Chemical Science

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Chiral organic contact ion pairs in metal-free catalytic enantioselective oxidative cross-dehydrogenative coupling of tertiary amines to ketones†

Cite this: DOI: 10.1039/c3sc50604e

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Received 4th March 2013
Accepted 19th March 2013

DOI: 10.1039/c3sc50604e

www.rsc.org/chemicalscience

A novel chiral organic contact ion-pair catalytic system has been developed for the transition-metal-free catalytic enantioselective oxidative cross-dehydrogenative coupling of tertiary amines to ketones for sp^3 C–H functionalization. This new strategy provides an efficient and environmentally friendly way to access diversify optically active C1-alkylated tetrahydroisoquinoline derivatives from simple starting materials under mild conditions.

Introduction

Recently, the oxidative coupling of two C–H bonds has emerged as an economical and ecofriendly tool available for forging new C–C bonds.[1] The prospect of concise synthesis of complex molecules from simple starting materials under mild conditions makes this strategy particularly attractive. Various sp^3 C–H bonds, such as benzylic and allylic C–H bonds,[2,3] α-C–H bonds of amines and ethers,[4,5] and the C–H bonds of alkanes[6] have been oxidized for direct coupling with other C–H bonds. However, the development of these transformations into a general, catalytic and enantioselective process has, to the best of our knowledge, remained elusive, especially for the oxidative coupling of tertiary amines.[7,8,39] Very recently, Chi and co-workers[8a] used a cooperative amine and metal catalysis to realize the enantioselective oxidative coupling of tertiary amines with aldehydes. However, this approach with cooperative catalysis was found to be unsuccessful for the reaction starting with simple ketones due to the disappointing results (less than 20% ee), as reported by Klussmann and co-workers[9a] as well as Xie and Huang.[9b] Therefore, the development of an alternative approach for the catalytic enantioselective oxidative coupling of tertiary amines with ketones is highly desired.

On the other hand, current oxidative coupling reactions usually require the use of transition metals, such as Cu,[10] Fe,[11] Pd,[12] Pt,[13] V,[14] Au,[15] Ru[16] and Rh.[17] However, transition metal-catalyzed transformations often suffer from some drawbacks in industrial applications such as high cost, air and moisture sensitivity, and may leave toxic trace metal contaminants. For these reasons, metal-free catalytic/mediated oxidative coupling reactions[18] have attracted considerable attention in recent years.

As increasing attention has been given to this new topic, chiral ion-pair catalysis has been introduced as a powerful strategy for asymmetric organic synthesis.[19] According to this concept, catalytic reactions that proceed *via* an intermediary ion-pair can be conducted asymmetrically *via* the use of a chiral enantiomerically enriched cation or anion incorporated into the catalyst. Present strategies mainly involve the use of cationic phase transfer catalysts,[20] chiral anion receptors,[21] and self-assembled supramolecular catalysts,[22] as well as Brønsted acids.[23] In this context, the recently introduced chiral anions have successfully been employed in the activation of various substrates through formation of a chiral contact ion pair between a chiral anion and a achiral cation, including carbocation,[24] oxocarbenium,[25] episulfonium ions,[26] and iminium ion.[27]

As pioneered by Murahashi *et al.*[28] Li *et al.*[29] and others,[30] one of the well-established methods for the construction of C–C bonds involving iminium ions is the oxidative coupling of tertiary amines with various nucleophiles. In addition, the iminium cationic intermediate could form a π-complex with copper anion, which has been structurally characterized,[31] although the nucleophilic addition to iminium ion gave the racemic product (eqn (1)). Inspired by the concept of chiral ion-pair catalysis, we wondered whether the copper anion of the π-complexes could be replaced by a chiral anion (**Y**) to form a chiral ion-pair and to conduct asymmetric transformations (eqn (2)).

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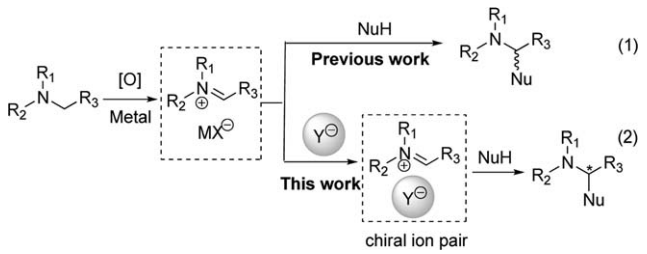
† Electronic supplementary information (ESI) available. CCDC reference number 911181. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3sc50604e

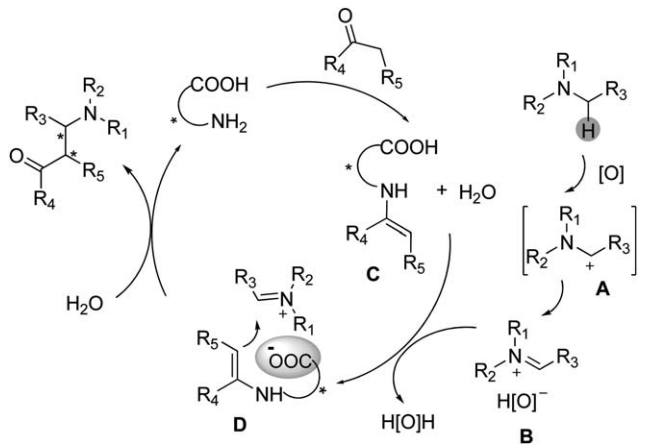
‡ These authors contributed equally to this work.



Results and discussion

As a natural extension of our continuing interest in chiral amines[32] and phase transfer catalysis,[33] we envisioned a catalytic cycle for an asymmetric version of this reaction involving an achiral cation and a chiral anion. Under oxidative conditions, a hydride can be abstracted from the α-C_{sp^3}–H bond of a tertiary amine to afford the radical cation **A**, which is subsequently transformed to an iminium cation as a key intermediate. The iminium cation can then form an achiral ion pair **B** with the hydrogenated oxidant anion.[34] The hydrogenated oxidant anion of **B** could then be replaced by the carboxylic acid anion of enamine intermediate **C** obtained from the ketone and primary amine of a chiral amino acid, to give the chiral ion pair **D**.[35] Finally, electrophilic attack of the iminium to the coordination sphere of the enamine occurs, to eventually afford the final product and regenerates the chiral amino acid catalyst (Scheme 1).

Tetrahydroisoquinoline derivatives, especially C1-alkylated tetrahydroisoquinolines with a stereocenter at the C1 position, are active determining building blocks with wide utility in organic synthesis and pharmaceutical chemistry.[36] Traditional methodologies for the formation of these privileged heterocycles mainly include the reduction of isoquinolines[37] and 1,5-hydride transfer/cyclization process.[38] However, asymmetric oxidative C_{sp^3}–H alkylation of amines, an alternative straightforward approach, which could afford chiral tetrahydroquinolines, has not been developed for their synthesis. As part of our continuous interest in amines functionalization,[39] we recently reported the first example on metal/organo-catalyzed asymmetric oxidative cross-coupling reactions of amines with olefins for the synthesis of chiral C1-alkene tetrahydroisoquinolines.[39a] Encouraged by this successful effort and aiming to develop other unprecedented transformations, herein we describe our recent contribution on oxidative coupling of tertiary amines with ketones for the synthesis of C1-alkylated tetrahydroquinolines.

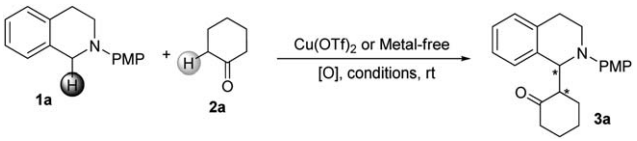


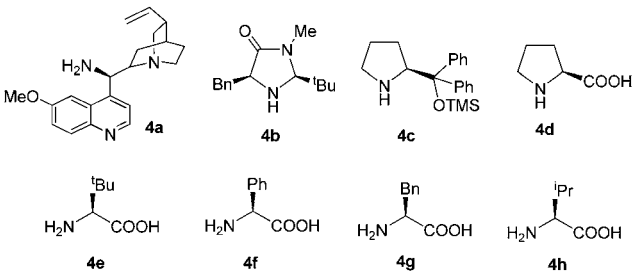
Scheme 1 Strategy for asymmetric metal-free oxidative coupling of amines *via* chiral ion-pair catalysis.

To explore the possibility of the proposed asymmetric metal-free oxidative coupling process, initially, we chose *N*-aryl tetrahydroisoquinolines as the tertiary amines to undergo oxidative coupling with cyclic ketones in the presence of a chiral primary or secondary amine and $Cu(OTf)_2$ in CH_2Cl_2 under oxidizing conditions at room temperature. The reaction gave the same yields and stereoselectivity when using the cooperative catalyst of **4a** with $Cu(OTf)_2$ or using **4a** alone (Table 1, entries 1 and 2; also see ESI†). The investigation of other chiral amines **4b–h** showed that **4g** was a better catalyst with regard to the diastereo- and enantioselectivity (Table 1, entries 3–9). To improve the enantioselectivity, various additives were then added to the reaction (Table 1, entries 10–14). To our delight, excellent conversion and enantioselectivity could be achieved when anhydrous ^{i}PrOH was added to the reaction (up to 66% yield, 13 : 1 d.r. and 90% ee; Table 1, entry 12), although the cooperative catalyst of **4g** with $Cu(OTf)_2$ gave only moderate results (Table 1, entry 13). Solvent optimization results showed that CH_2Cl_2 was a better solvent with regard to the enantioselectivity (see ESI†). The survey of oxidants indicated that 2,3-dichloro-5,6-dicyanoquinone (DDQ) was the best oxidant tested (Table 1, entries 15 and 16).

With the best reaction conditions established, the scope of substrates for this novel asymmetric transition-metal-free catalytic oxidative coupling reaction was then studied. In general, the reaction proceeded well to afford the desired products in good yields and good to excellent diastereo- and enantioselectivities. For the reaction with cyclohexanone (**2a**), a wide range of aromatic-substituted tetrahydroisoquinolines **1a–f** were examined, and it was observed that with both electron-withdrawing and electron-donating groups on the *para* and *ortho* position of the phenyl ring of **1** the desired oxidative coupling products were obtained in satisfactory yields of 65–81%, good to excellent diastereoselectivities of 3 : 1–13 : 1 and good to excellent enantioselectivities of 61–90% (Table 2, entries 1–6). After testing the generality of this concise oxidative coupling reaction with regard to the series of *N*-aryl tetrahydroisoquinolines with cyclohexanone (**2a**), various heterocyclic ketones were then investigated for the synthesis of diverse optically active C1-alkylated tetrahydroisoquinoline derivatives. When oxacyclic ketone and thiacyclic ketones, such as dihydro-2*H*-pyran-4(3*H*)-one (**2b**) and dihydro-2*H*-thiopyran-4(3*H*)-one (**2c**) were used to react with *N* substituted-aryl tetrahydroisoquinolines **1a** and **1g–j**, the reaction proceeded readily to give coupling products **3g–i** in good yield (67–77%) and good to excellent diastereo- and enantioselectivities (3 : 1–11 : 1 d.r. and 70–94% ee; Table 2, entries 7–12). The substituents with methoxy on the 6,7-position or chlorine on the 7-position of tetrahydroisoquinoline ring did not influence the reaction

Table 1 Optimization of reaction conditions[a]





Entry	Metal salt	4	[O]	Additive	Yield[b] (%)	d.r.[c]	ee[d] (%)
1	$Cu(OTf)_2$	**4a**	DDQ	None	68	3 : 1	31
2	None	**4a**	DDQ	None	65	4 : 1	35
3	None	**4b**	DDQ	None	33	6 : 1	30
4	None	**4c**	DDQ	None	27	5 : 1	−27
5	None	**4d**	DDQ	None	49	6 : 1	−34
6	None	**4e**	DDQ	None	70	7 : 1	70
7	None	**4f**	DDQ	None	66	7 : 1	48
8	None	**4g**	DDQ	None	71	9 : 1	82
9	None	**4h**	DDQ	None	64	8 : 1	75
10	None	**4g**	DDQ	4ÅMS	56	9 : 1	60
11	None	**4g**	DDQ	PhCOOH	58	7 : 1	38
12	None	**4g**	DDQ	^{i}PrOH	70	13 : 1	90
13	$Cu(OTf)_2$	**4g**	DDQ	^{i}PrOH	70	11 : 1	55
14	None	**4g**	DDQ	BnOH	65	9 : 1	67
15	None	**4g**	^{t}BuOOH	^{i}PrOH	43	9 : 1	30
16	None	**4g**	$PhI(OAc)_2$	^{i}PrOH	58	8 : 1	19

[a] The reaction was carried out with **1a** (0.1 mmol) and **2a** (0.4 mmol) in the presence of organocatalyst **4** (0.02 mmol), additive (0.02 mmol), oxidant (0.1 mmol) and anhydrous dichloromethane (1.0 mL) at rt for 48 h. [b] Yield of the isolated product. [c] The diastereomeric ratio, *anti*/*syn*, as determined by ^{1}H NMR spectroscopy. [d] The ee value for the major diastereomer was determined by HPLC on a chiral stationary phase.

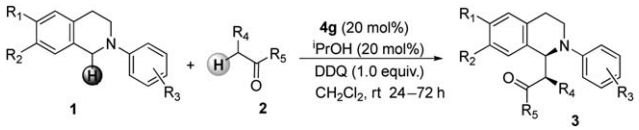
outcomes (Table 2, entries 13 and 14). However, the results were less satisfactory using acyclic ketones, such as butan-2-one (**2d**) to couple with **1a** because of the poor enantioselectivity (Table 2, entry 15). Similarly, the outcome was unsatisfactory using *N*-benzylaniline **1m** to couple with **2a** due to the poor reactivity (Table 2, entry 16). The absolute configuration of the two contiguous stereocenters of the products was determined by single-crystal X-ray diffraction of **3l** (Fig. 1 and ESI†).

The possible reaction pathways of this unique oxidative coupling of *N*-aryl tetrahydroisoquinolines with simple ketones are assumed to involve a single-electron transfer (SET) radical mechanism.[40] When DDQ reacts with the **1a**, a single-electron transfer from **1a** would occur to afford the radical cation, which is subsequently transferred to the iminium cation as a key intermediate. To check the intermediacy of a radical cation, the same equivalent of TEMPO or 2,6-di-*tert*-butyl-4-methylphenol (BHT) was respectively added to this reaction system. With addition of TEMPO, no significant change in the yield and stereoselectivity of the coupling product could be detected, and the addition product of *N*-aryl tetrahydroisoquinoline with TEMPO was not formed either (eqn (1), Scheme 2; also see ESI†). 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, the situation was changed when 2,6-di-*tert*-butyl-4-methylphenol (BHT) was added, for which the yield of the coupling product was decreased from 65 to 23%, although little influence on stereoselectivities was observed (eqn (2), Scheme 2; also see ESI†).

Conclusions

In summary, we have disclosed the first example on metal-free catalytic asymmetric oxidative coupling reaction of tertiary amines with simple ketones *via* a chiral ion-pair catalysis strategy for the construction of a C_{sp^3}–C_{sp^3} bond under mild conditions using an environmentally benign nontoxic and cheap natural α-amino acid as the catalyst with moderate to

Table 2 Investigating the scope of the procedure[a]



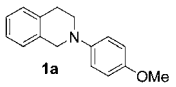
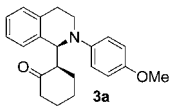
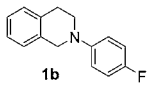
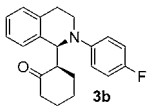
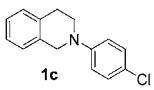
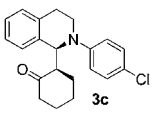
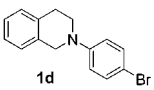
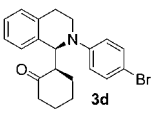
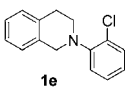
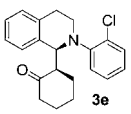
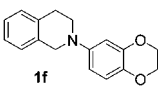
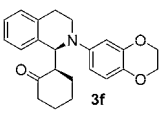
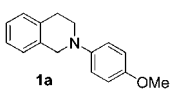
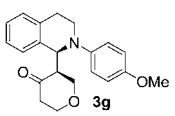
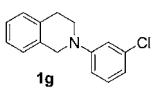
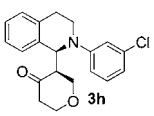
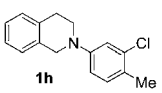
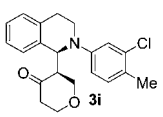
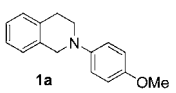
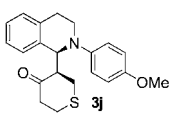
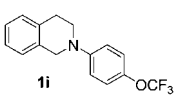
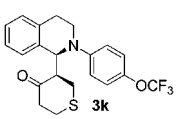
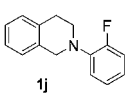
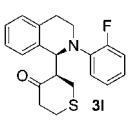
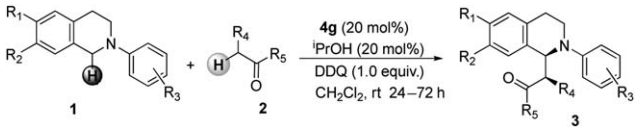
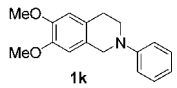
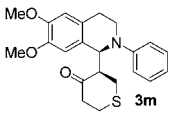
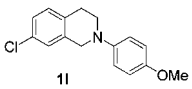
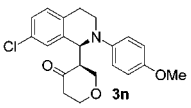
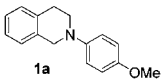
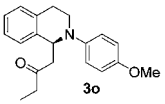
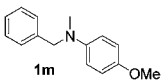
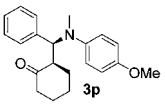
Entry	Substrate **1**	*t*/h	Product **3**	Yield[b] (%)	d.r.[c]	ee[d] (%)
1		48		65	13 : 1	90
2		48		78	13 : 1	90
3		48		75	3 : 1	84
4		48		72	3 : 1	78
5		48		81	5 : 1	88
6		48		69	3 : 1	61
7		36		73	3 : 1	94
8		36		77	11 : 1	83
9		36		71	8 : 1	90
10		24		75	7 : 1	90
11		24		70	6 : 1	80
12		24		67	6 : 1	70

Table 2 (*Contd.*)



Entry	Substrate **1**	*t*/h	Product **3**	Yield[b] (%)	d.r.[c]	ee[d] (%)
13	 **1k**	24	 **3m**	61	11 : 1	90
14	 **1l**	48	 **3n**	52	6 : 1	77
15	 **1a**	72	 **3o**	63		30
16	 **1m**	72	 **3p**	<10		n.d[e]

[a] The reaction was carried out with **1** (0.1 mmol) and **2** (0.4 mmol) in the presence of **4g** (0.02 mmol), ^{i}PrOH (0.02 mmol), DDQ (0.1 mmol) and anhydrous dichloromethane (1.0 mL) at rt for 24–72 h. [b] Yield of the isolated product. [c] The diastereomeric ratio, *anti*/*syn*, as determined by ^{1}H NMR spectroscopy. [d] The ee value for the major diastereomer, and the configuration was assigned by comparison of HPLC data and X-ray crystal data of **3l**. [e] n.d. = Not determined.

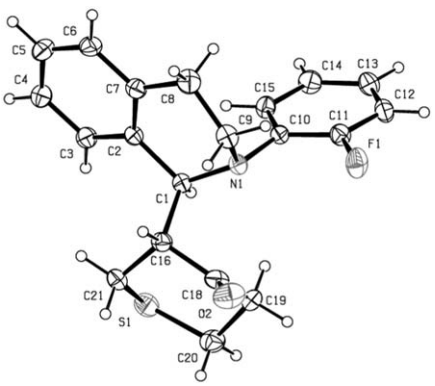
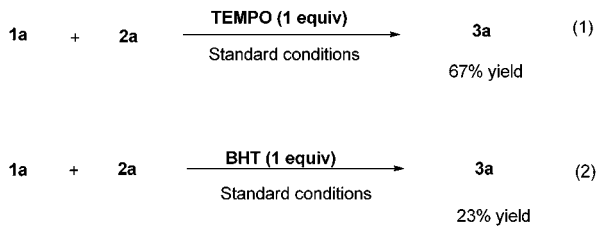


Fig. 1 X-Ray crystal structure of compound **3l**.



Scheme 2 Mechanistic experiments for metal-free catalytic asymmetric oxidative coupling.

good yields (52–81%) and good to excellent diastereo- and enantioselectivities (up to 13 : 1 d.r. and 94% ee). This method provides an alternative approach to current directing group (DG)-directed sp^3 C–H activation/alkylation and transition metal-catalyzed oxidative coupling reaction, and allowed the rapid construction of diverse optically active C1-alkylated tetrahydroisoquinoline derivatives in one step from basic starting materials and under a direct, efficient, mild and atom-economical process. The development of this concise metal-free chiral ion-pair catalysis system in other asymmetric oxidative coupling reactions and the mechanism study of this process are being pursued.

Acknowledgements

We are grateful for the grants from the National Natural Science Foundation of China (nos 91213302, 20932003 and 21272102) and the Key National S&T Program "Major New Drug Development" of the Ministry of Science and Technology of China (2012ZX09504001-003).

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