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A General Copper−BINAP-Catalyzed Asymmetric Propargylation of Ketones with Propargyl Boronates

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Supporting Information

ABSTRACT: An operationally simple copper−BINAP-catalyzed, highly enantioselective propargylation of ketones is presented. The methodology was developed as an enantioselective process for methyl ethyl ketone and shown to be applicable to a wide variety of prochiral ketones. The resulting homopropargyl adducts are versatile latent carbonyls from which γ-butyrolactones, β-hydroxy methyl ketones, and β-hydroxycarboxylates are readily obtained.

The synthesis of chiral tertiary alcohols represents a major challenge in asymmetric catalysis.[1] One of the most challenging substrates in this area is methyl ethyl ketone (MEK), for which there is minimal steric differentiation of the carbonyl's prochiral faces. To date, only low enantiocontrol has been realized with small-molecule catalysis (Figure 1).[2] Although enzymatic processes have been able to address this substrate, the enantiocontrol is only moderate in view of the fact that enzymatic processes normally proceed with excellent stereoinduction.[3] With this challenge in mind, we set out to develop a practical asymmetric catalytic propargylation focusing on MEK.

Chiral homopropargylic alcohols are valuable synthons because of the synthetic versatility provided by the alkyne moiety.[4] The asymmetric propargylation of aldehydes has seen significant development through the use of stoichiometric chiral reagents,[5] Barbier-type processes,[6] and the catalytic chiral Lewis acid-[7] and base-type[8] methodologies. Limited success[9] had been realized with the corresponding asymmetric propargylations of prochiral ketones until Soderquist and co-workers[10] were able to implement their chiral allenyl borolane reagents. Recently, Shibasaki and co-workers[11] developed copper−boron exchange into a highly enantioselective catalytic allylation of aldehydes and imines with chiral catalytic bis(phosphine)copper complexes. Furthermore, they implemented this concept for the asymmetric allylations and propargylations of ketones with allenyl boronates.[12] Although high enantioselectivity can be achieved in asymmetric propargylations of acetophenones with the use of their modular chiral bisphosphine ligands, only moderate enantiocontrol is realized with aliphatic prochiral ketones.[12] The development of a general highly enantioselective propargylation of aliphatic prochiral ketones as well as acetophenones is still needed. Recently, we showed that copper alkoxide−MeO-BIBOP[13] complexes are competent catalysts for highly enantioselective propargylations of aldehydes with trimethylsilyl (TMS)-propargyl boronates.[14] The need for a practical and general asymmetric catalytic propargylation of prochiral aliphatic ketones encouraged us to investigate this reaction further, focusing on the most challenging of prochiral aliphatic ketones, MEK. Herein we report a general copper alkoxide-catalyzed, highly enantioselective propargylation of ketones employing the commercially available BINAP ligand.

With MEK as a challenging model substrate, initial attempts at the asymmetric propargylation employing our previously reported copper(II) isobutyrate−MeO-BIBOP[14] catalyst system provided the desired homopropargylic alcohol **3a** with moderate enantioselectivity (69% ee; Table 1, entry 1). Attempts to improve the facial discrimination with this catalyst system were not successful,[15] and an extensive ligand, solvent, and catalyst survey[15] revealed copper(II) isobutyrate−BINAP-type catalysts to be superior for the facial discrimination, providing the adduct in 79−83% ee. Furthermore, decreasing the temperature of the reaction to −83 °C provided the desired product in 83% isolated yield with 95% enantiomeric excess for this challenging substrate.

After the optimal reaction parameters had been established, structurally diverse prochiral ketones were surveyed for the propargylation (Table 2). This methodology was found to be effective for prochiral ketones other than MEK, including cyclopropyl methyl ketone (**3b**). It was also amenable to a wide variety of acetophenone derivatives, providing the corresponding adducts in 93−98% yield with high enantioselectivity (94−96% ee) (entries 7−11). The chemistry was shown to display wide functional-group tolerance, as an ester (**1l**), pyridine (**1n**) and an *N*-tosyl indole (**1o**) were well-tolerated, providing the corresponding adducts in high yields (87−95%) with 91−95% enantiomeric excess. The methodology was not readily affected by the electronic nature of the acetophenone substrate, as both *p*-methoxyacetophenone (**1j**) and *p*-nitroacetophenone (**1i**) provided the corresponding addition products with high enantioinduction (95 and 93% ee, respectively). However, the reaction with benzofuran methyl ketone (**1p**) required a catalyst loading of 10 mol % and 35 h to reach complete conversion and proceeded with a decrease in enantiocontrol (84% ee).

The acetylene component of the chiral homopropargylic alcohol is a versatile functional group.[12] However, the acetylene can also be considered as a latent carbonyl, thus making this methodology an attractive alternative to the homoacetate and

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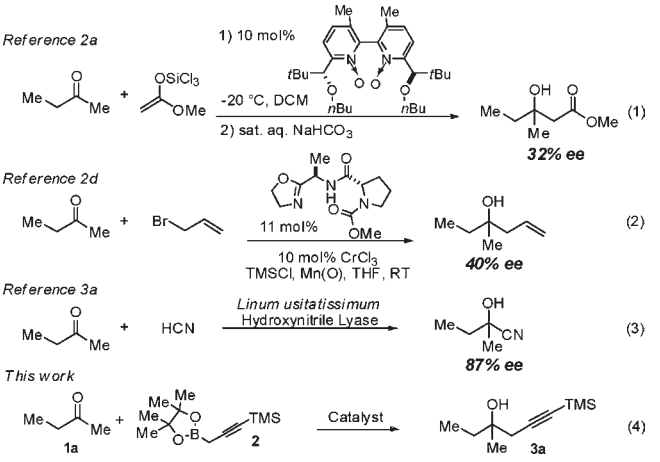
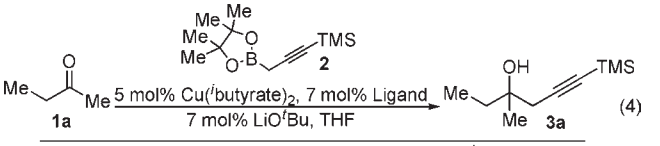
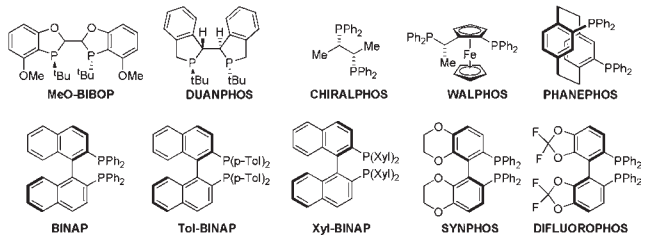


Figure 1. Highest reported enantioselective catalytic carbonyl additions with MEK.

Table 1. Initial Development of the Asymmetric Propargylation with Methyl Ethyl Ketone (1a)[a]



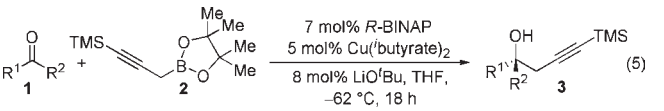
entry	ligand	temp.	conv.[b]	[ee%][c]
1	MeO-BIBOP	–25 °C	99%	69%
2	DUANPHOS	–25 °C	99%	10%
3	CHIRALPHOS	–25 °C	99%	10%
4	WALPHOS	–25 °C	99%	31%
5	PHANEPHOS	–25 °C	99%	23%
6	Tol-BINAP	–25 °C	99%	80%
7	Xyl-BINAP	–25 °C	99%	83%
8	SYNPHOS	–25 °C	99%	61%
9	DIFLUOROPHOS	–25 °C	99%	69%
10	BINAP	–25 °C	99%	79%
11	BINAP	–62 °C	99%[d]	90%
12	BINAP	–83 °C	99%[e]	95%



[a] Typical reaction conditions: 1.2 mmol of ketone, 1.7 mmol of propargyl boronate, 3 mL of THF. [b] Complete conversion was observed upon GC analysis. [c] Absolute stereochemistries; reported as enantiomeric excess as determined by chiral HPLC analysis. [d] Isolated yield 81%. [e] Isolated yield 83%

acetate aldol reactions.[2a,16] Treatment of chiral homopropargylic alcohol **3f** with catalytic palladium and stoichiometric copper[17] furnished γ-butyrolactone **4** in 92% isolated yield without erosion of the chiral center (eq 6 in Figure 2). The corresponding β-hydroxy methyl ketone **6** could also be accessed in 75% yield via terminal acetylene **5** by gold-catalyzed hydration (eq 7 in Figure 2).[18] Although ruthenium oxide-catalyzed oxidative

Table 2. Substrate Survey for the Cu–BINAP Asymmetric Propargylation[a]



entry	Substrate	Product	yield	ee[b]
1	1a	3a	81% (–62 °C) 83% (–83 °C)	90% ee 95% ee
2	1b	3b	96%	98% ee
3	1c	3c	77%	90% ee
4	1d	3d	91%	91% ee
5	1e	3e	87%	87% ee
6	1f	3f	91%	93% ee
7	1g	3g	98%	96% ee
8	1h	3h	98%	94% ee
9	1i	3i	85%	93% ee
10	1j	3j	94%	95% ee
11	1k	3k	98%	96% ee
12	1l	3l	93%	95% ee
13	1m	3m	96%	96% ee
14	1n	3n	87%	91% ee
15	1o	3o	95%	94% ee
16[c]	1p	3p	80%	84% ee

[a] Typical reaction conditions: 1.2 mmol of ketone, 1.7 mmol of propargyl boronate, 3 mL of THF. [b] Determined by chiral HPLC analysis. [c] 10 mol % catalyst, 35 h.

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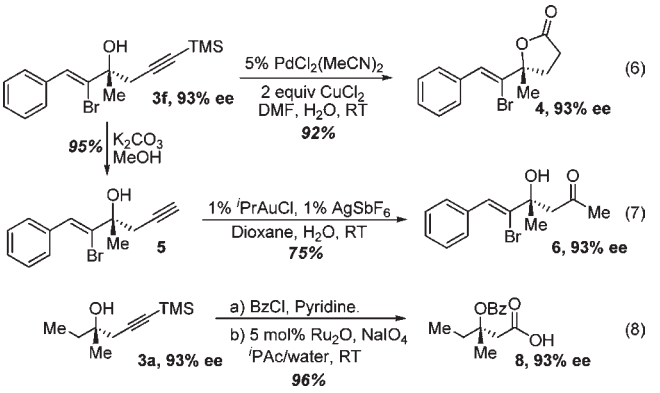
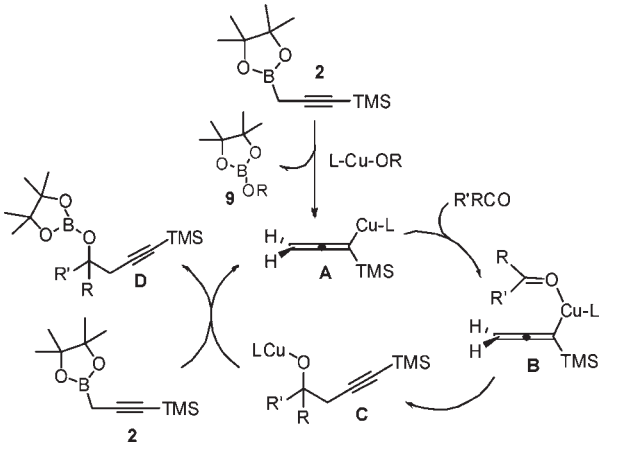


Figure 2. Derivatization of homopropargylic tertiary alcohols into homoacetate and acetate aldol products.

Scheme 1. Proposed Catalytic Cycle for the Propargylation of Ketones with Propargyl Borolane 2



cleavage is precedented for terminal acetylenes,[19] the corresponding cleavage with TMS-acetylene **3a** under the standard conditions (acetonitrile/water solvent system) was highly exothermic and gave a poor yield (40%). Performing the oxidative cleavage with a biphasic isopropyl acetate/water solvent system (eq 8 in Figure 2) offered the necessary control to provide the corresponding β-benzoate carboxylic acid **8** in 97% yield, thus allowing access to this challenging substrate[2a,20] with high enantiomeric excess (93% ee).

Scheme 1 presents a proposed catalytic cycle based on a previously demonstrated copper-alkoxide B/Cu exchange[12] with propargyl borolane **2** to form allenylcopper intermediate **A**.[14] After complexation with a ketone to form **B**, the stereochemically defining intermolecular propargylation[14] occurs, affording copper alkoxide **C.** A stereochemical model of **B** based on the copper–(*R*)-BINAP crystal structure of Anslyn[21] is presented in Figure 3, with the BINAP ligand represented as a space-filling model. The allenyl and ketone moieties are appended on the two available sites in the distorted tetrahedral copper–ligand complex. The ketone is oriented to position the more sterically demanding substituent away from the ligand, exposing the *Re* face for the intramolecular propargylation.[22] Following subsequent Cu/B

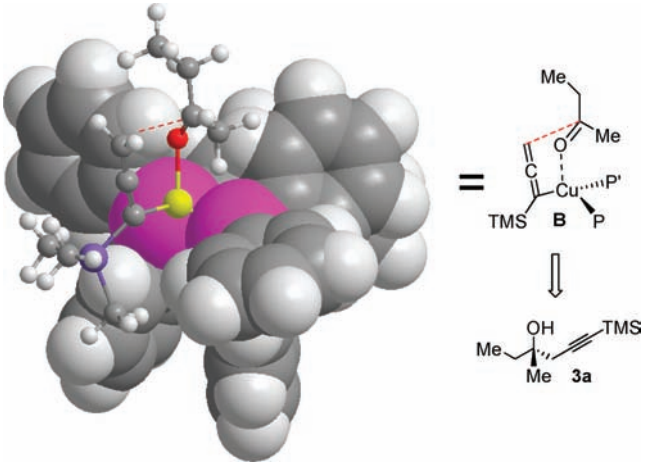


Figure 3. Stereochemical model of the propargylation of MEK with Cu–(*R*)-BINAP.

exchange with propargyl borolane **2**, intermediate **A** is regenerated to complete the catalytic cycle.

In conclusion, focusing on MEK as the paramount prochiral aliphatic ketone for the initial development of the enantioselective propargylation enabled the development of this methodology into a general system amenable not only to prochiral aliphatic ketones but also to a variety of acetophenones. The homopropargylic products have been shown to be versatile latent carbonyls, making this methodology a practical alternative to the asymmetric homoacetate and acetate aldol reactions.

■ ASSOCIATED CONTENT

Supporting Information. Optimization studies, experimental procedures, characterization data (^{1}H NMR and ^{13}C NMR spectra for all products), chiral HPLC data and copies of chromatograms, and determination of absolute stereochemistries. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

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(22) The stereochemical model was generated by replacing the appended counterions on the Cu−BINAP crystal structure with MEK and the TMS-allene unit. The BINAP ligand and the position of the carbonyl oxygen of MEK and C1 of the TMS-allene were frozen as found in the crystal structure. The distance between the terminus of the allene and the carbonyl carbon of MEK was constrained as 3.0 Å, after which a single-point energy minimization was performed using Spartan '08 (version 1.1.1).