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

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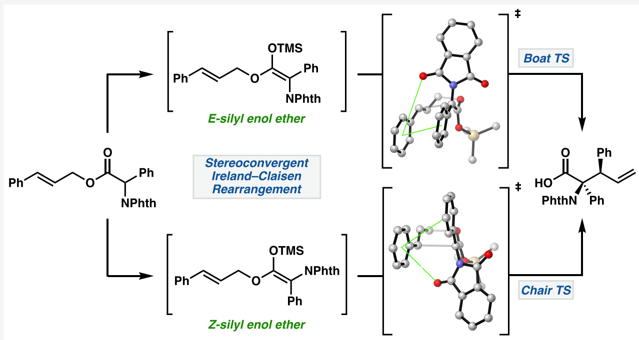
ABSTRACT: A dual experimental/theoretical investigation of the Ireland−Claisen rearrangement of tetrasubstituted α-phthalimido ester enolates to afford α-tetrasubstituted, β-trisubstituted α-amino acids (generally >20:1 dr) is described. For trans allylic olefins, the *Z*- and *E*-enol ethers proceed 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 *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.



■ INTRODUCTION

For over 40 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 has been 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 co-workers 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 co-workers utilized a chiral auxiliary approach to prepare chiral, nonracemic α-methyl-β-hydroxy allylic esters toward the synthesis of briarane natural products (Figure 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 co-workers investigated the diastereodivergent Ireland−Claisen rearrangement of tetrasubstituted α-alkoxy ester enolates toward the synthesis of α-alkoxy carboxylic acids (Figure 1C).[6] While the chelation-controlled, kinetic *Z*-selective enolization of α-alkoxy esters has been well established,[7] Zakarian and co-workers found that an *E*-selective enolization could be achieved with a judicious choice of base and solvent based on prior research from Langlois and co-workers.[8] While a variety of α-alkoxy carboxylic acid products were obtained with good to excellent diastereoselectivity, the level of control over enolate geometry

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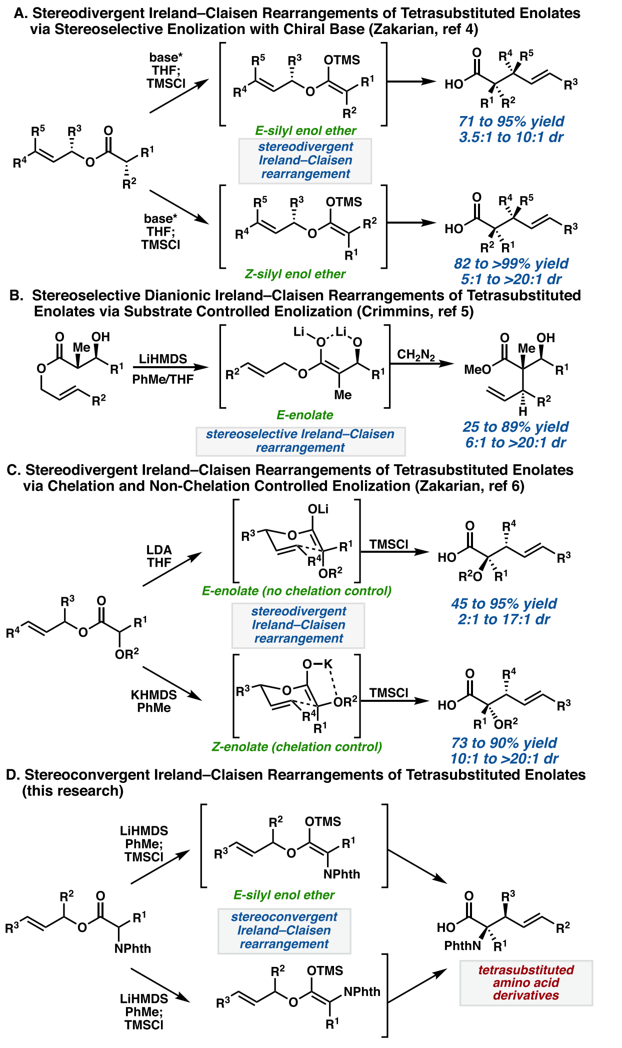


Figure 1. Stereoselective Ireland–Claisen rearrangements of fully substituted acyclic α,α-disubstituted esters.

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 the 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).

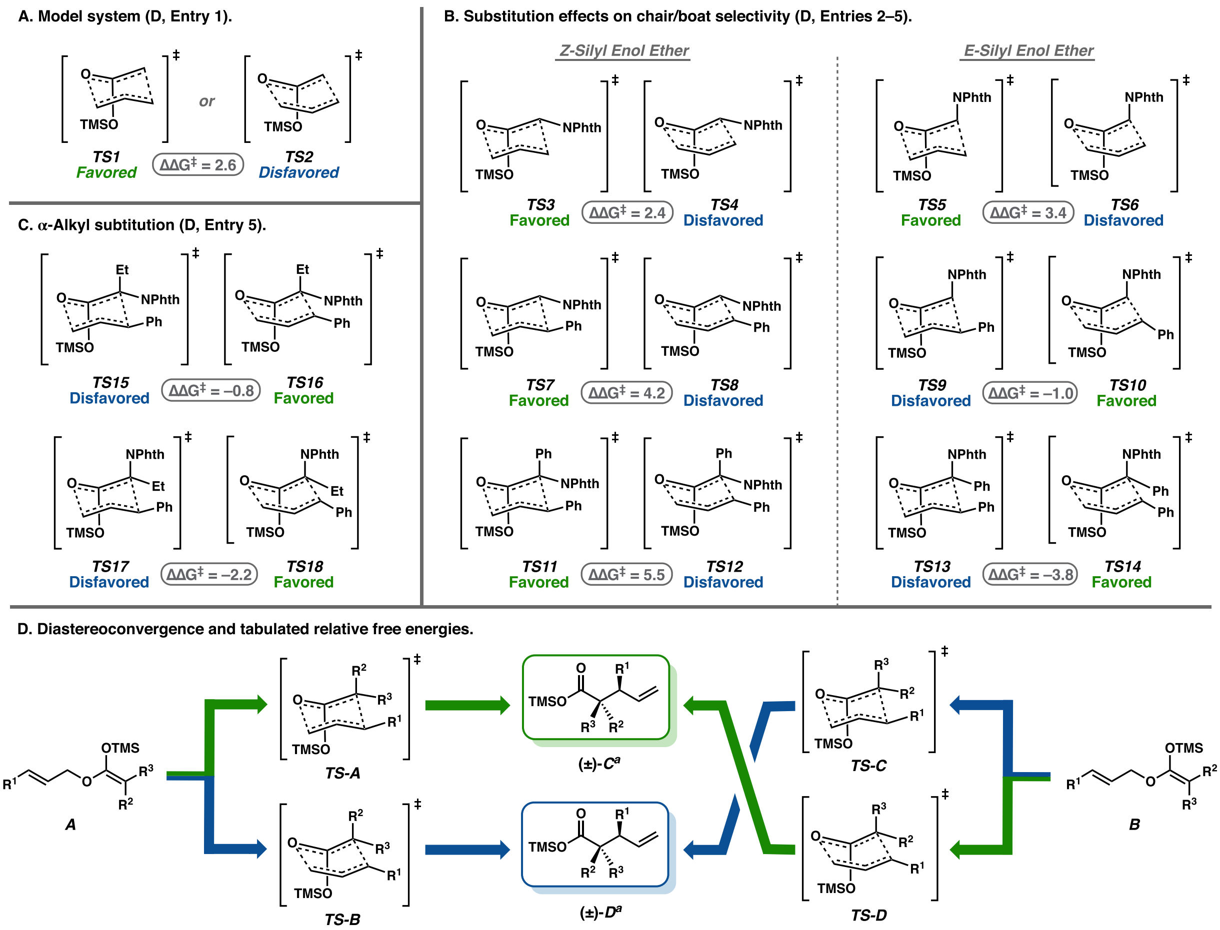
■ RESULTS AND DISCUSSION

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 multilevel 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 $\Delta\Delta G^{\ddagger}$ values 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.

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).[12] This reversal in preference for chair-like 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).

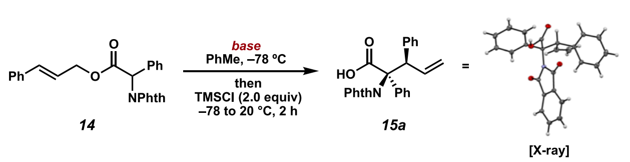
In contrast, high levels of selectivity for the chair-like transition state are anticipated for the fully substituted *Z*-silyl



Entry	R1	R2	R3	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. ΔΔG‡ (in kcal/mol) defined as ΔG‡(boat) − ΔG‡(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]Aabsolute stereochemistry drawn arbitrarily—opposite enantiomeric series than TS-B/D.

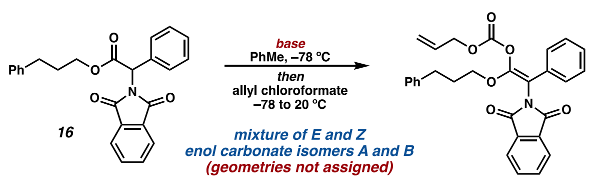
Table 1. Initial Investigation into Enolization Conditions[a]



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 of **14**, toluene (10 mL), base (2.00 mmol). [b]Isolated yields. [c]Determined by ^{1}H NMR analysis. [d]Me_2NEt (2.00 mmol).

Table 2. Enolate Trapping Experiments



		yield (%)	
entry	base	A	B
1	LiHMDS, Me_2NEt[d]	16	23
2	LiHMDS	43	27
3	KHMDS	55	24

[a]Conditions: 1.00 mmol of **16**, toluene (10 mL), base (2.00 mmol). [b]Isolated yields. [c]Determined by 1H NMR analysis. [d]Me_2NEt (2.00 mmol).

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 that the diastereoconvergent effect is significantly less pronounced when the *α*-

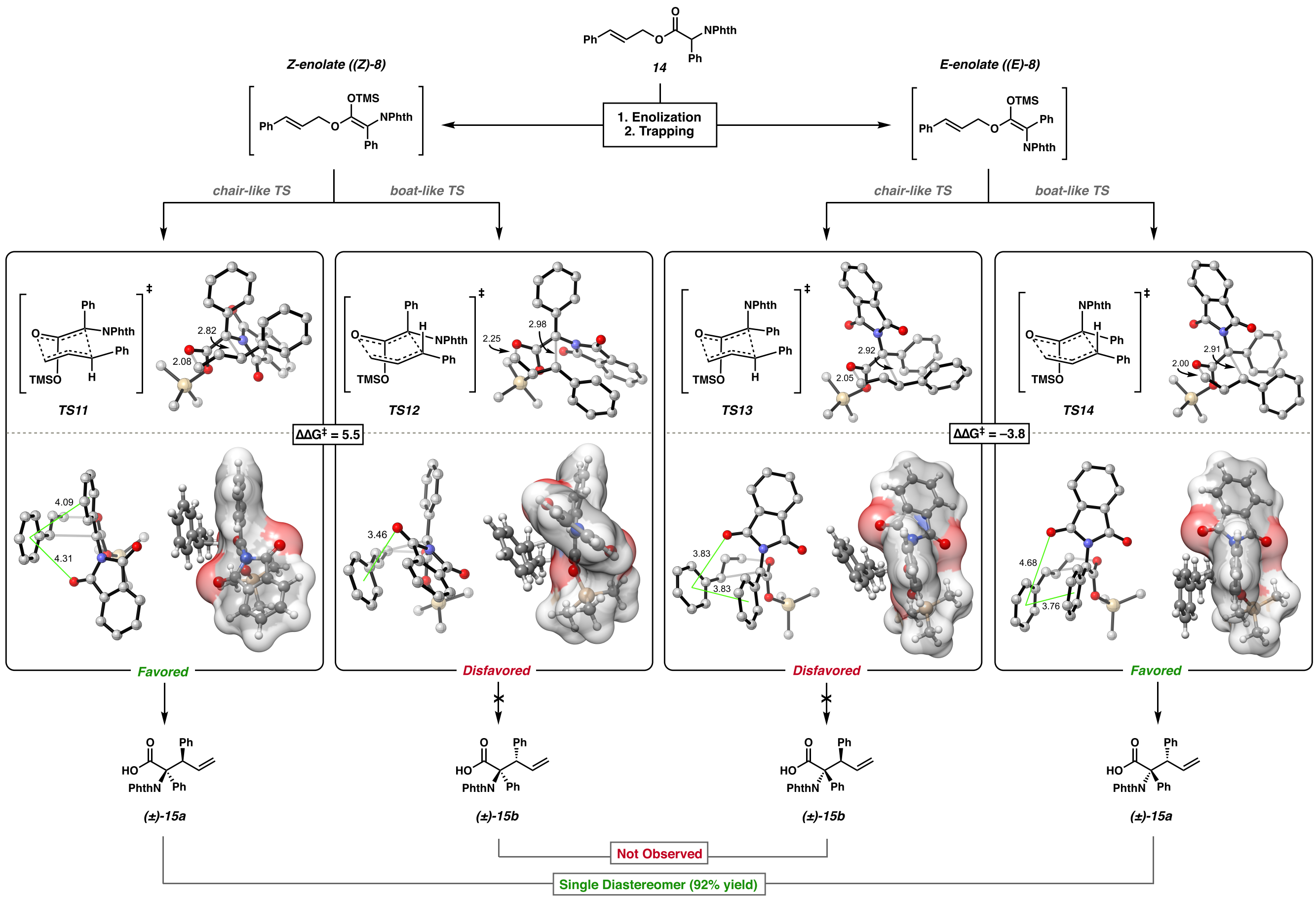


Figure 3. Origins of diastereoselectivity in the diastereoconvergent Ireland−Claisen rearrangement of (*E*/*Z*)-**8**. Relative free energies are given in kcal/mol. The surfaces depicted are solvent-excluded surfaces from van der Waals radii with a probe radius of 1.4 Å.

phenyl group is substituted for an α-ethyl substituent (Figure 2C, D entry 5).[13]

Initial Experimental Investigations. An Ireland−Claisen rearrangement of the computationally modeled α-phthalimido cinnamyl ester **14** leads to >20:1 diastereoselection with several different enolization conditions (Table 1). Enolization conditions of 1:1 LiHMDS/Me_2NEt (entry 1) were originally developed by Gosselin, Zhang, and co-workers[14] for the highly selective enolization of α,α-disubstitued aryl ketones. Additionally, Stoltz and Zhang demonstrated that 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 *tert*-butyl, phenyl, and ethyl esters.[15] 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.[16]

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, the analogous dihydro-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 nonequilibrating 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 homogeneous 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 that 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** undergoes a [3,3]-sigmatropic rearrangement

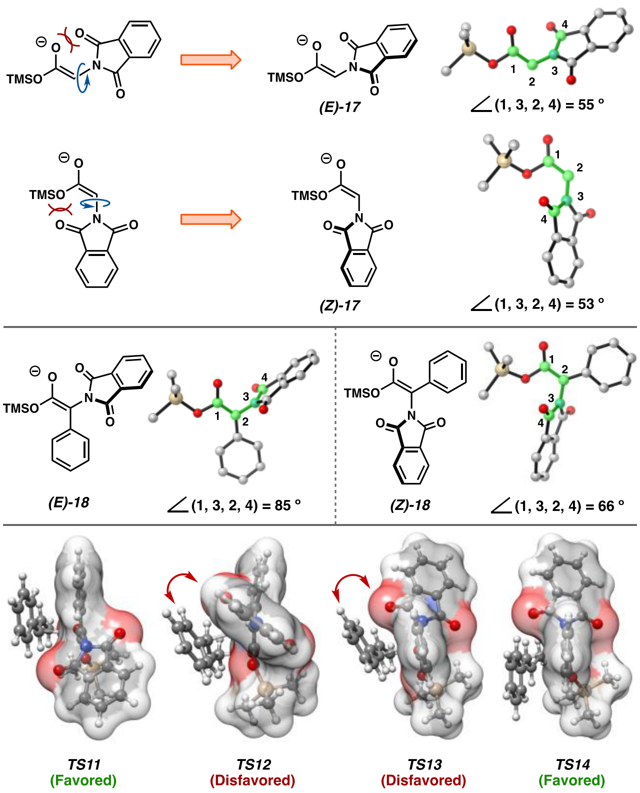


Figure 4. Geometric perturbations resulting from the out-of-plane rotation of the phthalimide moiety. Surfaces depicted are solvent-excluded surfaces from van der Waals radii with a probe radius of 1.4 Å.

preferentially through the chair-like transition state **TS11** ($\Delta\Delta G^{\ddagger}$ = 5.5 kcal/mol), while the *E*-enol ether **(*E*)-8** rearranges predominantly via the 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.

An 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). On examination of the generality of this effect, the *E*- and *Z*-olefin isomers of both the simplified trisubstituted analogue **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 optimal dihedral angles, defined between the planar enolate and phthalimide groups, of 55° and 53°, respectively. The rotation is further accentuated with the 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 in comparison to the electronic stabilization gained through

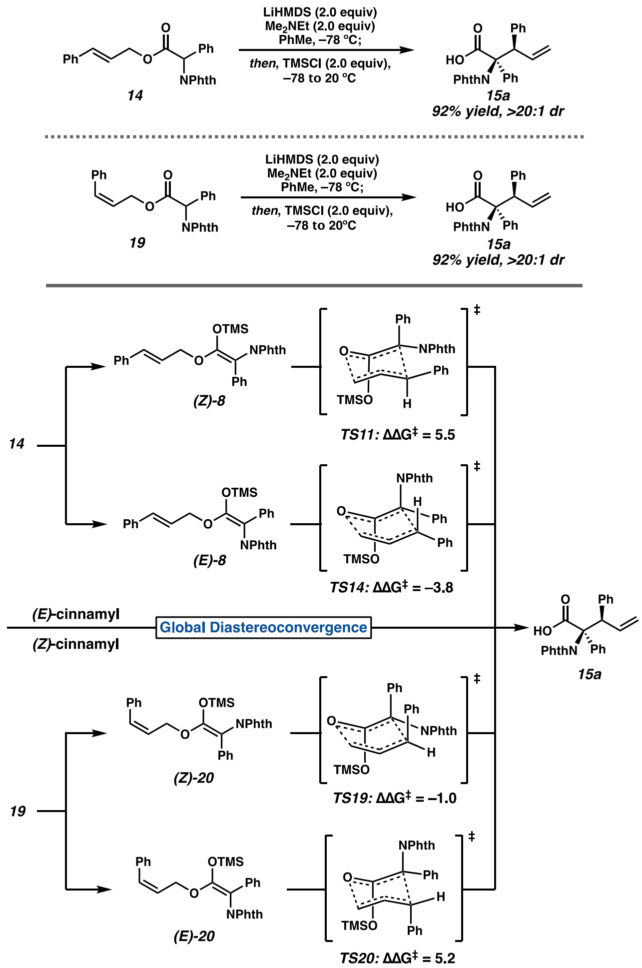


Figure 5. Global stereoconvergence in the Ireland−Claisen rearrangement of *Z*- and *E*-cinnamyl compounds **14** and **19**. Relative free energies are given in kcal/mol.

further conjugation with the enolate π system as achieved with coplanarity.

When one considers 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 the 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 also favor the boat-like transition state by 3.8 kcal/mol.

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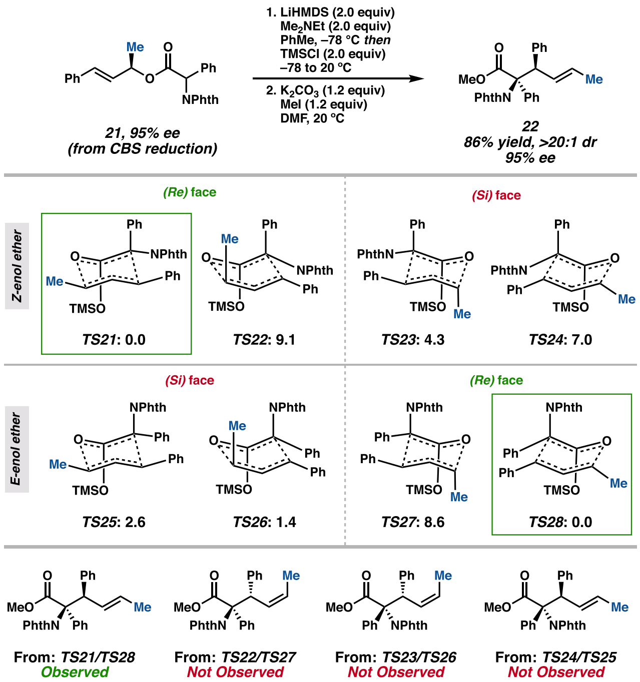

Figure 6. Chirality transfer in the diastereoconvergent Ireland–Claisen rearrangement. Relative free energies (in kcal/mol) of the eight possible stereochemically distinct transition states for the rearrangement of the *E*- and *Z*-silyl enol ethers derived from **21**.

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 the Supporting Information for details). An analysis analogous 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.[17] Hence, in addition to being individually less selective (calculated maximum dr values of 13:1 and 8:1), the overall diastereoselectivity is highly reliant on the *E*/*Z* selectivity of the initial enolization conditions.

On the basis of 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 diastereomer of product **15a** identical with that 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). The *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 rearrangement of *Z*-cinnamyl ester **19** affords the same diastereomeric outcome as that 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 the formation of a single stereoisomer of the 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.[18] In contrast to previous achiral examples, the approach of a chiral cinnamyl fragment from either the *Re* or *Si* face 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 regard 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 orientations of the methyl group (Figure 6). For the relevant chair-like transition 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 a Corey–Bakshi–Shibata (CBS) reduction. Indeed, nonselective enolization, trapping as the TMS enol ether, and warming to 20 °C afforded 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, with >20:1 dr and with complete retention of the 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 the 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

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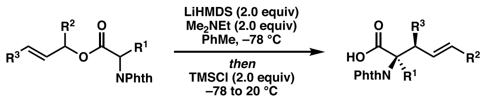
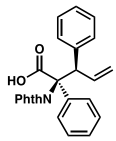
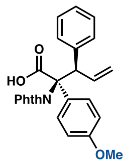
Table 3. Scope of the α,α-Disubstituted α-Phthalimido Ester Ireland–Claisen Rearrangement[a]



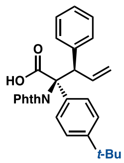
α-aryl substitution



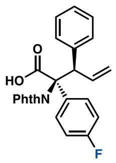
15a
92% yield, >20:1 dr
93% yield, >20:1 dr[b]



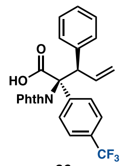
23
91% yield, >20:1 dr



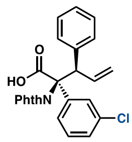
24
94% yield, >20:1 dr



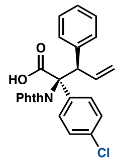
25
97% yield, >20:1 dr



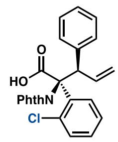
26
94% yield, >20:1 dr



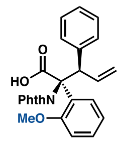
27
89% yield, >20:1 dr



28
96% yield, >20:1 dr

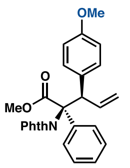


29[c]
95% yield, >20:1 dr

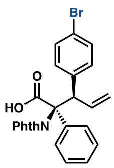


30[c]
87% yield, >20:1 dr

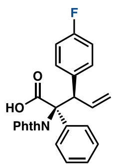
β-aryl substitution



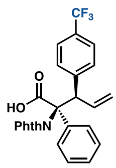
31
70% yield, >20:1 dr



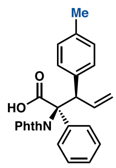
32
93% yield, >20:1 dr



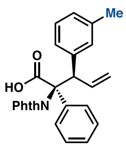
33
83% yield, >20:1 dr



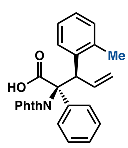
34
87% yield, >20:1 dr



35
88% yield, >20:1 dr

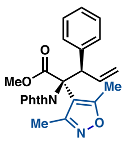


36
83% yield, >20:1 dr

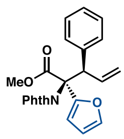


37
79% yield, >20:1 dr

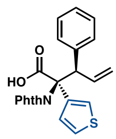
heterocycles



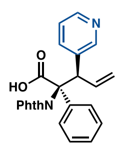
38
40% yield, >20:1 dr



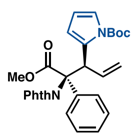
39
65% yield, >20:1 dr



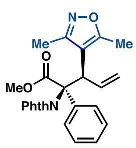
40
76% yield, >20:1 dr



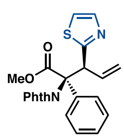
41
89% yield, >20:1 dr



42
71% yield, 10:1 dr



43
68% yield, >20:1 dr



44
38% yield, >20:1 dr

[a]Reactions were performed on a 1.00 mmol scale unless specified otherwise; 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 the Supporting Information for details). The 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.

tolerated in excellent yields. Chloro and methoxy *ortho*-substitutions were 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

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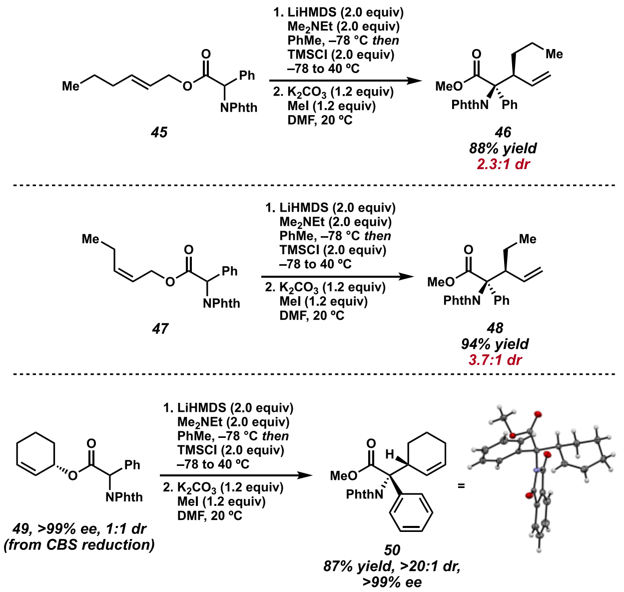

Figure 7. Ireland−Claisen rearrangement of tetrasubstituted α-phthalimido esters with alkyl-substituted allyl esters.

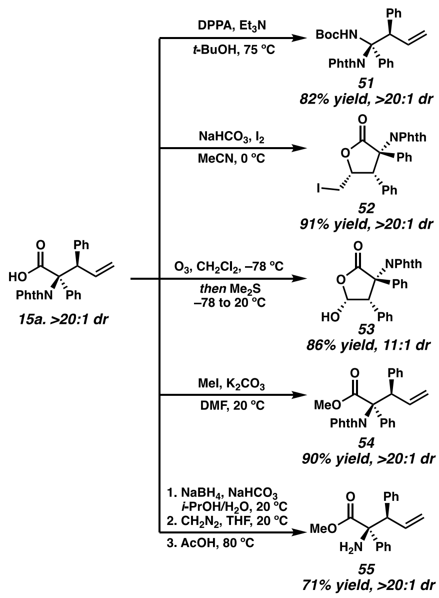

Figure 8. Derivatizations of the Ireland−Claisen rearrangement product **15a**.

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 diastereomer 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 by utilizing this diastereoconvergent methodology, alkyl-substituted allylic esters proved to be challenging substrates (Figure 7). The *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 the Ireland−Claisen rearrangement product **15a** afforded a range of densely functionalized small molecules (Figure 8). A Curtius rearrangement in *t*-BuOH provided the 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 being 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 an 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[19] reported by Davies[20] effected semireduction 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 multilevel 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 the representative rearrangement product **15a**. Further examination of the Ireland−Claisen rearrangement in other classes of tetrasubstituted silyl enol ethers is currently under way.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c11480.

Computational details, materials and methods, list of abbreviations, Ireland−Claisen Rearrangements of α-phthalidomido esters, Ireland−Claisen rearrangement of (*Z*)-3-phenylallyl 2-(1,3-dioxoisoindolin-2-yl)-2-phenylacetate (**19**), Ireland−Claisen rearrangements of Substrates Relevant to Figure 2, product derivatizations, preparation of allyl esters, investigation of enolization selectivity, X-ray crystallographic data for **15a**, **50**, and **52**, and NMR and IR spectra of new compounds (PDF)

QM energies (XLSX)

Cartesian coordinates of the calculated structures (ZIP)

Crystallographic data (CIF)

Crystallographic data (CIF)

Crystallographic data (CIF)

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Author Contributions

[‖]T.J.F. and A.Q.C. contributed equally.

Notes

The authors declare no competing financial interest.

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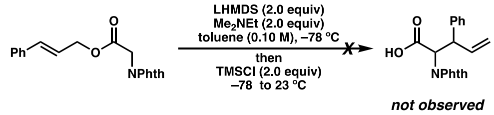

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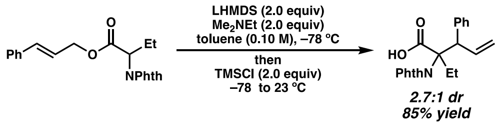
(13) Experimentally, a 2.7:1 dr is obtained (see the Supporting Information for details):



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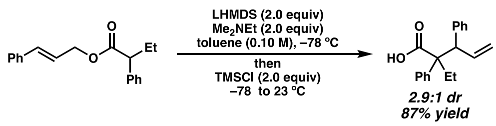
(17) Experimentally, a 2.9:1 dr is obtained (see the Supporting Information for details):



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