Communication

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Lewis Base/Copper Cooperatively Catalyzed Asymmetric α-Amination of Esters with Diaziridinones

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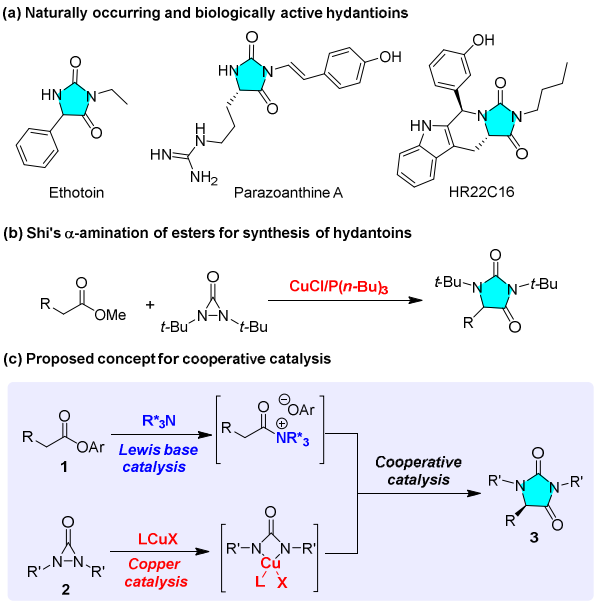
Supporting Information Placeholder

ABSTRACT: An enantioselective α-amination of esters by a Lewis base/copper (I) cooperative catalysis strategy has been developed. The transient chiral C1-ammonium enolate generated from pentafluorophenyl ester and nucleophilic Lewis base is nicely compatible with the copper intermediate formed from N,N-di-*t*-butyldiaziridinone and Cu(I) to allow for high levels of stereochemical control. The cooperative catalytic reaction leads to a diverse set of highly enantioenriched hydantoins in good yields with excellent enantioselectivities (91-98% ee).

Hydantoins, encountered as core structural elements in natural products and pharmaceuticals,[1] constitute a large family of biological molecules as exemplified by Ethotoin, Parazoanthine A, and HR22C16 (Scheme 1a).[2] In addition, flexible chemical transformations capable of occurring at the amide functionality provide chiral hydantoins with additional utilities in organic synthesis.[1b,3] The high value of hydantoins in the realm of synthetic and pharmaceutical chemistry[4] has driven the continuous investigations in the development of synthetic methods.[1b] However, a limited number of available approaches to create asymmetric catalytic synthesis of hydantoins fail to provide synthetically useful stereoselectivity.[5] In 2008, Shi and coworkers reported an elegant α-amination of esters enabled by copper catalysis to liberate hydantoins (Scheme 1b).[6] Notwithstanding the copper species adorned with ligands could exist in the entire catalytic process, a limited number of ligands are compatible with the stereoselectivity in the Cu(I)-catalyzed asymmetric diamination with diaziridinones.[7] As a consequence, circumventing the challenge in the stereochemical control of copper-catalyzed amination of esters entails an alternative strategy beyond the traditional chiral metal complex catalysis.

Asymmetric organocatalysis combined with metal catalysis has shown robust ability to allow the creation of asymmetric protocols which are unable to offer high levels of enantioselectivity by virtue of individual chiral metal catalysis.[8] Recently, we reported a highly stereoselective cooperative Lewis base/copper catalyzed α-propargylation of carboxylic acids.[9] Inspired by this achievement and other metal/Lewis base cooperative catalysis,[10] we discerned that integrating reactivities of an acylammonium and the copper diamide species that was considered a key intermediate in Shi's reaction[6,7] would lead to enantioenriched hydantoins (Scheme 1c). Herein, we will report the first asymmetric α-amination of esters enabled by chiral Lewis base and copper cooperative catalysis to access hydantoins in high optical purity.

Scheme 1. Cooperative Asymmetric α-Amination of Esters for the Synthesis of Hydantoins



In the proposed cooperative catalysis, an acylation reaction of the ester **1** with a nucleophilic Lewis base, such as a chiral tertiary amine, forms a chiral acylammonium **Ia**.[11] Simultaneously, as proposed by Shi and coworkers,[6,7,12] the cleavage of the N-N bond of N,N-diaziridinone (**2**) by the Cu(I) catalyst[13] generates a four-membered Cu(III) species **IIa** or a Cu(II) radical species **IIb**.[12g] At this stage, the acylammonium **Ia** was presumed to undergo a deprotonation reaction with the four-membered Cu(III) species **IIa** to give a chiral intermediate **III**. The reductive elimination of **III** would lead to a C-N coupling intermediate **IV** that undergoes an intramolecular amidation reaction to allow the catalyst turnover and to yield the enantioenriched hydantoin **3** (Scheme 2, left cycle). Alternatively, the α-amination involves initial generation of acylammonium **Ib**, which reacts with Cu(II) radical species **IIb** to give a radical intermediate **V**. This radical species would then undergo a cyclization to furnish the final product **3** and to regenerate the Lewis base and the copper catalyst (Scheme 2, right cycle). Since the Lewis base catalyst always locates proximal to the reactive carbon of intermediates that involve the creation of

Scheme 2. Mechanistic Hypothesis for Chiral Lewis Base/Copper Cooperatively Catalyzed Asymmetric α-Amination of Esters

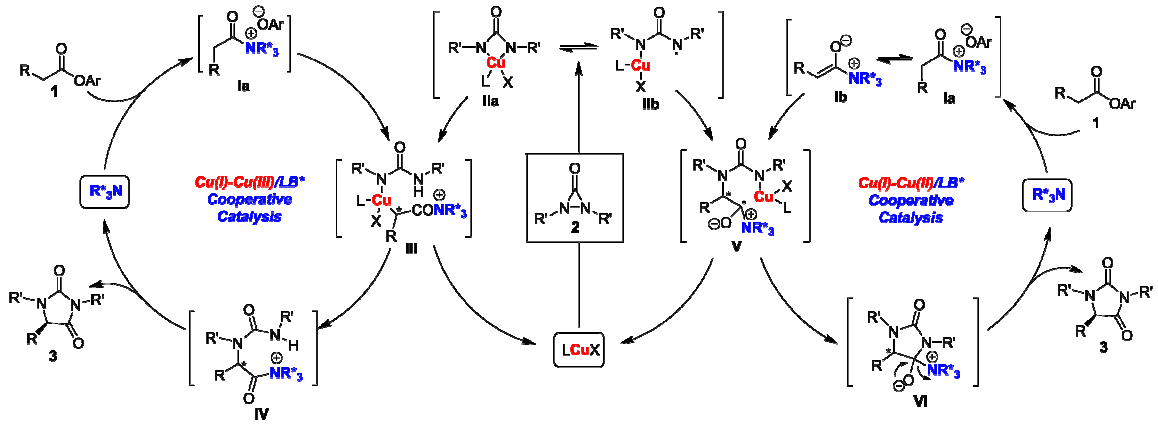
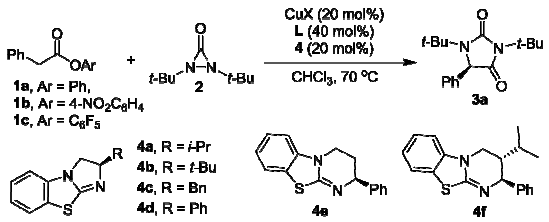


Table 1. Identification of Optimal Catalyst and Optimization of Reaction Conditions[a]



entry	1	CuX	L	4	Yield (%)[b]	*ee* (%)[c]
1	**1a**	CuCl	P(*n*-Bu)$_3$	**4a**	47	6
2	**1b**	CuCl	P(*n*-Bu)$_3$	**4a**	41	52
3	**1c**	CuCl	P(*n*-Bu)$_3$	**4a**	71	98
4	**1c**	CuBr	P(*n*-Bu)$_3$	**4a**	65	98
5	**1c**	CuI	P(*n*-Bu)$_3$	**4a**	62	98
6	**1c**	—	—	**4a**	n.d.	—
7	**1c**	CuCl	—	**4a**	22	86
8	**1c**	CuCl	PCy_3	**4a**	36	92
9	**1c**	CuCl	PPh_3	**4a**	73	95
10	**1c**	CuCl	P(4-MeC_6H_4)$_3$	**4a**	72	96
11	**1c**	CuCl	P(2-MeC_6H_4)$_3$	**4a**	55	91
12	**1c**	CuCl	P(2-furyl)$_3$	**4a**	36	80
13	**1c**	CuCl	$P(OPh)_3$	**4a**	35	89
14	**1c**	CuCl	P(*n*-Bu)$_3$	—	44	0
15	**1c**	CuCl	P(*n*-Bu)$_3$	**4b**	59	92
16	**1c**	CuCl	P(*n*-Bu)$_3$	**4c**	73	97
17	**1c**	CuCl	P(*n*-Bu)$_3$	**4d**	69	98
18	**1c**	CuCl	P(*n*-Bu)$_3$	**4e**	61	97
19	**1c**	CuCl	P(*n*-Bu)$_3$	**4f**	58	98

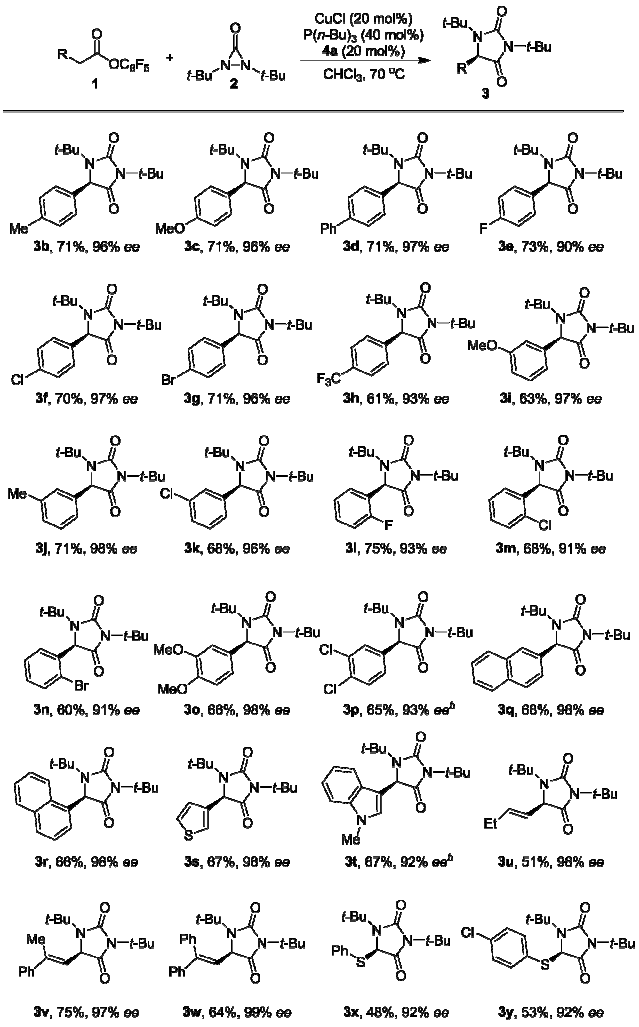
[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.6 mmol), CuCl (20 mol%), **L** (40% mmol), **4** (20 mmol%), $CHCl_3$ (1 mL), 70 °C, under Ar. [b]Isolated yield. [c]Determinted by HPLC and the absolute configuration of **3a** was assigned by single-crystal X-ray diffraction analysis (see Supporting Information).

ogenic center in either Cu(I)/Cu(III) or Cu(I)/Cu(II) catalytic cycle, the chiral Lewis base and copper cooperative catalysis would be able to provide a promising scenario to achieve asymmetric α-amination of esters.

The initial attempts to validate the proposed reaction focused on the compatibility of the aryl 2-phenylacetate reactivity with stereochemical control of chiral Lewis base. By using a modified benzotetramisole-type catalyst **4a**[11d,14] and a copper chloride-tributylphosphine complex, the asymmetric α-amination of aryl 2-phenylacetates **1a-1c** with N,N-di-*t*-butyldiaziridinone **2** proceeded smoothly to give the desired hydantoin **3a** (Table 1, entries 1-3). The enantioselectivity was significantly dependent on the nature of aryloxide leaving group. Gratifyingly, the pentafluorophenyl ester **1c** proved to the most effective and provided the highest yield and enantiomeric excess (entry 3, 71% yield, 98% ee). The copper salts affect the reaction conversion slightly, but were unable to alter the enantioselectivity (entries 3-5). Notably, the reaction does not proceed in the absence of the copper catalyst (entry 6). Interestingly, the phosphorus ligands exert profound impact on the reaction performance (entries 7-13). Tributylphosphine was not just able to enhance the catalytic activity of Cu(I), but imposed considerable influence on the stereochemical control, as indicated by the fact that both the reaction conversion and enantioselectivity considerably drooped without the ligand (entry 7). Moreover, the catalytic activity of Cu(I) complex largely depends on the electronic and steric feature of the phosphorus ligands (entries 8-13). Among the ligands screened, tributylphosphine turned out to be most compatible with the catalytic activity of copper and the stereoselectivity of chiral organocatalyst (entry 3 vs 7-13). In the absence of the chiral Lewis base, the reaction still proceeded, yet led to the racemic **3a** in a relatively lower yield (entry 14). However, the use of chiral phosphine ligands alone only provided almost racemic product **3a** (See Table S1 in Supporting Information for details). The copper-catalyzed reactions conducted with different Birman-type nucleophilic Lewis bases (**4a-f**) revealed that all of them were able to offer excellent levels of enantioselectivity notwithstanding the reaction conversion varied in correlation with the structure of chiral Lewis bases (entries 15-19). The (*R*)-*i*-Pr-BTM and (*R*)-Bn-BTM appeared to be best compatible with the reaction catalyzed by the copper complex of tributylphosphine (entries 3 and 16).

Having established the optimal reaction conditions, we investigated the generality of the cooperative catalytic reaction for acetyl acid pentafluorophenyl esters (Table 2). The variation in electron density of the phenyl group exerts little impact on the stereochemical outcome of reactions with *meta*- and *para*-substituted phenylacetyl acid pentafluorophenyl esters (**3b-3k**, 90-98% ee) while relatively lower enantioselectivities were observed for phenylacetyl acid pentafluorophenyl esters bearing a highly electron-withdrawing substituent (**3e** and **3h**).

Table 2. Substrate Scope[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.6 mmol), CuCl (20 mol%), P(*n*-Bu)$_3$ (40% mmol), **4** (20 mmol%), $CHCl_3$ (1 mL), 70 °C, under Ar. [b]at 60°C

In contrast, the alternation of electron density of the phenyl substituent was unable to considerably change the stereoselection in the amination reaction of *ortho*-substituted phenylacetyl acid pentafluorophenyl esters, yet still leading to chiral hydantoins **3l-3n** with excellent enantiomeric excesses. Disubstituted substrates were also tolerated to provide the desired products with excellent enantioselectivities (**3o** and **3p**). The reaction of naphthyl and hetereoaryl acetyl acid esters proceeded successfully to afford hydantoins **3q-3t** with high levels of enantioselectivity ranging from 92% to 98% ee. More importantly, the reaction conditions were amenable to a variety of 3-substituted butenoic acid pentafluorophenyl esters, which produced 5-vinyl hydantoins **3u-3w** in good yields of up to 75% and excellent enantioselectivities of up to 99% ee. 2-(Phenylthio)acetic acid esters appeared to be active reaction partners and provided uniformly high levels of enantioselectivity, although the yields were moderate (**3x** and **3y**). Although alkanoic substrates were ineffective under the conditions, 5-alkyl hydantoins can be alternatively accessed from catalytic hydrogenation of 5-vinyl hydantoins with maintained enantioselectivity (see Supporting Information).

In order to gain insight into the mechanism, the model reaction of **1c** with **2** (Table 1, entry 3) was monitoered by electron paramagnetic resonance (EPR) spectroscopy to identify if the radical speices was generated.[15] A triplet with a 1:1:1 intensity ratio was observed when N,N-di-*t*-butyldiaziridinone **2** was treated with CuCl-P(*n*-Bu)$_3$ (1:2) (Figure 1a), which suggested the existence of nitrogen radical intermediate **IIb**.[12g] A similar triplet with a 1:1:1 intensity ratio was also observed when the reaction was performed under the standard reaction conditions (Table 1, entry 3), which indicated that the process involved radical elementary steps (Figure 1b). The EPR experiments (see Supporting Information) suggested that the radical intermediate **IIb** might be the active copper species in the cooperative catalytic cycle (Scheme 2, right cycle). On the basis of our experimental results, a plausible transition state to account for the observed stereochemistry was proposed (Figure 1c).[16] The isopropyl group of the Lewis base catalyst effectively shields the *Si* face of the C1-ammonium (*Z*)-enolate, to permit the *Re* face open for the nitrogen radical intermediate **IIb** to undergo the enantioselective radical addition, and then followed by the subsequent lactamization to give experimentally observed product (*R*)-**3a** (Scheme 2).

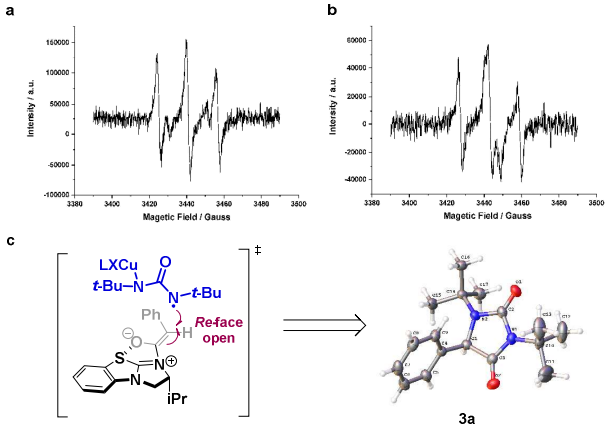
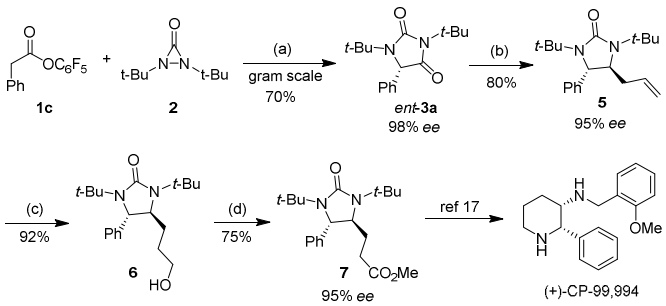


Figure 1. Mechanism Studies. (a) EPR spectrum for the reaction of N,N-di-*t*-butyldiaziridinone (2) and CuCl-P(*n*-Bu)$_3$ in chloroform. (b) EPR spectrum for the model reaction. (c) Proposed transition state and single-crystal X-ray structure of **3a**.

(+)-CP-99,994 is a high affinity NK_1 antagonist[17] and has been concisely accessed starting with the current reaction. As shown in Scheme 3, a gram-scale reaction of the pentafluorophenyl ester **1c** and **2** furnished hydantoin *ent*-**3a** in 71% yield and with 98% ee, almost identical to the results obtained in small scale (Table 1, entry 3). The reduction of *ent*-**3a** with $LiAlH_4$ and followed by a diastereoselective allylation with allyltributylstannane promoted by borontrifluoride led to **5** in 80% yield with 95% ee. The borylation with 9-borabicyclo[3.3.1]nonane (9-BBN) and oxidation with hydrogen peroxide under basic conditions converted the **5** to an alcohol **6**. The oxidation of **6** with pyridinium dichromate (PDC)

in methanol delivered an ester **7**, which could be transformed into (+)-CP-99,994 by following Shi's procedure.[18] In addition, The deprotection of the resulting hydantoin derivative **3a** smoothly provided corresponding product with maintained enantioselectivity (see Supporting Information).

Scheme 3. Asymmetric Formal Synthesis of (+)-CP-99,994[a]



[a]Reagents and Conditions: (a) CuCl (20 mol%), P(*n*-Bu)$_3$ (40 mol%), *ent*-**4a** (20 mol%), $CHCl_3$, 70 °C. (b) (i) $LiAlH_4$, THF, 0 °C to rt; (ii) $BF_3{\cdot}Et_2O$, allyltributylstannane, DCM, -78 °C. (c) (i) 9-BBN, THF, 60 °C; (ii) then H_2O_2, 30% NaOH. (d) PDC, MeOH, DMF, rt.

In summary, we have developed an asymmetric α-amination of esters by using chiral Lewis base and copper (I) cooperative catalysis, leading to a large family of highly enantioenriched hydantoins, which hold great potential applications in the preparation of biologically active molecules. The transient chiral C1-ammonium enolate generated from pentafluorophenyl ester and nucleophilic Lewis base is nicely compatible with the copper intermediate formed from N,N-di-*t*-butyldiaziridinone and Cu(I) to allow for high levels of stereochemical control that the use of chiral ligand is hard to enable. The future study will focus on the comprehensive exploration of the reaction mechanism and other asymmetric α-functionalization reactions of esters initiated with copper (I) complex.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data. 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 interests.

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