Iron-Catalyzed Nitrene Insertion Reaction for Facile Construction of Amide Compounds

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Abstract: A facile method for the construction of amide compounds from aldehydes by an iron-catalyzed nitrene insertion reaction has been developed. Both aryl and aliphatic aldehydes can directly afford the corresponding amides with an iron(II)-terpyridine (tpy) complex formed in situ as catalyst, and PhI=NTs as nitrogen source under mild reaction conditions. An ESI-MS study revealed the formation of [Fe(tpy)$_2$(NTs)]$^{2+}$ as a reaction intermediate.

**Key words:** nitrene, C–H insertion, iron, catalysis, amide

The amide group is a fundamental functionality in organic compounds that is prevalent in biologically active natural products and pharmaceuticals.[1] The most widely used synthetic route to amides is the coupling of carboxylic acids and amines;[2] however, this method usually requires addition of activation reagents for carboxylic acids, which sometimes complicates the reaction. Recently, a straightforward approach to amide formation through transition-metal-catalyzed nitrene insertion directly into the C–H bond of aldehydes was reported. Rhodium carboxylates,[3] ruthenium porphyrins,[4] and copper salts[5] have proven to be effective catalysts for this transformation.

Due to increasing concerns for the environment and sustainable development, there is growing interest in iron catalysis because of its natural abundance and biocompatibility.[6] We and other groups have demonstrated that iron complexes can catalyze various nitrene transfer reactions, including aziridination,[7] C–H insertion,[8] and imination.[9] In view of the importance of amides in organic chemistry, herein, we report iron-mediated nitrene insertion into the C–H bond of aldehydes for the construction of amide compounds.

Initially, we investigated the amidation of benzaldehyde using PhI=NTs as nitrene source. Treatment of benzaldehyde with this reagent, in the presence of 5 mol% anhydrous FeCl$_2$ in anhydrous MeCN at room temperature, afforded amide **2** in 9% isolated yield (Table 1, entry 1). Use of FeCl$_3$ (10 mol%) gave similar results under the same conditions (Table 1, entry 2). Other iron salts were

found to be inactive towards the amidation of benzaldehyde, and only a trace amount of amide **2** was detected in each case (Table 1, entries 3–7).

Table 1 Screening of Iron Salts for Amidation of Benzaldehyde with PhI=NTs
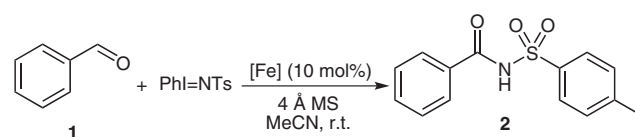
Entry[a,b]	Catalyst	Yield (%)[c]
1[d]	FeCl$_2$	9
2	FeCl$_3$	14
3	Fe(acac)$_3$	trace
4[e]	Fe(ClO$_4$)$_3$·6H$_2$O	trace
5[e]	Fe(ClO$_4$)$_2$·xH$_2$O	trace
6	Fe(OAc)$_2$	trace
7	Fe(OTf)$_2$	trace

[a] Reaction conditions: PhCHO (0.4 mmol), PhI=NTs (0.4 mmol), catalyst (10 mol%), 4 Å MS (120 mg; 30 mg/0.1 mmol substrate), MeCN (2 mL), r.t.
[b] All the iron salts dissolved well in MeCN except for Fe(OAc)$_2$.
[c] Isolated yield.
[d] 5 mol% catalyst loading.
[e] 240 mg 4 Å MS.

Our previous study showed that [Fe(Cl$_3$terpy)$_2$(ClO$_4$)$_2$] is effective in the catalysis of alkene aziridination and nitrene insertion into saturated C–H bonds, revealing the important effect of nitrogen-containing ligands on the iron-catalyzed nitrene transfer reactions.[7b] Therefore, we next set out to screen a variety of nitrogen-based ligands; the results were summarized in Table 2. Terpyridine was found to be the most effective ligand, affording 52% isolated yield (Table 2, entry 4). Chloro-substituted terpyridine also catalyzed the C–H insertion, albeit with lower yield compared with unsubstituted terpyridine (Table 2, entries 5 and 6). *tert*-Butyl substitution made the iron salt inactive towards the amidation (Table 2, entry 7). Compared with terpyridine, bipyridine was less effective, giving the amide in 18% yield (Table 2, entry 1). More rigid
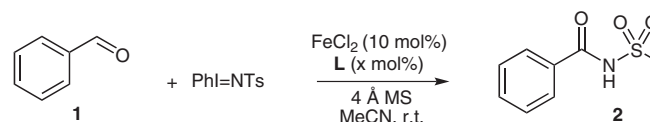
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bidentate nitrogen ligands, 1,10-phenanthroline and 2,9-dimethyl-1,10-phenanthroline, yielded the amide in 26 and 12% yield, respectively (Table 2, entries 2 and 3). Reducing the amount of terpyridine to 10 mol% had a minor effect on the reaction yield (Table 2, entry 8). Using terpyridine as ligand, changing the metal source from FeCl$_2$ to FeCl$_3$ afforded slightly lower yield (49%; Table 2, entry 9).

Phosphine-based ligands were also screened (Table 2, entries 10–18). The addition of Ph$_3$P, Cy$_3$P, and (n-Bu)$_3$P to the reaction did not lead to appreciable product yield

(Table 2, entries 10–12). However, Me$_3$P promoted the C–H insertion (20% product yield, Table 2, entry 13). Sterically encumbered P(t-Bu)$_2$(o-biphenyl) and P(Cy)$_2$(o-biphenyl-2′,4′,6′-tri-i-Pr) proved to be more effective, and use of these ligands significantly improved the reaction yield to 52 and 32%, respectively, albeit at the expense of longer reaction times compared with terpyridine (Table 2, entries 14–15). Bidentate phosphine ligands such as dppp and dppe led to lower yield compared with the sterically hindered monodentate phosphine ligands (Table 2, entries 16 and 17).

Table 2 Ligand Effects on Fe-Catalyzed Amidation of Benzaldehyde with PhI=NTs

Entry[a]	Ligand	x (mol%)	Yield (%)[b]
1		30	18
2		30	26
3		30	12
4		20	52
5		20	44
6		20	10
7		20	trace
8		10	52
9[c]		10	49

Table 2 Ligand Effects on Fe-Catalyzed Amidation of Benzaldehyde with PhI=NTs (continued)
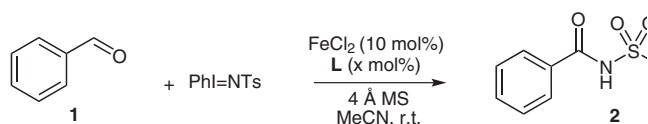
| Entry[a]	Ligand	x (mol%)	Yield (%)[b]
10[d]	PPh$_3$	20	trace
11[d]	PCy$_3$	20	trace
12[d]	P(n-Bu)$_3$	20	trace
13[d]	PMe$_3$	20	20
14[d]	P(t-Bu)$_2$(o-biphenyl)	20	52
15[d]	P(Cy)$_2$(o-biphenyl-2′,4′,6′-tri-i-Pr)	20	32
16[d]	dppp	10	27
17[d]	dppe	10	23
18[d]	P(t-Bu)$_2$(o-biphenyl)	10	49

[a] Reaction conditions: PhCHO (0.4 mmol), PhI=NTs (0.4 mmol), FeCl$_2$ (10 mol%), ligand, 4 Å MS (120 mg, 30 mg/0.1 mmol substrate), MeCN (2 mL), r.t., 8 h.
[b] Isolated yield.
[c] With FeCl$_3$ (10 mol%) as metal source.
[d] Reaction run at r.t. for 24 h.

Among the N and P donor ligands examined, terpyridine and P(t-Bu)$_2$(o-biphenyl) gave the best results. We chose terpyridine for further study because of its ease of preparation and high stability. With 10 mol% FeCl$_2$ and 10 mol% terpyridine as catalyst, the effects of solvent on the nitrene C–H bond insertion reaction was investigated, and acetonitrile proved to be the best solvent (see Table S1 in the Supporting Information).

Table 3 FeCl$_2$/Terpyridine-Catalyzed Amidation of Various Aldehydes with PhI=NTs
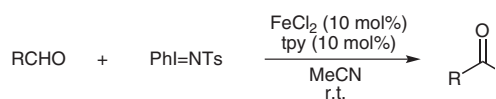
Entry[a]	Aldehyde	Yield (%)[b]
1		63
2		66
3		83
4		40
5		–[c]

Table 3 FeCl$_2$/Terpyridine-Catalyzed Amidation of Various Aldehydes with PhI=NTs (continued)
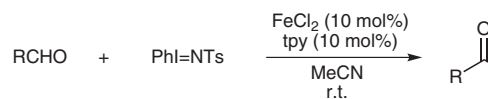
Entry[a]	Aldehyde	Yield (%)[b]
6		68
7		48
8		71
9		76
10		89
11		79
12		88
13		72

[a] Reaction conditions: aldehyde (0.4 mmol), PhI=NTs (0.4 mmol), FeCl$_2$ (10 mol%), tpy (10 mol%), 4 Å MS (120 mg, 30 mg/0.1 mmol substrate), MeCN (2 mL), r.t.
[b] Isolated yield.
[c] No desired product detected after 24 h.

Having established the optimal reaction conditions, we then explored the scope of the reaction with respect to aldehydes; the results are depicted in Table 3. Methoxyl-substituted benzaldehydes reacted smoothly with PhI=NTs under the optimal reaction conditions to afford the insertion products regardless of substitution position (Table 3, entries 1–3). 2,4,6-Trimethylbenzaldehyde also underwent the reaction smoothly to afford the product, albeit with a lower yield, probably because of steric hindrance (Table 3, entry 4). *p*-Chlorobenzaldehyde was inert in the reaction and no desired product was detected in the reaction mixture after 24 h (Table 3, entry 5). Both α- and β-naphthaldehyde underwent the reaction to afford the corresponding product amide with 68 and 48% isolated yield, respectively (Table 3, entries 6 and 7). Interestingly, the catalytic system seemed to be more suitable for preparing amides from aliphatic aldehydes than from aromatic aldehydes, and various substituted aliphatic aldehydes underwent the reaction well to afford the insertion products in up to 89% yield (Table 3, entries 8–13). It is noteworthy that when 3-phenylpropanal was used as substrate, no intermolecular benzylic C–H bond insertion product was found (Table 3, entry 13).

A plausible reaction mechanism was proposed as shown in Scheme 1. Similar to previous reports,[5] iron catalysts could decompose PhI=NTs to generate an iron imido/nitrene intermediate, which may undergo nitrene insertion into the C–H bond of an aldehyde to afford the corresponding amide. Attempts were made to characterize the reaction intermediate by monitoring the reaction mixture of PhI=NTs, FeCl$_2$, and terpyridine with ESI mass measurement. As shown in Figure 1, a prominent cluster peak (in positive-ion mode) at m/z 345.4 with peak separation of 0.5 units was observed. The cluster peak was consistent with $[Fe(tpy)_2(NTs)]^{2+}$ formulation (m/z calcd. for $C_{37}H_{29}N_7O_2SFe$: 345.6).
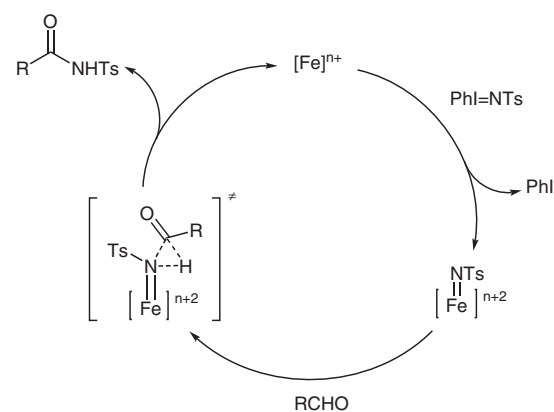
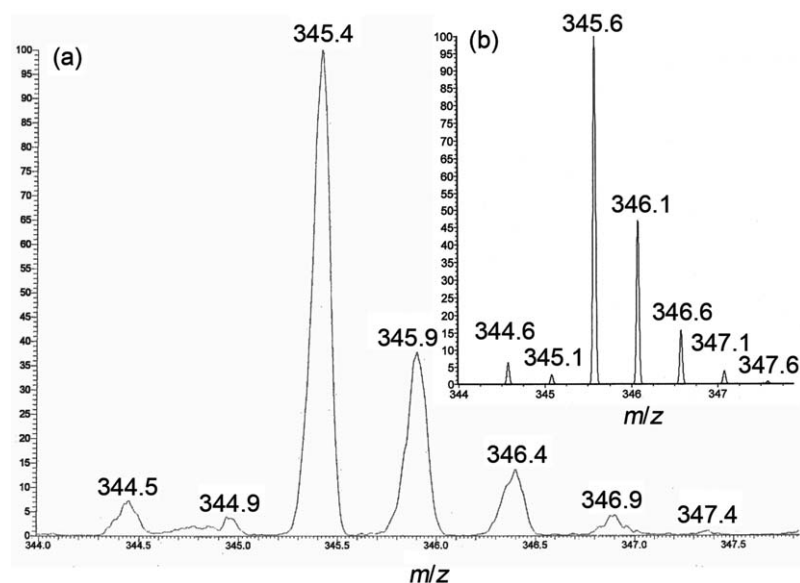**Scheme 1** Plausible reaction mechanism of iron-catalyzed nitrene C–H insertion reaction.

Figure 1 ESI-MS spectrum attributed to $[Fe(tpy)_2(NTs)]^{2+}$ ($C_{37}H_{29}N_7O_2SFe$). (a) Observed isotope pattern; (b) simulated isotope pattern.

In conclusion, we have developed a simple and efficient method for the construction of amide derivatives by iron-catalyzed nitrene insertion into the C–H bond of aldehydes. Both aryl and aliphatic aldehydes undergo the intermolecular nitrene C–H bond insertion reaction with inexpensive and biocompatible iron complex as catalyst to afford the corresponding amide derivatives under mild reaction conditions.

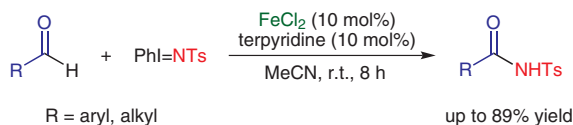**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

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