

Green chemistry: The development of cross-dehydrogenative coupling (CDC) for chemical synthesis*

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Abstract: Social, economic, and environmental concerns about chemical production have been increasing. These concerns all originate from the inefficiency of conventional chemical syntheses. On the basis of the “E-factor”, a concept of the “extended E-factor” is proposed in the article and is used to correlate various industrial sectors and the average number of synthetic steps involved in those sectors. Based on this analysis, the most fundamental way to eliminate waste formation is to develop new chemical reactivity that can greatly shorten the steps involved in a chemical synthesis. In classical organic transformations, a “functional group” is required. In efforts to develop new chemical reactivities that do not need extra steps for generating functional groups, we have recently developed various cross-dehydrogenative coupling (CDC) methodologies to construct functional molecules by directly using C–H bonds. This article describes the progress of our group’s research endeavor.

Keywords: green chemistry; E-factor; extended E-factor; C–C bond reaction; transition-metal-catalyzed; cross-coupling reactions; functional group chemistry.

INTRODUCTION

Over the past two centuries, the fundamental theories and reactivities in chemistry have been soundly established. Such theories and reactivities provided the foundation for the chemical enterprise that meets critical living needs such as food for the world populations, achieves various medical wonders that save millions of lives and improve people’s health, and produces essential material needs for modern life and the future needs of mankind. Just less than two centuries ago, organic compounds were believed to be accessible only through biological processes under the influence of “vital forces” [1], currently, molecules with great complexities can be synthesized readily. The total syntheses of natural products such as vitamin B₁₂ [2] and palytoxin [3] in the laboratory represent achievements comparable to the construction of the Great Pyramids.

Unfortunately, the great scientific and economic achievements of the modern era came with a price. The depletion of ozone in the stratospheric layer; the extinction of bio-species; the deterioration of water, air, and soil quality; the alarming global climate changes, combined with the fast-growing population and the rapid depletion of natural resources result in an unsustainable future for the planet Earth. Traditionally, environmental science has played the pivotal role in detecting environmental problems and finding ways to remediate them. Environmental policies have been surrounded by enforcing regu-

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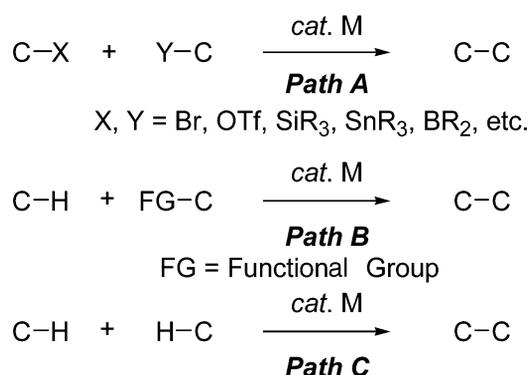
lations on the amount of pollutant emissions. The recent development of “green chemistry” [4] aims at developing fundamentally new and improved theories and chemical reactivities that can potentially achieve the same goal of economic development, whereas at the same time make chemicals (and materials) and processes inherently safer, cleaner, and cheaper. The concepts of atom-economy [5], ideal synthesis [6], and E-factor [7], together with the utilization of benign solvents such as water [8], CO₂ [9], and ionic liquids [10], provide the pillars of greener approaches for chemical synthesis. Among them, the E-factor elegantly shows the relative amount of total wastes generated per kg of the desired product among various industry sectors. As a first approximation [11], the differences between these industrial sectors are the number of chemical transformation steps involved. Taking this into consideration, an “extended E-factor” is showing in Table 1 [12]. Based on this analysis, the most fundamental and dramatic way to eliminate waste formation is to develop new chemical reactivity that can greatly shorten the steps involved in a chemical synthesis.

Table 1 Extended E-factor.^a

Industry segment	Product tonnage	Ratio kg by-product/kg product	# of steps <i>n</i>	Ratio/10 ^{<i>n</i>-1}
Oil refining	10 ⁶ –10 ⁸	ca. 0.1	1	0.1
Bulk chemicals	10 ⁴ –10 ⁶	<1–5	2	0.1–0.5
Fine chemicals	10 ² –10 ⁴	5–50	3	0.05–0.5
Pharmaceuticals	10 ¹ –10 ³	25–100+	4+	0.25–0.1

^aModified based on Roger Sheldon’s E-factor table.

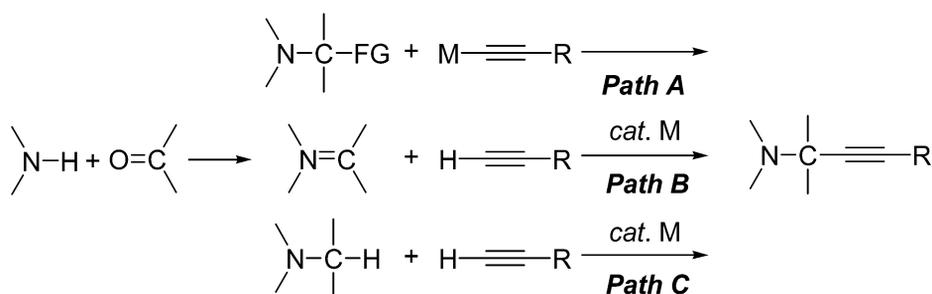
As a long-term objective of developing fundamentally new and challenging chemical reactivities toward green chemistry for chemical synthesis, we have focused on two aspects: (1) the development of C–C bond reactions in aqueous media that can potentially simplify protection and deprotection of functional groups incompatible to classical reactions; (2) the direct utilization of C–H bonds for C–C bond formations. In the realm of C–C bond formation reactions, transition-metal-catalyzed cross-coupling reactions of various reactive functional groups are newer and more powerful methods for the formation of C–C bonds (Scheme 1, path A) [13]. However, these well-developed cross-coupling reactions must use prefunctionalized starting materials. Therefore, for the formation of a single chemical bond, an extra step(s) is required to prepare the functionalized starting material from a raw material. Accordingly, transition-metal-catalyzed C–H bond activation and subsequent C–C bond formations have attracted much interest in recent years (Scheme 1, path B) [14]. Unfortunately, these reactions often still require a functionalized molecule to generate the desired cross-coupling product. On the basis of this progress, we questioned: Can we go beyond the current *functional group chemistry*? To explore such a possibility, we focused our attention on developing a cross-dehydrogenative coupling (CDC) methodology to construct functional molecules by directly using C–H bonds (Scheme 1, path C) [15]. Such a coupling will avoid the preparation of functional groups and thus make synthetic schemes shorter and more efficient, a highly desirable synthetic procedure for the next generation’s C–C bond formations [16]. Herein, we would like to present our progress and accomplishments.



Scheme 1 Various cross-coupling methods for the formation of C–C bonds.

CDC REACTIONS BETWEEN SP³ C–H AND SP C–H [15e]

As a start toward our objective, we first chose propargylic amines as our synthetic target. Propargylic amines are of great pharmaceutical interest and are synthetic intermediates for various nitrogen compounds [17]. Two main methods have been used to construct propargylic amines (Scheme 2): Path A is the stoichiometric nucleophilic reactions [18], and path B is the transition-metal-catalyzed reactions of alkynes and imines generated from aldehydes and amines. There are many excellent examples of these two methods. For examples, we [19] and others [20] have described the direct addition of a terminal alkyne to aldehyde and imines to afford propargyl alcohols and propargyl amines. With Cu(I)-pybox as a chiral catalyst, we developed a highly enantioselective imine addition in either water or toluene [21]. We also developed the coupling of alkynes with *N*-acylimines and *N*-acyliminium ions by a CuBr catalyst, and the gold- or silver-catalyzed coupling reaction of alkyne, aldehyde, and amine in water [22]. Although they are effective, these methods need a leaving group or imines formed from aldehyde and amine. With the development of more efficient methods in mind, our research objective was centered on directly constructing propargylic amines by the catalytic coupling of sp³ C–H adjacent to nitrogen with a terminal alkyne (path C) [15e].

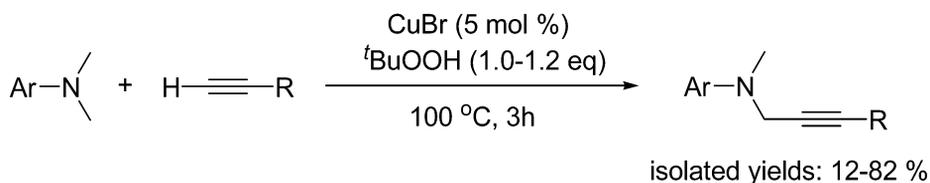


Scheme 2 Various methods for forming propargylamines.

To achieve this challenge, we used *N,N*-dimethylaniline and phenylacetylene as standard starting materials to find the optimal reaction conditions. Because a hydrogen acceptor is an essential reagent in this oxidative cross-coupling reaction, we chose O₂, H₂O₂, and some peroxides as the oxidant. To achieve this cross-coupling reaction, transition-metal catalysts are also important. There are two main reasons for this: (a) transition-metal catalysts usually efficiently promote cross-coupling reactions; and (b) they are required as an oxidant activator. We found that the desired product was obtained in good

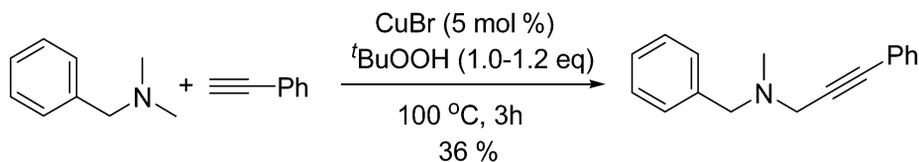
yield with the combination of a copper catalyst and *tert*-butyl hydroperoxide (TBHP). Thus, various copper salts were examined as catalysts for the alkylation of *N,N*-dimethylaniline. CuBr, CuBr₂, CuCl, and CuCl₂ proved to be most effective catalysts. No reaction was observed in the absence of a copper catalyst. To improve the yields, various ratios of *N,N*-dimethylaniline and alkynes as well as TBHP were examined. The best yield was obtained when the *N,N*-dimethylaniline:alkynes:TBHP ratio is 2:1:1. Based on the NMR spectrum of the crude reaction mixture, nearly 1 equiv of *N,N*-dimethylaniline remained after the reaction was completed. When the amount of *N,N*-dimethylaniline was reduced, however, the yields decreased. The yields were markedly decreased when the amount of TBHP was reduced to 0.5 and 0.25 equiv. The reaction did not proceed without TBHP either.

With the optimized reaction conditions in hand, various alkynes were reacted with amines (Scheme 3). Representative examples are shown in Scheme 3. The reaction of *N,N*-dimethylaniline (2 equiv) with phenylacetylene in the presence of a CuBr catalyst (5 mol %) and TBHP (1.0 equiv) at 100 °C for 3 h gave *N*-methyl-*N*-(3-phenylprop-2-ynyl)benzenamine in 74 % isolated yield. For aromatic alkynes, the reaction often provided good yields of the desired products. For aliphatic alkynes, the corresponding products were formed in lower yields. The reactions were found to tolerate functional groups such as alcohol and ester.

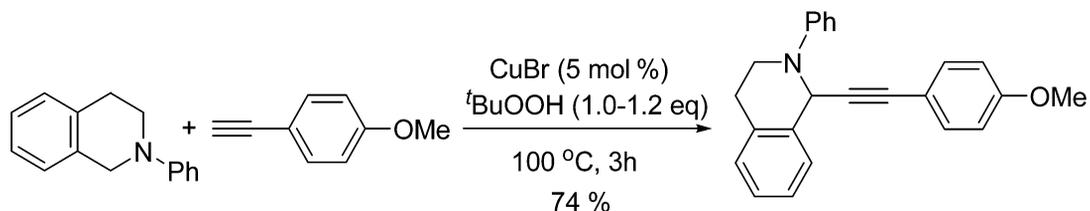


Scheme 3 Copper-catalyzed alkylation of amines.

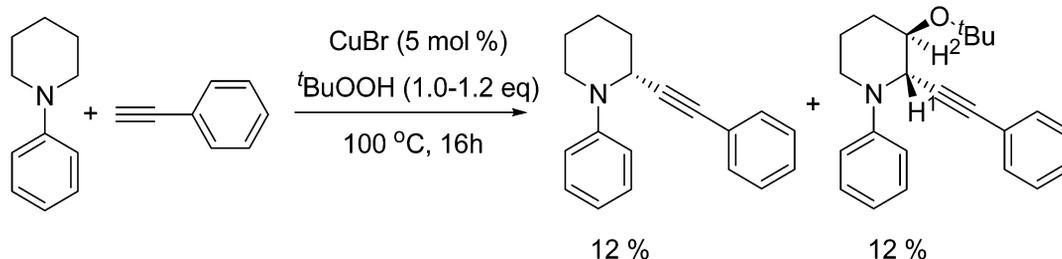
When benzyldimethylamine was reacted with phenylacetylene under the standard conditions, alkylation of the methyl group was the main product (Scheme 4). The minor product could not be isolated. Cyclic amines such as tetrahydroisoquinoline can be selectively converted into the corresponding C1-alkynylation compound in 74 % isolated yield (Scheme 5). 1-Phenyl-piperidine reacted with phenylacetylene in the presence of a catalytic amount of CuBr and 1 equiv of TBHP to give the desired direct alkylation product in 12 % yield together with a *tert*-butyloxy alkylation compound (12 %) (Scheme 6).



Scheme 4 Reaction of *N,N*-dimethylbenzylamine.



Scheme 5 Reaction of cyclic benzylamine.

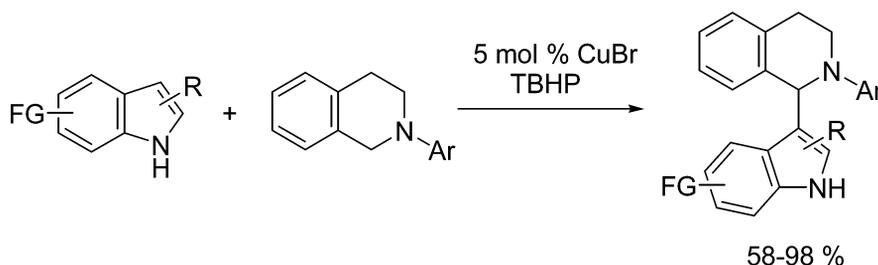


Scheme 6 Reaction of simple cyclic amine.

CDC REACTIONS BETWEEN SP³ C–H AND SP² C–H [15b]

Indoles and tetrahydroquinolines are common substructural units in natural products [23]. There are two main methods to synthesize indolyl tetrahydroisoquinolines: (1) the reactions of indoles with cotarnine [24]; and (2) the reactions of *N*-imidolylcycloimmonium salts with indoles followed by a catalytic hydrogenation [25]. However, these methods require multistep synthesis to generate the starting materials. To address this challenge as well as to extend the scope of CDC methodology, we decided to examine the synthesis of such alkaloids by directly using free (NH)-indoles and tetrahydroisoquinolines [26]. The desired product was successfully obtained when tetrahydroisoquinoline reacted with indole under our CuBr/TBHP system. The reaction was not sensitive to moisture and air. Even when the reaction was carried out in water under an atmosphere of air, the desired product was obtained in reasonable yield. The yield was improved when the temperature was raised to 50 °C. Using slightly excess amounts of **2a** and TBHP provided the best results.

Under the optimized reaction conditions, various indoles were reacted with tetrahydroisoquinolines. The desired products were formed in good to excellent yields (Scheme 7). The reactions selectively occurred at C3 position of indoles, if both C2 and C3 positions of indoles are unoccupied. When the C3 position of indoles is substituted, the C2-substituted products were obtained. Indoles with electron-withdrawing or -donating groups also worked well under present reaction conditions.



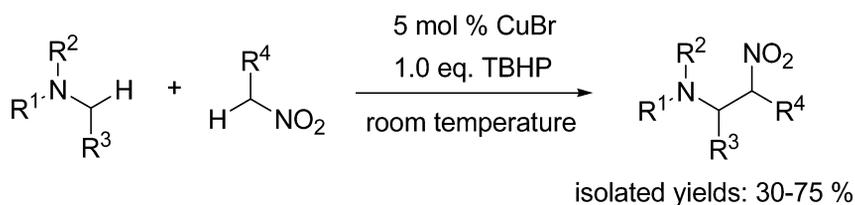
Scheme 7 CDC reactions of various indoles with tetrahydroisoquinolines.

CDC REACTIONS BETWEEN SP³ C–H AND SP³ C–H [15a,c]

With the success of the CDC reactions between sp³ C–H and sp C–H, as well as between sp³ C–H and sp² C–H, the next challenge for us is the CDC reactions of sp³ C–H and sp³ C–H. Vicinal diamines are also important compounds in biologically active natural products in medicinal chemistry, and more recently (as a core unit) are used as chiral auxiliaries and chiral ligands in asymmetric catalyses [27]. An efficient approach toward such compounds is via the nitro-Mannich (aza-Henry) reaction.

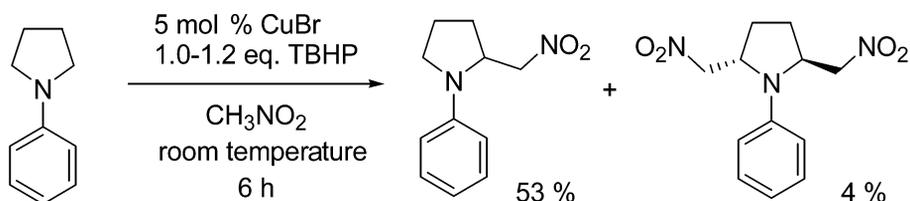
Our early efforts on this coupling were focused on the reaction of 1,2,3,4-tetrahydroisoquinoline with nitromethane, in which nitromethane was used as solvent. Various copper catalysts, such as CuCl,

CuBr, CuI, Cu(OTf), CuCl₂, CuBr₂, Cu(OTf)₂, and Cu(OAc)₂·H₂O, were examined under an ambient temperature, and the desired product was obtained in all cases. Again, CuBr was found to be the most effective catalyst. The desired product was obtained in over 90 % yield even when the amount of CuBr was reduced to 2 mol %. Under the optimized conditions, various β-nitroamine derivatives were generated by this new methodology (Scheme 8). 1,2,3,4-Tetrahydroisoquinoline derivatives and 4-substituted *N,N*-dimethylaniline gave excellent yields of the desired products based on NMR analysis of the reaction mixture. Moreover, when 1 equiv of nitromethane was used, the desired products were also obtained with good isolated yields (over 63 %). The use of nitroethane instead of nitromethane also gave the desired compounds with good isolated yields (the ratios of two diastereoisomers are 1.5-2:1). In the case of *N,N*-dimethylaniline, a low yield was obtained which was attributed to the formation of the demethylated compound and other unidentified by-products.



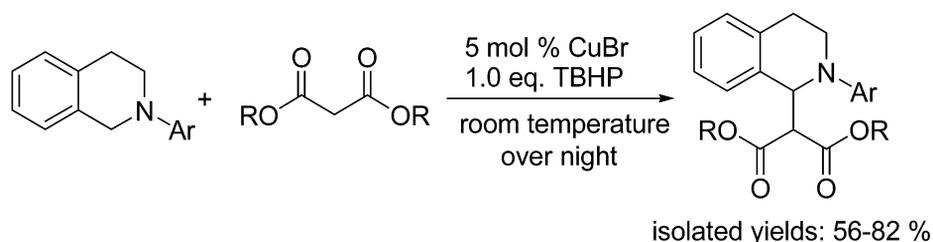
Scheme 8 CDC reactions of tertiary amines with nitroalkanes.

Other cyclic amines such as 1-phenyl-pyrrolidine also generated the desired product in good yield (Scheme 9). In this case, bis-CDC product is also formed in 4 % isolated yield along with the mono-CDC product.



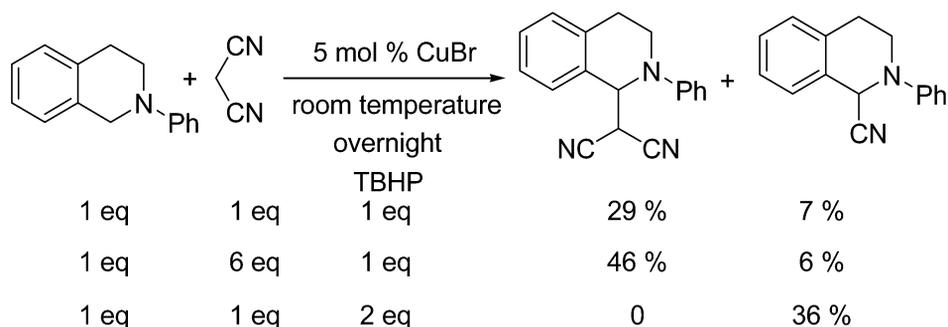
Scheme 9 Reaction of 1-phenyl-pyrrolidine with nitromethane.

Accordingly, various β-diester amine derivatives were obtained when stoichiometric tetrahydroisoquinolines and dialkyl malonates were used with 5 mol % CuBr together with 1 equiv TBHP under room temperature (Scheme 10) [15a]. To further improve the high efficiency of this new methodology, 1 mmol scale of the reaction was carried out with 0.5 mol % CuBr as the catalyst. The desired product was obtained in 72 % isolated yield.



Scheme 10 CDC reaction of tetrahydroisoquinolines with malonates.

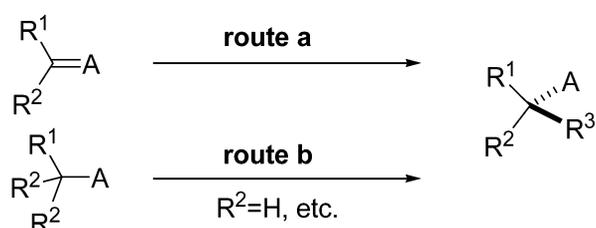
Next, we investigated the synthesis of β -dicyano tetrahydroisoquinolines by using malononitrile as the pronucleophile under the standard reaction conditions (Scheme 11). The desired product, β -dicyano tetrahydroisoquinoline, was obtained in 29 % isolated yield. Surprisingly, α -cyano product was also obtained as one of the unexpected by-products. The yield of β -cyano product was increased to 46 % along with 6 % of α -dicyano tetrahydroisoquinoline when 6 equiv of malononitrile were used. To form α -cyano product, ^-CN anion must be produced during the reaction. When excess TBHP (2 equiv of TBHP) was used, α -cyano product was obtained as the main product and β -dicyano tetrahydroisoquinoline was not observed by NMR.



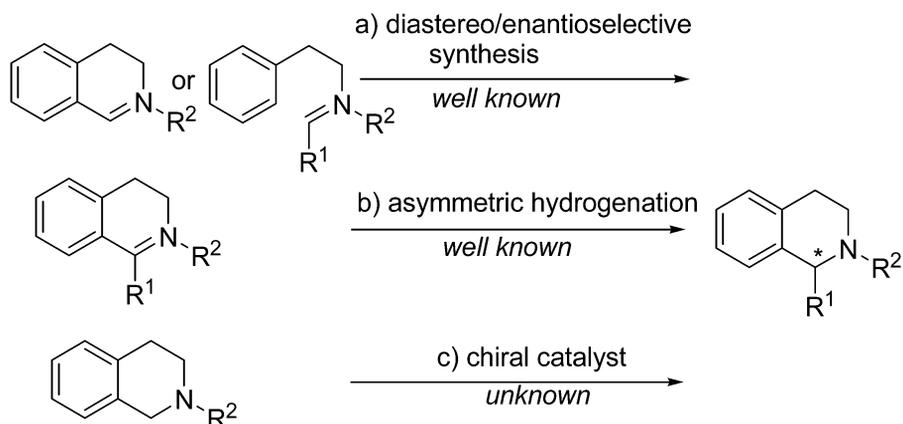
Scheme 11 CDC reaction of tetrahydroisoquinoline with malononitriles.

ASYMMETRIC CDC REACTIONS BETWEEN sp^3 C-H AND sp C-H [15d]

Enantioselective catalytic C–C bond formation has attracted much attention in both academic and industrial research. 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 12, route a). This is because most asymmetric syntheses are based on the reaction of double bonds (prochiral faces), being converted into chiral carbon centers. 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 recently [28]. 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 13, route b) [29]. With our first Cu-catalyzed alkylation of sp^3 C–H bonds adjacent to a nitrogen atom (Scheme 3) in hand [15e], it 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 12 Methods for constructing chiral carbon centers.



Scheme 13 Asymmetric strategies to C1-substituted tetrahydroisoquinolines.

Tetrahydroisoquinoline alkaloids with a stereocenter at C1 carbons exist widely in nature and are compounds of extensive interest owing to their biological and pharmacological properties. Various methodologies have been developed to construct this stereogenic center [30]. The main synthetic strategies are diastereoselective and enantioselective nucleophilic addition and Friedel–Crafts reaction (Scheme 13, route a) and asymmetric hydrogenation (Scheme 13, route b) of acyclic or cyclic imines or iminium intermediates, including Pictet–Spengler, Bischler–Napieralski, and Pomeranz–Frisch reactions. Although these methods have provided optically active C1-substituted tetrahydroisoquinoline derivatives, a more direct and simpler synthetic method (Scheme 13, route c) is still highly attractive.

Chiral bisoxazolines **1–4** [31] and QUINAP **5** and BINAP **6** were proved as good ligands in copper-catalyzed reactions in the literature. Therefore, various copper salts and chiral compounds **1–6** as ligands were examined under different conditions, such as different solvents and temperature. Ligand **1** was proved the best ligand in the reaction. Both Cu(I) and Cu(II) were found to be effective as the catalysts, however, slightly higher enantioselectivities were observed with Cu(I) catalysts. The use of Cu(OTf) provided better enantioselectivities than CuBr. The lowering of the reaction temperature (50 °C) is beneficial to the enantioselectivities. Various solvents can be used and the best enantioselectivity was obtained by using THF as solvent. The catalytic asymmetric alkylation also proceeds in water or without a solvent, both the yields and the enantioselectivities were decreased.

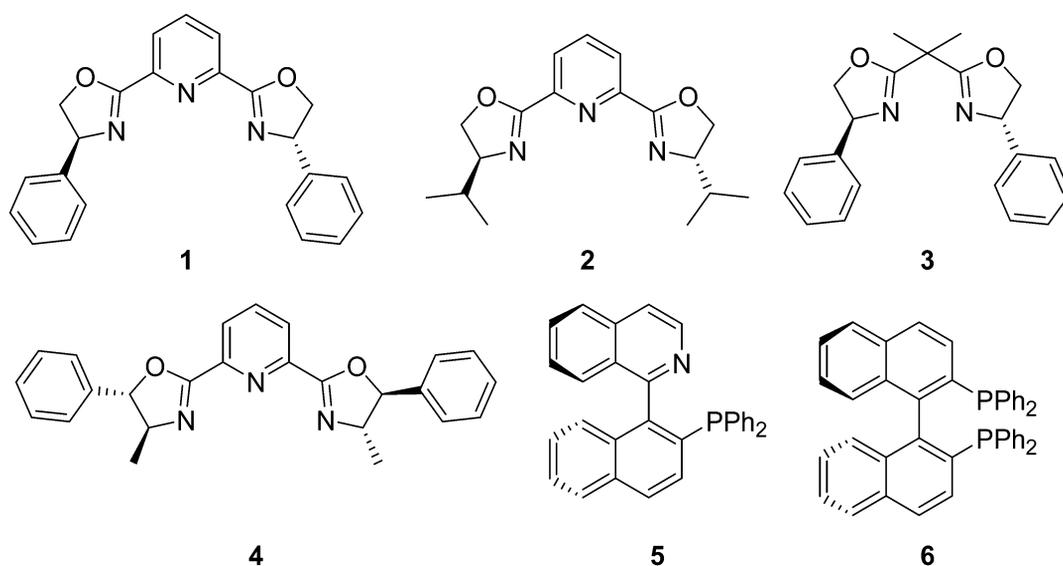
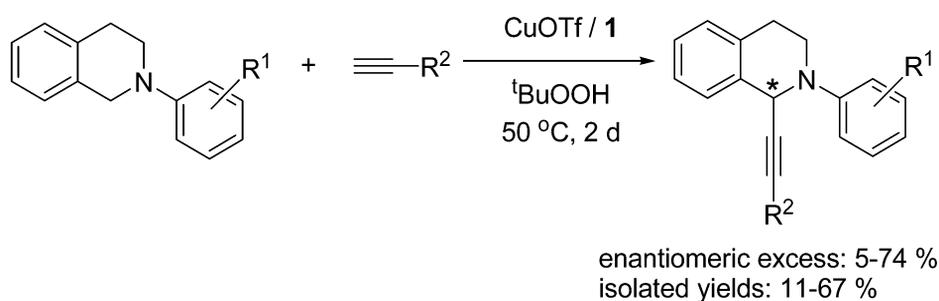


Fig. 1 Various chiral ligands.

Subsequently, a variety of substrates were examined by using the combination of Cu(I)OTf/**1** as the chiral catalyst (Scheme 14). For aromatic substituted alkynes, reactions usually provided both good yields and enantiomeric excesses. Electron-withdrawing groups or electron-donating group R^2 on aryl ring did not substantially influence the isolated yields and enantioselectivities of the desirable products. For aliphatic substituted alkynes, fair or low enantiomeric excess were obtained. Studies showed that the 4-substituted methoxy group on aryl ring R^1 did not influence the enantioselectivity of the reaction. Interestingly, the presence of an ortho methoxy substituent group on aryl ring (R^1) did improve the enantiomeric excess up to 74 %. The enhanced enantioselectivity is most likely due to the coordination of the oxygen in the ortho methoxy substituent to copper or the steric effect of the ortho substituent on the aryl ring.



Scheme 14 Enantioselectivity of coupling of tetrahydroisoquinolines with terminal alkynes.

CONCLUSION AND OUTLOOKS

As an effort to develop green chemistry for chemical synthesis, a new concept of cross-coupling reaction, CDC reaction, was established. Various nitrogen-containing compounds were obtained efficiently via CDC reactions under mild reaction conditions. The scope of such CDC reactions can be extended to other non-nitrogen systems [32]. Such reactions present the most direct and efficient synthetic meth-

ods of C–C bond formations and provide the pillar for the next generation of chemical synthesis with an eye on green chemistry.

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REFERENCES AND NOTES

1. P. Y. Bruce. *Organic Chemistry*, 4th ed., Pearson Education, Upper Saddle River, NJ (2004).
2. K. C. Nicolaou, E. J. Sorensen. *Classics in Total Synthesis*, VCH, Weinheim (1996).
3. R. W. Armstrong, J.-M. Beau, S. H. Cheon, W. J. Christ, H. Fujioka, W.-H. Ham, L. Hawkins, D. H. Jin, S. H. Kang, Y. Kishi, M. J. Martinelli, W. W. McWhorter Jr., M. Mizuno, M. Nakata, A. E. Stutz, F. X. Talamas, M. Taniguchi, J. A. Tino, K. Ueda, J. Uenishi, J. B. White, M. Yonaga. *J. Am. Chem. Soc.* **111**, 7530 (1989).
4. P. T. Anastas, J. C. Warner. *Green Chemistry Theory and Practice*, Oxford University Press, New York (1998).
5. (a) B. M. Trost. *Science* **254**, 1471 (1991); (b) B. M. Trost. *Angew. Chem., Int. Ed.* **34**, 259 (1995).
6. (a) P. A. Wender, S. T. Handy, D. L. Wright. *Chem. Ind.* 765 (1997); (b) P. A. Wender, B. L. Miller. In *Organic Synthesis: Theory and Applications*, T. Hudlicky (Ed.), p. 27, JAI Press, Greenwich, CT (1993).
7. R. A. Sheldon. *ChemTech* 38 (1994).
8. (a) C. J. Li. *Chem. Rev.* **93**, 2023 (1993); (b) C. J. Li, T. H. Chan. *Organic Reactions in Aqueous Media*, John Wiley, New York (1997); (c) P. A. Grieco (Ed.). *Synthesis in Water*, Thomson Science, Glasgow (1998); (d) C. J. Li. *Chem. Rev.* **105**, 3095 (2005).
9. P. G. Jessop, W. Leitner (Eds.). *Chemical Synthesis Using Supercritical Fluids*, Wiley-VCH, Weinheim (1999).
10. (a) P. Wasserscheid, T. Welton (Eds.). *Ionic Liquids in Synthesis*, Wiley-VCH, Weinheim (2002); (b) R. D. Rogers, K. R. Seddon (Eds.). *Ionic Liquids: Industrial Applications for Green Chemistry*, Oxford University Press, New York (2002); (c) P. Wasserscheid, W. Keim. *Angew. Chem., Int. Ed.* **39**, 3772 (2000).
11. The number of steps is based on an experience/impression of the authors regarding various industrial sectors.
12. First introduced in the C. J. Li's keynote speech at the Green Chemistry Symposium of the ACS Northern New Jersey Section, 13 June 2003.
13. F. Diederich, P. J. Stang (Eds.). *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH, New York (1998).
14. For representative reviews, see: (a) R. H. Crabtree. *J. Organomet. Chem.* **689**, 4083 (2004); (b) V. Ritleng, C. Sirlin, M. Pfeffer. *Chem. Rev.* **102**, 1731 (2002); (c) C. Jia, T. Kitamura, Y. Fujiwara. *Acc. Chem. Res.* **34**, 633 (2001); (d) G. Dyker. *Angew. Chem., Int. Ed.* **38**, 1698 (1999); (e) A. E. Shilov, G. B. Shul'pin. *Chem. Rev.* **97**, 2879 (1997); (f) B. A. Arndtsen, R. G. Bergman, T. A. Mobley, T. H. Peterson. *Acc. Chem. Res.* **28**, 154 (1995).
15. (a) Z. Li, C.-J. Li. *Eur. J. Org. Chem.* 3173 (2005); (b) Z. Li, C.-J. Li. *J. Am. Chem. Soc.* **127**, 6968 (2005); (c) Z. Li, C.-J. Li. *J. Am. Chem. Soc.* **127**, 3672 (2005); (d) Z. Li, C.-J. Li. *Org. Lett.* **6**, 4997 (2004); (e) Z. Li, C.-J. Li. *J. Am. Chem. Soc.* **126**, 11810 (2004).

16. For representative references, see: (a) sp^3 C–H and sp C–H: S.-I. Murahashi, N. Komiya, H. Terai, T. Nakae. *J. Am. Chem. Soc.* **125**, 15312 (2003); (b) sp^2 C–H and sp^2 C–H: Y. Hatamoto, S. Sakaguchi, Y. Ishii. *Org. Lett.* **6**, 4623 (2004); (c) T. Yokota, M. Tani, S. Sakaguchi, Y. Ishii. *J. Am. Chem. Soc.* **125**, 1476 (2003); (d) Z. Li, C.-J. Li. *J. Am. Chem. Soc.* **127**, 3672 (2005); (e) J. Tsuji, H. Nagashima. *Tetrahedron* **40**, 2699 (1984); (f) sp^2 C–H and sp^3 C–H: B. DeBoef, S. J. Pastine, D. Sames. *J. Am. Chem. Soc.* **126**, 6556 (2004); (g) sp C–H and sp C–H: K. C. Nicolaou, R. E. Zipkin, N. A. Petasis. *J. Am. Chem. Soc.* **104**, 5558 (1982).
17. H. Nakamura, T. Kamakura, M. Ishikura, J.-F. Biellmann. *J. Am. Chem. Soc.* **126**, 5958 (2004).
18. (a) T. Murai, Y. Mutoh, Y. Ohta, M. Murakami. *J. Am. Chem. Soc.* **126**, 5968 (2004); (b) J. H. Ahn, M. J. Joung, N. M. Yoon, D. C. Oniciu, A. R. Katritzky. *J. Org. Chem.* **64**, 488 (1999) and refs. therein.
19. (a) C. M. Wei, C.-J. Li. *Green Chem.* **4**, 39 (2002); (b) C. J. Li, C. M. Wei. *Chem. Commun.* 268 (2002); (c) Z. Li, C. Wei, L. Chen, R. S. Varma, C.-J. Li. *Tetrahedron Lett.* **45**, 2443 (2004); (d) X. Yao, C.-J. Li. *Org. Lett.* **7**, 4395 (2005); (e) C. Wei, C.-J. Li. *Lett. Org. Chem.* **2**, 410 (2005).
20. (a) R. Fassler, D. E. Frantz, J. Oetiker, E. M. Carreira. *Angew. Chem., Int. Ed.* **41**, 3054 (2002); (b) C. Fischer, E. M. Carreira. *Org. Lett.* **3**, 4319 (2001); (c) D. E. Frantz, R. Fassler, E. M. Carreira. *J. Am. Chem. Soc.* **121**, 11245 (1999); (d) M. Miura, M. Enna, K. Okuro, M. Nomura. *J. Org. Chem.* **60**, 4999 (1995).
21. (a) C. M. Wei, C.-J. Li. *J. Am. Chem. Soc.* **124**, 5638 (2002); (b) C. M. Wei, J. T. Mague, C.-J. Li. *Proc. Natl. Acad. Sci. (USA)* **101**, 5749 (2004); (c) C. Koradin, K. Polborn, P. Knochel. *Angew. Chem., Int. Ed.* **41**, 2535 (2002).
22. (a) CuBr: J. H. Zhang, C. M. Wei, C.-J. Li. *Tetrahedron Lett.* **43**, 5731 (2002); (b) Au: C. M. Wei, C.-J. Li. *J. Am. Chem. Soc.* **125**, 9584 (2003); (c) Ag: C. M. Wei, Z. Li, C.-J. Li. *Org. Lett.* **5**, 4473 (2003); (d) Y. Ju, C.-J. Li, R. S. Varma. *QSAR Comb. Sci.* **23**, 891 (2004); (e) Y. Luo, Z. Li, C.-J. Li. *Org. Lett.* **7**, 2675 (2005).
23. For a recent review, see: M. Somei, F. Yamada. *Nat. Prod. Rep.* **22**, 73 (2005).
24. K. A. Krasnov, V. G. Kartsev. *Russ. J. Org. Chem.* **38**, 430 (2002).
25. For a representative ref., see: R. P. Ryan, R. A. Hamby, Y.-H. Wu. *J. Org. Chem.* **40**, 724 (1975).
26. For representative refs., see: (a) R. D. Rieth, N. P. Mankad, E. Calimano, J. P. Sadighi. *Org. Lett.* **6**, 3981 (2004); (b) B. Sezen, D. Sames. *J. Am. Chem. Soc.* **125**, 5274 (2003); (c) B. Sezen, D. Sames. *Org. Lett.* **5**, 3607 (2003).
27. D. Lucet, T. Le Gall, C. Mioskowski. *Angew. Chem., Int. Ed.* **37**, 2580 (1998).
28. For asymmetric addition of aryl C–H bond, see: (a) R. K. Thalji, J. A. Ellman, R. G. Bergman. *J. Am. Chem. Soc.* **126**, 7193 (2004) and refs. therein; for asymmetric addition of alkynyl C–H bonds, see: (b) C. Wei, Z. Li, C.-J. Li. *Synlett* 1472 (2004); for asymmetric aldol-type addition, see: (c) C. Palomo, M. Oiarbide, J. M. Garcia. *Chem. Soc. Rev.* **33**, 65 (2004); (d) B. M. Trost, A. Fettes, B. T. Shireman. *J. Am. Chem. Soc.* **126**, 2660 (2004); (e) T. Ooi, M. Kameda, M. Taniguchi, K. Maruoka. *J. Am. Chem. Soc.* **126**, 9685 (2004) and refs. therein.
29. (a) H. M. L. Davies, C. Venkataramani. *Angew. Chem., Int. Ed.* **41**, 2197 (2002); (b) H. M. L. Davies, T. Hansen, M. R. Churchill. *J. Am. Chem. Soc.* **122**, 3063 (2000); (c) H. M. L. Davies, T. Hansen, D. W. Hopper, S. A. Panaro. *J. Am. Chem. Soc.* **121**, 6509 (1999).
30. (a) M. Chrzanowska, M. D. Rozwadowska. *Chem. Rev.* **104**, 3341 (2004); (b) K. W. Bentley. *Nat. Prod. Rep.* **21**, 395 (2004).
31. H. A. McManus, P. J. Guiry. *Chem. Rev.* **104**, 4151 (2004).
32. (a) Z. Li, C.-J. Li. *J. Am. Chem. Soc.* **128**, 56 (2006); (b) Y. H. Zhang, C.-J. Li. *Angew. Chem., Int. Ed.* **45**, 1949 (2006).