Highlight: Stereoselective Cross-Dehydrogenative Coupling Reactions Based on Sp^3 C—H Activation to Give Chiral Heterocyclic Compounds

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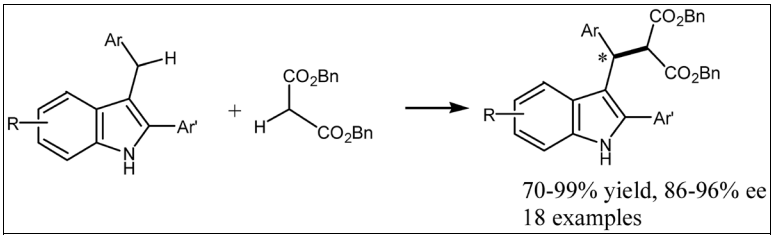

Stereoselective cross-dehydrogenative coupling (CDC) reactions based on sp^3 C—H activation for functionalization of heterocycles were introduced. It is an efficient, economical and convenient strategy for functionalization of heterocycles.

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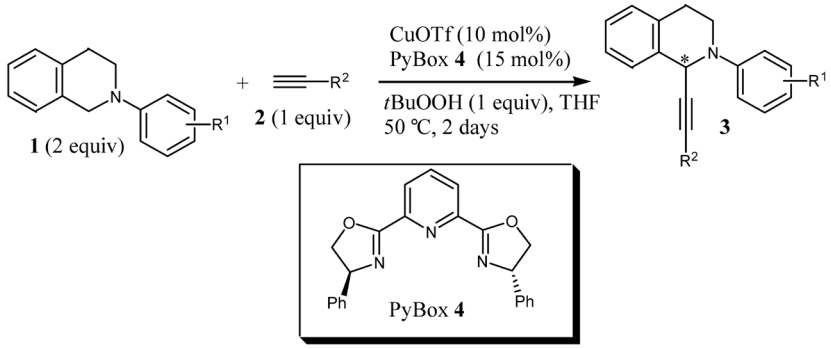
1. INTRODUCTION

Direct functionalization of C—H bonds has attracted much attention in chemistry field due to its many advantages [1(a–e)]. Cross-dehydrogenative coupling (CDC) reactions based on sp^3 C—H activation are gaining momentum, which allow the formation of new C—C bond from two different C—H bonds of readily available starting materials, provide shorter synthetic routes, release less wastes, and reduce cost [2(a,b)]. Many chiral heterocyclic compounds are prevalent in a variety of biologically active natural and non-natural compounds; stereocontrolled CDC reactions based on sp^3 C—H activation to give these compounds are thus important and worthwhile notice. In this Highlight, the challenging results for this purpose are discussed.

2. COPPER-CATALYZED SYNTHESIS OF TETRAHYDROISOQUINOLINE DERIVATIVES

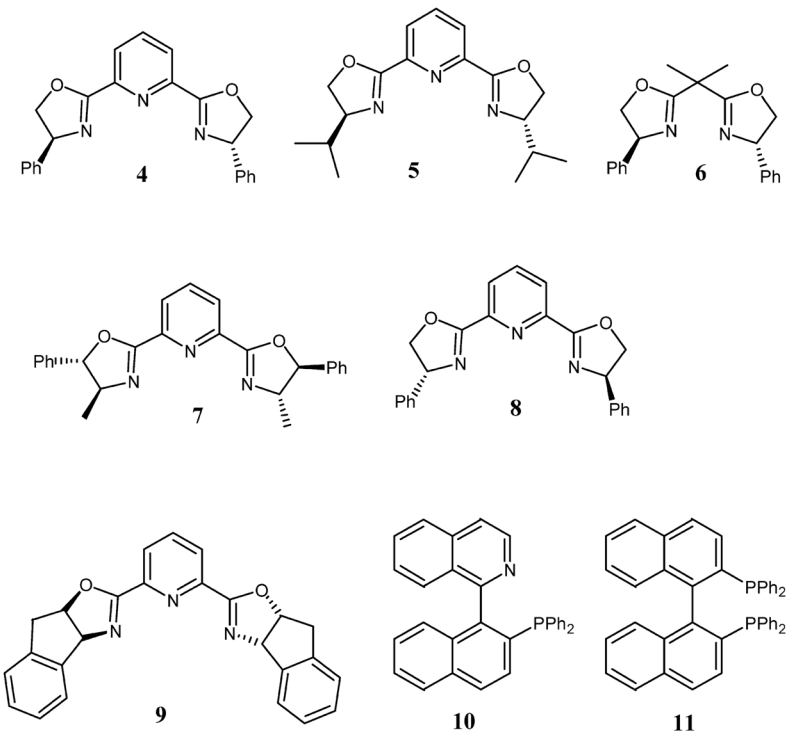
Tetrahydroisoquinoline (THIQ) alkaloids with a stereocenter at the C1 carbon possess biological and pharmacological properties [3]. Thus, the synthesis of optically active C1-substituted THIQs has great significance in medicinal studies. On the basis of the previous work of THIQ alkylation [2(b)], enantioselective synthesis of optically active C1-substituted THIQs **3** was achieved *via* CuOTf/PyBox **4**-catalyzed CDC reactions from THIQs **1** and terminal alkynes **2** (Scheme 1), which is a more direct and simpler synthetic method [4] developed by Li and coworkers [5] in 2004. A variety of chiral compounds including six chiral bisoxazolines (**4**–**9**), QUINAP **10**, and BINAP **11** were examined as ligands (Scheme 2), and PyBox **4** afforded the best enantioselectivity (63% ee) in the model reaction [5(a,b)]. For aromatic substituted alkynes, reactions provided both good yields and ee value. Electron-withdrawing or - donating group R^2 on the aryl ring did not substantially influence the isolated yields and enantioselectivities. For aliphatic substituted alkynes, fair or low enantiomeric excesses were obtained. The 4-substituted methoxy group on aryl ring (R^1) did not influence the enantioselectivity of the reaction, whereas the presence of an *o*-methoxy group on aryl ring (R^1) improved the enantiomeric excess up to 74%. The possible pathway is the formation of an imine-type intermediate (coordinated to copper) through the activation of sp^3 C—H adjacent to nitrogen and coupling with the copper activated

Scheme 1. Synthesis of optically active C1-substituted THIQ derivatives.

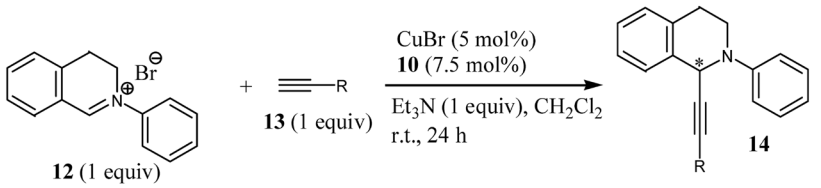


R^1 = H, R^2 = Ph, 67% yield, 63% ee; R^1 = H, R^2 = Hex, 65% yield, 26% ee;
R^1 = 4-MeO, R^2 = Ph, 59% yield, 60% ee; R^1 = 4-MeO, R^2 = Hex, 48% yield, 5% ee;
R^1 = 2-MeO, R^2 = Ph, 54% yield, 73% ee; R^1 = H, R^2 = 4-MeOPh, 65% yield, 41% ee;
R^1 = H, R^2 = 4-BrPh, 72% yield, 64% ee; R^1 = H, R^2 = TMS, 11% yield, 30% ee;
R^1 = 2-MeO, R^2 = 4-MeOPh, 56% yield, 69% ee; R^1 = 2-MeO, R^2 = 4-BrPh, 61% yield, 74% ee;
R^1 = 2-MeO, R^2 = Py, 57% yield, 36% ee

Scheme 2. Chiral ligands examined for the synthesis of THIQ derivatives.

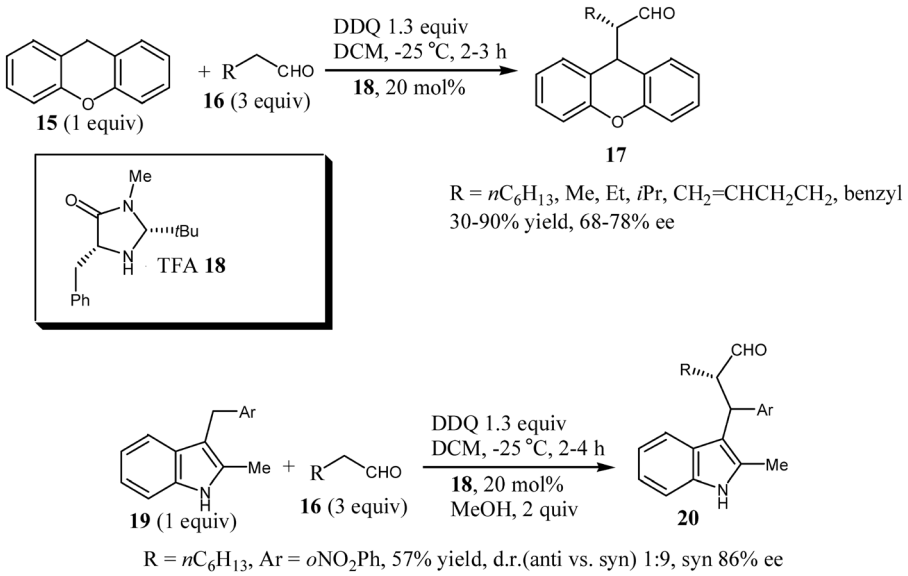


Scheme 3. Enantioselective reaction of dihydroisoquinolinium bromide with terminal alkynes.

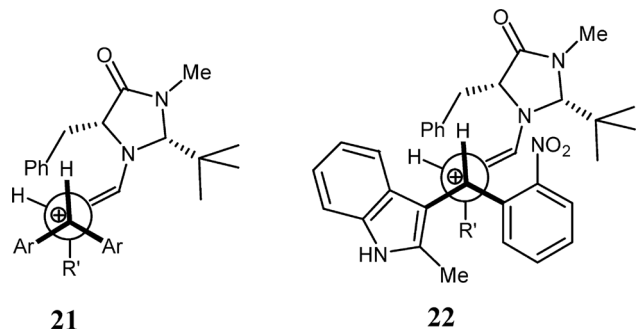


R = Ph, 83% yield, 75%ee; R = 4-$MeOC_6H_4$, 78% yield, 73%ee; R = 4-$BrOC_6H_4$, 80% yield, 81%ee;
R = Hex, 52% yield, 81%ee; R = TMS, 66% yield, 94%ee

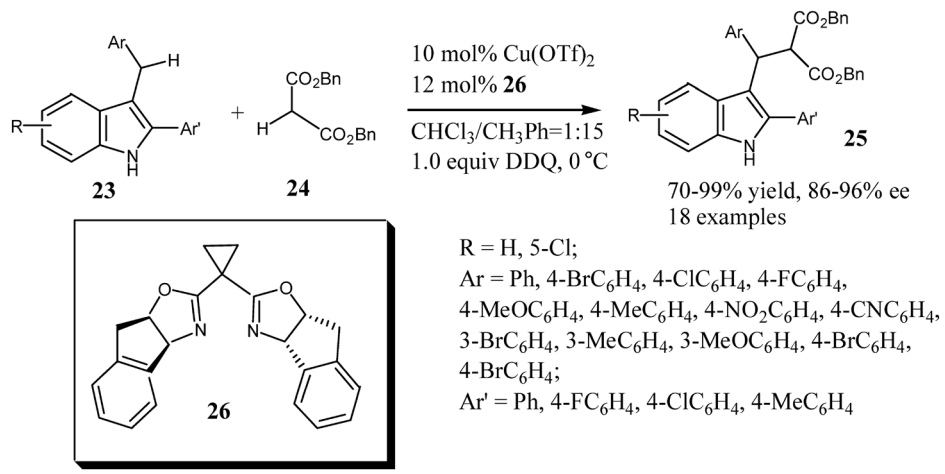
Scheme 4. Organocatalytic stereoselective CDC reactions.



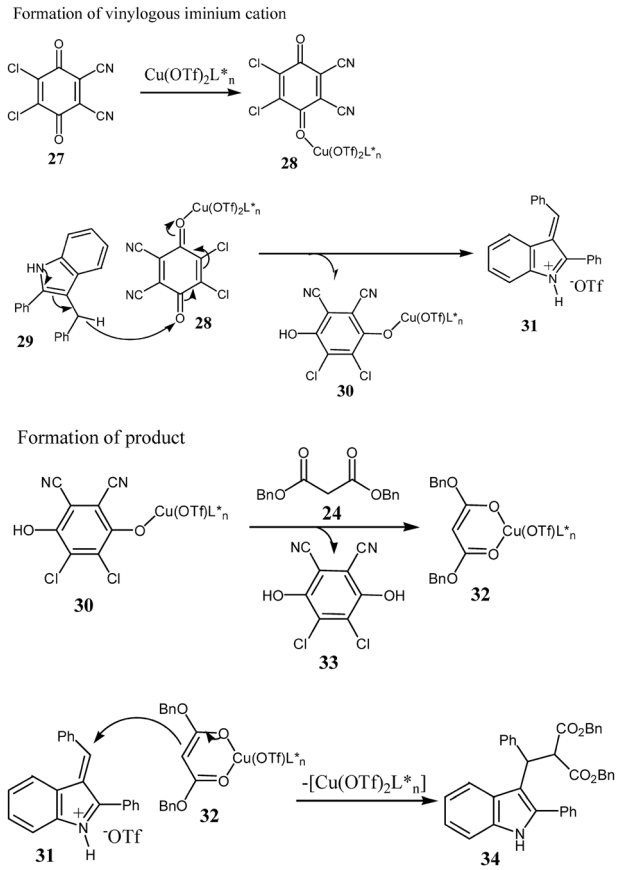
Scheme 5. Stereochemical models for organocatalytic CDC reactions.



Scheme 6. Enantioselective CDC reactions of 3-arylmethylindoles with dibenzylmalonate.

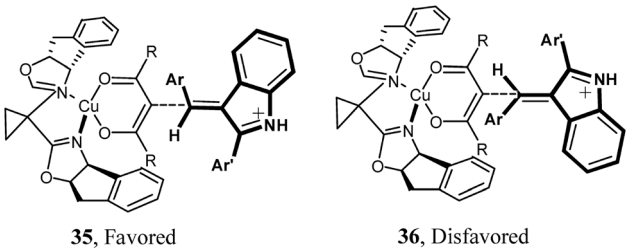


Scheme 7. Plausible pathway for CDC reactions of 3-arylmethylindoles with dibenzyl malonate.



terminal alkyne to give the product and regenerate the copper catalyst. It is also possible that *tert*-butylperoxide products were involved as intermediates [2,5(b)]. Although enantioselectivities (up to 73% ee) of this transformation are not very satisfactory, it is the first example for catalytic enantioselective version

Scheme 8. Reaction models for the conjugate addition.



35, Favored **36**, Disfavored

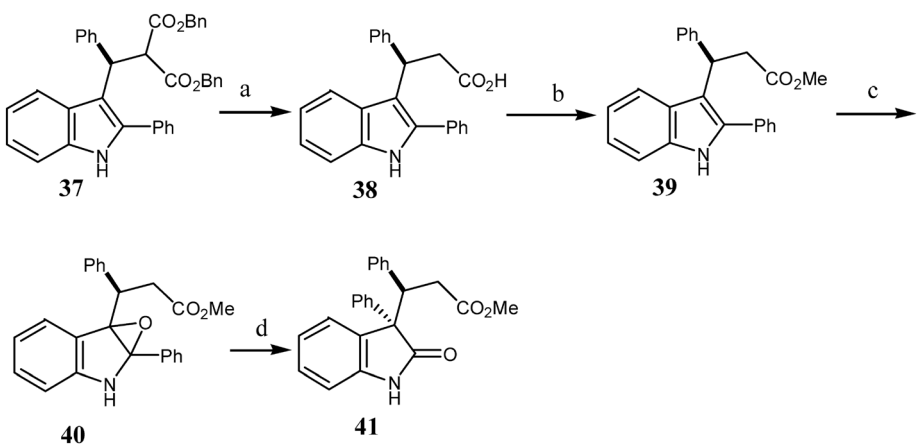
of CDC reactions based on sp^3 C—H activation, providing inspiration for late research.

It was hypothesized that dihydroisoquinolinium salt **12** might be the possible intermediate in the above reaction. To get the mechanistic insights of this CDC reaction (Scheme 1), Li *et al*. investigated the enantioselective reaction of dihydroisoquinolinium bromide **12** with terminal alkynes **13** in the presence of CuBr/QUINAP **10** [5(b)], giving good enantioselectivities and good yields of the desired products **14** (Scheme 3). It was found that triethylamine was essential in this reaction.

3. ORGANOCATALYTIC SYNTHESIS OF XANTHENE AND INDOLE DERIVATIVES

Metal-free organocatalytic stereoselective α-alkylation reactions of aldehydes **16** with xanthene **15** and indole **19** derivatives were developed by Cozzi and coworkers [6] in 2009 (Scheme 4). The MacMillan-type of catalyst (**18**) [7] promoted the CDC reactions based on sp^3 C—H activation. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) has been used as oxidant in many organic syntheses [8]. Xanthene **15** and indole **19** derivatives were proposed to give the corresponding carbocations by the oxidation of DDQ. Enamines derived from aldehydes and chiral catalysts (**18**) attack the

Scheme 9. Synthesis of an oxindole derivative with 94% ee. Reagents and conditions: (a) Pd/C, H_2, MeOH, 25°C, then Cu_2O, CH_3CN, 65°C, 74% yield; (b) $SOCl_2$, CH_3OH, 0–25°C, 79% 94% ee; (c) oxone, $NaHCO_3$, acetone/H_2O, 0°C, 92%; and (d) $Sc(OTf)_3$, toluene, 110°C, 81%, 94% ee.



carbocations in favored way (from less hindered face of the enamine **21** and **22**) (Scheme 5). In general, xanthene **15** reacts smoothly with different aldehydes **16**, resulting in high yield and good stereoselectivity of the desired products **17**. When an indole derivative **19** was tested, the reaction gave a moderate yield and good stereoselectivity. The absolute configuration (*S*) of the product, a xanthene derivative (R = Me) deduced from stereochemical models (Scheme 3) was in agreement with the assignment result by the chemical correlation. This protocol takes advantage of aldehyde group to subtly form chiral enamines; however, there is space for stereoselectivities to increase.

4. COPPER-CATALYZED SYNTHESIS OF INDOLE DERIVATIVES

Very recently, highly enantioselective CDC reactions of 3-arylmethylindoles **23** with dibenzyl malonate **24** were reported by Gong and coworkers (Scheme 6) [9]. The product **25** yields and ee value are both satisfactory (70–99% yield, 86–96% ee with 18 examples). A cationic rather than radical species was suggested to serve as the key intermediate, which was deduced from ESR studies [10]. The chiral copper complex facilitates the dehydrogenation of 3-arylmethylindole by coordinating to the oxygen of DDQ [11]. The vinylogous iminium cation **31** rather than a carbocation was assigned as the possible intermediate by DFT calculations. A chiral anion intermediate **32** generated from dibenzyl malonate enantioselectively attacks the vinylogous iminium cation **31** in a conjugate addition manner to give the chiral product **34** (Scheme 7). The observed stereochemistry was explained well by the proposed reaction models (Scheme 8); the transition state **35** is more favorably formed than **36** owing to the steric repulsion between the Ar group and phenyl ring of the chiral catalyst. Indole derivatives have widespread applications in organic synthesis [12]. A useful building block for the synthesis of alkaloid [13], one oxindole derivative **41** bearing quaternary stereogenic center at the 3-position was synthesized with 94% ee from one product **37** obtained from this asymmetric CDC reaction (Scheme 9). This successful and elegant work will stimulate further investigation of highly enantioselective functionalization of heterocycles *via* CDC reactions.

5. CONCLUSION

In summary, stereocontrolled CDC reactions based on sp^3 C—H activation to give chiral THIQ, xanthene, and indole derivatives have been developed notably. Two described examples used inexpensive copper catalysts, and another did not need metal catalyst. Although the three examples provide direct, simple, and economical synthetic routes to chiral heterocyclic compounds, stereoselectivities are not very satisfactory in alkynylation of THIQs by Li and coworkers [5] and α-alkylation of aldehydes by Cozzi and coworkers [6]. Choosing appropriate chiral ligands and optimizing reaction conditions might be useful for improving stereoselectivities. It is expected that various suitable heterocycle substrates will be tested for the functionalization *via* stereocontrolled CDC reactions based on sp^3 C—H activation in the future.

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