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Iron-Catalyzed Intermolecular Functionalization of Non-Activated Aliphatic C-H Bonds *via* Carbene Transfer

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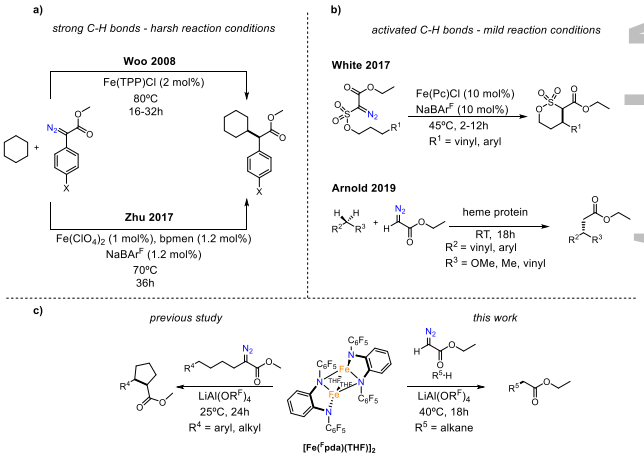
Abstract. The modification of strong C_{sp}^3-H bonds via iron carbene intermediates under mild reaction conditions has been an important challenge with attractive prospective in organic synthesis. In this work, we show the efficient combination of an electrophilic iron catalyst with a lithium Lewis acid for the functionalization of strong C_{sp}^3-H bonds of cyclic and linear alkanes by the activation of commercially available ethyl diazoacetate (EDA). The reaction proceeds with good yields, under mild reaction conditions (40 °C) and large excess of substrate is not needed. In addition, excellent activity is observed in the cyclopropanation of challenging aliphatic olefins.

Keywords: C-H functionalization; C-C bond formation; carbene transfer; iron catalyst; diazo compounds

Introduction

Direct and selective Csp^3-H functionalization via the construction of new Csp^3-Csp^3 bonds constitutes a powerful methodology to achieve the challenge of transforming hydrocarbons, inexpensive and abundant feedstock, into valuable molecules.[1] Particularly interesting are systems that perform these transformations under a catalytic regime.[2] Major limitations arise from the high bond dissociation energies (BDE) of Csp^3-H bonds, and the formation of highly stable metal-alkyl fragments upon C-H cleavage, precluding turnover in a catalytic cycle.[2] In this regard, metal-mediated insertion of carbene ligand fragments into C-H bonds is an effective strategy, which in particular cases is capable to functionalize methane, one of the molecules with the strongest Csp^3-H bonds.[3f] Typically, these reactive metallocarbene species are generated from reaction of diazo compounds with transition metal complexes, such as rhodium, silver, gold, cobalt, palladium and copper.[2,3] Because of sustainability considerations, iron is an appealing option to add to this list due to its inherent low toxicity and high earth-abundancy.[4] However, the iron catalyzed reaction has been developed only to a modest extent and reports are scarce.[5-10] Seminal studies started with the intramolecular functionalization of C-H bonds using stoichiometric amounts of a preformed iron-carbene compound.[5]

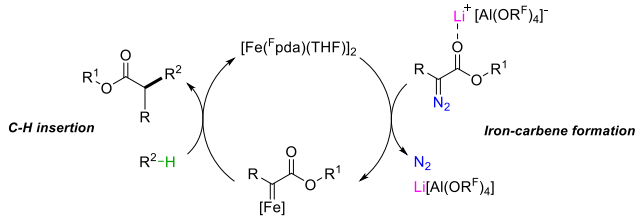


Scheme 1. a), b) Precedents in the literature on catalytic carbene transfer reactions. c) System used in the present work.

Subsequent reports allowed the functionalization of strong C-H bonds (>95 kcal·mol^{-1}) in both stoichiometric and catalytic fashion but applying harsh reaction conditions (Scheme 1a)[6] that are also compatible with decomposition of the diazo reagent, resulting in uncatalyzed C-H insertion.[7] Most importantly, these studies pinpoint to high energetic barriers for the iron mediated Csp^3-H insertion reactions, which have limited the scope to relatively weak C-H bonds. For instance, benzylic C-H bonds, allylic and those close to heteroatoms have been functionalized under milder reaction conditions in an

intermolecular and enantioselective manner using an engineered P450 enzyme (Scheme 1b),[8] and the intramolecular alkylation of diazo sulfonate substrates with an heme-like iron(III) phtalocyanine catalysts has been described.[9]

Overcoming these limitations, we have recently developed an iron-based system capable of delivering intramolecular functionalization of strong alkyl Csp^3-H bonds present in α-alkyl-α-diazo ester reagents under mild reaction conditions, upon pairing a very electrophilic iron compound $[Fe(^Fpda)(THF)]_2$ (1) (^{F}pda = N,N'-bis(pentafluorophenyl)-o-phenylenediamide) along with a Lewis acid salt $LiAl(OR^F)_4$ (OR^F = $(OC(CF_3)_3)$ (Scheme 1c).[10] Crucial aspects of this system are pre-activation of the carbene precursor via coordination of the Lewis acid to the carbonyl group, facilitating formation of the iron-carbene intermediate, and the highly electrophilic nature of the catalyst, which enables C-H insertion (Scheme 2).



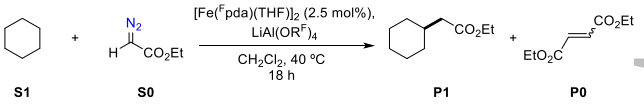
Scheme 2. Mechanism for the functionalization of diazo ester reagents using catalyst **1** and $LiAl(OR^F)_4$.

Building on this precedent, herein we report the intermolecular functionalization of aliphatic substrates via iron-carbene insertion. Upon slight modification of the original catalytic protocol, using stoichiometric amounts of Lewis acid and increasing the reaction temperature to 40 °C, we have enhanced the reactivity of our Fe/Li catalytic system being able now to react with the robust and commercially available ethyl diazoacetate (EDA) carbene precursor (Scheme 1c), which provides access to intermolecular alkylation of highly stable Csp^3-H bonds. Employing a series of alkanes, we tested the boundaries of our Fe/Li catalytic system in terms of activity, functionalizing C-H bonds with BDE values of 100 kcal·mol^{-1},[11] as well as in regards of selectivity, investigating the factors that govern site selectivity in substrates containing non-equivalent C-H bonds. In addition, we show that our Fe catalyst exhibits an outstanding activity in catalytic olefin cyclopropanation. External and internal aliphatic alkenes, recognized as challenging substrates for iron catalyzed carbene transfer reactions, undergo cyclopropanation in excellent yields under mild reaction conditions. Overall, we disclose our iron based system as a very powerful intermolecular carbene transfer agent to non-activated alkane and alkene moieties with potential applicability in organic synthesis.

Results and Discussion

We started our studies investigating the catalytic functionalization of cyclohexane (**S1**) because it has slightly smaller BDE values than linear alkanes, and because its simplicity facilitates the product analysis.[11] Capitalizing on our previous investigations, we probed alkylation of **S1** (1 equiv.) in dichloromethane using 2.5 mol% of **1**, 0.25 eq. of $LiAl(OR^F)_4$ and commercially available ethyl diazoacetate (1 equiv., EDA, **S0**) at 25 °C for 18 h, which led to exclusive formation of olefin **P0**, generated by a dimerization reaction. Slightly higher reaction temperatures (40 °C) gave the desired insertion product **P1** in small amounts, along with the olefin product **P0** as the major product (Table 1, entry 1). More significantly, when the lithium aluminate loading was increased to values of 0.5 to 1 equivalent, **P1** was formed in 27% yield (Table 1, entries 2-3). Final optimization was achieved using a small excess of **S0** (2 equiv.), which afforded a 61% yield of the alkylation product (Table 1, entry 4). Slow addition of EDA via syringe pump addition produced low yields, presumably because of catalyst deactivation at long reaction times. Mechanistically, the dimerization process is commonly accepted to occur via nucleophilic attack of EDA to the electrophilic metallocarbene fragment.[12] In addition, we previously demonstrated formation of a cationic adduct between diazo compounds and the lithium ion present in $LiAl(OR^F)_4$, which enhances the electrophilic nature of the carbene precursor.[10] Combining these two concepts, we rationalize that increasing the amount of lithium in the reaction media reduces the concentration of the more nucleophilic free EDA in solution, and hence it hampers the dimerization pathway.

Table 1. Optimization conditions for the functionalization of cyclohexane.



Entry	S1 (equiv.)	S0 (equiv.)	[Li] (equiv.)	Yield **P1** (%)[b]	Yield **P0** (%)[c]
1	1	1	0.25	3	67
2	1	1	0.5	26	19
3	1	1	1	27	15
4	1	2	1	61	42
5[d]	1	2	1	traces	traces

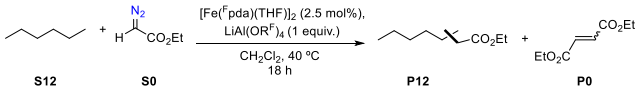
[a] Yields determined by GC, calibrated from commercially available **P1** and **P0**. [b] Yields based on cyclohexane. Recovering of S1 accounts for the balance of the reaction. [c] Yields based on ethyl diazoacetate. [d] Control experiment carried out in absence of $[Fe(^Fpda)(THF)]_2$.

Next, we explored the influence of the carbene fragment on the reaction outcome. Using methyl 2-phenyldiazoacetate as carbene precursor resulted in generation of the insertion product in a 26% yield along with a mixture of unidentified organic products,

more likely generated by decomposition of the diazo reagent due to its lower stability compared to EDA. Finally, a blank experiment showed that in absence of the metal catalyst, only traces amounts of **P1** and **P0** are formed.

Applying these optimized conditions to functionalization of the linear hexane produced a considerably lower yield of the alkylation product **P12** (Table 2, entry 1), favoring the dimerization compound. This is in agreement with the high BDE values inherent of saturated hydrocarbons,[11] which translates in kinetically retarded reactions. In line with this idea, increasing the concentration of **S12** in the reaction media (2.5 to 10 equiv.) resulted in formation of **P12** in 62% yield (Table 2, entries 2-4), where insertion occurs exclusively in secondary C-H bonds.

Table 2. Optimization conditions for the functionalization of hexane.



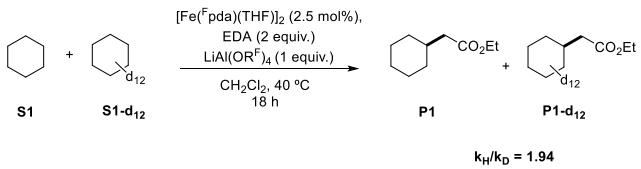
S12 S0 P12 P0

Entry	S12 (equiv.)	S0 (equiv.)	[Li] (equiv.)	Yield **P12** (%)	Yield **P0** (%)[c]
1	1	2	1	13[b]	53
2	2.5	1	1	46[c]	32
3	5	1	1	55[c]	18
4	10	1	1	62[c]	21

[a] Yields determined by NMR. [b] Yields based on *n*-hexane. [c] Yields based on ethyl diazoacetate.

These results are notable for two reasons; in first place they constitute the first examples of intermolecular iron catalyzed carbene transfer reactions to strong Csp^3-H bonds under mild conditions. In addition, no large excess of substrate is needed, highlighting a synthetic potential.[6]

Interestingly, further evidence of the formation of an iron-carbene intermediate necessary for the C-H activation process was deduced by the KIE value of 1.94, determined by product analysis of the competitive reaction between equimolar amounts of **S1** and **S1-d$_{12}$** (Scheme 3). Thus, this value is significantly different from photochemically generated free radical carbene specie (KIE = 1).[13] Moreover, supporting a concerted mechanism, the observed KIE is similar to the one found for concerted alkylation reaction iron-catalyzed[10] as well as for rhodium-carbene catalytic systems.[13]



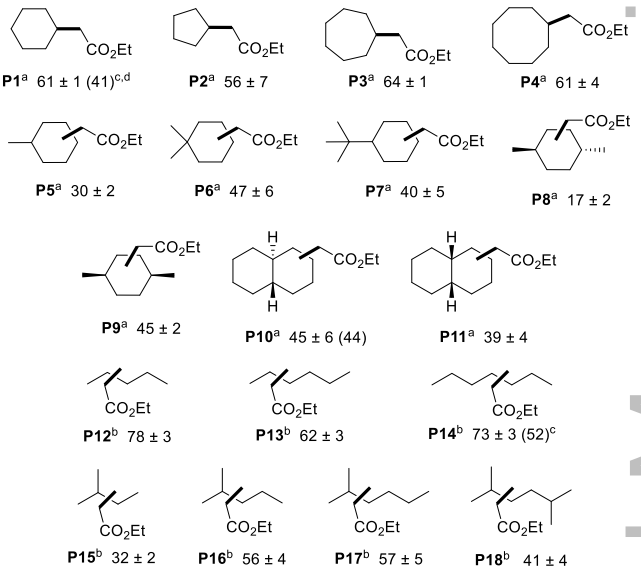
S1 S1-d$_{12}$ P1 P1-d$_{12}$

Scheme 3. Kinetic isotope effect study. [a] Reaction conditions: [Fe(^{F}pda)(THF)]$_2$ (2.5 mol%), cyclohexane (0.5 equiv.), cyclohexane-d^{12} (0.5 equiv.), ethyl diazoacetate (2 equiv.), LiAl(OR^F)$_4$ (1 equiv.), DCM (0.08M), 40 °C, 18h. k_H/k_D ratio determined by GC-MS.

Having established optimum reaction conditions for the alkylation of cyclic and linear alkane substrates, and after gaining confidence that the reactions proceed via the intermediacy of iron carbene species, we sought to investigate the substrate scope and selectivity properties of the reaction.

A variety of substrates containing non-activated aliphatic Csp^3-H bonds were investigated and product yields are collected in Table 3, while different aspects of the site selectivity observed in these reactions are displayed in Tables 4-7.

Table 3. Substrate scope of different alkenes.



[a] Reaction conditions: [Fe(^{F}pda)(THF)]$_2$ (2.5 mol%), alkane (1 equiv.), ethyl diazoacetate (2 equiv.), LiAl(OR^F)$_4$ (1 equiv.), DCM (0.08 M), 40 °C, 18 h. Average NMR yields of at least three runs based on the alkane. Isolated yields in brackets. [b] Reaction conditions: [Fe(^{F}pda)(THF)]$_2$ (2.5 mol%), alkane (10 equiv.), ethyl diazoacetate (1 equiv.), LiAl(OR^F)$_4$ (1 equiv.), DCM (0.08 M), 40 °C, 18 h. Average NMR yields of at least three runs based on the ethyl diazoacetate. [c] Isolated yields are relatively smaller due to the volatility of the products. [d] Catalysis performed in a 1 mmol scale.

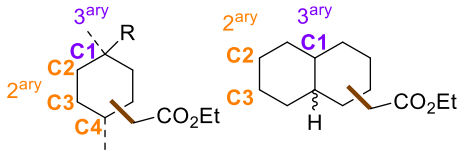
In terms of cycloalkanes, this catalytic system proved to be compatible with different ring size substrates, substituted cyclohexanes, and fused systems, generating the insertion products **P2**-**P11** in modest to good yields (17-64%). The simplest cyclic alkanes (C_5 (**S1**) to C_8 (**S4**)) undergo functionalization in good yields (56-64%). In addition, carbene transfer to alkyl substituted cyclohexanes (**S5**-**S9**) proceeds with smaller yields. In all cases, reactions occur at secondary and tertiary C-H bonds while primary sites remained unreactive. The comparatively reduced yields with respect to the simplest cycloalkanes can be

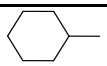
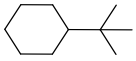
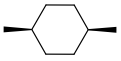
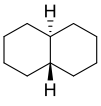
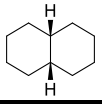
attributed to steric factors overriding electronic activating effects; despite the presence of electron-releasing alkyl groups should induce C-H activation by inductive effects, the most reactive positions (C_α and C_β) are hindered for reaction, being this situation most significant in the case of *trans*-1,4-dimethylcyclohexane **S8**, which is functionalized in a modest 17% yield. However, for the series of cyclohexanes where alkyl groups are installed at a single carbon (**S5-S7**), yields become larger as the inductive effect imparted by the substituents increases, as in the case of **S6** and **S7** (47 and 40% yield, respectively) compared to **S5** (30% yield).

Moving into linear substrates, alkanes of different lengths and branched were alkylated in comparable yields (32-78%) to the previous cyclic reagents. Again, steric hindrance imparted by substitution impacted negatively in yields when compared with the linear, unsubstituted alkanes. For instance, *n*-pentane, *n*-hexane and *n*-heptane (**S12-S14**) undergo alkylation in 62-78% yields, while their branched counterparts (**S15-S18**) are functionalized in 32-57% yield. Levering our Fe/Li catalytic system, we proved its applicability in synthesis by isolation of the three model reagents **P1**, **P10** and **P14** as pure products in moderate yields (41-52%) despite their high volatility.

Contrasting to the facile alkylation of non-activated C-H bonds, our system failed to functionalize deactivated C-H bonds present in electron-poor substrates as chlorocyclohexane, in accordance to the insertion reaction proceeding through an electrophilic iron-carbene intermediate.

Table 4. Regioselectivity of cyclic substrates.



Entry		Substrate	C1/C2/C3/C4[a]	$3^{ary}/2^{ary}$[b]
1	**S5**		21/20/42/17	79/21
2	**S6**		-/8/62/30	-
3	**S7**		-/1/73/26	-
4	**S8**		n.d.[c]	83/17
5	**S9**		n.d.[c]	96/4
6	**S10**		1/34/65	7/93
7	**S11**		30/27/43	68/32

[a] Ratio determined by GC of the reaction crude. [b] Values normalized by the number of C-H bonds. [c] Non-determined.

Analysis of the site selectivity observed in the reactions deserve special consideration. Results collected in Table 4 detail the site selectivity observed in the functionalization of the series of cyclic substrates **S5-S11**. As previously discussed, products resulting from primary C-H bond functionalization are not observed, and only products resulting from reaction at secondary and tertiary C-H bonds are observed. In addition, the normalized ratio for the activation of 3^{ary} over 2^{ary} bonds displays a preference for the formers and weaker C-H bonds. This selectivity pattern supports the involvement of the electrophilic iron-carbene as the active species of the process, which reacts preferentially with the more nucleophilic 3^{ary} C-H bonds. Exceptions to this trend are *tert*-butylcyclohexane (**S7**) and *trans*-decalin (**S10**); in both cases products resulting from functionalization of the tertiary C-H bonds are either not formed or detected in trace amount. This selectivity can be rationalized by considering that in both cases, these bonds are sterically shielded and thus steric factors prevail over the intrinsic electronic activation of tertiary C-H bonds.

In addition, in cyclohexanes where multiple, non-equivalent methylenic sites are available, insertion in C3 occurs preferentially in both mono and fused systems. Preferential functionalization of this site can be understood as the result of a balance between steric factors (favoring functionalization at the most distal places from the alkyl substituents), and electronics (inductive factors favoring functionalization at the closest positions). Beyond C3, the inductive effect is largely diminished and in consequence C4 is less activated. On the contrary, functionalization of C2 is disfavored under strict steric control. This situation is more noticeable going from substrate **S5** to **S7,** in which the increasing electron releasing nature and bulkiness of the substituent turns into higher yields for the functionalization at C3, whereas reaction at C2 is disfavored.

Monosubstituted cyclohexanes are interesting substrates because the alkyl substituent blocks the chair conformation, and C-H functionalization can take place at equatorial and axial C-H bonds. An analysis of the axial vs equatorial selectivity in the functionalization **S5** and **S7** is displayed in Table 5. Remarkably, equatorial C-H bonds are systematically preferentially functionalized over axial ones (Table 5) and the selectivity is systematically larger when functionalization takes place at C3 than at C4. In addition, equatorial selectivities are larger for **S7**, containing the bulkiest substituent. The combined selectivity parameters make functionalization of **S7** remarkable because the reaction shows a largely preferential site selectivity towards the equatorial C-H bond at C3.

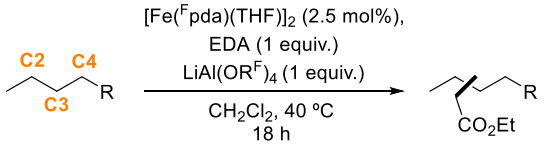
Table 5. Stereoselectivity of alkyl-substituted cyclohexanes.

Entry	Substrate	C3 (eq./ax.)	C4 (eq./ax.)
1	**S5**	(**4.25**/1)	(**3.25**/1)
2	**S7**	(**7**/1)	(**5.5**/1)

Collectively, selectivity patterns towards equatorial C-H bonds are reminiscent to other Csp^3-H functionalization reactions, proceeding through isoelectronic and electrophilic iron-oxo species, and initiated via a hydrogen atom transfer process.[14] In these cases, preferential HAT at equatorial C-H bonds is commonly understood as the result of a strain release that occurs after HAT and planarization of the incipient radical and because equatorial C-H bonds are sterically more accessible. The similar selectivity patterns observed in the current reactions may suggest that the steric discrimination is also dominating the selectivity in the current carbene transfer reaction. Of note, steric discrimination has also been highlighted as the major contributor in determining site selectivity towards C3 equatorial C-H bonds in carbene transfer reactions to monosubstituted cyclohexanes with bulky rhodium catalysts.[15]

For linear alkanes, the catalyst system preferentially functionalizes less congested methylenic positions following C2>C3>C4 order (Table 6), akin to catalytic rhodium-mediated insertions reported in the literature (Table 6).[13, 16]

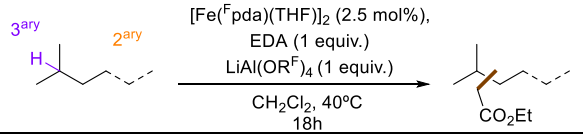
Table 6. Regioselectivity for linear alkanes.



Entry	Substrate	C2/C3/C4[a]	C2/C3/C4[b]
1	**S12**	79/21	69/31
2	**S13**	69/31	68/32
3	**S14**	57/30/13	61/26/13

[a] Ratio determined by GC of the reaction crude. [b] Average ratio of different rhodium complexes.[13,16]

Table 7. Regioselectivity for methyl-substituted *n*-alkanes.



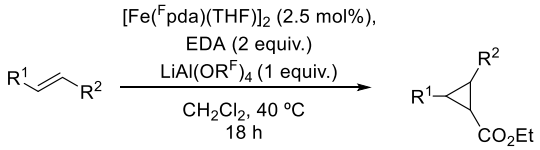
Entry	Substrate	$3^{ary}/2^{ary}$ [a]
1	**S15**	86:14
2	**S16**	85:15
3	**S17**	88:12
4	**S18**	>99:1

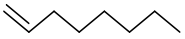
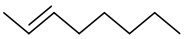
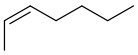
[a] Values normalized by the number of C-H bonds.

Similar to cycloalkanes, substituted linear hydrocarbons undergo preferential tertiary C-H alkylation, yielding a 9:1 ratio 3^{ary}:2^{ary} (Table 7, entries 1-3). Of notice, substrate **S18** undergoes only functionalization on tertiary C-H bond, due to the difficult access to methylenic sites for steric reasons. Most importantly, the observed regioselectivities contrast with alkylation reactions proceeding via free carbenes,[13] in which primary sites are also functionalized, pointing to the participation of iron-carbene active species in these transformations.

Encouraged by the versatility of our Fe/Li catalytic system, we extended our studies towards cyclopropanation reactions. The introduction of a cyclopropane ring in aromatic derivatives has been extensively studied, with excellent results on yield, stereo and enantioselectivities, using either porphyrinic systems,[17] artificial iron enzymes[18] and non-heme complexes.[19] This research has been also extended to the functionalization of vinyl and alkynyl substrates[20] as well as boronate-olefins.[21] We instead focused our attention in the challenging carbene transfer to non-activated terminal and internal aliphatic alkenes; in either *cis* or *trans* configurations, corresponding cyclopropanes were achieved in excellent yields (≥85%), although with low diastereoselectivity (Table 8).

Table 8. Cyclopropanation reaction of aliphatic alkenes. [a]



Entry	Substrate	Yield (%)	Diastereoselectivity (cis:trans)[b]
1	**S19** 	97±4 (85)[c]	39:61
2	**S20** 	88±6	n.d.[d]
3	**S21** 	88±5	53:47
4	**S22** 	89±3	63:28[e]

[a] Reaction conditions: $[Fe(^{F}pda)(THF)]_2$ (2.5 mol%), alkene (1 equiv.), ethyl diazoacetate (2 equiv.), $LiAl(OR^{F})_4$ (1 equiv.), DCM (0.08 M), 40 °C, 18 h. Average NMR yields of at least three runs based on the alkene. Isolated yields in brackets. [b] Ratio and stereochemistry determined by ^{1}H-NMR by comparison of previously reported products. [c] Isolated yield is relatively smaller due to the volatility of the product. [d] A ratio of 45:55 can be detected by GC, although no assignation of cis:trans isomers could be possible by ^{1}H-NMR. [e] Ratio corresponding to exo:endo isomers.

It is important to notice that the reactions proceed under mild conditions, using the alkene substrate as a limiting reagent. In addition, despite the availability of weak allylic C-H bonds, our Fe/Li system shows high chemoselectivity delivering cyclopropanation reaction over C-H insertions, especially in **S22** with the weakest allylic C-H bonds. These selectivity values are comparable to those obtained using EDA as carbene source, and rhodium or copper catalysts.[22] More interestingly, our system exhibits greater reactivity compared to previous iron-based cyclopropanation catalysis of aliphatic olefins, where high reaction temperatures (80 °C) or excess of alkene were required, or more significantly showing no reaction for internal alkenes; [23] this is only exceeded by engineered iron enzymes.[24]

Conclusion

In conclusion, we have shown that the pair formed by $[Fe(^{F}pda)(THF)]_2$ and $LiAl(OR^{F})_4$ activates a readily available azo compound (EDA) to catalytically perform the intermolecular alkylation of strong Csp^3-H bonds present in saturated lineal and cyclic hydrocarbons via metallocarbene intermediates under mild reaction conditions. Key for the success in these reactions is the use of the Lewis acid $LiAl(OR^{F})_4$ in stoichiometric amounts, which upon formation of a cationic complex between EDA and lithium reduces the nucleophilicity of the non-reacted carbene precursor, and hence suppresses the otherwise favorable dimerization process.

Regioselectivity of the reaction is controlled by an interplay of electronic and steric factors; in general, 3^{ary} bonds are functionalized preferentially over 2^{ary} ones highlighting C-H bond dissociation energy as a dominant factor, although selective methylene functionalization takes place in substrates where they are in competition with sterically hindered methyne sites. Among the available 2^{ary} sites, iron targets preferentially those less sterically congested, and sterics can also explain preferential functionalization of equatorial C-H bonds in substituted cyclohexanes. These selectivity trends, along with KIE study, strongly suggest reactions proceed via electrophilic iron-carbene intermediates that insert into the strong aliphatic C-H bonds of alkanes.

In addition, the Fe/Li system has also proved to be capable of promoting cyclopropanation reactions for non-activated alkenes with activity levels similar to copper and rhodium and overcoming the activity of up to date reported iron systems.

We note that the powerful reactivity and remarkable selectivity parameters exhibited by the current system are largely determined by the electronic and steric properties of this iron catalyst. We are aware that recent work has provided a multiparametric analysis of the factors that govern C-H site selectivity in carbene transfer to alkanes by copper, rhodium and silver catalysts, from where metal dependent trends have been derived.[25] Future work will be directed to place iron based catalysts in this frame. Furthermore, we envision that further elaboration of this catalyst will provide a novel generation with improved activity and selectivity and will open the path towards enantioselective transformations.

Experimental Section

General small scale catalytic procedure: To a solution of the $[Fe(^{F}PDA)(THF)]_2$ (2.5 mol%) in dichloromethane (1 mL) was added ethyl diazoacetate (0.16 mmol for cycloalkanes or alkenes; 0.08 mmol for *n*-alkanes) followed by addition of the alkane (0.08 mmol for cycloalkanes or alkenes; 0.8 mmol for *n*-alkanes) and $LiAl(OR^{F})_4$ [OR^{F}= $(OC(CF_3)_3]$ (0.08 mmol). The reaction was stirred at 40 °C for 18 h. After that time, the reaction mixture was filtered through a silica plug to remove paramagnetic impurities and rinsed with CH_2Cl_2 and Et_2O. 0.04 mmols of trimethoxybenzene were added as internal standard. All samples were analyzed by GC, GC-MS and ^{1}H-NMR to determine isomer ratios and yields.

General procedure for product isolation: To a solution of the $[Fe(^{F}pda)(THF)]_2$ (2.5 mol%) in dichloromethane (0.08M) was added ethyl diazoacetate (2 equiv. for cycloalkanes or alkene; 1 equiv. for *n*-alkanes) followed by addition of the alkane (1 equiv. for cycloalkanes or alkene; 10 equiv. for *n*-alkanes) and $LiAl(OR^{F})_4$ [OR^{F}= $(OC(CF_3)_3]$ (1 equiv.). The reaction was stirred at 40 °C for 18 h. The

desired product was isolated by flash chromatography (97:3 *n*-pentane:diethyl ether).

Kinetic isotopic effect: Following the general methodology described for small scale catalysis, to a solution of the $[Fe(^{F}pda)(THF)]_2$ (2.5 mol%) in dichloromethane (1 mL) was added ethyl diazoacetate (0.16 mmol) followed by the addition of a 1:1 mixture of cyclohexane and cyclohexane-d_{12} (0.04 mmol each). $LiAl(OR^F)_4$ [OR^F= $(OC(CF_3)_3$] (0.08mmol) was then introduced and the reaction was stirred at 40 °C for 1 hour. After that time, the resulting solution was filtered through a silica plug to remove paramagnetic impurities and the sample was analyzed by GC and GC-MS. 16% of product yield was determined by GC. The ratio of **P1** and **P1-d$_{12}$** gave a KIE value of 1.94.

Axial/equatorial functionalization determination: Axial/equatorial isomers of reaction crudes containing **P5-C3**, **P5-C4**, **P7-C3** and **P7-C4** were determined by comparison of their NMR data with those registered of independently synthetized products, and based on the different chemical shift of axial/equatorial protons. Thus, the presence of an axial proton correlates with an equatorial C-H bond functionalization, while the presence of an equatorial proton corresponds to an axial C-H bond functionalization. In addition, comparison of GC traces of reaction crudes and those of isolated products provided a more accurate assignation of each isomer and its ratio. **P5-C2** and **P7-C2** could be synthesized, but axial/equatorial isomers could not be assigned.

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FULL PAPER

Iron catalyzed intermolecular functionalization of non-activated aliphatic C-H bonds *via* carbene transfer

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