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Highly Enantioselective Synthesis of Indazoles with a C3-Quaternary Chiral Center Using CuH Catalysis

Yuxuan Ye,[1] Ilia Kevlishvili,[2] Sheng Feng,[1] Peng Liu,[2]* and Stephen L. Buchwald[1]*

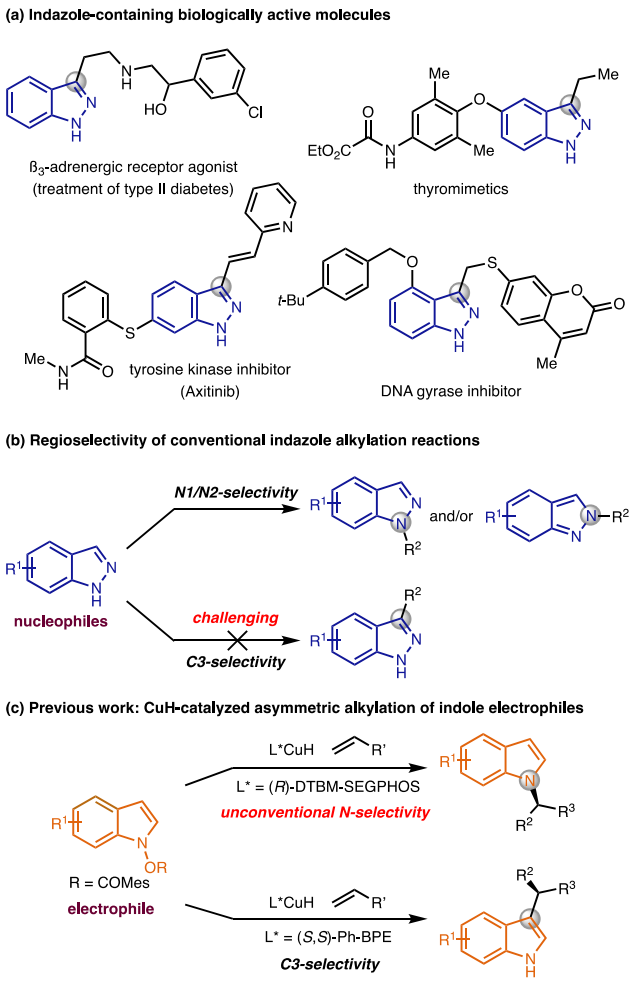
[1]Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States
[2]Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, United States

ABSTRACT: C3-substituted 1*H*-indazoles are useful and important substructures in many pharmaceuticals. Methods for direct C3-functionalization of indazoles are relatively rare, compared to reactions developed for the more nucleophilic N1 and N2 positions. Herein, we report a highly C3-selective allylation reaction of 1*H*-*N*-(benzoyloxy)indazoles using CuH catalysis. A variety of C3-allyl 1*H*-indazoles with quaternary stereocenters were efficiently prepared with high levels of enantioselectivity. Density functional theory (DFT) calculations were performed to explain the reactivity differences between indazole and indole electrophiles, the latter of which was used in our previously reported method. The calculations suggest that the indazole allylation reaction proceeds through an enantioselectivity-determining six-membered Zimmerman-Traxler-type transition state, rather than an oxidative addition/reductive elimination sequence, as we proposed in the case of indole alkylation. The enantioselectivity of the reaction is governed by both ligand-substrate steric interactions and steric repulsions involving the pseudoaxial substituent in the six-membered allylation transition state.

INTRODUCTION

The functionalization of nitrogen-containing heterocycles is a key area of research in organic synthesis due to the importance of these molecules in pharmaceutical applications.[1] In particular, the preparation of indazole derivatives is of great interest as a result of their versatile pharmacological activities[2] and their utility as indole bioisosteres in medicinal chemistry (Figure 1a).[3] The direct alkylation of indazoles is one of the most efficient methods to derivatize these molecules for medicinal chemistry studies. Conventionally, indazoles are employed as nucleophiles in these transformations, and either the N1- or N2-isomer is formed, depending on the reaction conditions.[4,5] Direct C3-alkylation processes, however, are rare due to the lack of nucleophilicity at the C3-position, even when the N1- or N2-position is protected (Figure 1b).[6]

Recently, we developed a method to prepare chiral alkylated indoles through a CuH-catalyzed nucleophilic alkylation reaction.[7] By employing *N*-(benzoyloxy)indoles as electrophiles and with the appropriate choice of ligand, selective N-alkylation or C3-alkylation was achieved (Figure 1c). Compared to conventional alkylation reactions, wherein indoles are used as nucleophiles,[8] the regioselectivity of this alkylation protocol was dictated by the catalyst, rather than the intrinsic nucleophilicities of the indole.[9] We envisioned that this umpolung strategy[10] could be expanded to other nitrogen-containing heterocycles, allowing us to achieve unconventional regioselectivity in the functionalization process of these heterocyclic molecules. Specifically, in the case of indazoles, we were hopeful that by employing *N*-(benzoyloxy)indazoles as electrophiles, the typically observed N1- or N2-regioselectivity in the nucleophilic substitution reactions could be overrode, and C3-alkylated indazoles might be accessed (Figure 1d).



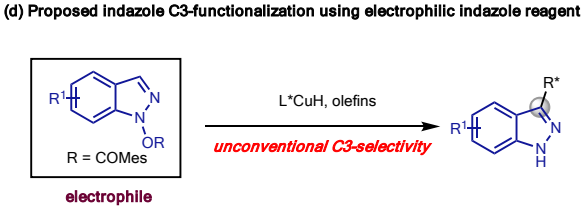


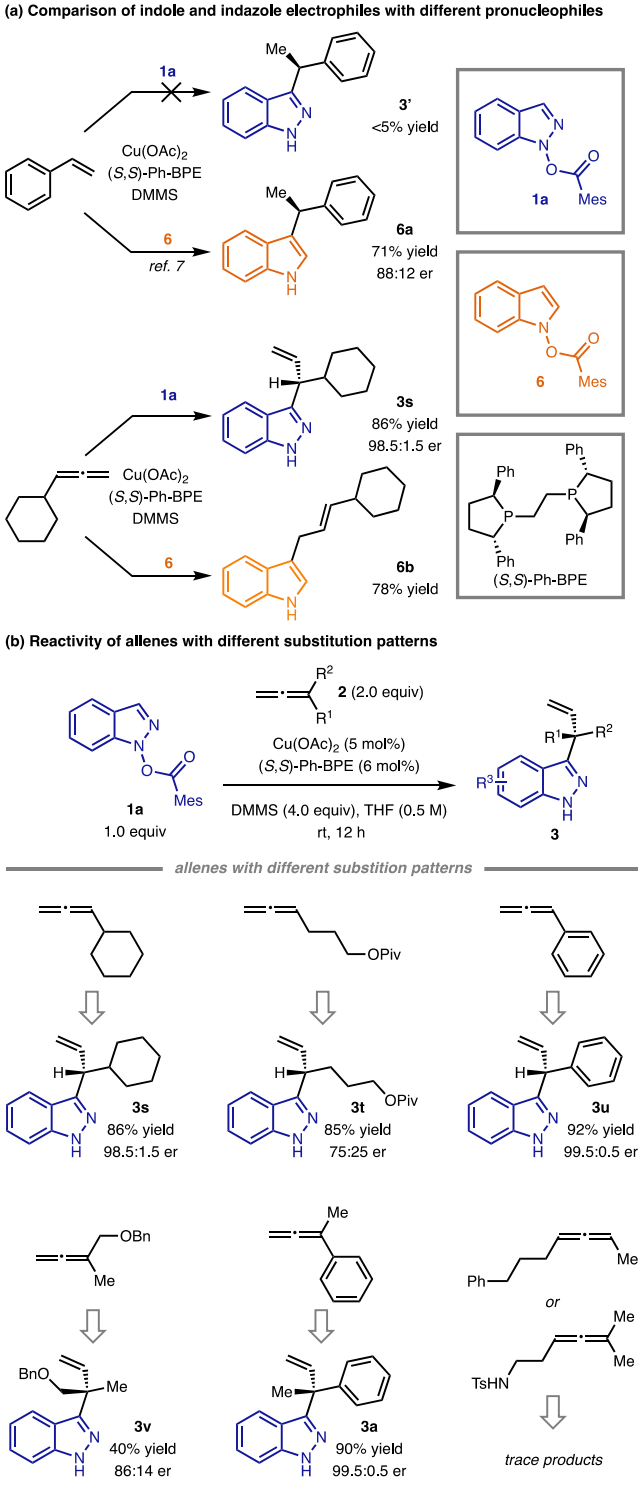
Figure 1. (a) Indazole-containing biologically active molecules. (b) Regioselectivity of conventional indazole alkylation reactions. (c) CuH-catalyzed asymmetric alkylation of indole electrophiles. (d) Proposed CuH-catalyzed asymmetric C3-allylation of indazole electrophiles. Mes: mesityl group.

RESULTS AND DISCUSSION

Initially, we attempted the coupling of a variety of readily accessible alkenes with indazole **1a** under the conditions previously developed for indole alkylation.[7] Less than 5% yield of the alkylated indazole products were formed in the cases of styrene (Figure 2a). However, when cyclohexylallene was employed,[11] it reacted efficiently with the indazole electrophile **1a**, providing the corresponding allyl indazole product (**3s**) in good yield with a high level of enantioselectivity. Notably, the reaction proceeded with excellent C3-regioselectivity. It is interesting that only the branched allyl indazole was formed, as the same reaction with the indole electrophile **6** produced the corresponding allyl indole product (**6a**) with exclusive selectivity for the linear isomer (Figure 2a). In addition, unlike the indole alkylation reaction,[7] wherein selective N-alkylation could be achieved using DTBM-SEGPHOS ligand, no N-allyl indazole product was observed with all the ligands tested (see the Supporting Information). The intriguing reactivity differences between indazole and indole electrophiles have important implications on the mechanisms of these reactions and were studied in detail with the aid of density functional theory (DFT) calculations (*vide infra*).

We further investigated the reactivity of other types of allenes in this reaction (Figure 2b). A monoalkyl-substituted allene with a substituent sterically smaller than cyclohexyl reacted efficiently albeit with decreased enantioselectivity (**3t**). A monoaryl-substituted allene could be coupled efficiently (**3u**). Furthermore, a 1,1-dialkylallene was successfully reacted with **1a** in moderate yield and useful enantioselectivity (**3v**). Finally, 1-aryl-1-alkylallene underwent the reaction with high efficiency, providing C3-allyl indazole (**3a**) in excellent yield and with a high level of enantioselectivity. However, neither 1,3-disubstituted allenes nor 1,1,3-trisubstituted allenes were suitable substrates.

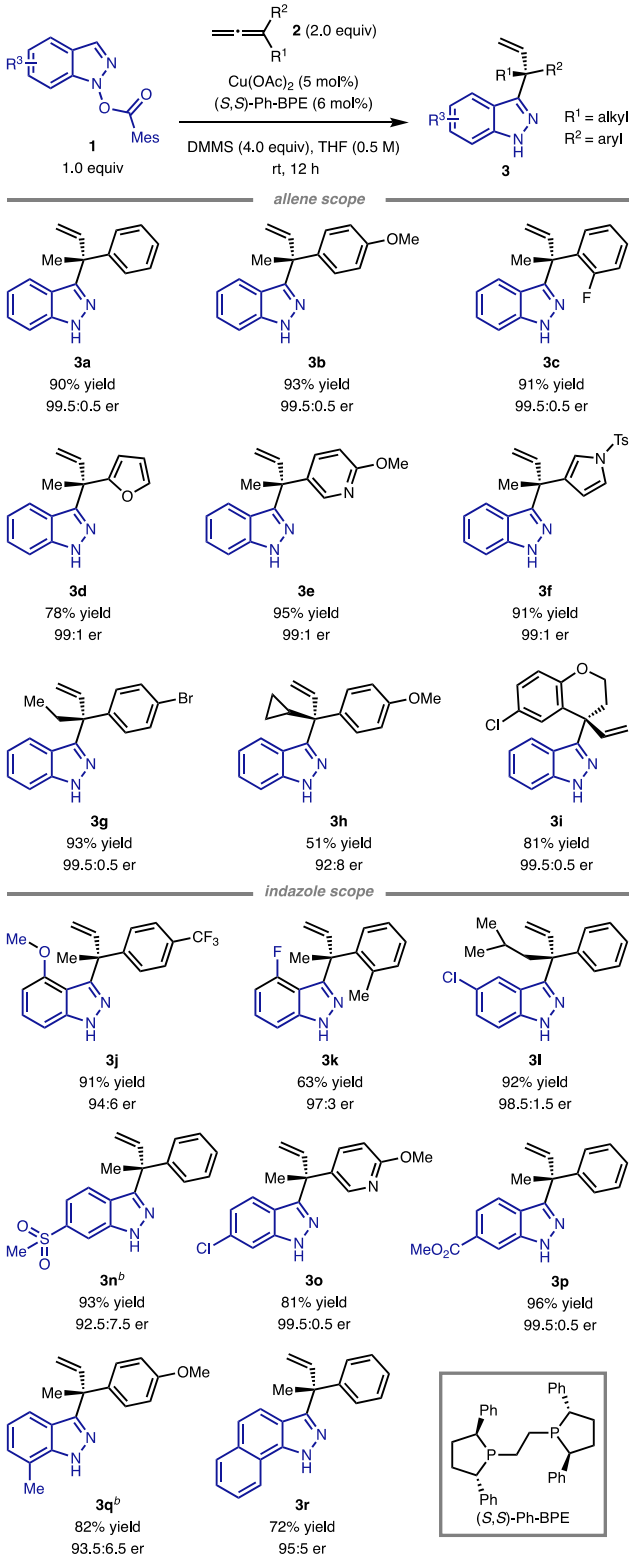
We considered 1-aryl-1-alkylallenes attractive coupling partners because the corresponding C3-allyl indazole products with an acyclic quaternary stereocenter are potentially valuable molecules in medicinal chemistry, and challenging to access using existing methods.[12] Therefore, a variety of 1-aryl-1-alkylallenes are tested in the reaction with *N*-(benzoyloxy)indazole electrophiles (Table 1). Substituents including 4-methoxy (**3b**), 2-fluoro (**3c**), 4-bromo (**3g**), 3-chloro (**3i**), 4-trifluoromethyl (**3j**), and 2-methyl (**3k**) on the phenyl ring of the allenes are well tolerated. Allenes containing heterocycles, such as furan (**3d**), 2-methoxypyridine (**3e**), and *N*-Ts-pyrrole (**3f**), are also compatible in the reaction. We observed a slight decrease in both efficiency and enantioselectivity with the increasing steric hindrance of alkyl substituents on the allenes. Methyl- (**3a**), ethyl- (**3g**), isobutyl- (**3l**), and cyclopropyl- (**3h**) substituted indazoles were prepared from the corresponding allenes with decreasing enantiomeric ratios (99.5:0.5 to 92:8). In addition, an indazole derivative with a fused dihydropyran (**3i**) was prepared from a chromane-derived allene efficiently.



Reactions were conducted on 0.10 mmol scale. Yields were determined by ^{1}H NMR or GC analysis of the crude reaction mixture. The absolute stereochemistry was signed by analogy to **3a** and confirmed by DFT calculations.

Figure 2. (a) Comparison of indazole and indole electrophiles with styrene and allene pronucleophiles. (b) Test of allenes with different substitution patterns in the indazole allylation reaction.

Table 1. Substrate Scope for the C3-Allylation of Indazole Electrophiles with 1-Aryl-1-Alkyl Allenes.[a]

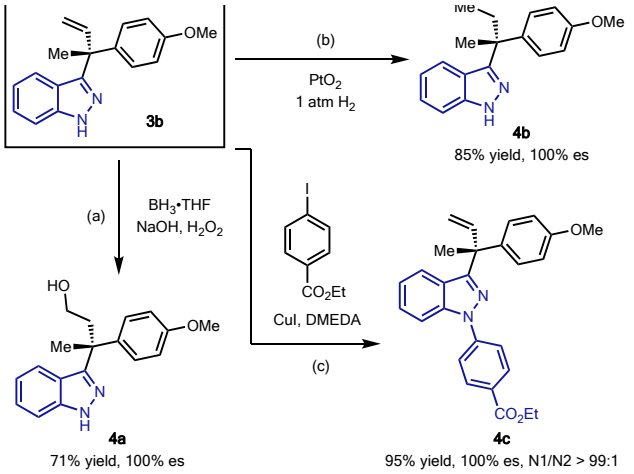


[a]All yields represent average isolated yields of two runs, performed with 0.50 mmol of indazole electrophile. [b]60 ºC.

The reaction is broadly tolerant of substituents appended to the indazole electrophiles, including 4-methoxy (**3j**), 4-fluoro (**3k**), 5-chloro (**3l**), 6-methylsulfonyl (**3n**), 6-chloro (**3o**), 6-carbomethoxy (**3p**), and 7-methyl (**3q**). Moreover, a benzoindazole electrophile was also found to be a competent coupling partner in this transformation (**3r**).

To briefly demonstrate the potential synthetic utility of these coupling products, indazole **3b** was converted to a primary alcohol in good yield under hydroboration-oxidation process (Scheme 1a). Furthermore, the terminal double bond of **3b** could be easily reduced to an ethyl group, generating a stereocenter containing both methyl and ethyl substituents with excellent enantioselectivity (Scheme 1b). An Ullmann coupling reaction of **3a** with an aryl iodide was performed successfully as well. Although transition-metal-catalyzed N-arylation of indazoles usually generates a mixture of N1- and N2-arylated products,[13] high N1-selectivity (N1:N2>20:1) of **3b** was observed in this case, presumably due to the steric hindrance of the C3-substituent (Scheme 1c).

Scheme 1. Further Functionalizations of Allylated Indazoles.[a]



[a]Reactions were conducted on 0.20 mmol scale. See the Supporting Information for detailed conditions.

As mentioned earlier, we noted prominent differences in reaction outcomes between indazole and indole electrophiles under copper hydride catalysis. To obtain more mechanistic understanding of the origin of reactivity differences, we computed the energy profiles of allylation reactions of **1a** and **6** with 1-phenyl-1-methylallene **2a** using density functional theory (DFT) calculations (Figure 3). Both reactions initiate via the hydrocupration of allene **2a** with copper hydride **7** with a 15.9 kcal/mol activation energy (**TS1a**, see the Supporting Information, Figure S1, for other less favorable hydrocupration pathways). This step leads to the irreversible formation of the *Z*-isomer of the terminal allylic copper species (**8**). Complex **8** can rapidly isomerize to form either diastereomers of the tertiary benzylic copper intermediate (**9**), which undergoes subsequent isomerization to afford the thermodynamically more stable *E*-isomer of the terminal allylic copper (**10**).[14] In the presence of the indole electrophile **6**, the most favorable reaction pathway proceeds through the SN2' type oxidative addition (**TS3'**, $\Delta G^{\ddagger} = 23.3$ kcal/mol with respect to **10**), leading to the formation of C3-allyl indole product with linear selectivity, which is consistent with the experimental results (Figure 2b). The competing SN2 type oxidative addition **TS4'**

leading to the N-allyl indole product is disfavored by 5.9 kcal/mol. These results are consistent with the previously studied ligand effects, where Ph-BPE ligand promoted the formation of C3-alkylated product.[7]

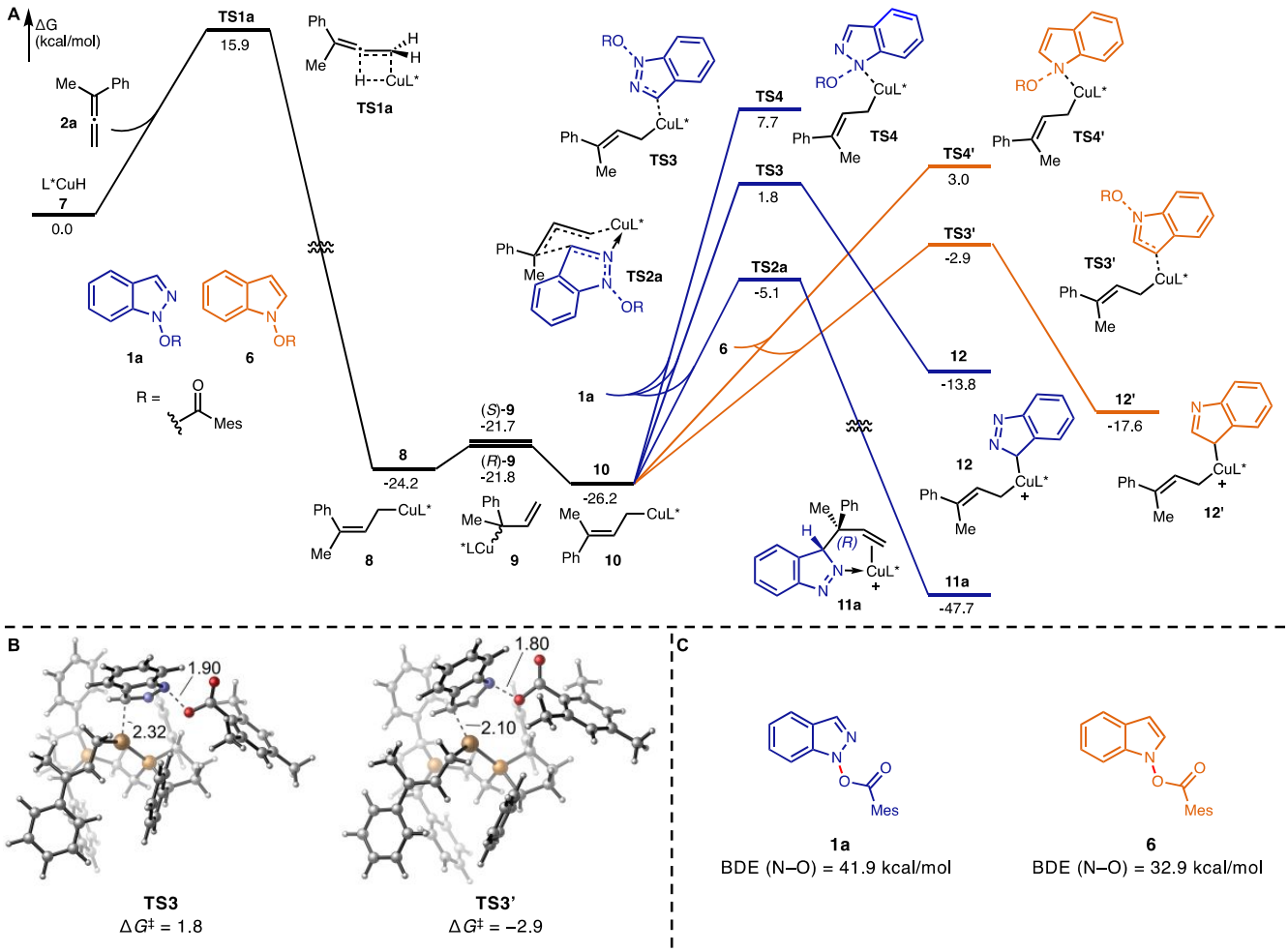


Figure 3. **A.** Energy profiles of the allylation of indazole (**1a**) and indole (**6**) electrophiles. **B.** Optimized structures of the C3-oxidative addition with indazole (**TS3**) and indole (**TS3'**) substrates. **C.** Calculated N-O bond dissociation enthalpies (BDEs) of **1a** and **6**.

In the reaction with the indazole electrophile (**1a**), we found that the SN2' oxidative addition (**TS3**) requires a higher activation barrier of 28.0 kcal/mol with respect to **10**, when compared to the reaction with indole (**TS3'**), and the product is thermodynamically destabilized by 3.6 kcal/mol (**12** versus **12'**). Since the C3 oxidative additions are endergonic, the transition states are more product-like and exhibit significant N–O bond elongations (Figure 3B). The computed kinetic and thermodynamic trends can therefore be attributed to the cleavage of a stronger N–O bond in the indazole electrophile, which is supported by calculated BDEs where the cleavage of the N–O bond in **1a** requires 9.0 kcal/mol higher energy than the corresponding bond cleavage in **6** (Figure 3C). In addition to the relatively high calculated energy barrier, this oxidative addition pathway would lead to the linear allylation products, which are inconsistent with the branched selectivity observed in experiment.

Our DFT calculations revealed a more feasible mechanism with indazole **1a** via a Zimmerman-Traxler type six-member transition state (**TS2a**).[15] This mechanism is favored because it forgoes the generation of the less stable Cu(III) intermediate. Furthermore, this transition state is stabilized by the presence of dative Cu–N2 bond, which is not available with the indole substrate. This model is consistent with the branched regioselectivity as well as the observed enantioselectivity in the reaction (Figure 4). The indazole electrophile **1a** can add at either face of the C=C bond of **8** or **10** (**TS2a-d**). Here, the C–C bond formation and the dissociation of 2,4,6-trimethylbenzoate anion are concerted processes, leading directly to 3*H*-indazole complexes (**11a-d**), which form the 1*H*-indazole product upon tautomerization. The enantioselectivity of the C3-allylation product is determined in the indazole addition step (**TS2**). Among the four competing transition states, **TS2c** and **TS2d** originating from the *Z*-allyl complex **8** are both disfavored (3.3 and 8.0 kcal/mol higher than **TS2a**, respectively) due to the pseudoaxial placement of the bulky phenyl group, which leads to increased repulsions with the indazole ring (Figure 4B). In **TS2a** and **TS2b**, the smaller methyl group is placed at the pseudoaxial position and thus the steric repulsions about the forming C–C bond are decreased. From intermediate **10**, the addition of the indazole to form product (*S*)-**3a** through **TS2b**

is 5.4 kcal/mol less favorable than the addition to form (*R*)-**3a** through **TS2a**. The relative instability of **TS2b** arises from unfavorable steric repulsions between the (*S*,*S*)-Ph-BPE ligand and the 2,4,6-trimethylbenzoate leaving group. In **TS2b**, the bulky leaving group is placed in the quadrant occupied by a "proximal" phenyl group on the ligand (Figure 4C). By contrast, in **TS2a**, the leaving group is in a less occupied quadrant with a "distal" phenyl group. The increased ligand-substrate steric repulsions in **TS2b** are evidenced by the more significant distortion of the Ph-BPE ligand in **TS2b** than in **TS2a** ($\Delta\Delta E_{\text{dist-Ph-BPE}}$ = 3.7 kcal/mol, see Figure S2).

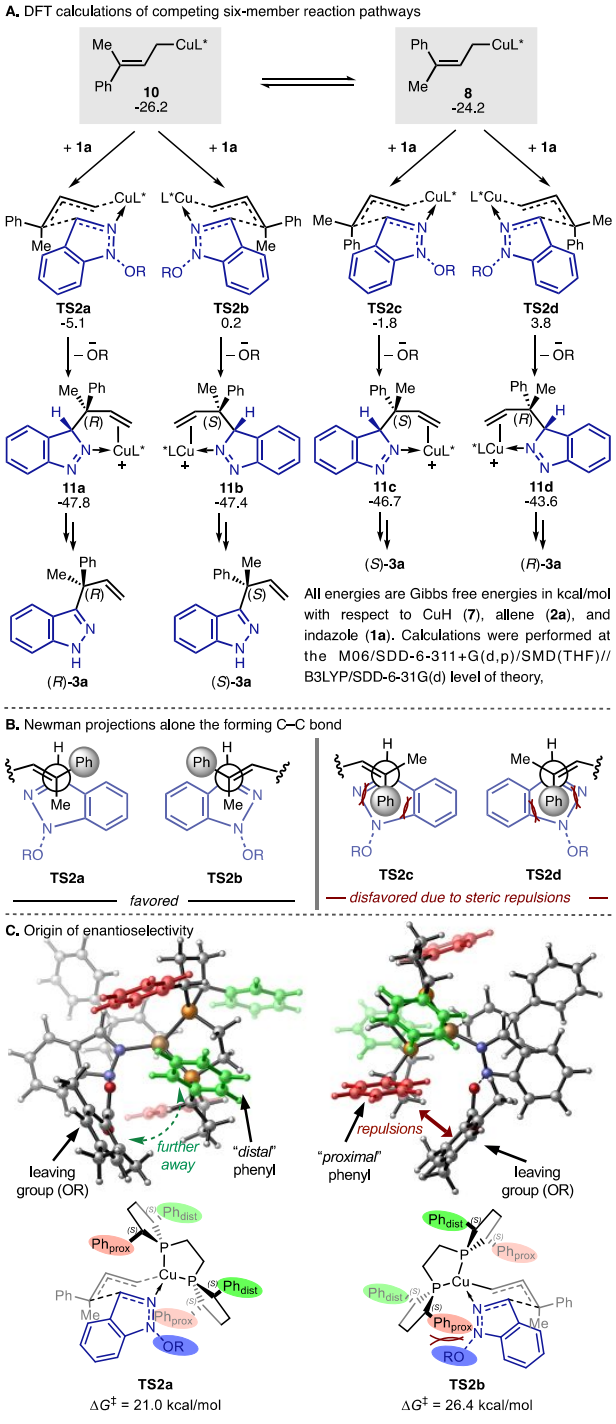
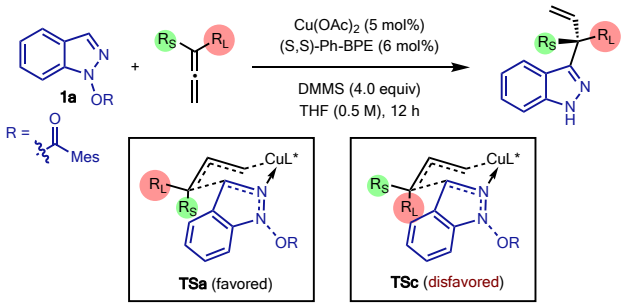


Figure 4. The origin of enantioselectivity in the C3-allylation with the indazole electrophile **1a**.

To further verify the mechanistic model, we calculated the enantioselectivities of the allylation reaction with allenes containing substituents of varying degrees of steric hindrance. The enantioselectivities were computed from transition states **TSa** and **TSc** arising from the same facial addition of **1a** to the *E*- and *Z*-isomers of the corresponding allylic copper species (Figure 5). The calculated enantioselectivity trend is in a good qualitative agreement with the experimental data (Figure 2). While reactions with allenes **2a** and **2s** are both highly enantioselective, using a less bulky primary alkyl allene (**2t**) almost completely diminishes the predicted *er*. Although this computed value is underestimated when compared to the observed *er*, both computational and experimental results demonstrated the role of steric effects of allene substituents on the *er* of the allylation product.



allene	R_S	R_L	predicted er	observed er
2a	Me	Ph	99.7:0.3	99.5:0.5 (**3a**)
2s	H	Cy	96:4	98.5:1.5 (**3s**)
2t	H	$(CH_2)_3OPiv^a$	42:58	75:25 (**3t**)

Figure 5. [a]R_L=*n*-Pr was used in calculations as a model of the 3-pivaloyloxypropyl group in **2t**. Computed enantioselectivities with different allene substrates.

CONCLUSIONS

In summary, we developed a method for the preparation of C3-allyl indazoles bearing quaternary stereocenters in high yield with excellent levels of enantioselectivity using CuH catalysis. Key to the success of this unique C3-selectivity in indazole allylation reaction is the use of an umpolung strategy: in contrast to the conventional use of indazoles as nucleophiles, electrophilic indazoles (*N*-(benzoyloxy)indazoles) are employed as electrophiles in the reaction. With the aid of DFT calculations, we discussed the fundamental reactivity differences between the indazole and the previously reported indole electrophiles. In addition, a mechanistic model was developed to account for the branched selectivity of the allyl indazole products, and explain the observed enantioselectivity in the reaction. Expanding this polarity reversal strategy to achieve novel reactivities in other nitrogen-containing heterocycle functionalization reactions is currently underway.

ASSOCIATED CONTENT

Supporting Information.

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

Experimental details and computational data (PDF)

Spectroscopic data (PDF)

AUTHOR INFORMATION

Corresponding Author

*sbuchwal@mit.edu
*pengliu@pitt.edu

Notes

The authors declare no competing financial interest.

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