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Copper–Catalyzed Cyclopropanol Ring Opening C_{sp^3} – C_{sp^3} Cross–Couplings with (Fluoro)Alkyl Halides

Zhishi Ye, Kristen E. Gettys, Xingyu Shen, and Mingji Dai

Department of Chemistry and Center for Cancer Research, Purdue University, 560 Oval Drive, West Lafayette, IN 47907, United States.

Abstract

Novel and general copper-catalyzed cyclopropanol ring opening cross-coupling reactions with difluoroalkyl bromides, perfluoroalkyl iodides, monofluoroalkyl bromides, and 2-bromo-2-alkylesters to synthesize various β -(fluoro)alkylated ketones are reported. The reactions feature mild conditions and excellent functional group compatibility, and can be scaled up to gram scale. Preliminary mechanistic studies suggest the involvement of radical intermediates. The difluoroalkyl-alkyl cross-coupling products can also be readily converted to more valuable and diverse gem-difluoro-containing compounds by taking advantage of the carbonyl group resulting from cyclopropanol ring opening.

Recently, significant progress has been made in the development of transition metal-catalyzed cross-coupling reactions of alkyl electrophiles and alkyl nucleophiles, including enantioselective variants. Most of the commonly used alkyl nucleophiles in these alkyl-alkyl cross-coupling processes are alkyl Grignard reagents, alkyl zinc reagents, and alkyl boron reagents.¹ Some of these reagents suffer from poor functional group compatibility, have to be generated in situ or right before use, and are not stable for long-term storage. Due to the importance of alkyl-alkyl cross-couplings in medicinal chemistry, natural product synthesis, and other related areas, there is a great need to expand the scope of alkyl nucleophiles. Furthermore, due to the importance of fluorinated molecules in medicinal chemistry and many other fields,² the demand for efficient and reliable methods for their synthesis has

Corresponding Author, mjdai@purdue.edu.

Supporting Information

Experimental procedures and characterization for new compounds are provided. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Notes

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increased dramatically. Despite recent advances,³ direct difluoroalkylation or monofluoroalkylation of alkyl nucleophiles have been limited⁴ in comparison to the introduction of such groups on aromatic systems⁵ and unsaturated systems such as olefins and alkynes.⁶ Efficient methods for direct fluoroalkyl-alkyl cross-coupling reactions are highly desirable. Recently, Fu et al. reported an elegant nickel-catalyzed alkyl-alkyl cross-coupling of fluorinated secondary electrophiles (cf. **1**→**2**, Scheme 1A).^{4a}

Cyclopropanols are important and useful functional groups and can be readily accessed via the Kulinkovich reaction or the Simmons-Smith protocols.⁷ They are bench stable and can be stored for a relatively long time. Due to its intrinsic ring strain, cyclopropanols are prone to ring opening reactions and are often viewed as homoenolate equivalents. Therefore, cyclopropanols could be important potential alkyl nucleophiles in alkyl-alkyl cross-coupling reactions. Moreover, the resulting coupling products would be equipped with a ketone functional group, which can be transformed to a variety of products due to the rich carbonyl chemistry. Currently, most of the transition-metal-catalyzed cyclopropanol ring opening cross-couplings focus on palladium-catalyzed C-C bond formation,⁸ which is significantly limited by the proclivity of β -H elimination. Copper, in comparison to palladium, is more abundant and cheaper, and less prone to β -H elimination chemistry.⁹ However, copper-promoted or copper-catalyzed cyclopropanol ring opening cross-coupling reactions have been very rare.¹⁰ Recently, Cha and coworkers have developed elegant S_N2' alkylations of the Zn(II)/Cu(I)-homoenolate derived from treating cyclopropanols with more than stoichiometric amount of CuCN and one equivalent of ZnEt₂ (cf. **3**→**4**, Scheme 1B)^{10c} and applied this chemistry in total synthesis of natural products.^{10d,e} We have developed copper-catalyzed cyclopropanol ring opening electrophilic cross-coupling reactions to synthesize various β -CF₃, β -SCF₃, and β -amino-substituted carbonyl products.^{11a,b} Herein, we report novel and unprecedented copper-catalyzed cyclopropanol ring opening alkyl-alkyl cross-coupling reactions with difluoroalkyl bromides, perfluoroalkyl iodides, monofluoroalkyl bromides, and 2-bromo-2-alkylesters as electrophiles (Scheme 1C). In addition to the catalytic nature, the selectivity of breaking the strained Walsh bond of unsymmetrical cyclopropanols is opposite from the previous cases,^{10c, 11b} which presumably due to a radical ring opening process of the cyclopropanols.

Due to the importance and prevalence of difluoroalkyl groups in bioactive molecules,¹² we started our exploration with 2-bromo-2,2-difluoroacetate (**11**) as the electrophilic coupling partner with cyclopropanols. After extensive reaction condition optimizations (see the Supporting Information), we discovered that (i) CuI is superior to CuCN, CuTc, and Cu(MeCN)₄PF₆; (ii) 2,2'-bipyridine or 9,10-phenanthroline ligand is critical; (iii) the reaction is very sensitive to solvent and MeCN is much better than other solvents such as THF, PhMe, DMF, DCE, 1,4-dioxane, and DMSO; (iv) a base is necessary to neutralize the acid generated in the reaction system. Under the conditions of catalytic amount of CuI/9,10-phenanthroline in MeCN at 80 °C with K₂CO₃ as base, optimal yields of 2,2-difluoro-1,5-dicarbonyl products¹³ (cf. **12**) could be obtained from various cyclopropanols and **11**.

We then investigated the substrate scope in terms of both cyclopropanols and the electrophilic bromodifluoroalkyl coupling partners (Figure 2, 3, and 4). To our satisfaction, the reaction has broad substrate scope and tolerates a variety of functional groups. Both aryl

and alkyl substituted cyclopropanols underwent the desired ring opening reactions with **11** to provide various β -difluoroalkylated ketone products in good to excellent yield (Figure 2). Alkyl/aryl ether (**12a**, **12c**, **12f**), benzoate (**12g**), TBS-ether (**12h**), α,β -unsaturated ester (**12j**) and aldehyde (**12k**), amide (**12l**), and epoxide (**12m**) are well tolerated. The reaction could also be conducted in gram-scale (**12a**, Figure 2).

We next explored unsymmetrical cyclopropanol substrates (cf. **3**, Figure 3). In this scenario, one question was apparent to us: which Walsh bond, the less substituted bond “a” or the more substituted bond “b”, would be selectively broken for the cross-coupling? It has been shown that radical promoted cyclopropanol ring opening tends to break bond “b” to provide more stable and more substituted β -alkyl radical¹⁴ and formation of metallo-homoenolate favors breaking bond “a” to generate less substituted metallo-homoenolate.^{10c,11b} In our case, the more substituted Walsh bond “b” was selectively cleaved and the difluoroalkylation occurred at the more substituted carbon, which indicates a radical cyclopropanol ring opening process. The selectivity is excellent for the cases of aryl substituted cyclopropanols and products **13a-c** were produced as the dominant products. While **13d** was produced in high selectivity (17/1), the selectivity dropped significantly in the case of **13e** (2.4/1). Additionally, aldehyde product **13f** could be obtained in good selectivity as well.

Other halodifluoroalkyl electrophiles such as 2-bromo-2,2-difluoroamides, (bromodifluoromethyl)phosphonates, and perfluoroalkyl iodides work smoothly under the reaction conditions (Figure 4). Morpholine- (**16a**), Bocprotected piperazine- (**16c**), benzoazepane- (**16d**), indoline- (**16e**), and azitidine-derived (**16j**) difluoroamides can be produced in good to excellent yield. With (bromodifluoromethyl)phosphonate as electrophile, a strong base, LiOtBu has to be used and the reaction yield was relatively low (**16k**, 32%). In the case of perfluoroalkylation (**16l** and **16m**), the corresponding alkyl iodides were used and good yields were obtained.

We then moved beyond difluoroalkyl electrophiles and explored the use of other alkyl electrophiles (Figure 5). To our delight, simply switching the base from K₂CO₃ to *i*Pr₂NH and using CuI or CuCl as catalyst, electrophiles such as 2-bromo-2-alkyl acetates and 2-bromo-2-fluoroacetates became effective coupling partners. We also observed some changes in comparison to the difluoroalkylation cases. Free alcohol (cf. **18j**) and terminal olefin (cf. **18h**), which are not compatible in the previous cases, are well tolerated in the slightly modified conditions. In general, good reaction yields could be obtained and a variety of functional groups including benzoate (**18e**), primary TBS-ether (**18f**), epoxide (**18g**), and aryl bromide (**18n**) are compatible under the reaction conditions.

One advantage of using cyclopropanols as nucleophilic alkyl cross-coupling partners is that the coupling products are equipped with a ketone functional group. Due to rich chemistry of carbonyl group, the coupling products can be converted to a diverse collection of products using standard carbonyl transformations. For example (Figure 6), Fisher indole synthesis was used to convert **12a** to indole-containing biaryl product **19** in 94% yield.¹⁵ Reductive amination followed by lactam formation provided α,α -difluorolactam **20** in excellent yield.¹⁶ When NaBH₄ was used, 3,3-difluoro-6-aryltetrahydropyran product **21** was obtained in 87% yield.¹⁷ These scaffolds are of great medicinal importance but are

otherwise challenging to access.¹⁵⁻¹⁷ The ketone carbonyl group could be reduced to a methylene group as well (cf. **12a**→**22**), which further expands the potential use of cyclopropanols as alkyl cross-coupling partners.

Mechanistically, both the conversion of **22** with a double bond to **23** and the formation of **24** when TEMPO was added to the reaction of **3aa** and **11** (Figure 7) suggesting the formation of a radical at the α -carbon bearing the two fluorine atoms presumable via a single electron transfer (SET) process between CuI and the bromides (**22** or **11**). The resulting Cu(II) salt would then oxidize cyclopropanols via another SET process to promote a radical cyclopropane ring cleavage as evidenced by the use of unsymmetrical cyclopropanols to generate a more stable β -alkyl radical for following cross-couplings.^{14,18}

In summary, we have developed a novel umpolung strategy for the synthesis of β -(fluoro)alkylated ketones via copper-catalyzed cyclopropanol ring opening Csp³-Csp³ cross-couplings with various alkyl halides including difluoroalkyl bromides, perfluoroalkyl iodides, monofluoroalkyl bromides, and 2-bromo-2-alkylesters. Many functional groups are tolerated under the mild reaction conditions. The reaction can also be scaled up. In addition to its catalytic nature, a different cyclopropane ring opening mode has been observed in comparison to the previous cases. Preliminary mechanistic studies indicate the involvement of radical intermediates. The coupling products could be converted to a diverse collection of important compounds. This chemistry demonstrates the significant potential of cyclopropanol and related systems as useful nucleophiles in alkyl-alkyl cross-coupling reactions. We are currently investigating the detailed reaction mechanisms as well as developing enantioselective versions of this type of transformation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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A. Ni-catalyzed alkyl-alkyl cross-couplings of fluorinated secondary electrophiles (Fu, et al.)

B. S_N2' alkylation of cyclopropanols via homoenolates (Cha, et al.)

C. This work: Cu-catalyzed ring opening (fluoro)alkyl-alkyl cross-couplings

Figure 1.
Selected examples and this work.

Figure 2.

Cyclopropanol substrate scope^a. ^[a] General reaction conditions: A solution of **3a** (0.1 mmol), **11** (0.4 mmol), CuI (0.01 mmol), phenanthroline (0.02 mmol), K₂CO₃ (0.2 mmol) were stirred in MeCN (1 mL) at 80 °C for 10-12 h. The reaction process was monitored by thin-layer chromatography. Isolated yield from flash chromatography was given; ^[b] gram scale.

Figure 3. Unsymmetrical cyclopropanol substrate scope^a. ^[a] Isolated yield with **13/14** ratio in parenthesis.

Figure 4.

Difluoroalkyl halides substrate scope^a. ^[a] Yield of isolated product; ^[b] *i*Pr₂NH as base; ^[c] LiO*t*Bu as base; ^[d] with perfluorobutyl iodide; ^[e] with perfluorohexyl iodide.

Figure 5. Other alkyl halides substrate scope^a. ^[a] Isolated yield; ^[b] CuI was used.

Figure 6.
Synthetic transformations of **12a**.

Figure 7.
Preliminary mechanistic studies.