Cu(I)-BOX Catalyzed Asymmetric 3-Component Reaction for the Synthesis of Trifluoromethylated Propargylic Ethers and Anilines

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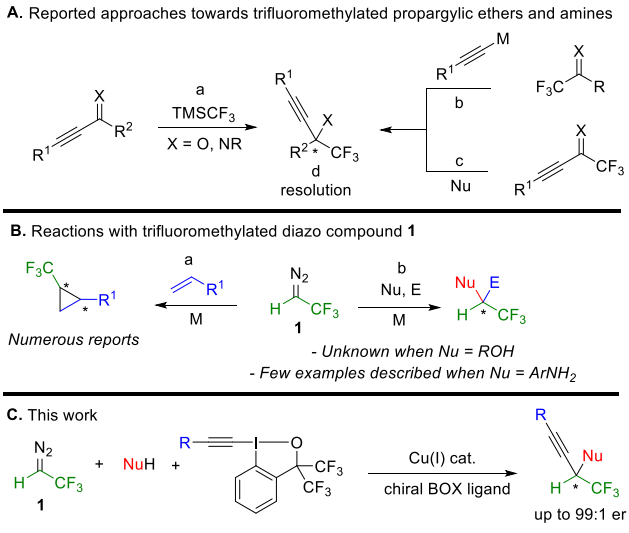
ABSTRACT: An asymmetric 3-component reaction between EthynylBenziodoXoles (EBxs), 2,2,2-trifluorodiazoethane and nucleophiles catalyzed by a Cu(I)Box catalyst is described. This protocol gives access to chiral trifluoromethylated propargylethers and anilines, which are valuable building blocks in synthetic and medicinal chemistry. The reaction proceeds with high enantioselectivity and yield with different nucleophiles such as primary, secondary and tertiary alcohols, as well as both electron-rich and electron-poor anilines. Aryl-, Alkyl- and silyl-substituted alkynes can be successfully introduced as electrophiles. In case of chiral substrates, high catalyst control was observed, leading to good diastereoselectivity.

The unique physico-chemical properties of the fluorine atom provide compounds with excellent pharmacokinetic properties, which make them important for drug design.[1,2] Moreover, organofluorine compounds are also frequently encountered in agrochemicals and materials.[3] Propargylic ethers and amines are synthetically important, as they combine the rigidity, electronic properties and easy post-functionalization of alkynes with the nucleophilic and hydrogen bonding properties of the heteroatoms.[4,5] Combined with a trifluoromethyl group, valuable building blocks for synthetic and medicinal chemistry are therefore obtained.[6] Due to the different bioactivity of enantiomeric compounds, the synthesis of enantioenriched trifluoromethylated carbinols and anilines has attracted especially attention recently (Scheme 1A).[7] Traditional approaches to these compounds are based on the use of chiral catalysts in (a) the addition of CF_3-based nucleophiles to ynones (*e.g.* Rupert-Prakash reagent),[7a,8] (b) the addition of acetylides onto carbonyl compounds or imines,[9,10] (c) the addition of carbon nucleophiles to trifluoromethylated alkynyl ketones and the reduction of the corresponding trifluoromethylated propargyl imines [11,12] or (d) *via* kinetic resolution of the propargyl alcohols.[6a] Nevertheless, in some cases stoichiometric amounts of strong bases, lower or higher temperatures, expensive catalysts (Rh, Pd, among others), and/or additives are needed. Furthermore, these protocols often present a narrow scope. Finally, most methods give access only to alcohols, requiring extra synthetic steps if the ethers are targeted. Therefore, the development of new stereoselective strategies for the synthesis of trifluoromethylated propargylic compounds is needed.

In this regard, Multi-Component Reactions (MCRs) have demonstrated their potential for the formation of chiral compounds with high molecular diversity and complexity.[13] Through the formation of a metal carbene, diazo compounds can react as nucleophiles and electrophiles at the same carbon center, allowing the formation of multiple chemical bonds in a single step.[14,15] Recently, fluorinated diazo compounds, such as 2,2,2-trifluorodiazoethane (HN_2CCF_3, **1**), have been used in the synthesis of trifluoromethylated compounds.[16] Nevertheless, enantioselective methods have been mostly limited to cyclopropanation.[17] In the case of MCRs, there are only examples of the use of amines as nucleophiles to access aziridines, triazolines or 1,2-diamines.[18] To the best of our knowledge, the use of alcohols as nucleophiles in asymmetric MCRs with fluorinated diazo compounds has never been reported.

Scheme 1. State of the art for the synthesis of fluorinated propargylic ethers and anilines and our approach



In 2016, our group reported an oxyalkynylation reaction of diazo compounds using EthynylBenziodoXolones (EBX) or their derivatives and a copper catalyst.[19] Later, enantioselective variation of this reaction were developed using BOX ligands.[20] Trifluoromethylated diazo compounds were not used in these early works. Interestingly, despite copper being one of the most

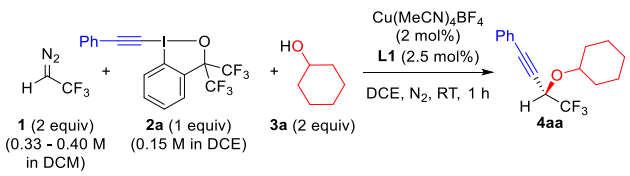
earth-abundant transition-metal catalysts, it has been only barely used in carbene-based enantioselective MCRs.[21] Recently, we could extend the use of copper catalysis to a 3-CR reaction between modified EBX derivatives, diazo compounds, and nucleophiles, such as alcohols[22] or anilines.[23] For the first time, trifluoromethylated diazo compounds could be used. However, the development of an enantioselective method has not yet been reported.

Herein, we describe the first asymmetric 3-CR between 2,2,2-trifluorodiazoethane (**1**), EBX derivatives and nucleophiles for the synthesis of trifluoromethylated propargylic ethers and anilines. The reaction proceeds with high enantioselectivity for non-chiral alcohols and anilines and high diastereoselectivity under catalyst control for chiral alcohols. In the case of alcohol nucleophiles, primary, secondary and tertiary alcohols could all be used, the latest being challenging targets for traditional etherification reactions.[24]

As a model system, we chose the 3-CR of 2,2,2-trifluorodiazoethane (**1**), EthynylBenziodoxole (EBx) **2a** and cyclohexanol (**3a**) (Table 1). After optimization, the enantioselective 3-CR could be performed using commercially available $Cu(MeCN)_4BF_4$ and BOX ligand **L1** at room temperature using DCE as solvent to give product **4aa** in 85% yield and 96:4 er after 1 h of reaction (Table 1, entry 1). On 0.20 mmol scale, **4aa** could be isolated in 83% yield. With indaBOX ligand **L2**, a quantitative yield, but lower selectivity was obtained (Table 1, entry 2). Using similar conditions than in our previous enantioselective oxyalkynylation work[20b] -generation of a cationic complex *in situ* from $CuCl/AgNTf_2$ in presence of **L1** or **L2**- led to similar results (Table 1, entries 3 and 4). Other counterions, such as SbF_6^-, PF_6^- or OTf^- gave **4aa** in similar or lower yields and er (Table 1, entries 5-7). Different Cu(I) catalysts, such as Cu(OTf)•PhMe, CuI or CuTc, (Table 1, entry 8 and Supporting Information) were also tested, but no improvement was observed. Using Cu(II) salts, such as $Cu(OAc)_2$ or $Cu(OTf)_2$ was also less efficient (Table 1, entries 9-10). A larger excess of **3a** did not lead to a significant improvement (Table 1, entry 11). Using only 1.5 equiv of **3a** afforded compound **4aa** in lower yield, but similar selectivity (Table 1, entry 12). Non-chlorinated solvents were also tested. No reaction was observed with MeCN and a lower yield and similar selectivity than with DCE when using PhMe. (Table 1, entries 13-14). Further solvents and conditions were also tested but did not lead to any improvements (see Supporting Information).

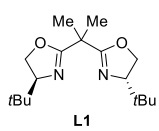
With these optimized conditions in hand, we explored the scope and limitations of the asymmetric reaction between **1**, **2a** and different alcohols **3a-3p** (Scheme 2). Enantiopure (*S*)-2-phenylethanol (**3b**) afforded compound **4ab** in good yield and diastereoselectivity (70% and 95:5 dr, respectively). Switching to tertiary alcohols, *tert*-butanol (**3c**) gave **4ac** in 72% yield and 96:4 er. *Tert*-amyl alcohol (**3d**) afforded the corresponding propargylic ether **4ad** in good yield (70%) and selectivity (94:6 er). The presence of an arene in the aliphatic chain (**3e-g**) was tolerated, yielding products **4ae-g** in 43-65% yield with 97:3-98:2 er. Cyclic alcohol **3h** gave **4ah** in 55% yield and 95:5 er. The use of adamantyl-substituted alcohols deserves a special attention since this structure can be found in pharmaceuticals.[25] In our case, trifluoromethylated propargylic ethers **4ai** and **4aj** containing adamantyl substituents were obtained in good yield and enantioselectivity.

Table 1. Optimization of the MCR reaction[a]

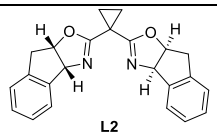


1 (2 equiv) (0.33 - 0.40 M in DCM) **2a** (1 equiv) (0.15 M in DCE) **3a** (2 equiv)

Entry	Modifications	Yield 4aa (%)	er
1	**none**	**85 (83)**[b]	**96:4**
2	**L2**	quant.	11:89
3	$CuCl/AgNTf_2$	75	93:7
4	$CuCl/AgNTf_2$ and **L2**	95	11:89
5	$Cu(MeCN)_4SbF_6$	89	92:8
6	$Cu(MeCN)_4PF_6$	69	89:11
7	$Cu(MeCN)_4OTf$	77	93:7
8	Cu(OTf)•PhMe	78	95:5
9	$Cu(OAc)_2$	69	85:15
10	$Cu(OTf)_2$	68	96:4
11	4 equiv of **3a**	88	94:6
12	1.5 equiv of **3a**	65	95:5
13	MeCN	n.d.	n.d.
14	PhMe	76	94:6



L1

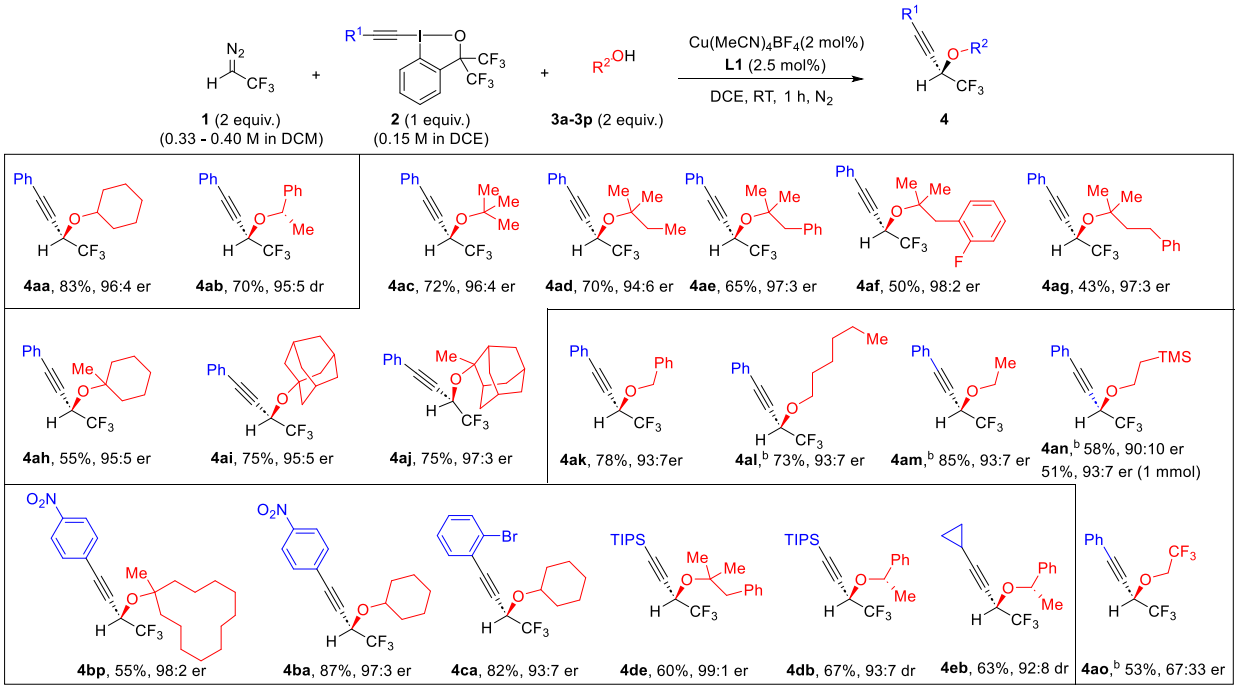


L2

Conditions: [a]The reactions were performed with 0.15 mmol of **2a**. The active chiral complex was formed mixing the Cu(I) catalyst with **L1** or **L2** in the reaction solvent during 1 h. The yield was determined by ^{19}F-NMR using 1 equiv of $PhCF_3$ as internal standard. The enantiomeric ratio (er) was determined by chiral HPLC. [b]Isolated yield at 0.20 mmol scale is indicated in brackets.

We then turned to primary alcohols. Benzyl alcohol (**3k**) was also well tolerated under the reaction conditions to give **4ak** in 78% and 93:7 er. However, when hexanol (**3l**) was submitted to the standard conditions, the desired product was obtained in good yield (84%), but lower selectivity (85:15 er). The use of a stoichiometric ratio between the Cu(I) salt and **L1** afforded compound **4al** in similar yield but higher enantioselectivity (93:7 er) (See SI, for more information). Ethanol (**3m**) afforded **4am** in 85% yield and 93:7 er. The presence of a trimethylsilyl group (**3n**) was also well tolerated under the optimized conditions to give **4an** in 58% yield and 90:10 er. This reaction was also performed at 1 mmol scale and product **4an** was obtained in similar yield (51%) and a slightly higher selectivity (93:7 er). Switching to less nucleophilic alcohols, such as trifluoroethanol (**3o**), we observed poor selectivity and moderate yield.[26]

Scheme 2. Scope of the 3-CR with 2,2,2-trifluorodiazoethane (1) and different alcohols (3) and EBxs (2).[a]

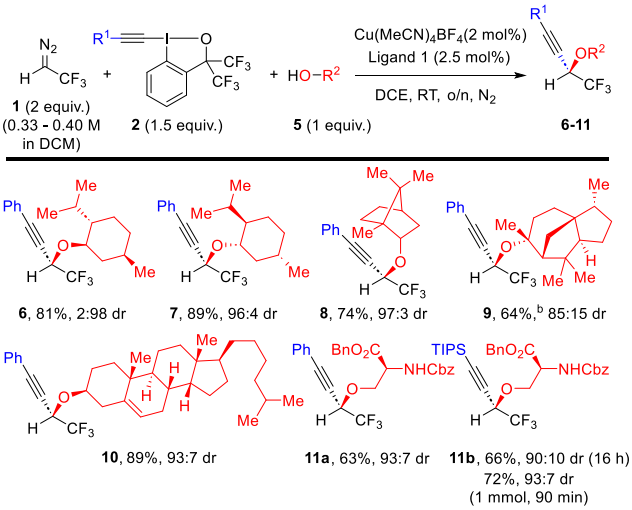


[a]The reactions were performed at 0.20 scale and isolated yield are given. The enantiomeric excess was obtained by chiral HPLC after flash column purification. The diastereomeric ratio was obtained from the crude reaction mixture by ^{19}FNMR. [b]2 mol% $Cu(MeCN)_4BF_4$ and 2 mol% **L1**.

Finally, we moved to the study of the substitution on the alkyne. We observed that a strong electron withdrawing nitro group in *para*-position of the phenyl ring led to high enantioselectivity, as showed with compounds **4bp** and **4ba** which were obtained in 55% yield/98:2 er and 87% yield/97:3 er, respectively. *Ortho*-substitution with a bromine group gave product **4ca** in 82% yield and 93:7 er. Importantly, silyl alkynes giving access to synthetically useful terminal alkynes were also tolerated. Product **4de** was obtained in moderate yield (60%), but excellent er (99:1). A 93:7 diastereoselectivity was obtained in the case of enantiopure alcohol **3b**. Compound **4eb** containing a cyclopropylalkyne was formed in 63% yield and 92:8 diastereoselectivity.

Valuable enantiopure alcohols are widely found in nature. Considering the impressive catalyst control observed with phenethyl alcohol (**2b**) using our method, we decided to investigate more complex substrates (Scheme 3). We first reoptimized the reaction for the use of the alcohol as limiting reagent (See SI for more information). The use of 1 equiv of (-)-menthol (**5a**) gave alkyne **6** in 81% yield and excellent diastereoselectivity (2:98 dr) after overnight reaction. When (+)-menthol (**5b**) was submitted to the same conditions, product **7** was obtained in 89% yield and 96:4 dr, displaying again an excellent catalyst control. Other terpene derived alcohols could also be used, giving products **8**-**10** in 64-89% yield and 85:15-97:3 dr. A lower selectivity was observed when starting from the chiral tertiary alcohol cedrol (**5d**) (product **9**, 85:15 dr). The reaction was also successful for a protected serine derivative **5f** as an example of chiral primary alcohol, and ether **11a** was obtained in 63% yield and 93:7 dr. The reaction of alcohol **5f** was also performed with TIPS-substituted reagent **2d,** giving compound **11b** in 66% yield and 90:10 dr. Compound **11b** was obtained in slightly higher yield and diastereoselectivity at the 1 mmol scale.

Scheme 3. Scope of the 3-CR with 2,2,2-trifluorodiazoethane (1) and chiral alcohols (5).[a]

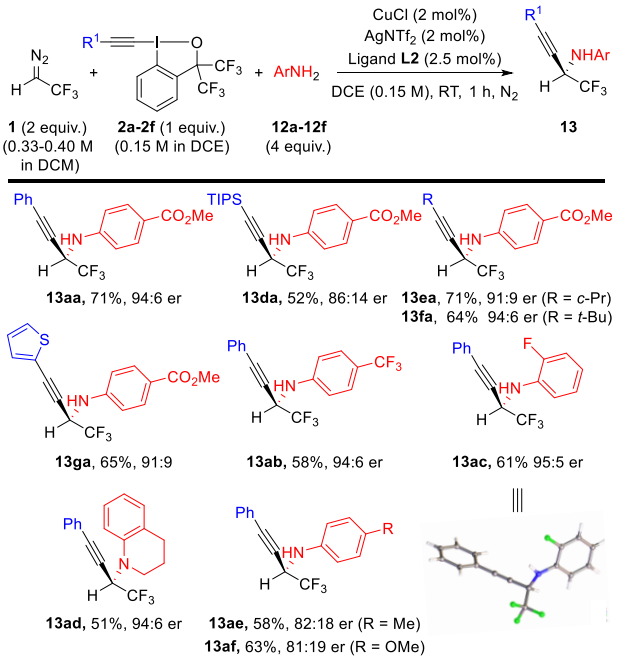


[a]Reaction conditions: Unless otherwise noticed, the reactions were performed at 0.25 mmol scale. Isolated yields by flash column chromatography are given. The diastereomeric ratio was obtained from the crude reaction mixture by ^{19}FNMR. [b]Using $Cu(MeCN)_4SbF_6$, 1 equiv of **2a** and 4 equiv. of alcohol **5e**.

Next, we move to the study of anilines as nucleophiles (Scheme 4) considering our previous work on the racemic process.[23] We chose as a model the reaction between **1**, **2a** and methyl 4-aminobenzoate (**11a**). Unfortunately, despite the good er obtained (98:2); the desired product (**12aa**) was obtained in only 66% yield with low reproducibility using

the conditions optimized for alcohols. After screening of different BOX ligands, Cu(I) catalysts, solvents, concentrations and temperatures, **L2** in combination with the cationic complex formed between CuCl/$AgNTf_2$ in DCE at room temperature afforded compound **13aa** in good yield (71%) and good enantioselectivity (94:6 er) with high reproducibility (See Supporting Information for further details on reaction optimization). When reagent **2d** was submitted to the re-optimized conditions, compound **13da** was obtained in 52% yield and 86:14 er. Alkyl substitution was also well tolerated on the alkyne. Both cyclopropyl (*c*-Pr) and *tert*-butyl (*t*-Bu)-substituted alkynes gave products **13ea** and **13fa** in 71% yield and 91:1 er and 64% yield and 94:6, respectively. Thiophene substituted alkyne **13ga** was obtained in 65% yield and 91:9 er. The scope of substituted anilines was then explored. Electron withdrawing groups, such as trifluoromethyl or *para*-fluoro gave the desired products **13ab** and **13ac**[27] in similar yield and selectivity. 1,2,3,4-Tetrahydroquinoline afforded compound **13ad** in moderated yield and good enantioselectivity. The presence of a methyl or methoxy in *para* position led to lower enantioselectivity (products **13ae** and **13af**).

Scheme 4. Scope of the 3-CR with 2,2,2-trifluorodiazoethane (1) and anilines (12).[a]

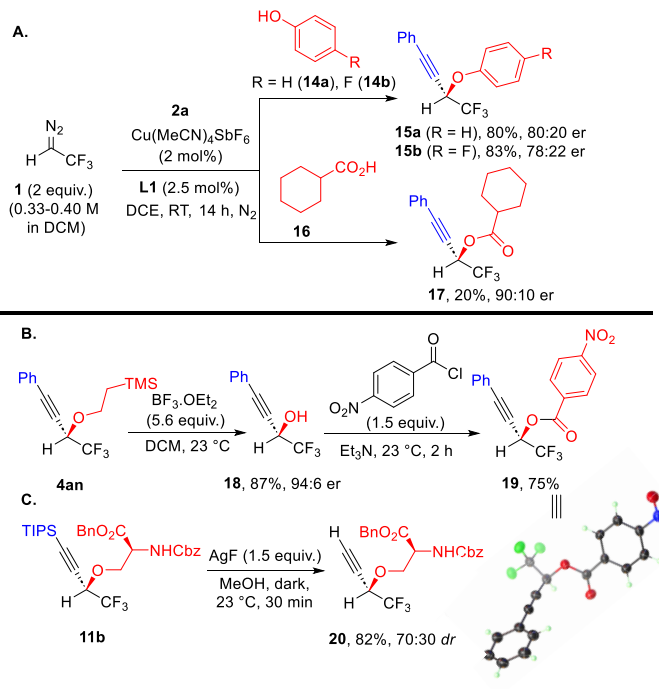


[a]The reactions were performed at 0.25 mmol scale. Isolated yields are given. The enantiomeric excess was obtained by chiral HPLC after PTLC

We also examined phenols and carboxylic acids as nucleophiles (Scheme 5A). In this case, the combination of $Cu(MeCN)_4SbF_6$ and an excess of the nucleophile afforded the best results. In the case of phenols **14a** and **14b**, compounds **15a** and **15b** were obtained in good yield and moderate selectivity. In contrast, using 2-cyclohexanecarboxylic acid (**16**), we were able to reach good enantioselectivity for ester **17**, but the reaction did not go to completion.

To determine the absolute configuration of the propargylic ether products, ether **4an** was deprotected using BF_3OEt_2 to give alcohol **18** in 87% yield (Scheme 5B). Compound **18** was reacted with *p*-nitrobenzoyl chloride to give compound **19**, which allow us to determine the absolute configuration via X-rays analysis.[28] Deprotection of the TIPS group was performed on compound **11b** by treatment with AgF, giving terminal alkyne **20** in 82% yield , albeit with a lower dr.

Scheme 5. Scope extension (A) and products modification (B and C).[a]



[a]Unless indicated otherwise, the reactions were performed at 0.20 mmol scale. Isolated yields are given. The enantiomeric excess was obtained by chiral HPLC after flash column purification.

In summary, we have developed the first asymmetric enantioselective 3-CR between hypervalent iodine reagents, 2,2,2-trifluorodiazoethane (**1**) and nucleophiles using a Cu(I) catalyst. Tertiary, secondary and primary alcohols as well as electron-rich and electron-poor anilines can be used as nucleophiles affording fluorinated propargylic ethers and anilines in up to 99:1 er. Alkyl-, aryl- and silyl-substituted EBxs could be used in the process, giving access to structurally diverse alkynes. With chiral substrates, high catalyst control was observed leading to high diastereoselectivity.

ASSOCIATED CONTENT

Optimization tables, experimental procedures and analytical data for all new compounds. ^{1}HNMR, ^{13}CNMR, ^{19}FNMR spectra and chiral HPLC traces are included.

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Author Contributions

N. R. performed the experiments, prepared and corrected the manuscript and supporting information. J. W. supervised the project, corrected and edited the manuscript and proofread the supporting information.

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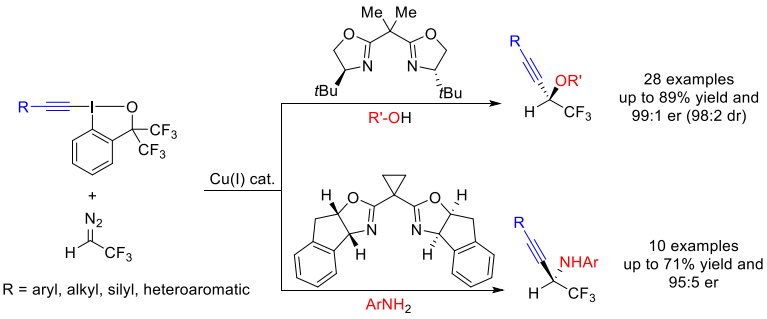
REFERENCES

(1) O'Hagan, D. Understandig organofluorine chemistry. An introduction to the C-F bond. *Chem. Soc. Rev.* **2008**, *37*, 308.
(2) (a) Chambers, R. D. Fluorine in Organic Chemistry; Wiley: Blackwell, 2044. (b) Müller, K.; Faeh, C.; Diederich, F. Fluorine in Pharmaceuticals: Looking Beyond Intuition. *Science* **2007**, *317*, 1881-1886. (c) Hagmann, W. K. The Many Roles for Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2008**, *51*, 4359-4369. (d) Swallow, S. In Fluorine in Pharmaceutical and Medicinal Chemistry: From Biophysical Aspects to Clinical Applications; Gouverneur, V.; Müller, K.; Ed.; Imperial College Press: London, **2012**. (e) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donneelly, D. J.; Meanwell, N. A. Applications of Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2015**, *58*, 8315-8359. (f) Inoue, M.; Sumii, Y.; Shibata, N. Contribution of Organofluorine Compounds to Pharmaceuticals. *ACS Omega* **2020**, *5*, 10633-10640.
(3) Zhang, C.; Yan, K. Fu, C.; Peng, H.; Hawker, C. J. Whittaker, A. K. Biological Utility of Fluorinated Compounds: from Materials Design to Molecular Imaging, Therapeutics and Environmental Remediation. *Chem. Rev.* **2022**, *122*, 167-208.
(4) Selected reviews for propargylic alcohols/ethers: (a) Nishibayashi, Y. Transition-Metal-Catalyzed Enantioselective Propargylic Substitution Reactions of Propargylic Alcohol Derivatives with Nucleophiles. *Synthesis* **2012**, *44*, 489-503. (b) Puri, S. Oxygen as a Heteroatom in Propargylic Alcohols: Reactivity, Selectivity, and Applications. *ChemistrySelect* **2020**, *5*, 9866-9877.
(5) Selected reviews for propargylic amines: (a) Arshadi, S.; Vessally, E.; Edjlali, L.; Hosseinzadeh-Khanmiri, R.; Ghorbani-Kalhor, E. N-Propargylamines: Versatile Building Blocks in the Construction of Thiazole Cores. Beilstein *J. Org. Chem.* **2017**, *13*, 625–638. (b) Irfana, J.; Chandra Nandi, G. C. Recent Advances in the A3 Coupling Reactions and their Applications. *Eur. J. Org. Chem.* **2019**, 2704–2720.
(6) Recent examples: (a) Boreux, A.; Lonca, G. H.; Riant, O.; Gagosz. Synthesis of Triflurometh yl-allenes by Gold-Catalyzed Rearrangement of Propargyl Benzyl Ethers. *Org. Lett.* **2016**, *18*, 5162-5165. (b) Noël, F.; Vukovic, V. D.; Yi, J.; Richmond, E.; Kravljanac, P.; Moran, J. Catalytic Synthesis of Trifluromethylated Allenes, Indenes, Chromenes, and Olefins from Propargylic Alcohols in HFIP. *J. Org. Chem.* **2019**, *84*, 15926-15947. (c) Posevins, D.; Bemejo-López, A.; Bäckwall, J.E. Iron-Catalyzed Cross-Coupling of Propargyl Ethers with Grignard Reagents for the Synthesis of Functionalized Allenes and Allenols. *Angew. Chem. Int. Ed.* **2021**, *60*, 22178-22183. (d) Kani, R.; Inuzuka, T.; Kubota, Y.; Funabiki, K. Synthesis of 1-Trifluoromethylated Propargylic Alcohols by Two Successive Reactions of Cyclopentylmagnesium Bromide in a One-Pot Manner. *Asian J. Org. Chem.* **2022**, *11*, e202100700.
(7) Selected reviews: (a) Rubiales, G.; Alonso, C.; Martínez de Marigorta, E.; Palacios, F. Nucleophilic trifluoromethylation of carbonyl compounds and derivatives. *Arkivoc* **2014** (*ii*), 362 – 406. (b) Noda, H.; Kumagai, N.; Shibasaki, M. Catalytic Asymmetric Synthesis of α-Trifluoromethylated Carbinols: A Case Study of Tertiary Propargylic Alcohols. *Asian J. Org. Chem.* **2018**, *7*, 599-612 and references therein.
(8) Liu, P.; Lei, Z.-L.; Peng, Y.-Y.;Liu, Z.-J.; Zhu, Q.-Z.; Liu, J.-T.; Wu, F. Diastereoselective Trifluoromethylation of Chiral α,β-Unsaturated N-tert-Butanesulfinyl Ketimines with Ruppert–Prakash Reagent: Asymmetric Synthesis of α-Tertiary Trifluoromethyl Allylic Amines. *Adv. Synth. Catal.* **2018**, *360*, 3418.
(9) (a) Motoki, R.; Kanai, M.; Shibasaki, M. Copper (I) Alkoxide-Catalyzed Alkynylation of Trifluoromethyl Ketones. *Org. Lett.* **2007**, *9*, 2997-3000. (b) Chinkov, A.; Warm, A.; Carreira, E. M. Asymmetric Autocatalysis Enables an Improved Synthesis of Efavirenz. *Angew. Chem., Int. Ed.* **2011**, *50*, 2957-2961. (c) Noda, H.; Amemiya, F.; Weidner, K.; Kumagai, N.; Shibasaki, M. Catalytic Asymmetric Synthesis of CF_3-Substituted Tertiary Propargylic Alcohols via Direct Aldol Reaction of α-N_3-Amide. *Chem. Sci.* **2017**, *8*, 3260-3269 (d) Park, D.; Jette, C. I.; Kim, J.; Jung, W.-O.; Lee, Y.; Park, J.; Kang, S.; Han, M. S.; Stoltz, B. M.; Hong, S. Enantioselective Alkynylation of Trifluoromethyl Ketones Catalyzed by Cation-Binding Salen Nickel Complexes. *Angew. Chem., Int. Ed.* **2019**, *59*, 775-779.
(10) (a) Xu, Y.; Dolbier, W. R. Synthesis of Trifluoromethylated Amines Using 1,1-Bis(dimethylamino)-2,2,2-trifluoroethane. *J. Org. Chem.* **2000**, *65*, 2134-2137. (b) Magueur, G.; Crousse, B.; Bonnet-Delpon, D. Direct Access to CF_3-Propargyl Amines and Conversion to Difluoromethyl Imines. *Tetrahedron Lett.* **2005**, *46*, 2219-2221. (c) Xiao,H.; Huang, Y.; Qing, F.-L. Highly Diastereoselective Synthesis of α-Trifluoromethylated α-Propargylamines by Acetylide Addition to Chiral CF_3-Substituted N-*tert*-Butanesulfinyl Ketimines. *Tetrahedron: Asymmetry* **2010**, *21*, 2949-2955. (d) Huang, G.; Yin, Z.; Zhang, X. Construction of Optically Active Quaternary Propargyl Amines by Highly Enantioselective Zinc/BINOL-Catalyzed Alkynylation of Ketoimines. *Chem. Eur. J.* **2013**, *19*, 11992-11998. (e) Morisaki, K.; Sawa, M.; Nomaguchi, J.-y.; Morimoto, H.; Takeuchi, Y.; Mashima, K.; Ohshima, T. Rh-Catalyzed Direct Enantioselective Alkynylation of α-Ketoiminoesters. *Chem. Eur. J.* **2013**, *19*, 8417-8420. (f) Morisaki, K.; Sawa, M.; Yonesaki, R.; Morimoto, H.; Mashima, K.; Ohshima, T. Mechanistic Studies and Expansion of the Substrate Scope of Direct Enantioseletive Alkynylation of α-Ketoimines Catalyzed by Adaptable(Phebox) Rhodium (III) Complexes. *J. Am. Chem. Soc.* **2016**, *138*, 6194-6203.
(11) Sasaki, S.; Yamauchi, T.; Kanai, M. ; Ishii, A.; Higashiyama, K.: Bisoxazoline-Catalyzed Asymmetric Nucleophilic Addition of Diethyl Zinc to Fluorinated Alkyl Ketones: Enantiofacial Control by Changing the Bisoxazoline Substituent. *Bull. Chem. Soc. Jpn.* **2015**, *88*, 200-208.
(12) (a) Du, W.-Q.; Zhang, J.-M.; Wu, R.; Liang, Q.; Zhu, S.-Z. One-pot Preparation of Fluorinated Propargylamines under Microwave Irradiation and Solvent-Free Conditions. *J. Fluorine Chem*. **2008**, *129*, 695-700. (b) Likhar, P. R.; Subhas, M. S.; Roy, S.; Kantam, M. L.; Sridhar, B.; Seth, R. K.; Biswas, S. Synthesis of Highly Substituted 2-Perfluoroalkyl Quinolines by Electrophilic Iodocyclization of Perfluoroalkyl Propargyl Imines/Amines. *Org. Biomol. Chem.* **2009**, *7*, 85-93. (c) Chen, M.-W.; Wu, B.; Chen, Z.-P.; Shi, L.; Zhou, Y.-G. Synthesis of Chiral Fluorinated Propargylamines via Chemoselective Biomimetic Hydrogenation. *Org. Lett.* **2016**, *18*, 4650. (d) Chen, M.-W.; Yang, Q.; Deng, Z.; Zhou, Y.; Ding, Q.; Peng, Y. Organocatalytic Asymmetric Reduction of Fluorinated Alkynyl Ketimines. *J. Org. Chem.* **2018**, *83*, 8688-8694. (e)

Miyagawa, M.; Takashima, K.; Akiyama, T. Asymmetric Reduction of Trifluoromethyl Alkynyl Ketimines by Chiral Phosphoric Acid and Benzothiazoline. *Synlett* **2018**, *29*, 1607-1610. (f) Trost, B. M.; Hung, C.-I.; Scharf, M. J. Direct CatalyticAsymmetric Vinylogous Additions of α,β-and β,γ-Butenolides to Polyfluorinated Alkynyl Ketimines. *Angew. Chem., Int. Ed.* **2018**, *57*, 11408-11412.
(13) (a) de Graaf, C.; Ruijter, E.; Orru, R. V. A. Recent Developments in Asymmetric Multicomponent Reactions. *Chem. Soc. Rev.* **2012**, *41*, 3969-4009. (b) Perez Herrera, R.; Marqués-López, E. Multicomponent Reactions: Concepts and Applications for Design and Synthesis. Wiley, 2015.
(14) (a) Guo, X.; Hu, W. Novel Multicomponent Reactions via Trapping of Protic Onium Ylides with Electrophiles. *Acc. Chem. Res.* **2013**, *46*, 2427-2440. (b) Chen, D. F.; Han, Z. Y.; Zhou, X. L.; Gong, L. Z. Asymmetric Organocatalysis Combined with Metal Catalysis: Concept, Proof of Concept, and Beyond. *Acc. Chem. Res.* **2014**, *47*, 2365-2377. (c) Zhang, D.; Hu, W. H. Asymmetric Multicomponent Reactions Based on Trapping of Active Intermediates. *Chem. Rec.* **2017**, *17*, 739-753.
(15) Wang, J.; Che, C-M.; Doyle, M. P. Transition Metal-Catalyzed Carbene Transformations. Wiley **2022**.
(16) Representative reviews: (a) Mykhailiuk, P. K. 2,2,2-Trifluorodiazoethane (CF_3CHN_2): A Long Journey since 1943. *Chem. Rev.* **2020**, *120*, 12718-12755. (b) Kumar, A.; Khan, W. A.; Ahamad, S.; Mohanan, K. Trifluorodiazoethane: A Versatile Building Block to Access Trifluoromethylated Heterocylces. *J. Heterocyclic Chem.* **2022**, *59*, 607-632.
(17) (a) Müller, P.; Grass, S.; Shahi, S. P.; Bernardinelli, G. Rh(II)-Catalyzed Asymmetric Carbene Transfer with Ethyl 3,3,3-trifluoro-2-diazopropionate. *Tetrahedron* **2004**, 60, 4755-4763. (b) Kotozaki, M.; Chanthamath, S.; Fujii, T.; Shibatomi, K.; Iwasa, S. Highly Enantioselective Synthesis of Trifluoromethyl Cyclopropanes by Using Ru(II)–Pheox Catalysts. *Chem. Commun.* **2018**, *54*, 5110 – 5113. (c) Zhang, Z.; Tian, C.; Wang, Z.; Sivaguru, P.; Steven P. Nolan, S. P.; Bi, X. Fluoroalkyl N Triftosylhydrazones as Easily Decomposable Diazo Surrogates for Asymmetric [2 + 1] Cycloaddition: Synthesis of Chiral Fluoroalkyl Cyclopropenes and Cyclopropanes. *ACS Catal.* **2021**, *11*, 8527−8537. (d) Altarejos, J.; Sucunza, D.; Vaquero, J. J.; Carreras, J. Enantioselective Copper-Catalyzed Synthesis of Trifluoromethyl-Cyclopropylboronates. *Org. Lett.* **2021**, *23*, 6174−6178.
(18) (a) Chai, Z.; Bouillon, J.-P.; Cahard, D. Chiral Brønsted Acid Catalyzed Diastereo- and Enantioselective Synthesis of CF_3-Substituted Aziridines. *Chem. Commun.* **2012**, *48*, 9471−9473. (b) Kumar, A.; Ahamad, S.; Kant, R.; Mohanan,K. Silver-Catalyzed Three-Component Route to Trifluoromethylated 1, 2, 3-Triazolines Using Aldehydes, Amines, and Trifluorodiazoehtane. *Org. Lett.* **2019**, *21*, 2962-2965. (c) Tan, X.-F.;Zhang, F.-G.; Ma, J.-A. Asymmetric Synthesis of CF_2-Functionalized Aziridines by Combined Strong Brønsted Acid Catalysis. *Beilstein J. Org.Chem.* **2020**, *16*, 638-644. d) Li, J.; Zhang, D.; Chen, J.; Ma, C.; Hu, W. Enantioselective Synthesis of Fluoroalkyl-Substituted *syn*-Diamines by the Asymmetric gem-Difunctionalization of 2, 2, 2-Trifluorodiazoethane. *ACS Catal.* **2020**, *10*, 4559-4565.
(19) Hari, D. P.; Waser, J. Copper-Catalyzed Oxy-Alkynylation of Diazo Compounds with Hypervalent Iodine Reagents. *J. Am. Chem. Soc.* **2016**, *138*, 2190-2193.
(20) (a) Hari, D. P.; Waser, J. Enantioselective Copper-Catalyzed Oxy-Alkynylation of Diazo Compounds. *J. Am. Chem. Soc.* **2017**, *139*, 8420-8423. (b) Hari, D.-P.; Schouwey, L.; Barber, V.; Scopelliti, R.; Fadaei-tirani, F.; Waser, J. Ethynylbenziodazolones (EBZ) as Electrophilic Alkynylation Reagents for the Highly Enantioselective Copper-Catalyzed Oxyalkynylation of Diazo Compounds. *Chem. Eur. J.* **2019**, *25*, 9522-9528.
(21) Selected review: Zhao, X.; Zhang, Y.; Wang, J. Recent Developments in Copper-Catalyzed Reactions of Diazo Compounds. *Chem. Commun.* **2012**, *48*, 10162-10173 and references therein.
(22) Pisella, G.; Gagnebin, A.; Waser, J. Three-Component Reaction for the Synthesis of Highly Functionalized Propargyl Ethers. *Chem. Eur. J.* **2020**, *26*, 10199-10204.
(23) Ramirez, N. P.; Pisella, G.; Waser, J. Cu(I)-Catalyzed gem-Aminoalkynylation of Diazo Compounds: Synthesis of Fluorinated Propargylic Amines. *J. Org. Chem.* **2021**, *86*, 10928-10938.
(24) Xiang, J.; Shang, M.; Kawamata, Y.; Lundberg, H.; Reisberg, S. H.; Chen, M.; Mykhailiuk, P.; Beutner, G.; Collins, M. R.; Davies, A.; Del Bel, M.; Gallego, G. M.; Spangler, J. E.; Starr, J.; Yang, S.; Blackmond, D. G.; Baran, P. S. Hindered Dialkyl Ether Synthesis with Electrogenerated Carbocations. *Nature* **2019**, *573*, 398–402.
(25) Wanka, L.; Iqbal, K.; Schreiner, P. R. The Lipophilic Bullet Hits the Targets: Medicinal Chemistry of Adamantane Derivatives. *Chem. Rev.* **2013**, *113*, 3516-3604.
(26) Less nucleophilic alcohols, such as HFIP did not show any reactivity.
(27) The absolute configuration of **12ac** was determined by X-ray analysis (CCDC number 2216834).
(28) CCDC number 2225295 .


Me Me
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CF3
R = aryl, alkyl, silyl, heteroaromatic
Cu(I) cat.
R'-OH
ArNH2
R
OR'
H
CF3
NHAr
28 examples
up to 89% yield and
99:1 er (98:2 dr)
10 examples
up to 71% yield and
95:5 er