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Catalytic C(sp³)-H Alkylation via an Iron Carbene Intermediate

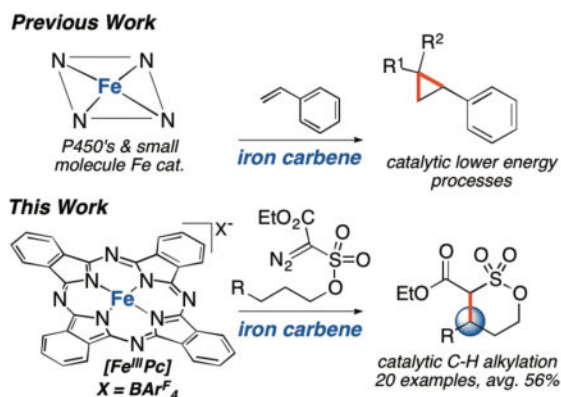
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Abstract

The catalytic transformation of a C(sp³)-H bond to a C(sp³)-C bond via an iron carbene intermediate represents a long-standing challenge. Despite the success of enzymatic and small molecule iron catalysts mediating challenging C(sp³)-H oxidations and aminations via high-valent iron oxos and nitrenes, C(sp³)-H alkylations via isoelectronic iron carbene intermediates have thus far been unsuccessful. Iron carbenes have been inert, or shown to favor olefin cyclopropanation and heteroatom-hydrogen insertion. Herein we report an iron phthalocyanine-catalyzed alkylation of allylic and benzylic C(sp³)-H bonds. Mechanistic investigations support that an electrophilic iron carbene mediates homolytic C-H cleavage and rebounds from the resulting organoiron intermediate to form the C-C bond; both steps are tunable via catalyst modifications. These studies suggest that for iron carbenes, distinct from other late metal carbenes, C-H cleavage is partially rate-determining and must be promoted to effect reactivity.

Graphical abstract



Iron is one of the most abundant elements, totaling one-third of the Earth's mass, and is emerging as an important metal for homogenous catalysis^{1a-f}. Iron small molecule catalysts have been demonstrated to catalyze challenging C-H oxidation and amination processes via

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Notes

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Supporting Information. The Supporting Information is available free of charge on the ACS Publications website at DOI: Experimental details and characterization data (PDF) Spectral data (PDF)

high-valent metal oxos and nitrenes^{1b,1c,1d,1f}. In contrast, no iron catalyst has been demonstrated to alkylate C(sp³)-H bonds via an isoelectronic metallocarbene intermediate.

Naturally occurring and engineered P450 enzymes form only inert carbenes or carbenes active for lower energy processes than C-H alkylation (e.g. cyclopropanations, heteroatom-hydrogen bond insertions)² (Fig. 1). Small molecule iron catalysts capable of forming carbenes also fail to catalyze C-H alkylation, favoring alternative reaction pathways³. Curiously, nearly all other late metals, including copper^{4a,4b}, cobalt^{4c}, silver^{4a}, palladium^{4d}, rhodium^{4e}, and ruthenium^{4f}, form metallocarbenes catalytically active for C-H alkylation. Herein we report an iron-catalyzed alkylation of allylic and benzylic C(sp³)-H bonds and provide evidence of an iron carbene intermediate. Distinct from other late metal carbenes, C-H cleavage is partially rate-determining and tunable via catalyst modifications.

Iron carbene complexes have been generated stoichiometrically at low temperatures, isolated^{5a}, and/or demonstrated to undergo C-H insertion in a separate step at elevated temperatures (e.g. 80°C)^{5b,c}. We hypothesized that one reason these reactions are not catalytic is due to the distinct energetic requirements for each step. At the elevated temperatures needed for C-H insertion, thermal decomposition of the diazoester or metal carbene into a free carbene may occur. Literature reports claiming iron-catalyzed C-H alkylation with methyl phenyldiazoacetate at 80°C are ambiguous^{6a} because this diazoester is reported and observed by us (Supplementary Information, SI) to show significant non-metal mediated alkylation reactivity at this temperature^{6b}.

We hypothesized that with iron, there is a higher kinetic barrier to C-H insertion than in rhodium and copper systems where metallocarbene formation is rate determining^{4a,7,8}. This difference may explain the predominance of lower energy pathways in iron carbene reactions, such as competitive dimerization to furnish olefins⁷. Reactivity and selectivity of metal carbenes is highly tunable^{4e,9a}; therefore, we aimed to electronically and sterically tune the catalyst and carbene precursor to form a metallocarbene intermediate reactive enough to insert into C(sp³)-H bonds at temperatures that mitigate deleterious pathways and do not decompose the diazoprecursor.

We first evaluated iron catalysts used for metallocarbene-mediated cyclopropanations and heteroatom-hydrogen insertions for the intramolecular alkylation of allylic C-H bonds (Table 1A)^{3,5b,10}. We examined a series of substituted diazo compounds (acceptor **1**, donor-acceptor **2**, acceptor-acceptor **3**) with varying degrees of electrophilicity and steric bulk^{9a}. With iron porphyrin and phthalocyanine catalysts, diazoester **1** converted to olefin dimer (**4**, 93% and 84%, respectively), suggestive of iron carbene formation^{9a}. Bulkier disubstituted carbene precursor **2** disfavored dimerization with all catalysts, but favored ketone product **5** over alkylation^{9a}.

We hypothesized that augmenting the electrophilicity of the disubstituted diazo compound would increase its reactivity by producing a strongly electrophilic metallocarbene that could more readily engage in higher energy C-H insertion pathways. Under rhodium catalysis, such electrophilic diazo compounds require very active catalysts to form the metallocarbene; however, once formed, the resulting carbene is more reactive towards C-H insertion^{9a}.

We next sought to investigate the mechanism and the involvement of an iron carbene intermediate in this reaction. We hypothesized that C–H alkylation occurs via an iron-bound carbene intermediate that, analogous to iron oxos^{1b,1f} and iron nitrenes^{1c,1d}, promotes homolytic cleavage of the C–H bond followed by recombination with the resulting carbon-centered radical to form the new C–C bond (Fig. 2A). Alternatively, [Fe^{III}Pc] could serve as a Lewis acid to decompose the diazosulfonate ester to a free carbene capable of inserting into proximal C–H bonds. We investigated unligated iron salts and UV light with no added catalyst, conditions demonstrated to form reactive free carbenes from acceptor-acceptor diazo species¹². FeCl₃ and FeCl₂ resulted in predominately recovered starting material (Fig. 2B), whereas irradiation of **6** with UV light (254 nm) gave compound **28**, generated from C–H insertion of the free carbene into the dichloromethane solvent (Fig. 2B). Product **28** is not observed under [Fe^{III}Pc]-catalysis, which is also run in dichloromethane. These divergent outcomes support the hypothesis that [Fe^{III}Pc]-catalyzed C–H alkylation does not proceed via free carbene intermediates.

We next sought to probe the involvement of an iron-bound carbene intermediate in both the C–H bond cleavage and C–C bond formation steps (Fig. 2C, 2D). In rhodium-catalysis proceeding via metallocarbene intermediates, varying the carboxylate ligands has been shown to influence both the intramolecular kinetic isotope effect (KIE) of C–H cleavage^{7,11,12b} and the selectivity of C–C bond formation^{4e,9a,13}. We observed a change in the KIE with varied ligand electronics: [Fe^{III}Pc] gave the highest KIE (5.0), followed by [Fe^{III}Cl₃Pc] (4.8) and [Fe^{III}Cl₁₆Pc] (4.5). These data support involvement of the iron complex in the C–H cleavage step. The larger KIE values for iron versus rhodium (1.8), support the proposed stepwise versus concerted mechanism (Fig. 2C)⁷. A stepwise mechanism accounts for the improved chemoselectivity of iron relative to rhodium catalysts for C–H insertion over cyclopropanation; a stabilized allylic radical is preferred over the secondary aliphatic radical formed during stepwise olefin oxidation processes^{1c,4c}.

We also probed the effect of ligand electronics on the C–C bond forming step. We performed a study on *Z*-olefin substrate **32** to determine if scrambling of the double bond geometry occurred during allylic C–H alkylation (Fig. 2D). Under Rh₂(OAc)₄ catalysis, no isomerization of the olefin was observed, consistent with a concerted mechanism of C–H insertion. In contrast, under [Fe^{III}Pc] catalysis we observed scrambling of olefin geometry, consistent with a stabilized carbon radical intermediate. The extent of olefin isomerization is dependent on the electronic substitution of the ligand, with the electron deficient chlorinated iron catalysts affording products with less isomerization than the unsubstituted phthalocyanine (10:1 vs 3:1). Under cobalt porphyrin catalysis, in the absence of a chiral pocket, isomerization during functionalization of *Z*-olefins occurs to a greater extent than in the iron system^{4c}. This suggests that C–H alkylation with iron proceeds with less free radical character than cobalt^{4c}. Electron withdrawing ligands may destabilize an iron-alkyl species prompting recombination at a faster rate.

We hypothesized that C–H insertion is rate-determining for iron-catalyzed alkylation, unlike rhodium and copper catalysis^{4a,7,8}. Intermolecular KIE studies that measured initial rates on parallel reactions with benzylic substrate **30** and **30-*d*₂** revealed a primary KIE of 3.1 under [Fe^{III}Pc] catalysis (Fig. 2C). This is consistent with C–H cleavage being part of the rate-

determining step of the reaction. Initial rate measurements with $[\text{Fe}^{\text{III}}\text{Cl}_{16}\text{Pc}]$ showed a lower KIE of 1.4 suggesting that with a more electron deficient iron catalyst, formation of the metallocarbene, which requires donation of electron density from the metal center to extrude nitrogen, competes energetically with C–H cleavage⁷.

We report an iron-catalyzed $\text{C}(\text{sp}^3)\text{--H}$ alkylation via a metallocarbene intermediate. $[\text{Fe}^{\text{III}}\text{Pc}]$ alkylates allylic and benzylic $\text{C}(\text{sp}^3)\text{--H}$ bonds with broad scope. Mechanistic studies demonstrate the ability to exert catalyst control on the reactivity and selectivity during C–H cleavage and functionalization. Future studies will be aimed at elucidating the nature of the iron carbene intermediate, as well as further development of this highly tunable species to access stronger aliphatic $\text{C}(\text{sp}^3)\text{--H}$ bond types and intermolecular C–H alkylations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

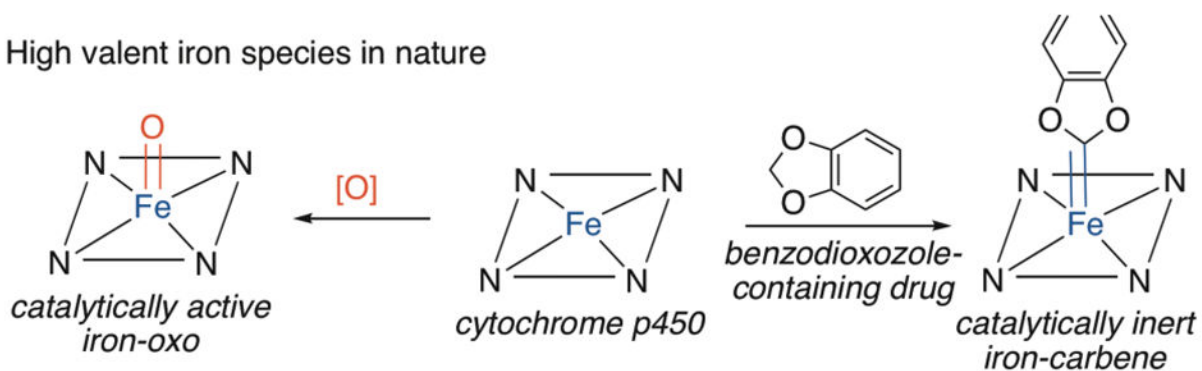
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A. High valent iron species in nature



B. Iron carbenes in C—C bond formation

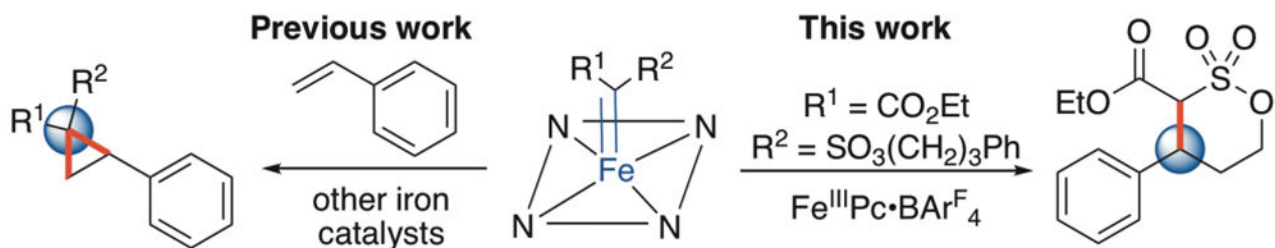


Figure 1.
Challenges of iron carbene C—H activation.

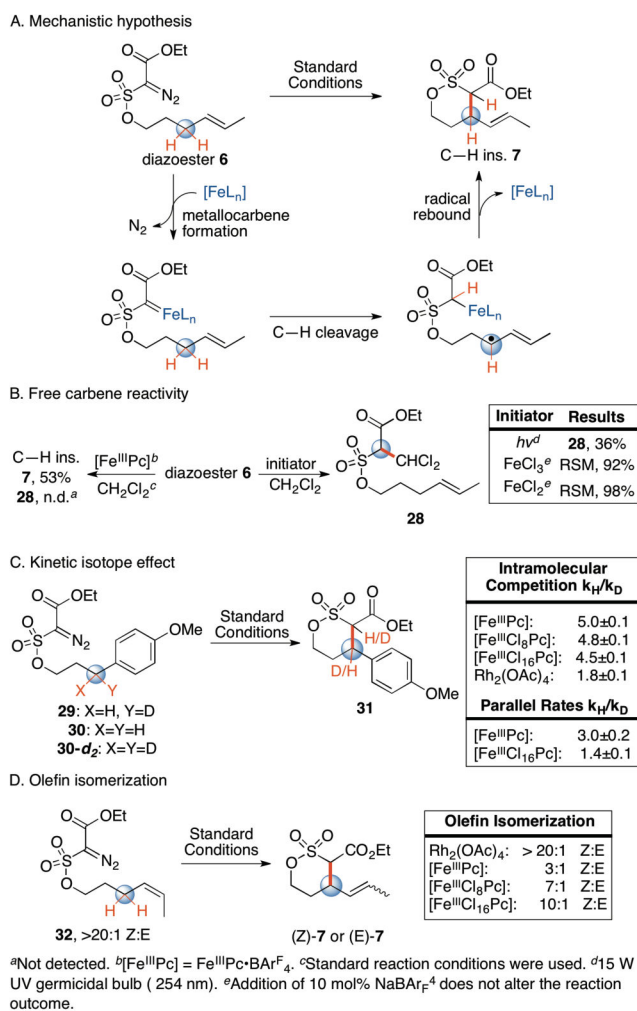
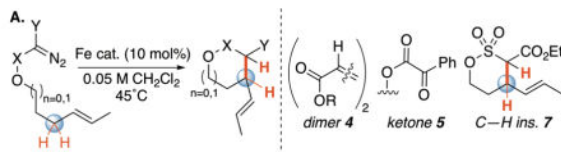


Figure 2.
Mechanistic studies.

Table 1

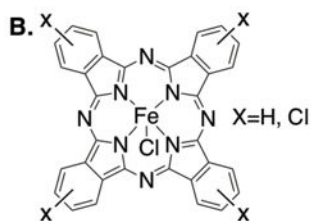
Reaction optimization.

A.



Catalyst:	1 ^a	2 ^a	3 ^a	6 ^b
Fe ^{III} Cl ₃ ·PyBOX	99% rsm	90% rsm	97% rsm	98% rsm
Fe ^{III} (TTP)Cl	93% dimer 4	4% ketone 5 95% rsm	96% rsm	98% rsm
[Fe ^{III} Pc]Cl	84% dimer 4	12% ketone 5 58% rsm	95% rsm	3% C—H ins. 7 97% rsm

B.



Catalysts:	Acceptor/acceptor 6:
[Fe ^{III} Pc]Cl, NaBAR ^F ₄	48% (53% ^c) C—H ins. 7
[Fe ^{III} Cl ₈ Pc]Cl, NaBAR ^F ₄	25% C—H ins. 7
[Fe ^{III} Cl ₁₆ Pc]Cl, NaBAR ^F ₄	38% C—H ins. 7

R = CH₂CH₂CH=CHCH₃. Reaction stirred for 24 hours unless otherwise noted. Pc = phthalocyanine; TPP = tetraphenylporphyrin; PyBOX = 2,6-bis[(4*R*)-4-phenyl-2-oxazolonyl]pyridine; NaBAR^F₄ = Sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate. Isolated yields are average of two runs. rsm = recovered starting material.

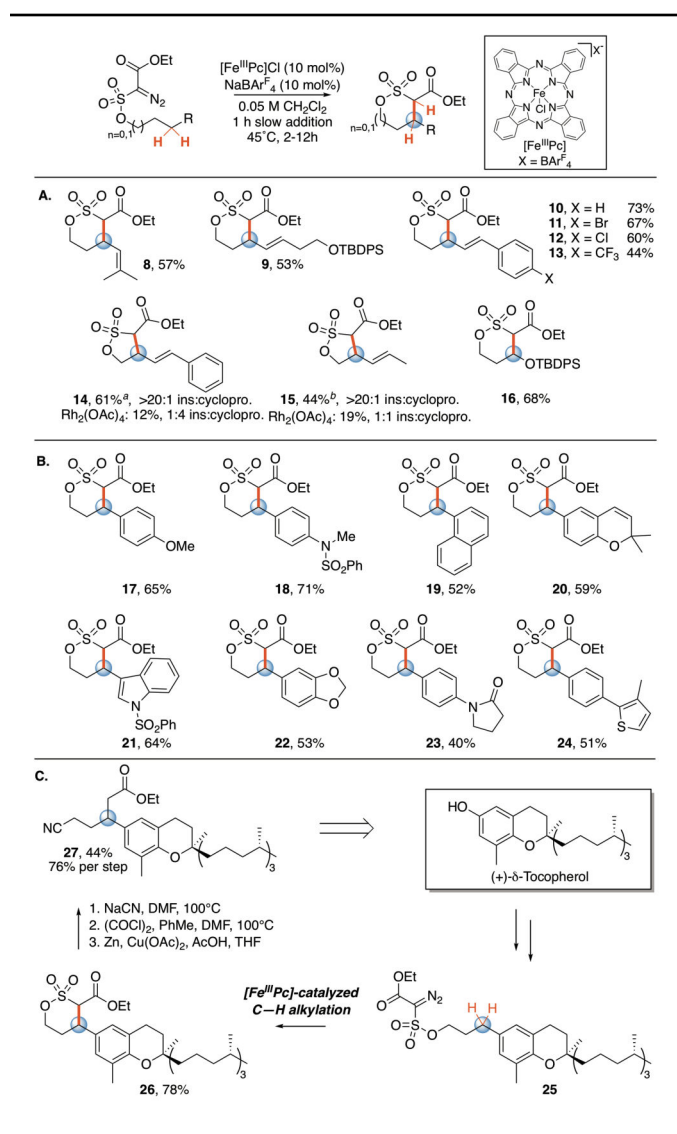
^a n = 0.

^b n = 1.

^c Run with a 1 h slow addition of substrate.

Table 2

Substrate scope.



* Isolated yields are the average of three runs. Products yields are based on a mixture of diastereomers.

^a d.r. = 11:1, relative stereochemistry not assigned.

^b d.r. = 10:1, relative stereochemistry not assigned.

For all other compounds, diastereomeric ratios range from 2:1 to 1:1.3 syn:anti. ins. = C—H insertion; cyclopro. = cyclopropanation; Rh₂(OAc)₄ = rhodium acetate dimer; TBDPS = tert-butyldiphenylsilyl; SO₂Ph = phenyl sulfonyl.