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Iron-Catalyzed Intramolecular C—H Amidation of *N*-Benzoyloxyureas

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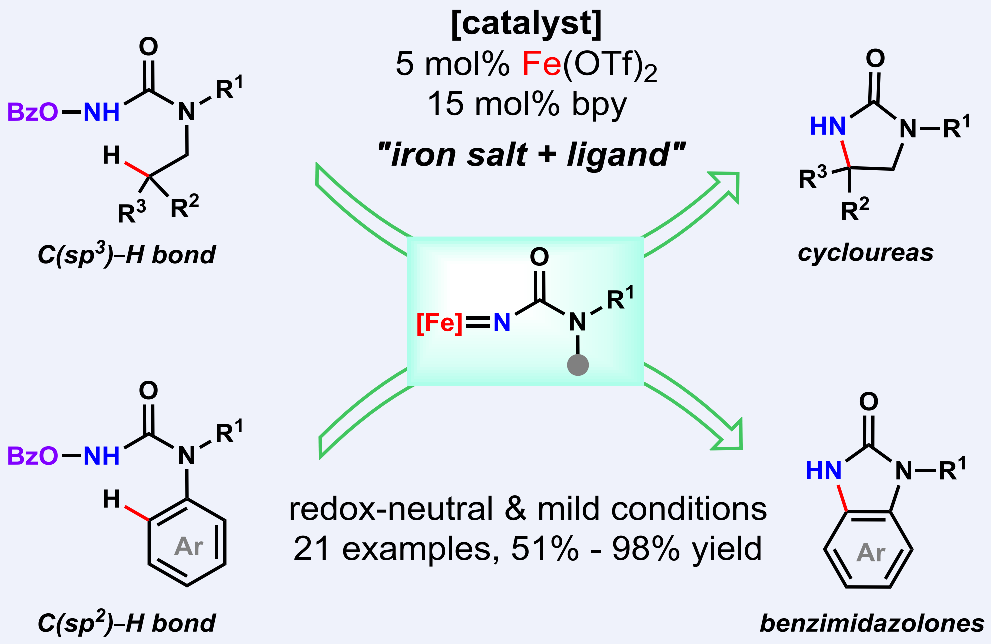
Keywords

C—H activation | Amination | Cyclization | Iron catalysis | Nitrene insertion

Main observation and conclusion

A redox-neutral Fe-catalyzed intramolecular C—H amidation of *N*-benzoyloxyureas is described. This methodology employs a simple iron complex *in situ* generated from Fe(OTf)$_2$ and bipyridine as the catalyst and *N*-benzoyloxyureas as the nitrene precursors without using exogenous oxidants. An array of cyclic ureas were synthesized *via* aliphatic C(sp^3)—H amidation in excellent yields. In addition, this catalytic system is also amenable to aryl C(sp^2)—H nitrene insertion to provide benzimidazolones in moderate yields.

Comprehensive Graphic Content



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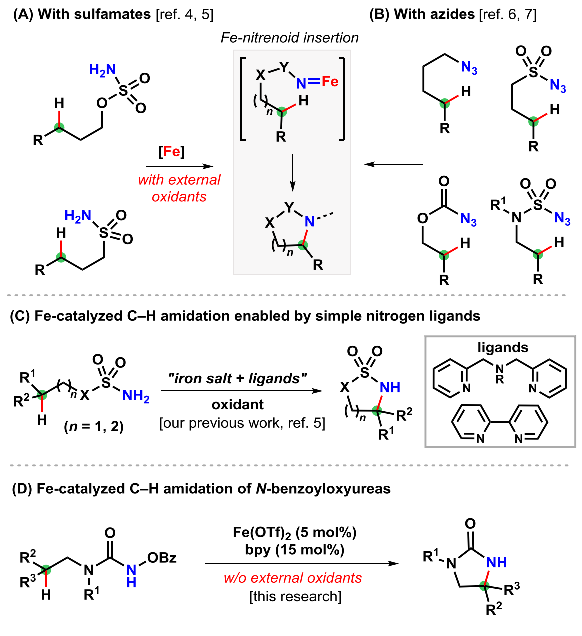
Background and Originality Content

Nitrogen-containing heterocycles are privileged scaffolds in pharmaceuticals and natural products.[1] Direct intramolecular C—H amination reaction provides straightforward access to these structural motifs and thus has drawn much attention and continued efforts.[2] Iron-catalyzed nitrene insertion is among the most attractive approaches of C—H amination due to the abundant and environmentally benign nature of iron.[3] In the last few decades, tremendously remarkable results have been disclosed with a variety of C(sp^3)—H bonds, both activated and inert, successfully aminated in high selectivities and reactivities. Sulfamates were commonly used as the nitrene precursors in iron-catalyzed amination reaction, but necessitated exogenous oxidants (*e.g.*, bis(trifluoroacetoxy)iodo]benzene (PIFA), Scheme 1A).[4-5] Significant advances were accomplished by a number of groups including Betley,[6a] Plietker,[6b] Che,[6c] and others,[7] employing azides to generate iron-nitreniod species (Scheme 1B). A remarkable recent example realized the amination of dioxazolones for the synthesis of γ-lactams reported by Chang group and remarkable reactivity was achieved using an iron(III) phthalocyanine catalyst.[8]

Due to their ready accessibility and relatively weak N—O bond, hydroxylamine derivatives were actively used as nitrogen-transfer reagents involving transition-metal-nitrenoid intermediacy under redox-neutral conditions.[9-10] However, their application in iron-catalyzed C—H amination has been rarely explored. To date, only a handful of examples were revealed by Morandi,[10a] Jiao,[10b] Singh,[10c] and Falck,[10d] but they were limited to aryl C—H bond amination reactions. Our group has a keen interest in developing practical amination strategies using a synthetically convenient "iron salt/ligand" protocol.[5] Notably, the amination of inert aliphatic primary, secondary, and tertiary C—H bonds of sulfamates in the presence of oxidants was enabled by handy catalysts *in situ* generated from cheap iron salts and readily available nitrogen ligands (*e.g.*, bipyridine, Scheme 1C).[5] Based on this precedence, we wondered whether the simple iron system is capable of catalyzing the amidation of hydroxylamine derivatives (Scheme 1D). Herein, we reported an efficient $Fe(OTf)_2$/bipyridine-catalyzed C—H amidation of *N*-benzoyloxyureas.[11] In this new transformation, both C(sp^3)—H and C(sp^2)—H bonds are feasible substrates delivering the cyclic ureas in moderate to excellent yields under external oxidant-free conditions.

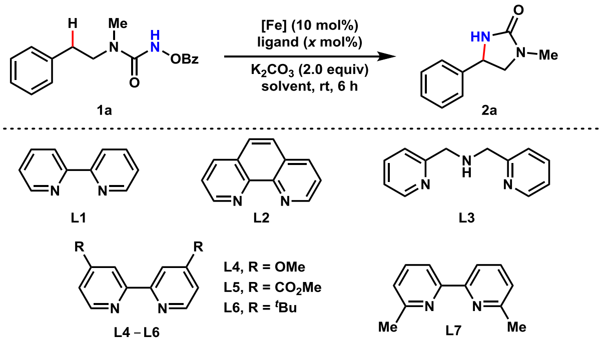
Scheme 1 C(sp^3)—H amination involving Fe-nitrenoid intermediacies



Results and Discussion

We commenced our study employing *N*-benzoyloxylurea **1a** as a model substrate. Much to our delight, cyclic urea **2a** was obtained in excellent yield (92%) with 10 mol% $FeCl_2$/bipyridine (**L1**) as the catalyst (entry 1). Further systematic optimization of the reaction conditions was carried out and the selected results are summarized in Table 1 (see Tables S1—S5 in Supporting Information for details). The reactions using 1,10-phenanthroline (**L2**) and a tridentate ligand (**L3**) provided 81% and 74% yields, respectively (entries 2 and 3). Bipyridines containing both electron-donating and electron-withdrawing substituents were studied (**L4**—**L6**, entries 4—6) and dramatically reduced reactivity was observed with electron deficient ligand (entry 5). 6,6'-Disubstituted bipyridine (**L7**) derived catalyst offered only 19% yield probably due to the steric effect. Varying the ratios of iron precursors *versus* ligands revealed that reducing the loading of ligands led to lower reactivity (*e.g.*, 47% yield with 10 mol% of **L1**, entry 9). After a brief screen of solvents, MeCN was superior albeit the reaction proceeded smoothly in CH_2Cl_2 (81%) and DCE (76%) (entries 10 and 11). Examination of a variety of iron salts revealed that $Fe(OTf)_2$ (96%, entry 12) was more efficient and a similar result was obtained with $FeBr_2$ (95%, entry 14). The reaction with reduced catalyst loading (5 mol%) was much less efficient, in turn only 54% yield of product was obtained (entry 15). Gratifyingly, the yield could be improved to 94% (91% isolated yield) upon heating of the reaction at 40 °C while maintained the catalyst loading (entry 16), which was identified as the optimal conditions.

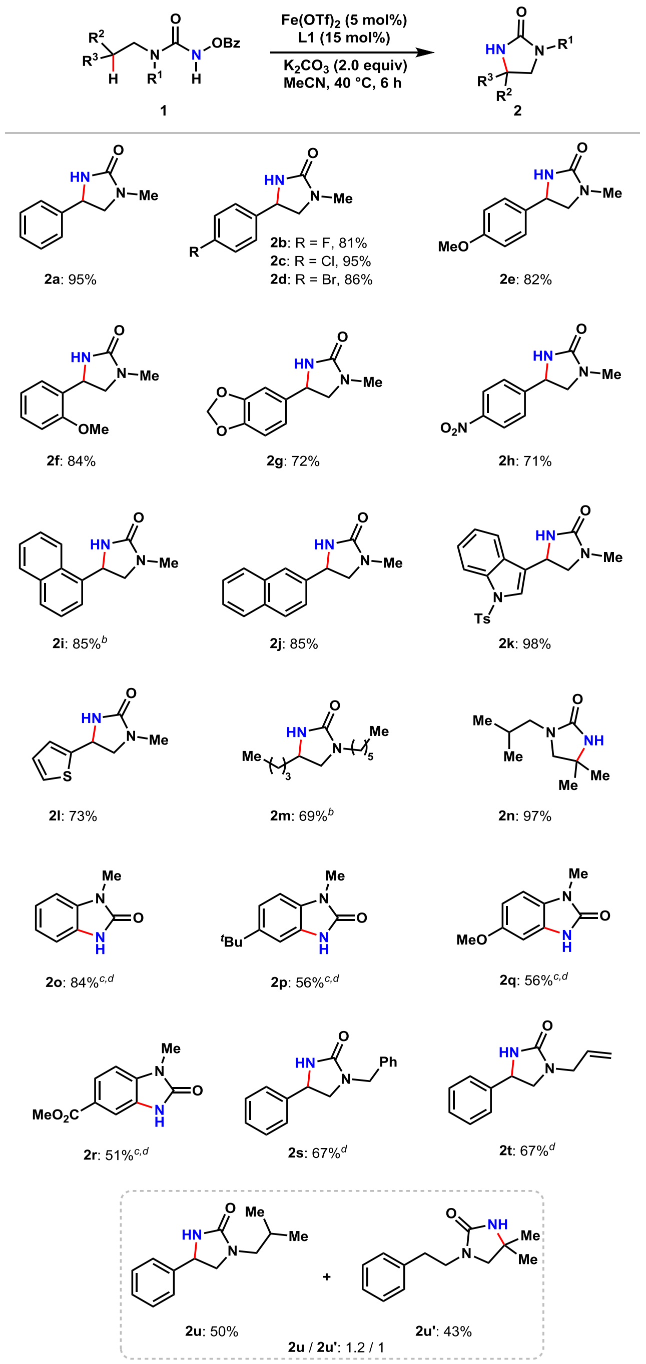
Table 1 Condition optimization



entry[a]	catalyst	ligand (*x* mol%)	solvent	yield[b]
1	$FeCl_2$	**L1** (30)	MeCN	92%
2	$FeCl_2$	**L2** (30)	MeCN	81%
3	$FeCl_2$	**L3** (20)	MeCN	74%
4	$FeCl_2$	**L4** (30)	MeCN	85%
5	$FeCl_2$	**L5** (30)	MeCN	35%
6	$FeCl_2$	**L6** (30)	MeCN	86%
7	$FeCl_2$	**L7** (30)	MeCN	19%
8	$FeCl_2$	**L1** (20)	MeCN	76%
9	$FeCl_2$	**L1** (10)	MeCN	47%
10	$FeCl_2$	**L1** (30)	CH_2Cl_2	81%
11	$FeCl_2$	**L1** (30)	DCE	76%
12	$Fe(OTf)_2$	**L1** (30)	MeCN	96% (93%)[c]
13	$Fe(ClO_4)_2$	**L1** (30)	MeCN	62%
14	$FeBr_2$	**L1** (30)	MeCN	95%
15[d]	$Fe(OTf)_2$	**L1** (15)	MeCN	54%
16[d,e]	$Fe(OTf)_2$	**L1** (15)	MeCN	94% (91%)[c]

[a] Reaction conditions: **1a** (0.1 mmol), [Fe] (0.01 mmol, 10 mol%), K_2CO_3 (2.0 equiv), rt, 6 h. [b] Determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [c] Isolated yield. [d] With 5 mol% $Fe(OTf)_2$. [e] At 40 °C.

Scheme 2 Substrate scope[a]



[a] Reaction conditions: **1** (0.4 mmol), Fe(OTf)$_2$ (0.02 mmol, 5 mol%), **L1** (0.06 mmol, 15 mol%), K$_2$CO$_3$ (2.0 equiv), 40 °C, 6 h. [b] 8 h. [c] In DCE (2 mL) for 8 h. [d] With **1** (0.2 mmol), Fe(OTf)$_2$ (10 mol%), and **L1** (30 mol%).

With the optimized conditions in hand, we next examined the scope of the reaction (Scheme 2). Substrates bearing halogen atom such as F, Cl, and Br at the *para*-position of the phenyl provided the corresponding cyclic ureas **2b**—**2d** in 81%—95% yields. Substrates with electron-donating groups (**2e**—**2g**) achieved 72%—84% yields. Whereas an electron-withdrawing nitro group-containing substrate delivered the desired product **2h** in lower yield (71%). Substrates **1i** and **1j** containing 1-naphthyl and 2-naphthyl, respectively, provided the corresponding products **2i** and **2j** smoothly. Heteroaromatic substrates, such as a tryptamine derivative (**2k**, 98%) and 2-thienylethylamine (**2l**, 73%), were also well tolerated. This method is also applicable to non-benzylic aliphatic C—H bonds (*e.g.*, **2m**, 69%; **2n**, 97%). It is noteworthy that the amidation of 3° C—H bonds is more efficient in comparison with 2° C—H bonds. Additionally, this method can be applied in the C(sp^2)—H amidation to produce benzimidazolones in synthetically useful yields (**2o**, 84%; **2p**, 56%; **2q**, 56%; **2r**, 51%). Other substituents on the nitrogen atom were also investigated. Bn and allyl substituted ureas delivered the corresponding products in declined yields (**2s**, 67% and **2t**, 67%). For the substrate **1u** bearing both benzylic and tertiary C—H bonds, a 1.2 : 1 mixture of products **2u** and **2u'** was obtained in excellent yield (93%) with the activated site slightly favored.

Conclusions

In conclusion, we have developed an intramolecular C—H amidation of *N*-benzoyloxyureas catalyzed by a simple "iron salt + ligand" strategy. With abundant and innocuous Fe(OTf)$_2$/bipyridine as the catalyst, both aliphatic C(sp^3)—H and aryl C(sp^2)—H bonds were successfully converted into a variety of cyclic ureas in moderate to excellent yields. This reaction features readily available catalyst, high reactivity and selectivity, and external oxidant-free conditions. We anticipant that this simple iron catalytic system offers an efficient and sustainable way to access privileged nitrogen-heterocycles.

Experimental

To an oven-dried 10 mL sealed tube were added Fe(OTf)$_2$ (0.02 mmol, 5 mol%), **L1** (0.06 mmol, 15 mol%), K$_2$CO$_3$ (0.8 mmol, 2.0 equiv), substrate **1** (0.4 mmol, 1.0 equiv) and MeCN (2.0 mL). The reaction was stirred at 40 °C for 6 h, filtered through a plug of celite, and washed with ethyl acetate. The filtrates were collected and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (200—300 mesh SiO$_2$) to give the desired products.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.202100005.

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