

Accepted Article

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201706804
Angew. Chem. 10.1002/ange.201706804

Link to VoR: <http://dx.doi.org/10.1002/anie.201706804>
<http://dx.doi.org/10.1002/ange.201706804>

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Cross-Coupling of α -carbonyl sulfoxonium ylides with C–H bondsManuel Barday,^[a] Christopher Janot,^[a] Nathan R. Halcovitch,^[b] James Muir,^[c] and Christophe Aïssa*^[a]

Abstract: The functionalization of carbon-hydrogen bonds in non-nucleophilic substrates using α -carbonyl sulfoxonium ylides has not been so far investigated, despite the potential safety advantages that those reagents would provide over diazo compounds or their *in situ* precursors. We describe the cross-coupling reactions of sulfoxonium ylides with C(sp²)-H bond of arenes and heteroarenes in the presence of a rhodium catalyst. The reaction proceeds by a succession of C–H activation, migratory insertion of the ylide into the carbon-metal bond and protodemetalation, the last step being turnover-limiting. The method is applied to the synthesis of benz[*c*]acridines when allied to an iridium-catalyzed dehydrative cyclization.

Metal-catalyzed reactions of sulfoxonium ylides are rare and underexploited.^[1] Specifically, the iridium-catalyzed formation of carbon-nitrogen and carbon-oxygen bonds from α -carbonyl sulfoxonium ylides has been optimized in industry in an effort to provide a safer alternative to the analogous diazo compounds, and thus avoid the risk of potential exothermic reactions linked to the release of nitrogen gas.^[2] This issue is particularly relevant in the context of relatively large scale applications at a late stage of drug development, as illustrated in the multi-kilogram synthesis of MK-7246, a drug candidate with potential application against respiratory disease [Figure 1a].^[2d] Iridium carbene **A** [Figure 1b] is a likely intermediate of these reactions and was also postulated to account for the iridium-catalyzed synthesis of pyrroles from α -carbonyl sulfoxonium ylides.^[3] In this case, the formation of a carbon-carbon bond plausibly proceeds *via* electrophilic substitution by the reactive α,β -unsaturated β -amino-esters substrates.

In contrast to the transformation depicted in Figure 1b, the cross-coupling of sulfoxonium ylides with organometallic intermediates generated by activation of C–H bonds *in less nucleophilic substrates* has not yet been investigated. We hypothesized that after group-directed cyclometallation involving metal-catalyzed C–H bond cleavage, **B** thus formed would undergo migratory insertion of α -carbonyl sulfoxonium ylides *via* intermediates **C** and/or **D** to give **E**. This intermediate would then liberate the cross-coupling products upon protodemetalation [Figure 1c]. Significantly, the realization of this design would

address the potential safety issues of the recently reported group-directed C–H functionalization reactions with diazo compounds^[4] and their *in situ* precursors such as triazoles^[5] or hydrazones.^[6] Moreover, it would complement the scope of recently reported rhodium-catalyzed annulation reactions with cyclopropenes^[7] and enynes,^[8] that also likely proceed by migratory insertion similar to the postulated evolution of **D** into **E**. Finally, it would also expand the scope of the well-established C–H insertion chemistry of metal-carbenoids generated from diazo compounds.^[9]

Herein, we show that α -carbonyl sulfoxonium ylides undergo efficient cross-coupling reactions with C(sp²)-H bond of arenes and heteroarenes in the presence of a rhodium catalyst that do not require a sacrificial oxidizing reagent. Data from control experiment supports the sequence of steps depicted in Figure 1c. Thus, the cross-coupling reaction described herein is strongly distinct from the single previous example of C–H functionalization by α -carbonyl sulfoxonium ylides,^[3] both in its scope and in terms of mechanism.

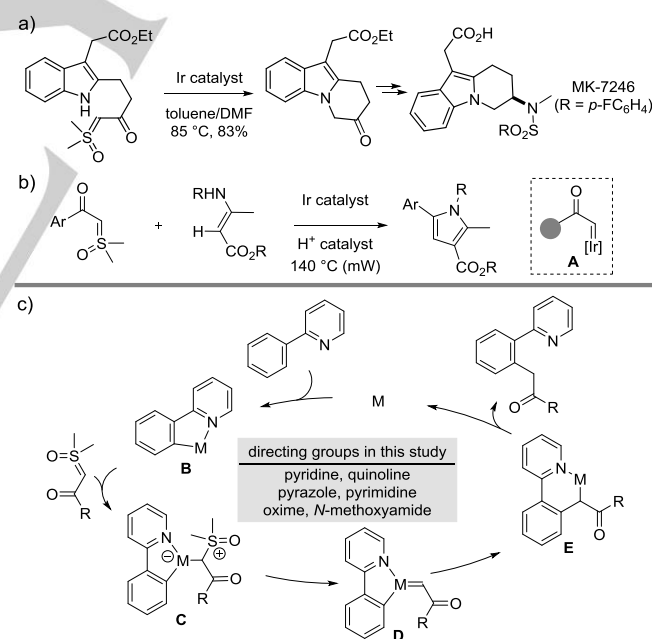


Figure 1. a) Iridium-catalyzed carbon-nitrogen bond formation from α -carbonyl sulfoxonium ylides. b) Postulated iridium-carbene intermediates from α -carbonyl sulfoxonium ylides during pyrrole synthesis. c) Hypothetical cross-coupling of α -carbonyl sulfoxonium ylides with C–H bonds (this work).

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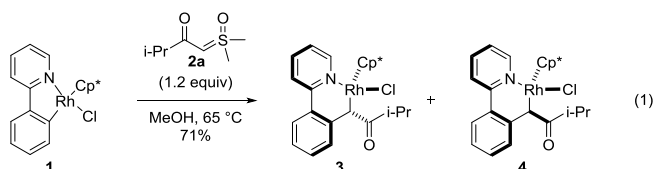
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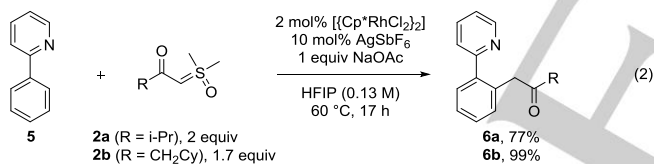
We were mindful that the envisioned migratory insertion from **B** to **E** was not known for α -carbonyl sulfoxonium ylides. Thus, we initially focused our attention on known rhodium complex **1**^[10] (Cp* = 1,2,3,4,5-pentamethylcyclopentadienyl) and observed its reaction with ylide **2a** to give a diastereomeric mixture of migratory

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insertion complexes **3** and **4** in good yield [Eq. (1)]. The ratio of **3** and **4** varied from 2.8:1 to 5:1, depending on the duration of the purification by flash chromatography. Compounds **3** and **4** are configurationally stable in the solid state and in solution at room temperature. Their structure was confirmed by X-ray crystallography.^[11]



Having established the crucial organometallic basis for the development of the catalytic reaction, we then observed that HFIP (1,1,1,3,3,3-hexafluoro-2-propanol) was essential for the efficient protodemetalation leading to catalyst turnover and product formation [Eq. (2) and Tables S1–S3]. The reaction could proceed without added base, but its presence enabled to reach full conversion and led to higher yield of isolated products. Another important factor was the amount of ylide. Thus, the yield of **6b** was quantitative when a 1.7 equiv of **2b** was used (Cy = cyclohexyl), whereas using 2 equiv of bulkier **2a** was necessary to reach full conversion and obtain **6a** in 77% yield. The reaction did not proceed at all without $[\text{Cp}^*\text{RhCl}_2]_2$, but the conversion into **6b** could reach 81% in the presence of this catalyst and in the absence of AgSbF_6 . Attempts to replace the rhodium catalyst with $[\text{Cp}^*\text{IrCl}_2]_2$, $[\text{Cp}^*\text{Co}]_2$, $[\text{Cp}^*\text{Co}(\text{CO})_2]$ or $[\text{Ru}(\textit{p}\text{-cymene})\text{Cl}_2]_2$ were unsuccessful.



Using ylides **2c–2k** with **5** revealed that aryl ketones **6c** and **6d** were obtained in excellent yields, whereas ylides with less electron-rich substituents led to slightly (**6e**) or more markedly (**6f**) decreased yields of products [Figure 2]. Heteroaryl ketones **6g** and **6h** could also be obtained in excellent yields after a more prolonged reaction. Furthermore, ylides **2i–2k** with a cyclopropane, protected piperidine or adamantyl R group all gave excellent yields of the desired products **6i**, **6j**, and **6k**, respectively. Electronic effects have a great influence on the rate of the reaction, whereby both electron-donating and electron-withdrawing groups in *para* position to the cleaved C–H bond in **7** and **8**^[12] led to lower yields of **6l** and **6m**, as compared to **6b**. The yield of **6l** was not further optimized. However, the yield of **6m** could be improved to 73% by performing the reaction at 90 °C. In addition, besides benzenic C–H bonds, the reaction was also amenable to the functionalization of heteroaromatic C–H bonds in **9–12**.^[12] Thus, indole **6n** was obtained in very good yield, whereas mono-substituted pyrrole **6o** was obtained in 75% yield. Bis-substitution at positions 2 and 5 was noticeable for **6p**. Remarkably, furyl **6q** was obtained in 63% yield as single regioisomer and without formation of doubly substituted product, whereas pyridin-2-one **6r** was obtained in 71% yield under modified conditions. Finally,

pyrazole, pyrimidine and methyloxime could also act as competent directing group although the reaction of **13–16**^[12] was more sluggish. Thus, it was necessary to increase the temperature to 90 °C in order to obtain **6s** in 84% yield. On the other hand, **6t** and **6v** were obtained in good yield after incomplete conversion, whereas **6u** was obtained in 93% yield. Replacing the rhodium and silver catalysts with the cationic rhodium complex $[\text{Cp}^*\text{Rh}(\text{MeCN})_3][\text{SbF}_6]_2$ (8 mol%) was also necessary in order to isolate **6w** in 90% yield. It is noteworthy that the primary alkylation products **6a–6w** are obtained directly without requiring decarboxylation, in contrast to previous group-directed Rh(III)-catalyzed C–H functionalization reactions with diazo derivatives.^[4c,13]

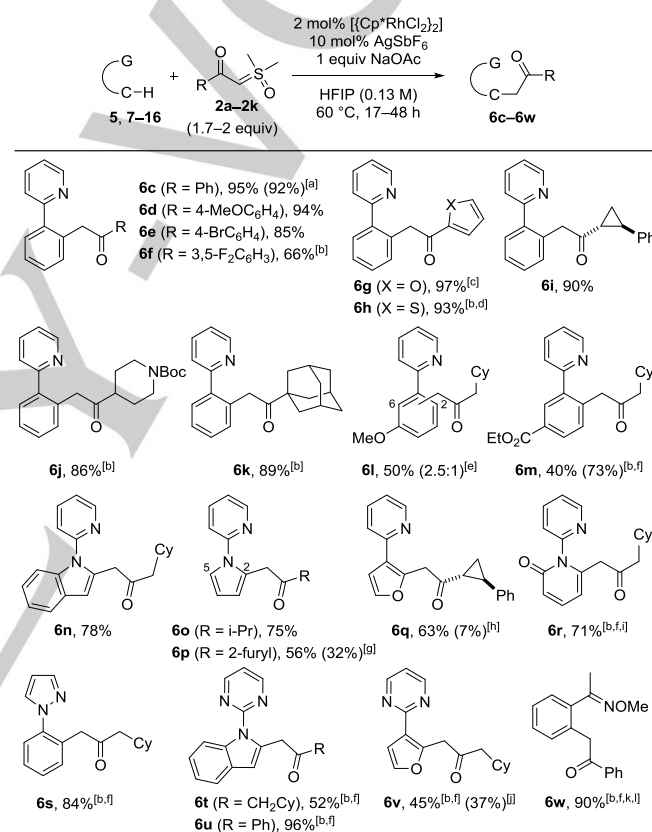
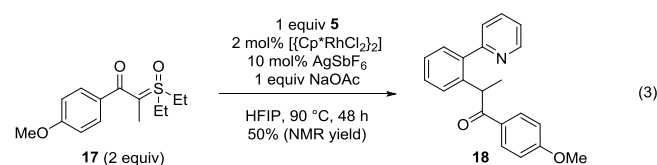


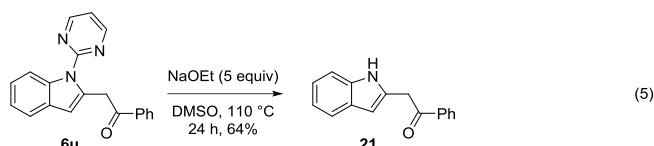
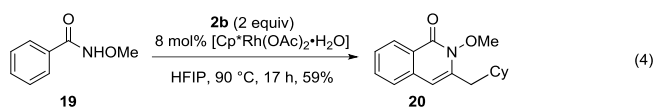
Figure 2. Rhodium-catalyzed cross-coupling of α -carbonyl oxosulfonium ylides with $\text{C}(\text{sp}^2)\text{-H}$ bonds. All yields given are for isolated products after 17 h from 0.34 mmol of **1** (1.7 equiv) except otherwise noted. [a] No NaOAc. [b] 2.0 equiv of **2**. [c] After 48 h. [d] After 24 h. [e] Ratio of regioisomers. [f] At 90 °C. [g] Yield of isolated product doubly substituted at positions 2 and 5. [h] Yield of recovered **11**. [i] $[\text{Cp}^*\text{Rh}(\text{OAc})_2\cdot\text{H}_2\text{O}]$ (8 mol%) was used as rhodium catalyst without AgSbF_6 . [j] Yield of recovered **15**. [k] $[\text{Cp}^*\text{Rh}(\text{MeCN})_3][\text{SbF}_6]_2$ (8 mol%) was used as rhodium catalyst without AgSbF_6 . [l] *Trans* and *cis* methyl oximes (3.5:1)



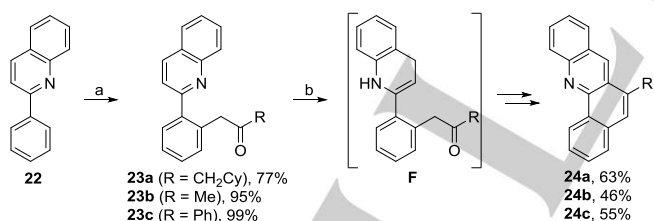
The effect of substitution at the ylide carbon atom was investigated with compound **17**. After 48 h at 90 °C, 85%

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conversion was reached and **18** was isolated alongside unidentified impurities in 50% NMR yield [Eq. (3)]. This decreased reactivity could be explained by the increased bulkiness of **17**.



Importantly, the C–H cross-coupling of sulfoxonium ylides described herein enables the rapid synthesis of valuable heterocycles. Thus, slightly modify conditions deliver 3-monosubstituted *N*-methoxylactam **20** after reaction of **19** and **2b** [Eq. (4)].^[14] Alternatively, the pyrimidine directing group that enabled the formation of **6u** can be cleaved to give **21** [Eq (5)]. Moreover, quinoline **23a** was obtained in 77% yield by cross coupling of **22** and **2b** and was then converted into benz[*c*]acridine **24a** in one step and 60% yield, after treatment with a catalytic amount of $[(\text{Cp}^*\text{IrCl}_2)_2]$ in a mixture of isopropanol and water (Scheme 1). This iridium-catalyzed dehydrative cyclization was discovered whilst attempting the transfer hydrogenation of the quinoline moiety^[15] and likely proceeds via 1,4-dihydroquinoline **F**, followed by attack of the enamine fragment on the ketone and rearomatization. Although serendipitous, this two-step sequence was also amenable to the synthesis of **24b** and **24c** in good overall yields. Significantly, this approach offers an attractive alternative to the drastic conditions typically used for the synthesis of benz[*c*]acridines,^[16] a motif frequently explored in drug discovery.^[17]



Scheme 1. Reagents and conditions: a) See Figure 2; b) $[(\text{Cp}^*\text{IrCl}_2)_2]$ (4 mol%), *i*-PrOH/H₂O (9.5:0.5), air, 90 °C.

In a preliminary study of the mechanism of the C–H cross-coupling of sulfoxonium ylides, we could verify that using rhodium complexes $[(\text{Cp}^*\text{RhCl}_2)_2]$ (2 mol%), **1** (4 mol%), or **3** (4 mol%) as rhodium source under the optimized conditions led to similar yields of **6a** (17–20% after 1 h, 72–77% after 17 h), which suggests that these rhodium complexes are all kinetically competent pre-catalysts of the reaction. We then attempted to garner further support for the catalytic cycle postulated in Figure 1c and made the following observations.

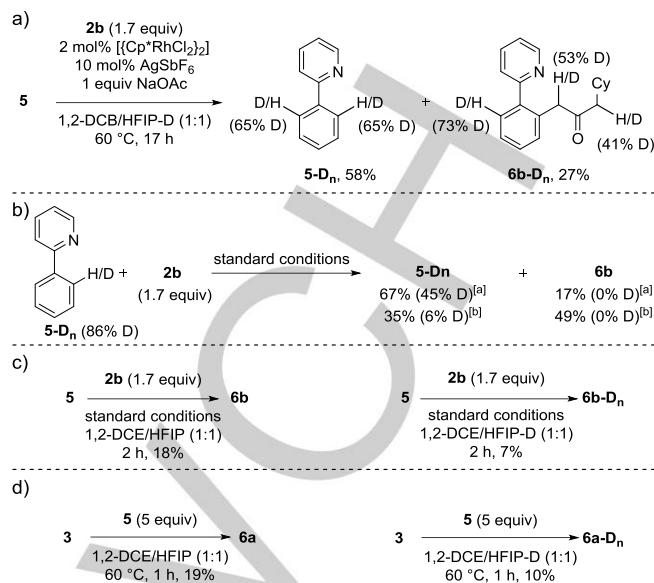


Figure 3. a) Deuterium-labelling experiment. b) Reversibility of C–H cleavage. c) Kinetic isotope effect under catalytic conditions. d) Kinetic isotope effect in the protodemetalation of complex **3**. Yields of isolated products. [a] After 1 h. [b] After 2 h.

First, we established that the C–H cleavage step is reversible. Thus, the reaction of **5** and **2b** under the optimized conditions but in a mixture of 1,2-dichlorobenzene (1,2-DCB) and HFIP-D ($(\text{CF}_3)_2\text{CHOD}$), led to an extensive incorporation of deuterium in recovered **5-D_n** and **6b-D_n** at the positions indicated in Figure 3a. Moreover, control experiments using **6b** as substrate revealed that i) the incorporation of deuterium at position β in **3a-D_n** can occur under the reaction conditions, and that ii) stirring **6b** in 1,2-DCB/HFIP-D at 60 °C for 16 h in the absence of any other reagent or catalyst is sufficient to enable deuterium incorporation in **6b** at the enolizable positions. Furthermore, when treating **5-D_n** and **2b** under the optimized conditions for 1–2 h, we observed an important loss of deuterium in recovered **5-D_n**, even at low conversion, whereas isolated **6b** did not contain deuterium [Figure 3b]. This result suggests that the C–H cleavage is not only reversible but also faster than the overall reaction leading to **6b**.

Second, a kinetic isotope effect ($k_{\text{H}}/k_{\text{D}}$) was observed when comparing the reactivity of a mixture of **5** and **2b** in the presence of HFIP or HFIP-D and a co-solvent (1,2-dichloroethane (1,2-DCE)). Thus, **6b** and **6b-D_n**^[18] were obtained after 2 h in 18% and 7% yield, respectively ($k_{\text{H}}/k_{\text{D}} = 2.6$ by initial conversion rates) [Figure 3c]. Similarly, in parallel experiments using complex **3**, the yields of isolated **6a** and **6a-D_n**^[18] were 19% in 10%, respectively, ($k_{\text{H}}/k_{\text{D}} = 1.9$ by initial conversion rates) [Figure 3d], which is in good agreement with the value found under catalytic conditions.

Third, we were able to mimic the last step of the postulated catalytic cycle^[19] and convert **3** into **6a** and **1** in 83% and 70% yield, respectively, by treating a solution of **3** in HFIP with **5** (5 equiv).

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Overall, these results are in support of the reaction sequence postulated in Figure 1c, whereby the C–H cleavage would be reversible and the protodemetalation turnover-limiting.

In conclusion, the cross-coupling described herein expands the traditional chemistry of sulfoxonium ylides^[20] and brings these reagents into the realm of metal-catalyzed C–H activation.^[21,22]

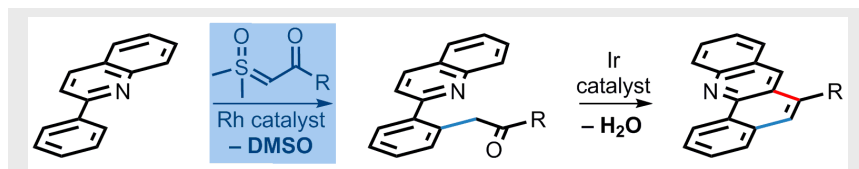
Acknowledgements

We are grateful to the University of Liverpool (studentships to M. B. and C. J.) and AstraZeneca (CASE award to C. J.) for financial support. We thank Umicore for the generous gift of rhodium salts.

Keywords: Sulfoxonium • Ylide • C–H activation • rhodium • homogeneous catalysis

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COMMUNICATION

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**Cross-Coupling of α -carbonyl
sulfoxonium ylides with C–H bonds**

The rhodium-catalyzed cross-coupling of sulfoxonium ylides with carbon-hydrogen bonds in hexafluoroisopropanol at 60–90 °C brings these reagents into the realm of C–H activation. When allied to an iridium-catalyzed dehydrative cyclization, this cross-coupling streamlines the synthesis of valuable heterocycles.