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Enantioselective Construction of Trifluoromethoxylated Stereogenic Centers by Nickel-Catalyzed Asymmetric Suzuki-Miyaura Coupling of Secondary Benzyl Bromides

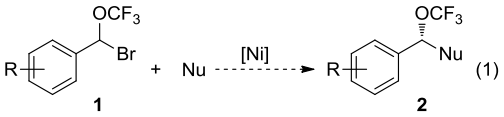
Weichen Huang,[a] Xiaolong Wan and Qilong Shen*[a]

Abstract: A method for the construction of trifluoromethoxy-containing stereogenic centers with high enantiometric excess via nickel-catalyzed Suzuki-Miyaura coupling of easily available α-bromobenzyl trifluoromethylethers **1a**-**f** with a variety of aryl pinacol boronates was described. The reaction conditions were mild and a variety of common functional groups such as fluoride, chloride, bromide, ester, enolizable ketone, nitro, cyano, amino and vinyl group were well tolerated. Furthermore, the reaction can be easily scaled up to gram quantities without erosion of the enantioselectivity.

Nowadays, it is generally accepted that fluorine and fluoroalkyl groups such as trifluoromethyl, difluoromethyl or trifluoromethylthio group have a "magic effect" in facilitating the search of lead compounds for new drug discovery in the fields of pharmaceutical and agrochemical industry.[1] Compared to these well-recognized fluoroalkyl groups, the trifluoromethoxy group (-OCF_3), however, is perhaps the least well understood,[2] even though it is commonly referred as "pseudo halogen".[3] Nevertheless, recently, this particular fluoroalkyl group has gained considerable attention because of its beneficial properties, which may improve the drug molecule's pharmacokinetics and efficacy, such as high lipophicicity (Hansch's hydrophobicity parameter π = 1.04) which is higher than that of trifluoromethyl group (π = 0.88),[4] and strong electron-withdrawing nature (inductive effect σ_I = +0.40).[5] Consequently, various stragegies that can access to the trifluoromethoxylated compounds have been actively pursued and a few elegant methods for the formation of alkyl or aryl trifluoromethylethers have been reported.[6,7]

Despite these tremendous achievements, methods that can build the CF_3O-containing stereogenic centers with high enantioselectivity remain extremely rare. To the best of our knowledge, up until now, only one method has been reported by Tang and co-workers for the construction of the CF_3O-containing stereogenic centers, whereas moderate enantioselectivities were observed.[8] Thus, development of new efficient protocol for the construction of tertiary stereogenic carbon centers bearing a trifluoromethoxy group with high enantioselectivity is urgently needed.

Inspired by the pioneer work from Fu's group on nickel-catalyzed asymmetric coupling of secondary alkyl halides with a variety of nucleophiles,[9-12] we envisaged that if a nickel-catalyzed asymmetric cross-coupling of racemic trifluoromethoxy-substituted secondary alkyl bromide such as compound **1** can be developed (Eq. 1), a general method for the formation of trifluoromethoxy-bearing stereogenic carbon centers could be provided for the medicinal chemists in search of high performance drug candidates. To achieve such a transformation, we are facing several formidable challenges: 1) Nickel-catalyzed Negishi asymmetric cross-couplings of benzylic bromides have previously been reported.[13] Analogous studies on asymmetric Suzuki-coupling reactions, however, has not be described; 2) α-Bromobenzyl methylethers were known to be unstable and easily underwent decomposition to form aldehydes;[14] while the electron-withdrawing trifluoromethyl group may increase the stability of α-bromobenzyl trifluoromethylethers, the stability of these compounds and the final products in the presence of Lewis acidic reagents or catalyst are questionable; 3) It has been reported previously that in the presence of a nickel catalyst, benzylic ethers underwent carbon-oxygen activation and further transformations.[15] In addition, since trifluoromethoxy group is considered as a "pseudo halogen", the selective activation of carbon-bromide bond over carbon-oxygen bond is not an easy task. Herein, we report that we have now developed a nickel catalyst that overcomes these challenges to catalyze the coupling of compounds **1a**-**f** with a variety of readily available aryl pinacol boronates with high enantiometric excess under mild conditions.



We began our investigation by optimizing the conditions of the nickel-catalyzed coupling reaction of compound **1a**, which was prepared by bromination of 4-methoxycarbonylbenzyl trifluoromethylether[16] using NBS. During the preparation of compound **1a**, we found that an electron-withdrawing substitution such as ester, ketone, cyano or nitro group stabilizes α-bromobenzyl trifluoromethylethers, while substrates with an electron-donating group such as methoxy or dimethylamino easily underwent decomposition to give the corresponding aldehydes. After initial considerable investigation, it was discovered that in the presence of 20 mol% $NiBr_2$•DME and 25 mol% pyridine-oxazoline ligand **L1**, reaction of **1a** with PhMgBr or Ph_2Zn occurred smoothly in full conversion after 12 h at 0 °C to give the coupled compound **2a** with a good enantioselectivity (91:9 e.r.). However, the yields for both reactions were low (38% and 15%, respectively). It was soon determined that the low yields were due to the side reaction of compound **2a** with aryl Grignard or Zinc reagent. These observations confirmed our previous speculation about the

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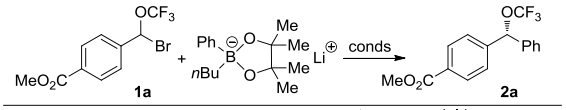
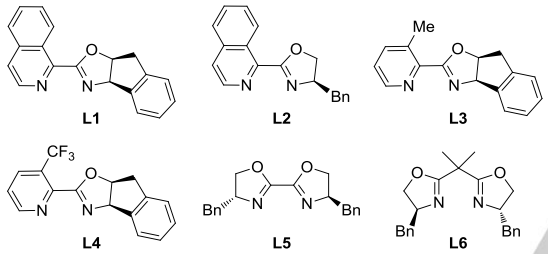
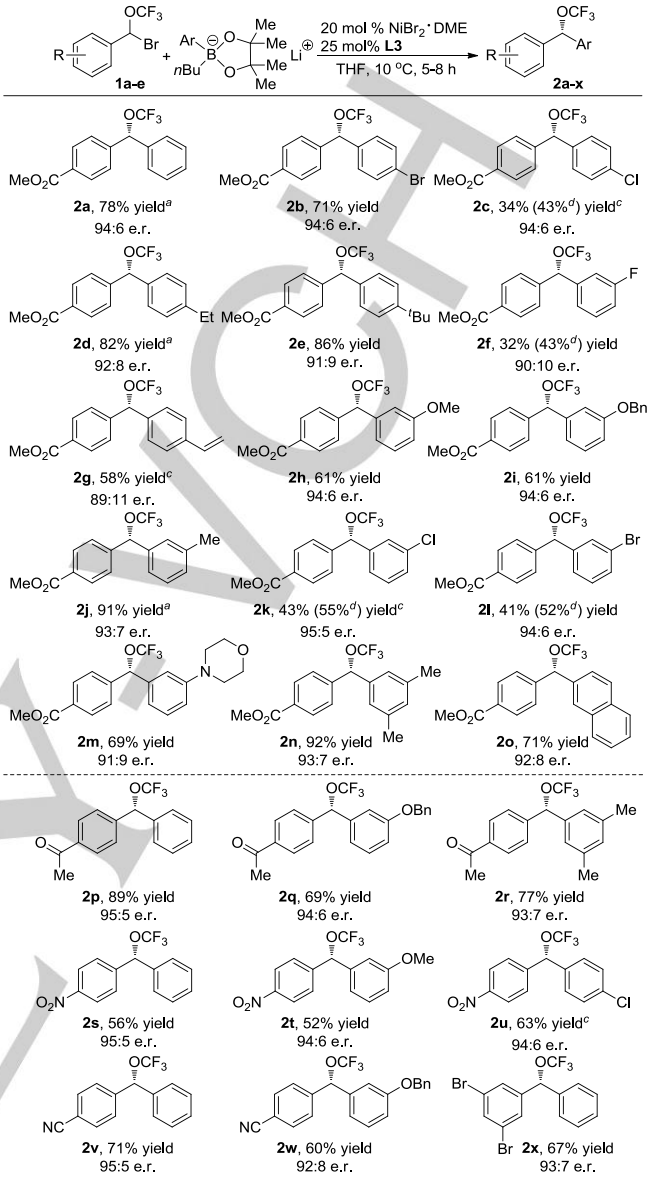


entry	[Ni]	ligand	solvent	temp (°C)	yield (%)[b]	e. r.
1	$NiBr_2$·DME	**L1**	THF	0 °C	81	93:7
2	$NiBr_2$·DME	**L1**	DME	0 °C	19	93:7
3	$NiBr_2$·DME	**L1**	dioxane	0 °C	-	-
4	$NiBr_2$·DME	**L1**	diglyme	0 °C	-	-
5	$NiBr_2$·DME	**L1**	triglyme	0 °C	-	-
6	$NiCl_2$·DME	**L1**	THF	0 °C	54	93:7
7	$Ni(OAc)_2$	**L1**	THF	0 °C	-	-
8	$NiBr_2$·DME	**L1**	THF	10 °C	73	93:7
9	$NiBr_2$·DME	**L1**	THF	-10 °C	73	93:7
10	$NiBr_2$·DME	**L1**	THF	-20 °C	71	91:9
11	$NiBr_2$·DME	**L1**	THF	0 °C	43[c]	93:7
12	$NiBr_2$·DME	**L1**	THF	0 °C	76[d]	93:7
13	$NiBr_2$·DME	**L1**	THF	0 °C	50[e]	91:9
14	$NiBr_2$·DME	**L2**	THF	0 °C	78	91:9
15	**$NiBr_2$·DME**	**L3**	**THF**	**0 °C**	**81**	**94:6**
16	**$NiBr_2$·DME**	**L3**	**THF**	**10 °C**	**83[f]**	**94:6**
17	$NiBr_2$·DME	**L4**	THF	0 °C	0	92:8
18	$NiBr_2$·DME	**L5**	THF	0 °C	0	-
19	$NiBr_2$·DME	**L6**	THF	0 °C	0	-



Scheme 1. Optimization of the conditions for nickel-catalyzed asymmetric Suzuki-coupling of α-bromo-4-methoxycarbonylbenzyl trifluoromethylether **1a** with phenylboronic pinacol ester. [a] Reaction conditions: compound **1a** (0.1 mmol), phenylboronic pinacol ester (0.15 mmol), nickel precursor (20 mol%), ligand (25 mol%) under conditions indicated in the scheme; [b] Yields were determined by ^{19}F NMR spectroscopy with trifluorotoluene as an internal standard; [c] 1.0 equivalent of **1a** was used; [d] 2.0 equivalents of **1a** was used; [e] MeLi was used; [f] The formation of homocoupling side product from compound **1a** was observed in 8% yield.



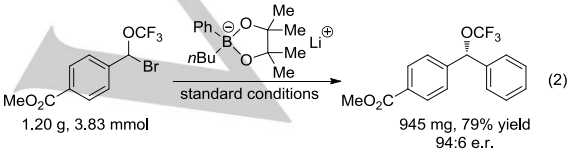
Scheme 2. Scope of nickel-catalyzed asymmetric Suzuki-coupling of α-bromo-benzyl trifluoromethylether **1a**-**e** with arylboronic pinacol ester. [a] Reaction conditions: compound **1a** (0.5 mmol), phenylboronic pinacol ester (0.75 mmol), *n*BuLi (0.75 mmol, 0.3 mL, 2.5 M in hexane), $NiBr_2$•DME (0.1 mmol), ligand **L3** (0.125 mmol) at 10 °C for 5 h ; Isolated yields; [b] Reactions conducted at 0 °C for 5 h; [c] Reactions conducted at 30 °C for 8 h; [d] Yields were determined by ^{19}F NMR spectroscopy with trifluorotoluene as an internal standard.

stability of the product in the presence of Lewis acidic reagents. To circumvent the use of Lewis acidic Grignard or Zinc reagents, we studied the reaction of **1a** with aryl boronic acid in the presence of a base. To our delight, when $PhB(OH)_2$ was employed as the nucleophile and K_2CO_3 was used as the base, the yield of the coupling reaction was improved to 81% when the reaction was conducted at 60 °C.[17] However, the enantioselectivity of the reaction decreased to 84:16 e.r.. To improve the enantioselectivity, we studied the reaction at lower temperature. Nevertheless, less than 10% conversion was observed when the reaction was conducted at 30 °C for 8 h.

It was postulated that sluggish reaction with aryl boronic acid at low temperature is because of the slow transmetallation step in the catalytic cycle. To facilitate the transmetallation, we studied the reaction of **1a** with lithium organoborate which was formed *in situ* by mixing phenylboronic acid pinacol ester with *n*BuLi.[18] Indeed, it was found that the reaction of **1a** with lithium organoborate in THF occurred smoothly in full conversion after 5.0 h at 0 °C to give the corresponding coupled product **2a** in 81% yield with 93:7 e.r. (Scheme 1, entry 1). The same reactions in other etheric solvents such as DME, dioxane, diglyme or triglyme were much less effective in terms of yields and enantioselectivities (Scheme 1, entries 2-5). The nickel catalyst precursor was important for the reaction. While the reaction catalyzed by a combination of $NiCl_2$•DME with ligand **L1** occurred in lower yield with comparable enantioselectivity, reaction using $Ni(OAc)_2$ as the catalyst precursor was completely ineffective at all (Scheme 1, entries 6-7). Further optimization in term of the reaction temperature and stoichiometry of the reagents disclosed that reactions conducted at 0 °C with 1.5 equivalents of lithium organoborate occurred in

high yields with good enantioselectivity (Scheme 1, entries 8-12). On the other hand, replacement of *n*BuLi with MeLi led to decrease both in yield and enantioselectivity (Scheme 1, entry 13). To further improve the enantioselectivity of the reaction, we evaluated the effects of the other dinitrogen ligand **L2**-**6**.[19] The enantioselectivity decreased when the ligand was switched from (1*R*,2*S*)-1-amino-2,3-dihydro-1*H*-inden-2-ol-derived ligand **L1** to pyridine-oxazoline ligand **L2** (Scheme 1, entry 14). Instead, increasing the steric hindrance at 3-position of the pyridyl moiety led to an increase in enantioselectivity (Scheme 1, entry 15). However, replacement of the methyl group in **L3** by an electron-withdrawing trifluoromethyl group led to a slight decrease in enantioselectivity (Scheme 1, entry 17). Finally, bisoxazoline ligands **L5**-**6** were completely ineffective at all (Scheme 1, entries 18-19). Nevertheless, reaction conducted at 10 °C gave slightly higher yields with similar enantioselectivity (Scheme 1, entry 16). Under these conditions, the main side product was the homocoupling compound of **1a** which was formed in 8% yield (Scheme 1, entry 16).

Under the optimized conditions of entry 15 or 16 in Scheme 1, we next examined the generality of the nickel-catalyzed asymmetric Suzuki-coupling of a variety of aryl boronic acid pinacol esters, as summarized in Scheme 2. In general, aryl boronic pinacol esters with both electron-rich and electron-poor groups at *mata*- or *para*-substituted positions reacted smoothly to give the corresponding compounds **2a**-**x** in good yields and high enantioselectivities. For example, reaction of α-bromo-4-methoxycarbonylbenzyl trifluoromethylether **1a** with 4-bromophenyl boronic pinacol ester gave compound **2b** in 71% yield with 94:6 e.r., while the same reaction with 3-methylphenyl boronic pinacol ester afforded the corresponding product **2j** in 91% yield with 93:7 e.r. (Scheme 2, **2b** and **2j**). Nevertheless, reactions of aryl boronic pinacol esters bearing a *meta*-fluoro, chloro or bromo substituent occurred in lower yields but with good enantioselectivities (Scheme 2, **2c**, **2f**, **2k**-**l**). In these cases, the homocoupling products were formed in roughly 20-30% yields. On the other hand, α-bromobenzyl trifluoromethylether (**1b**-**d**) with electron-withdrawing substituted groups such as ketone, cyano or nitro group reacted with various aryl boronic acid pinacol esters to afford the coupled products **2p**-**x** in high yields and high enantioselectivities (Scheme 2, **2p**-**x**). For example, reactions of both α-bromo-4-nitrobenzyl trifluoromethylether **1c** and α-bromo-4-cyanobenzyl trifluoromethylether **1d** with phenyl boronic pinacol ester under the optimized conditions to give the corresponding products in 56% and 71% yields, respectively, with excellent enantioselectivities (95:5 e.r.) (Scheme 2, **2s** and **2v**). Because of the mild conditions, a variety of common functional groups such as fluoride (**2f**), chloride (**2c**, **2k** and **2u**), bromide (**2b**, **2l** and **2x**), ester (**2a**-o), enolizable ketone (**2p**-**r**), nitro (**2s**-**u**), cyano (**2v**-w), amino (**2m**) and vinyl group (**2g**) were compatible. Finally, the reaction can be conducted at gram-scale quantities with comparable yield and enantioselectivity (Eq. 2).



(2)

To demonstrate the applicability of nickel-catalyzed asymmetric Suzuki-coupling reaction for the construction of the CF_3O-containing stereogenic centers, we applied this method to synthesize a trifluoromethoxy-substituted mimic of an inhibitor for the histone lysine methyltransferase enhancer of Zeste Homolog 2 (EZH2).[20] As shown in Figure 1, compound **3** was formed in 58% yield with 95:5 e.r. after recrystallization from Et_2O/CH_2Cl_2 via four step transformations from easily available α-bromo-4-*tert*-butoxybenzyl trifluoromethylether.

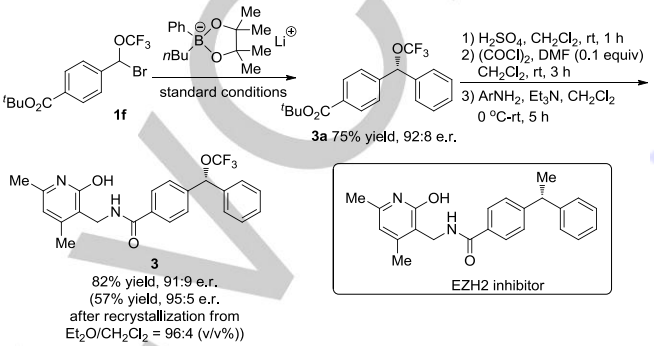


Figure 1. Preparation of trifluoromethoxylated derivatives of drug candidates.

In summary, we developed a nickel-catalyzed Suzuki-Miyaura coupling of easily available α-bromobenzyl trifluoromethylethers **1a**-**f** with a variety of aryl pinacol boronates with high enantiometric excess. The reactions were conducted under mild conditions that a variety of common functional groups such as fluoride, chloride, bromide, ester, enolizable ketone, nitro, cyano, amino and vinyl group were well tolerated. Furthermore, the reaction can be easily scaled up to gram quantities without erosion of the enantioselectivity. Studies to extend this method to the construction of CF_3O-containing quaternary stereogenic centers are currently undergoing in our laboratory.

Acknowledgements

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Keywords: Fluorine • trifluoromethoxy • nickel • asymmetric• cross-coupling

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[17] See Table S1 in supporting information for details about the optimization of the conditions for nickel-catalyzed Suzuki-coupling of compound **1a** with phenyl boronic acid.

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[19] See Table S2 in supporting information for details about the substitution effect of the ligand on enentioselectivity of the reaction.

[20] V. S. Gehling, R. G. Vaswani, C. G. Nasveschuk, M. Duplessis, P. Iyer, S. Balasubramanian, F. Zhao, A. C. Good, R. Campbell, C. Lee, L. A. Dakin, A. S. Cook, A. Gagnon, J.-C. Harmange, J. E. Audia, R. T. Cummings, E. Normant, P. Trojer, B. K. Albrecht, *Bioorg. Med. Chem. Lett.*, **2015**, *25*, 3644.

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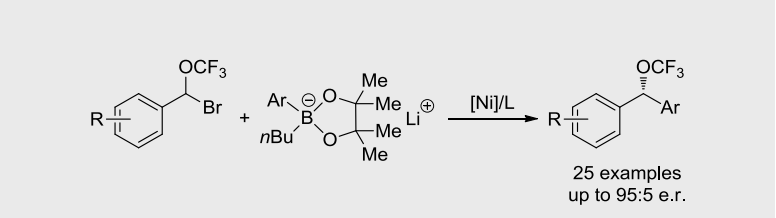
COMMUNICATION



A general method for the construction of trifluoromethoxy-containing stereogenic centers with high enantiometric excess via nickel-catalyzed Suzuki-Miyaura coupling of easily available α-bromobenzyl trifluoromethylethers **1a**-**f** with a variety of aryl pinacol boronates was described. The reaction conditions were mild and a variety of common functional groups such as fluoride, chloride, bromide, ester, enolizable ketone, nitro, cyano, amino and vinyl group were well tolerated.

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Enantioselective Construction of Trifluoromethoxylated Stereogenic Centers by Nickel-Catalyzed Asymmetric Suzuki-Miyaura Coupling of Secondary Benzyl Bromides