Cross-Coupling

Visible-Light-Promoted Asymmetric Cross-Dehydrogenative Coupling of Tertiary Amines to Ketones by Synergistic Multiple Catalysis

Qi Yang, Long Zhang, Chen Ye, Sanzhong Luo,* Li-Zhu Wu,* and Chen-Ho Tung

Abstract: Reported herein is an unprecedented photocatalytic asymmetric cross-dehydrogenative coupling reaction between tertiary amines and simple ketones, and it proceeds by synergistic multiple catalysis with substoichiometric amounts of a hydrogen acceptor. This process is enabled by a simple chiral primary amine catalyst through the coupling of a catalytic enamine intermediate and an iminium cation intermediate in situ generated from tetrahydroisoquinoline derivatives by coupled Ru/Co catalysis.

The direct cross-dehydrogenative coupling (CDC) of two C(sp³)-H bonds has recently become an enabling C-C bondformation strategy in synthetic chemistry.^[1-4] The development of catalytic enantioselective versions has since been actively pursued to include the asymmetric α -coupling of carbonyls, thus adding new variants to the fundamental α -carbonyl chemistry. Despite the advances, the successes with simple aldehydes and ketones have been rather limited.^[3,4] The elegant contributions from the groups of Rueping,^[4a] Chi,^[4f] and Wang^[4b,g] have verified the feasibility of chiral aminocatalysis in facilitating the reactions with aldehydes and ketones. These reactions were generally carried out with stoichiometric or excess amounts of strong oxidants, but the oxidative stability of the aminocatalysts remain an issue,^[4i,5] thus limiting another explorations along this line (Scheme 1 a). To overcome this oxidative constraint, we explored a tricatalytic hydrogen-transfer strategy for enantioselective CDC coupling by merging primary amine catalysis,^[5] photocatalysis,^[6–8] and cobalt catalysis^[9] under hydrogen-transfer conditions. In this reaction cycle, substoichiometric amounts of a nitro-compound act as the hydrogen acceptor, and circumvents the need for extra oxidants and

[*] Q. Yang, Dr. L. Zhang, Prof. Dr. S. Luo Key Laboratory for Molecular Recognition and Function Institute of Chemistry, Chinese Academy of Sciences Beijing, 100190 (China) and University of Chinese Academy of Sciences Beijing, 100049 (China) E-mail: luosz@iccas.ac.cn Homepage: http://luosz.iccas.ac.cn
C. Ye, Prof. Dr. L.-Z. Wu, Prof. Dr. C.-H. Tung Key Laboratory of Photochemical Conversion and Optoelectronic Materials, Technical Institute of Physics and Chemistry Chinese Academy of Sciences Beijing 100190 (China) E-mail: lzwu@mail.ipc.ac.cn

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 the author(s) of this article can be found under: http://dx.doi.org/10.1002/anie.201700572.

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Scheme 1. Direct CDC reaction. a) Oxidative coupling of tertiary amines to carbonyl compounds. b) Photocatalytic hydrogen-transfer asymmetric CDC reaction with substoichiometric hydrogen acceptor. PC = photocatalyst.

avoids the oxidative consumption of the amine catalyst under harsh oxidation conditions (Scheme 1 b). The current strategy makes possible a wide applicability and distinctive reactivity for a number of ketones and gives *syn*-diastereoselectivity for the reactions with cyclic ketones, which had not been seen in other asymmetric oxidative Mannich reactions of aldehydes and ketones.^[4f,g]

The asymmetric CDC reaction between N-phenyl-tetrahydroisoquinoline (1a) and cyclohexanone (2a) was first selected as the model reaction. Initial studies involved reactions with stoichiometric oxidants under either thermal or photocatalytic conditions, thus giving, unfortunately, either complicated reaction mixtures or no reaction (see Table S1 in the Supporting Information). At this point, we explored the photocatalytic hydrogen-transfer strategy by the combination with Ru/Co cocatalysts. To our delight, the reaction proceeded smoothly and we quickly identified an optimal tricatalytic system involving our chiral primary amine catalyst and Ru/Co complexes (Table 1, entry 1). Under these reaction conditions, conversion was complete within 24 hours and the desired product **3aa** was obtained with 83% yield, 8.8:1 d.r, and 99% ee (entry 1). Variation of cobalt catalysts (entries 2 and 3), photocatalysts (entries 4 and 5), primary amine catalysts (entries 6-9), temperature (entries 10 and 11), or the ratio between photocatalyst and cobalt catalyst (entries 12-14) led to a decrease in either the yield, d.r. value, or ee value. When m-NO2C6H4COOH was replaced by benzoic acid, the yield significantly decreased to 16% with 17% H₂ evolution (entry 15). We speculated that m-NO₂C₆H₄COOH was not only a weak acid additive, which had been shown to promote enamine formation as we

Table 1: Screening and optimization.[a]



Entry	Variation from standard conditions	Yield [%] ^{iej}	d.r. ¹⁹	ee [%] ^[0]
1	none	83 ^[e]	8.8:1	99
2	Co(dmgBF ₂) ₂ (H ₂ O) ₂ instead of Co-	60	4.0:1	97
	(dmgH) ₂ Cl ₂			
3	Co(dmgH)₂ClPy	70	3.2:1	97
4	Eosin Y	48	8.2:1	99
5	lr(ppy)₃	8	8.1:1	98
6	4b instead of 4a	48	1:3.0	60
7	4c	60	1:2.2	45
8	4 d	73	1:1.8	25
9	4e	55	1:3.6	15
10	2°C	77	4.2:1	93
11	RT	73	3.2:1	78
12	[PC]/[Co] = 1:10	59	5.1:1	96
13	[PC]/[Co]=2:10	65	5.4:1	95
14	[PC]/[Co]=3:10	81	5.9:1	98
15	40 mol% benzoic acid	16 ^[f]	3.5:1	95
16	40 mol% benzoic acid ^[g]	53 ^[h]	4.3:1	96
17	in air	58	6.8:1	97
18	in air ^[]	19	7.3:1	95
19	no Co(dmgH) ₂ Cl ₂	38	3.4:1	94
20	no Ru(bpy) ₃ Cl ₂ ·6H ₂ O	trace		
21	in the dark	n.r.		

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.3 mmol), **4a**/HOTf (20 mol%), m-NO₂C₆H₄COOH (40 mol%), Ru(bpy)₃Cl₂·6 H₂O (3 mol%), Co(dmgH₂)₂Cl₂ (8 mol%) were added to 1.0 mL solvent, then deaerated and irradiated for 24 h by 0.5 W blue LEDs. [b] Determined by ¹H NMR analysis using 1, 3, 5-trimethoxybenzene as an internal standard. [c] The diastereomeric ratio, *syn/anti*, was determined by ¹H NMR analysis. [d] Determined by HPLC analysis. [e] Yield of isolated product. [f] 17% yield of H₂. [g] 40 mol% nitrobenzene. [h] 95% yield of aniline was detected by GC. [i] No Co(dmgH)₂Cl₂ and m-NO₂C₆H₄COOH. Ad = adamantly, bpy = 2,2'-bipyridine, ppy = 2-phenylpyridine, PC = photocatalyst, n.r. = no reaction, Tf=trifluoromethanesulfonyl.

previously observed in similar catalysis,^[5] but also a hydrogen acceptor and underwent in situ hydrogenation.^[9e] This hypothesis was proved when m-NO₂C₆H₄COOH was replaced by nitrobenzene and benzoic acid, and a 95% yield of aniline was obtained with a slight reduction in the d.r. and *ee* values (entry 16). When the reaction took place in air, **1a** was competitively oxidized to the amide, 2-phenyl-3,4-dihydroisoquinolin-1-one, and the yield decreased dramatically (entry 17). When Co(dmgH)₂Cl₂ and *m*-NO₂C₆H₄COOH were further removed, **1a** was almost completely oxidized to 2-phenyl-3,4-dihydroisoquinolin-1-one with 19% yield (entry 18).^[10] Control experiments also revealed that photocatalyst, cobalt catalyst, and visible light

were essential for the reaction (entries 19–21), as either no reaction or poor yield was observed in their absence.

Under the optimized reaction conditions, the scope was then examined. As shown in Scheme 2, tetrahydroisoquinolines with variations on the phenyl moiety (R^1 and R^2 position) were tolerated in the reactions to afford the desired



Scheme 2. Scope with respect to tetrahydroisoquinolines. For the X-ray structure of **3 ac**, the thermal ellipsoids are shown at 30% probability.^[17]

syn-Mannich-type adducts with good to excellent diastereoand enantioselectivities (**3aa–k**). The absolute configuration was determined by single-crystal X-ray diffraction of **3ac** (see Table S3).^[17] It was noted that the diastereoselectivity was opposite to that observed in the study by Wang and coworkers,^[4g] which indicated a distinctive stereocontrol mode. Other tertiary amines or secondary amines were also examined, but led to either no desired reactions or complicated reaction mixtures (Scheme S2).

The reaction was not limited to cyclohexanones (Scheme 3). Tetrahydrothiapyrone and tetrahydropyranone also served as good nucleophiles in the reaction (**3ba-d**), though the products were easy to undergo racemization when isolated by silica gel column. Meanwhile, the reactions were successfully applied to other kinds of cyclic ketones in good to excellent yields with high d.r. and *ee* values (**3be-l**), which were not realizable in previous work.^[4] Eosin Y had been used to replace Ru(bpy)₃Cl₂·6 H₂O, and a similar outcome was obtained by prolonging reaction time (**3be-l**). Acyclic ketones had also been examined to give the desired adducts (**3bo-p**) with good yields but lower enantioselectivities.

We next explored the desymmetrization process of 4-substituted cyclohexanones. In this reaction, challenges mainly came from the difficulties in simultaneously controlling the diastereo- and enantioselectivities of C2 and remote C4 position (Scheme 4). To our delight, most of the substrates gave the desired products in good to excellent yields with high d.r. and *ee* values (**3ca-cf**). The absolute configuration of **3cd**

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Scheme 3. Scope with respect to ketones. [a] Eosin Y instead of $Ru(bpy)_3Cl_2 \cdot 6H_2O$ served as the photocatalyst. [b] Reaction at -5 °C. [c] Reaction at 5 °C.

was determined by single-crystal X-ray diffraction and others can be assigned accordingly (see Table S4).^[17] 3-Methylcyclohexanone and 4-ketalized cyclohexa-1,4-dione also worked well in the reaction with good d.r. and *ee* values (**3 cg-h**).

To probe the utility of our method in preparative synthesis, a scale-up reaction of **1a** with **2a** was performed by utilizing an organic dye photosensitizer in place of Ru-(bpy)₃Cl₂·6H₂O and decreasing the load of primary amine catalyst (10 mol%) and cobalt catalyst (5 mol%). Under these reaction conditions, conversion was complete within 48 hours with 72% yield, 7:1 d.r. and 96% *ee* (Scheme 5 a).

Experimentally, both butylated hydroxytoluene (BHT) and TEMPO, the typical radical inhibitors, slightly inhibited the reaction (Scheme 5b), and suggested the key bond-formation step was not radical in nature and the electron transfer was quite facile and fast. Indeed, we could identify and track the fast formation of the iminium cation intermediate **6** during the initial stage of reaction (see Schemes S3 and S4).^[41,11,12] The reaction could also be conducted in a two-stage light/dark manner with similar outcome (Scheme 5c). Those results indicated the subsequent C–C bond formation between the enamine intermediate **7** and **6** might be the rate-determining step in the whole reaction process.

To further shed light on the mechanism of amine oxidation, flash photolysis and emission quenching



Scheme 4. Scope with respect to substituted ketones (d.r.: ratio of the shown stereoisomer with all the other isomers). TEMPO = 2,2,6,6-tetramethylpiperidine-1-oxyl.

studies were carried out (see Figures S3-S9). No quenching of $*Ru(bpy)_{3}^{2+}$ luminescence was observed in the presence of either aminocatalyst 4a/TfOH, 1a, or m-NO₂C₆H₄COOH alone. Instead, we observed a strong quenching by Co- $(dmgH)_2Cl_2$ (Stern–Volmer constant of $1.1 \times 10^5 M^{-1}$) and a weak quenching effect by $1a/m-NO_2C_6H_4COOH$ together (Stern–Volmer constant is $3.1 \times 10^2 \text{ m}^{-1}$). These results strongly suggest that the reaction is initialized by oxidative quenching with a Co^{III} complex, instead of reductive quenching with 1a as previously reported.^[2e,4a,12] Electrochemical analysis showed that only Ru(bpy)₃³⁺ $(E_{1/2}^{III/II} = 1.29 V^{[13]}$ vs. SCE), not *Ru(bpy)₃²⁺ $(E_{1/2}^{*II/I} = 0.77 V$ vs. SCE),^[13] is able to oxidize 1a (0.88 V vs. SCE; see Figure S14), thus adding further support to an oxidation quenching process. The weak quenching efficiency with 1a/m-NO2C6H4COOH is also consistent with the observed low reactivity in the absence of the cobalt catalyst (Table 1, entry 19). In this context, an electron-donor-acceptor (EDA) complex between 1a and m-NO₂C₆H₄COOH can be invoked to account for the weak quenching effect in their co-existence.^[10b,12a,c] This process should be minor when CoIII complex is present.[14]



Scheme 5. The scale-up reaction and mechanistic insights.

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On the basis of the above observations, a plausible catalytic cycle is proposed in Scheme 6. Upon visible-light irradiation, the excited $*[Ru(bpy)_3]^{2+}$ is oxidized to $[Ru(bpy)_3]^{3+}$ by $[Co^{III}]$. Single-electron oxidation of the tertiary amine followed by hydrogen atom abstraction (HAT) or e/H^+ transformation results in the formation of the iminium cation **6**. The electron and proton are then captured by $[Co^{II}]$ to form $[Co^{I}]$ and $[Co^{III}-H]$, which hydrogenates m-NO₂C₆H₄COOH to complete the cycle. Meanwhile, interaction between the primary amine and ketone generated enamine intermediate **7**, which was proven by a previous investigation.^[5,15] Then **7** intercepts **6** to form the imine intermediate **9** through transition-state **8**.^[16] Finally, hydrolysis of **9** provides the desired product and allows the primary amine to re-enter the catalytic cycle.



Scheme 6. Plausible mechanism.

In summary, we have developed a visible-light-promoted asymmetric CDC-type coupling of tertiary amines to ketones enabled by a chiral primary amine catalyst, photocatalyst, and cobalt catalyst. The salient features of this synergistic multiple catalytic process involve the coupled tertiary amine oxidation and nitro-compound reduction by Ru/Co-mediated e/H shuttle as well as the realization of unprecedented *syn*selective C–C bond formation with high diastereo- and enantioselectivity. The consecutive low-barrier electrontransfer process, made possible by coupled Ru/Co catalysis, overcomes the high barriers of direct oxidation of substrates and avoids the undesired byproducts associated with typical oxidation processes. The current strategy would find more application in elusive asymmetric oxidative transformations.

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Conflict of interest

The authors declare no conflict of interest.

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- [17] CCDC 1532741 (3ac) and 1532659 (3cd) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

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Cross-Coupling

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Visible-Light-Promoted Asymmetric Cross-Dehydrogenative Coupling of Tertiary Amines to Ketones by Synergistic Multiple Catalysis

Working together: Synergistic multiple catalytic cycles enable an asymmetric cross-dehydrogenative coupling between tertiary amines and simple ketones with high diastereo- and enantioselectivity

under visible-light irradiation. This pro-

cess is enabled by a simple chiral primary amine catalyst through the coupling of a catalytic enamine intermediate and an iminium cation intermediate in situ generated from tetrahydroisoquinoline derivatives by Ru/Co catalysis.

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R-NH

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