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Catalytic Enantioselective Alkynylation of Prochiral sp^3 C–H Bonds Adjacent to a Nitrogen Atom

Zhiping Li and Chao-Jun Li*

Department of Chemistry, McGill University, 801 Sherbrooke Street West, Montreal, Quebec H3A 2K6, Canada

cj.li@mcgill.ca

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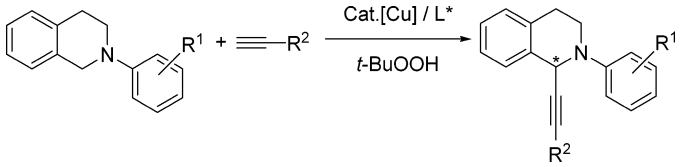
ABSTRACT

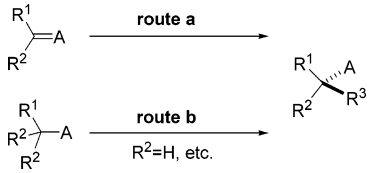


The construction of chiral carbon centers via the first catalytic asymmetric alkynylation of prochiral CH_2 groups was developed by using a copper-catalyzed double activation of sp^3 and sp C–H bonds. Optically active 1-alkynylated tetrahydroisoquinolines were obtained by this method.

C−C bond formation via C−H bond activation is one of the most challenging reactions in organic synthesis and has attracted great interest.[1] Enantioselective catalytic C−C bond formation via C−H bond activation will have a great impact on asymmetric synthesis both conceptually and practically. From the asymmetric synthetic concept point of view, a prochiral sp^2 carbon center is generally necessary as a precursor for constructing a chiral carbon center (Scheme 1, route a). This is because most asymmetric syntheses are based on the reaction of double bonds (prochiral faces) being converted into chiral carbon centers. Recently, important progress has been made in the asymmetric C−C bond formations based on the addition of various C−H bonds to prochiral double bonds.[2] On the other hand, an even bigger challenge is to achieve enantioselective C−C bond formations based on activation of sp^3 C−H bonds of prochiral CH_2 groups (Scheme 1, route b). Davies recently reported excellent examples of catalytic asymmetric insertions of diazo compounds into sp^3 C−H of acyclic[3a] and cyclic[3c] amines as well as sp^3 C−H of alkanes and tetrahydrofuran insertion into rhodium carbenoids.[3b]

Recently, we reported a Cu-catalyzed alkynylation of sp^3 C−H bonds adjacent to a nitrogen atom (Scheme 2).[4] This reaction provides a simple and effective catalytic method to construct proparylamines by using copper bromide and ^{t}BuOOH via a combination of sp^3 C−H bond and sp C−H bond activations followed by C−C bond formation. The success of this new reaction opens an opportunity to achieve catalytic asymmetric C−C bond formations based on reaction of sp^3 C−H bonds of prochiral CH_2 groups.

Scheme 1. Methods for Constructing Chiral Carbon Centers



(1) For representative reviews, see: (a) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (b) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633. (c) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698. (d) Shilov, A. E.; Shul′pin, G. B. *Chem. Rev.* **1997**, *97*, 2879. (e) Arndtsen, B. A.; Bergman, R. G.; Mobley, T. A.; Peterson, T. H. *Acc. Chem. Res.* **1995**, *28*, 154.

(2) For asymmteric addition of aryl C−H bond, see: Thalji, R. K.; Ellman, J. A.; Bergman, R. G. *J. Am. Chem. Soc.* **2004**, *126*, 7192 and references therein. For asymmetric addition of alkynyl C−H bonds, see: Wei, C.; Li, Z.; Li, C.-J. *Synlett* **2004**, 1472. For asymmetric aldol-type addition, see: (a) Palomo, C.; Oiarbide, M.; Garcia, J. M. *Chem. Soc. Rev.* **2004**, *33*, 65. (b) Trost, B. M.; Fettes, A.; Shireman, B. T. *J. Am. Chem. Soc.* **2004**, *126*, 2660. (c) Ooi, T.; Kameda, M.; Taniguchi, M.; Maruoka, K. *J. Am. Chem. Soc.* **2004**, *126*, 9685 and references therein.

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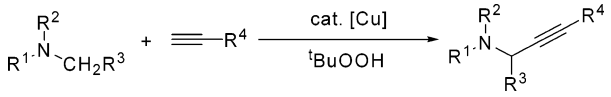
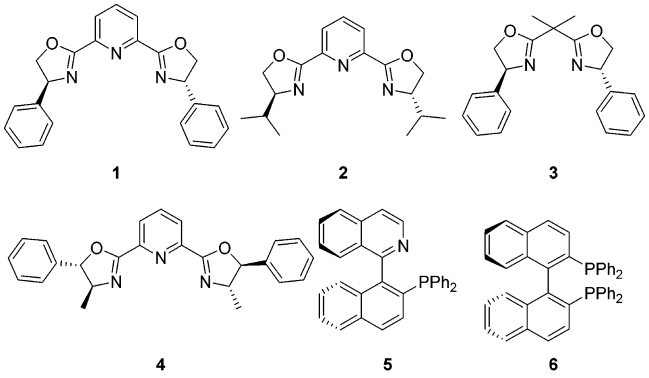
Scheme 2. Cu(I)-Catalyzed Alknylation of sp^3 C−H Bonds



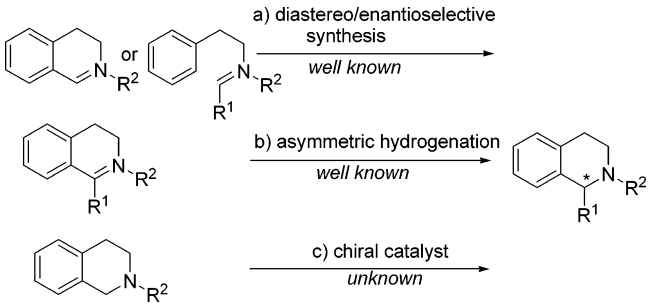
Tetrahydroisoquinoline alkaloids with a stereocenter at C-1 carbons exist widely in nature and are compounds of extensive interest due to their biological and pharmacological properties. Various methodologies have been developed to construct this stereogenic center.[5] The main synthetic strategies are diastereoselective and enantioselective nucleophilic addition and Friedel−Crafts reaction (Scheme 3, route a) and asymmetric hydrogenation (Scheme 3, route b) of acyclic or cyclic imines or iminium intermediates, including Pictet−Spengler reaction, Bischler−Napieralski reaction, and Pomeranz−Frisch reaction.[5a] Recently, Jacobsen and Taylor reported asymmetric catalysis of the acyl-Pictet−Spengler reaction by using chiral thiourea derivatives with electron-rich indoles.[6] Although these methods have provided optically active C-1-substituted tetrahydroisoquinoline derivatives, a more direct and simpler synthetic method is still highly attractive. Herein, we wish to report the development of a novel catalytic asymmetric 1-alkynylation of tetrahydroisoquinoline derivetives via the activation of sp^3 C−H bonds of prochiral CH_2 (Scheme 3, route c), leading to optically active C-1-substituted tetrahydroisoquinoline derivatives directly.

To begin our study, various copper salts and chiral compounds **1**−**6** as ligands were examined under different conditions, and the results are summarized in Table 1.



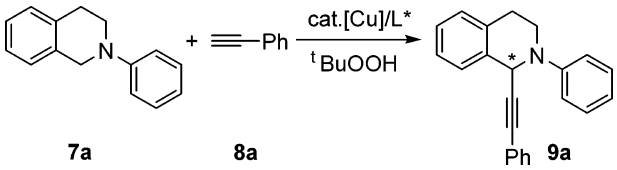
Using ligand **1**[7] as the standard, both Cu(I) and Cu(II) were found to be effective as the catalysts; however, slightly higher enantioselectivities were observed with Cu(I) catalysts (Table 1, entries 6, 8−10). The use of Cu(OTf) provided better

Scheme 3. Asymmetric Strategies to C_1-Substituted Tetrahydroisoquinolines



enantioselectivities than CuBr. The lowering of the reaction temperature is beneficial to the reaction. Various solvents can be used and the best enantioselectivity was obtained by using THF as solvent (Table 1, entries 3−7). The catalytic asymmetric alkynylation also proceeds in water or without solvent, both the yields and the enantioselectivities were decreased (Table 1, entries 1 and 5). Knochel and co-workers reported enantioselective syntheses of propargylamines in the presence of CuBr, (*R*)-Quinap, and 4 Å molecular sieves in both good yields and enantioselectivities.[8] However, chiral

Table 1. Effect of Conditions on the Enantioselectivity of Coupling of *N*-Benzene Tetrahydroisoquinoline with Phenylacetylene via sp^3 C−H Bond Activation[a]



7a **8a** **9a**

entry	catalyst	ligand	temp (°C)	solvent[b]	ee[c] (%)
1	CuOTf	**1**	80	no	19
2	CuOTf	**1**	80	toluene	21
3	CuOTf	**1**	50	toluene	42
4	CuOTf	**1**	50	1,2-dichloroethane	20
5	CuOTf	**1**	50	H_2O	18
6	CuOTf	**1**	50	1,4-dioxane	50
7	CuOTf	**1**	50	THF	56
8	CuBr	**1**	50	1,4-dioxane	18
9	$CuBr_2$	**1**	50	1,4-dioxane	12
10	$Cu(OTf)_2$	**1**	50	1,4-dioxane	40
11	CuOTf	**2**	50	dichloromethane	9
12	CuOTf	**3**	50	THF	14
13	CuOTf	**4**	50	THF	13
14	CuOTf	**5**	50	THF	20
15	CuBr	**5**	50	THF	4
16	CuOTf	**6**	50	THF	8
17	**CuOTf**	**1**	**50**	**THF**	**63**[d]

[a] 0.1 mmol of tetrahydroisoquinoline, 0.1 mmol of phenylacetylene, 0.01 mmol of copper salt, 0.015 mmol of ligand, and 0.1 mmol of ^{t}BuOOH (5−6 M in decane); reaction time is 2 days. [b] Solvents were used without distillation, except THF was distilled from sodium. [c] Enantiomeric excess was determined with HPLC by using a Chiralcel OD-H column and 95/5 hexane/isopropyl alcohol as eluent or 100 hexane. [d] Ca. 50 mg of 4 Å molecular sieves was used.

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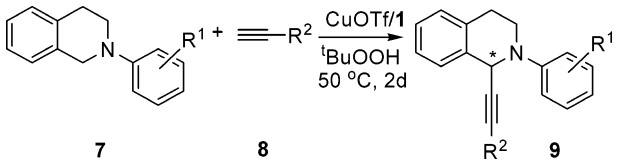
Table 2. Enantioselectivity of Coupling of Tetrahydroisoquinolines with Terminal Alkynes[a]



7 8 9

entry	R^1	R^2	compd	yield[b] (%)	ee[c] (%)
1	H	Ph	**9a**	67	63
2	H	4-MeOPh	**9b**	65	41
3	H	4-BrPh	**9c**	72	64
4	H	Hex	**9d**	65	26
5	H	TMS	**9e**	11	30
6	4-MeO	Ph	**9f**	59	60
7	4-MeO	Hex	**9g**	48	5
8	2-MeO	Ph	**9h**	54	73
9	2-MeO	4-MeOPh	**9i**	56	69
10	2-MeO	4-BrPh	**9j**	61	74
11	2-MeO	Py	**9k**	57	36

[a] 0.4 mmol of tetrahydroisoquinoline, 0.2 mmol of alkyne, 0.02 mmol of copper salt, 0.03 mmol of ligand, and 0.2 mmol of ^{t}BuOOH (5−6 M in decane). [b] Isolated yields were based on alkynes. [c] Enantiomeric excess was determined with HPLC by using a chiralcel OD-H column and 95/5 hexane/isopropyl alcohol or 100 hexane as eluent.

Quinap **4** is a less effective ligand in our reactions (Table 1, entries 14 and 15). Other ligands, ratios of catalysts and chiral ligands, and the amount of catalyst/ligand were also examined.[9]

Subsequently, a variety of substrates were examined by using the combination of Cu(I)OTf/**1** as the chiral catalyst (Table 2). For aromatic substituted alkynes, reactions usually provided both good yields and enantiomeric excesses. Electron-withdrawing groups or electron-donationg group R^2 on the aryl ring did not substantially influence the isolated yields and enantioselectivities of the desirable products (Table 2, entries 2 and 3 as well as entries 8−10). For aliphatic substituted alkynes, fair or low enantiomeric excesses were obtained (Table 2, entries 4, 5, and 7). Studies showed that the 4-substituted methoxy group on aryl ring (R^1) did not influence the enantioselectivity of the reaction (Table 2, entry 6). Interestingly, the presence of an *o*-methoxy substitutent group on aryl ring (R^1) did improve the enantiomeric excess up to 74% (Table 2, entry 10). The enhanced enantioselectivity is most likely due to the coordination of the oxygen in the *o*-methoxy substituent to copper or the steric effect of the ortho substituent on aryl ring.[10] In addition, these methoxy-substituted aryls can be removed readily.[11] The details of factors influencing the enantioselectivities of the reaction are under investigation and will be reported in due course.

In summary, the first enantioselective catalytic method for the coupling terminal alkynes with sp^3 C−H bonds of prochiral CH_2 group was developed. Biologically important chiral tetrahydroisoquinoline alkaloids were obtained by this novel asymmetric method. Application of this methodology in the synthesis of biologically active tetrahydroisoquinoline alkaloids is currently in progress.

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Supporting Information Available: Representative experimental procedure and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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