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Enantioselective Metal/Organo-Catalyzed Aerobic Oxidative sp^3 C−H Olefination of Tertiary Amines Using Molecular Oxygen as the Sole Oxidant

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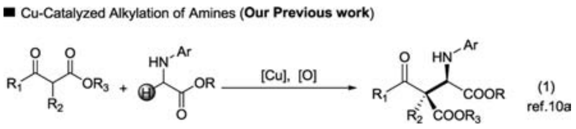
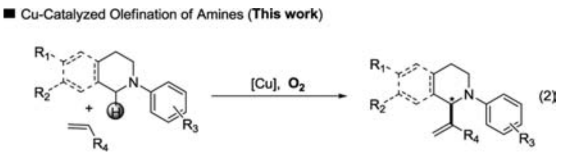
Supporting Information

ABSTRACT: An organocatalysis/copper-catalyzed asymmetric oxidative sp^3 C−H olefination reaction of tertiary amines with olefins using molecular oxygen as the sole oxidant under mild conditions was realized for the first time. This novel strategy provides an efficient and environmentally friendly way to access diversify optically active C_1-alkene tetrahydroisoquinoline derivatives.

The transition-metal-catalyzed C−H olefination reactions, which replace simple C−H bonds with readily derivatizable alkene functional groups, are uniquely powerful transformations available for forging new C−C bonds and play a fundamentally important role in modern organic synthesis.[1] Significant advances have been made in Pd-[2] and Rh-catalyzed[3] olefination of aromatic C−H bonds through C−H activation generally using a neighboring directing group (DG) in recent years. In contrast, the similar process at unactivated alkyl C−H sites remains undeveloped. To date, the only examples on sp^3 C−H olefination were disclosed by the groups of Yu[4] and Sanford[5] using a palladium catalysis and employing *N*-arylamide or pyridine as DG by means of metal insertion. However, a prominent challenge remaining in sp^3 C−H olefination is control of the enantioselectivity as regioselectivity must also be controlled simultaneously, which cannot be overcome via the existing DG-directed C−H activation due to the harsh reaction conditions;[6] therefore, the development of a complementary method is highly desired.

The oxidative coupling reaction has evolved to be one of the most efficient and atom-economical approaches to construct new bonds through direct coupling of two C−H or heteroatom−H bonds.[7] The prospect of concise synthesis of complex molecules from simple starting materials under mild conditions makes this reaction particularly attractive. Among this reaction, the oxidative coupling of amines with various nucleophile-catalyzed simple metal salts has received considerable attention,[8] and tremendous progress has been made in this fascinating field since the pioneering studies of Murahashi and Li.[9] However, the development of this transformation into a general, catalytic and enantioselective process still remains a great challenge and has never been achieved, especially for the coupling between amines and olefins. On the other hand, the current oxidative coupling reactions are usually environmentally unfriendly, using excess oxidant such as TBHP, Oxone, BQ, DDQ, IBX, $PhI(OAc)_2$, etc. Nevertheless, more economical and green oxidant—dioxygen with water as the only byproduct has not been widely employed in these reactions.[10] To the best of our knowledge, there have been no examples to date that report on the transition-metal or Lewis acid-catalyzed asymmetric oxidative coupling of amines under molecular oxygen. As our continuous interest in amines functionalization,[11] we recently reported the first example on copper-catalyzed asymmetric oxidative cross-coupling reactions of amines with activated methylenes for C_{sp3}−H alkylation of amines (eq 1).[11a,b] Encouraged by these successful efforts and aiming to develop other unprecedented transformations, herein we describe our contribution on enantioselective oxidative C_{sp3}−H olefination of amines using cooperative catalysts and utilizing dioxygen as a stoichiometric oxidant under mild conditions (eq 2).





As increasing attention has been given to this new topic, the combination of the transition metal/Lewis acid catalysis and organocatalysis in one process has emerged as a highly attractive strategy for developing new and valuable reactions, as it could potentially achieve unparalleled transformations not currently possible by use of the transition-metal/Lewis acid complex or the organocatalyst alone.[12] Since this concept was first introduced by Krische in 2003,[13] various transition metals/Lewis acid and several types of organocatalysts (including aminocatalysts,[14a,b] Bronsted acid,[14c,d] Lewis base[14e,f] and phase transfer catalyst[14g,h])

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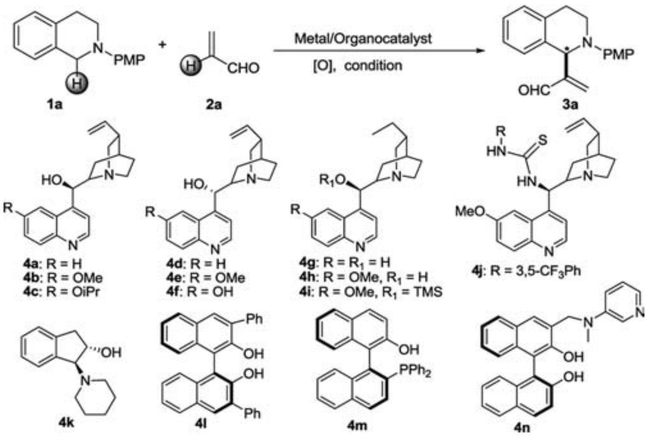
have been combined successfully for promoting a variety of unprecedented transformations. However, the combining transition metal/Lewis acid with bifunctional cinchona alkaloids has not been successfully developed. Thus, the design and discovery of this novel type of cooperative catalytic system to promote some undeveloped transformations, such as asymmetric oxidative cross-coupling reaction of amines and olefins, is particularly challenging.

Considering tetrahydroisoquinolines, especially C1-alkene tetrahydroisoquinolines with a stereocenter at the C1 position, are active determining building blocks with wide utility in organic synthesis and pharmaceutical chemistry,[15] we chose *N*-aryl tetrahydroisoquinolines as the tertiary amines to oxidative couple with olefins in the presence of a metal salt and an organocatalyst under the oxidizing conditions at room temperature. An initial survey of oxidant indicated that O_2 is a good oxidant, and the yield and enantioselectivity could be improved when molecular sieve was added to the reaction (Table 1, entries 1−5). The investigation of metals salts and organocatalysts **4a**−**n** showed that $Cu(OTf)_2$ and quinine (**4b**) were the best cooperative catalysts (Table 1, entries 6−20 and see the Supporting Information). Solvent optimization results showed that DCM was a better solvent with regard to the enantioselectivity (see the Supporting Information). The results of optimization of *N*-protecting groups of tetrahydroisoquinolines showed that *PMP*- is the best choice (for the detial, see the Supporting Information). To our delight, the best outcome for conversion and enantioselectivity could be achieved when anhydrous Na_2SO_4 was added to the reaction (up to72% yield and 90% ee; Table 1, entry 21). The reaction became slower and yield was decreased without molecular sieves, although little influence on stereoselectivity (Table 1, entry 22).

Table 1. Optimization of Reaction Condition[a]



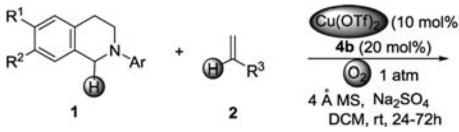
entry	metal	L*	oxidative	additive	yield (%)[b]	ee (%)[c]
1	$Cu(OTf)_2$	**4a**	O_2		68	28
2	$Cu(OTf)_2$	**4a**	^{t}BuOOH		<10	n.d.[d]
3	$Cu(OTf)_2$	**4a**	$PhI(OAc)_2$		80	20
4	$Cu(OTf)_2$	**4a**	DDQ		73	12
5	$Cu(OTf)_2$	**4a**	O_2	4 Å MS	71	51
6	AgOTf	**4a**	O_2	4 Å MS	55	−47
7	$Pd(OAc)_2$	**4a**	O_2	4 Å MS	36	24
8	$Cu(OTf)_2$	**4b**	O_2	4 Å MS	70	81
9	$Cu(OTf)_2$	**4c**	O_2	4 Å MS	54	−53
10	$Cu(OTf)_2$	**4d**	O_2	4 Å MS	52	−51
11	$Cu(OTf)_2$	**4e**	O_2	4 Å MS	59	−55
12	$Cu(OTf)_2$	**4f**	O_2	4 Å MS	<10	n.d.[d]
13	$Cu(OTf)_2$	**4g**	O_2	4 Å MS	61	50
14	$Cu(OTf)_2$	**4h**	O_2	4 Å MS	64	63
15	$Cu(OTf)_2$	**4i**	O_2	4 Å MS	n.d.	n.d.[d]
16	$Cu(OTf)_2$	**4j**	O_2	4 Å MS	n.d.	n.d.[d]
17	$Cu(OTf)_2$	**4k**	O_2	4 Å MS	67	50
18	$Cu(OTf)_2$	**4l**	O_2	Ph_3P	59	−13
19	$Cu(OTf)_2$	**4m**	O_2	4 Å MS	75	−45
20	$Cu(OTf)_2$	**4n**	O_2	4 Å MS	62	42
21	$Cu(OTf)_2$	**4b**	O_2	4 Å MS	72	90[e]
22	$Cu(OTf)_2$	**4b**	O_2	Na_2SO_4	56	88

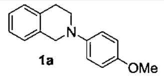
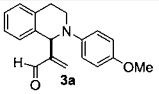
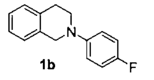
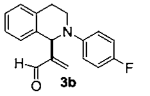
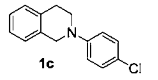
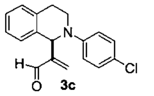
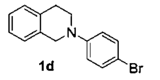
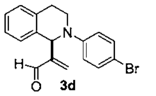
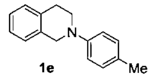
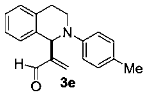
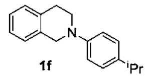
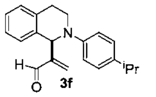
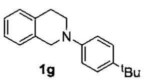
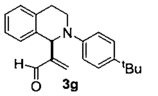
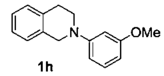
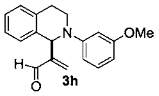
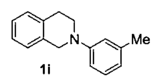
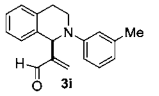
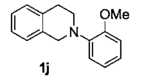
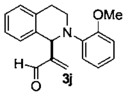
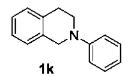
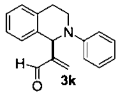
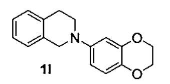
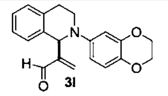
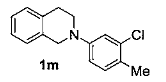
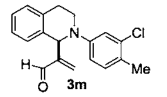
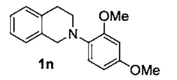
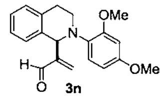
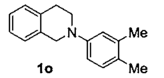
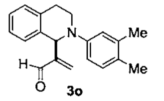
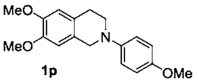
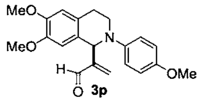
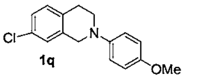
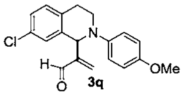
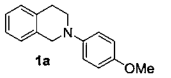
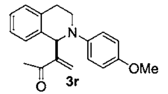
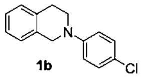
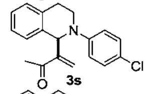
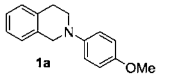
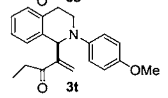
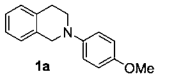
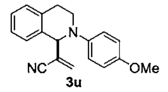
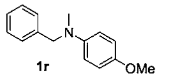
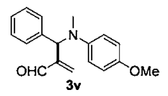
[a] Unless otherwise specified, the reaction was performed on a 0.1 mmol scale at room temperature (see the Supporting Information). [b] Isolated yield. [c] Determined by HPLC on chiral stationary phase. [d] Not determined. [e] Na_2SO_4 (0.3 mmol) was added to the reaction.

With the best reaction conditions established, the scope of substrates for the asymmetric copper/quinine-catalyzed oxidative coupling reactions was then studied. In general, the reaction proceeded well to afford the desired products in good yields and good to excellent enantioselectivities. For the reaction with acrylaldehyde (**2a**), a wide range of aromatic-substituted tetrahydroisoquinolines **1a**− **q** were examined, and it was observed that with both electron-withdrawing and electron-donating groups on the *para*, *meta* and *ortho* position of the phenyl ring of **1** the desired oxidative coupling products were obtained in satisfactory yields of 47−73% and excellent enantioselectivities of 85−99% (Table 2, entries 1−11). The coupling products of **2a** and aromatic-substituted tetrahydroisoquinolines **1** with double substituents on the *N*-aryl ring, respectively, were also isolated in good yield and high enantioselectivity (49−81% yields and 80−93% ee; Table 2, entries 12−15). The substituents with methoxy on the 6,7-position or chlorine on the 7-position of tetrahydroisoquinoline ring did not influence the reaction outcomes (Table 2, entries 16−17). After testing the generality of this novel oxidative coupling reaction with regard to the series of *N*-aryl tetrahydroisoquinolines with acrylaldehyde (**2a**), various olefins were then investigated for the synthesis of diverse optically active C1-alkene tetrahydroisoquinoline derivatives. When methylvinylketone (**2b**), ethylvinylketone (**2c**) and acrylonitrile (**2d**) were used to react with **1a** and **1b**, the reaction proceeded readily to give coupling products **3r**−**u** in good yield (48−77%) and good to excellent enantioselectivity (69−99% ee; Table 2, entries 18−21). However, the result was frustrated by using *N*-benzylaniline **1r** to couple with **2a** due to the weak reaction (Table 2, entry 22). The absolute configuration of products were determined to be *S* by using a single-crystal X-ray diffraction of **3q** (Figure 1).[16]

In summary, we have described a novel asymmetric oxidative cross-coupling reaction between simple amines and olefins for constructing $C_{sp2}-C_{sp3}$ bonds catalyzed by organo/metal cooperative catalysis under mild conditions using molecular oxygen as the terminal oxidant and with moderate to good yields (47−82%) and excellent enantioselectivities (up to 99% ee). This method provided an alternative approach to current DG-directed sp^3 C−H activation olefinations and allowed the rapid construction of diverse optically active C1-alkene tetrahydroisoquinoline derivatives in one step from basic starting materials and under a direct, efficient, mild and atom-economical process. The development of this novel cooperative catalysis system in other asymmetric oxidative coupling

Table 2. Investigating the Scope of the Procedure[a]



Entry	Substrate 1	t (h)	Product 3	Yield [%] [b]	ee [%] [c]
1	 1a	36	 3a	72	90
2	 1b	72	 3b	56	85
3	 1c	72	 3c	51	91
4	 1d	72	 3d	47	88
5	 1e	48	 3e	64	91
6	 1f	36	 3f	69	99
7	 1g	48	 3g	60	90
8	 1h	48	 3h	70	90
9	 1i	72	 3i	67	90
10	 1j	48	 3j	73	94
11	 1k	36	 3k	63	91
12	 1l	24	 3l	81	90
13	 1m	72	 3m	55	93
14	 1n	60	 3n	56	80
15	 1o	60	 3o	49	90
16	 1p	48	 3p	57	70
17	 1q	24	 3q	82	85
18	 1a	24	 3r	77	95
19	 1b	72	 3s	54	93
20	 1a	36	 3t	48	69
21	 1a	36	 3u	71	99
22	 1r	72	 3v	<10	n.d [d]

[a] Unless otherwise specified, the reaction was carried out with **1a** (0.1 mmol) and **2a** (0.2 mmol) in the presence of Cu(OTf)$_2$ (0.01 mmol) and **4b** (0.02 mmol), 4 A molecular sieve (100 mg), anhydrous Na$_2$SO$_4$ (0.3 mmol), and DCM (1.0 mL) under 1 atm molecular oxygen at room temperature for 24−72 h. [b] Isolated yield. [c] Determined by HPLC on chiral stationary phase and the configuration was assigned by comparison of HPLC data and X-ray crystal data of **3q**. [d] Not determined.

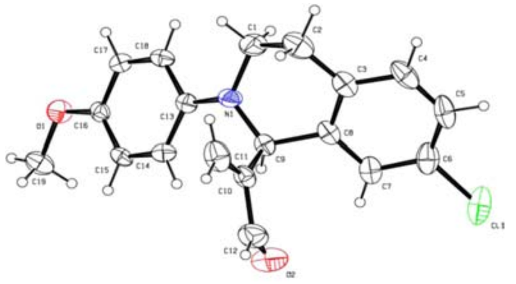


Figure 1. X-ray crystal data of compound **3q**.

reactions and the mechanism study of this process are being pursued.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details including product characterization and NMR-experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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