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C–H Activation

Highly Selective Trifluoromethylation of 1,3-Disubstituted Arenes through Iridium-Catalyzed Arene Borylation**

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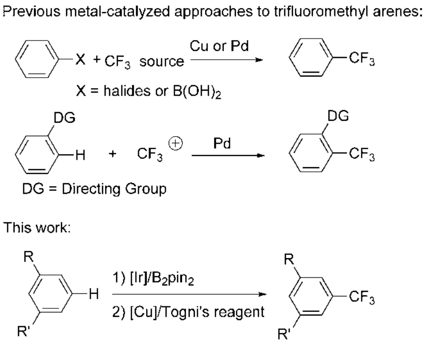
Dedicated to Professor Weiyuan Huang on the occasion of his 90th birthday

The trifluoromethyl group has evolved into an indispensable structural motif[1] for the pharmaceutical industry because of its unique size, electronic properties, and excellent metabolic stability, as evidenced by a large number of trifluoromethylated pharmaceuticals and drug candidates, such as the antidepressant Prozac,[2] the fungicide Trifloxystrobin,[3] and the herbicide Fusilade.[4] Consequently, development of new and efficient methods to introduce the trifluoromethyl group to small molecules are of high interest.[5]

Toward this end, several copper- and palladium-catalyzed trifluoromethylations of aryl halides or aryl boronic acids have been reported recently.[6–10] For example, Amii and co-workers reported the first copper-catalyzed trifluoromethylation of electron-poor aryl iodides with the Ruppert–Prakash reagent, CF_3SiEt_3, in the presence of CuI/1,10-phenanthroline (Scheme 1).[7] Buchwald and co-workers reported a palladium-catalyzed trifluoromethylation of aryl chlorides by use of sterically hindered electron-rich ligands.[8] Qing and Chu, and Buchwald and co-workers independently reported the copper-catalyzed trifluoromethylation of aryl boronic acids under oxidation conditions.[9,10] While these methods overcome the shortcomings of the classic Swarts reaction[11] or the [$CuCF_3$] strategy,[7,12] which requires harsh reaction conditions, stoichiometric amounts of organometallic reagents, and occurs with limited substrate scope, the trifluoromethyl group introduced by these catalytic methods was typically placed at the position of the C–X (X = halides or boron) bond of the prefunctionalized arenes. Such a prefunctionalization of substrates limits the application of these methodologies for the late-stage modification of drug candidates for structure–activity relationship (SAR) studies. A strategy that could convert the C–H bond of arenes into C–CF_3 bonds is thus highly desirable (Scheme 1). Yu and co-workers recently reported a palladium-catalyzed directed *ortho* trifluoromethylation of arenes,[13] but a method for the regioselective trifluoromethylation of arenes at a C–H bond without a directing group is unknown.



Scheme 1. Previous metal-catalyzed approaches to trifluoromethyl arenes.

Recent work from our laboratory has demonstrated that the copper-catalyzed trifluoromethylation of aryl and vinyl boronic acids with Togni's reagent proceeded under very mild reaction conditions;[14] Hartwig, Marder, Smith, Maleczka, and their co-workers have independently reported a series of reactions involving the iridium-catalyzed borylation of arenes and subsequent functionalization of the resulting boronic ester.[15] The regioselectivity of the products from the iridium-catalyzed borylation of arenes results from steric, rather than electronic control. For example, reactions of 1,3-disubstituted arenes under these conditions generate 3,5-disubstituted arene boronates. We envisioned that if these two catalytic reactions could be combined, a tandem C–H activation/trifluoromethylation strategy could be realized for a highly *meta*-selective preparation of trifluoromethyl arenes from readily available 1,3-disubstituted arenes. Herein, we report the development of such a one-pot method for the trifluoromethylation of arenes using the combination of the iridium-catalyzed borylation of arenes and copper-catalyzed trifluoromethylation of the resulting aryl boronates. The utility of this method is demonstrated by the efficient trifluoromethylation of some drug candidates through this one-pot *meta* trifluoromethylation. The introduction of a trifluoromethyl group into a molecule of interest at a late stage of a synthesis using mild reaction conditions could accelerate the discovery of a lead compound.

The trifluoromethylation of 4-biphenyl pinacolboronate with Togni's reagent[16] was chosen at the start of our investigation as a model reaction to identify conditions for

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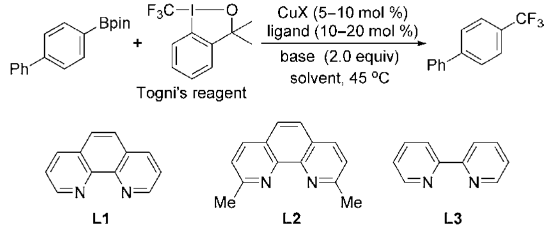
the conversion of pinacolboronate esters into trifluoromethylarenes. We first examined if our previously developed reaction conditions, wherein 5 mol % of CuI and 10 mol % of 1,10-phenanthroline (**L1**) were used as the catalyst, were suitable for the reaction of 4-biphenyl pinacolboronate with Togni's reagent (Table 1). Not surprisingly, the reaction occurred much more slowly than those with aryl boronic acids. Only 80 % conversion with a 58 % yield (^{19}F NMR spectroscopy) was observed after 24 hours at 45 °C (Table 1, entry 1). Switching the copper salt from CuI to copper(I) thiophene-2-carboxylate (CuTc) resulted in a much faster reaction with full conversion after 24 hours (Table 1, entry 4); other copper salts such as $[Cu(OTf)]_2$·benzene and $[Cu(MeCN)_4]PF_6$ did not improve the reaction yield (Table 1, entries 2 and 3). Interestingly, the reaction in the presence of water was much faster, probably because of the faster transmetalation of the aryl pinacolboronate to copper (Table 1, entry 5 versus 7 and entry 6 versus 10). For example, the reaction proceeded to full conversion after 48 hours in the presence of 1.0 equivalent of water when LiOH was used as the base, whereas only 28 % yield was observed in the absence of water (Table 1, entries 6 and 10). Reactions in the presence of other bases such as Li_2CO_3 or NaOH, however, afforded the desired product in less than 45 % yield (Table 1, entries 8–9). Finally, it was found that reactions in CH_2Cl_2 were much faster than those in other solvents and proceeded to full conversion after 4 hours at 45 °C to give the desired product in 97 % yield, as determined by ^{19}F NMR spectroscopy (Table 1, entries 10–16). Other dinitrogen ligands such as 2,9-dimethyl-1,10-phenanthroline (**L2**), 2,2′-bipyridine (**L3**), or tetramethylethylenediamine (TMEDA) were tested, but reactions under these conditions formed less than 81 % of the trifluoromethyl biphenyl (Table 1, entries 17–19). In the absence of the copper catalyst, less than 5 % of the trifluoromethylated product was observed.

Table 1: Optimization of the CuI/**L1**-catalyzed trifluoromethylation of 4-biphenyl pinacolboronate with Togni's reagent.[a,b]



Entry	Copper salt	Ligand	Base	Additive	Solvent	t [h]	Yield [%][c]
1	CuI	**L1**	K_2CO_3	–	diglyme	24	58
2	$[Cu(OTf)]_2·C_6H_6$	**L1**	K_2CO_3	–	diglyme	24	62
3	$(MeCN)_4CuPF_6$	**L1**	K_2CO_3	–	diglyme	24	13
4	CuTC	**L1**	K_2CO_3	–	diglyme	24	78
5	CuTC	**L1**	LiO*t*Bu	–	diglyme	48	< 5
6	CuTC	**L1**	LiOH	–	diglyme	48	28
7	CuTC	**L1**	LiO*t*Bu	H_2O	diglyme	48	33
8	CuTC	**L1**	NaOH	$2H_2O$	diglyme	48	13
9	CuTC	**L1**	Li_2CO_3	$2H_2O$	diglyme	48	42
10	CuTC	**L1**	LiOH	H_2O	diglyme	48	52
11	CuTC	**L1**	LiOH	H_2O	1,4-dioxane	48	54
12	CuTC	**L1**	LiOH	H_2O	DME	48	37
13	CuTC	**L1**	LiOH	H_2O	DMF	48	14
14	CuTC	**L1**	LiOH	H_2O	CH_2Cl_2	24	> 97
15	CuTC	**L1**	LiOH	H_2O	CH_2Cl_2	4	97
16	CuTC	**L1**	LiOH	H_2O	CH_2Cl_2	4	86[d]
17	CuTC	**L2**	LiOH	H_2O	CH_2Cl_2	48	47
18	CuTC	TMEDA	LiOH	H_2O	CH_2Cl_2	24	10
19	CuTC	**L3**	LiOH	H_2O	CH_2Cl_2	4	81

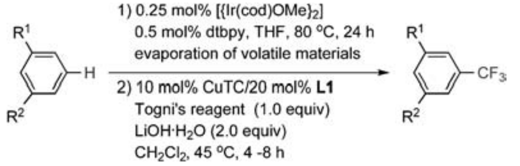
[a] Reaction conditions: 4-biphenyl pinacolboronate (0.2 mmol), Togni's reagent (0.2 mmol), CuX (10 mol %), ligand (20 mol %) and base (0.4 mmol) in specified solvent (1.0 mL) at 45 °C. [b] Reactions listed in entries 1–13 were conducted in Schlenk tubes with 5 mol % of CuX and 10 mol % of ligand, whereas reactions listed in entries 14–19 were conducted in sealed bombs. [c] Yields were determined by ^{19}F NMR analysis of the crude reaction mixture with 1-fluoronaphthalene as an internal standard. [d] 10 mol % of the ligand was used.

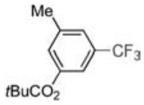
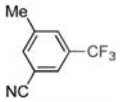
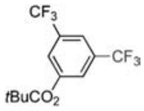
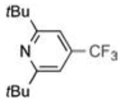
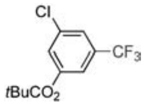
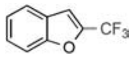
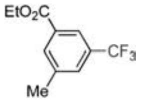
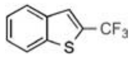
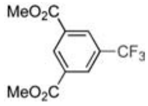
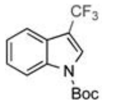
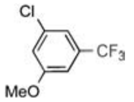
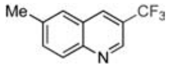
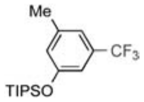
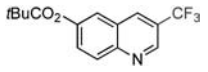
With the optimized reaction conditions for the trifluoromethylation of aryl pinacolboronate in hand, we studied a tandem sequence to convert 1,3-disubstituted arenes or heteroarenes into the corresponding trifluoromethylated arenes or heteroarenes. The borylation of 1,3-disubstituted arenes was conducted with 0.7 equivalents of bis(pinacolato)diboron (B_2pin_2) in the presence of 0.25 mol % of $[\{Ir(cod)OMe\}_2]$ (cod = 1,5-cyclooctadiene) and 0.5 mol % of di-*tert*-butylbipyridine (dtbpy) in THF at 80 °C for 24 hours. The resulting arylboronate esters were converted into the trifluoromethylated arenes by evaporation of the volatile materials, dissolution of the residue in CH_2Cl_2, addition of 10 mol % of CuTc, 20 mol % of 1,10-phenanthroline, 1.1 equivalents of Togni's reagent, and 2.0 equivalents of $LiOH·H_2O$, and then heating at 45 °C for 4–8 hours.

A variety of 1,3-disubstituted arenes were subjected to the C–H activation/trifluoromethylation conditions to give the corresponding 5-trifluoromethyl-1,3-disubstituted arenes in good to excellent yields, as summarized in Table 2. Arenes containing ester, protected phenoxy, chloride, and cyano groups were compatible with the reaction conditions and afforded the products in yields of 50–90 % (Table 2, entries 1–8). In addition, the reactions of a number of heteroarenes gave the trifluoromethylated product with excellent selectivity and yields. For example, the reaction of a 2,6-disubstituted pyridine produced the corresponding 4-trifluoromethyl pyridine in 90 % yield (Table 2, entry 9). Reactions of benzofuran and benzothiophene generated the 2-trifluoromethyl products in 72 % and 75 % yields, respectively (Table 2, entries 10 and 11). The reaction of Boc-protected indole gave the corresponding 3-trifluoromethyl-substituted product in good yield (Table 2, entry 12).

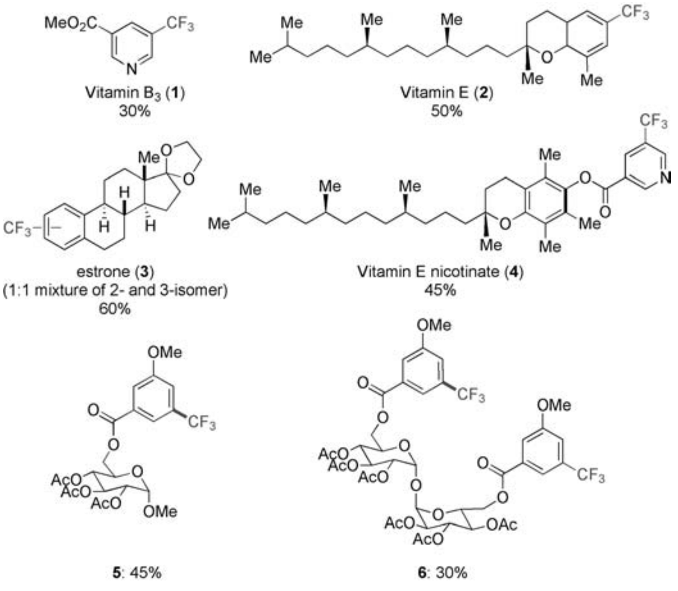
Late-stage modification of drug candidates is valuable for structure–activity relationship (SAR) studies since the complex target molecules are otherwise more challenging to obtain. We selected several pharmaceutical compounds to illustrate the advantage of late-stage trifluoromethylation compared to conventional synthesis to access complex trifluoromethylated molecules (Scheme 2). Biologically active molecules such as Vitamins B_3 and E, Vitamin E nicotinate, carbohydrates, and steroids are all compatible with the tandem C–H activation/trifluoromethylation procedure. It is worth mentioning that for all trifluoromethylated

Table 2: Trifluoromethylation of arenes by iridium-catalyzed borylation.



Entry	Product	Yield [%][a]	Entry	Product	Yield [%][a]
1	 Me CF$_3$ *t*BuCO$_2$	90	8	 Me CF$_3$ NC	70
2	 CF$_3$ CF$_3$ *t*BuCO$_2$	75	9	 *t*Bu N CF$_3$ *t*Bu	90
3	 Cl CF$_3$ *t*BuCO$_2$	75	10	 CF$_3$ O	72
4	 EtO$_2$C CF$_3$ Me	80	11	 CF$_3$ S	75
5	 MeO$_2$C CF$_3$ MeO$_2$C	87	12	 CF$_3$ N Boc	67[b]
6	 Cl CF$_3$ MeO	70	13	 Me CF$_3$ N	65[b]
7	 Me CF$_3$ TIPSO	50	14	 *t*BuCO$_2$ CF$_3$ N	50

[a] Yields of isolated product from the one-pot procedure (1.0 mmol scale). [b] Borylation with 1.0 mol% [{Ir(cod)OMe}$_2$] and 2.0 mol% dtbpy.



Scheme 2. Late-stage trifluoromethylation of complex small molecules.

compounds shown in Scheme 2, the trifluoromethylation was regioselective, and no constitutional isomers were observed in most cases. Only in the case of estrone were two isomers isolated in 1:1 ratio of inseparable isomers. The generally high regioselectivity of the sequential iridium-catalyzed C–H borylation and copper-catalyzed trifluoromethylation is an advantage over the other known trifluoromethylation reactions.

In summary, we have demonstrated the first copper-catalyzed trifluoromethylation of arylboronate esters and a sequential iridium-catalyzed C–H activation borylation and copper-catalyzed trifluoromethylation of arenes with a variety of functional groups. The advantage of this tandem procedure was demonstrated by application to a number of biologically active molecules. Mechanistic studies and synthetic applications of these transformations are ongoing in our laboratory.

Experimental Section

[{Ir(cod)(OMe)}$_2$] (1.7 mg, 0.25 mol%), dtbpy (1.45 mg, 0.540 mol%), and B$_2$pin$_2$ (186 mg, 0.730 mmol) were placed into an oven-dried sealed bomb. The bomb was evacuated and refilled with Ar three times. Under a positive flow of argon, dry THF (2.0 mL) and arene (1.0 mmol) were added. The reaction was stirred at 80 °C and monitored by GC/MS until the disappearance of the arene (24 h). After filtration through a short plug of celite, the volatiles were removed under vacuum and 4.0 mL of CH$_2$Cl$_2$ was added. The solution was transferred by a syringe into an oven-dried sealed bomb that contained CuTc (19 mg, 0.10 mmol), 1,10-phenanthroline (36 mg, 0.20 mmol), LiOH·H$_2$O (83 mg, 2.0 mmol), and Togni's reagent (363 mg, 1.10 mmol) under Ar. The reaction system was quickly degassed through three freeze/pump/thaw cycles and refilled with Ar. The reaction was stirred at 45 °C and monitored by ^{19}F NMR spectroscopy until the disappearance of Togni's reagent (typically 8 h). Brine (25 mL) and CH$_2$Cl$_2$ (10 mL) were added and the organic phase was separated. The aqueous phase was extracted with CH$_2$Cl$_2$ (5 × 10 mL) and the combined organic phases were dried over anhydrous Na$_2$SO$_4$, and concentrated in vacuo. The product was purified by flash chromatography on silica gel with n-pentane, and further purified by Kugelrohr distillation.

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