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Letter

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Sterically Controlled Cu-Catalyzed or Transition-Metal-Free Cross-Coupling of *gem*-Difluoroalkenes with Tertiary, Secondary, and Primary Alkyl Grignard Reagents

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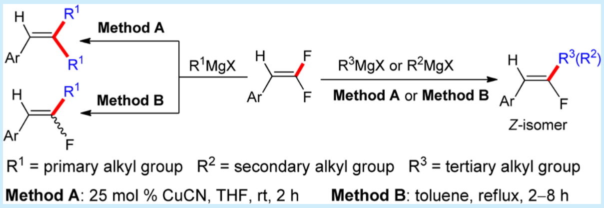
Supporting Information

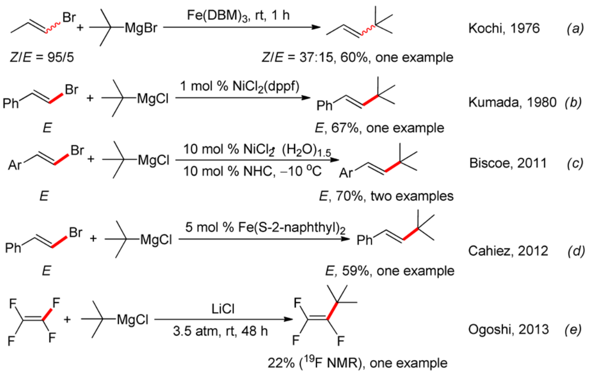
ABSTRACT: A robust copper-catalyzed or transition-metal-free cross-coupling of *gem*-difluoroalkenes with tertiary, secondary, and primary alkyl Grignard reagents has been developed. Remarkably, the tertiary and secondary alkylation of *gem*-difluoroalkenes proceeded very smoothly in the presence of 25 mol % of CuCN or under transition-metal-free conditions, affording the tertiary and secondary alkyl-substituted fluoroalkenes in good to excellent yields with excellent *Z* stereoselectivity.



The transition-metal-catalyzed reactions of aryl, alkenyl, and alkyl halides with Grignard reagents are powerful synthetic methods for the construction of C−C bonds.[1] Generally, primary alkyl, alkenyl, aryl, and even secondary alkyl Grignard reagents have been predominantly used as effective coupling partners,[2] whereas tertiary alkyl Grignard reagents are considered poor coupling partners owing to the large steric hindrance of the tertiary alkyl group, the isomerization of metal tertiary alkyl species, and the facile elimination of β-hydrogen.[3] Therefore, the coupling reactions of tertiary alkyl Grignard reagents with organic halides are still undeveloped.[4] Over the past decade, noteworthy progress has been brought about regarding the cross-coupling of tertiary alkyl Grignard reagents with organic halides such as aryl bromides,[5] alkyl halides,[6] chloroazacycles,[7] and alkynyl halides.[8] However, utilizing alkenyl halides as electrophiles to couple with tertiary alkyl Grignard reagents remains to be examined and only a few examples have been reported (Scheme 1a−e).[9]

The activation and functionalization of the C−F bond have attracted considerable attention in recent years.[10] The cleavage of the C−F bond is much more difficult due to the great strength of the C−F bond.[11] Although alkyl, vinyl, and aryl fluorides have been successfully coupled with different types of RMgX,[12] there has been only two reports in the literature on the coupling of tertiary alkyl Grignard reagents with less reactive organic fluorides. In 2013, Kambe reported the Co-catalyzed coupling of 1-fluorooctane with *t*-BuMgCl in the presence of 4 mol % of LiI and 1,3-butadiene and a moderate yield of the corresponding product was obtained (GC yield: 62%).[6] In the same year, Ogoshi also reported the LiCl-promoted monosubstitution reaction of tetrafluoroethene (TFE) with various Grignard reagents. However, when *t*-BuMgCl was employed as the substrate, the yield of the tertiary alkylation product dropped sharply (Scheme 1e).[9e] In continuation of our studies on the functionalization of the C−F bond of fluoroalkenes,[13] in this letter, we report the sterically controlled Cu-catalyzed or transition-metal-free coupling of *gem*-difluoroalkenes with tertiary, secondary, and primary alkyl Grignard reagents, which afforded various mono- or dialkylated multisubstituted alkenes depending on the Grignard reagents, reaction conditions, and substrates involved.

Scheme 1. Tertiary Alkylation of Alkenyl Halides



Generally, the cross-coupling of Grignard reagents with organic halides could be achieved by using palladium and nickel salts as catalysts.[1a,2a,14] 1,1-Dichoro- and dibromo-1-alkenes are valuable synthetic building blocks in organic synthesis and underwent facile Pd- or Ni-catalyzed coupling with Grignard reagents.[15] Recently, we reported the Pd- and Ni-catalyzed coupling reactions of *gem*-difluoroalkenes with aryl and primary alkyl Grignard reagents.[13c] We found that the catalytic system involving Pd(PPh$_3$)$_4$ was exceptionally effective for the coupling reaction of *gem*-difluoroalkenes with Grignard reagents without β-hydrogen atoms such as ArMgX, whereas NiCl$_2$(dppe) exhibited a superior reactivity in the cross-coupling of *gem*-

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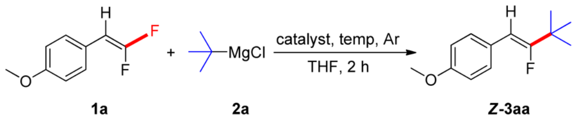
difluoroalkenes with Grignard reagents bearing *β*-hydrogen atoms such as *n*-C_4H_9MgX. However, when these two catalytic systems were applied to tertiary or secondary alkyl Grignard reagents, small amounts of cross-coupled products were observed (Table 1, entries 1−2).

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst (mol %)	2a (equiv)	temp	yield (%)[b]
1	$Pd(PPh_3)_4$ (25)	2.0	rt	10
2	$NiCl_2$(dppe) (25)	2.0	rt	2
3	$CuBr_2$ (25)	2.0	rt	13
4	$Cu(OAc)_2$ (25)	2.0	rt	31
5	Cu(OAc) (25)	2.0	rt	37
6	CuCl (25)	2.0	rt	38
7	CuBr (25)	2.0	rt	44
8	CuI (25)	2.0	rt	45
9	CuCN (25)	2.0	rt	99
10	CuCN (20)	2.0	rt	97
11	CuCN (15)	2.0	rt	85
12	CuCN (25)	1.8	rt	99
13	CuCN (25)	1.6	rt	75
14	none	2.0	rt	1
15	none	2.0	reflux	76
16	none	2.0	reflux (toluene)	99

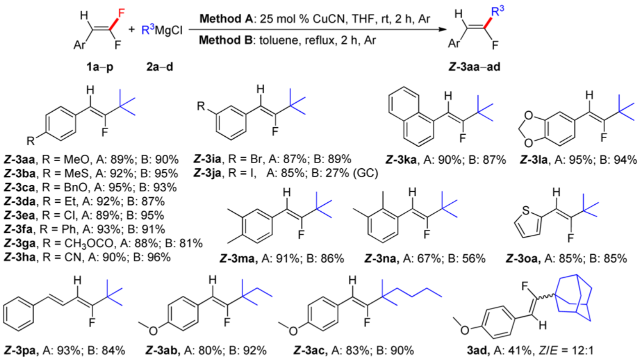
[a] Reaction conditions: **1a** (0.2 mmol), THF or toluene (3 mL), 2 h, Ar. [b] Yields determined by GC analysis and based on **1a**.

Recently, Cu-mediated or -catalyzed coupling reactions of organic halides with different types of Grignard reagents have attracted increasing attention because of the ready availability and lower commercial costs of copper salts.[16] Therefore, we initiated our studies by investigating the reactions of 1-(2,2-difluorovinyl)-4-methoxybenzene **1a** with *t*BuMgCl **2a** in the presence of various copper salts (Table 1). The screening of copper salts indicated that different copper species exhibited different efficiency in this coupling reaction and could afford the expected tertiary butylation product **Z-3aa** in low to moderate yields (entries 3−8). To our delight, when 25 mol % CuCN was used as a catalyst, the tertiary butylation product was formed in almost quantitative yield within 2 h at room temperature without any byproduct being observed. Even more surprisingly, the reaction proceeded with complete stereoselectivity to generate **Z-3aa** exclusively (entry 9). When the amount of CuCN declined to 20 mol %, the yield remained the same (entry 10). Further decrease of the amount of CuCN to 15 mol % resulted in a significantly reduced yield of **Z-3aa** (entry 11). It was found that 1.8 equiv of *t*BuMgCl **2a** was sufficient to carry out this reaction successfully (entry 12); however, when the amount of **2a** was reduced to 1.6 equiv, the yield of **Z-3aa** decreased significantly (entry 13).

The transition-metal-free coupling reaction of organic halides with Grignard reagents is a formidable challenge in the organic synthesis.[17] In addition, a survey of the literature revealed that there were only a few reports on the coupling reaction of organic fluoride with Grignard reagents under transition-metal-free conditions.[12c,18] However, successful examples of these coupling reactions are limited to substrates containing directing groups.[18c,d] Encouraged by the above success, we next examined the feasibility of tertiary butylation of *gem*-difluoroalkene under transition-metal-free conditions. Only a trace amount of **Z-3aa** was observed when the reaction was performed in THF without the addition of CuCN at rt (entry 14). Refluxing the reaction mixture in THF could afford **Z-3aa** in good yield (entry 15). Excitingly, when the reaction was performed in refluxing toluene, the yield of the desired **Z-3aa** was remarkably improved to 99% (entry 16). The configuration of the *Z*-isomer was determined by its $^3J_{H-F}$ coupling constant in the ^1H NMR spectra (ca. 40.0 Hz for the *Z* isomer and 26.0 Hz for the *E* isomer).

To gain insight into the tolerance of this reaction, we examined the scope of this reaction with respect to a variety of *gem*-difluoroalkenes and tertiary alkyl Grignard reagents under the two optimized reaction conditions (Table 1, entries 12 and 16). As shown in Scheme 2, this reaction exhibited good functional group compatibility and almost all *gem*-difluoroalkenes could afford tertiary alkylation products in good to excellent yields with excellent stereoselectivity. Generally, there was no significant difference in yield between methods A and B. Both *gem*-difluoroalkenes bearing a strong electron-donating group on the phenyl ring and *gem*-difluoroalkenes bearing a strong electron-withdrawing group could provide the coupled products in excellent yields (**Z-3aa** and **Z-3ha**). *gem*-Difluoroalkene having an *ortho* substituent on the phenyl ring has significant influence on the reaction, and only a moderate yield was obtained (**Z-3ma** versus **Z-3na**). The tolerance of chloride, bromide, and iodide substituents was particularly striking, which provides the opportunity for further modifications. 2-(2,2-Difluorovinyl)-thiophene (**1o**) and (*E*)-(4,4-difluorobuta-1,3-dien-1-yl)-benzene (**1p**) were also good substrates for this reaction. However, when aliphatic difluoroalkenes such as (4,4-difluorobut-3-en-1-yl)benzene were used as a substrate, no reaction was observed under the two reaction conditions. The replacement of *tert*-butylmagnesium chloride **2a** with *tert*-pentylmagnesium chloride **2b** and (2-methylpentan-2-yl)magnesium chloride **2c** also afforded excellent yields (**Z-3ab** and **Z-3ac**). In the case of adamantyl magnesium bromide **1d**, the reaction did not proceed smoothly and only 41% of **3ad** was formed. Importantly, the reaction of **1a** with **2a** could be scaled up from 1.0 to 10.0 mmol (**1a**, 1.7 g) without any loss in effectiveness (method A) and the **Z-3aa** was obtained in a nearly quantitative yield. Notably, 10 mol % CuCN was sufficient to accomplish the desired transformation.

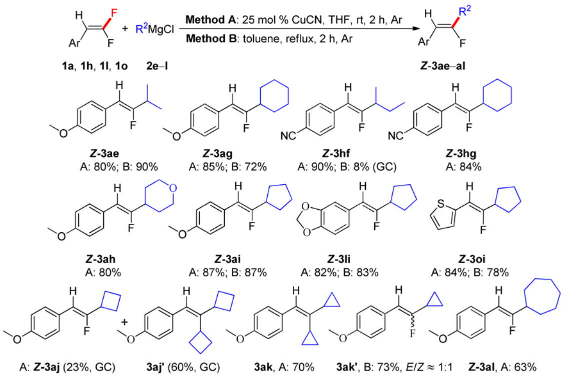
Scheme 2. Tertiary Alkylation of Various *gem*-Difluoroalkenes[a,b]



[a] Reaction conditions: (method A) **1a−p** (1.0 mmol), **2a−d** (1.8 mmol), 25 mol % CuCN, THF (5 mL), rt, 2 h, Ar; (method B) **1a−p** (1.0 mmol), **2a−c** (2.0 mmol), toluene (5 mL), reflux, 2 h, Ar. [b] Isolated yields.

To further examine the generality of this reaction, various secondary alkyl Grignard reagents were applied to the reaction with different *gem*-difluoroalkenes (Scheme 3). The Cu-catalyzed secondary alkylation of *gem*-difluoroalkenes proceeded efficiently and afforded secondary alkylation products in high yields with good stereoselectivity. However, compared to the coupling reaction of tertiary alkyl Grignard reagents, the coupling of secondary alkyl Grignard reagents with *gem*-difluoroalkenes was somewhat less efficient in terms of yield and stereoselectivity. Both cyclohexyl and cyclopentyl Grignard reagents proved to be efficient coupling partners, and cycloheptylmagnesium bromide **2l** is also a suitable coupling partner. When cyclobutylmagnesium bromide was used as a substrate, a mixture of the monocoupled product (*Z*-**3aj**) and dicoupled product (**3aj′**) was obtained. Interestingly, cyclopropylmagnesium bromide **2k** only afforded the double-cross-coupled product (**3ak**) in 70% yield and no monocoupled product was detected.

Scheme 3. Secondary Alkylation of *gem*-Difluoroalkenes[a,b]

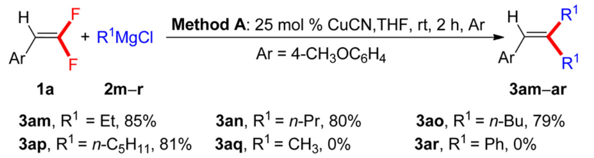


[a]Reaction conditions: method A: **1a**, **1h**, **1l**, **1o** (1.0 mmol), **2e–l** (1.8–3.0 mmol), 25 mol % CuCN, THF (5 mL), rt, 2 h, Ar. method B: **1a**, **1h**, **1l**, **1o** (1.0 mmol), **2e–g**, **2i** (1.8–3.0 mmol), **2k** (6.0 mmol), toluene (5 mL), reflux, 2 h, Ar. [b]Isolated yields.

Subsequently, we selected representative *gem*-difluoroalkenes and secondary alkyl Grignard reagents to investigate the secondary alkylation reaction under the transition-metal-free protocol (Scheme 3, method B). The results indicated that the secondary alkylation of *gem*-difluoroalkenes under transition-metal-free conditions also proceeded smoothly and gave comparable yields. However, the cyano group was not tolerated well, and only a small amount of product were detected according to GC-MS analysis (**Z-3hf**, 8%, method B). In addition, the reaction of cyclopropylmagnesium bromide **2k** with **1a** under transition-metal-free reaction conditions furnished a mixture of *E*/*Z*-fluorocyclopropylalkenes (**3ak′**, *E*/*Z* ≈ 1/1) in a modest yield.

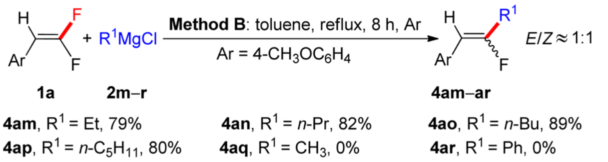
Inspired by the success in the coupling of *gem*-difluoroalkenes with tertiary and secondary alkyl Grignard reagents, to further extend the generality of this practical approach, we performed the reaction of *gem*-difluoroalkene (**1a** as example) with primary alkyl Grignard reagents with the two methods (Schemes 4 and 5). It was found that when the reactions of **1a** with EtMgCl (**2m**), *n*-PrMgCl (**2n**), *n*-BuMgCl (**2o**), or *n*-pentylMgCl (**2p**) were carried in the presence of 25 mol % CuCN (method A), dicoupled products were generated in good yields (Scheme 4, **3am–ap**). On the other hand, an excess amount of RMgX (6 equiv) and a longer reaction time (8 h) were required for the alkylation of *gem*-difluoroalkenes with primary alkyl Grignard reagents under transition-metal-free reaction conditions and a mixture of *E*/*Z*-monocoupled products was formed (Scheme 5, **4am–ap**). The coupling reaction of **1a** with CH_3MgCl (**2q**) and PhMgBr (**2r**) was unsuccessful under both reaction conditions.

Scheme 4. Cu-Catalyzed Primary Alkylation of *gem*-Difluoroalkene[a,b]



[a]Reaction conditions: **1a** (1.0 mmol), **2m–r** (3.0 mmol), 25 mol % CuCN, THF (5 mL), rt, 2 h, Ar. [b]Isolated yields.

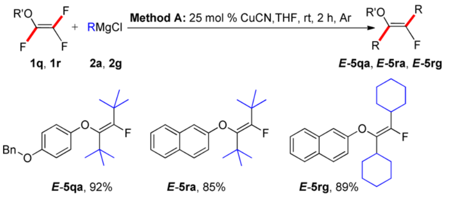
Scheme 5. Primary Alkylation of *gem*-Difluoroalkene under Transition-Metal-Free Conditions[a,b]



[a]Reaction conditions: **1a** (1.0 mmol), **2m–r** (6.0 mmol), toluene (5 mL), reflux, 8 h, Ar. [b]Isolated yields.

Alkylation of ((1,2,2-trifluorovinyl)oxy)arenes (Scheme 6, **1q**, **1r**) with tertiary and secondary alkyl Grignard reagents under Cu-catalyzed conditions produced dialkylation products (*E*-**5qa**, *E*-**5ra**, and *E*-**5rg**). The structure of *E*-**5qa** was determined by X-ray diffraction (see the Supporting Information, p 16). However, when EtMgCl (**2m**) was used as the coupling partner, no desired product was observed.

Scheme 6. Cu-Catalyzed Alkylation of ((1,2,2-Trifluorovinyl)oxy)arenes[a,b]

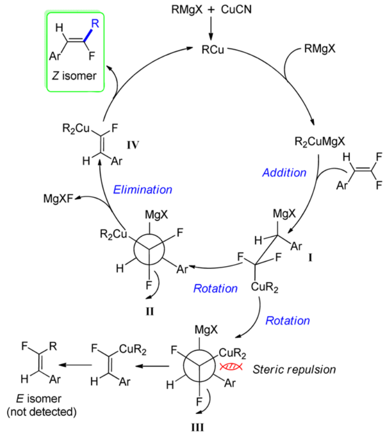


[a]Reaction conditions: **1q**, **1r** (1.0 mmol), **2a**, **2g** (3.0 mmol), 25 mol % CuCN, THF (5 mL), rt, 2 h, Ar. [b]Isolated yields.

Based on the above observations and earlier reports,[19] the mechanism for the Cu-catalyzed tertiary and secondary alkylation of *gem*-difluoroalkenes is proposed (Scheme 7). Initially, 2 equiv of RMgX reacted with CuCN to give dialkylcuprate magnesium halide (R_2CuMgX). The addition of R_2CuMgX to *gem*-difluoroalkene led to the generation of the key intermediate **I**. Rotation of the intermediate **I** by ±60° would result in the formation of two conformations, **II** and **III**. The intermediate **III** was relatively unstable because there might be steric repulsion between R_2Cu and the aryl group. Finally, the elimination of MgXF and RCu from the intermediate **II** and **IV**, respectively, afforded tertiary and secondary alkylated fluoroalkene with excellent *Z*-selectivity.

In addition, according to the literature reports,[17] we suggested that the mechanism of the reaction of *gem*-difluoroalkene with a

Scheme 7. Plausible Mechanism of Cu-Catalyzed Tertiary and Secondary Alkylation of *gem*-Difluoroalkenes



R = tertiary and secondary alkyl group

Grignard reagent under the transition-metal-free conditions might be involved in the formation of radical intermediates.

In summary, we have developed a new strategy for the cross-coupling of *gem*-difluoroalkenes with tertiary, secondary, and primary alkyl Grignard reagents in the presence of CuCN or under transition-metal-free conditions. The scope of the reactions is very broad with regard to both *gem*-difluoroalkenes and Grignard reagents, and various mono- or dialkylated multisubstituted alkenes could be obtained depending on the structure of the alkyl moiety in the Grignard reagents and reaction conditions. The steric effect played a key role in the formation of products. Remarkably, the tertiary and secondary alkylation of *gem*-difluoroalkenes in the presence of 25 mol % CuCN or under transition-metal-free conditions could afford the tertiary and secondary alkyl-substituted fluoroalkenes in high to excellent yields with excellent *Z*-stereoselectivity. It is noteworthy that *gem*-difluoroalkenes were all readily prepared from commercially available reagents following the known procedures.[20] Extension of this transformation to haloarenes and dihaloalkenes and further mechanistic studies are being investigated in our laboratories.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02026.

Crystallographic data for *E*-**5qa** (CIF)

Experimental details, spectroscopic data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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