JOC*Note*

Synthesis of Annulated 2*H*-Indazoles and 1,2,3- and 1,2,4-Triazoles via a One-Pot Palladium-Catalyzed Alkylation/Direct Arylation Reaction

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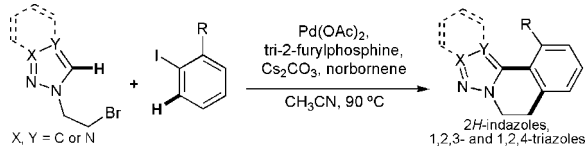
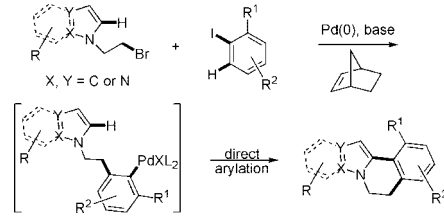


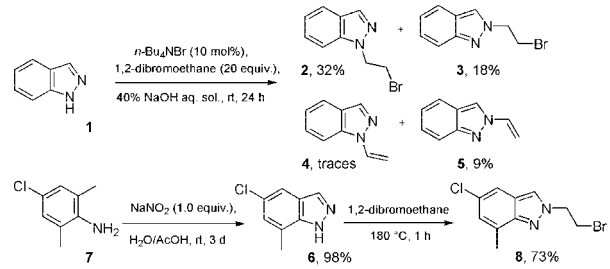
A variety of six-membered-ring annulated 2*H*-indazoles and 1,2,3- and 1,2,4-triazoles were synthesized in good to excellent yields from the corresponding bromoethyl azoles and aryl iodides. The annulation process involves a one-pot norbornene-mediated palladium-catalyzed sequence whereby an alkyl−aryl bond and an aryl−heteroaryl bond are successively formed through two C−H bond activations. Subsequent functionalizations of the resulting polycyclic through cross-coupling reactions are also presented.

Our group recently reported the palladium-catalyzed alkylation/direct arylation synthesis of a large variety of nitrogen-containing heterocycles: indoles, azaindoles, pyrroles, and pyrazoles.[1] The key step of this process is a norbornene-mediated palladium-catalyzed intermolecular ortho-alkylation of an aromatic C−H bond with a *N*-bromoalkyl heterocycle. The mechanism is based upon findings of Catellani and involves a Pd(II)/Pd(IV)[2] catalytic cycle[3] whereby an intramolecular direct arylation reaction[4] affords the desired annulated compounds (Scheme 1). Driven by these excellent results we sought to further expand the scope of this reaction. Herein are presented our results toward the synthesis of annulated indazoles and triazoles,[5] two widespread cores in pharmaceutical agents.[6,7]

SCHEME 1. Tandem Norbornene-Mediated Palladium-Catalyzed Alkylation/Direct Arylation Reaction



SCHEME 2. Synthesis of *N*-Bromoalkyl-2*H*-indazoles



Indazoles were examined under the annulation conditions. To tackle the synthesis of suitable starting materials, indazole **1** was alkylated with 1,2-dibromoethane.[8] Unfortunately a mixture of isomers **2** + **3** were formed, along with the elimination alkene byproduct **4** and **5** (Scheme 2). Favoring the alkylation at position 2 of the indazole core, as well as avoiding the alkene formed by elimination, turned out to be challenging issues that were difficult to overcome in the parent system. Indazole **6** appeared to be a better candidate to overcome the lack of regioselectivity observed for the alkylation reaction due to the steric hindrance arising from the methyl group. Compound **6** was synthesized from commercially available 4-chloro-2,6-dimethylaniline **7** in near-quantitative yield. Performing the alkylation reaction of **6** in the absence of a base with 1,2-dibromoethane as solvent at high temperature in a sealed tube proved to be particularly successful. The desired compound **8** was produced in 73% yield as a single regioisomer with no trace of the alkene byproduct (Scheme 2).

Our previous arylation conditions[9] that involved mixing all the reagents and then heating at reflux resulted in very low yields

(1) Blaszykowski, C.; Aktoudianakis, E.; Alberico, D.; Bressy, C.; Hulcoop, D.; Jafarpour, F.; Joushaghani, A.; Laleu, B.; Lautens, M. *J. Org. Chem.* **2008**, *73*, 1888, and references cited therein.

(2) For a discussion on Pd(II)/Pd(IV) reactions, see: Deprez, N. R.; Sanford, M. S. *Inorg. Chem.* **2007**, *46*, 1924, and references cited therein.

(3) Catellani, M. *Top. Organomet. Chem.* **2005**, *14*, 21, and references cited therein.

(4) For recent reviews, see: (a) Roger, J.; Doucet, H. *Org. Biomol. Chem.* **2008**, *6*, 169. (b) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (c) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (d) Fairlamb, I. J. S. *Chem. Soc. Rev.* **2007**, *36*, 1036. (e) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichim. Acta* **2007**, *40*, 35. (f) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200. (g) Godula, K.; Sames, D. *Science* **2006**, *312*, 67.

(5) To the best of our knowledge, direct arylation reactions on such heterocycles has only been previously reported for 1,2,3-triazoles: (a) Chuprakov, S.; Chernyak, N.; Dudnik, A. S.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 2333. (b) Do, H. Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404. (c) Iwasaki, M.; Yorimitsu, H.; Oshima, K. *Chem.−Asian J.* **2007**, *2*, 1430.

(6) (a) Elguero, J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W., Eds; Pergamon: New York, 1984; Vol. 5, p 167. (b) Cerecetto, H.; Gerpe, A.; Gonzalez, M.; Aran, V. J.; Ocariz, C. O. *Mini-Rev. Med. Chem* **2005**, *5*, 869. (c) Brase, A.; Gil, C.; Knepper, K. *Bioorg. Med. Chem.* **2002**, *10*, 2415.

(7) (a) Wamhoff, H. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W., Eds; Pergamon: New York, 1984; Vol. 5, p 669. (b) Polya, J. B. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W., Eds; Pergamon: New York, 1984; Vol. 5, p 733. (c) Whiting, M.; Muldoon, J.; Lin, Y. C.; Silverman, S. M.; Lindstrom, W.; Olson, A. J.; Kolb, H. C.; Finn, M. G.; Sharpless, K. B.; Elder, J. H.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 1435.

(8) Lopez, P.; Seipelt, C. G.; Merkling, P.; Sturz, L.; Alvarez, J.; Dölle, A.; Zeidler, M. D.; Cerdan, S.; Ballesteros, P. *Bioorg. Med. Chem.* **1999**, *7*, 517.

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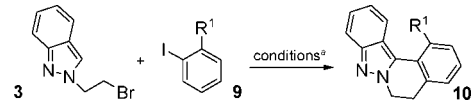
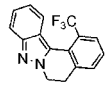
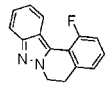
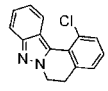
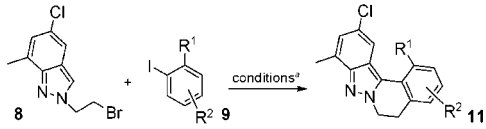
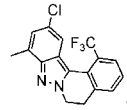
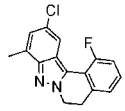
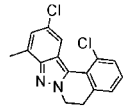
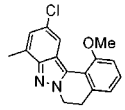
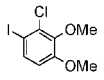
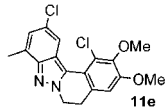
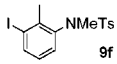
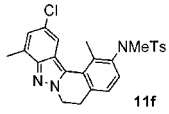
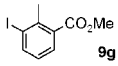
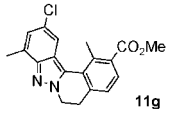
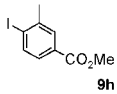
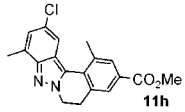
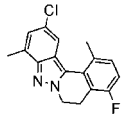
TABLE 1. Synthesis of Annulated 2*H*-Indazoles



entry	aryl iodide	product	isolated yield (%)
1			96
2			95
3			98[b]



4			94
5			63
6			84
7			44
8			81
9			55
10			78
11			55
12			53

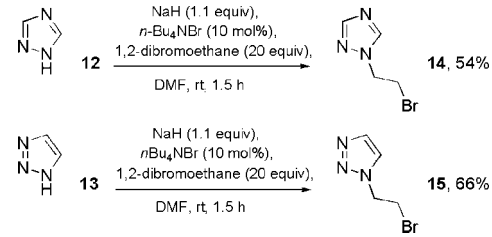
[a] Reactions were run under air atmosphere on a 0.2 mmol scale. Aryl iodide (1 equiv), $Pd(OAc)_2$ (10 mol %), tri-2-furylphosphine (22 mol %), Cs_2CO_3 (2 equiv), and norbornene (2 equiv) were heated at 90 °C in acetonitrile (0.2 M) for 24 h while a 0.3 M acetonitrile solution of bromoethylindazole (1.5 equiv) was added dropwise to the reaction mixture via syringe pump over 20 h. [b] Reaction run on 0.7 mmol scale.

of the desired compound due to formation of byproducts derived from the bromoethyl azole **3** (predominantly vinylazole **5**). After modifying the reaction conditions for the palladium-catalyzed annulation of indazole **3**, we found that a dropwise addition of a 0.2 M acetonitrile solution of **3** (1.5 equiv added over 20 h) to a solution of an aryl iodide of type **9** (1 equiv), palladium acetate (10 mol %), tri-2-furylphosphine (22 mol %), cesium carbonate (2 equiv), and norbornene (2 equiv) in acetonitrile (0.2 M) at 90 °C was best. Near-quantitative yields of the desired annulated heterocycles **10a**−**c** were obtained by reacting **3** with aryl iodides **9a**−**c** under those conditions (Table 1, entries 1−3). The straightforward synthesis of these tetracyclic nitrogen-containing heterocycles constitutes an interesting alternative to the elegant route recently reported by Kundu and co-workers.[10]

With these encouraging results in hand, we examined the scope of the reaction on the chloro-substituted indazole **8**. Reaction with both electron-rich and electron-poor aryl iodides (**9a**−**i**) afforded a variety of annulated 2*H*-indazoles in moderate to excellent yields (**11a**−**i**, 44−94%, Table 1, entries 4−12). Various substituents were tolerated under the reaction conditions including amine, chloride, ester, fluoro, methyl, methoxy, and trifluoromethyl. Changes in the electronic properties seemed to have little effect on the product yields. The 44% yield obtained for **11d** could seem disappointing at first glance but such low reactivity has been previously observed for annulation process conducted on **9d**.[1] Aryl palladium species bearing a methoxy group ortho to the palladium atom can indeed give stable five-membered palladacycles by a C−H activation reaction,[11] which can interfere with the catalytic cycle. This proposal is corroborated by the 81% yield obtained with aryl iodide **9e** bearing "non-coordinating" methoxy groups (entry 8). Comparison of entries 9 and 10 shows that having an ester substituent rather than a *N*-methyltosylamine at position 3 of the aryl iodide resulted in better reactivity. A higher yield was obtained with an ester group at position 3 rather than at position 4 (entries 10 and 11). Finally, a fluorine atom was the only functional group examined at the position meta to the iodide (**9i**) since it was previously shown[1,9] that introducing a group ortho to the C−H activation site resulted in poor yields of final product presumably due to steric interactions during the palladation of the C−H bond (entry 12).

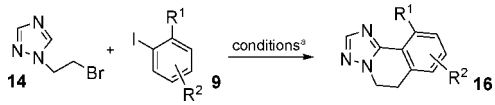
Triazoles were then examined as potential candidates for the annulation reaction. Upon treatment with an excess of 1,2-dibromoethane, 1,2,4-triazole **12** and 1,2,3-triazole **13** gave birth to their corresponding alkylated products **14** and **15**, as single regioisomers in 54% and 66% isolated yields, respectively (Scheme 3).

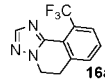
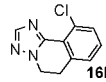
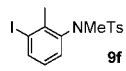
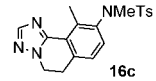
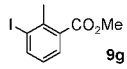
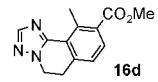
SCHEME 3. Synthesis of *N*-Bromoalkyltriazoles

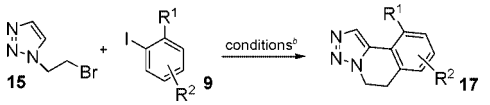


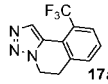
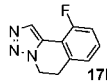
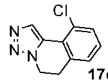
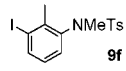
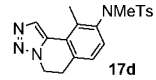
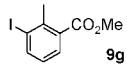
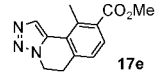
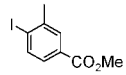
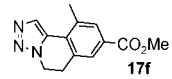
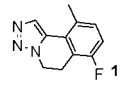
1,2,4-triazole **14** was submitted to the annulation process under the conditions previously described for the bromoalkyl indazoles but using an equimolar ratio between the aryl iodide **9** and the bromoalkyl triazole **14**.[12] The results are collected in Table 2 (entries 1−4). Once again, a variety of functional groups

TABLE 2. Synthesis of Annulated 1,2,4- and 1,2,3-Triazoles



entry	aryl iodide	product	isolated yield (%)
1	 **9a**	 **16a**	32
2	 **9c**	 **16b**	43
3	 **9f**	 **16c**	36
4	 **9g**	 **16d**	47



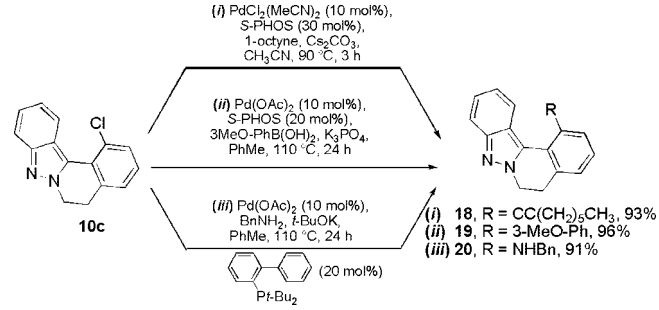
entry	aryl iodide	product	isolated yield (%)
5	 **9a**	 **17a**	71
6	 **9b**	 **17b**	85
7	 **9c**	 **17c**	89
8	 **9f**	 **17d**	81
9	 **9g**	 **17e**	90
10	 **9h**	 **17f**	76
11	 **9i**	 **17g**	64

[a] Reactions were run under air atmosphere on a 0.2 mmol scale. Aryl iodide (1 equiv), $Pd(OAc)_2$ (10 mol %), tri-2-furylphosphine (22 mol %), Cs_2CO_3 (2 equiv), and norbornene (2 equiv) were heated at 90 °C in acetonitrile (0.2 M) for 24 h while a 0.2 M acetonitrile solution of **14** (1.0 equiv) was added dropwise to the reaction mixture via syringe pump over 20 h. [b] Reactions were run under air atmosphere on a 0.3 mmol scale. Aryl iodide (1 equiv), $Pd(OAc)_2$ (10 mol %), tri-2-furylphosphine (22 mol %), Cs_2CO_3 (2 equiv), and norbornene (2 equiv) were heated at 90 °C in acetonitrile (0.2 M) for 24 h while a 0.3 M acetonitrile solution of **15** (1.5 equiv) was added dropwise to the reaction mixture via syringe pump over 20 h.

(trifluoromethyl, chloro, amine, and ester substituents) were tolerated on the aryl iodide but yields in annulated 1,2,4-triazoles **16a**−**d** remained modest (32−47%).[13] Nonetheless, it is noteworthy to mention that structural analogues of tricyclic 1,2,4-triazoles of type **16** have previously been shown to display high antifertility activity.[14]

In the case of 1,2,3-triazoles, working in slight excess of bromoalkylazole **15** resulted in a dramatic increase of the yield of these annulation reactions as aforementioned for indazoles. The substrate scope study was therefore conducted with 1.5 equiv of **15** added over 20 h by syringe pump to the mixture of the other reagents (aryl iodide, palladium acetate, tri-2-furylphosphine, norbornene, cesium carbonate) in acetonitrile at 90 °C. Relatively good yields of annulated 1,2,3-triazoles **17a**−**g** were achieved for all tested aryl iodides including a large variety of functional groups (64−90%, Table 2, entries 5−11).[15] No dramatic difference was noted between electron-withdrawing and electron-donating groups (entries 8 and 9). Nevertheless, an aryl iodide bearing an ester group at position 3 (**9g**) rather than at position 4 (**9h**) gave slightly better yield (90% vs. 76%, entries 9 and 10), which is consistent with what has been observed for 2*H*-indazoles.

SCHEME 4. Functionalization of Annulated Indazole 10c



We briefly studied the functionalization of our annulated compounds beginning with indazole **10c** through (i) Sonogashira coupling,[16] (ii) Suzuki coupling,[17] and (iii) Buchwald−Hartwig amination[18] reactions with 1-octyne, 3-methoxyphenylboronic acid, and benzylamine, respectively. Despite the steric hindrance around the coupling site of **10c**, these reactions proceeded particularly well and provided the expected compounds **18**, **19**, and **20** in high yields (93%, 96%, and 91%, respectively, Scheme 4).

The scope of these coupling reactions was then extended to indazoles **11a**,**b**,**e** (Scheme 5, vide infra). Compound **11e** appeared to be a suitable substrate to perform a double Sonogashira reaction with 1-octyne and yielded the desired product **21** in 78% yield (iv). Functionalizations at position 5 of the indazole core were then investigated. Suzuki coupling with

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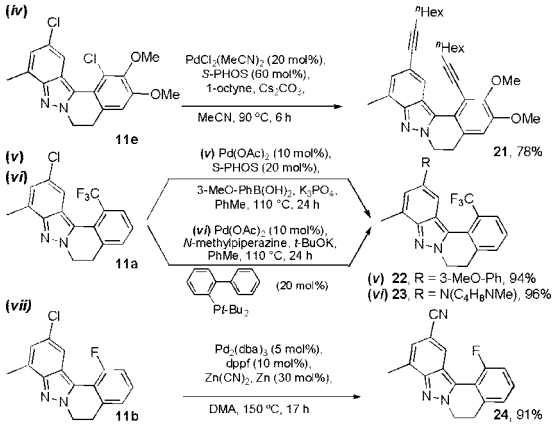
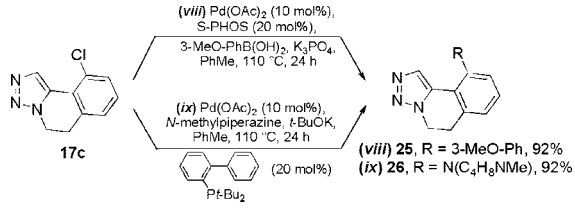
(10) Sawant, D.; Kumar, R.; Maulik, P. R.; Kundu, B. *Org. Lett.* **2006**, *8*, 1525.
(11) (a) Schiller, R.; Pour, M.; Fáková, H.; Kunes, J.; Císarová, I. *J. Org. Chem.* **2004**, *69*, 6761. (b) Dyker, G. *J. Org. Chem.* **1993**, *58*, 6426. (c) Dyker, G. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1023.
(12) Working with an excess of **14** did not bring any improvement.
(13) The formation of unproductive stable palladacycles (presumably due to the chelation ability of the triazole 4-nitrogen lone pair) might interfere with the catalytic cycle.
(14) Lerner, L. J.; Galliani, G.; Carminati, P.; Mosca, M. C. *Nature* **1975**, *256*, 130, and references cited therein.
(15) Differences observed between 1,2,4-and 1,2,3-triazoles toward the palladium-catalyzed annulation process remain elusive.
(16) Gelman, D.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 5993.
(17) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685.
(18) (a) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158. (b) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413.

SCHEME 5. Functionalization of Annulated Indazoles 11a,b,e



SCHEME 6. Functionalization of Annulated 1,2,3-Triazole 17c



3-methoxyphenylboronic acid (v) and Buchwald−Hartwig amination with *N*-methylpiperazine (vi) were conducted on indazole **11a** and gave the desired functionalized derivatives **22** and **23** in 94% and 96% yield, respectively. Finally compound **11b** was subjected to a palladium-catalyzed cyanation reaction[19] that afforded nitrile **24** in 91% yield (vii).

Suzuki coupling with 3-methoxyphenylboronic (viii) and an amination reaction with *N*-methylpiperazine (ix) were also achieved on **17c**. The desired functionalized triazoles **25** and **26** were both obtained in 92% yield (Scheme 6, vide infra).

In summary, a remarkable one-pot norbornene-mediated palladium-catalyzed annulation method whereby two C−H bond functionalizations occur was successfully applied to the synthesis of polycyclic 2*H*-indazoles and 1,2,3- and 1,2,4-triazoles with good to excellent yields. High functional group tolerance, readily available starting materials, and easy further functionalizations of the annulated products are key features of this methodology.

Experimental Section

General Procedure for the Synthesis of Annulated 2*H*-Indazoles and 1,2,3- and 1,2,4-Triazoles. A 5 mL round-bottomed flask equipped with a reflux condenser was charged with Cs_2CO_3 (2.0 equiv), $Pd(OAc)_2$ (10 mol %), tri-2-furylphosphine (22 mol %), norbornene (2.0 equiv), the aryl iodide (1.0 equiv), and CH_3CN (0.2 M). The resulting mixture was heated at 90 °C. A solution of *N*-bromoalkyl 2*H*-indazole or 1,2,3- or 1,2,4-triazole (1.5 or 1.0 equiv) in CH_3CN (0.3 or 0.2 M) was then added dropwise over 20 h via syringe pump. After addition, the mixture was heated at 90 °C for an additional 4 h. The resulting solution was then allowed to cool to room temperature, diluted with EtOAc, and finally filtered through a short plug of silica gel (EtOAc washings). Removal of the solvents gave a crude mixture that was purified by flash column chromatography over silica gel.

See the Supporting Information for details.

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

JO8017236

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