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Catalyst-Controlled Regiodivergence in Rearrangements of Indole-Based Onium Ylides

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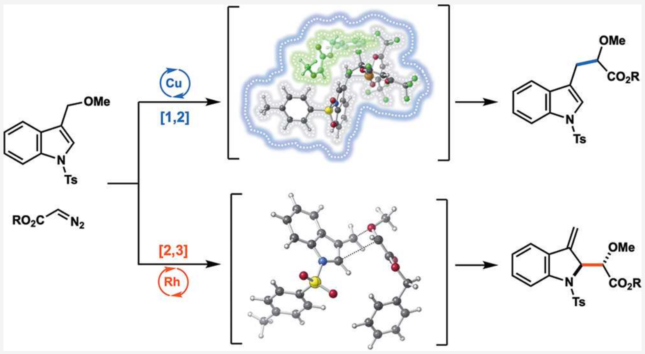
ABSTRACT: We have developed catalyst-controlled regiodivergent rearrangements of onium-ylides derived from indole substrates. Oxonium ylides formed *in situ* from substituted indoles selectively undergo [2,3]- and [1,2]-rearrangements in the presence of a rhodium and a copper catalyst, respectively. The combined experimental and density functional theory (DFT) computational studies indicate divergent mechanistic pathways involving a metal-free ylide in the rhodium catalyzed reaction favoring [2,3]-rearrangement, and a metal-coordinated ion-pair in the copper catalyzed [1,2]-rearrangement that recombines in the solvent-cage. The application of our methodology was demonstrated in the first total synthesis of the indole alkaloid (±)-sorazolon B, which enabled the stereochemical reassignment of the natural product. Further functional group transformations of the rearrangement products to generate valuable synthetic intermediates were also demonstrated.



■ INTRODUCTION

Molecular rearrangements are arguably some of the most effective reactions for the generation of new carbon−carbon bonds in the synthesis of complex molecules.[1] In recent years, advances in catalytic onium ylide rearrangements have paved the way for catalyst control of rearrangements that are traditionally unselective.[2,3] In this context, catalytic generation of onium ylides from diazocarbonyl compounds has served as a versatile platform for selective rearrangements (Scheme 1A). Despite many reports of catalytic onium ylide rearrangements of *aliphatic* systems,[4,5] only a few examples of analogous *aromatic* rearrangements are known which are limited to sulfonium (X = SR) and ammonium (X = NR$_2$) ylides.[6] The challenge of developing this class of rearrangements is partially due to the energetic penalty associated with disruption of aromaticity in the sigmatropic [2,3]-rearrangement (Scheme 1A).[7] A pioneering study on catalytic thia-Sommelet-Hauser rearrangement was reported by Wang and co-workers in 2008.[6c] In recent years, examples of controlled [1,2]- and [2,3]-rearrangements of ylides in aromatic systems have appeared in the literature.[8] Pan and co-workers reported rearrangements of sulfonium ylides where the selectivity for [1,2]- vs [2,3]-rearrangement is controlled by the solvent and substrate.[8a] Another report from Koenigs and co-workers shows a solvent controlled approach in rearrangements of sulfonium ylides formed from donor/acceptor carbenes.[8b] Alternatively, catalytic ylide-formation and aromatic [2,3]-rearrangements of oxonium systems (X = OR) are not known, presumably because of side reactions through nonylide pathways such as C−H insertion and cyclopropanation that compete with facile ylide formation.[9] Also, the examples for the [1,2]-rearrangement of oxonium ylides in the literature are generally limited to cyclic ylides.[4b−k] Catalytic methods for the selective formation of either [1,2]- or [2,3]-rearrangement products of aromatic systems from the same starting materials would provide a valuable new strategy for the synthesis of complex molecules.

Herein, we report the first catalyst-controlled regiodivergent aromatic rearrangements of indole-based oxonium ylides (Scheme 1B). With the proper choice of catalyst system, we can selectively generate the [1,2]- or [2,3]-rearrangement product. As our initial target for the rearrangements, we chose the indole-scaffold because of its prevalence in many natural products and medicinally valuable compounds.[10] In addition to exploring the scope of this reaction, we also performed DFT calculations to examine mechanisms and the origins of catalyst-controlled regiodivergence. Finally, to showcase the utility of

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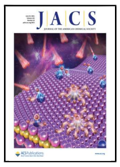

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Scheme 1. Catalyst Control of Regioselectivity in Onium Ylide Rearrangements

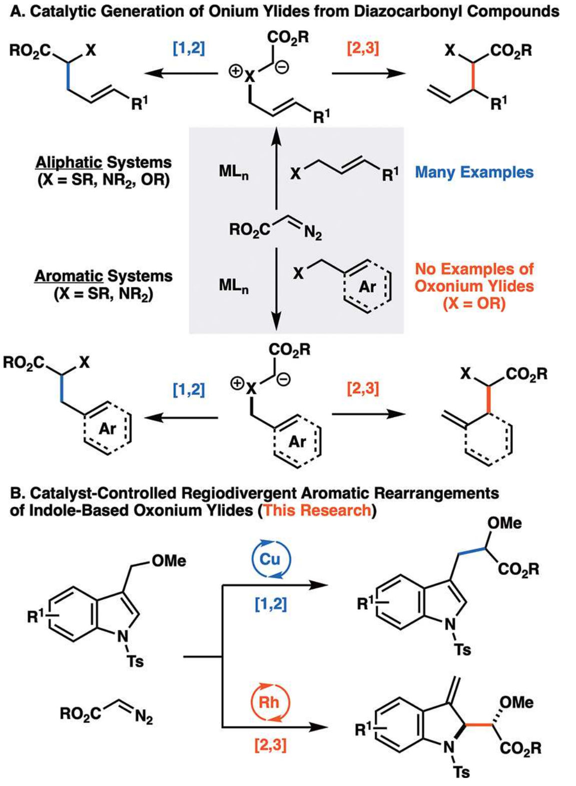
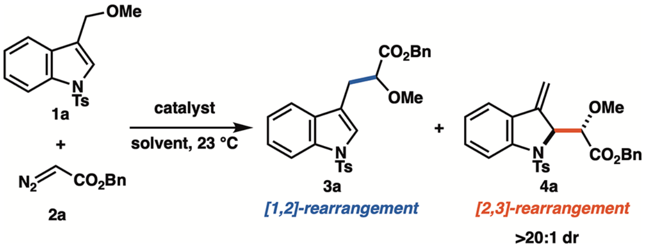


Table 1. Optimization of [1,2]- and [2,3]-Rearrangements[a]



Entry	Catalyst	Solvent	Conversion[b] (%)	Yield[c] (%)	3a:4a
1	$PdCl_2$	CH_2Cl_2	<5	<5	
2	AgOTf	CH_2Cl_2	<5	<5	
3	Ph_3PAuCl	CH_2Cl_2	<5	<5	
4	Cu(OTf)·benzene	CH_2Cl_2	5	5	82:18
5	CuCl	CH_2Cl_2	5	5	71:29
6	$CuCl_2$	CH_2Cl_2	8	7	75:25
7	CuOAc/$NaBAr_F$	CH_2Cl_2	26	18	76:24
8	$[Cu(MeCN)_4]PF_6$	CH_2Cl_2	42	38[d]	86:14
9	$Cu(hfacac)_2$	CH_2Cl_2	67	52[d]	92:8
10[e]	$Cu(hfacac)_2$	CH_2Cl_2	>95	78[d]	>95:5
11	$Rh_2(OAc)_4$	CH_2Cl_2	55	42[d]	<5:95
12	$Rh_2(cap)_4$	CH_2Cl_2	<5	<5	
13	$Rh_2(TFA)_4$	CH_2Cl_2	30	<5	
14	$Rh_2(TPA)_4$	CH_2Cl_2	56	23	32:68
15	$Rh_2(oct)_4$	CH_2Cl_2	44	33	10:90
16[e]	$Rh_2(OAc)_4$	CH_2Cl_2	92	26	<5:95
17	$Rh_2(OAc)_4$	DCE	41	36	<5:95
18	$Rh_2(OAc)_4$	$CHCl_3$	51	33	<5:95
19	$Rh_2(OAc)_4$	toluene	20	16	<5:95

[a]Reaction conditions: indole **1a** (0.16 mmol), benzyl diazoester **2a** (1.2 equiv, added using syringe pump as 0.2 M solution in solvent at a rate of 2 mL/h), copper catalyst (5 mol %) or rhodium catalyst (2 mol %). [b]Conversion of **1a**. [c]NMR yield using 1,3,5-trimethoxybenzene as internal standard. [d]Isolated yield. [e]2.4 equiv of **2a** was used.

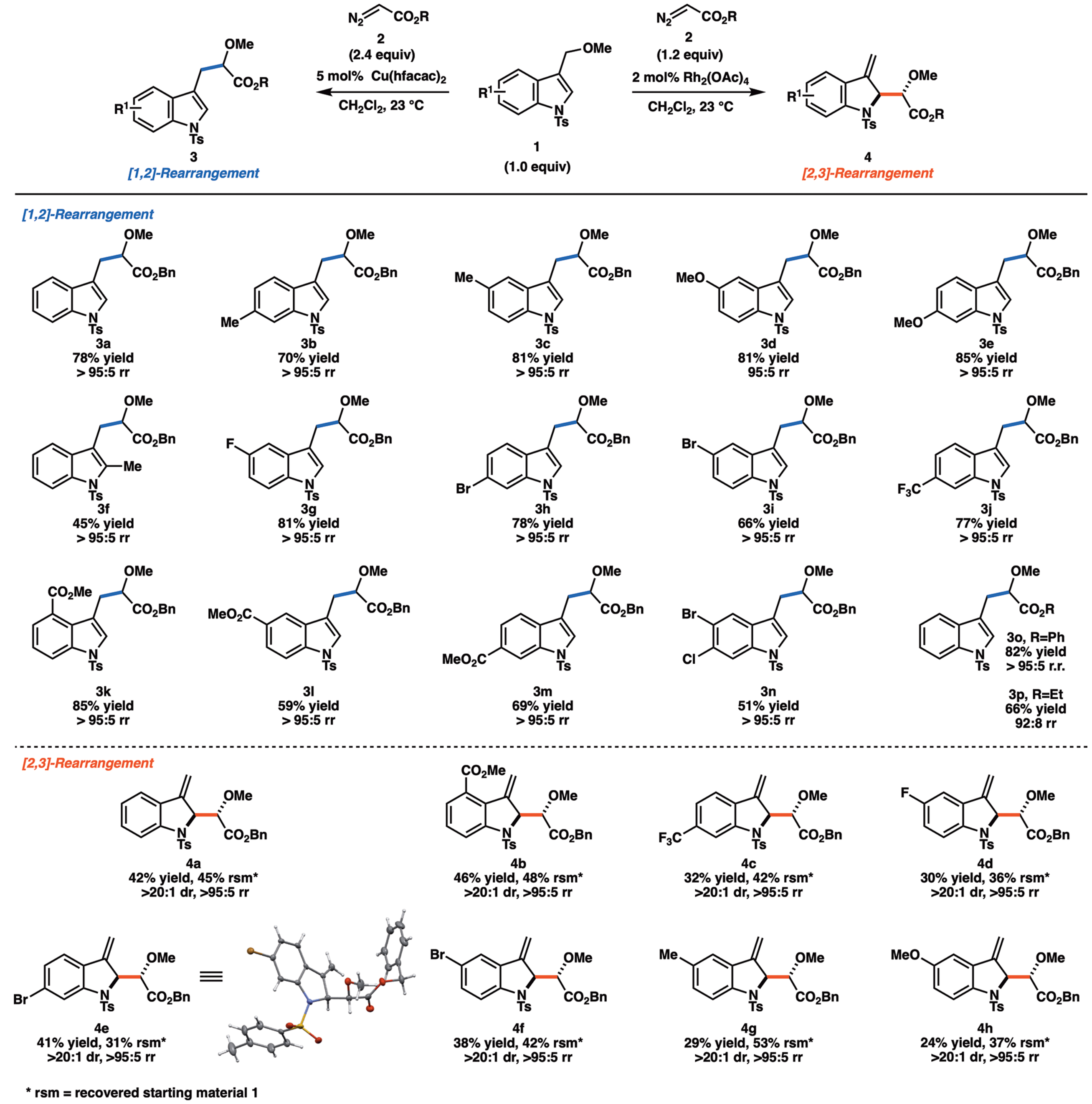
our method, we demonstrated the conversion of rearrangement products into the indole alkaloid sorazolon B and several valuable building blocks for drug discovery.

■ RESULTS AND DISCUSSION

Development of Regiodivergent Rearrangements. Our initial investigations began with the screening of various catalysts that are generally applied in carbene chemistry,[11] using 3-(methoxymethyl)-1-tosyl-1*H*-indole (**1a**) and benzyl diazoester (**2a**) as substrates (Table 1). While we did not observe any reactivity in the presence of palladium, silver, or gold catalysts (entries 1−3), CuOTf·benzene (5 mol %) afforded a mixture of [1,2]- and [2,3]-rearrangement products **3a** and **4a** (82:18 rr), respectively, in low yield (entry 4). Moreover, we were pleased to note that indoline **4a** bearing an exomethylene moiety (presumably from the [2,3]-rearrangement) was formed with excellent diastereoselectivity (>20:1 dr). Moving forward with this initial result that gave **3a** as the major product, we began optimizing the [1,2]-rearrangement of the oxonium ylides by screening additional copper sources. Other copper catalysts such as CuCl, $CuCl_2$, and CuOAc/$NaBAr_F$ gave similar or slightly improved yields, but relatively lower regioselectivities (entry 5−7). We were delighted to see an improved yield (38%) as well as regioselectivity (86:14 rr) with $[Cu(MeCN)_4]PF_6$ as catalyst (entry 8). The use of $Cu(hfacac)_2$ to perform the rearrangement further enhanced the yield (52%) and regioselectivity (92:8 rr) (entry 9). An examination of the conversion of the starting materials under these conditions revealed that the yield was limited by the incomplete consumption of indole **1a**, whereas the diazoester **2a** was completely consumed to give the desired products along with minor amounts of dibenzyl fumarate and dibenzyl maleate as the side products resulting from homodimerization. Increasing the amount of benzyl diazoester **2a** to 2.4 equiv resulted in >95% conversion of **1a** to provide the [1,2]-rearrangement product **3a** in 78% yield and >95:5 rr (entry 10).

Alternatively, when $Rh_2(OAc)_4$ (2 mol %) was used as the catalyst, we observed a switch in the regioselectivity that gave the [2,3]-rearrangement product **4a** as the major product (>95:5 rr) in 42% yield and >20:1 dr (entry 11). The screening of several other dirhodium carboxylate catalysts commonly used in metal-carbene transformations, such as $Rh_2(cap)_4$, $Rh_2(TFA)_4$, $Rh_2(TPA)_4$, and $Rh_2(oct)_4$,[12] failed to improve the yield for the reaction (entries 12−15). Similar to the copper-catalyzed [1,2]-rearrangement, an incomplete consumption of indole **1a** (55%) was identified as the reason for the moderate yields. However, increasing the amount of diazoester **2a** to 2.4 equiv diminished the yield of the [2,3]-rearrangement product **4a** to 26% (entry 16). We speculate that the reason for the lower yield with excess diazoester might be the propensity of the exomethylene group in **4a** to undergo cyclopropanation with excess highly reactive rhodium-carbene (see SI for details). We also examined other indole substrates besides methyl ether **1a** for optimization studies. While ethyl ether underwent the [2,3]-rearrangement, other alkyl and

Table 2. Products Generated by Regiodivergent [1,2]- and [2,3]-Rearrangements



[a] rsm = recovered starting material 1.

arylethers such as isopropyl and phenyl ethers did not give any conversion under the [2,3]-rearrangement conditions (see SI for details). Other N-protecting groups such as Me, Boc, and Ac were also screened during optimization for [2,3]-rearrangement, but most of these substrates did not show significant product formation (see SI for details). Further screening of different solvents also did not provide improvement in the yield (entries 17−19). As a result, the conditions with $Rh_2(OAc)_4$ (2 mol %) in CH_2Cl_2 at 23 °C were identified as optimal for the catalytic ylide-formation/aromatic [2,3]-rearrangement (entry 11).

Substrate Scope of Regiodivergent Rearrangements. With the optimized reaction conditions for both the copper-catalyzed ylide-formation/[1,2]-rearrangement and rhodium-catalyzed ylide-formation/[2,3]-rearrangement in hand (entries 10 and 11, Table 1), we next explored reaction scope (Table 2).

Indole substrates with a broad range of substituents at various positions on the heteroaromatic ring (**3a**−**3p**) worked efficiently under the [1,2]-rearrangement conditions. Electron-rich 5-and 6-substituted indole substrates provided high yields and excellent regioselectivities (**3b**−**3e**). Substitution at the 2-position generated the desired [1,2]-rearrangement product **3f**, albeit in slightly lower yield, but nonetheless gave excellent regioselectivity (>95:5 rr). Several electron-withdrawing substituents on the indole ring, including fluoro, bromo, trifluoromethyl, and ester groups (**3g**−**3m**), provided good yields and high regioselectivities. The reaction also progressed

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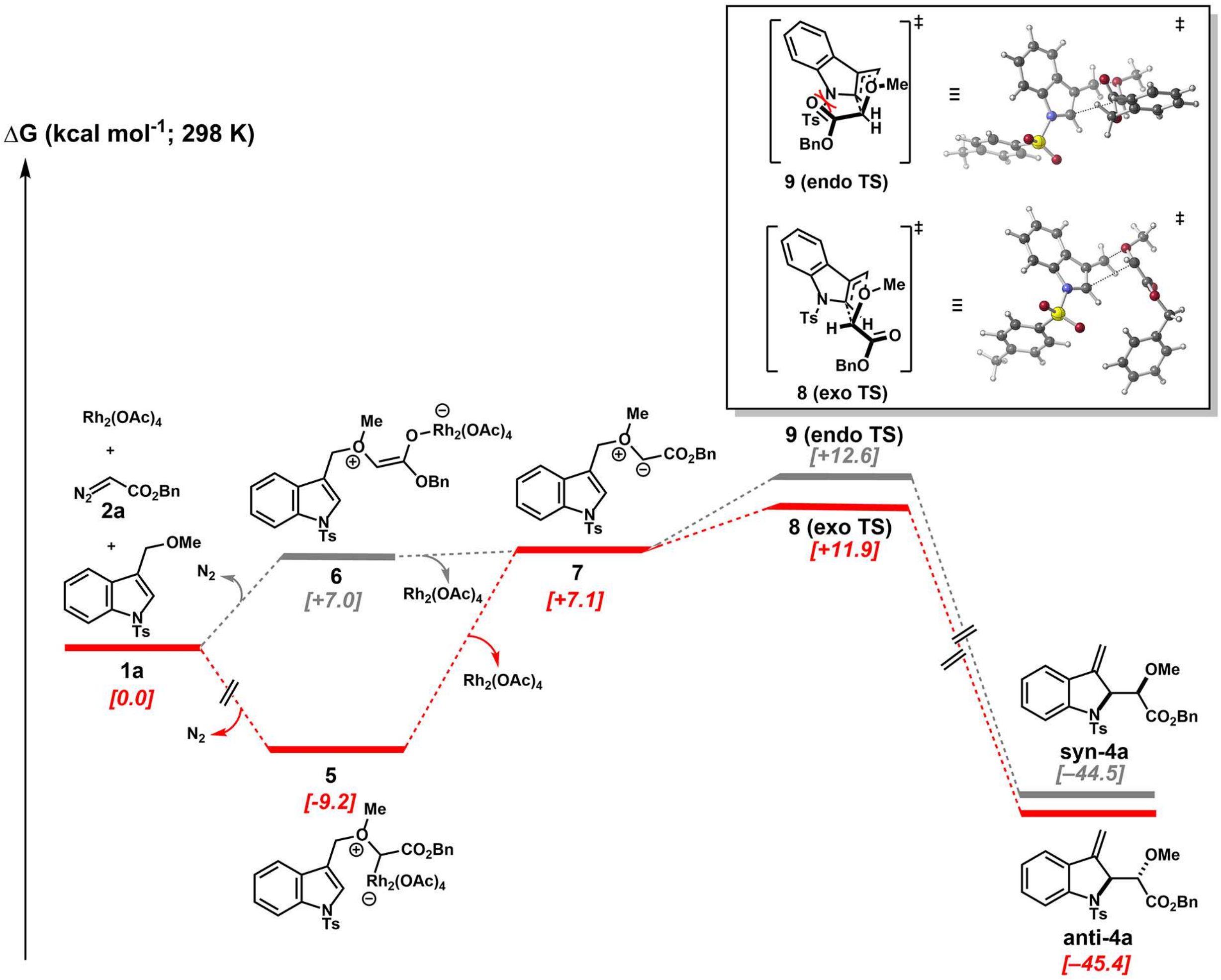


Figure 1. Computed (PWPB95-D3(BJ)/def2-QZVPP//IEFPCM(CH_2Cl_2)-B3LYP/6-31G(d), SDD) relative free energies (kcal/mol, italics) for minima and TSSs involved in the Rh-promoted reaction of **1a** and **2a**.

smoothly to generate dihalogenated product **3n** in 51% yield and >95:5 rr. In addition, other alkyl and aryl diazoesters were shown to be competent in generating [1,2]-rearrangement products in moderate to good yields (**3o** and **3p**).

Next, we explored the scope of the rhodium-catalyzed ylide-formation/[2,3]-rearrangement to provide various substituted indolines (**4**) that would be difficult to access in high selectivity by conventional methods.[13] Several electron-deficient indole rings with different substitution patterns underwent selective aromatic [2,3]-rearrangement to generate indolines (**4b**−**4f**) in moderate yields and with excellent regioselectivities. Electron-donating substituents on the indole ring led to comparatively lower isolated yields of the products (**4g** and **4h**); however, the [2,3]-rearrangement proceeded with excellent regioselectivity.[14] The rearrangement products were generally stable to rearomatization, presumably because of the electron-withdrawing tosyl protecting group similar to other known indolines.[13b,c] Notably, the [2,3]-rearrangement of all the substrates exhibited high diastereoselectivity (>20:1 dr). The relative stereochemistry of the major *anti*-diastereomer of product **4e** was confirmed by X-ray crystallography, and the relative stereochemistry of the major diastereomer of all other 2-substituted indolines was assigned by analogy.

Mechanistic Studies. To gain insight into the divergent mechanisms of the catalyst controlled ylide-formation/rearrangement reactions, a series of computational studies were performed using density functional theory at the PWPB95-D3(BJ)/def2-QZVPP//IEFPCM(CH_2Cl_2)-B3LYP/6-31G(d), SDD level (see SI for details).[15] The robustness of our chosen level of theory was evaluated through a series of tests with other functionals and basis sets (see SI for details); while there is some variation in predicted relative energies, these variations do not affect our mechanistic conclusions. 3-(Methoxymethyl)-1-tosyl-1*H*-indole **1a** was selected as the model substrate.

For the rhodium-catalyzed ylide-formation/[2,3]-rearrangement, we first examined the structure of the metal-bound oxonium ylide (Figure 1). Formation of the carbon-bound ylide **5** is predicted to be exergonic by 9.2 kcal/mol, whereas formation of the oxygen-bound ylide **6** is endergonic by 7.0 kcal/mol.

Our proposed pathway for a concerted [2,3]-rearrangement process is summarized in Figure 1. Dissociation of $Rh_2(OAc)_4$ prior to rearrangement generates free oxonium ylide **7**. Early dissociation of rhodium(II) complexes from ylides has been reported for other diazocarbonyl-mediated reactions.[4a,16] The most probable pathway to the product involves a metal-free [2,3]-rearrangement of oxonium ylide **7**, which leads to the observed product **4a** with the experimentally observed relative stereochemistry.[17] As expected, we were not able to find a transition state structure for the symmetry-forbidden metal-free [1,2]-rearrangement of oxonium ylide **7**.[18] The *relative*

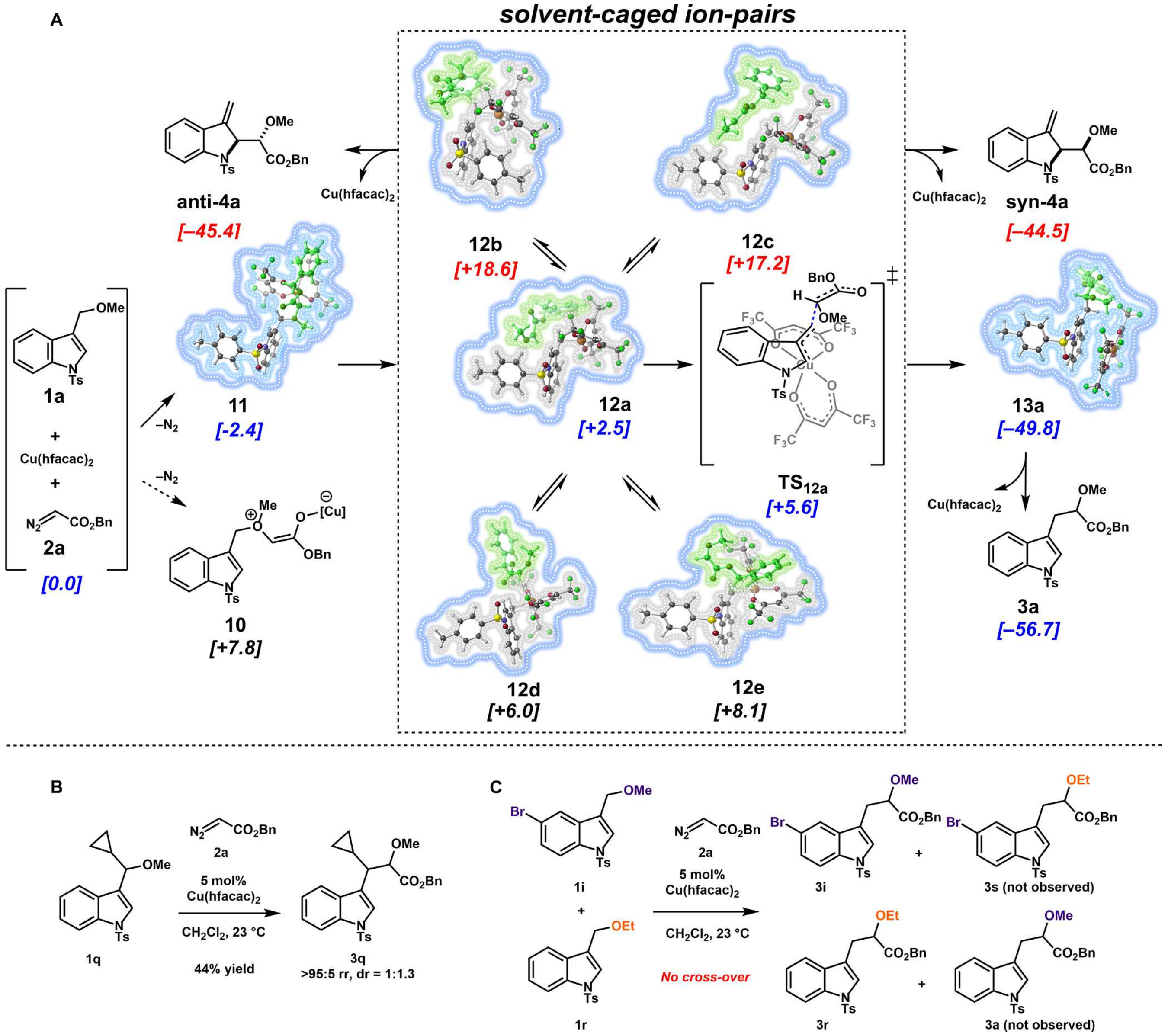


Figure 2. (A) Computed (PWPB95-D3(BJ)/def2-QZVPP//IEFPCM(CH_2Cl_2)-B3LYP/6-31G(d),SDD) relative free energies (kcal/mol, italics) for minima and TSSs involved in the Cu-promoted reaction of **1a** and **2a**. A selection of ion-pairs **12a**-**12e** were generated by scanning the bonds that form en route to the products. The energies for ion-pairs **12a**-**12e** are based on optimized complexes. Geometries of ion-pairs **12a**-**12e**, their preceding zwitterion **11**, and the recombination product **13a** shown in ball-and-stick images are included to facilitate comparison of overall shapes. For clarity in visual comparison, the enolate part of the ion-pair is highlighted in green and the indolyl part (highlighted in gray) is positioned the same way for each structure above. The solvent cage (not modeled explicitly) is depicted in blue with dotted lines. (B) Reaction conditions for radical probe experiment: indole **1q** (0.16 mmol), benzyl diazoester **2a** (1.2 equiv, added using syringe pump as 0.2 M solution in CH_2Cl_2 at a rate of 2 mL/h), Cu(hfacac)$_2$ (5 mol %), CH_2Cl_2, 23 °C. (C) Reaction conditions for crossover experiment: indole **1i** (0.08 mmol, 0.5 equiv), indole **1r** (0.08 mmol, 0.5 equiv) benzyl diazoester **2a** (1.2 equiv, added using syringe pump as 0.2 M solution in CH_2Cl_2 at a rate of 2 mL/h), Cu(hfacac)$_2$ (5 mol %), CH_2Cl_2, 23 °C.

stereochemistry of the major diastereomer of products arising from the [2,3]-rearrangement of indole-based onium ylides such as **7** is consistent with a preference for an *exo* transition state structure (**8**).[4d] Relative free energies calculated for the *exo* and *endo* transition states predicted a lower energy barrier for *exo* transition state **8** leading to the observed diastereomer *anti*-**4a**.

For the copper-catalyzed ylide-formation/[1,2]-rearrangement, we propose a mechanism that involves a stepwise process (Figure 2A).[4e,19] The preferential formation of the [1,2]-rearrangement product **3a** over the [2,3]-rearrangement product **4a** is an argument against pathways involving the early dissociation of copper from the initially generated metal-coordinated ylide **11**, since metal-free [1,2] rearrangement is predicted to have an extremely high barrier compared to that of the [2,3]-rearrangement (see SI). On the basis of our computational results, we favor an ion-pair fragmentation/recombination pathway for the copper-catalyzed reactions.[20] Other possible pathways were explored but were not consistent with our experimental results (see SI for details). For example, formation of simple radical-pairs cannot be ruled out on the basis of our computational results, but our experimental data argues against it. Specifically, cyclopropane containing substrate **1q** reacted with diazoester **2a** to yield the [1,2]-rearrangement product **3q** with the radical probe intact (Figure 2B).[21,22]

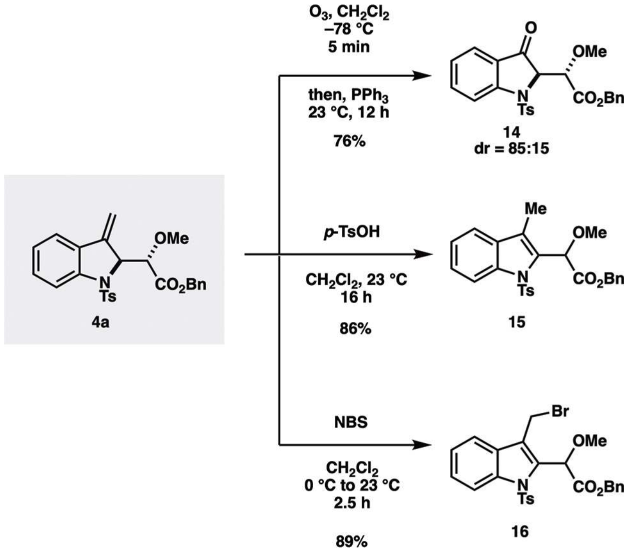
To gain insight into the key carbon−carbon bond formation event in the copper-catalyzed reaction, we considered ion-pair complexes (**12a**, **12b**, **12c**, **12d**, and **12e**) that could lead to the [1,2]-rearrangement product **3a** or the [2,3]-rearrangement product diastereomers *syn*-**4a** and *anti*-**4a** with minimal reorganization (Figure 2A).[23] In principle, these ion-pairs would be in equilibrium with each other and could recombine to form copper-bound recombination products (e.g., **13a**, Figure 2A).[24] However, recombination in a solvent cage is expected to be faster than equilibration between ion-pairs.[20g,25] Although a solvent cage was not explicitly modeled in our calculations, the formation of ion-pairs in a solvent cage is consistent with experimentally determined results. When substrates **1i** and **1r** were simultaneously subjected to the [1,2]-rearrangement conditions, we did not detect crossover products **3s** and **3a** (Figure 2C).

We were able to find a transition state structure (TS_{12a}) converting the ion-pair **12a** to **13a**, the $Cu(hfacac)_2$-bound experimentally observed product, with a 3.1 kcal/mol barrier. Subsequent dissociation of Cu catalyst yields **3a**. If **12a** was formed preferentially on the dissociation of the copper-coordinated oxonium ylide **11**, we propose that this ion-pair could rapidly recombine to the experimentally observed product (**12a** → **3a**) before equilibration with other ion-pairs. Comparisons of the various ion-pairs and metal-ylide intermediate **11** do indeed reveal greater conformational similarity between **11** and **12a** than either **12b**, **12c**, **12d**, or **12e** (Figure 2A; see SI for details). We also investigated the proposed stepwise ion-pair mechanism with other copper catalysts ($Cu(acac)_2$, $CuCl_2$, $Cu(hfacac)^+$, and $Cu(acac)^+$), and all qualitatively lead to similar results (see SI for details).

In summary, on the basis of our combined experimental and computational data, we favor a mechanism for the rhodium-promoted reaction where early catalyst dissociation occurs at the ylide stage, and products are formed via a metal-free [2,3]-sigmatropic rearrangement. For the copper-promoted reaction, we favor a mechanism where a copper-coordinated ion-pair is formed and rapidly recombines in a solvent cage to form the observed [1,2]-rearrangement product.

Synthetic Applications of Regiodivergent Rearrangements. The products generated through the [2,3]-rearrangement proved to be versatile substrates to access building blocks that are potentially useful for the synthesis of complex molecules (Scheme 2). For example, rearrangement product **4a** can undergo ozonolysis to yield indoxyl product **14**. In the presence of acid, the rearrangement product **4a** is rearomatized to furnish 2,3-disubstituted indole **15**. In the presence of an electrophilic source of bromine, it is selectively converted to 3-bromomethyl indole **16**.

Scheme 2. Synthetic Derivatization of [2,3]-Rearrangement Product



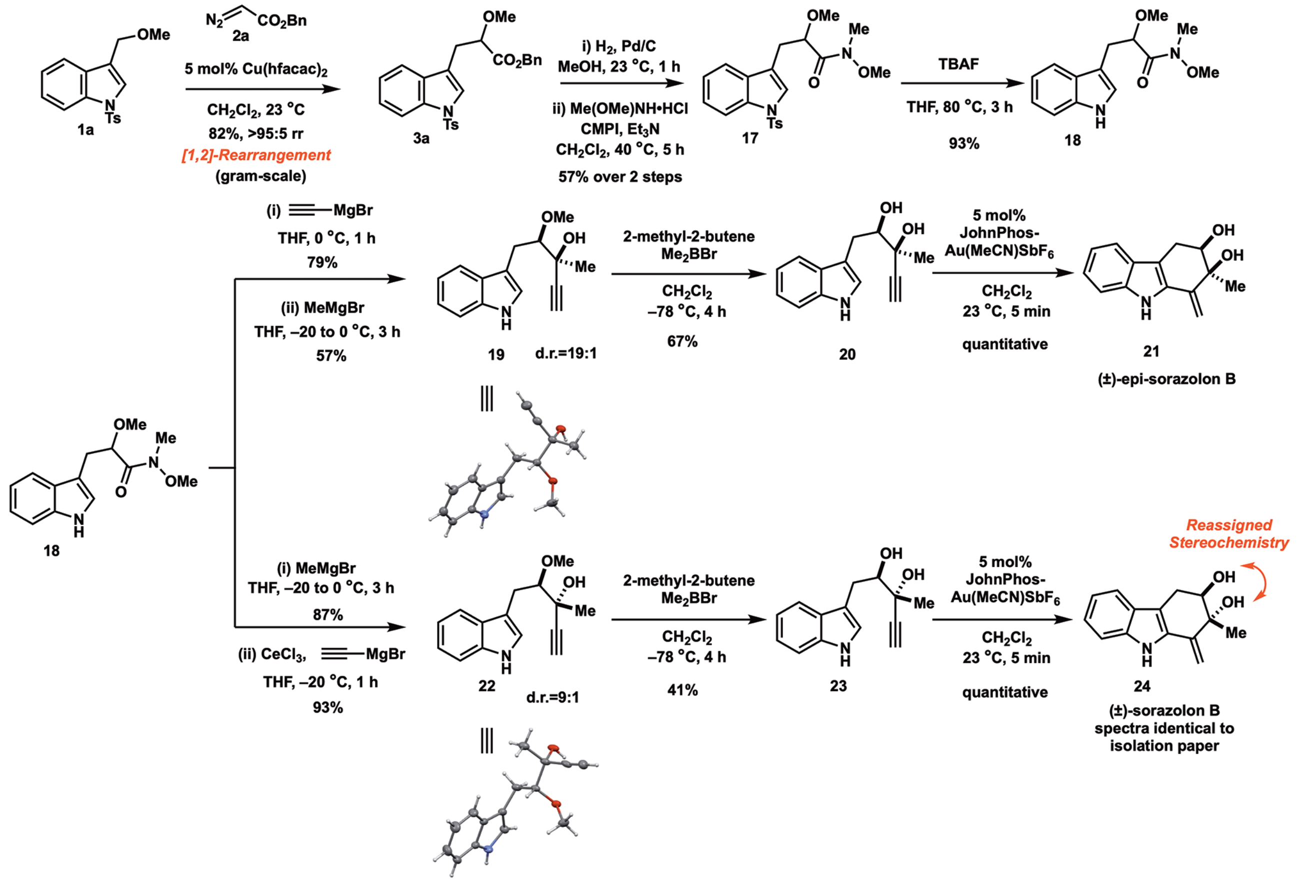
To demonstrate the synthetic utility of the [1,2]-rearrangement products, we incorporated this transformation into the first total synthesis of the indole alkaloid sorazolon B, which enabled a stereochemical reassignment of the natural product's structure that was reported in the original isolation paper (Scheme 3).[26] To commence the total synthesis, 3-(methoxymethyl)-1-tosyl-1*H*-indole (**1a**) was coupled with diazoester **2a** under the [1,2]-rearrangement conditions to furnish benzylester **3a** in 82% yield and >95:5 rr. The efficiency of the reaction was maintained on a gram scale. A two-step procedure converted benzylester **3a** to the Weinreb amide **17**. Subsequent removal of the *N*-tosyl group provided N−H indole **18** in 93% yield. To access the relative configuration for the proposed structure of sorazolon B (**21**), we treated the Weinreb amide **18** first with ethynylmagnesium bromide followed by methylmagnesium bromide, which generated tertiary alcohol **19** in 19:1 dr and 57% yield over the two steps. The relative configuration of the major diastereomer, which was confirmed by X-ray crystallography, was consistent with a Cram chelation controlled addition of methylmagnesium bromide.[27] Alcohol **19** was then converted to diol **20**, which was subjected to gold catalyzed 6-endo cyclization.[28] Although the resulting tricyclic skeleton of **21** was consistent with the proposed structure of sorazolon B, the NMR data of our synthetic sample did not match the corresponding data for the natural product.

We hypothesized that the relative configuration of the two stereogenic centers in sorazolon B may have been misassigned. To test this hypothesis, we switched the order of addition of Grignard reagents to the Weinreb amide **18**. An initial addition of methylmagnesium bromide followed by a Cram chelation controlled addition of ethynylmagnesium bromide yielded the tertiary alcohol **22** in 9:1 dr. The relative configuration of the major diastereomer was confirmed by X-ray crystallography. The treatment of methyl ether **22** with bromodimethylborane and 2-methyl-2-butene resulted in the formation of diol **23**. In the presence of $Au(MeCN)SbF_6$ and JohnPhos, diol **23** was converted to tricycle **24**, which had spectroscopic data that were identical with the data reported for sorazolon B in the original isolation paper.[26]

■ CONCLUSION

We developed catalyst-controlled regiodivergent rearrangements of onium-ylides derived from indole methyl ethers and diazoesters. While a copper catalyst promotes a regioselective [1,2]-rearrangement, a rhodium catalyst facilitates a regioselective and diastereoselective [2,3]-rearrangement. We present experimental and computational studies that support divergent mechanistic pathways for the two rearrangement processes. We also describe the synthetic utility of the two rearrangements by

Scheme 3. Synthesis and Stereochemical Reassignment of (±)-Sorazolon B from [1,2]-Rearrangement Product



demonstrating the functional group tolerance and scope of the reactions as well as the transformation of the rearrangement products to several indole-containing products. Finally, we applied the copper-catalyzed [1,2]-rearrangement in the first total synthesis of the indole alkaloid sorazolon B, which enabled the stereochemical reassignment of the natural product.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c00283.

Experimental details, characterization data, spectral data, and computational results (PDF)

Accession Codes

CCDC 2057316–2057318 and 2068211 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing 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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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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