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Highly Chemoselective *gem*-Difluoropropargylation of Aliphatic Alcohols

Toshitaka Okamura, [a] Syusuke Egoshi, [b] Kosuke Dodo, [b] Mikiko Sodeoka, [b] Yoshiharu Iwabuchi, [a] Naoki Kanoh[c]*

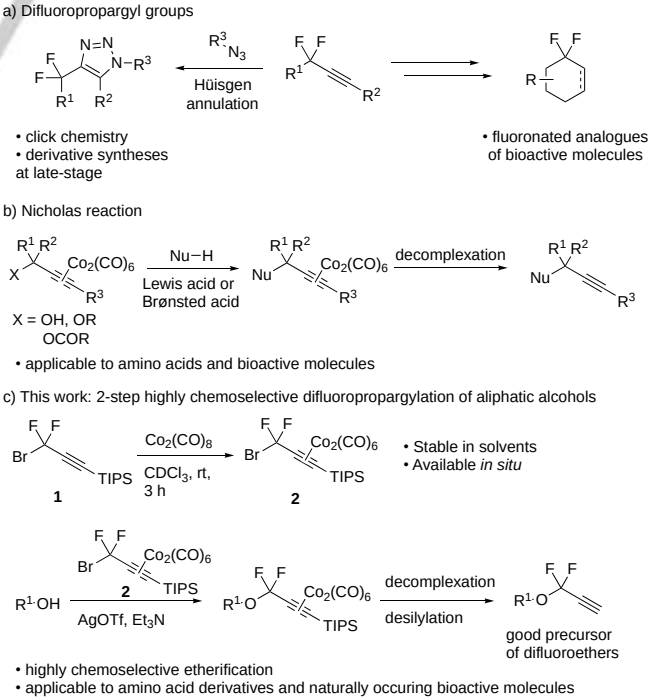
Abstract: Despite the potential of α-fluoroethers in medicinal chemistry, their synthetic methods, especially etherification of aliphatic alcohols, have been limited. Herein, we developed 2- and 3-step *gem*-difluoropropargylation of aliphatic alcohols including amino acid derivatives and naturally occurring bioactive molecules. Highly chemoselective etherification proceeded using the *gem*-difluoropropargyl bromide dicobalt complex in the presence of silver triflate and triethylamine. Decomplexation of dicobalt complexes was achieved by using cerium ammonium nitrate or *N,N,N'*-trimethylethylenediamine. The thus obtained *gem*-difluoropropargyl ethers were converted to various α-difluoroethers which are expected to be useful for medicinal chemistry.

Ether is one of the simplest and most prevalent functional groups in medicines and other organic compounds. Among the ethers, α-fluoroethers such as difluoromethyl ethers are important components because the introduction of fluorine atom(s) changes the chemical, physical, and biological properties of organic compounds.[1] For example, α-fluoroethers improved the lipophilicity and *in vivo* oxidative stability of drugs compared with alkyl ethers.[1a, 2] However, only a limited number of practical α-fluoroalkylation of aliphatic alcohols have been reported.[3] Because aliphatic alcohols are widely present in organic compounds,[4] it would be valuable to develop new etherification methods to introduce various fluoroalkyl units into them. In particular, if fluoroalkyl groups with various reactivities could be introduced, this would be useful for organic synthesis and derivative synthesis in drug discovery.[5]

Since alkynes have different reactivities and can be converted to various functional groups, it is highly useful to introduce alkynes into organic molecules.[5] Among the alkynes, the *gem*-difluoropropargyl unit has attracted attention because of its unusual reactivity and synthetic utility (Scheme 1a).[6] The *gem*-difluoropropargyl group is a better reactant in dipolar cycloaddition,[7] e.g., Hüisgen annulation, which is useful for derivative syntheses[8] and chemical biology,[9] than the normal propargyl group because of the fluorine effects. Difluoropropargyl groups are also used as synthetic precursors of difluoro-analogs of bioactive molecules. Hence some research groups have reported the introduction of *gem*-difluoropropargyl units using a metal-catalyzed cross-coupling reaction as well as under other conditions.[10] For example, Hammond's group reported nucleophilic difluoropropargylation including aliphatic alcohols although a solvent amount of nucleophile is needed in etherification. [10a]

Nicholas reaction, which utilizes cobalt-stabilized carbocations as active species, is a representative protocol for propargylation (Scheme 1b).[11] The cobalt-stabilized carbocations are usually generated from corresponding alcohols (X = OH), ethers (X = OR) or acetates (X = OCOR) using Lewis- or Brønsted acids, and react with various nucleophilic functional groups including aliphatic alcohols.[12] Recently, Nicholas reaction was applied to the propargylation of amino acids[13] and bioactive molecules.[14]

Herein, we report the electrophilic difluoropropargylation of aliphatic alcohols using a silver triflate (AgOTf) and a *gem*-difluoropropargyl bromide dicobalt complex **2**, which is easily prepared from triisopropylsilyldifluorobromopropyne (**1**)[15] and dicobalt octacarbonyl (Scheme 1c). This reaction is practical and easy to operate to obtain *gem*-difluoropropargyl dicobalt complex ethers that can be easily converted to *gem*-difuoropropargyl ethers by decomplexation. Our developed etherification proceeds chemoselectively in the presence of various nucleophilic functional groups and is successfully applied to bioactive molecules with multiple nucleophilic groups. The obtained *gem*-difluoropropargyl ethers have been applied to the synthesis of various difluorinated ethers using the reactivity of the alkynes.



Scheme 1. Overview of difluoropropargyl groups, Nicholas reaction, and the present work.

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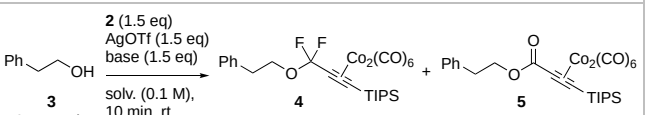
Firstly, we screened the conditions of etherification using **2** as a reagent and phenylethyl alcohol (**3**) as a model substrate (Table 1). When AgOTf was used as a Lewis acid and benzene as a solvent, the desired product **4** was obtained, but the major product was ester **5** (entry 1). We assumed that the formation of **5** occurred due to the elimination of fluorine atoms adjacent to the alkyne-dicobalt complex in **4** and insertion of H_2O under an acidic condition. Therefore, we next attempted addition of pyridine as a base and succeeded in obtaining the desired product **4** in 66% yield (entry 2). After the considerable screening of bases, we discovered that Et_3N gave a better yield (entry 3). Thus, we decided to use Et_3N as an optimal base. We changed the solvent and found that CH_2Cl_2 improved the yield (entry 4), and toluene was the best solvent (entry 5). Compared to AgOTf, the yield of **4** decreased with $AgNTf_2$ (entry 6) or $AgBF_4$ (entry 7). Based on these results, we decided that the conditions in entry 5 were optimal. Unlike Hammond's conditions, our conditions did not require a solvent amount of alcohols, and we expected that the conditions could be applied to a wider variety of alcohols.

Table 1. Optimization of the reaction conditions.



			Yield (%)[a]		
Entry	base	solvent	**4**	**5**	SM (**3**)
1	none	benzene	5	69	0
2	pyridine	benzene	66	7	0
3	Et_3N	benzene	85	0	9
4	Et_3N	CH_2Cl_2	88	0	0
5	Et_3N	toluene	99	0	0
6[b]	Et_3N	toluene	85	4	0
7[c]	Et_3N	toluene	<16	0	34

[a] Yield was determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as an internal standard. [b] $AgNTf_2$ was used instead of AgOTf. [c] $AgBF_4$ was used instead of AgOTf.

With the optimal conditions in hand, we next explored the substrate scope of this reaction (Figure 1). First, using substrates having non-nucleophilic functional groups, we attempted the functionalization of various alcohols (Figure 1a). Etherification of phenylethyl alcohol derivatives containing a methoxy group and a bromo group proceeded and gave the desired ethers in good yield (**6**: 84%; **7**: 84%). The reaction was easily scalable and the yield did not diminish with scaling (**6**: 1 mmol scale, 91%). When 4-nitro phenylethyl alcohol was used as a substrate, $AgNTf_2$, a stronger Lewis acid than AgOTf, was found to be effective probably because of the diminished nucleophilicity of alcohol by the nitro group (**8**: 60%). Benzyl alcohol derivatives could be functionalized in moderate yield under the optimal conditions (**9**: 64%; **10**: 63%). In these cases, dibenzyl ethers were also observed. *N*-Boc and *N*-Fmoc 4-hydroxypiperidines were tolerated under the optimal conditions (**11** and **12**), indicating that the optimal conditions are mild and could be applied to more complex molecules. Tertiary

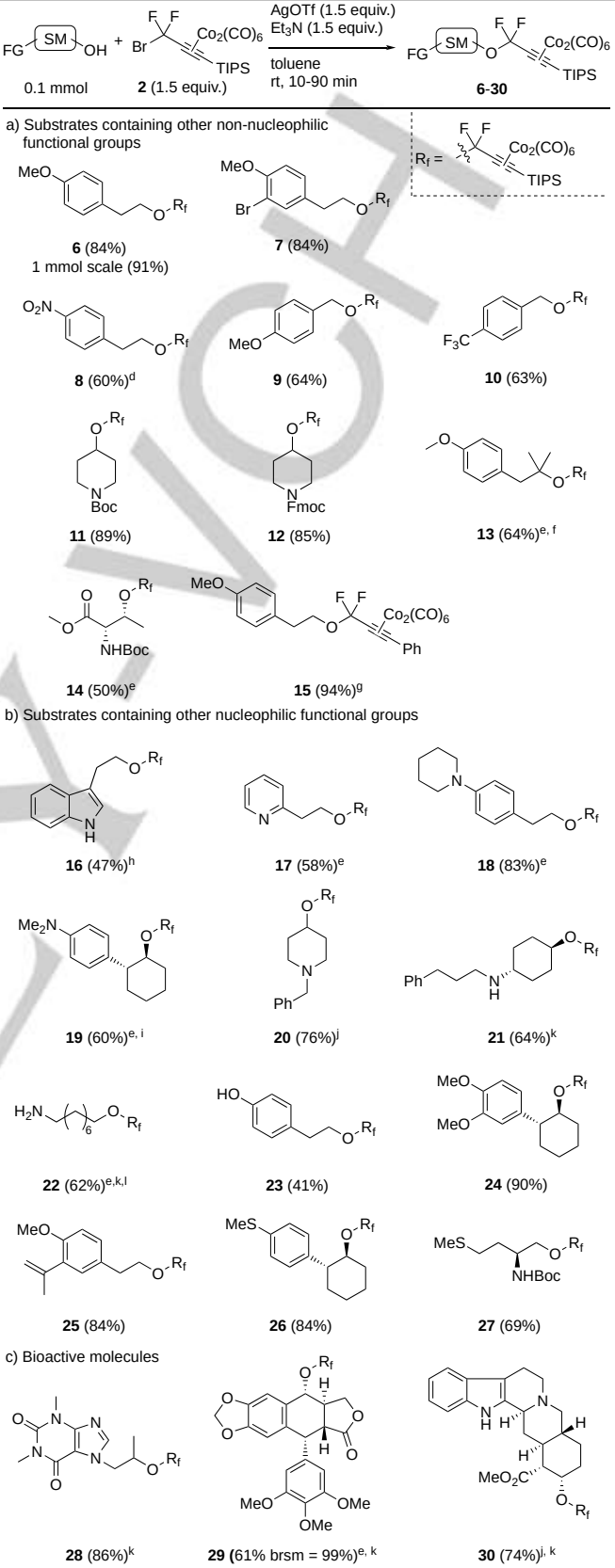


Figure 1. Substrate scope. [d] $AgNTf_2$ was used instead of AgOTf. [e] DTBMP was used instead of Et_3N. [f] Reagents were used at 2 equiv. [g] A phenyldifluorobromopropyne dicobalt complex was used. [h] Reagents were used at 1.2 equiv. [i] Benzene was used instead of toluene. [j] Et_3N was not added. [k] Toluene-CH_2Cl_2 was used. [l] The product was isolated after acetylation of the amino group.

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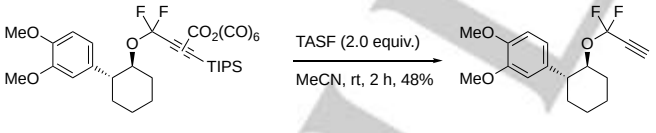
alcohol was etherified in good yield when larger amounts of **2** and DTBMP were used (**13**: 64%). The reaction was applied to a threonine derivative and gave **14** without epimerization. A Ph-substituted *gem*-difluoropropargyl bromide dicobalt complex was also used in this reaction and gave the ether **15** in 94% yield.

Next, we checked the applicability of substrates having other nucleophilic groups (Figure 1b). As briefly stated above, stable carbocations adjacent to an alkyne-dicobalt cluster react with various nucleophiles such as electron-rich aromatics,[14] amines,[16] sulfides,[17] and other nucleophiles[18] in the Nicholas reaction. Interestingly, our developed etherification proceeded in substrates containing other nucleophiles, such as indole NH (**16**), pyridine (**17**), and aniline (**18** and **19**). Moreover, secondary amine and tertiary amine, which are highly nucleophilic groups, did not interfere with the desired etherification and gave the desired ethers (**20** and **21**). Even with the primary amino group, the reaction proceeded with high aliphatic alcohol selectivity to give ether **22**. The phenolic hydroxyl group in substrate **23** did not react under these conditions. Electron-rich alkenes and aromatics, which are good reaction partners in the usual Nicholas reaction, did not interfere with this reaction (**24** and **25**). There was no problem with the presence of the sulfide (**26** and **27**). Although the detailed mechanism for the chemoselectivity has not been clarified yet, it is considered that the reaction proceeds by a mechanism different from the usual Nicholas reaction.

The present conditions were effective for the functionalization of bioactive molecules (Figure 1c). Proxyphylline with a xanthine skeleton was converted to **28** in excellent yield using CH_2Cl_2 as a co-solvent. Podophyllotoxin, which has a sterically hindered secondary alcohol, was also functionalized to give **29** without epimerization of the α-carbonyl position. Moreover, yohimbine with indole NH and tertiary amine underwent the etherification to give **30** in good yield.

Since the etherification described above using **2** succeeded in various alcohols, we then examined the conditions for decomplexation of dicobalt hexacarbonyl complexes and desilylation of the TIPS group for derivative synthesis. We devised three different approaches for this purpose. First, we used fluorides because decomplexation of the dicobalt complex and desilylation are known to proceed simultaneously.[18a] Along this line, 3,4-dimethoxyphenylcyclohexanol derivative **24** was converted to terminal alkyne **31** using TASF (Scheme 2).



24 **31**

Scheme 2. Decomplexation and desilylation using TASF.

Although this approach successfully gave the desired deprotection products, the yields were moderate at best. Therefore, stepwise deprotection approaches were next examined. After the screening of reagents and conditions, we found that cerium ammonium nitrate (CAN)[11b] was a suitable decomplexation reagent. We also found that the resulting TIPS group could be removed by tetrabutylammonium fluoride (TBAF) under -78 ºC (Figure 2). Under these conditions, compounds having an aryl group and a tertiary amine could be converted to the corresponding terminal *gem*-difluoropropargyl groups (**32** and **33**). A substrate having a base-sensitive Fmoc was also converted to **34** without byproduct formation. The decomplexation methods were effective for the production of amino acid derivative **35** and proxyphylline derivative **36**. The Ph-substituted *gem*-difluoropropargyl dicobalt complex was also converted to the corresponding alkyne **37**.

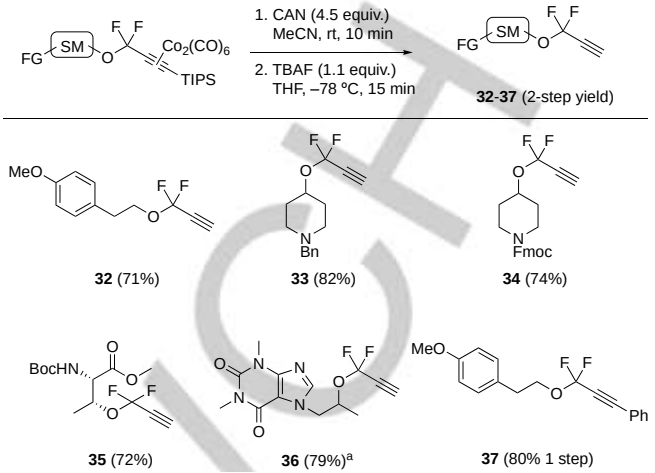
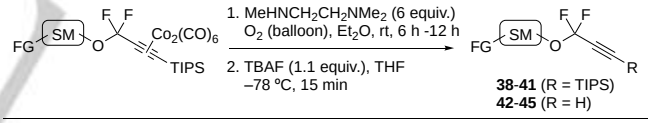


Figure 2. Decomplexation and desilylation of the obtained complexes using CAN and TBAF. [a] Acetone was used as a solvent in the first step.

When CAN decomposed the substrates in the first step, *N,N,N'*-trimethyl ethylenediamine was a good substitute for the decomplexation (Figure 3).[19] Using diamine in the presence of oxygen, various oxidant-sensitive derivatives could be decomplexed. These conditions were successfully applied to aniline derivative **38**, which was difficult to convert using CAN. Under these conditions, sulfide was well tolerated and gave the target product **39** in good yield. Podophyllotoxin derivative **40** with an electron-rich trimethoxybenzene and yohimbine derivative **41** with an indole were also tolerated under these conditions. In these substrates, the TIPS group was also removed by TBAF to give the terminal *gem*-difluoropropargyl ethers **42**-**45**.



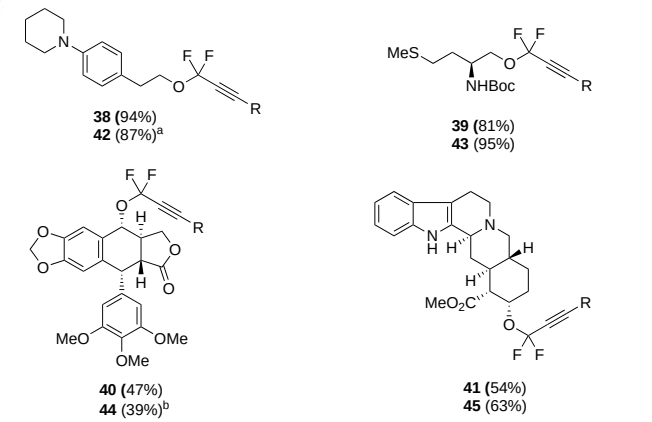
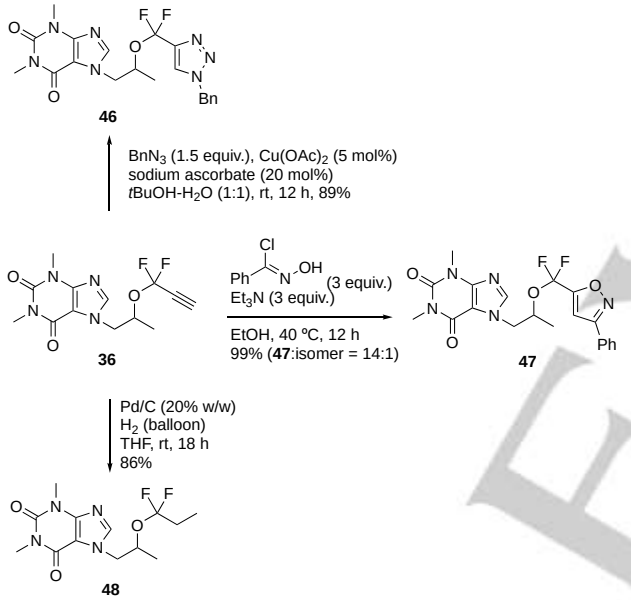


Figure 3. Decomplexation and desilylation of the obtained complexes using *N,N,N'*-trimethyl ethylenediamine and TBAF. [a] The yield was determined by ^{1}H-NMR using CH_2Br_2 as an internal standard. [b] An epimer of **44** was also obtained (40%).

The *gem*-difluoropropargyl group is a potentially useful functional group in chemical biology. For example, it is known that the Hüisgen annulation of terminal *gem*-difluoropropargyl groups and azides proceeds at the temperature of cell culture (e.g., ~37 ºC) without a copper catalyst.[10b, 10c] On the other hand, we are particularly interested in the Raman spectral property of *gem*-

difluoropropargyl groups. Many alkynes were found to be suitable Raman tags for live-cell imaging, and substituents on alkyne were known to effect the wavelength and intensity of the Raman signals.[20] We thus measured and compared the alkyne Raman signals of several *gem*-difluoropropargyl ethers and their non-substituted propargyl ones. Interestingly, alkyne Raman signals of *gem*-difluoropropargyl ethers appeared at higher wavenumbers compared to those of propargyl ethers, without changing their intensities (see the Supporting Information). These results suggested that *gem*-difluoropropargyl groups may be useful Raman tags for multi-imaging with several alkynes.

Finally, we applied *gem*-difluoropropargyl compounds to the synthesis of various α-difluoroethers by using proxyphylline derivative **36** (Scheme 3). As mentioned above, *gem*-difluoropropargyl groups react at ambient temperature with azides to give triazoles such as **46**.[7] When phenyl nitrile oxide was used as a reactant, isoxazole **47** was obtained with good selectivity. It was possible to convert **36** to the fluoropropyl ether **48** by reducing the alkyne.



Scheme 3. Syntheses of various difluoroethers.

In conclusion, we developed *gem*-difluoropropargylation of alcohols using complex **2**. Our developed methods could be applied to various substrates including several naturally occurring compounds and amino acid derivatives. Notably, complex **2** reacted with aliphatic alcohol selectively even if the substrates contained other nucleophilic functional groups. The introduced *gem*-difluoropropargyl dicobalt cluster was easily removed by CAN or *N,N,N'*-trimethylethylene diamine, and then desilylation by TBAF converted the resulting compound to useful terminal *gem*-difluoropropargyl groups. The Raman spectral property of *gem*-difluoropropargyl ethers was clarified, and the obtained *gem*-difluoropropargyl ethers were successfully converted to various α-difluoroethers. We hope that the method developed herein will provide new opportunities to use α-difluoroethers in drug development. Further studies using complex **2** to synthesize other difluoroethers are underway in our laboratory.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: difluoropropargylation • dicobalt complex•drug development

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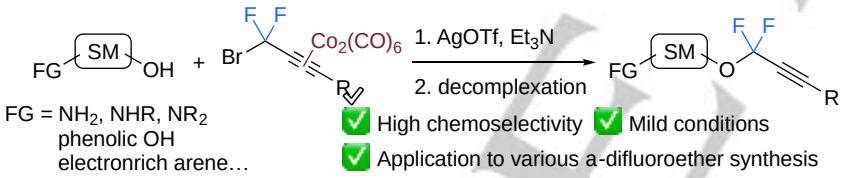

Highly chemoselective 2-step *gem*-difluoropropargylation of aliphatic alcohols was achieved by using *gem*-difluoropropargyl bromide dicobalt complex in the presence of silver triflate and triethylamine. The dicobalt complex could be easily decomplexed, and thus obtained *gem*-difluoropropargyl ethers were converted to various α-difluoroethers.

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