Oxidative Coupling

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Iron-Catalyzed Tertiary Alkylation of Terminal Alkynes with 1,3-Diesters via a Functionalized Alkyl Radical

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Dedicated to the 100th anniversary of Chemistry at Nankai University

Abstract: *Direct oxidative C(sp)−H/C(sp^3)−H cross-coupling offers an ideal and environmentally benign protocol for C(sp)−C(sp^3) bond formations. As such, reactivity and site-selectivity with respect to C(sp^3)−H bond cleavage have remained a persistent challenge. Herein is reported a simple method for iron-catalyzed/silver-mediated tertiary alkylation of terminal alkynes with readily available and versatile 1,3-dicarbonyl compounds. The reaction is suitable for an array of substrates and proceeds in a highly selective manner even employing alkanes containing other tertiary, benzylic, and C(sp^3)−H bonds alpha to heteroatoms. Elaboration of the products enables the synthesis of a series of versatile building blocks. Control experiments implicate the in situ generation of a tertiary carbon-centered radical species.*

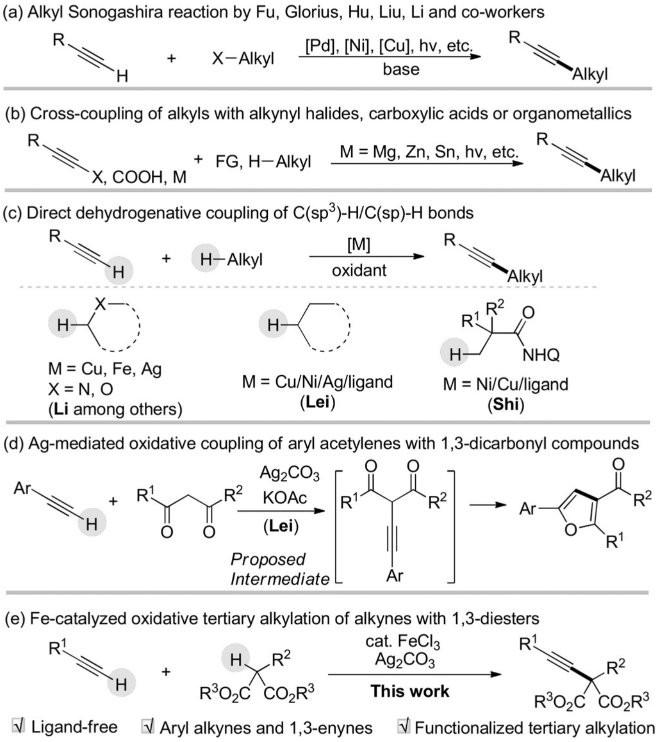

Figure 1. Transition metal-catalyzed cross-coupling for the construction of C(sp)−C(sp^3) bonds.

Introduction

Since the discovery of the Sonogashira reaction in 1975,[1] transition metal-catalyzed cross-couplings of terminal alkynes with organic (pseudo)halides represent one of the most reliable and general approaches to synthesize substituted alkynes.[2] Protocols that relied on the use of aryl or alkenyl electrophiles were the first to be developed for C(sp)−C(sp^2) bond formations. In comparison, use of the Sonogashira coupling reaction for construction of C(sp)−C(sp^3) bonds from terminal alkynes and alkyl halides poses a long-standing challenge. Advances in the application of alkyl halide coupling partners by the groups of Fu,[3] Glorius,[4] Hu,[5] Liu,[6] Li,[7] among others (Figure 1 a)[8] are noteworthy. Major impediments to such transformations include unwanted dimerization of terminal alkynes under oxidative conditions (Glaser–Hey coupling),[9] and β-hydride elimination of β-branched secondary or tertiary alkyl units.[10] As an alternative strategy to address these issues, catalytic C(sp)−C(sp^3) cross-couplings by engaging alkynyl halides, carboxylic acids, or organometallic alkynyl reagents have also received attention (Figure 1 b).[11] A common drawback of these methods is their reliance on functionalized precursors.

Oxidative functionalization of C(sp^3)−H bonds potentially provides an ecologically benign method for the installation of alkyl moieties,[12] but remains challenging. A cross-dehydrogenative coupling (CDC)[13] strategy, that is, the cross-couplings of C(sp)−H with C(sp^3)−H bonds, has been employed to access alkyl substituted alkynes (Figure 1 c).[14] CDC approaches were pioneered by Li's group employing a copper catalyst with stoichiometric peroxide. This method was selective for the cleavage of C(sp^3)−H bonds adjacent to heteroatoms.[14] In 2016, Lei and co-workers introduced a combined Cu/Ni/Ag catalytic system to couple terminal alkynes with unactivated alkanes,[15] such as cyclohexane and linear alkanes. This method required the alkane substrates as solvent or co-solvent and di-*tert*-butyl peroxide as oxidant. Not surprisingly, site-selectivity was also problematic. Shi's group addressed the site selectivity issue by using the 8-

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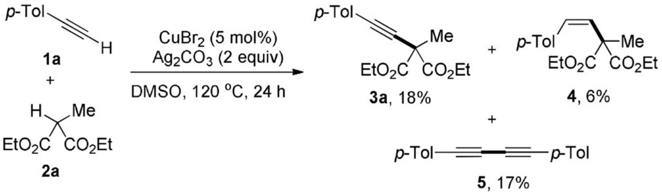
aminoquinoline directing group. This approach enabled the cross-coupling of terminal alkynes with primary C(sp^3)−H bonds.[16] Despite significant effort, the cross-coupling of tertiary C(sp^3)−H bonds with terminal alkynes remains largely underdeveloped.

Recently, our laboratory described a copper-catalyzed cross-coupling of alkenes with 1,3-dicarbonyl compounds,[17] wherein the intermediacy of a dicarbonyl radical was proposed.[18] Motivated by this oxidative C(sp^2)−H functionalization, we became interested in developing C(sp)−C(sp^3) cross-couplings from terminal alkynes and 1,3-dicarbonyl compounds.[19] A somewhat related reaction is Lei's elegant silver-mediated oxidative coupling of aryl acetylenes and 1,3-dicarbonyl compounds to generate furans. This reaction employed similar reagents (Figure 1 d) and it was proposed that alkylated alkynes were intermediates en route to furans. This hypothesis has not yet been verified to our knowledge.[20] Herein we present an iron-catalyzed tertiary alkylation of aryl alkynes and 1,3-enynes with 1,3-diesters that enables the streamlined synthesis of functionalized alkynes (Figure 1 e). This transformation avoids nucleophilic addition of 1,3-diesters to terminal alkynes with the formation of alkene-containing products.[21] Mechanistically, we propose that the reaction proceeds via a radical oxidative coupling pathway.[22]

Results and Discussion

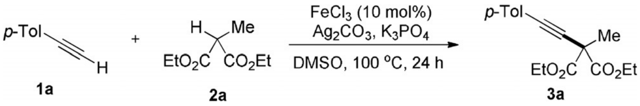
At the outset, the cross-coupling of C(sp)−H/C(sp^3)−H bonds was evaluated by selecting *p*-tolylacetylene (**1a**) and diethyl methylmalonate (**2a**) as the model substrates. Copper salts exhibited superior catalytic performance in promoting alkylation of alkenes in our previous studies.[17] Exploratory studies using $CuBr_2$ as catalyst and Ag_2CO_3 as oxidant, however, gave a low chemical yield of the dehydrogenative product **3a**, together with *cis*-hydroalkylation byproduct **4** and undesired dimerization by-product **5** (Scheme 1, percentages refer to yields of isolated products). This competitive reductive pathway for the formation of disubstituted alkenes[23] was viewed as potentially problematic and inspired us to consider use of other metals.

After an extensive survey of reaction parameters (see the Supporting Information for details), we arrived at the optimized conditions that involved 10 mol % $FeCl_3$ with Ag_2CO_3 as the oxidant and K_3PO_4 base in DMSO (0.08 M) at 100 °C, affording the desired product **3a** in 76 % isolated yield (Table 1, entry 1). Control experiments showed that both $FeCl_3$ and Ag_2CO_3 were essential for the coupling and the base greatly improved the efficiency (Table 1, entries 2–4). Other common Lewis acids like $FeCl_2$, $CuCl_2$, $ZnCl_2$, $AlCl_3$, and $BF_3{\cdot}OEt_2$, gave inferior results (Table 1, entry 5). A series of silver salts were examined as oxidants, but none were competitive with Ag_2CO_3 (Table 1, entries 6–8). Peroxides, which have been extensively utilized in oxidative C−H/C−H cross-coupling reactions, gave no conversion (Table 1, entry 9). Replacing K_3PO_4 with other bases such as K_2CO_3, KOAc, and Cy_2NH, was found to be detrimental to the product yield. Solvent effects were also evaluated. Among polar aprotic solvents examined, dimethyl sulfoxide proved to be optimal (Table 1, entry 11).



Scheme 1. Preliminary results for direct coupling of C(sp^3)−H/C(sp)−H bonds.

Table 1: Optimization of the reaction conditions.[a]



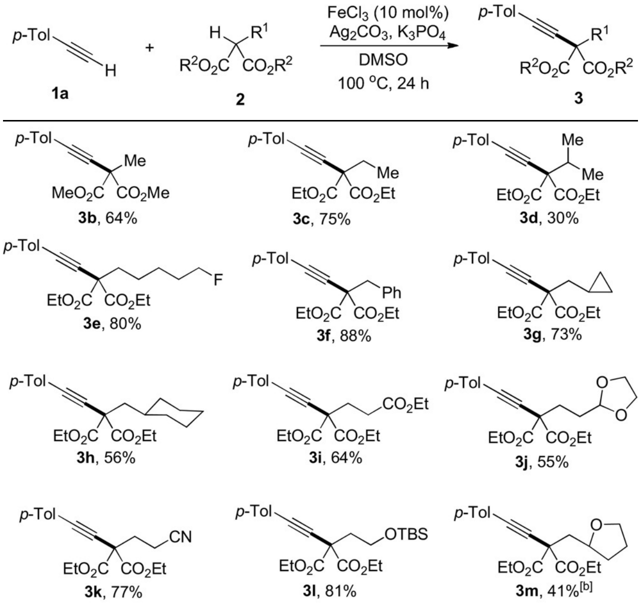
Entry	Variation from the standard conditions	Yield [%][b]
1	none	76
2	no $FeCl_3$	trace
3	no Ag_2CO_3	0
4	no K_3PO_4	17
5	Lewis acids instead of $FeCl_3$	0–60
6	Ag_2O as an oxidant	12
7	AgOAc as an oxidant	18
8	$AgNO_3$ as an oxidant	trace
9	DTBP as an oxidant	0
10	other bases instead of K_3PO_4	14–55
11	other solvents instead of DMSO	7–40

[a] Reaction conditions unless otherwise noted: **1a** (0.2 mmol), **2a** (0.4 mmol), $FeCl_3$ (10 mol %), Ag_2CO_3 (0.4 mmol), K_3PO_4 (0.4 mmol), DMSO (2.5 mL), 100 °C, 24 h. [b] Yield of isolated product.

With the optimized reaction conditions in hand, we began to explore the generality and selectivity of the Fe-catalyzed C(sp)−H/C(sp^3)−H bond coupling by using tolyl acetylene (**1a**) as coupling partner (Table 2). Dimethyl methylmalonate proved to be amenable to this oxidative cross-coupling, delivering the corresponding product **3b** in 64 % yield. Extending the chain attached to the α-position of the malonate to ethyl resulted in an increase in the yield to 75 % (**3c**). In contrast, the more sterically demanding isopropyl derivative exhibited diminished reactivity, but still permitted isolation of the product **3d** (30 % yield). Tertiary alkylation of tolyl acetylene (**1a**) with various malonate derivatives bearing desirable functionality, such as fluoride, benzyl, cyclopropyl, cyclohexyl, ester, acetal, nitrile, silyl ether, and tetrahydrofuranyl motifs, proceeded efficiently, providing access to functionalized alkynes (**3e**–**3m**) with yields ranging from 41 to 88 %. It is noteworthy that substrates bearing C−H bonds that are susceptible to hydrogen atom transfer processes, such as those positioned at benzylic centers or C−H bonds alpha to oxygen, were compatible with the reaction conditions. In the case involving ethyl 2-methylacetoacetate, no evidence of the coupling product was detected. This result showed that the diester moiety appeared to be uniquely suitable under these reaction conditions.[24]

Next, we turned our attention to the scope of the aryl alkynes (Table 3). The functional group compatibility of the

Table 2: Substrate scope with regard to α-substituted malonates.[a]

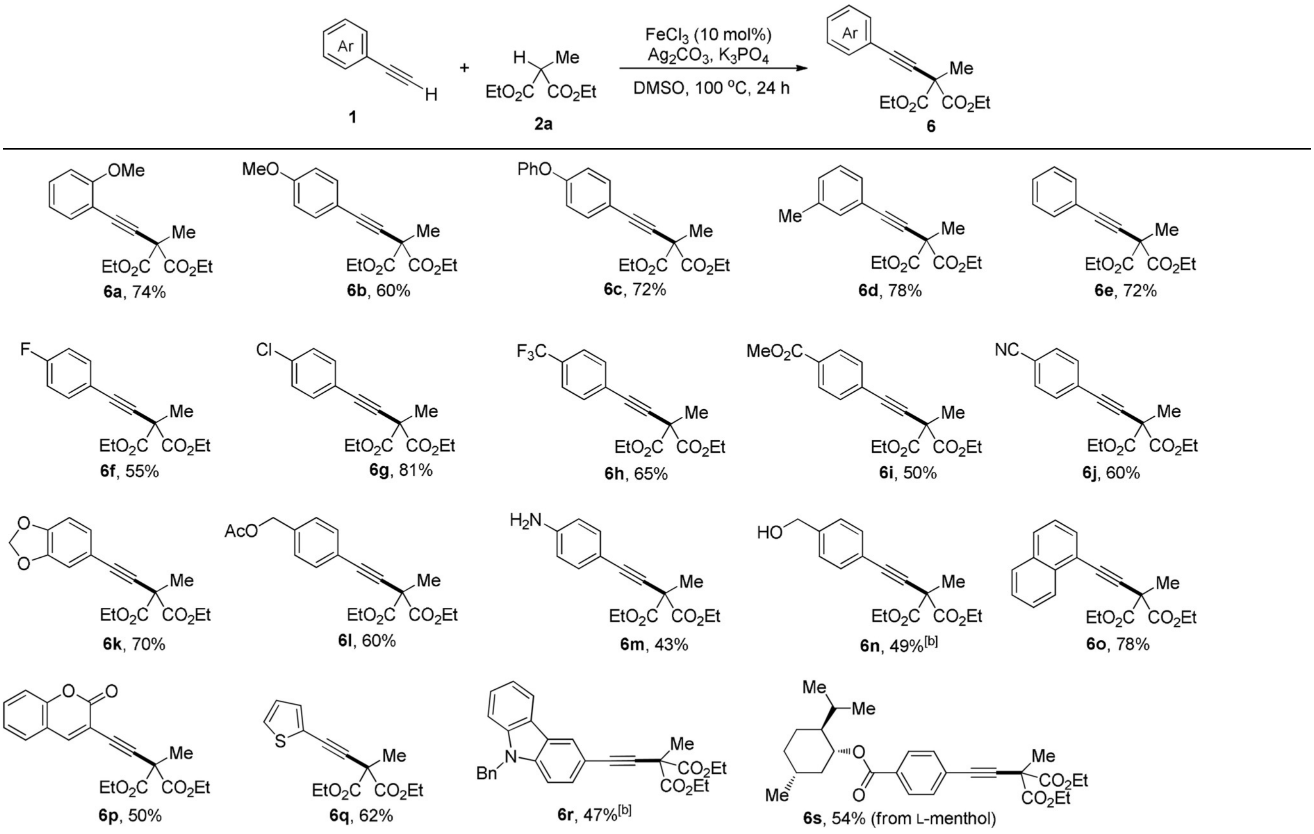


[a] Reaction conditions: **1 a** (0.2 mmol), **2** (0.4 mmol), $FeCl_3$ (10 mol%), Ag_2CO_3 (0.4 mmol), and K_3PO_4 (0.4 mmol) in DMSO (2.5 mL) at 100°C for 24 h. Isolated yields. [b] Reaction was conducted at 90°C with 20 mol% $FeCl_3$.

alkynes was probed by examination of electronically varied substituents at the *ortho*-, *meta*-, and *para*-positions. We were pleased to observe that the catalytic efficiency could accommodate aryl acetylenes with different electronic and steric properties. Functional groups, such as ether, halides, trifluoromethyl, methoxycarbonyl, cyano, acetal, ester, and even free amino groups, were well tolerated, giving internal alkynes in 43–81% yields (**6a**–**6m**). The potentially oxidizable benzyl alcohol-tethered alkyne was also tolerated in the reaction (**6n**, 49% yield). Moreover, a naphthalene ring as well as pharmaceutically relevant heterocycles, including coumarin, thiophene, and carbazole, readily participated in these couplings to deliver the desired products in 50–78% yields (**6o**–**6r**). The synthetic applicability was further highlighted by the late-stage modification of an L-menthol derivative, in which the corresponding alkylated product **6s** was obtained in 54% yield. No deterioration of the stereochemistry was detected. Unfortunately, less reactive alkyl alkynes, as exemplified by 1-heptyne, do not participate in this dehydrogenative cross-coupling process under our current conditions.

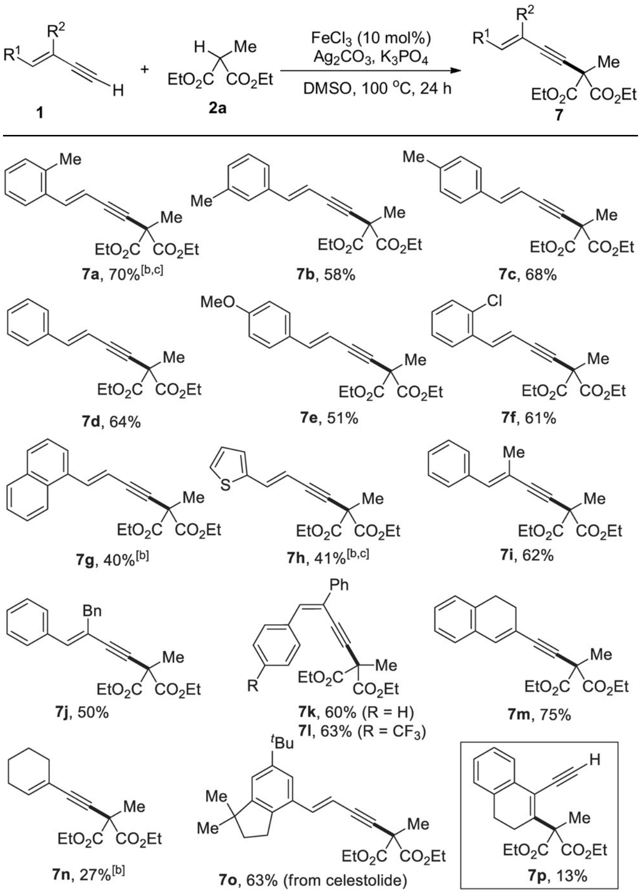
Inspired by the fruitful tertiary alkylation of aryl alkynes, we were interested in investigating the functionalization of 1,3-enyne substrates. As revealed in Table 4, a series of 1,3-enynes bearing aryl groups were chemoselectively alkylated without competing reaction at the alkene. This is particularly noteworthy because addition of radicals is reported to occur more readily at alkenes than alkynes.[25] Electron-neutral H

Table 3: Substrate scope with regard to (hetero)aryl alkynes.[a]



[a] Reaction conditions: **1** (0.2 mmol), **2 a** (0.4 mmol), $FeCl_3$ (10 mol%), Ag_2CO_3 (0.4 mmol), and K_3PO_4 (0.4 mmol) in DMSO (2.5 mL) at 100°C for 24 h. Isolated yields. [b] Reaction was conducted at 90°C.

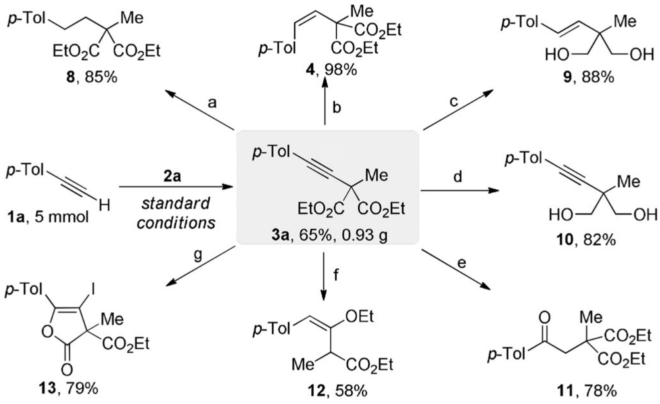
Table 4: Substrate scope with regard to 1,3-enynes.[a]



[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $FeCl_3$ (10 mol%), Ag_2CO_3 (0.4 mmol), and K_3PO_4 (0.4 mmol) in DMSO (2.5 mL) at 100°C for 24 h. Isolated yields. [b] Reaction was conducted at 90°C. [c] With 20 mol% $FeCl_3$.

and Me (58–70%), -donating 4-OMe (51%) and -withdrawing 2-Cl (61%) groups on the aryl rings were well tolerated under the standard conditions. Likewise, naphthyl- and thiophenyl-substituted enynes were competent in the couplings, furnishing the desired products **7g** and **7h** in 40–41% yield. Disubstituted 1,3-enynes (**7i**–**7m**) successfully yielded alkylation products with 62–75% yields with no detectable isomerization of the double bond. The alkyl-substituted enyne, 1-ethynylcyclohex-1-ene, furnished the expected product **7n**, albeit in 27% yield. The different yields between the products **7m** and **7n** indicate that the extended π-conjugation on the substrates has a noticeable effect on their reactivity. Successful tertiary alkylation of a celestolide derivative was achieved to afford the desired product in 63% yield (**7o**). An exception to the reactivity pattern of enynes was found in the reaction of enyne **1pa**, which was derived from 1-tetralone. In this case, alkylation occurred on the alkene site to give **7p** in low yield (13%). We attribute this result to the stability of the radical intermediate formed upon addition of the malonate-derived radical to the double bond, which is stabilized by being both benzylic and propargylic.

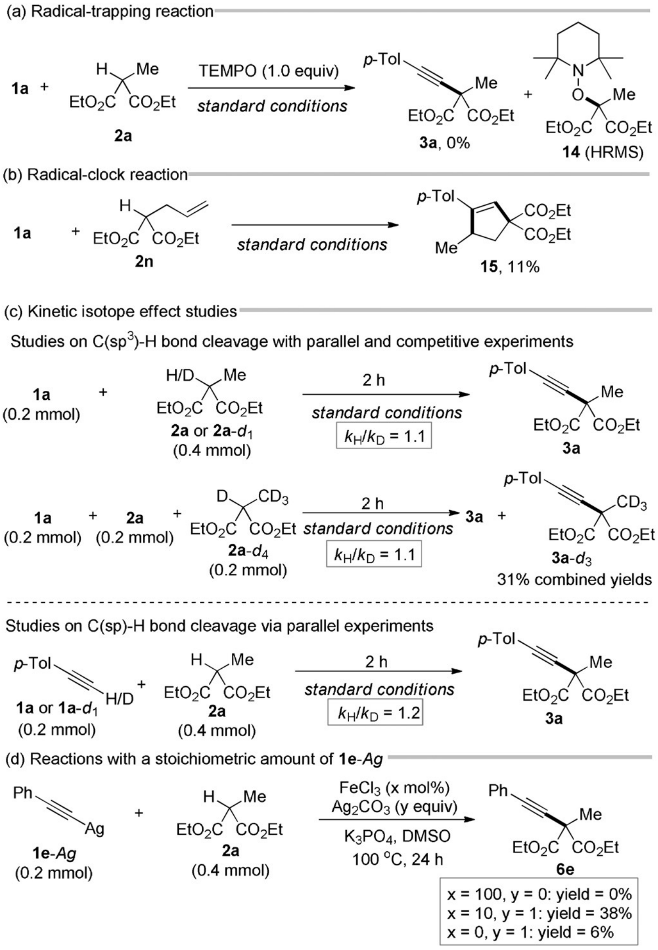
To showcase the synthetic value of the coupling protocol, a gram scale synthesis of **3a** was performed and several derivatives were synthesized (Scheme 2). The scale up of **3a** validated the robustness of the present catalytic C(sp)−C(sp^3) coupling reaction. Hydrogenation of the acetylene moiety using palladium on charcoal afforded the ethyl compound **8** (path a, 85% yield). Semi-reduction of the internal alkyne with HCO_2H, K_2CO_3, and catalytic $PdCl_2$ provided the corresponding *cis*-alkene **4** in nearly quantitative yield (path b). Treatment of **3a** with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) resulted in the formation of *trans*-alkene **9** (path c, 88% yield). Moreover, the diester reduction with $LiAlH_4$ in diethyl ether smoothly yielded 1,3-diol **10** without touching the alkyne (path d, 82%). Direct hydration took place in the presence of catalytic trifluoromethanesulfonic acid to furnish ketone **11**[26] (path e, 78% yield). Interestingly, compound **3a** could be readily converted into vinyl ether **12** (58% yield), as shown in path f, by means of alcoholic sodium ethoxide through a successive hydroethyoxylation/decarboxylation reaction path.[27] Electrophilic cyclization of **3a** with iodine at room temperature occurred cleanly to produce the highly functionalized furanone **13** in path g (79% yield).[28] This vinyl iodide product is primed for further functionalization through cross-coupling methods.



Scheme 2. Derivatization of tertiary alkyl-substituted alkynes. Reaction conditions: [a] H_2 balloon, Pd/C, MeOH, rt, 2 h; [b] $PdCl_2$, HCO_2H, K_2CO_3, 1,4-dioxane, 80°C, 24 h; [c] Red-Al, THF, 0→60°C, 12 h; [d] $LiAlH_4$, Et_2O, rt, 2 h; [e] H_2O, CF_3SO_3H, CF_3CH_2OH, 60°C, 20 h. [f] NaOEt, EtOH, 60°C, 3 h; [g] I_2, DCM, rt, 2 h.

To gain insight into the reaction pathway, a series of experiments were performed. When the radical inhibitor 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO) was added to the reaction under the standard conditions, none of the alkyne alkylation was observed. Analysis of the crude reaction mixture by MS indicated that some radical trapping product **14** could be detected (Scheme 3a). Moreover, under the standard conditions, the reaction of **1a** with malonate **2n** bearing a pendent alkene unit delivered a cyclopentene **15** as the sole product via a tandem C(sp)−C(sp^3) coupling followed by a 5-*exo*-trig cyclization process (Scheme 3b). These observations strongly support the intermediacy of a tertiary carbon-centered radical species that adds to the alkyne to form a new radical.

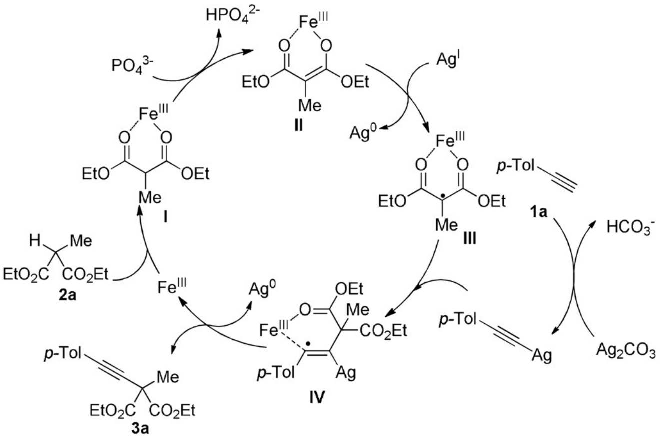
Kinetic isotope effect studies were also performed to shed light on the C−H bond cleavage step. To this end, deuterium-labeled methylmalonates **2a**-d_1 and **2a**-d_4 as well as alkyne **1a**-d_1 were prepared and subjected to the coupling conditions



Scheme 3. Mechanistic studies of the Fe-catalyzed oxidative coupling of C(sp)−H/C(sp^3)−H bonds.

(Scheme 3c). Parallel experiments with **2a** and deuterium-labeled methylmalonates **2a**-d_1 and **2a**-d_4 exhibited an identical KIE value of $k_H/k_D = 1.1$. The low KIEs suggest that cleavage of the C(sp^3)−H bond is not turnover-limiting. Two parallel experiments with **1a** and **1a**-d_1 were then conducted, giving a measured KIE value of 1.2. This KIE indicates that C(sp)−H bond cleavage is also not involved in the turnover-limiting step. No reaction occurred when silver phenylacetylide was treated with **2a** and 1 equiv $FeCl_3$ in the absence of Ag_2CO_3. This result suggests that $FeCl_3$ is not acting as an oxidant to initiate a radical chain reaction (Scheme 3d). In contrast, when the preformed silver phenylacetylide was subjected to the reaction conditions with Ag_2CO_3 and catalytic $FeCl_3$, the expected product **3a** was obtained in 38% yield. Finally, under the standard conditions, but in the absence of $FeCl_3$, only trace coupling product was detected.

On the basis of the aforementioned experimental results and literature precedents,[29] we propose a reaction pathway (Scheme 4). The initial step is envisioned to be coordination of the diester **2a** to $FeCl_3$ to give complex **I**, which is deprotonated by phosphate anion to generate enolate **II**. Deprotonation likely has a low barrier, consistent with the observed KIEs. Enolate **II** is subsequently oxidized by Ag^I to deliver tertiary carbon-centered radical species **III**. Concurrently, C(sp)−H bond activation of the terminal alkyne by silver occurs to afford the silver acetylide complex. Based on the KIEs, this step also has a relatively low barrier. The next step is proposed to involve radical addition of intermediate **III** to the silver acetylide, resulting in formation of a vinyl radical species **IV**. Support for this step is the radical-trapped cyclopentene **2n**, as depicted in Scheme 3b. Vinylic radicals are generally very reactive, inspiring us to postulate that the radical is stabilized by iron. Based on Pearson's rules of hard and soft acids and bases,[30] we anticipate that Fe^{III} prefers to coordinate to the 1,3-diester while the softer Ag^I favors activation of the alkyne. We cannot rule out, however, that the Fe^{III} bonds to the alkyne during the radical addition step. Finally, homolysis of the Ag−C bond with simultaneous regeneration of the alkyne π-bond and silver metal furnishes the C(sp)−C(sp^3) coupling product **3a** and liberates the iron catalyst. The fact that other Lewis acids, such as $ZnCl_2$ and $AlCl_3$ (Table S1), cannot change oxidation states but still promote this process suggests that $FeCl_3$ is behaving as a Lewis acid.



Scheme 4. Proposed mechanism.

Conclusion

In summary, we have developed a practical protocol for the iron-catalyzed oxidative cross-dehydrogenative coupling between C(sp) centers of terminal alkynes and C(sp^3) centers of 1,3-diesters that enables the assembly of functionalized tertiary alkyl-substituted alkynes. This simple procedure has the advantage that it does not require functionalized precursors or expensive ligands. Both aryl alkynes and 1,3-enynes are viable substrates in this catalytic system. Excellent functional group compatibility and diverse synthetic modifications further highlight the strengths of this transformation. Mechanistic studies reveal that neither C(sp^3)−H nor C(sp)−H bond cleavage is turnover-limiting. It is proposed that a tertiary carbon-centered radical species and silver acetylide complex are generated in situ and react via radical intermediates. Further studies toward developing novel C(sp^3)−H bond functionalization reactions focusing on environmentally benign oxidative strategies are underway in our laboratories.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: 1,3-diesters · alkynes · iron catalysis · radical · tertiary alkylation

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