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Copper Catalyzed Asymmetric Propargylation of Aldehydes

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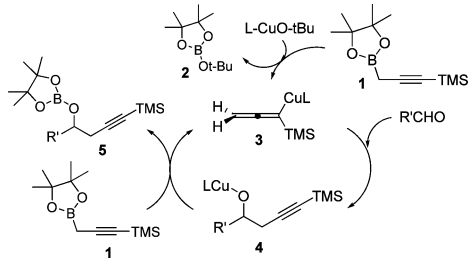
Chiral homopropargylic alcohols are versatile and valuable synthetic intermediates due to the alkyne functional group which provides a convenient synthetic handle for coupling or derivation.[1] The enantioselective propargylation of aldehydes with a chiral allene reagent[2] or intermediate[3] has shown broad synthetic utility. Propargylations utilizing a catalytic amount of a chiral source are limited to a Barbier type addition,[1d,e,4] or asymmetric Lewis acid or base catalysis with a metalloallene reagent.[5,6] Recently, we reported the zinc catalyzed propargylation of aldehydes with a propargyl borolane based on a B/Zn exchange mechanism.[7] However, propargylations with allenyl-zinc species with chiral amino-alcohol ligands were shown to proceed with only modest enantioselectivity.[8] Alternatively, if a copper alkoxide catalyst is able to promote this mechanism, then a chiral phosphine ligand could be utilized to effect asymmetric induction. Herein, we report the discovery of a highly enantioselective and site selective copper alkoxide catalyzed propargylation of aldehydes with a propargyl borolane.

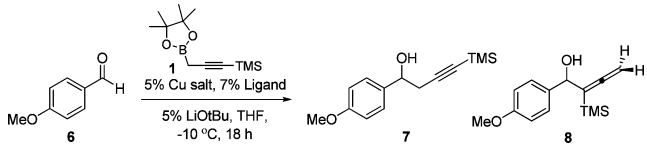
The proposed catalytic cycle is based on a Cu-alkoxide mediated B/Cu exchange with the propargyl borolane **1** to generate an allenyl Cu intermediate **3** (Scheme 1). After propargylation of an aldehyde,

Scheme 1. Proposed Mechanism for a Cu Catalyzed Propargylation of Aldehydes with a Propargyl Borolane



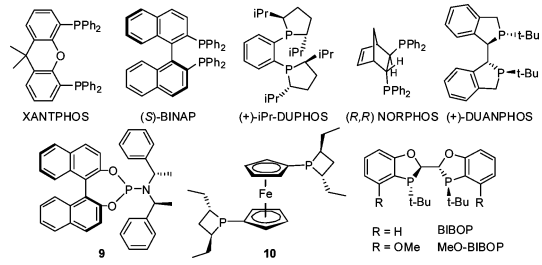
a Cu-alkoxide species would be regenerated, and a catalytic cycle would be established. The two key operations in this catalytic cycle have been separately demonstrated in an analogous B/Cu exchange with an allyl borolane reagent[9] and propargylation with an allenyl copper species.[3b] Consistent with this model, a slow background reaction between the parent aldehyde **6** and the borolane reagent **1** was observed with or without a catalytic copper halide catalyst. Based on the previously shown B/Cu exchange with a Cu(I) alkoxide complex,[9b,10] the use of catalytic Cu(I)-*tert*-butoxide was attempted which rapidly promoted the propargylation of *p*-anisaldehyde with moderate site selectivity for the alkynyl over the allenyl product (Table 1). The use of phosphine ligands dramatically improves the site selectivity for the homopropargylic alcohol, and an enantioselective reaction was achieved by utilizing our recently disclosed air stable BIBOP ligands.[11] Variation of the copper

Table 1. Optimization of the Cu Catalyzed Propargylation[a]



entry	Cu salt	ligand	conv.[b]	**7**:**8**.[c]	[ee][d]
1[e,f]	none	none	31%	1: 2	–
2[e]	CuCl	none	51%	3: 1	–
3	CuCl	none	100%	4:1	–
4	CuCl	XANTPHOS	100%	>100:1	–
5	CuCl	BINAP	100%	2:1	26%
6	CuCl	*i*Pr-DUPHOS	100%	3:1	2%
7	CuCl	NORPHOS	100%	36:1	20%
8	CuCl	DUANPHOS	100%	21:1	40%
9	CuCl	**9**	100%	55:1	34%
10	CuCl	**10**	100%	12:1	63%
11[g]	CuCl	BIBOP	100%	93:1	82%
12[g]	$Cu(OAc)_2H_2O$	BIBOP	100%	87:1	88%
13[g]	$Cu(isobutyrate)_2$	BIBOP	100%	86:1	89%
14[g]	$Cu(isobutyrate)_2$	MeO-BIBOP	100%[h]	49:1	98%

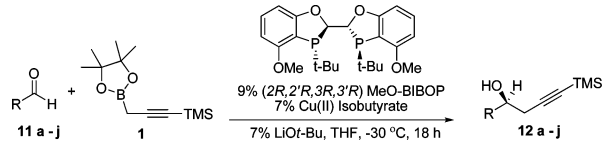
[a] 1.5 equiv of **1**. [b] Molar conversion. [c] Site selectivity between **7** and **8**. [d] Absolute enantiomeric excess determined by chiralcel OJ-H HPLC. [e] No LiO*t*Bu. [f] 20 °C. [g] Reactions conducted at −30 °C with 7% Cu salt, 9% ligand, and 7% LiO*t*Bu. [h] 97% Isolated yield. See Supporting Information for detailed optimization tables and ligand screen.

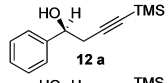
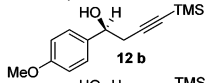
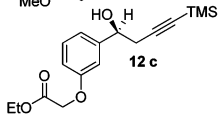
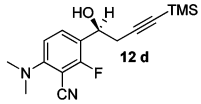
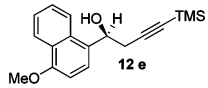
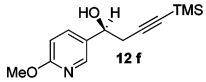
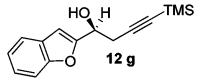
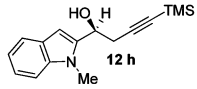
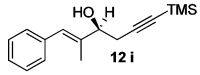
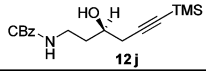


precatalyst moderately improved the enantioselectivity. A more pronounced effect on the enantioselectivity was observed when the methoxy derivative (MeO-BIBOP) of the parent BIBOP ligand was employed.

After establishing highly enantioselective conditions, the scope of the copper catalyzed asymmetric propargylation was examined (Table 2). High enantioselectivities (93−99% ee) and yields were achieved for aromatic and alkenyl aldehydes. Only a slight decrease in enantioselectivity (90% ee) was observed for the aliphatic aldehyde (entry 10). The method demonstrated good tolerance toward numerous functional groups. For example, esters, nitriles, an aryl fluoride, and a carbamate showed no impact on the asymmetric propargylation. Heterocycles and substrates bearing a Lewis basic functional group that have the potential to coordinate to Lewis acidic metals were also

Table 2. Substrate Scope for the Asymmetric Propargylation[a]



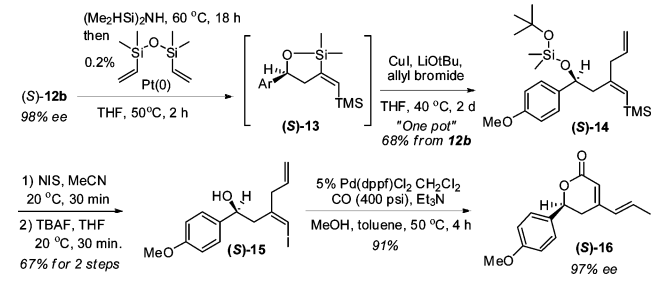
entry	product	yield[b]	ee[c]
1	 **12 a**	99%	**97%**
2	 **12 b**	97%	**98%**
3	 **12 c**	95%	**99%**
4	 **12 d**	94%	**96%**
5	 **12 e**	98%	**97%**
6	 **12 f**	93%	**97%**
7	 **12 g**	77%	**93%**
8	 **12 h**	86%	**97%**
9[d]	 **12 i**	96%	**97%**
10	 **12 j**	95%	**90%**

[a] 1.5 equiv of **1**. [b] Isolated yields. [c] Enantiomeric excess determined by chiralcel OJ-H, OD-H, or chiralpak AD-H HPLC. [d] Reaction performed at −30 to 0 °C for 48 h. See Supporting Information for determination of absolute configuration.

tolerated. The more sterically demanding α-methyl cinnamaldehyde (entry 9) required a slightly higher temperature (0 °C) for complete conversion but also proceeded in high enantioselectivity and yield.

Typically, the terminal trimethylsilyl substituent of alkynes is utilized as a protecting group which after deprotection provides access for further derivatization.[1] In addition to this utility, this silyl substituent can also provide a useful synthetic handle.[1c,12] For example, utilization of this functional group within chiral trimethylsilyl homopropargylic alcohols provides a convenient avenue for the preparation of synthetically useful dihydropyranones (Scheme 2). Hydroxy directed hydrosilylation of homopropargylic alcohol **12b** with Karstedt's catalyst utilizing Denmark and Pan's conditions[13] *in situ* provided siloxane **13** which when subjected to alkylation with Takada and co-workers' procedure[14] furnished the Z-vinyl silane **14** in reasonable yield. *Ipso*-substitution[15] of vinyl silane **14** with NIS stereospecifically afforded the vinyl iodide **15** after deprotection. Palladium catalyzed carbonylation of the vinyl iodide **15** proceeded with olefin isomerization to provide dihydropyranone **16** in excellent yield without racemization.

Scheme 2. Application toward the Synthesis of Chiral Dihydropyranone **16**



In conclusion, the highly enantioselective copper catalyzed propargylation of aldehydes with a propargyl borolane reagent provides an operationally simple method for the preparation of synthetically useful chiral homopropargylic alcohols.

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

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JA103312X