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Cobalt-Catalyzed Asymmetric Cross-Coupling Reaction of Fluorinated Secondary Benzyl Bromides with Lithium Aryl Boronates/$ZnBr_2$

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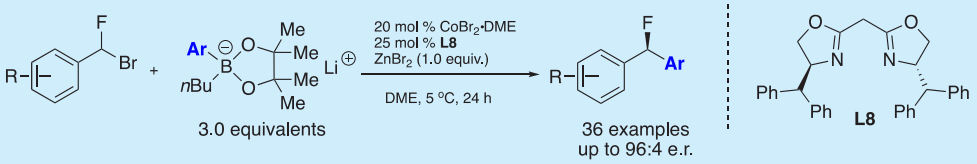

ABSTRACT: A cobalt-catalyzed asymmetric cross-coupling of α-bromo-α-fluorotoluene derivatives with a variety of aryl zincates derived from lithium aryl *n*-butyl pinacol boronates and $ZnBr_2$ under mild reaction conditions was described. In addition to mild reaction conditions, another advantage includes the compatibility of various common functional groups such as fluoride, chloride, bromide, cyano, or ester groups. Furthermore, this protocol was successfully applied to the enantioselective synthesis of three fluorinated derivatives of biologically active compounds or drug molecules.

In the past two decades, transition-metal-catalyzed asymmetric cross-coupling reaction between a racemic secondary alkyl electrophile and an organometallic nucleophile has emerged as a powerful strategy for the construction of stereodefined tertiary carbon centers.[1] The majority of reported approaches typically employ a combination of a nickel(II) precursor and a nitrogen based bidentate or tridentate ligand as the catalyst to enable the high enantioselectivity,[2] owing largely to Fu and co-workers' seminal discovery in 2005.[3] Unlike nickel, even though cobalt represents one of the earth abundant, first row transition metals that are able to catalyze the cross-coupling of alkyl halides,[4−6] few cobalt-catalyzed asymmetric $C(sp^3)-C(sp^2)$ bond-forming cross-coupling reactions have been reported previously (Figure 1). To the best of our knowledge, only two

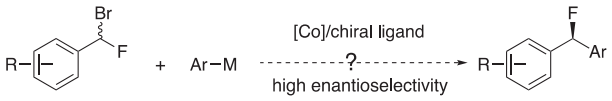

Figure 1. Cobalt-asymmetric cross-coupling of fluorinated secondary alkyl halides.

examples of cobalt catalysis in such asymmetric cross-coupling reactions have been reported recently, wherein the substrates of these reactions were limited to racemic α-bromoesters.[7]

Fluorinated organic compounds have been found to be of enormous value in many fields, especially in the pharmaceutical industry,[8] mainly due to fluorine's unique and "magical" effect on the compound's physical, chemical, and biological properties.[9] In fact, 18 out of 42 small-molecule drugs in 2018, as well as 11 out of 23 in 2019, approved by the US Food and Drug Administration (FDA) in 2019 were fluorinated.[10] Consequently, development of an efficient method for the strategic incorporation of fluorine into target molecules, particularly in a stereoselective fashion, is of utmost importance.[11] More specifically, α-fluorinated diarylmethane,[12] a potential pharmacophore for new drug discovery as it is considered a metabolically more stable bioisostere of diphenylmethanol,[13] which is also known as benzhydrol, is a key structural motif in a number of biologically active natural occurring compounds[14] and has thus attracted increasing attention. Interestingly, while a few methods for the preparation of racemic α-fluorinated diarylmethanes have been reported previously,[15] methods for the construction of stereodefined α-fluorinated diarylmethanes are unknown and remain an ongoing urgent challenge. In this respect, we envisaged that an enantioselective coupling of a racemic fluorinated secondary benzylic halide with an organometallic nucleophile represents a potentially broadly applicable approach for the preparation of these fluorinated drug-like molecules.[16]

Nevertheless, to develop a cobalt-catalyzed asymmetric cross-coupling reaction of fluorinated secondary benzylic halides, we faced three formidable challenges: (1) As we mentioned earlier, only two examples of such asymmetric

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reactions have been reported previously,[7] which indicates that the factors in controlling the enantioselectivity were largely unknown and the choice of the suitable spectator ligand remains something of an art. (2) It was reported that cobalt-catalyzed coupling reaction of alkyl halides occurred quickly in the absence of any added ligand.[4] Consequently, this background reaction may significantly decrease the enantioselectivity of the reaction. (3) The difference in the atomic radius of the fluorine and hydrogen atoms is small. Thus, it is difficult to differentiate the facial selectivity of the α-fluorinated alkyl radical. Herein, we report that we have now overcome these challenges and developed the first cobalt-catalyzed asymmetric cross-coupling of easily available α-bromo-α-fluorotoluene derivatives with a variety of aryl pinacol boronates in the presence of zinc bromide with excellent enantioselectivities. Furthermore, this protocol was successfully applied to the enantioselective synthesis of three fluorinated derivatives of biologically active compounds or drug molecules.

We initially chose the reaction of methyl 4-(bromofluoromethyl) benzoate **1a** with an organometallic nucleophile in the presence of a combination of 20 mol % of $CoBr_2$·DME and 25 mol % of commercial bisoxazoline ligand **L1** as a model reaction to optimize the reaction conditions. Not surprisingly, reactions using PhMgBr as the nucleophile occurred after 24 h at 5 °C occurred sluggishly to give the desired product in 26% yield with low enantioselectivity (62:38 e.r.), while reactions of **1a** with PhZnBr or Ph_2Zn did not take place at all. In contrast, when an "ate' type nucleophile phenyl zincate, *in situ* generated from a combination of 3.0 equiv of lithium phenyl *n*-butyl pinacol boronate and 1.0 equiv of $ZnBr_2$ was used,[17] the reaction occurred to full conversion to give the desired coupled product in 60% with 81:19 e.r. (eq 1). As a control, we also studied the same reaction in the absence of $ZnBr_2$. However, the desired coupled product was not observed under otherwise identical conditions (Figure 2).[18]

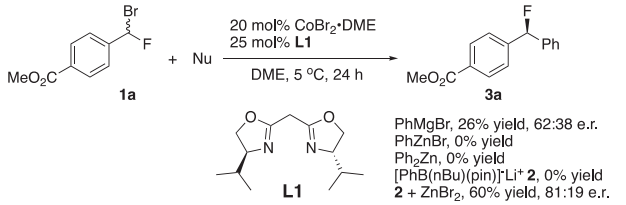
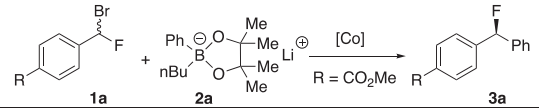


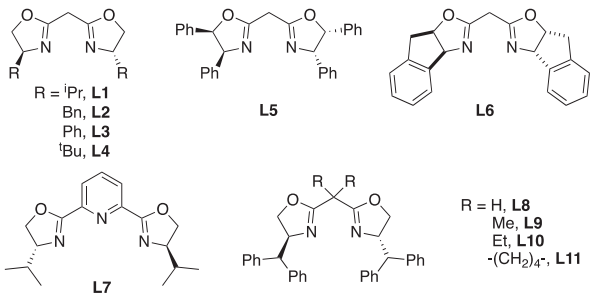
Figure 2. Initial screening of cobalt-catalyzed asymmetric coupling of 4-(bromofluoromethyl) benzoate **1a** with various nucleophiles using **L1** as the ligand.

With these initial results in hand, we then systematically screened the reaction parameters to improve the yield and enantioselectivity of the reaction, as summarized in Scheme 1. A quick survey of the reaction conditions disclosed that the choice of a suitable chiral ligand was crucial in delivering the reaction's high yields and enantioselectivity. Switching the isopropyl group in bisoxazoline ligand to a benzyl (**L2**), phenyl (**L3**), or *tert*-butyl group (**L4**) led to a decrease in enantioselectivity (Scheme 1, entries 2−4). The enantioselectivity was slightly improved when 4,5-diphenyl-substituted bisoxazoline ligand **L5** was used as the ligand, and reaction using indene-derived ligand **L6** gave much lower enantioselectivity, while reaction with tridentate ligand **L7** was not

Scheme 1. Optimization of the Conditions for Cobalt-Catalyzed Asymmetric Coupling of 4-(Bromofluoromethyl)benzoate 1a with Phenyl Zincate[a]



entry	[Ni]	ligand	additive	solvent	temp (°C)	yield (%)[b]	e.r
1	$CoBr_2$·DME	**L1**	$ZnBr_2$	DME	5	60	81:19
2	$CoBr_2$·DME	**L2**	$ZnBr_2$	DME	5	72	55:45
3	$CoBr_2$·DME	**L3**	$ZnBr_2$	DME	5	60	75:25
4	$CoBr_2$·DME	**L4**	$ZnBr_2$	DME	5	30	52:48
5	$CoBr_2$·DME	**L5**	$ZnBr_2$	DME	5	68	86:14
6	$CoBr_2$·DME	**L6**	$ZnBr_2$	DME	5	18	55:45
7	$CoBr_2$·DME	**L7**	$ZnBr_2$	DME	5	0	-
8	$CoBr_2$·DME	**L8**	$ZnBr_2$	DME	5	84	95:5
9	$CoBr_2$·DME	**L9**	$ZnBr_2$	DME	5	23	80:20
10	$CoBr_2$·DME	**L10**	$ZnBr_2$	DME	5	51	77:23
11	$CoBr_2$·DME	**L11**	$ZnBr_2$	DME	5	60	67:33
12	$CoBr_2$·DME	**L8**	$ZnBr_2$	DME	5	54	95:5 [c]
13	$CoBr_2$·DME	**L8**	$ZnBr_2$	DME	5	83	94:6 [d]
14	$CoBr_2$·DME	**L8**	$ZnCl_2$	DME	5	46	93:7
15	$CoBr_2$·DME	**L8**	ZnI_2	DME	5	54	93:7
16	$CoBr_2$·DME	**L8**	$MgBr_2$	DME	5	0	-
17	CoI_2	**L8**	$ZnBr_2$	DME	5	70	93:7
18	$CoCl_2$	**L8**	$ZnBr_2$	DME	5	54	92:8
19	$Co(OAc)_2$	**L8**	$ZnBr_2$	DME	5	48	94:6
20	$CoBr_2$·DME	**L8**	$ZnBr_2$	diglyme	5	74	94:6
21	$CoBr_2$·DME	**L8**	$ZnBr_2$	triglyme	5	69	93:7
22	$CoBr_2$·DME	**L8**	$ZnBr_2$	dixoane	5	0	-
23	$CoBr_2$·DME	**L8**	$ZnBr_2$	THF	5	0	-
24	$CoBr_2$·DME	**L8**	$ZnBr_2$	DMA	5	53	77:23
25	$CoBr_2$·DME	**L8**	$ZnBr_2$	CH_2Cl_2	5	0	0
26	$CoBr_2$·DME	**L8**	$ZnBr_2$	DME	rt	70	93:7
27	$CoBr_2$·DME	**L8**	$ZnBr_2$	DME	-10	42	92:8
28	$CoBr_2$·DME	**L8**	$ZnBr_2$	DME	5	46	95:5 [e]



[a]Reaction conditions: compound **1a** (0.1 mmol), lithium phenyl *n*-butyl boronic pinacol ester (0.3 mmol), additive (0.1 mmol), cobalt precursor (20 mol %), ligand (25 mol %) for 24 h under conditions otherwise indicated in the scheme. [b]Yields were determined by ^{19}F NMR spectroscopy with 1-fluoronaphthlene as an internal standard. [c]0.5 equiv of $ZnBr_2$ was used. [d]1.5 equiv of $ZnBr_2$ was used. [e]$CoBr_2$·DME (10 mol %), **L8** (12.5 mol %).

effective at all (Scheme 1, entries 5−7). Considering that ligand **L1** was structurally more modifiable than ligand **L6**, we chose to synthesize various **L1** derivatives to improve the enantioselectivity of the reaction. Notably, when the isopropyl group in the bisoxazoline ligand was switched to more sterically hindered ligand **L8**, the enantioselectivity was significantly improved to 95:5 (Scheme 1, entry 8). Additional studies showed that the smaller bite methylene group of the bisoxazoline ligand resulted in a remarkable decrease in enantioselectivity (Scheme 1, entries 9−11).

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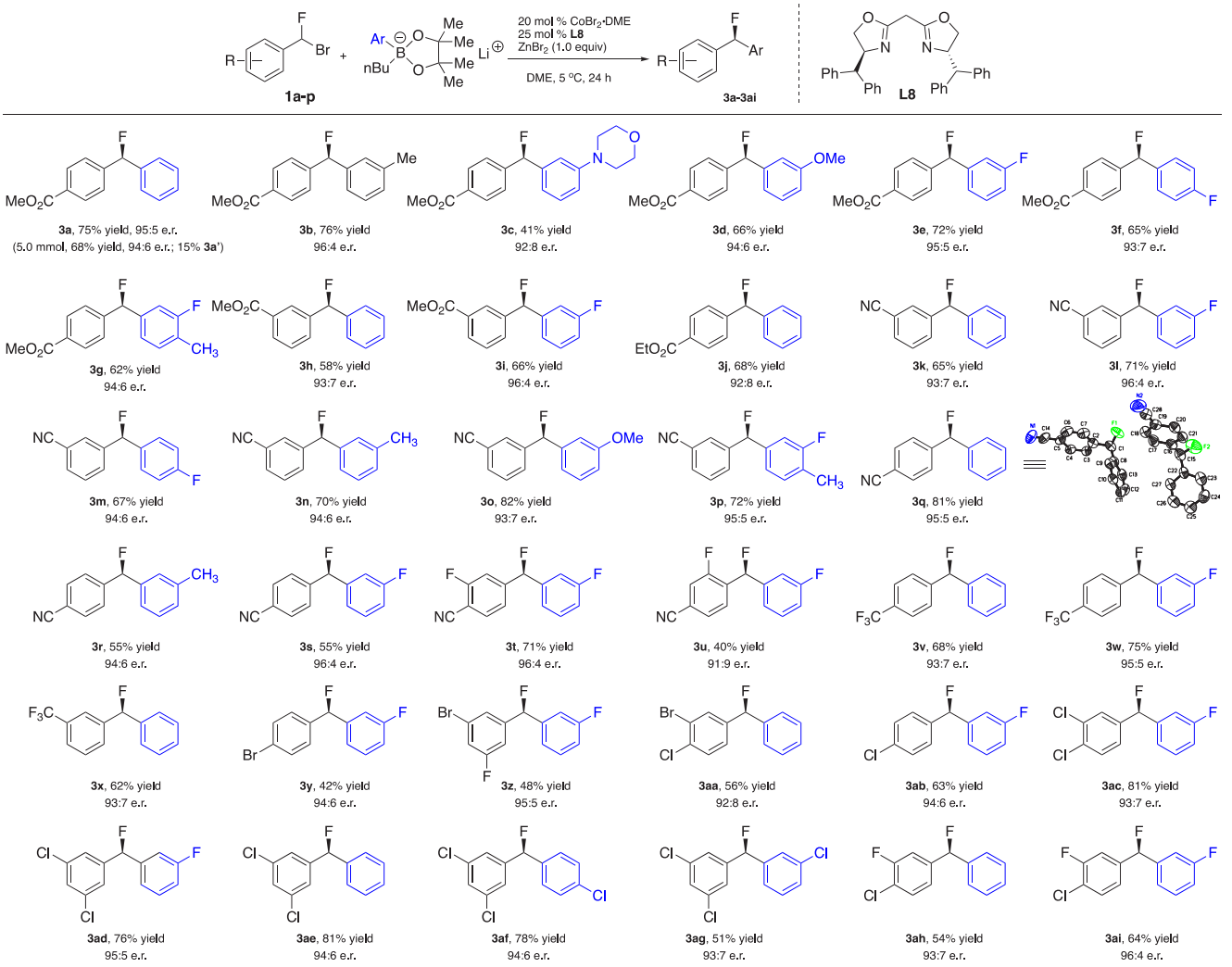
Scheme 2. Scope of Cobalt-Catalyzed Asymmetric Coupling of α-Bromo-α-fluorotoluene Derivatives 1a−m with Lithium Aryl *n*-Butyl Boronic Pinacol Ester[a,b]



[a]Reaction conditions: compound **1** (0.3 mmol), aryl *n*-butyl boronic pinacol boronate **2** (0.9 mmol), $CoBr_2$·DME (20 mol %), ligand **L8** (25 mol %), and $ZnBr_2$ (0.3 mmol) in DME at 5 °C for 24 h. [b]Isolated yields and e.r. were determined by chiral HPLC analysis.

Under the optimized conditions (Scheme 1, entry 8), we next examined the generality of the cobalt-catalyzed asymmetric coupling with a variety of lithium aryl *n*-butyl pinacol boronates and different α-bromo-α-fluorotoluene derivatives. As shown in Scheme 2, in general, α-bromo-α-fluorotoluene derivatives with electron-poor substituents such as the ester, cyano, trifluoromethyl group or weakly electron-donating substituents such as chloride or bromide reacted smoothly to give the corresponding products **3a−3ai** in good yields and good to excellent enantioselectivities. For examples, reactions of both methyl 4-(bromofluoromethyl)benzoate **1a** and 4-(bromofluoromethyl)benzonitrile **1d** with lithium phenyl *n*-butyl boronate **2a** gave the corresponding products **3a** and **3q** in 75% and 81% yields with 95:5 e.r., respectively (Scheme 2, **3a** and **3q**). Nevertheless, α-bromo-α-fluorotoluene derivatives with strong electron-donating substituents such as 1-(bromofluoromethyl)-4-methoxybenzene were unstable and easily underwent decomposition to give aldehydes. Likewise, lithium aryl *n*-butyl boronates with electron-poor or weakly electron-rich aryl groups reacted to give the desired products in good to excellent enantioselectivities. For example, lithium aryl *n*-butyl boronates with *meta*-methoxy, *meta*-fluoride, or *para*-fluoride reacted with compound **1a** to afford the desired products in 66%, 72%, and 65% yields with 94:6, 95:5, and 93:3 e.r., respectively (Scheme 2, **3d−f**). Reactions of lithium aryl *n*-butyl boronates with electron-rich aryl groups, however, gave the desired products in low yields, mainly due to the unstable nature of those electron-rich arylated products. Since no strong base was used in the reaction, common functional groups such as esters (**3a−j**), cyanos (**3k−u**), or halogens (**3y−3ai**) were compatible. Notably, the reaction could be easily scaled up. Reaction of 5.0 mmol of compound **1a** with lithium phenyl *n*-butyl boronate **2a** occurred to give the desired product in 68% yield with 94:6 e.r. with a side product dimethyl 4,4′-(1,2-difluoroethane-1,2-diyl)dibenzoate **3a′** in 15% yield[19] (Scheme 2, **3a** and **3a′**). The absolute configuration of compound **3q** was determined to be *S* by X-ray diffraction of its single crystals, and the configurations of the remaining compounds were assigned based on the same mechanistic assumption (Scheme 2, **3q**).

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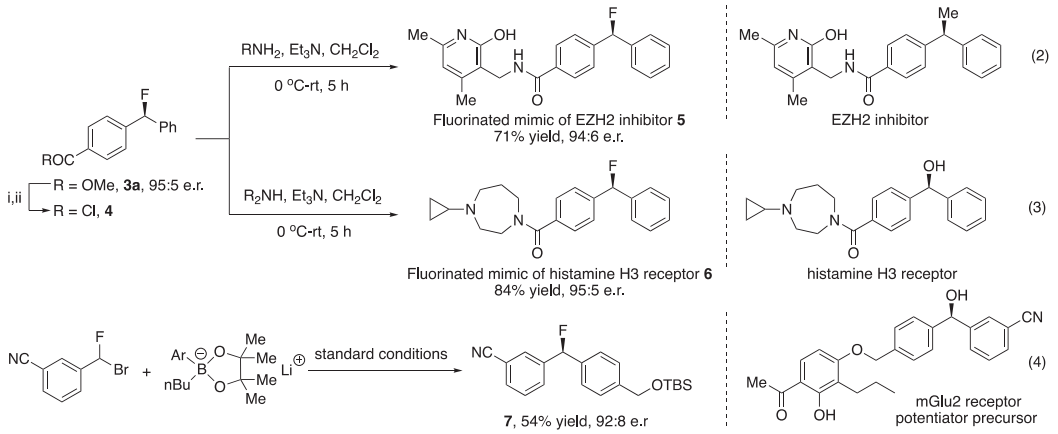
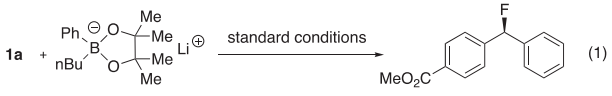


Figure 3. Preparation of fluorinated mimics of drug-like compounds. (i) LiOH, MeOH/H_2O, rt, 24 h; (ii) $(COCl)_2$, DMF (0.1 equiv), CH_2Cl_2, rt, 3 h.

In general, cobalt-catalyzed coupling reaction of alkyl halides was proposed to form an alkyl radical via single-electron-transfer (SET) of an alkyl halide to the cobalt complex.[4] To probe whether a free alkyl radical was generated in the current protocol, we conducted two sets of experiments (eq 1). In the first experiment, the reaction of compound **1a**



TEMPO (1.0 equiv): 0% yield
BHT (1.0 equiv): 20% yield
1,4-dinitrobenzene (1.0 equiv): 0% yield

with lithium phenyl *n*-butyl boronate **2a** was conducted in the presence of 1.0 equiv of radical inhibitor (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) or butylated hydroxytoluene (BHT) under otherwise identical conditions. It was found that reaction in the presence of TEMPO was completely shut down, while the yield of the reaction in the presence of BHT was decreased significantly to 20%. In addition, a doublet peak at −104.80 ppm in ^{19}F NMR spectroscopy showed up for the reaction with TEMPO, which was further characterized by a high resolution mass spectrometer (ESI) to be TEMPO-R (MS(ESI): 324.4) wherein the R group was the benzylic radical generated from compound **1a**. In a second experiment, the same reaction was conducted in the presence of 1.0 equiv of an SET inhibitor 1,4-dinitrobenzene. Again, the reaction was fully shut down. Furthermore, in several cases, the dimers of the benzylic radical that was supposed to be generated from the benzylic bromides were observed. These results suggest that the cobalt-catalyzed asymmetric cross-coupling of the fluorinated secondary benzylic bromides likely involves a free alkyl radical intermediate.

To assess whether the enantioselectivity of the reaction resulted from kinetic resolution of the α-bromo-α-fluorotoluene derivatives, we monitored the enantio-excess of compound **1a** at a different period of the reaction by quenching an aliquot of the reaction mixture with an acid and subsequently analyzing the organic layer by HPLC. It was found that compound **1a** remained racemic at 2.0, 5.0, or 12 h, respectively. These results clearly ruled out the possibility of a kinetic resolution process.

The above-mentioned initial mechanistic experiments indicate that the current cobalt-catalyzed asymmetric cross-coupling reaction is a catalyst-controlled enantioselective reaction via a benzylic radical intermediate, even though further detailed mechanistic studies are required to further elucidate the mechanism of the reaction.

Finally, to demonstrate the applicability of the current protocol, we applied this methodology to synthesize a few fluorine-substituted mimics of potentially drug-like compounds (Figure 2). Compound **5**, which is a fluorinated mimic of an inhibitor for the histone lysine methyltransferase enhancer of zeste homologue 2 (EZH2),[20] was prepared in 53% overall yield with 95:5 e.r. via a four-step transformation from easily available methyl 4-(bromofluoromethyl)benzoate **1a** (eq 2 in Figure 3). Likewise, a fluoride-substituted compound **6**, which is a mimic of histamine H3 receptor,[21] was synthesized from the same starting material after four steps in 64% overall yield and 95:5 e.r. (eq 3 in Figure 3). Furthermore, we applied this method to synthesize compound **7**, a key intermediate of a fluoride-substituted analog of Lilly's mGlu2 receptor potentiators, a compound for the acute treatment of migraine headaches,[22] in 84% yield with 92:8 e.r. (eq 4 in Figure 3). These examples clearly showed the potential of the current protocol in the preparation of enantio-enriched fluorinated drug analogs.

In summary, we developed a cobalt-catalyzed asymmetric cross-coupling reaction of α-bromo-α-fluorotoluene derivatives with a variety of aryl zincates that were *in situ* generated from lithium aryl *n*-butyl pinacol boronates with $ZnBr_2$ under mild conditions, which may serve as a versatile, efficient, and convenient approach for the rapid access of optically pure α-fluorinated diarylmethane derivatives. Furthermore, this reaction, which exhibits some advantages over nickel catalysis in some respects, greatly strengthens the arsenal of the cobalt-catalyzed asymmetric cross-coupling reactions of secondary alkyl halides. Studies to extend this protocol to cobalt-catalyzed asymmetric cross-coupling reactions of other secondary alkyl halides and nucleophiles are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01363.

^1H, ^{19}F, ^{13}C NMR and HPLC spectra of compounds **3a**−**3ai**, **5**−**7**; X-ray structure of **3q** (PDF)

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Accession Codes

CCDC 1983499 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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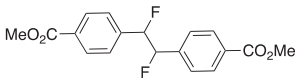

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