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C–H Activation

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Catalytic Asymmetric Activation of a C_{sp^3}–H Bond Adjacent to a Nitrogen Atom: A Versatile Approach to Optically Active α-Alkyl α-Amino Acids and C1-Alkylated Tetrahydroisoquinoline Derivatives[**]

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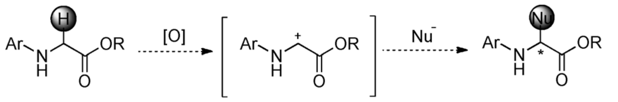
The catalytic enantioselective activation of a C_{sp^3}–H bond to form a new C–C bond provides a potent strategic approach for the synthesis of numerous complex chiral molecules, and is at the forefront of current chemical research.[1] Despite the substantial progress that has been made in this field, this transformation to date has largely been achieved by metal carbene and nitrene insertion.[2] However, a variety of deficiencies such as the use of expensive transition metals, harsh reaction conditions, and poor stereoselectivities have limited the laboratory and industrial applications of these methods. Thus, the development of an alternative approach is particularly appealing.

It was not until very recently that the cross-dehydrogenative coupling (CDC) of C–H bonds to give new C–C bonds was developed.[3] This reaction is more atom economical and environmentally friendly than other cross-coupling reactions, and can be considered as a complementary strategy to the existing direct C–H bonds activations. Considerable advances in this field have recently been achieved.[4,5] However, a catalytic enantioselective variant of this transformation has, to the best of our knowledge, remained elusive, especially for the catalytic asymmetric alkylation of an α-C_{sp^3}–H bond adjacent to a nitrogen atom, even though it presents a powerful method for amine functionalization. In view of this limitation, and considering that under oxidizing conditions, a hydride can be abstracted from the C–H bond adjacent to a nitrogen atom to form a cationic intermediate that could react with a nucleophile, thus leading to the formation of a new C–C bond (Scheme 1), we embarked on the study of asymmetric CDC reactions for the α alkylation of secondary and tertiary amines, for the synthesis of optically active α-alkyl α-amino acids and C1-alkylated tetrahydroisoquinolines.



Scheme 1. Catalytic asymmetric activation of C–H bonds adjacent to a nitrogen atom.

Glycine is the most simple and least expensive natural amino acid, and contains a prochiral carbon at the α position. Therefore, the development of a method for the direct α-C–H functionalization of glycine would provide a convenient way to generate large arrays of diverse α-amino acid derivatives,[6] which are of great importance and have applications in the synthesis of biologically active peptides, natural products, and organocatalysts. Recently, Li and co-workers introduced functionalities such as aryl, vinyl, alkynyl, and indolyl specifically to the α position of relatively unreactive glycine amides.[7] However, glycine esters, unlike glycine amides, did not undergo the CDC reaction, and an alkyl group could not be introduced. Huang and Xie recently used a transition metal/amine catalyst under oxidative conditions to solve this problem, but either the enantioselectivity or yield was poor.[8] The importance of optically active amino acid derivatives and the lack of successful systems for catalytic asymmetric CDC reactions of glycine derivatives with β-ketoesters, combined with our long-standing interest in the synthesis of amino acids,[9] lead us to focus on the study of CDC reactions of glycine esters with α-substituted β-ketoesters. Based on the concept that the catalytic oxidation of α-C_{sp^3}–H bonds of secondary amines provides reactive imines,[10] and considering that the nucleophilic addition to imines has been studied clearly,[11] we believe there is a possibility for this reaction to proceed.

As 2,3-dichloro-5,6-dicyanoquinone (DDQ) has been widely used as an efficient oxidant in several recent oxidative coupling reactions,[12] we started our study with the DDQ-mediated CDC reaction of ethyl 2-oxocyclopentanecarboxylate (**1a**) with *N-para*-methoxyphenyl glycine ester (**2a**) in the presence of 10 mol% of $Cu(OTf)_2$ and 12 mol% of a chiral bisoxazoline (BOX) ligand **4a** in dichloromethane. The reaction gave a moderate yield but poor enantioselectivity (Table 1, entry 1). However, the replacement of **4a** with other ligands, such as **4b**, **4c**, and **4e**, gave no significant improvement to the stereoselectivity (Table 1, entries 2–4). To our delight, when **4f** was used as a ligand, both the stereoselectivity and yield were enhanced (78% *ee*, 75% yield, 4:1 d.r.;

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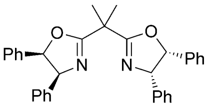
Table 1: Optimization of the reaction conditions.[a]

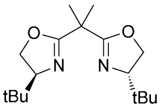
1a **2a** **3a**

Entry	Metal	L*	Solvent	t [h]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	$Cu(OTf)_2$	**4a**	CH_2Cl_2	8	47	4:1	15
2	$Cu(OTf)_2$	**4b**	CH_2Cl_2	8	62	3:1	23
3	$Cu(OTf)_2$	**4c**	CH_2Cl_2	8	58	7:3	25
4	$Cu(OTf)_2$	**4d**	CH_2Cl_2	8	71	3:1	45
5	$Cu(OTf)_2$	**4e**	CH_2Cl_2	12	75	4:1	78
6	$Cu(OAc)_2$	**4e**	CH_2Cl_2	12	57	3:2	35
7	$CuCl_2$	**4e**	CH_2Cl_2	12	48	2:1	17
8	$Zn(OTf)_2$	**4e**	CH_2Cl_2	12	69	4:1	33
9	$Mg(OTf)_2$	**4e**	CH_2Cl_2	12	64	2:1	56
10	$Sc(OTf)_3$	**4f**	CH_2Cl_2	12	51	3:2	27
11	$Yb(OTf)_3$	**4f**	CH_2Cl_2	12	54	7:3	21
12	$Cu(OTf)_2$	**4e**	Tol	12	79	4:1	52
13	$Cu(OTf)_2$	**4e**	THF	12	80	4:1	84
14	$Cu(OTf)_2$	**4e**	THF	24	78	5:1	91[e]

[a] Unless otherwise specified, the reaction was performed on a 0.1 mmol scale at room temperature (see the Supporting Information). [b] Yield of the isolated product. [c] The diastereomeric ratio, *anti*/*syn*, as determined by ^1H NMR spectroscopy. [d] The *ee* value for the major diastereomer. [e] The reaction was carried out at −40 °C. PMP = *para*-methoxyphenyl, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran.



4a



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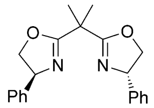
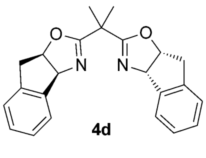
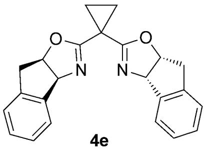


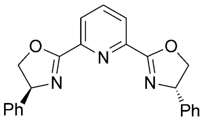
4c



4d

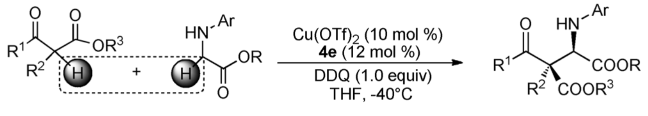


4e



4f

Table 2: Investigation of the scope of the procedure.[a]



1 **2** **3**

Entry	1	R^1	R^2	R^3	2	R	Ar	3	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**1a**	$(CH_2)_3$		Et	**2a**	Et	4-$MeOC_6H_4$	**3a**	78	5:1	91
2	**1a**	$(CH_2)_3$		Et	**2b**	Et	2,4-$MeOC_6H_3$	**3b**	73	6:1	92
3	**1a**	$(CH_2)_3$		Et	**2c**	Et	4-ClC_6H_4	**3c**	65	3:2	84[e]
4	**1a**	$(CH_2)_3$		Et	**2d**	Et	4-BrC_6H_4	**3d**	61	3:2	80[e]
5	**1a**	$(CH_2)_3$		Et	**2e**	Et	C_6H_5	**3e**	82	4:1	86
6	**1a**	$(CH_2)_3$		Et	**2f**	Me	4-$MeOC_6H_4$	**3f**	79	5:1	90
7	**1a**	$(CH_2)_3$		Et	**2g**	Bn	4-$MeOC_6H_4$	**3g**	72	2:1	96
8	**1b**	$(CH_2)_3$		Me	**2e**	Et	C_6H_5	**3h**	60	7:1	89
9	**1b**	$(CH_2)_3$		Me	**2b**	Et	2,4-$MeOC_6H_3$	**3i**	74	2:1	84
10	**1c**	$(CH_2)_3$		*i*Pr	**2a**	Et	4-$MeOC_6H_4$	**3j**	77	2:1	91
11	**1c**	$(CH_2)_3$		*i*Pr	**2f**	Me	4-$MeOC_6H_4$	**3k**	63	7:3	88
12	**1d**	$(CH_2)_3$		*t*Bu	**2a**	Et	4-$MeOC_6H_4$	**3l**	49	5:1	91[e]
13	**1e**	$(CH_2)_3$		Bn	**2a**	Et	4-$MeOC_6H_4$	**3m**	81	6:1	90
14	**1f**	$(CH_2)_3$		Allyl	**2a**	Et	4-$MeOC_6H_4$	**3n**	79	5:1	92
15	**1g**	$(CH_2)_4$		Et	**2a**	Et	4-$MeOC_6H_4$	**3o**	71	2:1	90[e]
16	**1h**	Me	Me	Et	**2a**	Et	4-$MeOC_6H_4$	**3p**	82	2:1	90[e]
17	**1i**	Ph	H	Et	**2a**	Et	4-$MeOC_6H_4$	**3q**	68	3:1	90[f]
18	**1j**	Et	Me	Et	**2a**	Et	4-$MeOC_6H_4$	**3r**	70	3:2	81[e]

[a] Unless otherwise specified, the reaction was carried out with **1** (0.2 mmol) and **2** (0.1 mmol) in the presence of $Cu(OTf)_2$ (0.01 mmol), **4e** (0.012 mmol), and tetrahydrofuran (2.0 mL) at −40 °C for 24 h. [b] Yield of the isolated product. [c] The diastereomeric ratio, *anti*/*syn*, as determined by ^1H NMR spectroscopy. [d] The *ee* value for the major diastereomer. [e] The reaction was carried out at 0 °C. [f] The *ee* value for the minor diastereomer. Bn = benzyl.

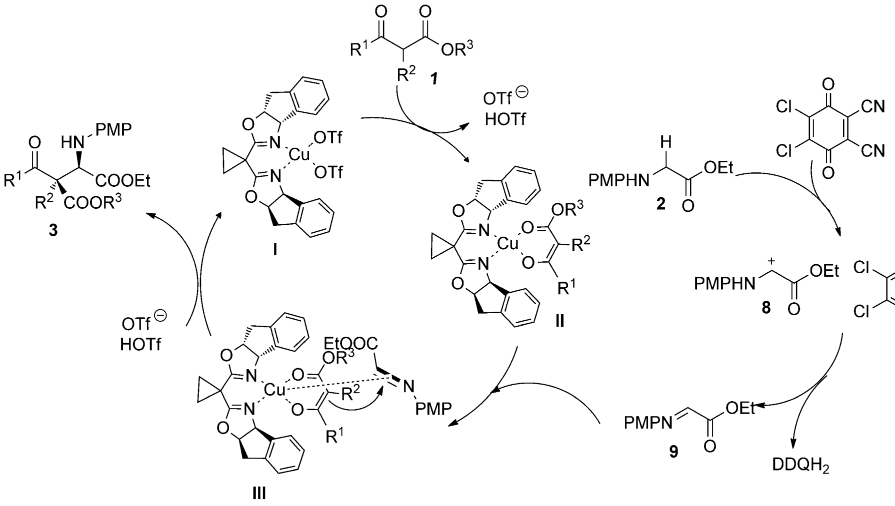
Table 1, entry 5). Other copper salts (Table 1, entries 6 and 7) and alternative transition metal trifluoromethanesulfonic salts (Table 1, entries 8–11) led to less-satisfactory reactions. Solvent optimization results showed that THF was a better solvent with regard to the enantioselectivity (up to 84 % *ee*; Table 1, entries 12 and 13). The best outcome for conversion and enantioselectivity was achieved when the reaction was carried out at −40 °C (Table 1, entry 14).

With the best reaction conditions established, the generality of this novel CDC reaction was investigated (Table 2). In general, the reaction proceeded smoothly to afford the desired products in good yields and good to excellent diastereo- and enantioselectivities. For the reaction with ethyl 2-oxocyclopentanecarboxylate (**1a**), a wide range of aromatic-substituted glycine esters **2a**–**2e** were examined (Table 2, entries 1–5), and it was observed that with both electron-withdrawing and electron-donating groups on the 4-position of the phenyl ring of **2** the desired α-alkyl α-amino acid derivatives were obtained in satisfactory yields of 61–82 % and excellent enantioselectivities (80–92 % *ee*). When the corresponding methyl ester **2f** and benzyl ester **2g** were employed instead of ethyl ester **2a**, coupling products **3f** and **3g**, respectively, were also isolated in good yield and high enantioselectivity (Table 2, entries 6–7).

After testing the generality of this novel CDC reaction with regard to the series of *N*-aryl glycine esters **2a**–**2g** with ethyl 2-oxocyclopentanecarboxylate **1a**, various β-ketoesters were then studied for the synthesis of diverse optically active α-alkyl α-amino acid derivatives. For the five-membered-ring cyclic substrate, when ethyl, methyl, isopropyl, *tert*-butyl, benzyl, and allyl esters **1a**–**f** were used the reaction proceeded readily to give coupling products **3b**–**o** in good yield (49–81 %), moderate diastereoselectivity (d.r. 2:1–7:1), and excellent enantioselectivity (84–92 % *ee*; Table 2, entries 8-14).

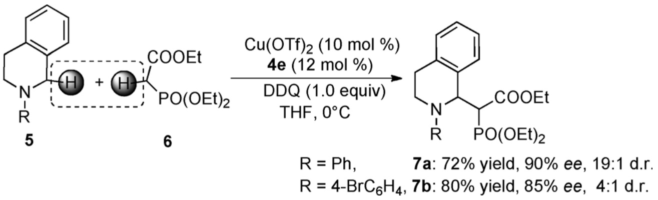
More importantly, six-membered-ring cyclic substrate, ethyl 2-oxocyclohexanecarboxylate **1g** was also a suitable substrate for this novel CDC reaction (Table 2, entry 15). In addition, the less-reactive acyclic substrates **1h**–**j** also reacted completely with **2a** to afford the desired products in good diastereoselectivity and excellent enantioselectivity. The absolute configuration of products was determined from the X-ray structure of a known compound (see the Supporting Information for details).

Encouraged by the outstanding results achieved above, we wished to extend the application of this effective catalytic system to the asymmetric synthesis of other useful organic molecules, such as C1-alkylated tetrahydroisoquinolines, with their potential versatility as active determining building blocks with wide utility in organic synthesis and pharmaceutical chemistry.[13] Also, the efficient construction of the optically pure form of these compounds have not been achieved, to date. Owing to our continuous interest in phosphorus-containing nucleophiles,[14] we chose acetyl phosphates, which are Horner–Wadsworth–Emmons (HWE) reagents with relatively low reactivity,[15] to react with *N*-aryl tetrahydroisoquinolines under the same reaction conditions. Satisfactorily, the reaction generally proceeded smoothly to afford various C1-alkylated tetrahydroisoquinolines **7** in good yields (72–80 %) and excellent diastereo- and enantioselectivities (up to 19:1 d.r., up to 90 % *ee*; Scheme 2).



Scheme 3. Proposed mechanism for the one-pot asymmetric oxidative reaction.

The possible reaction pathways are presumed to involve single-electron transfer (SET).[16] When DDQ reacts with the *N*-PMP glycine esters **2**, a single-electron transfer from **2** would occur to afford the radical cation **8**, and then hydrogen transfer would proceed to provide iminium **9**. To check the intermediacy of a radical cation TEMPO, a radical inhibitor, was added to this reaction system; there was no significant change in the yield of the coupling product and the addition product of *N*-aryl glycine esters with TEMPO was not formed. These results indicate that a radical cation might be involved but that the irreversible hydrogen transfer could be so rapid that TEMPO cannot capture this radical cation, however, a little of this radical cation can be captured by 2,6-di-*tert*-butyl-4-methylphenol (BHT; about 20 %, the yield of **3** decreased from 78 to 59 %). After formation of the iminium intermediate **9**, the electrophilic addition to the prepared chiral lewis-acid-bonded nucleophile **II**, occurs to give the final product **3** (Scheme 3). To support the proposed mechanism, the iminium intermediate **9** was synthesized by oxidation of *N*-PMP glycine esters **2** with DDQ, and then iminium **9** was added to a mixture of **4e**, Cu(OTf)$_2$, and 2-oxocyclopentanecarboxylate **1a** in THF. To our delight, the reaction proceeded well to afford the final coupling product without any loss of enantioselectivity or yield (see the Supporting Information for the details).



Scheme 2. The CDC reaction for the asymmetric synthesis of chiral C1-alkylated tetrahydroisoquinolines.

In summary, we have developed a one-pot, oxidative, and enantioselective cross-coupling reaction of *N*-substituted glycine esters with α-substituted β-ketoesters for the synthesis of various α-alkyl α-amino acids catalyzed by a chiral BOX/Cu^{II} complex. More importantly, this novel strategy was extended to asymmetric synthesis of C1-alkylated tetrahydroisoquinolines by the reaction of Horner–Wadsworth–Emmons reagents with *N*-aryl tetrahydroisoquinolines.

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