Title

Arynes and Cyclic Alkynes as Synthetic Building Blocks for Stereodefined Quaternary Centers

Journal

Journal of the American Chemical Society, 140(24)

ISSN

0002-7863

Authors

Picazo, Elias
Anthony, Sarah M
Giroud, Maude
et al.

Publication Date

2018-06-20

DOI

10.1021/jacs.8b02875

Peer reviewed

Published in final edited form as:
J Am Chem Soc. 2018 June 20; 140(24): 7605–7610. doi:10.1021/jacs.8b02875.

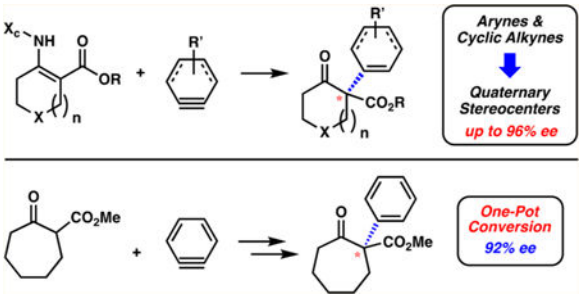
Arynes and Cyclic Alkynes as Synthetic Building Blocks for Stereodefined Quaternary Centers

Elias Picazo[†], **Sarah M. Anthony**[†], **Maude Giroud**, **Adam Simon**, **Margeaux A. Miller**, **K. N. Houk**[*], and **Neil K. Garg**[*]
Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095, United States

Abstract

We report a facile method to synthesize stereodefined quaternary centers from reactions of arynes and related strained intermediates using β-ketoester-derived substrates. The conversion of β-ketoesters to chiral enamines is followed by reaction with in situ generated strained arynes or cyclic alkynes. Hydrolytic workup provides the arylated or alkenylated products in enantiomeric excesses as high as 96%. We also describe the one-pot conversion of a β-ketoester substrate to the corresponding enantioenriched α-arylated product. Computations show how chirality is transferred from the *N*-bound chiral auxiliary to the final products. These are the first theoretical studies of aryne trapping by chiral nucleophiles to set new stereocenters. Our approach provides a solution to the challenging problem of stereoselective β-ketoester arylation/alkenylation, with formation of a quaternary center.

Graphical Abstract



[*]**Corresponding Authors** houk@chem.ucla.edu, neilgarg@chem.ucla.edu.
[†]**Author Contributions** E.P. and S.M.A. contributed equally.

Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT
Supporting Information
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b02875.
Detailed experimental procedures, compound characterization data, and computational analysis (PDF)
Data for $C_{21}H_{25}NOS$ (CIF)

INTRODUCTION

Arynes have historically been avoided as synthetic intermediates as a result of their high reactivity.[1,2] However, recent studies have demonstrated that arynes can be generated under mild reaction conditions,[3] trapped regioselectively using predictive models,[4] and employed in a host of synthetic applications. The utility of arynes is evident, as they have now been used to synthesize natural products, ligands, materials, agrochemicals, and pharmaceutical agents (e.g., **1**−**3**, Figure 1a).[1,5]

The majority of reported synthetic applications of arynes are intermolecular reactions that lead to achiral or racemic products.[5d,e,6] We questioned if arynes and related strained intermediates could instead serve as building blocks to generate enantioenriched products bearing quaternary centers. Only two methodologies leading to intermolecular, stereoselective aryne trappings have been reported and are limited to the synthesis of tertiary stereocenters.[7,8]

We considered the reaction manifold in which β-ketoesters **4**[9] would be trapped with strained alkynes **5**, to give their corresponding α-arylated products **6** with formation of a quaternary stereocenter (Figure 1b).[10] As prior efforts to achieve this direct functionalization in a racemic sense were accompanied by an undesired C−C bond fragmentation,[11] we considered a two-step, alternative approach. First, β-ketoesters **4** would be treated with amines **7** to afford the corresponding enamines **8**.[12] Trapping of the enamines **8** with in situ-generated arynes (or strained cyclic alkynes) would give the α-arylated or alkenylated products **6** after hydrolysis in the same pot.[13] The use of a chiral amine (i.e., **7**) in this process would ultimately give rise to enantioenriched products **6** bearing quaternary stereocenters.[10,14] It should be noted that the enantioselective α-arylation of β-ketoesters has remained a challenging synthetic problem.[15] Promising developments include the use of hypervalent iodine reagents (racemic or modest enantioenrichment),[16] the Cu-catalyzed, enantioselective coupling of 2-methyl acetates with 2-iodotrifluoroacetanilides,[17] and the Pd-catalyzed α-arylation of malonates and cyanoacetates (racemic).[18] A general method for the stereo-controlled α-arylation or -alkenylation of β-ketoesters has not been disclosed.

We report the development of the synthetic sequence shown in Figure 1b, which provides a facile method to achieve the stereoselective α-arylation/alkenylation of β-ketoesters.[9] In addition to providing access to adducts bearing stereodefined quaternary centers, this methodology demonstrates that highly reactive arynes and related intermediates can serve as building blocks to access enantioenriched products by intermolecular trapping. In addition, the origins of stereoselectivity have been revealed by a computational investigation of these reactions.

RESULTS AND DISCUSSION

Development of a Racemic and Stereospecific Reaction to Generate Quaternary Centers.

To commence our studies, we selected β-ketoester **9** as an initial substrate for the two-step arylation procedure (Figure 2). As the use of enamines and arynes to construct quaternary stereocenters was unknown, we first pursued a racemic transformation. Benzylamine was

condensed with ketoester **9** to yield enamine **10** quantitatively. Next, enamine **10** was used to trap benzyne, which was generated in situ from silyl triflate **11** (1.5 equiv) in DME at 30 °C (6 h). After quenching with 1 M $HCl_{(aq)}$, we were delighted to obtain the desired α-arylated product **12** in 92% yield with introduction of a quaternary center.[19] Furthermore, we surveyed several other highly reactive intermediates to gauge the possibility of utilizing substituted benzynes and cyclic alkynes. The use of fused arynes 2,3-naphthalyne and *N*-Boc-4,5-indolyne[20] provided arylated products **13** and **14**, respectively.[21] In addition, trapping with known heterocyclic alkynes[22] delivered tetrahydropyridine **15** and dihydropyran **16** in 67% and 74% yields, respectively. Regioselectivities for the formation of **14**−**16** were in accord with the distortion/interaction model.[20,22] These results represent a facile means to install aryl and vinyl moieties onto a cyclic β-ketoester with quaternary center formation.

Having developed the racemic arylation/alkenylation reaction, we turned our attention to the discovery of a diastereoselective variant to access enantioenriched products (Table 1).[23] Thus, a series of enantioenriched chiral amines, readily prepared using Ellman auxiliary chemistry (i.e., **18**− **24**),[24,25] were condensed with ketoester **9** to access enamines **17**. Subsequent arylation under the conditions depicted in Figure 2 furnished **12** in enantioenriched form. Utilization of phenyl derivative **18** resulted in the formation of **12** in good yield and 74% enantiomeric excess (ee) (entry 1). Employing amine **19**, bearing a cyclohexyl moiety, gave the desired product in a lower ee of 30% (entry 2). Recognizing the importance of the aryl fragment, we examined 1- and 2-naphthyl derived amines **20** and **21**, which provided **12** in 80% and 56% ee (entries 3 and 4, respectively). With improved results in the case of **20**, we examined anthracenyl amines **22**−**24** (entries 5− 7). As the use of ethyl derivative **23** furnished **12** with the best combination of yield and ee (entry 6), **23** was selected for subsequent studies. It should be noted that the Ellman-approach provides both enantiomers of **23**, which, in turn, permits access to each enantiomer of the products depicted subsequently.[26,27]

Scope of Methodology.

With a suitable chiral amine identified, we evaluated several cyclic alkynes in the stereoselective arylation/alkenylation reaction to form quaternary stereocenters (Figure 3). The reaction was tolerant of substituted benzyne intermediates and extended aryl units, giving rise to arylated products **28** and **13**, respectively.[28] Moreover, trapping of an indolyne intermediate delivered heterocycle-containing product **14**. When applied to non-aromatic, strained alkynes, the methodology provided alkenylated products in good yields and stereoselectivities. For example, trapping of cyclohexyne[29] provided cyclohexene derivative **29** in good yield and 86% ee. Additionally, by employing heterocyclic alkynes, products **15** and **16** were obtained in excellent yields and comparable stereoselectivities. As shown in Figure 4, the methodology is also tolerant of variation in the nucleophilic component. For example, replacement of the ethyl ester with a benzyl ester in the parent substrate gave rise to arylated product **32** in 71% yield and 86% ee. Furthermore, piperidinone and tetrahydropyranone derivatives could be employed to access heterocyclic products (i.e., **33**−**35**). Enamines derived from 7-membered ring β-ketoesters could also be utilized, as shown by the formation of arylated products **36** and **37** with excellent stereoselectivity.

Lastly, the formation of ketoester **38** demonstrates the viability of utilizing this methodology for the α-arylation of acyclic β-ketoesters.

One-Pot, Stereoselective Arylation.

As one final application of this methodology, we developed a one-pot variant of the methodology to convert ketoester substrate **39** to α-arylated product **36**, with recovery of the chiral auxiliary (Figure 5). β-Ketoester **39** was reacted with amine **23** to generate enamine **40** in situ. Addition of CsF and silyl triflate **11**, followed by stirring at 30 °C for 6 h, and subsequent acid-mediated hydrolysis yielded the desired α-arylated product **36**. When performed on mmol scale, the reaction gave **36** in 68% yield and 92% ee, in addition to 67% recovered amine **23**. This protocol provides a promising means to achieve the direct, asymmetric α-arylation of β-ketoesters.

Computational Analysis of Chirality Transfer.

Density functional theory (DFT) calculations were performed to understand how stereochemical information is transferred from the chiral auxiliary to the newly formed quaternary stereocenter. Our laboratories have studied reactions of arynes in nucleophilic additions using computations,[4] but no theoretical studies of aryne trapping by chiral nucleophiles to set new stereocenters have been reported. All calculations described here utilize the M06–2X[30]/def2-TZVPP-SMD[31] (diethyl ether)//B3LYP[32]/6–31+G(d,p) level of theory (see the SI for a discussion of the computational methods and results with other density functionals).

We first calculated the stereocontrolling transition structures for the reaction of benzyne and enamine **(*S*)-41**, which possesses the 1-naphthyl group at the chiral center. The stereochemistry-controlling transition structures are shown in Figure 6. Each pathway has a low barrier ($\Delta G^{\ddagger}$ = 9.6 and 11.6 kcal/mol, respectively). TS1 leads to the experimentally preferred stereoisomer, **(*S*)-12**, whereas **TS2** yields the minor enantiomer, **(*R*)-12**.[33] The difference in free energy of activation ($\Delta\Delta G^{\ddagger}$) is 2.0 kcal/mol, within error of the experimentally observed selectivity of 80% ee ($\Delta\Delta G^{\ddagger}$ = 1.3 kcal/mol). In both **TS1** and **TS2**, an intramolecular hydrogen bond between the NH and ester carbonyl is present. Axial-attack by benzyne occurs in both cases, as expected from the preference the forming bond to be staggered with respect to the allylic CH bonds (known previously as the Fürst-Plattner rule).[34] Though attack is axial in both cases, and the chiral group is in its favored conformation, the interaction of the CH at the stereogenic center is disfavorable in the minor TS.

In **TS2**, there is a close-contact H−H interaction of 2.1 Å between the chiral center of the enamine and methylene of the six-membered ring. This contact is alleviated in **TS1**, with an H−H interaction distance of 2.4 Å. Our laboratory has previously examined the transmission of chirality in the reaction of a similar chiral enamine with acrylonitrile, which similarly revealed the importance of torsional interactions between forming bonds and allylic bonds.[34] In that case, the same conformations and their energies were found for the chiral enamine with a phenyl ring instead of naphthyl. Torsional strain[35] controls the stereoselectivity of this reaction, where the enamine conformations remain the same for both stereoisomeric transition states.

One might expect that the stereoselectivity cannot be modulated by the size of the substituent, but as found here, enamine **25** has improved enantioselectivity with the larger 9-anthracenyl substituent. We calculated the stereochemistry-controlling transition structures for the reaction of chiral enamine 25 and benzyne using methyl groups in place of ethyl groups to simplify computations.[36] The two lowest-energy transition structures leading to the major and minor stereoisomers are shown in Figure 7. **TS3** leads to the experimentally preferred stereoisomer, **(*S*)-12**, whereas **TS4** yields the minor enantiomer. The difference in free energy of activation ($\Delta\Delta G^{\ddagger}$) is 2.5 kcal/mol, within error of the experimentally observed selectivity of 84% ee ($\Delta\Delta G^{\ddagger}$ = 1.5 kcal/mol) and 0.5 kcal/mol higher than observed with **20**. Axial-attack by benzyne again occurs for the two half-chair conformers of the cyclohexene. However, here the conformation of the enamine stereogenic group differs between the stereoisomeric transition structures. Whereas the conformation of **TS3** is analogous to that in **TS1**, the enamine in **TS4** is in a higher-energy conformation because the face being blocked to form the (*R*)-isomer is obstructed by the anthracene group. This conformation yields a higher-energy penalty than the torsional strain found in **TS2**, which enables an increase in enantiospecificity.

CONCLUSIONS

We have developed the first methodology that allows for arynes and related strained intermediates to be trapped intermolecularly for the formation of stereodefined quaternary centers. The strategy relies on the facile conversion of β-ketoesters to chiral enamines, which undergo nucleophilic trapping of in situ generated strained arynes or cyclic alkynes. Hydrolysis in the same pot provides the arylated products in good to excellent enantiomeric excesses (up to 96% ee). This strategy circumvents a previously known undesired C−C bond fragmentation, while providing a general solution to the challenging problem of stereoselective β-ketoester arylation/alkenylation, with formation of a quaternary center. In addition, a one-pot procedure for the conversion of a β-ketoester substrate to the corresponding enantioenriched α-arylated product was developed. Finally, computations show how chirality transfer is achieved from the chiral auxiliary to the final products, a type of conformational transmission operating in the trapping of arynes by chiral nucleophiles. We expect these studies will enable further developments of intermolecular, stereoselective reactions of highly reactive aryne and cyclic alkyne intermediates.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

The authors are grateful to the University of California, Los Angeles for financial support. We are grateful to the NIH-NIGMS (F31-GM117945 to E.P.), the Foote Family (E.P.), the Swiss National Science Foundation for an Early Mobility Postdoctoral Fellowship (M.G.), the UCLA Cota-Robles Fellowship Program (E.P.), and the CBI training program (USPHS National Research Service Award 5T32GM008496 to M.A.M. and A.S.). Dr. J. Moreno (UCLA) is acknowledged for experimental assistance, and we thank the Nelson laboratory (UCLA) for use of instrumentation. These studies were supported by shared instrumentation grants from the NSF (CHE-1048804) and the National Center for Research Resources (S10RR025631). This work used computational and storage services associated with the Hoffman2 Shared Cluster provided by UCLA Institute for Digital Research and Education's Research Technology Group.

REFERENCES

(1). For reviews regarding benzyne and related reactive intermediates, see: (a) Pellissier H; Santelli M Tetrahedron 2003, 59, 701–730.(b) Wenk HH; Winkler M; Sander W Angew. Chem., Int. Ed 2003, 42, 502–528.(c) Sanz R Org. Prep. Proced. Int 2008, 40, 215–291.(d) Bronner SM; Goetz AE; Garg NK Synlett 2011, 2599–2604.(e) Tadross PM; Stoltz BM Chem. Rev 2012, 112, 3550–3557. [PubMed: 22443517] (f) Gampe CM; Carreira EM Angew. Chem., Int. Ed 2012, 51, 3766–3778.(g) Bhunia A; Yetra SR; Biu AT Chem. Soc. Rev 2012, 41, 3140–3152. [PubMed: 22278415] (h) Yoshida H; Takaki K Synlett 2012, 23, 1725–1732.(i) Dubrovskiy AV; Markina NA; Larock RC Org. Biomol. Chem 2013, 11, 191–218. [PubMed: 23132413] (j) Wu C; Shi F Asian J. Org. Chem 2013, 2, 116–125.(k) Hoffmann RW; Suzuki K Angew. Chem., Int. Ed 2013, 52, 2655–2656.(l) Goetz AE; Garg NK J. Org. Chem 2014, 79, 846–851. [PubMed: 24410270] (m) Goetz AE; Shah TK; Garg NK Chem. Commun 2015, 51, 34–45.(n) Yoshida S; Hosoya T Chem. Lett 2015, 44, 1450–1460.(o) Bhojgude SS; Bhunia A; Biju AT Acc. Chem. Res 2016, 49, 1658–1670. [PubMed: 27560296]

(2). For the quantification of benzyne's high electrophilicity, see: Fine Nathel NF; Morrill LA; Mayr H; Garg NK J. Am. Chem. Soc 2016, 138, 10402–10405. [PubMed: 27480639]

(3). For Kobayashi's generation of arynes from o-silyltriflate precursors, see: Himeshima Y; Sonoda T; Kobayashi H Chem. Lett 1983, 12, 1211–1214.

(4). For the aryne distortion/interaction model, see: (a) Cheong PH-Y; Paton RS; Bronner SM; Im G-YJ; Garg NK; Houk KN J. Am. Chem. Soc 2010, 132, 1267–1269 [PubMed: 20058924] (b) Im G-YJ; Bronner SM; Goetz AE; Paton RS; Cheong PH-Y; Houk KN; Garg NK J. Am. Chem. Soc 2010, 132, 17933–17944 [PubMed: 21114321] (c) Goetz AE; Bronner SM; Cisneros JD; Melamed JM; Paton RS; Houk KN; Garg NK Angew. Chem., Int. Ed 2012, 51, 2758–2762(d) Bronner SM; Mackey JL; Houk KN; Garg NK J. Am. Chem. Soc 2012, 134, 13966–13969 [PubMed: 22876797] (e) Medina JM; Mackey JL; Garg NK; Houk KH J. Am. Chem. Soc 2014, 136, 15798–15805. [PubMed: 25303232] (f) Picazo E; Houk KN; Garg NK Tetrahedron Lett 2015, 56, 3511–3514. [PubMed: 26034336]

(5). For select examples of synthetic applications, see: (a) Mauger CC; Mignani GA Org. Process Res. Dev 2004, 8, 1065–1071(b) Lin JB; Shah TK; Goetz AE; Garg NK; Houk KN J. Am. Chem. Soc 2017, 139, 10447–10455 [PubMed: 28675700] (c) Surry DS; Buchwald SL Angew. Chem., Int. Ed 2008, 47, 6338–6361(d) Ross SP; Hoye TR Nat. Chem 2017, 9, 523–530. [PubMed: 28537589] (e) Corsello MA; Kim J; Garg NK Nat. Chem 2017, 9, 944–949. [PubMed: 28937679]

(6). Intramolecular aryne trappings, although less common, have been used to construct complex natural product frameworks. See references 1, 5, and the following recent examples: (a) Goetz AE; Silberstein AL; Corsello MA; Garg NK J. Am. Chem. Soc 2014, 136, 3036–3039 [PubMed: 24524351] (b) Neog K; Borah A; Gogoi P J. Org. Chem 2016, 81, Chem. 2017, 2883–2915.

(7). For the intermolecular trapping of benzyne with dienes bearing the Oppolzer sultam (with later cleavage of the auxiliary) to generate tertiary stereocenters, see: (a) Dockendorff C; Sahli S; Olsen M; Milhau L; Lautens M J. Am. Chem. Soc 2005, 127, 15028–15029 [PubMed: 16248633] (b) Webster R; Lautens M Org. Lett 2009, 11, 4688–4691. [PubMed: 19778014]

(8). For the intermolecular trapping of arynes with Schöllkopf reagents (with later hydrolysis) to generate tertiary stereocenters, see: (a) Jones EP; Jones P; Barrett AGM Org. Lett 2011, 13, 1012–1015 [PubMed: 21302900] (b) Jones EP; Jones P; White AJP; Barrett AGM Beilstein J. Org. Chem 2011, 7, 1570–1576. [PubMed: 22238534]

(9). β-Keto esters are commonly seen in bioactive molecules, so methods to synthesize functionalized derivatives are valuable. A Reaxys search reveals there are 53,683 known β-keto esters with biological activity (1 24, 2018).

(10). Methodologies to generate quaternary stereocenters, especially with control of absolute stereochemistry, remain highly sought after. For pertinent reviews, see: (a) Quasdorf KW; Overman LE Nature 2014, 516, 181–191. [PubMed: 25503231] (b) Liu Y; Han S-J; Liu W-B; Stoltz BM Acc. Chem. Res 2015, 48, 740–751. [PubMed: 25715056] (c) Shockley SE; Holder JC; Stoltz BM Org. Process Res. Dev 2015, 19, 974–981. [PubMed: 27293370] (d) Zeng X-P; Cao Z-Y; Wang Y-H; Zhou F; Zhou J Chem. Rev 2016, 116, 7330–7396. [PubMed: 27251100]

(11). For the α-arylation of β-ketoesters, with concomitant C–C bond fragmentation, see: Tambar UK; Stoltz BM J. Am. Chem. Soc 2005, 127, 5340–5341. [PubMed: 15826170]

(12). Enamines derived from β-ketoesters were considered well suited, as they are stable on neutral alumina and can be purified prior to use.

(13). For pioneering studies of racemic enamine arylations, see: (a) Kuehne ME J. Am. Chem. Soc 1962, 84, 837–847.For the α-arylation of enamines with arynes to give functionalized achiral enamines, see: (b) Ramtohul YK; Chartrand A Org. Lett 2007, 9, 1029–1032. [PubMed: 17309270] (c) Li R; Wang X; Wei Z; Wu C; Shi F Org. Lett 2013, 15, 4366–4369. [PubMed: 23957502]

(14). For select previous studies on the enantioselective functionalization of enamines bearing chiral auxiliaries, see: (a) Tomioka K; Ando K; Takemasa Y; Koga K J. Am. Chem. Soc 1984, 106, 2718–2719.(b) Christoffers J; Mann A Chem. - Eur. J 2001, 7, 1014–1027. [PubMed: 11303862] (c) Camara C; Joseph D; Dumas F; d'Angelo J; Chiaroni A Tetrahedron Lett 2002, 43, 1445–1448.(d) Fujimoto T; Endo K; Tsuji H; Nakamura M; Nakamura E J. Am. Chem. Soc 2008, 130, 4492–4496. [PubMed: 18331035]

(15). A related breakthrough, albeit not using β-ketoesters, is the α-arylation of oxindoles using Pd catalysis; see: (a) Altman RA; Hyde AM; Huang X; Buchwald SL J. Am. Chem. Soc 2008, 130, 9613–9620. [PubMed: 18588302] (b) Taylor AM; Altman RA; Buchwald SL J. Am. Chem. Soc 2009, 131, 9900–9901. [PubMed: 19580273] (c) Li P-F; Buchwald SL Angew. Chem., Int. Ed 2011, 50, 6396–6400.

(16). (a) Beringer FM; Forgione PS; Yudis MD Tetrahedron 1960, 8, 49–63.(b) Ochiai M; Kitagawa Y; Takayama N; Takaoka Y; Shiro M J. Am. Chem. Soc 1999, 121, 9233–9234.(c) Oh CH; Kim JS; Jung HH J. Org. Chem 1999, 64, 1338–1340.

(17). Xie X; Chen Y; Ma D J. Am. Chem. Soc 2006, 128, 16050–16051. [PubMed: 17165754]

(18). For the Pd-catalyzed α-arylation of malonates, see: Beare MA; Hartwig JF J. Org. Chem 2002, 67, 541–555. [PubMed: 11798329]

(19). By employing the N-deutero derivative of 10 in this transformation, we observe deuterium incorporation on the ortho position of the aromatic ring of 12. For details, see the SI.

(20). For the synthesis and regioselective trappings of indolynes accessed from silyltriflate precursors, see references 4a and 4b.

(21). For reasons not fully understood, the racemic arylation of the indolyne was lower yielding than the corresponding stereoselective arylation reaction.

(22). For the synthesis and regioselective trappings of these strained cyclic alkynes, see: (a) McMahon TC; Medina JM; Yang Y-F; Simmons BJ; Houk KN; Garg NK J. Am. Chem. Soc 2015, 137, 4082–4085. [PubMed: 25768436] (b) Shah TK; Medina JM; Garg NK J. Am. Chem. Soc 2016, 138, 4948–4954. [PubMed: 26987257]

(23). Other strategies for this transformation were pursued, such as the use of Cu/BOX as a catalyst for the arylation reaction. Additionally, many other classes of amines, such as amino acids and amino acid derivatives were examined in the arylation reaction, but led to either poor yields and/or poor stereochemical outcomes.

(24). For a review on Ellman's chiral sulfinamides, see: (a) Ellman JA; Owens TD; Tang TP Acc. Chem. Res 2002, 35, 984. [PubMed: 12437323] Procedure followed to synthesize chiral anthracenyl amines: (b) Rodriguez-Hernandez R; Hernandez-Castillo T; Huizar-Trejo KE Synthesis 2011, 2817–2821.

(25). Chiral auxiliaries have seen widespread use to install important stereocenters in drugs and complex targets. For a recent review, see: (a) Farina V; Reeves JT; Senanayake CH; Song J Chem. Rev 2006, 106, 2734–2793. [PubMed: 16836298] For examples using chiral sulfinamides, see: (b) Pflum DA; Krishnamurthy D; Han Z; Wald SA; Senanayake CH Tetrahedron Lett 2002, 43, 923–926.(c) Han ZS; Herbage MA; Mangunuru HPR; Xu Y; Zhang L; Reeves JT; Sieber JD; Li Z; DeCroos P; Zhang Y; Li G; Li N; Ma S; Grinberg N; Wang X; Goyal N; Krishnamurthy D; Lu B; Song JJ; Wang G; Senanayake CH Angew. Chem., Int. Ed 2013, 52, 6713–6717.For examples of chiral auxiliaries used in drug development see: (d) Zhang W-Y; Sun C; Hunt D; He M; Deng Y; Zhu Z; Chen C-L; Katz CE; Niu J; Hogan PC; Xiao X-Y; Dunwoody N; Ronn M Org. Process Res. Dev 2016, 20, 284–296.

(26). For the crystallographic data used to assign the absolute stereochemistry of amine 23 and its enantiomer, see the SI.

(27). The choice of enantiomer of 23 used in subsequent experiments was made arbitrarily, as both were prepared in gram quantities.

(28). The regioselective formation of 28 is consistent with previously observed trends in the trapping of 3-methylbenzyne; see: Aithagani SK; Dara S; Munagala G; Aruri H; Yadav M; Sharma S; Vishwakarma RA; Singh PP Org. Lett 2015, 17, 5547–5549. [PubMed: 26562479]

(29). For a study involving the generation and trapping of cyclohexyne, see: Medina JM; McMahon TC; Jiménez-Osés G; Houk KN; Garg NK J. Am. Chem. Soc 2014, 136, 14706–14709. [PubMed: 25283710]

(30). Zhao Y; Truhlar DG Theor. Chem. Acc 2008, 120, 215–241.

(31). Marenich AV; Cramer CJ; Truhlar DG J. Phys. Chem. B 2009, 113, 6378–6396. [PubMed: 19366259]

(32). (a) Vosko SH; Wilk L; Nusair M Can. J. Phys 1980, 58, 1200–1211.(b) Lee C; Yang W; Parr RG Phys. Rev. B: Condens. Matter Mater. Phys 1988, 37, 785–789.(c) Becke AD J. Chem. Phys 1993, 98, 5648–5652.(d) Stephens PJ; Devlin FJ; Chabalowski CF; Frisch MJ J. Phys. Chem 1994, 98, 11623–11627.

(33). The stereochemical outcome predicted by the computational analysis was validated experimentally. For the determination of product absolute stereochemistry, see the SI.

(34). Lucero MJ; Houk KN J. Am. Chem. Soc 1997, 119, 826–827.

(35). Wu YD; Houk KN; Paddon-Row MN Angew. Chem., Int. Ed. Engl 1992, 31, 1019–1021.

(36). From the results provided in Table 1, entries 5 and 6, the use of methyl vs ethyl has a negligible impact on stereoselectivity.

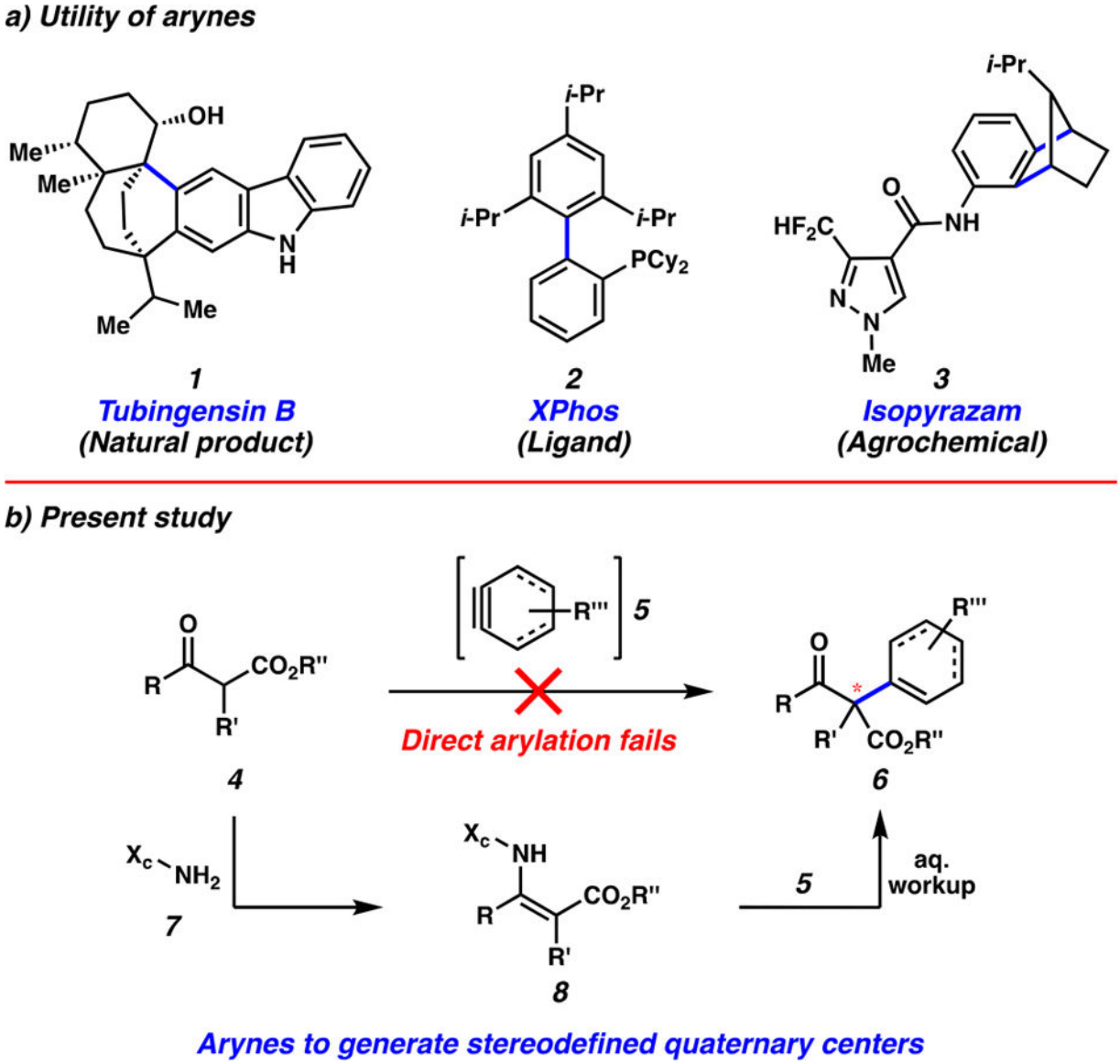


Figure 1.

Synthetic applications of arynes and strategy for the stereoselective arylation of β-ketoesters.

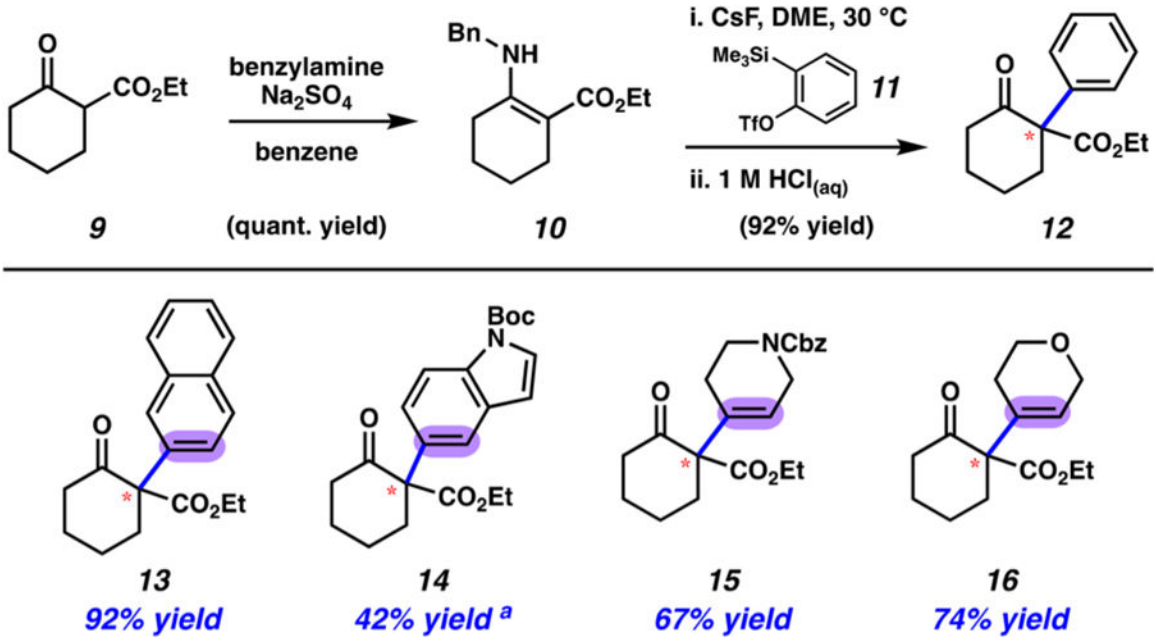


Figure 2.

Discovery of methodology for the arylation/vinylation of *β*-ketoesters in racemic fashion. Conditions for enamine formation: ketoester **9** (1.0 equiv), benzylamine (1.5 equiv), Na_2SO_4 (5:1 by wt.), benzene (0.7 M), 80 °C, 16 h. Conditions for arylation/alkenylation unless otherwise stated: (i) enamine **10** (1.0 equiv), silyl triflate (1.5 equiv), CsF (7.5 equiv), DME (0.1 M), 30 °C, 6 h; (ii) 1 M $HCl_{(aq)}$, 23 °C, 30 min. Yields reflect the average of two isolation experiments. *a*Aryne trapping performed for 3 h.

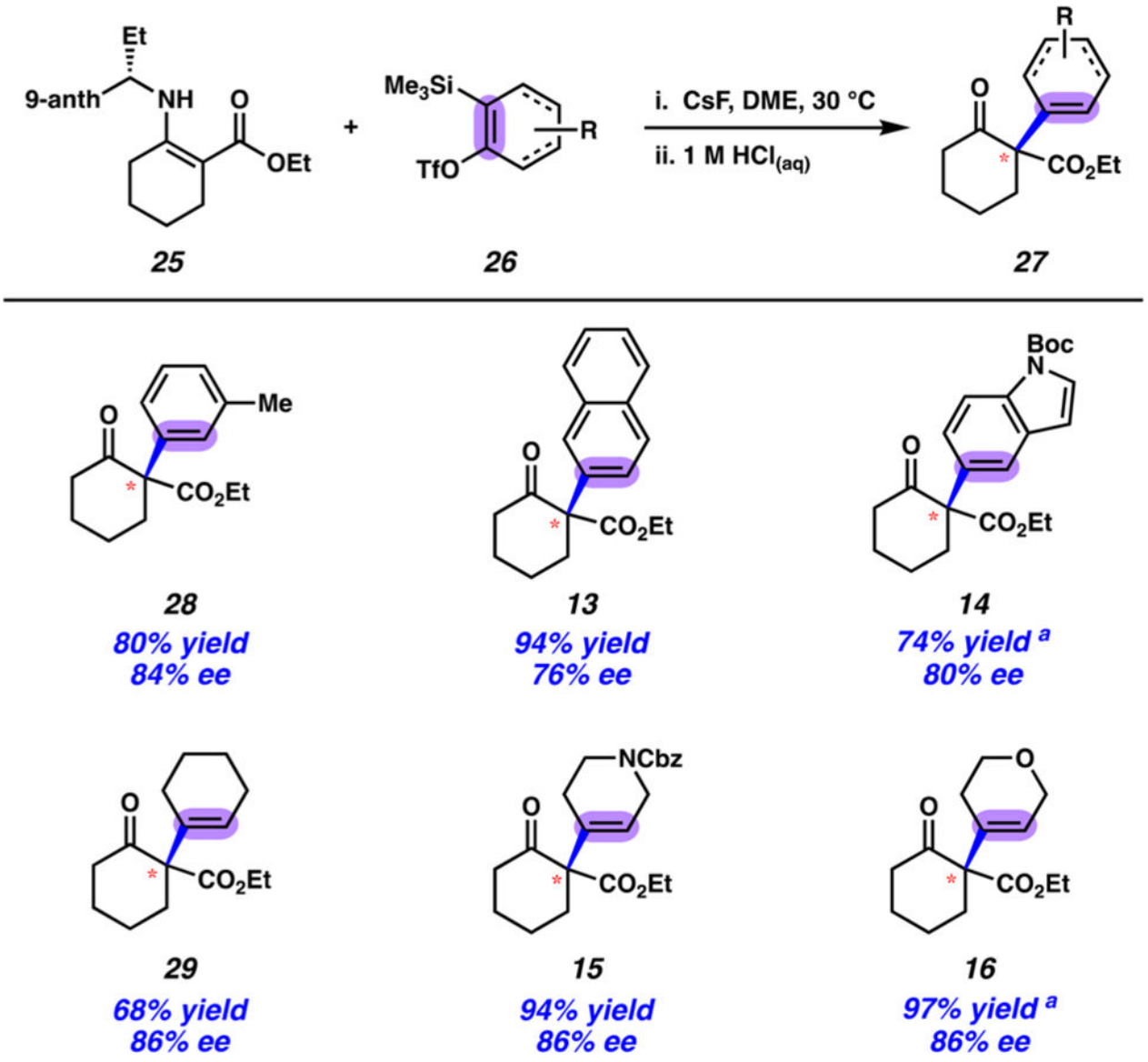


Figure 3.

Variation of the electrophile. Conditions unless otherwise stated: (i) enamine **25** (1.0 equiv), silyl triflate **26** (1.5 equiv), CsF (7.5 equiv), DME (0.1 M), 30 °C, 6 h; (ii) 1 M $HCl_{(aq)}$, 23 °C, 30 min. Yields reflect the average of two isolation experiments. [a]Aryne or cyclic alkyne trapping performed for 3 h.

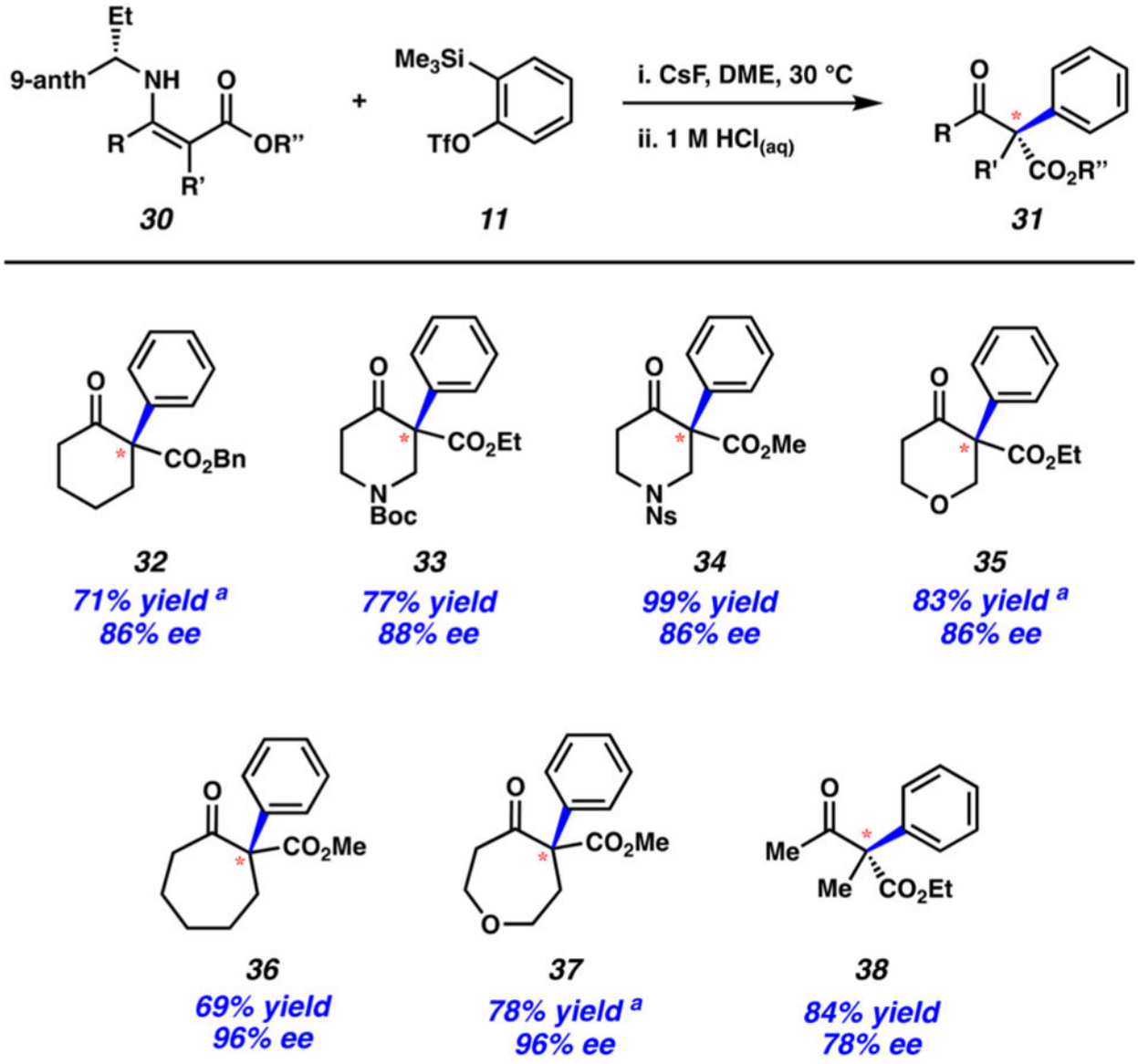


Figure 4.

Variation of the nucleophilic component **30** in the trapping with **11**. Conditions unless otherwise stated: (i) enamine **30** (1.0 equiv), silyl triflate 11 (1.5 equiv), CsF (7.5 equiv), DME (0.1 M), 30 °C, 3 h; (ii) 1 M $HCl_{(aq)}$, 23 °C, 30 min. Yields reflect the average of two isolation experiments. [a]Aryne trapping performed for 6 h.

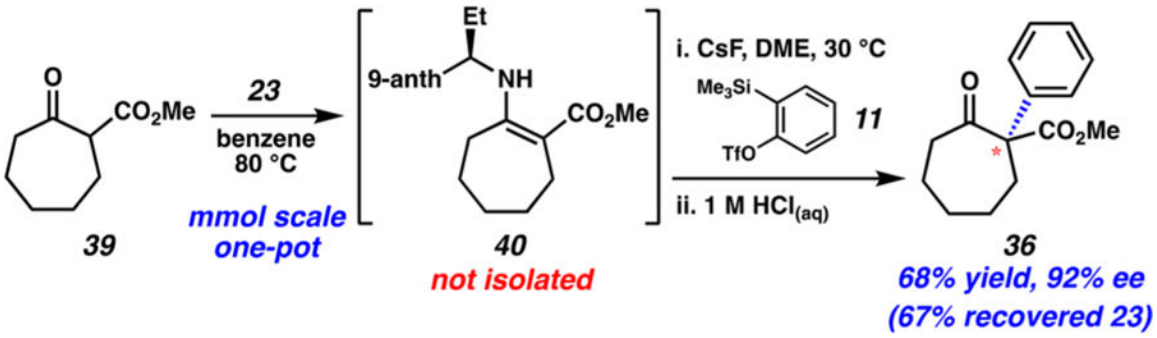


Figure 5.

One-pot, mmol-scale arylation reaction to furnish **36**. Conditions for enamine formation: ketoester **39** (1.0 equiv), amine **23** (1.0 equiv), benzene (0.7 M), 80 °C, 16 h, followed by evaporation of benzene solvent. Conditions for arylation: (i) silyl triflate **11** (1.5 equiv), CsF (7.5 equiv), DME (0.1 M), 30 °C, 6 h; (ii) 1 M $HCl_{(aq)}$, 23 °C, 12 h.

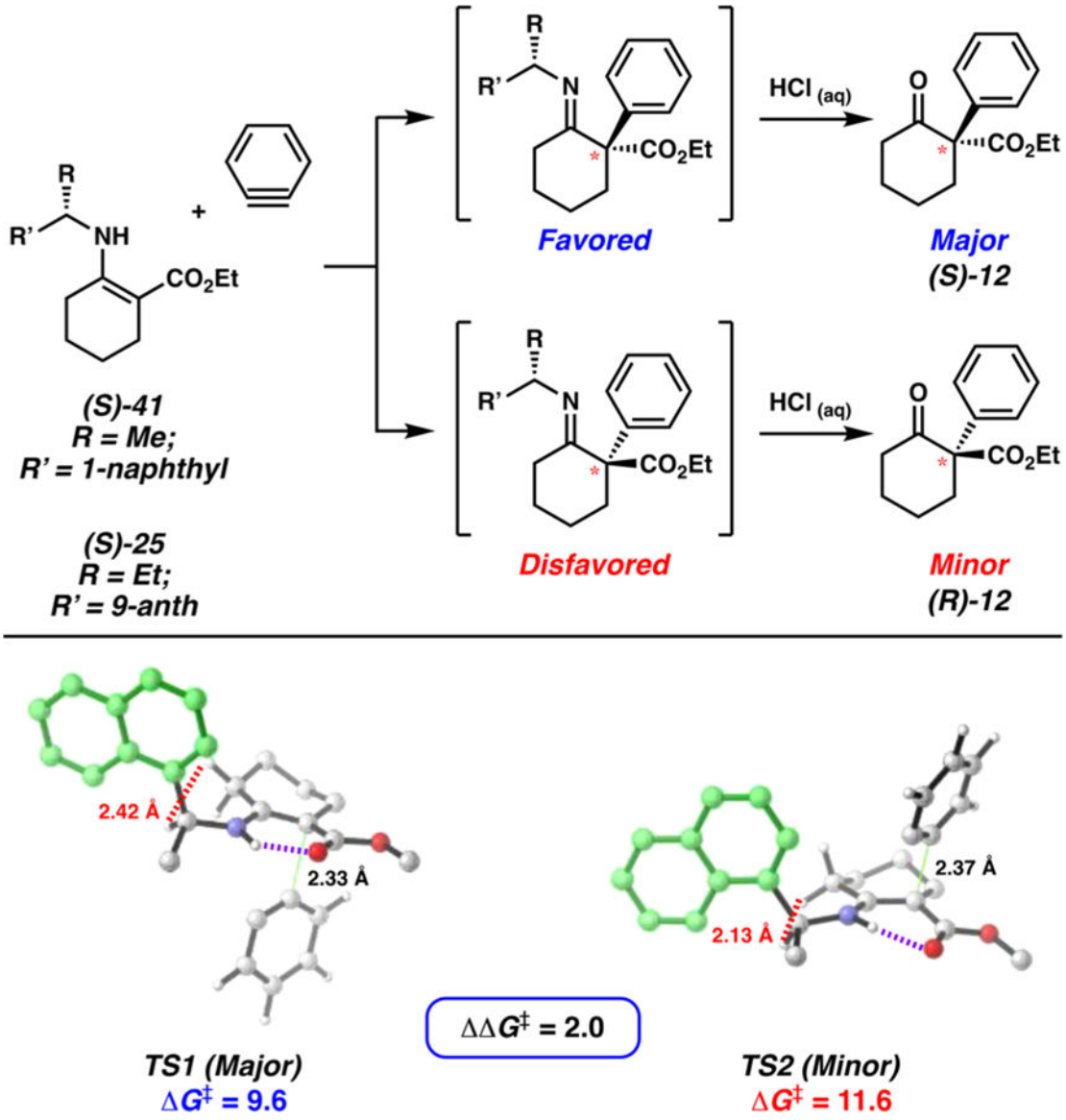


Figure 6.

Lowest-energy transition structures **TS1** and **TS2** for the addition of benzyne and the chiral enamine derived from amine 20 (M06–2X/def2-TZVPP-SMD (diethyl ether)//B3LYP/6–31+G(d,p)). Free energy activation barriers ($\Delta G^{\ddagger}$) are compared to separated intermediates. The difference in free energies of activation ($\Delta\Delta G^{\ddagger}$), relative to **TS1**, is reported in kcal/mol.

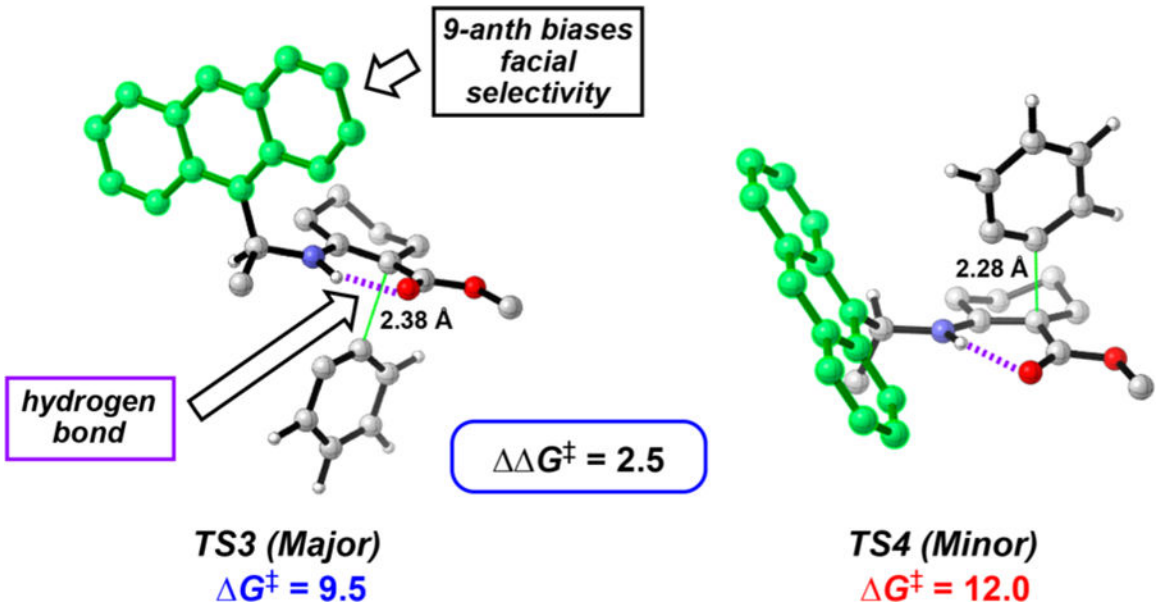
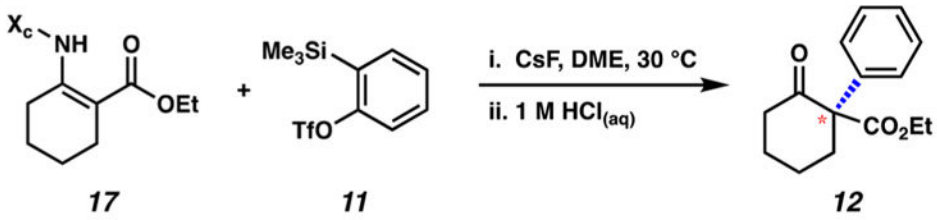


Figure 7.

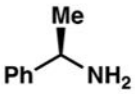
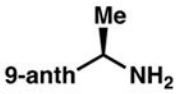
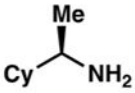
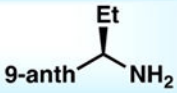
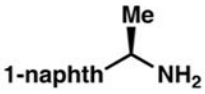
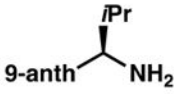
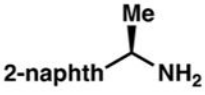
Lowest-energy transition structures **TS3** and **TS4** for the addition of benzyne and chiral enamine **25** (M06–2X/def2-TZVPP− SMD (diethyl ether)//B3LYP/6–31+G(d,p)). Free energy activation barriers ($\Delta G‡$) are compared to separated intermediates. The difference in free energies of activation ($\Delta\Delta G^{‡}$), relative to **TS3**, is reported in kcal/mol.

Table 1.

Survey of Chiral Auxiliaries To Give Optically Enriched Ketone 12[a]



17 11 12

Entry	X_c–NH_2	Yield	ee	Entry	X_c–NH_2	Yield	ee
1	 18	87%	74%	5	 22	71%	94%
2	 19	64%	30%	6	 23	96%	84%
3	 20	72%	80%	7	 24	100%	66%
4	 21	79%	56%				

[a]Reaction conditions: (i) enamine 17 (1.0 equiv), silyl triflate 11 (1.5 equiv), CsF (7.5 equiv), DME (0.1 M), 30 °C, 6 h; (ii) 1 M $HCl_{(aq)}$, 23 °C, 30 min.