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Catalytic asymmetric cross-dehydrogenative coupling: activation of C–H bonds by a cooperative bimetallic catalyst system†

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A cooperative bimetallic catalyst system was applied in the catalytic asymmetric cross-dehydrogenative coupling of β-ketoesters and xanthene. Various optically active xanthene derivatives bearing a quaternary stereogenic carbon center were obtained in moderate to good yields (up to 90%) with excellent enantioselectivities (up to 99% ee). Meanwhile, a transition-state model was proposed to explain the origin of the asymmetric induction.

Catalytic asymmetric cross-dehydrogenative coupling reaction (CDC reaction) has attracted great attention because it provides efficient methods to construct versatile and useful building blocks.[1] Under oxidative conditions, two C–H bonds could be directly coupled to form a new C–C bond without prior installation of functional groups. For the activation of sp^3 C–H bond in this reaction, the generation of a carbocation mediated by an oxidant is the key step.[2] Therefore, seeking stable carbocations *in situ* is extremely significant. CDC reactions of amines or ethers, which could stabilize the carbocation by an α-heteroatom, with nucleophiles have been widely reported.[1,3] However, the asymmetric oxidative coupling of an unreactive benzylic C–H bond has remained a challenge due to the instability of the generating carbocation.[4] Xanthene, which contains a benzylic C–H bond, is pharmaceutically and biochemically active and has been widely used as dyes and fluorescent materials.[5] At present, only two examples of asymmetric CDC reaction of xanthene with aldehydes have been described subsequently by Cozzi's[4a] and Jiao's groups.[4c] MacMillan-type organocatalysts were used to promote the process with up to 93% ee.

With regard to chiral catalysts used for sp^3 C–H-activation-based asymmetric C–C bond formation *via* CDC reaction, chiral mono-metal complexes,[3,4b] organocatalysts[4a,c] and metal–organic cooperative catalysts[6] have been employed. In recent years, bimetallic cooperative catalysis has emerged as an attractive strategy to achieve high efficiency and selectivity in asymmetric reactions[7] due to the distinct multiple functionalities in a simultaneous manner. However, to the best of our knowledge, this approach has not been applied in catalytic asymmetric CDC reactions. We herein developed a catalytic asymmetric CDC reaction of α-substituted β-ketoesters with xanthene. By using a chiral Ni^{II}–Fe^{II} hetero-bimetallic cooperative catalyst system, good yields and excellent enantioselectivities were achieved for various optically pure xanthene derivatives bearing a quaternary stereogenic carbon center.

Initially, we examined the CDC reaction between *tert*-butyl indanone carboxylate **1a** as a representative pronucleophile and xanthene using TBHP as the oxidant. A series of metal salts such as Cu^{I}, Zn^{II}, Fe^{II} and Ni^{II} chelated with L-proline-derived *N*,*N*′-dioxide **L1**[8] were used to catalyze the coupling reaction (Table 1, entries 1–4). To our delight, the desired product **3a** was obtained in 47% yield with 77% ee by using nickel(II) as the central metal. Nevertheless, a considerable amount of byproduct **3a**′ from α-hydroxylation of β-ketoester **1a** was also detected (Table 1, entry 4). Comparatively, iron(II) salt gave a higher yield of **3a** but as a racemate (Table 1, entry 3). Then we modified the catalysts with different nickel salts (Table 1, entries 5–7), and found that the counterions had a crucial influence on the reaction. NiF_2 did not promote the reaction at all (Table 1, entry 5), whereas excellent enantioselectivity (97% ee) and moderate yield were obtained with $NiBr_2$ (Table 1, entry 7). The structure of the *N*,*N*′-dioxide ligands was also found to affect both the reactivity and enantioselectivity. Although the combination of **L5** and $NiBr_2$ promoted the reaction with up to 99% ee, only moderate yield of the desired product **3a** was generated as the result of the side reaction (Table 1, entry 11). Considering the high yield catalyzed by **L**-Fe(II), and the excellent enantiomeric excess catalyzed by **L5**-$NiBr_2$, we next examined the CDC reaction with a bimetallic cooperative catalyst. Firstly, a mixture of 10 mol% of $NiBr_2$, 10 mol% of $Fe(BF_4)_2\cdot 6H_2O$, and 20 mol% of **L5** was composed to catalyze this reaction. It was found to our delight that the yield of the product **3a** was obviously improved, but with a small loss of enantiomeric excess (87% yield, 79% ee; Table 1, entry 12 *vs.* 11). Then the amount of Fe(II) species was decreased to minimize the disadvantage to the enantioselectivity. Entries 13 and 14 showed that the enantiomeric excess enhanced gradually upon reducing the amount of $Fe(BF_4)_2\cdot 6H_2O$ with the high yield of **3a** maintained. When 1 mol% of

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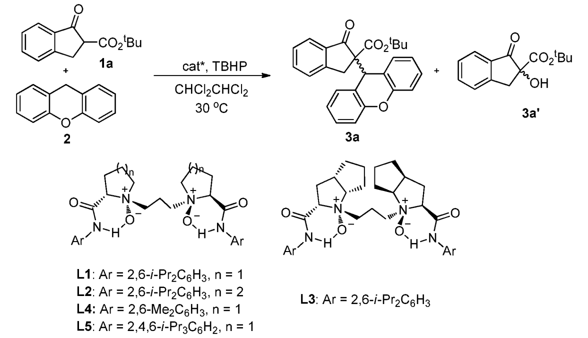
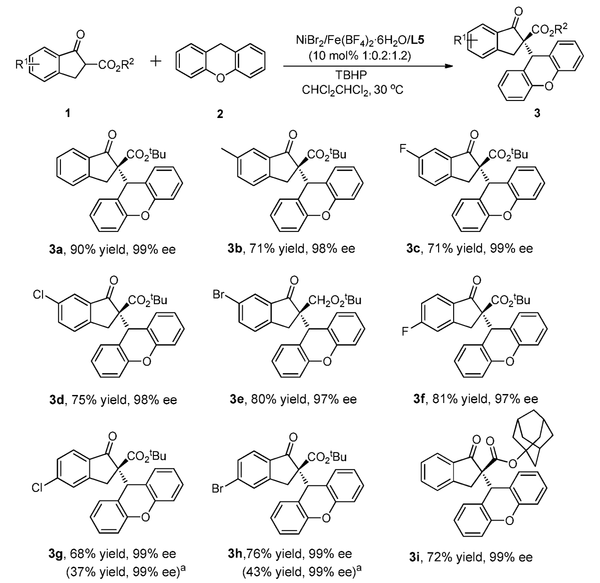
Table 1 Optimization of the reaction conditions



Entry[a]	Metal	Ligand	Yield of **3a**[b] (%)	ee of **3a**[c] (%)
1	CuBr	**L1**	67 (20)	0
2	$Zn(BF_4)_2 \cdot 6H_2O$	**L1**	34 (16)	0
3	$Fe(BF_4)_2 \cdot 6H_2O$	**L1**	88 (<5)	0
4	$Ni(BF_4)_2 \cdot 6H_2O$	**L1**	47 (29)	77
5	NiF_2	**L1**	Trace (-)	—
6	$NiCl_2$	**L1**	46 (24)	75
7	$NiBr_2$	**L1**	49 (36)	97
8	$NiBr_2$	**L2**	33 (47)	96
9	$NiBr_2$	**L3**	25 (63)	85
10	$NiBr_2$	**L4**	42 (50)	33
11	$NiBr_2$	**L5**	51 (40)	99
12[d]	$NiBr_2/Fe(BF_4)_2 \cdot 6H_2O$	**L5**	87 (<5)	79
13[e]	$NiBr_2/Fe(BF_4)_2 \cdot 6H_2O$	**L5**	88 (<5)	93
14[f]	$NiBr_2/Fe(BF_4)_2 \cdot 6H_2O$	**L5**	90 (<5)	99
15[g]	$NiBr_2/Fe(BF_4)_2 \cdot 6H_2O$	**L5**	66 (23)	99

[a] Unless otherwise noted, all reactions were performed with L-metal (10 mol%, 1 : 1), **1a** (0.10 mmol), **2** (0.11 mmol), TBHP (^{t}BuOOH; 20 μL 5.0–6.0 M in decane) at 30 °C for 24 h. The yields in parentheses are the isolated yields of **3a**′. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Ni(II)/Fe(II)/**L5** (10 mol%, 1/1/2). [e] Ni(II)/Fe(II)/**L5** (10 mol%, 1/0.5/1.5). [f] Ni(II)/Fe(II)/**L5** (10 mol%, 1/0.2/1.2). [g] Ni(II)/Fe(II)/**L5** (10 mol%, 1/0.1/1.1).



3a, 90% yield, 99% ee
3b, 71% yield, 98% ee
3c, 71% yield, 99% ee
3d, 75% yield, 98% ee
3e, 80% yield, 97% ee
3f, 81% yield, 97% ee
3g, 68% yield, 99% ee (37% yield, 99% ee)[a]
3h,76% yield, 99% ee (43% yield, 99% ee)[a]
3i, 72% yield, 99% ee

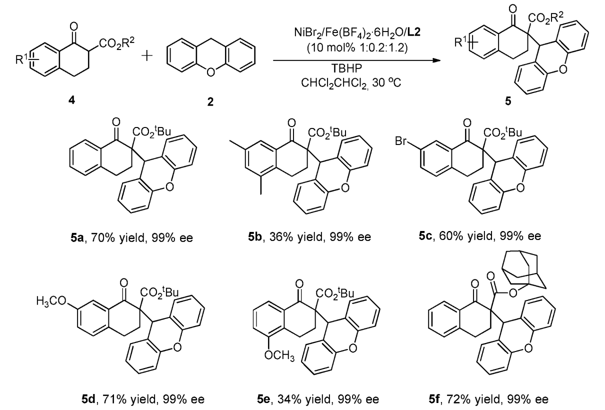
Fig. 1 Substrate scope for the 1-indanone derivatives. Unless otherwise noted, all reactions were performed with $NiBr_2/Fe(BF_4)_2 \cdot 6H_2O$/**L5** (10 mol%, 1 : 0.2 : 1.2), **1** (0.10 mmol), **2** (0.11 mmol), TBHP in decane (5.0–6.0 M, 20 μL) at 30 °C for 10 h. Relative and absolute stereochemical configurations were determined by X-ray analysis and circular dichroism spectrum. The results in parentheses were obtained by using $NiBr_2$/**L5** (10 mol%, 1 : 1) as the catalyst.

$Fe(BF_4)_2 \cdot 6H_2O$ was added, a slight increase in the CDC product was observed, although the byproduct was inhibited simultaneously (Table 1, entry 15 *vs.* entry 11). Therefore, 2 mol% of $Fe(BF_4)_2 \cdot 6H_2O$, 10 mol% of $NiBr_2$ and 12 mol% of **L5** as the catalyst were optimized to initiate the CDC reaction (Table 1, entry 14).

With the optimal conditions established, the scope of the reaction was then probed (Fig. 1). High yields with excellent ee values were observed for a range of substituted indanone pronucleophiles bearing *tert*-butyl ester substituents (68–90% yield, 97–99% ee, **3a–3h**). The electronic effect has no influence on the enantioselectivity, and the yields were slightly affected by either the electron-donating or -withdrawing substituent. In two instances, the acceleration of the reactivity with the assistance of $Fe(BF_4)_2$ was further confirmed. The yields of the products were significantly increased in the presence of the cooperative bimetallic catalyst system (for **3g** from 37% to 68%, and for **3h** from 43% to 76%). In addition, the substrate with the more hindered substituent located on the ester side could also give the corresponding product **3i** with good results (72% yield, 99% ee). In all cases, a small amount of α-hydroxylation byproduct **3** and 9*H*-xanthen-9-one from xanthene were detected.

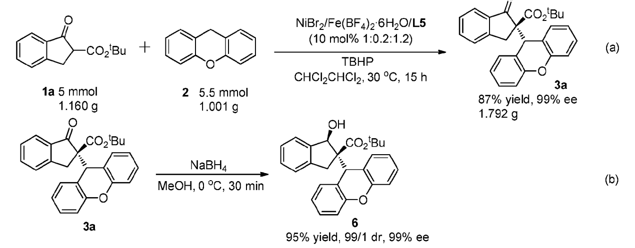
To extend the application of this protocol, further examination of the substrates was focused on forming 1-tetralone derivatives. However, under the same reaction conditions (Table 1, entry 14), xanthene was directly oxidized to 9*H*-xanthen-9-one by TBHP, and a trace amount of the desired CDC product **5a** was generated. To our delight, after a slight modification of the ligand, by altering the ligand **L5** to **L2**, and increasing the amount of xanthene and TBHP, the corresponding coupling product **5a** was obtained in 70% yield with 99% ee. For the 7-substituted-1-tetralone derivatives **5c** and **5d** and **5f**, promising yields with excellent enantiomeric excess were obtained. While 5-methoxy-1-tetralone **5b** and 5,7-dimethyl-1-tetralone **5e** displayed low yields (Fig. 2).

To show the synthetic utility of the catalyst system, the gram-scaled reaction was performed with a gram quantity of β-ketoester **1a**. As shown in Scheme 1a, the reaction proceeded smoothly to give the desired product **3a** in 87% yield with 99% ee. Due to the potential biological activities of β-hydroxy esters and xanthene,

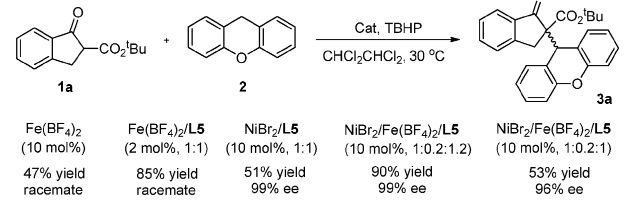


5a, 70% yield, 99% ee
5b, 36% yield, 99% ee
5c, 60% yield, 99% ee
5d, 71% yield, 99% ee
5e, 34% yield, 99% ee
5f, 72% yield, 99% ee

Fig. 2 Substrate scope for the 1-tetralone derivatives. All the reactions were performed with $NiBr_2/Fe(BF_4)_2 \cdot 6H_2O$/**L2** (10 mol%, 1 : 0.2 : 1.2), **4** (0.10 mmol), **2** (0.20 mmol), TBHP in decane (5.0–6.0 M, 40 μL) at 30 °C for 20 h.



Scheme 1 (a) Gram-scaled version of the reaction, (b) the synthesis of β-hydroxy esters.



Scheme 2 Control experiments.

the reduction of **3a** was probed, which generated a single diastereoisomer of β-hydroxy ester **6** in excellent yield without the loss of enantioselectivity (Scheme 1b).

Control experiments were then performed to understand the activation model of the reaction (Scheme 2). The use of 10 mol% of Fe(BF$_4$)$_2$ promoted the reaction with 47% yield. The combination of 2 mol% of the ligand **L5** and Fe(BF$_4$)$_2$ resulted in high isolated yield although no stereocontrol was found (85% yield). When the reaction was carried out with the cooperation of 2 mol% **L5**–Fe(BF$_4$)$_2$ in the presence of 10 mol% **L5**–NiBr$_2$, the yield of the product **3a** was improved from 51% to 90% with the 99% ee value maintained. Furthermore, a significant loss of yield was observed by slightly decreasing the amount of the chiral ligand **L5**. On the basis of the results described above, we conclude that the **L5**–NiBr$_2$ complex plays an important role in the chiral induction of the reaction, and at the same time the **L5**–Fe(BF$_4$)$_2$ complex accelerates the reaction rate for the generation of product **3a** (see ESI† for details). Meanwhile, based on the absolute configuration of product **3d**, a possible asymmetric catalytic model was proposed. Carbocations preferred to attack the Re face rather than the Si face of β-ketoester chelated with Ni/**L5**, because the latter is strongly shielded by the nearby aromatic ring and the *tert*-butyl of β-ketoester which results in the *R*-configured product (Fig. 3).

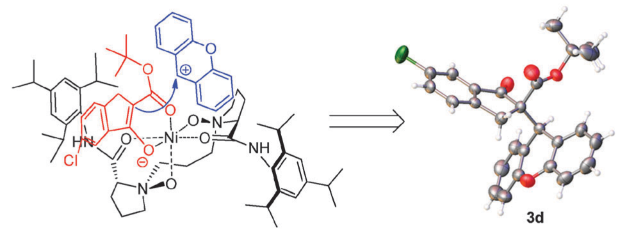


Fig. 3 Proposed transition-state model and the absolute configuration of **3d**.

In summary, we have developed a one-pot and highly enantioselective oxidative cross-dehydrogenative coupling reaction of α-substituted β-ketoesters with xanthene catalyzed by a cooperative bimetallic catalyst system. Various optically active xanthene derivatives bearing a quaternary stereogenic carbon center were obtained in moderate to good yields (up to 90%) with excellent ee values (up to 99% ee) under mild conditions. Meanwhile, a transition-state model was proposed to explain the origin of the asymmetric induction and more proof for the catalyzed mechanism is underway in our group.

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