NIH Public Access
Author Manuscript
Tetrahedron Lett. Author manuscript; available in PMC 2013 September 12.

Published in final edited form as:
Tetrahedron Lett. 2012 September 12; 53(37): 4938–4941. doi:10.1016/j.tetlet.2012.06.138.

o-(Trialkylstannyl)anilines and Their Utility in Stille Cross-Coupling: Direct Introduction of the 2-Aminophenyl Substituent

Enver Cagri Izgu[a] and **Thomas R. Hoye**[a,*]
[a]Department of Chemistry, 207 Pleasant Street, SE, University of Minnesota, Minneapolis, Minnesota 55455

Abstract

We have developed shelf- and air-stable ortho-stannylated aniline reagents that can directly be coupled with alkenyl and aryl halides via Stille cross-coupling. We report i) the efficient preparation of *o*-(tributylstannyl)aniline (**2a**) and *o*-(trimethylstannyl)aniline (**2b**), ii) the comparison of the reactivities of **2a** and **2b** with those of related organostannanes in cross-coupling reaction with an alkenyl halide, and iii) the cross-coupling of **2a** and **2b** with a series of arylhalides and triflate.

Keywords

Cross-coupling; Ortho-metalation; Aniline; Organostannanes

The 2-aminophenyl substituent is an important structural entity in organic and medicinal chemistry. The essential features of cross-coupling partners suitable for installation of such a moiety are shown in Figure 1. In principle, the 2-aminophenyl partner can be either the acceptor (panel A) or donor (panel b) and the most direct access to the desired anilino cross-coupling product is when the nitrogen functionality in these reactants is the free amino (–NH_2) group.

Examples of molecules of medicinal relevance that contain an embedded 2-aminoarene subunit are shown in Figure 2. In the synthesis of each of these compounds, the 2-aminophenyl units were installed by an aryl-aryl cross-coupling reaction (see arrow in each structure).[ia–d] The key reagent for these transformations was either the boronic acid **1a** or its pinacolate ester **1b** (Figure 3). These are commercially available but relatively expensive (ca. $100/g). Their preparation via borylation with $(RO)_2B\text{-}B(OR)_2$[iia,b] or $(RO)_2B\text{-}H$[iic,d] uses rather exotic reagents, ligands, and/or conditions.[iii]

Faced with the need to effect introduction of a 2-aminophenyl substituent in the course of a natural product synthesis project, we had occasion to explore a new class of reagents—namely the 2-aminophenylstannanes **2a** and **2b** (Figure 3). We could find no reports in the

© 2012 Elsevier Ltd. All rights reserved.

*Corresponding author. Tel.: 612-625-1891; fax: 612-626-7541; hoye@umn.edu.

Supplementary data
Supplementary data associated with this article can be found in the online version at http//dx.doi.org/#########. It includes all experimental procedures and spectroscopic characterization data for all new compounds.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

literature describing any 2-aminophenylstannanes. We viewed **2a** and **2b** as potentially general and valuable synthons for Stille cross-coupling[iv] reactions. We have developed a high-yielding, multigram synthesis of each reagent. These organostannanes have proven to be robust (shelf- and air-stable) and, in our hands, additionally advantageous compared to the boron-based analogs **1**. They can be coupled with alkenyl and aryl halides under neutral conditions, a feature that is often advantageous in complex molecule settings.

Our investigations into the synthesis of **2a** are summarized in Scheme 1. First, we explored reduction of *o*-(tributylstannyl)-nitrobenzene (**2d**[v]) with Sn(II)Cl_2/EtOH, Fe(0)/EtOH, or Pd/C, H_2 (1 atm)/DCM or EtOH. We recovered starting material using the first two conditions, and we observed only the formation of nitrobenzene with the last. Next, we considered di-debenzylation[vi] of *N,N*-dibenzyl-2-(tributylstannyl)aniline (**6**). However, stannylation of the iodo-precursor **5** via lithium halogen exchange with *n*-BuLi gave *N,N*-dibenzyl-2-butylaniline as the only identifiable product. We then examined directed-ortho-metallation[vii] of the anilide, 4-methoxy-*N*-phenylbenzamide (**7**). However, stannylation occurred, instead, primarily at the 2-position of the 4-methoxyphenyl moiety of the starting anilide **7**.

We then explored lithiation[viii] and stannylation of *N*-Boc aniline (**9**). We found Stanetty's protocol for the lithiation (*t*-BuLi, Et_2O, −40 °C)[viiib] to be more serviceable[ix] for the efficient preparation of the desired aniline precursor **2c**,[x] following quenching with *n*-Bu_3SnCl. We explored a number of conditions for removal of the Boc group in **2c**. Purification of **2a** on either silica gel or alumina (basic or neutral) was problematic. Gratifyingly, the TMSOTf-mediated Boc-cleavage developed by Sakaitani and Ofune[xi] smoothly provided *o*-(tributylstannyl)aniline (**2a**) with excellent yield and in a high state of purity. This material (oil) has been stored on the benchtop with no protection from light, air, or moisture for over a year, and no significant deterioration is observable in its ^{1}H NMR spectrum. Access to **2b** involves a similar protocol from **9** (Me_3SnCl was used to quench the initial lithiated *N*-Boc aniline) and proceeds with similar overall yield.

We then studied the performance of **2a** and **2b** vis-à-vis the known 2-*N*-Boc- and 2-nitro-phenylstannanes (**2c** and **2d**) in coupling reactions with *N*-alkyl bromomaleimide (**10**) as the alkenyl halide. To test the relative efficiency and reactivity of Stille cross-couplings with organotin reagents containing different nitrogen-based functional groups, we studied the reactions of **2a–d** (Table 1, graphic) with *N*-hexyl bromomaleimide (**10**) as the halide partner. Indeed, it was thecross coupling of a 2-aminophenyl moiety with this specific type of halide that was the motivating impetus for this study. The results are presented in entries 1–6 of Table 1. The isolated yields were excellent even when using a nearly 1:1 stoichiometric ratio. Although the nitro compound **2d** reacted somewhat sluggishly under our standard conditions (entry 5), addition of CuI led to a significant improvement (entry 6).[xiii] We also performed a series of competition studies[xiv] designed to determine the relative reactivity of **2a**, **2c**, and **2d** (Table 1, entries 7–9). When imide **10** was treated simultaneously with an excess of **2a** and the nitro compound **2d** (10 equiv each, entry 7), anilinoimide **11a/b** (**11a** = **11b; 11**, N* = NH_2) was observed as the sole coupling product, imide **10** was fully consumed, and **2a** was ca. 10% consumed (GC/MS integration). The reactivity of **2a** was also compared to that of the *N*-Boc protected derivative **2c** (entry 8). Again, anilinoimide **11a/b** was the exclusive product. These results show that **2a** is very effective in this additive-free Stille cross-coupling reaction and is more reactive than either **2c** or **2d**. Although other explanations are possible, these observations are consistent with a more rapid transmetalation to the RPd(II)Br species by the amine-bearing organostannane **2a**. A similar explanation has been invoked in an earlier study by Farina.[xv]

We have also explored the scope of the cross-coupling of **2a** using various alkenyl and aryl halides (Table 2). Use of the Stille cross-coupling conditions championed by Baldwin and

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

co-workers,[xvi] namely, $Pd(PPh_3)_4$–CuI–CsF in DMF, provided significantly higher product yields for substrates exhibiting low reactivity (**12a** in entry 1, and **12e–h** in entries 5–8) under typical conditions. Coupling of **2a** with the (multifunctional) bromodihydropyrrole **12a**[xvii] provided the 2-(aminophenyl)-dihydropyrrole **13a** in 62% yield (entry 1). While aryl iodides **12b–e** (entries 2–5) underwent cross-coupling reactions efficiently, aryl bromides **12f** and **12g** gave 2-(aryl)anilines **13f** and **13e** in somewhat lower yields (ca. 65%, entries 6–7, respectively). Similar to the case of **12a**, phenyl triflate (**12h**) was unreactive under the $Pd_2(dba)_3$•$CHCl_3$–$AsPh_3$ (with or without CuI additive). The coupling efficiency with this partner significantly increased, again, using Baldwin's conditions, which resulted in 80% isolated yield of 2-(phenyl)aniline (entry 8).

In conclusion, we have shown that the *o*-anilinostannanes **2a** and **2b** are facile participants in Stille cross-coupling reactions. Each has been efficiently synthesized on multigram scale. Their cross-coupling reactivity toward *N*-hexyl bromomaleimide (**10**) is greater than that of either the *N*-Boc or nitro analog **2c** or **2d**, respectively. The efficient preparations of **2a** and **2b** and their good substrate scope in Stille cross-couplings make these organostannanes important and practical building blocks for general use in organic synthesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

These studies were supported by the National Institute of General Medical Sciences (GM-65597) and the National Cancer Institute (CA-76497) of the United States National Institutes of Health.

References and notes

i. (a) Murugesan N, Gu Z, Stein PD, Bisaha S, Spergel S, Girotra R, Lee VG, Lloyd J, Misra NR, Schmidt J, Mathur A, Stratton L, Kelly YF, Bird E, Waldron T, Liu ECK, Zhang R, Lee H, Serafino R, Abboa-Offei B, Mathers P, Giancarli M, Seymour AA, Webb ML, Moreland S, Barrish JC, Hunt JT. J Med Chem. 1998; 41:5198–5218. [PubMed: 9857090] (b) Kranich R, Busemann AS, Bock D, Schroeter-Maas S, Beyer D, Heinemann B, Meyer M, Schierhorn K, Zahlten R, Wolff G, Aydt EM. J Med Chem. 2007; 50:1101–1115. [PubMed: 17302397] (c) Wagner FF, Comins DL. Org Lett. 2006; 8:3549–3552. [PubMed: 16869657] (d) Banwell MG, Edwards AJ, Jolliffe KA, Smith JA, Hamel E, Verdier-Pinard P. Org Biomol Chem. 2003; 1:296–305. [PubMed: 12929425]

ii. (a) Appukkuttan P, Van der Eycken E, Dehae W. Synlett. 2003:1204–1206.(b) Yamamoto T, Morita T, Takagi J, Yamakawa T. Org Lett. 2011; 13:5766–5769. [PubMed: 21978296] (c) Baudoin O, Guénard D, Guéritte F. J Org Chem. 2000; 65:9268–9271. [PubMed: 11149887] (d) Baudoin O, Cesario M, Guénard D, Guéritte F. J Org Chem. 2002; 67:1199–1207. [PubMed: 11846663]

iii. Earlier reports for the synthesis of **1a** involved nitration of phenylboronic acid followed by catalytic hydrogenation; Verbit L, Levy JS, Rabitz H, Kwalwasser W. Tetrahedron Lett. 1966; 10:1053–1055.Groziak MP, Ganguly AD, Robinson PD. J Am Chem Soc. 1994; 116:7597–7605.

iv. (a) Stille JK. Pure Appl Chem. 1985; 57:1771–1780.(b) Stille JK. Angew Chem Int Ed. 1986; 25:508–524.

v. Kosugi M, Ohya T, Migita T. Bull Chem Soc Jpn. 1983; 56:3855–3856.

vi. (a) Gonzáles-Morales A, Díaz-Countiño D, Fernandez-Zertuche M, García-Barradas O, Ordóñez M. Tetrahedron: Asymmetry. 2004; 15:457–463.(b) Theodora, W.; Greene, TW.; Wuts, PGM. Protective Groups in Organic Synthesis. 3. J. Wiley & Sons, Inc; New York, NY: 1999. p. 579

vii. (a) Snieckus V. Heterocycles. 1980; 14:1649–1676.(b) Snieckus V. Chem Rev. 1990; 90:879–933. and references cited therein.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

viii. (a) Muchowski JM, Venuti MC. J Org Chem. 1980; 45:4798–4801.(b) Stanetty P, Koller H, Mihovilovic M. J Org Chem. 1992; 57:6833–6837.

ix. In our hands performing the lithiation and quenching sequence in THF at −78 °C[viiia,x] resulted in variable yields (ca. 20–55%).

x. (a) Salituro FG, McDonald IA. J Org Chem. 1988; 53:6138–6139.(b) Iwao M, Takehara H, Furukawa S, Watanabe M. Heterocycles. 1993; 36:1483–1488.

xi. Sakaitani M, Ohfune Y. J Org Chem. 1990; 55:870–876.

xii. Initial screening of catalysts and additives for the coupling of **2a** or **2b** with imide**10** showed that $Pd_2(dba)_3$•$CHCl_3$/$AsPh_3$ was superior to $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$/LiCl, or $Pd_2(dba)_3$•$CHCl_3$/PPh_3.

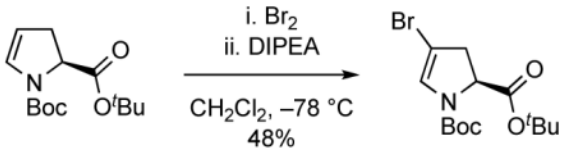
xiii. Farina V, Kapadia S, Krishnan B, Wang C, Liebeskind LS. J Org Chem. 1994; 59:5905–5911.

xiv. Anslyn, EV.; Dougherty, DA. Modern Physical Organic Chemistry. University Science Books; Sausalito, CA: 2006. p. 473-474.

xv. Farina V. Pure Appl Chem. 1996; 68:73–78.

xvi. Mee SP, Lee V, Baldwin JE. Angew Chem Int Ed. 2004; 43:1132–1136.

xvii. Compound **12a** was prepared by a one-pot bromination-elimination procedure from the enecarbamate precursor 16 (see the Supplementary data for further details).



16 **12a**

Enecarbamate **16** was obtained in 54% yield over three steps from commercially available L-pyroglutamic acid following the pathway reported by Gross U, Nieger M, Brase S. Org Lett. 2009; 11:4740–4742. [PubMed: 19764736]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

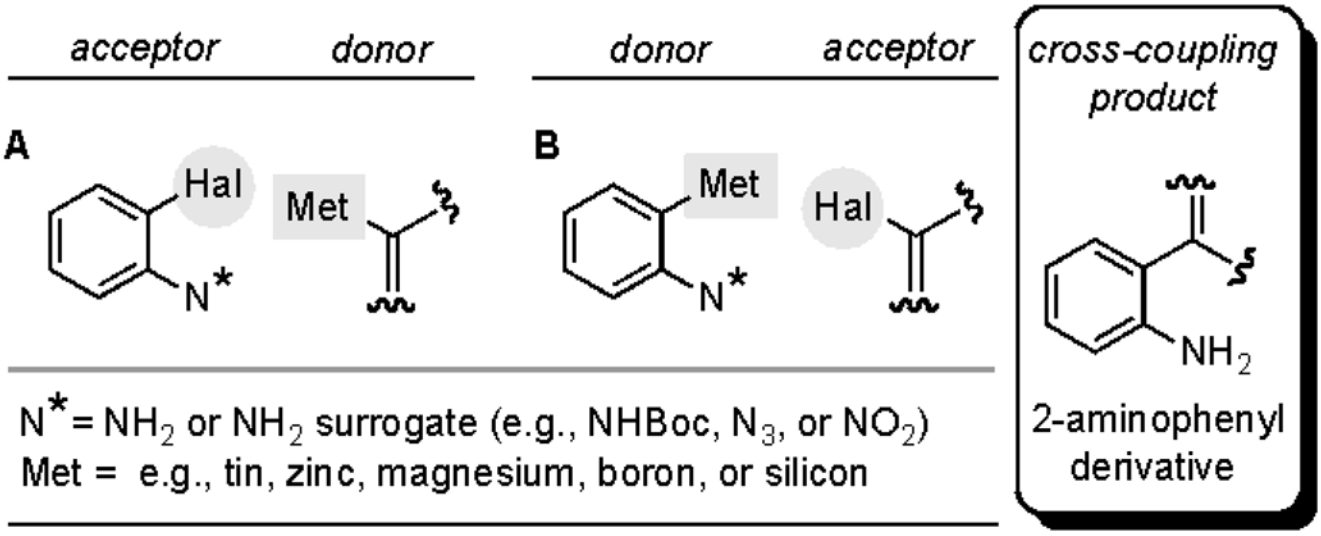


Figure 1.
Cross-coupling strategies for preparation of 2-aminophenyl derivatives.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

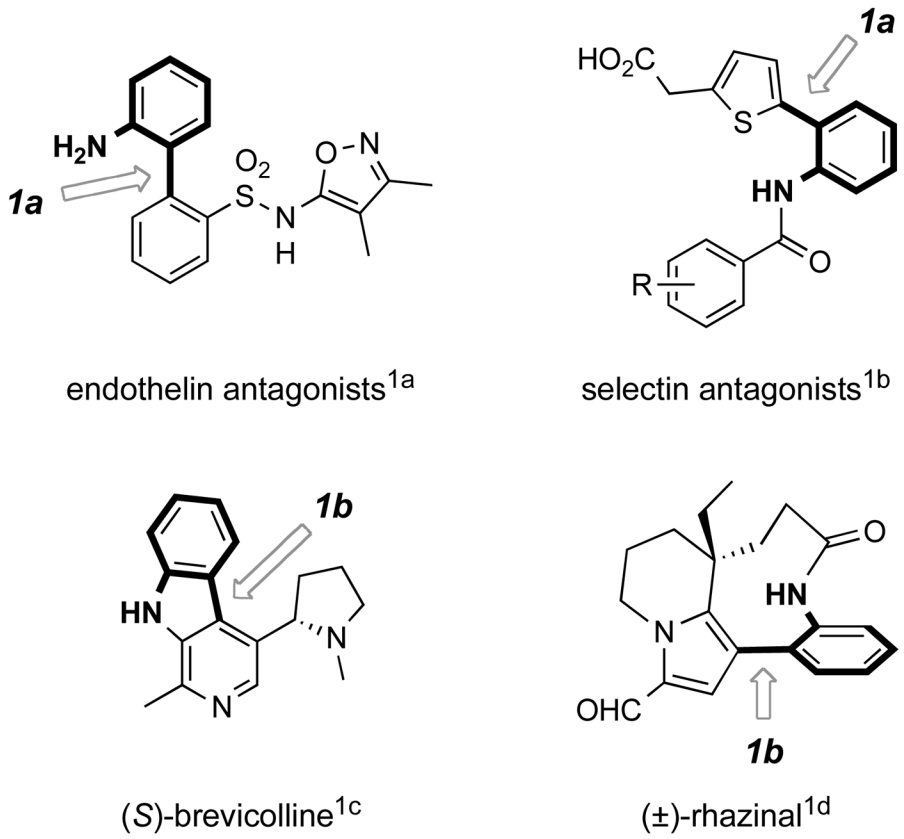


Figure 2.
Examples of biologically relevant compounds synthesized via a 2-aminophenylation cross-coupling reaction.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

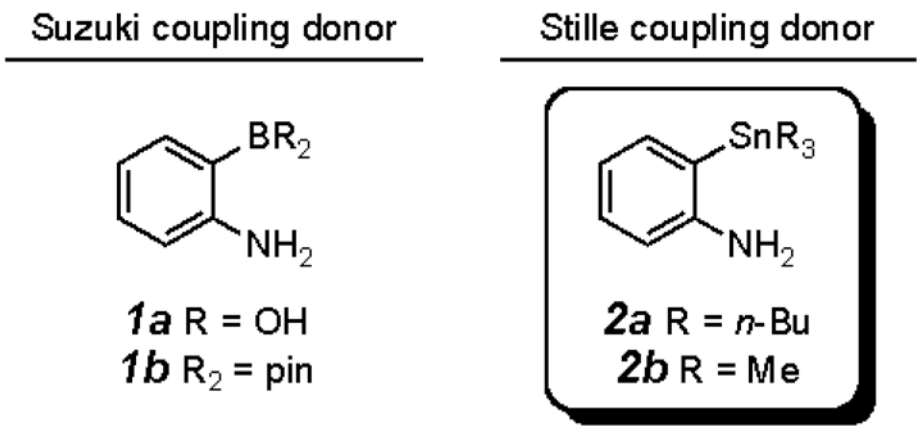


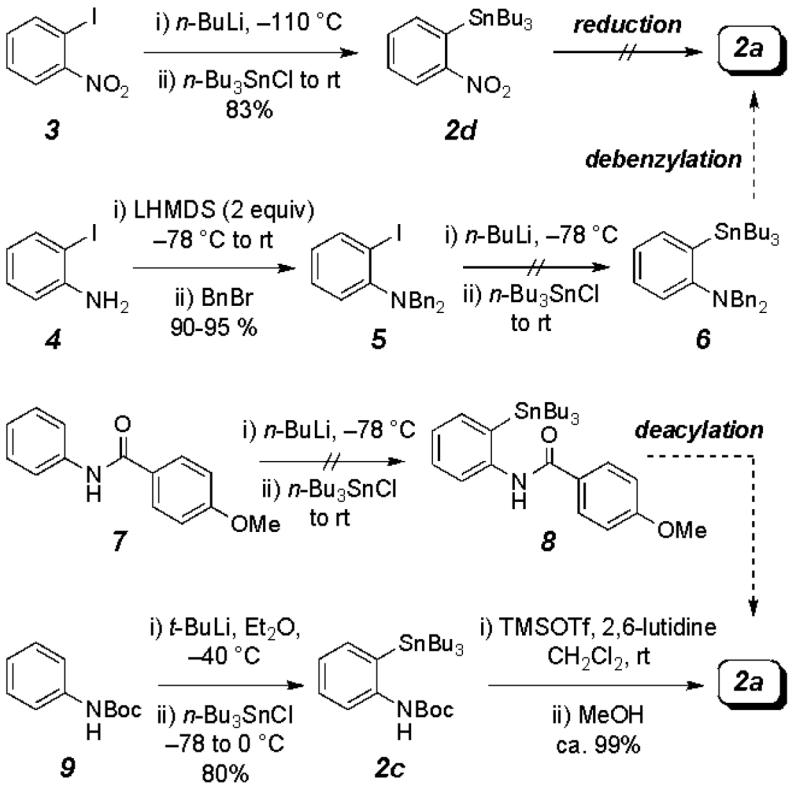
Figure 3.

Free anilino cross-coupling building blocks: known boron reagents[ii] (**1**) and new tin reagents (**2**).

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript



Scheme 1.
Synthesis of *o*-(tributylstannyl)aniline (**2a**)

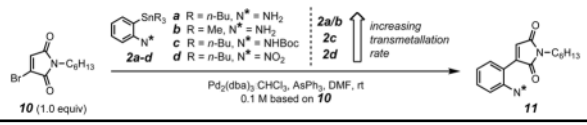
NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table 1

Stille Cross-Couplings of **2a–d** with imide **10**[a]



Entry[b]	Aryl stannane	Equiv	Time (h)	Conversion of *10* (%)	*11*, Yield[c]
1	**2a**	1.1	12.0	90	**11a/b**, 82 %
2	**2b**	1.1	12.0	90	**11a/b**, 85 %
3	**2a**	1.1	0.5	> 99	**11a/b**, 94 %
4	**2c**	1.1	12.0	> 99	**11c**, 91%
5	**2d**	1.1	24.0	20	**11d**, 13 %
6[d]	**2d**	1.1	24.0	> 99	**11d**, 85%
7	**2a** + **2d**	10.0	0.5	> 99	**11a/b**[e]
8	**2a** + **2c**	10.0	0.5	> 99	**11a/b**[e]
9	**2c** + **2d**	10.0	12.0	> 99	**11c**[e]

[a]One-hundred mg of **10** was used in the experiments reported in entries 1–6; ten mg in entries 7–9.

[b]$Pd_2(dba)_3 \cdot CHCl_3$ (1 mol%),[xii] $AsPh_3$ (4 mol%) in entries 1–2, $Pd_2(dba)_3 \cdot CHCl_3$ (5 mol%), $AsPh_3$ (20 mol%) in entries 3–9.

[c]Isolated yields for entries 1–6.

[d]CuI (10 mol%) was added.

[e]Only product that was observed by GC-MS analysis; yield was not determined.

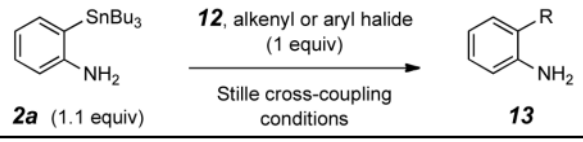
NIH-PA Author Manuscript

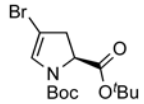
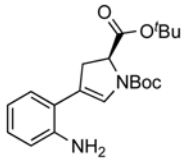
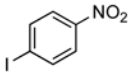
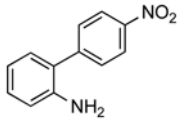
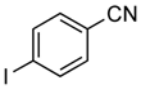
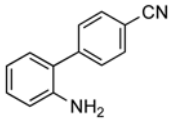
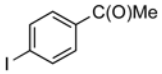
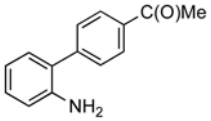
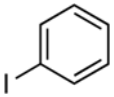
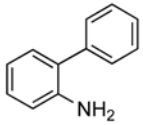
NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table 2

Stille Cross-Couplings of **2a** with alkenyl and aryl halides **12**[a]

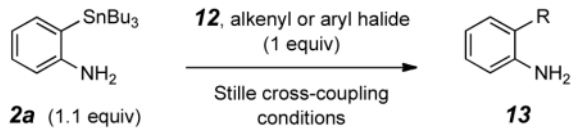


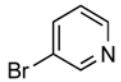
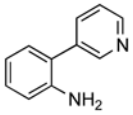
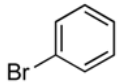
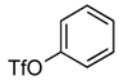
Entry	12	Catalyst (mol%)	Additives (equiv)	13	Yield (%)
1	 12a	$Pd(PPh_3)_4$(5)	CuI (0.1); CsF (2.0)	 13a	62
2	 12b	$Pd_2(dba)_3{\bullet}CH_3Cl_3$ (5)	$AsPh_3$ (0.2)	 13b	86
3	 12c	$Pd_2(dba)_3{\bullet}CH_3Cl_3$ (5)	$AsPh_3$ (0.2)	 13c	84
4	 12d	$Pd_2(dba)_3{\bullet}CH_3Cl_3$ (5)	$AsPh_3$ (0.2)	 13d	73
5	 12e	$Pd(PPh_3)_4$ (10)	CuI (0.2); CsF (2.0)	 13e	82

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript



Entry	*12*	Catalyst (mol%)	Additives (equiv)	*13*	Yield (%)
6	 ***12f***	$Pd(PPh_3)_4$ (10)	CuI (0.2); CsF (2.0)	 ***13f***	66
7	 ***12g***	$Pd(PPh_3)_4$ (10)	CuI (0.2); CsF (2.0)	***13e***	63
8	 ***12h***	$Pd(PPh_3)_4$ (10)	CuI (0.2); CsF (2.0)	***13e***	80

[a]All reactions were performed in DMF (purged with Ar for ca. 10 min prior to addition of the catalyst and additives) at room temperature and were quenched with saturated aqueous NaCl solution after 24 hours.