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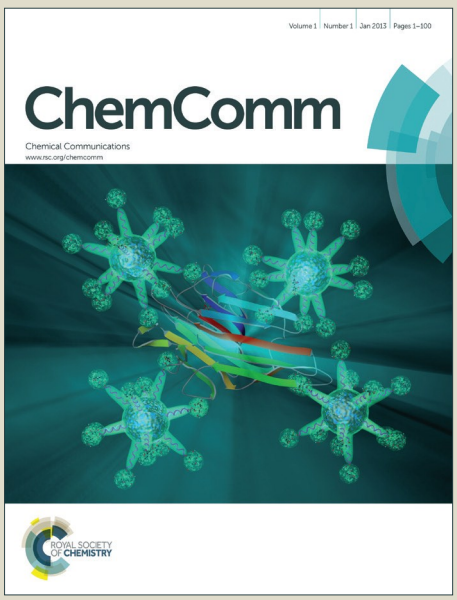

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Journal Name

COMMUNICATION

Copper(II)/Amine Synergistically Catalyzed Enantioselective Alkylation of Cyclic *N*-Acyl Hemiaminals with Aldehydes†

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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The first catalytic asymmetric alkylation of *N*-acyl quinoliniums with aldehydes has been described. A copper/amine synergistic catalytic system has been developed, allowing the addition of functionalized aldehydes to a wide range of electronically varied *N*-acyl quinoliniums in good yields with excellent enantiocontrol. The synergistic catalytic system was also effective for *N*-acyl dihydroisoquinoliniums and β-cabboliniums, demonstrating the general applicability of the protocol in the enantioselective alkylation of diverse cyclic *N*-acyl hemiaminals.

Enantioenriched α-substituted tetrahydroquinolines are important synthetic intermediates and common units in numerous pharmacologically active alkaloids.[1] The catalytic asymmetric addition to iminiums represents one of the most efficient and attractive approaches to access the structure. Numerous methods have been reported for the enantioselective nucleophilic addition to isoquinoliniums.[2] However, the studies on quinolinium ions are still underdeveloped. Shibasaki established the first catalytic asymmetric addition of TMSCN to quinoliniums generated in situ through the Reissert reaction of quinolines and 2-furoyl chloride.[3] Inspired by the seminal work, Takemoto[4] and Arndtsen[5] disclosed enantioselective vinylation and alkynylation of quinoliniums with cinnamyl boronates and terminal alkynes, respectively. Quinolinium ions can also be generated through the collapse of *N*-acyl hemiaminals like 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinolines, as demonstrated by the enantioselective vinylation and arylation with cinnamyl boronates and arylboroxines by Schaus[6] and Doyle,[7] respectively. However, no example of catalytic asymmetric alkylation of quinoliniums has been disclosed to date.

The catalytic enantioselective addition of aldehydes to a variety of electrophiles, including carbonyls, imines, alkyl halides, alkenes, and oxocarbenium ions, have been extensively investigated during the past decade.[8-9] However, the addition of aldehydes to *N*-acyliminium ions has not been well explored, which might be ascribed to the high reactivity of the unstable intermediates. Jørgensen developed an enantioselective intramolecular reaction of aldehydes and isoquinoliniums.[2g] Albeit excellent enantiocontrol, only modest reaction efficiency was obtained (18-41%). Recently, Cozzi reported an enantioselective addition of aldehydes to isoquinoliniums promoted by the Hayashi–Jørgensen catalyst.[2f] Moderate diastereoselectivity and excellent enantioselectivity were observed, and synthetic utility of the method was demonstrated by the total synthesis of a 13-alkyl-tetrahydroprotoberberine alkaloid. However, the reaction efficiency was still a problem, with only 9–23% yields obtained for functionality-containing aldehydes. Herein we report the first highly enantioselective alkylation of quinolinium with a wide range of aldehydes.

Initially, Cozzi's protocol on the enantioselective addition of aldehydes to isoquinoliniums was applied to the alkylation of quinoliniums generated in situ through the Reissert reaction of methyl chloroformate and quinoline (Table 1, Scheme 1).[2f] However, no reaction was observed. We ascribed the observation to the low stability of the *N*-acyl quinolinium intermediate and the insufficient nucleophilicity of the chiral enamine. In such case, the quinoliniums generated in a high concentration would decompose back to quinolines before the attack of the catalytic amount of the enamine. Additionally, the chiral amine catalysis system might not be compatible with the Reissert-type activating model.[2f] We envisioned that the generation of the quinolinium and enamine components in a synergetic manner might be a solution to the problem.[10]

The coupling of 2-ethoxy-1-methoxycarbonyl-1,2-dihydroquinoline (EMDQ) **1a** and pentanal **2a** was selected as the model reaction for optimization employing secondary amine as the catalyst (Table 1). No reaction took place when free amine **A** was used (Table 1, entry 2). Decomposition of **1a** to quinoline was observed when Brønsted acid like TFA was introduced, with no desired **3a** detected (Table 1, entry 3). $Yb(OTf)_3$ (10 mol%) was found to promote the coupling, with **3a** isolated in 32% yield with 5% ee for the major isomer (Table 1, entry 4). The choice of Lewis acid additive proved to be crucial to the efficiency and selectivity of the reaction, with $Cu(OTf)_2$ as the ideal candidate (entries 4-10). An extensive screen of chiral imidazolidinones **A-F** and the Hayashi-Jørgensen catalysts **G** and **H** revealed that amine **E** was the best

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†Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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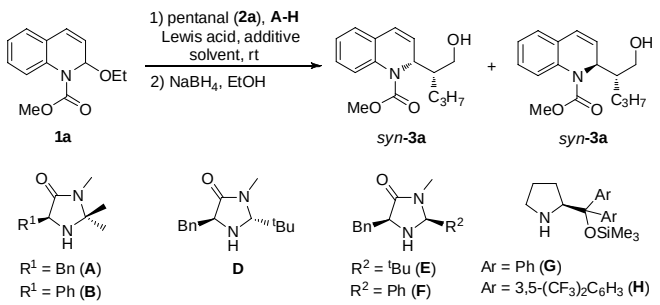
Table 1 Reaction condition optimization[a]



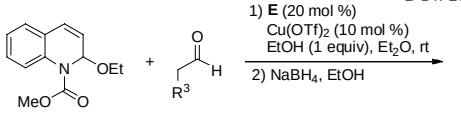
Entry	Amine	Lewis acid	Yield[b] (%)	dr[c]	ee[d] (%, *syn*)	ee[d] (%, *anti*)
1[e]	**A**	—	< 5	n.d.	n.d.	n.d.
2	**A**	—	< 5	n.d.	n.d.	n.d.
3	**A**·TFA	—	< 5	n.d.	n.d.	n.d.
4	**A**	$Yb(OTf)_3$	32	55:45	5	0
5	**A**	$Sc(OTf)_3$	< 5	n.d.	n.d.	n.d.
6	**A**	$La(OTf)_3$	< 5	n.d.	n.d.	n.d.
7	**A**	CuOTf	20	63:37	15	11
8	**A**	$Cu(OTf)_2$	41	60:40	18	15
9	**A**	$CuCl_2$	33	58:42	9	13
10	**A**	$CuBr_2$	40	55:45	12	10
11	**B**	$Cu(OTf)_2$	46	67:33	22	20
12	**C**	$Cu(OTf)_2$	35	52:48	24	6
13	**D**	$Cu(OTf)_2$	31	62:38	56	29
14	**E**	$Cu(OTf)_2$	33	64:36	80	66
15	**F**	$Cu(OTf)_2$	< 5	n.d.	n.d.	n.d.
16	**G** or **H**	$Cu(OTf)_2$	< 5	n.d.	n.d.	n.d.
17	**E**·TFA	$Cu(OTf)_2$	30	58:42	73	60
18[f]	**E**	$Cu(OTf)_2$	60	62:38	86	69
19[g]	**E**	$Cu(OTf)_2$	62	70:30	77	62
20[h]	**E**	$Cu(OTf)_2$	76	72:28	98	96
21[h,i]	**E**	$Cu(OTf)_2$	59	71:29	98	97
22[h,j]	**E**	$Cu(OTf)_2$	91	74:26	99	99

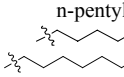
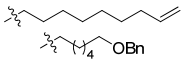
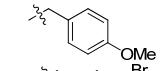
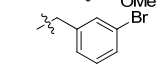
[a]General conditions: **1a** (0.1 mmol), **2a** (0.3 mmol), amine (0.02 mmol), Lewis acid (0.01 mmol) and additive (0.1 mmol) in $ClCH_2CH_2Cl$ (1.0 mL) at rt, unless stated otherwise. [b]Isolated yield. [c]Determined by ^1H NMR spectroscopy. [d]Determined by HPLC analysis on a chiral stationary phase. [e]Quinoline and methyl chloroformate were used as starting materials. [f]Toluene as the solvent. [g]THF as the solvent. [h]Et_2O as the solvent. [i]H_2O as the additive. [j]EtOH as the additive. n.d. = not determined. TFA = trifluoroacetic acid. Tf = trifluoromethanesulfonyl.

choice in terms of the diastereo- and enantioselectivity, though the reaction efficiency was still modest, with the decomposition of **1a** to quinoline as the major side pathway (Table 1, entries 11-17). Next, the solvent effect was investigated. When Et_2O was employed as the solvent, improved d.r. (*syn*/*anti* = 78:28) and excellent ee (98%/96%) were observed; notably, the decomposition side pathway was well blocked and the yield was optimized to 76% (Table 1, entries 18-20). A suitable additive was also beneficial to the efficiency and enantiocontrol (Table 1, entries 21-23), and the reaction with 1 equiv of EtOH afforded **3a** in 91% yield with 99% ee for both isomers (Table 1, entry 22).

The scope of the catalytic enantioselective alkylation of **1a** with a variety of aldehydes was explored (Table 2).[11] In general, the coupling proceeded smoothly providing desired α-substituted dihydroquinolines **3a-3i** in good to excellent yields (76%-91%) with moderate diastereocontrol and good to excellent enantiocontrol for both isomers (80%-99% ee). Aldehydes bearing diverse functional groups, such as halide (**2d**), olefin (**2e**), benzyl ether (**2f**), and electronically varied aryl moties (**2g-2i**), were well compatible with

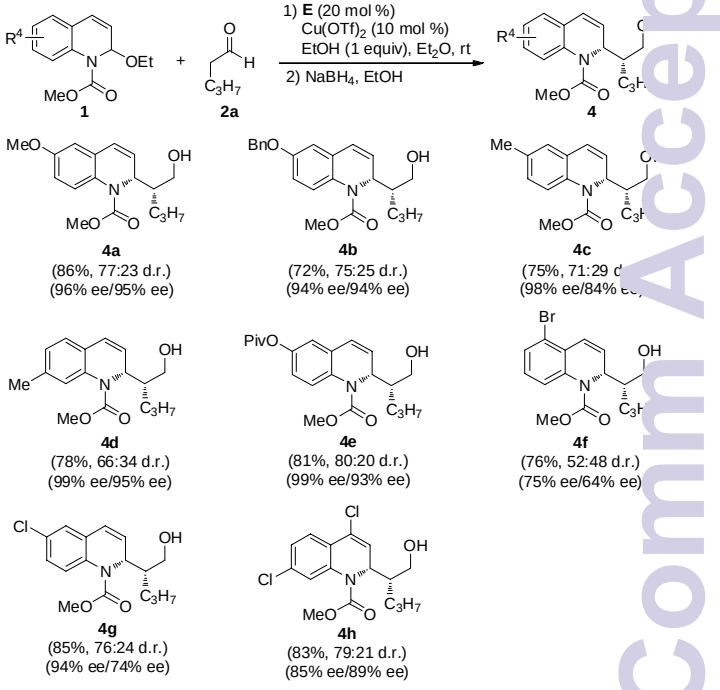
Table 2 The scope of the aldehyde[a]



Entry	3	R^3	Yield[b] (%)	dr[c]	ee[d] (%, *syn*/*anti*)
1	**3a**	n-propyl	91	74:26	99/99
2	**3b**	Me	85	72:28	85/94
3	**3c**	n-pentyl	82	70:30	95/90
4	**3d**		90	80:20	98/93
5	**3e**		78	64:36	97/91
6	**3f**		85	60:40	93/80
7	**3g**	Bn	90	82:18	99/95
8	**3h**		76	79:21	99/93
9	**3i**		88	81:19	99/89

[a]General conditions: **1a** (0.1 mmol), **2** (0.3 mmol), **E** (0.02 mmol), $Cu(OTf)_2$ (mmol) and EtOH (0.1 mmol) in Et_2O (1.0 mL) ar rt for 6-12 h. [b]Isolated yield. [c]Determined by ^1H NMR spectroscopy. [d]Determined by HPLC analysis on a chiral stationary phase.

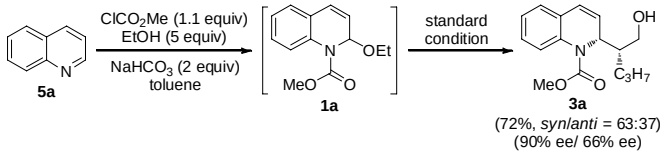
the synergistic catalytic system. Compared with the moderat efficiency of the alkylation of isoquinoliniums with the same type of aldehydes,[2f] the method developed herein displays the capabili in creating diversely functionalized molecules in high efficiency.



Scheme 1 The Scope of the EMDQs.

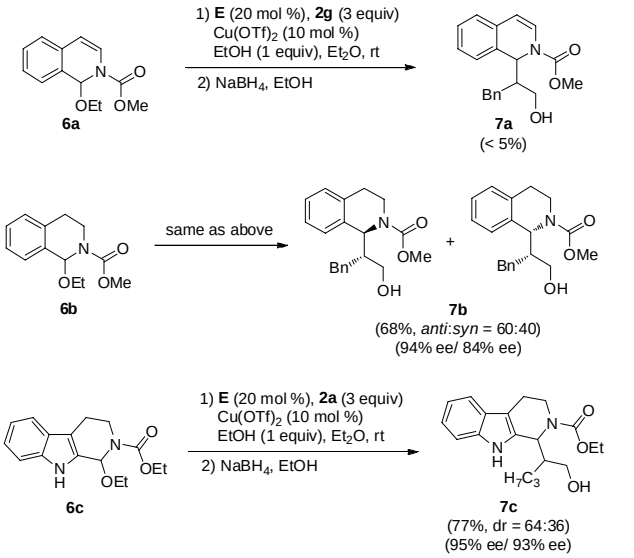
The scope of EMDQs **1** was next examined (Scheme 1). I general, good yields and excellent enantiocontrol were observed f the reaction involving a variety of electronically varied EMDQs with different substitution patterns. Substitutions at the 4, 6, and positions on the quinoline rings were well tolerated (**1a-1e** and **1g-1h**). Substitution at the 5 position gave a diminished ee (**1f**). Th efficiency and enantioselectivity were found to be not sensitive t

different electronic substituents on the EMDQ. Various functional groups including benzyl ether (**1b**), carboxylate (**1e**), bromide (**1f**), and chloride (**1g** and **1h**) were compatible with the mild catalysis system, which will be beneficial for further diversification.



Scheme 2 One-Pot Alkylation of the Quinoline.

Given that quinolines are precursors for the preparation of EMDQs, developing a one-pot protocol directly using quinolines as the starting point would be highly desired. Treatment of quinoline **5a** with methyl chloroformate, EtOH, and $NaHCO_3$, followed by exposure to the standard coupling condition, delivered **3a** with moderate diastereoselectivity (*syn*/*anti* = 63:37) and good enantioselectivity (90%/66% ee) in 72% yield (Scheme 2).



Scheme 3 One-Pot Alkylation of the Quinoline.

While the previously reported alkylations of isoquinoliniums with aldehydes displayed excellent enantiocontrol, functionality-containing aldehydes were not well tolerated due to the incompatibility of the Hayashi-Jørgensen catalyst with the acyl chloride, and the low stability of the isoquinolinium ion.[2f] The success of the synergistic catalytic system on the alkylation of quinoliniums prompted us to apply the concept to the reaction of isoquinoliniums. In light of the low yield (9%) for the known protocol with 3-phenylpropanal **2g**, the aldehyde was selected as the coupling partner for preliminary study. While isoquinoline-based hemiaminal **6a** was not a suitable component, tetrahydroisoquinoline-derived **6b** proved to be a competent partner with **2g**, affording **7b** in 68% yield with high enantiocontrol (94%/84% ee).[11] Additionally, the alkylation of tetrahydro-β-carboline-based **6c** gave **7c** in 77% yield with excellent enantioselectivities (95%/93% ee), demonstrating the general applicability of the synergistic catalytic system in the alkylation of diverse *N*-acyl hemiaminals.

In conclusion, the first catalytic asymmetric alkylation of *N*-acyl hemiaminals with aldehydes has been described. The $Cu(OTf)_2$/amine synergistic catalytic system allowed nucleophilic addition of diverse functionalized aldehydes to a wide range of electronically varied *N*-acyl quinoliniums in good yield with excellent enantiocontrol. The synergistic catalytic system was also effective for *N*-acyl dihydroisoquinoliniums and β-carboliniums, demonstrating the general applicability of the protocol in the enantioselective alkylation of diverse *N*-acyl hemiaminals.

We gratefully acknowledge the National Science Foundation of China (21202093, 21472112), the Program for New Century Excellent Talents in University (NCET-13-0346), and the Shandong Science Fund for Distinguished Young Scholars (JQ201404), Young Scientist Foundation Grant of Shandong Province (BS2013YY001), and the Fundamental Research Funds of Shandong University (2014JC00[illegible], 2015JC035) for financial support.

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11 See the Supporting Information for the absolute and relative configuration assignment. We thank an anonymous reviewer for the suggestion on the determination of the configuration.