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Palladium-Catalyzed Negishi Coupling of #-CF3 Oxiranyl Zincate: Access to Chiral CF3-substituted Benzylic Tertiary Alcohols

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Palladium-Catalyzed Negishi Coupling of α-CF_3 Oxiranyl Zincate: Access to Chiral CF_3-substituted Benzylic Tertiary Alcohols

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Supporting Information Placeholder

ABSTRACT: We report a Pd-catalyzed stereospecific α-arylation of optically pure 2,3-epoxy-1,1,1-trifluoropropane (TFPO). This method allows for the direct and reliable preparation of optically pure 2-CF_3-2-(hetero)aryloxiranes, which are precursors to many CF_3-substituted tertiary alcohols. The use of continuous-flow methods has allowed the deprotonation of TFPO and subsequent zincation at higher temperature compared to that under traditional batch conditions.

Introduction

The strongly electron-withdrawing trifluoromethyl (CF_3) group can dramatically affect the physical and biological properties of compounds, such as lipophilicity and metabolic stability.[1] These unique effects have led to the prevalence of CF_3 group in synthetically prepared bioactive molecules.[2] In particular, chiral CF_3-substituted tertiary alcohols and their derivatives are present in a diverse range of therapeutic drugs (Scheme 1a). Yet, efficient and general methods for their preparation in optically pure form are still limited. Previous methods mostly rely on enantioselective addition of nucleophiles to trifluoromethylketones or nucleophilic trifluoromethylation of prochiral ketones (Scheme 1b).[3] Although high enantioselectivities are often observed, these methods provide access to only a few, specialized classes of CF_3-substituted tertiary alcohols.

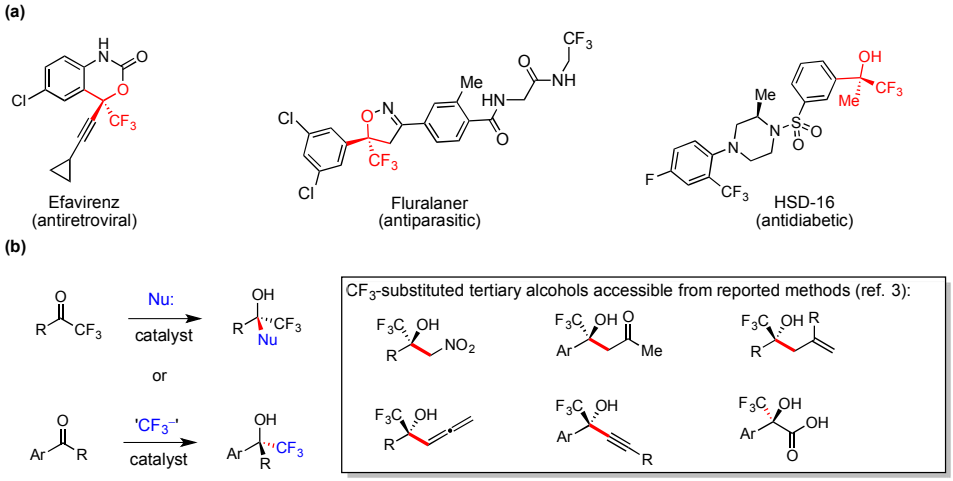
The nucleophilic ring-opening of enantioenriched 2-substituted 2-trifluoromethyloxiranes may provide an alternative, more general, approach to the stereoselective synthesis of chiral CF_3-substituted tertiary alcohols (Scheme 2a). The functionalization of enantioenriched α-trifluoromethyl oxiranyl anion **2**, which could be generated by stereoretentive metalation of optically pure 2,3-epoxy-1,1,1-trifluoropropane (TFPO, **1**), represents an attractive means of accessing these intermediates since both enantiomers of **1** are readily accessible from hydrolytic kinetic resolution of the racemic oxirane[4]. In 2002, Uneyama and coworkers reported the stereoselective trapping of **2** with a variety of electrophiles, including aldehydes and MeI, to give the 2-alkylated epoxides.[5] However, the arylation of **2** proved challenging. The authors reported a single example of a Negishi coupling between the zincated α-trifluoromethyl oxiranyl anion and an aryl iodide.[6] In this case, a modest yield was obtained despite the use of a high catalyst loading and an excess of aryl iodide (The enantiomeric excess of the product was not reported, Scheme 2b).

In contrast to the extensive progress in the Negishi coupling of primary and secondary alkylzinc species,[7] the coupling of tertiary alkylzinc reagents is relatively rare.[8] Problems in the coupling of tertiary alkylzincs include the slow rate of transmetallation of the bulky nucleophile and competitive β-hydride elimination. These challenges are further exacerbated in the case of α-CF_3 oxiranyl zincates, since the strongly electron-withdrawing CF_3 group further reduces the nucleophilicity of the alkylzinc species. We hypothesized that a bulky biaryldialkylphosphine ligand would promote the transmetallation step by forming a coordinatively unsaturated $L_1Pd(Ar)X$ intermediate, which should be less hindered and exhibit higher reactivity toward transmetallation with the organozinc species.[9] Herein, we report the successful development of a highly effective and general catalyst system for the Negishi coupling of α-CF_3 oxiranyl zincate with aryl bromides or chlorides to access 2-aryl-2-trifluoromethyloxiranes in essentially optically pure form (>99% ee or >99:1 dr).

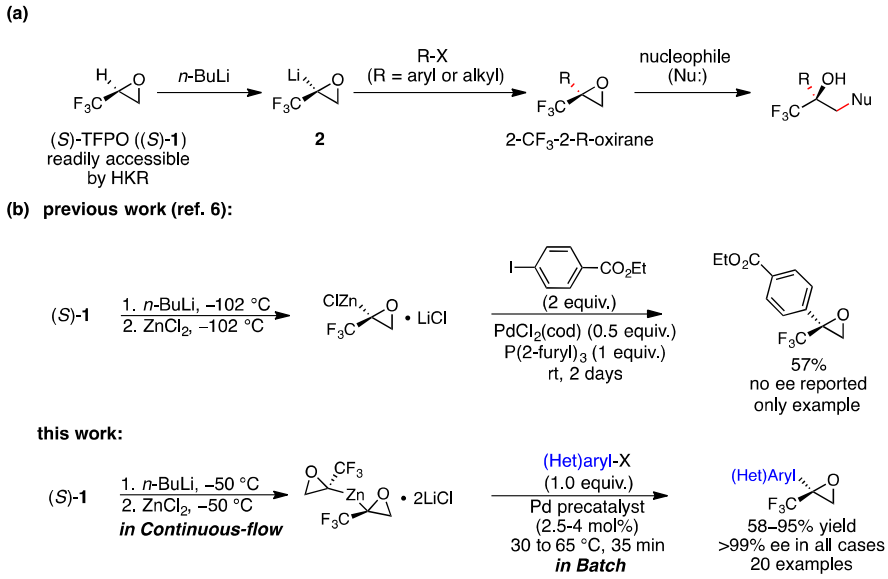
Result and discussion

We initially investigated a series of G3-palladacycle precatalysts[10] bearing various biaryldialkylphosphine ligands for the Negishi coupling of **3a** with α-CF_3 oxiranyl zincate **I** (Table 1). Among the precatalysts evaluated[11], the palladacycle based on CPhos (**P1**), previously reported to be an excellent catalyst in the Negishi coupling of secondary alkylzincs,[12] was found to be the only catalyst that promoted the formation of the desired coupling product **4a**, albeit in trace yield (entry 1). Significant improvement was observed by adding one equivalent LiCl, presumably by forming a more reactive high-order alkylzincate species $RZnCl_3^{2-}$ (**II**) (entry 2).[13] A further improvement in yield was observed when the amount of $ZnCl_2$ was reduced to 0.6 equiv (entry 3), perhaps by favoring the formation of dialkylzincate $R_2ZnCl_2^{2-}$ (**III**) as the dominant alkylzinc spe cies.[14] Based on the observation that α-CF_3 oxiranyl zincate species are much less basic than typical organozinc reagents,[15] we hypothesized that a precatalyst bearing a more acidic anilino group would be more readily activated via deprotonation. This led us to investigate the G5-precatalyst (**P2**).[16] Indeed, the use of **P2** showed higher reactivity than **P1** (entry 4). By comparison, less readily deprotonated G4-precatalyst **P3** gave a much lower yield (entry 5). Finally, using toluene as cosolvent and slow addition of a solution of the organozinc resulted in further improvement to provide **4a** in excellent yield (entry 6 and 7).

Scheme 1. (a) Examples of CF_3-substituted tertiary alcohols and derivatives in pharmaceuticals (b) Enantioselective addition to trifluoromethylketones or trifluoromethylation of ketones



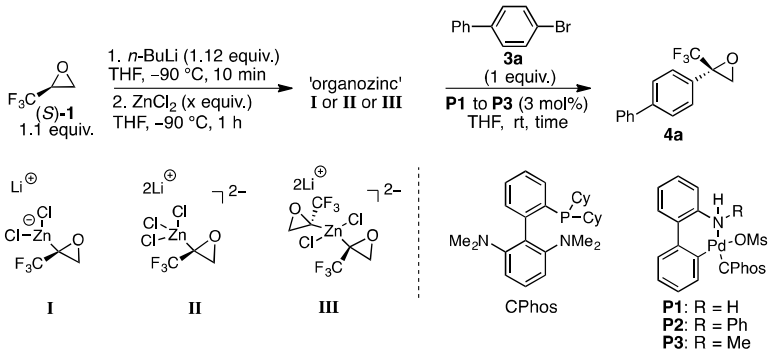
Scheme 2. (a) Synthesis of CF_3-substituted tertiary alcohols via α-CF_3 oxiranyl anion (b) Negishi coupling of α-CF_3 oxiranyl zincate with aryl halides



The highly unstable nature of oxiranyl anions necessitates their generation and subsequent electrophilic trapping at very low temperatures under batch conditions (often below −90 °C). This is difficult to achieve using standard cryogenic equipment and poses a major challenge for the scale-up of reactions. Recently, continuous-flow systems have been shown to provide several advantages for reactions involving thermally unstable intermediates.[17] With more efficient mixing and heat transfer, reactions under continuous-flow conditions may be performed at considerably higher temperatures compared to batch conditions. Yoshida and coworkers reported the development of continuous-flow systems for electrophilic trapping of various oxiranyl anions at −78 to −48 °C.[18] More recently, we[19] and the Knochel group[20] independently developed systems for the deprotonation and zincation of aromatic rings to form (hetero)aryl zincates in continuous-flow followed by Negishi coupling. We sought to transfer the generation of **III** into a continuous-flow system, aiming to increase the reaction temperature and improve the scalability of the process. We found that deprotonation of (*S*)-**1** and subsequent zincation could be conducted at −50 °C in continuous-flow (Scheme 3). The organozincate **III** generated was added directly into the batch reactor for Negishi coupling to provide **4a** in excellent yield.

Using this continuous-flow to batch system we explored the substrate scope of this Negishi coupling reaction (Table 2). Substrates bearing various electrophilic functional groups successfully underwent cross-coupling to provide the epoxides in good yield (**4b** to **4e**). Examples of acidic functional groups such as an alcohol (**4i**), carbamate (**4j**), and sulfonamide (**4k**), are compatible with this transformation. A variety of brominated or chlorinated heterocycles, including quinoline, pyridine, azaindole, and benzothioazole, are also competent partners, providing the epoxide product in moderate to good yield (**4m** to **4r**). We believe that the lower yields realized with substrates **4j**, **4n**, **4o** and **4q** are mostly due to lower yielding Negishi coupling reactions. The NMR yields with these substrates, which were determined before purification, were also lower compared to other substrates. We also note that, in general,

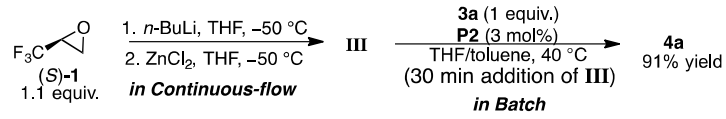
Table 1. Optimization of the Negishi coupling[a]



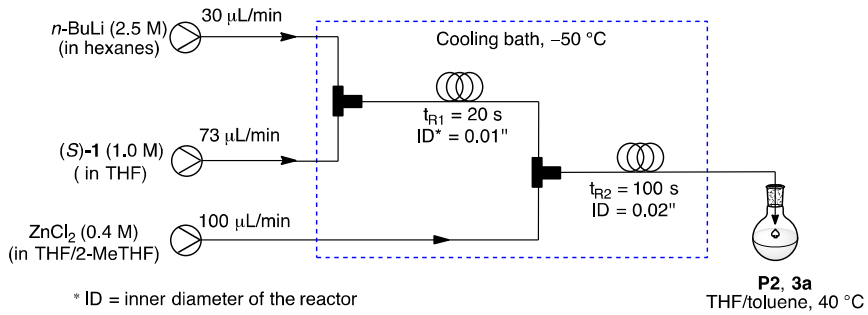
entry	precat.	$ZnCl_2$ (equiv.)	alkylzinc	time (h)	solvent	Yield[d] of **4a**
1	**P1**	1.1	**I**	12	THF	2%
2[b]	**P1**	1.1	**II**	12	THF	13%
3	**P1**	0.6	**III**	2	THF	41%
4	**P2**	0.6	**III**	2	THF	69%
5	**P3**	0.6	**III**	2	THF	11%
6	**P2**	0.6	**III**	2	THF/toluene	74%
7[c]	**P2**	0.6	**III**	0.5	THF/toluene	90% (>99% ee[e])

[a] Reactions were conducted on 0.5 mmol scale, see SI for details of the experiments. [b] 1 equivalent LiCl added. [c] Slow addition of organozinc solution over 30 minutes at 40 °C. [d] Yields were determined by ^{19}F NMR analysis using α,α,α-trifluoromethyltoluene as an internal standard. [e] Enantiomeric excesses are determined by chiral HPLC.

Scheme 3. Continuous-flow to batch system



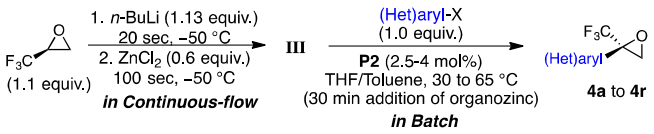
Setup of the continuous-flow to batch system

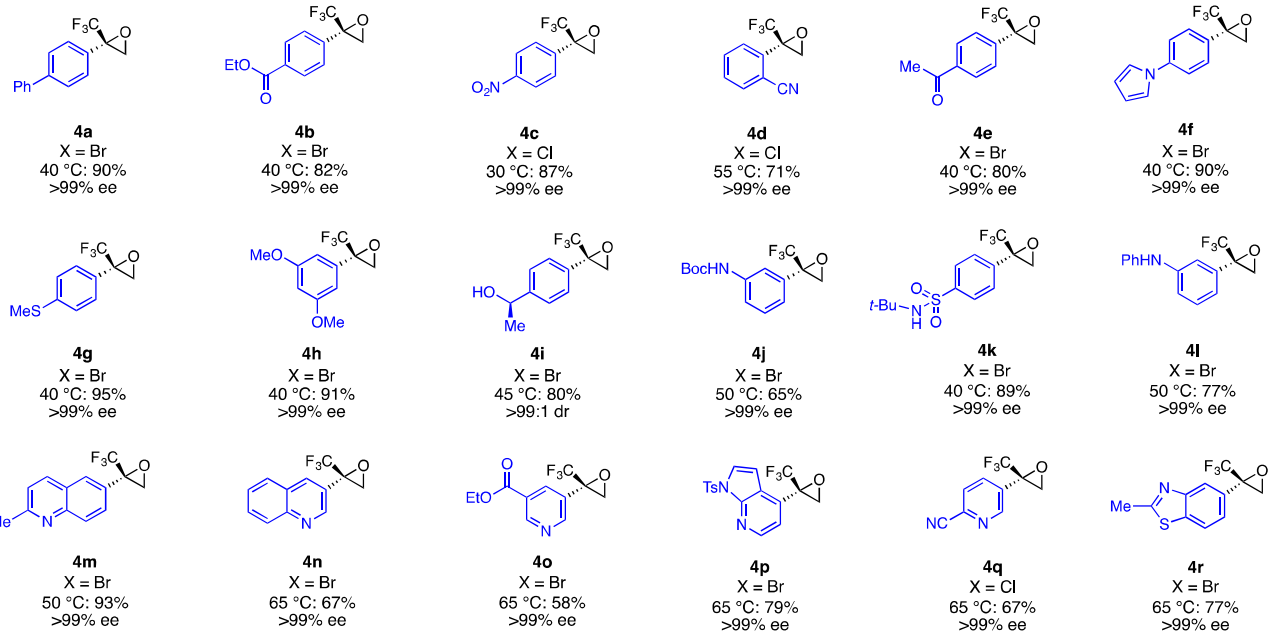


the transformation of pyridine-containing substrates is more challenging and gives lower yields of product. Importantly, no erosion in enantiopurity was ever observed during the course of metalation and arylation; thus in all cases examined, the products were isolated with >99% ee or >99:1 dr. The absolute configuration of the epoxide product was determined by X-ray crystallographic analysis of **4g**.

As previously mentioned, the optically pure 2-aryl-2-trifluoromethyloxiranes obtained from this method represent attractive substrates for ring-opening reactions with various nucleophiles. To illustrate this point, optically pure amino alcohol **5** and homopropargyl alcohol **6** were obtained in high yield by the ring-opening of **4m** with cyclopropylamine and alkynyllithium, respectively (Scheme 4a). Additionally, *N*-tosyl 2-aryl-2-CF_3-aziridine **7** was synthesized in two steps and 75% yield from **4m**. Chiral diol **8**, a precursor to Mosher's acid,[21] was prepared from bromobenzene (**3s**) and (*S*)-**1** in two steps and 70% yield with 1 mol% catalyst loading (Scheme 4b). HSD-016[22], a drug candidate for the treatment of type-2 diabetes, has been previously prepared from **3t** in 37% yield over five steps, four of which were used to prepare epoxide **4t**. The Negishi coupling of **3t** with organozinc **III** afforded **4t** in a single step (68% isolated yield, >99:1 dr) (Scheme 4c), exemplifying the potential utility and efficiency of this method for the construction of medicinally relevant molecules.

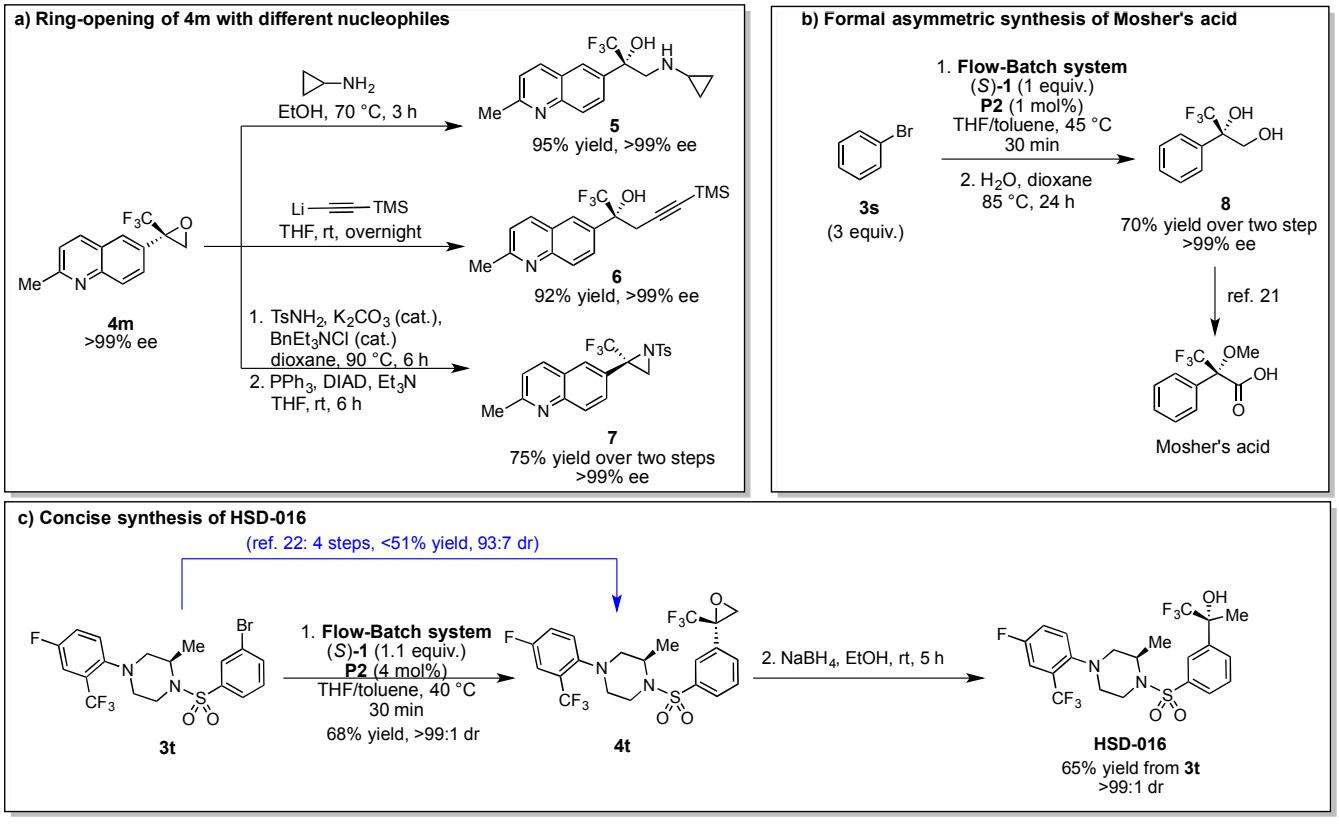
Table 2. Substrate scope[a]





[a] Reactions were conducted on 2 mmol scale. Yields are of isolated products and are the average of two runs. Enantiomeric excesses are determined by chiral HPLC.

Scheme 4. Synthetic applications of the Negishi coupling of α-CF_3 oxiranyl anion



Conclusion

In summary, we have developed an efficient Pd-catalyzed arylation of TFPO by using a high-order dialkylzincate and a precatalyst that is effectively activated by the weakly basic zincate. A continuous-flow to batch system has also been developed. This three-step process allows for the generation of α-CF_3 oxiranyl zincate at much higher temperature compared to the batch conditions. This method demonstrates excellent compatibility with functional groups and reliably provides 2-aryl-2-trifluoromethyloxiranes in exceptionally high enantiomeric excess. With the rich chemistry of epoxides, this process constitutes a general approach to various CF_3-substituted tertiary alcohols and related molecules.

ASSOCIATED CONTENT

Supporting Information.
The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and characterization data for all compounds (PDF)
Crystallographic data for **4g** (CIF)

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Notes

The authors declare the following competing financial interest(s): MIT has or has filed patents on ligands that are described in the paper from which SLB and former/current coworkers receive royalty payments.

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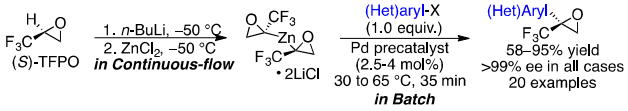
(S)-TFPO
1. n-BuLi, –50 °C
2. ZnCl2, –50 °C
in Continuous-flow
• 2LiCl
(Het)aryl-X
(1.0 equiv.)
Pd precatalyst
(2.5-4 mol%)
30 to 65 °C, 35 min
in Batch
(Het)Aryl
58–95% yield
>99% ee in all cases
20 examples