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Organocatalytic Asymmetric Intermolecular Dehydrogenative α-Alkylation of Aldehydes Using Molecular Oxygen as Oxidant

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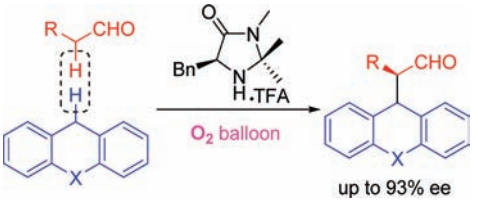
ABSTRACT



An organocatalytic enantioselective intermolecular oxidative dehydrogenative α-alkylation of aldehydes via benzylic C−H bond activation has been developed. The asymmetric reaction is smoothly fulfilled by using simple and green molecular oxygen as the oxidant. Two hydrogen dissociations make this transformation more environmentally benign because of high atom efficiency.

In the past decade, organocatalysis has experienced dramatic growth.[1] The magical performance of organocatalysis encouraged chemists to discover more efficient approaches for construction of optically active compounds. Among them, the organocatalytic asymmetric α-alkylation of carbonyl comounds, especially of aldehydes, has long been a challenging task.[2] Recently, the intramolecular α-alkylation of aldehydes has been disclosed by List[3] and others.[4] In contrast, the organocatalytic enantioselective intermolecular α-alkylation of aldehydes has been rarely reported. MacMillan and co-workers made a significant contribution on the asymmetric intermolecular α-alkylation of aldehydes via a radical process by their organo-SOMO catalysis or merging photocatalysis and

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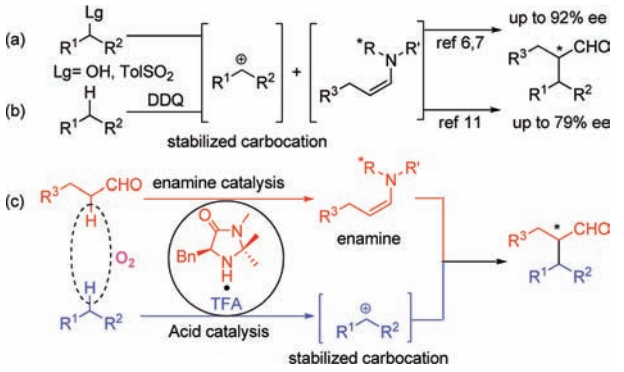
Scheme 1. Strategies for Enantioselective α-Alkylation of Aldehydes



enamine catalysis.[5] Another important S_N1-type enantioselective intermolecular α-alkylation of aldehydes, with a stabilized carbocation generated from an alcohol with the acid involved in the enamine catalysis,[6,7] or by dissociation of arylsulfonyl[8] group (a, Scheme 1), has been developed by Cozzi[6] and Melchiorre.[8] Our recent studies have also shown the enantioselective tandem reduction and alkylation of α,β-unsaturated aldehydes with a stabilized carbocation generated in situ from loss of a hydroxyl group.[9]

On the other hand, a stabilized carbocation can be produced from the benzylic C−H bond under different oxidative conditions.[10,11] Recently, Li and co-workers have developed the cross-dehydrogenative coupling (CDC reaction).[11] However, the enantioselective α-alkylation of aldehydes with a potential electrophile via C−H bond activation is more challenging, mainly because of the stability of the produced carbocation and the potential side reaction between the carbocation and the generated water during the formation of the enamine.[12] In 2009, Cozzi's group first realized the organocatalytic stereoselective alkylation of aldehydes via benzylic C−H bond activation using DDQ as the oxidant (b, Scheme 1).[13]

The utilization of molecular oxygen as an oxidant has attracted considerable attention because of its readily availability and its inexpensive and environmental benign character.[14,15] More recently, a *nonasymmetric* oxidative α-alkylation of *ketones* with benzylic C−H bond activation using molecular oxygen as oxidant promoted by Brønsted acid was reported by Klussmann et al.[16] Considering that the free acid could be generated in the enamine catalytic process,[6,9] we envisioned that the enantioselective α-alkylation of aldehydes might be realizable in a simple and green way using molecular oxygen as the oxidant under enamine catalysis and acid catalysis (c, Scheme 1). Herein, we describe an organocatalytic asymmetric oxidative dehydrogenative α-alkylation of aldehydes via benzylic C−H bond activation using molecular oxygen as the oxidant.

To validate our hypothesis, we embarked on the investigation with the reaction of commercially available xanthene **1a** with hexanal **2a** in the presence of catalyst **A** in CH_3NO_2 under O_2 (1.0 atm). Interestingly, the desired product **3aa** was obtained in 63% yield with 56% ee (enantiomeric excess) (entry 1, Table 1). Encouraged by this result, we screened a range of the MacMillan catalysts[1c,e] **B**−**E**, under the same reaction conditions. The results showed that catalyst **B** is an effective organocatalyst for this transformation, which gave **3aa** in 81% yield with 73% ee (entry 2, Table 1). When pyrrolidine derivatives **F**−**H** (either the free amine or their salts of TFA and PhCOOH) were employed as the catalysts, the reactions did not work or only gave traces of the desired product **3aa** (entries 6−8). Different reaction temperatures were subsequently surveyed. When the reaction was performed at −5 °C, the ee value was improved to 80% and the yield to 76% (entry 9, Table 1). Lowering the reaction temperature to −15 °C raised the ee value to 87% but decreased the yield to 33% (entry 10). Different solvents were then screened. The results indicate that the reactions in CH_3NO_2 performed the best in terms of yield and ee value (entries 11−16, Table 1). Gratifyingly, H_2O as an additive had a significant effect on this asymmetric α-alkylation. When 10 equiv of H_2O was employed, the desired alkylation product **3aa** was obtained in 71% yield

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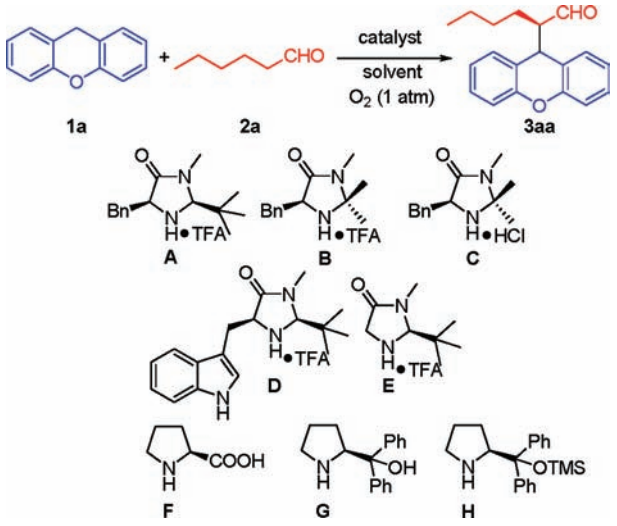
Table 1. Reaction of Xanthene **1a** and Hexanal **2a** in the Presence of Different Conditions[a]



entry	catalyst	solvent	temp (°C)	yield[b] (%)	ee[c] (%)
1	**A**	CH_3NO_2	5	63	56
2	**B**	CH_3NO_2	5	81	73
3	**C**	CH_3NO_2	5	trace	
4	**D**	CH_3NO_2	5	40	18
5	**E**	CH_3NO_2	5	73	42
6	**F**	CH_3NO_2	5	trace	
7	**G**	CH_3NO_2	5	nr	
8	**H**	CH_3NO_2	5	nr	
9	**B**	CH_3NO_2	−5	76	80
10	**B**	CH_3NO_2	−15	33	87
11	**B**	DCM	−5	21	82
12	**B**	DCE	−5	29	83
13	**B**	toluene	−5	trace	
14	**B**	xylene	−5	nr	
15	**B**	THF	−5	nr	
16	**B**	CH_3CN	−5	81	70
17[d]	**B**	CH_3NO_2	−5	71	92
18[e]	**B**	CH_3NO_2	5	trace	

[a] All reactions were carried out on the scale of **1a** (0.2 mmol), **2a** (0.6 mmol), catalyst (0.04 mmol) in 1 mL of solvent at the appointed temperature under O_2 (1 atm) for 4 days. [b] Isolated yields; nr = no reaction. [c] The ee value was determined by chiral HPLC analysis. [d] The reaction was carried out in 1 mL of dry CH_3NO_2 and 10 equiv of H_2O. [e] The reaction was carried out under N_2.

with 92% ee (entry 17, Table 1). The reaction under N_2 did not work (entry 18, Table 1).

With the optimized conditions in hand, the scope of this transformation was then investigated (Table 2). A wide range of aliphatic aldehydes smoothly underwent this asymmetric transformation generating the desired alkylation products **3** in moderate to good yield (48−77%) with excellent ee values (81−92%) (entries 1−6, Table 2). The yields and ee values in the reaction of isovaleraldehyde **2g** were unsatisfactory, possibly due to steric hindrance in the aldehyde (entry 7, Table 2). Aldehydes containing olefins were tolerated in this transformation generating **3ah** in

Table 2. Reaction of Xanthene **1a**, Thioxanthene **1b**, and 10-Methyl-9,10-dihydroacridine **1c** with Different Aldehydes[a]

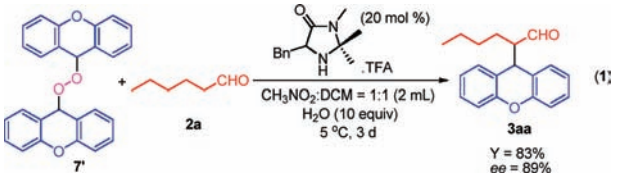
entry	1	2(R)		temp (°C)	3	yield[b] (%)	ee[c] (%)
1	**1a**	C_4H_9	**2a**	−5	**3aa**	71	92
2	**1a**	Me	**2b**	+5	**3ab**	61	81
3	**1a**	Et	**2c**	+5	**3ac**	62	90
4	**1a**	C_3H_7	**2d**	−5	**3ad**	77	90
5	**1a**	C_5H_{11}	**2e**	+5	**3ae**	48	89
6	**1a**	C_6H_{13}	**2f**	+5	**3af**	65	83
7	**1a**	^{i}Pr	**2g**	+5	**3ag**	40	69
8	**1a**	allyl	**2h**	+5	**3ah**	67	87
9	**1a**	benzyl	**2i**	+5	**3ai**	64	92
10[d,e]	**1a**	*p*-MeO-benzyl	**2j**	−5	**3aj**	82	86
11[d,f]	**1a**	*p*-Me-benzyl	**2k**	+5	**3ak**	81	80
12[g]	**1a**	*o*-NO_2-benzyl	**2l**	+5	**3al**	82	93
13[d]	**1b**	C_4H_9	**2a**	−5	**3ba**	24	76
14[h]	**1c**	C_4H_9	**2a**	+5	**3ca**	52	45

[a] All reactions were carried out on the scale of **1** (0.2 mmol), **2** (0.6 mmol), catalyst **B** (0.04 mmol), and H_2O (10 equiv) in 1 mL of dry CH_3NO_2 at the appointed temperature under O_2 (1 atm) for 4 days. [b] Isolated yields. [c] The ee value was determined by chiral HPLC analysis. [d] The commercial CH_3NO_2 (1 mL) was directly used. [e] Isolated yield based on 51% conversion of xanthene. [f] Isolated yield based on 48% conversion of xanthene. [g] Isolated yields based on 49% conversion of xanthene. [h] The reaction was carried out in 1 mL of dry DCM with the addition of 10 equiv of H_2O.

67% yield with 87% ee value (entry 8). Moreover, this method proved to be effective for a range of aldehydes substituted with phenyl groups, leading to excellent ee values (80−93%) (entries 9−12, Table 2). The reaction using thioxanthene **1b** and 10-methyl-9,10-dihydroacridine **1c** as the substrates could also execute this transformation under these conditions but in moderate enantiomeric excesses, respectively (entries 13 and 14, Table 2). The absolute configuration of compound **3ai** was determined to be *R* by comparison of the elution order of the products from a chiral phase HPLC column to those reported in the literature.[13]

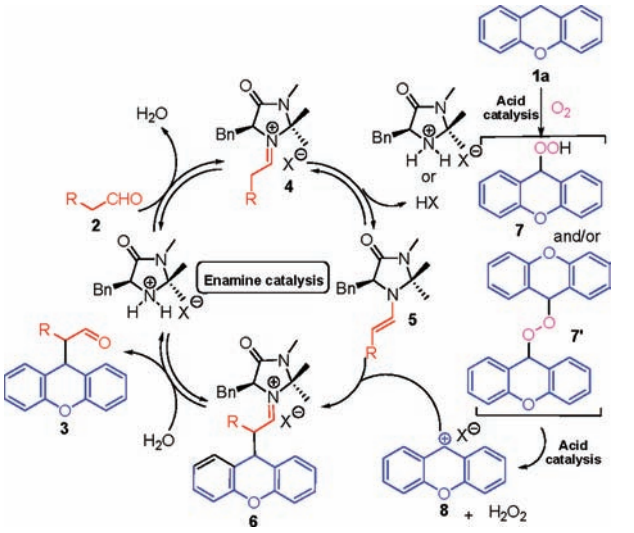
A plausible mechanism for the asymmetric transformation is illustrated in Scheme 2. We believe that the mechanism includes two catalytic cycles: enamine catalysis and acid catalysis. The enamine catalytic cycle involves condensation of the ammonium salt catalysts and the saturated aldehydes **2** to generate iminium intermediates **4**, which are converted to the activated nucleophilic enamine species **5** by deprotonation with the release of free acid (HX). Subsequently, the nucleophilic enamine species **5** react with carbocations **8** to form new iminium intermediates **6**. Finally, the products **3** are produced by hydrolysis of **6** with formation of the ammonium salt catalysts to complete the catalytic cycle. In the acid catalytic cycle, the

substrates **1** could be oxidized to peroxides **7** and/or **7′** by a radical pathway with O_2.[16,17] The peroxides **7** and/or **7′** could then produce stabilized carbocations **8**[16] catalyzed by the free acid (HX) generated in the enamine catalysis or by the ammonium salts serving as Brønsted acids.[18] The formed carbocations **8** immediately participate in the enamine catalysis cycle to execute this transformation. Further investigation showed that the isolated xanthene peroxide **7′** could directly react with **2a** at 5 °C to produce **3aa** in 83% yield with 89% ee (eq 1). This result indicates that the peroxides **7′** which could be generated from **7** under acidic conditions[16,17] may be the key intermediates of this transformation.



In summary, we have developed an organocatalytic asymmetric intermolecular oxidative dehydrogenative α-alkylation of aldehydes via benzylic C−H bond activation. The asymmetric reaction is smoothly effected by using simple and green dioxygen as the oxidant. Two hydrogen dissociations make this transformation more environmentally benign via high atom efficiency. Furthermore, that the ammonium salt catalysts play dual roles not only as enamine catalysts but also as acid catalysts, to broaden the research into the areas of ammonium salt catalysis and the cross-dehydrogenative coupling using dioxygen as the oxidant. Further studies on the scope, the mechanism, and the synthetic applications are ongoing in our laboratory.

Scheme 2. Proposed Catalytic Cycles for the Enantioselective Transformation



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Supporting Information Available. Experimental details, NMR spectra, and HPLC analysis of the products. This material is available free of charge via the Internet at http://pubs.acs.org.