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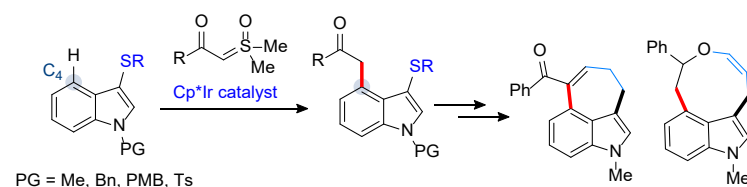
Thioether-Directed C4-Selective C–H Acylmethylation of Indoles Using α -Carbonyl Sulfoxonium Ylides

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Supporting Information Placeholder



ABSTRACT: Site-selective direct functionalization of indole benzenoid core has been a great challenge due to its inherently poor reactivity. We herein demonstrate an iridium-catalyzed C4-selective acylmethylation of indoles using α -carbonyl sulfoxonium ylides as carbene precursors. This method exhibits high efficiency and broad functional group compatibility. The directing group was easily removed or converted to other functionalities after the catalysis. The potential synthetic utility of the coupling products was highlighted by constructing medium-sized polycyclic indoles.

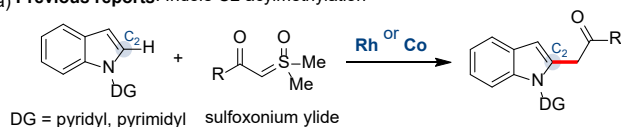
Indoles and their derivatives are definitely important structural motifs with promising applications in various research fields involving biochemistry, medicinal chemistry, materials science, etc.¹ In this regard, site-selective functionalization of the indole core adopting transition metal catalysts has attracted significant attention² because of the wide prevalence of functionalized indoles in biologically active compounds and natural products. Particularly, the selective functionalization of the indole benzenoid core (C4–C7), which are inherently less reactive than the pyrrol ring (C2 and C3), remains as a tremendous challenge. Over the past decades, some catalytic approaches involving alkylation,³ alkenylation,⁴ alkynylation,⁵ arylation,⁶ amination,⁷ and borylation⁸ have been achieved in the presence of appropriate directing groups.

Meanwhile, transition-metal-catalyzed insertion reactions of carbenoid species have emerged as efficient synthetic tools for the C–C and C–heteroatom bond formations.⁹ α -Diazo carbonyls have been widely utilized as carbene precursors for the installation of sp^3 -carbon fragments. Other carbene surrogates such as hydrazones^{9a,10} and triazole^{10,12} derivatives have also functioned for the catalysis; however, a potential safety risk of the vigorous nitrogen gas release from these reagents is inevitable. Accordingly, it has been of great demand to establish stable, user-friendly, and efficient carbene sources. In analogy to the diazo-derived carbenoids, sulfoxonium ylides were optimized as the safer alternative in the carbene insertion chemistry due to their operational simplicity and stability even in relatively harsh reaction conditions.^{9a,13,14} More recently, the groups of Aïssa and Li independently introduced the use of sulfoxonium ylides for the coordination-assisted C–H functionalization strategy under Cp^*Rh catalysis.¹⁵ A series of arenes and heteroarenes successfully underwent the direct acylmethylation. Afterward,

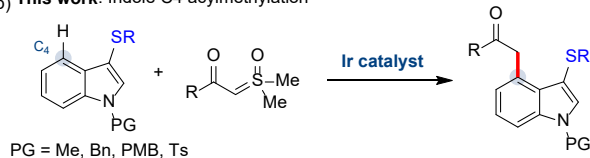
Wang *et al.* reported a similar transformation using an analogous Cp^*Co catalyst.¹⁶ These leading contributions prompted the synthetic community to explore the utility of the ylide reagents. To date, many catalytic reactions have been established utilizing the reagents as the coupling partners^{17,18} as well as the bifunctional directing groups.¹⁹ However, to the best of our knowledge, direct C–H acylmethylation onto the indole benzene ring has not been realized, whereas the C2-selective reaction is well-explored with pyridine and pyrimidine directing groups placed at the indole nitrogen atom (Scheme 1a).^{15,16}

Scheme 1. Schematic Representation of the Site-Selective Direct Acylmethylation

(a) **Previous reports:** Indole C2 acylmethylation



(b) **This work:** Indole C4 acylmethylation

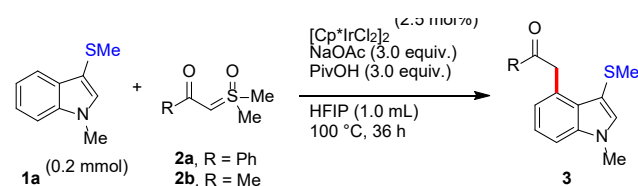


As recent contributions to the direct C–H functionalization of the indole benzenoid core, we developed a Rh-catalyzed C4-selective alkenylation^{4c,4f} and Ir-catalyzed C4/C7-selective alkynylation^{5a} with the aid of thioether directing groups. A notable feature of these reaction systems is that the sulfur directing

groups can readily be removed or be replaced with other functionalities after the catalysis. In this [letter](#), we [report](#) the first C4-selective acylmethylation of indoles adopting the sulfoxonium ylides as the carbene precursors (Scheme 1b). This transformation does not require any external oxidant and, intriguingly, is currently achievable only with the aid of sulfur directing groups. The significance of this work is demonstrated by the post-functionalization of the coupling products into some medium-sized polycyclic indoles.

As an initial attempt, we examined the reaction of 1-methyl-3-(methylthio)-1*H*-indole (**1a**) with a representative benzoyl sulfoxonium ylide **2a** (Table 1).²⁰ Under the standard reaction conditions adopting [Cp*IrCl₂]₂ (2.5 mol %) catalyst, NaOAc and PivOH additives in HFIP solvent,²¹ the C4-functionalized product **3aa** was obtained in 85% yield (62% isolated yield) (entry 1). The structure of **3aa** was confirmed by X-ray crystallographic analysis.²² The desired coupling product was not obtained in the absence of the iridium catalyst (entry 2). An analogous rhodium complex [Cp*RhCl₂]₂ was totally ineffective to the present transformation (entry 3). Considerable decrease of the productivity was inevitable without the additives (entries 4 and 5), and a slightly lower yield was obtained with decreased amounts of the additives (entry 6).

Table 1. Optimization Study for the C4-Selective Acylmethylation of **1a**^a



entry	deviation from the standard conditions	yield ^b
1	2a None	85% (62%)
2	2a w/o [Cp*IrCl ₂] ₂	n.d
3	2a [Cp*RhCl ₂] ₂ instead [Cp*IrCl ₂] ₂	Trace
4	2a w/o NaOAc	50%
5	2a w/o PivOH	20%
6	2a 2.0 equiv each NaOAc and PivOH	68%
7	2a KOAc instead of NaOAc	40%
8	2a LiOAc instead of NaOAc	n.d
9	2a CsOAc instead of NaOAc	n.d
10	2a with AgSbF ₆ (10 mol %)	(25%)
11	2b None	(85%)

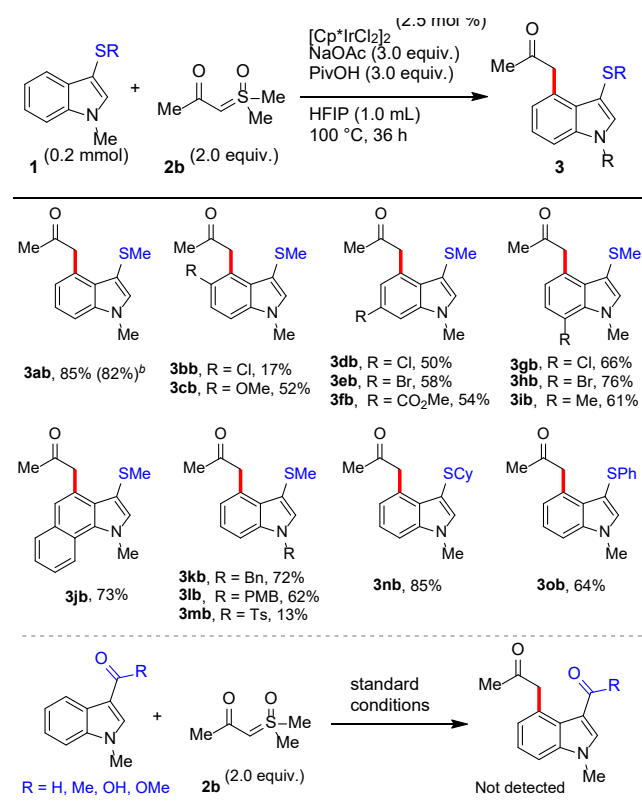
^a Standard conditions: **1a** (0.20 mmol), **2** (0.20 mmol), [Cp*IrCl₂]₂ (2.5 mol %), NaOAc (0.6 mmol), PivOH (0.6 mmol) in HFIP (1.0 mL) at 100 °C for 36 h. ^b Determined by NMR analysis. Isolated yields are in parentheses. HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol, n.d. = not detected

Use of KOAc instead of NaOAc resulted in poor product yield (entry 7), whereas other acetate salts LiOAc and CsOAc obstructed the reaction (entries 8 and 9). In the presence of AgSbF₆ as an anion-exchange agent, the product yield considerably dropped to 25% (entry 10). Other solvents such as TFE (trifluoroethanol), DCE (dichloroethane), PhCF₃, THF, and 1,4-dioxane were not suitable for the present transformation (not

shown). The use of acetyl sulfoxonium ylide **2b** as the carbene source instead of **2a** significantly improved the reaction efficiency to afford the target product **3ab** in 85% isolated yield (entry 11).

With the optimal reaction conditions (Table 1, entry 11) in hand, we evaluated the scope of various C3-SMe indoles for the C4-selective acylmethylation with the sulfoxonium ylide **2b** (Scheme 2). This protocol was rather sensitive to the steric bulkiness around the C4 position since 5-chloroindole **1b** reacted sluggishly to provide **3bb** in 17% yield, whereas 5-methoxyindole **1c** gave the corresponding product in 52% yield. C6-substituted indoles **1d** (6-Cl), **1e** (6-Br), and **1f** (6-CO₂Me) were well tolerated to give the desired products in higher 50-58% yields. The reaction was also successful with C7-substituted indoles **1g** (7-Cl), **1h** (7-Br), and **1i** (7-Me) as well as a benzo-fused indole **1j**, leading to the exclusive formation of the C4-functionalized indoles **3gb-3jb** in high yields. Unfortunately, indoles bearing a substituent at the C2 position could not participate in the reaction (not shown).

Scheme 2. Scope of Indoles^a



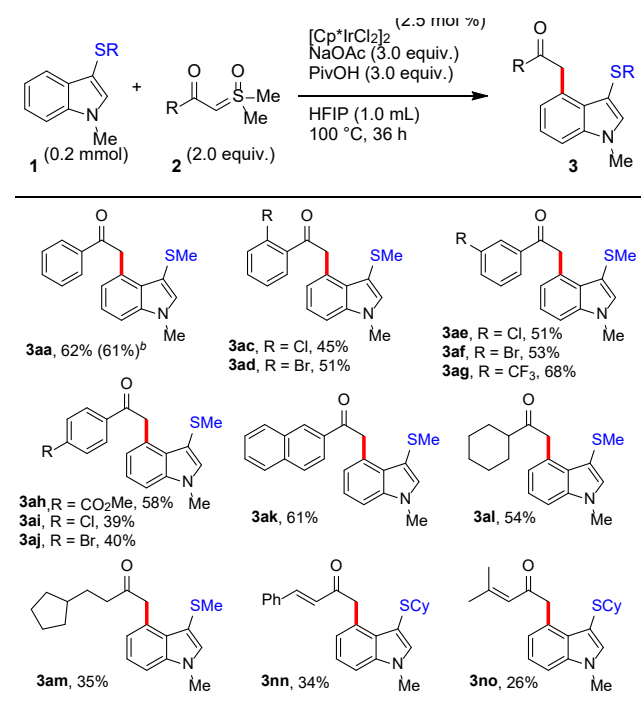
^a Reaction conditions: **1** (0.2 mmol), **2b** (0.4 mmol), [Cp*IrCl₂]₂ (2.5 mol %), NaOAc (0.6 mmol), PivOH (0.6 mmol) in HFIP (1.0 mL) at 100 °C for 36 h. ^b Isolated yield in 1.0 mmol scale.

We then examined the effect of some protecting groups on the indole nitrogen atom. *N*-Benzyl (**1k**) and *N*-*p*-methoxybenzyl (**1l**) indoles exhibited similar reactivity as compared to **1a**, whereas an electron deficient *N*-tosyl (**1m**) group retarded the reaction. These protecting groups were practically more attractive due to their ease of removal. With respect to the sulfur directing group, SCy (**1n**) and SPh (**1o**) were also effective to trigger the selective C–H activation at the C4 position. In sharp contrast, other well-established carbonyl directing groups such

as aldehyde, ketone, carboxylic acid and ester all failed to stimulate the reaction at the C4 as well as at the C2 positions. These substrates were totally recovered unreacted under the standard conditions, vividly highlighting the peculiar utility of the sulfur directing groups. This might be attributed to the sufficient stabilization of the 5-membered rhodacycle, formed via C–H activation at the C4, by the coordination of the sulfur atom.

We prepared a series of sulfoxonium ylides **2c–2o** and screened for the present catalytic system (Scheme 3). For the substituted benzoyl sulfoxonium ylides, functional groups involving chloro (**2c**, **2e**, **2i**), bromo (**2d**, **2f**, **2j**), trifluoromethyl (**2g**), and ester (**2h**) on the benzene ring were well tolerated to give the corresponding C4-functionalized indoles in moderate to high yields. In addition, sulfoxonium ylides bearing 2-naphthyl (**2k**), cyclohexyl (**2l**), and primary alkyl (**2m**) moieties were smoothly converted to the target compounds. Although cinnamyl (**2n**) and 3-methylcrotonyl (**2p**) ylides were not productive with the standard SMe directing group (**1a**), interestingly, the desired coupling products were obtained in moderate yields with the aid of SCy (**1n**) director.

Scheme 3. Scope of Sulfoxonium Ylides ^a

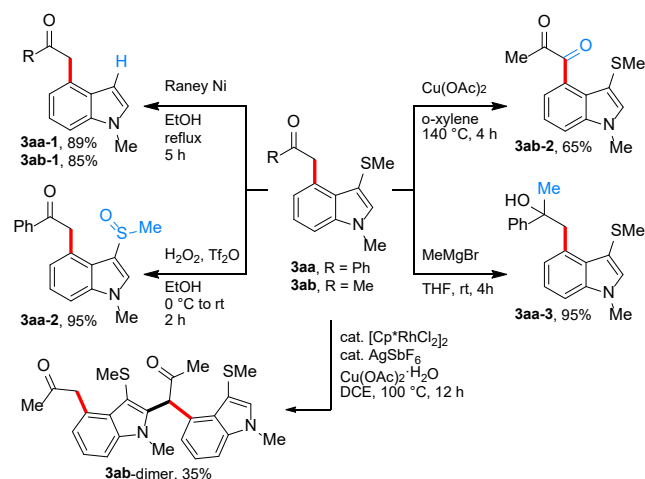


^a Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), [Cp*IrCl₂]₂ (2.5 mol %), NaOAc (0.6 mmol), PivOH (0.6 mmol) in HFIP (1.0 mL) at 100 °C for 36 h. ^b Isolated yield of 1.0 mmol scale.

In recent years, removability of directing groups from the substrates has emerged as an important criteria for the chelation-assisted transformations.²³ To our delight, the SMe group of the coupling products **3aa** and **3ab** was easily removed upon treatment with Raney Ni to give **3aa-1** and **3ab-1** in high yields, keeping the installed functionality at the C4 untouched (Scheme 4).²⁴ Such an orthogonal reactivity between the thioether and the acylmethyl groups prompted us to test some additional derivatization reactions. The SMe was preferentially oxidized into the sulfoxide **3aa-2** under the conditions using H₂O₂/Tf₂O, whereas the reaction with Cu(OAc)₂·H₂O induce the benzylic oxidation²⁵ to form an α-diketone **3ab-2**. Alkylation of **3aa** using a Grignard reagent furnished the tertiary alcohol **3aa-3** in

excellent yield. Additionally, we found that the dimerization of **3ab** took place in the presence of a Cp*Rh catalyst and Cu(OAc)₂·H₂O as oxidant to give **3ab-dimer** in 35% yield.²⁶ The connectivity was unambiguously determined by X-ray crystallographic analysis.²²

Scheme 4. Derivatization of the C4-Functionalized Indoles



The ease of the SMe group removal is practically beneficial for the post-functionalization because the nucleophilic indole C3 site would facilitate the installation of additional functionalities. Indeed, polycyclic indole derivatives with a conjunction of the C3 and C4 positions are frequently found as key structural motifs in many natural products and bioactive compounds (Figure 1);²⁷ however, limited synthetic methods have been available for the construction of the medium size ring scaffolds. In order to demonstrate the utility of the developed catalytic system, we challenged ourselves to convert **3aa-1** and **3ab-1** to some C3-C4 looped molecules.

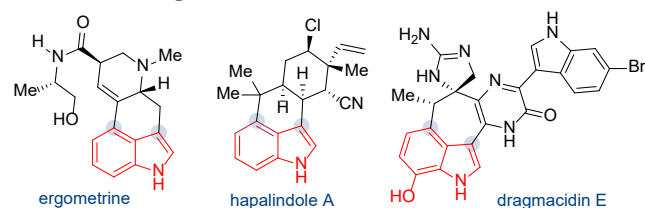
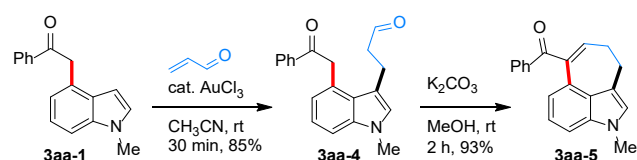


Figure 1. Examples for C3-C4 looped indole derivatives in natural products and bioactive compounds.

As the first example, Michael addition of **3aa-1** to acrolein in the presence of AuCl₃ as catalyst produced the corresponding aldehyde **3aa-4** (Scheme 5).²⁸ This was further treated with K₂CO₃ in methanol to ensure the intramolecular aldol condensation, furnishing a seven-membered ring product **3aa-5** in 93% yield.

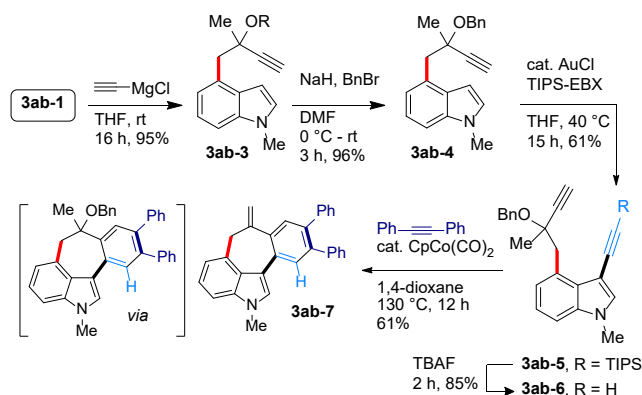
Scheme 5. Synthesis of a Seven-Membered Tricyclic Molecule



Our second approach employed the cobalt-catalyzed alkyne trimerization (Scheme 6).²⁸ The acetyl variant **3ab-1** was converted to the alkynol **3ab-3** using ethynyl magnesium chloride.

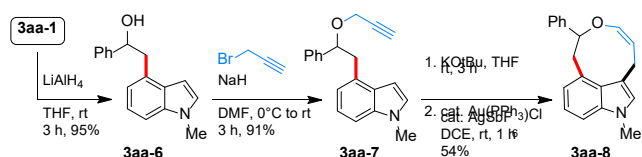
The hydroxyl group was protected as the benzyl ether (**3ab-4**), followed by the gold-catalyzed direct C3-alkynylation **3ab-5** in 61% yield. Subsequent silyl deprotection and [2 + 2 + 2] cycloaddition with diphenylacetylene afforded the tetracyclic compound, which was converted to the corresponding alkene **3ab-7** via the elimination of a benzyl alcohol.

Scheme 6. Synthesis of a Seven-Membered Tetracyclic Molecule



Among the series of medium-sized cyclic architectures, nine-membered systems are still one of the most difficult rings to access because of the significant entropic and enthalpic penalties.^{31,32} Accordingly, we tackled this issue relying on the intramolecular hydroarylation under gold catalysis (Scheme 7).³³ Reduction of the carbonyl moiety within **3aa-1** by LiAlH₄ furnished the alcohol **3aa-6**, which was further transformed to the corresponding propargyl ether **3aa-7** upon treatment with propargyl bromide. Thereafter, this precursor was converted to the allenyl ether intermediate in situ and subjected to the gold-catalyzed intramolecular cyclization. Gratifyingly, the desired nine-membered tricyclic product **3aa-8** was obtained as a pure *cis*-isomer in synthetically meaningful 54% yield.

Scheme 7. Synthesis of a Nine-Membered Tricyclic Molecule.



In conclusion, we have developed the direct C4-selective acylmethylation of indole using α -carbonyl sulfoxonium ylides as carbene precursors under iridium catalysis. Intriguingly, the current transformation was only achievable with the aid of sulfur directing groups. Various functional groups on the indoles as well as on the ylides were well tolerated under the catalytic conditions. The synthetic utility of the coupling products was highlighted by applying to the construction of C3-C4 looped medium size ring scaffolds, which are ubiquitous in many biologically important compounds.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website, including detailed experimental procedures, characterization data for all products, crystal structure images, and copy of NMR spectra as a PDF file.

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Notes

The authors declare no competing financial interest.

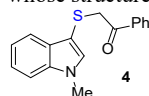
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REFERENCES

- (1) (a) Andreani, A.; Rambaldi, M. *J. Heterocycl. Chem.* **1988**, *25*, 1519-1523. (b) Galliford, C. V.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 8748-8758. (c) Kochanowska-Karamyan, A. J.; Hamann, M. T. *Chem. Rev.* **2010**, *110*, 4489-4497. (d) Taylor, R. D.; MacCoss, M.; Lawson, A. D. J. *J. Med. Chem.* **2014**, *57*, 5845-5859. (e) Zhang, M.-Z.; Chen, Q.; Yang, G.-F. *Eur. J. Med. Chem.* **2015**, *89*, 421-441.
- (2) For recent reviews on selective C-H functionalization of indoles: see, (a) Petrini, M. *Chem. Eur. J.* **2017**, *23*, 16115-16151. (b) Leitch, J. A.; Bhoonah, Y.; Frost, C. G. *ACS Catal.* **2017**, *7*, 5618-5627. (c) Kalepu, J.; Gandeepan, P.; Ackermann, L.; Pilarski, L. T. *Chem. Sci.* **2018**, *9*, 4203-4216. (d) Yang, Y.; Shi, Z. *Chem. Commun.* **2018**, *54*, 1676-1685. (e) Shah, T. A.; De, P. B.; Pradhan, S.; Punniyamurthy, T. *Chem. Commun.* **2019**, *55*, 572-587.
- (3) Alkylation: (a) Chen, X.; Zheng, G.; Li, Y.; Song, G.; Li, X. *Org. Lett.* **2017**, *19*, 6184-6187. (b) Borah, A. J.; Shi, Z. *Chem. Commun.* **2017**, *53*, 3945-3948. (c) Leitch, J. A.; McMullin, C. L.; Mahon, M. F.; Bhoonah, Y.; Frost, C. G. *ACS Catal.* **2017**, *7*, 2616-2623. (d) Biswas, A.; Samanta, R. *Eur. J. Org. Chem.* **2018**, 1426-1436. (e) Borah, A. J.; Shi, Z. *J. Am. Chem. Soc.* **2018**, *140*, 6062-6066. (f) Pan, C.; Huang, G.; Shan, Y.; Li, Y.; Yu, J.-T. *Org. Biomol. Chem.* **2020**, *18*, 3038-3042.
- (4) Alkenylation: (a) Lanke, V.; Prabhu, K. R. *Org. Lett.* **2013**, *15*, 6262-6265. (b) Lanke, V.; Bettadapur, K. R.; Prabhu, K. R. *Org. Lett.* **2016**, *18*, 5496-5499. (c) Xu, L.; Zhang, C.; He, Y.; Tan, L.; Ma, D. *Angew. Chem. Int. Ed.* **2016**, *55*, 321-325. (d) Lv, J.; Wang, B.; Yuan, K.; Wang, Y.; Jia, Y. *Org. Lett.* **2017**, *19*, 3664-3667. (e) Okada, T.; Sakai, A.; Hinoue, T.; Satoh, T.; Hayashi, Y.; Kawauchi, S.; Chandrababunaidu, K.; Miura, M. *J. Org. Chem.* **2018**, *83*, 5639-5649. (f) Kona, C. N.; Nishii, Y.; Miura, M. *Org. Lett.* **2018**, *20*, 4898-4901.
- (5) Alkynylation: (a) Kona, C. N.; Nishii, Y.; Miura, M. *Angew. Chem. Int. Ed.* **2019**, *58*, 9856-9860. (b) Fang, S.; Jiang, G.; Li, M.; Liu, Z.; Jiang, H.; Wu, W. *Chem. Commun.* **2019**, *55*, 13769-13772.
- (6) Arylation: (a) Yang, Y.; Qiu, X.; Zhao, Y.; Mu, Y.; Shi, Z. *J. Am. Chem. Soc.* **2016**, *138*, 495-498. (b) Yang, Y.; Li, R.; Zhao, Y.; Zhao, D.; Shi, Z. *J. Am. Chem. Soc.* **2016**, *138*, 8734-8737. (c) Yang, Y.; Gao, P.; Zhao, Y.; Shi, Z. *Angew. Chem. Int. Ed.* **2017**, *56*, 3966-3971. (d) Qiu, X.; Deng, H.; Zhao, Y.; Shi, Z. *Sci. Adv.* **2018**, *4*, eaau6468. (e) Qiu, X.; Wang, P.; Wang, D.; Wang, M.; Yuan, Y.; Shi, Z. *Angew. Chem. Int. Ed.* **2019**, *58*, 1504-1508. (f) Thrimurtulu, N.; Dey, A.; Singh, A.; Pal, K.; Maiti, D.; Volla, C. M. R. *Adv. Synth. Catal.* **2019**, *361*, 1441-1446.
- (7) Amination: (a) Kim, Y.; Park, J.; Chang, S. *Org. Lett.* **2016**, *18*, 1892-1895. (b) Song, Z.; Antonchick, A. P. *Org. Biomol. Chem.* **2016**, *14*, 4804-4808. (c) Lanke, V.; Prabhu, K. R. *Chem. Commun.* **2017**, *53*, 5117-5120. (d) Kim, Y.; Park, Y.; Chang, S. *ACS Cent. Sci.* **2018**, *4*, 768-775. (e) Biswas, A.; Bera, S.; Poddar, P.; Dhara, D.; Samanta, R. *Chem. Commun.* **2020**, *56*, 1440-1443.

- (8) Borylation: (a) Robbins, D. W.; Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 4068-4069. (b) Feng, Y.; Holte, D.; Zoller, J.; Umemiya, S.; Simke, L. R.; Baran, P. S. *J. Am. Chem. Soc.* **2015**, *137*, 10160-10163. (c) Amaike, K.; Loach, R. P.; Movassaghi, M. *Org. Synth.* **2015**, *92*, 373-385.
- (9) For recent reviews, see: (a) Jia, M.; Ma, S. *Angew. Chem. Int. Ed.* **2016**, *55*, 9134-9166. (b) Xia, Y.; Qiu, D.; Wang, J. *Chem. Rev.* **2017**, *117*, 13810-13889. (c) Zhu, D.; Chen, L.; Fan, H.; Yao, Q.; Zhu, S. *Chem. Soc. Rev.* **2020**, *49*, 908-950.
- (10) For a comprehensive report, see: Qiu, D.; Mo, F.; Zhang, Y.; Wang, J. *Adv. Organomet. Chem.* **2017**, *67*, 151-219.
- (11) For selected early reports, see: (a) Chuprakov, S.; Hwang, F.; Gevorgyan, V. *Angew. Chem. Int. Ed.* **2007**, *46*, 4757-4759. (b) Chuprakov, S.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 4463-4466. (c) Horneff, T.; Chuprakov, S.; Chernyak, N.; Gevorgyan, V.; Fokin, V. V. *J. Am. Chem. Soc.* **2008**, *130*, 14972-14974. (d) Miura, T.; Yamauchi, M.; Murakami, M. *Chem. Commun.* **2009**, 1470-1471. (e) Chuprakov, S.; Kwok, S. W.; Zhang, L.; Lercher, L.; Fokin, V. V. *J. Am. Chem. Soc.* **2009**, *131*, 18034-18035.
- (12) For reviews, see: (a) Chattopadhyay, B.; Gevorgyan, V. *Angew. Chem. Int. Ed.* **2012**, *51*, 862-872. (b) Gulevich, A. V.; Gevorgyan, V. *Angew. Chem. Int. Ed.* **2013**, *52*, 1371-1373. (c) Davies, H. M. L.; Alford, J. S. *Chem. Soc. Rev.* **2014**, *43*, 5151-5162. (d) Anbarasan, P.; Yadagiri, D.; Rajasekar, S. *Synthesis*, **2014**, *46*, 3004-3023. (e) Jiang, Y.; Sun, R.; Tang, X.; Shi, M. *Chem.-Eur. J.* **2016**, *22*, 17910-17924.
- (13) For an early review, see: Burtoloso, A. C. B.; Dias, R. M. P.; Leonarczyk, I. A. *Eur. J. Org. Chem.* **2013**, 5005-5016.
- (14) For selected examples, see: (a) Baldwin, J. E.; Adlington, R. M.; Gudfrey, C. R. A.; Gollinsa, D. W.; Vaughan, J. G. *J. Chem. Soc. Chem. Commun.* **1993**, 1434-1435. (b) Müller, P.; Fernandez, D.; Nury, P.; Rossier, J.-C. *Helv. Chim. Acta* **1999**, *82*, 935-945. (c) Mangion, I. K.; Nwamba, I. K.; Shevlin, M.; Huffman, M. A. *Org. Lett.* **2009**, *11*, 3566-3569. (d) Mangion, I. K.; Ruck, R. T.; Rivera, N.; Huffman, M. A.; Shevlin, M. *Org. Lett.* **2011**, *13*, 5480-5483; (e) Molinaro, C.; Bulger, P. G.; Lee, E. E.; Kosjek, B.; Lau, S.; Gauvreau, D.; Howard, M. E.; Wallace, D. J.; O'Shea, P. D. *J. Org. Chem.* **2012**, *77*, 2299-2309. (f) Vaitla, J.; Bayer, A.; Hopmann, K. H. *Angew. Chem. Int. Ed.* **2017**, *56*, 4277-4281.
- (15) (a) Barday, M.; Janot, C.; Halcovitch, N. R.; Muir, J.; Aïssa, C. *Angew. Chem. Int. Ed.* **2017**, *56*, 13117-13121. (b) Xu, Y.; Zhou, X.; Zheng, G.; Li, X. *Org. Lett.* **2017**, *19*, 5256-5259.
- (16) Ji, S.; Yan, K.; Li, B.; Wang, B. *Org. Lett.* **2018**, *20*, 5981-5984.
- (17) Recent examples: (a) You, C.; Pi, C.; Wu, Y.; Cui, X. *Adv. Synth. Catal.* **2018**, *360*, 4068-4072. (b) Xu, G.-D.; Huang, K. L.; Huang, Z.-Z. *Adv. Synth. Catal.* **2019**, *361*, 3318-3323. (c) Nie, R.; Lai, R.; Lv, S.; Xu, Y.; Guo, L.; Wang, Q.; Wu, Y. *Chem. Commun.* **2019**, *55*, 11418-11421. (d) Li, H.; Wu, C.; Liu, H.; Wang, J. *J. Org. Chem.* **2019**, *84*, 13262-13275. (e) Li, C.; Li, M.; Zhong, W.; Jin, Y.; Li, J.; Wu, W.; Jiang, H. *Org. Lett.* **2019**, *21*, 872-875. (f) Yu, J.; Wen, S.; Ba, D.; Lv, W.; Chen, Y.; Cheng, G. *Org. Lett.* **2019**, *21*, 6366-6369.
- (18) Recent examples on annulation reactions (see the Supporting Information for all references): (a) Oh, H.; Han, S.; Pandey, A. K.; Han, S. H.; Mishra, N. K.; Kim, S.; Chun, R.; Kim, H. S.; Park, J.; Kim, I. S. *J. Org. Chem.* **2018**, *83*, 4070-4077. (b) Hoang, G. L.; Streit, A. D.; Ellman, J. A. *J. Org. Chem.* **2018**, *83*, 15347-15360. (c) Wu, X.; Xiong, H.; Sun, S.; Cheng, J. *Org. Lett.* **2018**, *20*, 1396-1399. (d) Hu, P.; Zhang, Y.; Xu, Y.; Yang, S.; Liu, B.; Li, X. *Org. Lett.* **2018**, *20*, 2160-2163. (e) Halskov, K. S.; Witten, M. R.; Hoang, G. L.; Mercado, B. Q.; Ellman, J. A. *Org. Lett.* **2018**, *20*, 2464-2467. (f) Liang, Y.-F.; Yang, L.; Rogge, T.; Ackermann, L. *Chem.-Eur. J.* **2018**, *24*, 16548-16552. (g) Zhou, C.; Fang, F.; Cheng, Y.; Li, Y.; Liu, H.; Zhou, Y. *Adv. Synth. Catal.* **2018**, *360*, 2546-2551. (h) Xie, H.; Lan, J.; Gui, J.; Chen, F.; Jiang, H.; Zeng, W. *Adv. Synth. Catal.* **2018**, *360*, 3534-3543. (i) Chen, G.; Zhang, X.; Jia, R.; Li, B.; Fan, X. *Adv. Synth. Catal.* **2018**, *360*, 3781-3787. (j) Shi, X.; Wang, R.; Zeng, X.; Zhang, Y.; Hu, H.; Xie, C.; Wang, M. *Adv. Synth. Catal.* **2018**, *360*, 4049-4053. (k) Hu, P.; Zhang, Y.; Liu, B.; Li, X.; *Org. Chem. Front.* **2018**, *5*, 3263-3266. (l) Xu, Y.; Zheng, G.; Yang, X.; Li, X. *Chem. Commun.* **2018**, *54*, 670-673.
- (19) For recent examples, see: (a) Xu, Y.; Yang, X.; Zhou, X.; Kong, L.; Li, X. *Org. Lett.* **2017**, *19*, 4307-4310. (b) Zhou, M.-D.; Peng, Z.; Wang, H.; Wang, Z.-H.; Hao, D.-J.; Li, L. *Adv. Synth. Catal.* **2019**, *361*, 5191-5197. (c) Yu, Y.; Wu, Q.; Liu, D.; Yu, L.; Tan, Z.; Zhu, G. *Org. Chem. Front.* **2019**, *6*, 3868-3873. (d) Chen, X.; Wang, M.; Zhang, X.; Fan, X., *Org. Lett.* **2019**, *21*, 2541-2545. (e) Wu, X.; Xiao, Y.; Sun, S.; Yu, J.-T.; Cheng, J. *Org. Lett.* **2019**, *21*, 6653-6657. (f) Hanchate, V.; Kumar, A.; Prabhu, K. R. *Org. Lett.* **2019**, *21*, 8424-8428. (g) Wang, P.; Xu, Y.; Sun, J.; Li, X. *Org. Lett.* **2019**, *21*, 8459-8463. (h) Lou, J.; Wang, Q.; Zhou, Y.-G.; Yu, Z. *Org. Lett.* **2019**, *21*, 9217-9222. (i) Kommagalla, Y.; Ando, S.; Chatani, N. *Org. Lett.* **2020**, *22*, 1375-1379. (j) Hanchate, V.; Devarajappa, R.; Prabhu, K. R. *Org. Lett.* **2020**, *22*, 2878-2882.
- (20) In entries 4, 5, 7, and 10, considerable amount of byproducts were observed. A major byproduct (up to 25% yield) was **4** whose structure is shown below.



- (21) For reviews on the use of HFIP, see: (a) Bégué, J.-P.; Bonnet-Delpon, D.; Crousse, B. *Synlett* **2004**, *1*, 18-29. (b) Shuklov, I. A.; Dubrovina, N. V.; Börner, A. *Synthesis* **2007**, *19*, 2925-2943.
- (22) The CCDC numbers are 1998209 (**3aa**) and 1998210 (**3ab-dimer**).
- (23) For reviews, see: (a) Rousseau, G.; Breit, B. *Angew. Chem. Int. Ed.* **2010**, *50*, 2450-2494. (b) Rej, S.; Chatani, N. *Angew. Chem. Int. Ed.* **2019**, *58*, 8304-8329.
- (24) Unoh, Y.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2015**, *17*, 704-707.
- (25) For selected reviews on Cu-mediated aerobic oxidation, see: (a) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem. Int. Ed.* **2011**, *50*, 11062-11087. (b) Allen, S. E.; Walvoord, R. R.; Padilla-Sallinas, R.; Kozłowski, M. S. *Chem. Rev.* **2013**, *113*, 6234-6458.
- (26) A possible mechanism of the dimerization is (1) formation of a rhodium enolate species through the deprotonation of **3ab**, (2) electrophilic metalation of another **3ab** molecule at the indole C2 position, and (3) reductive elimination.
- (27) (a) Bonjouklian, R.; Smitka, T. A.; Mynderse, J. S.; Foster, R. S.; Jones, N. D.; Swartzendruber, J. K.; Deeter, J. B. *J. Org. Chem.* **1987**, *52*, 1036-1043. (b) Stratmann, K.; Moore, R. E.; Bonjouklian, R.; Deeter, J. B.; Patterson, G. M. L.; Shaffer, S.; Smith, C. D.; Smitka, T. A. *J. Am. Chem. Soc.* **1994**, *116*, 9935-9942. (c) Jimenez, J. I.; Huber, U.; Moore, R. E.; Patterson, G. M. L. *J. Nat. Prod.* **1999**, *62*, 569-572; (d) Bennett, J. W.; Klich, M. *Clin. Microbiol. Rev.* **2003**, *16*, 497-516; (e) Gul, W.; Hamann, M. T. *Life Sci.* **2005**, *78*, 442-453. (f) Baran, P. S.; Maimone, T. J.; Richter, J. M. *Nature*, **2007**, *446*, 404-408. (g) Richter, J. M.; Ishihara, Y.; Masuda, T.; Whitefield, B. W.; Llamas, T.; Pohjakallio, A.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 17938-17954. (h) Wallwey, C.; Li, S.-M. *Nat. Prod. Rep.* **2011**, *28*, 496-510. (i) Quasdorf, K. W.; Hutters, A. D.; Lodewyk, M. W.; Tantillo, D. J.; Garg, N. K. *J. Am. Chem. Soc.* **2012**, *134*, 1396-1399. (j) Chen, J.-J.; Han, M.-Y.; Gong, T.; Yang, J.-L.; Zhu, P. *RSC Adv.* **2017**, *7*, 27384-27396.
- (28) Li, Z.; Shi, Z.; He, C. *J. Organomet. Chem.* **2005**, *690*, 5049-5054.
- (29) For a review on the cobalt-catalyzed alkyne trimerization, see: Gandon, V.; Aubert, C.; Malacria, M. *Chem. Commun.* **2006**, 2209-2217.
- (30) Brand, J. P.; Charpentier, J.; Waser, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 9346-9349.
- (31) For a recent review, see: Huber, T.; Wildermuth, R. E.; Magauer, T. *Chem. Eur. J.* **2018**, *24*, 12107-12120.
- (32) (a) Majumdar, K. C.; Chattopadhyay, B. *Synlett* **2008**, 979-982. (b) Majumdar, K. C.; Chattopadhyay, B. *Synthesis* **2009**, 2385-2392.

(33) Kona, C. N.; Shinde, M. H.; Ramana, C. V. *Org. Biomol. Chem.*
2015, *13*, 5358-5362.