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Author manuscript

Org Lett. Author manuscript; available in PMC 2023 April 18.

Published in final edited form as:

Org Lett. 2022 May 27; 24(20): 3726–3730. doi:10.1021/acs.orglett.2c01381.

## Diastereoselective Indole-Dearomative Cope Rearrangements by Compounding Minor Driving Forces

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### Abstract

Reported herein is the discovery of a diastereoselective indole-dearomative Cope rearrangement. A suite of minor driving forces promote dearomatization: (i) steric congestion in the starting material, (ii) alkylidene malononitrile and stilbene conjugation events in the product, and (iii) an unexpected intramolecular  $\pi$ - $\pi^*$  stack on the product side of the equilibrium. The key substrates are rapidly assembled from simple starting materials, resulting in many successful examples. The products are structurally complex and bear vicinal stereocenters generated by the dearomative Cope rearrangement. They also contain a variety of functional groups for interconversion to complex architectures.

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Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.2c01381>.

Experimental procedures and characterization data ( $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR,  $^{19}\text{F}$  NMR, HRMS, X-ray, and HPLC traces) (PDF)

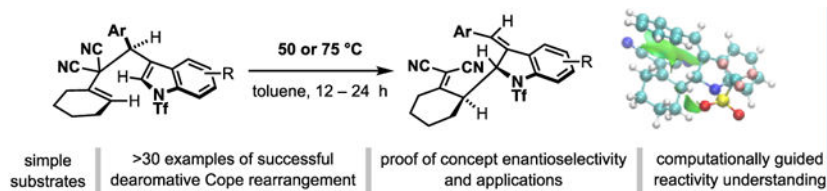
Accession Codes

CCDC 2149755 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif), or by emailing [data\\_request@ccdc.cam.ac.uk](mailto:data_request@ccdc.cam.ac.uk), or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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The authors declare no competing financial interest.

## Graphical Abstract



Aromatic sigmatropic rearrangements involving dearomatized intermediates and/or products<sup>1,2</sup> often leverage a heteroatom to facilitate and favor dearomatization and/or aromatic functionalization. This is because of the generally favorable kinetics and thermodynamics of such systems. There is a rich variety of “heteroatomic 1,5-diene” substrate classes reported (Figure 1A),<sup>3–10</sup> including many “named reactions” (aromatic Claisen<sup>11</sup> and Sommelet–Hauser<sup>12,13</sup> rearrangements and Fischer indole synthesis<sup>14</sup>). The aromatic Cope rearrangement is significantly more limited with few modern examples that can be applied to complex molecule synthesis.<sup>15</sup> The most common strategy for driving forward an aromatic Cope rearrangement is utilizing strain release (Figure 1B, eq 1).<sup>16–18</sup> There are also reports related to anion acceleration (Figure 1B, eq 2).<sup>19</sup> A relatively new strategy pertains to synchronized aromaticity (Figure 1B, eq 3).<sup>20</sup> Considering the relative dearth of methods for achieving aromatic Cope rearrangement, there is a need to identify new methods of value to complex molecule synthesis. These methods should be characterized by (a) desirable kinetic and thermodynamic profiles, (b) stereocontrol about the [3,3] rearrangement, and (c) yields of valuable complex molecules from (d) readily available sources. Our previous work resulted in the discovery of 3,3-dicyano-1,5-dienes (and related substrates) that have low [3,3] kinetic barriers (19–25 kcal/mol) and high thermodynamic favorability ( $G = -5$  kcal/mol) and yield useful building blocks containing vicinal stereocenters.<sup>21–23</sup> These findings suggest that other more challenging Cope substrate classes may be positively impacted by related engineering strategies.<sup>24</sup> Herein, we report the discovery of a readily available class of substrates capable of undergoing thermodynamically favorable indole-dearomatative Cope rearrangement.

Vicinal stereocenter-generating, dearomatative Cope rearrangement was first observed on substrate **1a** (Scheme 1A). This substrate has some rationally designed features that we hypothesized would favor the desired dearomatative Cope rearrangement. In addition to facilitating substrate synthesis, the 3,3-dicyano moiety would stabilize the transition state and the product side of the equilibrium through resonance conjugation. For similar reasons, the 4-phenyl group would facilitate and partially counteract the penalty for indole dearomatization. Together, the 3,3-dicyano moiety and the 4-phenyl group weaken the C3–C4 bond via torsional strain and/or steric congestion. Thus, both substrate-destabilizing features and product-stabilizing features are designed into the starting material. It was found that at increased temperatures [1,3] Cope product **2a** was favored (Scheme 1A, entry 1), likely via a solvent-caged radical route. A crossover experiment supports this.<sup>25</sup> However, temperatures ranging from rt to 100 °C produced the desired [3,3] product *trans*-**3a** with two new vicinal stereocenters and *trans*-stilbene geometry exclusively (Scheme 1A, entries 2–5). This stereochemistry was assigned on the basis of detailed NMR analysis.<sup>25</sup> Notably,

the transformation proceeded with high diastereoselectivity at 75 °C (Scheme 1A, entry 3) but was less selective at 100 °C (Scheme 1A, entry 2). The stereochemistry observed is rationalized by a closed, chairlike transition state, though the outcome also suggests that the 4-phenyl group is positioned pseudoaxially in this model (see Figure 2). During the optimization studies, we also examined the effect of the N-protecting group and found that *N*-Ts-**1a** was less reactive under the optimized conditions and yielded a 5:1 diastereomeric mixture of Cope products (Scheme 1A, entry 6). Similarly, *N*-Boc-**1a** was unreactive to [3,3] under the standard conditions, and at increased temperatures, only the formal [1,3] product was observed (Scheme 1A, entry 7). To probe the significance of the 4-phenyl group on Cope rearrangement reactivity, we prepared substrates that bear a 4-methyl group and an unsubstituted methylene (Scheme 1B). Neither of these substrates was reactive up to 150 °C, providing qualitative support for the idea that the 4-phenyl group has a unique impact on the kinetics and thermodynamics of this dearomative transformation.

The thermodynamic favorability of this indole-dearomatizing Cope rearrangement and the observed *trans*-stilbene diastereoselectivity is intriguing. To support our substrate design hypotheses and initial observations, we turned to DFT computation (Figure 2). Recall that the observed diastereomers *trans*-**3a** and *cis*-**3a** are *trans*- and *cis*-stilbene isomers, respectively, and are thus derived from chair transition states differing by either pseudoaxial or pseudoequatorial positioning of the phenyl group (Figure 2A, eqs 1 and 2). The computational data support the idea that the chair-pseudoaxial-phenyl transition state leading to the major observed *trans*-stilbene product *trans*-**3a** (Figure 2A, eq 1) is kinetically favored over the chair-pseudoequatorial-phenyl transition state toward the minor observed diastereomer *cis*-**3a** (Figure 2A, eq 2);  $G^\ddagger = 1.8$  kcal/mol (Figure 2A, eq 1 vs eq 2). On the basis of a noncovalent interaction (NCI) analysis,<sup>26,27</sup> both pathways (eqs 1 and 2) are exergonic. The key distinguishing feature in favor of eq 1 is an aromatic  $\pi$ - $\pi^*$  interaction (secondary orbital overlap) between the developing alkylidene malononitrile and *trans*-stilbene functional groups.<sup>28</sup> This interaction is significantly weaker in the pathway where the phenyl group is positioned pseudoequatorially (eq 2), especially in the product (see the Supporting Information for complete NCI analysis). For the sake of continuity, we also modeled the Cope rearrangements that proceed through boat transition states where the phenyl group is positioned either pseudoaxially (Figure 2A, eq 3) or pseudoequatorially (Figure 2A, eq 4), thus having the *trans*-stilbene or *cis*-stilbene geometry, respectively, in the product (Figure 2A, eqs 3 and 4). In both cases, the reactive conformer and the transition state were found to be higher in energy than the comparative transformations that proceed via chair conformations, which agrees with the experimental findings. The calculations also support that the most kinetically and thermodynamically favored dearomative Cope rearrangement pathway (Figure 2A, eq 1) is kinetically favored over the radical [1,3] rearrangement ( $G^\ddagger = 3.6$  kcal/mol), in agreement with our experimental findings (Scheme 1A). On the basis of these findings, the favorability for dearomatization is achieved through the combination of three minor contributing structural features: C3–C4 congestion in the starting material, alkylidene malononitrile and stilbene conjugation events in the product, and an aromatic  $\pi$ - $\pi^*$  interaction.

With a method in hand for achieving indole-dearomatizing Cope rearrangement, we turned to examine the scope of the transformation (Scheme 2). Standard conditions involved heating substrates **1a–1bb** in toluene at 75 °C. However, if diastereomers were observed, we often performed the reaction at 50 °C, which normally improved diastereoselectivity. As shown in Scheme 2, we examined a variety of alkylidene malononitriles **4** and indole-phenylmethanol-derived electro-philic **5** (bromides or carbonates). Scheme 2A summarizes the scope with respect to various alkylidenemalononitriles. While model cyclohexyl scaffold **3a** reached full conversion within 15 h, it was found that various cyclic scaffolds bearing functional groups at position 4 often influenced the thermodynamics such that equilibrium mixtures of Cope “starting materials” **1** and Cope “products” **3** were observed. Nonetheless, respectable yields of protected piperidine (**3b**, 48% yield), tetrahydrothiopyran (**3c**, 83% yield), and ketal-protected cyclohexanone (**3d**, 53% yield) could be isolated at 75 °C. In these cases, the Cope equilibrium isomers were separable, allowing for recycling of the starting material. However, the difluorocyclohexanone-containing product **3e** was poorly favored thermodynamically (and inseparable from the respective starting material). Next, we found that tetralone (**3f** and **3g**)- and cycloheptanone (**3h**)-based scaffolds were highly reactive toward indole-dearomatizing Cope rearrangement. This can be rationalized by strain release (endocyclic cycloheptene to exocyclic cycloheptene) and an increased level of conjugation, respectively, upon dearomative [3,3]. Similarly, azepane (**3i**) and tropane (**3j**) were favorable substrates. Finally, acyclic substrates exemplified by **3k** were also reactive to indole-dearomative Cope rearrangement. Scheme 2B summarizes the scope with respect to the various indole-phenylmethanol-derived electrophiles. Electron-withdrawing and -donating groups were generally tolerated about the indole portion of the scaffold (**3l–3r**). 7-Azaindole scaffold **3t** had acceptable thermodynamic favorability for dearomative Cope rearrangement, though the *cis–trans* diastereoselectivity was low (2:1). The phenyl portion of the scaffold was similarly tolerant to electronic changes. For example, both 4-fluorophenyl (**3u**) and 4-methoxyphenyl (**3v**) reached >85% conversion with good, isolated yields and diastereoselectivity. Finally, examples **3w–3z** contain either electronically “paired” (e.g., F-/MeO- or MeO-/F-) or “dissonant” (e.g., F-/F- or MeO-/MeO-) arene–indole rings. We found that in all cases that conversion and isolated yields were high and diastereoselectivity ranged from excellent to modest. An X-ray structure of **3w** was also obtained, further validating the structural assignments. The final examples in Scheme 2B utilized tetralone-based scaffolds (**3aa** and **3bb**).

To complete our initial studies of the indole-dearomatizing Cope rearrangement, we examined how scaffolds can be made enantioselectively as well as ways in which the Cope products can be derivatized (Scheme 3). With regard to enantioselectivity (Scheme 3A), we envisaged a Pd-catalyzed kinetic resolution of the racemic electrophile **5a** to the enantioenriched Pd- $\pi$ -indolyl intermediate.<sup>29,30</sup> Indeed, it was found that Pd<sub>2</sub>dba<sub>3</sub>/(*R*)-SEGPHOS provided proof-of-concept enantioselectivity [46% yield of (–)-**3d**, 70% ee] for this sequence. Under these reaction conditions, the Cope product was observed directly. With regard to the functional group interconversion (Scheme 3B), we found that the alkylidene malononitrile moiety on **3a** or **3c** could be reduced efficiently with Hantzsch ester<sup>31</sup> to a malononitrile moiety, which, in turn, could be converted to an ester under mild conditions.<sup>32</sup> The dearomatized indole portion of the scaffolds could be rearomatized under

Lewis acid-catalyzed or oxidative conditions, thus yielding **7a** and **7b** following  $K_2CO_3$ /MeOH-promoted *N*-triflate deprotection. Under the same conditions in similar yields, we were also able to prepare *trans*-3,4-disubstituted heterocycle **7c**.

Described herein is a new platform for achieving indole-dearomative Cope rearrangement. The key structural features for the kinetically and thermodynamically favorable dearomative transformation, as determined through computational analysis, are a suite of minor contributing features, including steric congestion of the starting material, product stabilization through resonance conjugation, and  $\pi$ - $\pi^*$  aromatic stacking between the newly generated alkylidenemalononitrile and the *trans*-stilbene. Thus, compounding individual minor substrate-destabilizing and product-stabilizing effects results in thermodynamically favorable dearomatization. The understanding that minor driving forces built into a substrate can amount to a successful transformation that is normally considered kinetically and thermodynamically unfavorable will allow for much continued study, both fundamental and applied.<sup>33</sup>

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## ACKNOWLEDGMENTS

The authors gratefully acknowledge the National Institute of General Medical Sciences (R35 GM137893-01) for providing support for this research. The authors thank the Mass Spectrometry Research and Education Center and its funding source (National Institutes of Health Grant S10 OD021758-01A1).

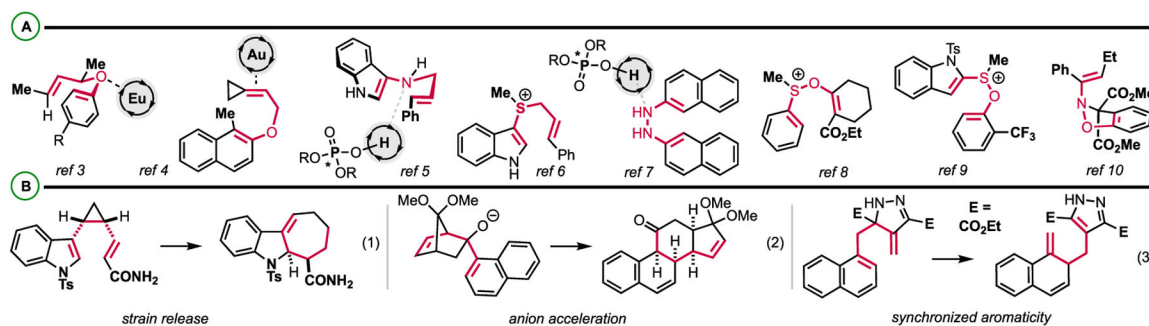
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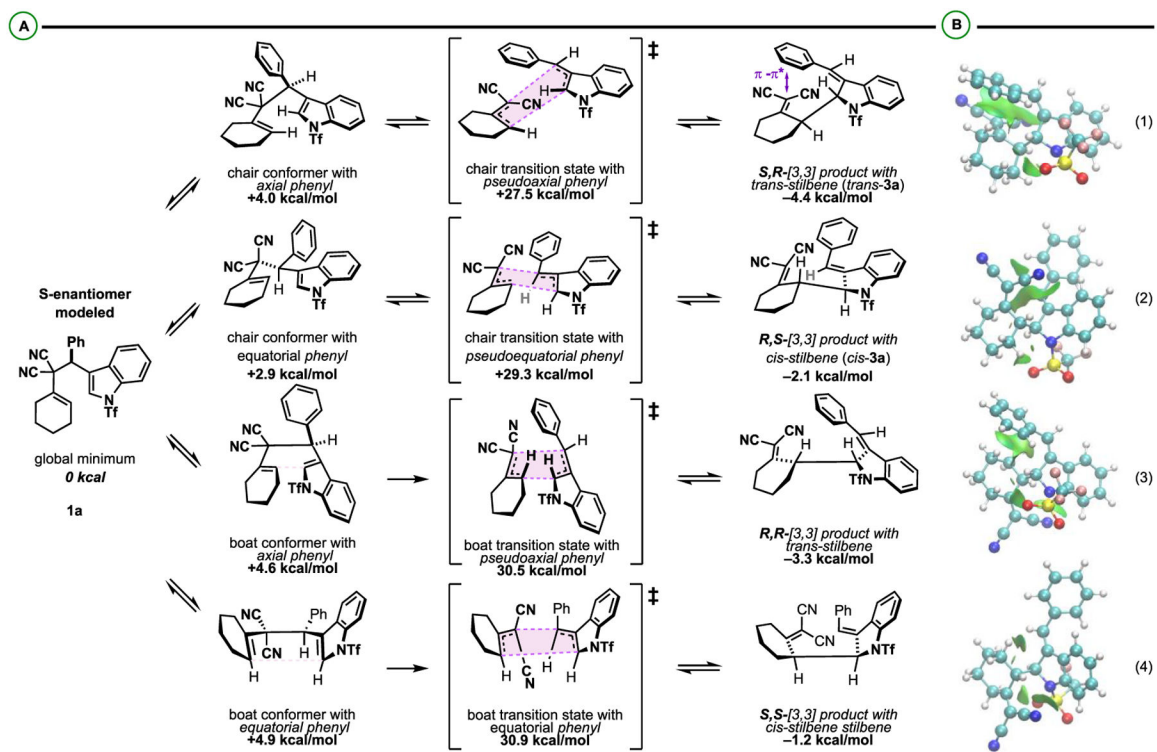


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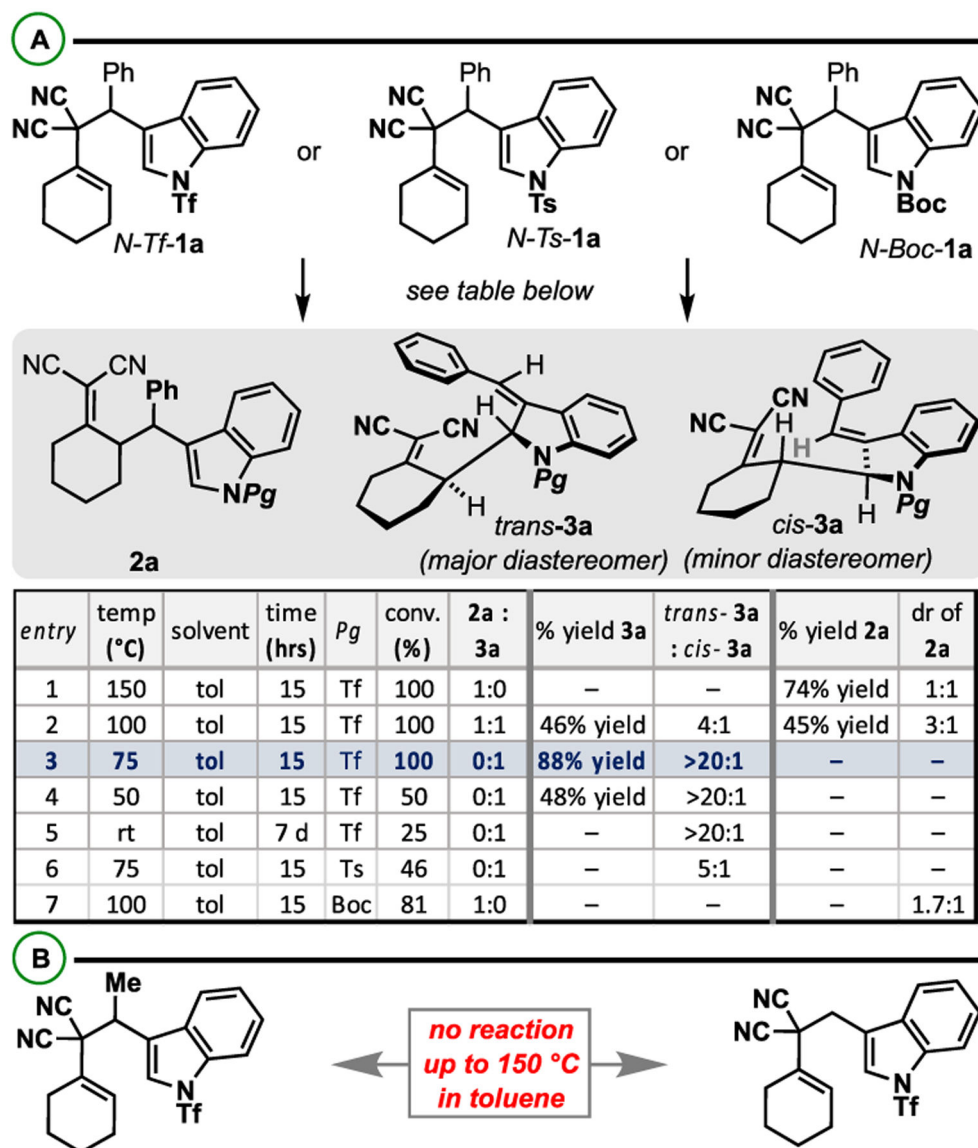


**Figure 1.**  
Aromatic sigmatropic rearrangements. (A) There is a rich diversity of heteroatomic substrate classes. (B) State-of-the-art aromatic Cope rearrangements.



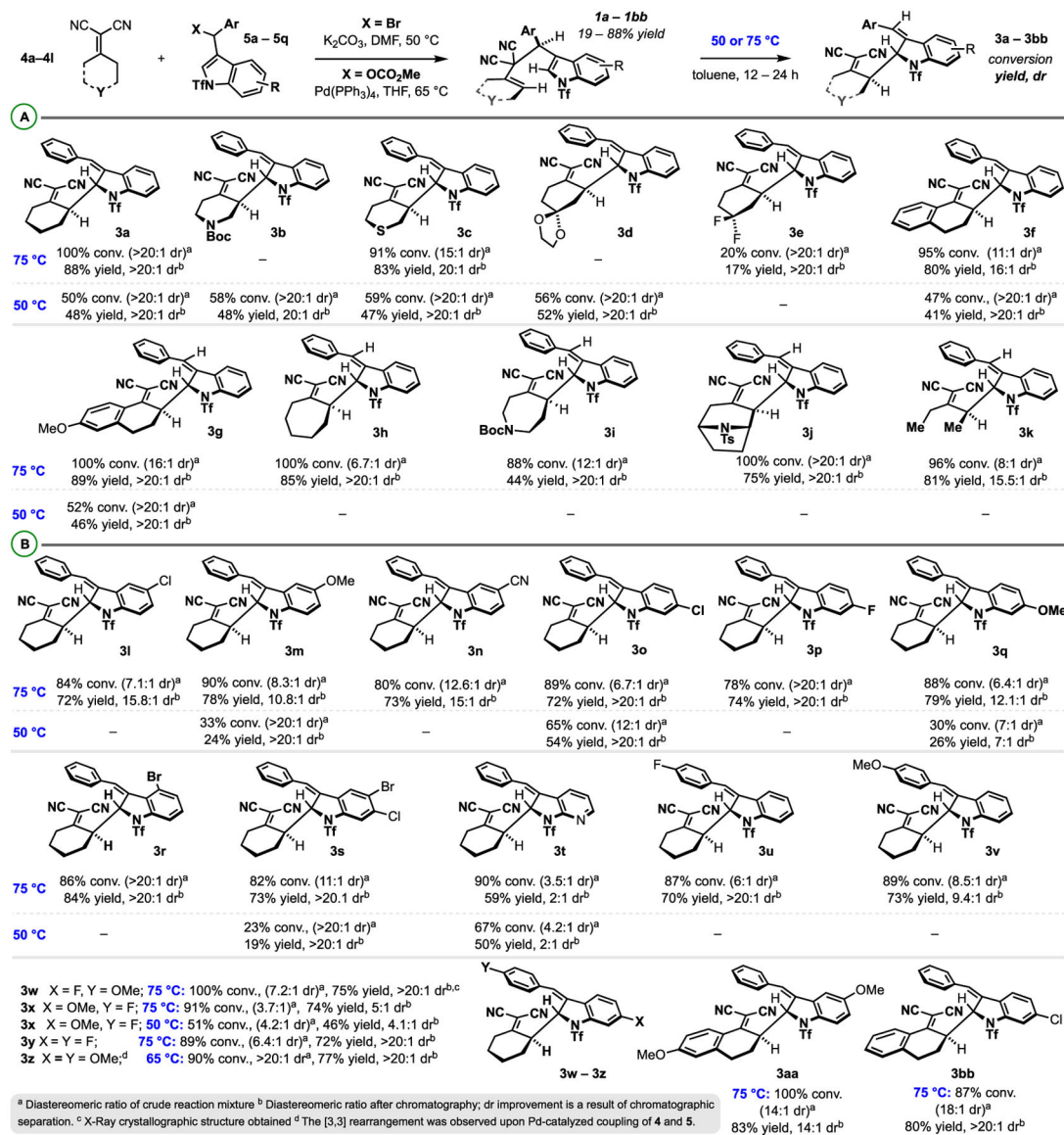


**Figure 2.** (A) Computational investigation of dearomative [3,3]. (B) Dearomatized diastereomers with plotted NCI regions.



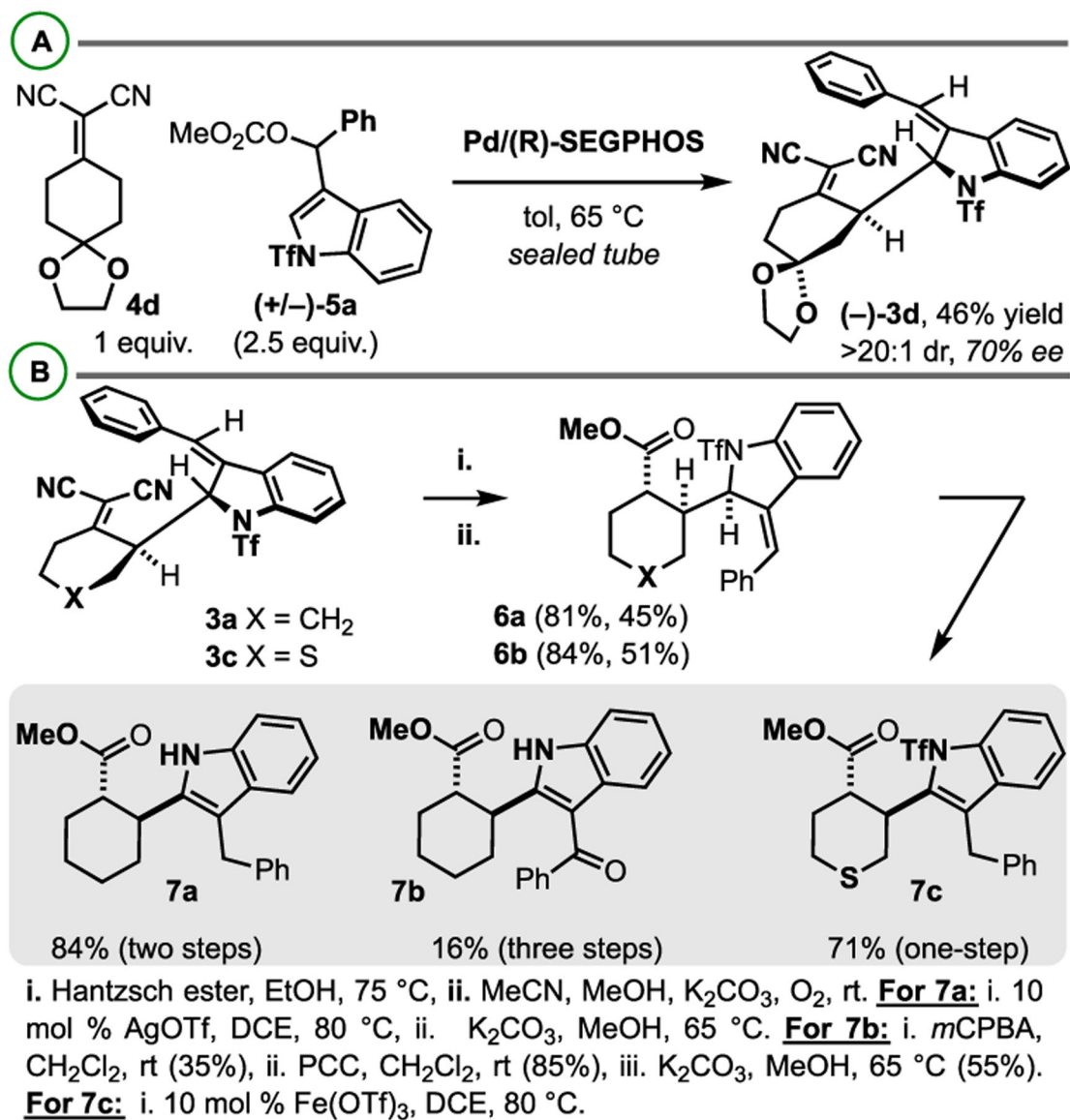
Scheme 1.

(A) [1,3] vs [3,3] Cope Rearrangements and (B) Probing the Impact of the 4-Phenyl Group on Rearrangement Reactivity



## Scheme 2.

Studies of the Scope of (A) Variable Alkyldenemalononitriles and (B) Variable Indole-phenylmethanol-Derived Electrophiles



## Scheme 3.

(A) Toward an Enantioselective Variant and (B) Functional Group Interconversion Reactions