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Communication

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Copper(I)-Catalyzed Enantioselective Addition of Enynes to Ketones

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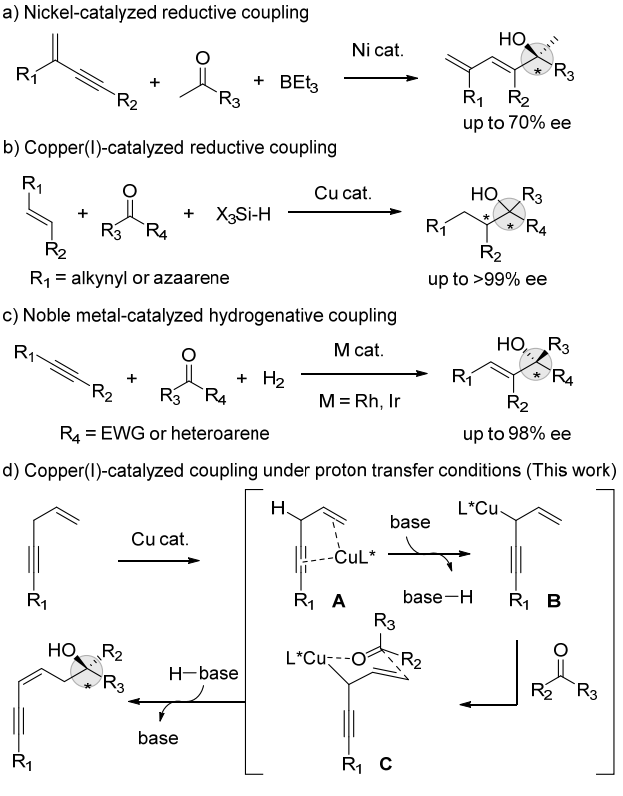
Supporting Information Placeholder

ABSTRACT: A copper(I)-catalyzed enantioselective addition of enynes to ketones was developed. The method allows facile construction of enantiomerically-enriched tertiary alcohols using skipped enynes as stable hydrocarbon pronucleophiles. The combination of a soft copper(I)-conjugated Brønsted base catalyst with a chiral diphosphine ligand, (*S,S*)-Ph-BPE, enabled chemoselective deprotonation of the skipped enynes in the presence of ketones bearing intrinsically more acidic α-protons. The catalytically-generated chiral allylcopper species enantio-, diastereo-, regio-, and chemo-selectively reacted with ketones, thereby demonstrating excellent substrate generality with functional group tolerance. The skipped enyne moieties of the pronucleophiles were exclusively converted to *cis*-conjugated enynes, which will eventually allow for further versatile transformations.

Catalytic asymmetric nucleophilic addition of hydrocarbons to ketones is a fundamentally important transformation, producing enantiomerically-enriched tertiary alcohols, which are a frequently encountered structural motif in biologically active natural products and pharmaceuticals.[1] The general requirement of preformed reactive organometallic reagents along with the generation of stoichiometric amounts of metal salts waste, however, often limit the overall synthetic efficiency and functional group tolerance. Transition metal-catalyzed asymmetric reductive coupling of stable hydrocarbons with ketones has led to considerable effort to override the limitations of preformed organometallic reagents. The pioneering work of Jamison disclosed nickel-catalyzed asymmetric alkenylation of ketones using BEt_3 as a terminal reductant, which circumvents the prior preparation of reactive organometallic reagents (Scheme 1a).[2] Lam realized a copper-catalyzed asymmetric addition of C(sp^3)-nucleophiles derived from alkenylazaarenes using $PhSiH_3$ as a reductant (Scheme 1b).[3] Related copper catalysis was further applied to conjugated enyne pronucleophiles by Buchwald for asymmetric propargylation of ketones.[4] A more atom-economical hydrogenative approach using a rhodium or iridium catalyst was reported by Krische (Scheme 1c),[5] although the approach is limited to activated ketones (such as α-keto esters) or heteroaromatic ketones.

A redox-neutral asymmetric coupling reaction between hydrocarbon pronucleophiles and ketones under proton transfer conditions is an ideal approach that does not require stoichiometric amounts of bases and additives. Difficulties in deprotonating hydrocarbons to generate organometallic reagents, however, have hampered the development of such reactions.[6] Only a combination of relatively acidic terminal alkynes (C(sp)-pronucleophiles) and activated ketones has been developed,[7] and asymmetric addition of C(sp^3)-nucleophiles has remained unexplored. Herein we report a copper-catalyzed asymmetric addition of enynes to ketones under proton transfer conditions (Scheme 1d). The reaction does not require stoichiometric amounts of bases and additives, and proceeds with good functional group tolerance.

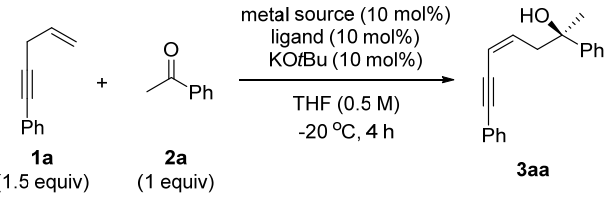
Scheme 1. Catalytic Asymmetric Coupling of Hydrocarbons with Ketones.



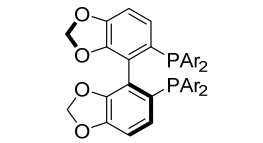
To catalytically generate reactive organocopper species via deprotonation of hydrocarbons, we first evaluated whether a soft-soft interaction between copper(I) catalyst and C-C multiple bonds could acidify adjacent C(sp^3)-H protons.[8,9] Thus, skipped enynes were selected as pronucleophiles to maximize the interaction with the copper(I) catalyst, where a C-C double bond as well as a triple bond can coordinate to the copper(I) catalyst (Scheme 1d: **A**). Allylcopper species **B** generated through deprotonation would attack ketones via six-membered transition state **C**.[10] The

products, conjugated enynes, are an important structural motif due to their synthetic versatility and prevalence in biologically relevant molecules.[11] Previously reported methods using skipped enynes as pronucleophiles in organic synthesis, however, required harsh conditions. Medlik utilized a stoichiometric amount of MeLi for selective monometalation of skipped enynes followed by alkylation at the methylene position.[12] Later, Yamaguchi developed a $GaCl_3$-promoted ethynylation reaction of skipped enynes using silylchloroacetylenes as electrophiles.[13] Although ethynylation can proceed with a catalytic amount of $GaCl_3$, the high temperature (150 °C) required in the presence of a strong Lewis acid sharply limits the functional group tolerance.

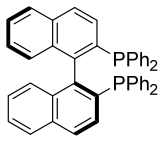
Table 1. Optimization of Copper(I)-Catalyzed Asymmetric Addition of Enyne to Ketone.[a]



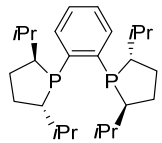
Entry	Metal source	Ligand	Yield (%)	*trans/cis*	ee (%)
1	-	-	trace	-	-
2	$CuClO_4(MeCN)_4$	**L1**	trace	-	-
3	$CuClO_4(MeCN)_4$	**L2**	trace	-	-
4	$CuClO_4(MeCN)_4$	**L3**	trace	-	-
5	$CuClO_4(MeCN)_4$	**L4**	31	1/>20	95
6	$AgClO_4$	**L4**	20	1/>20	87
7	CuCl	**L4**	trace	-	-
8	CuOAc	**L4**	trace	-	-
9[b]	MesCu	**L4**	93	1/>20	92
10[b,c]	MesCu	**L4**	90	1/>20	97
11[b,d,e]	MesCu	**L4**	72	1/>20	94



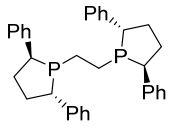
(*S*)-DTBM-SEGPHOS (**L1**)
Ar = 3,5-(*t*Bu)$_2$-4-MeO-C$_6$H$_2$



(*S*)-BINAP (**L2**)



(*S,S*)-*i*Pr-DUPHOS (**L3**)



(*S,S*)-Ph-BPE (**L4**)

[a]General reaction conditions: **1a** (0.15 mmol), **2a** (0.1 mmol), MesCu (0.01 mmol), and ligand (0.01 mmol) were reacted in THF (200 μL) at -20 °C for 4 h. Yields were determined by ^{1}H NMR analysis of the crude mixture using 1,3,5-trimethylbenzene as an internal standard. [b]Without KO*t*Bu. [c]-30 °C. [d]5 mol% catalyst loading. [e]Reaction time was 6 h.

Based on the above-mentioned working hypothesis, we initiated our investigation using acetophenone (**2a**) and 1-phenyl-4-penten-1-yne (**1a**; 1.5 equiv) as substrates (Table 1). The use of 10 mol% KO*t*Bu in the absence of a copper(I) catalyst was completely ineffective (entry 1). Examination of a variety of chiral ligands using $CuClO_4(MeCN)_4$ as a copper source in combination with KO*t*Bu (10 mol%), generating chiral CuO*t*Bu complexes in the reaction mixture,[14] revealed that only (*S,S*)-Ph-BPE (**L4**) exhibited moderate reactivity and excellent enantioselectivity and *trans/cis*-selectivity (entry 5). Neither a possible regio-isomer *via* internal addition nor the *trans*-isomer was observed. Use of $AgClO_4$, instead of $CuClO_4(MeCN)_4$, led to lower reactivity and enantioselectivity (entry 6). While other copper(I) sources, such as CuCl (entry 7) and CuOAc (entry 8), produced only a trace amount of the product, mesitylcopper (MesCu) without additional base was identified to be the optimal choice (entry 9). Decreasing the temperature to -30 °C further improved the enantioselectivity to 97% ee (entry 10) without a significant loss of catalyst activity. The catalyst loading could be reduced to 5 mol% and the product was obtained still in high yield with comparable enantioselectivity (entry 11).

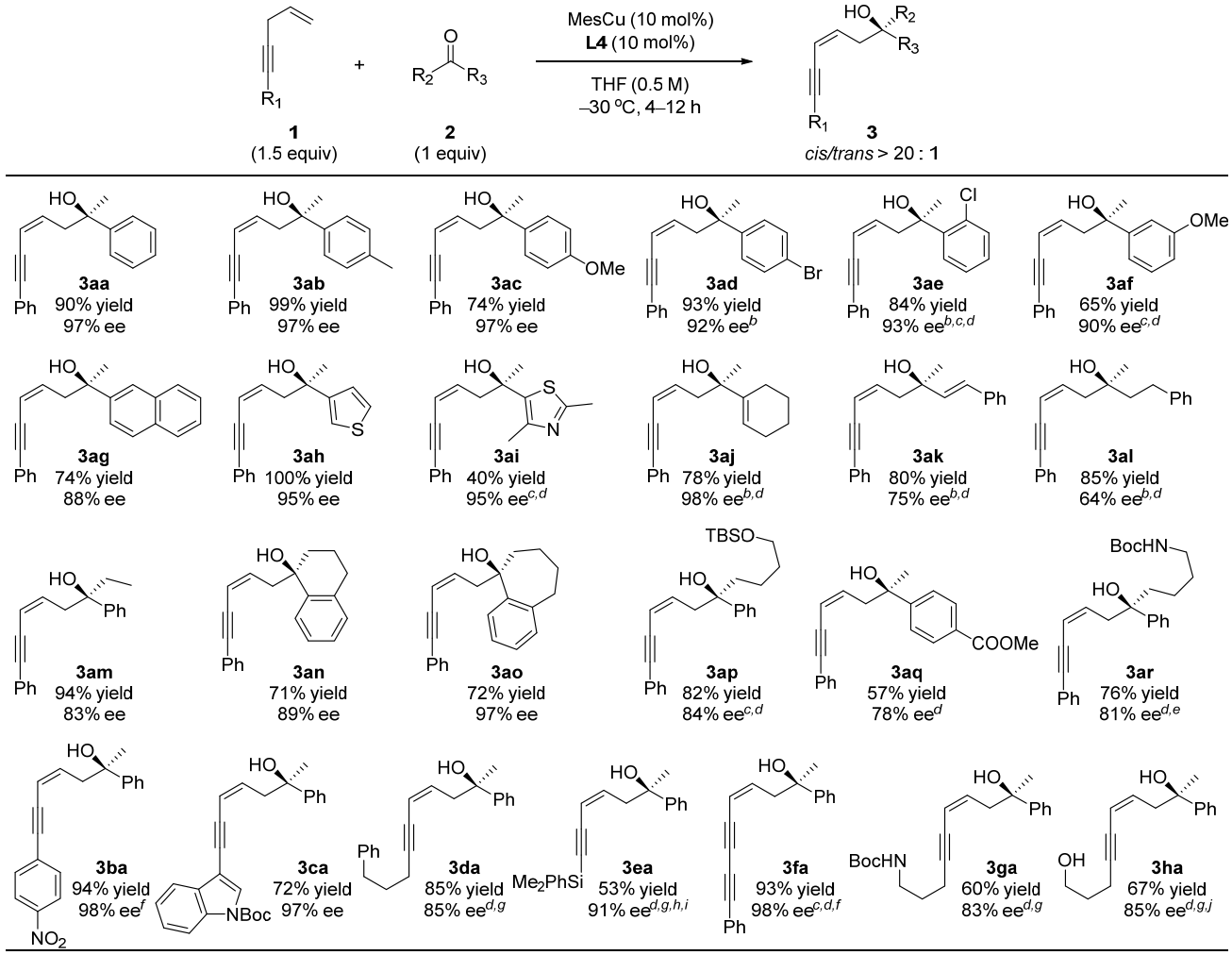
Having established the optimal conditions, we next examined the substrate scope (Table 2). With **1a** as a pronucleophile, ketone electrophiles were evaluated first (**2a**-**2r**). Products were obtained in high yield and with excellent enantioselectivity for aryl ketones containing electron-donating groups or halogen substituents at the *para* position (**3ab**, **3ac**, and **3ad**). Substrates with a substitution at the *ortho* or *meta* position were less reactive than other aryl ketones. Using Mg(O*i*Pr)$_2$ as a cocatalyst,[15] however, **3ae** and **3af** were produced in good yield with excellent enantioselectivity. A ketone with a bulky naphthyl group was also applicable (**3ag**: 74% yield, 88% ee). Additionally, heteroaryl ketones, which potentially inhibit the reaction by coordinating to the copper catalyst, were competent (**3ah** and **3ai**). On the other hand, a ketone with a strong electron-withdrawing group, *p*-nitroacetophenone, was totally unreactive probably due to great acidity of the α-protons of the ketone, hampering deprotonation of **1a**.[16]

Enones (**2j** and **2k**) also served as appropriate electrophiles: potential byproducts derived from 1,4-addition of the allylcopper nucleophile to enones were not detected in either case. Moreover, an aliphatic ketone (**2l**) was applicable, resulting in satisfactory yield, albeit with moderate enantioselectivity (**3al**). The reaction was effective not only for methyl ketones but also for longer chain ketones, in which it is more difficult to differentiate the steric factors between the two substituents of the carbonyl group. Propiophenone (**2m**), cyclic α-tetralone (**2n**) and 1-benzosuberone (**2o**) underwent the asymmetric carbonyl addition with high yield and satisfactory enantioselectivity. Moreover, ketones bearing functional groups were also competent. A siloxy group (**2p**) and an ester group (**2q**) were unaffected under the reaction conditions. It is also noteworthy that a substrate bearing a protic NH functional group (**2r**) produced chiral tertiary alcohols with high enantioselectivity.[17]

We then examined the scope of skipped enyne pronucleophiles. In addition to the phenyl-substituted enyne (**1a**), the terminal substituents of enynes can cover a *p*-nitrophenyl group (**1b**), an indole moiety (**1c**), an aliphatic substituent (**1d**), a silicon substituent (**1e**), and a conjugated diyne (**1f**), which showed broad adaptability for facile construction of an array of compounds containing a variety of conjugated enyne moieties. The protic functional groups on the pronucleophile side were also amenable to the reaction, affording the products with satisfactory enantioselectivity (**3ga** and **3ha**).

The conjugated enyne-containing tertiary alcohol products offer multiple possibilities for further transformations.[18,19] Representative examples are shown in Scheme 2. Hydrogenation of the enyne moiety of **3ar** produced **4**, which is difficult to access in an enantiomerically enriched form by other methods, in 91% yield. The conjugated enyne moiety could be regio- and stereoselectively transformed to the *cis*-diene moiety under palladium-catalyzed hydrosilylation conditions to give **5** in high yield.[20] These transformations proceeded without any epimerization.

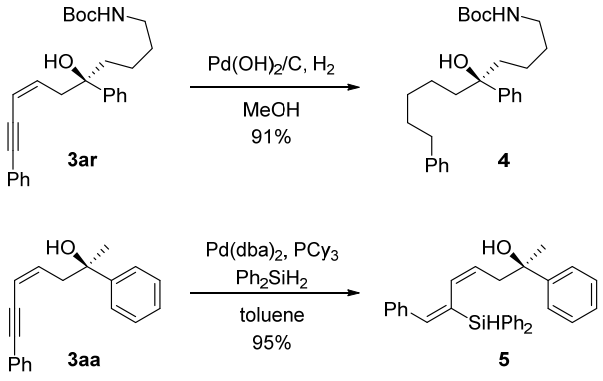
Table 2. Substrate Scope of Copper(I)-Catalyzed Asymmetric Addition of Conjugated Enynes to Ketones.[a]



[a]General reaction conditions: **1a** (0.15 mmol), **2a** (0.1 mmol), MesCu (0.01 mmol), and (*S,S*)-Ph-BPE (0.01 mmol) were reacted in THF (200 μL) at -30 °C. [b]-45 °C. [c]0.2 equiv of $Mg(OiPr)_2$ was added. [d]Reaction time was 12 h. [e]0.5 equiv of Cs_2CO_3 was added. [f]-40 °C. [g]-10 °C. [h]0.4 equiv of $Mg(OiPr)_2$ was added. [i]500 μL of THF was used as solvent. [j]20 mol% of MesCu/(*S,S*)-Ph-BPE was used.

In summary, we developed the first catalytic enantioselective C-C bond-forming reaction via *in situ* generation of nucleophilic organometallic species through deprotonation of the non-acidic C(sp^3)-H bond of hydrocarbons without adjacent electron-withdrawing groups.[21] The catalytically generated chiral allylcopper(I) species exhibited high nucleophilicity, enantioselectivity, and functional group-tolerance even in the presence of protic functional groups. The products containing unique conjugated *cis*-enyne moieties[22] serve as versatile building blocks in organic synthesis. Studies toward switching the *cis*/*trans* stereoselectivity and regio-selectivity of this method to further diversify the product structures are on-going in our laboratory.

Scheme 2. Transformation of the Products.



ASSOCIATED CONTENT

Supporting Information

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

Experimental details and characterization data (PDF)

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Notes

The authors declare no competing financial interests.

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(16) Skipped enyne **1a** isomerized to the corresponding conjugated enyne **6** when deprotonation proceeded (see Supporting Information). Since **1a** was recovered without isomerization in 95% yield after the reaction, deprotonation of **1a** was not likely to proceed when *p*-nitroacetophenone was present.

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(21) Preliminary mechanistic studies and a proposed catalytic cycle are described in Supporting Information. Two main mechanistic features supported by the experiments are: (a) the reaction would proceed through allylcopper species **B**, not allylcuprate species; and (b) allylcopper species **B** would pre-equilibrate through metallotropic rearrangement prior to the addition to ketones.

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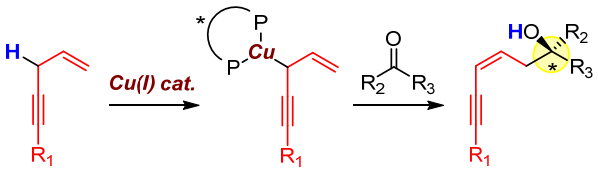

- *C(sp^3)-hydrocarbon addition*
- *H$^+$ transfer conditions*
- *up to 98% ee (25 examples)*
- *cis- & regio-selective*