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Iron-Catalyzed Carbenoid Insertion into C(sp^3)–H Bonds

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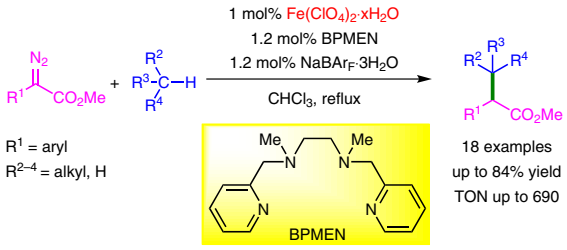

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Abstract An iron-catalyzed carbenoid insertion into C–H bonds of alkanes was developed with high activity (turnover numbers up to 690 in a gram-scale experiment) and chemoselectivity. This non-heme iron-catalyzed C(sp^3)–H insertion reaction provides an efficient strategy for C–H functionalization.

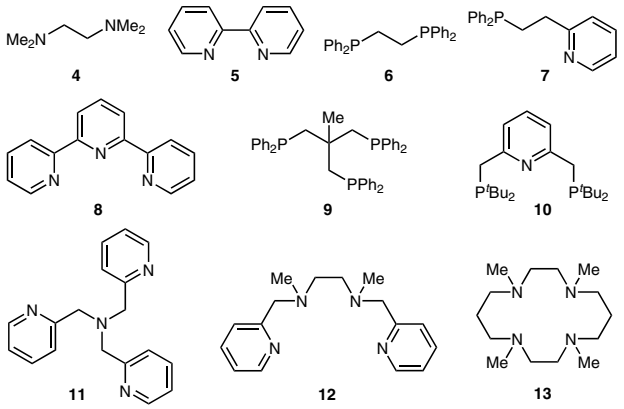
Key words iron catalysis, carbenoid insertion, C–H functionalization, chemoselectivity, diazo compounds, alkanes

The direct functionalization of inert C(sp^3)–H bonds is a state-of-the-art and challenging topic in modern organic chemistry.[1] Transition-metal-catalyzed carbenoid insertion into C(sp^3)–H bonds is a classic and efficient C–H functionalization strategy.[2] However, this transformation has traditionally involved dirhodium(II) complexes as catalysts.[3] Recently, several iridium complexes were also developed as catalysts in this reaction.[4] The limited availability as well as high price and toxicity of precious metals has driven academia and industry to develop base metals, especially iron, as alternative catalysts for this important transformation.[5,6] Few iron-mediated carbenoid insertions into C(sp^3)–H have been developed using iron porphyrins as catalysts or stoichiometric reagents.[7] As iron porphyrin has a special planar coordinative structure, it is difficult to tune its reactivity and selectivity through ligand modifications. Thus, the development of non-heme iron catalysts for C(sp^3)–H insertion reaction is highly desired. As part of our continuing efforts to develop iron-catalyzed reactions,[8] we herein report a non-heme iron-catalyzed C(sp^3)–H insertion reaction using the iron complex of tetradentate nitrogen ligand BPMEN (*N*,*N*′-dimethyl-*N*,*N*′-bis(pyridin-2-ylmethyl)ethane-1,2-diamine, **12**) as a catalyst, which exhibited higher activity (turnover numbers, TON up to 690 in a gram-scale experiment) than the iron porphyrin catalysts[7a] in C(sp^3)–H insertion reaction.

The initial experiment was performed with methyl α-diazophenylacetate (**1a**) and cyclohexane (**2a**) in chloroform at 70 °C, in the presence of 10 mol% iron catalyst generated in situ from $Fe(ClO_4)_2{\cdot}xH_2O$, TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine, **4**), and $NaBAr_F$ (sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate; Table 1, entry 1). The desired C–H functionalization product **3aa** was isolated with 36% yield, although carbene dimerization was observed as a competing reaction. Increasing the amount of TMEDA to 24 mol% led to a slight increase in yield. We then studied different types of bidentate and tridentate ligands **5**–**10**, but no significant improvement in yield was observed (entries 2–7). Several tetradentate ligands **11**–**13** were then examined (entries 8–10). To our delight, when ligand BPMEN (**12**) was used, the yield of the product **3aa** increased markedly to 69% (entry 9). In the absence of any ligand, only a trace amount of **3aa** was generated, with carbene dimers[9] being the predominant products (entry 11).

To further improve the reactivity and selectivity of this C–H functionalization process, the reaction conditions were optimized by using ligand **12** (Table 2). First, several iron precursors were evaluated, with $Fe(ClO_4)_2$ giving the best yield (entries 1–8). The amount of additive was then studied. $NaBAr_F$ with 12 mol% loading proved to be most suitable (entry 1 vs. entries 9 and 10). The absence of chloroform was not favorable in terms of reaction rate and yield (entry 11). Gratifyingly, increasing the bath temperature from 70 to 95 °C significantly improved both the reaction rate and the yield of the desired product **3aa** (80%, entry 12). Reducing the catalyst loading to 1 mol% gave the same level of yield, but a longer reaction time was required (entry 13). Even 0.1 mol% iron catalyst was sufficient to achieve a

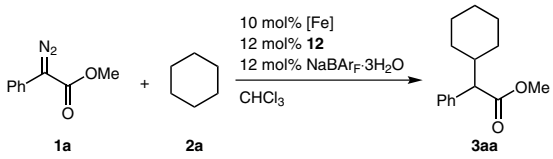
Table 1 Iron-Catalyzed C–H Functionalization of Cyclohexane: Ligand Evaluation[a]



Entry	Ligand	Time (h)	**3aa** (%)[b]	**1a** (%)[b]
1	**4**	48	36 (43)[c]	–
2	**5**	20	11	–
3	**6**	48	37	–
4	**7**	40	44	–
5	**8**	48	32	6
6	**9**	48	38	16
7	**10**	48	30	–
8	**11**	48	62	7
9	**12**	48	69	–
10	**13**	48	37	42
11	none	10	trace	–

[a] Reaction conditions: $Fe(ClO_4)_2$ (0.03 mmol), ligand (0.036 mmol), $NaBAr_F$ (0.036 mmol), **1a** (0.3 mmol), **2a**/$CHCl_3$ (3:1 mL), bath temperature = 70 °C.
[b] Isolated yield (**3aa**) or recovery (**1a**).
[c] The yield in parentheses was obtained using 24 mol% TMEDA.

Table 2 Iron-Catalyzed C–H Functionalization of Cyclohexane: Optimization of Reaction Conditions[a]



Entry	[Fe]	Temp (°C)[b]	Time (h)	**3aa** (%)[c]	**1a** (%)[c]
1	$Fe(ClO_4)_2·xH_2O$	70	48	69	–
2	$Fe(OTf)_2$	70	48	54	11
3	$Fe(OAc)_2$	70	48	62	9
4	$FeSO_4·7H_2O$	70	48	56	12
5	$Fe(BF_4)_2·6H_2O$	70	48	24	–
6	$FeCl_2$	70	48	51	16
7	$Fe(ClO_4)_3·6H_2O$	70	48	45	–
8	$FeCl_3$	70	48	51	24
9[d]	$Fe(ClO_4)_2·xH_2O$	70	48	58	10
10[e]	$Fe(ClO_4)_2·xH_2O$	70	36	47	–
11[f]	$Fe(ClO_4)_2·xH_2O$	70	48	60	8
12	$Fe(ClO_4)_2·xH_2O$	95	10	80	–
13[g]	$Fe(ClO_4)_2·xH_2O$	95	36	82	–
14[h]	$Fe(ClO_4)_2·xH_2O$	95	60	73	–

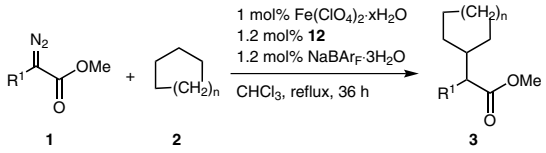
[a] Reaction conditions: [Fe] (0.03 mmol), **12** (0.036 mmol), $NaBAr_F$ (0.036 mmol), **1a** (0.3 mmol), **2a**/$CHCl_3$ (3:1 mL).
[b] Bath temperature.
[c] Isolated yield or recovery.
[d] In the absence of $NaBAr_F$.
[e] Using 24 mol% $NaBAr_F$.
[f] In the absence of $CHCl_3$.
[g] Using 1 mol% catalyst.
[h] Using 0.1 mol% catalyst.

satisfactory result (entry 14). Notably, this process displayed a high chemoselectivity, with only trace amounts of carbene dimers observed. Moreover, despite the crystallization water in iron precursors and $NaBAr_F$, no O–H insertion product was detected in the reaction.[8a]

The generality and substrate scope of the reaction were investigated under the optimized reaction conditions. A variety of α-diazo esters **1a–m** smoothly underwent the reaction with cyclohexane (**2a**) to afford the corresponding products **3aa–ma** in good yields (Table 3, entries 1–13). Diazo compounds **1f** and **1h**, which have 3-chloro and 3-methoxy substituents on their phenyl rings, respectively, gave slightly lower yields (entries 6 and 8). The steric bulk of the *ortho* substituents of α-aryl-α-diazoacetates **1i–k** did not affect the yield of reaction (entries 9–11). α-Diazo-α-(2-naphthyl)acetate **1m** was also a suitable substrate for the reaction (entry 13). Other cycloalkanes including cyclopentane (**2b**), cycloheptane (**2c**), and cyclooctane (**2d**), also reacted smoothly to furnish the desired products **3ab–ad** in good yields (entries 14–16). The iron catalyst Fe/BPMEN exhibited high sensitivity to the diazo compounds, and the reaction only afforded complex reaction mixture when benzyl α-diazoacetate or benzyl α-diazopropionate was used.

The Fe/BPMEN-catalyzed C–H functionalization of alkanes is easy to scale-up. A gram-scale reaction of **1a** and **2a** was carried out with 0.1 mol% catalyst, and 1.0 g (69% yield) of the desired product **3aa** was isolated (Scheme 1). It should be noted that the diazo compound can be added in one potion in all the above reactions, which indicates that the reaction has excellent chemoselectivity. In contrast,

Table 3 Iron-Catalyzed C–H Functionalization of Cycloalkanes: Substrate Scope[a]

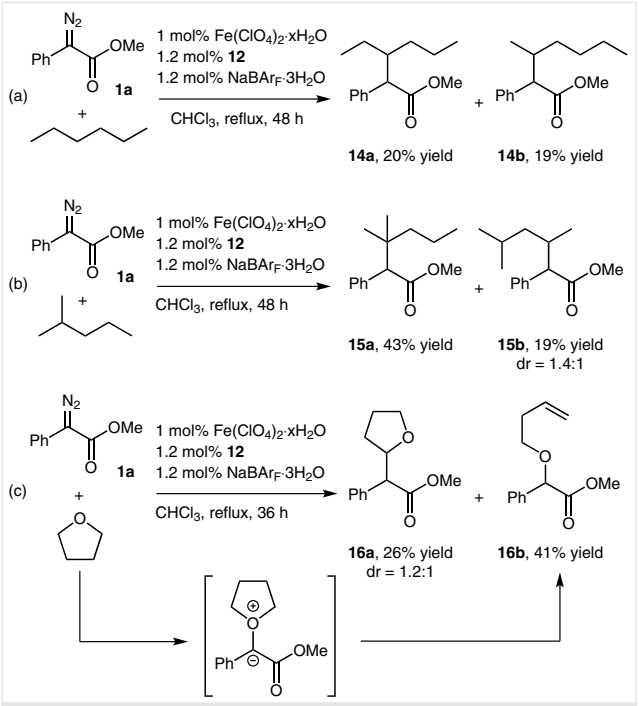


Entry	R^1	1	*n*	2	3	Yield (%)[b]
1	Ph	**1a**	2	**2a**	**3aa**	82
2	4-ClC_6H_4	**1b**	2	**2a**	**3ba**	73
3	4-PhC_6H_4	**1c**	2	**2a**	**3ca**	77
4	4-MeC_6H_4	**1d**	2	**2a**	**3da**	84
5	4-$MeOC_6H_4$	**1e**	2	**2a**	**3ea**	71
6	3-ClC_6H_4	**1f**	2	**2a**	**3fa**	56
7	3-MeC_6H_4	**1g**	2	**2a**	**3ga**	76
8	3-$MeOC_6H_4$	**1h**	2	**2a**	**3ha**	61
9	2-FC_6H_4	**1i**	2	**2a**	**3ia**	76
10	2-ClC_6H_4	**1j**	2	**2a**	**3ja**	73
11	2-MeC_6H_4	**1k**	2	**2a**	**3ka**	77
12	3,4-$O_2CH_2C_6H_3$	**1l**	2	**2a**	**3la**	72
13	2-naphthyl	**1m**	2	**2a**	**3ma**	66
14[c]	Ph	**1a**	1	**2b**	**3ab**	72
15	Ph	**1a**	3	**2c**	**3ac**	84
16	Ph	**1a**	4	**2d**	**3ad**	78

[a] Reaction conditions: $Fe(ClO_4)_2·xH_2O$ (0.003 mmol), **12** (0.0036 mmol), $NaBAr_F$ (0.0036 mmol), **1** (0.3 mmol), **2**/$CHCl_3$ (3:1 mL).
[b] Isolated yield.
[c] Reaction time: 60 h.

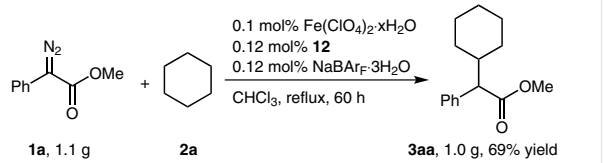
slow addition of diazo compound was generally required in the C–H insertion reactions catalyzed by other metal catalysts to avoid carbene dimerization.[2–4]

In addition to cycloalkanes, linear and branched alkanes are also suitable substrates for the reaction. The C–H insertion of *n*-hexane occurred at the secondary C–H bonds under the standard conditions (Scheme 2 a). When 2-methylpentane was subjected to the reaction, the tertiary C–H insertion product **15a** was obtained as the major product (Scheme 2 b).[10] Notably, no product of carbene insertion into the primary C–H bonds was observed in these reactions. In addition, the reaction of tetrahydrofuran under standard conditions led to two products, the C–H insertion product **16a** and the ylide rearrangement product **16b** in approximately 1:1.6 ratio (Scheme 2 c). This chemoselectivity is reversed in comparison with the previously reported iron porphyrin-catalyzed reaction (**16a**/**16b** = 3.4:1).[7a] The major diastereomer of **16a** was methyl (*S**)-2-phenyl-2-((*R**)-tetrahydrofuran-2-yl)acetate, which is consistent with the reaction catalyzed by Rh_2(S-DOSP)$_4$.[3b]

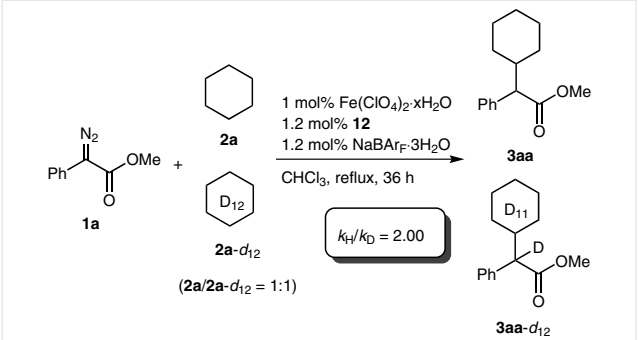


Scheme 2 Iron-catalyzed C–H functionalization of other hydrocarbon substrates

To gain an insight into the reaction mechanism, we conducted kinetic isotope effect (KIE) experiments (Scheme 3). A primary KIE (k_H/k_D = 2.00) was observed, which is consistent with that reported in the rhodium-catalyzed C(sp^3)–H insertion and implies that the C–H bond cleavage might be involved in the rate-limiting step.[11] A detailed mechanism study is under way in our laboratory.



Scheme 1 Gram-scale synthesis



Scheme 3 Kinetic isotope effect experiments

In summary, the non-heme iron-catalyzed carbene insertion into C(sp^3)–H bonds of alkanes has been realized.[12] The readily available iron complex of BPMEN was found to be a powerful and highly chemoselective catalyst for the reaction. The easy modification of BPMEN leaves rooms for the development of iron catalysts with tunable reactivity and selectivity. This iron-catalyzed C–H insertion reaction provides an efficient strategy for C–H functionalization of alkanes.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588743.

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(12) **Methyl 2-cyclohexyl-2-phenylacetate (3aa); Typical Procedure:** Powered $Fe(ClO_4)_2{\cdot}xH_2O$ (1.0 mg, 0.003 mmol, 1 mol%), ligand **12** (1.0 mg, 0.0036 mmol, 1.2 mol%), and $NaBAr_F$ (3.4 mg, 0.0036 mmol, 1.2 mol%) were introduced into an oven-dried Schlenk tube in an argon-filled glovebox. After $CHCl_3$ (1 mL) was injected into the Schlenk tube, the solution was stirred at 25 °C under argon atmosphere for 4 h. Cyclohexane (**2a**; 3 mL) and methyl α-diazophenylacetate (**1a**; 52.9 mg, 0.3 mmol) were then successively introduced into the system. The resulting mixture was stirred at a bath temperature of 95 °C for 36 h. After concentration in vacuo, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 30:1 v/v) to give methyl 2-cyclohexyl-2-phenylacetate (**3aa**) as a colorless oil. Yield: 57.2 mg (0.246 mmol, 82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.20 (m, 5 H), 3.64 (s, 3 H), 3.22 (d, *J* = 10.7 Hz, 1 H), 2.08–1.94 (m, 1 H), 1.83–1.57 (m, 4 H), 1.33–0.99 (m, 5 H), 0.79–0.68 (m, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.4, 137.8, 128.5, 128.4, 127.1, 58.8, 51.7, 41.0, 32.0, 30.4, 26.3, 26.0, 25.9.