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Global Diastereoconvergence in the Ireland–Claisen Rearrangement of Isomeric Enolates: Synthesis of Tetrasubstituted α-Amino Acids

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Abstract

A dual experimental/theoretical investigation of the Ireland–Claisen rearrangement of tetrasubstituted α-phthalimido ester enolates to afford α-tetrasubstituted, β-trisubstituted α-amino acids (generally >20:1 dr) is described. For trans allylic olefins, the *Z* and *E*-enol ethers proceed through chair and boat transition states, respectively. For cis allylic olefins, the trend is reversed. As a result, the diastereochemical outcome of the reaction is preserved regardless of the geometry of the enolate or the accompanying allylic olefin. We term this unique convergence of all possible olefin isomers as *global diastereoconvergence*. This reaction manifold circumvents limitations in present-day technologies for the stereoselective enolization of α,α-disubstituted allyl esters. Density functional theory paired with state-of-the-art local coupled-cluster theory (DLPNO-CCSD(T)) was employed for the accurate determination of quantum mechanical energies.

Keywords

diastereoconvergence; Ireland–Claisen; Tetrasubstituted amino acid

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‡These authors contributed equally. All authors have given approval to the final version of the manuscript.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Supporting Information (PDF)

QM Energies (.xlsx)

Coordinates of structures (.xyz)

INTRODUCTION

For over forty years, the Ireland–Claisen rearrangement has been a mainstay for the construction of a diversity of carbon–carbon bonds in organic synthesis.[1] The ubiquity of the Ireland–Claisen rearrangement can be attributed to the relative ease of accessing the requisite allylic ester and the robust and predictable stereochemical outcome of the rearrangement. Consequently, the Ireland–Claisen rearrangement has been an indispensable tool for the construction of sterically encumbered vicinal stereogenic centers. Despite the utility of the Ireland–Claisen rearrangement, one longstanding challenge is the implementation of fully substituted acyclic allyl ester enolates derived from α,α-disubstituted esters. This is presumably a consequence of the difficulty in controlling the enolate geometry in tetrasubstituted ester-derived systems. The Ireland–Claisen rearrangement typically proceeds through a predictable and well-defined chair-like transition state, thus, *E*- and *Z*-enolate geometries lead to diastereomeric products, necessitating a highly selective enolization protocol for efficient diastereoselection.

Few examples of fully substituted, acyclic enolates in highly diastereoselective Ireland–Claisen rearrangements have been reported to date.[2] Zakarian and coworkers established the first effective protocol for the selective enolization of chiral α,α-disubstituted esters utilizing chiral Koga-type[3] bases to impart *E*/*Z* enolization selectivity (Figure 1A).[4] Although this protocol enables the selective generation of either *E*- or *Z*-tetrasubstituted ester enolates under mild conditions to access both diastereomeric series of rearrangement products, the utilization of allylic esters with highly enantioenriched or enantiopure α-stereocenters is required and each substrate requires optimization of the chiral base. Crimmins and coworkers utilized a chiral auxiliary approach to prepare chiral, non-racemic α-methyl-β-hydroxy allylic esters toward the synthesis of briarane natural products (Scheme 1B).[5] In this approach, enolization selectivity is imparted by chelation and steric approach control to provide Ireland–Claisen rearrangement products with generally excellent diastereoselectivity.

More recently, Zakarian and coworkers investigated the diastereodivergent Ireland–Claisen rearrangement of tetrasubstituted α-alkoxy ester enolates toward the synthesis of α-alkoxy carboxylic acids (Scheme 1C).[6] While the chelation-controlled, kinetic *Z*-selective enolization of α-alkoxy esters has been well established,[7] Zakarian and coworkers found an *E*-selective enolization could be achieved with judicious choice of base and solvent based on prior research from Langlois and coworkers.[8] While a variety of α-alkoxy carboxylic acid products were obtained with good to excellent diastereoselectivity, the level of control over enolate geometry is highly substrate dependent, particularly for *E*-selective enolization.

We address the limitations of enolate geometry control by developing a system wherein both enolate geometries converge to a single diastereomer of product, rendering the enolization selectivity inconsequential (Figure 1D). This was accomplished in the context of tetrasubstituted amino acid synthesis wherein intramolecular interactions of an α-phthalimide group with an *E*-phenyl substituted allyl olefin serves to overturn the inherent preference for the chair-like transition state from the *E*-silyl enol ether ($\Delta\Delta G^{\ddagger} = -3.8$ kcal/mol). In contrast, these interactions reinforce the energetic preference for the chair-like

transition state from the *Z*-silyl enol ether ($\Delta\Delta G^{\ddagger}$ = 5.5 kcal/mol). Consequently, in the case of a *Z*-phenyl substituted allyl olefin, the *E*-silyl enol ether rearranges via a chair-like transition state, while from the *Z*-silyl enol ether a boat-like transition state is favored.

The ability to incorporate an enantioenriched allylic stereogenic center in the Ireland–Claisen rearrangement allows for the transfer of chirality with generally excellent stereochemical fidelity. We demonstrate that chirality transfer is conserved within the divergent transition state preference from *E*-and *Z*-silyl enol ethers. In this study, we detail the computational design and modeling and experimental investigation of the Ireland–Claisen rearrangement of tetrasubstituted α-phthalimido ester enolates toward the synthesis of non-natural tetrasubstituted α-amino acid derivatives bearing vicinal stereogenic centers (Figure 1D).

RESULTS AND DISCUSSION

Quantum mechanical evaluation of the diastereoconvergent Ireland–Claisen rearrangement.

Quantum Mechanics (QM) calculations were carried out in order to probe the energetic requirements for a diastereoconvergent transformation. A multi-level approach was employed in which geometries, thermodynamic corrections, and solvation free energies are obtained via density functional theory (DFT) with final electronic energies obtained from calculations with domain based local pair natural orbital coupled-cluster theory (DLPNO-CCSD(T)). Reported energies are relative Gibbs free energies in kcal/mol calculated at 298.15 K with the DLPNO-CCSD(T)/cc-pVTZ/SMD(Toluene)//B3LYP-D3(BJ)/6–31G(d) level of theory. Throughout the text, signed $\Delta\Delta G^{\ddagger}$ defined as $\Delta G^{\ddagger}$(boat) – $\Delta G^{\ddagger}$(chair) are provided. All computations were carried out using the ORCA program.[9] Full computational details as well as comparisons between DFT and coupled-cluster methods are included in the Supporting Information section.

In a fully simplified model system, i.e. the trimethylsilyl enol ether derived from allyl acetate (**1**), an energetic preference of 2.6 kcal/mol is observed for the chair-like (**TS1**) over the boat-like transition state (**TS2**) (Figure 2A, D entry 1). A diastereoconvergent rearrangement will occur in the case of *E/Z* mixtures of tetrasubstituted enolates when the sum of the interactions between the substituents for one enolate geometry overcomes the intrinsic preference for a chair-like transition state to the extent that the boat-like transition state is significantly favored. The groups of Houk, Neier, and Aviyente described a preference for a boat-like transition state in the Ireland–Claisen rearrangement of cyclohexenyl esters which was attributed to steric interactions between the enolate and cyclohexenyl fragments.[10] In the case of acylic, tetrasubstituted enol ethers, these interactions are diminished.

We examined stereoconvergence in the Ireland–Claisen rearrangement in the context of the synthesis of valuable tetrasubstituted α-amino acid building blocks. The α-phthalimido group was chosen as a stable, easily removed, bis-protected α-amine.[11] Introduction of the α-phthalimido group imparts a minimal effect on the chair/boat selectivities, with a preference for the chair-like (**TS3/TS5**) over boat-like transition state (**TS4/TS6**) for both

E- and *Z*-silyl enol ethers (***(E/Z)*-3**) of 3.4 and 2.4 kcal/mol, respectively (Figure 2B, D entry 2). While introduction of substitution in the form of a phenyl group at the terminus of the allylic olefin slightly increases the preference for the chair-like transition state from ***(Z)*-5** to 4.2 kcal/mol, the boat-like transition state is 1.0 kcal/mol lower in energy than the chair-like transition state from enol ether ***(E)*-5** (Figure 2B, D entry 3). This reversal in preference for chair versus boat-like transition state for the α-phthalimido *E*-silyl enol ethers is further exacerbated with additional substitution of the silyl enol ether. In fact, the boat-like transition state (**TS14**) derived from the corresponding α-phenyl-α-phthalimido *E*-silyl enol ether (***(E)*-8**) is computed to be 3.8 kcal/mol lower in energy than its chair counterpart (**TS13**) (Figure 2B, D entry 4).

In contrast, high levels of selectivity for the chair-like transition state are anticipated for the fully substituted *Z*-silyl enol ether (***(Z)*-8**), with the chair-like transition state (**TS11**) favored over the boat-like transition state (**TS12**) by 5.5 kcal/mol (Figure 2B, D entry 4). As a result, for the fully substituted system, the diastereoselectivity of the ensuing Ireland–Claisen rearrangement is anticipated to be independent of the *E/Z* selectivity in the enolization and trapping of the requisite tetrasubstituted silyl enol ether. Note the diastereoconvergent effect is significantly less pronounced when the α-phenyl group is substituted for an α-ethyl substituent (Figure 2C, D entry 5).[12]

Initial experimental investigations.

Ireland–Claisen rearrangement of computationally modeled α-phthalimido cinnamyl ester **14** leads to >20:1 diastereoselection with under several different enolization conditions (Table 1). Enolization conditions of 1:1 LiHMDS/Me_2NEt (entry 1) were originally developed by Gosselin, Zhang, and coworkers[13] for the highly selective enolization of α,α-disubstitued aryl ketones. Additionally, Stoltz and Zhang demonstrated these conditions can be applied to the selective enolization and trapping of a variety of acyclic α-aryl substituted carboxylic acid derivatives including α-ethyl-α-phenyl *t*-butyl, phenyl, and ethyl esters.[14] Enolization with LiHMDS (entry 2) and KHMDS (entry 3) without additives results in identical yields and diastereoselectivity. Notably, phthalimide protected amino acid **15a** is obtained without column chromatography and the relative stereochemistry was confirmed unambiguously by X-ray crystallography, matching the computationally predicted outcome.[15]

Direct observation of and quantification of the ratio of enolate geometries formed in situ proved challenging due to the facile nature of the rearrangement at low temperature and heterogeneous reaction mixture. Thus, analogous di-hydro-α-phthalimide substituted ester **16** was examined as a surrogate to **14** that is incapable of undergoing rearrangement. A variety of kinetic enolate trapping reagents (e.g. TMSCl, TMSOTf, Ts_2O, Tf_2O) were studied employing the same enolization conditions (vide supra). These trapping experiments failed due to the inability to form or isolate the resulting enol ethers, however, moderate yields of allyl enol carbonate isomers **A** and **B** were obtained with allyl chloroformate as an *O*-acylating reagent (Table 2). In each enolization and *O*-acylation control, a mixture of two isomeric enol carbonates was generated in varying *E*/*Z* ratios. Despite variable yields and selectivities, these results demonstrate that under each set of non-equilibrating

enolization conditions, a mixture of enolates is generated. These yields do not necessarily reflect the true enolization selectivity due to the difficulty of *O*-acylation of the in situ-generated enolate. Although the reaction yield and diastereoselectivity of the Ireland–Claisen rearrangement of cinnamyl ester **14** is consistent for various enolization methods, our study proceeded with 1:1 LiHMDS/Me_2NEt as the standard enolization procedure as in practice this affords the cleanest reaction profile and most homogenous reaction mixture — necessitating only an acid/base extraction to afford the rearranged products in high purity in most cases.

Origins of stereoselectivity in diastereoconvergent mechanism.

The invariance of olefin geometry of the in situ-generated trimethylsilyl enol ethers in the diastereomeric selectivity of the subsequent Ireland–Claisen rearrangement to **15a**, suggests a diastereoconvergent mechanism is indeed occurring. Kinetic enolization of **14** with LiHMDS/Me_2NEt and trapping with TMSCl affords a mixture of *E/Z* silyl enol ethers **(*Z*)-8** and **(*E*)-8**. Upon warming from −78 °C, *Z*-enol ether **(*Z*)-8** under-goes the [3,3]-sigmatropic rearrangement preferentially through chair-like transition state **TS11** ($\Delta\Delta G^{\ddagger}$ = 5.5 kcal/mol), while *E*-enol ether **(*E*)-8** rearranges predominantly via boat-like transition state **TS14** ($\Delta\Delta G^{\ddagger}$ = −3.8 kcal/mol), yielding tetrasubstituted product **9** as a single diastereomer. With barrier heights of 19.6 and 19.9 kcal/mol for the rearrangement of **(*Z*)-8** and **(*E*)-8**, respectively, no appreciable resolution of the *E/Z*-silyl enol ether mixture is anticipated. Furthermore, these barrier heights are consistent with the experimentally observed reaction times considering gradual warming from −78 to 20 °C.

Initial inspection of **TS11**–**TS14** reveals a commonality in which the planar phthalimide motif of the enolate fragment is rotated out of the plane defined by the olefin of the enolate (Figure 3). Examining the generality of this effect, the *E*- and *Z*-olefin isomers of both the simplified trisubstituted analog (**17**) and tetrasubstituted enolate (**18**), corresponding to the enolate fragments encountered in **TS11**–**TS14,** were optimized as the enolate anion (Figure 4). Indeed, a similar torsion around the N–C(olefin) bond is observed. The simplified trisubstituted enolates **(*E*)-17** and **(*Z*)-17**, present an optimal dihedral angle, defined between the planar enolate and phthalimide groups, of 55° and 53°, respectively. The rotation is further accentuated with introduction of an aryl substituent as in the case of α-phenyl tetrasubstituted enolates **(*E*)-18** and **(*Z*)-18** with dihedral angles of 85° and 66°, respectively (Figure 4). As is observed in **TS11–TS14**, the α-phenyl substituent remains nearly coplanar with the enolate fragment. This perturbation is likely the result of the steric/electrostatic repulsion between the phthalimide oxygen and enolate oxygen atoms presenting a larger destabilizing force than the electronic stabilization gained through further conjugation with the enolate π system as achieved with coplanarity.

Considering that the planar enolate and allyl fragments adopt a nearly parallel orientation in the transition state, the out-of-plane phthalimide substituent of the enolate scaffold is well poised to interact with substitution on the allyl fragment. Hence, the phthalimide group plays a key role in determining the stereochemical outcome of the reaction. Specifically, in the case of *Z*-silyl enol ether **(*Z*)-8**, eclipsing interactions between the equatorial, out-of-plane phthalimide group and phenyl ring of the cinnamyl fragment are encountered in the boat-like

transition state (**TS12**), resulting in a distortion of the transition state geometry. This adverse NPhth–Ph(cinnamyl) eclipsing interaction is largely relieved in the chair-like transition state (**TS11**). Hence, a substantial preference for the chair-like transition state (**TS11**) of 5.5 kcal/mol is afforded. In contrast, in the pericyclic transition states derived from *E*-silyl enol ether **(*E*)-8**, the phthalimide occupies an axial orientation. As a result, the chair-like transition state (**TS13**) bears the costly NPhth–Ph(cinnamyl) eclipsing interaction, which is greatly reduced in the boat-like transition state (**TS14**). The net interactions are substantial enough in magnitude to not only overcome the inherent preference for a chair-like transition state, but further favor the boat-like transition state by 3.8 kcal/mol.

To further highlight the role that the phthalimide moiety has in the stereocontrol of the rearrangement, control calculations were carried out in which the α-phthalimide of **(*E*/*Z*)-8** is replaced with an ethyl group (See Supporting Information for details). An analogous analysis to that of **TS11**–**TS14** revealed that the magnitude of $\Delta\Delta G^{\ddagger}$ of the chair/boat selectivity is reduced for both enolate geometries. Critically, with the α-phthalimide replaced with an α-ethyl substituent, the key diastereoconvergence of the transformation is lost as the chair-like transition state is favored for both *E*- and *Z*-silyl enol ethers by 1.5 and 1.2 kcal/mol, respectively.[16] Hence, in addition to being individually less selective (calculated maximum dr of 13:1 and 8:1), the overall diastereoselectivity is highly reliant on *E*/*Z* selectivity of the initial enolization conditions.

Based on our working stereochemical model, if the NPhth–Ph(cinnamyl) eclipsing interaction is indeed the dominant element of stereocontrol, then inversion of the axial/equatorial positioning of the phenyl group of the cinnamyl fragment, i.e. employing the *Z*-cinnamyl ester (**19**), leads to an inversion in the chair/boat transition state preference for *both* of the corresponding *E*- and *Z*-silyl enol ethers. In this case, the double-inversion in stereoselectivity affords the identical diastereomerof product **15a** as obtained from *E*-cinnamyl ester **14**.

With respect to the *E*-cinnamyl system, a global inversion in the chair/boat transition state preference for both *E*/*Z* silyl enol ethers is predicted (Figure 5). *Z*-silyl enol ether **(*Z*)-20** preferentially rearranges through a boat-like transition state (**TS19**) ($\Delta\Delta G^{\ddagger}$ = −1.0 kcal/mol), while for *E*-silyl enol ether **(*E*)-20**, the chair-like transition state (**TS20**) is preferred ($\Delta\Delta G^{\ddagger}$ = 5.2 kcal/mol). As anticipated, the Ireland–Claisen rearrangment of *Z*-cinnamyl ester **19** affords the same diastereomeric outcome as with *E*-cinnamyl ester **14**. In total, the diastereoselectivity of the transformation is invariant to any combination of the *E*/*Z* geometry of both olefins of the in situ-generated silyl enol ether. We term this effect *global diastereoconvergence* — i.e. all possible stereoisomers derived from permutations of stereochemical elements of the reagent lead to formation of a single stereoisomer of product. To the best of our knowledge, this constitutes the first example of a globally diastereoconvergent Ireland–Claisen rearrangement of an acyclic, tetrasubstituted silyl enol ether.

A powerful feature of the Ireland–Claisen rearrangement is its ability to relay stereochemical information from a chiral center in the substrate to the absolute stereochemistry of the rearranged product. In contrast to previous achiral examples, the approach of a chiral

cinnamyl fragment from either the *Re* or *Si* faces of the enol ether gives rise to diastereomeric transition states. For a mixture of *E/Z* silyl enol ethers this gives rise to eight unique transition states which we modeled with regards to enantioenriched α-phthalimido ester **21** (Figure 6).

Analogous to our previous discussion, the *Z*- and *E*-silyl enol ethers derived from **21** preferentially rearrange via chair-like (**TS21**) and boat-like (**TS28**) transition states, respectively. While the NPhth–Ph(cinnamyl) eclipsing interaction drives the chair/boat selectivity in each silyl enol ether geometry, differentiation between the two diastereotopic chair-like (**TS21** and **TS23**) and boat-like (**TS26** and **TS28**) transition states must be achieved for effective chirality transfer. This component of the stereoselectivity arises in the energetic differences between axial and equatorial orientation of the methyl group (Figure 6). For the relevant chair-like transitions states (**TS21** and **TS23**) derived from the *Z*-enol ether of **21**, the 1,3-diaxial interactions imposed from the methyl group occupying an axial orientation carry an energetic penalty of 4.3 kcal/mol. Likewise, for the pair of boat-like transition states in the rearrangement of the *E*-enol ether (**TS26** and **TS28**) a preference of 1.4 kcal/mol is found for the equatorial orientation of the methyl group. As a result, the system exhibits diastereoconvergence with respect to chirality transfer. To experimentally demonstrate this, we synthesized the enantioenriched α-phthalimido ester from the requisite alcohol, in turn prepared via Corey–Bakshi–Shibata (CBS) reduction. Indeed, non-selective enolization, trapping as the TMS enol ether, and warming to 20 °C affords the desired α,α-disubstituted acid. The crude acid was subsequently transformed to methyl ester **22**, which was isolated in 86% yield over two steps, >20:1 dr, and with complete retention of enantiomeric excess (95% ee) (Figure 6).

Substrate scope of the diastereoconvergent Ireland–Claisen rearrangement.

A variety of differentially substituted α-aryl, α-phthalimido esters were examined in the Ireland–Claisen rearrangement to explore the scope of this transformation (Table 3). The reaction was highly compatible with a broad scope of differentially substituted esters, affording tetrasubstituted amino acid derivatives bearing an adjacent tertiary stereogenic center with generally >20:1 diastereoselectivity. Additionally, the rearrangement could be performed with standard substrate **14** on a 5.00 g (12.6 mmol) scale with identical yield and diastereoselectivity. In some cases, the carboxylic acid products were transformed into the corresponding methyl ester to circumvent challenges in substrate acid/base purification or decomposition of the parent carboxylic acid. With respect to the α-aryl group, a variety of both electron rich and electron deficient aryl rings were tolerated in excellent yields. Chloro and methoxy *ortho*-substitution was also well tolerated in the rearrangement, affording highly sterically encumbered amino acid derivatives **29** and **30** in excellent yields with >20:1 dr. Variation of the allylic olefin aryl group was also well tolerated, providing differentially substituted β-aryl groups in high yield and diastereoselection. Methyl *ortho*-substitution was also well tolerated, affording carboxylic acid **37** as a single diasteromer in 79% yield. In addition to these substrates, a variety of different heterocycles were incorporated, affording rearrangement products in generally >20:1 dr and moderate to excellent yield.

While a broad scope of rearrangement products could be prepared utilizing this diastereoconvergent methodology, alkyl-substituted allylic esters proved to be challenging substrates (Figure 7). *E*-hexenyl ester **45** afforded methyl ester **46** in 2.3:1 dr. A modest improvement in diastereoselectivity is observed with *Z*-pentenyl ester **47** which was isolated as methyl ester **48** in 3.7:1 dr. On the other hand, excellent diastereoselectivity and enantioretention (>99% ee) was observed with *(S)*-cyclohex-2-en-1-ol derived ester **49**. The relative and absolute stereochemistry of cyclohexene **50** was determined by single crystal X-ray diffraction.

Derivatizations of the Ireland–Claisen Rearrangement Product.

Derivatization of Ireland–Claisen rearrangement product **15a** afforded a range of densely functionalized small molecules (Figure 8). Curtius rearrangement in *t*-BuOH provided bench-stable, differentially protected aminoacetal **51** in 82% yield. Iodolactonization afforded lactone **52** in an excellent 91% yield as a single diasteromer with the relative configuration confirmed by single crystal X-ray diffraction. Ozonolysis with reductive quenching provided cyclized product **53** in 11:1 dr and 86% yield. Methyl esterification with MeI/K_2CO_3 generated ester **54** in excellent 90% yield. Removal of the phthalimide proved challenging under standard hydrazine-mediated protocols due to competitive olefin reduction and slow phthalhydrazide removal. A modified Ganem protocol[17] reported by Davies[18] affected semi-reduction of the phthalimide. Methyl esterification followed by AcOH-mediated phthalide removal afforded α-amino acid methyl ester **55**.

CONCLUSIONS

We have computationally modeled and experimentally developed a globally diastereoconvergent Ireland–Claisen rearrangement of α-phthalimido esters that is invariant to the geometry of the silyl enol ether and allylic ester olefin. A local coupled-cluster theory (DLPNO-CCSD(T)) and DFT multi-level approach was employed for the accurate determination of quantum mechanical energies. The scope of the rearrangement is broad with respect to aryl and heteroaryl substitution, and a variety of α-phthalimide-protected α-tetrasubstituted amino acids bearing a vicinal tertiary stereogenic center are isolated with generally excellent (>20:1) diastereoselection in good to excellent yields. Additionally, transfer of chirality with stereodefined α-phthalimido esters affords rearrangement products with excellent retention of chiral information. A range of densely substituted small molecules can be readily prepared from representative rearrangement product **15a**. Further examination of the Ireland–Claisen rearrangement in other classes of tetrasubstituted silyl enol ethers is currently under way.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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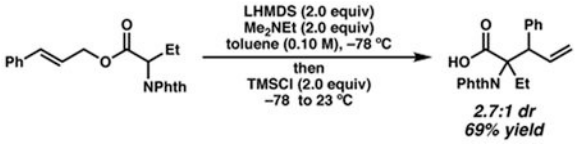
(12). Experimentally, a 2.7:1 dr is obtained (see Supporting Information for details):



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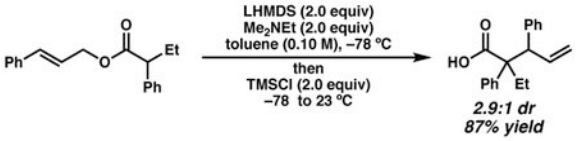
(16). Experimentally, a 2.7:1 dr is obtained (see Supporting Information for details):



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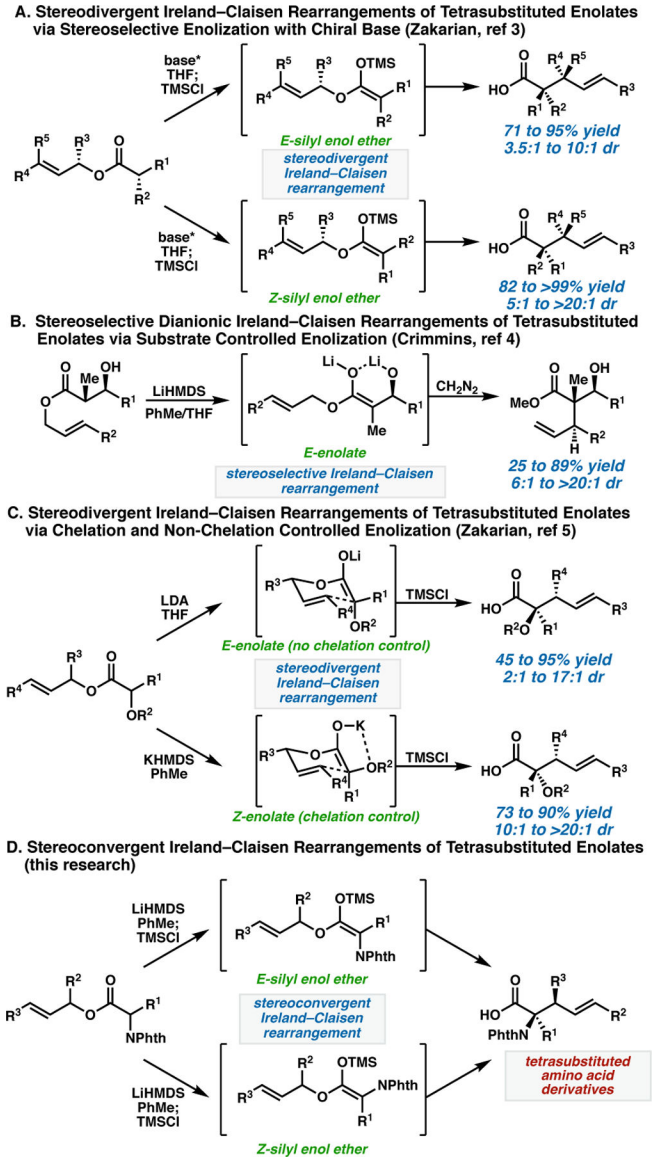
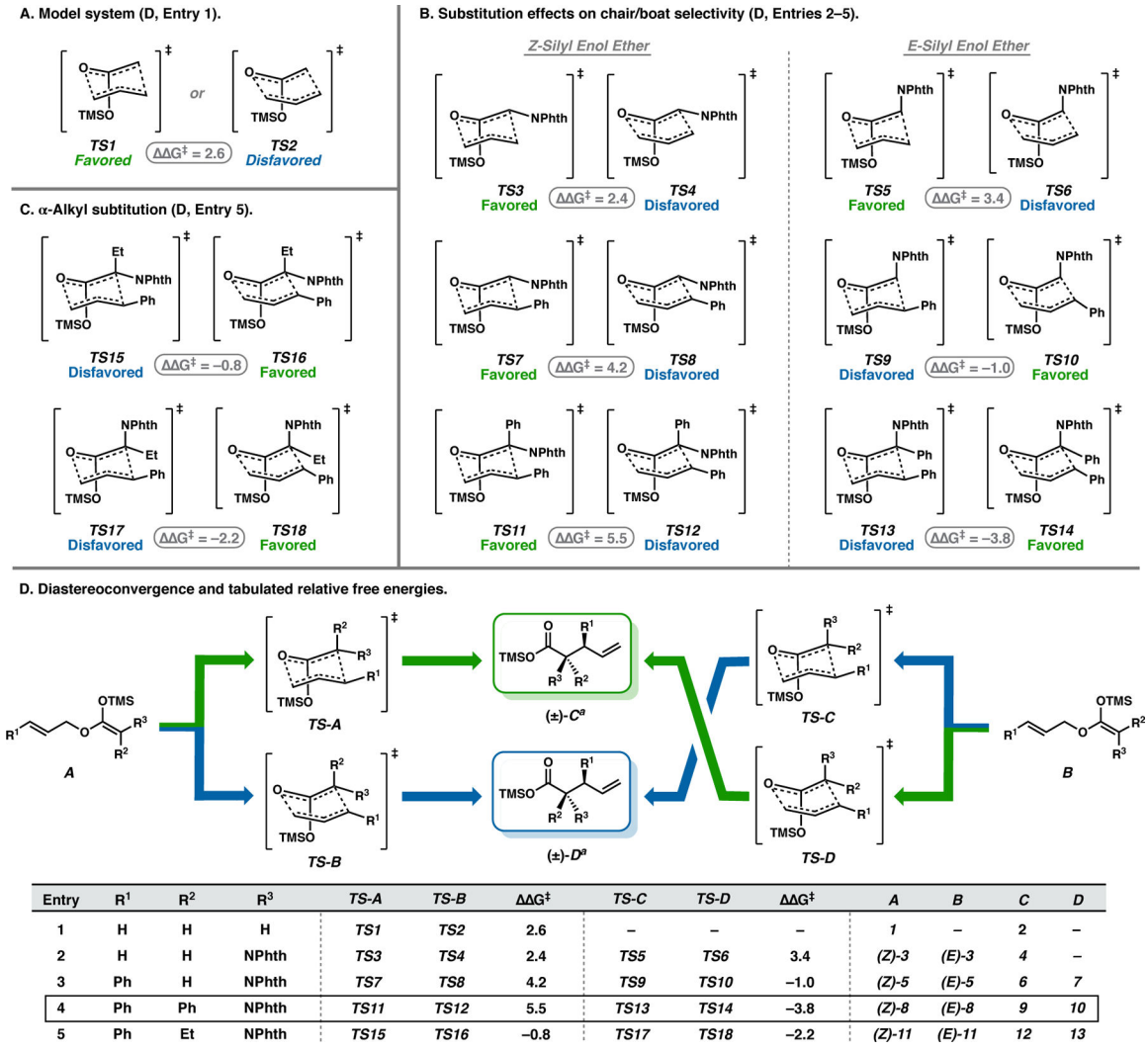


Figure 1.

Stereoselective Ireland–Claisen rearrangements of fully substituted acyclic α,α-disubstituted esters.



Entry	R^1	R^2	R^3	TS-A	TS-B	ΔΔG‡	TS-C	TS-D	ΔΔG‡	A	B	C	D
1	H	H	H	*TS1*	*TS2*	2.6	–	–	–	*1*	–	2	–
2	H	H	NPhth	*TS3*	*TS4*	2.4	*TS5*	*TS6*	3.4	*(Z)-3*	*(E)-3*	*4*	–
3	Ph	H	NPhth	*TS7*	*TS8*	4.2	*TS9*	*TS10*	–1.0	*(Z)-5*	*(E)-5*	*6*	*7*
4	Ph	Ph	NPhth	*TS11*	*TS12*	5.5	*TS13*	*TS14*	–3.8	*(Z)-8*	*(E)-8*	*9*	*10*
5	Ph	Et	NPhth	*TS15*	*TS16*	–0.8	*TS17*	*TS18*	–2.2	*(Z)-11*	*(E)-11*	*12*	*13*

Figure 2.

$\Delta\Delta G^{\ddagger}$ (in kcal/mol) defined as $\Delta G^{\ddagger}$ (boat) – $\Delta G^{\ddagger}$ (chair) (A) Innate preference for chair-like TS. (B) Effect of substitution pattern on diastereoconvergence in the Ireland–Claisen rearrangement. (C) Probing α-alkyl substitution. (D) Diastereoconvergence, compound labels, and tabulated relative free energies [a]Absolute stereochemistry drawn arbitrarily – opposite enantiomeric series than TS-B/D.

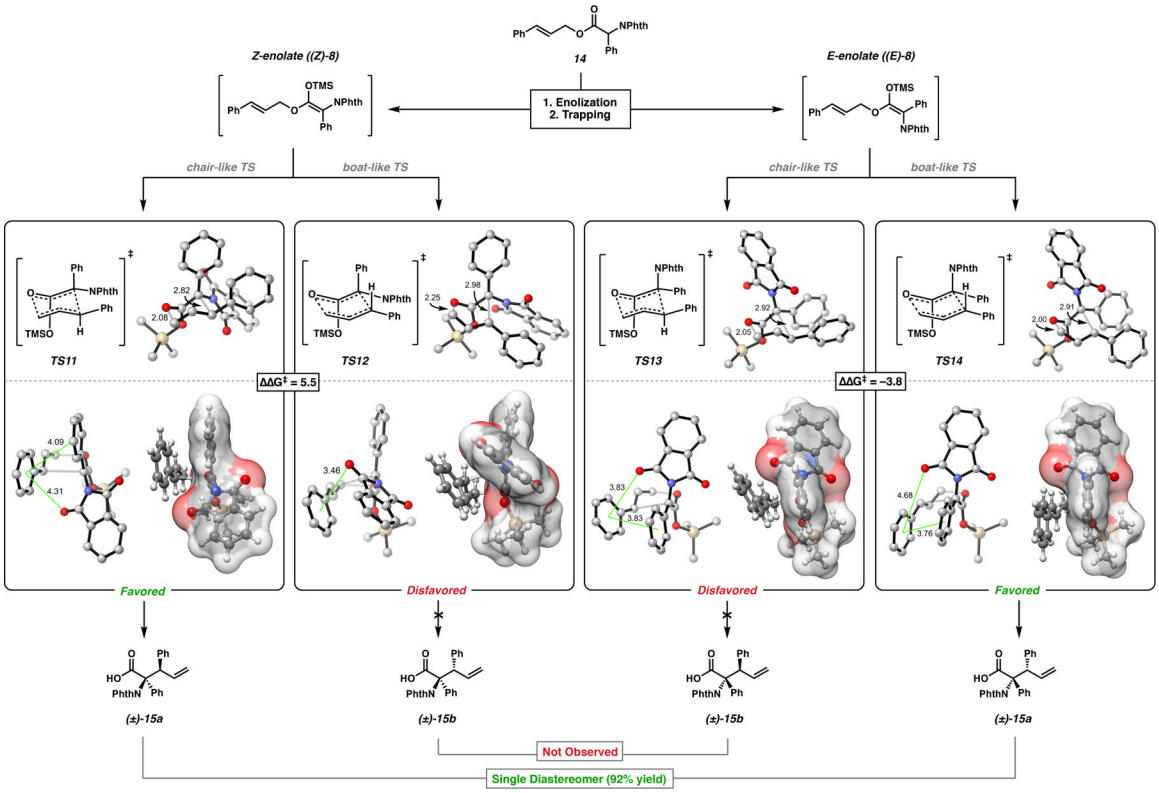


Figure 3.

Origins of diastereoselectivity in the diastereoconvergent Ireland–Claisen rearrangement of **(*E*/*Z*)-8**. Relative free energies given in kcal/mol.

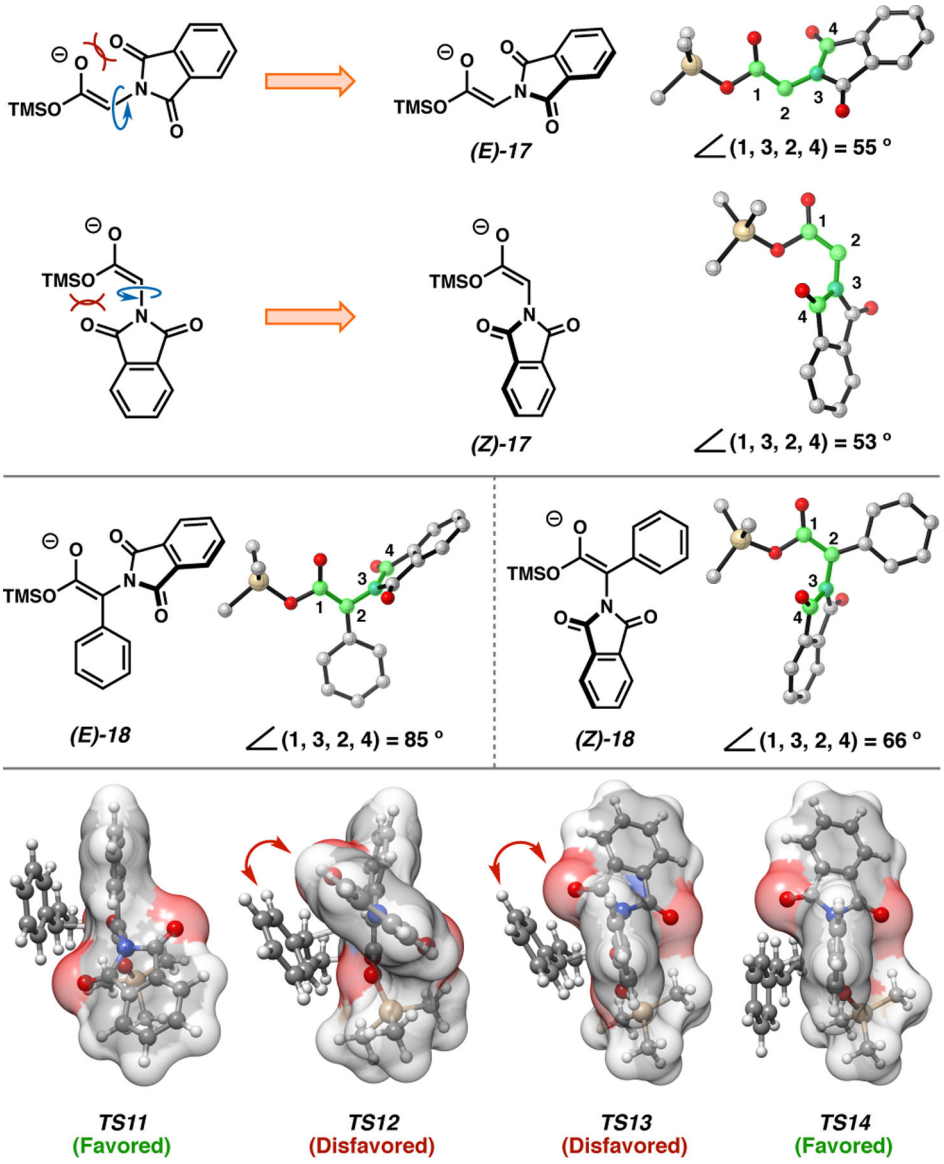


Figure 4.
Geometric perturbations resulting from the out-of-plane rotation of the phthalimide moiety.

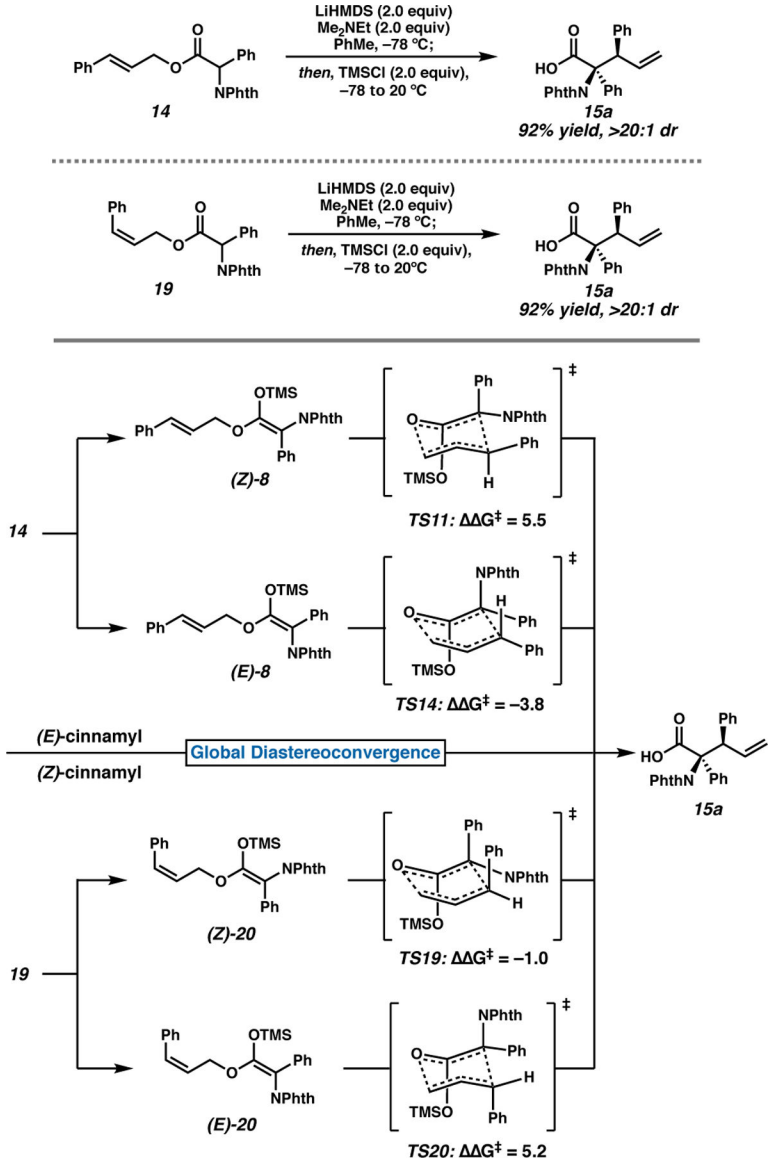


Figure 5.

Global stereoconvergence in the Ireland–Claisen rearrangement of *Z*- and *E*-cinnamyl compounds **14** and **19**. Relative free energies given in kcal/mol.

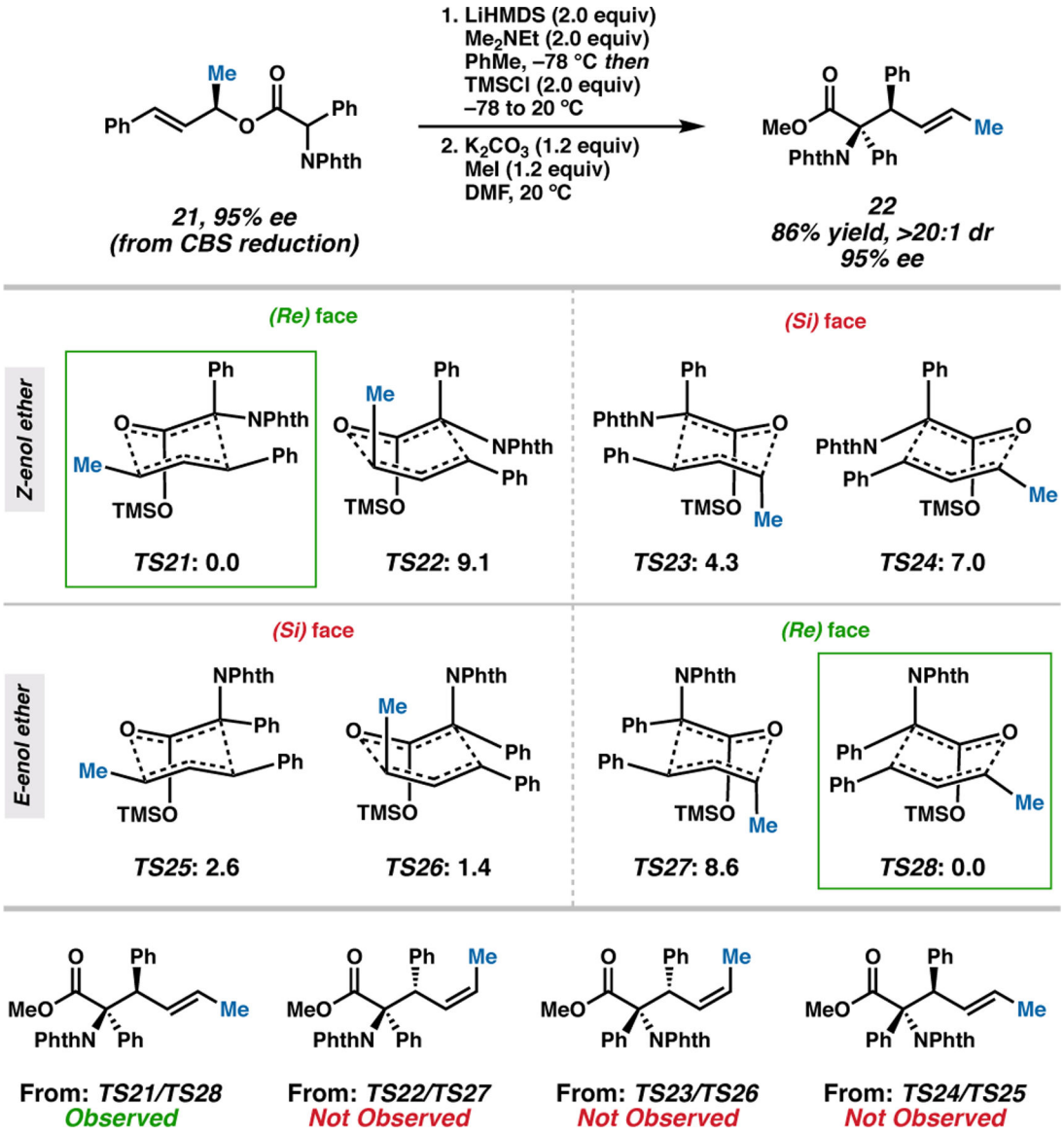


Figure 6.

Chirality transfer in the diastereoconvergent Ireland–Claisen rearrangement. Relative free energies (in kcal/mol) of the eight possible stereochemically distinct transition states for the rearrangement of the *E*- and *Z*-silyl enol ethers derived from **21**.

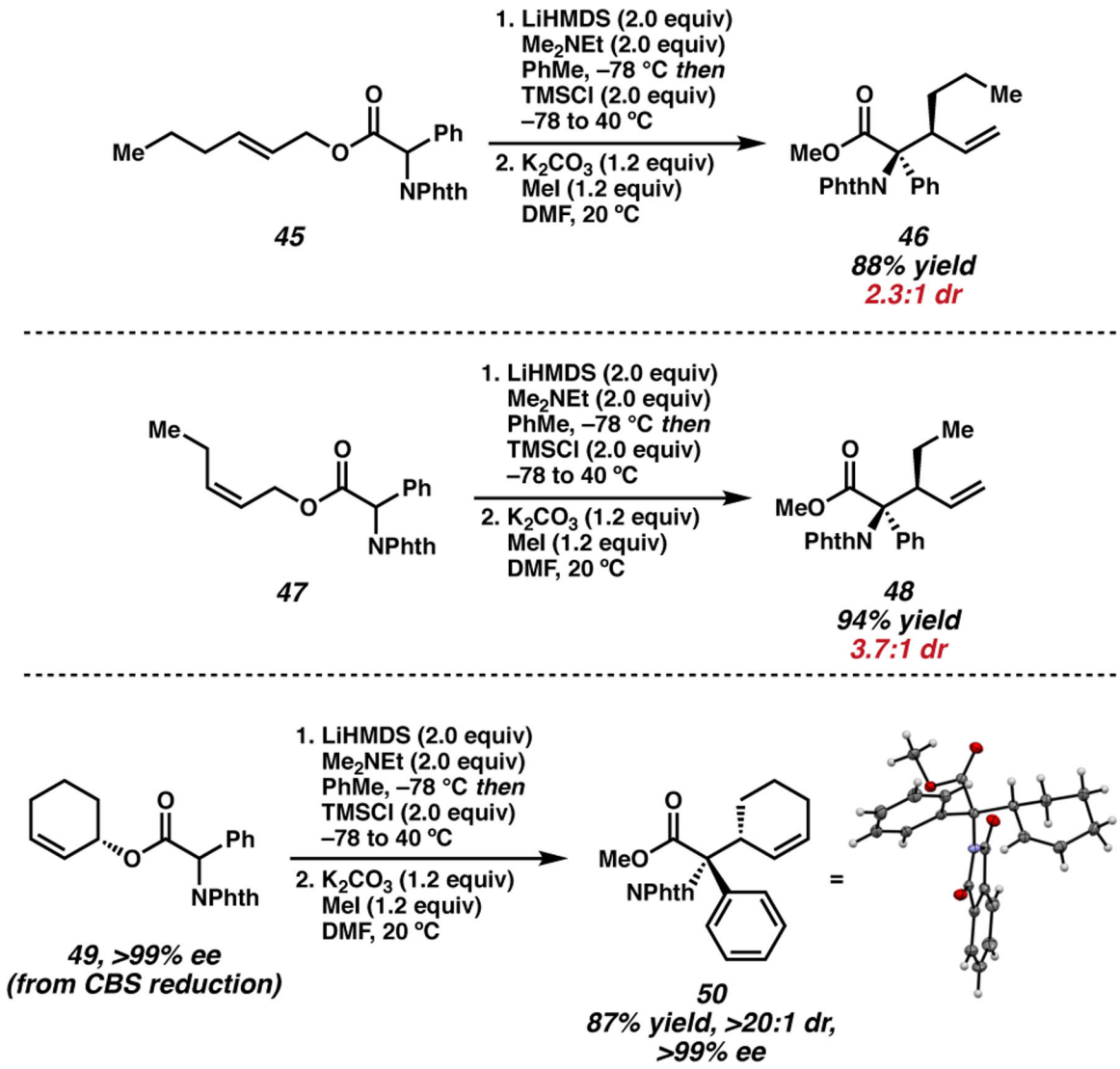


Figure 7.

Ireland–Claisen rearrangement of tetrasubstituted α-phthalimido esters with alkyl substituted allyl esters.

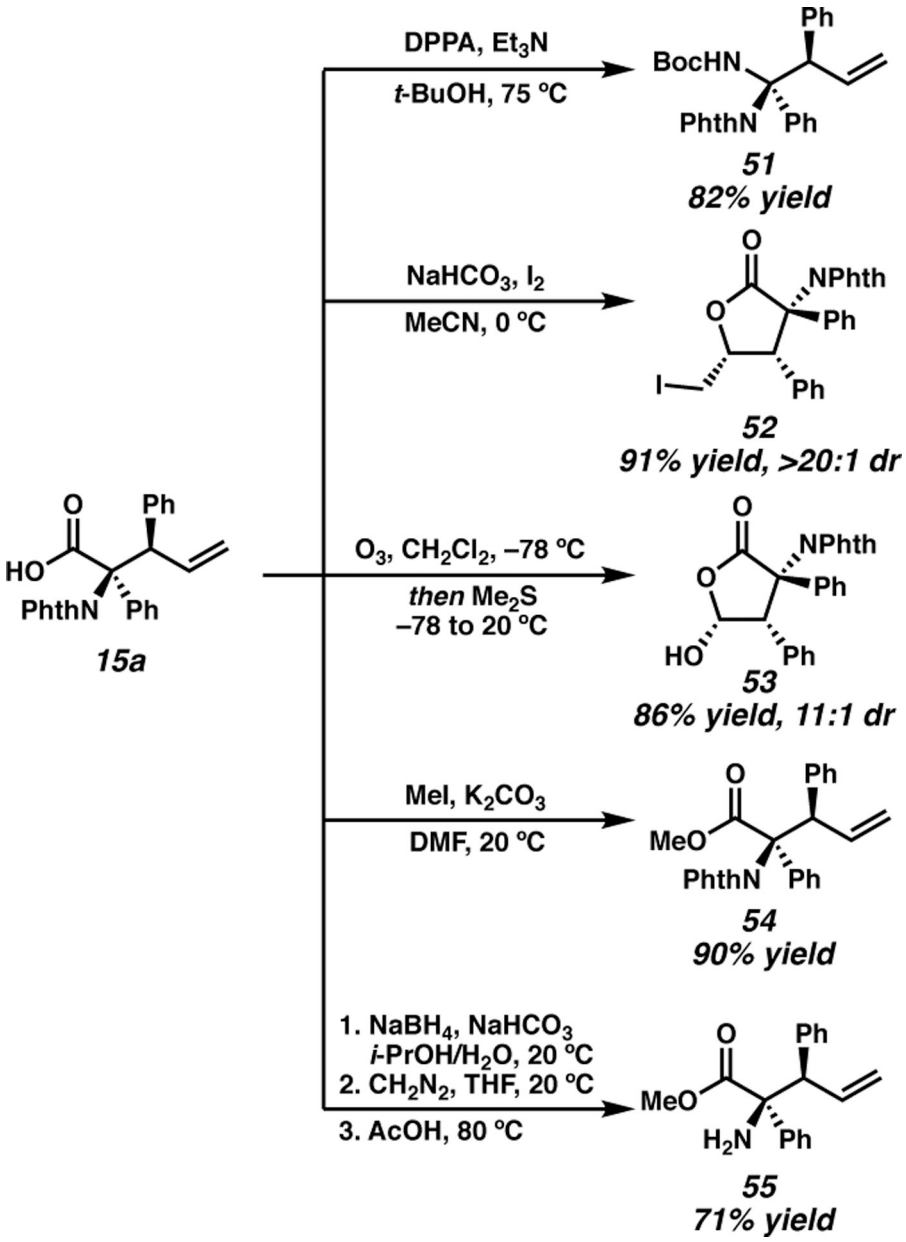
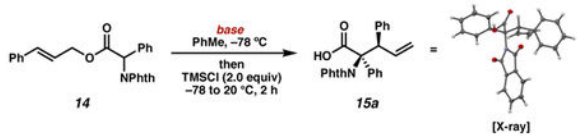


Figure 8.
Derivatizations of the Ireland–Claisen rearrangement Product **15a.**

Table 1.

Initial investigation into enolization conditions.[a]



Entry	Base	% Yield 15a[b]	dr[c]
1	LiHMDS, Me_2NEt[d]	92	>20:1
2	LiHMDS	90	>20:1
3	KHMDS	90	>20:1

[a] Conditions: 1.00 mmol **14**, toluene (10 mL), base (2.00 mmol)

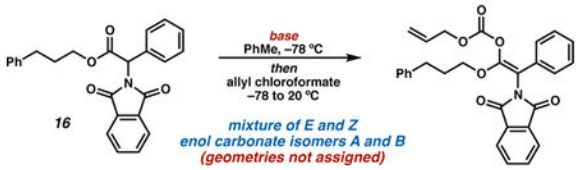
[b] Isolated yields.

[c] Determined by ^1H NMR analysis.

[d] Me_2NEt (2.00 mmol).

Table 2.

Enolate trapping experiments.



Entry	Base	% Yield isomer A	% Yield isomer B
1	LiHMDS, Me_2NEt[d]	16	23
2	LiHMDS	43	27
3	KHMDS	55	24

[a] Conditions: 1.00 mmol **16**, toluene (10 mL), base (2.00 mmol)

[b] Isolated yields.

[c] Determined by ^1H NMR analysis.

[d] Me_2NEt (2.00 mmol).

Table 3.

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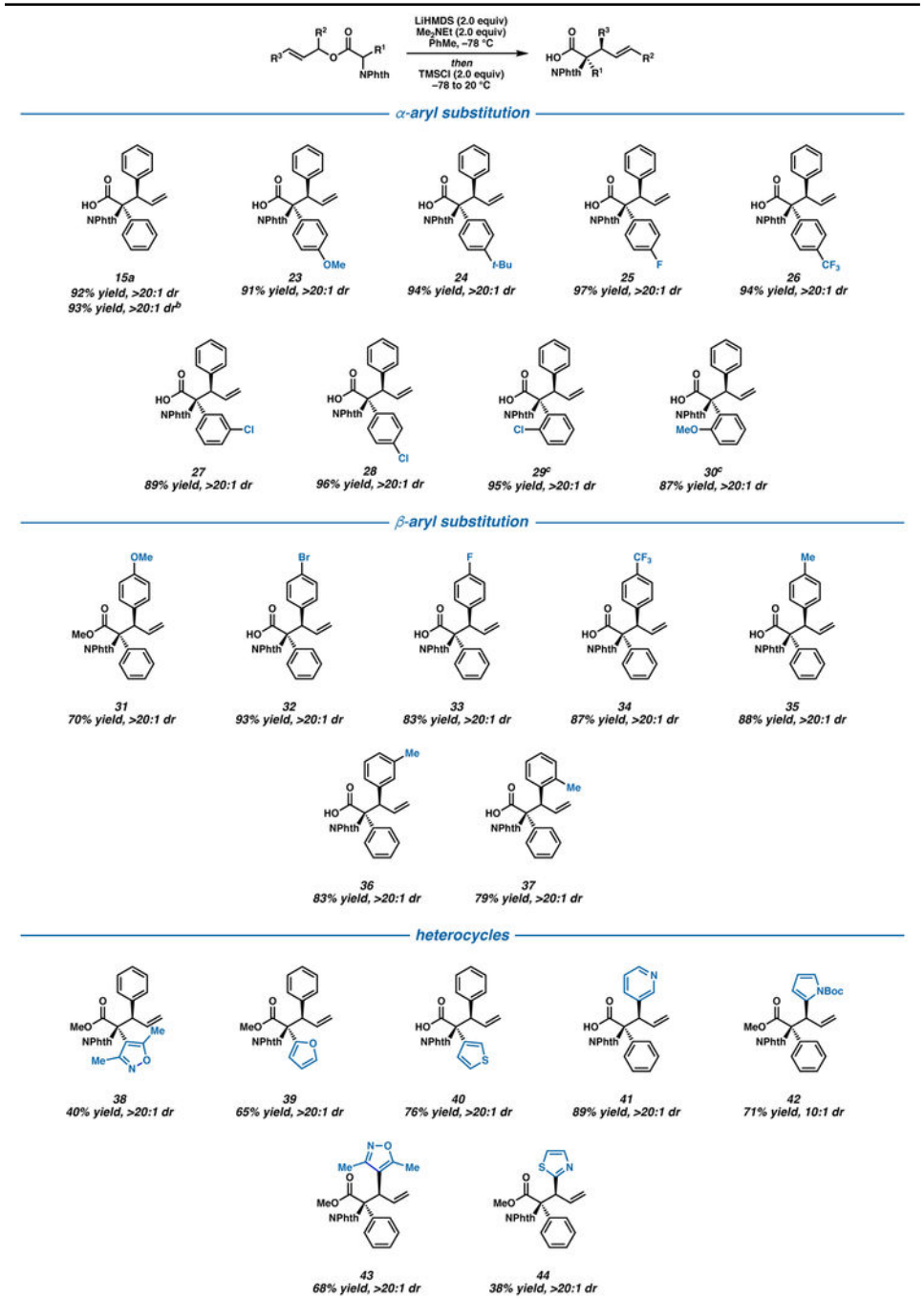
Scope of the α,α-disubstituted α-phthalimido ester Ireland–Claisen rearrangement.[a]



[a] Reactions performed on a 1.00 mmol scale, yields are of isolated products. Diastereomeric ratios were determined by ^{1}H NMR spectroscopy. In some cases, the crude products were converted to the corresponding methyl ester for isolation (see Supporting Information for details). Relative configuration was assigned by single crystal X-ray diffraction of **15a**, all others are assigned by analogy.

[b] Reaction performed on a 5.00 g (12.6 mmol) scale.

[c] Rearrangement performed at 40 °C.