Cooperative Catalysis

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Cross-Dehydrogenative Coupling Reactions by Transition-Metal and Aminocatalysis for the Synthesis of Amino Acid Derivatives**

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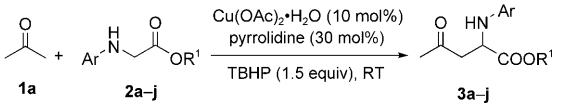
The direct cross-dehydrogenative coupling (CDC) of C–H bonds has become a potent strategy for C–C bond formation. As CDC reactions avoid prefunctionalization of the substrates, they are more atom-economical and environmentally friendly than other cross-coupling reactions.[1] Several research groups have reported CDC reactions of various sp^3 C–H bonds, such as benzylic and allylic C–H bonds,[2,3] α-C–H bonds of tertiary amines[4] and ethers,[5] and C–H bonds of alkanes,[6] with other C–H bonds. As far as we know, there are only two successful examples of CDC reactions for the synthesis of amino acid derivatives, although these compounds are so important in terms of their biological activity. Li and co-workers developed CDC reactions of *N*-acetylglycine esters and *N*-aryl glycine amides with malonates and alkynes in the presence of $Cu(OAc)_2$ (2.0 equiv) and catalyzed by CuBr, respectively.[7,8] However, they reported that *N*-aryl glycine esters, unlike *N*-aryl glycine amides, could not undergo a CDC reaction.[7] Owing to the importance of amino acid derivatives and the lack of successful CDC reactions of glycine derivatives with ketones, we embarked on a study of CDC reactions of N-substituted glycine esters with unmodified ketones for the synthesis of amino acid derivatives.

In recent years, cooperative metal and organocatalysis has received considerable attention, since it can potentially enable unprecedented transformations currently impossible with a metal catalyst or an organocatalyst alone.[9] Owing to their significance and in continuation of our recent investigation on cooperative metal and organocatalysis,[10] we planned to carry out the investigation on CDC reactions by cooperative catalysis. In the last decade, a lot of interest has been paid to C–H activation with metal catalysts and subsequent C–C bond formation with nucleophiles.[1] At the same time, enamines have become crucial reactive intermediates in organocatalysis as elegant nucleophiles for C–C bond formation. However, there have been only a few reports on the application of aminocatalysis to C–C bond formation after C–H activation by transition-metal catalysis.[4i,l] In 2009, Klussmann and co-workers developed a CDC reaction of tertiary amines with methyl ketones by dual catalysis by a vanadium complex and proline.[4i] Almost all tertiary-amine substrates that underwent the CDC reaction efficiently were tetrahydroisoquinoline derivatives. To the best of our knowledge, there is no successful and disclosed example of a CDC reaction of secondary amines with ketones. Herein, we present our preliminary results on the synthesis of amino acid derivatives by CDC reactions of N-substituted glycine esters with unmodified ketones by cooperative transition-metal and aminocatalysis.

Initially, we screened different N substituents on glycine esters and various organocatalysts, transition-metal catalysts, ligands, solvents, oxidants, and additives (see the Supporting Information). The experiments demonstrated that for optimal results, the reaction should be performed by the cooperative catalysis of $Cu(OAc)_2{\cdot}H_2O$ (10 mol%) and pyrrolidine (30 mol%) with *tert*-butyl hydroperoxide (TBHP; 1.5 equiv) at ambient temperature under neat conditions in air. Under the optimized conditions, acetone reacted with the *N*-4-methylphenylglycine ester **2a** smoothly to give the desired coupling product **3a** in 73% yield (Table 1, entry 1). If either pyrrolidine or $Cu(OAc)_2{\cdot}H_2O$ was present, no coupling product **3a** was obtained. A series of *N*-aryl glycine esters **2a–f** were then examined in the CDC reaction. The reaction

Table 1: Cooperative catalytic CDC reaction mediated by TBHP.[a]



(1)

2a: Ar = 4-MeC_6H_4, R^1= Et
2b: Ar = C_6H_5, R^1= Et
2c: Ar = 4-$MeOC_6H_4$, R^1= Et
2d: Ar = 4-ClC_6H_4, R^1= Et
2e: Ar = 4-BrC_6H_4, R^1= Et
2f: Ar = 3-MeC_6H_4, R^1= Et
2g: Ar = 4-MeC_6H_4, R^1= Me
2h: Ar = 4-MeC_6H_4, R^1= *i*Pr
2i: Ar = 4-MeC_6H_4, R^1= *t*Bu
2j: Ar = 4-MeC_6H_4, R^1= Bn

Entry	Ar	R^1	*t* [h]	Product	Yield [%][b]
1	4-MeC_6H_4	Et	10	**3a**	73
2	C_6H_5	Et	20	**3b**	54
3	4-$MeOC_6H_4$	Et	8	**3c**	46
4	4-ClC_6H_4	Et	20	**3d**	63
5	4-BrC_6H_4	Et	10	**3e**	58
6	3-MeC_6H_4	Et	12	**3f**	75
7	4-MeC_6H_4	Me	16	**3g**	77
8	4-MeC_6H_4	*i*Pr	10	**3h**	74
9	4-MeC_6H_4	*t*Bu	16	**3i**	62
10	4-MeC_6H_4	Bn	12	**3j**	71

[a] Reaction conditions: **2** (0.15 mmol), acetone (0.75 mL), $Cu(OAc)_2{\cdot}H_2O$ (10 mol%), pyrrolidine (30 mol%), TBHP (1.5 equiv, 5.5 M in decane). [b] Yield of the isolated product. Bn = benzyl.

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of acetone with various *N*-aryl glycine esters **2a–f**, but not the corresponding *N*-4-nitrophenylglycine ester,[11] resulted in the desired *N*-aryl amino acid derivatives in satisfactory yields of 46–75% (Table 1, entries 1–6). *N*-Aryl amino acids are core structures in many biologically significant compounds and medicinally important agents.[12]

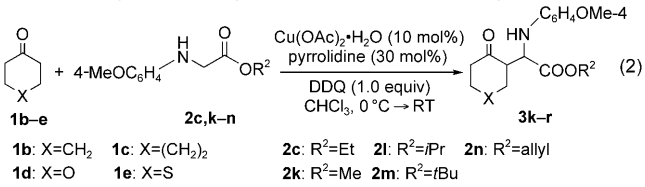
When the corresponding methyl or isopropyl ester **2g**,**h** was employed instead of ethyl ester **2a**, coupling products **3g**,**h** were also isolated in satisfactory yield (Table 1, entries 7 and 8). However, the reaction of *tert*-butyl ester **2i** proceeded in lower yield than the reactions of the ethyl, methyl, and isopropyl esters **2a**,**g**,**h** (Table 1, entry 9). The reason for this lower yield may be the steric hindrance of *tert*-butyl group, as the CDC reaction of *N*-aryl glycine ester **2** with TBHP seems to be sensitive to steric effects. It was significant that when the glycine benzyl ester **2j**, which contains an readily activated C–H bond in the benzyloxy moiety,[5a,b,13] was used, the CDC reaction showed a good regioselectivity to give the expected coupling product **3j** in 71% yield (Table 1, entry 10).

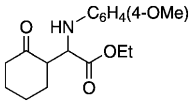
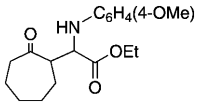
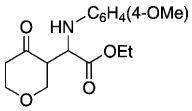
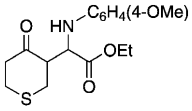
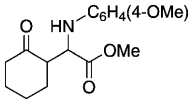
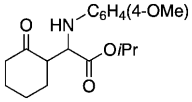
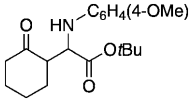
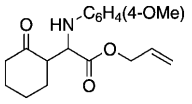
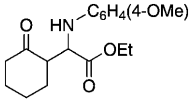
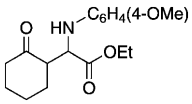
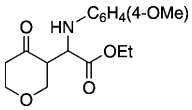
When cyclohexanone (**1b**) was employed instead of acetone in this CDC reaction with **2a**, none of the desired coupling product was isolated. However, when TBHP was replaced with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as the oxidant, the CDC reaction of cyclohexanone with the *N*-4-methoxyphenylglycine ester **2c** proceeded readily to give the coupling product **3k** in 83% yield (Table 2, entry 1). Without $Cu(OAc)_2 \cdot H_2O$, **3k** was also obtained, but in decreased yield (68%) with decreased diastereoselectivity (d.r. 1.1:1; see the Supporting Information). Thus, we continued to study the CDC reaction with $Cu(OAc)_2 \cdot H_2O$ as a transition-metal catalyst. When the *N*-4-methylphenylglycine ester **2a** or *N*-4-chlorophenylglycine ester **2d** was used as a substrate with cyclohexanone, the coupling product was not formed or was formed in just 28% yield under the same reaction conditions (see the Supporting Information for details). In further experiments, the *N*-4-methoxyphenylglycine ester **2c** underwent smooth CDC reactions with different cycloketones to furnish the desired coupling products **3l–n** in satisfactory yields (51–72%) under very mild conditions in air (Table 2, entries 2–4).

As in most CDC reactions, the diastereoselectivities observed for the novel CDC reaction were not high (Table 2, entries 1–11). If the substituent on ester **2c** was switched from an ethyl to a methyl group, the yield decreased significantly to 64% (Table 2, entry 5). When isopropyl, *tert*-butyl, and allyl esters **2l–n** were used, the reaction proceeded readily to give coupling products **3p–r** in good yield (Table 2, entries 6–8). We also found that without pyrrolidine, the yields of coupling products **3k** and **3m** decreased significantly from 83 and 72% to 76 and 56%, respectively (Table 2, entries 10 and 11). The CDC reaction may proceed in the absence of pyrrolidine because the *N*-4-methoxyphenylglycine esters **2c**, **3k**, and **3m** are secondary amines and might perform autocatalysis of the CDC reaction.[14]

To gain insight into these CDC reactions, we carried out preliminary studies on the mechanistic pathway. We found that if 2,6-di-*tert*-butyl-4-methylphenol (BHT), a radical inhibitor, was added to the reaction system with TBHP [Eq. (1)], the yield of the coupling product **3a** decreased dramatically from 73 to less than 5%. The key intermediate in this transformation, the α-*tert*-butyldioxyl secondary amine **4**, was identified by ^{1}H NMR spectroscopy and MS, although it

Table 2: Cooperative catalytic CDC reaction mediated by DDQ.[a]



Entry	Product		*t* [h]	d.r.[b]	Yield [%][c]
1		**3k**	18	2:1	83
2		**3l**	48	1:3	51
3[d]		**3m**	12	1:1	72
4[e]		**3n**	40	4:1	63
5		**3o**	24	9:5	64
6		**3p**	20	2:1	83
7		**3q**	24	5:1	75
8		**3r**	20	2:1	80
9[f]		**3k**	15	9:5	78
10[g]		**3k**	18	2:1	76
11[d,g]		**3m**	12	1:1	56

[a] Reaction conditions: **2** (0.15 mmol), **1** (15.0 equiv), $Cu(OAc)_2 \cdot H_2O$ (10 mol%), pyrrolidine (30 mol%), DDQ (1.0 equiv), $CHCl_3$ (1.0 mL). [b] Diastereomeric ratio: *anti*/*syn*. [c] Yield of the isolated product. [d] The reaction was performed with 10.0 equivalents of the cycloketone. [e] The reaction was performed with 5.0 equivalents of the cycloketone. [f] The reaction was performed at room temperature. [g] The reaction was performed in the absence of pyrrolidine.

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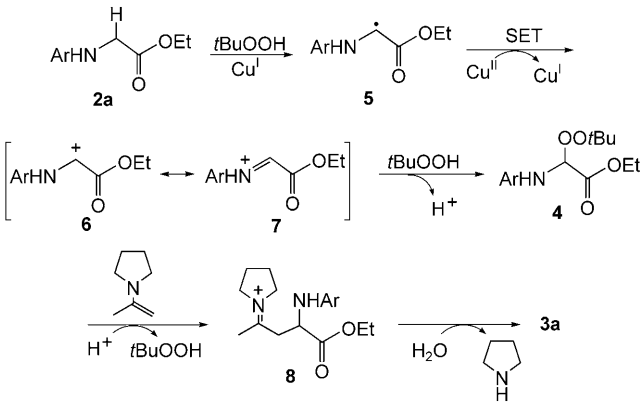
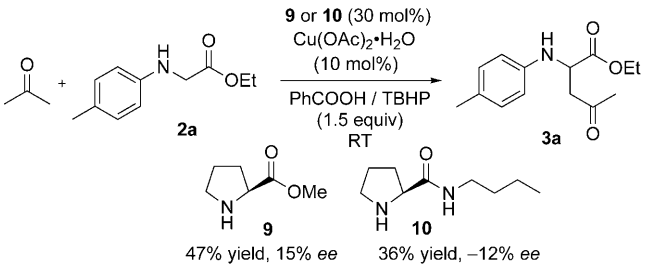
was unstable (see the Supporting Information for details).[15] Thus, the reaction may proceed by a radical mechanism via the peroxide intermediate **4** (Scheme 1). Initially, a *tert*-butoxyl radical generated by the copper-catalyzed decomposition of TBHP[16] may abstract a α hydrogen atom of **2a** to form radical **5**. Single-electron transfer (SET) from **5** leads to carbocation **6**, which can tautomerize to iminium ion **7**. Nucleophilic attack of *t*BuOOH on **7** then forms the peroxide **4** with a bulky *tert*-butyl group. Subsequent nucleophilic attack of an enamine derived in situ from acetone and pyrrolidine on the peroxide intermediate **4** under acid catalysis generates the iminium ion **8**. The failure of the CDC reaction when cyclohexanone was used instead of acetone may be due to steric hindrance from the *tert*-butyl group in **4**. Finally, the hydrolysis of **8** gives the coupling product **3a** and regenerates pyrrolidine.



Scheme 1. Plausible mechanism of the cooperative catalytic CDC reaction mediated by TBHP.

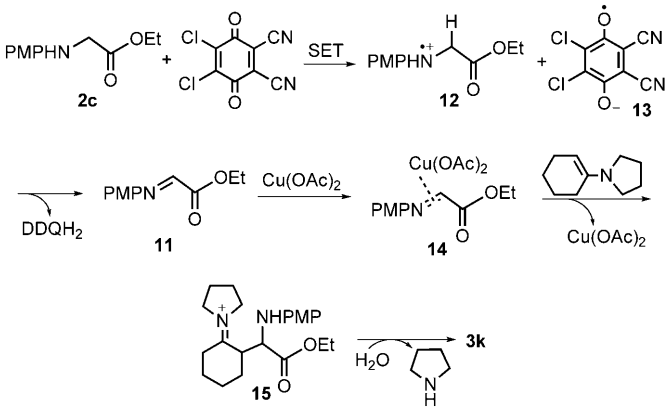
For the development of an asymmetric CDC reaction mediated by TBHP under cooperative catalysis for the synthesis of amino acids, we initially examined various chiral ligands. No enantioselectivity was observed with any of the chiral ligands employed (see the Supporting Information for details). The formation of racemic products is consistent with the above mechanism (Scheme 1), in which the only role of the metal is the generation of carbocation **6** through a radical pathway. We then tested various chiral organocatalysts in the CDC reaction of the *N*-4-methylphenylglycine ester **2a** with acetone. The coupling product **3a** was obtained with 15% *ee* when the chiral pyrrolidine ester **9** was used in the presence of the additive PhCOOH (Scheme 2; see also the Supporting Information). When the chiral pyrrolidine amide **10**, which has an active hydrogen atom for the formation of a hydrogen bond, was used as the organocatalyst, the reverse enantioselectivity (−12% *ee*) was observed (Scheme 2; see also the Supporting Information). The observed asymmetric induction indicates that the chiral organocatalysts participate in the formation of enamines in situ, which also supports the proposed mechanism.

When BHT was used as a radical inhibitor in the reaction mediated by DDQ [Eq. (2)], the yield of the coupling product **3k** decreased greatly from 83 to 18%. Moreover, in the



Scheme 2. Asymmetric induction in the cooperative catalytic CDC reaction mediated by TBHP.

absence of cyclohexanone, the imine intermediate **11** derived from **2c** was formed in 57% yield under the catalytic conditions described in Equation (2) (see the Supporting Information for details). These results suggest that the CDC reaction may proceed by a radical pathway via the imine intermediate **11** (Scheme 3). First, the transfer of a single electron from the nitrogen atom of **2c** to DDQ gives a radical cation **12** and a radical anion **13**. The weaker electron-donating conjugation effects of the methyl or chloro group in *N*-4-methylphenyl- and *N*-4-chlorophenylglycine esters **2a**,**d** relative to the methoxy group in **2c** probably make it difficult for these substrates to transfer a single electron, so that the corresponding coupling product is not formed or is formed in only 28% yield, respectively (see the Supporting Information for details). Second, the anionic and radical oxygen atoms in the DDQ radical anion **13** abstract the N-bonded hydrogen atom and α-hydrogen atom of radical cation **12**, respectively, to generate imine **11** and $DDQH_2$. Coordination of the copper salt to imine **11** may activate this intermediate and improve diastereoselectivity. The coordinated imine **14** then undergoes nucleophilic attack by an enamine derived from cyclohexanone and pyrrolidine to generate iminium ion **15**. Finally, hydrolysis of **15** leads to the coupling product **3k** and regenerates pyrrolidine. It can be deduced from the two mechanistic pathways that the different oxidants in these CDC reactions determine the formation of different key intermediates (such as **4** and **11**); the key intermediates in turn determine the substrate selectivity.



Scheme 3. Plausible mechanism of the cooperative catalytic CDC reaction mediated by DDQ.

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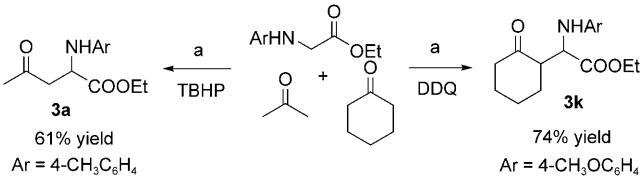
To improve our understanding of the substrate selectivities of the CDC reactions with different oxidants, we added cyclohexanone to the reaction mixture of acetone with **2a** in the presence of TBHP under the reaction conditions in Equation (1). The expected product **3a** of coupling with acetone was isolated in 61 % yield, and no coupling product of cyclohexanone was observed (Scheme 4; see the Supporting



Scheme 4. Substrate selectivity of the CDC reactions with different oxidants. Reaction conditions: a) $Cu(OAc)_2{\cdot}H_2O$ (10 mol %), pyrrolidine (30 mol %), room temperature (with TBHP or DDQ).

Information for details). When a mixture of cyclohexanone and acetone with **2c** was subjected to the catalytic conditions in the presence of DDQ [Eq. (2)], the expected product **3k** of coupling with cyclohexanone was isolated in a 74 % yield, and no coupling product of acetone was observed. The only small decrease in the yield relative to that observed in the absence of acetone (78 %; Table 2, entry 9) indicates that the presence of acetone in the reaction system hardly interferes with the CDC reaction of cyclohexanone and **2c**.

In summary, we have developed a facile approach to *N*-aryl amino acid derivatives that involves the coupling of *N*-aryl glycine esters with unmodified ketones under the cooperative catalysis of $Cu(OAc)_2{\cdot}H_2O$ and pyrrolidine in the presence of TBHP or DDQ in air under mild conditions. We have also proposed possible SET mechanisms for the CDC reactions of secondary amines on the basis of radical-inhibition experiments and the identification of key reactive intermediates. We conclude that the oxidant used for C–H activation determines the substrate selectivity of the CDC reaction. Further studies on the CDC reactions of secondary amines for the synthesis of amino acid derivatives by cooperative transition-metal and aminocatalysis under ambient conditions are under way. For example, we aim to extend the scope of the reaction in terms of possible reactants, elucidate the reaction mechanisms, and develop asymmetric versions of the reaction.

Experimental Section

CDC of *N*-aryl glycine esters with acetone: An *N*-aryl glycine ester **2a–j** (0.15 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (3.0 mg, 0.015 mmol, 10 mol %) were added to a solution of pyrrolidine (3.2 mg, 0.045 mmol, 30 mol %) in acetone (0.75 mL), and the resulting mixture was stirred for 5–10 min. A 5.5 M solution of TBHP (41 µL, 0.225 mmol, 1.5 equiv) in decane was then added, and the reaction mixture was stirred at room temperature in air for the time indicated in Table 1. When the reaction was finished, a standard workup afforded the desired *N*-aryl glycine ester derivative **3a–j.**

CDC of *N*-4-methoxyphenylglycine esters with cycloketones: An *N*-4-methoxyphenylglycine ester **2c**,**k–n** (0.15 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (3.0 mg, 0.015 mmol, 10 mol %) were added to a solution of the cycloketone **1b–e** (5–15 equiv) and pyrrolidine (3.2 mg, 0.045 mmol, 30 mol %) in $CHCl_3$ (1.0 mL), and the resulting mixture was stirred at 0 °C for 5–10 min. DDQ (34.1 mg, 0.15 mmol) was then added at 0 °C in portions. The reaction mixture was stirred at 0–5 °C in air for 6 h, and at room temperature for the time indicated in Table 2. When the reaction was finished, a standard workup afforded the desired *N*-aryl glycine ester derivative **3k–r.**

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