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Modular Synthesis of Indoles from Imines and *o*-Dihaloarenes or *o*-Chlorosulfonates by a Pd-Catalyzed Cascade Process

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Abstract: A detailed study of the scope of a new Pd-catalyzed synthesis of indoles from 1,2-dihaloarenes and *o*-halobenzene sulfonates and imines is described. The cascade reaction comprises an imine α-arylation followed by an intramolecular C−N bond-forming reaction promoted by the same Pd catalyst. The reaction with 1,2-dibromobenzene shows wide scope and allows the introduction of aryl, alkyl, and vinyl substituents at different positions of the five-membered ring of the indole. The regioselective synthesis of indoles substituted in the six-membered ring can be carried out by employing *o*-dihalobenzene derivatives with two different halogens, taking advantage of the different reactivities of I, Br, and Cl in oxidative addition reactions. This paper also introduces a method for the efficient cleavage of the *N*-*t*-butyl group, thus allowing for the preparation of N−H indoles through the same methodology. Finally, the reaction with *o*-halosulfonates has been studied. The best substrates are *o*-chlorononaflates, which lead to indoles in very high yield. The reaction is particularly appropriate for the synthesis of the challenging 6-substituted indoles. In view of the availability of *o*-chlorophenols, which are direct precursors of the chlorononaflates, this reaction represents an efficient entry into indoles substituted in the six-membered ring. The concept is illustrated by the preparation of a 4,6-disubstituted indole from naturally occurring anethole.

Introduction

The indole structure is probably the heterocyclic nucleus that concentrates the most interest because of its presence in a plethora of natural products and molecules with biological activity.[1] Although nowadays there are a large number of methodologies for the synthesis and structural modification of the indole scaffold,[2] the development of alternative approaches that may allow for the straightforward preparation of structurally diverse indoles is a field of constant interest.[3]

In recent years, methodologies for the synthesis of indoles based on transition-metal-catalyzed reactions, and in particular on Pd-catalyzed processes, have gained great interest.[4] Of particular appeal are the methods in which the five-membered ring is formed through Pd-catalyzed cascade processes. These approaches enable the synthesis of indoles with diverse substitution in the five-membered ring and therefore may find wide application in drug discovery programs. Figure 1 schematically presents some of these methodologies, including (a) reaction of *o*-haloanilines with internal alkynes,[5] (b) cyclization of *o*-alkynylanilines by aminopalladation/reductive elimination,[6] (c) C−N/C−N bond-forming reactions of *o*-halo-*β*-sulfonylstyrenes with primary amines,[7] (d) C−N/Suzuki and C−N/Heck sequences of *o*-amino-*gem*-dihalostyrenes,[8] and (e) C−N/Heck sequences with *o*-haloanilines.[9]

In the context of our interest in Pd-catalyzed C−C and C−N bond-forming reactions, we have recently described a novel approach to the indole skeleton through a Pd-catalyzed C−C/

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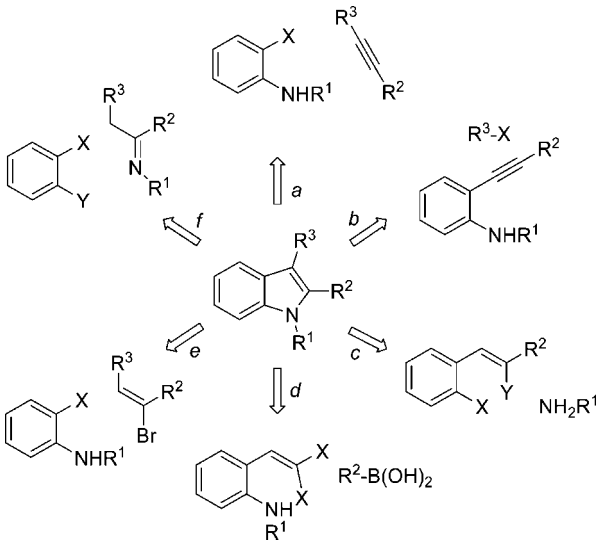
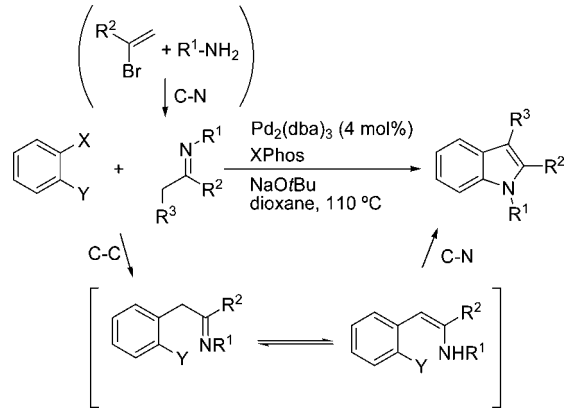
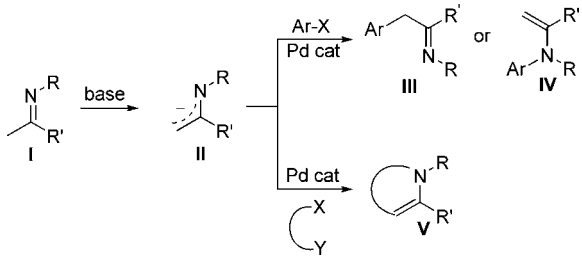


Figure 1. Main strategies for the synthesis of indoles through Pd-catalyzed cascade processes.

Scheme 1. Synthesis of Indoles by Pd-Catalyzed C−C/C−N and C−N/C−C/C−N Sequences

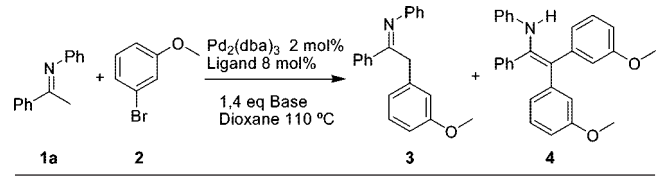


Scheme 2. Possible Pathways for Pd-Catalyzed Arylation of Azaallylic Anions



C−N cascade from 1,2-dihaloarenes and imines that involves an imine α-arylation followed by an intramolecular C−N bond-forming reaction (Scheme 1).[10] This strategy [method (f) in Figure 1] represents an alternative disconnection in the synthesis

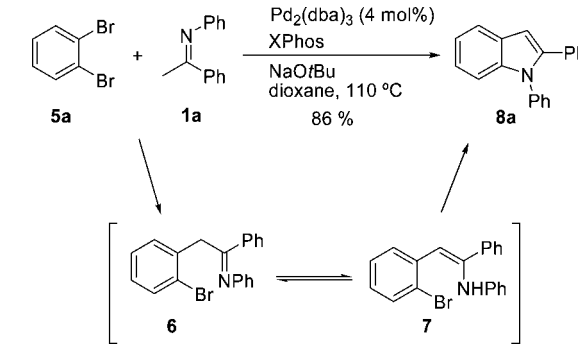
Table 1. Pd-Catalyzed Arylation of Imine **1a** under Different Reaction Conditions[a]



entry	ligand	base	*t* (h)	conversion (%)[b]	**3**/**4** ratio[c]
1	XPhos	NaOtBu	14	100	0:100
2	XPhos	Cs_2CO_3	4	≪100	70:30
3	XPhos	Cs_2CO_3	14	100	30:70
4	XPhos	LDA	14	100	75:25
5	XPhos	LHMDS	20	–	–
6	XPhos	K_3PO_4	14	100	30:70
7	Binap	Cs_2CO_3	14	–	–
8	S-phos	Cs_2CO_3	14	–	–
9	Johnphos	Cs_2CO_3	14	–	–
10	Davephos	Cs_2CO_3	14	100	75:25
11	Xantphos	Cs_2CO_3	14	100	71:29
12	(*o*-Tolyl)$_3$P	Cs_2CO_3	14	–	–
13[d]	XPhos	Cs_2CO_3	6	<100	15:85
14[d]	XPhos	Cs_2CO_3	14	100	0:100(78%)[e]

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), base (0.7 mmol), $Pd_2(dba)_3$ (2 mol %), ligand (4 mol %), dioxane (1 mL), 110 °C. [b] Conversion determined by GC and referred to the disappearance of **2**. [c] Ratio in the reaction crude, as determined by ^{1}H NMR. [d] Carried out with 2 equiv of **2** and 2.4 equiv of Cs_2CO_3. [e] Isolated yield after column chromatography.

Scheme 3. Indolization Reaction from Imine **1** and Dibromobenzene **5**



of the five-membered ring of indoles.[11] Moreover, a three component C−N/C−C/C−N cascade can be implemented starting from alkenyl halides, amines, and dihaloarenes (Scheme 1). It is noteworthy that in both types of reactions, the same Pd catalyst promotes each individual C−C or C−N bond-forming reaction.

A particular strength of this indole synthesis is the modularity, since the indole skeleton is built from three readily available fragments: the 1,2-dihaloarene and the amine and ketone or alkenyl halide that are employed to prepare the imine. Therefore, it might be possible to prepare a wide variety of indoles employing this methodology.

For this reason, and encouraged by our preliminary results,[10] we carried out a comprehensive study of the scope of this novel approach to the synthesis of the indole core. The results presented herein indicate that this methodology is truly reliable and very general. Notably, we have been able to expand the

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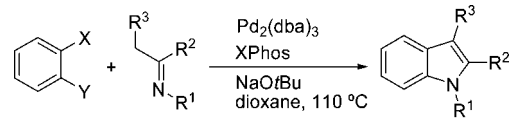
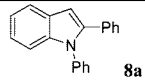
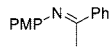
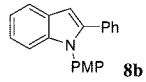
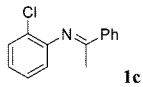
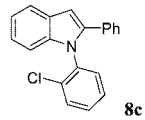
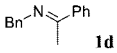
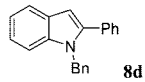
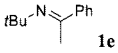
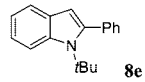
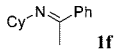
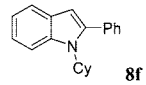
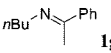
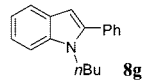
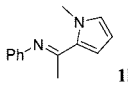
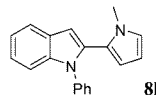
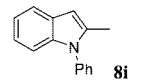
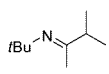
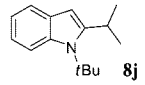
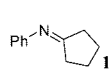
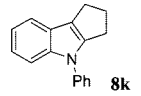
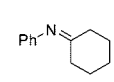
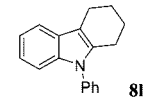
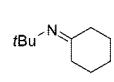
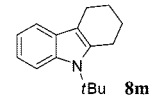
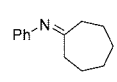
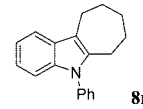
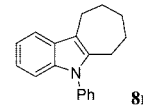
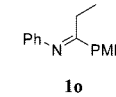
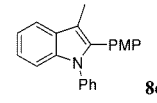
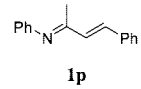
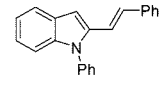
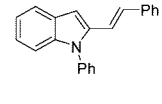
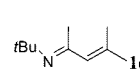
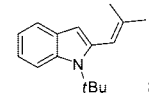
Table 2. Synthesis of Indoles from 1,2-Dihalobenzenes **5** and Structurally Diverse Imines[a]



5 **1** **8**

Entry	Dihaloarene **5**	Imine **1**	Indole **8**	Yield[b] %
1	 **5a**	 **1a**	 **8a**	86
2	 **5b**	**1a**	**8a**	80
3[c]	**5a**	 **1b**	 **8b**	80[c]
4	**5a**	 **1c**	 **8c**	77
5	**5a**	 **1d**	 **8d**	56
6	**5a**	 **1e**	 **8e**	72
7	**5a**	 **1f**	 **8f**	80
8	**5a**	 **1g**	 **8g**	52
9	**5a**	 **1h**	 **8h**	82
10	**5a**	 **1i**	 **8i**	77
11	**5b**	 **1j**	 **8j**	55
12	**5a**	 **1k**	 **8k**	86
13	**5a**	 **1l**	 **8l**	66
14	**5a**	 **1m**	 **8m**	50
15	**5a**	 **1n**	 **8n**	80
16	 **5c**	**1n**	 **8n**	87
17[c]	**5a**	 **1o**	 **8o**	66
18	**5a**	 **1p**	 **8p**	83
19	**5b**	**1p**	 **8p**	75
20	**5a**	 **1q**	 **8q**	78
21	**5a**	**1r**	**8r**	63
22	**5d**	**1p**	**8u**	71
23	**5a**	**1a**	**8a**	83[d]

[a] Reaction conditions: **1** (1 mmol), **5** (1 mmol), [$Pd_2(dba)_3$] (2 mol %), XPhos (4 mol %), NaOtBu (2.8 mmol), dioxane (2 mL), 110 °C, 14 h. Reaction times were not optimized. [b] Isolated yield after column chromatography. [c] PMP = *p*-methoxyphenyl. [d] Reaction was carried out on a 30 mmol scale.

reaction to encompass *o*-chlorosulfonates, which are readily available from phenols, widening the applicability of the reaction. Thus, we present in this paper a very general and highly convergent synthesis of substituted indoles that allows for the introduction of high structural diversity in almost every position of the indole skeleton.

Results and Discussion

Imine α-Arylation. At the outset of this project, we wanted to investigate the reactivity of the azaallylic anion in Pd-catalyzed arylation reactions. Although azaallyllic anions have been extensively studied in heterocyclic chemistry,[12] no example of their use in transition-metal-catalyzed reactions had previously been reported. Initially, two competitive pathways for the Pd-catalyzed arylation of imine **I** through the formation of anion **II** could be conceived (Scheme 2): (i) a C−C bond-forming

(12) Mangelinckx, S.; Giubellina, N.; De Kimpe, N. *Chem. Rev.* **2004**, *104*, 2353.

α-arylation[13] to give imine **III** and (ii) a C−N bond-forming arylation to yield enamine **IV**. Moreover, the ambidentate nucleophilic nature of the anion **II** might allow it to participate in two sequential events, enabling its use in the synthesis of heterocycles.

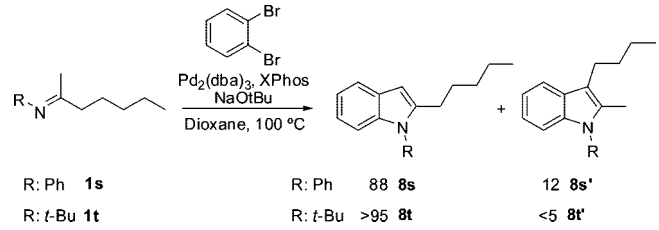
We chose as model system for our initial experiments the reaction of the imine **1a** with *m*-bromoanisole (**2**). This reaction was studied by employing an array of catalytic systems, bases, and reaction conditions. Selected examples are presented in Table 1. In most of the examples, the reaction afforded a mixture of the monoarylated imine **3** and the diarylated enamine **4** in a ratio that varied depending on the particular reaction conditions.[14] The most active ligand for this transformation turned out to be XPhos, which drove the reactions to complete conversion regardless of the base employed (entries 1−6). However, the use of an equimolar amount of imine **1a** and aryl halide **2** always led to a mixture of monoarylated imine **3** and diarylated enamine **4**. As expected, when the reaction was conducted with imine **1a** and halide **2** in a 1:2 ratio, the diarylated enamine **4** was isolated in very high yield. Davephos is also a competent ligand for this transformation. Interestingly, the reaction with Davephos showed higher selectivity toward the monoarylation, and employing equimolar amounts of reactants **1a** and **2** yielded a **3**/**4** ratio of 75:25. Nevertheless, we were not able to devise reaction conditions to exclusively achieve the monoarylation of the acetophenone imine **1**.

Synthesis of Indoles from 1,2-Dibromobenzene. At the present point of development, the α-arylation of imines appears to be a transformation of limited synthetic usefulness because of the difficulty in controlling the monoarylation when the reactions are conducted with equimolar amounts of reagents. However, we envisioned that the ability of imines to participate in such Pd-catalyzed C−C bond-forming reactions might be employed to design Pd-catalyzed cascades that can take advantage of the ambidentate nature of the azaallylic anion.

Therefore, we decided to investigate the reaction of 1,2-dibromobenzene **5a** with imine **1a**. We expected that after the initial C-arylation reaction to form **6**, an intramolecular C−N bond-forming reaction on the enamine tautomer **7** might occur, leading to the formation of an indole in a completely new approach (Scheme 3).

After some experimentation, we found that the cascade indolization could indeed be carried out by employing $Pd_2(dba)_3$ as the Pd source, XPhos as the supporting ligand, and NaO*t*Bu as the base in dioxane at 110 °C. The reaction is very demanding in terms of base and ligand. Under these reaction conditions, replacement of NaO*t*Bu by milder bases such as Cs_2CO_3 or K_3PO_4 did not lead to the formation of the indole. Similarly, substitution of XPhos by other ligands, even ones with similar electronic and steric requirements, such as Davephos, led to a dramatic drop in the conversion of the reaction.

Scheme 4. Influence of the Substituent at the Nitrogen in the Synthesis of 2-Alkylindoles



With a proper reaction protocol in hand, we carried out a study of the scope of the reaction with regard to the structure of the imine. A set of selected examples is presented in Table 2.

The results in Table 2 show that the indolization reaction can be accomplished with a variety of imines of different natures. Moreover, 1,2-dichlorobenzene can be employed as the dihalogenated system with results very similar to those for 1,2-dibromobenzene (entries 1, 2). By means of substitution at the nitrogen atom of the imine, this methodology allows for the very easy preparation of *N*-aryl- (entries 1−4) and *N*-alkyl-substituted (entries 5−8) indoles. Bulky substituents, such as ortho-substituted aromatics, can be introduced efficiently. The selectivity observed in the reaction of entry 4 is noteworthy, as the intermolecular α-arylation of the imine with 1,2-dibromobenzene is preferred over a possible intramolecular α-arylation by the *o*-chloroarene. In regard to the *N*-alkylindoles, the reaction can be effected with imines derived from primary (R^1 = Bn, Bu; entries 5, 8), secondary (R^1 = Cy, entry 7), and tertiary amines (R^1 = *t*-Bu, entry 6). Noteworthy is the ability to prepare *t*-Bu-substituted indoles, as very few methods allow for the synthesis of *N*-substituted indoles carrying sterically demanding substituents.[7b,15] Interestingly, better results in terms of yield and reaction time were generally obtained for indoles bearing secondary or tertiary substituents at the nitrogen than for the primary-alkyl-substituted ones.

The scope of the reaction with regard to the substituents at positions 2 and 3 of the indole was also examined. The use of imines derived from methyl ketones leads to 1,2-disubstituted indoles. For instance, indoles bearing aromatic and heteroaromatic substituents at the 2-position can be synthesized with very high yields (entries 1−9). Furthermore, the reaction with α,β-unsaturated imines gives rise to 2-vinylindoles (entries 18−22).

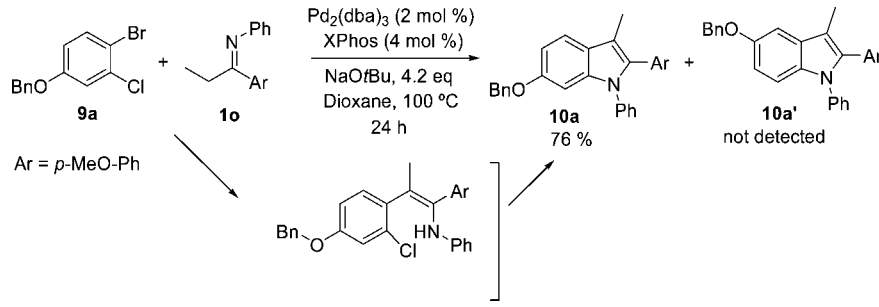
The preparation of 2-alkylindoles is also possible. For instance, the reaction with the imine derived from acetone provides a 2-methylindole (entry 10). Of note are the reactions of *n*-alkyl methyl ketones (Scheme 4). In this case, two regioisomeric indoles can be formed, depending on the regioselectivity of the initial C−C bond-forming reaction. The reaction of 1,2-dibromobenzene with the *N*-phenyl imine **1s** derived from 2-heptanone occurred with moderate regioselectivity, giving rise to a 7:1 mixture of regioisomeric indoles **8s** and **8s′**. Notably, when the same reaction was carried out with the *N*-*t*-butyl imine **1t**, total regioselectivity was achieved, leading exclusively to the 2-substituted indole **8t**. Clearly, the steric bulk of the *t*-butyl substituent drives the α-arylation of the imine to the less substituted position. This is an interesting result, since the Fischer indole synthesis, the most standard method for the preparation of indoles from ketones,[16] gives precisely the opposite regioisomer. Moreover, as will be

(13) For some leading references on the α-arylation of carbonyl compounds, see: (a) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1740. (b) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473. (c) Hamada, T.; Chieffi, A.; Åhman, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1261. (d) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 212. (e) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234. (f) Martín, R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 7236. (g) Vo, G. D.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2008**, *47*, 2127.

(14) A more detailed study on the arylation of imines, to provide an interesting synthetic methodology, will be published elsewere.

(15) Schirok, H. *Synthesis* **2008**, 1404.

Scheme 5. Regioselectivity of the Indolization Reaction



discussed later in this paper, the *t*-butyl group, which directs the regioselectivity of the indolization, can be easily cleaved to provide the corresponding N−H indoles.

Other types of 2,3-disubstituted indoles can be obtained by selection of proper imines. For instance, imine **1o** derived from a propiophenone leads to the 2-aryl-3-methyl-substituted indole **8o** (Table 2, entry 17). Moreover, the reaction can be carried out with imines **1k**−**n** derived from cyclic ketones, providing the corresponding tricyclic N-substituted derivatives **8k**−**n** (Table 2, entries 12−16).

It is worth noting that the indolization reaction can be performed on a multigram scale under similar reaction conditions. For instance, the reaction of **2a** with **1a** on a 30 mmol scale (Table 2, entry 23) provided 6.7 g of indole **5a** (83% isolated yield).

Regioselectivity of the Process: Regioselective Synthesis of Indoles Substituted on the Benzene Ring. The relative reactivities of different C−I, C−Br, and C−Cl bonds in oxidative addition processes is of great importance in Pd-catalyzed cascade or sequential reactions. The remarkable chemoselectivity allows one to perform a reaction on an aryl bromide or iodide in the presence of an aryl chloride, which can be employed in a subsequent coupling reaction. In our case, the I > Br > Cl reactivity trend can be employed in order to regioselectively synthesize indoles substituted on the benzene ring. The regioselectivity of the obtained indole corresponds to the system in which the initial C−C bond formation occurs in the position occupied by the more reactive halogen. A clear demonstration of this principle is shown in Scheme 5. The reaction of 1-bromo-2-chloro-4-benzyloxybenzene **9a** with imine **1o** leads exclusively to the 6-substituted indole **10a,** without formation of the regioisomeric 5-substituted indole **10a′**.

Therefore, the regioselectivity of the process is controlled by the first oxidative addition reaction, which occurs at the position occupied by the more reactive halogen. To date, we have not observed any exceptions to this general rule, as presented in Table 3. Thus, indoles carrying an alkyl, alkoxy, or fluoro substituent at either the 4-, 5-, or 6-position of the indole ring can be synthesized with total regioselectivity simply by choosing the appropriate starting dihaloarene. The examples presented in Table 3 show that the regioselective synthesis of indoles from bromochloroarenes and iodochloroarenes occurs with the same scope as the reaction with 1,2-dibromobenzene discussed previously.

Chloro-Substituted Indoles. The presence of a halogen in the benzene ring of the indole is particularly valuable, since it can be transformed into virtually any other substituent by applying cross-coupling techniques. We envisioned that our methodology might allow us to prepare indoles bearing a chlorine substituent at the challenging 4-position by choosing the appropriate dichloroiodo- or dichlorobromo-substituted arenes (Scheme 6).

Thus, we studied the reaction with the bromo and iodo derivatives **11** and **12**. No conversion was detected with 1-bromo-2,6-dichlorobenzene **11a** under the standard reaction conditions, giving rise to the recovery of the starting materials. Nevertheless, the reaction could be achieved successfully by employing 1,3-dichloro-2-iodobenzene **11b**, leading to the desired 4-chloro-substituted indoles **10l**−**n** (Scheme 6). Moreover, reaction with 1,2-dichloro-3-iodobenzene **12b** gave the desired 7-chloroindole **10o**, albeit in only moderate yield.

N−H Indoles. Our methodology does not allow the direct preparation of N−H indoles, since the required N−H imines are generally not stable compounds. Therefore, we decided to investigate protecting groups for N−H that could be introduced into the starting imine and removed after the formation of the indole. This task turned out to be nontrivial, since most of the classical protecting groups for indole N−H[17] are not easily incorporated into the imine or failed in the indolization reaction. For instance, under the reaction conditions studied, *N*-Tosyl and *N*-acyl imines did not undergo α-arylation and therefore did not produce the indoles. *N*-allyl imines produced the indole in very low yield, as a result of the partial isomerization of the allyl imine into the 2-azadiene under the basic reaction conditions. Finally, *N*-benzyl imines provided the indoles with acceptable yields, but the cleavage of benzyl groups on indoles is not always straightforward.

Next we considered using imines derived from *t*-butylamine. Although the *t*-butyl group is not considered a regular protecting group for indole N−H, we envisioned that the *N*-*t*-Bu deprotection might occur upon treatment with an appropriate acid.[18] As presented above, imines derived from *t*-butylamines are in fact optimum substrates for our indolization reaction, giving rise to the corresponding indoles in very high yields (Tables 2 and 3).

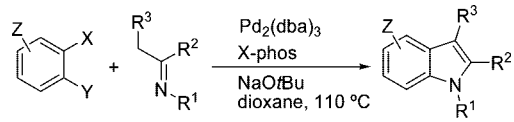
Cleavage of the *N*-*t*-Bu substituent was studied under different acidic reaction conditions. After some experimentation, we

(16) (a) For a review of the Fischer indole synthesis, see: Hughes, D. L. *Org. Prep. Proced. Int.* **1993**, *25*, 607. (b) Hutchins, S. M.; Chapman, K. T. *Tetrahedron Lett.* **1996**, *37*, 4869. (c) Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 6621–6622. (d) Rosenbaum, C.; Baumhof, P.; Mazitschek, R.; Müller, O.; Giannis, A.; Waldmann, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 224. (e) Mun, H.-S.; Ham, W.-H.; Jeong, J.-H. *J. Comb. Chem.* **2005**, *7*, 130.

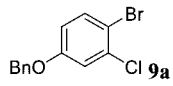
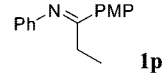
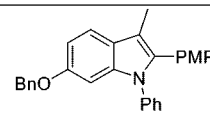
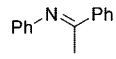
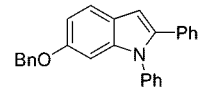
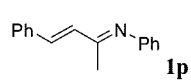
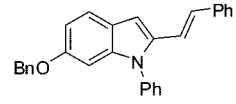
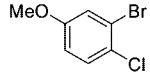
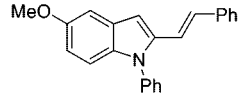
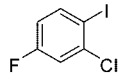
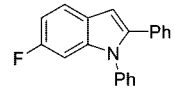
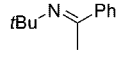
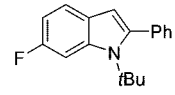
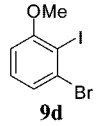
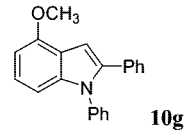
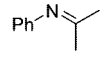
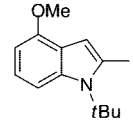
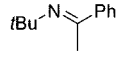
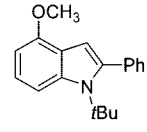
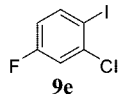
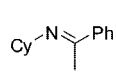
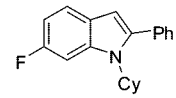
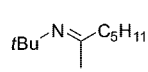
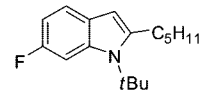
(17) Wuts, P. G. M.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis*, 4th ed.; Wiley-VCH: Weinheim, Germany, 2006.

(18) For previous examples of the cleavage of the *t*-Bu group in indole derivatives, see: (a) Jones, R. A.; Marriott, M. T. P.; Rosenthal, W. P.; Sepulveda Arques, J. *J. Org. Chem.* **1980**, *45*, 4515. (b) Barnerjee, R.; Basu, C.; Chene, P.; Roy, S. *J. Peptide Res.* **2002**, *60*, 88. (c) Bundy, G. L.; Banitt, L. S.; Dobrowolski, P. J.; Palmer, J. R.; Schwartz, T. M.; Zimmermann, D. C.; Lipton, M. F.; Mauragis, M. A.; Veley, M. F.; Appell, R. B.; Clouse, R. C.; Daugs, E. D. *Org. Process Res. Dev.* **2001**, *5*, 144.

Table 3. Regioselective Synthesis of Indoles from Asymmetrically Substituted *O*-Dihalobenzene Derivatives **9** and Imines **1**[a]



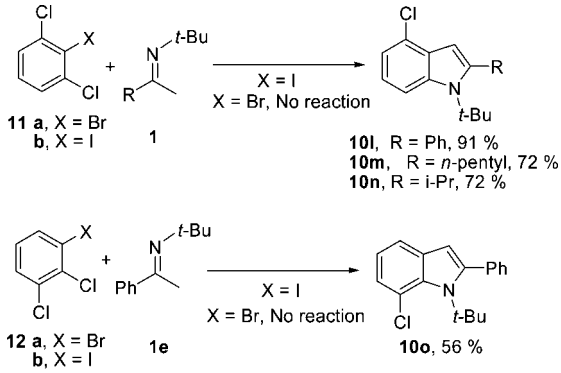
9 **1** **10**

Entry	Dihalogen **9**	Imine **1**	Indole **10**	Yield[b] %
1[c]	 **9a**	 **1p**	 **10a**	76
2	**9a**	 **1a**	 **10b**	57
3	**9a**	 **1p**	 **10c**	60
4	 **9b**	**1p**	 **10d**	74
5	 **9c**	**1a**	 **10e**	83
6	**9c**	 **1e**	 **10f**	83
7	 **9d**	**1a**	 **10g**	64
8	**9d**	 **1j**	 **10h**	45
9	**9d**	 **1e**	 **10i**	76
10	 **9e**	 **1f**	 **10j**	72
11	**9e**	 **1t**	 **10k**	60

[a] Reaction conditions: **1** (1 mmol), **9** (1 mmol), [$Pd_2(dba)_3$] (2 mol %), XPhos (4 mol %), NaOtBu (2.8 mmol), dioxane (2 mL), 110 °C, 14 h. Reaction times were not optimized. [b] Isolated yield after column chromatography. [c] PMP = *p*-methoxyphenyl.

found that 2,3-disubstituted indoles such as **8m** could be cleanly deprotected by treatment with TFA in refluxing CH_2Cl_2. On the other hand, 2-substituted indoles such as **8e**, which are prone to dimerize under acidic conditions, required more controlled conditions. Nevertheless, the deprotection step can be conducted by treatment with $AlCl_3$ in refluxing methylene chloride (Scheme

Scheme 6. Regioselective Synthesis of Chloroindoles from Dichloroiodobenzene Derivatives **11b** and **12b**[a]



[a] Reaction conditions: **1** (1 mmol), **9** (1 mmol), [$Pd_2(dba)_3$] (2 mol %), XPhos (4 mol %), NaOtBu (2.8 mmol), dioxane (2 mL), 110 °C, 14 h.

Scheme 7. Deprotection of *t*-Butylindoles under Thermal Conditions

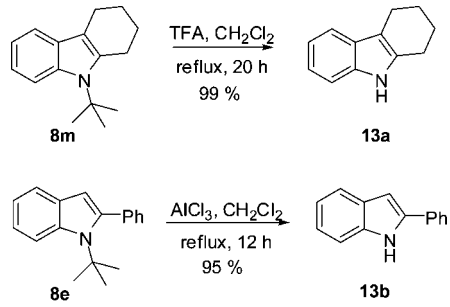
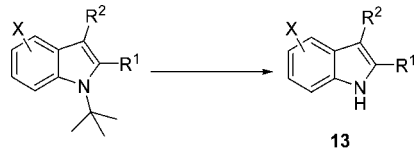
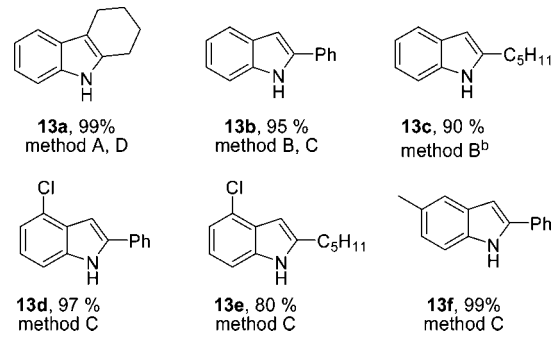


Table 4. Deprotection of *t*-Butylindoles under Microwave or Thermal Heating Conditions[a]





[a] Reaction conditions: (A) indole (0.5 mmol), TFA (0.8 mL), CH_2Cl_2 (2 mL), 0 °C to reflux, 12 h; (B) indole (0.5 mmol), $AlCl_3$ (1.3 equiv), CH_2Cl_2 (2 mL), 0 °C to reflux, 12 h; (C) indole (0.5 mmol), $AlCl_3$ (1.3 equiv), CH_2Cl_2 (0.5 mL), microwave irradiation, 80 °C, 10 min; (D) indole (0.2 mmol), TFA (0.8 mL), CH_2Cl_2 (2 mL), microwave irradiation, 80 °C, 15 min. [b] $AlCl_3$ (2.6 equiv).

7). Interestingly, the relatively long reaction times required for the deprotection can be dramatically reduced to as little as 10 min by carrying out the cleavage reaction using microwave heating. With this experimental procedure, the *t*-butyl group was efficiently cleaved from each of a set of indoles bearing different substitution patterns to produce the corresponding N−H indoles **13** with very high yields (Table 4).

Scheme 8. General Scheme for the Synthesis of Indoles from Imines and Phenols

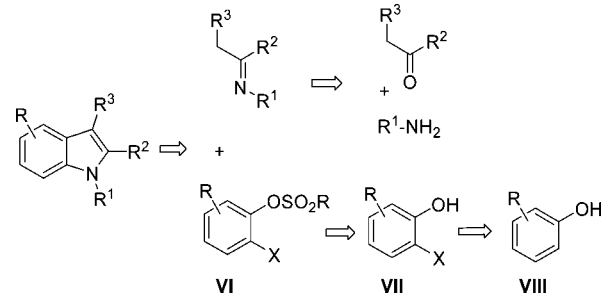
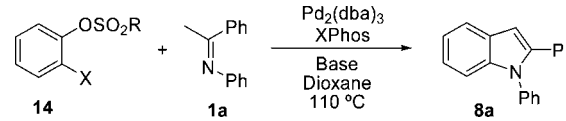


Table 5. Influence of the Halosulfonate **14** and the Base in the Indolization[a]



entry	R	X	sulfonate	base	conversion (%)[b]
1	CF_3	I	**14a**	LiO*t*Bu	0
2	*p*-Tol	I	**14b**	LiO*t*Bu	0
3	CF_3	Br	**14c**	LiO*t*Bu	0
4	*p*-Tol	Br	**14d**	LiO*t*Bu	0
5	CF_3	Cl	**14e**	LiO*t*Bu	32
6	*p*-Tol	Cl	**14f**	LiO*t*Bu	0
7	CF_3	Cl	**14e**	Cs_2CO_3	0
8	CF_3	Cl	**14e**	NaO*t*Bu	0
9	CF_3	Cl	**14e**	LiO*t*Bu	100 (80)[c,d]

[a] Reaction conditions: **1a** (0.5 mmol), **14** (0.75 mmol), $Pd_2(dba)_3$ (4 mol %), XPhos (16 mol %), base (2.4 equiv), dioxane (2 mL), 110 °C, 14−24 h. [b] Relative to the amount of imine. [c] The chlorotriflate **14e** was slowly added with a syringe pump over 6 h. [d] Isolated yield is indicated in parentheses.

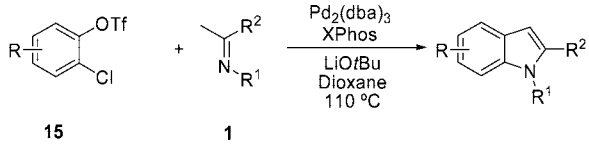
Indoles from *o*-Chlorosulfonates. As we have shown in this paper, convergence and modularity are particular advantages of this synthesis of indoles, allowing the introduction of an array of different substituents R^1, R^2, and R^3 at every position of the five-membered ring as a result of the ready availability of the starting imines, which can be easily prepared from amines and ketones, vinyl halides, or acetylenes.

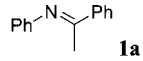
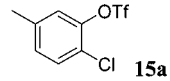
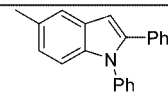
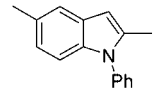
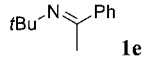
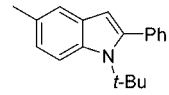
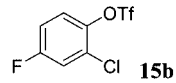
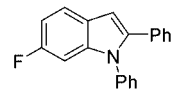
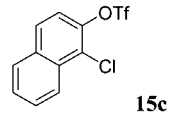
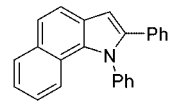
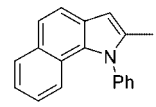
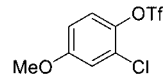
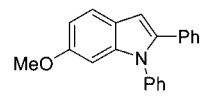
With regard to substitution on the six-membered ring, *o*-dihalobenzene derivatives with two different halogens are needed to ensure the regioselective transformation. However, the relatively limited availability of these disubstituted arenes may represent a drawback in the generality of this reaction.

To expand the applicability of this synthesis of indoles, we decided to investigate the incorporation of *o*-halobenzene sulfonates **VI** as substitutes for the *o*-dihaloarenes. If this modification were possible, the actual starting materials would be the *o*-halophenols **VII**, which are very abundant commercially or otherwise easily prepared from phenols **VIII** (Scheme 8).

To this end, we started our investigation by considering the reactions of imine **1a** with each of the six *o*-halobenzene sulfonates **14** (resulting from combining Cl, Br, and I with triflate and tosylate) under a large set of reaction conditions, including variation of the bases, ligands, solvents, and temperatures. A set of representative results is presented in Table 5. Very frustrating results were obtained in most of the cases, since the imine **1a** was usually recovered unaltered. The only promising reactions occurred with *o*-chlorobenzene triflate **14e**. When the reaction was carried out with LiO*t*Bu as the base,

Table 6. Synthesis of Imines from Chlorotriflates[a]



Entry	Imine **1**	Triflate **15**	Indole **16**	addn. rate (mL/h)[d]	Yield[b,c] [%]
1	 **1a**	 **15a**	 **16a**	0.16	78
2	 **1l**	**15a**	 **16b**	0.1	45
3	 **1e**	**15a**	 **16c**	0.1	70
4	**1a**	 **15b**	 **10e**	0.1	65
5	**1a**	 **15c**	 **16d**	0.12	66
6	**1i**	**15c**	 **16e**	0.12	26
7	**1a**	 **15d**	 **16f**	0.12	36

[a] Reaction conditions: **1** (0.5 mmol), **15** (0.75 mmol), $Pd_2(dba)_3$ (4 mol %), XPhos (16 mol %), base (2.4−4.8 equiv), dioxane (2 mL), 110 °C, 14−24 h. [b] Relative to the amount of imine. [c] Isolated yield. [d] 0.75 mmol of triflate **15** in 1 mL of dioxane was slowly added with a syringe pump at the indicated rate.

$Pd_2(dba)_3$ as the Pd source, and XPhos as the supporting ligand for Pd in dioxane at 110 °C (Table 5, entry 5), formation of the indole was observed in a very low yield, with only 32% conversion of the imine **1**. The low yield obtained in this reaction can be easily understood in view of the sensitivity of triflates to metal alkoxides. An extensive search of alternative bases (milder, stronger, or less nucleophilic) was carried out, but Li*t*OBu was the only base that led to the formation of indole to any extent. With regard to the ligand, the use of XPhos was also required, since no indole formation was observed when other mono- or bidentate phosphines of N-heterocyclic carbenes were employed.[19]

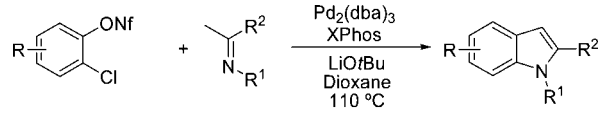
After some experimentation, we found that the reaction could be driven to nearly complete conversion with respect to the imine as the limiting regent by very slow addition of the chlorotriflate **14e**, in an attempt to synchronize the rate of the addition with the rate of the catalytic cycle. This similarity of rates would minimize the exposure of the triflate to the alkoxide.[20] Employing this approach with a triflate/imine ratio of 1.5:1 yielded the indole in a remarkable 80% yield (Table 5, entry 9).

We studied the scope of this reaction by examining the participation of different *o*-chlorotriflates **15** having diverse substitution in the aromatic ring with a set of imines **1**. As Table 6 indicates, a variety of indoles with different substituents in the benzene ring can be prepared. The reactions are completely regioselective. The regioisomer obtained corresponds to that in which the first reaction, the imine α-arylation, occurs at the carbon that holds the triflate. This observation is consistent with

(19) The reaction of imine **1a** with chlorotriflate **14** was examined with the following ligands: tricyclohexylphosphine, 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl (Davephos), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos), and Josiphos. The following commercial complexes of Pd with N-heterocyclic carbenes were also tested: PEPPSI-IPr, PEPPSI-SIPr.

(20) Slow addition had previously been employed in the original procedures for the amination of aryl triflates. See: (a) Louie, J.; Driver, M. S.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1997**, *62*, 1268. (b) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1264.

Table 7. Synthesis of Indoles from Chlorononaflates **17**[a]



17 **1** **16**

Entry	Imine **1**	Nonaflate **17**	Indole **16**	Yield[b,c] (%)
1	**1a**	**17a**	**8a**	92
2	**1a**	**17b**	**16a**	86
3	**1e**	**17b**	**16c**	93
4	**1t**	**17b**	**16g**	65
5	**1b**	**17b**	**16h**	89
6	**1h**	**17b**	**16i**	88
7	**1a**	**17c**	**10e**	81
8	**1b**	**17c**	**16j**	64
9	**1h**	**17c**	**16k**	78
10	**1a**	**17d**	**16f**	80
11	**1b**	**17d**	**16l**	63
12	**1b**	**17e**	**16m**	71
13	**1a**	**17f**	**16n**	64
14	**1e**	**17f**	**16o**	79
15	**1u**	**17c**	**16p**	83
16	**1u**	**17g**	**16q**	66
17	**1u**	**17b**	**16r**	88
18	**1u**	**17h**	**16s**	87
19	**1f**	**17h**	**16t**	75
20	**1q**	**17h**	**16u**	61
21	**1a**	**17i**	**16v**	62
22	**1a**	**17j**	**16w**	78
23	**1a**	**17k**	**16x**	80
24	**1a**	**17l**	**16y**	72

[a] Reaction conditions: **1** (0.5 mmol), $Pd_2(dba)_3$ (4 mol %), XPhos (16 mol %), base (4.8 equiv), dioxane (1 mL), 0.75 mmol of **17** in 1 mL of dioxane (addition rate, 0.1 mL/h), 110 °C, 10−20 h. [b] Relative to the amount of imine. [c] Isolated yield.

the known higher reactivity of aryl triflates than aryl chlorides toward oxidative addition reactions.[21]

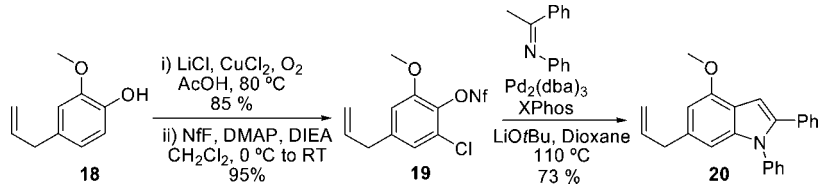
The reaction tolerates the presence of neutral and electron-withdrawing groups in the aromatic ring. Of note is the preparation of benzoindole **16d** (Table 6, entry 5), obtained from the corresponding chlorotriflate **15c**, which is readily available from 2-naphthol.[22]

It should be pointed out that this reaction presents some severe limitations. First of all, in order to achieve high conversion, a study of the addition rate of the triflate had to be conducted for each individual reaction. Moreover, very low yields were obtained in some cases, such as when chlorotriflates with electron-rich substituents were employed.

The limited scope and low yields of the reactions with chlorotriflates **15**, which are the result of the instability of **15** in the presence of alkoxides, prompted us to examine the reactions with *o*-chlorobenzene nonaflates **17** (Ar−ONf = $Ar-OSO_2CF_2CF_2CF_2CF_3$). Aryl and alkenyl nonaflates are competent partners in Pd-catalyzed cross-coupling reactions,[23,24]

(21) Littke, A. F.; Dai, C.; Fu, C. G. *J. Am. Chem. Soc.* **2000**, *122*, 4020.
(22) (a) Ginsburg, D. *J. Am. Chem. Soc.* **1951**, *73*, 2723. (b) Zhang, Y.; Shibatomi, K.; Yamamoto, H. *Synlett* **2005**, 2837.
(23) With respect to cross-coupling reactions with aryl nonaflates, for Suzuki−Miyaura, see: (a) Blettner, C. G.; Konig, W. A.; Stenzel, W.; Schotten, T. *J. Org. Chem.* **1999**, *64*, 3885. For Negishi, see: (b) Rottlander, M.; Knochel, P. *J. Org. Chem.* **1998**, *63*, 203. For silanol coupling, see: (c) Denmark, S. E.; Sweis, R. F. *Org. Lett.* **2002**, *4*, 3771. For amination, see: (d) Anderson, K. W.; Mendez-Perez, M.; Priego, J.; Buchwald, S. L. *J. Org. Chem.* **2003**, *68*, 9563. (e) Tundel, R. E.; Anderson, K. W.; Buchwald, S. L. *J. Org. Chem.* **2006**, *71*, 430. (f) Bolm, C.; Hildebrand, J. P.; Rudolph, J. *Synthesis* **2000**, *7*, 911.
(24) Högermeier, J.; Reissig, H.-U. *Chem.—Eur. J.* **2007**, *13*, 2410, and references cited therein.

Scheme 9. Regioselective Synthesis of 4,6-Disubstitued Indole **20**



with reactivities similar to those of triflates, but aryl nonaflates are more stable toward decomposition by nucleophilic bases such as alkoxides.[25,26]

We carried out some preliminary experiments indicating that *o*-chlorobenzene nonaflates provided indoles in a similar way as the analogous triflates. Importantly, the greater stability of the nonaflates in the presence of the alkoxide base favored the indolization reaction, and higher conversion was generally achieved. Thus, after some experimentation in order to tune the reaction conditions, a study of the scope of the reaction was carried out (Table 7).

The reactions of nonaflates turned out to possess certain advantages in comparison with the reactions of triflates. First of all, the reaction yields were always higher with nonaflates than with triflates, and importantly, the indolization reaction occurred with a wider scope in regard to both coupling partners. Furthermore, although slow addition of the nonaflate to the reaction was still necessary in order to achieve complete conversion of the imine, the very precise tuning of the addition rate for each reaction that was required for the chlorotriflates was not needed here. Indeed, most of the reactions presented in Table 7 were carried out with the same addition rate of the nonaflate solution. Only the reaction involving the *t*-butoxycarbonyl-substituted nonaflate **17i** required a lower addition rate in order to obtain the indole **16v** in good yield.

A variety of structurally diverse imines can participate in the reaction, and consequently, indoles bearing an alkyl (entry 4), aryl (entries 1−3, 5, 7, 8, 10−14, 19), heteroaryl [either π-excessive (entries 6, 9) or π-deficient (entries 15−18)], or vinyl (entry 20) substituent at the 2-position can be prepared. Additionally, aryl and alkyl substituents can be placed at the N-position.

Moreover, the reaction is fairly general in regard to substituents on the benzene ring; neutral, electron-donating, and electron-withdrawing groups are all tolerated. With respect to functional-group compatibility, under the reaction conditions devised, nonaflates substituted with functionalities that might be sensitive under strongly basic conditions, such as carboxylic esters, nitriles, and aldimines, gave rise to the corresponding indoles in good yields (entries 21−24). Indoles substituted at the 4- (entries 13, 14) or 7-positions (entry 12), which might have been more difficult to form by this method for steric reasons, were also prepared efficiently. Additionally, while chlorotriflates with electron-rich substituents performed poorly (Table 6, entry 7), the analogous nonaflates provided the indoles in good yields (Table 7, entries 10 and 11).

It is noteworthy that this methodology is particularly convenient for the synthesis of indoles with certain substitutions in the benzene ring that are difficult to obtain by typical methods. In particular, 6-substituted indoles,[27] whose regioselective synthesis employing standard methodologies is not straightforward, are ideal targets because of the easy preparation of the chlorophenol precursors (entries 7−11, 15, 16, 18−24). Moreover, the reactions are completely regioselective, and again, the regioisomer obtained corresponds to that resulting from formation of the C−C bond at the nonaflate position.

To further illustrate the potential of this method in the regioselective preparation of indoles substituted on the benzene ring, 4-methoxy-6-allylindole derivative **20,** which features an unusual 4,6-disubstitution, was synthesized from chlorononaflate **19** (Scheme 9). The latter was easily prepared from anethole **18**, a naturally occurring phenol, by ortho chlorination[28] followed by formation of the nonaflate.

It must be emphasized that the regioselective synthesis of indoles with these type of substitution patterns is not straightforward using the conventional methodologies:[29] methods based on nitrogenated benzene derivatives, such as the Fischer synthesis, give rise to mixtures of regioisomers,[16a,30] and those derived from ortho-substituted anilines require polysubstituted benzene derivatives that are not readily available. However, the ability to construct the indole ring in a regioselective manner by employing phenols (which are abundant) as starting materials opens the door to the generation of new classes of structurally diverse indoles.

Summary

We have reported a new modular synthesis of indoles starting with imines and *o*-dihalobenzenes or *o*-chloroarylsulfonates. The reaction involves two Pd-catalyzed processes, an imine C-arylation and an intramolecular amination, both promoted by the same Pd catalyst. We have carefully studied the scope of the reaction and showed that this methodology allows for the regioselective synthesis of indoles with a variety of substituents at almost any position of either ring. In addition, the reaction is not restricted to N-substituted indoles: we have discovered that the *t*-butyl group can be easily removed from the indole nitrogen and therefore employed as a protecting group.

A particularly remarkable advance is the use of *o*-chlorosulfonates instead of dihaloderivatives. The use of nonaflates instead of triflates was found to be important in making the indole synthesis efficient. In view of the wide availability of chlorophenols, which are the precursors to chlorononaflates, this methodology may represent a valuable entry into structurally

(25) Zhang, X.; Sui, Z. *Tetrahedron Lett.* **2003**, *44*, 3071.
(26) The α-arylation of ketones with aryl triflates has recently been reported (see: Liao, X.; Weng, Z.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 195.), but to the best of our knowledge, aryl nonaflates have not previously been employed in α-arylation reactions.
(27) For a recent regioselective synthesis of 6-substituted indoles through the Neber rearrangement, see: (a) Taber, D. F.; Tian, W. *J. Am. Chem. Soc.* **2006**, *128*, 1058.
(28) Menini, L.; Gusevskaya, E. V. *Appl. Catal., A* **2006**, *309*, 122.
(29) For a regioselective synthesis of indoles from *o*-nitrohalobenzene derivatives, see:Rutherford, J. L.; Rainka, M. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 15168.
(30) (a) Robinson, B. *The Fischer Indole Synthesis*; Wiley: Chichester, U.K., 1982. (b) Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10251. (c) Chae, J.; Buchwald, S. L. *J. Org. Chem.* **2004**, *69*, 3336.

diverse indoles that are regioselectively substituted on the benzene ring and that have been previously unavailable through conventional methodologies. For these reasons, we believe that this new methodology for the synthesis of the important indole substructure may find wide applicability in organic synthesis and in particular in programs oriented toward drug discovery.

Experimental Section

General Procedure for the Synthesis of Indoles 8 and 10 from 1,2-Dihaloarenes. A reaction tube under a nitrogen atmosphere was charged with XPhos (19.6 mg, 0.04 mmol, 4 mol %), $Pd_2(dba)_3$ (dba = dibenzylideneacetone) (18.3 mg, 0.02 mmol, 2 mol %), sodium *tert*-butoxide (268 mg, 2.8 mmol, 2.8 equiv), and dioxane (2 mL). After 1 min, the dihaloarene was added under nitrogen and heated to 110 °C. After 5 min, imine **1** (1 mmol) was added under nitrogen. The reaction mixture was stirred at 110 °C until complete disappearance of the dihaloarene had occurred, as determined by GC−MS. The mixture was cooled to room temperature, taken up in hexanes (15 mL), and filtered through Celite. The solvents were evaporated under reduced pressure, and the resulting residue was purified by column chromatography.

General Procedure for the Synthesis of Indoles 10 and 16 from *O*-Chlorononaflates. A reaction tube under a nitrogen atmosphere was charged with XPhos (39.6 mg, 0.08 mmol, 16 mol %), $Pd_2(dba)_3$ (18.3 mg, 0.02 mmol, 4 mol %), lithium *tert*-butoxide (192 mg, 2.4 mmol, 4.8 equiv), the imine (0.5 mmol) and dioxane (1 mL). The mixture was heated with stirring at 110 °C. A solution of chlorononaflate **17** (0.75 mmol) in 1 mL of dioxane was added with a syringe pump over a period of 10 h (0.1 mL/h). The reaction was kept at 110 °C for an additional period of 4−10 h, until complete dissapearance of the imine had occurred (GC−MS monitoring). The mixture was cooled to room temperature and quenched with 10 mL of water, and the organics were extracted with methylene chloride (3 × 10 mL). The organic layers were combined, washed with brine (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by column chromatography.

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Supporting Information Available: Experimental procedures, characterization data, complete ref 1a, and copies of the NMR spectra for all of the new compounds synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

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