Copper-Phosphido Catalysis: Enantioselective Coupling of Phosphines and Cyclopropenes

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ABSTRACT: We describe a copper-catalyst that promotes the addition of phosphines to cyclopropenes at ambient temperature. A range of cyclopropylphosphines bearing different steric and electronic properties can now be accessed in high yields and enantioselectivities. A combined experimental and theoretical mechanistic study supports insertion of a Cu(I)-phosphido intermediate into the strained olefin. Density functional theory calculations reveal migratory insertion as the stereodetermining step of the pathway, with final product formation occurring via a *syn*-protodemetalation. Enrichment of phosphorus stereocenters is demonstrated via a DyKAT process.

By inventing strategies to forge C–P bonds, chemists enable rapid access to organophosphorous architectures for diverse applications in medicine and catalysis.[1] The cyclopropylphosphine motif attracts attention due to its unique steric and electronic profile. For example, a cyclic analogue of fosmidomycin shows enhanced antibiotic activity against E. coli, presumably due to restricted rotation.[2] In the realm of catalysis, Takasago's cyclopropyl phosphine ligand, cBRIDP outperforms its vBRIDP in Suzuki-Miyaura cross coupling; the cyclopropyl's electron-richness accelerates oxidative addition, while its sterics aid reductive elimination (Figure 1A).[3] Considering ways to construct cyclopropyl phosphines, we focused on hydrophosphination: the direct addition of a P–H bond across a C–C multiple bond.[4] Hydrophosphination represents an attractive and atom-economical platform[5] for control of stereochemistry at carbon and/or phosphorous. While progress has been made, stereoselective methods remain rare.[6] Further studies are warranted to extend additions beyond use of alkynes,[7] oxa-bicycles,[8] and Michael acceptors (Figure 1B).[9] Driven by strain release,[10] cyclopropenes show high reactivity in various applications.[11,12] The hydrofunctionalization of cyclop ropenes has enabled a direct access to a diverse range of enantiomerically enriched rings.[12]

Organophosphorous partners bearing P-H bonds with a wide range of acidities (pKa 9.0 to 22.4) can be activated with transition metal-catalyts. Secondary phosphines lie at the upper end of this pKa range but are greatly acidified upon coordination to a transition metal. Deprotonation results in a metal-phosphido complex with high nucleophilicity, and recent studies have revealed impressive versatility of catalytically generated Cu-phosphido complexes. Glueck elucidated mechanistic and structural details, while Yin demonstrated catalytic transformations using Cu-phosphidos. Encouraged by these studies, we imagined using Cu-phosphido catalysis for the enantioselective hydrophosphination of cyclopropenes. Previous cyclopropene studies using both phosphine oxides and phosphites all gave ring-opening to afford allylic phosphine oxides and allylic phosphonates. At the start of our studies, there was only one transformation, using phosphine oxides and cyclopropenes catalyzed by palladium which provided the ring-retained cyclopropyl phosphine product, albeit as a racemic mixture Coinciding with our efforts, the Wang group was independently pursuing the enantioselective addition of phosphines to cyclopropenes by Pd-catalysis.

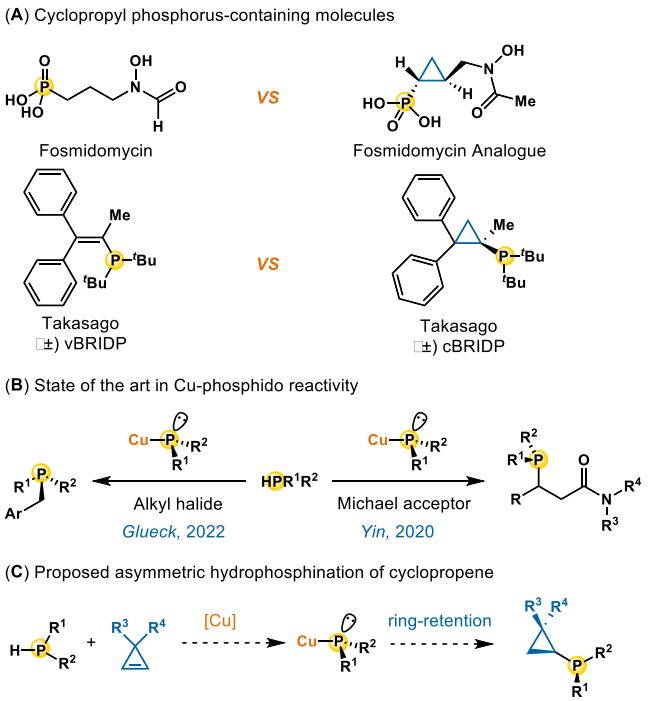
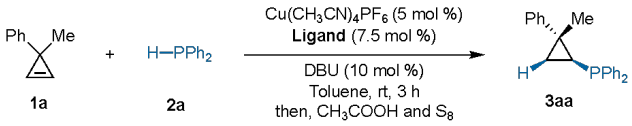


Figure 1. Inspiration for asymmetric hydrophosphination of cyclopropenes.

While promising, their scope is limited strictly to ester-bearing cyclopropenes and requires use of a precious metal. Herein, we report an enantioselective addition of phosphines to cyclopropenes via Cu-phosphido catalysis. Supported by detailed experimental and theoretical studies, we propose that

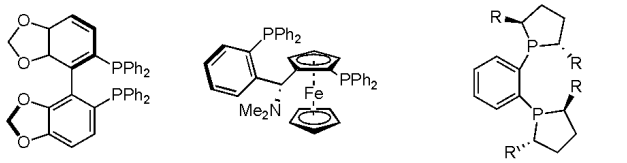
this complementary process occurs by the insertion of a phosphide intermediate into cyclopropenes. The protocol involves ambient temperatures and features the use of an earth abundant metal to access a wide range of cyclopropyl phosphines. Furthermore, we provide insights into ligand trends for selectivity on the basis of buried volume analysis.

Table 1. Ligand effects on asymmetric hydrophosphination of 1a[a]



1a 2a 3aa

entry	variations	yield (%)	*er*
1	—	93	98:2
2	without $Cu(CH_3CN)PF_6$	—	—
3	without DBU	—	—
4	no (R,R)-i-Pr-DuPhos	77	—
5	6 mol% ((R,R)-i-Pr-DuPhos	91	79:21
6	**L1** instead of **L5**	90	85:15
7	**L2** instead of **L5**	82	64:36
8	**L3** instead of **L5**	70	90:10
9	**L4** instead of **L5**	73	92:8



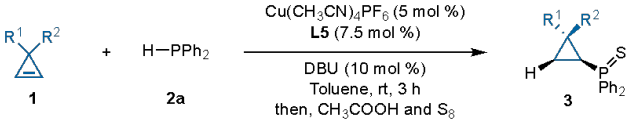
R-SEGPHOS (**L1**) Taniaphos (**L2**) (R,R)-DuPhos
R = Me(**L3**), Et(**L4**) ^{i}Pr(**L5**)

[a]Reaction conditions: 1a (0.12 mmol), 2a (0.10 mmol), $Cu(CH_3CN)_4PF_6$ (5.0 mol%), ligand (7.5 mol%), DBU (10 mol%), toluene (0.40 mL), 3 h. Yield determined by GC-FID analysis of the reaction mixture, which was referenced to 1,3,5-trimethoxybenzene internal standard. Enantioselectivity determined by chiral SFC.

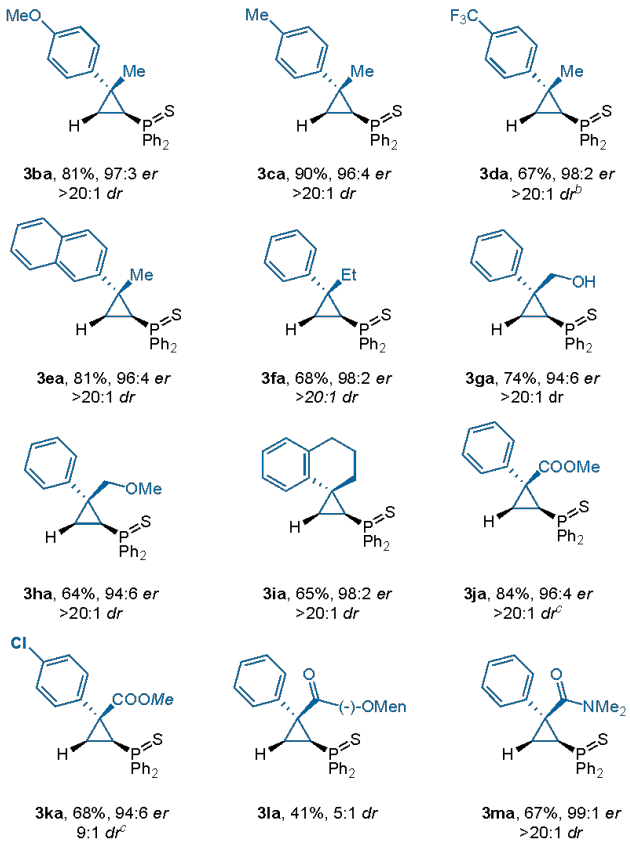
In our initial studies, we surveyed phosphine oxides and found that it was difficult to achieve high enantioselectivity (Table xx SI). In contrast, diphenyl phosphine (2a) gave promising results with both Pd and Cu. Therefore, we choose diphenyl phosphine (2a) and cyclopropene 1a as model substrates. Although the Wang group reported that cyclopropene 1a does not transform under with their standard conditions,4g we found that the SEGPHOS ligand family with Pd(OAc)2 provides cyclopropyl phosphine 3aa in 86 % yield with 97:3 er (Table S1).18 In previous studies using copper catalysis, Yin's group has demonstrated the superiority of Taniaphos ligands for the Cu-catalyzed alkylation of secondary phosphines.9f However, Taniaphos ligands were ineffective in this cyclopropene hydrophosphination (Table 1, entry 7). Instead, we found the DuPhos ligand family was most promising (Table 1, entry 8,9). Higher selectivity was correlated with larger R-substituents on the ligand (92% yield, 98:2 er). The addition of base is necessary to promote the formation of copper phosphido (Table 1, entry 3). With further tuning of the reaction stoichiometry, we developed a convenient and practical protocol for the asymmetric coupling of phosphines and cyclopropenes.

Due to the unique structure of cyclopropyl phosphine compounds, the product is relatively air stable.[3] For the convenience of handling and analysis, the cyclopropyl phosphine products were oxidized with sulfur to generate the corresponding phosphine sulfides. Compared to the scope of hydrophosphination developed by Wang group, we achieved a wider scope of 12 unique cyclopropene partners with different functionalities, electronics and sterics as summarized in Table 2.

Table 2. Hydrophosphination of various cyclopropenes.[a]



1 2a 3



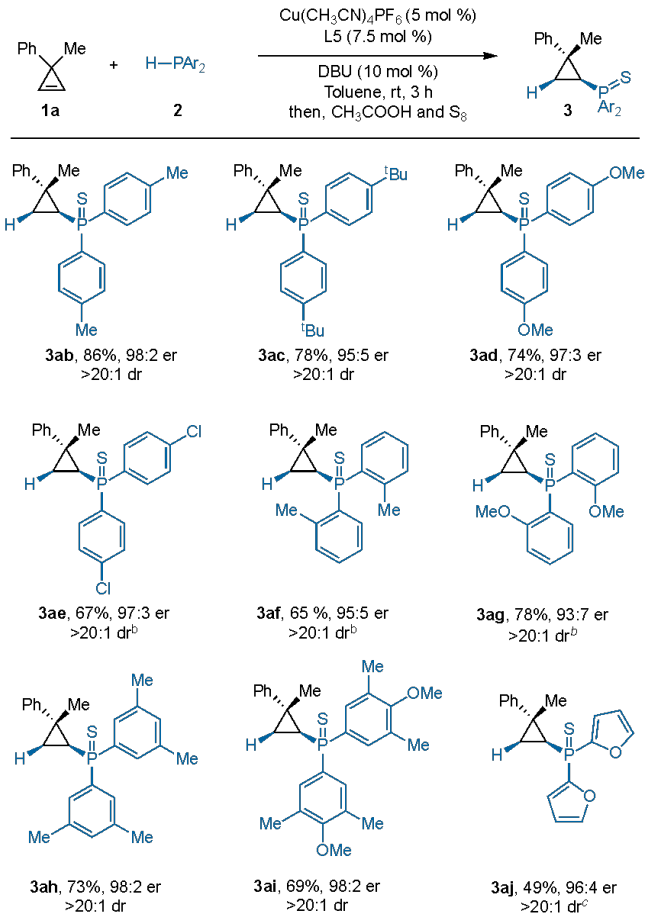
3ba, 81%, 97:3 *er* >20:1 *dr*
3ca, 90%, 96:4 *er* >20:1 *dr*
3da, 67%, 98:2 *er* >20:1 *dr*[b]
3ea, 81%, 96:4 *er* >20:1 *dr*
3fa, 68%, 98:2 *er* >20:1 *dr*
3ga, 74%, 94:6 *er* >20:1 dr
3ha, 64%, 94:6 *er* >20:1 *dr*
3ia, 65%, 98:2 *er* >20:1 *dr*
3ja, 84%, 96:4 *er* >20:1 *dr*[c]
3ka, 68%, 94:6 *er* 9:1 *dr*[c]
3la, 41%, 5:1 *dr*
3ma, 67%, 99:1 *er* >20:1 *dr*

[a]Reaction conditions: **1** (0.12 mmol), **2a** (0.10 mmol), $Cu(CH_3CN)_4PF_6$ (5.0 mol%), ligand (7.5 mol%), DBU (10 mol%), toluene (0.40 mL), 3 h. Isolated yield of **3**. Diastereomeric ratios (*dr*) were determined from ^{1}H NMR analysis of the unpurified reaction mixture. Enantioselectivity determined by chiral SFC. [b]Reaction time is 24 hours. [c]$Pd(OAC)_2$ (5.0 mol%) and (*R*)-DM-SEGPHOS (6.0 mol%), 60 °C instead of standard condition, see SI for details.

Cyclopropenes with alcohol (**3ga**) and methyl ether (**3ha**) substituents undergo the transformation with moderate yields (64-74%) and high stereoselectivities (>20:1 *dr*, 94:6 *er*). Spiro compounds with quaternary carbons are common in natural products[19] and are difficult to construct enantioselectively.[20] With this transformation, we successfully obtained hydrophosphinated tetralin (**3ia**) by desymmetrization of the

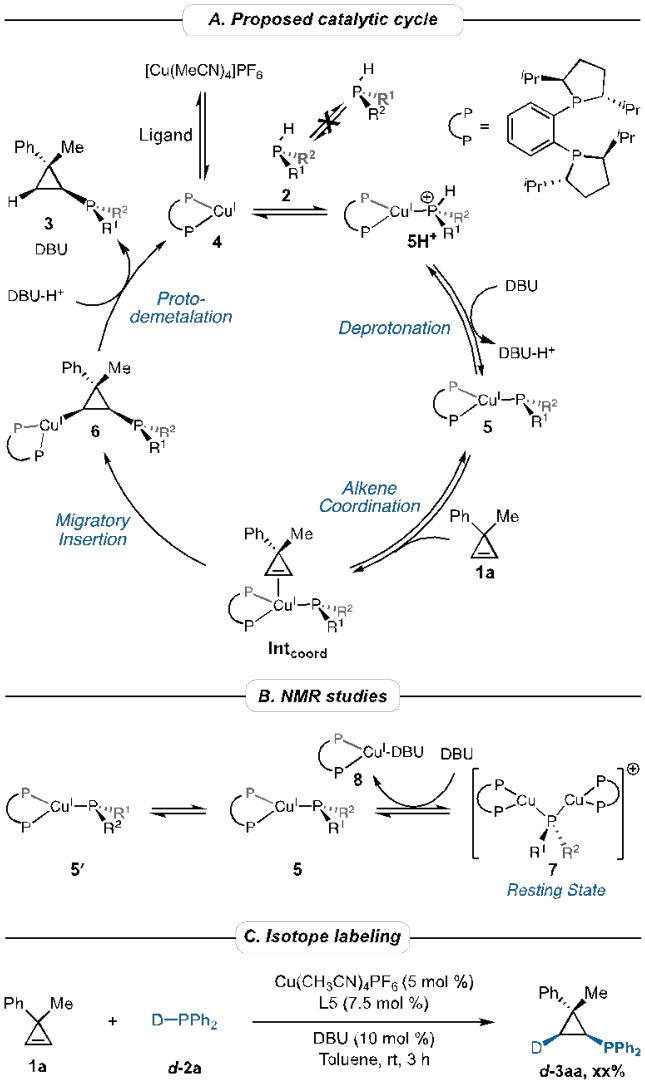
corresponding cyclopropene. Interestingly, ester cyclopropene **3ja** gives no enantioselectivity (50:50 *er*) with Cu standard condition, but high enantioselectivity was obtained by using Pd and DM-SEGPHOS. Therefore, cyclopropene **3ka** with p-Cl phenyl substituent was also desymmetrized using Pd and DM-SEGPHOS to provide corresponding cyclopropyl phosphine with moderate yield (68%) and stereoselectivity (9:1 *dr*, 94:6 *er*). The chlorine substituent provides an extra handle for further derivatization of the phosphine product. In addition, we desymmetrized menthol ester cyclopropene (**3la**) with moderate diastereoselectivity (5:1 *dr*). An amide substituted cyclopropene (**3ma**) also undergoes hydrophosphination with moderate yield (67%) and excellent stereoselectivity (>20:1 *dr*, 99:1 *er*).

Table 3. Hydrophosphination of **1a** with various phosphines.[a]



[a]Reaction conditions: **1** (0.12 mmol), **2a** (0.10 mmol), $Cu(CH_3CN)_4PF_6$ (5.0 mol%), ligand (7.5 mol%), DBU (10 mol%), toluene (0.40 mL), 3 h. Isolated yield of **3**. Diastereomeric ratios (*dr*) were determined from ^1H NMR analysis of the unpurified reaction mixture. Enantioselectivity determined by chiral SFC. [b]Reaction performed for 12 hours. [c]Reaction performed at 80 °C for 12 hours.

Our method also encompasses a range of different phosphine compounds and affords both good yields and stereoselectivity, as shown in Table 3. Phosphines bearing electron donating Me, tBu, and OMe groups at the para position (**3ab**, **3ac**, **3ad**) show moderate to high yields (74-86 %) and high enantioselectivities (95:5-98:2 *er*). Electron poor phosphines are also well-tolerated (**3ae**). Even phosphines with ortho substituted (**3af**, **3ag**), 3,5-substituted (**3ah**) and 3,4,5-substituted aromatic rings (**3ai**) transform in 65-78% yield and high enantioselectvities (93:7-98:2 *er*). Our method additionally tolerates heterocyclic phosphines, such as 2-furyl **2j**, which gives **3aj** (49% yield, 96:4 *er*) at elevated temperature (80 °C, 12 hours).

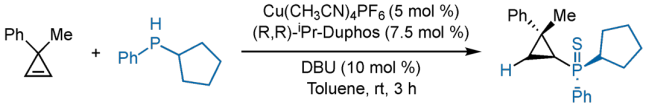


Scheme 1. A. Catalytic cycle for the asymmetric hydrophosphination of cyclopropenes via copper catalysis, as deduced from concurrent theoretical and experimental mechanistic findings. **B.** NMR identification of the off-cycle dimerization of monomeric Cu-phosphido complex. **C.** Isotope labeling experiment to probe stereoselectivity in hydrophosphination reaction.

Based on literature precedent[9f,17d,17e] and our own observations, we propose the general catalytic cycle in Scheme 1. Initially, $Cu(CH_3CN)_4PF_6$ binds to (*R*,*R*)-^{i}Pr-DuPhos to generate a mono(chelate) species **4** followed by the monocoordination of phosphine (**2**) to generate copper phosphido complex **5**. In related studies, Glueck has proposed that the steric bulk of the ligand prevents coordination of the secondary phosphine to generates **5**.[17d] Therefore, phosphine complexation coupled with deprotonation is a probable step

for the formation of **5**. A key step in the cycle involves addition of copper phosphido intermediate (**5**) to the cyclopropene (**1a**). We imagined that **5** could either undergo either direct nucleophilic attack[21] or insertion into the cyclopropene □-bond.[22] Lastly, elimination of the copper catalyst to regenerate **4** and release the final hydrophosphinated cyclopropane product **3** completes the catalytic cycle.

To investigate our proposed catalytic cycle (Scheme 1A), we performed a series of experimental mechanistic studies. Firstly, we studied the rate by variable time normalization analysis. We were surprised by the first order dependance of the DBU concentration and the fractional order dependance of the copper catalyst concentration on the reaction rate. In stark contrast to prior reports where addition of base to a mixture of $Cu(CH_3CN)_4PF_6$, bidentate phosphine ligand, and secondary phosphine results in a complicated mixture, our ^{31}P NMR data shows immediate and clean formation of a new species, which we have characterized as a Cu-phosphido dimer **7** (Scheme 1B), where the lone pair of the X-type phosphido ligand of **5** acts as an L-type ligand to form a ⌈2 bridge to another unit of Cu-DuPhos mono-chelate **4** via a three-center four-electron bond. We propose this species to be the catalyst resting state due to its persistence and remarkable stability under reaction conditions. In line with this observation, our kinetics studies, and similar observations made by Appel and coworkers while studying copper hydride catalysis,[23] we propose the DBU acts as not only a base but also an L-type ligand. The DBU undergoes ligand substitution with the dimeric resting state **7** to liberate the catalytically active monomeric copper phosphide **5**. This hypothesis is further supported by ^{31}P NMR studies which reveal decomposition of the dimer **7** with concomitant formation of an unidentified species in the presence of large excesses of DBU. Finally, the reaction performed with *d*-**2a** revealed that the hydrophosphination proceeds via a formal syn-addition of the P–H bond across the cyclopropene double bond (Scheme 1C).[24]



1a **rac-2k** **3ak**, 58%, 3:1 dr, 96:4/88:12 er

Scheme 2. Dynamic kinetic asymmetric transformation.

With this mechanism in mind, we examined the possibility of setting a phosphorus stereocenter via a dynamic kinetic asymmetric transformation (DyKAT).[25] As outlined in the proposed mechanism, pyramidal inversion of the secondary phosphine is impractically slow at room temperature while epimerization of copper phosphido **5** with **5'** occurs rapidly.[26] We subjected asymmetrically substituted phosphine **2k** to the reaction conditions to test this hypothesis and observed a 3:1 *dr* for the inseparable cyclopropyl phosphine products with *er* of 96:4 and 88:12 respectively (Scheme 2). Based on our prior results, we assume desymmetrization of the cyclopropene is achieved effectively but with low control over the configuration of the phosphorus stereocenter, in line with a recent report from Glueck using a similar catalyst system for asymmetric alkylation of secondary phosphines.[17d,17e] A dimeric resting state was again observed by ^{31}P NMR studies of phosphine **2k**, thwarting attempts to compare the *dr* of the monomeric copper phosphido catalyst to the Curtin-Hammett controlled product distribution.

To support the proposed mechanism and elucidate a detailed pathway for the enantioselective hydrophosphination of cyclopropenes, we performed a density functional theory (DFT) analysis on the title reaction of 3-methyl-3-phenylcyclopropene (**1a**) and diphenylphosphine (**2a**) catalyzed by copper-^{i}Pr-Duphos complex (**4**). DFT computations were performed utilizing ωB97XD/def2TZVP PCM(toluene)// B97D/def-2SVP level of theory as implemented in Gaussian 16.[27-33] Thermal corrections were computed using Grimme's quasi-rigid rotor harmonic oscillator approximation.[34] IRC calculations were performed to confirm that transition structures (TSs) connected minima along the potential energy surface. A thorough exploration of the catalyst conformational space was performed using CREST. In addition, a detailed exploration of TS conformations was performed for the selectivity-determining step (see Supporting Information page S5 for details)

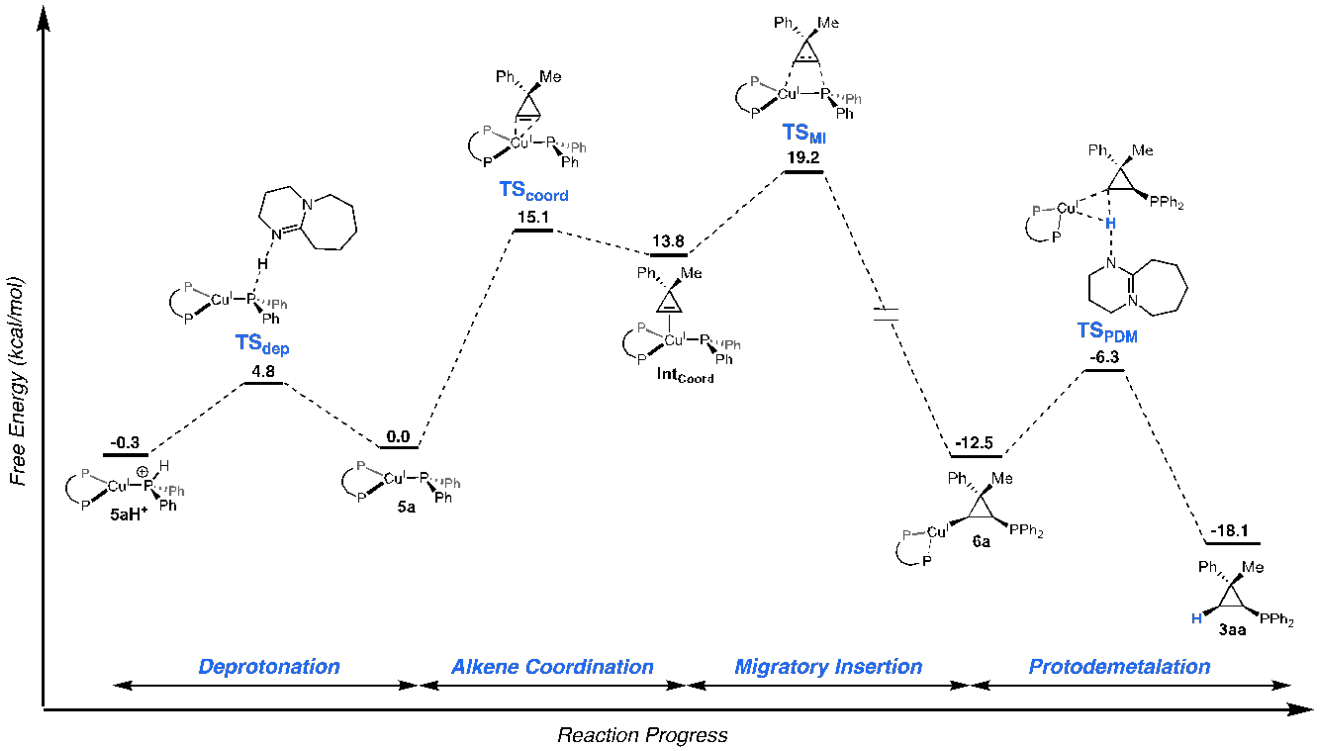


Figure 2. Reaction coordinate diagram depicting the relative barriers of deprotonation, alkene coordination, migratory insertion and protodemetalation in the hydrophosphination of cyclopropene. Migratory insertion is the stereoselectivity determining step.

Our computational study sought to identify both the turnover-limiting and stereoselectivity-determining steps of the catalytic cycle and to explain the origins of experimentally observed stereoselectivity. The potential energy surface for the lowest energy pathway resulting from our investigation is shown in Figure 2. The reaction is initiated via the coordination of diphenyl phosphine **2a** to Cu-Duphos to give the Cu-$HPPh_2^+$ complex **5aH**$^+$. Deprotonation of this cationic complex **5aH**$^+$ by DBU is a low barrier step (**TS**$_{Dep}$, $\Delta G^{\ddagger}$ = 4.8 kcal/mol) that leads to the reversible formation of Cu-phosphido intermediate **5a** (chosen as the reference structure in the reaction coordinate). Following deprotonation, **5a** binds cyclopropene **1a** via π-coordination transition structure **TS**$_{Coord}$ ($\Delta G^{\ddagger}$ = 15.1 kcal/mol) to generate Cu-alkene complex **Int**$_{Coord}$. The subsequent 1,2-migratory insertion into the cyclopropene π-bond (**TS**$_{MI}$) has a free energy barrier of 19.2 kcal/mol relative to **5a** and represents a highly exothermic step in the pathway, which results in a stable, significantly lower energy copper coordinated cyclophosphinated intermediate **6a** – residing 12.5 kcal/mol below the monomeric resting state **5a**. The reaction pathway then proceeds through a facile stereo-retentive protodemetalation (**TS**$_{PDM}$, $\Delta G^{\ddagger}$ = -6.3 kcal/mol relative to **5a**) – a copper mediated protonation from DBU occurs syn to the diphenylphosphine substituent – to concomitantly regenerate **4** and afford the *syn*-hydrophosphinated cyclopropene product **3aa** (transferred proton shown in blue).[35-37] This protodemetalation step (**TS**$_{PDM}$) proceeds through a unique three-center, two-electron bond transition structure (C–Cu bond-breaking is 2.11 Å and C–H bond forming distance is 1.42 Å), consistent with the exclusive *syn* addition observed when the reaction is performed with *d*-**2a** (Figure 3 and Scheme 1c) (vide supra). Incidentally, several alternative pathways for protodemetalation were also explored computationally (See Supporting Information page S6). A *syn*-protodemetalation TS analogous to **TS**$_{PDM}$, whereby copper mediates the proton transfer from a protonated PPh_2 on the adjacent carbon, was found to be 25 kcal/mol higher in energy than **TS**$_{PDM}$.

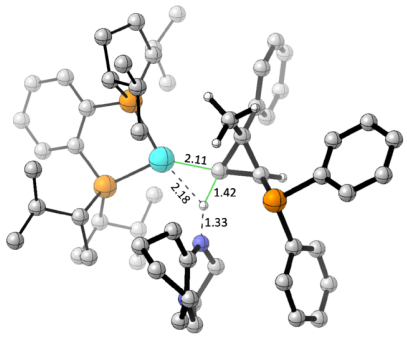
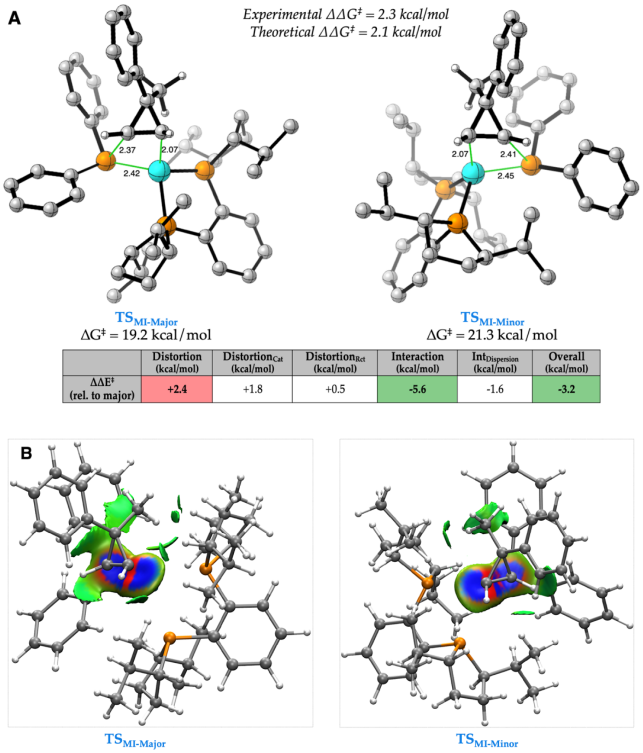


Figure 3. Three-center, two-electron bond transition structure for the product-forming *syn*-protodemetalation of Cu-Duphos from cyclopropene via DBU-H$^+$.

Analysis of the potential energy surface indicates that **TS**$_{MI}$ is the enantio- and diastereoselectivity-determining step in the hydrophosphination reaction. To investigate catalyst-substrate interactions that dictate the enantioselectivity in this reaction, a conformational search was conducted on **TS**$_{MI}$ for transition structures that lead to the formation of both the major and minor enantiomers of **3aa**. The lowest energy transition structure which leads to the major enantiomer (Figure 4A, **TS**$_{MI\text{-}Major}$) is favored by 2.1 kcal/mol with respect to the lowest energy structure for the minor enantiomer (Figure 4A, **TS**$_{MI\text{-}Minor}$). At 298 K, a $\Delta\Delta G^{\ddagger}$ of 2.1 kcal/mol corresponds to a predicted *er* of 97.5:2.5, which is in excellent agreement with

the experimental *er* of 98:2 ($\Delta\Delta G^{\ddagger}$ of 2.3 kcal/mol) for the title reaction.



	Distortion (kcal/mol)	$Distortion_{Cat}$ (kcal/mol)	$Distortion_{Rct}$ (kcal/mol)	Interaction (kcal/mol)	$Int_{Dispersion}$ (kcal/mol)	Overall (kcal/mol)
ΔΔE‡ (rel. to major)	+2.4	+1.8	+0.5	-5.6	-1.6	-3.2

Figure 4. (A) Lowest energy TSs of the enantioselectivity-determining step with experimental and theoretical free energy barriers after Boltzmann weighting. Also shown are components of the energy decomposition analysis relative to the major enantiomer. ΔDistortion of the catalyst (Cat) and reactants (Rct) versus overall ΔInteraction (including ΔDispersion) are highlighted. **(B)** Non-covalent interaction (NCI) plots depict dispersive interactions (shown in green) between Cu-DuPhos and PPh_2 with cyclopropene reactants for each TS leading to the major and minor enantiomers of product (Isosurface of 0.009).

To further evaluate the origin of enantioselectivity, a distortion-interaction analysis was performed on **$TS_{MI\text{-}Major}$** and **$TS_{MI\text{-}Minor}$**.[38-40] Distortion energy describes the energy required to distort reactants and catalysts from their respective ground states into the necessary transition state conformations. Energy decomposition revealed that the major enantiomer suffers a greater degree of distortion energy, 2.4 kcal/mol ($\Delta\Delta E^{\ddagger}$) more than the minor enantiomer (Figure 4A). The majority (1.8 kcal/mol) of this 2.4 kcal/mol difference in distortion energy arises from the distortion of the diphenyl phosphine and Cu-DuPhos catalyst, while the remaining 0.6 kcal/mol arises from distortion of the cyclopropene substrate. Despite distortion energy favoring the minor enantiomer, advantageous interaction energy favors the major enantiomer by 5.6 kcal/mol. Interaction energy describes how the distorted catalyst and reactant fragments interact with one another within the TS, a portion of this can be accounted for as dispersion energy. The major enantiomer exhibits favorable dispersions in the form of significant CH—π interactions between the diphenylphosphine and the cyclopropene methyl group as well as moderate dispersions amongst the Cu-DuPhos isopropyl groups and the cyclopropene substrate (Figure 4B). A visual comparison of the dispersion interactions in the enantioselectivity-determining transition states shows that **$TS_{MI\text{-}major}$** enjoys more stabilizing dispersion interactions than **$TS_{MI\text{-}minor}$** (as evidenced by the greater green areas in the NCI plots of the two TSs shown in Figure 4B).[41,42] In addition to the favorable dispersions imparted by its isopropyl groups in **$TS_{MI\text{-}Major}$**, the Cu-DuPhos catalyst also serves to add steric bulk to the catalytic pocket, blocking more than three-fourths of the pocket when coordinated to PPh_2, forcing the cyclopropene substrate to bind in the same location for both enantiomers (see Supporting Information page C9).

From this analysis, steric interactions have been identified to play a key role in controlling stereoselectivity. Using this information, we chose to investigate the buried volume and steric maps for intermediate **5a** with **L1**, **L3**, **L4** and **L5** as ligands.[43-44] The buried volume analysis reveals that ligand **L1** (Figure 5A) has a slightly smaller available free volume compared to the best ligand **L5** (Figure 5C). However, **L5** is more fluctional compared to the rigid biphenyl backbone of **L1**, thereby accommodating the incoming cyclopropene more readily. This leads to an overall reduction in the background reaction of **L5**, compared to **L1**, thus enabling better enantioselectivity in **L5**. Similarly, despite having the same backbone as **L5** (R=iPr), ligands **L3** (R=Me, Figure 5B) and **L4** (R=Et) have more available free volume, leading to overall poorer steric control and slightly lower enantioselectivity.[45]

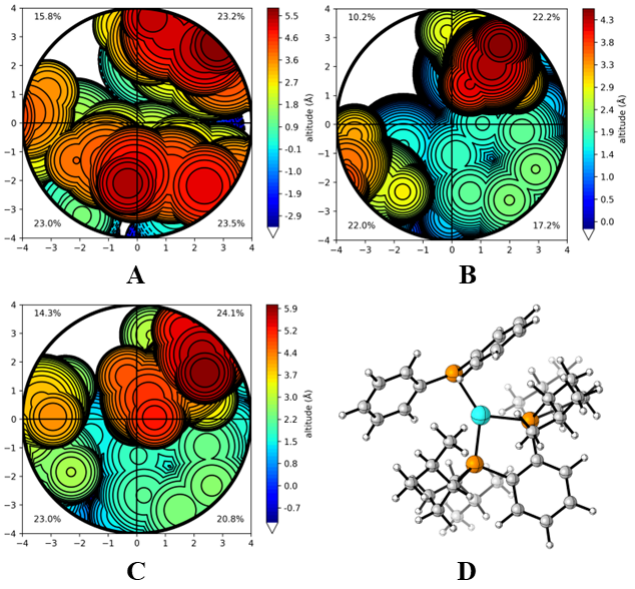


Figure 5. Steric maps depicting the catalytic pocket prior to coordination of cyclopropene when the ligand on copper is **(A)** R-SEGPHOS (**L1**), **(B)** (R,R)-Me-DuPhos (**L3**), or **(C)** (R,R)-^{i}Pr-DuPhos (**L5**). The orientation of the copper-phosphido complexes in these steric maps is depicted in **D**.

In conclusion, we report asymmetric hydrophosphination of cyclopropenes in high enantio- and diastereoselectivities. Mechanistic studies reveal an unusual dimeric resting state and a surprising rate enhancement effect from DBU, which plays an important role in forming the catalytically active monomer. Enrichment of phosphorus stereocenters is additionally demonstrated through a DyKAT of an unsymmetrically substituted secondary phosphine. Both the enantio- and diastereoselectivity of the product is determined during the migratory insertion step. An analysis of the relevant

TSs indicate that selectivity is controlled by a combination of dispersion and steric interactions. Future studies will focus on achieving higher control of this phosphorus stereocenter and elaborating the cyclopropyl phosphine products to afford mono- or bidentate phosphine ligands. We expect insight from these studies to guide the development of related strategies in copper catalysis, hydrofunctionalization, and phosphine synthesis.

ASSOCIATED CONTENT

Supporting Information

(Word Style "TE_Supporting_Informati**on").** (Word Style "TE_Supporting_Informati**on").** A listing of the contents of each file supplied as Supporting Information should be included. For instructions on what should be included in the Supporting Information as well as how to prepare this material for publication, refer to the journal's Instructions for Authors.

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Notes

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ABBREVIATIONS

CCR2, CC chemokine receptor 2; CCL2, CC chemokine ligand 2; CCR5, CC chemokine receptor 5; TLC, thin layer chromatography.

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[45] There is little difference between the buried volumes of L3 and L4, corresponding with the little difference in the observed ee for L3 and L4 (see Supplementary Information Table S2 for buried volumes and all steric maps).