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A Palladium-Catalyzed Domino Reaction To Access 3-Amino-2*H*-indazoles from Hydrazines and 2-Halobenzonitriles

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c02766 Read Online

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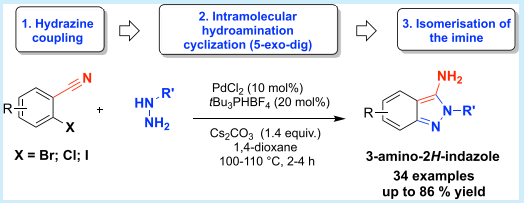
ABSTRACT: The development of a novel selective synthesis of 3-amino-2*H*-indazoles from readily available 2-halobenzonitriles is presented. The reaction proceeds through a domino reaction sequence, consisting of a regioselective palladium-catalyzed coupling of monosubstituted hydrazines with 2-halobenzonitriles, followed by an intramolecular hydroamination through a 5-exo-dig cyclization and subsequent isomerization to directly afford a wide variety of substituted 2*H*-indazole analogues in good to excellent yields.



Major advances in the identification of novel drug targets and structural biology have provided better insight into 3D structures and chemical environments of particular target families. In order to translate this knowledge into small molecule ligands, with suitable steric and electronic properties to bind the receptor, efficient drug syntheses strategies are needed. Heterocyclic compounds have proven to be highly effective ligands for a number of targets;[1−3] however, many potentially interesting substituents or substitution patterns are incompatible with traditional synthetic routes and the synthesis of well-defined highly functionalized heterocycles still frequently represents an ongoing challenge for synthetic chemists.[4−7] The indazole scaffold has been gaining increased attention in drug discovery as a privileged scaffold[8] and is known to interact with a variety of targets, in particular kinases. This culminated not only in the launch of Pazopanib **1**[9] but also more recently in the approval of the PARP 1/2 inhibitor Niraparib **3**[10,11] (Figure 1). Furthermore, the indazole scaffold can serve as an effective isostere for other structures such as indoles, benzimidazoles, and benzothiazoles.[12−14] The direct regioselective access to N-substituted 2*H*-indazoles is challenging with only a few efficient syntheses, as most synthetic approaches lead to either mixtures of 1*H*- and 2*H*-indazoles or the thermodynamically favored 1*H*-indazole.[15−20]

The functionalization of the 3-position of indazoles and in particular 2*H*-indazoles is intrinsically difficult and the focus of very recent research efforts. Apart from steric hindrance, the electronic environment disfavors smooth substitutions and a limited set of reliable transformations are described. In this context, our lab has previously developed a novel methodology for constructing 3-amino-2*H*-indazoles via a Cadogan-type reaction, allowing further functionalization, e.g. acylation, reductive amination, and diazotation.[18] To surmount limitations in building block availability, especially of 2-nitrobenzonitrile derivatives, and broaden the scope of accessible substitution patterns, we aimed to develop a direct palladium-catalyzed regioselective reaction sequence starting from commercially available materials for the preparation of 3-amino-2*H*-indazoles **12**.[16,21]

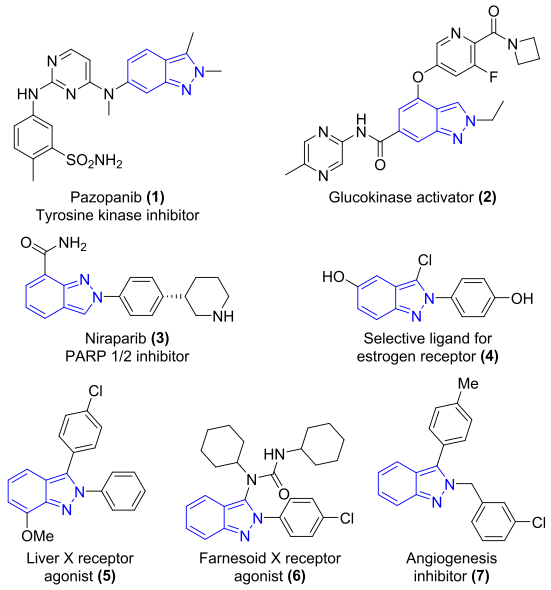


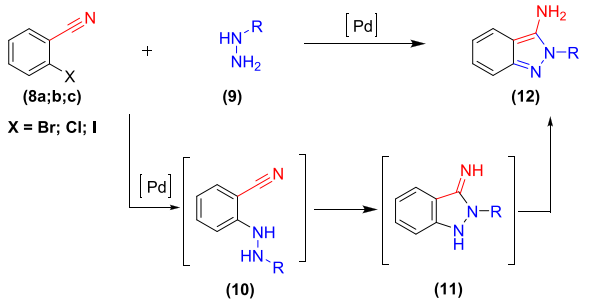
Figure 1. Marketed 2*H*-indazole drug Pazopanib **1**,[9] glucokinase activator **2**,[13] and Niraparib **3**,[10,11] selective 2*H*-indazole-based estrogen receptor ligand **4**,[22] liver X receptor agonist **5**,[23] farnesoid X receptor agonist **6**,[24] and angiogenesis inhibitor **7**.[25]

Received: August 18, 2020

https://dx.doi.org/10.1021/acs.orglett.0c02766
Org. Lett. XXXX, XXX, XXX−XXX

Here we describe the development of a novel and direct synthesis for the selective construction of 3-amino-2*H*-indazoles **12** based on a Pd-catalyzed domino reaction using readily available 2-halobenzonitriles **8** and monosubstituted hydrazines **9** (Scheme 1).

Scheme 1. Strategy for the Palladium-Mediated Access to 3-Amino-2*H*-indazoles

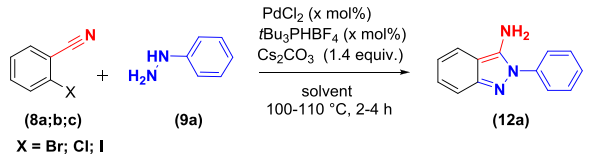


Although a number of transition-metal-catalyzed couplings between aryl halides and amides, amines, hydrazides, and hydrazones are known, only a few couplings employing hydrazines have been published.[15−17,21,26] We therefore set out to develop a regioselective transition-metal-catalyzed coupling of monosubstituted hydrazines **9** with 2-halobenzonitriles **8**, to provide the *N*,*N*′-disubstituted hydrazines **10** needed for the cyclization to **12**.

The subsequent hydroamination/5-exo-dig-cyclization step toward the formation of the 3-imino-1,2-dihydro-3*H*-indazole **11** was a further critical step, as other cyclization pathways, e.g. (6-endo-dig) and (5-endo-dig), are also favored by the Baldwin rules giving rise to other products like 1,2-dihydro-(aza)cinnolines and *N*-azaindole. We started by screening for suitable reaction conditions for the coupling of 2-bromo (**8a**), 2-chloro (**8b**), or 2-iodobenzonitrile (**8c**) and phenyl hydrazine (**9a**) to afford 2-phenyl-3-amino-2*H*-indazole (**12a**) in the presence of palladium, phosphine ligand and a base. By varying the palladium source, solvents, and base, we found the desired coupling to proceed smoothly within just a few hours and with complete regioselectivity employing a $PdCl_2$/*t*Bu_3PHBF_4 (1:2) catalyst at 110 °C and Cs_2CO_3 as base. The optimal solvents were found to be 1,4-dioxane and toluene.

Decreasing the catalyst loading to 5 mol % still afforded the desired 3-amino-2*H*-indazole **12a** in good yield (Table 1, entries 7−10), but 5 equiv of phenyl hydrazine (**9a**) were required for high yields (Table 1, entries 11 and 12 and SI Table S1). Albeit the catalyst loading could be decreased to 5 mol % without a significant drop in yield (Table 1, entries 7 and 8), 10 mol % with 3.5 equiv as well as 2 equiv of hydrazine generally provided the most robust conditions for further development without strict handling precautions. 2-Bromo, 2-chloro, and 2-iodobenzonitriles (**8a−c**) were found to react similarly with phenyl hydrazine (**9a**) to afford 2-phenyl-3-amino-2*H*-indazole (**12a**) (Table 1, entries 2−5). The free choice of halogen is clearly a major synthetic advantage, as it significantly increases the pool of available 2-halobenzonitriles substrates. Control experiments in the absence of either palladium, ligand, or base led in all cases to no detectable amounts of indazole **12a** confirming that the reaction is indeed palladium-catalyzed (see Table S2, Supporting Information)

Table 1. Optimization of Reaction Conditions[a]



N	X	Cat. mol %	Lig. mol	Ph-NH-NH_2 (equiv)	Solvent	Yield (%)
1	Br	10	20	2	toluene	85
2	Br	10	20	2	1,4-dioxane	86
3	Cl	10	20	2	1,4-dioxane	67
4	I	10	20	2	1,4-dioxane	63
5	Br	10	20	3.5	toluene	95
6	Br	10	20	3.5	1,4-dioxane	66
7	Br	5	10	3.5	toluene	67
8	Br	5	10	3.5	1,4-dioxane	60
9	Br	7	14	4.7	toluene	68
10	Br	7	14	4.7	1,4-dioxane	63
11	Cl	5	10	5	1,4-dioxane	91
12	Br	10	20	5	1,4-dioxane	74

[a]All reactions were performed in anhydrous solvent at 100−110 °C for 2−4 h. Yield of the isolated product after flash chromatography on silica gel or reversed phase HPLC.

With these optimized reaction conditions, we then explored the scope of the reaction using various monosubstituted hydrazines **9** and reacting them with 2-bromo- or 2-chlorobenzonitrile (**8a** and **b**) (Scheme 2). The 2*H*-indazoles **12** were formed in good to moderate yields (Scheme 2, **12a−v**), and importantly the domino reaction sequence was also found to proceed with nonaromatic hydrazines as well (Scheme 2). Although full conversion was observed by LCMS, the isolated yield was moderate after the purification. Besides free hydrazines their corresponding HCl salts could also be employed in the reaction when additional Cs_2CO_3 is added (Scheme 2). This result is of great practical significance, as most commercially available hydrazines are sold as their more stable hydrochloride salts, eliminating the need to liberate and handle the free hydrazines.

To further expand the scope of the domino reaction, a variety of hydrazines with electron-donating or -withdrawing groups at different positions were reacted. Electron-withdrawing groups such as CF_3, F, OCF_3, methane sulfonyl, naphtyl, or nitrile in the 4-position attached to the phenyl hydrazine accelerate the reaction, and the desired products were obtained in good to excellent yields of up to 83% while, e.g., Cl substitution formed the desired products **12h** and **12r** in moderate yield (Scheme 2). Some electron-donating substituents such as benzyloxy formed the corresponding 3-amino-2*H*-indazole in moderate to good yield (Scheme 2), whereas isopropyl, methyl, and dioxolyl afforded good yields (Scheme 2) except for the 2-ethyl substituted hydrazine which only provided a 34% yield, presumably due to increased steric hindrance (Scheme 2).

To explore the scope and versatility of this synthesis with regard to substituted 2-halobenzonitriles **8**, we performed the reaction with phenyl hydrazine (**9a**). Several substituted 2-halobenzonitriles bearing methyl, methoxy, monofluoro, difluoro, CF_3, chloro, and unprotected amine groups were compatible with the reaction conditions and produced the desired 3-amino-2*H*-indazoles **13** in very good to moderate yields. The use of methyl substituents in the 6- and 4-position

https://dx.doi.org/10.1021/acs.orglett.0c02766
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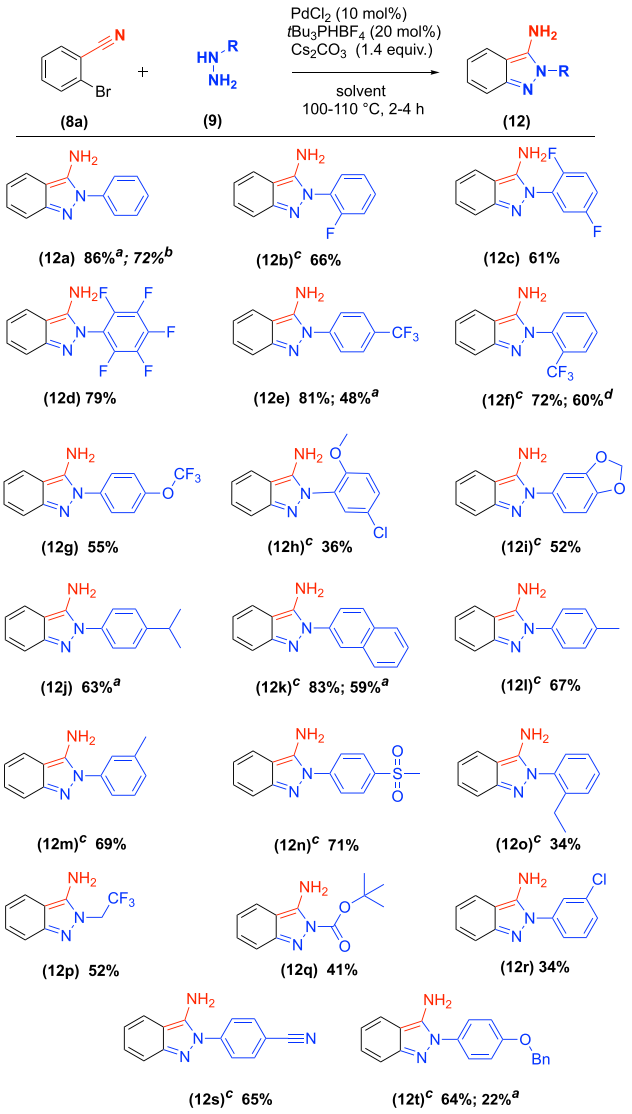
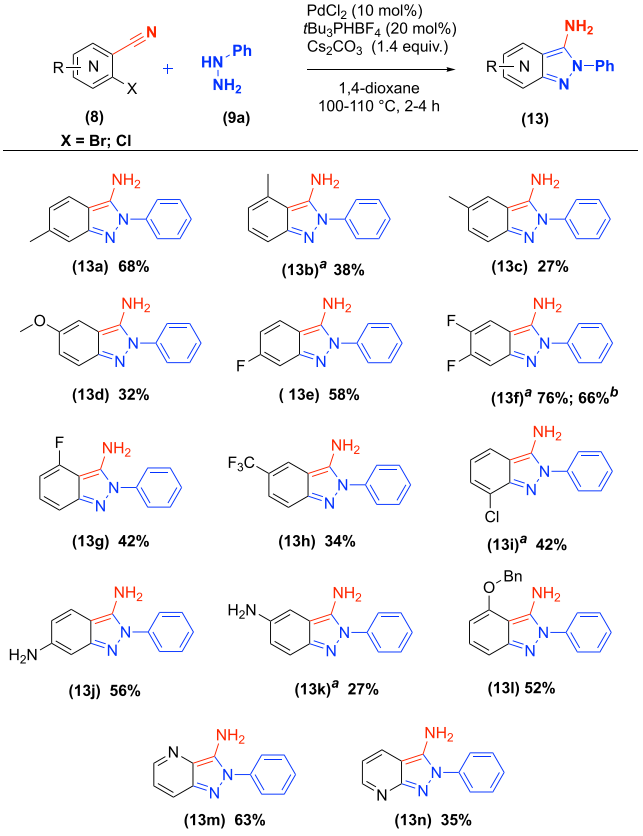
Scheme 2. Substrate Scope for Hydrazines[a]



[a]All reactions were performed with **8a** (1 equiv), hydrazine **9** (2 equiv), and Cs_2CO_3 (1.4 equiv) in 1,4-dioxane at 100−110 °C for 2-4 h. Yield of the isolated product after flash chromatography on silica gel or reversed phase HPLC. [b]Reactions were performed in toluene. [c]The reaction was carried out on a 10 mmol scale. [d]The reaction was performed with hydrazine as HCl salt and Cs_2CO_3 (2.7 equiv). [e]The reaction was carried out on a 5 mmol scale.

Scheme 3. Substrate Scope for 2-Halobenzonitriles[a]



[a]All reactions were performed with **9a** (2 equiv) and **8**, X = Br (1 equiv) in 1,4-dioxane at 100−110 °C for 4 h. Yield of the isolated product after flash chromatography on silica gel or reversed phase HPLC. [b]The reaction was performed with **8**, X = Cl (1 equiv). [c]The reaction was carried out on a 5 mmol scale with **8**, X = Cl.

led to products **13a** and **13b**, respectively, in yields of up to 68% while methyl, CF_3, and amine substituents in the 5-position (Scheme 3, **13c**, **h**, and **k**) formed the desired 2*H*-indazole in only low yield. However, for example, the unprotected amine in 4-amino-2-bromobenzonitrile was well tolerated and afforded 2*H*-indazole **13j** in good yield (56%) as well as a benzyloxy substitution in 4-position **13l** (52%). 3-Amino-2*H*-indazoles mono- or disubstitued by fluorine were obtained in good yields (Scheme 3, **13e−g**), while the reaction carrying a chloro substituent was less efficient (42%, Scheme 3, **13i**). Moreover, pyridines were converted to their highly interesting aza-3-amino-2*H*-indazole **13m−n** congeners in 63% and 35% yield, respectively.

In summary, we have established a simple and versatile synthesis of 3-amino-2*H*-indazole analogues through a one-pot sequence. The domino reaction proceeds through a regioselective coupling of 2-halobenzonitriles with monosubstituted hydrazines, followed by a reductive cyclization and isomerization to the desired 3-amino-2*H*-indazoles. Moreover, with this versatile and flexible procedure, it is possible to incorporate a variety of functionalities such as halides, as well as amine and protected hydroxyl groups, which are valuable attachment points for subsequent functionalization. This practical one-pot procedure is a novel approach to 3-amino-2*H*-indazoles directly accessing this compound class in good yields. The reaction closes a gap in current synthetic methodology as it is performed under mild conditions and, therefore, tolerates a variety of substrates and substituents.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02766.

Experimental procedures and spectral data (PDF)

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https://dx.doi.org/10.1021/acs.orglett.0c02766
Org. Lett. XXXX, XXX, XXX−XXX

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank Dr. Edgar Specker, Leibniz-Forschungsinstitut für Molekulare Pharmakologie (FMP), and Dipl. Ing. Jérôme Paul, Leibniz-Forschungsinstitut für Molekulare Pharmakologie (FMP), for recording the HRMS spectra and Dr. Peter Schmieder, Leibniz-Forschungsinstitut für Molekulare Pharmakologie (FMP), for NMR assistance. We are grateful to the Philipp Schwartz Initiative of the Alexander von Humboldt Foundation for a fellowship to Dr. Rana Alsalim.

■ REFERENCES

(1) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014**, *57*, 10257−10274.

(2) Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. Combining Molecular Scaffolds from FDA Approved Drugs:Application to Drug Discovery. *J. Med. Chem.* **2017**, *60*, 1638−1647.

(3) Smith, B. R.; Eastman, C. M.; Njardarson, J. T. Analysis of the Elemental Composition of U.S. FDA Approved Drug Architectures. *J. Med. Chem.* **2014**, *57*, 9764−9773.

(4) Taylor, A. P.; Robinson, R. P.; Fobian, Y. M.; Blakemore, D. C.; Jones, L. H.; Fadeyi, O. Modern advances in heterocyclic chemistry in drug discovery. *Org. Biomol. Chem.* **2016**, *14*, 6611−6637.

(5) Cabrele, C.; Reiser, O. The Modern Face of Synthetic Heterocyclic Chemistry. *J. Org. Chem.* **2016**, *81*, 10109−10125.

(6) Cacchi, S.; Fabrizi, G. Update 1 of: Synthesis and Functionalization of Indoles Through Palladium-Catalyzed Reactions. *Chem. Rev.* **2011**, *111*, PR215−PR283.

(7) Platon, M.; Amardeil, R.; Djakovitch, L.; Hierso, J.-C. Progress in palladium-based catalytic systems for the sustainable synthesis of annulated heterocycles: a focus on indole backbones. *Chem. Soc. Rev.* **2012**, *41*, 3929−3968.

(8) Gaikwad, D. D.; Chapolikar, A. D.; Devkate, C. G.; Warad, K. D.; Tayade, A. P.; Pawar, R. P.; Domb, A. J. Synthesis of indazole motifs and their medicinal importance: An overview. *Eur. J. Med. Chem.* **2015**, *90*, 707−731.

(9) Bukowski, R. M.; Yasothan, U.; Kirkpatrick, P. Pazopanib. *Nat. Rev. Drug Discovery* **2010**, *9*, 17−18.

(10) Jones, P.; Wilcoxen, K.; Rowley, M.; Toniatti, C. Niraparib: A Poly(ADP-ribose) Polymerase (PARP) Inhibitor for the Treatment of Tumors with Defective Homologous Recombination. *J. Med. Chem.* **2015**, *58*, 3302−3314.

(11) Zhang, S.-G.; Liang, C.-G.; Zhang, W.-H. Recent Advances in Indazole-Containing Derivatives: Synthesis and Biological Perspectives. *Molecules* **2018**, *23*, 2783.

(12) Vidyacharan, S.; Adhikari, C.; Krishna, V. S.; Reshma, R. S.; Sriram, D.; Sharada, D. S. A robust synthesis of functionalized 2*H*-indazoles via solid state melt reaction (SSMR) and their antitubercular activity. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 1593−1597.

(13) Pfefferkorn, J. A.; Tu, M.; Filipski, K. J.; Guzman-Perez, A.; Bian, J.; Aspnes, G. E.; Sammons, M. F.; Song, W.; Li, J.-C.; Jones, C. S.; Patel, L.; Rasmusson, T.; Zeng, D.; Karki, K.; Hamilton, M.; Hank, R.; Atkinson, K.; Litchfield, J.; Aiello, R.; Baker, L.; Barucci, N.; Bourassa, P.; Bourbounais, F.; D'Aquila, T.; Derksen, D. R.; MacDougall, M.; Robertson, A. The design and synthesis of indazole and pyrazolopyridine based glucokinase activators for the treatment of Type 2 diabetes mellitus. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 7100−7105.

(14) Okuzumi, T.; Fiedler, D.; Zhang, C.; Gray, D. C.; Aizenstein, B.; Hoffman, R.; Shokat, K. M. Inhibitor hijacking of Akt activation. *Nat. Chem. Biol.* **2009**, *5*, 484−493.

(15) Genung, N. E.; Wei, L.; Aspnes, G. E. Regioselective Synthesis of 2*H*-Indazoles Using a Mild, One-Pot Condensation−Cadogan Reductive Cyclization. *Org. Lett.* **2014**, *16*, 3114−3117.

(16) Halland, N.; Nazaré, M.; R'kyek, O.; Alonso, J.; Urmann, M.; Lindenschmidt, A. A General and Mild Palladium-Catalyzed Domino Reaction for the Synthesis of 2*H*-Indazoles. *Angew. Chem., Int. Ed.* **2009**, *48*, 6879−6882.

(17) Halland, N.; Nazaré, M.; Alonso, J.; R'Kyek, O.; Lindenschmidt, A. A general and mild domino approach to substituted 1-aminoindoles. *Chem. Commun.* **2011**, *47*, 1042−1044.

(18) Bel Abed, H.; Schoene, J.; Christmann, M.; Nazaré, M. Organophosphorus-mediated N−N bond formation: facile access to 3-amino-2*H*-indazoles. *Org. Biomol. Chem.* **2016**, *14*, 8520−8528.

(19) Schoene, J.; Bel Abed, H.; Schmieder, P.; Christmann, M.; Nazaré, M. A General One-Pot Synthesis of 2*H*-Indazoles Using an Organophosphorus−Silane System. *Chem. - Eur. J.* **2018**, *24*, 9090−9100.

(20) Schoene, J.; Gazzi, T.; Lindemann, P.; Christmann, M.; Volkamer, A.; Nazaré, M. Probing 2*H*-Indazoles as Templates for SGK1, Tie2, and SRC Kinase Inhibitors. *ChemMedChem* **2019**, *14*, 1514−1527.

(21) Crawford, S. M.; Lavery, C. B.; Stradiotto, M. BippyPhos: A Single Ligand With Unprecedented Scope in the Buchwald−Hartwig Amination of (Hetero)aryl Chlorides. *Chem. - Eur. J.* **2013**, *19*, 16760−16771.

(22) De Angelis, M.; Stossi, F.; Carlson, K. A.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. Indazole Estrogens: Highly Selective Ligands for the Estrogen Receptor *β*. *J. Med. Chem.* **2005**, *48*, 1132−1144.

(23) Aganda, K. C. C.; Kim, J.; Lee, A. Visible-light-mediated direct C3-arylation of 2*H*-indazoles enabled by an electron-donor−acceptor complex. *Org. Biomol. Chem.* **2019**, *17*, 9698−9702.

(24) Richter, H. G. F.; Benson, G. M.; Bleicher, K. H.; Blum, D.; Chaput, E.; Clemann, N.; Feng, S.; Gardes, C.; Grether, U.; Hartman, P.; Kuhn, B.; Martin, R. E.; Plancher, J. M.; Rudolph, M. G.; Schuler, F.; Taylor, S. Optimization of a novel class of benzimidazole-based farnesoid X receptor (FXR) agonists to improve physicochemical and ADME properties. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1134−1140.

(25) Chen, H.-S.; Huang, L.-J.; Kuo, S.-C.; Lee, F.-Y.; Shih, M.-L.; Teng, C.-M. Synthesis of substituted 2*H*-indazole derivatives as anti-angiogenic agents. EP1659115, 2006.

(26) DeAngelis, A.; Wang, D.-H.; Buchwald, S. L. Mild and Rapid Pd-Catalyzed Cross-Coupling with Hydrazine in Continuous Flow: Application to the Synthesis of Functionalized Heterocycles. *Angew. Chem., Int. Ed.* **2013**, *52*, 3434−3437.