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Palladium(II)-Catalyzed Enantioselective Synthesis of α-(Trifluoromethyl)arylmethylamines

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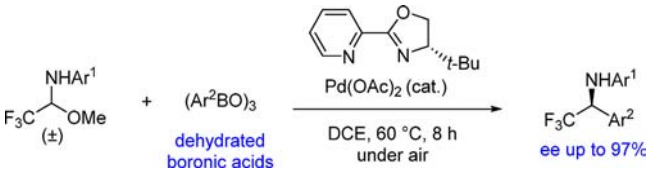
ABSTRACT



Trifluoromethylacetaldimines, generated in situ from the corresponding *N,O*-acetals, undergo 1,2-addition of arylboroxines under palladium(II) catalysis to generate a variety of α-(trifluoromethyl)arylmethylamines with good to high enantioselectivity (up to 97% ee). The pyridine-oxazolidine (PyOX) class of ligands was found to be particularly suitable for this transformation, which proceeds without exclusion of ambient air and moisture.

The transition-metal-catalyzed addition of organoboron reagents to imines has emerged as a versatile method for the preparation of diversely substituted amines in an enantioselective fashion.[1] Among the catalytic systems capable of effecting this transformation, complexes of rhodium(I) with chiral dienes or phosphorus-based ligands have most often been employed.[1,2] In comparison, there are few reports featuring the use of the less expensive palladium(II) as the catalyst for this transformation.[3]

In view of the prevalence of organofluorine compounds in medicinal chemistry, as well as the occurrence of α-(trifluoromethyl)amines in several biologically active molecules,[4] we sought to develop an enantioselective method for the synthesis of this class of compounds. Herein, we report that readily available *N,O*-acetals of trifluoroacetaldehyde react with arylboroxines and a Pd(II)/(*S*)-PyOX complex to afford enantioenriched secondary amines.

Much recent interest in trifluoromethylated amines can be associated with their use as amide bond isosteres, with a recent report of a cathepsin K inhibitor drug candidate.[5] Previous reports on the asymmetric synthesis of α-(trifluoromethyl)amines are in the fields of catalytic hydrogenation of imines,[6] cinchona alkaloid-catalyzed isomerization of trifluoromethylated imines,[7] and nucleophilic

(1) (a) Ramadhar, T. R.; Batey, R. A. In *Boronic Acids: Preparation and Applications in Organic Synthesis, Medicines and Materials*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, Germany, 2011; Vol. 2, pp 427−477. (b) Sun, Y.-W.; Zhu, P.-L.; Xu, Q.; Shi, M. *RSC Adv.* **2013**, *3*, 3153–3168. (c) Marques, C. S.; Burke, A. J. *ChemCatChem* **2011**, *3*, 635–645.

(2) Selected recent examples: (a) Jung, H. H.; Buesking, A. W.; Ellman, J. A. *J. Org. Chem.* **2012**, *77*, 8541–8548. (b) Nishimura, T.; Noishiki, A.; Tsui, G. C.; Hayashi, T. *J. Am. Chem. Soc.* **2012**, *134*, 5056–5059.

(3) (a) Chen, J.; Lu, X.; Lou, W.; Ye, Y.; Jiang, H.; Zeng, W. *J. Org. Chem.* **2012**, *77*, 8541–8548. (b) Marques, C. S.; Burke, A. J. *Eur. J. Org. Chem.* **2010**, *9*, 1639–1643. (c) Dai, H.; Lu, X. *Tetrahedron Lett.* **2009**, *50*, 3478–3481. (d) Ma, G. N.; Zhang, T.; Shi, M. *Org. Lett.* **2009**, *11*, 875–878. (e) Dai, H.; Lu, X. *Org. Lett.* **2007**, *9*, 3077–3080.

(4) (a) Lim, J.; Taoka, B.; Otte, R. D.; Spencer, K.; Dinsmore, C. J.; Altman, M. D.; Chan, G.; Rosenstein, C.; Sharma, S.; Su, H.-P.; Szewczak, A. A.; Xu, L.; Yin, H.; Zugay-Murphy, J.; Marshall, C. G.; Young, J. R. *J. Med. Chem.* **2011**, *54*, 7334–7349. (b) O'Shea, P. D.; Chen, C.-Y.; Gauvreau, D.; Gosselin, F.; Hughes, G.; Nadeau, C.; Volante, R. P. *J. Org. Chem.* **2009**, *74*, 1605–1610. (c) Zhang, N.; Ayral-Kaloustian, S.; Nguyen, T.; Afragola, J.; Hernandez, R.; Lucas, J.; Gibbons, J.; Beyer, C. *J. Med. Chem.* **2007**, *50*, 319–327. (d) Grunewald, G. L.; Caldwell, T. M.; Li, Q.; Criscione, K. R. *J. Med. Chem.* **1999**, *42*, 3315–3323.

(5) Black, W. C.; Bayly, C. I.; Davis, D. E.; Desmarais, S.; Falgueyret, J. P.; Leger, S.; Li, C. S.; Masse, F.; McKay, D. J.; Palmer, J. T.; Percival, M. D.; Robichaud, J.; Tsou, N.; Zamboni, R. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4741–4744.

(6) (a) Chen, M. W.; Duan, Y.; Chen, Q.-A.; Wang, D.-S.; Yu, C.-B.; Zhou, Y. G. *Org. Lett.* **2010**, *12*, 5075–5077. (b) Henseler, A.; Kato, M.; Mori, K.; Akiyama, T. *Angew. Chem., Int. Ed.* **2011**, *50*, 8180–8183. (c) Gosselin, F.; O'Shea, P. D.; Roy, S.; Reamer, R. A.; Chen, C.; Volante, R. P. *Org. Lett.* **2006**, *7*, 355–358.

(7) (a) Liu, M.; Li, J.; Xiao, X.; Xie, Y.; Shi, Y. *Chem. Commun.* **2013**, *49*, 1404–1406. (b) Wu, Y.; Deng, L. *J. Am. Chem. Soc.* **2012**, *134*, 14334–14337.

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additions to fluorinated or nonfluorinated imines (Figure 1).[8] Despite these important developments, asymmetric addition to imines generally relies on N-activating groups that are cleavable under particularly harsh conditions[8c,d] or on chiral auxiliaries.[8a,b,12]

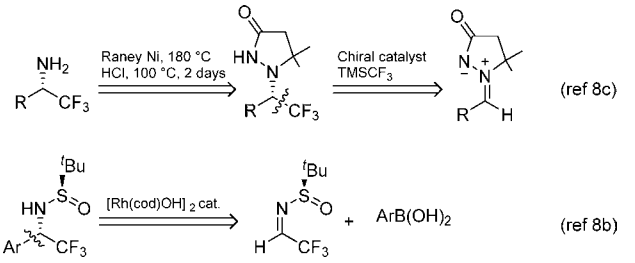


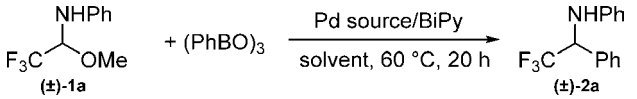
Figure 1. Previous examples of α-(trifluoromethyl)amine synthesis by asymmetric addition to imines.

We began our work examining the racemic addition to aniline-derived *N*,*O*-acetal **1a** using phenylboroxine (Table 1). At the outset, we observed that a catalytic amount of $Pd(OAc)_2$ along with 2,2′-bipyridine (BiPy) as a ligand furnished the desired amine **2a** in good yield, using DCE as the solvent (Table 1, entry 1). DCM and trifluorotoluene (TFT) could also be used, albeit with diminished yields (Table 1, entries 2 and 3); other common solvents were ineffective (Table 1, entries 4−6). It was also observed that $Pd(TFA)_2$ could be employed with similar results as with $Pd(OAc)_2$ (Table 1, entry 7). In a control experiment, $Pd_2(dba)_3$ led to no observable product by ^{19}F NMR analysis of the reaction mixture (Table 1, entry 8). Under the optimized contidions, the reaction could effectively be scaled up to a 2.5 mmol scale (Table 1, entry 1).

Although commercial phenylboronic acid was used in our preliminary experiments, it was found that different lots gave inconsistent results. In fact, the boroxine/boronic acid/water ratio of such samples can vary from batch to batch and over time.[9] We hypothesized that dehydrating the boronic acids to their corresponding boroxines would circumvent the problem. Indeed, the use of boroxines enabled completely reproducible results.[10]

We then turned our attention to finding an appropriate chiral ligand for this reaction. A number of privileged structures were screened under our optimized conditions: while BOX (L_1-L_2) or PyBOX (L_3-L_4) ligands were unsuitable (Table 2, entries 1−4), pyridine-oxazoline (PyOX) ligands (L_5-L_8)[3c] were compatible with the reaction and afforded increasing levels of enantioselectivity with increasing steric bulk of the R side chain (Table 2, entries 5−8). As the analogue bearing a *tert*-butyl side chain (L_8) yielded the desired amine with highest enantioselectivity (92% ee), it was selected to examine the scope of the reaction (Table 3).

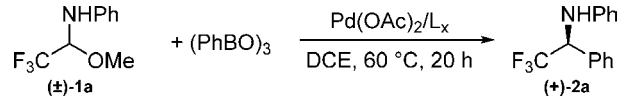
Table 1. Optimization of the Reaction Conditions[a]



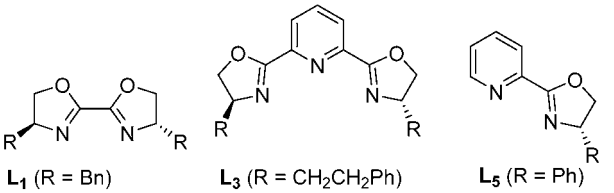
entry	Pd source	solvent	yield (%)[b]
1	**$Pd(OAc)_2$**	**DCE**	**73 (77)**[c]
2	$Pd(OAc)_2$	DCM	63
3	$Pd(OAc)_2$	TFT	51
4	$Pd(OAc)_2$	dioxane	–
5	$Pd(OAc)_2$	toluene	–
6	$Pd(OAc)_2$	acetonitrile	–
7	$Pd(TFA)_2$	DCE	71
8	$Pd_2(dba)_3$[d]	DCE	–

[a] Reaction conditions: *N*,*O*-acetal (0.20 mmol, 1 equiv); phenylboroxine (0.20 mmol, 1 equiv); Pd source (0.010 mmol, 5 mol %); BiPy (0.012 mmol, 6 mol %); solvent (1.1 mL); under air. [b] Yield of isolated product after flash chromatography. [c] 2.5 mmol scale reaction. [d] Control experiment with a Pd(0) source.

Table 2. Screening of Chiral Ligands[a]



entry	ligand	yield (%)[b]	ee (%)[c]
1	L_1	–	n.d.
2	L_2	–	n.d.
3	L_3	–	n.d.
4	L_4	–	n.d.
5	L_5	80	76
6	L_6	82	80
7	L_7	80	86
8	L_8	**83**	**92**



L_1 (R = Bn)
L_2 (R = *i*-Pr)

L_3 (R = CH_2CH_2Ph)
L_4 (R = *i*-Pr)

L_5 (R = Ph)
L_6 (R = Bn)
L_7 (R = *i*-Pr)
L_8 (R = *t*-Bu)

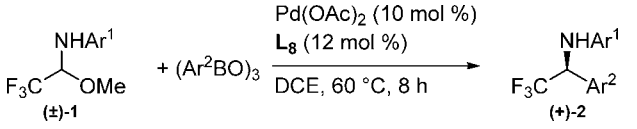
[a] Reaction conditions: *N*,*O*-acetal (0.20 mmol, 1 equiv); phenylboroxine (0.20 mmol, 1 equiv); $Pd(OAc)_2$ (0.010 mmol, 5 mol %); ligand (0.012 mmol, 6 mol %); solvent (1.1 mL); under air. [b] Yield of isolated product after flash chromatography. [c] Determined by HPLC on a chiral stationary phase. See Supporting Information for details.

(8) (a) Xu, J.; Liu, Z.-J.; Yang, X.-J.; Wang, L.-M.; Chen, G.-L.; Liu, J.-T. *Tetrahedron* **2010**, *66*, 8933–8937. (b) Truong, V. L.; Pfeiffer, J. Y. *Tetrahedron Lett.* **2009**, *50*, 1633–1635. (c) Kawai, H.; Kusuda, H.; Nakamura, S.; Shiro, M.; Shibata, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6324–6327. (d) Lauzon, C.; Charette, A. B. *Org. Lett.* **2006**, *8*, 2743–2745.

(9) Boronic acids trimerize to form boroxines upon standing, with release of water. See *Boronic Acids: Preparation and Applications in Organic Synthesis, Medicines and Materials*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, Germany, 2011; pp 1−123.

(10) For examples of the use of boroxines in 1,2-addition reactions, see ref 2.

Table 3. Pd(II)-Catalyzed Enantioselective Synthesis of α-(Trifluoromethyl)amines[a]



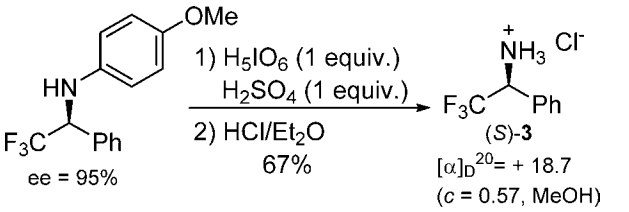
entry	Ar^1	Ar^2	**2**, yield (%)[b]	ee (%)[c]
1	Ph	Ph	**2a**, 83 (85)[d]	92 (93)[d]
2	4-$MeOC_6H_4$	Ph	**2b**, 85	93
3		Ph	**2c**, 59	97
4	4-BrC_6H_4	Ph	**2d**, 86	95
5	4-ClC_6H_4	Ph	**2e**, 86	96
6	4-$COOEtC_6H_4$	Ph	**2f**, 75	94
7	3-BrC_6H_4	Ph	**2g**, 81	95
8	2-$MeOC_6H_4$	Ph	**2h**, 77 (65)[e]	63 (71)[e]
9	4-$NO_2C_6H_4$	Ph	n.r.	-
10	4-$MeOC_6H_4$	4-MeC_6H_4	**2i**, 87	92
11	4-$MeOC_6H_4$	4-PhC_6H_4	**2j**, 84	95
12	4-$MeOC_6H_4$	4-^{t}Bu	**2k**, 80	95
13	4-$MeOC_6H_4$	4-$MeOC_6H_4$	**2l**, 91	84
14	4-$MeOC_6H_4$	4-$BnOC_6H_4$	**2m**, 89	76
15	4-$MeOC_6H_4$	4-FC_6H_4	**2n**, 86[f]	96
16	3-BrC_6H_4	4-$MeOC_6H_4$	**2o**, 59	92
17	4-$COOEtC_6H_4$	3-MeC_6H_4	**2p**, 86	95

[a] Reaction conditions: *N*,*O*-acetal (0.20 mmol, 1 equiv); boroxine (0.20 mmol, 1 equiv); $Pd(OAc)_2$ (0.020 mmol, 10 mol %); ligand (0.024 mmol, 12 mol %), solvent (1.1 mL); under air. [b] Yield of isolated product after flash chromatography. [c] Enantiomeric excesses determined by HPLC on a chiral stationary phase. [d] Reaction ran on a 1 mmol scale. [e] $\mathbf{L_6}$ was used. [f] Reaction time was 48 h.

The influence of substituents on the *N*-aryl ring was studied. Notably, all reactions were performed without rigorous exclusion of air and moisture. Using phenylboroxine as the nucleophile, *N*,*O*-acetals bearing electron-rich or neutral aryl rings gave good to high yields of product (77−85%) (Table 3, entries 1, 2, and 8) with the exception of dioxolane-bearing amine **2c**, generated in lower yield (59%) (Table 3, entry 3). Substrates with moderately electron-deficient aromatic rings furnished products in comparable yields (75−86%) (Table 3, entries 4−7). However, introduction of a nitro group at the 4 position shut down reactivity (Table 3, entry 9). In all of the successful examples, high enantioselectivity was achieved with the exception of *ortho*-substituted product **2h** (63% ee). Interestingly, in the latter case, switching to the less hindered ligand $\mathbf{L_6}$ proved beneficial as the ee increased to 71%.

The scope of boroxines was then studied with an *N*,*O*-acetal bearing a 4-MeO aryl substituent. It was found that

Scheme 1. Removal of the Amine PMP Group[a]



[a] Step 1: MeCN/H_2O (1:1), rt, 16 h. See Supporting Information for details.

electron-neutral or moderately electron-rich boroxines reacted to give the desired amines in high yield and enantioselectivity (Table 3, entries 10−12). Boroxines with a more electron-donating substituent reacted equally well but with diminished enantiocontrol (Table 3, entries 13 and 14). However, the switch to a substrate bearing a 3-Br substituent restored a high level of enantioselectivity (Table 3, entry 13 vs 16). A fluorinated boroxine was also tolerated but necessitated a longer reaction time to reach complete conversion (Table 3, entry 15). Under our optimized conditions, other electron-poor boroxines (e.g., 3-chlorophenyl, 4-(acetyl)phenyl) and an *ortho*-substituted boroxine (2-methyl) did not display any reactivity.

The *p*-methoxyphenyl (PMP) group of α-(trifluoromethyl)amine **2b** could be removed under modified literature conditions (Scheme 1).[11] Oxidative cleavage followed by workup and acidification furnished the hydrochloride salt (*S*)-**3** in 67% yield. The absolute stereochemistry was assigned by comparison of the optical rotation with that found in the literature ($[\alpha]_D^{25} = +26.5$ (c = 0.65, MeOH)) for 94% ee.[12]

In summary, a Pd(II)-catalyzed enantioselective synthesis of α-(trifluoromethyl)arylmethylamines has been developed, starting from readily available *N*,*O*-acetals of trifluoroacetaldehyde. A variety of fluorinated benzylamines could be synthesized in up to 97% ee and 91% yield. Efforts are underway to extend this reaction to the addition of other classes of nucleophiles.

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Supporting Information Available. Detailed experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(11) Verkade, J. M M.; van Hemert, L. J. C.; Quaedflieg, P. J. L. M.; Alsters, P. L.; van Delft, F. L.; Rutjes, F. P. J. T. *Tetrahedron Lett.* **2006**, *47*, 8109–8133.

(12) Prakash, G. K. S.; Mandal, M.; Olah, G. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 589–590.