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Communication

Editing Tetrasubstituted Carbon: Dual C−O Bond Functionalization of Tertiary Alcohols Enabled by Palladium-Based Dyotropic Rearrangement

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Cite This: J. Am. Chem. Soc. 2024, 146, 11061−11066
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ABSTRACT: Many elegant asymmetric syntheses of enantioenriched tertiary alcohols have been developed, and both the transition metal-catalyzed and the radical-based peripheral functionalization of tertiary alcohols have attracted intensive research interest in recent years. However, directly editing tetrasubstituted carbons remains challenging. Herein, we report a Pd-catalyzed migratory fluoroarylation reaction that converts tertiary alcohols to α-fluorinated tertiary alkyl ethers in good to excellent yields. An unprecedented 1,2-aryl/Pd^{IV} dyotropic rearrangement along the C−O bond, integrated in a Pd^{II}-catalyzed domino process, is key to the dual functionalization of both the hydroxyl group and the tetrasubstituted carbon. This reaction, which is compatible with a broad range of functional groups, generates a tertiary alkyl fluoride and an alkyl-aryl ether functional group with inversion of the absolute configuration at the tetrasubstituted stereocenter.

Tertiary alcohol is a ubiquitous structural motif widely present in natural products and pharmaceuticals.[1] Not surprisingly, a variety of methods have been developed for the preparation of these building blocks in enantioenriched form.[2,3] In addition to O-functionalization (O-arylation/alkylation/acylation), two other strategies have been developed for remote functionalization of substituents attached to tetrasubstituted carbon: (a) 1,5-hydrogen atom abstraction (1,5-HAT) of in situ generated alkoxy radicals to generate translocated carbon-centered radicals for subsequent transformation;[4,5] (b) transition metal-catalyzed remote C−H bond activation using hydroxy groups as directing groups.[6] Despite the great progress recorded in this field, direct editing of tetrasubstituted carbon of tertiary alcohols remains underdeveloped.

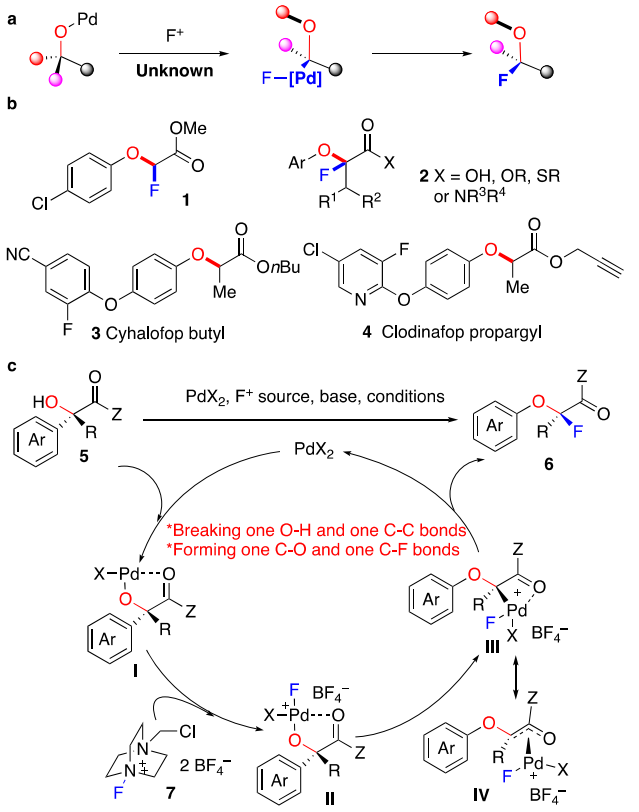
Type I dyotropic rearrangements are a class of pericyclic valence isomerization reactions in which two σ-bonds simultaneously migrate intramolecularly.[7,8] Our group[9−14] and others[15,16] recently reported a 1,2-aryl(alkyl)/Pd dyotropic rearrangement and devised several carbofluorination and oxyfluorination reactions by incorporating this elementary step into a Pd^{II}-catalyzed domino process. The C−C bond served as a stationary phase in all these examples.[9−16] As a continuation of this research program, we wondered whether this 1,2-positional exchange process could occur along the C−O bond of tertiary alcohols (Scheme 1a). Owing to the easy access to alkoxy-Pd^{II} complexes, this synthetic transformation would allow dual functionalization of both the hydroxyl group and the tetrasubstituted carbon of tertiary alcohols. We were particularly interested in the fluorination reaction, as this reaction converts tertiary alcohols to α-fluorinated tertiary alkyl ethers, which are structural units found in bioactive compounds.[17,18] For example, aryloxy-2-fluoroacetic acid derivatives **1**[19] and **2**[20] are synthetic auxins,[21] and compound **2** is known to exhibit remarkable herbicidal activity with the added benefit of being more crop tolerant than the widely used aryloxyphenoxypropanoic acid class of herbicides such as cyhalofop butyl (**3**) and clodinafop propargyl (**4**) (Scheme 1b).[18] While a variety of synthetic methodologies, including S_N2,[22−24] S_N1,[25−27] decarboxylative fluorination,[28−31] and *gem*-difunctionalization of α-diazoketone,[32,33] have been developed to access monofluoroalkyl ethers, the synthesis of α-fluorinated tertiary alkyl ethers has been reported only sporadically,[27,33] and no asymmetric synthesis has been reported to date. In this context, the direct conversion of easily available homochiral tertiary alcohols[1,2] to enantioenriched fluorinated tertiary alkyl ethers would be of particular interest (Scheme 1a).

The proposed transformation involves cleavage of a C−C bond with concurrent formation of a tertiary C−F bond[34] and alkylation/arylation of the hindered hydroxyl group. To accomplish this task, we targeted the conversion of amides **5**, readily accessible from 2-aryl-2-hydroxyalkanoic acids, to 2-aryloxy-2-fluoroalkanoic acid derivatives **6**. The hypothetical reaction sequence exploiting a previously unknown 1,2-aryl/Pd dyotropic rearrangement along the C−O bond as the key step is outlined in Scheme 1c. Ligand exchange between PdX_2 and alcohol **5** (or its deprotonated form) would afford palladium alkoxide complex **I**, which could subsequently be oxidized to Pd^{IV} species **II** in the presence of an appropriate F^+ reagent.[35] The 1,2-aryl/Pd dyotropic rearrangement of the latter would furnish α-carbon-bound Pd species **III**, which could exist in the

Received: February 27, 2024
Revised: April 2, 2024
Accepted: April 4, 2024
Published: April 8, 2024

https://doi.org/10.1021/jacs.4c02924
J. Am. Chem. Soc. 2024, 146, 11061−11066

Scheme 1. Pd-Based Dyotropic Rearrangement along the C−O Bond[a]

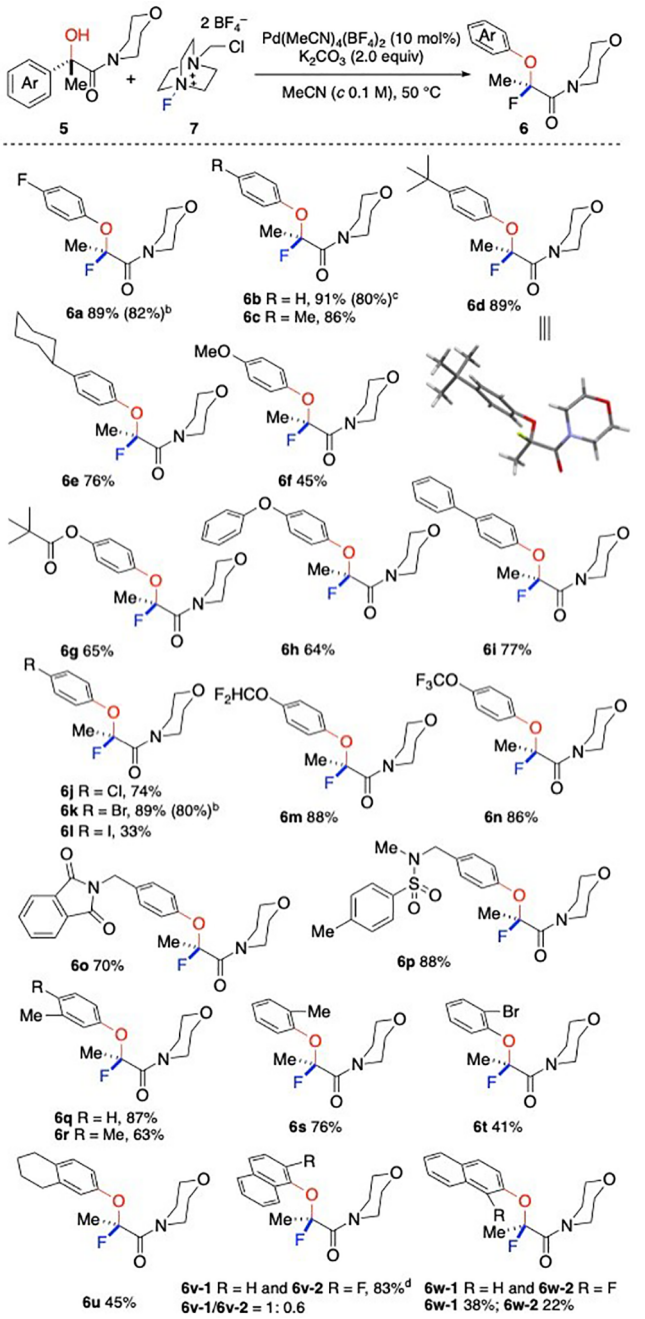


[a](a) Pd-based dyotropic rearrangement along the C−O bond; (b) selected examples of bioactive fluoroalkyl aryl ethers; (c) reaction design and underlying mechanistic hypothesis.

form of the π-oxyallylPd complex **IV**. We assumed that this could provide the driving force for the desired rearrangement reaction. A C−F bond-forming reductive elimination from **III** would then provide product **6**.[36−39] We report herein the realization of this endeavor and document that the reaction occurs with stereoinversion at the tetrasubstituted carbon without eroding the enantiopurity.

Pd^{II} intermediate **I** is known to undergo β-carbon elimination and intramolecular C−H activation,[40−44] and Pd^{IV} species **II** could in principle also undergo the same types of reactions.[45,46] Therefore, both the oxidation of Pd^{II} and the dyotropic rearrangement of the resulting Pd^{IV} should proceed faster than the competitive manifolds mentioned above to drive the reaction toward the desired pathway. Gratifyingly, stirring an acetonitrile solution of **5a** and Selectfluor (**7**) (2.0 equiv) in the presence of K_2CO_3 (2.0 equiv) and a catalytic amount of $Pd(OAc)_2$ (10 mol %) at 50 °C for 24 h indeed afforded product **6a** in 57% yield (Scheme 2). 4-Fluoroacetophenone (**8a**, structure not shown), presumably resulting from the β-carbon elimination of the Pd-alkoxide complex, was also generated in 28% yield. Encouraged by these preliminary results, we fine-tuned the conditions to favor the production of **6a**. Key observations are noted as follows (see SI for details). In the absence of K_2CO_3, a complex reaction mixture was obtained, while replacing CH_3CN with 1,2-dichloroethane (1,2-DCE) led to no reaction. The addition of dtbpy (4,4′-di-*tert*-butyl-2,2′-bipyridine) favored the β-carbon elimination pathway affording **8a** in 42% yield, whereas the

Scheme 2. Dual C−O Bond Functionalization: Scope of the Migrating Group[a]



[a]Reagents and conditions: Selectfluor (2.0 equiv) was used. Unless otherwise specified, the reaction was performed on a 0.2 mmol scale, and the yield refers to the isolated pure product. [b]Reaction was performed on a 5.0 mmol scale. [c]Reaction was performed on a 1.0 mmol scale. [d]Yield of two inseparable products. Selectfluor = 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate). The unwedged bold and hashed lines in compounds **5** and **6** depict only the relative stereochemistry. Both substrates **5** and products **6** are racemates in these examples.[47] The same applies to Schemes 3 and 4.

presence of silver triflate (AgOTf) slightly increased the yield of **6a**. Increasing the reaction temperature reduced the yields of both **6a** and **8a**. Other Pd sources, such as $Pd(OCOCF_3)_2$, $Pd(OPiv)_2$, $Pd(OCOAd)_2$, and $PdCl_2(CH_3CN)_2$, were found

https://doi.org/10.1021/jacs.4c02924
J. Am. Chem. Soc. 2024, 146, 11061−11066

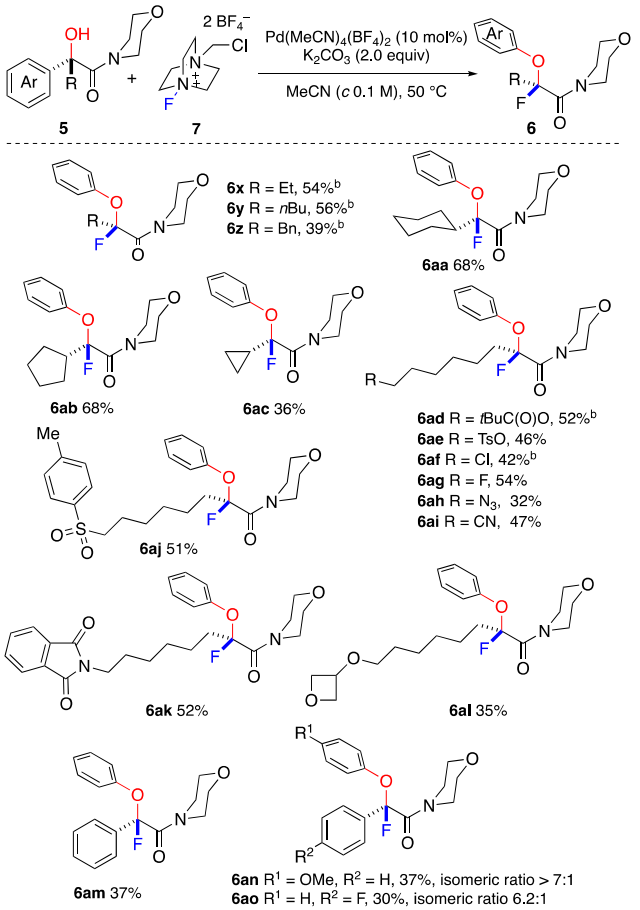
to be less efficient than $Pd(OAc)_2$. However, when $Pd(CH_3CN)_4(BF_4)_2$ was employed as a catalyst, the desired compound **6a** was formed in 89% isolated yield. Control experiments showed that both the palladium salt and Selectfluor were required for the reaction to occur. Overall, heating an acetonitrile solution of **5a**, Selectfluor (2.0 equiv), $Pd(CH_3CN)_4(BF_4)_2$ (10 mol %), and K_2CO_3 (2.0 equiv) was determined to be the optimum conditions.

With the optimum conditions in hand [Selectfluor (2.0 equiv), $Pd(CH_3CN)_4(BF_4)_2$ (10 mol %), K_2CO_3 (2.0 equiv), CH_3CN (*c* 0.1 M), 50 °C], the versatility and efficiency of this transformation were examined by first varying the nature of the migrating aryl group (Scheme 2). The phenyl group and the 4-methyl-, 4-*tert*-butyl-, and 4-cyclohexyl-substituted phenyl groups in substrate **5** participated in the migration to afford the fluorinated aryl alkyl ethers in excellent yields (**6b**–**6e**). The substrate bearing a 4-methoxyphenyl substituent afforded a more complex reaction mixture, probably due to the competitive electrophilic fluorination of the electron-rich arene.[48] The desired product **6f** was, nevertheless, isolated in 45% yield. On the other hand, compound **6g**, which has a less electron-donating 4-pivaloyl group, was formed in 65% yield. The phenoxyphenyl group underwent a 1,2-shift efficiently to afford **6h** in 64% yield, as did the biaryl group (**6i**, 77%). The presence of halogen substituents (Cl, Br, and I) was compatible with the reaction conditions, providing compounds **6j**–**6l** and **6t** amenable to further transformations. In addition to 4-fluorophenyl (**6a**), 4-difluoromethoxy- and 4-trifluoromethoxy-substituted phenyls participated in the 1,2-dyotropic rearrangement to furnish **6m** and **6n** in yields of 88% and 86%, respectively. The phthalimide and *N*-tosyl groups were also tolerated (**6o**, **6p**). The *meta*-, *ortho*-, and disubstituted phenyl groups underwent a 1,2-shift without event (**6q**–**6t**). Bicyclic arenes, such as tetrahydronaphthyl, 1-naphthyl, and 2-naphthyl groups, migrated smoothly to afford the desired products (**6u**, **6v**, **6w**). In the last two cases, products resulting from the concurrent monofluorination of the aromatic ring were formed as minor products.

We next examined the scope of the nonmigrating group (Scheme 3). The conditions were generally applicable to a variety of alkanoic acid derivatives, including linear (**6x**–**6z**) and *β*-branched amides (**6aa**, **6ab**, and **6ac**). The fact that 2-cyclopropyl-2-fluoro-1-morpholino-2-phenoxyethan-1-one (**6ac**) was accessible indicated that radical intermediates might not be involved in this process. Diverse functional groups, such as esters (**6ad**), tosylate (**6ae**), alkyl chloride (**6af**), fluoride (**6ag**), azido (**6ah**), cyano (**6ai**), and sulfone (**6aj**), and heterocycles, such as phthalimide (**6ak**) and oxetane (**6al**), were compatible with the reaction conditions. Finally, the morpholinyl amide of 2-hydroxy-2,2-diarylacetic acid participated in the reaction to afford **6am**, **6an**, and **6ao** in moderate yields. In the latter two cases, the more electron-rich aryl groups preferentially migrated to afford **6an** and **6ao**, respectively, as major isomers. This migratory preference is unusual because the *π*-electrons of the aromatic ring are in principle not involved in the dyotropic rearrangement, unlike those involving a phenonium intermediate.

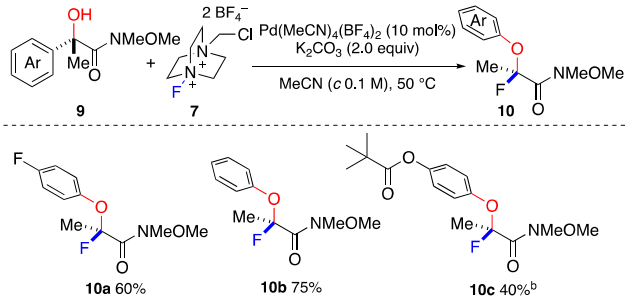
Finally, the rearrangement of the less coordinating Weinreb amides **9** was also briefly examined.[10,49] As shown in Scheme 4, the reaction occurred readily under standard conditions. However, the yields of the rearranged products (**10a**–**10c**) were generally lower than those of their morpholinyl amide counterparts (cf. Scheme 2, **6a**, **6b**, **6g**). Since similar reactivity

Scheme 3. Dual C–O Bond Functionalization: Scope of the Nonmigrating Group[a]



[a]Reagents and conditions: Selectfluor (2.0 equiv) was used. Unless otherwise specified, the reaction was performed on a 0.2 mmol scale, and the yields refer to the isolated pure products. [b]Reaction was performed at 80 °C.

Scheme 4. Dual C–O Bond Functionalization of Weinreb Amides[a]



[a]Reagents and conditions: Selectfluor (2.0 equiv) was used. Unless otherwise specified, the reaction was performed at the 0.2 mmol scale, and the yield refers to the isolated pure product. [b]Reaction was performed at 60 °C.

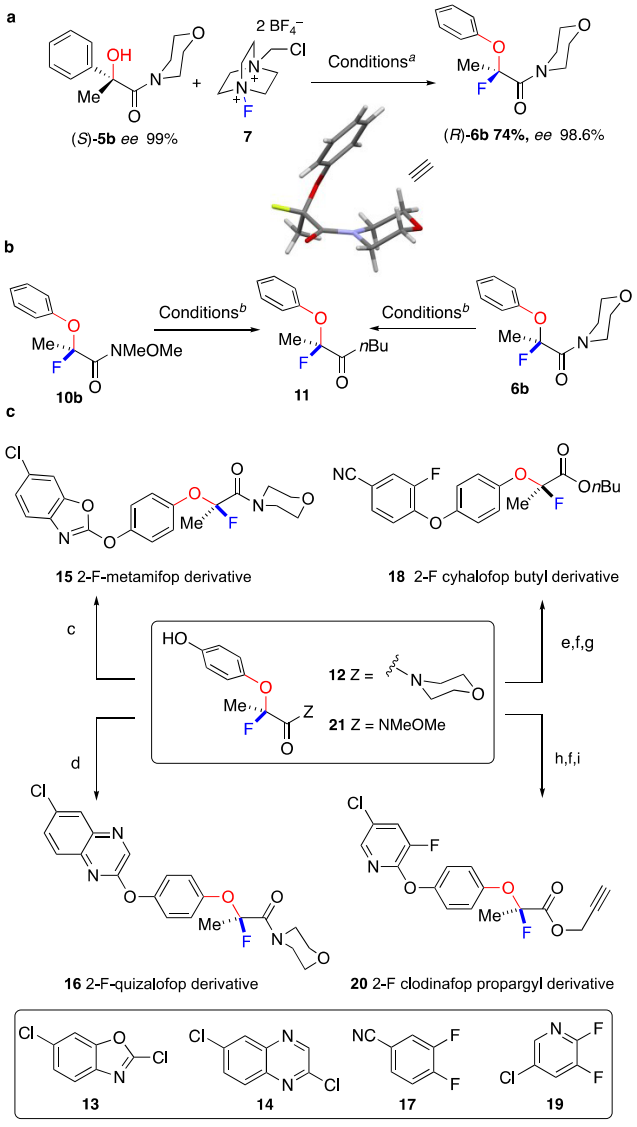
profiles of Weinreb amides and morpholinyl amides were observed in the subsequent post-transformations, no further condition optimization was performed to increase the yields of products **10**.

The rearrangement of amide (*S*)-**5b** (99% ee), which is easily accessible from commercially available (*S*)-2-hydroxy-2-

https://doi.org/10.1021/jacs.4c02924
J. Am. Chem. Soc. 2024, 146, 11061–11066

phenylpropanoic acid, was examined to probe the stereochemical outcome of this reaction. Under standard conditions, (*S*)-**5b** was converted to **6b**, whose absolute configuration was determined to be *R* by X-ray crystallographic analysis (Scheme 5a). The inversion of the absolute configuration is in line with the concerted migration of the dyotropic rearrangement (cf. Scheme 1c). The enantiomeric excess (ee) of product (*R*)-**6b** was determined to be 98.6%, indicating the excellent stereochemical fidelity of the transformation. The result indicates that the $\eta^3-\eta^1$ rearrangement of the Pd-oxa-π-allylic complex (Scheme 1c, III and IV) proceeds without racemization in this instance, consistent with the established literature precedents.[50] Whereas stereoinversion of a tertiary alcohol with a hydroxyl group or its activated form as a leaving group has been reported,[51−53] the mechanism by which an aryl group acts formally as a nucleofuge has, to the best of our knowledge, not been reported. Since enantioenriched α-hydroxy acids are readily accessible, the present method is well suited for the synthesis of homochiral α-fluorinated tertiary alkyl ethers.

Scheme 5. Stereoselectivity of the Dyotropic Rearrangement and Post-transformations[a]



[a]Reagents and conditions: (*S*)-**5b** (0.1 mmol), $Pd(CH_3CN)_4(BF_4)_2$ (10 mol %), K_2CO_3 (2.0 equiv), Selectfluor (2.0 equiv), CH_3CN, 50 °C, 21 h. [b]*n*BuLi (2.0 equiv), THF, −78 °C, 1 h, 79% from **10b**, 78% from **6b**. [c]2,6-Dichlorobenzo[*d*]oxazole (**13**, 2.0 equiv), K_2CO_3 (4.0 equiv), CH_3CN (*c* 0.06 M), 70 °C, 18 h, 93%. [d]2,6-Dichloroquinoxaline (**14**, 2.0 equiv), K_2CO_3 (4.0 equiv), CH_3CN (*c* 0.06 M), 70 °C, 21 h, 72%. [e]3,4-Difluorobenzonitrile (**17**, 2.0 equiv), K_2CO_3 (4.0 equiv), DMF (*c* 0.06 M), 70 °C, 21 h, 80%. [f]LiOH (excess), THF/H_2O (v/v = 2:1), 0 °C to rt. [g]1-Iodobutane (5.0 equiv), K_2CO_3 (4.0 equiv), acetone, 45% over two steps. [h]5-Chloro-2,3-difluoropyridine (**19**, 2.0 equiv), K_2CO_3 (4.0 equiv), CH_3CN (*c* 0.06 M), 70 °C. [i]Propargyl bromide (5.0 equiv), K_2CO_3 (4.0 equiv), acetone, rt, 19 h, 68% over two steps.

The reaction of Weinreb amide **10b** with *n*BuLi afforded ketone **11** in 79% yield. Morpholinyl amide **6b** was converted to ketone **11** in a similar yield (Scheme 5b).[54,55] Finally, the selective hydrolysis of pivaloyl ester in **6g** (K_2CO_3, MeOH, 0 °C) afforded phenol **12** in 97% yield. The S_NAr reactions of **12** with 2,6-dichlorobenzo[*d*]oxazole (**13**) and 2,6-dichloroquinoline (**14**) afforded **15** (a metamifop analog) and **16** (a quizalofop analog) in yields of 93% and 72%, respectively (Scheme 5c). A sequence of S_NAr reactions of **12** with 3,4-difluorobenzonitrile (**17**) followed by hydrolysis of the amide and esterification of the resulting carboxylic acid with 1-iodobutane furnished a 2-fluoro analog of cyhalofop butyl **18**. The same three-step sequence using 5-chloro-2,3-difluoropyridine (**19**) as an electrophilic partner of **12** provided a 2-fluoro analog of clodinafop propargyl **20**. Finally, by applying the same synthetic sequence to Weinreb amide **21**, which was prepared from **10c**, compound **20** was obtained in a similar overall yield.

In summary, we developed a Pd^{II}-catalyzed domino process involving an unprecedented 1,2-aryl/Pd^{IV} dyotropic rearrangement along the C−O stationary phase. Applying to tertiary alcohols, migratory fluoroarylation occurs to provide α-fluorinated tertiary alkyl-aryl ethers. This reaction, which is compatible with a broad range of functional groups, generates a tertiary alkyl fluoride and an alkyl-aryl ether motif with inversion of the absolute configuration at the tetrasubstituted stereocenter. Apart from the implication of this elementary step in the fundamentals of organometallic chemistry, we believe that the transformation enriches the toolbox of tertiary alcohol editing methodologies that could find application in synthetic and medicinal chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.4c02924.

Experimental procedures and characterization data, additional experimental details, crystallographic data of **6d** and (*R*)-**6b**, copies of the chiral SFC chromatograms, ^1H, ^{13}C, and ^{19}F NMR spectra (PDF)

Accession Codes

CCDC 2296492 and 2324152 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

https://doi.org/10.1021/jacs.4c02924
J. Am. Chem. Soc. 2024, 146, 11061−11066

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T.D. and B.Y. contributed equally to this work. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank EPFL (Switzerland) and Swiss National Science Foundation for financial support. This publication was created as part of NCCR Catalysis, a National Centre of Competence in Research funded by the Swiss National Science Foundation (SNSF 180544). We thank Dr. F. Fadaei-Tirani and Dr. R. Scopelliti for the X-ray structural analysis of compounds **6d** and (*R*)-**6b**.

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https://doi.org/10.1021/jacs.4c02924
J. Am. Chem. Soc. 2024, 146, 11061−11066