JOC Article

Palladium-Catalyzed Annulation of Haloanilines and Halobenzamides Using Norbornadiene as an Acetylene Synthon: A Route to Functionalized Indolines, Isoquinolinones, and Indoles

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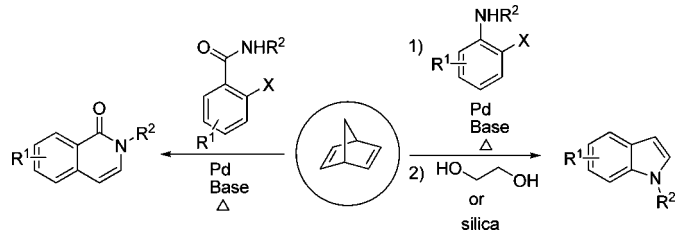
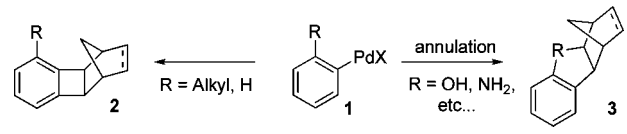


A general procedure for the palladium-catalyzed annulation of substituted haloanilines with norbornadiene gives functionalized indolines in 51−98% yield. These indolines can be rapidly converted to benzenoid-substituted indoles and tricyclic indolines. Extension to the use of substituted halobenzamides gives functionalized isoquinolinones in up to 86% yield.

Introduction

Indoles are the principal motif in a variety of pharmaceuticals and natural products.[1] Countless reports have been devoted to developing indole syntheses,[2] including our own efforts using *gem*-dihalovinylanilines.[3] As part of our ongoing interest in finding novel ways of synthesizing heterocycles, we now report a short and efficient route to indolines and indoles through a palladium-catalyzed annulation of norbornadiene with *o*-haloanilines. We have recently reported the annulation of haloaryl heterocycles with strained alkenes.[4] In this study, norbornadiene was used as an acetylene synthon for the synthesis of fused aromatic heterocycles. We considered that annulation onto a heteroatom rather than a heterocycle would provide an interesting approach toward the synthesis of a range of indole and indoline scaffolds (Scheme 1). This approach would allow for ready variation of the substituents in the benzenoid ring of the indole, which few methods can easily accomplish.[5]

SCHEME 1. Annulation Strategies with Aryl Halides



We have previously reported the annulation of 2-iodo-*N*-acetylaniline with norbornene as a side product in the palladium-catalyzed *ortho*-alkylation/Heck reaction (eq 1).[6] Similarly, Catellani,[7] Larock,[8] and Saito[9] have reported the annulation of iodophenols and iodoanilines with norbornene. Catellani also reported the annulation of an iodophenol with norbornadiene in 46% yield.[7] However, to the best of our knowledge, the

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(5) For syntheses of indoles in which the substituents on the benzenoid ring are easily varied, see: (a) Dunetz, J. R.; Danheiser, R. L. *J. Am. Chem. Soc.* **2005**, *127*, 5776. (b) Trost, B. M.; McClory, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 2074. (c) Siu, J.; Baxendale, I. R.; Ley, S. V. *Org. Biomol. Chem.* **2004**, *2*, 160. (d) Cho, C. S.; Lim, H. K.; Shim, S. C.; Kim, T.-J.; Chin, H.-J. *Chem. Commun.* **1998**, *9*, 995.

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(8) Emrich, D. E.; Larock, R. C. *J. Organomet. Chem.* **2004**, *689*, 3756.

(9) Saito, K.; Katsuhiko, O.; Sano, M.; Kiso, S.; Takeda, T. *Heterocycles* **2002**, *57*, 1781.

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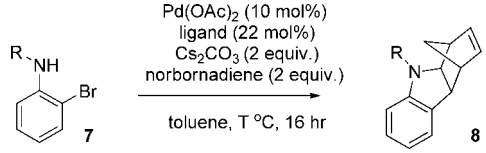
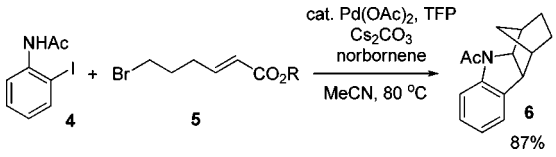
TABLE 1. Optimization of Annulation of Haloanilines with Norbornadiene



entry	R (**7**)	ligand	*T* (°C)	**8**	yield (%)
1	Me (**7a**)	tri(2-furyl)phosphine	80	**8a**	
2	Ts (**7b**)	tri(2-furyl)phosphine	80	**8b**	
3	Bz (**7c**)	tri(2-furyl)phosphine	80	**8c**	
4	Boc (**7d**)	tri(2-furyl)phosphine	80	**8d**	60
5	Boc (**7d**)	tricyclohexylphosphine	80	**8d**	
6	Boc (**7d**)	tricyclohexylphosphine	110	**8d**	50
7	Boc (**7d**)	tri(2-furyl)phosphine	110	**8d**	40[a]
8[b]	Boc (**7d**)	tricyclohexylphosphine	120	**8d**	82
9[b]	Boc (**7d**)	tri-*tert*-butylphosphonium tetrafluoroborate	120	**8d**	90

[a] Impure product. [b] With 6 equiv of alkene.

annulation of haloanilines with norbornadiene has not been reported. There are considerable advantages associated with selective monofunctionalization of this diene.



(1)

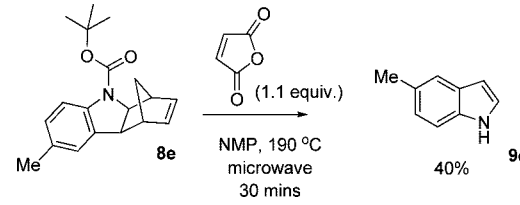
Results and Discussion

Synthesis of Annulated *o*-Bromoanilines. Re-examining the reaction in eq 1, we found that it proceeded equally well in the absence of the alkyl bromide **5**. However, a simple switch from norbornene to norbornadiene resulted in very poor yields. To improve the yield of the annulation product, we examined the effect of changing the nitrogen protecting group (Table 1). Alkyl, sulfonyl, or amide protecting groups led to either recovery of starting material or decomposition products (entries 1−3). Pleasingly, the Boc-protected aniline gave **8** in 60% yield. Treatment of unprotected anilines provides annulated products in moderate yield but low purity. To promote the amination, we increased the electron-donating properties and steric bulk of the ligand by the use of tricyclohexylphosphine.[10] Interestingly, consumption of starting material was observed at both 80 and 110 °C (entries 5 and 6), while formation of product was only observed at 110 °C. Though this suggests that a competing process might be occurring at lower temperatures, we were only able to recover starting material from these low conversion reactions and were unable to identify the remainder of the mass balance.

However, increasing the temperature and the equivalents of norbornadiene allowed us to generate the desired product in 82% yield (entry 8). A further increase in yield to 90% is obtained using a $^{t}Bu_3P$ ligand precursor (entry 9).

The annulation is tolerant of a variety of functionality including electron-donating (Table 2, entries 2, 5, and 6) and electron-withdrawing (entries 3, 4, and 7−10) groups at various positions around the benzenoid ring. Among the results, some examples deserve further comment. Substrate **7i**, bearing a potentially hindering methyl group, gives the annulated product in 89% yield (entry 6). Whereas the aryl chloride **7o** gives a good yield of the annulated product **8o** under the reaction conditions (entry 12), chlorine functionality elsewhere in the ring does not seem well tolerated. Thus, substrate **7g** gives a low yield with $^{t}Bu_3PHBF_4$, but using the DavePhos ligand[11] a 51% yield of the desired compound was obtained (entry 4). The structure of **8h** was confirmed by X-ray crystallography.[12] Notably, **8e** has been synthesized on a gram scale in 92% yield.

Synthesis of Benzenoid-Substituted Indoles. We next investigated the retro Diels−Alder reactions of our annulated products as this would give rise to a variety of benzenoid-substituted indoles.[13] Even though the present reaction is performed at a higher temperature than our previously reported annulation of bromoarylheterocycles leading to retro Diels−Alder products,[4] no retro Diels−Alder indole products were formed under the reaction conditions. The annulated compounds **8** were found to be stable up to 200 °C under microwave irradiation. At this high temperature under the sealed conditions, we were concerned that the retro Diels−Alder reaction may be reversible.[14] Therefore, substrate **8e** was heated with microwave irradiation at 190 °C in the presence of a competitive dienophile according to a strategy used by Mander and co-workers in the synthesis of sordaricin.[15,16] Gratifyingly, indole **9e** was formed, but only in a 40% yield (eq 2).



(2)

Noting that the indole had lost its protecting group, we considered that the stability of the molecule at high temperatures might be caused by the presence of the carbamate. We therefore aimed to find conditions that would allow in situ deprotection of the annulation products and subsequent retro Diels−Alder reaction.

We developed two sets of conditions that enabled the synthesis of indoles **9** from annulation products **8**: treatment with silica gel in xylenes at 170 °C or heating in ethylene glycol at 170 °C. Removal of Boc protecting groups by reflux in toluene in the presence of silica has previously been reported,[17] but deprotection via heating in ethylene glycol is to the best of

(10) Electron-rich, bulky phosphanes promote aromatic aminations: (a) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413. (b) Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553. (c) Zapf, A.; Beller, M. *Chem. Commun.* **2005**, 431. (d) Watanabe, M.; Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **2000**, *41*, 481.

(11) For the use of the DavePhos ligand in aminations, see: Harris, M. C.; Geis, O.; Buchwald, S. L. *J. Org. Chem.* **1999**, *64*, 6019.

(12) For X-ray crystal data, see the Supporting Information.

(13) This would create a novel two-step approach to indole synthesis. A related method is the Larock indole synthesis, whereby indoles can be produced in one step from *o*-haloanilines and acetylenes. Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652.

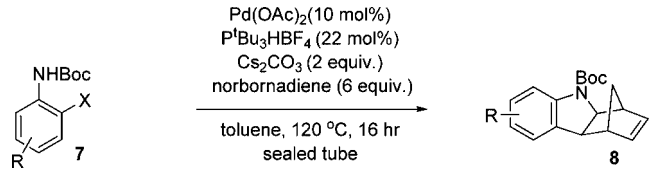
(14) [4 + 2] cycloadditions between indole and cyclopentadiene have been reported: (a) Davies, H. M. L.; Dai, X. *J. Org. Chem.* **2005**, *70*, 6680. (b) Sato, S.; Fujino, T.; Isobe, H.; Nakamura, E. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1288.

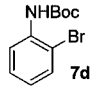
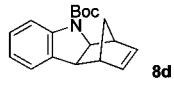
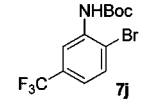
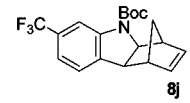
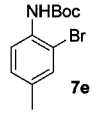
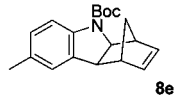
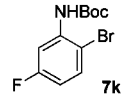
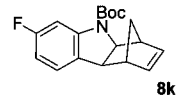
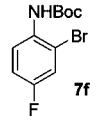
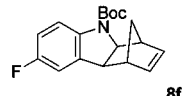
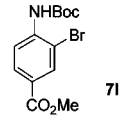
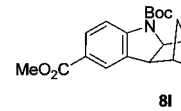
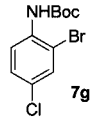
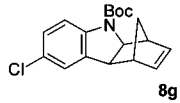
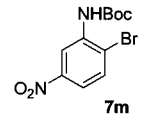
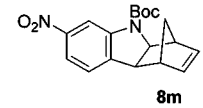
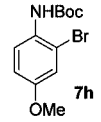
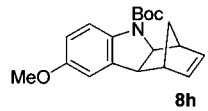
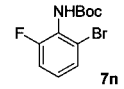
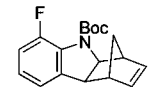
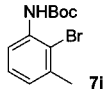
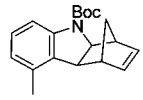
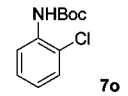
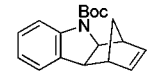
(15) Mander, L. N.; Thomson, R. J. *J. Org. Chem.* **2005**, *70*, 1654.

(16) For examples of retro-Diels−Alder reactions used to obtain heterocyclic compounds, see: (a) Burgess, K. L.; Lajkiewicz, N. J.; Sanyal, A.; Yan, W.; Snyder, J. K. *Org. Lett.* **2005**, *7*, 3795. (b) Marques, M. M. B.; Lobo, A. M.; Prabhakar, S.; Branco, P. S. *Tetrahedron Lett.* **1999**, *40*, 3795. (c) Sha, C.-K.; Yang, J.-F.; Chang, C.-J. *Tetrahedron Lett.* **1996**, *37*, 3487. (d) Arai, Y.; Kontani, T.; Koizumi, T. *Chem. Lett.* **1991**, *12*, 2135. (e) Magnus, P.; Cairns, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 217.

(17) Apelqvist, T.; Wensbo, D. *Tetrahedron Lett.* **1996**, *37*, 1471.

TABLE 2. Scope for Annulation of Anilines with Norbornadiene



entry	substrate	product	yield (%)	entry	substrate	product	yield (%)
1	 7d	 8d	90	7[e]	 7j	 8j	81
2	 7e	 8e	98(92)[a]	8	 7k	 8k	88
3	 7f	 8f	91	9	 7l	 8l	72
4[b]	 7g	 8g	51	10	 7m	 8m	74
5[c]	 7h	 8h	77	11	 7n	 8n	91
6[d]	 7i	 8i	89	12	 7o	 8o	71

[a] Reaction performed on a 1 g (3.5 mmol) scale. [b] DavePhos was used as the ligand instead of $P^tBu_3HBF_4$. [c] Structure of product confirmed by X-ray crystallography. [d] After 48 h. [e] After 24 h.

our knowledge unknown. Given the high synthetic utility of the indole products, we investigated the generality of these conditions (Table 3).

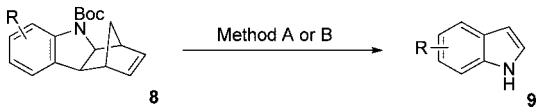
Using the ethylene glycol conditions, a range of substituted indoles were prepared from annulation products **8**. Notably substrate **8m** containing a nitro group meta to the indoline nitrogen provided indole **9m** in 92% yield. However, substrates containing either a methoxy or chlorine para to the indole nitrogen, or fluorine adjacent to the indole nitrogen, gave lower yields of indoles **9g**, **9h**, and **9n**. In these latter cases, yields were improved by using the silica gel in xylenes method, which seems to be more general.

Synthesis of Annulated *o*-Benzamides. We sought to extend this methodology to the preparation of isoquinolinones. We found that *N*-benzyl-*o*-bromobenzamide in the presence of norbornadiene can be cyclized to isoquinolinones **11**, though accompanied by byproducts **12**−**14**. Since the palladium-catalyzed dimerization of these compounds to the phenanthridinones **13** was already reported,[18] we searched to find conditions to improve the yield of the isoquinolinone product **11**. The proposed mechanism for the formation of isoquinolinone **11** and the byproducts **12**−**14** is shown in Scheme 2.

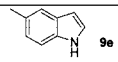
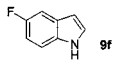
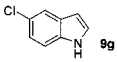
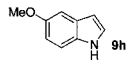
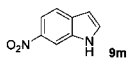
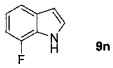
The catalytic cycle starts at a Pd(0) species which is formed in situ from $Pd(OAc)_2$. After oxidative addition of the substrate to give a Pd(II) species, two pathways are possible. In one pathway, dimerization with a second *o*-halobenzamide leads to the aforementioned phenanthridinone **13**. In the second pathway, carbopalladation with norbornadiene can occur to give either one of two products. In the presence of a base, either the amide N−H proton can be abstracted to form a seven-membered heteropalladacycle or an ortho C−H proton can be abstracted to form the five-membered palladacycle. The former case can reductively eliminate to form the norbornadiene adduct **12**, which can undergo a retro-Diels−Alder reaction to form the

(18) (a) Ferraccioli, R.; Carenzi, D.; Motti, E.; Catellani, M. *J. Am. Chem. Soc.* **2006**, *128*, 722. (b) Furuta, T.; Kitamura, Y.; Hashimoto, A.; Fujii, S.; Tanaka, K.; Kan, T. *Org. Lett.* **2007**, *9*, 183.

TABLE 3. Scope of Indole Formation



8 9

entry	8	9	Method A (%)[a]	Method B (%)[b]
1	**8e**	 **9e**	80	80
2	**8f**	 **9f**	81	71
3	**8g**	 **9g**	53	68
4	**8h**	 **9h**	53	97
5	**8m**	 **9m**	92	53
6	**8n**	 **9n**	52	62

[a] Ethylene glycol (3 mL), 170 °C, 12 h. [b] SiO_2 (1 pipet measure), xylenes, 170 °C, 12 h.

desired isoquinolinone **11**. Reductive elimination in the latter case leads to the cyclobutene product **14**.

In analogy to our results with *o*-bromoanilines, the synthesis of **11** is sensitive to the protecting group on the benzamide nitrogen. Only *N*-alkyl-substituted benzamides led to the desired products, while other common protecting groups such as Boc, tosyl, or phenyl led to decomposition of the starting material. The benzyl group (Bn) proved to be the best alkyl protecting group for the benzamide. The norbornadiene adduct **12** decomposed to the isoquinolinone **11** at 130 °C (Table 4, entry 1 vs entry 2). Diluting the reaction mixture and increasing the ratio of solvent to norbornadiene also increased product yields (entries 3 and 4). Using norbornadiene as solvent led to exclusive formation of annulated product **12** (entry 5). Since dimerization products were present in large amounts in the aforementioned cases, the less reactive *N*-benzyl-*o*-chlorobenzamide was synthesized and tested (entries 6−9). The initial reactions produced the desired isoquinolinone in 51% yield, together with 38% of the cyclobutane adduct which arises from C−H activation of the ortho position (entry 6). Toluene was found to be the best solvent, with DMF and acetonitrile giving only the phenanthridinone product (entries 7 and 8). An 8:1 solvent ratio in favor of toluene gave the optimal conditions with a 55% yield of isoquinolinone **11**.

Several *N*-benzyl-*o*-chlorobenzamides were synthesized and subjected to the optimized reaction conditions to explore the scope of the methodology (Table 5). Compared to the unsubstituted benzamide **11a** (entry 1), introduction of an ortho-blocking group produced a much cleaner reaction resulting in 86% yield of product (entry 2). Increasing the electron density of the ring resulted in a slower oxidative addition, with the *o*-methoxy product isolated in 43% yield (entry 3) and the dimethoxy product in 30% based on recovered starting material (entry 4). Electron-withdrawing substituents had a negative effect on the yield with a *p*-nitro group leading to a messy reaction from which only traces of the desired product could be isolated (entry 5). Introducing a second chloro substituent as a removable ortho-blocking group led to the exclusive formation of the cyclobutene product **14**; this could be overcome by changing to a less electron-rich phosphine ligand (PPh_3), giving 35% yield of the product (entry 6). Similarly, the use of a fluoro substituent encouraged product dimerization; thus, changing the ligand to PPh_3 gave 44% of the isoquinolinone. In the latter case the electron density of the metal center is reduced by using a less electron rich ligand, and thus, a second oxidative addition of the substrate is discouraged.

SCHEME 2. Proposed Mechanism for the Formation of Isoquinolinone 11 and Byproducts 12−14

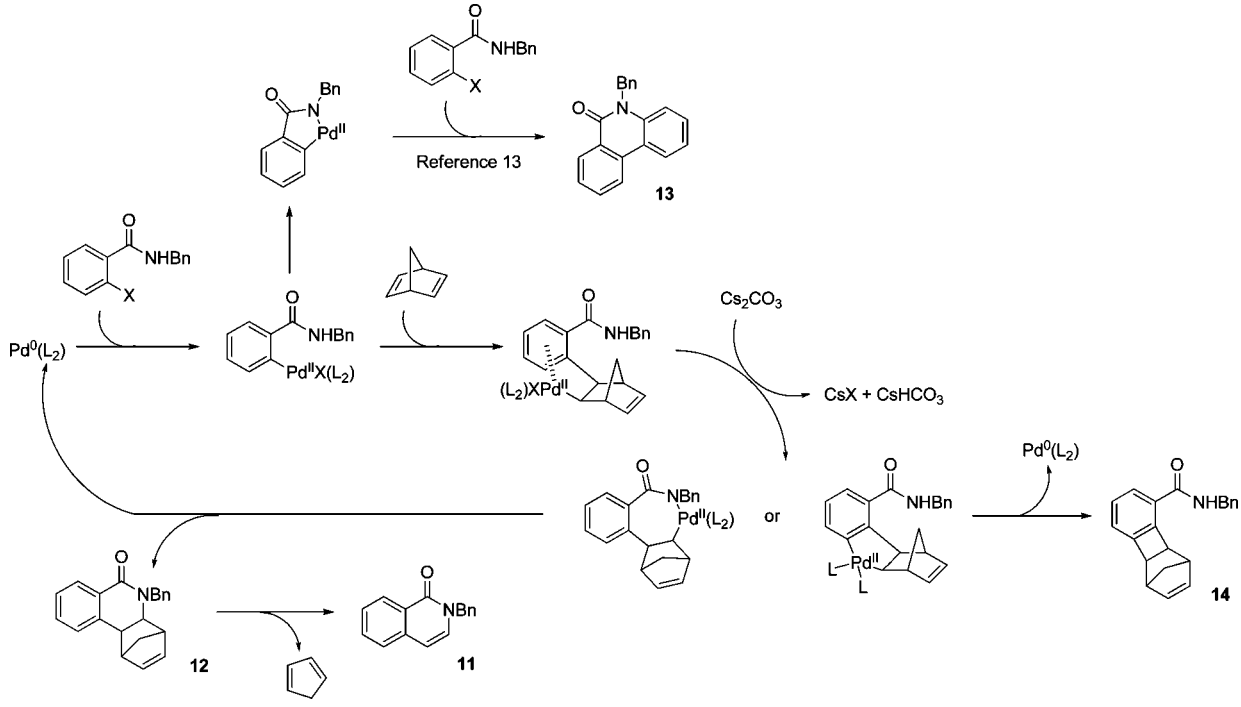
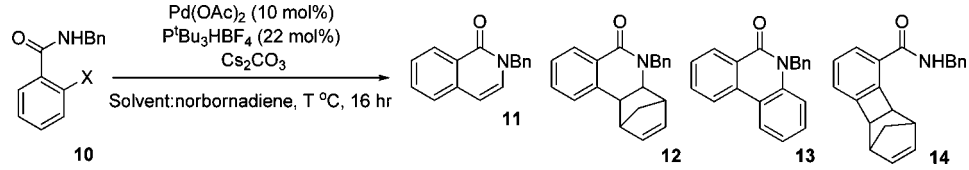


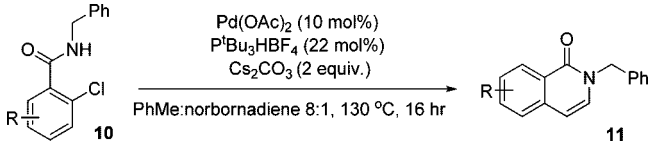
TABLE 4. Optimization for the Annulation of *o*-Halobenzamides with Norbornadiene



					yield (%)			
entry	X	solvent[a] (ratio)	Cs_2CO_3 (equiv)	*T* (°C)	**11**	**12**	**13**	**14**
1	Br	PhMe/Nbd (1:1)	2	130	38	inseparable 3:1 ratio		
2	Br	PhMe/Nbd (1:1)	2	110		50% inseparable mixture		
3	Br	PhMe/Nbd (2:1)	1.3	130	36		22	
4	Br	PhMe/Nbd (4:1)	2	130	30	18		
5	Br	Nbd	1.3	100		36		
6	Cl	PhMe/Nbd (2:1)	1.3	130	51			38
7	Cl	DMF/Nbd (2:1)	1.3	130			56	
8	Cl	CH_3CN/Nbd (2:1)	1.3	130			32	
9	Cl	PhMe/Nbd (8:1)	1.3	130	55			28

[a] Nbd = norbornadiene.

TABLE 5. Scope for the Annulation of *ortho*-Halobenzamides with Norbornadiene

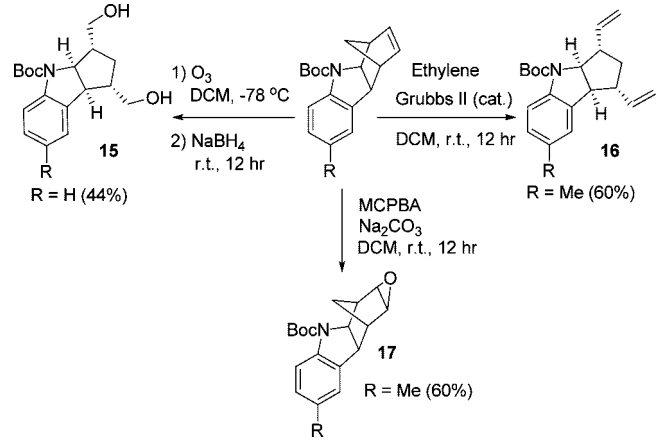


entry	substrate	product	yield (%)
1	**10a**	**11a**	55
2	**10b**	**11b**	86
3	**10c**	**11c**	43
4[a]	**10d**	**11d**	30
5	**10e**	**11e**	traces
6[b]	**10f**	**11f**	35
7[b]	**10g**	**11g**	44

[a] Based on recovered starting material. [b] With PPh_3.

Synthesis of Tricyclic Indolines. Cleavage of the alkene in annulation products **8** would provide tricylic indolines. These indolines are privileged structures in pharmaceuticals as they are present in androgen receptor modulators, antipsychotics, antiobesity agents, and 5-HT2 receptor ligands.[19] To exemplify this strategy, ozonolysis of **8d** under reductive conditions provides the tricyclic indoline **15** in 44% yield (Scheme 3). Alternatively, cross-metathesis of **8e** with ethylene gives the tricyclic indoline **16** in 60% yield. The reactivity of the norbornyl alkene was further demonstrated by *exo*-epoxidation to furnish the epoxide **17** in 60% yield.

SCHEME 3. Synthetic Utility of Products



Conclusions

In summary, we have developed conditions for the annulation of haloanilines and halobenzamides with norbornadiene and showed that the reaction is tolerant of a variety of functionality. Coupled with a retro-Diels−Alder reaction, the current methodology gives a new and highly efficient route to synthesize substituted indoles or isoquinolinones. Furthermore, the annulated haloaniline products can be rapidly converted to tricyclic indolines through ozonolysis or metathesis reactions.

Experimental Section

General Procedure for the Annulation of Haloanilines (8d−o). The substrate (0.2 mmol) was combined with $Pd(OAc)_2$ (4.9 mg, 0.02 mmol), $P^tBu_3HBF_4$ (11.6 mg, 0.04 mmol), Cs_2CO_3

(130.0 mg, 0.4 mmol), and the alkene (6 equiv) in a sealed tube. Toluene (2 mL) was added and the reaction vessel flushed with nitrogen. After the tube was sealed, the reaction mixture was heated at 120 °C overnight. Once cooled, the reaction was diluted with DCM and then filtered through Celite, washing with DCM. The solvent was removed in vacuo to provide the crude products, which were purified by flash column chromatography.

General Procedure for Indole Formation (9e−n). Procedure A. (2-Bromo-4-methylphenyl)carbamic acid *tert*-butyl ester (50 mg, 0.17 mmol) was suspended in ethylene glycol (3 mL) and the mixture heated at 170 °C overnight. The reaction was quenched with water (10 mL) and the mixture extracted with ether (3 × 20 mL), the combined organic layers were dried ($MgSO_4$) and filtered, and then the solvent was removed in vacuo. The resulting oil was purified by flash column chromatography (hexane/ethyl acetate 10:1) to yield the title compound as a white solid (17.8 mg, 81%).

Procedure B. (2-Bromo-4-methylphenyl)carbamic acid *tert*-butyl ester (50 mg, 0.17 mmol) was suspended in xylenes (3 mL), 1 pipet measure of silica added, and the mixture heated at 170 °C overnight in a sealed tube. Once cooled, the reaction was diluted with DCM and then filtered through Celite, washing with DCM. The solvent was removed in vacuo to provide the crude product. Purification by flash column chromatography (hexane/ethyl acetate 10:1) yielded the title compound as a white solid (17.3 mg, 79%).

(19) (a) Pedram, B.; Van Oeveren, C. A.; Zhi, L.; Zhao, S.; Shen, Y. International Patent PCT/US2006/023111, 2006. (b) Gao, H.; Stack, G. P.; Sabb, A. L. International Patent PCT/US2003/012691, 2003. (c) Bentley, J. M.; Davidson, J. E. P.; Mansell, H. L.; Monck, N. J. T. International Patent PCT/EP2001/011814, 2001.

General Procedure for the Annulation of Halobenzamides (10a−g). The substrate (0.2 mmol) was combined with $Pd(OAc)_2$ (4.9 mg, 0.02 mmol), $P^tBu_3HBF_4$ (11.6 mg, 0.04 mmol), Cs_2CO_3 (130.0 mg, 0.4 mmol), and the alkene (1 mL, 5 equiv) in a sealed tube. After toluene (4 mL) was added, the reaction vessel was flushed with nitrogen and the tube was sealed. After the reaction mixture was stirred for 5 min at room temperature, the reaction was heated at 130 °C overnight. Once cooled, the reaction was diluted with DCM and then filtered through Celite, washing with DCM. The solvent was removed in vacuo to provide the crude products, which were purified by flash column chromatography.

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Supporting Information Available: Experimental procedures, characterization data, and crystallographic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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