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Development of a Late-Stage Diversification Strategy for the 4- and 5-Positions of 4,5,6-Trisubstituted Indazoles

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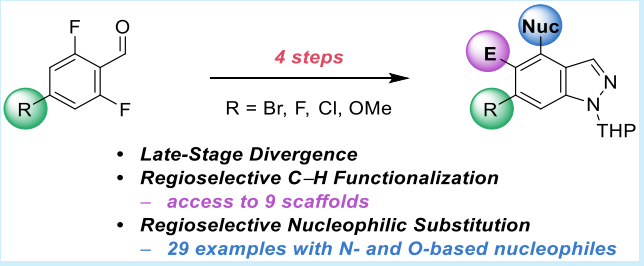
ABSTRACT: Indazoles represent a privileged motif in drug discovery. However, the formation of highly substituted indazoles can require the execution of lengthy synthetic routes with minimal opportunities to introduce diversity. In this report, we disclose the development of a late-stage diversification strategy for the 4- and 5-positions of 4,5,6-trisubstituted indazoles. A regioselective C−H functionalization and subsequent nucleophilic aromatic substitution provide two sequential points of diversification. The synthetic sequence delivers rapid access to an array of 4,5,6-trisubstituted indazoles in only four steps from readily available starting materials.



Nitrogen-containing heterocycles are ubiquitous in medicinal chemistry and marketed pharmaceuticals.[1] Indazoles represent an important class of bicyclic heterocycles due to their 1,2-donor−acceptor arrangement. A prodigious amount of research has focused on the construction and application of indazoles in biologically active molecules.[2−5] Although observed sparingly in nature,[6−8] indazole-containing compounds have been utilized in an array of therapeutic areas, including as antibacterial,[9] anticancer,[10−12] anti-inflammatory,[13] antiprotozoal,[14] and antiviral[15] agents (Figure 1). Given the utility of the indazole scaffold, the ability to incorporate a range of diversity, in a unified manner, would greatly facilitate the examination of structure−activity and structure−property relationships in a drug discovery program possessing this core.

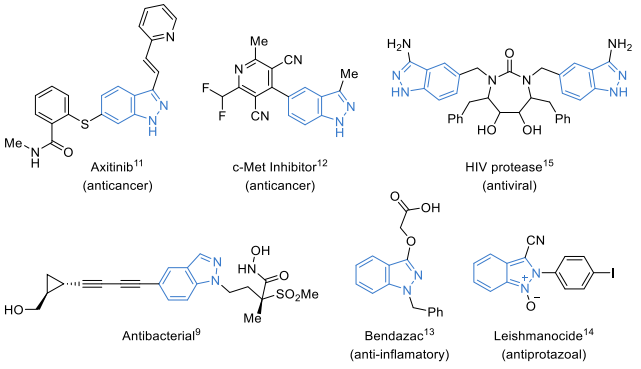


Figure 1. Representative examples of bioactive compounds containing the indazole motif.

The syntheses of indazoles have utilized a wide array of chemical methods.[16−18] Traditionally, indazoles have been synthesized through the cyclization of *o*-toluidine diazonium salts[19,20] or the intramolecular cyclization of arylhydrazones.[21] Transition-metal-catalyzed/mediated formations of 1*H*-indazoles are also prevalent in the literature.[22] Much of this work focuses on the formation of mono- and disubstituted indazoles; however, Tsui and co-workers reported the synthesis of highly substituted indazoles using a palladium-catalyzed cycloaddition of alkynes with pyrazoles to form 4,5,6,7-tetrasubstituted indazoles.[23]

The late-stage functionalization of indazoles generally requires the early introduction of a cross-coupling handle that can survive the indazole formation step.[24−26] The development of methods beyond cross-coupling strategies for the derivatization of indazoles has remained largely unexplored, with the majority of reported methodologies taking advantage of the inherent reactivity at the C3-position.[27,28] Direct alkenylation of both 1*H*- and 2*H*-indazoles at the C3- and C7-positions has been achieved using palladium and rhodium catalysis.[29,30] Methods for direct C−H functionalization of the arene ring of indazoles have remained somewhat elusive. Herein, we report the synthesis of 4,5,6-trisubstituted

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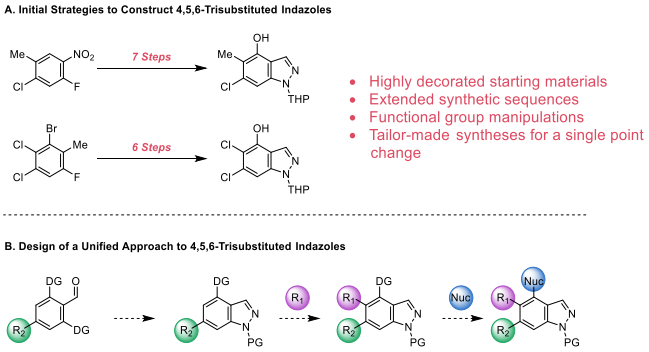
Scheme 1. Initial Efforts Towards the Synthesis of 4,5,6-Trisubstituted Indazoles Compared with a More Unified Route



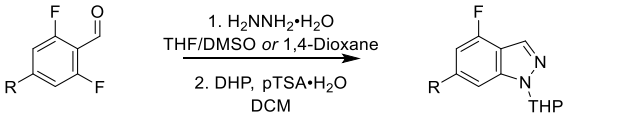
indazoles via the unification of direct C−H functionalization methodology and a late stage-diversification strategy.

Our interest in the syntheses of a diverse array of 4,5,6-trisubstituted indazoles stemmed from a recent need to broadly evaluate the structure−activity relationship (SAR) of this motif as a key pharmacophore in one of our lead-optimization campaigns. Regrettably, the syntheses of these functionalized indazoles proved to be lengthy and inefficient. Moreover, each synthesis had to be tailor-made for the specific indazole-containing target (Scheme 1A). It became evident that a unified synthesis of 4,5,6-trisubstituted indazoles with the potential for late-stage diversification at the 4- and 5-positions would be highly enabling.

We took inspiration in our route design from the broad availability of 2,6-difluorobenzaldehydes (Scheme 1B). Moreover, the *C*2 symmetry of these molecules permits their cyclization with hydrazine to the corresponding 4,6-disubstituted indazoles without a need to establish regiocontrol. Direct C−H functionalization at the C5-position would serve as our first point of diversification. Subsequent nucleophilic aromatic substitution at C4 would further expand the collection of indazoles that can be accessed through this synthetic sequence.

Our initial efforts focused on optimizing the formation of 1*H*-indazoles **2a−d** (Scheme 2) from the corresponding 2,6-difluorobenzaldehyde starting material. Inspired by the work of Lukin and co-workers,[21] a one-pot, two-step sequence was examined. The aryl hydrazone is preformed in tetrahydrofuran (THF) followed by solvent exchange to dimethyl sulfoxide (DMSO) and ring closure to furnish our desired indazole. By adapting previously reported conditions for a one-step hydrazone formation, ring closure provided access to the target indazole using 1,4-dioxane as solvent.[31] Subsequent THP-protection provided the protected 1*H*-indazole.[32] This sequence was successful with both electron-withdrawing (**2a−2c**) and electron-donating (**2d**) groups at the C4-postion, albeit with depreciated yield for the electron-rich substrate.

Scheme 2. Formation of Indazoles 2a−d Using Aryl Aldehydes and Hydrazine Followed by THP-Protection



2a (R = Br): 57% yield (2 steps)
2b (R = F): 85% yield (1 step)
2c (R = Cl): 75% yield (2 steps)
2d (R = OMe): 15% yield (2 steps)

With the requisite 4,6-disubstituted indazoles in hand, our attention turned to the regioselective C−H functionalization of the C5-position. Although ^{1}H NMR analysis indicated that the C7-proton is likely most acidic,[33] we speculated that the C4-fluorine could serve as a directing group to achieve deprotonation at the C5-position.[34−41] Quenching the anion with an electrophilic chlorinating agent would provide desired indazole **3c**.

Our initial efforts using indazole **2c** employed magnesium bases due to the lower propensity of aryl-magnesium species to form benzyne at elevated temperatures (Table 1, entries 1−3).[42] Unfortunately, no product was detected when using $Mg(NiPr_2)_2$ or TMPMgCl·LiCl (entries 1 and **2**). Using $(TMP)_2Mg·2LiCl$ as the base (entry 3) delivered the desired chlorination product in low conversion. We then assessed lithium bases and found that LDA performed well, delivering the desired product in 44% yield (entry 4) with a high level of regioselectivity (>20:1, **3c**:**3c**′). Complete consumption of the starting material was critical for purification as separation of **2c** and **3c** was challenging. The use of hexachloroacetone as the electrophilic chlorinating agent (entry 5) proved unfruitful, as **3c** was isolated in diminished yield. It is known that LiCl can aid in the reduction of aggregates in lithiation reactions.[43−46] The addition of LiCl in this transformation provided a cleaner reaction profile, furnishing the desired product in 68% yield, while maintaining high levels of regioselectivity (entry 6). Employing *n*-BuLi as the base flipped the regioselectivity to favor chlorination at the 7-position (entry 7), delivering **3c**′ as the major regioisomer in good yield. It is known that THP protecting groups have demonstrated the ability to serve as *o*-directing groups in *o*-lithiations.[47,48] Additionally, due to steric effects of the THP group, the 7-position could be more accessible to *n*BuLi than LDA. Finally, a slight exotherm was observed upon addition of the electrophile, which we speculated could impact the stability of the anion. As such, inverse addition, wherein the indazole anion was added to a precooled solution of the electrophile, was applied (entry 8). This protocol provided a moderate increase in yield and an improved reaction profile to deliver **3c** in 81% isolated yield. Additional optimization studies focused on reducing the loading of reagents to deliver a more process-friendly protocol.

With optimized conditions in hand, the scope of the regioselective C−H chlorination was evaluated (Scheme 3). Chlorination of indazoles containing either electron-withdrawing or electron-donating C6-functional groups was successful (**3a−d**), with **3c** being obtained on >40 g scale. We subsequently found that the lithiated species could be quenched with a variety of electrophiles to achieve C5-

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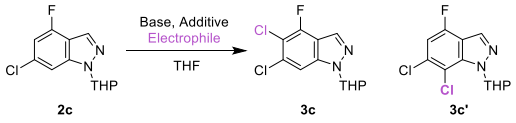
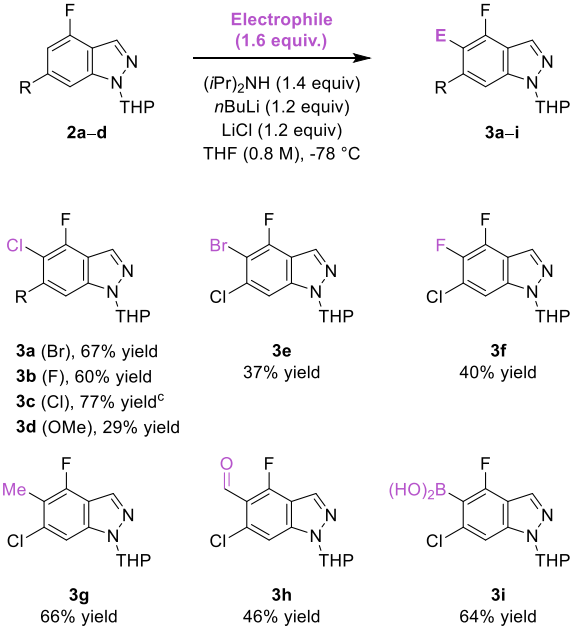
Table 1. Selected Conditions for Optimization of the Directed Lithiation and Anion Quenching with Chlorinating Reagent[a,b,c]



Entry	Substrate	Base (equiv)	Additive	"E" (equiv)	Temp	2c:3c	yield	c:c'
1	**2c**	$Mg(NiPr_2)_2$ (1.0)	None	C_2Cl_6 (2.0)	-20−0 °C	>20:1	ND	ND
2	**2c**	TMPMgCl•LiCl (1.1)	None	C_2Cl_6 (1.4)	-20−0 °C	>20:1	ND	ND
3	**2c**	$(TMP)_2Mg$•2LiCl (1.0)	None	C_2Cl_6 (2.0)	-20−0 °C	10:1	ND	3:1
4	**2c**	LDA (1.4)	None	C_2Cl_6 (1.4)	-78 °C	1:20	44%	>20:1
5	**2c**	LDA (1.4)	None	$CO(CCl_3)_2$ (1.4)	-78 °C	1:3	38%	>20:1
6	**2c**	LDA (1.4)	LiCl (1.4)	C_2Cl_6 (2.0)	-78 °C	1:20	68%	>20:1
7	**2c**	*n*BuLi (1.2)	LiCl (1.2)	C_2Cl_6 (1.6)	-78 °C	1:10	70% (1:5 *rr*)	1:5
8	**2c**	LDA (1.4)	LiCl (1.4	C_2Cl_6 (2.0)	-78 °C	<1:20	81%[d]	>20:1

[a]Reported yields are of isolated material. [b]Ratios of starting material: product (**2**:**3**) determined by ^{1}H NMR analysis of crude material. [c]Ratio of regioselectivity (c:c′) determined by ^{1}H NMR analysis of crude material. [d]Inverse addition performed.

Scheme 3. Substrate Scope of the Regioselective Directed Lithiation and Electrophilic Quenching[a,b]



[a]Reported yields are of isolated material. [b]Unless otherwise noted, reactions were conducted on 1.0 mmol scale. [c]Reaction to produce **3c** was conducted on 49 g scale.

diversification. Bromination with dibromoethane and fluorination with NFSI provided **3e** and **3f**, in 37% and 40% yield, respectively. Methylation with iodomethane delivered **3g** in 66% yield. Formylation with DMF proceeded in moderate yield (**3h**). Borylation with trimethylborate delivered **3i** in 64% yield, providing a functional group handle for subsequent cross-coupling reactions.

We next turned our attention to the nucleophilic aromatic substitution of the 4-fluoro group with *N*- and *O*-based nucleophiles (Scheme 4). Utilizing **3b** as the indazole substrate, it was found that heteroaryl amines undergo nucleophilic substitution (**4a**−**h**). Using benzimidazole, substitution product **4a** was isolated in 90% yield.[49] Employing 1*H*-indazole as the nucleophile delivered desired product **4b** in good yield as the major isomer,[50] with small amounts of the product of *N*-2 substitution detected.[32,51] Using pyrazole and 2-methylimidazole delivered the desired substitution products, **4d** and **4e**, in >95% yield and 90% yield, respectively. 1,2,4-Triazoles also served as functional nucleophiles, delivering **4f** and **4g** in good yield. It is postulated that, in the deprotonated form, a destabilizing effect from the adjacent lone pair amplifies the nucleophilicity of *N*-1, favoring reactivity at this position. To our delight, **4g** was crystalline, which permitted us to obtain an X-ray crystal structure, allowing unambiguous assignment of both the *N*-selectivity of the triazole and the regioselectivity on the indazole fluorine of **3b**. It is reasoned the 4-position of the indazole is more electrophilic due to electronics of the carbonyl-like C3-position. The regioselectivities of the other products were assigned in accordance with this result. Using 3-aminopyrazole as the nucleophile delivered **4h** in 70% yield as the major isomer, with minor isomers of nitrogen substitution occurring. Surveying amides led to the evaluation of 2-pyrrolidinone, which provided **4i** in 82% yield with *N*-selectivity. Extrapolation of our standard reaction conditions (Cs_2CO_3, room temperature) to aliphatic amines proved unsuccessful. However, it was found that the desired S_NAr reaction occurred at an elevated temperature (90 °C) with excess amine (no exogenous base) to provide the corresponding products **4j** and **4k** in moderate yield. Hydroxylation of **3b** with water delivered **4l** in >95% yield. Aliphatic alcohols served as nucleophiles in this transformation, furnishing **4m**−**o** in excellent yields. Employing **3c** as the indazole provided similar reactivity and selectivity as observed with **3b**. Again, we saw good reactivity from heteroaryl *N*-based nucleophiles (**5a**−**h**). When using 4-azaindazole as the nucleophile, product **5c** was formed with

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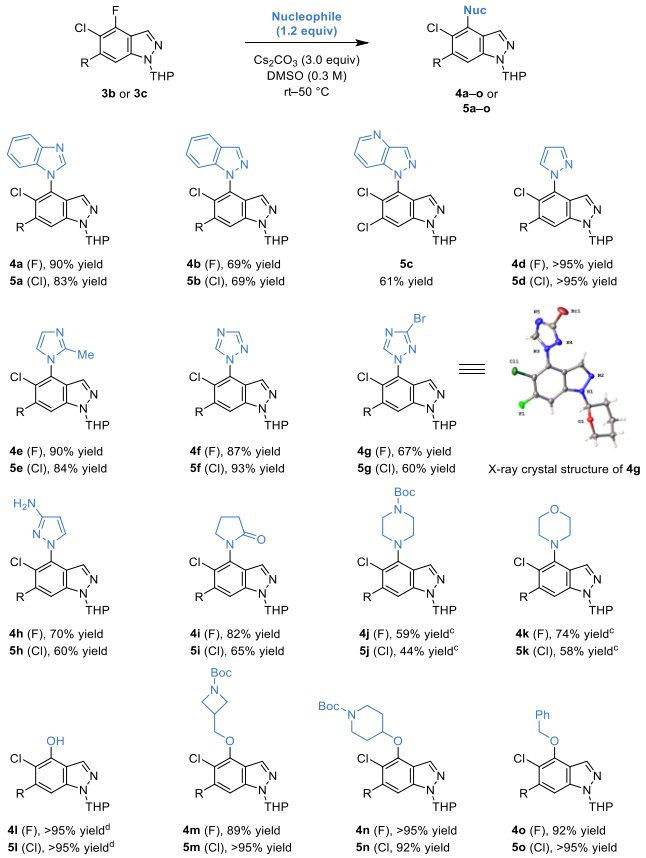
Scheme 4. Substrate Scope of Substitution Reaction with *N*- and *O*-Based Nucleophiles[a,b]



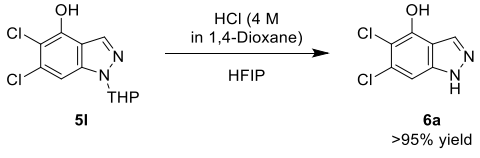
[a]Reported yields are of isolated material. [b]Unless otherwise noted, reactions were conducted on 0.3 mmol scale. [c]5 equiv of the amine was used and the reactions were conducted at 90 °C. [d]Reactions conducted on 1 mmol scale.

the same regiochemistry (*N*-1 attack) as seen when using indazole (**4b** and **5b**).[52] As before, 2-pyrrolidinone attack proceeded to form **5i** in 65% yield. It was also observed that aliphatic amines required the same reaction parameter adjustment as before, furnishing **5j** and **5k** in diminished yields. *O*-Based nucleophiles participated in the transformation with **3c** to similar levels as observed with **3b**, delivering substitution products **5l–o** in high yields.

Lastly, facile deprotection of **5l** using strong acid delivered 4,5,6-trisubstituted indazole **6a** in quantitative yield (Scheme 5).

In conclusion, we have developed a route to access a variety of highly functionalized 4,5,6-trisubstituted indazoles in only four steps from commercially available materials. Central to this approach is the regioselective C–H functionalization of the C5-position with a variety of electrophiles. Nucleophilic aromatic substitution at the C4-position delivers an additional handle for regioselective functionalization with *N*- and *O*-based nucleophiles. These transformations offer two sequential points of diversification and obviate the need for tailor-made indazole syntheses. This approach is highly enabling for rapid SAR determination thus further enhancing medicinal chemists' synthetic toolbox. Further studies evaluating the regioselectivity in the directed lithiation are ongoing in our laboratory.

Scheme 5. Deprotection To Furnish 4,5,6-Trisubstituted Indazole 6a



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03440.

Experimental procedures and characterization data for all novel compounds (PDF)

Accession Codes

CCDC 2038443 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(52) See Supporting Information for characterization and regiochemical assignment of **5b** and **5c** using NMR studies.

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