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Catalytically Generated Allyl Cu(I) Intermediate via Cyclopropene Ring-Opening Coupling en Route to Allylphosphonates

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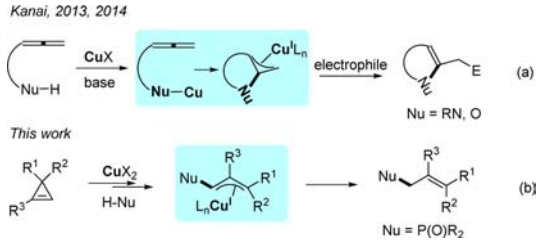
Supporting Information

ABSTRACT: An efficient generation of functionalized allyl copper(I) species via cyclopropene ring-opening coupling reaction is reported, which enables stereoselective access to allylphosphonates. Mechanistic studies uncovered stereochemistry to be controlled by both ligand and substrate electronics, with the latter likely arising from pronounced arene-Cu(I) interaction in electron-deficient substrates. The study unravels a novel approach to access functionalized nucleophilic allylcopper species upon which three-component coupling reactions might be developed.

Intensive studies on the allylation of carbonyl derivatives with semimetallic reagents (boron, silicon, stannane, etc.), one of the most useful transformations in organic synthesis,[1] identified Cu(I) catalysis to be exceptionally efficient, wherein nucleophilic allyl Cu(I) intermediates are invoked as reactive species.[1f] Due to the limited availability of stereodefined, multisubstituted allylic reagents, direct access to multisubstituted allylcopper(I) intermediate offers a straightforward alternative. Stoichiometric generation of allylic copper(I) intermediates via carbo-[2] and silacupration[3] of dienes with in situ formed organocuprates offers an entry to multisubstituted alkenes and allylic derivatives. A lack of functional group tolerance due to employment of strongly basic organometallic reagents, however, is an intrinsic limitation. Many recent efforts have therefore been made to develop processes to form allylcopper(I) species via addition of catalytically generated X−Cu(I) (X = heteroatom) species with unsaturated carbon−carbon bonds. This approach encompasses the advantage of high efficiency and atom economy as well as enabling of multicomponent processes. X−Cu(I) intermediates where X is Lewis acidic or neutral elements such as B or Si demonstrated exceptional reactivities, as shown in numerous reports on intermolecular bora-[4] and silylcupration[5] of allenes as viable routes to allyl Cu(I) intermediate generation, highlighting the advantage of this strategy in the construction of complex molecular architectures. Despite these remarkable advances, the generation of allyl Cu(I) intermediates via heteroatomcupration where heteroatoms are nucleophilic centers (such as N and O) still represents an unmet challenge. Intramolecular version of such process has recently been attained by Kanai and coworkers with allenes (Scheme 1a);[6] however, intermolecular nucleocupration remains elusive.

Scheme 1. Catalytic Processes for Generation of Nu-Containing Allylcopper(I) Intermediates



Cyclopropene (CPE) is a highly strained yet readily available unsaturated carbocycle that exhibits rich reactivity patterns under transition-metal catalysis.[7] Recently, noble metals, notably rhodium and gold, catalyzed CPE ring-opening reactions have been well documented.[8] In contrast, a paucity of reports on earth-abundant first-row transition-metals catalyzed CPE ring-opening prevails. This is reflected in the fact that only one or a couple of examples have been reported each for Ni-,[9] Cu-,[10] and recently, Zn-catalyzed[11] CPE ring-opening initiated reactions. Based on our long-standing interest in copper catalysis,[12] we conceived a copper-catalyzed strain-driven CPE nucleocupration[13]/β-carbon elimination[14] sequence to access the functionalized allyl Cu(I) intermediate. Herein, we report that catalytic generation of this intermediate can be realized under ambient conditions and the application of the approach enables stereoselective synthesis of allylphosphonates (Scheme 1, b).

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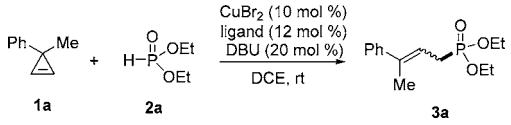
Multisubstituted functionalized alkene is a key functional moiety in organic and medicinal chemistry. Organophosphates are widely used olefination reagents in the Horner−Wadsworth−Emmons (HWE) reaction that allow a high degree of stereochemical control over the generated carbon−carbon double bond.[15] At the onset of this study, we examined the reactivity of 3-phenyl-3-methylcyclopropene **1a** under the catalysis of various copper salts in the presence of diethyl phosphite **2a** as a model nucelophile. We envisioned that the incipient catalytically generated allylcopper(I) species might be sufficiently basic to deprotonate the phosphonate **2a**, suggesting a substoichiometric base-initiated process. Initial optimization identified $CuBr_2$ as the optimal catalyst, which, with 0.2 equiv of DBU as base, afforded product **3a** with high yield and a selectivity of 9/1 at room temperature (entry 1, Table 1). A control experiment performed without base led to

Table 1. Ligand Effects[a]



1a 2a 3a

entry	ligand	yield (%)	E/Z[b]
1		90	9/1
2	TMEDA	76	8/1
3	P(*o*-tol)$_3$	98	9/1
4	DAP	70	13/1
5	dppf	60	16/1
6	dppbz	85	24/1
7	xantphos	75	20/1

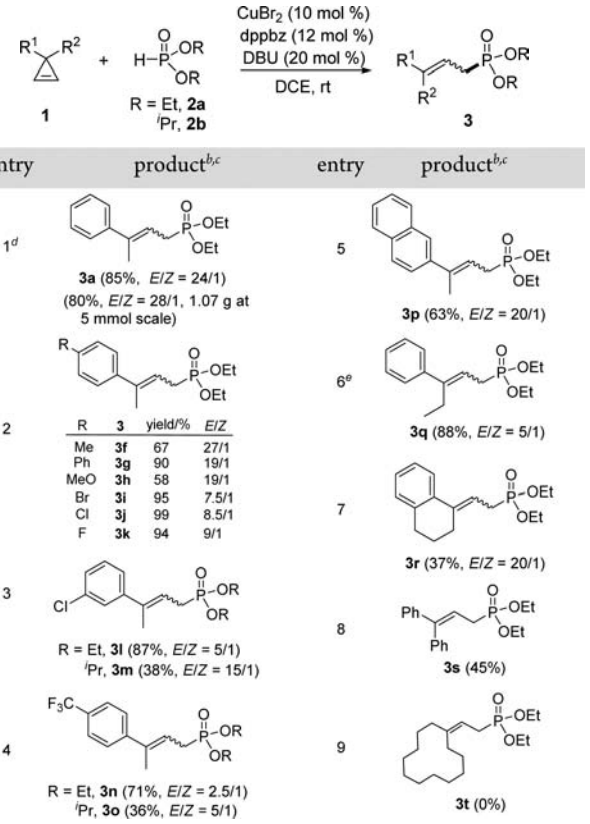
[a]Conditions: cyclopropene **1a** (0.30 mmol, 1.5 equiv), diethyl phosphite **2a** (0.20 mmol), DBU (0.04 mmol, 20 mol %), $CuBr_2$ (0.02 mmol, 10 mol %), ligand (0.024 mmol, 12 mol %), DCE (2 mL), rt. [b]Ratios of isolated products due to the unidentifiable crude NMR residue.

no conversion. To further optimize the selectivity, the effects of various phosphine and nitrogen based ligands were studied. Notably, additional ligands indeed imparted significant influences with respect to both reactivity and selectivity. Specifically, TMEDA led to lower yield and selectivity (entry 2). The use of sterically hindered P(*o*-tol)$_3$ achieved almost quantitative yield but a similar selectivity (entry 3). With DAP (2,9-bis(*p*-anisyl)-1,10-phenanthroline) and dppf, the selectivities were improved at the sacrifice of yields. Delightfully, with dppbz, **3a** was obtained in 85% yield and 24/1 selectivity and thus used as the optimal conditions in the following studies. The reactivities of several P-based nucleophiles were also examined under the optimized conditions (Scheme 2).

Although the diisopropyl phosphite **2b** led to higher selectivities and a slight drop of yield, the reaction of diisobutyl phosphite **2c** afforded the product **3c** with almost quantitative yield and high (>20/1) selectivity. Neither diphenyl phosphite (**2d**) nor diphenylphosphine oxide (**2e**) gave better selectivities.

Substrate scope studies revealed that a wide range of functionalities with distinct electronic properties were compatible, affording the corresponding products with high yields (Table 2). Notably, CPEs bearing electron-neutral and

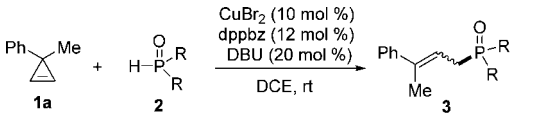
Table 2. Substrate Scope Studies[a]



[a]Conditions: cyclopropene (0.30 mmol, 1.5 equiv), phosphine reagent (0.20 mmol, 1.0 equiv), copper (0.02 mmol, 10 mol %), dppbz (0.024 mmol, 12 mol %), DBU (0.04 mmol, 20 mol %) in DCE (2 mL). [b]Isolated yields. [c]E/Z ratios were determined by ^{1}H NMR spectroscopy. [d]The gram-scale reaction was performed with 5 mol % of $CuBr_2$/6 mol % of dppbz as catalyst. [e]2 equiv of cyclopropene was used.

electron-rich aryl groups afforded products with high E/Z ratios (**3a,f−h**, entries 1 and 2), while those bearing electron-withdrawing groups (EWGs) retrieved the corresponding products with decreased selectivities (**3i−k**, entry 2). Substrates bearing moderately strong (3-Cl) and strong (4-CF_3) EWGs on the aryl moiety afforded products with much lower selectivities (entries 3 and 4). The reactions of these reactants with the more sterically hindered diisopropyl phosphite **2b** were found to be more selective, and product **3m** was obtained with a selectivity of 15/1 (entry 3). However, the strategy was not as effective for 4-CF_3-substituted substrate, as only a moderate improvement of selectivity was obtained for **3o** (entry 4). Variations on the aryl and alkyl moieties showed that 2-naphthyl (instead of phenyl), ethyl (instead of methyl), and bicyclic systems were also readily applicable (entries 5−7). 3,3-Diaryl substrate was also viable, giving the allylic phosphonate product **3r** in 45% yield. 3,3-Dialkylcyclopropene was not

Scheme 2. Reactivities of Different P-Based Nucleophiles



1a 2 3

R = O^{i}Pr, **2b**
O^{i}Bu, **2c**
OPh, **2d**
Ph, **2e**

R = O^{i}Pr, **3b** (74%, *E*/*Z* > 20/1)
O^{i}Bu, **3c** (97%, *E*/*Z* > 20/1)
OPh, **3d** (98%, *E*/*Z* = 5/1)
Ph, **3e** (89%, *E*/*Z* = 10/1)

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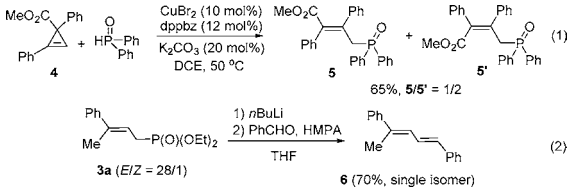
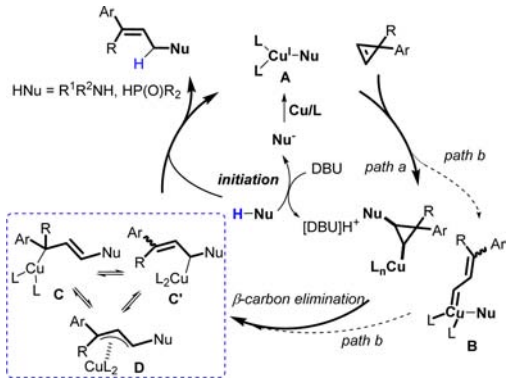
reactive (entry 9), and substrate decomposition was observed. A gram-scale reaction readily afforded **3a** in 80% yield and 28/1 selectivity under a reduced catalyst loading (entry 1). Furthermore, preliminary studies revealed that at slightly elevated temperature less electron-rich 3-EWG-substituted cyclopropene **4** produced the diastereoisomeric products **5**/**5′** in moderate yields, which were facilely separated on silica (eq 1). Their configurations were determined by NOESY experiments of **5**. Cycloisomerization, a facile transformation of these substrates,[16] did not occur owing to the mildness of the conditions. As an exemplified synthetic application, HWE reaction of **3a** with benzaldehyde afforded diene **6** in high yield and exclusive stereoselectivity (eq 1).



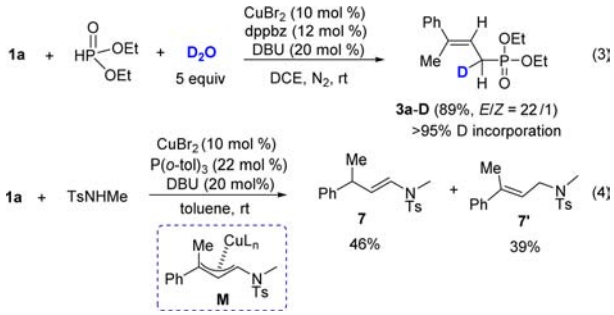
On the basis of the above observations and some related literature,[17] a plausible mechanism was outlined in Scheme 3.

Scheme 3. Plausible Catalytic Cycle for Copper-Catalyzed Stereoselective Ring-Opening Coupling of Cyclopropene



First, DBU deprotonation of **2a** facilitates the formation of P−Cu(I) complex **A**. Cyclopropene phosphoracupration[13] followed by β-carbon elimination[14] leads to η^1-allyl copper species **C** and **C′**, possibly equilibrating via η^3-allyl copper **D**.[1f] Protonation of the allylcopper species with the nucleophile **2a** releases the product **3** and regenerates catalyst **A** (path a). An alternative pathway involving first generation of vinylcopper carbenoid species **B** followed by intra- or intermolecular attack of the nucleophile **Nu** to form allyl copper intermediates could not be strictly excluded at the current stage.[10] Consistent with the mechanistic proposal, an isotope-labeling experiment performed with added D_2O (5 equiv) resulted in high deuterium incorporation in the product **3a-D** (eq 3). Subjecting **3a** to a mixture of **2a** and D_2O under the conditions of entry 2 resulted in no isotope incorporation, disclaiming the proposition of catalytic DBU-promoted H/D exchange.

The reaction of *N*-phenylsulfonamide under slightly modified conditions afforded a mixture of constitutional isomers enamide **7** and allylic amide **7′** in 46% and 39% yields, respectively (eq 4), supporting the possible existence of equilibrating η^1-allyl copper species **C** and **C′**. Furthermore, the observation that 3,3-dialkylcyclopropenes are unreactive (entry 9, Table 2)



might reflect the requirement of a suitably stabilized allylcopper intermediate.

Hammett analysis was then conducted to examine if the stereoselectivity correlates with electronic effects. Plotting the logarithmic selectivity ratios of substituted products **3** (**3a,f**–**k,l,n**) over that of **3a** (Table 2) against the substituents' Hammett constants σ_R[18] (Figure 1) revealed a rough

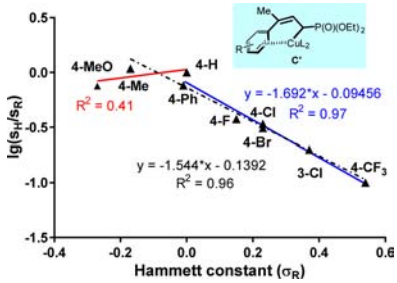


Figure 1. Hammett analysis of reaction selectivity. Hammett linear correlations with electron-rich to -neutral (red line), electron-rich to deficient (dashed line), as well as electron-neutral to -deficient substrates (blue line).

correlation by electron-releasing and -neutral groups (4-MeO, 4-Me, and H) (red line) and a significant correlation by electron-releasing to electron-withdrawing groups but with obvious trend discrepancy (dashed line). Omitting 4-Me led to better correlation (blue line), lending more support for the role of EWGs in deviating from the trend in favor of the *Z*-isomer. This effect could be attributed to appreciable Cu(I)−arene interaction in the allylcopper species (**C** and **D**) in EWG-substituted substrates.[19] This trend is opposite to those observed in cationic Cu(I)− and Cu(II)−arene complexes, where electron-donating groups facilitate charge transfer,[19a,b] implying a possible interaction engaging the electron-rich Cu(I) center in **C**/**C′** to be dominated by d−π^* interaction. The interaction presumably disfavors the ligation of exogenous ligands, thereby overriding the ligand and steric effects in electron-deficient substrates (entry 4, Table 2). Indeed, dppbz was not as effective in improving the *E*/*Z* ratio in the reaction of **3n**, as only marginal improvement was observed when PCy_3 was employed (from 2.5/1 to 3/1, data not shown). A detailed mechanistic investigation is warranted and is currently ongoing.

In conclusion, we have realized an efficient generation of allylcopper(I) species via cyclopropene ring-opening coupling. As a preliminary synthetic application, a stereoselective access to allylphosphonates was established. Mechanistic studies not only provided clues for the putative allylcopper(I) species but revealed a noteworthy dependence of stereochemistry on ligand and substrate electronic effects. The present work unravels a novel approach to access functionalized allyl Cu(I) species

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upon which three-component coupling reactions might be developed. Endeavors toward this direction are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02307.

Detailed experimental procedure, characterization data, and NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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