Asymmetric Catalysis

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Oxidative and Enantioselective Cross-Coupling of Aldehydes and Nitromethane Catalyzed by Diphenylprolinol Silyl Ether

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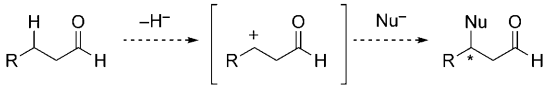
Activation of the C–H bond and transformation of this bond into a new C–C bond is one of the fundamental transformations in organic chemistry.[1,2] Recently, great progress has been achieved in the field of the activation of unreactive C–H bonds, in which organometallic reagents play a central role. Moreover, it is one of the great synthetic challenges not only to transform the unreactive C–H bond into a new C–C bond but also to control the absolute configuration of the newly generated stereogenic center.

There are many methods for the transformation of a C–H bond at the α position of an aldehyde that involve an enolate as a reactive intermediate [Eq. (1)]. On the other hand, the substitution of a proton at the β-carbon atom of the aldehyde with a functional group in a one-pot operation—this operation is a synthetic equivalent of C–H activation at the β-carbon center of the aldehyde—is a difficult transformation even with the use of organometallic reagents. To the best of our knowledge, there has been no successful enantioselective version of this transformation. If a hydride can be abstracted from the C–H bond at the β position of the aldehyde, a cationic intermediate would be formed that would react with a nucleophile leading to the formation of a new C–C bond [Eq. (2)]. One-pot transformation of C–H bond at the β-carbon atom of the aldehyde into a new C–C bond is not known.

(1)

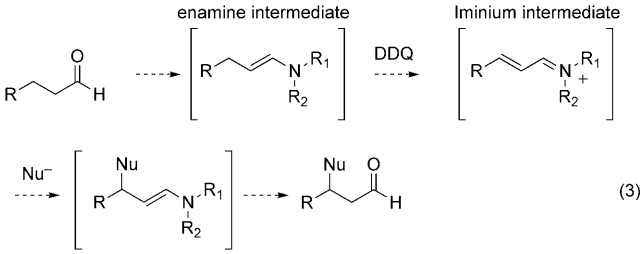


(2)

In 1987, Hayashi and Mukaiyama reported a one-pot procedure for an oxidative carbon–carbon bond-forming reaction[3] using 2,3-dichloro-5,6-dicyanoquinone (DDQ) as an oxidant for the coupling of allyl ethers and TMSCN in the presence of $LiClO_4$. This reaction afforded the desired product in good yields. Recently, several oxidative coupling reactions using DDQ as an oxidant have been developed.[4]

The field of organocatalysis has developed very rapidly,[5] and many synthetically useful asymmetric transformations have been reported, in which enamines[6] and iminium ions[7] are key reactive intermediates. Organocatalysts have been used for domino reactions,[8] and one of the typical organocatalyst-mediated domino reactions is the reaction of an iminium ion and subsequent reaction of an enamine species. However, there is no precedent in the literature where an enamine formed from a saturated aldehyde and chiral amine gives access to a reactive α,β-unsaturated iminium intermediate.

If the enamine, generated from an aldehyde and an amine, reacts with a hydride-abstracting reagent, it would afford an iminium ion [Eq. (3)]. Because the enamine is an electron-rich alkene and DDQ can act as a hydride-abstracting reagent from an allylic hydrogen, there is a possibility for this reaction to proceed. Because the iminium ion is known to be a reactive intermediate, it would react with a nucleophile to afford a β-substituted aldehyde after hydrolysis. By the use of a suitable organocatalyst, asymmetric induction might be expected. Use of an organocatalyst would then allow the functionalization of unreactive C–H bonds. The successful realization of this scenario will be described herein.



(3)

First, we had to investigate whether the iminium ion could be generated by the reaction of aldehyde, organocatalyst, and a hydride-abstracting reagent. We chose 3-phenylpropanal and DDQ as a model aldehyde and a hydride-abstracting reagent, respectively. Diphenylprolinol trimethylsilyl ether **1a**[9] was selected as an organocatalyst, which was independently developed by our group[10] and Jørgensen's group (Scheme 1).[11] After treatment of the aldehyde and an

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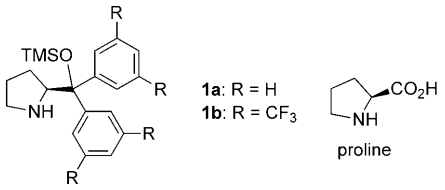
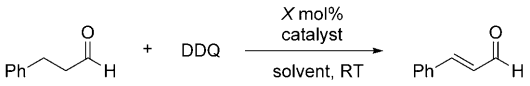


Scheme 1. Organocatalysts used in the present study. TMS = trimethylsilyl.

equimolar amount of DDQ with a catalytic amount of organocatalyst **1a**, the reaction was quenched with aqueous $NaHCO_3$ and cinnamaldehyde was isolated as the product,[12] thus indicating that the hydride abstraction had proceeded. The effect of solvent and amount of the catalyst were examined and the results are summarized in Table 1. Both THF and toluene were effective solvents. The reaction was completed within 1 hour at room temperature in quantitative yield when 20 mol% of catalyst **1a** was used (Table 1, entries 5 and 6).

Table 1: The effect of solvent and amount of catalyst in the reaction of 3-phenylpropanal and DDQ catalyzed by an amine catalyst.[a]



Entry	Catalyst	Solvent	Amount of catalyst [mol%]	Amount of DDQ [equiv]	*t* [h]	Yield [%][b]
1	**1a**	CH_2Cl_2	10	2	48	44
2	**1a**	toluene	10	2	48	77
3	**1a**	THF	10	1.5	48	75
4	**1a**	CH_2Cl_2	20	1	4	85
5	**1a**	toluene	20	1	1	quant.
6	**1a**	THF	20	1	1	quant.
7	proline	THF	20	1	1	66
8	**1b**	THF	20	1	1	quant.

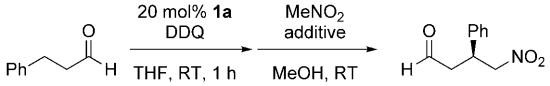
[a] Reaction conditions: 3-phenylpropanal (0.4 mmol), DDQ, and catalyst in solvent (1.6 mL) at room temperature. [b] Yield of isolated product. THF = tetrahydrofuran.

The amine catalyst is essential for this oxidation, as no reaction proceeded without amine catalyst **1a**. Other chiral amines such as proline and trifluoromethyl substituted diarylprolinol silyl ether **1b** were also effective for this oxidation, and afforded cinnamaldehyde in 66% yield and quantitatively, respectively (Table 1, entries 7 and 8). Other achiral amines like pyrrolidine was not as effective, and afforded the product in 29% yield.[13] A tertiary amine was not suitable, as no reaction proceeded in the presence of Et_3N, and cinnamaldehyde was obtained in about 5% yield when the reaction was catalyzed by pyridine.

As we already knew that **1a** would be an effective catalyst in the subsequent reaction of nitromethane and α,β-unsaturated aldehyde,[14] catalyst **1a** was selected as the chiral amine catalyst.

Because the first hydride abstraction preceded efficiently, a one-pot oxidative carbon–carbon bond-formation reaction was examined. As γ-nitro aldehyde is a synthetically important chiral building block, nitromethane was selected as a nucleophile. We have already reported the asymmetric Michael reaction of nitromethane with α,β-unsaturated aldehydes catalyzed by diphenylprolinol silyl ether **1a**,[14] in which MeOH was an effective solvent. Hence, MeOH was used in the second reaction; however, the reaction scarcely proceeded. Benzoic acid was identified as an effective additive in the Michael reaction of nitromethane and α,β-unsaturated aldehydes, and the reaction of allyl ether and TMSCN with DDQ was accelerated in the presence of $LiClO_4$.[3] These observations encouraged us to investigate the effect of additives, the study is summarized in Table 2.

Table 2: Effect of the additive in the reaction of 3-phenylpropanal and nitromethane catalyzed by **1a**.[a]



Entry	Additive	*t* [h][b]	Yield [%][c]	*ee* [%][d]
1	p-$NO_2C_6H_4OH$	48	< 5	n.d.
2	$PhCO_2H$	48	< 5	n.d.
3	$NaHCO_3$	48	38	90
4	Et_3N	48	50	85
5	Na_2HPO_4	48	36	93
6	NH_4OAc	48	36	92
7	LiOAc	24	57	93
8	NaOAc	24	76	92

[a] Reaction conditions: 3-phenylpropanal (0.4 mmol), DDQ (0.4 mmol), catalyst **1a** (0.08 mmol), THF (1.6 mL), $MeNO_2$ (4.0 mmol), additive (0.96 mmol), MeOH (0.8 mL). [b] The reaction time for the addition reaction of nitromethane. [c] Yield of isolated product. [d] Determined by HPLC on a chiral stationary phase. n.d. = not determined.

Although acids such as *p*-nitrophenol and benzoic acid scarcely promote the reaction, the use of a weak base was effective. The reaction was found to be promoted by $NaHCO_3$, Et_3N, LiOAc,[14c] NH_4OAc, and NaOAc. The NaOAc was a suitable additive and afforded the product in good yield with excellent enantioselectivity. Upon the addition of NaOAc, immediate precipitation occurred and this would correspond to the formation of a sodium salt of hydroquinone. The effective removal of the acidic hydroquinone would be one of the key roles of this additive. The absolute configuration of the reaction product was determined by comparison with the product synthesized by our previous procedure.[14a] Once we had established the one-pot procedure, the method was applied to a domino reaction. Our studies focus on the reaction of 3-phenylpropanal in the presence of DDQ, diphenylprolinol silyl ether **1a**, and nitromethane. Several solvents and additives were tested. However, good results have not been obtained so far.

Once the best reaction conditions for the one-pot reaction were found, the generality of the reaction was investigated, the results are summarized in Table 3. As for the β substituent of α,β-unsaturated aldehyde, not only the phenyl group (Table 3, entry 1) but also the electron-rich *p*-methoxyphenyl and electron-deficient *p*-bromo- and *p*-nitrophenyl groups

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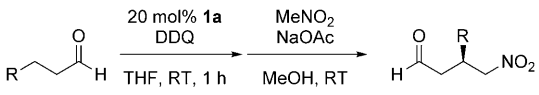
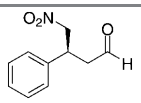
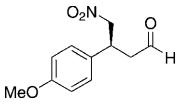
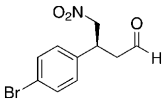
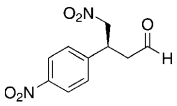
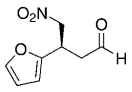
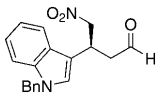
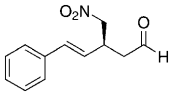
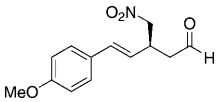
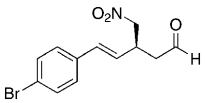
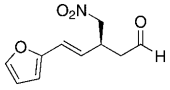
Table 3: The generality of the one-pot, oxidative asymmetric Michael reaction.[a]



Entry	Product	*t* [h][b]	Yield [%][c]	*ee* [%][d]
1		12	75	92
2		12	77	95
3		12	66	95
4		12	65	94
5		20	62	94
6		12	70	92
7		4	78	91
8		3	80	92
9		4	71	90
10		8	64	85

[a] Reaction conditions: aldehyde (0.4 mmol), DDQ (0.4 mmol), catalyst **1a** (0.08 mmol), THF (1.6 mL), $MeNO_2$ (4.0 mmol), NaOAc (0.96 mmol), MeOH (0.8 mL). [b] The reaction time for the addition reaction of nitromethane. [c] Yield of isolated product. [d] For the determination of enantiomeric excess, see the Supporting Information. Bn = benzyl.

were suitable (Table 3, entries 2–4), where hydride abstraction and subsequent asymmetric Michael reaction proceeded efficiently to afford the product with excellent enantioselectivity. In addition to the aromatic group, heteroaromatic groups such as furyl and indole were successfully employed as a β substituent of α,β-unsaturated aldehyde (Table 3, entries 5 and 6). Moreover, β-aryl and β-heteroaryl substituted α,β-unsaturated aldehydes, pent-4-enal derivatives were also suitable substrates. As for the substituents at the 5-position of pent-4-enal, aromatic groups with both electron-rich and electron-deficient substituents were used to afford the products with excellent enantioselectivity (Table 3, entries 7–10).

The reaction is thought to proceed via two reaction paths (Scheme 2). The first oxidation path is rather fast (within 1 h; Table 1), while the second addition reaction of nitromethane is slow (within 3–20 h; Table 3). Organocatalyst **1a** reacts with the aldehyde to afford enamine **2** along with the generation of water. Enamine **2** reacts with DDQ, which abstracts a hydride, to provide iminium ion **3**, and **3** reacts with water to afford α,β-unsaturated aldehyde **4** with the regeneration of catalyst **1a**. α,β-Unsaturated aldehyde **4** reacts with catalyst **1a** to generate iminium ion **5**, which reacts with nitromethane to afford enamine **6**. Enamine **6** reacts with water to give the product **7** with regeneration of catalyst **1a**. Iminium ion **5** is also generated directly from iminium ion **3** by reaction with NaOAc. 4,5-Dichloro-3,6-dihydroxy-1,2-benzenecarbonitrile is too acidic and addition of NaOAc is essential for the conversion of iminium ion **3** into **5**, with the elimination of the sodium salt of hydroquinone derivative from the reaction mixture by the precipitation.

When DDQ reacts with the enamine **2**, single electron transfer[4e,15] from enamine **2** would occur to afford a radical cation, from which hydrogen transfer would proceed to provide iminium ion **3**. To check the intermediacy of a radical cation, we performed the reaction of 3-phenylpropanal and DDQ in the presence of several equivalents of the radical trap reagent TEMPO. Although the yield of cinnamaldehyde was dependant on the amount of TEMPO,[16] the hydride abstraction proceeded to afford cinnamaldehyde with the recovery of 3-phenylpropanal, in which no addition product of 3-phenylpropanal and TEMPO was formed. We also conducted the experiment with allyltrimethylsilane as a radical trap, as it is reported to be a suitable SOMOphile by MacMillan and coworkers.[17] When 3-phenylpropanal, DDQ, allyltrimethylsilane (2.5 equiv), and **1a** (20 mol%) were stirred in THF, cinnamaldehyde was obtained in 95% yield without formation of the addition product with the allyl moiety. These results indicate that a radical cation might be involved, but the irreversible hydrogen transfer would be very rapid.

In summary, we have developed a one-pot, oxidative and enantioselective cross-coupling reaction of aldehydes and nitromethane catalyzed by diphenylprolinol silyl ether. There are several noteworthy features in the present reaction. 1) The proton at the β-carbon atom of an aldehyde was substituted with nitromethyl (CH_2NO_2) enantioselectively. 2) This reaction is a synthetic equivalent of C–H activation at the β-carbon atom of an aldehyde. 3) β-Substituted γ-nitro aldehyde, an important synthetic intermediate, can be synthesized with excellent enantioselectivity. 4) Oxidative C–C bond-forming reactions can be successfully performed without a metal by the use of organic oxidizing reagent. 5) The secondary amine catalyst **1a** plays two different roles: one is the generation of an enamine and the other is the generation of an α,β-unsaturated iminium ion. 6) This is the first, enantioselective one-pot transformation of a C–H bond at the β-carbon atom of aldehyde into a new C–C bond.

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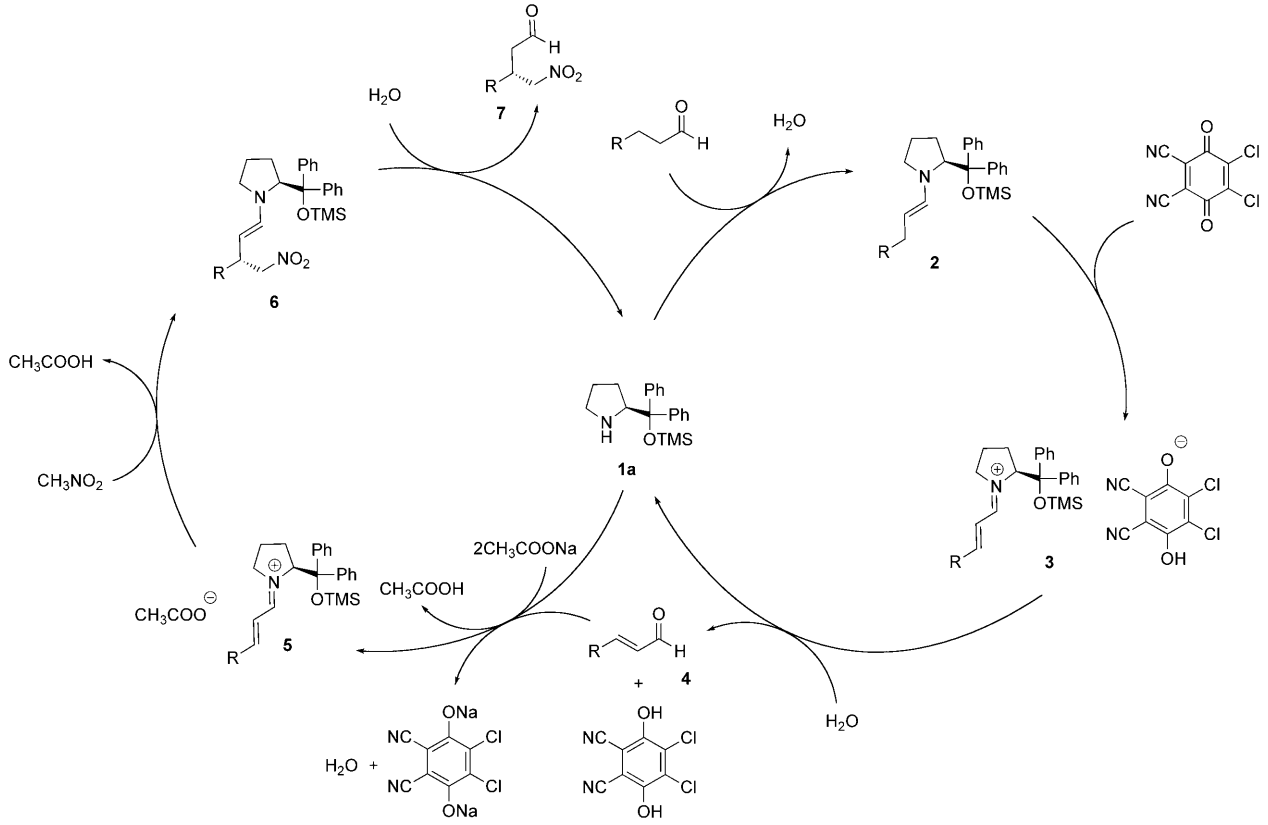

Scheme 2. Proposed reaction mechanism for the asymmetric, oxidative reaction.

Keywords: asymmetric catalysis · cross-coupling · one-pot reaction · organocatalysis · oxidative reaction

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