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Stereoconvergent Negishi Arylations of Racemic Secondary Alkyl Electrophiles: Differentiating between a CF_3 and an Alkyl Group

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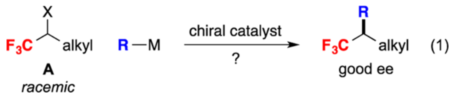
Supporting Information

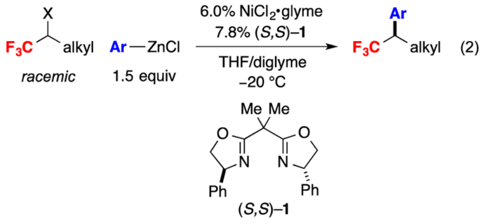
ABSTRACT: In this report, we establish that a readily available nickel/bis(oxazoline) catalyst accomplishes a wide array of enantioconvergent cross-couplings of arylzinc reagents with CF_3-substituted racemic secondary alkyl halides, a process that necessitates that the chiral catalyst be able to effectively distinguish between a CF_3 and an alkyl group in order to provide good ee. We further demonstrate that this method can be applied without modification to the catalytic asymmetric synthesis of other families of fluorinated organic compounds.

The incorporation of a trifluoromethyl (CF_3) group in an organic molecule can lead to substantially altered properties, including biological activity, as compared to a nonfluorinated compound.[1] Whereas significant advances have been described in the synthesis of molecules that contain an Ar–CF_3 bond,[2] progress in the development of general methods for the synthesis of compounds that include a C_{sp^3}–CF_3 bond has been more limited, particularly in the case wherein the carbon that bears the CF_3 group is a tertiary stereogenic center.[3,4] Examples of catalytic asymmetric reactions that generate the latter class of compounds include the α-trifluoromethylation of aldehydes,[5] the conjugate addition to CF_3-containing electron-deficient alkenes,[6] the trifluoromethylation of allylic electrophiles,[7] and the hydrogenation of CF_3-substituted alkenes;[8] these methods often require a suitable additional functional group (e.g., carbonyl, alkenyl, or aryl substituent) to achieve the desired bond formation and good enantioselectivity. The development of a general approach that proceeds in high ee without the need for such a functional group could thus complement existing strategies.

Recently, we have established that chiral nickel catalysts can accomplish enantioconvergent cross-coupling reactions of a number of racemic secondary electrophiles.[9] These methods have typically employed alkyl halides that either are activated (e.g., benzylic or allylic) or include a directing group (e.g., a carbonyl or a sulfonamide). In order to achieve the objective outlined above, we decided to pursue the development of a general method for the stereoconvergent cross-coupling of an electrophile of type **A** (eq 1);[10,11] to furnish good enantioselectivity in such a process, the catalyst must effectively differentiate between a CF_3 and an alkyl group,[12,13] which was not achieved in the only previous report of such a cross-coupling.[14]



In this report, we establish that cross-couplings of CF_3-substituted racemic alkyl electrophiles can indeed be achieved with good enantioselectivity, without the need for an additional activating/directing group elsewhere in the molecule. Specifically, we establish that a nickel/bis(oxazoline) catalyst can effect asymmetric Negishi arylations of secondary alkyl halides (eq 2).



The data in Table 1 illustrate the impact of various reaction parameters on the efficiency of this stereoconvergent cross-coupling.[15] If either of the catalyst components ($NiCl_2$·glyme or bis(oxazoline) ligand **1**, each of which is commercially available and can be handled in air) is omitted, little or no carbon–carbon bond formation is observed (entries 2 and 3). Other ligands, including related bis(oxazolines), a pybox, and a 1,2-diamine,[16] furnish lower ee's and yields (entries 4–7). The use of less of the organozinc nucleophile, a lower catalyst loading, or THF (without diglyme) as the solvent results in no erosion in enantioselectivity but in a modest loss in yield (entries 8–10). At room temperature, side reactions such as hydrodebromination and debromodefluorination become significant (entry 11). This enantioconvergent Negishi arylation is not highly water-sensitive: the addition of 0.1 equiv of water has no deleterious effect on either ee or yield (entry 12).

Next, we explored the scope of this new method for the catalytic enantioselective synthesis of stereogenic centers that bear a CF_3 substituent (Table 2).[17] Although the use of an ortho-substituted arylzinc reagent leads to a modest yield of the desired cross-coupling product (entry 1), an array of meta- and para-substituted nucleophiles, either electron-rich or electron-poor, generally furnish very good ee's and yields (entries 2–11). Functional groups such as an aryl ether,[18] an aryl halide (Br, Cl, and F),[19] an aryl thioether,[20] and oxygen and nitrogen

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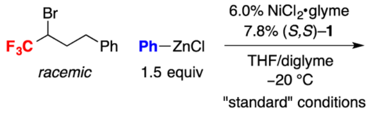
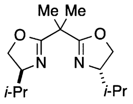
Table 1. Stereoconvergent Negishi Arylations of Fluorinated Electrophiles: Effect of Reaction Parameters[a]

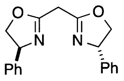


entry	variation from the "standard" conditions	ee (%)	yield (%)[b]
1	none	95	89
2	no $NiCl_2$·glyme	–	<2
3	no (*S,S*)-**1**	–	3
4	(*S,S*)-**2**, instead of (*S,S*)-**1**	33	26
5	(*S,S*)-**3**, instead of (*S,S*)-**1**	40	27
6	(*R,R*)-**4**, instead of (*S,S*)-**1**	–	<2
7	(*S,S*)-**5**, instead of (*S,S*)-**1**	11	4
8	1.1 equiv of Ph–ZnCl	95	78
9	3.0% $NiCl_2$·glyme, 3.9% (*S,S*)-**1**	94	72
10	THF only	95	82
11	rt, instead of −20 °C	86	15
12	0.1 equiv of H_2O added	95	88

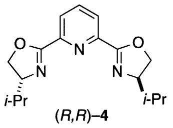
[a] All data are the average of two experiments. [b] The yields were determined through analysis by ^{19}F NMR spectroscopy (with the aid of an internal standard).



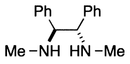
(*S,S*)–**2**



(*S,S*)–**3**

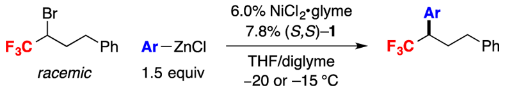


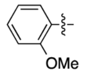
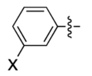
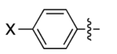
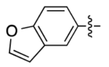
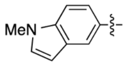
(*R,R*)–**4**



(*S,S*)–**5**

Table 2. Stereoconvergent Negishi Arylations of Fluorinated Electrophiles: Scope with Respect to the Nucleophile[a]



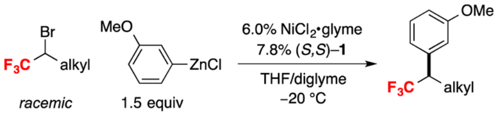
entry	Ar	ee (%)	yield (%)[b]
1		87	50
2	 X = OMe	96	90
3	Me	95	90
4	CF_3	97	87
5	F	96	79
6	Cl	96	86
7	 X = H	95	86
8	Me	95	89
9	SMe	94	52
10	F	96	84
11	Br	95	87
12		94	60
13		94	68

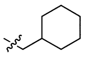
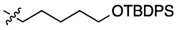
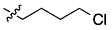
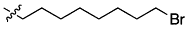
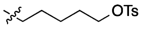
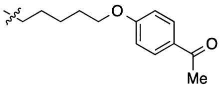
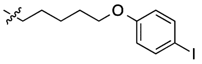
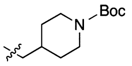
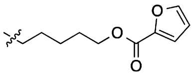
[a] All data are the average of two experiments. [b] Yield of purified product.

heterocycles are compatible with the coupling conditions. On a gram scale (1.34 g of product), the stereoconvergent Negishi reaction illustrated in entry 2 of Table 2 proceeds in 96% ee and 91% yield; it is noteworthy that this cross-coupling is not especially air-sensitive—when conducted in a capped vial under air, the product is generated with similar efficiency (96% ee, 87% yield).

With regard to the electrophilic coupling partner, the scope of this method for enantioselective Negishi cross-couplings of fluorinated secondary alkyl halides is also fairly broad (Table 3).[21] It is worth noting that, in the case of entry 1, the catalyst must effectively differentiate between a CF_3 and a CH_3 group in order to deliver the product in very good ee.[12] A variety of functional groups are compatible with the reaction conditions, including a silyl ether, a primary alkyl chloride,[22] a primary alkyl bromide,[23] a primary alkyl tosylate,[24] an aryl ether,[18] a ketone, an aryl iodide,[19] a carbamate, an ester, and a furan.

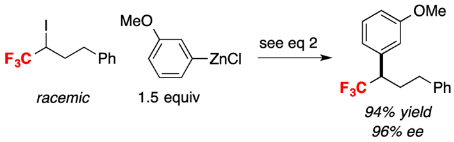
Table 3. Stereoconvergent Negishi Arylations of Fluorinated Electrophiles: Scope with Respect to the Electrophile[a]



entry	alkyl	ee (%)	yield (%)[b]
1	Me	91	81
2	*n*-Oct	95	88
3		96	81
4		94	77
5		96	89
6		96	80
7		97	91
8		96	89
9		95	60
10		97	82
11		96	81

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

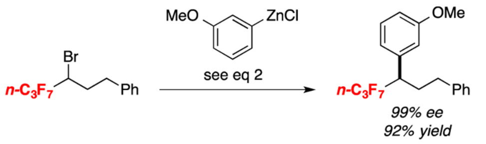
The choice of electrophile is not limited to alkyl bromides. Thus, without modification we can apply to a racemic secondary alkyl iodide the method that we have developed for stereoconvergent cross-couplings of bromides (eq 3).[25]



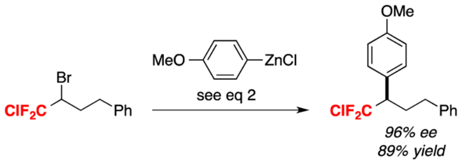
(3)

Significantly, the method can also be applied to electrophiles that bear an electron-withdrawing group other than CF_3. Thus, excellent enantioselectivity is observed with an array of fluorinated substituents, including perfluoroalkyl, CF_2Cl, CF_2COPh, and CF_2CO_2Et (eqs 4–7).[26]

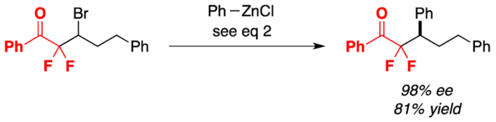
In conclusion, we have developed a versatile stereoconvergent Negishi arylation of racemic secondary alkyl halides wherein a chiral nickel catalyst differentiates between a CF_3 and an alkyl substituent in order to deliver a high enantiomeric excess. In contrast to many other catalytic asymmetric processes that generate tertiary stereocenters that bear a CF_3 substituent, this method does not require an extraneous



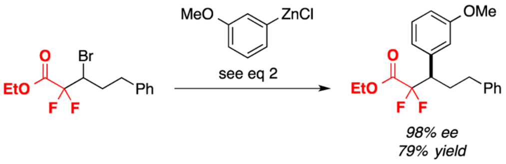
(4)



(5)



(6)



(7)

activating/directing group; furthermore, this approach is effective at producing a variety of other enantiomerically enriched fluorinated compounds under the same conditions. From a practical perspective, it is noteworthy that both of the catalyst components are commercially available and can be handled in air and that the method is not particularly air- or water-sensitive. Further studies of nickel-catalyzed cross-couplings of alkyl electrophiles are underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and compound characterization data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b04725.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For leading references, see: (a) *Fluorine in Pharmaceutical and Medicinal Chemistry: From Biophysical Aspects to Clinical Applications*; Gouverneur, V., Müller, K., Eds.; Imperial College Press: London, 2012. (b) Zhu, W.; Wang, J.; Wang, S.; Gu, Z.; Aceña, J. L.; Izawa, K.; Liu, H.; Soloshonok, V. A. *J. Fluorine Chem.* **2014**, *167*, 37−54.

(2) For discussions and leading references, see: (a) Cho, E. J.; Senecal, T. D.; Kinzel, T.; Zhang, Y.; Watson, D. A.; Buchwald, S. L. *Science* **2010**, *328*, 1679−1681. (b) Alonso, C.; Martínez de Marigorta, E.; Rubiales, G.; Palacios, F. *Chem. Rev.* **2015**, *115*, 1847−1935.

(3) For discussions and leading references, see: (a) Yang, X.; Wu, T.; Phipps, R. J.; Toste, F. D. *Chem. Rev.* **2015**, *115*, 826−870. (b) References 1b and 2b. (c) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214−8264. (d) Xu, J.; Liu, X.; Fu, Y. *Tetrahedron Lett.* **2014**, *55*, 585−594.

(4) For a few examples of target compounds, see: (a) Proline derivative: Del Valle, J. R.; Goodman, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 1600−1602. (b) Qiu, X.-l.; Qing, F.-l. *J. Org. Chem.* **2002**, *67*, 7162−7164. (c) Nucleoside analogue: Jeannot, F.; Gosselin, G.; Standring, D.; Bryant, M.; Sommadossi, J.-P.; Loi, A. G.; La Colla, P.; Mathé, C. *Bioorg. Med. Chem.* **2002**, *10*, 3153−3161. (d) Estradiol derivative: Blazejewski, J.-C.; Wilmshurst, M. P.; Popkin, M. D.; Wakselman, C.; Laurent, G.; Nonclercq, D.; Cleeren, A.; Ma, Y.; Seo, H.-S.; Leclercq, G. *Bioorg. Med. Chem.* **2003**, *11*, 335−345.

(5) For example, see: (a) Nagib, D. A.; Scott, M. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 10875−10877. (b) Allen, A. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 4986−4987.

(6) For a recent example, see: Massolo, E.; Benaglia, M.; Orlandi, M.; Rossi, S.; Celentano, G. *Chem. - Eur. J.* **2015**, *21*, 3589−3595.

(7) For a recent example, see: Nishimine, T.; Fukushi, K.; Shibata, N.; Taira, H.; Tokunaga, E.; Yamano, A.; Shiro, M.; Shibata, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 517−520.

(8) For example, see: Dong, K.; Li, Y.; Wang, Z.; Ding, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 14191−14195.

(9) (a) For the initial report, see: Fischer, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594−4595. (b) For the most recent study, see: Choi, J.; Martín-Gago, P.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 12161−12165.

(10) For examples of metal-catalyzed cross-coupling reactions of CF_3CH_2OTs and CF_3CH_2I (*primary* alkyl electrophiles), see: (a) Zhao, Y.; Hu, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 1033−1036. (b) Liang, A.; Li, X.; Liu, D.; Li, J.; Zou, D.; Wu, Y.; Wu, Y. *Chem. Commun.* **2012**, *48*, 8273−8275. (c) Feng, Y.-S.; Xie, C.-Q.; Qiao, W.-L.; Xu, H.-J. *Org. Lett.* **2013**, *15*, 936−939. (d) Leng, F.; Wang, Y.; Li, H.; Li, J.; Zou, D.; Wu, Y.; Wu, Y. *Chem. Commun.* **2013**, *49*, 10697−10699.

(11) To the best of our knowledge, there are no examples of metal-catalyzed cross-couplings of perfluorinated alkyl nucleophiles with unactivated alkyl electrophiles, which could represent a complementary route to the products illustrated in eq 1.

(12) For an early example of an enantioselective reaction wherein differentiation between a CF_3 and a CH_3 group is achieved, see: Feigl, D. M.; Mosher, H. S. *Chem. Commun.* **1965**, 615−616.

(13) For a recent review on the influence of fluorine in asymmetric catalysis, see: Cahard, D.; Bizet, V. *Chem. Soc. Rev.* **2014**, *43*, 135−147.

(14) Liang, Y.; Fu, G. C. *Angew. Chem., Int. Ed.* **2015**, *54*, 9047−9051.

(15) Notes: (a) The method described in ref 14 is not effective for the arylation process illustrated in Table 1, furnishing poor ee and yield. (b) PhZnCl is generated from PhLi. If PhZnCl is produced instead from PhMgCl, then the arylation proceeds in 95% ee and 81% yield. Ph_2Zn is not effective under these conditions, furnishing 88% ee and a 9% yield.

(16) These families of ligands have previously been employed in stereoconvergent nickel-catalyzed cross-couplings of alkyl electrophiles: (a) Bis(oxazoline): Lou, S.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 1264−1266. (b) Pybox: Reference 9a. (c) 1,2-Diamine: Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 6694−6695.

(17) Notes: (a) During the course of these couplings, we have not observed kinetic resolution of the electrophile (<5% ee), consumption of the cross-coupling product, or erosion in the ee of the product. (b) In a preliminary study under our standard conditions, a thienylzinc, a pyridylzinc, and an alkenylzinc reagent were not suitable cross-coupling partners. (c) Hydrodebromination of the electrophile is the predominant side reaction.

(18) For examples of the reactivity of aryl ethers in nickel-catalyzed cross-couplings, see: Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346−1416.

(19) For examples of the reactivity of aryl halides (I, Br, Cl, and F) in nickel-catalyzed cross-couplings, see: Han, F.-S. *Chem. Soc. Rev.* **2013**, *42*, 5270−5298.

(20) For early examples of nickel-catalyzed cross-couplings of an aryl thioether, see: (a) Wenkert, E.; Ferreira, T. W.; Michelotti, E. L. *J. Chem. Soc., Chem. Commun.* **1979**, 637−638. (b) Okamura, H.; Miura, M.; Takei, H. *Tetrahedron Lett.* **1979**, *20*, 43−46. (c) Takei, H.; Miura, M.; Sugimura, H.; Okamura, H. *Chem. Lett.* **1979**, 1447−1450.

(21) In a preliminary study under the standard conditions, an attempt to cross-couple an electrophile wherein alkyl = cyclohexyl was not successful.

(22) For an early example of a nickel-catalyzed cross-coupling of a primary alkyl chloride, see: Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2002**, *124*, 4222−4223.

(23) (a) For an early example of a nickel-catalyzed cross-coupling of a primary alkyl bromide, see: Devasagayaraj, A.; Stüdemann, T.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1996**, *34*, 2723−2725. (b) The lower reactivity of the primary alkyl bromide may be due to activation of the secondary alkyl bromide by the CF_3 substituent (ref 14).

(24) For an early example of a nickel-catalyzed cross-coupling of a primary alkyl tosylate, see ref 22.

(25) Under the same conditions, the corresponding alkyl tosylate, alkyl chloride, and alkyl triflate are not useful coupling partners (<5% yield).

(26) For recent references to the synthesis/utility of chlorodifluoromethyl- and difluorocarbonyl-containing compounds, see: (a) Salomon, P.; Zard, S. Z. *Org. Lett.* **2014**, *16*, 2926−2929. (b) Han, C.; Salyer, A. E.; Kim, E. H.; Jiang, X.; Jarrard, R. E.; Powers, M. S.; Kirchhoff, A. M.; Salvador, T. K.; Chester, J. A.; Hockerman, G. H.; Colby, D. A. *J. Med. Chem.* **2013**, *56*, 2456−2465. (c) Ge, S.; Arlow, S. I.; Mormino, M. G.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 14401−14404.

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