Confronting the Challenging Asymmetric Addition of Vinyl Arene Pronucleophiles into Ketones: Ligand-Controlled Regiodivergent Processes Through a Dearomatized Allyl-Cu Species

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ABSTRACT: The selective reductive coupling of vinyl arenes and ketones represents a versatile approach for the rapid construction of enantiomerically enriched tertiary alcohols. Herein, we demonstrate a CuH-catalyzed regiodivergent coupling of vinyl arenes and ketones, in which the selectivity is controlled by the ancillary ligand. This approach leverages an *in situ* generated benzyl- or dearomatized allyl-Cu intermediate, yielding either the dearomatized or exocyclic addition products, respectively. The method exhibits excellent regio-, diastereo- and enantioselectivity, and tolerates a range of common functional groups and heterocycles. Computational studies suggest that the regio- and enantioselectivity are controlled by the ancillary ligand, while the diastereoselectivity is enforced by steric interactions between the alkyl-Cu intermediate and ketone substrates in a six-membered cyclic transition state.

The enantioselective coupling of two prochiral molecules constitutes an effective strategy for the construction of multiple vicinal stereogenic centers in a single operation.[1-12] In particular, the reaction between prochiral vinyl heterocycles and ketones provides rapid entry to enantiomerically enriched tertiary alcohols, which are prominent substructures in pharmaceuticals and natural products (Figure 1A).[12-14] Prototypical approaches to form enantioenriched tertiary alcohols have relied on utilizing stoichiometric chiral auxiliaries to relay stereochemical information to the product.[15] Catalytic asymmetric approaches to access tertiary alcohols generally promote the 1,2-addition of preformed organometallic reagents with a chiral Lewis acid or base catalyst.[16-25] The application of these protocols, however, is frequently complicated by the pregeneration of a stoichiometric amount of highly reactive carbon nucleophiles, limiting the functional group compatibility. To this end, utilization of olefinic pronucleophiles in conjunction with a catalytic metal-hydride represents a versatile approach and obviates the need for preformed organometallic species.[7-9, 26-33]

Our group and others have developed asymmetric CuH-catalyzed carbonyl 1,2-addition reactions utilizing *in situ* generated allyl-Cu intermediates.[34-37] This strategy has accommodated a range of olefinic pronucleophiles,[38] including enynes,[12] 1,3-dienes,[3-4] and allenes.[5, 39] Among these transformations, the allyl-Cu species is proposed to engage the carbonyl substrate through a conserved six-membered cyclic transition state (**I**, Figure 1B).[3, 5] However, despite the extensive studies employing these classes of aliphatic olefins, only highly activated vinyl arenes, such as 2-alkenyl azaarenes, have been successfully utilized as pronucleophiles to couple to ketones (Figure 1C). This asymmetric 1,2-addition involves a proposed chair-like transition state in which the Cu-atom is coordinated by the aza-group.[40] We hypothesized that highly selective coupling between unactivated vinyl aromatic compounds and ketones will likely proceed through the intermediacy of a closed six-membered cyclic transition state, composed of the *in situ* generated allyl-Cu type intermediate and ketone.[41-42] A single example of the reductive coupling of a vinyl arene and ketone was reported by our group; however, our attempts to extend this protocol to other substituted styrenes and ketones were unsuccessful (see Scheme S1 in Supporting Information).[10, 12, 35, 43-47] The inability to access a six-membered transition state likely forces this reaction to proceed through an unselective four-membered transition state. We envision that the reduced resonance stabilization of a vinyl heteroarene substrate may produce two equilibrating η^1-benzyl-Cu species (**II** and **III**, Figure 1D), in which the position of the Cu species could be controlled by the steric environment of the ancillary ligand. In the presence of a ketone, an analogous Zimmerman-Traxler-type transition state could be accessed in a regiodivergent fashion (**II** and **III**).[42, 47-65] In particular, **III** provides a dearomative pathway, and the corresponding product allows access to saturated heterocyclic compounds. Accordingly, we describe the ligand-controlled, regiodivergent asymmetric coupling between vinyl heteroarenes and ketones enabled by CuH catalysts.

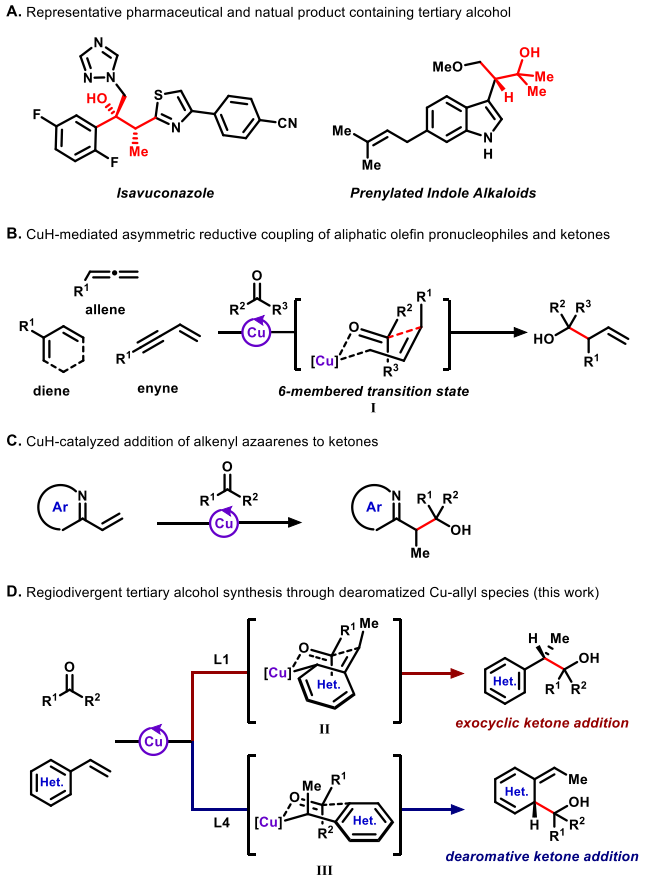
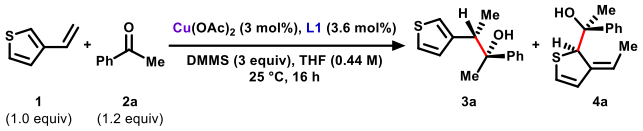


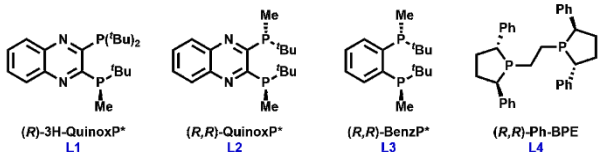
Figure 1. (A) Representative pharmaceutical and natural products containing tertiary alcohol functional groups. (B) CuH-mediated coupling between aliphatic olefin pronucleophiles and ketones through a cyclic, six-membered transition state. (C) Previously reported alkenyl arene to ketone featuring highly activated vinyl azarenes. (D) A catalytic approach to ligand-controlled, regiodivergent coupling between vinyl heteroarenes and ketones using CuH supported by asymmetric bisphosphines.

We commenced our investigation by examining the reductive coupling of commercially available 3-vinylthiophene (**1**) to acetophenone (**2a**). Employing several P-stereogenic ligands (**L1–L3**),[66-68] the exocyclic product **3a** was formed exclusively (>20:1 rr) in moderate yield and enantioselectivity (entry 1–3, Table 1). We identified the *C1*-symmetric (*R*)-3H-QuinoxP* (**L1**) as an optimal ligand for this transformation, which provided **3a** with excellent regio-, diastereo-, and enantioselectivity. Lowering the reaction temperature, modifying the copper salt, or reaction solvent were deleterious toward the reaction result (entry 4–6, and Table S1).[66-69] Decreasing the catalyst loading to 3 mol% of Cu along with 3.6 mol% of **L1** was sufficient to achieve full conversion (see SI, Table S1). To inhibit the competing ketone reduction, **2a** could be slowly introduced into the reaction mixture, and the use of an addition rate of 6 μL/min (entry 7) was optimal. While the product yield increased with slower addition, a concomitant decrease in enantioselectivity was observed (see SI, Table S2). Therefore, for operational simplicity, unless otherwise noted, the ketone substrates were added in one portion. To test our aforementioned hypothesis involving a ligand-controlled bifurcation of reactivity, further screening of asymmetric phosphine ligands (see SI, Table S1) revealed the dearomatized product (**4a**) as a minor regioisomer when chiral bisphosphine (*R,R*)-Ph-BPE (**L4**, entry 8) was employed. Therefore, we sought to explore the substrate scope of this ligand-controlled transformation targeting both the exocyclic and dearomative pathways utilizing **L1** and **L4** as the ancillary ligands, respectively.

Table 1. Optimization of the Regio-, Diastereo- and Enantioselective Coupling of 3-Vinylthiophene (1) and Acetophenone (2a)[a]



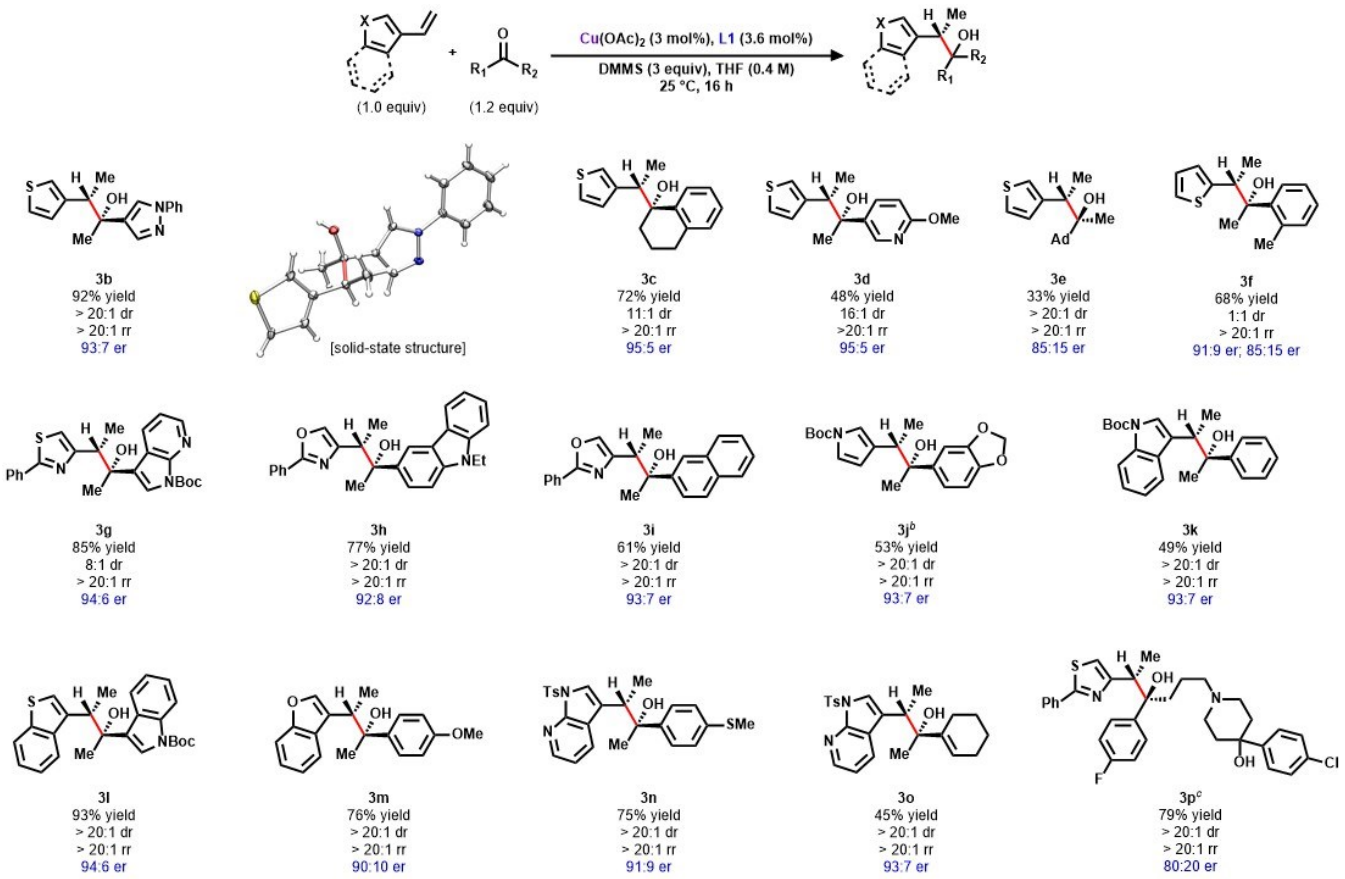
	variation from standard conditions	yield	rr	dr	er
1	none	65%	>20:1	>20:1	95:5
2	**L2**	42%	>20:1	3:1	95:5
3	**L3**	57%	>20:1	5:1	95:5
4	−30 °C	28%	>20:1	>20:1	95:5
5	CuOAc	52%	>20:1	3:1	N.D.
6	CuI	0	–	–	–
7[b]	slow addition of **2a** (6 μL/min)	69%	>20:1	>20:1	95:5
8	**L4**	>99%	6:1	2:1[c]	>99:1[c]



[a]Reaction conditions: 0.20 mmol 3-vinylthiophene (**1**, 1.0 equiv), 0.24 mmol acetophenone (**2a**, 1.2 equiv), and THF (0.4 M); reaction yields, regioisomeric and diastereomeric ratios were determined by ^{1}H NMR spectroscopy of the crude reaction mixture using 1,1,2,2-tetrachloroethane as an internal standard (see SI for details). Enantiomeric ratio (er) was determined by chiral supercritical fluid chromatography (SFC). N.D.: not determined. [b]**2a** was added as a THF solution (1.2 M) to a THF solution of **1** (0.8 M) (see SI for experimental details). [c]Determined for the major regioisomer.

With the optimized reaction conditions identified for the formation of **3a**, we assessed the functional group tolerance and scope of compatible heterocycles in the exocyclic addition pathway. The reaction proceeds effectively with substrates bearing both electron-rich and -deficient heterocycles commonly found in pharmaceuticals (Table 2),[70-72] including a thiophene (**3b–f**), pyridine (**3d**), pyrazole (**3b**), thiazole (**3g**, **3p**), pyrrole (**3j**), indole (**3k–l**), benzothiophene (**3l**), benzofuran (**3m**), oxazole (**3h–i**), azaindole (**3g**, **3n–o**), and carbazole (**3h**). The relative and absolute configuration of the major enantiomer was determined by obtaining the solid-state structure of two examples (**3b**, **3i**; see SI, Figure S4–5). The products were assigned as the *anti*-addition product, with the resulting tertiary alcohol as *R*-configuration and *S*- at the adjacent stereocenter. Acetophenone derivatives featuring *ortho*- (**3f**), *meta*- (**3j**) and *para*-substituents (**3j**, **3m–n**) are all suitable coupling partners.

Table 2. Substrate Scope of the Exocyclic Addition of Vinyl Arenes to Ketones[a]



[a]All yields represent the average of two isolated yields with 0.50 mmol of vinyl heteroarene; regioisomeric (rr) and diastereomeric ratios (dr) were determined by ^{1}H NMR spectroscopy. Enantiomeric ratio (er) was determined by chiral SFC. [b]Ketone substrate was added as a THF solution (2.5 M) with 1 μL/min addition rate. [c]Additional amount of THF (0.2 M) and DMMS (5 equiv) was employed.

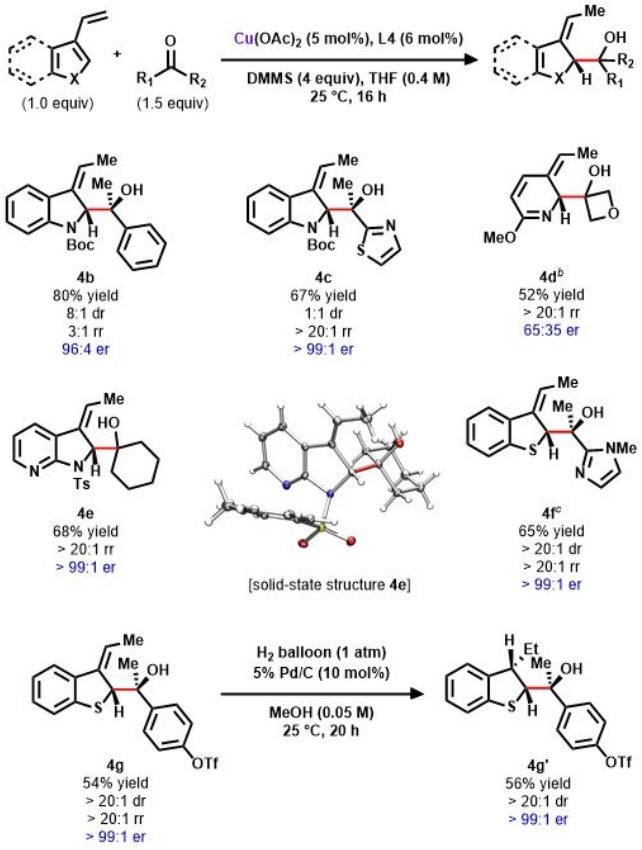
Utilization of a cyclic ketone, 1-tetralone, resulted in good enantio- and diastereoselectivity (**3c**), while an *α,β*-unsaturated aliphatic ketone yielded exclusively the 1,2-addition product (**3o**).[73-75] The reaction conditions also tolerate coordinating groups, such as a thioether (**3n**), pyridine-type nitrogen atoms (**3b**, **3d**, **3g–i**, **3n–p**), and a tertiary amine (**3p**) present in antipsychotic haloperidol. A dialkyl ketone was coupled with **1** to yield **3e**, albeit with lower yield and enantioselectivity.

Intrigued by the significant amount of dearomatized product **4a** observed with **L4** as the ancillary ligand (entry 8, Table 1), we sought to optimize the reaction scope for the dearomative reaction mode. While the coupling between *tert*-butyl 3-vinyl-1*H*-indole-1-carboxylate (**5**) and acetophenone (**2a**) generated exclusively the exocyclic product with **L1** (cf. Table 2, **3k**), utilizing **L4** provided the dearomatized product **4b** as the major regioisomer (Table 3). Furthermore, by employing **L4** as the ancillary ligand, a variety of dearomatized heterocycles were obtained in a regioselective manner. A range of heterocyclic substrates, including an indole (**4b–c**), thiazole (**4c**), pyridine (**4d**), azaindole (**4e**), imidazole (**4f**), and benzothiophene (**4f–g**), were well tolerated. A highly reactive 3-oxetanone could be effectively coupled (**4d**) utilizing this protocol; however, slow addition of the ketone substrate was necessary to minimize the undesired 1,2-reduction pathway. The relative and absolute configuration of the major enantiomer was determined by obtaining the solid-state structure of **4e** (see SI, Figure S6) in conjunction with computational modelling (*vide infra*).[3-4, 46] The products were assigned as the *anti*-addition product, with the resulting tertiary alcohol as *R*-configuration. The exocyclic alkene was revealed in the more sterically strained *Z*-configuration, prompting a more detailed analysis of the proposed chair-like transition state by DFT calculations (*vide infra*). Notably, the generation of dearomatized product features excellent enantiocontrol, > 99:1 er in several cases (**4c**, **4e–g**). To further highlight the synthetic utility of this dearomative transformation, a third stereogenic center could be formed through diastereoselective olefin reduction, targeting highly substituted hydrogenated heterocycles. Hydrogenation of **4g** using Pd/C stereospecifically generated the *cis*-product **4g'**. When the coupling of vinyl arenes and ketones was conducted on a 5.0 mmol scale, significant heat release was detected. An ice-water bath was utilized to facilitate heat transfer, and preparation of both the exocyclic (**3a**) and dearomatized products (**4g**) were isolated with comparable isolated yield and selectivity on large scale (eq. 1–2).

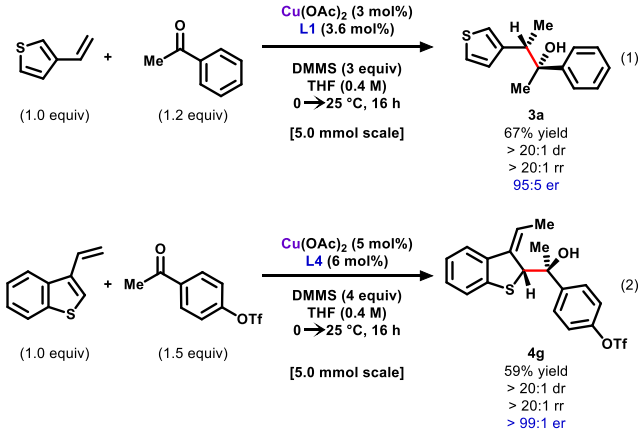
To explore the origins of the ligand-controlled regiodivergent reaction outcome, density functional theory (DFT) calculations were carried out to study the free energy profiles of the reaction between **5** and **2a** featuring both **L1** and **L4** as the ancillary ligands. The calculations were performed at the M06/6-311+G(d,p)-SDD(Cu)/SMD(THF)//B3LYP-D3/6-31G(d)–SDD(Cu)/SMD(THF) level of theory (see SI for

computational details). The hydrocupration of **5** with **L1** and **L4**-supported Cu catalysts is irreversible (see Figures S8–9), leading to allyl-Cu intermediates (*S*)-**Int-1** and (*R*)-**Int-1'**, respectively (Figure 3A). The more energetically accessible hydrocupration transition state is consistent with

Table 3. Substrate Scope of the Dearomative Addition of Vinyl Arenes to Ketones[a]



[a]All yields represent the average of two isolated yields with 0.50 mmol of vinyl heteroarenes; regioisomeric (rr) and diastereomeric ratios (dr) were determined by ^{1}H NMR spectroscopy. Enantiomeric ratio (er) was determined by chiral SFC. In order to out compete the ketone reduction, a slightly excess amount of ketone (1.5 equiv) was used. [b] 2.0 equiv of ketone substrate was added as a THF solution (2.2 M) with 3 μL/min addition rate. [c]Modified amount of ketone (1.2 equiv) was employed.



the crystallographically determined absolute configurations of the corresponding carbon atoms (**3b, 3i** and **4d**, *vide supra*), assuming subsequent stereoretentive 1,3-Cu-migration and ketone trapping steps (*vide infra*). Alternative hydrocupration pathways are disfavored by placing the heteroarenes in the more sterically encumbered quadrants of the asymmetric ligands.

Due to the facile 1,3-Cu-migration from (*S*)-**Int-1** and (*R*)-**Int-1'** to their respective dearomatized intermediates (*R*)-**Int-2** and (*S*)-**Int-2'** (Figure 3A), both the regio- and diastereoselectivity of the transformation are under Curtin-Hammett control. Therefore, the experimentally observed regioisomeric and diastereomeric ratios are determined by the relative energies of the Zimmerman-Traxler-type ketone addition transition states. Our calculations revealed a 5.1 kcal/mol preference toward the generation of **3k** (**TS-2**) using **L1** and a 1.7 kcal/mol kinetic barrier difference favoring the production of dearomatized **4b** (**TS-3'**) employing **L4**, in excellent agreement with the regioselectivity observed in both cases experimentally (>20:1 rr for **L1**; 3:1 rr for **L4**). The divergent regioselectivity is controlled by matching of the chair-like activated complex and the chiral pockets created by the ligands as well as the stabilizing C–H/π interactions between the two.

In the dearomative transition states, the ketone-based Me group occupies an axial position and is placed in a quadrant occupied by either a ^{t}Bu group on **L1** (**TS-3**) or a Ph group on **L4** (**TS-3'**). The substrate-ligand steric repulsion with the ^{t}Bu group on **L1** destabilizes **TS-3**, which features a short H···H distance of 1.96 Å; whereas the **L4**-supported **TS-3'** experiences diminished substrate-ligand steric repulsion along with stabilizing C–H/π interaction between the olefin-based Me group and Ph group on the ligand (Figure 3B). In the exocyclic addition transition states (**TS-2** and **TS-2'**), the axial ketone-based Me group occupies a less crowded quadrant, and thus the most significant interactions arise between the heterocycle and ligand. In the **L1**-supported **TS-2**, the distance between the ligand-based ^{t}Bu C–H bond and the indole π-system is 2.59 Å, indicating a stabilizing C–H/π interaction. By contrast, C–H/π or π/π interaction was not observed in **TS-2'**, where the Ph group on **L4** is relatively far away from the heteroaryl substrate (Figure 3B).

In the most favorable exocyclic and dearomative ketone addition transition states (**TS-2** and **TS-3'** with **L1** and **L4**, respectively), the larger Ph group on the ketone prefers the equatorial position to avoid repulsions with the heteroaryl groups[76] (see Figure 3C for higher energy transition states with Ph group at the axial position). This orientation of ketone within the six-membered cyclic transition states determines the diastereoselectivity of the reaction.

The origin of the selective generation of *Z*-dearomatized products is due to the preferred orientation of the olefin-based Me group at the axial position in the six-membered cyclic transition state (**TS-3'**). An equatorial arrangement (**TS-5'**) forces the Me group into an unfavorable eclipsed conformation against the heteroarene (Figure 3C), diminishing the accessibility to the *E*-stereoisomer of the product.

In summary, we have developed a protocol for the selective reductive coupling between vinyl heteroarenes and ketones to rapidly construct enantioenriched tertiary

alcohols with adjacent stereocenters. The transformation exhibits regiodivergent reactivity controlled by the ancillary ligand employed, yielding either the exocyclic or dearomatized addition product. This method is tolerant of a wide range of important functional groups prevalent in pharmaceuticals and biologically active natural products. The mechanism through which the chiral catalyst exerts enantio- and diastereocontrol was elucidated by theoretical investigations.

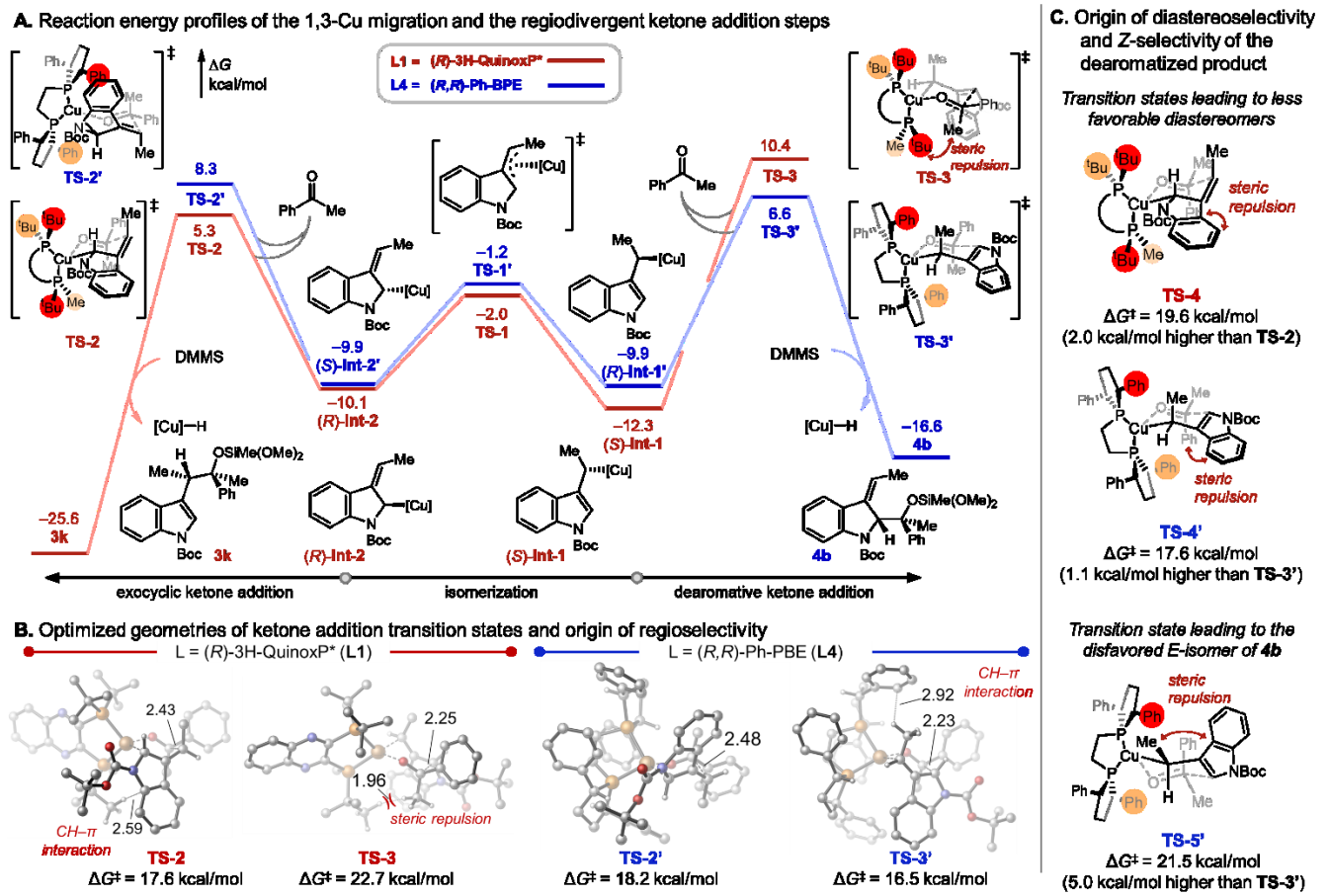


Figure 3. Computational studies of the mechanism and selectivity of the regiodivergent reductive coupling between **5** and **2a** using (*R*)-3H-QuinoxP* (**L1**, red) and (*R,R*)-Ph-BPE (**L4**, blue). Bond distances are in Å. Gibbs free energies are with respect to LCuH and the starting materials in (A) and with respect to the alkyl-Cu species (*S*)-**Int-1** and (*R*)-**Int-1'** in (B) and (C).

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge via the Internet at http://pubs.acs.org.

Experimental procedures and characterization data for all new compounds, including NMR spectra, SFC, and X-ray crystallographic information, computational details, and Cartesian coordinates of all computed structures (PDF)

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Notes

The authors declare no competing financial interest

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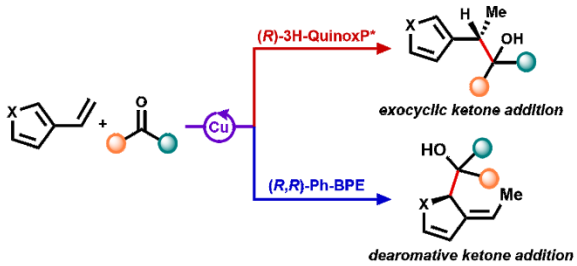
(R)-3H-QuinoxP*
(R,R)-Ph-BPE
Cu
X
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exocyclic ketone addition
dearomative ketone addition