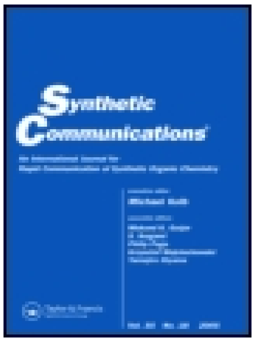


Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: https://www.tandfonline.com/loi/lsyc20

Palladium-catalyzed cross-coupling of benzylzinc reagents with 2-bromo-3,3,3-trifluoropropene

An-Jun Wang, Yue-Guang Lou, Liang Zhao, Fei-Hu Gou, Lian Wang, Yanbo Yu, Jiwei Gu & Chun-Yang He

To cite this article: An-Jun Wang, Yue-Guang Lou, Liang Zhao, Fei-Hu Gou, Lian Wang, Yanbo Yu, Jiwei Gu & Chun-Yang He (2019): Palladium-catalyzed cross-coupling of benzylzinc reagents with 2-bromo-3,3,3-trifluoropropene, Synthetic Communications, DOI: 10.1080/00397911.2019.1663540

To link to this article: https://doi.org/10.1080/00397911.2019.1663540

SYNTHETIC COMMUNICATIONS®
https://doi.org/10.1080/00397911.2019.1663540

Palladium-catalyzed cross-coupling of benzylzinc reagents with 2-bromo-3,3,3-trifluoropropene

An-Jun Wang*, Yue-Guang Lou*, Liang Zhao, Fei-Hu Gou, Lian Wang, Yanbo Yu, Jiwei Gu, and Chun-Yang He

Key Laboratory of Biocatalysis and Chiral Drug Synthesis of Guizhou Province, Generic Drug Research Center of Guizhou Province, School of Pharmacy, Zunyi Medical University, Zunyi, China

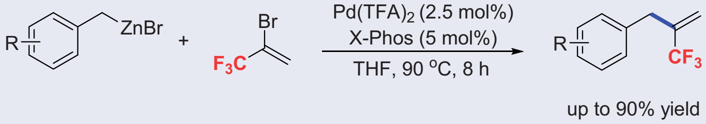
ABSTRACT

α-Trifluoromethyl alkenes can be used as peptide isosteres, moreover, the pre-installed vinyl group make it possible that transformation to diverse fluorine-containing unities. However, the cross-coupling of benzyl group with α-trifluoromethyl alkenes has yet to be developed. In this report, we describe a general method for the cross-coupling of benzylzinc reagents with 2-bromo-3,3,3-trifluoropropene (BTP) to afford diverse α-trifluoromethylalkene derivatives by using $Pd(TFA)_2$ as catalyst. This method takes advantage of cheap industrial available fluorine building blocks and easily prepared benzylzinc reagents to generate α-trifluoromethylalkene derivatives, which features with mild reaction conditions, wide substrate scope and feasibility of product transformations.

ARTICLE HISTORY
Received 15 August 2019

KEYWORDS
Trifluoromethylation; BTP; benzylzinc reagents; palladium-catalyzed

GRAPHICAL ABSTRACT



Introduction

Due to the unique properties of fluorine atom (small size, high electronegativity, inertness of C-F bonds), fluorinated compounds are of paramount importance in pharmaceuticals, agrochemicals, and materials science.[1–7] During the last 10 years, the demand for fluorinated molecules is rapidly increasing. Therefore, it is of great importance to develop novel and effective synthetic methods for the construction of fluorine-containing organic compounds.[8–21]

2-Bromo-3,3,3-trifluoropropene (BTP) is a readily available versatile organo-fluorine building block, which has been widely used in various coupling/addition reactions under various conditions.[22–25] The pre-installed vinyl group make it possible that

---

CONTACT Chun-Yang He hechy2002@163.com Key Laboratory of Biocatalysis and Chiral Drug Synthesis of Guizhou Province, Generic Drug Research Center of Guizhou Province, School of Pharmacy, Zunyi Medical University, Zunyi, 563003, China.

Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/lsyc.
*Both author contributed equally to this work.

Supplemental data for this article can be accessed on the publisher's website.

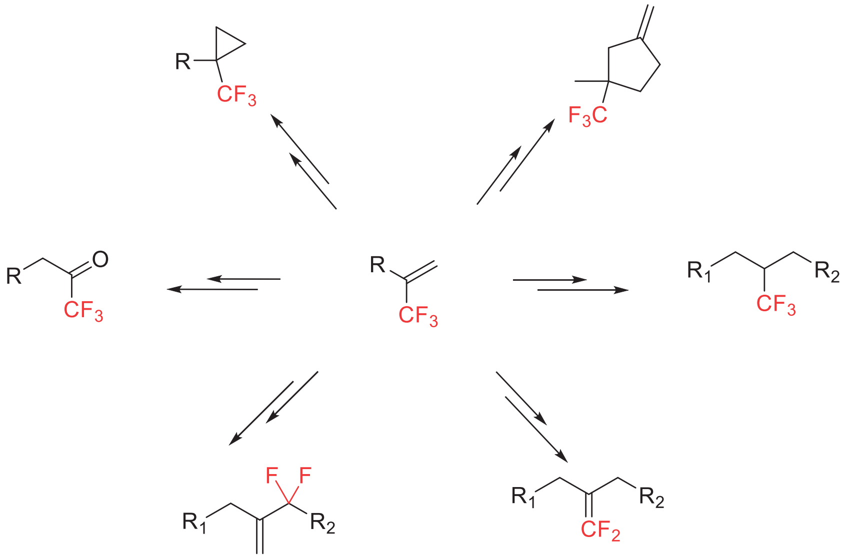


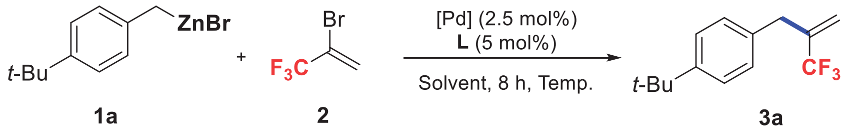
Figure 1. Diversity transformation of 3,3,3-trifluoropropene containing structures.

transformation to diverse fluorine-containing unities (Figure 1).[26–29] More important, α-trifluoromethyl alkenes can be used as peptide isosteres,[30–33] which are important medicinally relevant moieties in pharmacologically active compounds. Therefore, it is of great interesting to introduce such structure into organic compounds. However, to the best of our knowledge, the cross-coupling of benzyl group with α-trifluoromethyl alkenes has yet to be developed. Alkylzinc reagents are important alkylmetal reagents, which can be easily prepared therefore have many applications in organic synthesis.[34–36] Inspired by our previous reports,[37] we envision that the cross-coupling of benzylzinc reagents with 2-bromo-3,3,3-trifluoropropene *via* palladium catalyst is also feasible. As part of our ongoing studies on the development of green strategies for fluoroalkylation,[38–40] herein, we present an efficient protocol to construct trifluoromethyl substituted terminal alkenes by the cross-coupling of benzylzinc reagents with BTP. The resulting products can be well suited to obtain diverse fluorinated compounds by subsequent simple transformations.

Results and discussion

To begin this study, (4-(tert-butyl)benzyl)zinc bromide (**1a**) and 2-bromo-3,3,3-trifluoropropene **2** (2.0 equiv.) were chosen as model substrates to test the transformation of this protocol. After initial failures, we found that the combination of $Pd(OAc)_2$ (2.5 mol %) with PPh_3 in THF at 110 °C provide product **3a** with 16% yield (Table 1, entry 1). Inspired by this result, a variety of different phosphine ligands were screened, to our delight, the yield increased to 71% when X-Phos was used (Table 1, entries 2–5). After a survey of the solvents utilized, other solvents, such as MeCN, DMF, Dioxane and DMA were less effective compared to THF (Table 1, entries 6–9) and no reaction occurred when DMSO was used. Comparable yield can still be obtained when the reaction performed at 90 °C, and the reactivity decreased dramatically when the temperature further decreased to 80 °C (Table 1, entries 11-12). Then, under these conditions, a

Table 1. Optimization of palladium-catalyzed cross-coupling of (4-(tert-butyl)benzyl)zinc bromide (**1a**) with 2-bromo-3,3,3-trifluoropropene (**2**).[a]



Entry	Pd	L	Temp. (°C)	Solvent	Yield (%)[b]
1	$Pd(OAc)_2$	PPh_3	110	THF	16
2	$Pd(OAc)_2$	Xantphos	110	THF	9
3	$Pd(OAc)_2$	DPPM	110	THF	7
4	$Pd(OAc)_2$	DPPP	110	THF	Nr
5	$Pd(OAc)_2$	X-Phos	110	THF	71
6	$Pd(OAc)_2$	X-Phos	110	MeCN	16
7	$Pd(OAc)_2$	X-Phos	110	DMA	37
8	$Pd(OAc)_2$	X-Phos	110	Dioxane	60
9	$Pd(OAc)_2$	X-Phos	110	DMF	44
10	$Pd(OAc)_2$	X-Phos	110	DMSO	Nr
11	$Pd(OAc)_2$	X-Phos	90	THF	75
12	$Pd(OAc)_2$	X-Phos	80	THF	40
13	$Pd(PPh_3)_4$	X-Phos	90	THF	42
14	$Pd_2(dba)_3$	X-Phos	90	THF	56
15	$Pd(dppf)Cl_2$	X-Phos	90	THF	34
16	$PdCl_2$	X-Phos	90	THF	55
17	$Pd(TFA)_2$	X-Phos	90	THF	87(81)

[a] Reaction conditions (unless otherwise specified): **1a** (0.2 mmol, 1.0 equiv.), **2a** (2.0 equiv.), solvent (2.0 mL).
[b] NMR yield determined by ^{19}F NMR using fluorobenzene as an internal standard (isolated yield in parentheses).

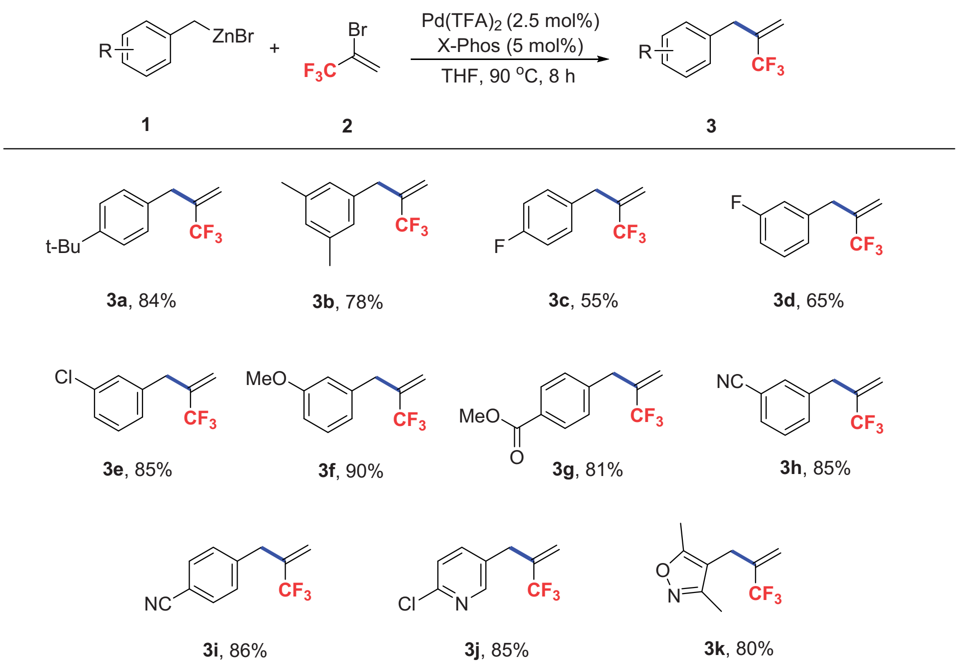
variety of catalyst systems were tested, only moderate yield was obtained when $Pd(PPh_3)_4$, $Pd_2(dba)_3$ or $Pd(dppf)Cl_2$ were used (Table 1, entries 13–15), the yield further increased to 87% when the catalyst switch to $Pd(TFA)_2$ (Table 1, entry 17).

The optimized cross-coupling conditions were applied to a series of different benzylzinc substrates. As summarized in Table 2, the reaction proceeds in moderate to high yield with benzylzinc agents bearing electron-withdrawing, electron-neutral and electron-donating substituents on the aromatic ring. Alkyl or dialkyl substituted benzylzinc reagents undergo the desired transformation smoothly (**3a–b**). Fluoro or chloro substituted benzylzinc reagents were also suitable substrates, providing compound **3c–e** in moderate to good yields. Benzylzinc reagents with methoxyl, ester or cyano on the aromatic ring proceeded this reaction well (**3f–i**). Additionally, heteroaromatic was also tolerated in this reaction to give the desired product in good yield (Table 2, **3j–k**).

Experiments

General procedure for the palladium-catalyzed cross-coupling of benzylzinc reagents (**1**) with 2-bromo-3,3,3-trifluoropropene (**2**): To a 25 mL of Schlenk tube were added $Pd(TFA)_2$ (2.5 mg, 2.5 mol %), X-Phos (7.2 mg, 5 mol %). The reaction tube was evacuated and backfilled with argon for three times, then THF (2.0 mL), benzylzinc reagent **1** (solution, 0.3 mmol, 1.0 equiv) and 2-bromo-3,3,3-trifluoropropane **2** (0.6 mmol, 2.0 equiv) were added subsequently. The Schlenk tube was screw capped and put into a preheated oil bath (90 °C). After stirring for 8 h, the reaction mixture was cooled to room temperature, diluted with EtOAc (50 mL) and filtered with a pad of Celite. The

Table 2. Palladium-catalyzed cross-coupling of benzylzinc reagents with 2-bromo-3,3,3-trifluoropropene.[a]



3a, 84%
3b, 78%
3c, 55%
3d, 65%
3e, 85%
3f, 90%
3g, 81%
3h, 85%
3i, 86%
3j, 85%
3k, 80%

[a] Reaction conditions (unless otherwise specified): **1** (0.3 mmol, 1.0 equiv), **2** (0.6 mmol, 2.0 equiv), THF (2.0 mL).

filtrate was washed with water (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified with silica gel chromatography to give the pure product.

Conclusion

In conclusion, this communication demonstrates a general approach for palladium-catalyzed cross-coupling of benzylzinc reagents with 2-bromo-3,3,3-trifluoropropene. This protocol used cheap industrial fluorine building blocks and easily prepared alkylzinc reagents to generate α-trifluoromethylalkene derivatives. This transformation features synthetic simplicity, mild reaction conditions and high functional group tolerance, providing a facile route for applications in medicinal chemistry.

Funding

The National Natural Science Foundation of China [No. 81760624, 21702241, 21762053], Young Elite Scientists Sponsorship Program by Cast of the China Association for Science and Technology [No. 2015-41], the Programs of Guizhou Province [No. 2017-1225, 2018-1427] are warmly acknowledged for funding this work.

ORCID

Jiwei Gu http://orcid.org/0000-0002-4908-7544
Chun-Yang He http://orcid.org/0000-0002-0599-7335

References

[1] Hiyama, T. *Organofluorine Compounds, Chemistry and Applications*; Springer-Verlag: Berlin, Heidelberg, **2000**.

[2] (a) Ojima, I. *Fluorine in Medicinal Chmeistry and Chemical Biology*; Wiley-Blackwell: Oxford, UK, **2009**. (b) Hussain, H.; Al-Harrasi, A.; Al-Rawahi, A.; Green, I. R.; Gibbons, S. *Chem. Rev.* **2014**, *114*, 10369–10428.

[3] (a) Gaspar, A.; Matos, M. J.; Garrido, J.; Uriarte, E.; Borges, F. *Chem. Rev.* **2014**, *114*, 4960–4992. DOI: 10.1021/cr400265z. (b) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308–319.

[4] Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320–330. DOI: 10.1039/b610213c.

[5] Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881–1886. DOI: 10.1126/science.1131943.

[6] Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432–2506. DOI: 10.1021/cr4002879.

[7] Preshlock, S.; Tredwell, M.; Gouverneur, V. *Chem. Rev.* **2016**, *116*, 719–766. DOI: 10.1021/acs.chemrev.5b00493.

[8] Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470–477. DOI: 10.1038/nature10108.

[9] Charpentier, J.; Fruh, N.; Togni, A. *Chem. Rev.* **2015**, *115*, 650–682. DOI: 10.1021/cr500223h.

[10] Xu, X.-H.; Matsuzaki, K.; Shibata, N. *Chem. Rev.* **2015**, *115*, 731–764. DOI: 10.1021/cr500193b.

[11] Feng, Z.; Xiao, Y.-L.; Zhang, X. *Acc. Chem. Res.* **2018**, *51*, 2264–2278. DOI: 10.1021/acs.accounts.8b00230.

[12] Chu, L.; Qing, F.-L. *Acc. Chem. Res.* **2014**, *47*, 1513–1522. DOI: 10.1021/ar4003202.

[13] Shao, X.; Xu, C.; Lu, L.; Shen, Q. *Acc. Chem. Res.* **2015**, *48*, 1227–1236. DOI: 10.1021/acs.accounts.5b00047.

[14] Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475–4521. DOI: 10.1021/cr1004293.

[15] Besset, T.; Schneider, C.; Cahard, D. *Angew. Chem. Int. Ed. Engl.* **2012**, *51*, 5048–5050. DOI: 10.1002/anie.201201012.

[16] Ni, C.; Hu, M.; Hu, J. *Chem. Rev.* **2015**, *115*, 765–825. DOI: 10.1021/cr5002386.

[17] An, L.; Xiao, Y.-L.; Zhang, S.; Zhang, X. *Angew. Chem. Int. Ed. Engl.* **2018**, *57*, 6921–6925. DOI: 10.1002/anie.201802713.

[18] Gao, X.; Xiao, Y.-L.; Wan, X.; Zhang, X. *Angew. Chem. Int. Ed. Engl.* **2018**, *57*, 3187–3191. DOI: 10.1002/anie.201711463.

[19] Zhang, B.; Zhang, X. *Chem. Commun. (Camb.)* **2016**, *52*, 1238–1241. DOI: 10.1039/c5cc08394j.

[20] Feng, Z.; Min, Q.-Q.; Fu, X.-P.; An, L.; Zhang, X. *Nat. Chem.* **2017**, *9*, 918–923. DOI: 10.1038/nchem.2746.

[21] Feng, Z.; Min, Q.-Q.; Zhang, X. *Org. Lett.* **2016**, *18*, 44–47. DOI: 10.1021/acs.orglett.5b03206.

[22] Phelan, J. P.; Wiles, R. J.; Lang, S. B.; Kelly, C. B.; Molander, G. A. *Chem. Sci.* **2018**, *9*, 3215–3220. DOI: 10.1039/c7sc05420c.

[23] Obijalska, E.; Pawelec, M.; Mlostoń, G.; Capperucci, A.; Tanini, D.; Heimgartner, H. *Eur. J. Org. Chem.* **2018**, *2018*, 3716–3723. DOI: 10.1002/ejoc.201701752.

[24] Fuchibe, K.; Hatta, H.; Oh, K.; Oki, R.; Ichikawa, J. *Angew. Chem. Int. Ed. Engl.* **2017**, *56*, 5890–5893. DOI: 10.1002/anie.201701985.

[25] Nagaki, A.; Tokuoka, S.; Yoshida, J.-I. *Chem. Commun. (Camb.)* **2014**, *50*, 15079–15081. DOI: 10.1039/c4cc06709f.

[26] Zhao, Q.; Besset, T.; Poisson, T.; Bouillon, J.-P.; Pannecoucke, X. *Eur. J. Org. Chem.* **2016**, *2016*, 76–82. DOI: 10.1002/ejoc.201501217.

[27] Trost, B. M.; Debien, L. *J. Am. Chem. Soc.* **2015**, *137*, 11606–11609. DOI: 10.1021/jacs.5b07573.

[28] Ichitsuka, T.; Fujita, T.; Ichikawa, J. *ACS Catal.* **2015**, *5*, 5947–5950. DOI: 10.1021/acscatal.5b01463.

[29] Liu, Y.; Zhou, Y.; Zhao, Y.; Qu, J. *Org. Lett.* **2017**, *19*, 946–949. DOI: 10.1021/acs.orglett.7b00168.

[30] Xiao, J.; Weisblum, B.; Wipf, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 5742–5743. DOI: 10.1021/ja051002s.

[31] Inokuchi, E.; Narumi, T.; Niida, A.; Kobayashi, K.; Tomita, K.; Oishi, S.; Ohno, H.; Fujii, N. *J. Org. Chem.* **2008**, *73*, 3942–3945. DOI: 10.1021/jo702318d.

[32] Kobayashi, K.; Narumi, T.; Oishi, S.; Ohno, H.; Fujii, N. *J. Org. Chem.* **2009**, *74*, 4626–4629. DOI: 10.1021/jo9005602.

[33] Fustero, S.; Chiva, G.; Piera, J.; Sanz-Cervera, J. F.; Volonterio, A.; Zanda, M.; Ramirez de Arellano, C. *J. Org. Chem.* **2009**, *74*, 3122–3132. DOI: 10.1021/jo9001867.

[34] Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417–1492. DOI: 10.1021/cr100327p.

[35] Tilly, D.; Chevallier, F.; Mongin, F.; Gros, P. C. *Chem. Rev.* **2014**, *114*, 1207–1257. DOI: 10.1021/cr400367p.

[36] Huo, S. *Org. Lett.* **2003**, *5*, 423–425. DOI: 10.1021/ol0272693.

[37] Lou, Y.-G.; Wang, A.-J.; Zhao, L.; He, L.-F.; Li, X.-F.; He, C.-Y.; Zhang, X. *Chem. Commun.* **2019**, *55*, 3705–3708. DOI: 10.1039/C8CC10212K.

[38] He, C.-Y.; Kong, J.; Li, X.; Li, X.; Yao, Q.; Yuan, F.-M. *J. Org. Chem.* **2017**, *82*, 910–917. DOI: 10.1021/acs.joc.6b02316.

[39] (a) Huang, Y.; Lei, Y.-Y.; Zhao, L.; Gu, J.; Yao, Q.; Wang, Z.; Li, X.-F.; Zhang, X.; He, C.-Y. *Chem. Commun.* **2018**, *54*, 13662–13665. DOI: 10.1039/C8CC07759B. (b) Zhao, L.; Huang, Y.; Wang, Z.; Zhu, E.; Mao, T.; Jia, J.; Gu, J.; Li, X.-F.; He, C.-Y. *Org. Lett.* **2019**, *21*, 6705–6709.

[40] Mao, T.; Zhao, L.; Huang, Y.; Lou, Y.-G.; Yao, Q.; Li, X.-F.; He, C.-Y. *Tetrahedron. Lett.* **2018**, *59*, 2752–2754. DOI: 10.1016/j.tetlet.2018.06.003.