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# Copper(0)/$PPh_3$-Mediated Bisheteroannulations of *o*-Nitroalkynes with Methylketoximes Accessing Pyrazo-Fused Pseudoindoxyls

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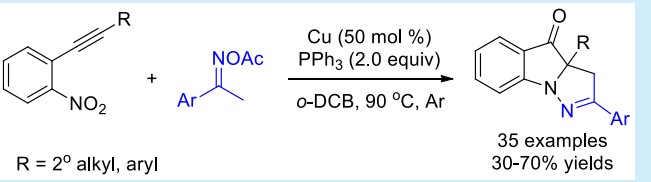
**ABSTRACT:** A copper(0)/$PPh_3$-mediated cascade bisheteroannulation reaction of *o*-nitroalkynes with methylketoximes has been developed that provides viable access to a diverse range of pyrazo-fused pseudoindoxyl compounds. Synthetically useful functional groups including sensitive C−I bonds are compatible with this system. Mechanistic studies suggest a reaction cascade involving sequential $PPh_3$-mediated deoxygenative cycloisomerization and copper-catalyzed [3 + 2] pyrazo-annulation.

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Nitrogen-containing heterocycles are privileged core skeletons that continually constitute key units of numerous naturally occurring alkaloids and pharmacologically active compounds. Specifically, pseudoindoxyls featuring the 2,2-disubstituted indolin-3-one core structure appear in diverse pharmaceutical agents such as Halichrome A, LipidGreen, Cephalinone, isatisine A, and Duocarmycins A, etc. (Figure 1).[1] Consequently, the development of synthetic methods for pseudoindoxyl formation has drawn considerable interest in molecular synthesis.[2]

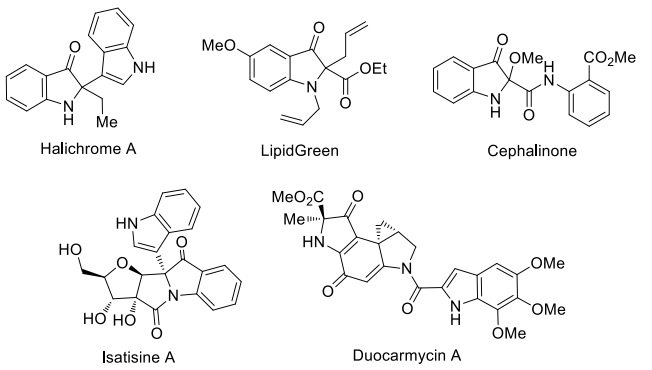


**Figure 1.** Valuable indolin-3-one molecules.

Indole oxidation to indol-3-ols followed by a semipinacol rearrangement provides a powerful route to 2,2-disubstituted indolin-3-ones.[3] In the past decade, a number of mild and sustainable oxidative systems have been developed to enable effective methods for this event.[4] Alternatively, the intramolecular cyclization of *o*-nitroalkynes is also a viable strategy for the construction of pseudoindoxyl compounds under generally redox-neutral reaction systems, which was actually pioneered more than one century ago. Given the development of mild transition metal catalysis in the last few decades, cycloisomerization of *o*-nitroalkynes was ingeniously designed to initiate cascade reactions in both intramolecular and intermolecular manners. Hence, transformations involving *o*-nitroalkyne cycloisomerization followed by nucleophilic addition (Figure 2a),[5] 1,3-dipolar cycloaddition (Figure 2b),[6]

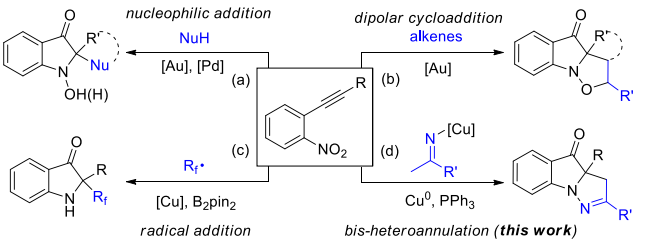


**Figure 2.** Pseudoindoxyl formation by cascade cycloisomerization reactions of *o*-nitroalkynes.

and radical addition (Figure 2c)[7] have been achieved to provide viable access to diverse pseudoindoxyls. Of them, stereoselectivity of the quaternary carbon could also be successfully controlled.[5a,6a,c] With the well-established imino radical formation from ketoximes to construct nitrogen-containing heterocycles,[8] we proposed a cascade reaction involving *o*-nitroalkyne cycloisomerization and subsequent radical addition/pyrazole annulations through copper-mediated N−N bond formation. The key challenge of this domino transformation should be to capture the formal conflict between the initial reductive cycloisomerization and the

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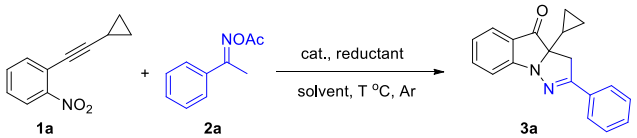
following oxidative N−N bond generation in one pot. Herein, in our systematic studies, we have demonstrated that the mild oxidative property of ketoxime internal oxidants combined with copper catalysis could enable the oxidative N−N coupling in the $PPh_3$-based reductive system (Figure 2d).

Initially, we set up the bisheteroannulation of 1-(cyclopropylethynyl)-2-nitrobenzene (**1a**) and acetophenone oxime acetate (**2a**) to screen the reaction conditions (Table 1). In the presence of copper catalyst (CuCl, 20 mol %) and reductant ($PPh_3$, 1.0 equiv), the reaction performed in $CH_3CN$ afforded the target pseudoindoxyl product **3a** in 26% yield (entry 1). Solvent screening among others featured that *ortho*-dichlorobenzene (*o*-DCB) was superior to others (entries 2−5), furnishing **3a** in 38% yield (entry 4). Low-polarity media such as toluene quenched the desired transformation (entry 2). Other copper catalysts were then tested (entries 6−10). While CuBr diminished the yield to 22% (entry 6), copper(II) salts proved catalytically inactive (entries 8 and 9), suggesting a reduction-initiated cascade process of the bisheteroannulation. In view of these observations, we rationally employed copper powder as the catalyst, which therein enhanced the reactivity to 45% yield (entry 10). Increasing either catalyst loading or the amount of reductant improved the present reaction, with combinational use of Cu (50 mol %) and $PPh_3$ (2.0 equiv) to give the best results (entries 11 and 12, 70% yield). Other reductants including $PBu_3$, $B_2Pin_2$, $Mo(CO)_6$, and $Et_3SiH$, some of which were successfully used previously for reductive cycloisomerization of *o*-nitroalkynes, found all inferior to $PPh_3$ (entries 13 and 16). The reaction at 90 °C gave the same efficiency (entry 17), while further lowering to 80 °C led to a substantial decrease of reactivity (entry 18, 55% yield). Control experiments revealed that the copper catalyst is a basic necessity for the bisheteroannulation (entry 19), and the reaction in the absence of phosphorus reductant with 2.0 equiv of copper powder worked, albeit in low yield (entry 20). The reaction carried out under an air atmosphere also significantly decreased the yield (entry 21). Finally, the 1 mmol scale reaction featured diminished reactivity to afford **3a** in 42% yield (entry 12).

**Table 1. Optimization of Reaction Conditions.**[a]




1a 2a 3a

| entry | catalyst (mol %) | reductant (equiv) | solvent | temp. (°C) | yield[b] 3a (%) |
|---|---|---|---|---|---|
| 1 | CuCl (20) | $PPh_3$ (1.0) | $CH_3CN$ | 100 | 26 |
| 2 | CuCl (20) | $PPh_3$ (1.0) | toluene | 100 | trace |
| 3 | CuCl (20) | $PPh_3$ (1.0) | PhCl | 100 | 22 |
| 4 | CuCl (20) | $PPh_3$ (1.0) | *o*-DCB | 100 | 38 |
| 5 | CuCl (20) | $PPh_3$ (1.0) | DMF | 100 | 15 |
| 6 | CuBr (20) | $PPh_3$ (1.0) | *o*-DCB | 100 | 22 |
| 7 | CuI (20) | $PPh_3$ (1.0) | *o*-DCB | 100 | trace |
| 8 | $CuCl_2$ (20) | $PPh_3$ (1.0) | *o*-DCB | 100 | trace |
| 9 | $CuBr_2$ (20) | $PPh_3$ (1.0) | *o*-DCB | 100 | trace |
| 10 | Cu (20) | $PPh_3$ (1.0) | *o*-DCB | 100 | 45 |
| 11 | Cu (20) | $PPh_3$ (2.0) | *o*-DCB | 100 | 51 |
| 12 | Cu (50) | $PPh_3$ (2.0) | *o*-DCB | 100 | 70, 42[c] |
| 13 | Cu (50) | $PBu_3$ (2.0) | *o*-DCB | 100 | 64 |
| 14 | Cu (50) | $B_2Pin_2$ (2.0) | *o*-DCB | 100 | 23 |
| 15 | Cu (50) | $Mo(CO)_6$ (2.0) | *o*-DCB | 100 | trace |
| 16 | Cu (50) | $Et_3SiH$ (2.0) | *o*-DCB | 100 | 52 |
| 17 | Cu (50) | $PPh_3$ (2.0) | *o*-DCB | 90 | 70 |
| 18 | Cu (50) | $PPh_3$ (2.0) | *o*-DCB | 80 | 55 |
| 19[d] | | $PPh_3$ (2.0) | *o*-DCB | 90 | ND |
| 20 | Cu (200) | | *o*-DCB | 90 | 11 |
| 21[e] | Cu (50) | $PPh_3$ (2.0) | *o*-DCB | 90 | 48 |

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.2 mmol), catalyst, reductant, solvent (1.5 mL), 100 °C, 5 h, under Ar, unless otherwise noted. [b]Isolated yield. [c]1.0 mmol scale. [d]In the absence of Cu. [e]Under air.

With the optimized reaction conditions in hand, we next probe the substrate scope of the copper-powder-mediated reductive bisheteroannulation (Figure 3). With respect to oxime acetates derived from acetophenones, the corresponding products were generally obtained in moderate yields (**3a**−**3v**), with a broad array of compatible functionalities including alkyl, alkoxy, halogen, and even nitro. Notably, the C($sp^2$)−I bond, which is highly sensitive to the copper-based reductive system, was well tolerated in the present catalysis (**3j**), with no

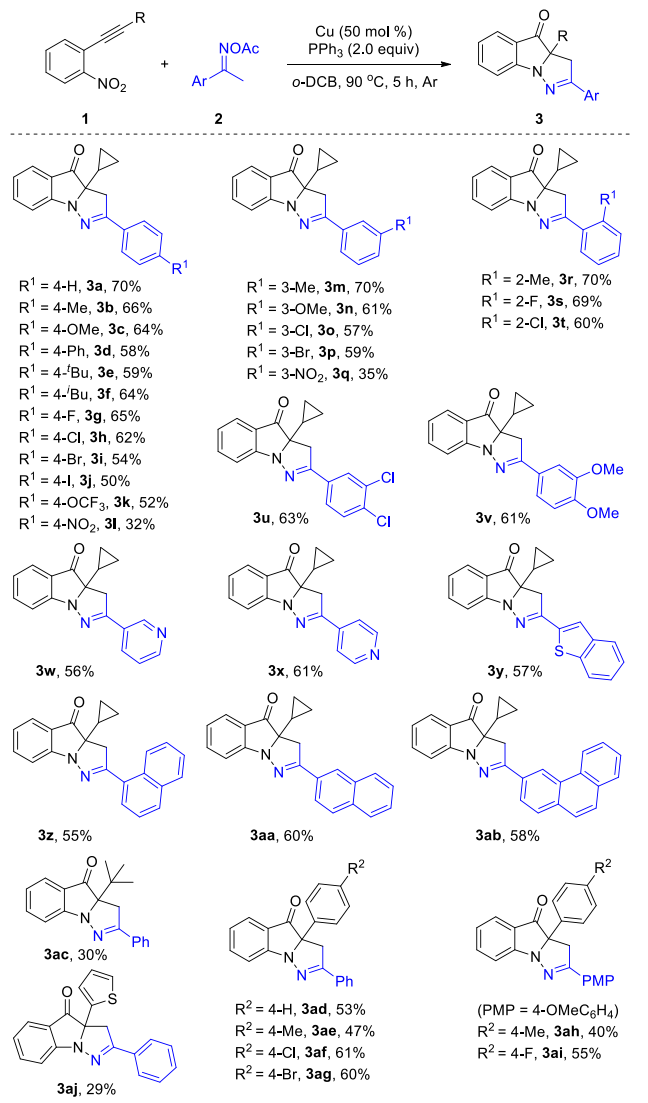



**Figure 3.** Substrate scope of the copper-mediated bisheteroannulations.



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detection of dehalogenative product. However, nitro-substituted acetophenone oximes resulted in relatively lower yields of products (**3l**, **3q**), along with probably formation of anilines that led to a mixed complex mass. The inhibitory influence of sterically hindered substrates, i.e., ortho-substituted acetophenone oximes, was not observed (**3r**−**3t**); therein, the expected pseudoindoxyl products were generated in similar yields with para- and meta-substituted reactants. Heteroaryl methylketoximes bearing pyridinyl and benzothiophenenyl moieties also displayed modest reactivities (**3w**−**3y**). In correspondence with acetophenone oximes, naphthyl and phenanthrenyl substrates were expectedly accommodated with the present copper catalysis (**3z**−**3ab**).

Subsequently, we tested a range of *o*-nitroalkynes. The substrates attached with a primary or tertiary alkyl group at the alkyne moiety dramatically decreased the yield. For example, the *tert*-butyl *o*-nitroalkyne afforded the corresponding product **3ac** in only 30% yield. Comparably, diarylacetylenes showed modest reactivities, thus providing a feasible access to 2-aryl pseudoindoxyl products (**3ad**−**3ai**). The *o*-nitroalkyne bearing a thienyl moiety generated the corresponding product in 29% yield.

The major side product of this bisheteroannulation reaction was generated by the monocyclization, in which the N−N bond was not formed and workup of the reaction mixture afforded pseudoindoxyls bearing a ketone moiety. For example, besides the formation of **3aj**, the thienyl reactant also generated monocyclization product **4c** as the side product (Figure 4). This kind of product was dominant especially when

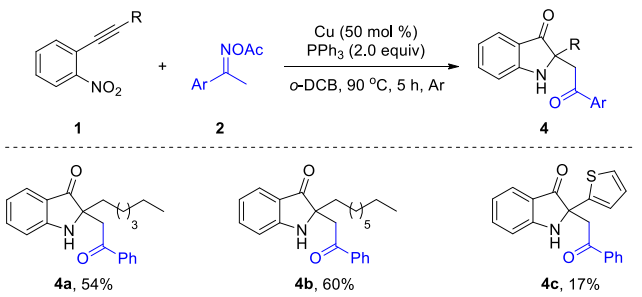


**Figure 4.** Formation of pseudoindoxyls **4**.

the *o*-nitroalkynes attached with a primary alkyl. Hence, the hexyl and octyl substrates afforded pseudoindoxyls **4a** and **4b**, respectively, in moderate yields, along with the formation of bisheteroannulation products in only trace amounts.

Based on the results reported in the literature,[5a,6a,7b,9] we postulated that our copper/$PPh_3$-based system could reduce *o*-nitroalkynes to trigger a reductive cycloisomerization reaction, with then the resultant indol-3-one containing an imine fragment coupled with methylketoximes to generate the dihydropyrazole ring. The results of control experiments suggest this to be rational, with the roles of $PPh_3$ and copper catalyst clarified to independently work in both reaction steps (Figure 5a,b). The addition of $PPh_3$ also has an obvious inhibitory effect on the later [3 + 2] pyrazolannulation that is expected to be a redox-neutral process. Finally, elusive results were obtained when conducting the reactions with a radical scavenger, where an additional 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) featured no significant influence on the yield, and by contrast, 3,5-di-*tert*-butyl-4-hydroxytoluene (BHT) quenched the transformation (Figure 5c).

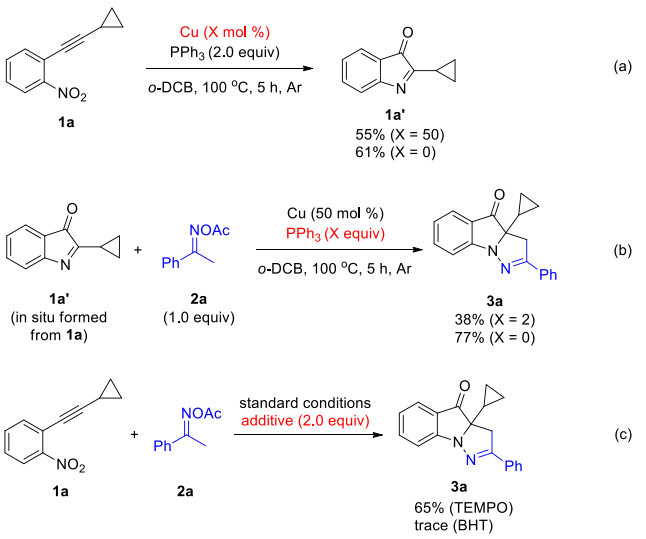


**Figure 5.** Control experiments.

Given the above results, a plausible reaction mechanism is illustrated in Figure 6. Direct nitro deoxygenative reduction by

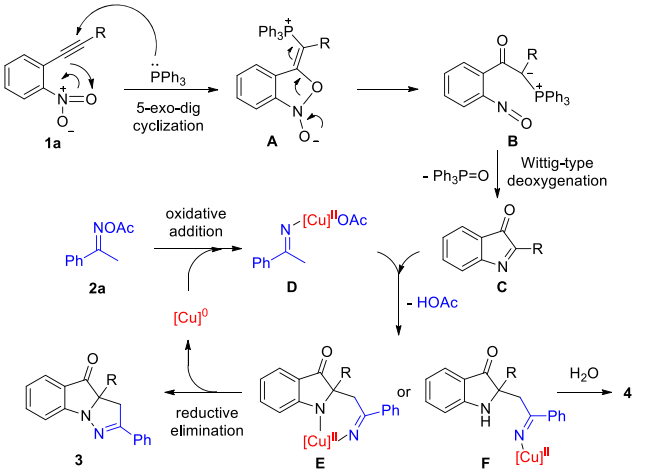


**Figure 6.** Possible reaction mechanism.

$PPh_3$ is impossible in our system.[10] Hence, we propose that the initial step should be the nucleophilic attack of the $PPh_3$ base to an alkyne moiety, which induces the 5-exo-dig cyclization of **1**.[11] Then, intramolecular charge transfer of the cyclic intermediate **A** leads to the phosphorus ylide **B**, which furnishes indol-3-one **C** via Wittig-type deoxygenation. Simultaneously, in the presence of copper powder, oxime acetate **2a** results in the imino-copper(II) species **D** by oxidative addition of copper(0) into the N−O bond.[8b] Subsequently, migration insertion of **D** across the C═N bond of **C** occurs to generate the cyclocopper intermediate **E**, with the final N−N bond reductive elimination[12] producing the pyrazolo[1,5-*a*]indolone product **3**. We suspect a steric bulky group is required to push the copper center close to both nitrogen atoms, hence enabling the N−N bond formation. Otherwise, the interaction of **C** and **D** leads to the formation of intermediate **F** by nucleophilic addition. The subsequent workup of **F** gives the monocyclic product **4**.

In summary, we have developed a viable copper powder/triphenylphosphine-based reductive system that enables


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bisheteroannulation of *o*-nitroalkynes with methylketoxime acetates. This protocol provides convenient access to structurally and pharmacologically significant pseudoindoxyl compounds with generally moderate yields and tolerates important functionalities including nitro and iodine being sensitive to copper-based reductive systems. Mechanistically, the reaction cascade involves triphenylphosphine-mediated deoxygenative cyclization and copper-catalyzed [3 + 2] formal annulations.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02180.

Experimental procedures, characterization data, and $^{1}H$ NMR and $^{13}C$ NMR spectra for all new products (PDF)

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### Author Contributions

†H.M. and Z.X. contributed equally to this work.


### Notes

The authors declare no competing financial interest.

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