Synthetic Methods

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Enantioselective Oxidative Cross-Dehydrogenative Coupling of Tertiary Amines to Aldehydes**

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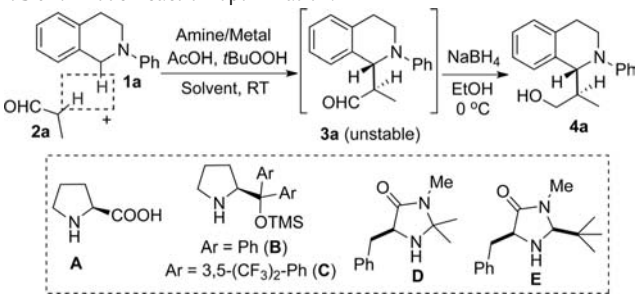
The direct oxidative cross-dehydrogenative coupling (CDC) of two C–H bonds can be an efficient and relatively clean strategy in organic synthesis.[1] Various sp^3 C–H bonds, such as benzylic and allylic C–H bonds,[2,3] the α-C–H bonds of amines and ethers,[4,5] and the C–H bonds of alkanes[6] can be oxidized for direct reaction with carbon nucleophiles. Among these reactions, the oxidation of tertiary amines to generate iminium intermediates, as pioneered by Murahashi et al.,[7] Li et al.[8] and others,[9–11] has received considerable attention. Carbonyl compounds, such as 1,3-dicarbonyls,[8e,f,h,10b,g] α,β-unsaturated ketones,[8f] and simple ketones[2c,11] have been successfully coupled with tertiary amines by using metal catalysis, acid catalysis, metal/organic cooperative catalysis, or photoredox catalysis. In all of these reactions, the development of enantioselective catalysis remains a challenge.[12] Very recently, Wang and co-workers used metals together with chiral bisoxazoline ligands to realize enantioselective reactions of activated carbonyl nucleophiles (such as 1,3-dicarbonyls and acetyl phosphates) to oxidatively generate iminiums or their analogues.[4d] However, this approach with chiral ligands was found to be unsuccessful for reactions starting with simple ketone nucleophiles, as reported by Klussmann and co-workers[11a] as well as Xie and Huang.[4c] Approaches that use asymmetric enamine catalysis[13] for the activation of carbonyl compounds have led to disappointing results (for example, less than 20% *ee*) as well[4c,11a,c,d]. As part of a larger program for developing sustainable oxidation chemistry,[14] we herein report an enantioselective oxidative coupling reaction of aldehydes and tertiary amines under cooperative amine and metal catalysis. The racemic version of this reaction was also realized by using metal catalysts alone (without amine catalysts), on account of its potential utility and the very different optimized conditions, relative to the enantioselective reactions.

We examined metal-catalyzed oxidative coupling reactions between *N*-phenyltetrahydroisoquinoline (**1a**) and propionaldehyde (**2a**) in the presence of *t*BuOOH without an amine catalyst.[15] An initial survey of solvents and catalysts indicated that DMF is a good solvent and $CuBr_2$ is an effective metal catalyst (Table 1, entries 1–3, see also the Supporting Information). The amino aldehyde product **3a** is unstable and, thus, was isolated as the corresponding amino alcohol product **4a** in 72% yield after reduction with $NaBH_4$ in situ, albeit with no diastereoselectivity (Table 1, entry 3). Under these conditions, various amines, such as *N*-aryl tetrahydroisoquinolines **1** and *N*,*N*-dialkyl anilines, and aldehydes **2** were used to obtain the corresponding racemic amino alcohols **4** in acceptable yields. Aldehydes with longer carbon chains required elevated reaction temperatures. *N*,*N*-dialkyl anilines gave the corresponding products in lower yields (Table S6 and Scheme S3 in the Supporting Information).

Table 1: Model reaction optimization.[a]



Entry	Solvent	Amine/Metal	*t* [h]	Yield [%][b]	d.r.[c] [*syn*/*anti*]	*ee* [%][d] [*syn*/*anti*]
1[e]	solvents[f]	–/CuBr	24	< 5	n.d.	–
2[e]	DMF	–/CuBr	24	65	49:51	–
3[e]	**DMF**	**–/$CuBr_2$**	**24**	**72**	**53:47**	**–**
4[e]	DMF	**A**/$CuBr_2$	24	63	50:50	4/3
5	DMF	**B**/$CuBr_2$	24	60	44:56	35/37
6	DMF	**C**/$CuBr_2$	24	65	43:57	48/51
7	$CHCl_3$	**C**/$CuBr_2$	10	52	23:77	70/67
8	Et_2O	**C**/$CuBr_2$	24	56	50:50	97/94
9	$CHCl_3/Et_2O$	**C**/$CuBr_2$	17	60	36:64	96/91
10[g]	**$CHCl_3/Et_2O$**	**C/$CuBr_2$**	**17**	**66**	**36:64**	**96/92**
11[g]	$CHCl_3/Et_2O$	–/$CuBr_2$	17	< 5	n.d.	n.d.
12[g]	$CHCl_3/Et_2O$	**A**/$CuBr_2$	17	< 5	n.d.	n.d.
13[g]	$CHCl_3/Et_2O$	**B**/$CuBr_2$	17	42	36:64	70/67
14[g]	$CHCl_3/Et_2O$	**D**/$CuBr_2$	17	< 5	n.d.	n.d.
15[g]	$CHCl_3/Et_2O$	**E**/$CuBr_2$	17	< 5	n.d.	n.d.

[a] Reaction conditions: amine (0.03 mmol), AcOH (0.03 mmol), $CuBr_2$ (0.01 mmol), **1a** (0.1 mmol), **2a** (0.5 mmol), *t*BuOOH in decane (0.15 mmol), and solvent (1.0 mL). [b] Combined yield of isolated **4** (*syn* and *anti*). [c] Determined by ^1H NMR spectroscopy and HPLC on a chiral stationary phase. [d] Determined by HPLC on a chiral stationary phase. [e] No AcOH was used. [f] DMSO, MeOH, toluene, THF, CH_2Cl_2, $CHCl_3$ and Et_2O. [g] 50 mol% AcOH was used. n.d. = not determined, TMS = trimethylsilyl.

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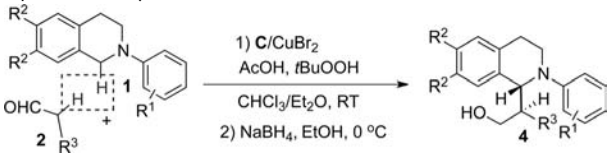
We used a chiral amine combined with $CuBr_2$ as a cooperative catalytic system to develop the enantioselective reaction between **1a** and **2a**. The reaction catalyzed by (*S*)-proline/$CuBr_2$ in DMF gave the desired product in 63% yield and in a 1:1 diastereomeric ratio (d.r.), with virtually no enantioselectivity (4%/3% *ee*) (Table 1, entry 4). The reaction with diphenylprolinol-based silyl ether catalyst **B**, in the presence of 30 mol% of AcOH, gave product **4a** with low *ee* values (35%/37%; Table 1, entry 5). The *ee* values were improved by using catalyst **C** (48%/51% *ee*; Table 1, entry 6). For reactions that were carried out in DMF (Table 1, entry 6), the low *ee* values were largely caused by the racemic background reaction that is not catalyzed by the amine. To suppress the racemic background reaction, we screened solvents for this cooperative system with catalyst **C** (Table 1, entries 7–9, see also the Supporting Information). The reaction in $CHCl_3$ was complete a in shorter time and gave products with improved d.r. (*syn*/*anti* = 23:77), but with moderate *ee* values (Table 1, entry 7). Fortunately, with Et_2O as the solvent, the reaction proceeded smoothly and gave **4a** with high enantioselectivity (97%/94% *ee*), moderate yield (56%), but with poor diastereoselectivity (1:1, Table 1, entry 8). Finally, we found that the mixture of solvents $CHCl_3$/Et_2O (1:1, v/v) provided the coupling product with an improved d.r., as well as good yields and high enantioselectivity (Table 1, entry 9). Increasing the loading of AcOH to 50 mol% led to a higher yield of the product (Table 1, entry 10). Accordingly, a cooperative catalytic system that consists of **C**, $CuBr_2$, AcOH, and a solvent mixture of $CHCl_3$/Et_2O (1:1, v/v) is the optimal system for this reaction. The desired product **4a** was be obtained in 66% yield, with an improved d.r. (36:64) and in 96%/92% *ee* after 17 h at room temperature (Table 1, entry 10). Given the sensitivity of the d.r. and *ee* values to the reaction conditions (such as solvents and acid co-catalysts, Table 1, see also the Supporting Inforation) and the high instability of the aldehyde Mannich product **3a** toward side reactions (such as decompositions) and racemization, the d.r. and *ee* values that were obtained are quite impressive for this class of oxidative coupling reactions.

Under the optimized conditions, the scope of substrates for the asymmetric oxidative coupling reactions was then studied. *N*-aryl tetrahydroisoquinolines **1** with different R^1 and R^2 substituents were investigated in the reaction with **2a**. The reactions proceeded readily with both electron-withdrawing and donating R^1 substituents on the *N*-aryl ring of **1** at room temperature, to afford **4** with high enantioselectivity (88–94% *ee*, for the major *anti* isomers) and in moderate to good yields (52–71%, Table 2, entries 1–5). The R^2 substituents on the tetrahydroisoquinoline ring did not influence the reaction outcomes (Table 2, entries 6–8). Aldehydes that have longer carbon chains, such as *N*-butyraldehyde and *N*-valeraldehyde, were examined. The desired products were obtained with good enantioselectivity, but in lower yields (Table 2, entries 9 and 10). The use of 3-phenylpropionaldehyde as the aldehyde substrate also gave similar results (lower yield and *ee* values). Prolonging the reaction time only slightly improved the reaction yields (largely as a result of the instability of **3** before reduction) and led to lower *ee* values because of product racemization (Table 2, entries 9–11).[16] The CDC reaction is believed to involve a single-electron transfer (SET) radical mechanism (see the Supporting Information).[7b,17,18]

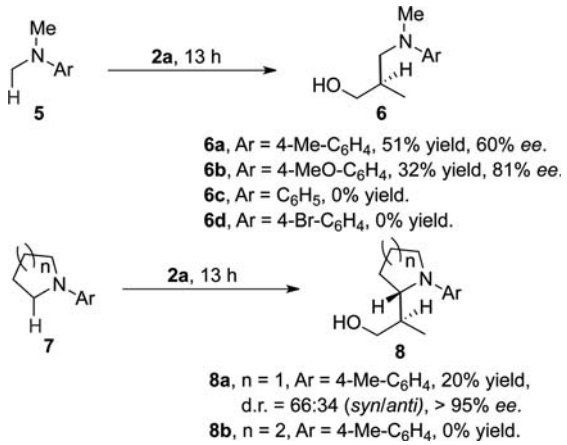
Table 2: Asymmetric oxidative coupling reaction with metal/organic cooperative catalysis.[a]



Entry	R^1, R^2, R^3	*t* [h]	**4**	Yield [%][b]	d.r.[c] [*syn*/*anti*]	*ee* [%][d] [*syn*/*anti*]
1	H, H, Me	17	**4a**	66	36:64	96/92
2	4-Me, H, Me	11	**4b**	71	28:72	94/92
3	4-MeO, H, Me	11	**4c**	64	29:71	86/88
4	4-Br, H, Me	12	**4d**	60	41:59	99/94
5	2-MeO, H, Me	12	**4e**	52	22:78	52/88
6	H, MeO, Me	12	**4f**	67	25:75	86/87
7	4-Br, MeO, Me	12	**4g**	61	31:69	n.d./94
8	4-Me, MeO, Me	12	**4h**	68	26:74	n.d./84
9	H, H, Et	17	**4j**	44	36:64	89/84
		26	**4j**	46	35:65	86/82
10	H, H, *n*Pr	17	**4k**	43	34:66	81/77
		26	**4k**	47	35:65	75/73
11	H, H, Bn	13	**4i**	31	62:38	88/72
		42	**4i**	37	57:43	67/46

[a] Reaction conditions: **C** (0.03 mmol), AcOH (0.05 mmol), $CuBr_2$ (0.01 mmol), **1** (0.1 mmol), **2** (0.5 mmol), *t*BuOOH in decane (0.15 mmol), and $CHCl_3$/Et_2O (1:1, v/v, 1.0 mL). [b] Combined yield of isolated **4** (*syn* and *anti*; inseparable by chromatography on a silica gel column for most substrates). [c] Determined by ^{1}H NMR spectroscopy and HPLC on a chiral stationary phase. [d] Determined by HPLC on a chiral stationary phase; the absolute configuration was determined by the Mosher method (see the Supporting Information).

We also examined other tertiary amine substrates besides tetrahydroisoquinolines (Scheme 1). Anilines substituted with electron-donating functionalities gave the desired prod-



Scheme 1. CDC reactions of anilines and aliphatic cyclic amines. Reaction conditions are the same as used in Table 2. The stated yield is the yield of isolated product. The *ee* values were determined by HPLC on a chiral stationary phase. The d.r. was determined by ^{1}H NMR spectroscopy and HPLC on a chiral stationary phase.

ucts **6a** and **6b** in low to moderate yields (Scheme 1), whereas electron-deficient anilines were unsuitable substrates for the oxidative reactions and products **6c** and **6d** were not obtained (Scheme 1). With aliphatic cyclic amines, the size of the ring was found to affect the outcome of the reaction. The reaction of an *N*-aryl pyrrolidine with **2a** gave the desired product **8a** with an excellent *ee* value (95% *ee*), albeit in low yield. No detectable product was formed in the reaction with an *N*-aryl piperidine (Scheme 1, **8b**). Other amine substrates that were examined but did not react well are summarized in the Supporting Information. It appears that intrinsic limitations on tertiary amine substrates remain a problem in nearly all of the oxidative coupling reactions.[8–11]

In summary, we have developed an enantioselective, direct, oxidative cross-dehydrogenative coupling reaction of tertiary amines with aldehydes. With only a metal catalyst, efficient racemic reactions were also realized. This method allows optically active β-amino alcohols that contain tetrahydroisoquinoline[19] units to be synthesized. To our knowledge, a highly enantioselective oxidative coupling reaction of tertiary amines and non-activated carbonyl compounds that is catalyzed by metal/organic cooperative catalysis has not been reported previously. Additional studies to improve the diastereoselectivity of such reactions and to develop other asymmetric oxidative coupling reactions are being pursued.

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[12] To our knowledge, only three successful examples of enantioselective CDC reactions of tertiary amines have been reported. One is an alkynylation of tertiary amines in which the best *ee* value of 74% is obtained (Refs. [8b,g]); another is a reaction of tertiary amines with activated carbonyl compounds, which included two examples with up to 90% *ee* (Ref [4d]). In the above two reports, copper salts together with chiral bisoxazoline ligands were employed as the catalysts. The third example is a biocatalytic enantioselective reaction (Ref. [9g]).

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[16] Product racemization was also found by Klussmann in the case of the ketone, see: Ref. [11a].

[17] N. J. Leonard, G. W. Leubner, *J. Am. Chem. Soc.* **1949**, *71*, 3408 – 3411.

[18] In the absence of amine catalysts in DMF, the aldehyde prenucleophile is presumably activated as its enol form.

[19] For the synthesis and biological activities of isoquinoline alkaloids, see: a) M. Chrzanowska, M. D. Rozwadowska, *Chem. Rev.* **2004**, *104*, 3341 – 3370; b) K. W. Bentley, *Nat. Prod. Rep.* **2004**, *21*, 395 – 424.

