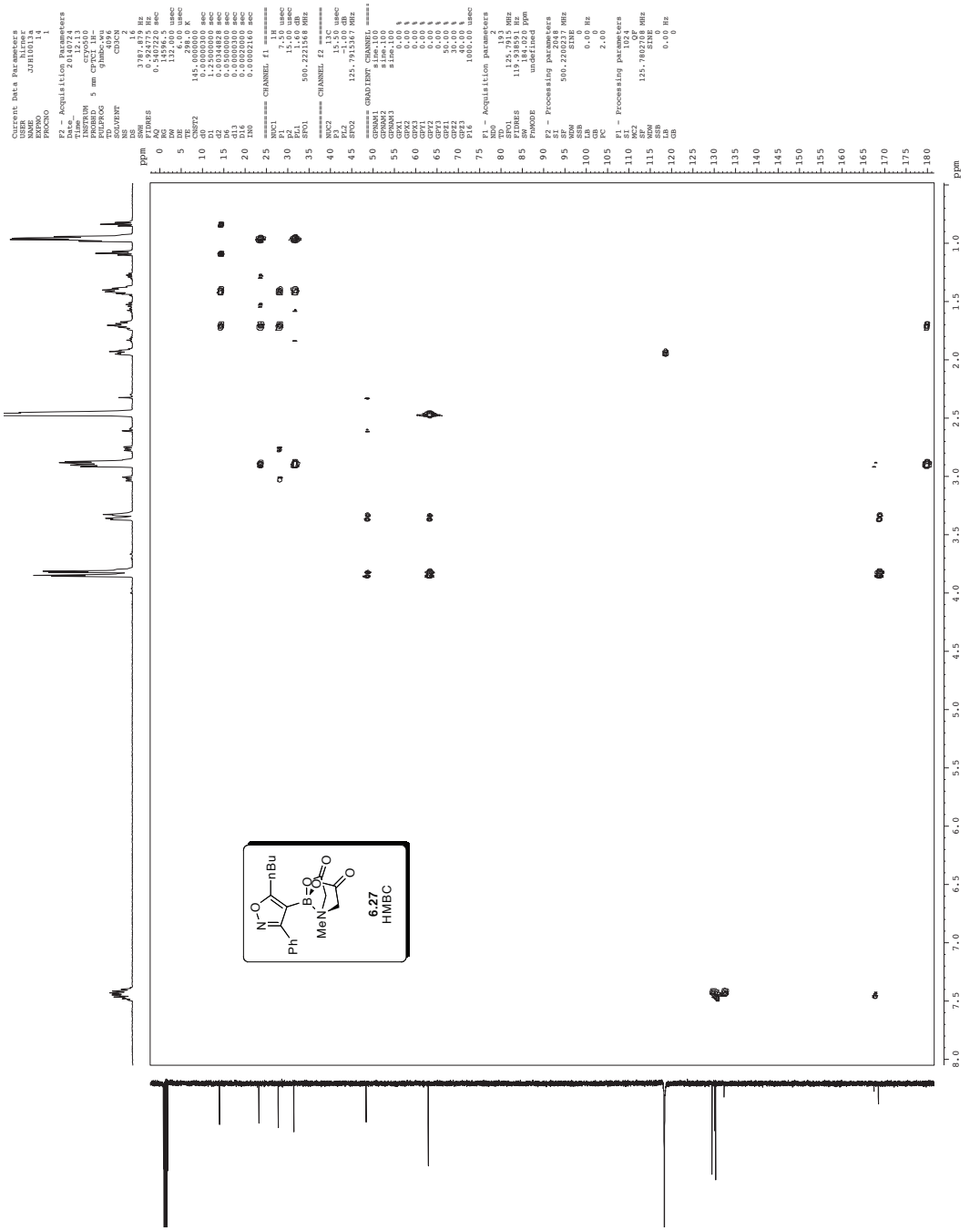
6.27
^{11}B NMR

10.584

```
Current Data Parameters
USER                hirner
NAME             JJH10013a
EXPNO                   11
PROCNO                   1

F2 - Acquisition Parameters
Date_            20140724
Time                11.51
INSTRUM               av600
PROBHD    5 mm TBI 1H/13
PULPROG    zgdc30bs.prd
TD                   35448
SOLVENT              CD3CN
NS                      96
DS                       0
SWH             11867.089 Hz
FIDRES              0.334775 Hz
AQ                1.4935924 sec
RG                    2050
DW                  42.133 usec
DE                   8.71 usec
TE                  298.1 K
D1              1.00000000 sec
D11             0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
SFO1            192.5497836 MHz
NUC1                    11B
P1                    15.60 usec
P2                    31.20 usec

F2 - Processing parameters
SI                    65536
SF              192.5455613 MHz
WDW                     EM
SSB                      0
LB                    4.00 Hz
GB                       0
PC                    1.00
```




6.27
13C NMR
Ph
nBu
MeN
1.817
1.669
13.992
23.221
27.747
31.405
48.381
62.945
118.318
129.510
130.143
130.360
132.330
167.500
168.536


6.27
HMBC