Cyclic Sulfoxonium Ylides: Synthesis and Chemospecific Reactivity in the Catalytic Alkylation of Indoles

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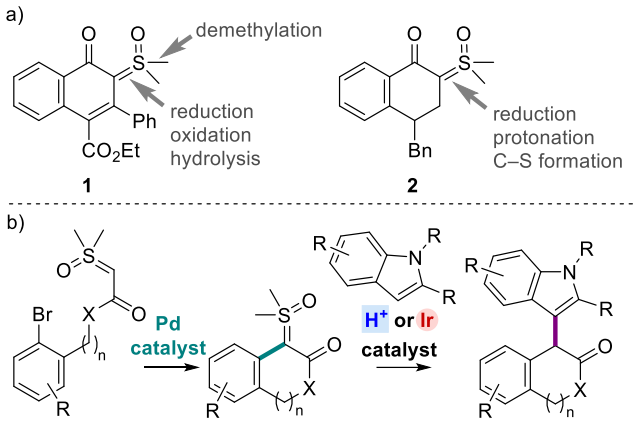
Abstract: The study of the reactivity of cyclic sulfoxonium ylides has been so far neglected, in particular for reactions that forms carboncarbon bond at the ylide carbon atom. Herein, we describe the synthesis of cyclic sulfoxonium ylides by palladium-catalyzed intramolecular arylation and the reactivity of these ylides in the C3-alkylation of indoles in the presence of either an acid catalyst or an iridium catalyst. This study revealed that acid catalysis is only efficient for cyclic sulfoxonium ylides in which the tether is a six-membered lactone, whereas iridium catalysis was better suited to the reaction of cyclic sulfoxonium ylides in which the tether is a five-membered ring ketone or lactone. The observed chemospecificity might be due to the relative basicity of the ylides under acid catalysis and to the steric hindrance around an iridium carbene intermediate when the reaction is conducted with the iridium catalyst.

Introduction

Sulfoxonium ylides have recently gained renewed attention as potential surrogates of diazo compounds in both metal- and acid-catalyzed reactions.[1–6] These studies have been focused on *acyclic* α-carbonyl sulfoxonium ylides, whereas the potential reactivity of their *cyclic* congeners remains vastly unknown. Hence, only rare examples of cyclic sulfoxonium ylides have been prepared where the sulfoxonium moiety is in an *exo* position to a ring. Thus, methods to access these ylides include the decomposition of the parent diazo compounds or iodoniums in the presence of dimethyl sulfoxide,[7–9] and intramolecular carbonylative palladium-catalyzed cross-coupling of aryl iodides,[10] among others.[11,12] Recently, more systematic methods were disclosed that relied either on intermolecular rhodium-catalyzed cross coupling of α-carbonyl sulfoxonium ylides and diazo compounds to access ylides **1**,[13] or on light-mediated cycloaddition of aliphatic alkenes and iodonium-sulfoxonium ylides to access **2** (Scheme 1a).[14] However, the reactivity of the cyclic sulfoxonium ylides made in these studies was examined only briefly. Hence, oxidation, reduction, protonation, hydrolysis, S-demethylation and C–S bond formation with a thiol were the only transformations demonstrated, whilst carbon-carbon bond formation at the ylide carbon atom was not reported.

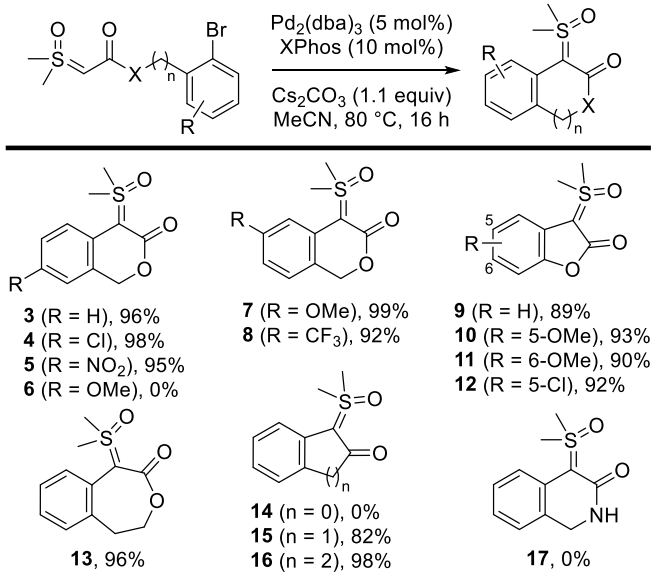
Following on previous reports of intermolecular palladium-catalyzed cross-coupling of α-carbonyl sulfoxonium ylides of aryl bromides,[15,16] we envisioned that the intramolecular variant of that reaction would give rapid access to cyclic sulfoxonium ylides, which in turn would enable the study of their reactivity (Scheme 1b). Herein, we focused our attention on C–C bond forming reactions with the regioselective alkylation of indoles with cyclic sulfoxonium ylides under two sets of catalytic conditions, namely acid-catalysis[17] and iridium-catalysis.[18–20] Importantly, we discovered a chemospecific reactivity of cyclic sulfoxonium ylides under these two sets of catalytic conditions that is dependent on the length and nature of the tether: a six-membered lactone tether is optimal under acid catalysis, whereas five-membered ketone and lactone tethers are the best under iridium catalysis.



Scheme 1. a) Limited reactivity of cyclic sulfoxonium ylides (previous work). b) Synthesis of cyclic sulfoxonium ylides by intramolecular cross-coupling of aryl bromides and subsequent acid- or iridium-catalyzed alkylation of indoles (this work).

Results and Discussion

Following on previous work by the Aïssa group,[15,16] the optimization of the intramolecular arylation of sulfoxonium ylides for the synthesis of cyclic compound **3** (Scheme 2) was straightforward (see Table S1 in the Supporting Information). Gratifyingly, five-, six- and seven-membered ring lactones **3**–**5** and **7**–**13** could be obtained in good yields (Scheme 2). Similarly, cyclic ketones **15** and **16** were made accessible by this method. However, neither 4-membered ring ketone **14** nor lactam **17** were formed under the optimized reaction conditions. Moreover, six-membered ring lactone **6** was not formed, where an electron-rich methoxy group is in *para* position to the ylide carbon, whereas the same arrangement was not problematic in five-membered ring lactone **11**. The absence of product in the case of **6** is in agreement with the previously reported palladium-catalyzed intermolecular cross-coupling of α-carbonyl sulfoxonium ylides with *para*-bromoanisole that delivered unstable adducts.[15,16] Hence, the excellent yield of compound **11** might be explained by enhanced stability, which could possibly be understood in terms of resonance structure, as the delocalization of the negative charge of the ylide carbon atom into the carbonyl leads to an aromatic benzofuran resonance form.

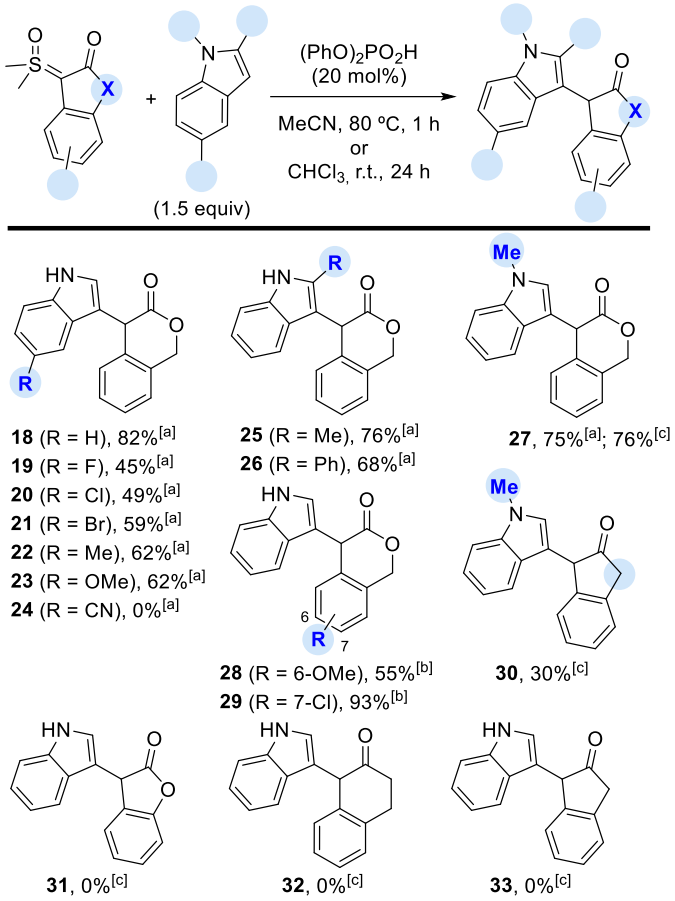


Scheme 2. Intramolecular arylation of sulfoxonium ylides.

Previously, the Burtoloso group described the intermolecular acid-catalyzed C3-alkylation of indoles with α-carbonyl sulfoxonium ylides.[17] We were thus eager to extend this methodology to the cyclic sulfoxonium ylides obtained above, which would significantly expand the chemistry so far reported for these valuable reagents. We were pleased to bring these plans to fruition. Hence, cyclic sulfoxonium ylide **3** was converted into **18**–**23** when treated with a slight excess of

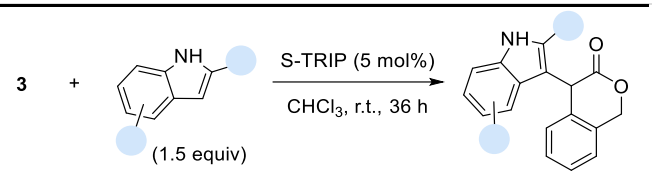
unprotected indoles in the presence of a catalytic amount of diphenyl phosphate at 80 °C in a microwave oven (Scheme 3). Substitution at position 2 or at the nitrogen atom of the indole was well tolerated, as illustrated with the good yields of compounds **25**–**27**. Similarly, electronic variations on the benzene ring of the cyclic sulfoxonium ylide were also tolerated, as shown with compounds **28** and **29** that were formed smoothly by treating the reactants with the acid catalyst in chloroform at room temperature for 16 hours. However, the most electron-poor indole we examined failed to give any of compound **24**, likely because this indole is not sufficiently nucleophilic. Surprisingly, the desired products **31**–**33** were not found in the complex mixtures obtained after reaction of cyclic sulfoxonium ylides **9**, **15** and **16** with unprotected indole. Similarly, **30** was only obtained in 30% yield when *N*-Me indole and **15** were treated in the presence of the acid catalyst at 80 °C, but the same product was not formed at all at room temperature.

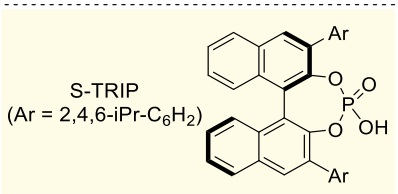
Moreover, we were pleased to observe excellent asymmetric induction in the reaction of sulfoxonium ylide **3** with indoles conducted in the presence of a chiral acid catalyst at room temperature (Table 1). The best results were obtained for unsubstituted indole (entry 1), 5-methoxyindole (entry 3) and 2-methyl indole (entry 4). Overall, the yields and enantiomeric ratios of these reactions involving *cyclic* sulfoxonium ylides compare favorably with those previously obtained under similar conditions with *acyclic* sulfoxonium ylides, as exemplified with **34** and **35** (entries 6 and 7).[17] It is also noteworthy that the reaction of cyclic sulfoxonium ylides were faster.

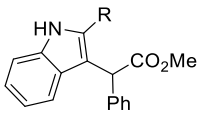


Scheme 3. Acid-catalyzed C3-alkylation of indoles with cyclic sulfoxonium ylides. [a] In MeCN, at 80 °C (microwave heating), 1 h. [b] In $CHCl_3$, at room temperature, 24 h. [c] In MeCN, at 80 °C (oil bath), 16 h.

Table 1. Enantioselectivity of the reactions catalyzed by *S*-TRIP.





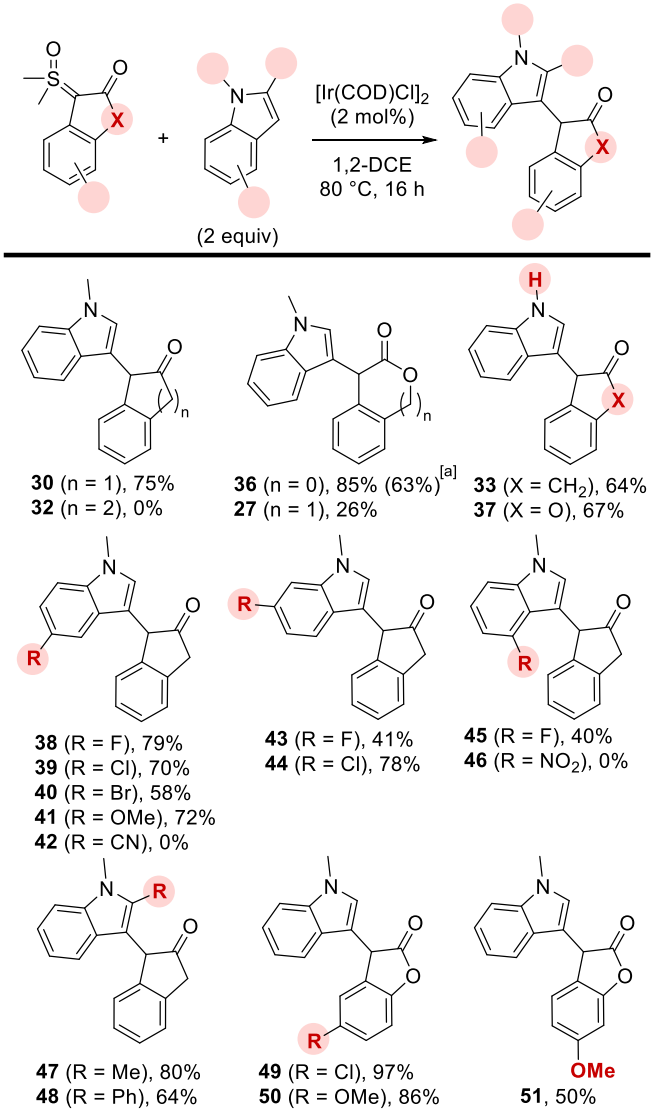


34 (R = H)
35 (R = Me)

Entry	Product	Yield[a]	Enantiomeric ratio[b]
1	**18**	94%	86:14
2	**19**	73%	67:33
3	**23**	91%	85:15
4	**25**	87%	92:8
5	**26**	22%	95:5
6	**34**	37%[c,d]	85:15[c,d]
7	**35**	35%[c,d]	76:24[c,d]

[a] Yield of isolated product. [b] Determined by chiral HPLC. [c] From reference 17. [d] 5 mol% S-TRIP, r.t., 168 h.

In an attempt to solve the issues encountered in the acid-catalyzed reactions of cyclic sulfoxonium ylides **9**, **15** and **16**, we turned our attention to iridium-catalyzed reactions.[18–20] Gratifyingly, we could isolate **30** in 75% yield after treating **15** with 2 mol% of $[Ir(COD)Cl]_2$ and *N*-Me indole in refluxing 1,2-dichloroethane. Using less than 2 equivalents of indole led to a lower yield of the product. Surprisingly, treating the 6-membered ring sulfoxonium ylide **16** under the same conditions did not allow for the isolation of **32**. The same difference of reactivity between 5-membered and 6-membered ring sulfoxonium ylides was evident in the case of ester derivatives **9** and **3**. Hence, **36** could be isolated in 85% yield, whereas **27** was isolated in only 26% yield. Moreover, the reaction could be conducted on the gram-scale to afford **36** in 63% yield. The reaction was amenable to the use of unprotected indole to give **33** and **37** in good yields. Similarly, substitution at positions 4–6 of *N*-Me indole gave **38**–**41** and **43**–**45** without clearly identifiable electronic effect. Only in the case of strongly electronically deactivated 5-CN and 4-NO_2 *N*-Me indoles did we fail to obtain **42** and **46**, respectively. Moreover, substitution at position 2 of the indole was well tolerated, as shown with **47** and **48**. However, the reaction is sensitive to electronic variation in the cyclic sulfoxonium ylides as 5-OMe and 5-Cl derivatives **10** and **12** gave **49** and **50** in high yields, respectively, whereas more electron-rich ylide **11** gave **51** in 50% yield only. We also conducted the reaction in the presence of a chiral iridium catalyst that previously gave positive results in the intramolecular cyclopropanation of sulfoxonium ylides,[21] but no induction of enantioselectivity was observed in the reaction of *N*-Me indole and ylide **9** (Figure 1). Finally, it is noteworthy that the *cyclic* sulfoxonium ylides used in this iridium-catalyzed alkylation of indoles appear to be more reactive than their *acyclic* congeners under the same conditions, as shown with compounds **52** and **53** (Figure 2).



Scheme 4. Iridium-catalyzed C3-alkylation of indoles with cyclic sulfoxonium ylides. COD: cyclooctadiene; 1,2-DCE: 1,2-dichloroethane.

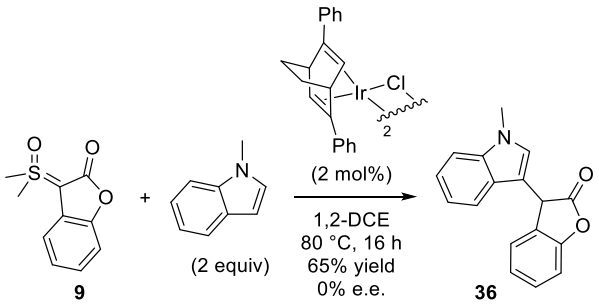


Figure 1. Evaluation of a chiral iridium catalyst to promote C3-alkylation of indoles with cyclic sulfoxonium ylides.

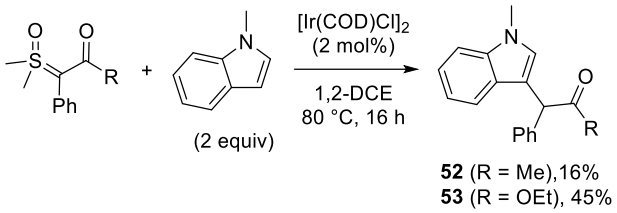


Figure 2. Evaluation of acyclic sulfoxonium ylides in iridium-catalyzed alkylation of indoles.

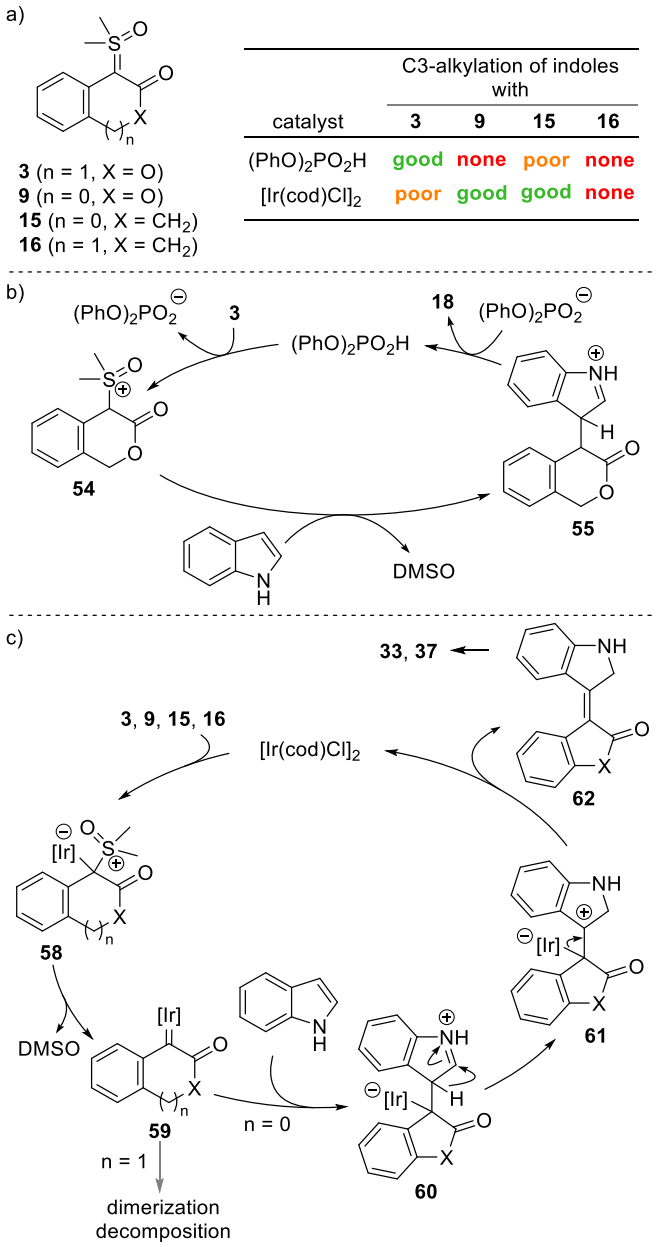


Figure 3. (a) Contrasted reactivity of cyclic sulfoxonium ylides. (b) Proposed mechanism for the acid-catalyzed C3-alkylation of indoles with cyclic sulfoxonium ylides. (c) Proposed mechanism for the iridium-catalyzed C3-alkylation of indoles with cyclic sulfoxonium ylides.

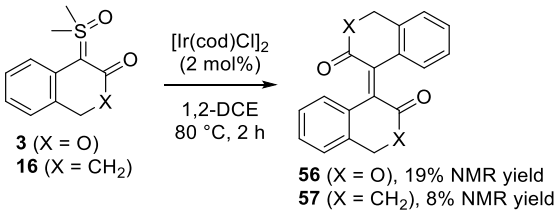


Figure 4. Iridium-catalyzed dimer formation.

Overall, we observed a remarkable chemospecific reactivity for cyclic sulfoxonium ylides **3**, **9**, **15**, and **16** in the acid-catalyzed and iridium-catalyzed C3-alkylation of indoles (Figure 3a). The lack of reactivity of **15** and **16** in the acid-catalyzed reaction might be explained by the lower pKaH of these ylides as compared to **3** and **9**.[22] Moreover, the 5-membered ring **9** might also have a lower pKa than **3** because of the aromatic character of the O-centered enolate resonance form. Thus, **3** would give sulfoxonium **54** that would then undergo reaction with indole to give **55** before rearomatization to give **18** (Figure 3b).[17] In the iridium-catalyzed reaction, **3** and **16** were unsatisfactory, and thin layer chromatography of the crude indicated the presence of many decomposition products that could not be identified. We were curious to examine the reactivity of these two substrates in the presence of the iridium catalyst but in the absence of indole. After 2 hours of reaction, we found that **3** was fully converted into dimer **56** besides other compounds that could not be identified by NMR (Figure 4), whereas **16** was recovered in 22% NMR yield besides **57** in 8% NMR yield when treated under the same conditions. Unfortunately, in both cases, some decomposition of the starting ylide was not captured by NMR of the crude mixture. It is noteworthy that the extensive decomposition of **3** and **16** was not observed when heating these ylides in 1,2-DCE at 80 °C in the absence of iridium catalyst, which strongly supports the conclusion that the decomposition of **3** and **16** is iridium-catalyzed. This decomposition in the absence of indoles after 2 hours of heating was complete in the case of the 16-hour reactions of the same substrates in the presence of indoles and explained the non-formation of **32** and the low yield of **27** as depicted in Scheme 4.

The decreased reactivity of **16** as compared to that of **3** might be understood by considering Mayr's nucleophilicity scale, which suggests that the lactone **3** should be more nucleophilic than the ketone **16**.[23,24] Although recent theoretical studies suggest that the formation of metal carbenes from α-carbonyl sulfoxonium ylides is a two-step process involving facile coordination of the ylide carbon atom to the metal followed by rate-limiting elimination of DMSO,[25] the efficiency of formation of an iridium carbene from **3**, **9**, **15**, and **16** does not appear to fully explain their difference of reactivity.[18–21, 26–28] Instead, it is more likely that after attack of the iridium catalyst by these substrates and elimination of DMSO from **58**, iridium carbenes **59** would be formed in all cases (Figure 1c). Then, dimerization [21, 26] and other unidentified decomposition pathways would be predominant in the case of the six-membered ring intermediates (n = 1), whereas indole would react productively with the five-membered ring intermediates **59** (n = 0) to give **60**, which would give **33** and **37** after a sequence consisting of 1,2-hydride shift to **61**, elimination to **62** and rearomatization. The greater steric hindrance around the iridium carbene **59** when n = 1 might explain the difference of behavior observed between five- and six-membered ring cyclic sulfoxonium ylides.

Conclusion

In conclusion, we have expanded the scope of the palladium-catalyzed cross-coupling of sulfoxonium ylides with aryl bromides to easily prepare cyclic sulfoxonium ylides. The C3-alkylation of indoles with these ylides can be performed with either an acid catalyst or with an iridium catalyst, but it is important to choose the method wisely for optimal results. Acid catalysis performed best when the tether of the cyclic sulfoxonium ylide was a six-membered ring lactone, whereas iridium catalysis was optimal when the tether is a five-membered ring ketone or lactone. The cyclic ylides that feature a six-membered ring ketone as tether were not productive in either of the two catalytic regimes. It is proposed that the difference of reactivity under acid catalysis might be best explained by the relative basicity of the ylides. In addition, the difference of reactivity between cyclic sulfoxonium ylides under iridium catalysis might be explained by the difference in steric hindrance around an iridium carbene intermediate. The chemistry of cyclic sulfoxonium ylides, and in particular the formation of C–C bond from these cyclic substrates, had been hitherto neglected. We anticipate that the result of this study will contribute to a better understanding of the reactivity of these ylides and inspire further developments.

Experimental Section

Essential Experimental Procedures

***General Procedure for Intramolecular Palladium-Catalyzed Cross-Coupling of Sulfoxonium Ylides*.** Under nitrogen, a J-Young Schlenck tube was charged with XPhos (9.5 mg, 0.02 mmol, 0.1 equiv), Pd_2dba_3 (9 mg, 0.01 mmol, 0.05 equiv),

and Cs_2CO_3 (72 mg, 0.22 mmol, 1.1 equiv). Acetonitrile (0.5 mL) was then added, and the mixture was stirred at room temperature for 10 min. Then, sulfoxonium ylide (0.2 mmol, 1 equiv) was added, the inner wall of the Schlenck tube was rinsed with acetonitrile (0.5 mL), and the tube was then sealed, placed in a preheated oil bath set at 80 °C, and stirred for 16 h. The crude was then filtered over celite at room temperature using dichloromethane to transfer all the material and for rinsing. After evaporation of all volatiles under vacuum, purification by flash chromatography (silica gel; ethyl acetate) afforded desired cyclic sulfoxonium ylide.

***Organocatalyzed C-H functionalization of indoles*.** Conventional heating: To a flame-dried and argon-purged 2 mL reaction vial with a Teflon coated septum screw-top was added sulfoxonium ylides (0.10 mmol, 1.0 equiv.), 0.5 mL of acetonitrile, indole (0.15 mmol, 1.5 equiv.), and diphenyl phosphate (5.0 mg, 0.02 mmol, 0.2 equiv.). The reaction was stirred at 80˚C for 16 hours. The product was purified by flash column chromatography in EtOAc/Hexanes. Microwave: To a flame-dried and argon-purged 4 mL glass microwave vial equipped with a magnetic stir bar were added the sulfoxonium ylides (0.10 mmol, 1.0 equiv.), 0.3 mL of acetonitrile, indole (0.15 mmol, 1.5 equiv.), and diphenyl phosphate (5.0 mg, 0.02 mmol, 0.2 equiv.). The microwave vial was capped with a Teflon microwave cap and the reaction was heated for 60-90 min to 80 °C MW. The resulting mixture was purified by flash column chromatography using silica gel and an appropriate mixture of hexane/ethyl acetate as the eluent. Asymmetric reaction: To a 2 mL reaction vial with a Teflon coated septum screw-top was added sulfoxonium ylide (0.1 mmol, 1.0 equiv.), 0.2 mL of $CHCl_3$, and phosphoric acid catalyst (S)-TRIP (3.76 mg, 0.005 mmol, 0.05 equiv). The reaction was stirred at rt for twenty minutes before the addition of indole (0.15 mmol 1.5 equiv.). The reaction was stirred at room temperature for 1-3 days until consumption of all sulfur ylide substrate. The crude mixture was purified by flash column chromatography using silica gel and hexane/ethyl acetate as the eluent. The *ee* value was determined by chiral HPLC analysis of the purified product (AD-H column: 85:15 hexane/*i*-PrOH, 0.9 mL/min).

Iridium catalyzed C-H functionalization reactions. Method A: Under nitrogen, a J-Young Schlenck tube was charged with sulfoxonium ylide substrate (0.1 mmol), indole (0.2 mmol, 2 equiv.) and solvent 1,2-DCE (0.3 mL). The system was degassed by 3 cycles of freeze-pup-thaw and filled back with nitrogen. The catalyst $[Ir(COD)Cl]_2$ (0.002 mmol, 2 mol%) was then added, the tube was sealed and the mixture was stirred at 80 ºC for 16h. After evaporation of all volatiles under vacuum, purification by flash chromatography (silica gel; ethyl acetate/hexane) afforded the desired N-H insertion or C-H functionalization product. Method B: Under nitrogen, a J-Young Schlenck tube was charged with sulfoxonium ylide substrate (0.1 mmol) and indole (0.2 mmol, 2 equiv.) A stock solution of $[Ir(COD)Cl]_2$ (6.67 $mmol.\mu L^{-1}$) in DCE was prepared, and 0.3 mL of this solution (0.002 mmol, 2 mol% of catalyst in 0.3 mL of solvent) was added to the reaction tube. The tube was sealed, and the mixture was stirred at 80 ºC for 16h. After evaporation of all volatiles under vacuum, purification by flash chromatography (silica gel; ethyl acetate/hexane) afforded the desired C-H functionalization product.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Acknowledgements

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[1] J. Vaitla, A. Bayer, *Synthesis* **2019**, *51*, 612-628.
[2] X. Wu, S. Sun, J. T. Yu, J. Cheng, *Synlett* **2019**, *30*, 21-29.
[3] G. D. Bisag, S. Ruggieri, M. Fochi, L. Bernardi, *Org. Biomol. Chem.* **2020**, *18*, 8793-8809.
[4] A. Kumar, M. S. Sherikar, V. Hanchate, K. R. Prabhu, *Tetrahedron* **2021**, *101*, 132478.
[5] C. A. D. Caiuby, L. G. Furniel, A. C. B. Burtoloso, *Chem. Sci.* **2022**, *13*, 1192-1209.
[6] P. Bhorali, S. Sultana, S. Gogoi, *Asian J. Org. Chem.* **2022**, *11*, e202100754.
[7] F. Dost, J. Gosselck, *Tetrahedron Lett.* **1970**, *11*, 5091-5093.
[8] J. Vaitla, K. H. Hopmann, A. Bayer, *Org. Lett.* **2017**, *19*, 6688-6691.
[9] J. Lu, L. Li, X.-K. He, G.-Y. Xu, J. Xuan, *Chin. J. Chem.* **2021**, *39*, 1646-1650.

[10] Y. Yuan, X.-F. Wu, *Org. Lett.* **2019**, *21*, 5310-5314.
[11] J. Ide, Y. Kishida, *Chem. Pharm. Bull.* **1968**, *16*, 793-798.
[12] S. Zhu, K. Shi, H. Zhu, Z-K. Jia, X.-F. Xia, D. Wang, L.-H. Zou, *Org. Lett.* **2020**, *22*, 1504-1509.
[13] X. Chen, M. Wang, X. Zhang, X. Fan, *Org. Lett.* **2019**, *21*, 2541-2545.
[14] L. Li, K. Deng, Y. Xing, C. Ma, S.-F. Ni, Z. Wang, Y. Huang. *Nat Commun* https://doi.org/10.1038/s41467-022-34401-7
[15] C. Janot, P. Palamini, B. C. Dobson, J. Muir, C. Aïssa, *Org. Lett.* **2019**, *21*, 296-299.
[16] C. Janot, J.-B. Chagnoleau, N. R. Halcovitch, J. Muir, C. Aïssa, *J. Org. Chem.* **2020**, *85*, 1126-1137.
[17] A. N. Leveille, R. Echemendía, A. E. Mattson, A. C. B. Burtoloso, *Org. Lett.* **2021**, *23*, 9446-9450.
[18] D. Clare, B. C. Dobson, P. A. Inglesby, C. Aïssa, *Angew. Chem. Int. Ed.* **2019**, *58*, 16198-16202.
[19] C. A. D Caiuby, M. P. de Jesus, A. C. B. Burtoloso, *J. Org. Chem.* **2020**, *85*, 7433−7445.
[20] J. Vaitla, A. Bayer, K. H. Hopmann, *Angew. Chem. Int. Ed.* **2017**, *56*, 4277−4281.
[21] L, Vidal, P.-P. Chen, E. Nicolas, A. Hackett, C. M. Robertson, K. N. Houk, C. Aïssa, *Org. Lett.* **2022**, *24*, 8503–8508.
[22] Y. Fu, H. J. Wang, S. S. Chong, Q. X. Guo, L. Liu, *J. Org. Chem.* **2009**, *74*, 810–819.
[23] H. Mayr, T. Bug, M. F. Gotta, N. Hering, B. Irrgang, B. Janker, B. Kempf, R. Loos, A. R. Ofial, G. Remennikov, H. Schimmel, *J. Am. Chem. Soc.* **2001**, *123*, 9500–9512.
[24] A. I. Leonov, D. S. Timofeeva, A. R. Ofial, H. Mayr, *Synthesis* **2019**, *51*, 1157–1170.
[25] D. Zhang, X. He, T. Yang, S. Liu, *ChemistryOpen* **2022**, *11*, e202100254.
[26] I. K. Mangion, I. K. Nwamba, M. Shevlin, M. A. Huffman, *Org. Lett.* **2009**, *11*, 3566−3569.
[27] J. Li, H. He, M. Huang, Y. Chen, Y. Luo, K. Yan, Q. Wang, Y. Wu, *Org. Lett.* **2019**, *21*, 9005−9008.
[28] S.-S. Zhang, H. Xie, B. Shu, T. Che, X.-T. Wang, D. Peng, F. Yang, L. Zhang, *Chem. Commun.* **2020**, *56*, 423−426.