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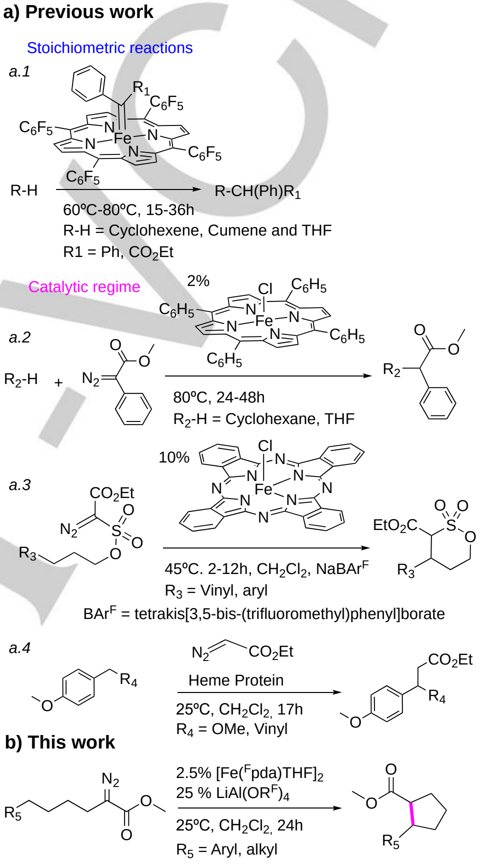
Electrophilic iron catalyst paired with a lithium cation enables selective functionalization of non-activated aliphatic C-H bonds via metallocarbene intermediates

Alberto Hernán-Gómez,*[a] Mònica Rodríguez,[a] Teodor Parella,[b] Miquel Costas*[a]

Abstract: Combining an electrophilic iron complex [Fe(^{F}pda)(THF)]$_2$ (**3**) [^{F}pda = *N,N'*-bis(pentafluorophenyl)-*o*-phenylenediamide] compound with pre-activation of α-alkyl substituted α-diazoesters reagents by the Lewis acid LiAl(OR^F)$_4$ [OR^F= (OC(CF$_3$)$_3$] provides unprecedented access to selective iron catalyzed intramolecular functionalization of strong alkyl C(sp^3)-H bonds. Reactions occur at 25°C, via α-alkyl-metallocarbene intermediates, and with activity/selectivity levels similar to rhodium carboxylate catalysts. Mechanistic investigations reveal a crucial role of the lithium cation in the rate determining formation of the electrophilic iron-carbene intermediate, which then proceeds via concerted insertion into the C-H bond.

Introduction

Carbon-carbon C(sp^3)-C(sp^3) bond formation methodologies are fundamental in many synthetic transformations. Among the different existing strategies,[1] the formal metal mediated insertion of carbene fragments into C(sp^3)-H bonds[2] is an appealing methodology due to its greater atom economy when compared with the most extended cross-coupling procedures, employing organometallic coupling partners (boron, zinc or Grignard reagents).[1a, b] Despite the robustness of C(sp^3)-H bonds,[3] making difficult their chemical manipulation, a variety of transition metal carbene species (copper, cobalt, silver, palladium, rhodium, and ruthenium), generated from diazo reagents, are capable of catalyzing these insertion reactions.[4] In contrast, iron systems, which are attractive from a sustainability perspective,[5] have shown modest activity being limited to less demanding processes, including cyclopropanation reactions,[6] and alkylation of C(sp^2)-H,[7] heteroatom –hydrogen,[8] and relatively weak allylic and benzylic (BDE < 90 Kcal/mol) C(sp^3)-H bonds (Scheme 1).[9] Pioneer studies by Che[10] proved the feasibility of iron (III) porphyrins to effect this methodology by stoichiometric functionalization of cyclohexene, cumene and tetrahydrofuran, using diphenyldiazomethane as carbene precursor at high temperatures (60°C - 80°C) (Scheme 1 a.1).



Scheme 1. State of art of iron-carbene mediating C(sp^3)-H functionalization.

Updating this strategy to a catalytic version, Woo[11] reported intermolecular insertion of carbene fragments, generated from methyl phenyldiazoacetate, into the C-H bonds of cyclohexane and tetrahydrofuran, mediated by an iron (III) porphyrin catalyst at 80°C (Scheme 1 a.2). Although this study opened a new ground for iron chemistry, it was later reported that these diazoester compounds undergo formal carbene insertion in the absence of iron, although in lower yields.[12] More recently, intramolecular alkylation of weak allylic and benzylic C(sp^3)-H bonds has been reported using a heme-like iron (III) phtalocyanine catalysts, and intermolecular enantioselective alkylation of activated C(sp^3)-H bonds (benzylic and adjacent to heteroatom) has been described by laboratory-evolved P-450 enzymes (Scheme 1 a.3 and a.4).[9] This scenario contrasts to the one operating for the isoelectronic iron oxos,[13] and iron nitrenes[14] in which upon ligand design, functionalization of less reactive C(sp^3)-H bonds (BDE C-H > 90 Kcal/mol) is well stablished.[3] We hypothesized that replacing the porphyrin (or related), by ligands of highly electrophilic character will led to formation of electron-poor iron-carbene species by

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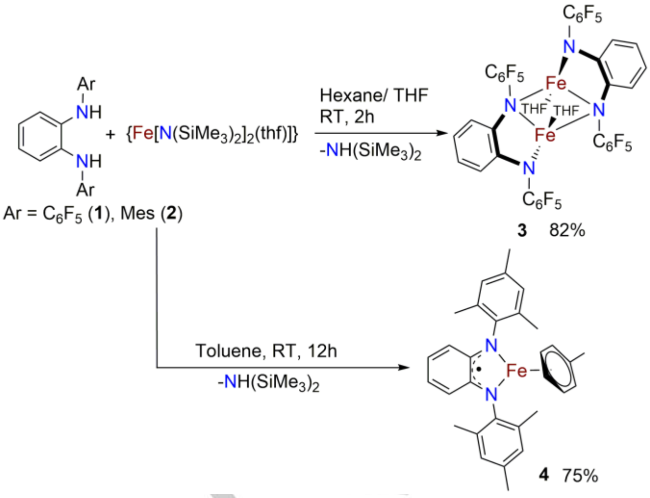
reaction with diazo compounds, being able to overcome energetically demanding C-H alkylation processes under mild conditions.

In our aim to develop iron-carbene species with the ability to functionalize strong C(sp^3)-H bonds, herein we report an electrophilic iron complex [Fe(^{F}pda)(THF)]$_2$ (**3**) [^{F}pda = *N,N'*-bis(pentafluorophenyl)-*o*-phenylenediamide], which is arranged in an unique dimeric fashion within *ortho*-phenylenediamide iron chemistry, which traditionally has been dominated by formation of the more stable [FeL$_2$] fragment, as described by Wieghardt.[15] For comparison reasons, the related complex [Fe(^{Mes}pda)(Tol)] (**4**) [^{Mes}pda = *N,N'*-bis(2,4,6-trimethylphenyl)-*o*-phenylenediamine], displaying poorer electrophilic nature, has been also investigated. Effectively, we disclose unprecedented iron catalyzed intramolecular carbene insertion into a variety of non-activated aliphatic C-H bonds, via iron-carbene intermediates (Scheme 1b), under mild conditions (25ºC). The reaction is critically based on two novel aspects; a) pre-activation of the diazoester reagent by the Lewis acid LiAl(OR^F)$_4$ [OR^F= (OC(CF$_3$)$_3$], which enables formation of the iron-carbene species under mild conditions, and b) the electrophilic character of complex **3**, which permits functionalization of non-activated aliphatic C-H bonds. Remarkably **3** exhibits activity and selectivity levels comparable to rhodium carboxylate catalysts.

Results and Discussion

Catalysts synthesis and characterization. *Ortho*-phenylenediamine ligands **1** and **2** were synthesized by nucleophilic aromatic substitution between lithium 1,2-phenylendiamide and hexafluorobenzene for compound **1**, and Buchwald-Hartwig amination of 1,2-dibromobenzene with 2,4,6-trimethylaniline in the case of **2**, according to previous reports in the literature.[16]



Scheme 2. Synthesis of compounds **3** and **4**.

Metallation of **1** with the bisamide iron compound {Fe[N(SiMe$_3$)$_2$]$_2$(thf)} in a mixture THF/hexane (1:9) at room temperature led to the formation of [Fe(^{F}pda)(thf)]$_2$ (**3**), as a pale orange solid in 82% yield (Scheme 2). Similarly, reaction of ligand **2** and {Fe[N(SiMe$_3$)$_2$]$_2$(thf)} using toluene as a solvent media, resulted in isolation of a dark purple solid identified as compound [Fe(^{Mes}pda)(toluene)] (**4**) (75% yield) (Scheme 2). Single crystal X-ray analysis of compound **3** (Figure 1a, Table 1) reveals a dimeric structure in the solid state formed by two units of [Fe(^{F}pda)(thf)] and with a central {Fe$_2$N$_2$} core, where the iron centers are connected by two bridging nitrogen atoms of two ^{F}pda ligands. Fulfilling their coordination sphere the metallic centers are terminally coordinated by the second nitrogen atom of the *N,N'*-bidentate ligands, and by a molecule of THF. Inspection of the monomeric asymmetric unit [Fe(^{F}pda)(thf)] reveals two significantly different Fe-N bond distances, Fe1-N1 2.112 (1) and Fe1-N2 1.969 (1), attributed to the bridging character of N1 between Fe1 and Fe1', while N2 coordinates terminally to Fe1. Similarly, within the {Fe$_2$N$_2$} core two different Fe-N bond distances are observed, being the previous Fe1-N1 bond distance longer than the one formed between the same N1 and the neighboring iron atom Fe1'-N1 2.069(1). These Fe-N bond distances are within the range of high spin Fe(II) compounds supported by bidentate ligands (Fe-N> 2.0 Å).[17] In contrast, compound **4** (Figure 1b, Table 1) exhibits a monomeric η^6-toluene adduct with ^{Mes}pda acting as a terminal *N,N'*-bidentate ligand and with shorter Fe-N bonds (average 1.87(1) Å).

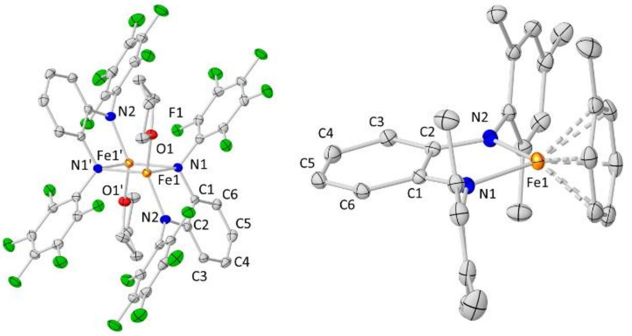


Figure 1. Molecular structures of a) compound **3** and b) compound **4** with thermal ellipsoids at 50% probability. Hydrogen atoms are omitted for clarity.

Table1. Selected bond distances of compounds **3** and **4**.

Bond distances / Angles	3	4
Fe1-O1	2.017(1)	-
Fe1-N1	2.112(1)	1.881(2)
Fe1-N'1	2.069(1)	-
Fe1-N2	1.969(1)	1.867 (2)
Fe-C$_{\text{Tol average}}$	-	2.09(1)
N1-C1	1.446(2)	1.359(4),
N2-C2	1.399(2)	1.359(4),
C1-C2, ,	1.411(2)	1.426(4),
C1-C6	1.390(3),	1.410(4),
C2-C3	1.399(3),	1.414(4),
C3-C4	1.388(3)	1.375(4),
C4-C5	1.380(3),	1.407(4),
C5-C6	1.392(3)	1.382(4);

The different nature of the formed complexes with the non-nitrogen donor ligands, THF σ-adduct in **3** and toluene π-adduct in **4**, points to different electronic configuration of each iron complex due to the "redox-active" nature of the *N,N'*-

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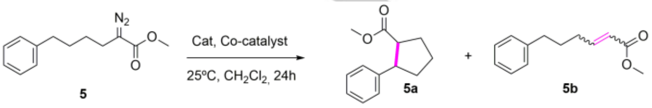
bidentate employed ligands. The latter is confirmed by comparison of the metrical data of the ligand backbones of **3** and **4**, following Wieghardt´s structural approach to determine the redox form of the ligand and metal in complexes supported by *ortho*-phenylene diamine ligands.[15] Thus compound **3** displays an aromatic phenylene ring (C-C$_{average}$ 1.39(1) Å) and single C-N bonds (C-N$_{average}$ 1.42(2) Å), whereas species **4** exhibits subtle dearomatization on the phenylene ring with two sets of C-C bonds (average C$_\alpha$-C$_\alpha$ and C$_\alpha$-C$_\beta$ 1.417(8) Å; C$_\beta$-C$_{\gamma\ average}$ 1.378(5) Å), as well as shorter C-N bond distances (C-N$_{average}$ 1.359(4) Å). These data are consistent with a dianionic *ortho*-phenylenediamide bidentate ligand binding an Fe^{2+} metallic center in complex **3**, similarly to the homoleptic [Fe(^{F}pda)$_2$][AsPh$_4$] previously reported by Wieghardt, although in this case two ^{F}pda^{2-} coordinate the same metallic center.[15b] Key for the isolation of compound **3** relies on the use of the iron base {Fe[N(SiMe$_3$)$_2$]$_2$(thf)}, which precludes the presence of an excess of dianionic diamide ligand, as when the lithiated diamide is used as transmetallating reagent, and ultimately avoids formation of the [FeL$_2$] fragment.

In contrast, compound **4** is better described as an iron (I) *ortho*-diiminosemiquinonate with metrical data similar to the [Fe(^{Ipr}pda)(Tol)] compound reported by Song.[18] In agreement with the electronic structures suggested by X-ray crystallography, ^{1}H NMR characterization in C$_6$D$_6$ solution displayed different magnetic behavior for the two complexes. Compound **4** is diamagnetic and its spectrum displays six signals in the range 7 – 2 ppm, assigned to the *N,N'*-chelating ligand, and four high shielded resonances (5.14, 4.89 and 4.82 and 1.78 ppm) consistent with a η^6-toluene adduct. The observed diamagnetic behavior of **4** can be rationalized in terms of an antiferromagnetically coupling between the structurally deduced Fe^I (d^7) metallic center with the unpaired electron on the *ortho*-diiminosemiquinonate ligand, as it was reported for the isostructural [Fe(^{Ipr}pda)(Tol)].[18] In contrast, in C$_6$D$_6$ species **3** displays a paramagnetic behavior showing two resonances at 25 and 15 ppm, accounting for the four aromatic protons at the backbone of the bisamide ligand, and a solution magnetic moment μ$_{eff}$ = 4.71 (3) μ$_B$ per dimer at room temperature. Confirming retention of the solid state structure of **3** in C$_6$D$_6$ solution, when its ^{1}H NMR spectrum was registered in [D$_8$]-THF, a shift of the latter signals, assigned to the dimer (25 and 15 ppm), was observed towards higher field (-18 and -22 ppm), in agreement with THF coordination to the iron centers and breaking up of the dimer to generate a monomer species. Thus, the deduced spin-only value for compound **3** in C$_6$D$_6$, which is lower than the expected for two uncoupled high-spin iron (II) (6.9 μ$_B$), can be attributed to antiferromagnetic coupling between the two vicinal iron atoms (2.615(1) Å) of the dimer.

Catalytic carbene transfer reactions. To begin our investigations on C-H alkylation, we tested the catalytic activity of compounds **3** (2.5 mol%) and **4** (5 mol%) in the intramolecular C-H alkylation of diazoester **5** in CH$_2$Cl$_2$ at 25°C for 24 hours (Table 1, entries 1-2). The reactions provided poor conversions (7-8%) of **5** into the desired **5a** product, where intramolecular alkylation has taken place at the benzylic position, and the α, β-unsaturated ester side product **5b**, generated in a β-hydride migration process, or alternatively by two consecutive hydrogen atom abstraction (HAT) steps, as it has been recently reported by De Bruin for intramolecular C-H alkylation catalysis via radical cobalt-carbene intermediates. [19]

Table 2. Optimization for catalytic functionalization of diazo reagent **5**.[a]



Entry	Catalyst (%)	Co-Catalyst (%)	5	5a (*anti*:*syn*)	5b (E:Z)
1	**3** (2.5)	-	92%	2% (75:25)	3% (47:53)
2	**4** (5)	-	93%	-	5% (45:55)
3	**3** (2.5)	LiAl(OR^F)$_4$ (5)	52%	31% (87:13)	12% (32:68)
4	**4** (5)	LiAl(OR^F)$_4$ (5)	82%	7% (89:11)	8% (35:65)
5	**3** (2.5)	LiAl(OR^F)$_4$ (15)	42%	40% (86:14)	15% (27:73)
6	**3** (2.5)	LiAl(OR^F)$_4$ (25)	4%	60% (76:24)	35% (19:81)
7	**3** (2.5)	LiAl(OR^F)$_4$ (50)	-	51% (84:16)	48% (42:58)
8	**3** (2.5)	LiAl(OR^F)$_4$ (75)	-	48% (78:22)	48% (47:53)
9	**3** (2.5)	LiAl(OR^F)$_4$ (100)	-	45% (83:17)	50% (46:54)
10	-	LiAl(OR^F)$_4$ (25)	>99%	-	-
11	**3** (2.5)	NaBAr^F (25)	89%	7% (85:15)	-
12	[Fe(OTf)$_2$(PyTACN)] (5)	LiAl(OR^F)$_4$ (25)	>99%	-	-
13	[Rh(OAc)$_2$]$_2$ (2.5)	-	-	68% (93:7)	31% (1:99)
14	Tp^{Br3}Cu(NCMe) (5)	-	-	6% (>99:1)	92% (37:63)

[a] Reaction conditions: [**5**] = 0.08 mM. Yields of **5a**, **5b**, and diastereomeric ratios were determined by ^{1}H NMR spectroscopy using dibromomethane as internal standard.

Despite this lack of reactivity, during the addition of diazo compound **5** over the CH$_2$Cl$_2$ solution of **3** we observed an immediately color change from orange to dark brown. Analysis of the mixture resulting from the reaction of stoichiometric amounts of diazoester **5** and iron species **3** by infrared spectroscopy shows a band shift to a lower value (Δυ = 13 cm^{-1}) of the C=O functional group (Figures 2a-2c), while the band assigned to the N=N functional group is modified in a more modest extend (Δυ = -8 cm^{-1}). These observations suggest that the iron compound is unable to effect formation of the metallocarbene intermediate upon nitrogen release of the diazo compound, and instead a novel adduct species through the binding of the O donor atom of the carbonyl group [Fe-O(C)] present in the diazo reagent to the Lewis acid Fe^{II} atom of **3** is formed. This scenario is reminiscent to the one recently reported for the C(sp^2)-H bond alkylation reactions via non heme iron-carbene species. In this case, computational studies rationalize the high reaction temperatures (80°C) required by dissociation of an unproductive Fe-O(C) adduct formed between the iron catalyst and the oxygen atom of the carbonyl group of ethyl diazoacetate.[7a]

Lithium activation of the azo reagent. We hypothesized that the undesired Fe-O(C) interaction can be disfavored by addition of a

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stronger Lewis acid than the iron centers present in compounds **3** and **4**.

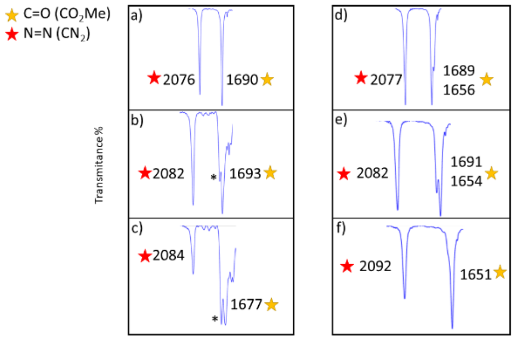

Figure 2. Expanded IR spectra displaying C=O and N_2 bands of a) diazoester **5**, b) reaction mixture of **5** and **3** (1:0.5), c) reaction mixture of **5** and **3** (1:1), d) reaction mixture of **5** and $LiAl(OR^F)_4$ (1:0.05), e) reaction mixture of **5** and $LiAl(OR^F)_4$ (1:0.15) and f) reaction mixture of **5** and $LiAl(OR^F)_4$ (1:0.25). * band belonging to compound **3**. For full spectra see supporting information

Indeed, repeating the infrared spectroscopy monitoring of the mixture formed by compound **5** and variable amounts of the lithium salt $LiAl(OR^F)_4$ [OR^F= ($OC(CF_3)_3$] (5-25 mol%), we observed a split in two of the investigated C=O bands, assigned to free **5** (1690 cm^{-1}) and lithium bound **5** (1654 cm^{-1}) (Figures 2d-2f). According to this assignation, the intensity of the free diazo band systematically decreased to depletion in favor of the adduct band as the concentration range of $LiAl(OR^F)_4$ increased from 5 to 25 mol%. Beyond 25 mol% concentration of lithium aluminate no changes were observed in the IR spectra. Of relevance to these observations, this coordination mode reproduces the one observed for the interaction of lactones with lithium inorganic salts, which occurs through the carbonyl group.[20] In parallel, within the range of $LiAl(OR^F)_4$ concentrations studied, the N=N stretching frequency experiences a 15 cm^{-1} shift to higher energies, which can be rationalized by an additional, but weaker, interaction between a lithium cation and **5** through the negatively polarized carbon bearing the diazo fragment Li-C(N_2). In solution, a dynamic binding of lithium to the diazoester **5** can be deduced by ^1H NMR study of the previously described reaction mixtures within the concentration range 5-25 mol% of $LiAl(OR^F)_4$, which display only one set of broad signals of the diazoester reagent (Figures S127-S128, supporting information). Further evidence for the strong binding of the diazo compound **5** to lithium is provided by mass spectroscopy analysis of a reaction mixture of **5** and $LiAl(OR^F)_4$ (1:0.25), which exhibits peaks at m/z = 471.2585 and 239.1384, corresponding to a mono- and bis-adduct between **5** and the lithium cation (Figures S129-S131, supporting information). Collectively, the data suggests the formation of a strong adduct between **5** and lithium, through the carbonyl group, which may be used to liberate the iron center, setting it ready for carbene formation.

Li-promoted carbene transfer reactivity. In agreement with the above described analysis, repeating the intramolecular C-H alkylation reaction of **5** catalysed by 2.5 mol% of **3** and 5 mol% of **4**, now in presence of 5 mol% of $LiAl(OR^F)_4$ [OR^F= ($OC(CF_3)_3$] resulted in enhanced conversions of **5** at 25°C (Table 2, entries 3-4), exhibiting **3** the highest reactivity and selectivity with a 48% conversion and a 72:28 ratio (**5a**:**5b**), while **4** only rendered a 18% conversion with a 47:53 ratio (**5a**:**5b**). Seeking to increase the yield of product **5a** we optimized the loading of lithium salt $LiAl(OR^F)_4$ (Table 2, entries 5-9), resulting in nearly quantitative conversion of **5**, the best **5a**/**5b** ratio, and a high **5a** diastereomeric ratio (76/24, *syn:anti*) at 25 mol% concentration (Table 2, entry 6). Of notice this lithium concentration actually matches the absence of free diazo compound observed by infrared studies. Proving the synergistic partnership between Fe and Li, when the lithium aluminate $LiAl(OR^F)_4$ is reacted with diazo compound **5** at 25 °C in the absence of catalyst **3**, no **5a** or **5b** product was observed (Table 2, entry 10). Under the optimized conditions we investigated the influence of each component in the catalytic reaction. Other alkali metal salts, such as $NaBAr^F$, have been used in more facile C(sp^3)-H insertion reactions via iron-carbene species, playing a mere role as trapping reagents of the halogen atoms connected to the iron center, and generating a cationic and hence more reactive iron species.[7, 9b] In our case replacing $LiAl(OR^F)_4$ by $NaBAr^F$ (Table 2, entry 11) turned into lower reactivity observing only 7% yield of **5a**, proving sodium to be a less affective co-catalyst in agreement with the softer nature as a Lewis acid compared to lithium cation.

Highlighting the importance of low coordinate iron centers to develop these C-H insertion reactions, when catalyst **3** was substituted by an iron complex supported by a polydentate amino-based ligand [$Fe(OTf)_2$(PyTACN)] (PyTACN = 1-(2-pyridylmethyl)-4,7-dimethyl-1,4,7-triazacyclononane, Table 2, entry 12),[7] no product **5a** was formed recovering the starting material **5**. This catalyst has been recently shown to activate ethyl diazoacetate to effect chemoselective arene alkylation of alkyl arenes via a formal carbene insertion reaction: Reactions require 80°C to proceed and did not display sp^3 alkylation, even in the presence of weak tertiary C-H bonds. In addition, and for comparison reasons the studied cyclization was also subjected to rhodium catalysis,[19] which in our hands using 2.5 mol% of $[Rh(OAc)_2]_2$ provided similar results to our iron-lithium catalytic system (Table 2, entry 13). Drawing a comparison to iron catalysis in terms of sustainability, the earth-abundant copper metal supported by trispyrazolylborate compounds have emerged as powerful catalysts able to functionalize unreactive hydrocarbons,[21] however alkylation of **5** using the electron-deficient $Tp^{Br3}Cu(NCMe)$ (Tp^{Br3} = (hydrotris(3,4,5-tribromo)pyrazolylborate)] species rendered almost exclusively the undesired **5b** product (Table 2, entry 14).

Substrate scope. With the optimized conditions in hand, we next investigated the viability of this catalytic Fe/Li system in intramolecular C-H alkylation of diazo substrates with varying degrees of electrophilicity (**6**-**8,** Table 3) and containing bonds of different strength (**9**-**19**, Table 3).

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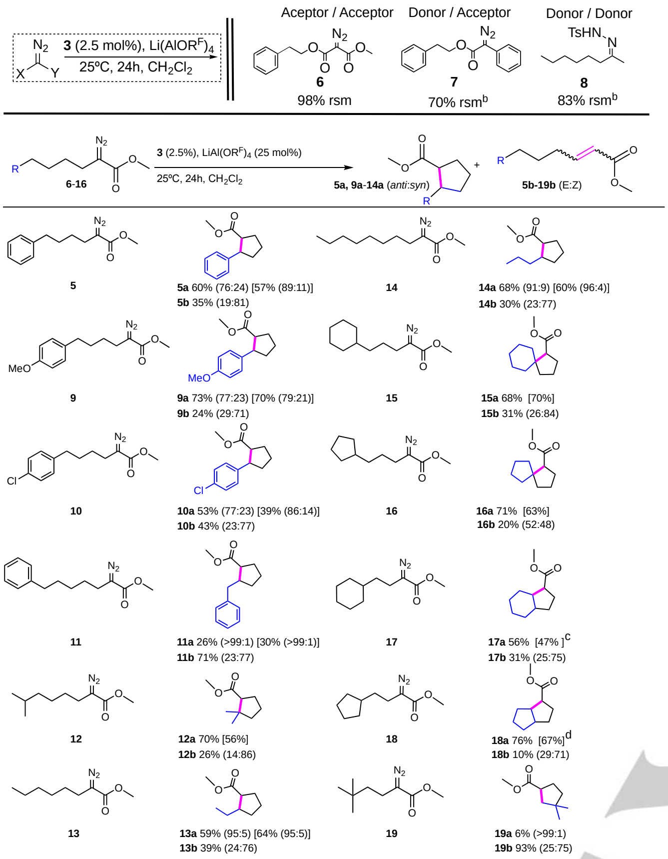
Table 3. Substrate scope [a]

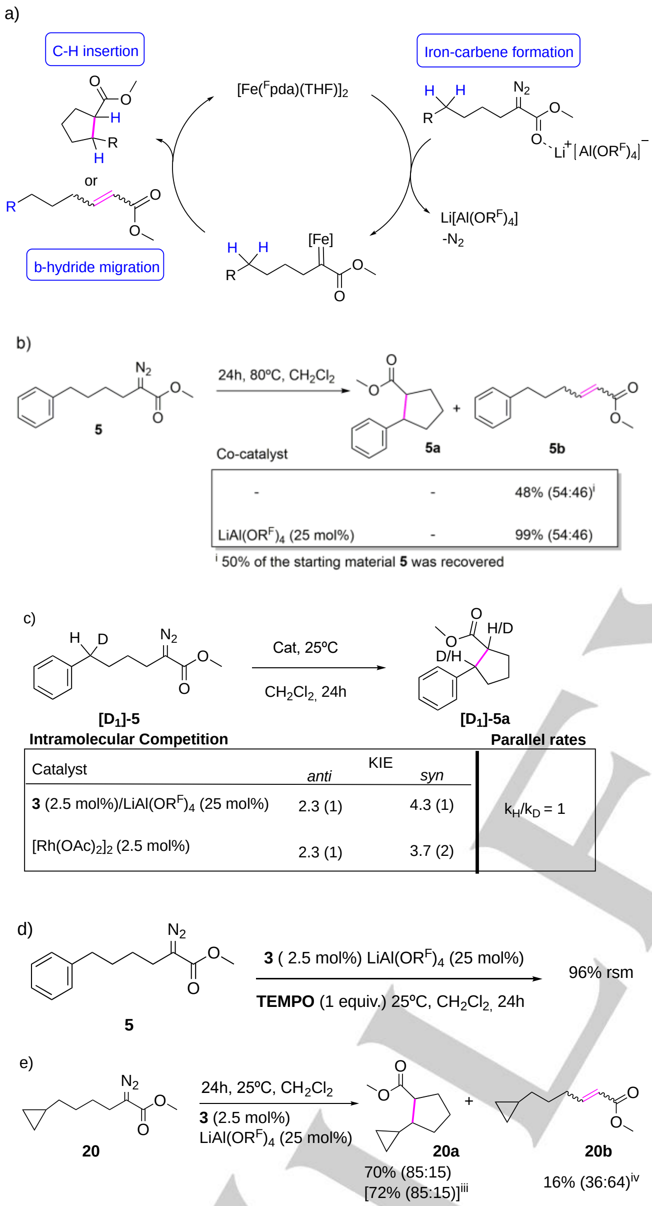


[a] Reaction conditions: [**5-19**] = 0.08 mM. Conversions of **6-8** were determined by ^{1}H NMR spectroscopy using dibromomethane as internal standard. Yields of **5a, 9a-19a** and **5b,9b-19b**, were determined by ^{1}H NMR spectroscopy using dibromomethane as internal standard. Diastereomeric ratios were determined by GC and ^{1}H NMR spectroscopy. *Anti* diastereomer for products **5a, 9a-14a** was determined to be the major isomer by NMR characterization. Isolated yields for 1 mmol scale reactions are reported in brackets and their corresponding diasteromeric ratios determined by GC and ^{1}H NMR spectroscopy. rsm = recovered starting material; [b] Non-identified products; [c] d.r. (63:25:12), d.r. for isolated yield (68:29:3) determined by GC and ^{1}HNMR spectroscopy, relative stereochemistry was not determined; [d] d.r (94:6) determined by GC, relative stereochemistry was not determined.

Modification of the electronic properties of the diazo reagent resulted in no reaction in the case of acceptor/acceptor substrate **6**, and in low conversion of the donor/acceptor compound **7** towards a mixture of unidentified compounds. In addition, we also explored other carbene sources such as *N*-tosylhydrazone **8** which gives rise to the corresponding diazo reagent in situ upon deprotonation using a base (LiO^{t}Bu), as it has successfully used in cobalt catalysis.[4d-g] However this methodology proved to be incompatible with the developed Fe/Li system.

Extending the study to donor/acceptor diazo reagents structurally similar to **5** and containing benzylic C-H bonds, using the electron-rich *para*-methoxy aryl diazoester reagent **9** led to the corresponding cyclopentane product **9a** in a high isolated yield 70%, while the electron-poor *para*-chloro substituted compound **10** was transformed to **10a** in a diminished 39% isolated yield. Both compounds **9a** and **10a** are formed in similar and modest diastereomeric ratio (d.r.) 77:23. Again, the differences observed in yields are in agreement with involvement of an electrophilic iron-carbene as the active species, with enhanced reactivity as the nucleophilicity of the reactive C-H bond increases. Notably, directed by the formation of a favorable five-membered ring a strong alkyl C-H bond is functionalized over the weaker benzylic C-H bond, forming the five-membered ring **11a**, albeit in a modest yield 30%. These catalytic C-H alkylation reactions compared well with the only previous report in the literature for the catalytic intramolecular functionalization of benzylic C-H bonds via iron carbene intermediates, as the latter required heating (45°C) and higher catalyst loading (10 mol%) to carry out these reactions under similar reaction times and yields.[9b] In addition, these results (Table 3, **5a, 9a-11a**) suggest that formation of olefin side products is substrate-dependent, becoming this reaction more competent as the functionalization of the desired C-H bond is less favorable, as observed for substrates **10** and **11** in which the α,β-unsaturated ester product is generated in higher yields. Of relevance, reactions exhibit an excellent mass balance; for each substrate, the sum of yields of alkylated product and the α,β-unsaturated ester account for the total amount of initial substrate. Encouraged by the formation of **11a** under mild conditions, we next explored functionalization of strong C-H bonds found in alkyl derivatives. Starting with a less demanding one, catalyst **3** in combination with LiAl(OR^F)$_4$ was able to produce cyclization upon functionalization of a tertiary C-H bond present in diazoester reagent **12**, generating **12a** in 56% isolated yield. A similar yield (64%) was obtained for cyclopentane derivative **13a**, when substrate **13** containing a more challenging secondary C-H bond was subjected to the catalytic Fe/Li system. As was observed for benzylic C-H bonds, formation of a five-membered ring primes over the possibility of forming larger size rings as in the case of diazoester **14**, which renders **14a** in 60% yield. More importantly, formation of cyclopentane derivatives **11a**-**14a** occurs in an excellent diastereomeric ratio (*anti:syn* ≥ 95:5). Beyond monocyclic products, the developed methodology gives access to bicyclic spirocompounds (**15a**, **16a**) and fused ring products (**17a**, **18a**) in moderate to good yields (47-70%). Contrastingly, catalyst **3** in combination with the lithium salt activates the most challenging primary C-H bonds present in substrate **19** in nearly stoichiometric yield (6%).

Mechanistic analyses. We envisioned that the reaction will proceed via a concerted alkylation process (Figure 3a), in which the iron-carbene is formed by nitrogen extrusion from the corresponding lithium-diazoester adduct, and then effects insertion into the C-H bond forming a new C-C and C-H bond simultaneously, releasing the organic product and re-generating the active catalyst. Nevertheless, two alternative scenarios can be proposed, such as formation of free carbene species able to effect the observed C-H insertion reactions or a hydrogen atom transfer initiated radical stepwise process, as in the case of iron mediated C-H oxidation,[13] amination,[14] and a recently described iron-phthalocyanine catalyzed alkylation.[9b] To distinguish between these three possibilities, we subjected our system to a variety of mechanistic analyses. First, generation of a free carbene was thermally (80°C) achieved, and resulted in exclusive formation of the undesired product **5b** in a 48% yield (Figure 3b). Under the same conditions (80°C and absence of iron catalyst), addition of the Lewis acid LiAl(OR^F)$_4$, afforded exclusively **5b** in quantitative yields (Figure 3b). This acceleration is in agreement with the observed interaction Li-C(N_2) by IR spectroscopy, which at high temperatures favors formation of a free carbene. The lack of formation of **5a** in absence of iron catalyst **3** provides strong support for the necessary formation of an iron-carbene intermediate as the active species responsible for the C-H alkylation reactions.



^{iii} Reaction conditions: [**19**] = 0.08 mM. Yields determined by ^{1}H NMR spectroscopy using dibromomethane as internal standard. Diastereomeric ratios (*anti*:*syn*) determined by GC; ^{iv} Diastereomeric ratios (E:Z) determined by ^{1}H NMR.

Figure 3. a) Proposed mechanism of reaction; b) Generation of free carbene via thermal decomposition, c) Plot of Ln[**5**] vs time (h) for C-H alkylation reaction of **5** catalyzed by 2.5 mol% of 3 and 25 mol% of LiAl(OR^F)$_4$; d) Intramolecular KIE, e) C-H alkylation using radical probe **17**.

Next, to shed light on the nature of the C-H activation step, intramolecular kinetic isotope effect (KIE) was explored via alkylation of the partially deuterated diazoester reagent [D_1]-**5**. This experiment revealed two different values for each diastereomer, being the isotopic effect lower in the case of the major *anti* isomer [KIE = 2.3 (1)] than the one observed for the *syn* isomer [KIE = 4.3 (1)] (Figure 3c). For comparison reasons diazoester [D_1]-**5** was also subjected to catalytic alkylation using the dimeric [Rh(OAc)$_2$]$_2$ catalysts, well-known to operate through C-H insertion,[22] which afforded again two KIE values of 2.3 (1) for the *anti* isomer, and 3.7 (1) for the *syn* isomer (Figure 3d). The similar KIE values for both catalysts support the proposed concerted mechanism. In addition, the different results for each diastereomer in both metal-mediated reactions reflect two different transition states for the concerted insertion, as it has been also observed in previous rhodium mediated carbene insertion reactions.[23] To confirm the absence of radical intermediates, the radical trap TEMPO was added to the optimized alkylation reaction of diazo reagent **5**, however this experiment led to fully recovery of the starting material (Figure 3d). This can be reasoned by preliminary reaction between the catalyst **3** and TEMPO, rendering a species unable to form an iron-carbene active species. We next explored cyclization of the radical clock substrate **19,** which leads to the cyclopentane **19a** in 72% yield, conserving intact the cyclopropyl fragment (Figure 3e). Hydride shift product **19b**, accounts for the rest of the starting material. The lack of rearranged products is consistent with an insertion reaction, devoid of long lived radical or carbocationic intermediates.

Once the concerted mechanism was established, we explored the nature of the rate determining step by kinetic studies. ^{1}H-NMR spectroscopy monitoring of the C-H alkylation of substrate **5** under the optimized conditions (2.5 mol% of **3** and 25 mol% of LiAl(OR^F)$_4$) reveals a first order dependence on the diazoester reagent (Figure S135). In addition, a KIE value of 1 was determined by product analysis of the competitive reaction between equimolar amounts of **5** and [D_1]-**5** at low substrate conversion (15%) (Figure 3c). Finally, variable time normalization analysis[24] for the intramolecular insertion reaction at **5**, at different concentrations of LiAl(OR^F)$_4$) (25-40mol%) revealed a fractional 1.5 order (Figure S136), suggesting participation of more than one lithium cation through a coordination-dissociation equilibrium process. This is in agreement with the IR studies, which show that **5** interacts with lithium through the carbonyl group Li-O(C), and the carbon negatively polarized Li-C(N_2), requiring the latter to be replaced by iron for the formation of the iron-carbene species. Overall, these data are consistent with a rate-limiting iron-carbene formation, preceded by competition between a second lithium cation and iron for the C(N_2) center in an equilibrium process, shifted towards the interaction with iron due to the irreversible iron-carbene formation.

Conclusion

In conclusion, we describe an electrophilic iron complex **3** which in combination with LiAl(OR^F)$_4$ as co-catalyst activates diazoesters under mild reaction conditions, resulting in intramolecular C(sp^3)-H alkylation of a variety of benzyl and alkyl C-H bonds, leading to a variety of carbocyclic cyclopentanes as well as bicyclic spiro and fused ring compounds. High stereoselectivity is observed in the alkylation of the strong aliphatic sites. Mechanistic studies strongly suggest that the reactions proceed via highly reactive iron-carbene active species. Key to its formation is the binding of the carbonyl group of the diazoester reagent to lithium Li-O(C). Presumably, this reaction blocks formation of unproductive Fe-O(C) species, favoring interaction of the diazo moiety with the iron center, previous replacement of a second lithium cation interacting with the diazo reagent via Li-C(N), which then triggers release of nitrogen and formation of the reactive iron-carbene in the rate determining step. In addition these studies show a close similarities to rhodium based carbene transfer reactions, which entail a concerted metallocarbene insertion into the C-H bond, forming the new C-C and C-H bonds, suggesting that the current iron based system also operates via a C-H insertion process. Most relevant, the current systems extend the substrate scope of iron carbene species towards site selective alkylation of strong aliphatic C-H bonds, opening transformations so far only accessible with precious metals. Key to this finding is the tuning of the ligand architecture to endorse the iron center with a highly electrophilic character. Considering the structural versatility of this class of ligands, and the high level of diastereoselectvity observed in the functionalization of aliphatic sites, the development of catalyst dependent site and enantioselective transformations, akin those stablished for rhodium carbenes is envisioned.

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Keywords: Iron • carbene • C-H activation

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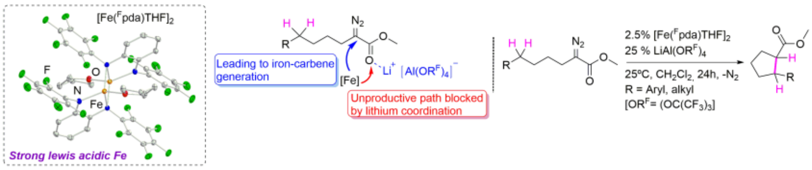
RESEARCH ARTICLE



Iron-carbene gets access to strong Csp^3-H bonds: Pairing a strong lewis acidic iron catalyst with pre-activation of diazo reagents using the lithium salt LiAl(OR^F)$_4$ [OR^F= (OC(CF$_3$)$_3$] renders electrophilic iron-carbenes capable to insert in non-activated aliphatic C-H bonds.

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Electrophilic iron catalyst paired with a lithium cation enables selective functionalization of non-activated aliphatic C-H bonds via metallocarbene intermediates

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