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Iron-Catalyzed Intramolecular Amination of Aliphatic C−H Bonds of Sulfamate Esters with High Reactivity and Chemoselectivity

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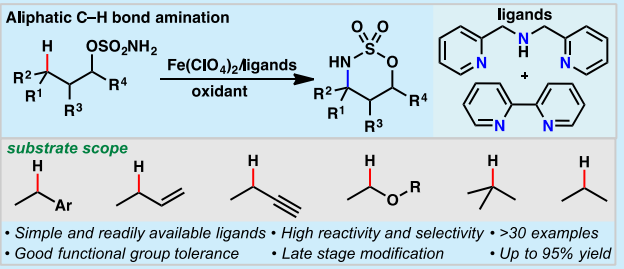
Supporting Information

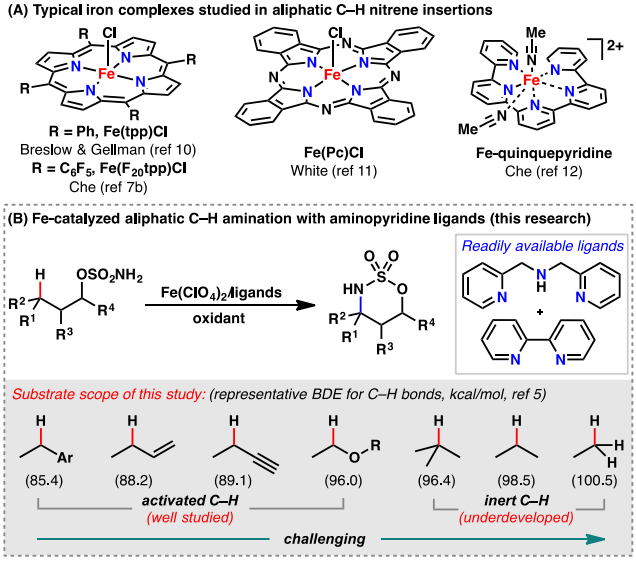
ABSTRACT: It is challenging to develop simple and low cost catalytic systems while maintaining high reactivity and selectivity. An iron-catalyzed intramolecular C−H amination of sulfamate esters using simple and cheap ligands is reported with general substrate scope (31 examples, up to 95% yield). The addition of second ligand, bipyridine, is able to accelerate the reaction and increase the yield. The ready availability of these iron catalysts provides a promising approach to selective introduction of nitrogen into hydrocarbon feedstock.



Nitrogen-containing motifs are prevalent in synthetic intermediates, pharmaceuticals, and agrochemicals.[1,2] The importance of nitrogen that strongly influences bioactivity inspired chemists to develop a wide array of C−N forming methods,[2] among which direct amination of ubiquitous hydrocarbons has a significant impact on the synthesis of amines and *N*-heterocycles.[3,4] However, aliphatic C−H bonds are among the least reactive in organic transformations because of their thermodynamic and kinetic stability.[5] Although substantial advances have been made on noble metal catalyzed C−H amination via nitrenoid intermediates in the last decades,[3,6] the search for highly efficient but low cost catalytic methods that enable direct hydrocarbon functionalization is a longstanding ambition of synthetic chemists. Correspondingly, many efforts have been devoted to the development of catalysts based on relatively nontoxic and largely abundant first-row transition metals and, in particular, on iron.[7−9]

In 1982, Breslow and Gellman reported the first example of nitrene insertion to the aliphatic C−H bond using iron−porphyrin complex (Fe(tpp)Cl, Scheme 1A).[10] With sulfamate substrates, the White group successfully demonstrated a site-selective intramolecular nitrene insertion using phthalocyaninato-iron catalyst (Fe(Pc)Cl) combined with silver salt, albeit primarily with activated substrates (i.e., allylic, benzylic).[11] Concurrently, Che and co-workers efficiently realized the amination of a variety of hydrocarbons, including nonactivated C(sp^3)−H bonds, utilizing an impressive iron−quinquepyridine complex.[12] Remarkable progress in C−H aminations of aliphatic azides was also achieved by Betley,[13a] Driver,[6d] De Bruin and Van Der Vlugt,[13b] Plietker,[13c] Che,[13d] and others.[4i] Although those are great achievements in iron−nitrenoid insertion chemistry, there are still important challenges to be addressed. First, inert C(sp^3)−H bonds have been proven to be problematic with low reactivity, and there are very limited examples that tolerate such types of substrates.[12,13d] Moreover, the amination of aliphatic C−H bonds enriched with functional groups has not been well demonstrated. Second, ligands in iron-catalyzed amination of sulfamate esters studied to date are mainly limited to very unique frameworks (Scheme 1A), which make them challenging to synthesize and modify,

Scheme 1. Iron-Catalyzed Intramolecular C−H Aminations of Sulfamate Esters



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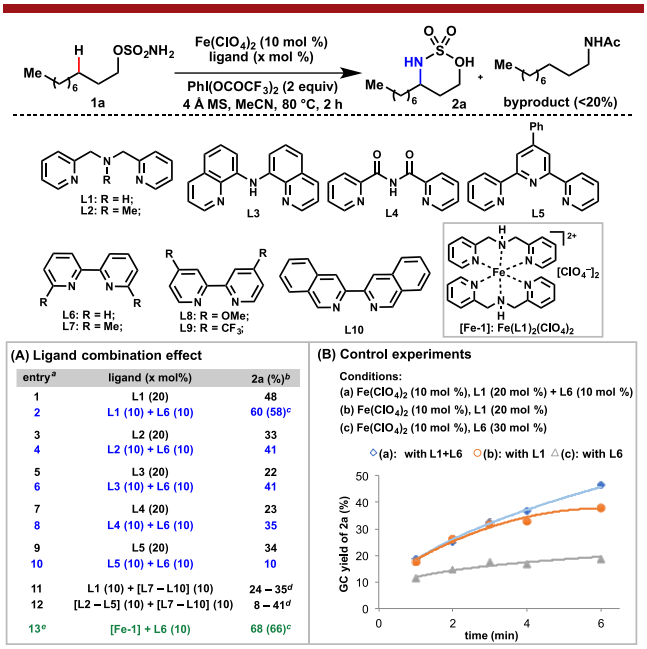
therefore inherently hampering the access of structurally diverse catalysts and the synthetic application of the methodologies. Since ligand is always found to play a key role in tuning the reactivity and selectivity, discovery of active iron complex derived from simple ligands could quickly provide viable catalysts to facilitate the amination. Our attention was drawn by the fact that a large collection of simple aminopyridine analogues have been widely studied as ligands in iron-catalyzed C−H oxidation[14] but scarcely investigated in amination.[15] Inspired by the remarkable reactivity of the iron−quinquepyridine complex,[12] we sought to mimic its stereoelectronic and coordinating environment with a combination of simple tridentate ligand and bidentate ligand. This finally led us to find that employing a mixture of ligands of aminopyridine **L1**[16] and bipyridine **L6** allows selective C−H amination reaction with a wide range of C(sp^3)−H bonds.

With aliphatic sulfamate ester **1a** as a model substrate, extensively condition optimizations by screening of iron sources, oxidants, ligands, and solvents were carried out (Tables S1−S4). We were pleased to find that in situ prepared catalyst from $Fe(ClO_4)_2$ and **L1** provided product **2a** in 48% yield (entry 1 in Figure 1a). When equimolar amounts of **L1** and **L6** were employed as ligands,[17] an increased yield was obtained (60%, entry 2). Encouraged by these results, we next studied the ligand combination strategies using catalysts generated in situ from $Fe(ClO_4)_2$ and equimolar amounts of tridentate ligand (from **L1** to **L5**) and **L6**, the enhancement of reactivity was observed except for ligand **L5** (entries 3−10). Cross combinations between each tridentate ligand (**L1**−**L5**) with each of bidentate ligand (**L6**−**L10**) were carried out but failed to further increase the yield (entries 11 and 12, Figure 1a and Table S4). Iron precursors with different anions, such as bromide, triflate, perchlorate, tetrafluoroborate, etc., were also screened, and $Fe(ClO_4)_2$ showed higher reactivity (entries 29−36, Table S4). Finally, employing 10 mol % of iron complex [**Fe-1**], which was preformed from **L1** and $Fe(ClO_4)_2$ in MeCN and isolated by recrystallization,[18a] and 10 mol % of **L6** improved the NMR yield of **2a** to 68% (66% isolated, entry 13) and was thus identified as the optimal conditions. It is worth mentioning that a byproduct (decylacetamide) formed from the reaction of substrate **1a** with MeCN was observed but in less than 20% yield under all the screened conditions (NMR yield, see the SI).



entry[a]	ligand (x mol%)	2a (%)[b]
1	L1 (20)	48
2	L1 (10) + L6 (10)	60 (58)[c]
3	L2 (20)	33
4	L2 (10) + L6 (10)	41
5	L3 (20)	22
6	L3 (10) + L6 (10)	41
7	L4 (20)	23
8	L4 (10) + L6 (10)	35
9	L5 (20)	34
10	L5 (10) + L6 (10)	10
11	L1 (10) + [L7 − L10] (10)	24 − 35[d]
12	[L2 − L5] (10) + [L7 − L10] (10)	8 − 41[d]
13[e]	[Fe-1] + L6 (10)	68 (66)[c]

Figure 1. Condition optimizations. (a) Reaction conditions: **1a** (0.2 mmol), $PhI(OCOCF_3)_2$ (0.4 mmol), and 4 Å MS (50 mg) in MeCN (2.5 mL) at 80 °C for 2 h. (b) NMR yield using 1,3,5-trimethoxybenzene as an internal standard. (c) Isolated yield. (d) See Table S4 for details. (e) Without the use of $Fe(ClO_4)_2$.

To further understand the possible role of the additional ligand **L6**, control experiments with three in situ formed catalysts, namely, (a) $Fe(ClO_4)_2$/(**L1** + **L6**), (b) $Fe(ClO_4)_2$/**L1**, and (c) $Fe(ClO_4)_2$/**L6**, were carried out (Figure 1B). Although all three complexes are found to be capable of promoting the amination, the reaction with combined ligands (conditions a) was found to be faster than others and provided the desired product in 46% yield in 6 min. The addition of **L6** accelerates the rate of the reaction probably due to the formation of new catalytic species. Theoretically, if ligand exchange is fast and reversible, three different iron complexes in equilibrium with one another could be formed using two ligands, including homocombinations $[Fe(\mathbf{L1})_2(ClO_4)_2]$ and $[Fe(\mathbf{L6})_3(ClO_4)_2]$ and the corresponding heterocombination $[Fe(\mathbf{L1})(\mathbf{L6})(ClO_4)_2]$.[18b] Indeed, three peaks at m/z 262.0706, 227.0784, and 205.5573 were obtained by HRMS studies assignable to $[Fe(\mathbf{L6})_3]^{2+}$ (calcd m/z 262.0700), $[Fe(\mathbf{L1})_2]^{2+}$ (calcd m/z 227.0779), and $[Fe(\mathbf{L1})(\mathbf{L6})]^{2+}$ (calcd m/z 205.5568), respectively (Figure S1).[19]

To prove the general applicability of this strategy, we first explored the substrates with strong C−H bonds (Scheme 2a). A shorter carbon chain substrate **1b** provided product **2b** in 66% yield. Distal functional groups, such as chloride (**2c**, 63%), bromide (**2d**, 70%), silyl ether (**2e**, 56%), ester (**2f**, 65%), tosylate (**2g**, 54%), and phthalamide (Phth) (**2h**, 60%), were all reasonably tolerated. Cyclopropane-containing product **2i** was obtained in 68% yield.[20] Amination of sterically hindered tertiary C−H bonds (**1j** and **1k**) delivered the corresponding products **2j** (60%) and **2k** (52%). Bicyclic and spirocyclic heterocycles (**2l**−**r**) were formed from the corresponding sulfamates. Quaternary carbon containing bicyclic **2l** and **2m** were synthesized in 54% and 80% yield with excellent diastereoselectivity. Cyclobutane derivatives are found in a variety of natural products,[21] and direct functionalization methods are appealing. Here, efficient amination of the cyclobutane ring was achieved to provide **2n** (86%) as single isomer. Adamantane-derived product **2o** was also obtained in excellent yield (95%).

The high degree of functional group compatibility of this catalyst is further demonstrated by substrates with activated C−H bonds (Scheme 2b). Amination product **2p**, a synthetic precursor to a neurotoxic agent saxitoxin,[22] was obtained in 46% yield from enantioenriched glycerol-derived sulfamate ester **1p**. It is noteworthy that ethereal substrate reacted at the more reactive C−H bond, resulting in the formation of five-membered product **2q** in 49% yield. The amination of the allylic C−H bonds of **1r** and **1s** occurred in moderate yield (**2r** and **2s**). Although chemoselectivity of metal−nitrenoid insertion toward the C−H bond and olefin is often a significant challenge, a high selectivity (10:1, amination vs aziridination) was observed with substrate **1s**.[4,23] Propargylic (**2t**) C−H bond amination was performed in moderate yield. The amination of a variety of benzylic substrates containing both electron-rich and electron-withdrawing groups provided

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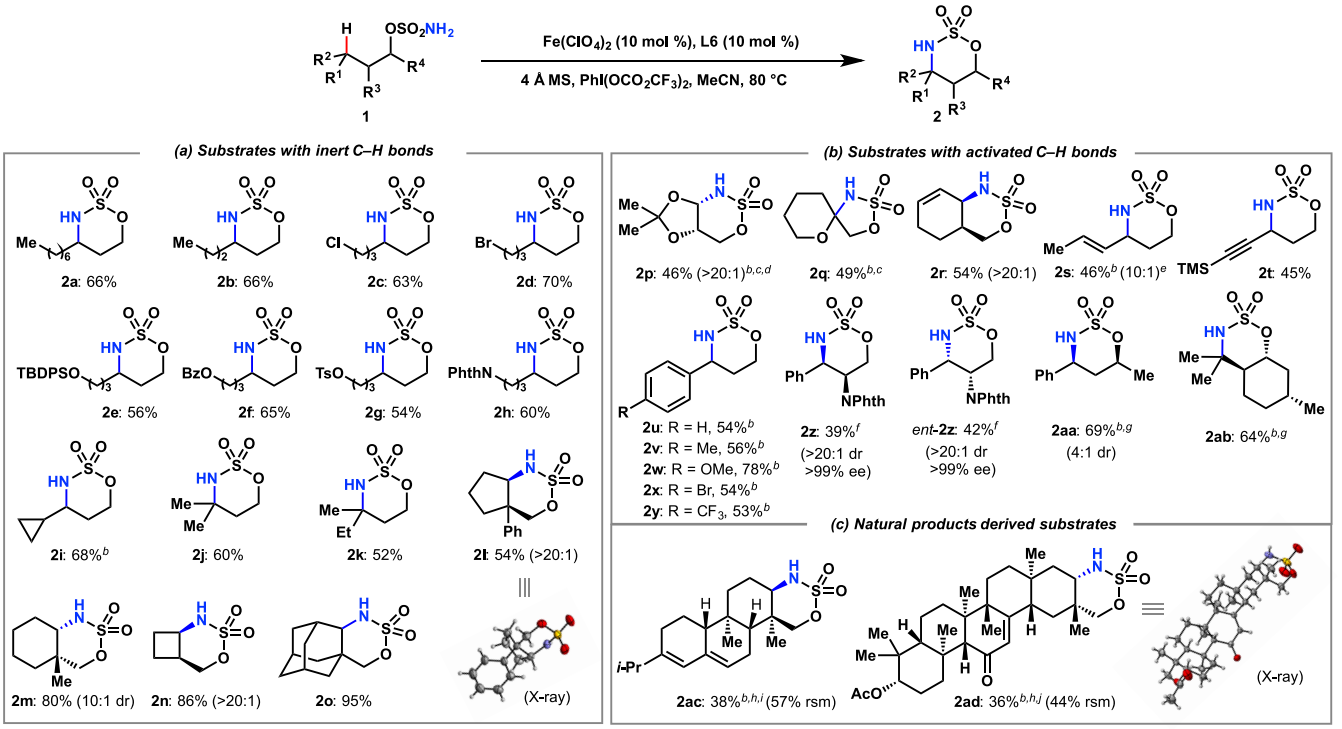
Scheme 2. Substrate Scope[a]



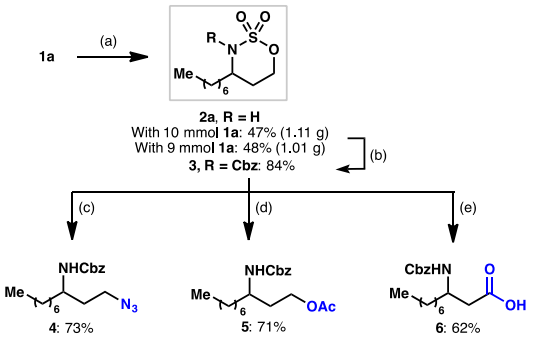
[a]Reaction conditions: **1** (0.4 mmol), PIFA (0.8 mmol), 4 Å MS (100 mg), MeCN (5 mL), 80 °C; see the SI for details. [b]$PhI(OPiv)_2$ (2 equiv) was used instead of PIFA. [c]60 °C. [d]0.3 mmol scale. [e]The ratio of amination vs aziridination products. [f]With $Fe(ClO_4)_2$ (10 mol %) and **L6** (30 mol %) as catalyst. [g]Without the use of **L6**. [h]With [**Fe-1**] (20 mol %) only. [i]0.2 mmol scale. [j]0.1 mmol scale.

products **2u**–**y** in 53–78% yield. Notably, the ability to access both enantiomers of 1-hydroxyl-2,3-diamine (**2z** and *ent*-**2z**) in a stereospecific manner by this method is very attractive given the ready availability of optically pure amino alcohols. Secondary alcohol-derived sulfamate esters **1aa** and **1ab** were functionalized to **2aa** and **2ab** in 69% (4:1 dr) and 64% yield, respectively. Finally, this methodology was applied in C–H functionalization of natural product derivatives (Scheme 1c). Abietic acid (**1ac**) and glycyrrhetic acid (**1ad**) derivatives gave regiospecific C–H amination products **2ac**–**ad** in 36–38% yield, leaving the alkene and enone groups unaffected.

To further showcase the application of this method, gram-scale synthesis and product derivatizations were performed (Scheme 3). Reaction with 9–10 mmol of substrate **1a** provided 1.0–1.1 g of **2a** in 47–48% yield with 8.5 mol % of the catalyst. Next, starting from **2a**, a variety of useful building blocks such as 3-amino azide **4** (73%), 1,3-amino alcohol derivative **5** (71%), and *β*-amino acid **6** (62%) were accessed successfully.

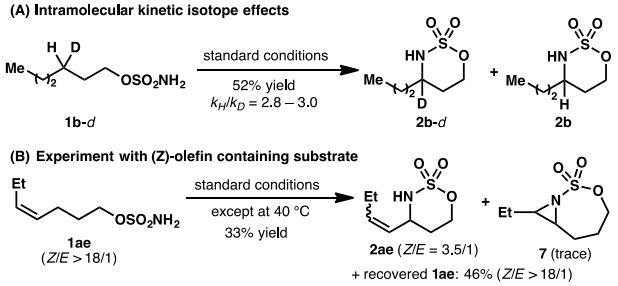
Preliminary experimental investigations were performed to shed light on the mechanism. First, a primary intramolecular kinetic isotope effect (KIE = 2.8–3.0, Scheme 4A) was obtained, which is similar to previously reported results.[11] Second, with (*Z*)-olefin substrate **1ae**, only isomerization of double bond was observed in the corresponding amination product **2ae** but not in the recovered starting material,[6g] together with a trace amount of aziridination product **7** (Scheme 4B). Third, for C–H bonds with different BDEs (i.e., **2r**, Scheme 2), the intramolecular amination exclusively occurred at the allylic position. These data are consistent with previous observations involving an iron–nitrenoid

Scheme 3. Gram-Scale Synthesis and Product Derivatization[a]



[a]Conditions: (a) standard conditions except with 8.5 mol % of catalyst; (b) CbzCl, NaH, THF, 30 °C, 6 h; (c) NaN_3, DMSO, 30 °C; (d) KOAc, DMF, 30 °C; (e) (i) MeCN, H_2O, 75 °C, 24 h; (ii) TEMPO (10 mol %), NaClO (2 mol %), $NaClO_2$.

Scheme 4. Preliminary Mechanistic Investigations



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engaged H atom abstraction followed by a fast radical rebounding pathway.[4a,d,12]

In conclusion, we have reported an iron-catalyzed intramolecular C−H bond amination with cheap and commercially available ligands. A variety of substrates bearing inert secondary and tertiary aliphatic C−H bonds as well as relatively weaker benzylic, allylic, propargylic, and ethereal C−H bonds are aminated in moderate to good yield. Importantly, the addition of second ligand was found able to enhance the reactivity of the catalyst. The readily accessible ligands and iron source offer diverse catalysts and variable alternations for iron-catalyzed C−H functionalization.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00660.

Additional data and experimental details, including Table S1−S4 and Figure S1; characterization and spectra of all new compounds (PDF)

Accession Codes

CCDC 1849958, 1849976, and 1849979−1849980 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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