Communication

#-C–H Functionalization of #-Bonds Using Iron Complexes: Catalytic Hydroxyalkylation of Alkynes and Alkenes

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α-C–H Functionalization of π-Bonds Using Iron Complexes: Catalytic Hydroxyalkylation of Alkynes and Alkenes

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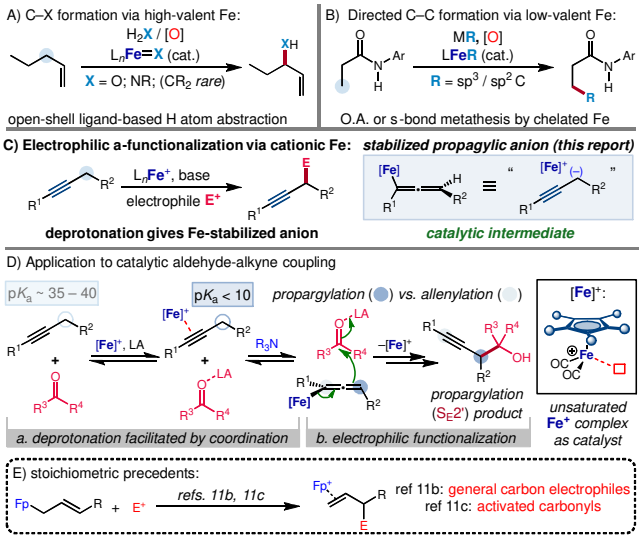
Supporting Information Placeholder

ABSTRACT: The discovery of catalytic systems based on earth-abundant transition metals for the functionalization of C–H bonds enables streamlined and sustainable solutions to problems in synthetic organic chemistry. In this Communication, we disclose an iron-based catalytic system for the functionalization of propargylic and allylic C–H bonds. Inexpensive and readily-available cyclopentadienyliron(II) dicarbonyl complexes were employed as catalysts for a novel deprotonative activation mode for C–H functionalization, an approach that allows for the direct union of unsaturated building blocks with aryl aldehydes and other carbonyl electrophiles to deliver a range of unsaturated alcohol coupling products under operationally simple and functional group tolerant reaction conditions.

The discovery of new strategies and methods for the functionalization of readily available hydrocarbon resources using abundant reagents and sustainable catalysts is an important goal in contemporary synthetic organic chemistry.[1] The use of complexes based on iron, the most earth-abundant transition metal, is a particularly attractive area of investigation which has seen intensive development in recent years.[2] In one approach, inspired by a variety of enzyme active sites found in nature, high-valent iron species are used to perform the catalytic *O*- and *N*-functionalization of C–H bonds.[3] A wide variety of electron-rich C–H bonds are susceptible to this oxidative process. However, this approach is rarely used for the formation of C–C bonds (Scheme 1A). In a more recently developed catalytic approach, metalation facilitated by chelating directing groups or by 1,5-hydrogen-atom transfer has enabled the iron-catalyzed oxidative coupling of C-H bonds with main-group organometallic reagents.[4] Although this approach allows for the installation of more general carbon-based fragments, a directing group effect appears to be required for good reactivity (Scheme 1B).[4c] These complementary strategies have given rise to an impressive array of iron-catalyzed transformations of C–H bonds. Nevertheless, the formation of C–C bonds via catalytic C–H functionalization in the absence of a directing group continues to represent a synthetic challenge, not only for iron chemistry but for transition-metal catalysis in general.

Viewed broadly, strategies for the functionalization of unreactive C–H bonds typically involve the removal of a hydrogen atom (H•) or hydride anion (H^-) equivalent. As an alternative, we considered the possibility of C–H bond cleavage through the removal of a proton (H^+), facilitated by coordination of an electron-deficient metal fragment to a neighboring π-bond. The resultant organometallic complex could be conceptualized as a metal-stabilized propargylic anion equivalent, capable of undergoing subsequent reactions with electrophiles to afford the net α-functionalization product (Scheme 1C). [5]

Scheme 1. Approaches for Fe-catalyzed C–H functionalization

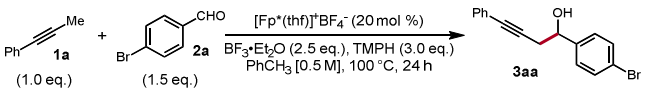


Considering their wide availability from petrochemical feedstocks, simple alkenes and alkynes are attractive starting materials for C–H functionalization processes. Although several well-developed reactions for the introduction of functional groups at the allylic position are now available,[6] the intermolecular formation of C–C bonds still represents a challenge. On the other hand, the corresponding functionalization of alkynes at the propargylic position without concomitant transformation of the C–C triple bond remains mostly unaddressed, with only a handful of propargylic C–H functionalization reactions having been reported.[7,8] A few intramolecular amination reactions by nitrenoid insertion are known.[7c,7d] Intermolecular processes generally require the use of directing or activating groups on the alkyne or its partner,[8a,8b] or rely on radical chemistry whose regioselectivity would likely suffer in contexts where comparably weak C–H bonds are present.[7b]

We hypothesized that a mode of C–H functionalization in which the hydrogen departs as a proton, rather than hydride or hydrogen atom, would be particularly suitable for the propargylic functionalization of internal alkynes, given the higher intrinsic acidity of a propargylic C–H bond (pK_a ~ 35 to 40) compared to an allylic one (pK_a ~ 43).[9] As part of our research group's interest in developing methods to forge C–C bonds from readily available building blocks, we targeted the coupling of internal alkynes and aldehydes to demonstrate the synthetic utility and prospects of this new approach. Although alkynes and aldehydes have served as coupling partners in other transition-metal catalyzed coupling reactions, the proposed coupling at the propargylic position, without isomerization or reduction of the triple bond, would be a here-

tofore unreported outcome.[10] To implement this strategy, we considered the use of inexpensive and readily-prepared cyclopentadienyliron(II) dicarbonyl complexes and their substituted derivatives ($Cp^RFe(CO)_2 = Fp^R$) as potential catalysts .[11] Seminal work by Rosenblum and coworkers on $Fp(\eta^2\text{-alkene})^+$ complexes suggests that coordination leads to a dramatic increase in acidity of the allylic position (from pK_a ~43 to <10, Scheme 1D). Moreover, the neutral σ-allyliron complexes formed upon deprotonation react with a range of carbon and heteroatom electrophiles to furnish the product of net α-functionalization of the olefin (Scheme 1E).[11b,11c] Despite the remarkable reactivity, no catalytic applications of this chemistry have been reported. On the other hand, aside from a report detailing the deprotonation of a $Fp(\eta^2\text{-alkyne})^+$ complex to form an σ-allenyliron complex[11f] and a report of the reaction of the parent σ-allenyl-Fp with a cationic troponeiron tricarbonyl complex,[11g] the chemistry of alkyne-derived Fp^R complexes is otherwise underexplored. Nevertheless, we felt that reported stoichiometric reactivity patterns offered a tantalizing starting point for the development of catalytic systems for the functionalization of internal alkynes.

Table 1. Optimization of reaction conditions



entry	change from standard condition	yield (%)[a]
1	*none*	89 (81)[b]
2	2,4,6-collidine *instead of* TMPH	64
3	DBU *or* Barton's base *instead of* TMPH	0
4	Proton Sponge, PMP, *or* iPr_2NEt *instead of* TMPH	0
5	$^iPr_2NH$ *instead of* TMPH	0
6	pyridine *instead of* TMPH	0
7	$Sc(OTf)_3$, $Al(OTf)_3$ *instead of* $BF_3{\cdot}Et_2O$	0
8[c]	Fe^{2+}, Zn^{2+}, *or* Ag^+ *instead of* $Fp^*(thf)BF_4$	0
9	$Fp(thf)BF_4$ *instead of* $Fp^*(thf)BF_4$	0
10[d]	$Fp^R(thf)BF_4$ *instead of* $Fp^*(thf)BF_4$	24
11	1.5 eq. $BF_3{\cdot}Et_2O$, 2.0 eq. TMPH	61
12	10 mol % $Fp^*(thf)BF_4$ *instead of* 20 mol %	70
13	80 °C *instead of* 100 °C	74
14	$PhCF_3$ *instead of* $PhCH_3$ as solvent	82
15	$Fp^*(thf)BF_4$, $BF_3{\cdot}Et_2O$ or TMPH *omitted*	0

[a]Yields were determined by ^1H NMR using 1,1,2,2-tetrachloroethane as the internal standard. [b]Isolated yield (0.3 mmol scale). [c]$Fe(BF_4)_2{\cdot}6H_2O$, $Zn(NTf_2)_2$, or $AgBF_4$ (20 mol %). [d] Fp^R = (1,3-*t*-$Bu_2C_5H_3$)$Fe(CO)_2$. TMPH = 2,2,6,6-tetramethylpiperidine, PMP = 1,2,2,6,6-pentamethylpiperidine, Barton base = 2-*t*-butyl-1,1,3,3-tetramethylguanidine, Proton Sponge = 1,8-bis(dimethylamino)-naphthalene.

At the outset, we were aware that in addition to identification of a suitable cyclopentadienyl ligand, we also needed to select a compatible Lewis acid for activation of the aldehyde and base for the deprotonation of the alkyne. In particular, a hindered amine is needed to prevent irreversible deactivation of both the iron catalyst and Lewis acidic activator. Simultaneously, it must retain the ability to abstract the α-proton from the $Fp^R(\eta^2\text{-alkyne})^+$ complex. Moreover, competitive intramolecular cyclization of the homopropargylic alcohol product may present an additional complication,[12] as Fp^+ is known to activate triple bonds for nucleophilic attack.[11i] In this Communication, we report the successful development of the desired catalytic coupling process, in spite of these obstacles. A judicious choice of catalyst, reagent, and reaction conditions eventually led to the development of an operationally simple catalytic protocol for the coupling of aldehydes and internal alkynes to deliver a wide range of homopropargylic alcohol products.[13,14]

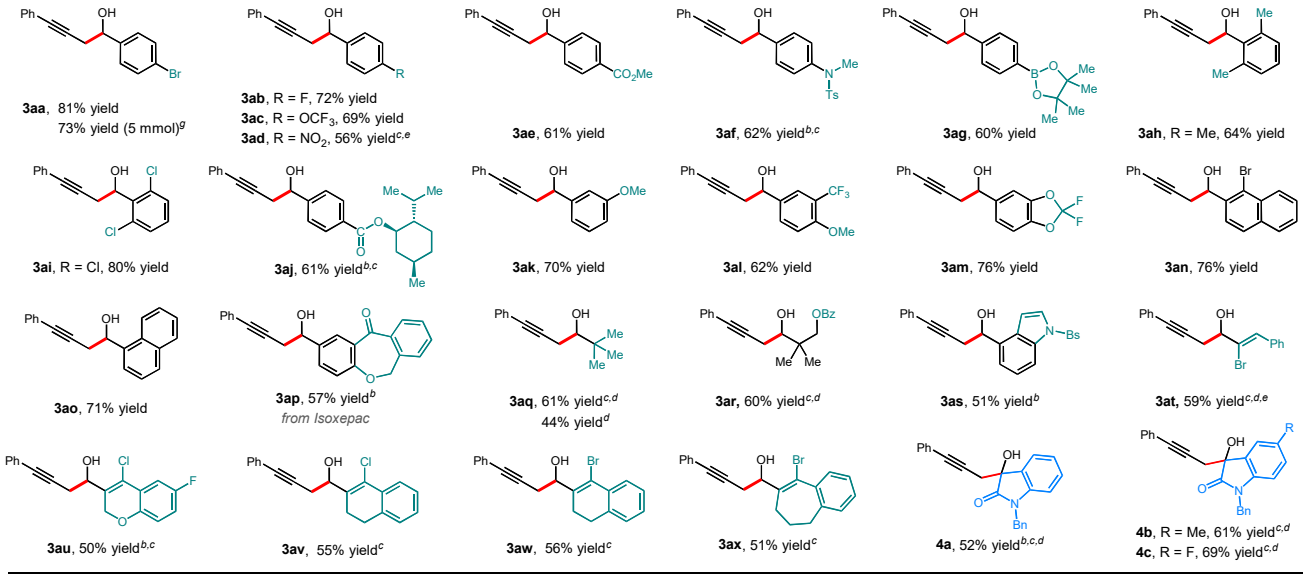
We began our initial search for a catalytic coupling procedure by examining the behavior of 1-phenyl-1-propyne (**1a**) and 4-bromobenzaldehyde (**2a**) as model alkyne and aldehyde coupling partners, respectively (Table 1). We also selected boron trifluoride etherate as a convenient and readily available Lewis acid for the activation of the carbonyl moiety. Bearing in mind the interplay between the amine base and the Lewis acidic Fe catalyst, we prioritized the examination of combinations of hindered base and hindered Fe complexes for desired reactivity. Among an extensive series of combinations examined, the combination of 2,2,6,6-tetramethylpiperidine (TMPH) as the amine base and $[Fp^*(thf)]^+BF_4^-$ ($Fp^* = (C_5Me_5)Fe(CO)_2^+$) as the precatalyst for cationic Fe was the most successful combination (Table 1, entry 1). While the use of 2,4,6-collidine in place of TMPH (entry 2) also delivered a significant amount of product under catalytic conditions, most other bases yielded no desired product (entries 3-6). Application of another hindered Fp^R-based catalyst (Fp^R = (1,3-*t*-$Bu_2C_5H_3$)$Fe(CO)_2$) was partially successful (entry 10), but replacement with the unsubstituted cationic Fp complex (entry 9), another cationic transition metal catalyst (entry 8), or use of another Lewis acid activator was ineffective (entry 7). Control experiments showed the necessity of Fe complex, Lewis acid, and base (entry 15).

These conditions were used to examine the generality of the catalyst system with respect to the two coupling partners (Table 2). A collection of aryl aldehydes (Table 2, top), ranging from mildly electron-rich (**3af**, **3ao**) to highly electron-poor (**3ad**, **3ae**) could be used as coupling partners. 2,6-Substitution (**3ah**, **3ai**) was tolerated, as was the presence of a diaryl ketone (**3ap**), esters (**3ae**, **3aj**), a difluoroacetal (**3am**), a pinacol ester (**3ag**), and a sulfonamide (**3af**). Non-enolizable alkyl aldehydes (**3aq**, **3ar**), an electron-rich heteroaryl aldehyde (**3as**), as well as simple (**3at**) and cyclic (**3au**-**3ax**) α,β-unsaturated aldehydes could also be used as the aldehyde coupling partner. During the course of examination of the aldehyde scope, it was found that for less reactive starting materials, the addition of $Zn(NTf_2)_2$ (10 mol %) led to improved yields (e.g., **3aq**). As a further example of the generality of this process, we examined *N*-benzylated isatins as coupling partners. In these cases, the ketonic carbonyl group of the isatins functioned as the electrophile to deliver the tertiary homopropargylic alcohol in moderate to good yields (**4aa**-**4ac**).

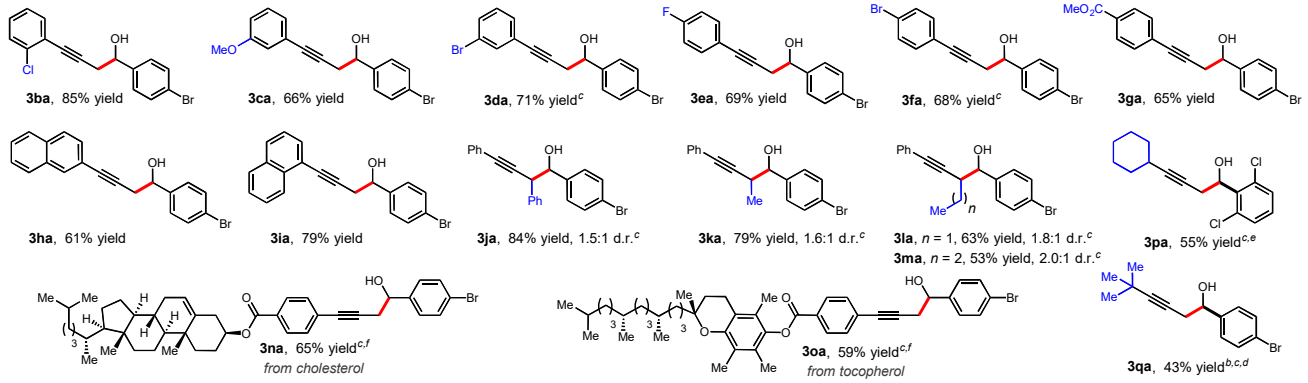
The scope of the coupling with respect to alkynes was then evaluated (Table 2, bottom). A range of mildly electron-rich (**3ha**) to moderately electron-poor (**3ga**) aryl methyl acetylenes could be coupled under these conditions, as could higher aryl alkyl acetylenes (**3ja**-**3ma**), albeit with little control over the diastereoselectivity of the coupling (1.6 to 2.0:1 d.r.). Complex scaffolds derived from cholesterol and tocopherol could likewise be used (**3na**, **3oa**). With a higher catalyst loading, certain hindered dialkyl acetylenes (**3pa**) could also be successfully employed.[15,16]

Table 2. Reaction scope for homopropargylic alcohol [a]

The scope of electrophile



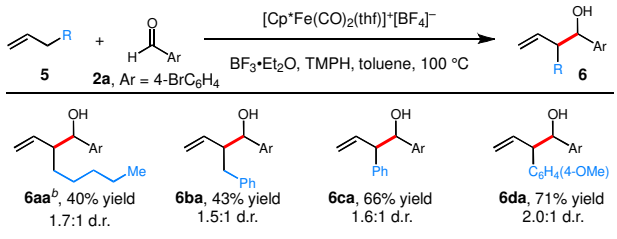
The scope of alkyne



[a]Condition: **1a** (0.3 mmol), **2** (1.5 eq.), Fp*(thf)BF_4 (20 mol %), BF_3·Et_2O (2.5 eq.), TMPH (3.0 eq.), toluene (0.6 mL), 100 °C. [b]**1a** (2.0 eq.), **2** (0.3 mmol), [c]$Zn(NTf_2)_2$ (10 mol %) was added. [d]80 °C, DCE. [e]30 mol % Fp*(thf)BF_4. [f]0.1 mmol scale. [g]15 mol % Fp*(thf)BF_4, 5 mol% $Zn(NTf_2)_2$.

After exploring the scope of the alkyne component, we wondered whether our optimized conditions would be applicable to olefin substrates. Applying our optimized conditions to terminal olefins, we were pleased to find that our conditions resulted in allylic functionalization of these substrates to furnish the homoallylic alcohol products (Table 3). Notably, even unactivated olefins (**6aa**, **6ba**) delivered the coupling product, though substrates with additional electronic activation (**6ca**, **6da**) provided higher yields of coupling product. These examples represent rare instances of the catalytic allylic C–H functionalization of olefins with carbonyl derivatives reported to date.

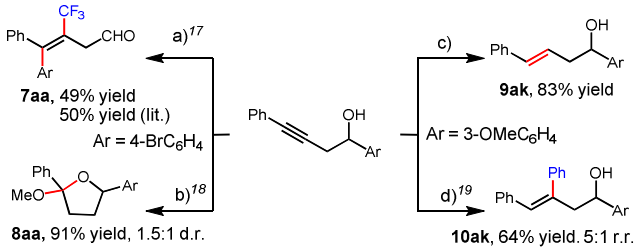
Table 3. Scope of alkenes for homoallylic alcohol synthesis[a]



[a]Condition: **5** (2.0 eq.), **2a** (0.3 mmol), Fp*(thf)BF_4 (20 mol %), BF_3·Et_2O (2.0 eq.), TMPH (3.0 eq.), toluene (0.6 mL), 100 °C. [b]$Zn(NTf_2)_2$ (10 mol %) was added.

To showcase the utility of this transformation, two of the products (**3aa**, **3ak**) were derivatized using literature methods to produce several elaborated structures (Scheme 3), including a tetrasubstituted trifluoromethyl alkene (**7aa**), a tetrahydrofuran (**8aa**), and two stereodefined alkenyl alcohols (**9ak**, **10ak**).

Scheme 3. Divergent transformations of products

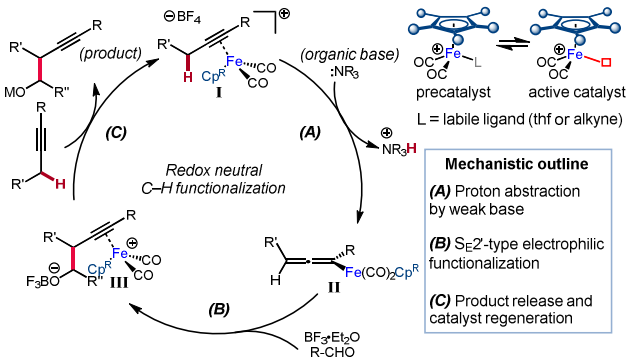


Conditions: a) CuI (10 mol %), Togni's reagent II (2.0 equiv), $CHCl_3$, 30 °C; b) Ph_3PAuBF_4 (5 mol %), TsOH (10 mol %), MeOH, rt; c) $LiAlH_4$, THF, reflux; d) $Ni(acac)_2$•xH_2O (10 mol %), PPh_3 (10 mol %), $PhB(OH)_2$ (2.0 equiv), Cs_2CO_3 (20 mol %), dioxane:EtOH = 4:1, 90 °C

At present, Scheme 4 represents a working model of the catalytic cycle of our coupling reaction. The cycle begins with a cationic alkyne-iron π-complex of type **I** (Cp^R = substituted cyclopentadienyl). The amine base would then abstract the propargylic proton to give a neutral allenyliron σ-complex of type **II**. Subsequently, the electrophilic func-

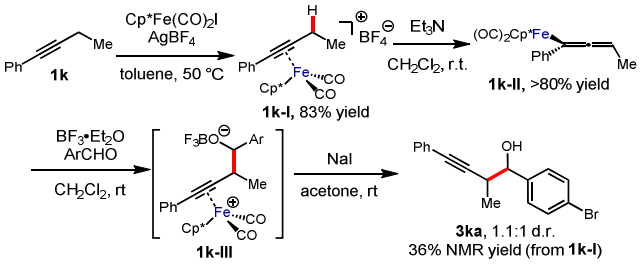
tionalization of **II** would give a cationic alkyne-iron complex of type **III**, which would then undergo ligand exchange with the starting alkyne to liberate the coupling product and close the catalytic cycle.

Scheme 4. Proposed catalytic cycle



To provide some evidence of this hypothesized catalytic cycle, we investigated each of the elementary steps therein (Scheme 5). We began our investigation by exploring the stoichiometric reactivity of the Fp*-alkyne complex **1k-I** ($[Cp^*Fe(CO)_2(alkyne)]^+[BF_4]^-$), which was prepared in high yield by heating a toluene suspension of $Cp^*Fe(CO)_2I$ and $AgBF_4$ with 1-phenyl-1-butyne (3.0 equiv) at 50 °C. Next, Fp*-alkyne complex **1k-I** was treated with Et_3N to give the σ-allenyliron complex **1k-II** in >80% yield. Finally, **1k-II** was reacted with aldehyde **2a** in the presence of BF_3·Et_2O to deliver the organic product **3ka** with an overall NMR yield of 36%. Notably, each of the proposed catalytic intermediates could be identified spectroscopically (Scheme 5 and SI).

Scheme 5. Stoichiometric mechanistic experiments.



In summary, we have developed an iron-catalyzed functionalization of propargylic and allylic C–H bonds to deliver a range of unsaturated alcohol coupling products. These transformations represent initial explorations of a novel strategy for propargylic and allylic C–H functionalization. Investigations into new synthetic applications and efforts to improve the robustness, rate, and stereoselectivity of the catalyst system are ongoing in our laboratories.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic data for the substrates and products (PDF), and crystallographic data (CIF) for **3aa** (CCDC 1961289), **4b** (CCDC 1961290). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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(16) In all cases, examination of the crude product by ^{1}H NMR and TLC or LC-MS showed only the formation of the homopropargylic alcohol product (S_E2'); the allenylcarbinol product (S_E2) was not detected. This is consistent with the proposed mechanism given in ref. 11(g). Computational studies to elucidate the origins of this selectivity are currently underway.

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