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A Highly Selective Tandem Cross-Coupling of *gem*-Dihaloolefins for a Modular, Efficient Synthesis of Highly Functionalized Indoles

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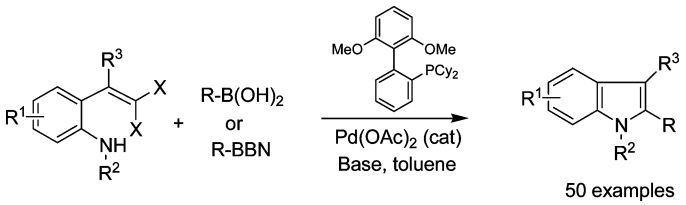

A highly efficient method of indole synthesis using *gem*-dihalovinylaniline substrates and an organoboron reagent was developed via a Pd-catalyzed tandem intramolecular amination and an intermolecular Suzuki coupling. Aryl, alkenyl, and alkyl boron reagents are all successfully employed, making for a versatile modular approach. The reaction tolerates a variety of substitution patterns on the aniline leading to indoles with group at C_2-C_7. The orthogonal approach of the sequential copper- and palladium-mediated synthesis of 1,2-diarylindoles exploited the wide availability of diverse organoboron reagents.

Introduction

Over the past three decades, many advancements have been made in the field of Pd-catalyzed C−C bond forming reactions. In particular, organoboron (Suzuki−Miyaura),[1] organostannane (Stille),[2] organozinc (Negishi),[3] and organosilane (Hiyama)[4] based couplings with halogenated substrates have become very reliable processes. Palladium is the most widely used catalyst for forming carbon−heteroatom bonds under very mild conditions,[5] an important transformation for the pharmaceutical industry since many biologically active molecules contain heterocycles. Although significant progress has been made in improving specific Pd-catalyzed reactions by developing new ligands or reaction conditions, less effort has been expended to integrate multiple couplings of a multihalogenated substrate. Tandem reactions can increase the efficiency and modularity of chemical transformations by reducing the number of steps and also exploiting the versatility of the catalyst. The fundamental questions associated with these powerful coupling combinations, such as selectivity, compatibility, and relative rates have rarely been reported in the literature.

An interesting dihalosystem we selected to investigate is *gem*-dihaloolefins. *gem*-Dibromovinyl compounds can be obtained conveniently from an aldehyde (or activated ketone) using CBr_4/PPh_3 (Ramirez olefination used in the Corey−Fuchs reaction).[6] The ylide CCl_2PPh_3,[7] which can be prepared from the reaction of PPh_3 and *in situ*-generated CCl_2 carbene (*t*-BuOK and $CHCl_3$), provides straightforward access to *gem*-dichlorovinyl compounds.

Stepwise functionalization of *gem*-dihaloolefin systems has been shown to occur with good stereoselectivity.[8] Potentially more efficient tandem reactions are rarely used,[9] in particular when carbon−heteroatom bond formation is involved.[10] Inspired by our success with a double Heck reaction using dibromoaryl substrates to achieve orthogonal functionalization (Scheme 1),[11] we envisaged a modular heterocycle synthesis via an intramolecular C−heteroatom bond formation and intermolecular cross

(1) (a) Suzuki, A. *J. Organomet. Chem.* **2002**, *653*, 83. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (c) Suzuki, A. in *Boronic Acids*; Hall, D. G, Ed.; Wiley-VCH: Weinheim, 2005; p 123.

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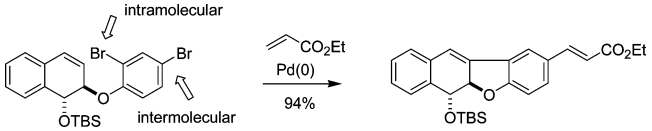
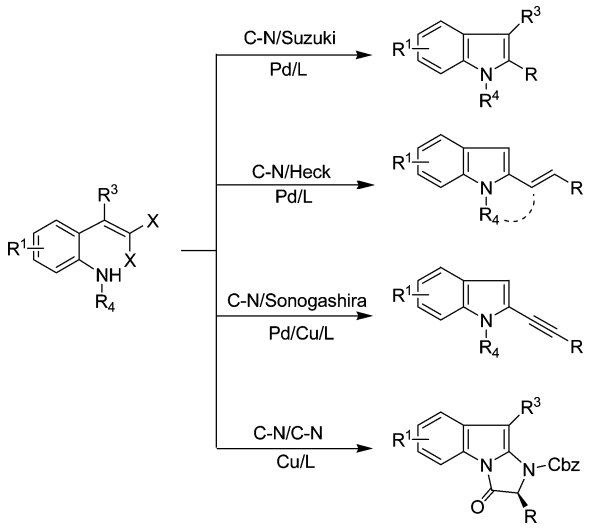
SCHEME 1. Tandem Intra- and Intermolecular Heck Reaction



SCHEME 2. Tandem Cross-Couplings of *gem*-Dihalovinylanilines

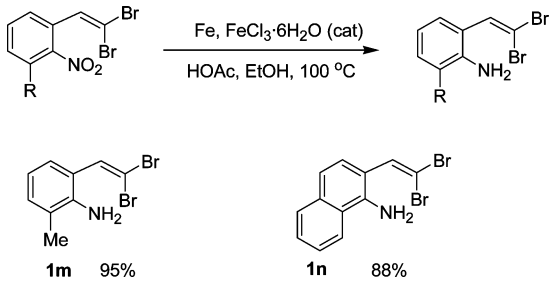


coupling. Recently, we have reported a Pd-catalyzed indole synthesis[12] via a C−N/Suzuki[13] or C−N/Heck[14] or C−N Sonogashira combinations[15] and a Cu-catalyzed double C−N bond formation[16] (Scheme 2). We have applied the methodology in the synthesis of azaindoles and thienopyrroles[17] as well as a family of KDR kinase inhibitors.[18] Here, we report on the scope and the mechanism of the indole synthesis via the C−N/Suzuki sequence as well as efficient routes to the starting *gem*-dibromovinyloanilines.

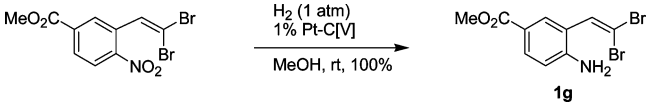
Results and Discussion

Substrate Synthesis. The Ramirez olefination is sensitive to amine or amide functional groups, so we sought to use

SCHEME 3. Reduction of Hindered Nitrobenzenes Using Fe/$FeCl_3$·$6H_2O$



SCHEME 4. Selective Reduction of Nitrobenzenes Using Pt-Catalyzed Hydrogenation



o-nitrobenzaldehydes as our starting materials. A one-pot two-step procedure between CBr_4/PPh_3 and 2-nitrobenzaldehydes followed by reduction of the nitro group using $SnCl_2$·$2H_2O$ in refluxing ethanol provided a very convenient preparation of *gem*-dibromovinylanline **1a** on scales up to 50 g (55%) (Table 1). Many substrates bearing either an electron-donating or an electron-withdrawing group at C-3, C-4, or C-5 position were prepared in good yield. This procedure is superior to the multiple step routes from either 2′-aminobenzyl alcohol or 2-cyanobenzaldehyde.[10b,19] In addition to the commercially available inexpensive *o*-nitrobenzaldehydes, additional substrates could be prepared via a range of literature routes.[20]

Practical Nitro Group Reduction. The inherent inefficiency of $SnCl_2$·$2H_2O$ to reduce sterically hindered nitro groups made a search for other reagents necessary, and iron powder in the presence of a catalytic amount of $FeCl_3$·$6H_2O$[21] provided a useful approach for these substrates (Scheme 3).

There are many practical drawbacks regarding the use of traditional reducing agents such as Sn(II) or Fe metal, including large amounts of metal oxide waste (3−7 equiv), and difficulties with workup on a large scale. We therefore searched for a better method of reduction such as catalytic hydrogenation by screening numerous heterogeneous transition metal catalysts. In most cases, the double bond and halogens posed significant challenges for a selective reaction since traditional catalysts including Pd/C (1 to 10% Pd), Ru/C, Rh/C, Pearlman's catalyst (20%), and Raney nickel failed to produce the desired product, although the starting material was consumed. One commercially available selective catalyst we found was 1% vanadium-doped platinum on carbon (abbreviated as 1% Pd−C[V]), which is a straightforward method reported by Solvias (Scheme 4).[22] The presence of vanadium serves to minimize contamination by the undesired hydroxyamine formed in the reduction process, affording the aniline product in excellent yield. Analytically pure product was obtained after removal of the catalyst and solvent, with no need for chromatographic purification.

(8) Using Grigard or organozinc reagents: (a) Minato, A.; Suzuki, K.; Tamao, K. *J. Am. Chem. Soc.* **1987**, *109*, 1257. (b) Minato, A. *J. Org. Chem.* **1991**, *56*, 4052. (c) Zeng, X.; Qian, M.; Hu, Q.; Negishi, E. *Angew. Chem., Int. Ed.* **2004**, *43*, 2259. (d) Tan, Z.; Negishi, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 762. Using organoboron reagents: (e) Roush, W. R.; Mariaty, K. J.; Brown, B. B. *Tetrahedron Lett.* **1990**, *31*, 6509. (f) Molander, G. A.; Yokoyama, Y. *J. Org. Chem.* **2006**, *71*, 2493. Using organotin: (g) Shen, W.; Wang, L. *J. Org. Chem.* **1999**, *64*, 8873. (h) Uenishi, J.; Kawahama, R.; Yonemitsu, O.; Tsuji, J. *J. Org. Chem.* **1998**, *63*, 8965.

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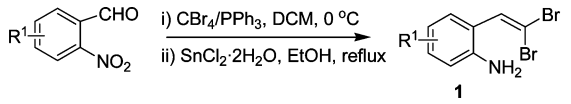
(20) (a) Vetelino, M. G.; Coe, J. W. *Tetrahedron Lett.* **1994**, *35*, 219. (b) Meshram, H. M.; Ganesh, Y. S. S.; Madhavi, A. V.; Eshwaraiah, B.; Yadav, J. S.; Gunasekar, D. *Synth. Commun.* **2003**, *33*, 2497. (c) Makosza, M.; Owczarczyk, Z. *J. Org. Chem.* **1989**, *54*, 5094.

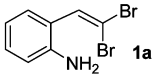
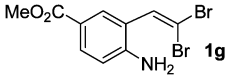
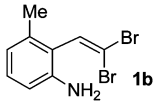
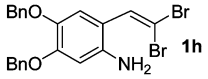
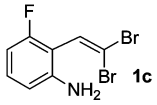
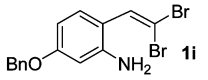
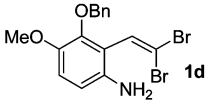
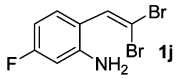
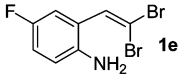
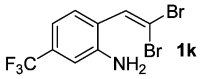
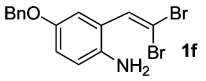
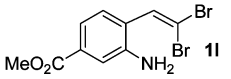
(21) Crich, D.; Rumthao, S. *Tetrahedron* **2004**, *60*, 1513.

(22) (a) Baumeister, P.; Blaser, H.-U.; Studer, M. *Catal. Lett.* **1997**, *49*, 219. (b) Strem catalogue (2004−2006) number: 78−1512.

TABLE 1. A One-Pot Two-Step Procedure for the Synthesis *o-gem*-Dibromovinylanilines

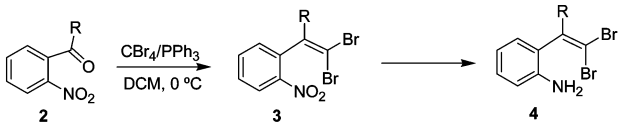


1

entry	Product	yield (%)[a]	entry	Product	yield (%)[a]
1	 **1a**	88	7	 **1g**	88
2	 **1b**	69	8	 **1h**	41
3	 **1c**	81	9	 **1i**	82
4	 **1d**	72	10	 **1j**	80
5	 **1e**	76[b]	11	 **1k**	78
6	 **1f**	76	12	 **1l**	63

[a] Isolated yield. [b] Two step procedure first step yield 95%, second steps 80% in CF_3CH_2OH.

SCHEME 5. Preparation of Substrates from Ketone



2 **3** **4**

	R	yield of **3**	yield of **4**: H_2, 1%Pt-C[V]	yield of **4**: $SnCl_2·2H_2O$
a	$-CF_3$	88%	82%	89%
b		54%	89%	0%

***gem*-Dihaloolefins from Ketones.**

The synthesis of *gem*-dibromoaniline substrates needed for 3-substituted indoles can be achieved using the CBr_4/PPh_3 method with activated ketones such as trifluoromethyl **2a** or alkynyl **2b** ketones. Reduction of the nitro group for the non-sensitive CF_3 substrate **3a** gave comparable yields using $SnCl_2·2H_2O$ or 1% Pt/ C[V]-catalyzed hydrogenation (Scheme 5). However, reduction of the alkynyl substrate **3b** using $SnCl_2·2H_2O$ resulted in no formation of the desired product **3b**, while the Pt−C[V] catalyst showed excellent selectivity for the nitro group, leaving the double bond, triple bond, and halogens intact.

Benzophenones showed no reactivity under the Ramirez olefination conditions, so an alternative route to obtain the *gem*-dibromoalkene **9** was through a Wittig olefination followed by sequential bromination/dehydrobromination/bromination (Scheme 6).[23] Comparison of different reduction methods showed that hydrogenation, using the Pt−C[V] catalyst, was again superior.

gem-Dichlorovinylaniline substrates were synthesized using the CCl_2PPh_3 ylide according to a modified literature procedure, in which freshly prepared *t*-BuOK was replaced by a *t*-BuOH·*t*-BuOK adduct to eliminate the use of hazardous potassium metal (Scheme 7). The *t*-BuOH·*t*-BuOK adduct can be prepared by simply heating commercially available *t*-BuOK in anhydrous *t*-BuOH for 30 min before removal of excess *t*-BuOH under vacuum. This complex was stable at −20 °C for long periods of time without significant reduction of the yield. To ensure complete conversion of the reaction and to significantly increase the yield, an excess of the ylide (1.5−2.0 equiv) was used instead of the stoichiometric amount reported in the original procedure.[24] One of the biggest advantages of using this method is that the protocol works extremely well for relatively nonactivated ketones such as **11b**, for which the CBr_4/PPh_3 protocol was ineffective.

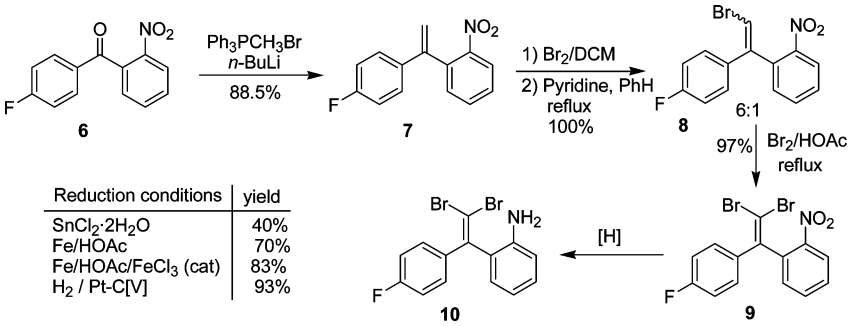
Optimization of the Tandem C−N/Suzuki Reaction. Initially, we chose to optimize the tandem C−N/Suzuki coupling reaction using acetamide **14** and $PhB(OH)_2$ since Pd-catalyzed amidation takes place under milder conditions than amination. The latter usually requires the use of strong base such as *t*-BuOK, which would likely result in E2-elimination of the *gem*-dihaloolefins.

After an exhaustive screening process of each reaction parameter, we were able to obtain *N*-acetylindole product **15a** in 72% isolated yield (Scheme 8) using the conditions described in Table 2. During the course of our studies, a report appeared outlining a very similar reaction to a 2-phosphinyl and 2-arylindoles. In analogy with our studies, Bisseret found that with a ligand such as dppf an acyl group was required to provide *N*-acetyl-2-methoxyphenylindole in 52% yield; otherwise no product was isolated.[10b] Unfortunately, the reaction was very

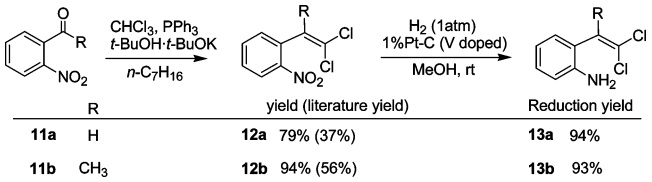
(23) Kobrich, G.: Trapp, H.; Akhtar, A. *Chem. Ber.* **1968**, *101*, 264.

(24) Olah, G. A.; Yamada, Y. *J. Org. Chem.* **1975**, *40*, 1107.

SCHEME 6. Preparation of Substrate 10



SCHEME 7. Preparation of *gem*-Dichlorovinyl Substrates



R		yield (literature yield)	Reduction yield
11a	H	**12a** 79% (37%)	**13a** 94%
11b	CH_3	**12b** 94% (56%)	**13b** 93%

SCHEME 8. Tandem Cross-Coupling of *N*-Acyl Substrate 14

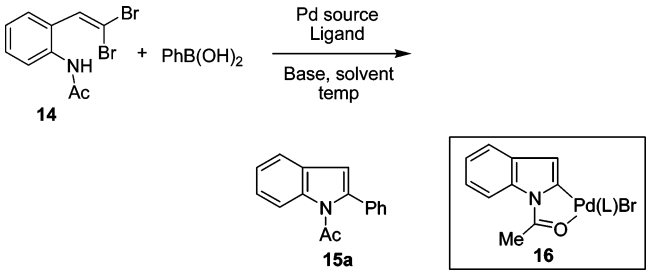
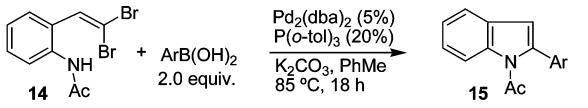
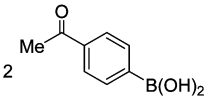
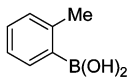


TABLE 2. Scope of *N*-Acetyl Indole Synthesis via a Tandem Amidation/Suzuki Reaction



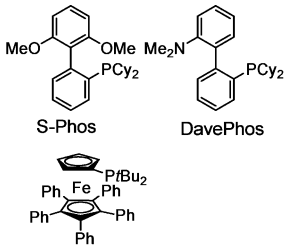
entry	$ArB(OH)_2$	product	yield [a]
1	$PhB(OH)_2$	**15a**	72
2		**15b**	23
3		**15c**	17

[a] Isolated yield.

limited in scope. The use of either sterically hindered or electron poor arylboronic acids produced the corresponding 2-arylated products in low yield (Table 2, entries 2 and 3). We speculated that formation of intermediate **16**, where coordination of Pd to the carbonyl group slows down transmetallation of the boronic acid to the palladium, takes place and limits catalyst turnover.

We then examined other substrates lacking an *N*-acetyl group to avoid coordination and isolated the tandem coupling product 2-phenylindole **17a**, albeit in slightly poorer yield (58%) (Scheme 9). Fortunately, the tandem coupling of **1a** with the sterically hindered *o*-tolyl boronic acid worked just as well as the phenylboronic acid. Encouraged by these results, we explored the effect of ligand and base with free aniline substrates.

TABLE 3. Ligand Screening for the Tandem Reaction between 1a and $PhB(OH)_2$



entry	ligand	yield (%)[a,b]	entry	ligand	yield (%)[a,b]
1	P(*o*-tol)$_3$	63	6	P(*t*-Bu)$_3$	47
2	PPh_3	55	7	S-Phos	80
3	P(*p*-CF_3Ph)$_3$	51	8	DavePhos	72
4	P(*p*-MeOPh)$_3$	67	9	Q-Phos	29
5	dppf	34			

[a] Yield was measured by CG using *n*-dodecane as internal standard. [b] $Pd_2(dba)_3$ (2.5%), ligand (10%), and K_3PO_4 (5 equiv.) at 90 °C in PhMe.

It was found that while K_3PO_4 was slightly more effective than K_2CO_3, the phosphine ligand has a more profound effect. In general, bidentate phosphine ligands such as dppf were less efficient, presumably since partial dissociation of the ligand is necessary for key step(s) of the tandem sequence (Table 3). Recent studies showed that P(*t*-Bu)$_3$ or Q-Phos[25] display very diverse utility in C−N and C−C coupling. However, in our case they did not give acceptable results. Fortunately, Buchwald's biphenylphosphine family of ligands showed the best reactivity and yields, especially the recently developed S-Phos ligand for Suzuki coupling reactions.[26]

Further optimization studies showed that $Pd(OAc)_2$ was more effective than $Pd_2(dba)_3$, and $K_3PO_4 \cdot H_2O$ was slightly better than K_3PO_4. In both cases, finely powdered base is important for complete conversion, and a reaction temperature of 90−100 °C is optimal. Under the optimized conditions, the desired product **1a** was obtained in 84% isolated yield using 1% $Pd(OAc)_2$ and 2% S-Phos.

Scope of the Tandem Coupling Reaction. We evaluated a variety of boronic acids (Table 4) under the optimal conditions.

SCHEME 9. Initial Results of Tandem Cross-Couplings Using Free Amine Substrate 1a

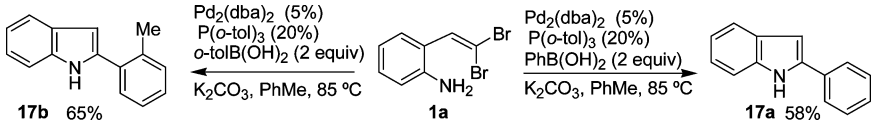
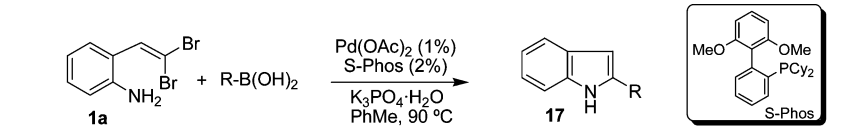
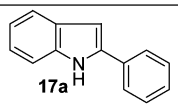
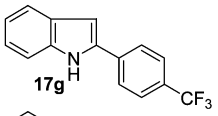
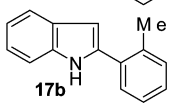
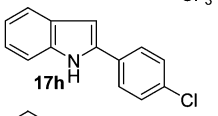
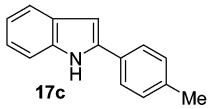
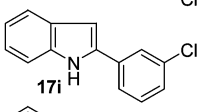
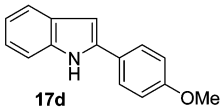
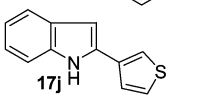
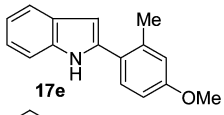
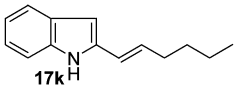
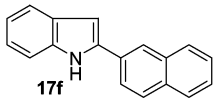
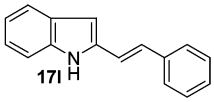


TABLE 4. Scope of the Tandem Coupling Reaction with Different Boronic Acids



entry	product	yield (%)[a]	entry	product	yield (%)[a]
1	 **17a**	84%	7	 **17g**	75%
2	 **17b**	82%	8	 **17h**	57%
3	 **17c**	88%	9	 **17i**	60%
4	 **17d**	83%	10	 **17j**	86%
5	 **17e**	79%	11	 **17k**	80%
6	 **17f**	82%	12	 **17l**	68%

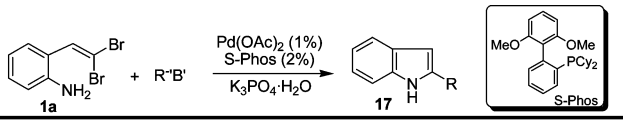
[a] Isolated yield.

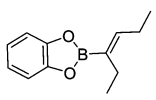
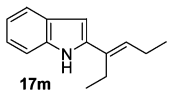
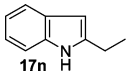
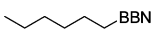
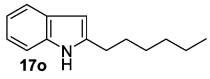
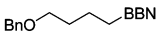
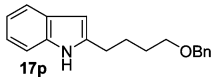
Arylboronic acids of different electronic and steric properties were tolerated and generally afforded very good yields (Table 4, entries 2−7) Significantly lower yields were obtained when chlorophenylboronic acids (Table 4, entries 8 and 9) were used, presumably due to a competing additional Suzuki coupling of the aryl chloride to generate undesired biphenyl byproducts under the highly reactive catalyst system. Use of a heteroarylboronic acid such as 3-thienylboronic acid (Table 4, entry 10) was also effective. As well, extension to alkenylboronic acids (Table 4, entries 11 and 12) was successful, giving the desired 2-alkenylindole in good yield.

Alkenyl boronate esters derived from hydroboration of a disubstituted alkyne can also be used to afford a trisubstituted alkene **17m** in good yield (Table 5, entry 1). One of the merits of the Suzuki−Miyaura coupling reaction is its ability to couple both sp^2 and sp^3 carbons.[27] Therefore, we decided to examine commercially available trialkylboron or functionalized alkyl 9-BBN reagents (prepared *in situ* by premixing a terminal alkyne and 9-BBN overnight in THF at 20 °C). Coupling under mild reaction conditions (60 °C in THF) gave the desired 2-alkylindoles in good yield (Table 5, entries 2−4).

The ability to incorporate a range of functional groups is essential for a general and practical indole synthesis. Therefore, substituted *ortho-gem*-dibromovinylanilines **1** were evaluated with phenylboronic acid under the optimal reaction conditions.

TABLE 5. Scope of the Tandem Coupling Reaction Varying Organoboron Reagents

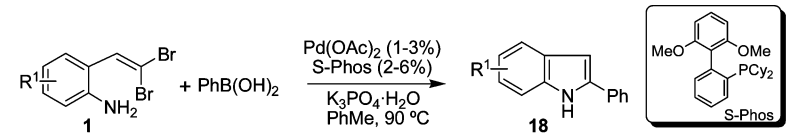


entry	R-'B'	product	yield (%)[a]
1		 **17m**	73%[b]
2		 **17n**	77%[c]
3		 **17o**	79%[c]
4		 **17p**	77%[c]

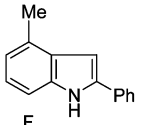
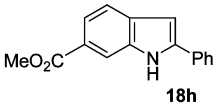
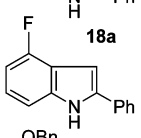
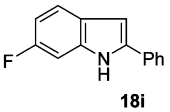
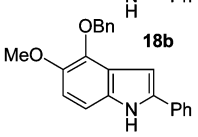
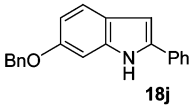
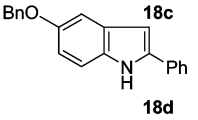
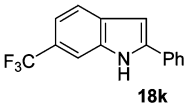
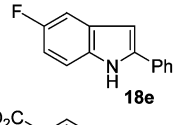
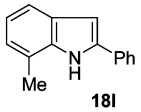
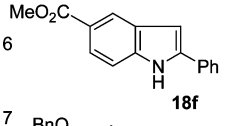
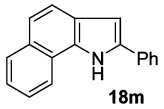
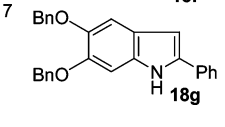
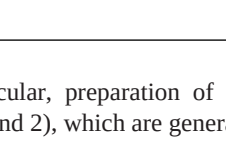
[a] Isolated yield. [b] In PhMe at 90 °C. [c] In THF at 60 °C.

Substitution at each of the 4−7 positions of the indole was examined with functional groups of varying electronic properties. The method proved to be very general and efficient (Table

TABLE 6. Scope of the Tandem Coupling Reaction Varying Aniline Substitution



1 18

entry	product	yield (%)[a]	entry	product	yield (%)[a]
1	 **18a**	77%	8	 **18h**	90%
2		88%	9	 **18i**	80%
3	 **18b**	72%	10	 **18j**	72%
4	 **18c**	86%	11	 **18k**	90%
5	 **18d**	87%	12	 **18l**	89%
6	 **18e**	87%	13	 **18m**	77%
7	 **18f**	57%			
	 **18g**				

[a] Isolated yield.

6, entries 1−13). In particular, preparation of 4-substituted indoles (Table 6, entries 1 and 2), which are generally regarded as challenging targets by traditional Fischer indole methods, were prepared from their corresponding anilines in good yield. The compatibility with a broad spectrum of electron-withdrawing and electron-donating functionalities, presumably due to the distance from the reaction site, provides access to a large number of indole derivatives.

We also sought to extend our method toward the preparation of synthetically important 2,3-disubstituted indoles.[28] Using the standard conditions, various 3-alkyl, aryl, or alkynyl substituted indoles (Table 7, entries 1−3) could be obtained from the corresponding dihalovinyl substrates in good to excellent yields. This method provides the first reliable stereoselective functionalization of tetrasubstituted *gem*-dibromoolefin systems. In particular, we note that use of *ortho-gem-di*chlorovinylanilines (Table 7, entries 4 and 5) gave nearly quantitative yields of the desired indole, suggesting that Pd(0)-oxidative addition into the C−Cl bond is more selective than into the corresponding C−Br bond.

N-Substituted Indoles *via* Sequential Orthogonal Coupling. Since a variety of N-substituted indoles tend to be biologically active, we decided to explore the scope of the tandem coupling reaction with substituents on the aniline nitrogen. Alkylation of the aniline substrate using benzyl bromide gave the desired *N*-benzyl substrate **20a** in good yield. Another convenient and mild method to alkylate the NH_2 group is by reductive amination. For example, the *N*-isopropyl group in substrate **20b** can be introduced using 2-methoxypropene and $NaBH(OAc)_3$ in the presence of HOAc.[29] The third method of preparing an N-substituted substrate was through a S_NAr reaction of 4-nitrofluorobenzene **22**, which can be easily prepared from the corresponding ketone **21** (Scheme 11).

We also explored an orthogonal approach to synthesize 1,2-disubstituted or 1,2,3-trisubstituted indoles since these compounds generally exhibit a broad range of applications in pharmaceuticals (COX-II inhibitors,[30] estrogen agonists and

(25) Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553.

(26) (a) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871. (b) Barder, T. E.; Buchwald, S. L. *Org. Lett.* **2004**, *6*, 2649. (c) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685. (d) Billingsley, K. L.; Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 3484.

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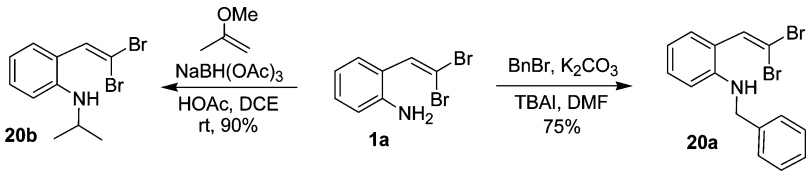
(28) (a) Hu, W.; Guo, Z.; Chu, F.; Bai, A.; Yi, X.; Cheng, G.; Li, J. *Bioorg. Med. Chem.* **2003**, *11*, 1153. (b) Guo, Z.; Cheng, G.; Chu; F. (P. R. China). U.S. Pat. Appl. Publ. US 2004058977; *Chem. Abstr.* **2004**, *140*, 270734. (c) Liu, Y.; Gribble, G. W. *Tetrahedron Lett.* **2000**, *41*, 8717.

(29) Reddy, T. J.; Leclair, M.; Proulx, M. *Synlett* **2005**, 583.

(30) Gungor, T.; Teulon, J.-M. (Laboratoires UPSA, Fr.), WO 9,805,-639, 1998; *Chem. Abstr.* **1998**, *128*, 180330.

SCHEME 10. Preparation of *N*-Alkyl Substrates Using S_N2 Reactions



SCHEME 11. Preparation of *N*-Alkyl Substrate 23 Using an S_NAr Reaction

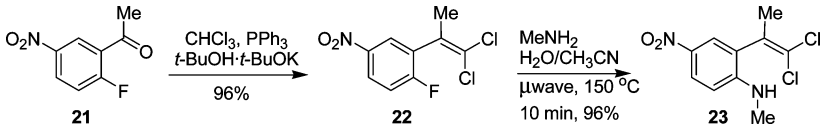
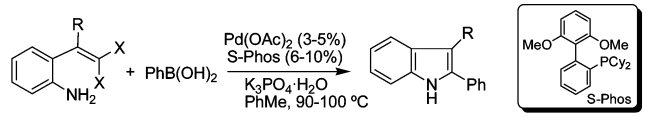
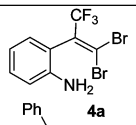
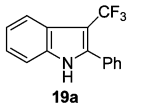
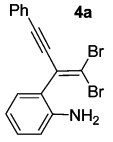
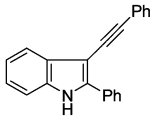
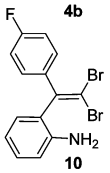
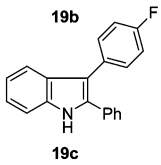
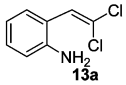
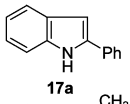
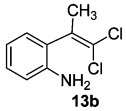
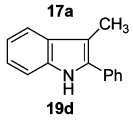


TABLE 7. Scope of the Tandem Coupling Reaction



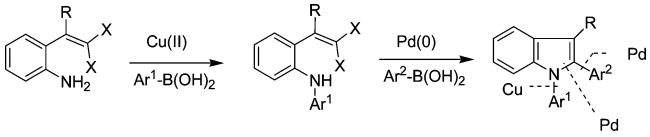
entry	substrate	product	yield (%)[a]
1	 **4a**	 **19a**	79%
2	 **4b**	 **19b**	77%
3	 **10**	 **19c**	90%
4	 **13a**	 **17a**	95%
5	 **13b**	 **19d**	96%

[a] Isolated yield.

antagonists[31]) and materials (electroluminescence[32]). In order to introduce an aryl group on the nitrogen, we attempted to use an orthogonal approach to perform an oxidative C−N coupling using an aryl boronic acid under Cu(II)-catalysis pioneered by Lam and co-workers.[33] This would result in an interesting metal-controlled sequential coupling, potentially useful for the synthesis of 1,2-diarylindole libraries (Scheme 12).

Applying the conditions developed by Batey [$Cu(OAc)_2 \cdot H_2O$ (20 mol %), 4 Å MS, CH_2Cl_2, 40 °C, O_2),[34] N-arylated product

SCHEME 12. Sequential Arylations for 1,2-Diarylindole Preparation



was obtained in low yields, which we speculated was due to lack of catalyst turnover of Cu(II). Under Buchwald's conditions [$Cu(OAc)_2$ (20%), myristic acid (40%), 2,6-lutidine (1 equiv), PhMe, rt], a TON of 2 was obtained,[35] presumably because our aniline substrates are significantly more hindered than those examined by Buchwald and Batey. Considering the low cost of the copper (II) complex, a stoichiometic amount was used, and the temperature was also raised to 40−60 °C. Under these more forcing conditions, nearly complete conversion of the aniline was observed. The major byproduct of the reaction is the parasitic C−O coupling between either the boronic acid and acetate or the boronic acid and myristic acid.

The optimal Cu(II)-mediated coupling conditions were applied to bromo substrate **1a** as well as the chloro substrate **13b**. Both halides were equally effective, tolerating a wide range of aryl boronic acids with various electronic and steric properties (Table 8). This route also provides convenient access to a large number of N-arylated substrates **24** and **25**.

Both the *N*-benzyl, *N*- and N-arylated *gem*-dibromoanilines were subjected to the tandem coupling reaction, and in all cases gave very good to excellent yields of the *N*-arylindoles (Table 9). The N-arylated *gem*-dichloro substrates **25** were similarly subjected to the tandem coupling reaction conditions, also affording the 1,2,3-trisubstituted indole products in good to excellent yields (Table 10). We were particularly pleased to observe that highly hindered indoles such **27d** and **27e** were obtained in very good yields. Our approach allows for the facile and rapid generation of a diverse library using a limited number of reagents by simply switching the addition sequence of the boronic acids in the reactions.

Mechanism of the Tandem Coupling. An important question in the tandem coupling is to determine if the Suzuki (Path I) or a Buchwald−Hartwig coupling (B−H) (Path II) is faster or if they have similar rates (Scheme 13). It was not possible to observe any intermediates during the reaction using analytical methods such as GC-MS. In addition, no reaction was observed in the absence of boronic acid. Therefore, we turned to indirect ways to explore the mechanism.

(31) (a) Von Angerer, E.; Strohmeier, J. *J. Med. Chem.* **1987**, *30*, 131. (b) Von Angerer, E.; Biberger, C.; Schneider, M. (Schering A.-G., Germany), WO 9,603,375, 1996; *Chem. Abstr.* **1996**, *125*, 33474.

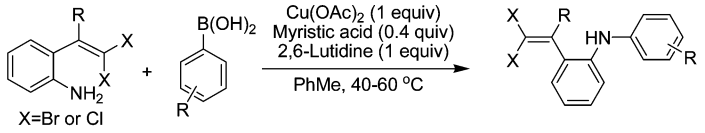
(32) Lin, T.-s. (Lightronik Technology Inc., Taiwan), US 6,790,539, 2004; *Chem. Abstr.* **2004**, *140*, 136161.

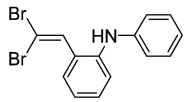
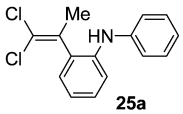
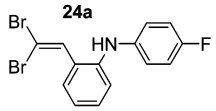
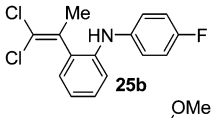
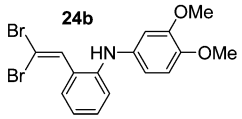
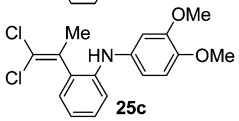
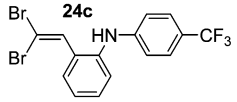
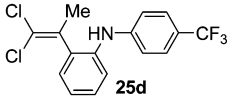
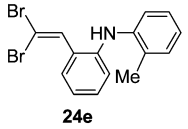
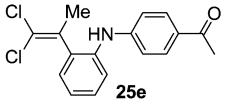
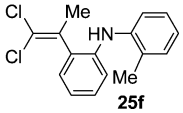
(33) Chan, D. M. T.; Lam, P. Y. S. In *Boronic Acids*; Hall, D. G., Eds.; Wiley-VCH: Weinheim, 2005; p 205.

(34) Quach, T. D.; Batey, R. A. *Org. Lett.* **2003**, *5*, 4397.

(35) Antilla, J. C.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 2077.

TABLE 8. Scope of Cu-mediated Oxidative Coupling of Aniline Substrates and Arylboronic Acids



entry	product	yield (%)[a]	entry	product	yield (%)[a]
1	 **24a**	89%	7	 **25a**	98%
2	 **24b**	69%	8	 **25b**	65%
3	 **24c**	56%	9	 **25c**	88%
4	 **24d**	84%	10	 **25d**	69%
5	 **24e**	69%	11	 **25e**	70%
			12	 **25f**	70%

[a] Isolated yield.

We began by preparing intermediates **28** and **29**, which could be on the reaction pathway based on the two mechanisms. The vinyl bromide **28** was prepared using a stereoselective Suzuki coupling of **30** with $PhB(OH)_2$, followed by reduction of the nitro group with $SnCl_2 \cdot 2H_2O$ (Scheme 14). 2-Bromoindole (**29**) was prepared using a known ortho-lithiation protocol starting from indole.[36]

Subjecting intermediate **28** to the reaction conditions in the presence of 1 equiv of $PhB(OH)_2$ gave a mixture of the intramolecular C−N coupling product **17a** and an intermolecular Suzuki product **31** (Scheme 15). Only 1 equiv of $PhB(OH)_2$ was selected in order to reflect the amount of boronic acid that would typically be present at partial conversion in the usual catalytic reaction. The double Suzuki product **31** has never been observed as a byproduct of the tandem coupling reaction even when 2 equiv of boronic acid was used, which suggests that **28** is not a likely intermediate under the reaction conditions.

On the other hand, the Suzuki coupling between 2-bromoindole (**29**) and $PhB(OH)_2$ (1.5 equiv) proceeded quantitatively using $Pd(OAc)_2$ and S-Phos (Scheme 16), which is in accord with Path II.

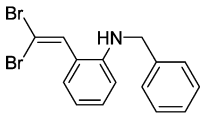
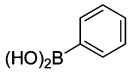
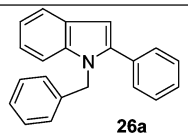
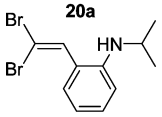
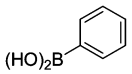
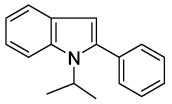
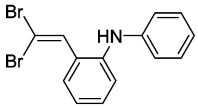
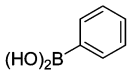
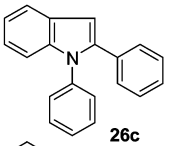
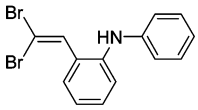
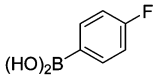
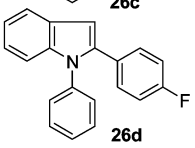
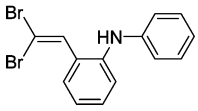
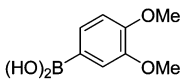
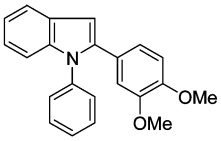
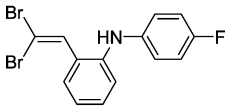
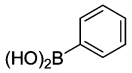
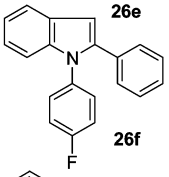
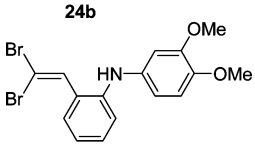
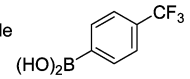
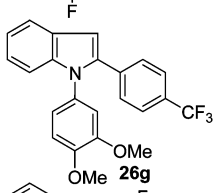
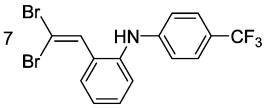
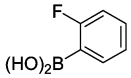
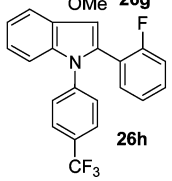
These studies indicate that the C−N bond formation could be the first coupling step, but it is important to note that many steps precede the coupling. If the C−N bond formation is indeed faster than the Suzuki coupling, it implies that the first palladium oxidative addition occurs on the (*Z*)-C−Br bond, which is in contrast to previous cross coupling reactions with *gem*-dibromoalkenes. It is possible that prior coordination to the aniline nitrogen is important in directing the oxidative addition. Another mechanistic possibility is dehydrobromination of the dibromoalkene to form a bromoalkyne. To probe this question, we prepared a deuterated analogue (**34**) of **1a** (Scheme 17) from methyl 2-nitrobenzoate (**32**). The deuterium incorporation at the vinyl position of **34** is over 98% since there is no detectable signal in the ^1H NMR spectrum.

Subjecting the deuterium labeled *ortho-gem*-dibromovinylaniline (**34**) under the standard reaction conditions gave the expected indole product with 16% deuterium leaching at C-3 (Scheme 18). Likewise, the ND_2-substrate **35**, which is obtained from **1a** by deuterium exchange with D_2O gave the product with some deuterium incorporation at C-3 (19%) in the presence of $K_3PO_4 \cdot D_2O$. A control experiment that showed no deuterium exchange at C-3 in 2-phenylindole was seen under the reaction conditions. These phenomena are not explicable by invoking a direct Buchwald−Hartwig C−N reaction and imply a second process may complete with C−N coupling. However, it seems highly unlikely that a direct dehydrobromination is the major pathway since the percentage of deuterium loss is minimal (Scheme 19, Path I).

We believe the dominant process is a direct Buchwald-Hartwig C−N coupling (Scheme 19, Path I) accompanied by a

(36) Bergman, J.; Venemalm, L. *J. Org. Chem.* **1992**, *57*, 2495.

TABLE 9. Scope of 1,2-Disubstituted Indoles.

entry	substrate	$ArB(OH)_2$	product	yield[a]
1	 **20a**		 **26a**	82%
2	 **20b**		 **26b**	71%
2	 **24a**		 **26c**	92%
3	 **24a**		 **26d**	86%
4	 **24a**		 **26e**	60%
5	 **24b**		 **26f**	90%
6	 **24c**		 **26g**	81%
7	 **24d**		 **26h**	82%

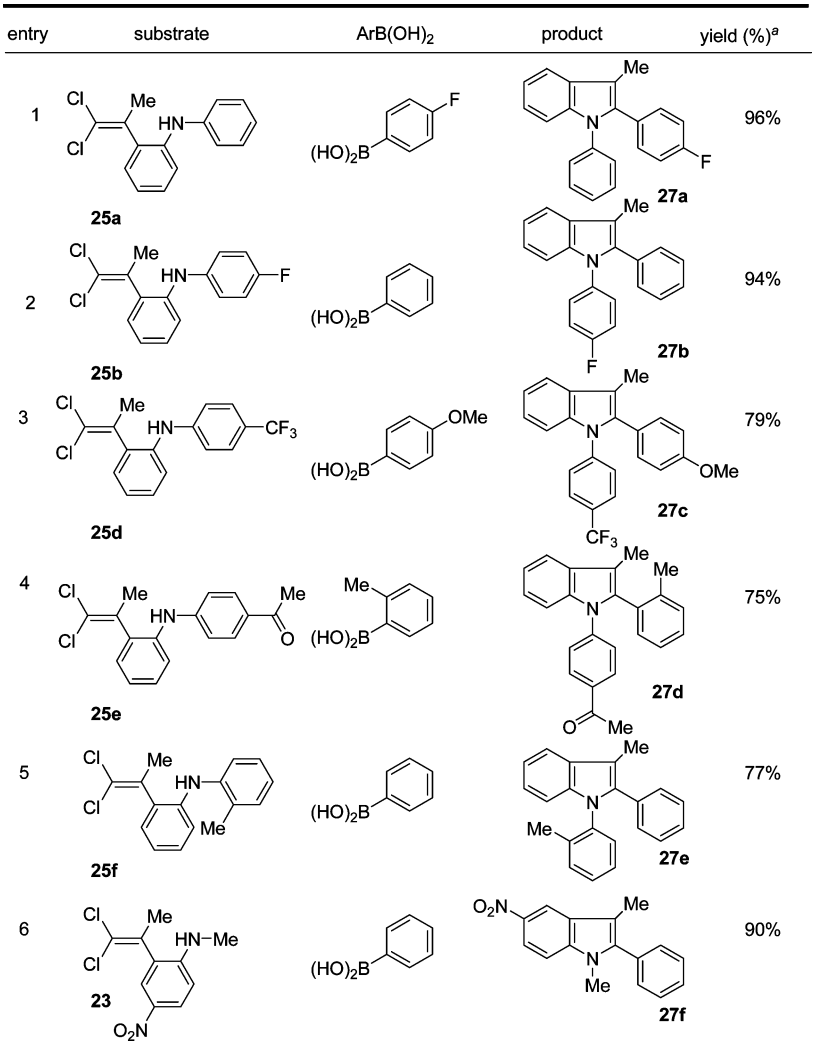
[a] Isolated yield.

minor pathway involving an alkyne intermediate (Path II). For the latter pathway, Pd(0) begins the catalytic cycle by undergoing oxidative addition into the *trans*-C−Br bond, which is well precedented (Scheme 19, Path II). Instead of a Suzuki coupling, the vinylpalladium intermediate **37** undergoes a β-hydride elimination to give the bromoalkyne intermediate **38** complexed to DPd(II)Br.[8g] A Pd(II)-mediated 5-*endo-dig* cyclization then gives the 2-bromoindole **38**, which subsequently undergoes Suzuki coupling with the phenylboronic acid. Proton exchange of DPd(II)Br with a proton source such as the boronic acid or the amine may be responsible for the observed deuterium leaching.[37] The observation that 2,3-disubstituted indoles can be formed in high yield from the tetrasubstituted *gem*-dibromoolefin substrates such as **10** (Table 7, entry 3) is evidence that the direct Buchwald-Hartwig coupling pathway is efficient and β-elimination is not a necessary event en route to the final indole product. The level of leaching in **34** and **35** suggests direct coupling is a very facile process.

In summary, we have developed a highly efficient method of indole synthesis using *gem*-dihalovinylaniline substrates and an organoboron reagent via a Pd-catalyzed tandem intramolecular amination and intermolecular Suzuki coupling. The indole synthesis methodology we developed using *gem*-dihalovinyl substrates is compatible with a variety of aryl, alkenyl, and alkyl boron reagents, making it a versatile, modular approach. The tolerance for a variety of substitution patterns on the indole has been very thoroughly examined at positions 2−7, providing products that are difficult to make by existing

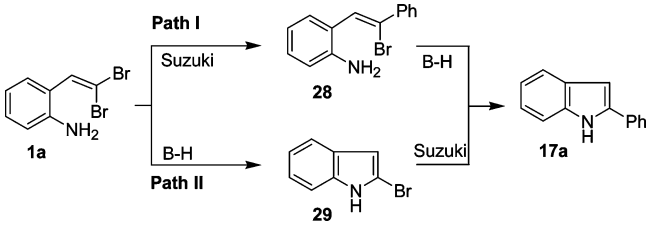
(37) (a) Kudo, K.; Hidai, M.; Murayama, T.; Uchida, Y. *J. Chem. Soc., Chem. Commun.* **1970**, 1701−1702. (b) Leoni, P.; Sommovigo, M.; Pasquali, M.; Midollini, S.; Braga, D.; Sabatino, P. *Organometallics* **1991**, *10*, 1038.

TABLE 10. Scope of 1,2,3-Trisubstituted Indoles

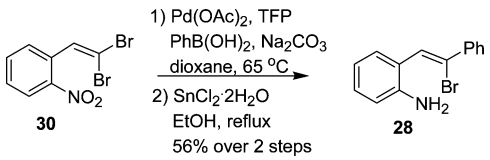


[a] Isolated yield.

SCHEME 13. Possible Mechanistic Pathways for the Tandem Cross-Couplings



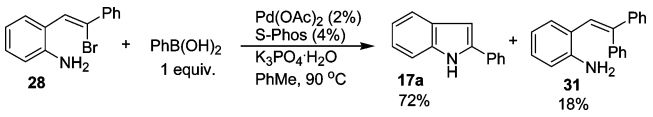
SCHEME 14. Preparation of the Proposed Intermediate 28



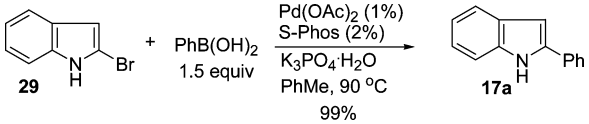
methods. The orthogonal approach of the sequential copper- and palladium-mediated synthesis of 1,2-diarylindoles exploited the wide availability of diverse organoboron reagents.

The mechanistic studies conducted show that two different pathways are likely in operation. One is via an initial alkynyl formation which then undergoes a 5-*endo-dig* cyclization to generate the C−N bond followed by Suzuki coupling. The other pathway is a direct Buchwald-Hartwig amination followed by a Suzuki coupling.

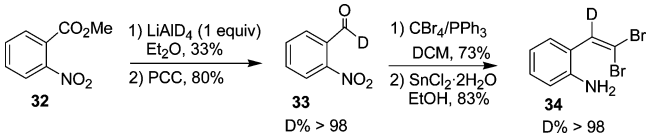
SCHEME 15. Intramolecular C−N Coupling of 28 in the Presence of PhB(OH)2



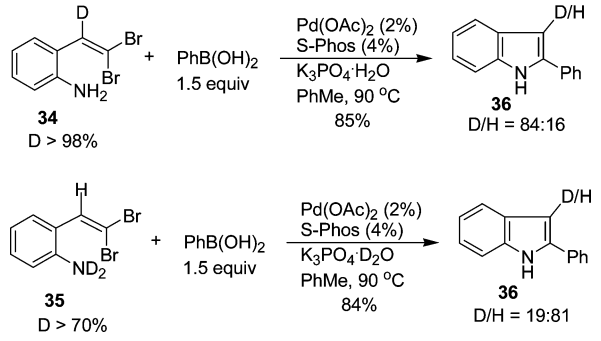
SCHEME 16. Suzuki Coupling of 29 with PhB(OH)2



SCHEME 17. Preparation of Deuterated Substrate 34



SCHEME 18. Deuterium Labeling Studies



Experimental Section

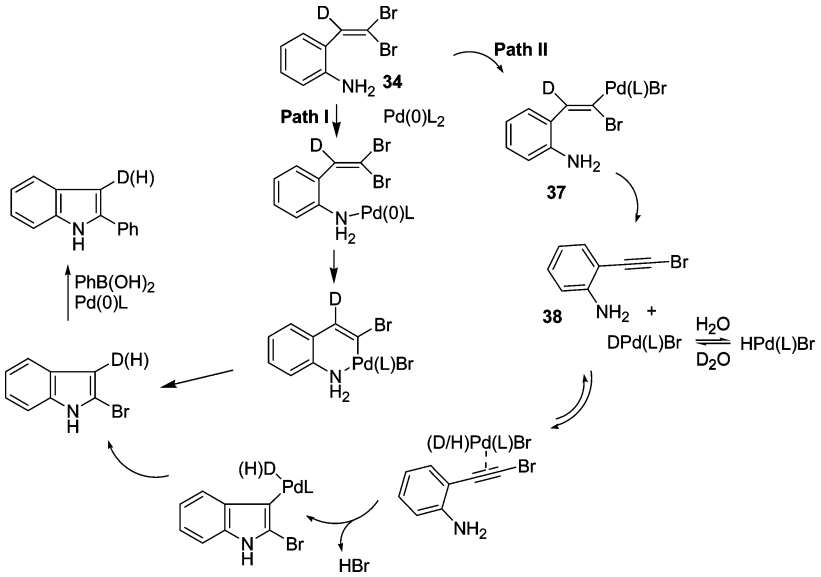
2-Phenyl-1*H*-indole (17a). General Procedure A for the Pd-Catalyzed Tandem Coupling. A 10-mL round-bottomed flask was charged with **1a** (0.277 g, 1 mmol), $PhB(OH)_2$ (0.183 g, 1.5 mmol), and powdered $K_3PO_4 \cdot H_2O$ (1.15 g, 5 mmol), and the mixture was purged with argon for at least 10 min. A separate 10-mL round-bottomed flask was charged with $Pd(OAc)_2$ (2.3 mg, 1 mol %) and S-Phos (8.2 mg, 2 mol %) and purged with argon for at least 10 min. Toluene (5 mL) was added to the catalyst flask, and the mixture was stirred at rt for 3 min. The homogeneous catalyst solution was then cannulated to the reactant flask, and the heterogeneous mixture was stirred at rt for 2 min and heated to 90 °C. After heating at 90 °C for 6 h, the mixture was cooled to rt and diluted with Et_2O (15 mL). After aqueous workup, the mixture was purified by flash chromatography (10% EtOAc in hexanes) to afford **17a** as a white crystalline solid (0.163 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (1H, br), 7.65−7.61 (3H, m), 7.43 (2H, t, J = 7.8 Hz), 7.38 (1H, d, J = 8.0 Hz), 7.31 (1H, t, J = 7.8 Hz), 7.19 (1H, td, J^t = 7.4 Hz, J^d = 1.2 Hz), 7.12 (1H, td, J^d = 6.8 Hz, J^d = 1.2 Hz), 6.82 (1H, d, J = 1.3 Hz).

2-Hex-1-enyl-1*H*-indole (17k). General procedure A for the Pd-catalyzed tandem coupling was followed. A mixture of **1a** (0.139 g, 0.5 mmol), *trans*-1-hexenylboronic acid (0.128 g, 1 mmol), $K_3PO_4 \cdot H_2O$ (0.58 g, 2.5 mmol), and a catalyst solution ($Pd(OAc)_2$ (2.3 mg, 2 mol %) and S-Phos (8.2 mg, 4 mol %) in PhMe (2.5 mL)) was heated at 90 °C for 5 h. After an aqueous workup, the crude material was purified by flash chromatography (5% EtOAc in hexanes) to afford **17k** as a white crystalline solid (0.080 g, 80%). R_f = 0.23 (5% EtOAc/hexanes). mp 70−72 °C (hexanes). IR (neat, cm^{-1}): 3420, 3382, 2925, 2867, 1453, 1413, 1342, 1293, 1233. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (1H, br), 7.53 (1H, d, J = 7.9 Hz), 7.27 (1H, d, J = 8.1 Hz), 7.13 (1H, ddd, J = 7.6. 7.6, 1.1 Hz), 7.06 (1H, ddd, J = 7.4. 7.4, 0.9 Hz), 6.39 (1H, d, J = 14.3 Hz), 6.38 (1H, s), 6.03 (1H, ddd, J = 16.1, 7.0, 7.0 Hz), 2.23 (2H, dddd, J = 7.2, 7.2, 7.2, 1.1 Hz), 1.50−1.33 (4H, m), 0.93 (3H, t, J = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 136.6, 130.5, 129.2, 122.3, 120.9, 120.5, 120.1, 110.6, 101.5, 32.9, 31.6, 22.5, 14.2. HRMS (EI) calcd for $C_{14}H_{17}N$ ([M]$^+$) 199.1361. Found: 199.1365.

2-(4-Benzyloxybutyl)-1*H*-indole (17p). General Procedure B for the Pd-Catalyzed Tandem Coupling. To a flame-dried round-bottomed flask under N_2 was added 9-BBN solution (0.5 M, 1.65 mL, 0.825 mmol), followed by dropwise addition of but-3-enyloxymethylbenzene (0.122 g, 0.75 mmol). The mixture was stirred at rt overnight (12 h). A separate round-bottomed flask was charged with **1a** (0.139 g, 0.50 mmol), $K_3PO_4 \cdot H_2O$ (0.58 g, 2.5 mmol), $Pd_2(dba)_3$ (4.6 mg, 2 mol % Pd), and S-Phos (10.3 mg, 5 mol %). After the mixture was purged with N_2 for over 10 min, the alkyl 9-BBN solution was cannulated into the flask, followed by addition of H_2O (10 μL). The reaction mixture was stirred at 60 °C for 4 h. The mixture was then cooled to −20 °C, to which H_2O_2 (30%, 0.5 mL) was added. The mixture was slowly warmed to rt and stirred for another 30 min. After a usual aqueous workup, the product was purified by flash chromatography (10% EtOAc in hexanes) to afford **17p** as white crystalline product (0.108 g, 77%). R_f = 0.20 (15% EtOAc/hexanes). mp 48−50 °C. IR (neat, cm^{-1}): 3394, 2935, 2864, 1550, 1494, 1455, 1412, 1367, 1284, 1122. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (1H, br), 7.51 (1H, d, J = 7.7 Hz), 7.34−7.25 (5H, m), 7.23 (1H, d, J = 7.4 Hz), 7.12−7.02 (2H, m), 6.22 (1H, s), 4.51 (2H, s), 3.53 (2H, t, J = 5.9 Hz), 2.77 (2H, t, J = 7.1 Hz), 1.87−1.80 (2H, m), 1.79−1.71 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.8, 138.6, 136.0, 129.0, 128.6, 127.9, 127.9, 121.1, 119.9, 119.7, 110.5, 99.7, 73.3, 70.4, 29.3, 28.0, 26.5. Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.60; H, 7.74; N, 5.11.

4-Fluoro-2-phenyl-1*H*-indole (18b). General procedure A for the Pd-catalyzed tandem coupling was followed. A mixture of 2-(2,2-dibromovinyl)-3-fluoro-phenylamine (0.152 g, 0.515 mmol), $PhB(OH)_2$ (0.092 g, 0.75 mmol), $K_3PO_4 \cdot H_2O$ (0.58 g, 2.5 mmol), and a catalyst solution ($Pd(OAc)_2$ (1.2 mg, 1 mol %) and S-Phos (4.2 mg, 2 mol %) in PhMe (2.5 mL)) was heated at 90 °C for 14 h. After an aqueous workup, the crude material was purified by flash chromatography (7.5% EtOAc in hexanes) to afford a white crystalline solid (0.096 g, 88%). R_f = 0.14 (7.5% EtOAc/hexanes). mp 65−67 °C. IR (neat, cm^{-1}): 3453, 1583, 1487, 1453, 1404,

SCHEME 19. Proposed Mechanistic Pathways for the Tandem C−N/C−C Cross-couplings



1358, 1340, 1226, 1066. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (1H, br), 7.65−7.61 (2H, m), 7.46−7.40 (2H, m), 7.33 (1H, dddd, J = 7.3, 7.3, 1.2, 1.2 Hz), 7.16 (1H, dd, J = 8.2, 0.9 Hz), 7.09 (1H, ddd, J = 7.9, 7.9, 4.9 Hz), 6.88 (1H, dd, J = 2.5, 0.8 Hz), 6.79 (1H, ddd, J = 10.3, 7.7, 1.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.5 (J_{C-F} = 247 Hz), 139.4 (J_{C-F} = 11.2 Hz), 138.1, 132.0, 129.3, 128.3, 125.4, 122.9 (J_{C-F} = 7.4 Hz), 118.6 (J_{C-F} = 22.3 Hz), 107.2 (J_{C-F} = 3.7 Hz), 105.2 (J_{C-F} = 18.9 Hz), 96.0 (J_{C-F} = 0.6 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ −122.1. Anal. Calcd for $C_{14}H_{10}NF$: C, 79.60; H, 4.77; N, 6.63. Found: C, 79.37; H, 5.13; N, 6.63.

3-(4-Fluorophenyl)-2-phenyl-1*H*-indole (19c). General procedure A for the Pd-catalyzed tandem coupling was followed. A mixture of 2-[2,2-dibromo-1-(4-fluorophenyl)vinyl]-phenylamine (0.125 g, 0.337 mmol), $PhB(OH)_2$ (0.062 g, 0.505 mmol), $K_3PO_4 \cdot H_2O$ (0.35 g, 1.5 mmol), and a catalyst solution ($Pd(OAc)_2$ (2.2 mg, 3 mol %) and S-Phos (8.8 mg, 6 mol %) in PhMe (1.5 mL)) was heated at 100 °C for 2 h. After an aqueous workup, the crude material was purified by flash chromatography (10% EtOAc in hexanes) to afford an off-white crystalline solid (0.087 g, 90%). R_f = 0.21 (10% EtOAc in hexanes). mp 143−145 °C. IR (neat, cm^{-1}): 3411, 3055, 1601, 1553, 1510, 1452, 1327, 1221. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (1H, br), 7.62 (1H, d, J = 7.9 Hz), 7.42−7.29 (8H, m), 7.24 (1H, t, J = 7.3 Hz), 7.15 (1H, t, J = 7.5 Hz), 7.06 (2H, t, J = 8.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8 (J_{CF} = 245 Hz), 136.0, 134.4, 132.7, 131.8 (J_{C-F} = 8.4 Hz), 131.2 (J_{C-F} = 3.1 Hz), 129.0, 128.9, 128.3, 128.0, 123.0, 120.7, 119.7, 115.7 (J_{C-F} = 21.5 Hz), 114.2, 111.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ −116.4. HRMS (EI) calcd for $C_{20}H_{14}NF$ ([M]$^+$) 287.1110. Found: 287.1113.

[2-(2,2-Dibromovinyl)phenyl]phenylamine (24a). General procedure for $Cu(OAc)_2$-mediated coupling: A tube (24 × 150 mm) of Carousel reaction station was charged with **1a** (0.277 g, 1 mmol), $PhB(OH)_2$ (0.244 g, 2 mmol), $Cu(OAc)_2$ (0.182 g, 1 mmol), myristic acid (0.092 g, 0.4 mmol), 2,6-lutidine (125 μL, 1.07 mmol), and toluene (3 mL). The mixture was stirred at 40 °C under an O_2 atmosphere for 21 h. The mixture was diluted with Et_2O (10 mL) and Et_3N (1.5 mL), stirred at rt for 15 min, filtered through a short silica gel column, and eluted with a copious amount of Et_2O (∼30 mL). The crude material was further purified by flash chromatography (2.5% EtOAc in hexanes) to afford the desired product as a solid (0.3134 g, 89%). R_f = 0.28 (5% EtOAc in hexanes). mp 75−77 °C. IR (neat, cm^{-1}): 3407, 3035, 1597, 1577, 1506, 1455, 1311, 1214. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (1H, d, J = 7.7 Hz), 7.39 (1H, s), 7.30−7.23 (4H, m), 7.03−6.94 (4H, 4 m), 5.47 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0, 141.0, 134.3, 129.9, 129.7, 129.6, 126.4, 121.8, 121.4, 118.7, 118.2, 93.1. HRMS (EI) calcd for $C_{14}H_{11}NBr_2$ ([M]$^+$) 350.9258. Found: 350.9253.

[2-(2,2-Dichloro-1-methylvinyl)phenyl]phenylamine (25a). The general procedure for $Cu(OAc)_2$-mediated coupling was followed using **13b** (0.105 g, 0.52 mmol), phenylboronic acid (0.122 g, 1 mmol), $Cu(OAc)_2$ (0.091 g, 0.5 mmol), myristic acid (0.046 g, 0.2 mmol), and 2,6-lutidine (62.5 μL, 0.54 mmol) in toluene (1.5 mL). The mixture was stirred at 40 °C for 6.5 h under an O_2 atmosphere. The crude material was further purified by flash chromatography (2.5% EtOAc in hexanes) to afford the desired product as an oil (0.1415 g, 98%). R_f = 0.20 (2.5% EtOAc in hexanes). IR (neat, cm^{-1}): 3411, 3046, 1593, 1505, 1451, 1308. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.25 (3H, m), 7.21 (1H, ddd, J = 7.6, 7.6, 1.7 Hz), 7.10 (1H, dd, J = 7.6, 1.6), 7.07−7.04 (2H, m), 6.98−6.93 (2H, m), 5.45 (1H, s), 2.14 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2, 139.9, 134.2, 130.2, 129.6, 129.1, 129.0, 121.7, 121.4, 118.9, 118.8, 118.0, 22.2. HRMS (EI) calcd for $C_{15}H_{13}NCl_2$ ([M]$^+$) 277.0425. Found: 277.0426.

2-(4-Fluorophenyl)-1-phenyl-1*H*-indole (26d). General procedure A for the Pd-catalyzed tandem coupling was followed. A mixture of [2-(2,2-dibromovinyl)-phenyl]-phenylamine (0.109 g, 0.31 mmol), 4-$FPhB(OH)_2$ (0.065 g, 0.45 mmol), $K_3PO_4 \cdot H_2O$ (0.35 g, 1.5 mmol), and a catalyst solution ($Pd(OAc)_2$ (2.2 mg, 3 mol %) and S-Phos (8.1 mg, 6 mol %) in PhMe (1.5 mL)) was heated at 100 °C for 2 h. After an aqueous workup, the crude material was purified by flash chromatography (2% EtOAc in hexanes) to afford a white solid (0.076 g, 86%). R_f = 0.25 (2.5% EtOAc in hexanes). mp 121−122 °C (Lit: 123−124 °C).[38] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69−7.65 (1H, m), 7.25−7.16 (10H, m), 7.09 (2H, t, J = 8.5 Hz), 6.79 (1H, s). ^{19}F NMR (376 MHz, $CDCl_3$) δ −114.2.

1-(4-Fluorophenyl)-3-methyl-2-phenyl-1*H*-indole (27b). General procedure A for the Pd-catalyzed tandem coupling was followed. A mixture of [2-(2,2-dichloro-1-methylvinyl)-phenyl]-(4-fluorophenyl)-amine (0.088 g, 0.297 mmol), $PhB(OH)_2$ (0.055 g, 0.45 mmol), $K_3PO_4 \cdot H_2O$ (0.35 g, 1.5 mmol), and a catalyst solution ($Pd(OAc)_2$ (2.2 mg, 3 mol %) and S-Phos (8.1 mg, 6 mol %) in PhMe (1.5 mL)) was heated at 100 °C for 1 h. After an aqueous workup, the crude material was purified by flash chromatography (2.5% EtOAc in hexanes) to afford a white solid (0.0838 g, 94%). R_f = 0.28 (2.5% EtOAc in hexanes). mp 108−110 °C. IR (neat, cm^{-1}): 3053, 2916, 1603, 1510, 1457, 1364, 1217. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68−7.64 (1H, m), 7.31−7.18 (8H, m), 7.15−7.11 (2H, m), 7.02 (2H, t, J = 7.5 Hz), 2.40 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3 (J_{C-F} = 246 Hz), 137.9, 137.2, 134.9 (J_{C-F} = 3.2 Hz), 132.1, 130.8, 129.6 (J_{C-F} = 8.3 Hz), 129.2, 128.3, 127.5, 122.8, 120.4, 119.2, 116.2 (J_{C-F} = 22.7 Hz), 111.0, 110.3, 9.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ −115.0. HRMS (EI) calcd for $C_{21}H_{16}NF$ ([M]$^+$) 301.1267. Found: 301.1260. Anal. Calcd for $C_{21}H_{16}NF$: C, 83.70; H, 5.35; N, 4.65. Found: C, 83.91; H, 5.26; N, 4.64.

2-(4-Fluorophenyl)-3-methyl-1-phenyl-1*H*-indole (27a). General Procedure C for the Pd-Catalyzed Tandem Reaction. A 5-mL round-bottomed flask was charged with [2-(2,2-dichloro-1-methylvinyl)-phenyl]-phenylamine (0.056 g, 0.2 mmol), 4-$FPhB(OH)_2$ (0.042 g, 0.30 mmol), and a powdered mixture of $K_3PO_4 \cdot H_2O$/KOH (mol/mol = 1:2, 0.072 g, 0.6 mmol), and the mixture was purged with argon for at least 10 min. To a separate 5-mL round-bottomed flask was charged with $Pd(OAc)_2$ (1.34 mg, 3 mol %) and S-Phos (3.3 mg, 6 mol %) and purged with argon for at least 10 min. Toluene (1 mL) was added to the catalyst flask, and the mixture was stirred at rt for 3 min. The homogeneous catalyst solution was then cannulated to the reactant flask, and the heterogeneous mixture was stirred at rt for 2 min. After heating at 100 °C for 1 h, the mixture was cooled to rt and diluted with Et_2O (5 mL). After an aqueous workup, the crude material was purified by flash chromatography (2.5% EtOAc in hexanes) to afford a white crystalline solid (0.058 g, 96%). R_f = 0.22 (2.5% EtOAc in hexanes). mp 154−155 °C. IR (neat, cm^{-1}): 3053, 1995, 1499, 1452, 1362, 1217. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66−7.64 (1H, m), 7.35−7.26 (4H, m), 7.23−7.13 (6H, m), 6.96 (2H, ddd, J = 7.7, 7.7, 2.0 Hz), 2.38 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1 (J_{C-F} = 248 Hz), 138.7, 137.8, 136.1, 132.4 (J_{C-F} = 7.7 Hz), 129.3, 129.1, 128.4 (J_{C-F} = 3.1 Hz), 128.1, 127.0, 122.8, 120.4, 119.1, 115.3 (J_{C-F} = 21.5 Hz), 110.9, 110.5, 9.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ −114.4. HRMS (EI) calcd for $C_{21}H_{16}NF$ ([M]$^+$) 301.1267. Found: 301.1257.

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Supporting Information Available: Experimental procedure and characterization data for rest of substrates and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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