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# Cu-Catalyzed Denitrogenative Transannulation of 3-Aminoindazoles To Assemble 1-Aminoisoquinolines and 3-Aminobenzothiophenes

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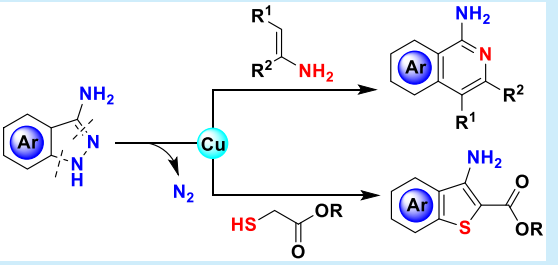
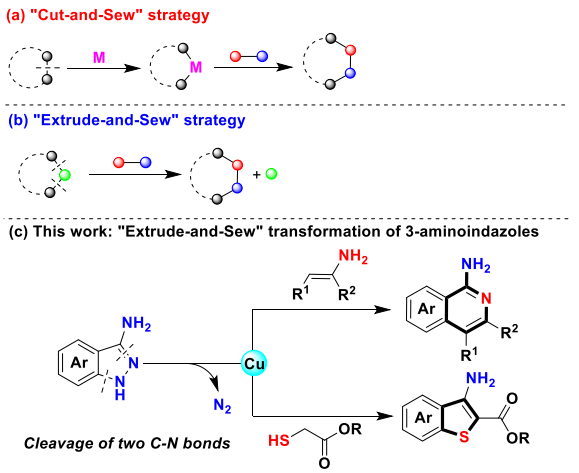
Supporting Information

**ABSTRACT:** We disclose a novel Cu-catalyzed denitrogenative transannulation of 3-aminoindazoles to afford diverse functionalized 3-aminobenzothiophenes and 1-aminoisoquinolines, in which denitrogenative transannulation of 3-aminoindazoles is reported for the first time. This transformation proceeds via an "extrude-and-sew" strategy with an unprecedented radical reactivity of 3-aminoindazoles.




The development of new strategies for successive multiple bond cleavage and multiple bond formation to forge complex molecules is an important goal in organic chemistry. Recently, a variety of "cut-and-sew" reactions have been developed by organic chemists[1] as the "cut-and-sew" tactics could rapidly construct complex molecules by incorporating two skeletons and reorganizing bond connections. This "cut-and-sew" strategy typically involves oxidative addition of transition metals into strained C−C bonds followed by 2$\pi$ unit insertion (Scheme 1a). Although most excellent "cut-and-sew" transformations design and prepare special strained substrates, displaying high atom economy and providing an efficacious and direct approach to access intricate frameworks, it is still a powerful tool to acquire complicated compounds.[1] Another alternative tactic involves cleavage of two bonds and extrusion of a small molecule (such as CO, $N_2$, $CO_2$, etc.) from the parent substrates, followed by introduction of a new group from another reactant, named "extrude-and-sew" transformations (Scheme 1b).[2] 3-Aminobenzothiophene and 1-aminoisoquinoline derivatives are widely found as privileged core structural motifs in many bioactive compounds.[3,4] Meanwhile, they also serve as versatile building blocks for the generation of isoquinoline and benzothiophene derivatives.[5,6] In this letter, we demonstrate a novel "extrude-and-sew" transformation of 3-aminoindazoles to assemble the valuable 3-aminobenzothiophene and 1-aminoisoquinoline derivatives.

**Scheme 1. "Cut-and-Sew" Transformations and "Extrude-and-Sew" Transformations**




Since the research groups of Gevorgyan,[7] Fokin,[8] and Murakami[9] reported the pioneering studies on denitrogenation reaction of triazoles to generate highly electrophilic $\alpha$-imino metal carbenoid species, during the past decades, myriads of work based on the transition-metal-catalyzed denitrogenative transannulation of triazoles have been reported for the synthesis of azo-heterocyclic compounds.[10,11] In addition to the triazoles, the denitrogenative transannulation of benzotriazinones was also developed,[12] in which diverse isoquinolone derivatives were produced via regioselective insertion of benzotriazinones with various unsaturated compounds. In 2018, Murakami disclosed a Rh-catalyzed enantioselective denitrogenative transannulation of 1*H*-tetrazoles with styrenes for the construction of 3,5-diaryl-

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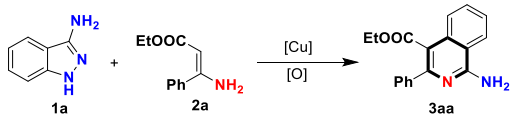
2-pyrazolines.[13a] In the same year, Chattopadhyay demonstrated an excellent Ir-catalyzed intramolecular transannulation of tetrazoles.[13b] Very recently, Chattopadhyay's group also disclosed the Fe(II)-mediated intermolecular denitrogenative transannulation of 1,2,3,4-tetrazoles, overriding traditional click chemistry.[13c] Although the denitrogenative transannulations of triazoles, benzotriazinones, and tetrazoles have been previously studied, the denitrogenative transannulation of 3-aminoindazoles has never been reported so far. As part of our ongoing interest in exploring new reactions of 3-aminoindazoles,[14] herein, we describe a novel Cu-catalyzed denitrogenative transannulation of 3-aminoindazoles to afford diverse functionalized 3-aminobenzothiophenes and 1-aminoisoquinolines (Scheme 1c).

To experimentally verify our hypothesis, we selected the commercially available 3-amino-1*H*-indazole (**1a**) as a model substrate to react with (*Z*)-ethyl 3-amino-3-phenyl acrylate (**2a**). At the outset, when the reaction was performed in the presence of $Cu(OAc)_2$ and *tert*-butyl peroxybenzoate (TBPB) in $CH_3CN$ at 60 °C using $K_2CO_3$ as the base, desired product ethyl 1-amino-3-phenylisoquinoline-4-carboxylate (**3aa**) was obtained in 47% yield (Table 1, entry 1). Subsequently, the model reaction was subjected to various oxidants to investigate the effect of the oxidants (Table 1, entries 2−10). Among the oxidants tested, *tert*-butyl hydroperoxide (TBHP) demonstrated the optimal efficiency (Table 1, entry 3). We then screened

**Table 1. Optimization of the Reaction Conditions**



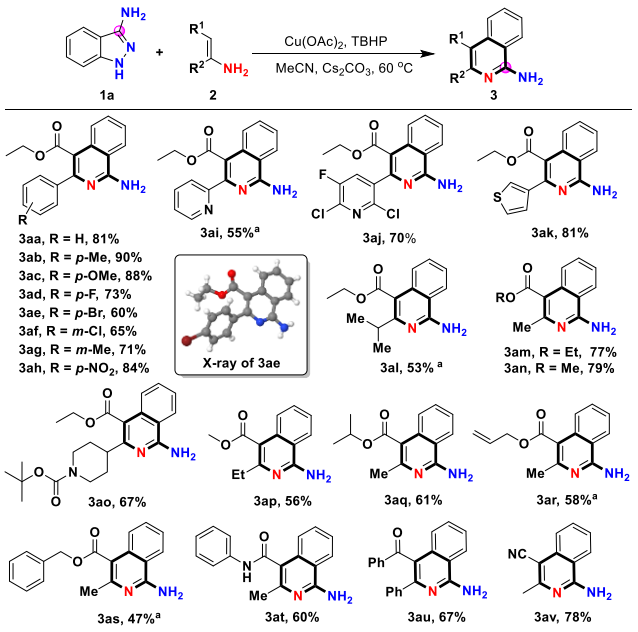

| entry[a] | [Cu] | oxidant | base | yield (%) of **3aa**[b] |
|---|---|---|---|---|
| 1 | $Cu(OAc)_2$ | TBPB | $K_2CO_3$ | 47 |
| 2 | $Cu(OAc)_2$ | DTBP | $K_2CO_3$ | 27 |
| 3 | $Cu(OAc)_2$ | TBHP | $K_2CO_3$ | 61 |
| 4 | $Cu(OAc)_2$ | $O_2$ | $K_2CO_3$ | 31[c] |
| 5 | $Cu(OAc)_2$ | $K_2S_2O_8$ | $K_2CO_3$ | 36 |
| 6 | $Cu(OAc)_2$ | $Na_2S_2O_8$ | $K_2CO_3$ | 25 |
| 7 | $Cu(OAc)_2$ | LPO | $K_2CO_3$ | <10 |
| 8 | $Cu(OAc)_2$ | PIFA | $K_2CO_3$ | trace |
| 9 | $Cu(OAc)_2$ | IBX | $K_2CO_3$ | 22 |
| 10 | $Cu(OAc)_2$ | PhIO | $K_2CO_3$ | 43 |
| 11 | $CuCl_2$ | TBHP | $K_2CO_3$ | 18 |
| 12 | CuI | TBHP | $K_2CO_3$ | 56 |
| 13 | $CuBr_2$ | TBHP | $K_2CO_3$ | 43 |
| 14 | $Cu(OAc)_2$ | TBHP | DBU | trace |
| 15 | $Cu(OAc)_2$ | TBHP | NaOAc | 10 |
| 16 | $Cu(OAc)_2$ | TBHP | NaOH | 58 |
| 17 | $Cu(OAc)_2$ | TBHP | $Li_2CO_3$ | 22 |
| 18 | $Cu(OAc)_2$ | TBHP | $K_3PO_4$ | 65 |
| 19 | $Cu(OAc)_2$ | TBHP | $Cs_2CO_3$ | 81[d] |
| 20[e] | $Cu(OAc)_2$ | TBHP | $Cs_2CO_3$ | 62 |
| 21[f] | $Cu(OAc)_2$ | TBHP | $Cs_2CO_3$ | 73 |
| 22[g] | $Cu(OAc)_2$ | TBHP | $Cs_2CO_3$ | 60 |

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.2 mmol), [Cu] (20 mol %), oxidant (2 equiv), base (2 equiv), under air, 60 °C, 20 h. [b]GC yield. [c]When $O_2$ balloon was used for 24 h, the yield of **3aa** was 58%. [d]Isolated yield. [e]$Cs_2CO_3$ (3 equiv). [f]80 °C. [g]RT; LPO = lauroyl peroxide; PIFA = [bis(trifluoroacetoxy)iodo]benzene; IBX = 2-iodylbenzoic acid.

several copper catalysts. Disappointingly, only marginal improvements were obtained when other Cu salts, such as $CuCl_2$, CuI, and $CuBr_2$, were used in place of $Cu(OAc)_2$ (Table 1, entries 11−13). To enhance the reaction yield, we also inspected a series of bases (Table 1, entries 14−19). Organic bases, such as DBU, just lead to a stagnant reaction. The yield of **3aa** was significantly increased to 81% when $Cs_2CO_3$ was employed as the base (Table 1, entry 19). The attempt to increase the amount of $Cs_2CO_3$ resulted in a lower yield of **3aa** (Table 1, entry 20). The model reaction failed to deliver higher yields whether we increased or decreased the temperature (entries 21 and 22).

Having identified the optimal reaction conditions, the scope of this Cu-catalyzed oxidative transannulation of 3-aminoindazoles to afford 1-aminoisoquinoline derivatives was evaluated (Scheme 2). A variety of functionalized enamines

**Scheme 2. Substrate Scope with Respect to Enamines***




*All reactions unless otherwise stated were carried out with **1** (0.3 mmol), **2** (0.2 mmol), $Cu(OAc)_2$ (20 mol %), $CsCO_3$ (2 equiv), and TBHP (2 equiv) in MeCN (1.0 mL) heated at 60 °C for 20 h. [a]**1** (0.2 mmol), **2** (0.4 mmol).

were surveyed initially. The electronic effects of the substituents on the aromatic rings of the *β*-enamine esters had no significant effect on the reaction yields, and the corresponding 1-aminoisoquinolines (**3aa**−**3ah**) were obtained in good to high yields. The structure of **3ae** was unambiguously confirmed by X-ray crystallographic analysis. Heteroaromatic *β*-enamine esters such as **2i**−**2k** were tolerable under the standard conditions, as well, delivering the targeted products **3ai**−**3ak** in 55, 70, and 81% yield, respectively. In addition to the aromatic *β*-enamine esters, the alkyl-substituted *β*-enamine esters **2l**−**2s** were also good candidates in this denitrogenative transannulation, affording the expected 1-aminoisoquinolines **3al**−**3as** in moderate to good yields. (*Z*)-3-Amino-*N*-phenylbut-2-enamide **2t** could be engaged in this reaction, as well, and product **3at** was achieved in 60% yield. Enamines bearing ketone and nitrile were also found to be good "sew" partners, providing the desired 1-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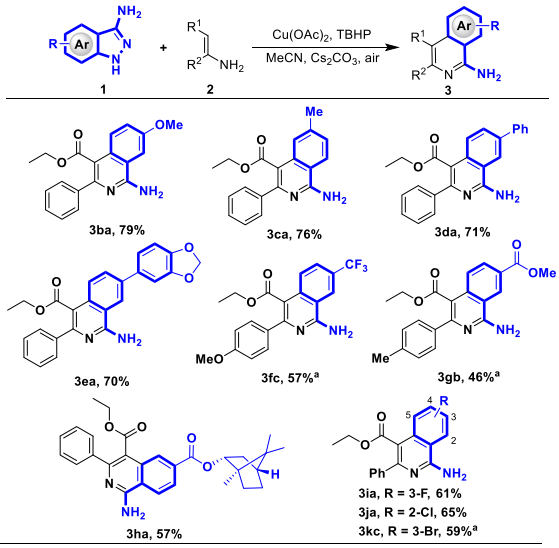
aminoisoquinolines **3au** and **3av** in 67 and 78% yields, respectively.

Subsequently, the scope with regard to 3-aminoindazoles was inspected (Scheme 3). Different substituted 3-aminoindazoles

**Scheme 3. Substrate Scope with Respect to 3-Aminoindazoles***

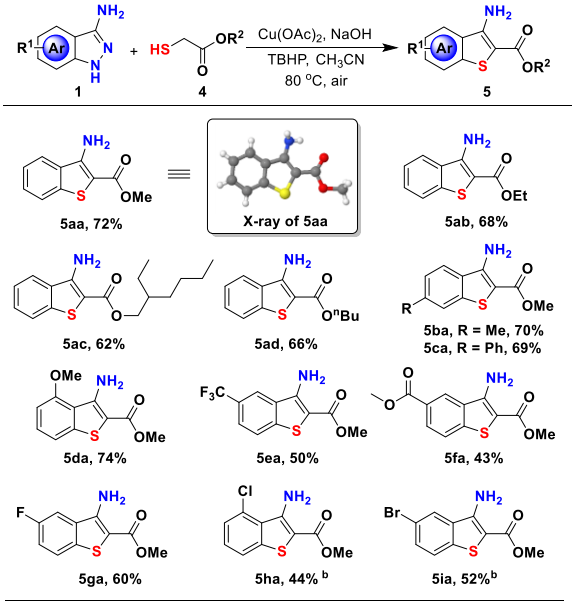



*All reactions unless otherwise stated were carried out with **1** (1.5 equiv), **2** (0.2 mmol), $Cu(OAc)_2$ (20 mol %), $Cs_2CO_3$ (2 equiv), and TBHP (2 equiv) in MeCN (1.0 mL) heated at 60 °C for 20 h. [a]**1** (2 equiv).

could be successfully transformed into the targeted 1-aminoisoquinolines under this novel Cu-catalyzed denitrogenative transannulation of 3-aminoindazoles. 3-Aminoindazole derivatives that bear either electron-donating or electron-withdrawing groups on the aromatic rings were very compatible, rendering the targeted products (**3ba**−**3ea**, **3fc**, **3gb**) in 46−79% yields. Borneo-(−)-derived 3-aminoindazole was proven to be a good donor in this denitrogenative transannulation, enabling the production of **3ha** in 57% yield. Halo-substituted 3-aminoindazoles, such as fluoro, chloro, and bromo, could work smoothly under the optimal conditions, furnishing the desired products (**3ia**, **3ja**, **3kc**) in 61, 65, and 59% yield, respectively.

Inspired by the successful preparation of 1-aminoisoquinolines through this Cu-catalyzed denitrogenative transannulation of 3-aminoindazoles, we then moved our focus to explore other reagents as the "sew" partners. The mercaptoacetates aroused our attention. If the mercaptoacetates could be transformed under this "extrude-and-sew" reaction, the valuable 3-aminobenzothiophenes would be acquired. To verify our hypothesis, the reaction of 3-amino-1*H*-indazole (**1a**) and methyl 2-mercaptoacetate (**4a**) was carried out. The expected product 3-aminobenzothiophene **5aa** was generated indeed with good yield when the reaction was performed at 80 °C using NaOH as the base. As shown in Scheme 4, in addition to methyl 2-mercaptoacetate, the ethyl, 2-ethylhexyl, and butyl 2-mercaptoacetates were good "sew" partners in this transformation, as well, delivering the targeted products (**5ab**−**5ad**) in 68, 62, and 66% yield, respectively. Next, we evaluated this denitrogenative transannulation reaction by using methyl 2-mercaptoacetate (**4a**) in conjunction with a round of 3-aminoindazoles, and

**Scheme 4. Substrate Scope for the Synthesis 3-Aminobenzothiophenes[a]**

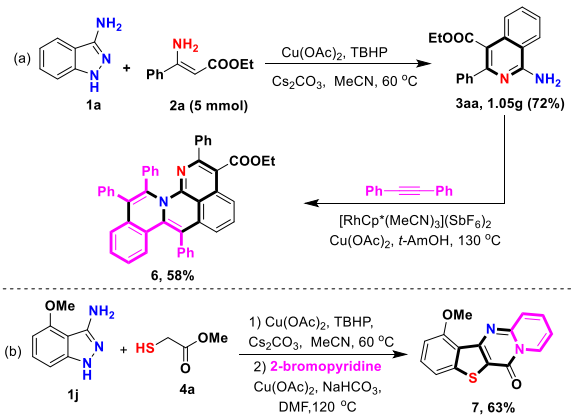



[a]All reactions unless otherwise stated were carried out with **1** (1.5 equiv), **4** (0.3 mmol), $Cu(OAc)_2$ (20 mol %), NaOH (3 equiv), and TBHP (2 equiv) in MeCN (1.0 mL) heated at 80 °C for 22 h. [b]2 equiv of $K_2CO_3$ was used.

corresponding 3-aminobenzothiophenes (**5ba**−**5ia**) were achieved in moderate to good yields.

The denitrogenative transannulation of 3-aminoindazoles can be readily scaled up without a loss of efficiency (Scheme 5). The

**Scheme 5. Larger Synthesis and Synthetic Applications**




product 1-amino-3-phenylisoquinoline-4-carboxylate (**3aa**) could be gained in 72% yield when **1a** (7.5 mmol) and **2a** (5 mmol) were exposed to the standard conditions. The products of this denitrogenative transannulation reaction could be conveniently derivatized. An extended fused ring system **6** could be constructed via Rh-catalyzed dual C−H activation with 1,2-diphenylethyne.[5d] In addition, the copper-catalyzed domino reaction between **5ca** and 2-bromopyridine could produce a good yield of 6*H*-benzo[4,5]thieno[3,2-*d*]pyrido[1,2-*a*]-pyrimidin-6-one **7** (Scheme 5), which is an analogue of benzo[*b*]thiophenes having antimicrobial activity.[15]

To gain a deeper understanding of these transformations, we conducted several control experiments. When unsubstituted, 3-



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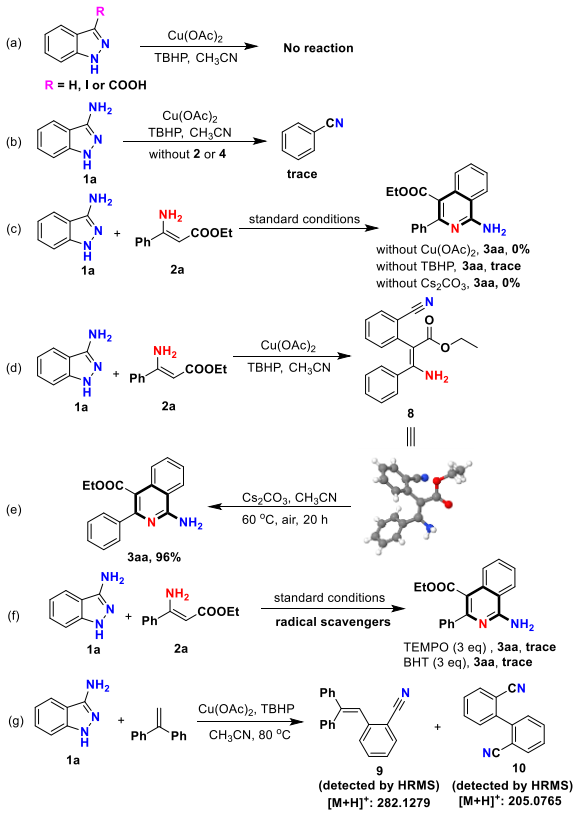
iodo, and 3-carboxylic acid indazoles were used as substrates, no ring-opening products were observed (Scheme 6a), which

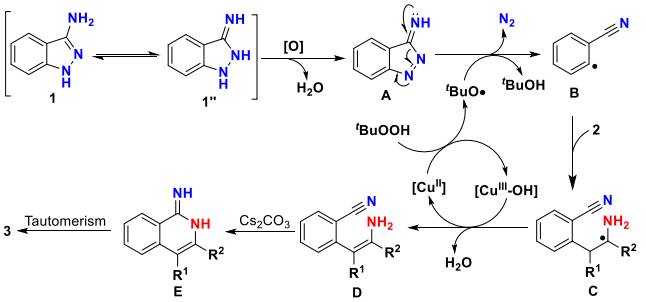
**Scheme 6. Primary Mechanism Studies**




suggested that the $NH_2$ group installed on the C3 position of indazoles is indispensable for this ring opening of the indazole ring. When 3-amino-1*H*-indazole (**1a**) was submitted to the reaction conditions without the "sew" partners mercaptoacetates or enamines, a trace amount of benzonitrile was detected by GC-MS (Scheme 6b). No product was observed when the reaction was performed without Cu salt, oxidant, or base (Scheme 6c), which suggested that the Cu salt, oxidant, and base were all required for this transformation. When the reaction was carried out in the absence of $Cs_2CO_3$, compound **8** was isolated, the structure of which was unequivocally confirmed by X-ray crystal analysis. When **8** was used as starting material to expose under the basic conditions, 96% yield of **3aa** was acquired, which manifested that **8** was a key intermediate in this transformation (Schemes 6d and 6e). When 3 equiv of the common radical probes TEMPO and BHT were added to the reactions under the identified conditions, a trace amount of **3aa** was observed (Scheme 6f). In addition, compound **9** and radical dimer compound **10** were detected by HRMS when 1,1-diphenylethylene and 3-aminoindazole **1a** were exposed under the conditions without base, indicating that a radical process might be involved in this denitrogenative transannulation reaction (Scheme 6g).

On the basis of these experiment results, a possible reaction mechanism for this Cu-catalyzed denitrogenative transannulation of 3-aminoindazoles is depicted in Scheme 7. First, 3-aminoindazole **1** suffers from oxidation to afford compound **A** with the assistance of oxidant. Meanwhile, the low-valent Cu(II) species donates an electron to TBHP to form the Cu(III) species and the *tert*-butoxyl radical.[16] Then, the *tert*-butoxyl radical

**Scheme 7. Proposed Reaction Mechanism**




abstracts a hydrogen atom from compound **A**, which successively undergoes extrusion of one molecular nitrogen to generate the radical intermediate **B**. Addition of the aryl radical **B** to the enamine **2** provides the radical intermediate **C**, which is subjected to the oxidation by the Cu(III) species and deprotonation of the in situ generated carbocation species, giving compound **D**. In the meantime, the Cu(II) species is regenerated to continue the catalytic cycle. Compound **D** goes through the intramolecular nucleophilic attack to render compound **E**. Finally, tautomerism of compound **E** furnishes the desired product **3**.

In summary, we have successfully developed a novel Cu-catalyzed denitrogenative transannulation of 3-aminoindazoles for the construction of 1-aminoisoquinolines and 3-aminobenzothiophenes. Diverse functionalized 1-aminoisoquinoline and 3-aminobenzothiophene derivatives were obtained in good yields via an "extrude-and-sew" strategy with wide substrate scope. Compared to previous work for denitrogenative transannulation, most of these excellent transformations undergo the ionic mechanism. However, our current denitrogenative transannulation of 3-aminoindazoles proceeds via a radical pathway. This protocol is readily scaled up without loss of its efficiency. Further applications of this novel denitrogenative transannulation of 3-aminoindazoles are underway in our group.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02288.

General experimental procedures and spectroscopic data for the corresponding products (PDF)

### Accession Codes

CCDC 1831421, 1842359, and 1844187 contain 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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