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

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**Supporting Information**

**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.

Iron is one of the most abundant elements, totaling one-third of the Earth’s mass, and is emerging as an important metal for homogeneous catalysis. Iron small molecule catalysts have been demonstrated to catalyze challenging C−H oxidation and amination processes via high-valent metal oxos and nitrenes. 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 (e.g., cyclopropanations, heteroatom-hydrogen bond insertions) (Figure 1). Small molecule iron catalysts capable of forming carbenes also fail to catalyze C−H alkylation, favoring alternative reaction pathways. Curiously, nearly all other late metals, including copper, cobalt, silver, palladium, rhodium, and ruthenium, 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, and/or demonstrated to undergo C−H insertion in a separate step at elevated temperatures (e.g., 80 °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 because this diazoester is reported and observed by us (Supporting Information, SI) to show significant nonmetal mediated alkylation reactivity at this temperature.

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. This difference may explain the predominance of lower energy pathways in iron carbene reactions, such as competitive dimerization to furnish olefins. Reactivity and selectivity of metal carbenes is highly tunable; 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 diazo precursor.

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). We examined a series of substituted diazo compounds (acceptor, donor−acceptor, donor−acceptor 3) with varying degrees of electrophilicity and steric bulk. With iron porphyrin and phthalocyanine catalysts, diane 1 converted to olefin dimer (4, 93% and 84%, respectively), suggestive of iron carbene formation. Bulkier disubstituted carbene precursor 2 disfavored dimerization with all catalysts, but favored ketone product 5 over alkylation.

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*Received:* July 20, 2017  
*Published:* September 12, 2017
We hypothesized that augmenting the electrophilicity of the disubstituted diazo compound would increase its reactivity by producing a strongly electrophilic metal carbene 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 metal carbene; however, once formed, the resulting carbene is more reactive toward C–H insertion.9a Acceptor–acceptor diazoester 3 resulted in predominately recovered starting material. Upon examination of the 13C shifts of the α-carbon of various acceptor–acceptor diazo precursors, we observed that sulfonate esters appeared to be the most electrophilic and thus investigated their diazo esters (6) for C–H alkylation reactivity.9b The catalyst with the greatest π-accepting character, iron phthalocyanine chloride ([FeIII]Cl), formed C–H alkylated δ-sultone product 7 in low yield (3%) but with excellent selectivity (97% rsm). Examination of noncoordinating counterions to render the iron catalyst more electrophilic led to a significant increase in yield with both AgSbF6 (45%, SI) and NaBArF4 (48%) (Table 1B). Adding the substrate to [FeIII]Cl over an hour further increased the yield (53%). Catalysts with halogenated phthalocyanine ligand frameworks formed C–H alkylated product in lower yield than the unsubstituted, commercial catalyst (e.g., [(FeIII]Cl2Pc]Cl). Iron(II) phthalocyanine and iron porphyrin complexes gave very little or no C–H alkylation (see SI), highlighting the significance of the FeIII oxidation state and the ligand framework.10 NaBArF4 alone gave no product (see SI).

Allylic C–H alkylations are rare under both noble and base metal catalysis. Specifically, under rhodium and copper catalysis, chemoselectivity issues arise wherein cyclopropanation of the olefin competes with C–H insertion.4a,e,9 We investigated the scope of this iron-catalyzed reaction across a range of allylic diazosulfonate esters (Table 2A). Bulky trisubstituted olefins, olefins with proximal, protected oxygen functionality, and styrenyl substrates all undergo alkylation in preparative yields (8–13). Consistent with an electrophilic metal carbene intermediate, [FeIII]Pc]-catalyzed C–H alkylation is sensitive to substrate electronics (13 vs 10).4c,11 This contrasts observations with metalloradical intermediates invoked in cobalt catalysis, where substrate electronics do not affect reactivity.4c Chemoselectivity for iron-catalyzed allylic C–H alkylation is maintained with more proximal olefins where cyclopropanation would form the geometrically preferred 6-membered sultone9b (14, 15). In contrast, rhodium catalysis shows poor chemoselectivity for C–H insertion, forming cyclopropanated products. We also demonstrate one example of ethereal C–H alkylation (16).

Benzylic C(sp3)–H bonds were evaluated under these reaction conditions and shown to readily undergo alkylation (Table 2B). Substrates containing electron rich aryl rings are alkylated in high yield (17, 18), with no cyclopropanation observed even for a naphthene-containing substrate (19). [FeIII]Pc] promotes C–H alkylation adjacent to chromene and indole heterocycles (20, 21), and tolerates lactam and

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**Table 1. Reaction Optimization**

<table>
<thead>
<tr>
<th>Catalysts</th>
<th>Acceptor/acceptor:</th>
<th>Donor/acceptor:</th>
<th>Selectivity</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>FeIII[TPP]Cl</td>
<td>3:1</td>
<td>4</td>
<td>93% dimer</td>
<td>99% yield</td>
</tr>
<tr>
<td>FeIII[TPP]Cl</td>
<td>1:1</td>
<td>4</td>
<td>4% ketone</td>
<td>96% yield</td>
</tr>
<tr>
<td>FeIII[Pc]Cl</td>
<td>3:1</td>
<td>5</td>
<td>84% dimer</td>
<td>98% yield</td>
</tr>
</tbody>
</table>

**Table 2. Substrate Scope**

<table>
<thead>
<tr>
<th>Substrate</th>
<th>C–H Alkylation</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>7</td>
<td>C–H ins. 7</td>
</tr>
<tr>
<td>8</td>
<td>9</td>
<td>C–H ins. 7</td>
</tr>
<tr>
<td>10, X = H</td>
<td>72%</td>
<td>C–H ins. 7</td>
</tr>
<tr>
<td>11, X = Br</td>
<td>47%</td>
<td>C–H ins. 7</td>
</tr>
<tr>
<td>12, X = Cl</td>
<td>60%</td>
<td>C–H ins. 7</td>
</tr>
<tr>
<td>13, X = CF3</td>
<td>44%</td>
<td>C–H ins. 7</td>
</tr>
</tbody>
</table>

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*isolated yields are the average of three runs. Products yields are based on a mixture of diastereomers. 9a = 11.1, relative stereochemistry not assigned. 9b = 10.1, relative stereochemistry not assigned. For all other compounds, diastereomeric ratios range from 2:1 to 1:13.3 syn/ant. ins. = C–H insertion; cycloprop = cyclopropanation; R30(DA)Cl2 = rhodium acetate dimer; TBDDS = tert-butylidiphenylsilyl; SO2Ph = phenyl sulfonyl.*
thiophene motifs (23, 24). A substrate containing a benzodioxole moiety is readily alkylated (22), despite the activated methylenedioxy functionality.

We investigated the application of this reaction to the late-stage functionalization of δ-tocopherol, a chromane antioxidant (Table 2C). Tocopherol derivative 25 was subjected to [FeIIIPc]-catalyzed C–H alkylation and furnished 26 in 78% yield. The δ-sultone motif has been demonstrated to be readily derivitized. Accordingly, a three-step elaboration of the δ-sultone via nuclophilic displacement yielded 27, bearing an unsymmetrical tertiary center with two new functional group handles, in 44% overall yield.

Next, we 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 and iron nitrenes, promotes homolytic cleavage of the C–H bond followed by recombination with the resulting carbon-centered radical to form the new C–C bond (Figure 2A). Alternatively, the iron carbene intermediate, as well as further development of stepwise versus concerted mechanism (Figure 2C). 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.

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 (Figure 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 [FeIIIPc] 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, the absence of a chiral pocket, isomerization during functionalization of Z-olefins occurs to a greater extent than in the iron system. This suggests that C–H alkylation with iron proceeds with less free radical character than cobalt. 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. Intermolecular KIE studies that measured initial rates on parallel reactions with benzylic substrate 30 and 30-d2 revealed a primary KIE of 3:1 under [FeIIIPc] catalysis (Figure 2C). This is consistent with C–H cleavage being part of the rate-determining step of the reaction. Initial rate measurements with [FeCl3] 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 cleavage.

We report an iron-catalyzed C(sp3)–H alkylation via a metallocarbene intermediate. [FeIIIPc] alkylates allylic and benzylic C(sp3)–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 C(sp³)–H bond types and intermolecular C–H alkylations.

■ ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b07602.

Experimental details and characterization data and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support provided by the NIGMS MIRA (R35 GM122525). J.R.G. is a National Science Foundation and Springborn Graduate Fellow. C.I.W. is an Illinois Distinguished Graduate Fellow. We thank L. Zhu for assistance with NMR and Dr. J. R. Clark for checking our experimental procedure.

■ REFERENCES


