Homogeneous Catalysis Hot Paper

International Edition: DOI: 10.1002/anie.201503297
German Edition: DOI: 10.1002/ange.201503297

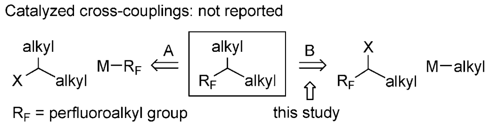
Nickel-Catalyzed Alkyl–Alkyl Cross-Couplings of Fluorinated Secondary Electrophiles: A General Approach to the Synthesis of Compounds having a Perfluoroalkyl Substituent**

*Yufan Liang and Gregory C. Fu**

Abstract: *Fluorinated organic molecules are of interest in fields ranging from medicinal chemistry to polymer science. Described herein is a mild, convenient, and versatile method for the synthesis of compounds bearing a perfluoroalkyl group attached to a tertiary carbon atom by using an alkyl–alkyl cross-coupling. A nickel catalyst derived from* $NiCl_2$*·glyme and a pybox ligand achieves the coupling of a wide range of fluorinated alkyl halides with alkylzinc reagents at room temperature. A broad array of functional groups is compatible with the reaction conditions, and highly selective couplings can be achieved on the basis of differing levels of fluorination. A mechanistic investigation has established that the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) inhibits cross-coupling under these conditions and that a TEMPO–electrophile adduct can be isolated.*

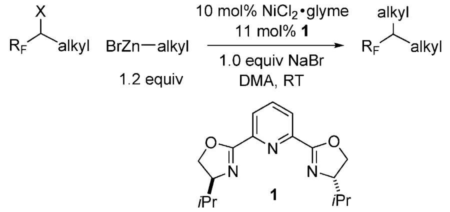
Because fluorinated organic compounds exhibit different properties, including different biological activities, when compared with their nonfluorinated counterparts, interest in the synthesis of fluorinated molecules has increased rapidly in recent years.[1] Whereas impressive progress has been described in the development of general strategies for the preparation of fluorinated aromatic compounds (e.g., Ar–F and Ar–CF_3),[2,3] current approaches to the synthesis of molecules which include a C_{sp3}–R_F bond (R_F = a perfluoroalkyl group) are generally narrow in scope.[3b,4]

For target compounds wherein a perfluoroalkyl group is attached to an sp^3-hybridized tertiary carbon atom,[5,6] alkyl–alkyl cross-coupling with a perfluorinated nucleophile (M-R_F) represents a potentially attractive and versatile approach [Eq. (1); pathway A].[7] Although there are scattered reports of stoichiometric cross-couplings of fluorinated nucleophiles with alkyl electrophiles, catalyzed processes have been limited to activated electrophiles (e.g., allylic, benzylic, and propargylic).[8]



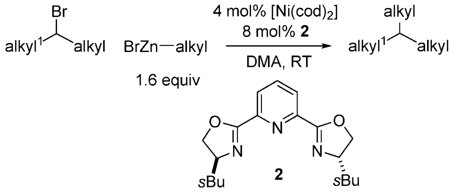
(1)

To the best of our knowledge, an alternative strategy in which a secondary alkyl electrophile, which includes a perfluoroalkyl substituent, is cross-coupled with an alkylmetal reagent [Eq. (1); pathway B] has not been described,[9] perhaps because of the deleterious effect of the perfluoroalkyl group at one or more stages in the catalytic cycle.[10,11] In this report, we provide a method that accomplishes this transformation with secondary alkyl halides bearing a variety of perfluoroalkyl substituents [Eq. (2); DMA = *N,N*-dimethylacetamide].



(2)

Because of their ready accessibility and their high functional-group compatibility, alkylzinc reagents are attractive partners for cross-coupling processes.[12] Several years ago, we reported a nickel/pybox-based method for coupling unactivated secondary alkyl bromides with alkylzinc reagents in good yield [Eq. (3); cod = 1,5-cyclooctadiene].[13] When we applied these conditions to the cross-coupling of an alkyl bromide bearing a perfluoroalkyl substituent, we obtained a low yield of the desired product [8%; Eq. (4)]. Debromodefluorination (-BrF)[14] and hydrodebromination of the electrophile were significant side reactions.



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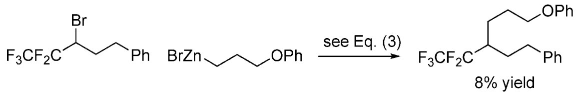

(4)

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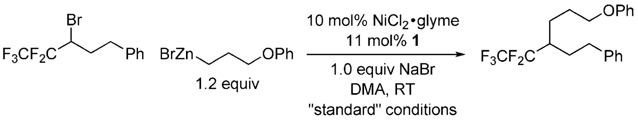
[**] Support has been provided by the National Institutes of Health (National Institute of General Medical Sciences: R01-GM62871) and the Gordon and Betty Moore Foundation (Caltech Center for Catalysis and Chemical Synthesis). We thank Dr. Nathan D. Schley for helpful discussions.

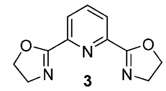
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201503297.

Table 1: Alkyl–alkyl cross-coupling of a fluorinated secondary electrophile: Effect of reaction parameters.[a]



Entry	Variation from the “standard” conditions	Yield [%][b]
1	none	79
2	no NaBr	28
3	LiBr, instead of NaBr	75
4	KBr, instead of NaBr	66
5	CsBr, instead of NaBr	61
6	(nBu)$_4$NBr, instead of NaBr	74
7	NaI, instead of NaBr	59
8	NaCl, instead of NaBr	66
9	NaF, instead of NaBr	27
10	**3**, instead of **1**	5
11	**4**, instead of **1**	<1
12	**5**, instead of **1**	7
13	**6**, instead of **1**	17
14	**7**, instead of **1**	<1
15	$+0.1$ equiv H_2O	79
16	under air in a closed vial	60
17	40 °C, instead of RT	72
18	0 °C, instead of RT	75
19	1.0 equiv of organozinc reagent	71
20	5.0 mol% $NiCl_2$·glyme, 5.5 mol% **1**	64
21	no $NiCl_2$·glyme	<1
22	no **1**	49

[a] All data are the average of two experiments. [b] The yields were determined by ^{19}F NMR spectroscopy with the aid of an internal standard.



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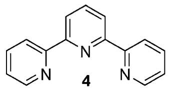

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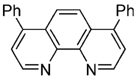

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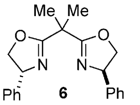

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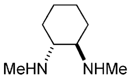
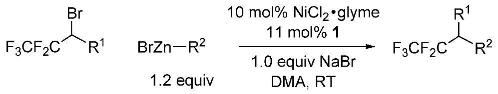
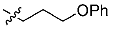
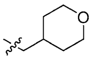
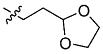
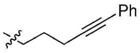
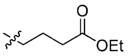
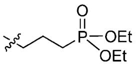
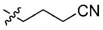
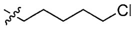
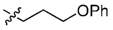


7 (racemic)

Nevertheless, by modifying the reaction conditions, we can achieve the desired alkyl–alkyl cross-coupling of a fluorinated secondary electrophile in good yield (Table 1, entry 1). The presence of the bromide ion is particularly helpful, with NaBr being the most useful source among those that we have examined (entries 1–6).[15] The addition of either NaI or NaCl also has a substantial beneficial effect (entries 7 and 8), whereas NaF does not (entry 9). A variety of other ligands, both tridentate and bidentate, furnish significantly lower yields compared with that obtained with the pybox ligand **1** (entries 10–14).[16] The optimized method is not affected by the presence of a small amount of water (entry 15) and is only modestly sensitive to air (entry 16). Changes in temperature (0–40 °C), as well as the use of a smaller amount of the nucleophile (1.0 equiv), lead to only a small loss in coupling efficiency (entries 17–19). Cutting the catalyst loading in half results in a moderate decrease in yield (entry 20). In the absence of $NiCl_2$·glyme, essentially no product is formed (entry 21), whereas, in the absence of the ligand, cross-coupling is less efficient (entry 22). $NiCl_2$·glyme and **1** are both commercially available and can be handled in the air.

Table 2: Alkyl–alkyl cross-couplings of fluorinated secondary electrophiles: Scope.[a]



Entry	R^1	R^2	Yield [%][b]
1	CH_2CH_2Ph		74
2	CH_2CH_2Ph		55
3	CH_2CH_2Ph		61
4	CH_2CH_2Ph		59
5	CH_2CH_2Ph		66
6	CH_2CH_2Ph		70
7	CH_2CH_2Ph		77
8			64

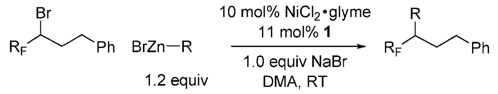
[a] All data are the average of two experiments. [b] Yield of purified product.

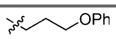
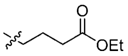
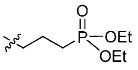
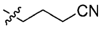
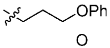
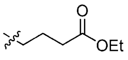
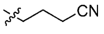
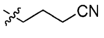
The scope of this new alkyl–alkyl cross-coupling process is fairly broad (Table 2).[17] Thus, functional groups such as an ether, an acetal, an alkyne, an ester, a phosphonate, a nitrile, and a primary alkyl chloride are compatible with the reaction conditions. Electrophiles which bear higher order perfluoroalkyl substituents are also suitable coupling partners (Table 3).

This method is not limited to cross-couplings of alkyl bromides. Thus, under the same reaction conditions, the Negishi reaction of a fluorinated alkyl iodide proceeds in fairly good yield [Eq. (5)].[18]

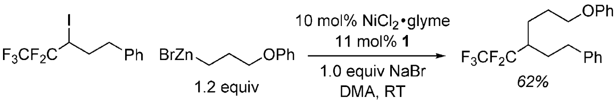
Among perfluoroalkyl groups, trifluoromethyl (CF_3) is the most commonly encountered, and considerable effort has

Table 3: Alkyl–alkyl cross-couplings of fluorinated secondary electrophiles: Scope with respect to the perfluoroalkyl group.[a]



Entry	R$_F$	R	Yield [%][b]
1	nC_3F_7		65
2	nC_3F_7		54
3	nC_3F_7		51
4	nC_3F_7		69
5	nC_4F_9		67
6	nC_4F_9		54
7	nC_4F_9		69
8	nC_9F_{19}		66

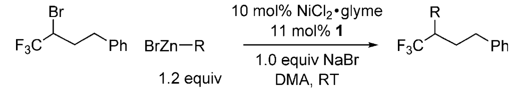
[a] All data are the average of two experiments. [b] Yield of purified product.

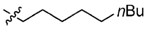
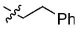
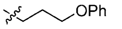
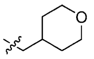
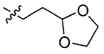
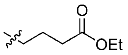
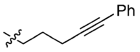
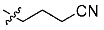
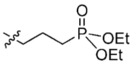


(5)

therefore been dedicated to the development of approaches to the synthesis of various scaffolds that bear this substituent.[3b,4] Although some progress has been described in the generation of targets which include a trifluoromethyl group attached to a tertiary carbon atom, there is still a need for a general method that proceeds in good yield.[3b,4,19] As illustrated in Tables 4 and 5,[20] our cross-coupling conditions provide versatile access to such compounds and are compatible with a wide array of functional groups (e.g., ether, acetal, ester, alkyne, nitrile, phosphonate, primary alkyl bromide, primary alkyl tosylate, furan, aryl iodide, carbamate, and ketone). On a gram scale, in the presence of 5 mol % NiCl$_2$·glyme/5.5 mol % **1**, the alkyl–alkyl Negishi coupling depicted in entry 8 of Table 4 proceeds in 80 % yield (1.22 g of product).

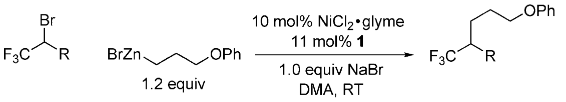
Table 4: Alkyl–alkyl cross-couplings to generate trifluoromethyl-substituted products: Scope with respect to the nucleophile.[a]

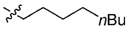
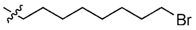
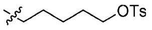
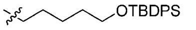
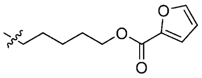
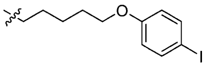
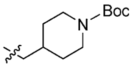
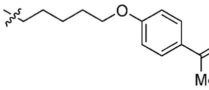


Entry	R	Yield [%][b]
1		79
2		78
3		83
4		74
5		72
6		83
7		67
8		83
9		89

[a] All data are the average of two experiments. [b] Yield of purified product.

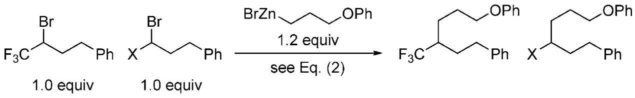
Table 5: Alkyl–alkyl cross-couplings to generate trifluoromethyl-substituted products: Scope with respect to the electrophile.[a]



Entry	R	Yield [%][b]
1		86
2		79
3		76
4[c]		72
5		83
6[c]		81
7		80
8		86

[a] All data are the average of two experiments. [b] Yield of purified product. [c] Nucleophile: BrZnCH$_2$CH$_2$CH$_2$CH$_2$CN. Boc = *tert*-butoxycarbonyl, TBDPS = *tert*-butyldiphenylsilyl, Ts = 4-toluenesulfonyl.

Table 6: Selective alkyl–alkyl cross-couplings based on fluorine substitution.



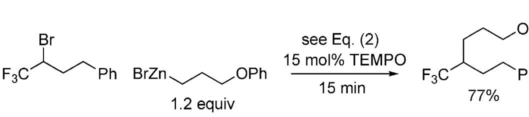
Unreacted (%)		X	Yield [%]	
0	97	CF$_2$H	88	3
0	>99	CFH$_2$	87	<1
0	99	CH$_3$	87	1

The yields and conversions were determined through analysis by ^{19}F NMR spectroscopy and gas chromatography with the aid of internal standards.

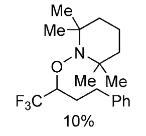
We have observed that, under our standard cross-coupling conditions, replacement of the CF$_3$ substituent of the electrophile with a CF$_2$H group leads to a significantly slower reaction. The enhanced reactivity of the CF$_3$-substituted electrophile enables unusual and highly selective Negishi reactions in the presence of less fluorinated electrophiles (Table 6).[21]

For the array of nickel-catalyzed cross-couplings of alkyl halides that we have developed, we have suggested that the electrophile may react to furnish an alkyl radical during the oxidative-addition step of the catalytic cycle.[22] For the present method, we have determined that the addition of 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO)[23] substantially inhibits carbon–carbon bond formation [Eq. (6)]. A side product of this Negishi reaction is a TEMPO-electrophile adduct [Eq. (7)], potentially generated from the coupling of TEMPO with an alkyl radical.[24]

In conclusion, we have developed a mild and simple nickel-catalyzed cross-coupling method for synthesizing a broad array of compounds which include a tertiary carbon atom bearing a perfluoroalkyl substituent, thereby providing



(6)



(7)

a general approach to the synthesis of this family of target molecules. A wide variety of functional groups are compatible with the reaction conditions, and the catalyst components are commercially available. The rate of cross-coupling is remarkably sensitive to the level of fluorination of the electrophile, and enables the unusual and highly selective reaction of a substrate which bears a CF$_3$ group in the presence of the corresponding CF$_2$H-substituted compound. In a mechanistic study, we have established that the presence of TEMPO, a radical trap, inhibits carbon–carbon bond formation, and we have isolated a TEMPO-electrophile adduct. Additional studies of nickel-catalyzed cross-couplings of alkyl electrophiles are underway.

Keywords: cross-coupling · fluorine · homogeneous catalysis · nickel · zinc

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 9047–9051
Angew. Chem. **2015**, *127*, 9175–9179

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[17] Notes: a) Under our standard reaction conditions, the cross-coupling product is stable (e.g., no C−F bond cleavage is observed), and a secondary alkylzinc reagent (cyclopentyl-ZnBr) was not a suitable coupling partner; b) The cross-coupling illustrated in entry 3 of Table 2 proceeds with 28% *ee*.

[18] Under our standard reaction conditions, the corresponding secondary alkyl chloride and secondary alkyl tosylate are not suitable substrates.

[19] For a recent report of oxidative coupling between secondary alkylboronic acids and TMS-CF$_3$ (10 mol% Cu(OTf)$_2$·0.5(PhH),

40 mol% 3,4,7,8-tetramethyl-1,10-phenanthroline, 3 equiv AgF, 1 equiv Ag(OTs), and 3 equiv KF in DMF at 50°C; 35–54% yield), see: J. Xu, B. Xiao, C.-Q. Xie, D.-F. Luo, L. Liu, Y. Fu, *Angew. Chem. Int. Ed.* **2012**, *51*, 12551–12554; *Angew. Chem.* **2012**, *124*, 12719–12722.

[20] Under our standard reaction conditions: a) For the reaction illustrated in entry 1 of Table 4, the corresponding alkyl iodide couples in 57% yield, whereas the chloride and the tosylate are ineffective cross-coupling partners; b) Debromodefluorination is the predominant side reaction; c) An allylic, benzylic, propargylic, and hindered (alkyl = Cy) electrophile, as well as a secondary alkylzinc (cyclopentyl-ZnBr) and a perfluoroalkylzinc reagent, were not suitable coupling partners; d) The cross-coupling illustrated in entry 5 of Table 4 proceeds in 20% *ee*.

[21] Nevertheless, the cross-coupling of the difluoromethyl-substituted electrophile which is illustrated in Table 6 can be achieved in good yield (70%) under related conditions (10 mol% $NiCl_2$·glyme, 11 mol% **1**, 1 equiv KBr, DMA/DMF, RT). For a review on difluoromethylation, see: J. Hu, W. Zhang, F. Wang, *Chem. Commun.* **2009**, 7465–7478.

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[24] Notes: a) After the TEMPO (15 mol%) has been consumed, cross-coupling resumes; b) In the absence of $NiCl_2$·glyme or of the organozinc reagent, the adduct of TEMPO with the electrophile was not observed; c) Addition of the TEMPO-electrophile adduct to a cross-coupling reaction does not inhibit carbon–carbon bond formation; d) The TEMPO-electrophile adduct is stable to the cross-coupling conditions.

Received: April 11, 2015
Revised: May 3, 2015