Iron-Catalyzed Cross-Coupling of Propargyl Ethers with Grignard Reagents for the Synthesis of Functionalized Allenes and Allenols

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Abstract: Herein we disclose an iron-catalyzed cross-coupling reaction of propargyl ethers with Grignard reagents. The reaction was demonstrated to be stereospecific and allows for a facile preparation of optically active allenes via efficient chirality transfer. Various tri- and tetrasubstituted fluoroalkyl allenes can be obtained in good to excellent yields. In addition, an iron-catalyzed cross-coupling of Grignard reagents with α-alkynyl oxetanes and tetrahydrofurans is disclosed herein, which constitutes a straightforward approach towards fully substituted β- or γ-allenols, respectively.

Allenes constitute an interesting class of compounds and have attracted considerable attention in synthetic organic chemistry in recent years.[1] Functionalized allenes are frequently used as building blocks in organic synthesis and they occur in a range of natural products and pharmaceuticals.[2] An interesting feature with functionalized allenes is that they can possess axial chirality.

We[3–5] and others[6] have recently developed a large number of diverse synthetic methods that rely on the use of various allene-based starting materials. The development of new procedures for the preparation of allenes is therefore highly desirable. A common route towards functionalized allenes involves the copper- or iron-catalyzed SN2 reaction between Grignard reagents and propargyl substrates.[7] Copper-catalyzed cross-couplings between propargylic substrates and Grignard reagents are well known, but to date there are only few reports on the corresponding iron-catalyzed cross-couplings and they mainly rely on the use of sulfonates[8] or halides[9] as leaving groups. Fürstner has reported a related method for the preparation of α-allenols that utilize alkynyl epoxide with its high ring strain as the nucleophile (Scheme 1a).[10] In addition, our group has recently disclosed a practical method for the preparation of highly substituted allenes[11a] and α-allenols[11b] via iron-catalyzed cross-coupling of propargyl carboxylates and Grignard reagents (Scheme 1b). In the present work we have studied iron-catalyzed cross-coupling of less reactive propargylic ethers with Grignard reagents. With methoxy as leaving group the stereospecificity (> 99% syn-displacement) is the highest ever reported in an iron-catalyzed SN2 substitution of propargylic substrates. Importantly, the low reactivity of the alkoxy group compared to conventional leaving groups allows the presence of fluoroalkyl groups. The use of cyclic analogues, α-alkynyl oxetanes and tetrahydrofurans as substrates led to synthetically useful allenols.

Our investigations began with the screening of various leaving groups in the reaction of trifluoromethyl group-containing propargyl substrates 1 in the presence of Fe(acac)3 as the catalyst (Table 1). Unexpected formation of gem-difluoro 1,3-enyne 3 was observed (60% yield) in the case of the acetate as the leaving group (1aa) and only 20% yield of the desired trifluoromethyl allene 2aa was obtained (entry 1, Table 1). Formation of 3 is thought to proceed via a propargyl radical intermediate.[12,13] Also, other oxygen-based leaving groups tested, such as pivalate, carbonate, phosphonate, and mesylate provided the desired allene 2aa in poor yields together with the 1,3-enyne 3 as the main product (entries 2–5). These results demonstrate the compatibility problems with fluoroalkyl group-containing substrates in these attempted SN2-type cross-coupling reactions. In a try to circumvent this problem we tested methoxy as the leaving group. Interestingly, this leaving group suppressed the unde-
Optimization of the reaction conditions. 

Table 1: Optimization of the reaction conditions.

| Entry | Substrate (1) | Catalyst | Yield of 2aa [%][b] | Yield of 3 [%][b] |
|-------|---------------|----------|---------------------|------------------|
| 1     | 1aa (R = Ac)  | Fe(acac)₃ | 20                  | 60               |
| 2     | 1ab (R = Piv) | Fe(acac)₃ | 15                  | 58               |
| 3     | 1ac (R = CO₂Me) | Fe(acac)₃ | 19                  | 69               |
| 4     | 1ad (R = P(O)(OEt)₂) | Fe(acac)₃ | 25                  | 67               |
| 5     | 1ae (R = Ms)  | Fe(acac)₃ | 18                  | 47               |
| 6     | 1af (R = Me)  | Fe(acac)₃ | 94 (89)             | n.d.             |
| 7     | 1af          | Fe(OAc)₂ | 92                  | n.d.             |
| 8     | 1af          | Fe(OAc)₂ | –[d]               | –[d]             |
| 9     | 1af          | Fe(acac)₃ | 92                  | n.d.             |
| 10    | 1af          | Fe(acac)₃ | 91                  | n.d.             |
| 11    | 1af          | CuBr     | –[e]               | –[e]             |

[a] Reaction conditions: 0.2 M solution of propargylic substrate 1 (0.3 mmol) in PhMe, catalyst (5 mol%) with dropwise addition of Grignard reagent. [b] Determined by NMR using anisole as the internal standard. Isolated yield in parentheses.  
[c] ≥ 99.9 %. [d] 1af was recovered in 93 % yield. [e] Using 20 mol % of TMEDA as an additive.  
[f] Using 20 mol % of IMes·HCl as an additive.  
[g] 1af was recovered in 96 % yield. acac = acetylacetonate. TMEDA = N,N,N,N-tetramethylethylenediamine.

sired formation of the elimination product 3, and the allene product 2aa was now obtained in 94 % yield with no detectable amounts of the side product 3 (entry 6). FeCl₃ as the catalyst showed similar performance as that of Fe(acac)₃ in this reaction, albeit providing the desired allene in a slightly decreased 92 % yield (entry 7). Fe(OAc)₂, as the catalyst failed to give the desired product in this transformation (entry 8). Screening of some commonly used additives did not lead to any increase in yield of allene 2aa (entries 9 and 10). The use of CuBr as the catalyst in place of Fe(acac)₃ did not lead to any detectable amounts of the desired product 2aa (entry 11). This observation not only shows that iron is superior to copper as the catalyst in this reaction but also rules out that the reaction is catalyzed by trace amounts of copper in the commercially available Fe(acac)₃.[14]

With the optimized reaction conditions in hand, we further studied the reactivity of various fluorinated propargylic methyl ethers 1 (R = fluoroalkyl) in this transformation (Table 2). The use of other Grignard reagents such as n-BuMgCl and PhMgBr in the reaction with 1af afforded the corresponding trifluoroalkyl allenes 2ab and 2ac in 43 % and 62 % yields, respectively (entries 2 and 3, Table 2). The observed lower yield of product 2ab is most likely due to competing β-hydride elimination in the alkyliron intermediate initially formed from Fe(acac)₃, and the Grignard reagent. Allenes 2b and 2c, containing masked alcohol and aldehyde functionalities, respectively, were prepared in good to high yields from the corresponding substrates 1b and 1c (entries 4 and 5). Pentafluoropyridyl group-containing substrate 1d afforded the corresponding allene 2d in 72 % yield (entry 6). Interestingly, TBS-protected CF₃ and CHF₂ group-containing α-allenols 2e and 2f were prepared in 85 % and 77 % yields, respectively, using the newly developed methodology (entry 7). The β-enamines 2g and 2h were obtained from the corresponding 1g and 1h in 88 % and 75 % yields, respectively (entries 8 and 9). The cross-coupling reaction with substrate 1i afforded allene product 2i without any formation of cyclopentyl moiety-containing products that would be expected from cyclization of an intermediate propargyl radical species (entry 9). Furthermore, cyclopropyl-substituted propargyl methyl ether 1j as the substrate gave 2j in 56 % yield, and, interestingly, did not result in any side products arising from the radical ring-opening of the cyclopropane ring (entry 10). The use of propargyl methyl ether 1k gave the desired allene 2k in a low 17 % yield, possibly due to an unfavorable coordination of the pyridine moiety to the metal center (entry 11).

The use of 1 equiv of TEMPO as an additive in the reaction of 1af with PhMgBr did not completely shut down the reaction, but afforded the desired allene product 2ac in 34 % yield (see the Supporting Information). These results strongly suggest, that carbon-centered radical intermediates are either extremely short-lived or are not involved in the reaction process.

We were delighted to find that the use of cyclic ether 4a as the substrate in the reaction led to formation of the CF₃ group-containing γ-allenol 5a in an excellent 88 % yield [Eq. (1)]. γ-Allenols are highly desired substrates for many transition-metal-catalyzed transformations as well as important building blocks in the total synthesis of natural products.[13] The examples of preparation of γ-allenols currently found in the literature typically involve multistep syntheses.

Because of the demand of new efficient methods for the preparation of functionalized allenols we decided to investigate additional α-alkynyl tetrahydrofurans 4 as substrates in this reaction (Table 3). Tetrahydrofurans 4b–4e containing alkyl substituents in the R¹ and R² positions afforded the corresponding γ-allenols 5b–5e in 56–85 % yields under the standard reaction conditions (entries 2 and 3, Table 3). Interestingly, the reaction tolerates the presence of a free hydroxyl group in substrate 4e and afforded the diol product 5e in a moderate 56 % yield. α-Alkynyl tetrahydrofuran 4f, containing a hydrogen atom in the R² position, gave the desired trisubstituted γ-allenols 5fa and 5fb in good yields (entries 4 and 5). Substrates 4g and 4h bearing an aryl group in the R² position furnished the corresponding products 5g and 5h in 65 % and 67 % yields, respectively (entries 6 and 7). Trisubstituted γ-allenol 5i was prepared by cross-coupling of 4i with MeMgBr under the standard reaction conditions in a moderate 55 % yield (entry 8).

To the best of our knowledge, the use of α-alkynyl oxetanes as substrates has not previously been explored in the Fe-catalyzed cross coupling with Grignard reagents.
Table 2: Preparation of fluoroalkyl allenes 2.[4]

| Entry | Substrate (1) | R'MgX | Product (2) | Yield of 2 [%][5] |
|-------|---------------|--------|-------------|------------------|
| 1     | Ph            | MeMgBr | Ph            | 89               |
| 2     | taf           | n-BuMgCl | 43[6]       |
| 3     | taf           | PhMgBr | 62[6]       |
| 4     | TBSO           | MeMgBr | 74          |
| 5     |               | MeMgBr | 92          |
| 6     |               | MeMgBr | 72          |
| 7     | TBSO           | MeMgBr | 2e: 85      |
| 8     |               | MeMgBr | 2f: 77      |
| 9     |               | MeMgBr | 2h: 75      |
| 10    |               | MeMgBr | 56          |
| 11    |               | PhMgBr | 1j[4]       |

[a] Reaction conditions: 0.2 M solution of propargyl methyl ether 1 (0.3 mmol) in PhMe, Fe(acac)3 (5 mol%) with dropwise addition of Grignard reagent (1.5 equiv). [b] Isolated yield. [c] Using 10 mol% of TMEDA as an additive. [d] 2.0 equiv of PhMgBr was used and the reaction time was 4 h. [e] The reaction time was 12 h and 1k was recovered in 43% yield.

To demonstrate the scalability of the herein described iron-catalyzed synthesis of fluoroalkyl allenes we performed the transformation of propargyl ether 1e on a gram-scale (Scheme 3a). The desired trifluoromethylmethyl allene 2e was obtained in an excellent 88% yield. To show-case the potential synthetic utility of the obtained fluoroalkyl allenes, 2h was subjected to the regio- and stereoselective palladium-catalyzed oxidative borylation reaction[10] to give the trifluoromethyl group-containing borylated triene product 8 in 67% yield (Scheme 3b).

We also investigated the stereochimistry of the iron-catalyzed Grignard reaction (Scheme 3c). Enantiomerically enriched substrates 11-a were conveniently prepared via an enzymatic kinetic resolution of the corresponding secondary propargyl alcohols, followed by methylation using methyl iodide (see the Supporting Information). Interestingly, products 21-a were formed under the standard reaction conditions with excellent transfer of chirality from the corresponding propargyl ethers 11-a in good yields. Propargylic substrate (R)-21 gave the allene product (R)-21. The structure and absolute configuration of (R)-21 was established by X-ray crystallography of its ester derivative (R)-9 (DNB = 2,5-dinitrobenzoyl). These results show that a syn-SN2 displacement of the methoxy group by the aryl group has occurred, which, in line with the radical probe experiments, rules out the involvement of carbon-based radical species generated from the substrate (R)-11.

We also investigated the preparation non-fluorinated allenes 2o-2s using propargyl methyl ethers 1o-1s as substrates under the standard reaction conditions (Scheme 4). Substrates 1o-1p bearing alkyl substituents in R1, R2 and R3 positions all afforded the corresponding tetrasubstituted allene products 2o-2p in good yields with high selectivity. Trisubstituted allene 2q was prepared in 92% yield by reacting TMS group-containing Grignard reagent with propargyl methyl ether 1q. Cross-coupling of ester group-containing substrates 1r and 1s with MeMgBr afforded allenes 2r and 2s in 51% and 73% yields, respectively.

Scheme 2. Preparation of β-allenols 7. Reaction conditions: 0.2 M solution of oxetane 6 (0.3 mmol) in PhMe, Fe(acac)3 (5 mol%) with dropwise addition of Grignard reagent (1.5 equiv).[5] Using 10 mol% of TMEDA as an additive.

Scheme 3. Preparation of fluoroalkyl allenes 2. Reaction conditions: 0.2 M solution of propargyl methyl ether 1 (0.3 mmol) in PhMe, Fe(acac)3 (5 mol%).
In the iron-catalyzed coupling reaction it is thought that the Grignard reagent initially reacts with the iron catalyst Fe(acac)$_3$ to generate a reduced organoiron complex, probably an “ate” complex. [17,18] Based on the observed transfer of chirality, the reaction is proposed to proceed via a syn-SN2 attack of the initially generated organoiron intermediate on substrate 1 (oxidative addition) to generate Int-B via Int-A (Scheme 5). Reductive elimination from Int-B would give

Table 3: Preparation of γ-allenols 5.^[a]^[b][c][d]

| Entry | Substrate (4) | R'MgX | Product (5) | Yield of 5 [%][e] |
|-------|---------------|-------|-------------|------------------|
| 1     |               | MeMgBr| ![Image](image1) | 88               |
| 2     |               | BnMgCl| ![Image](image2) | ![Image](image3) | ![Image](image4) | 5b: 73, 5c: 68 |
| 3     |               | MeMgBr| ![Image](image5) | ![Image](image6) | ![Image](image7) | ![Image](image8) | 5d: 85, 5e: 56% |
| 4     | ![Image](image9) | BnMgCl| ![Image](image10) | 71               |
| 5     | 4f            | MeMgBr| ![Image](image11) | 68               |
| 6     |               | PhMgBr| ![Image](image12) | 65%[f]          |
| 7     |               | MeMgBr| ![Image](image13) | 67               |
| 8     |               | MeMgBr| ![Image](image14) | 55               |

[a] Reaction conditions: 0.2 M solution of tetrahydrofuran 4 (0.3 mmol) in PhMe, Fe(acac)$_3$ (5 mol %) with dropwise addition of Grignard reagent (1.5 equiv). [b] Isolated yield. [c] 2.5 equiv of MeMgBr was used. [d] 2.0 equiv of PhMgBr was used and the reaction time was 1 h.

Scheme 3. Additional experiments.

Scheme 4. Preparation of non-fluorinated allenes 2. Reaction conditions: 0.2 M solution of methyl ether 1 (0.3 mmol) in PhMe, Fe(acac)$_3$ (5 mol %) with dropwise addition of Grignard reagent (1.5 equiv).
trisubstituted allene product 2 with the observed axial chirality.

In conclusion, we have developed a facile method for cross-coupling of propargyl ethers with Grignard reagents that involves the use of a nontoxic and commercially available iron catalyst. Interestingly, the method allows for the preparation of highly substituted fluoroalkyl allenes as well as for the preparation of β- and γ-allenols (from readily available α-alkynyl cyclic ethers). The preparation of fluoroalkyl allenes was scalable up to gram-scale and the use of enantiomerically enriched starting materials led to formation of the desired chiral allenes via a syn-S_{2}2′ process with excellent transfer of chirality. To the best of our knowledge this is the highest stereospecificity ever reported in an iron-catalyzed SN2 process with excellent transfer of chirality. To the best of our knowledge this is the highest stereospecificity ever reported in an iron-catalyzed SN2 process with excellent transfer of chirality.

Scheme 5. Proposed reaction mechanism.

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Conflict of Interest

The authors declare no conflict of interest.

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A method for facile synthesis of highly substituted allenols and fluoroalkyl allenes via iron-catalyzed cross-coupling reaction of propargyl ethers with Grignard reagents is disclosed. Various tri- and tetrasubstituted fluoroalkyl allenes and β-/γ-allenols were obtained in good to excellent yields. The reaction was demonstrated to be stereospecific occurring with syn-SN2' displacement of the methoxy group by the Grignard reagent.