Cross-Coupling of α-Carbonyl Sulfoxonium Ylides with C–H Bonds

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Abstract: The functionalization of carbon–hydrogen bonds in non-nucleophilic substrates using a-carbonyl sulfoxonium ylides has not been so far investigated, despite the potential safety advantages that such reagents would provide over either diazo compounds or their in situ precursors. Described herein are the cross-coupling reactions of sulfoxonium ylides with C(sp²)–H bonds 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 acarbonyl sulfoxonium ylides has been optimized in industry 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 multikilogram synthesis of MK–7246, a drug candidate with potential application against respiratory disease (Figure 1a).[2d] The 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 a-carbonyl sulfoxonium ylides.[3] In this case, the formation of a carbon–carbon bond plausibly proceeds by electrophilic substitution by the reactive a,b-unsaturated b-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 a-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] reactions which 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 carbeneoids generated from diazo compounds.[9]

Herein, we show that a-carbonyl sulfoxonium ylides undergo efficient cross-coupling reactions with a C(sp²)–H bond of both arenes and heteroarenes in the presence of a rhodium catalyst, which does not require a sacrificial oxidizing reagent. Data from control experiments support the sequence of steps depicted in Figure 1c. Thus, the crosscoupling reaction described herein is strongly distinct from the single, previous example of C–H functionalization by α-carbonyl sulfoxonium ylides,[3] both in scope and in terms of mechanism. 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 the known rhodium complex 1[10] [Cp*]=1,2,3,4,5-pentamethylcyclcopentadienyl] and observed its reaction with the ylide 2a to give a diastereomeric mixture of the migratory 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. The compounds 3 and 4 are configurationally stable in the solid state and in solution at room temperature. Their structures were 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); see Tables S1–S3 in the Supporting Information]. The reaction could proceed without added base, but its presence enabled full conversion and led to higher yield of the isolated products. Another important factor was the amount of ylide. Thus, the yield of 6b was quantitative when 1.7 equivalents of 2b were used (Cy=cyclohexyl), whereas using 2 equivalents of the bulkier 2a was necessary to reach full conversion and obtain 6a in 77% yield. The reaction did not proceed at all without [{Cp*RhCl2}], but the conversion into 6b reached 81% in the presence of this catalyst and in the absence of AgSbF6. Attempts to replace the rhodium catalyst with either [{Cp*IrCl2}], [{Cp*CoI2}], [{Cp*Co(CO)}2], or [{Ru(p-cymene)Cl2}] were unsuccessful.

Using the ylides 2c–k with 5 revealed that the aryl ketones 6c and 6d were obtained in excellent yields, whereas ylides with less electron-rich substrituents led to either slightly (6e) or more markedly (6f) decreased product yields (Figure 2). The heteroaryl ketones 6g and 6h were obtained in excellent yields after a prolonged reaction. Furthermore, the ylides 2i–k, having a cyclopropane, protected piperidine, and adamantly group, respectively, all gave excellent yields of the desired corresponding products 6i, 6j, and 6k. Electronic effects have a great influence on the rate of the reaction, whereby both electron-donating and electron-withdrawing groups in the 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 aryl 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 the monosubstituted pyrrole 6o was obtained in 75% yield. Disubstitution at positions 2 and 5 was noticeable for 6p. Remarkably, the furyl 6q was obtained in 63% yield as a single regioisomer and without formation of the doubly substituted product, whereas the pyridin-2-one 6r was obtained in 71% yield under modified reaction conditions. Finally, pyrazole, pyrimidine, and methyloxime could also act as competent directing groups although the reactions of 13–16 [12] were more sluggish. Thus, it was necessary to increase the temperature to 90 °C to obtain 6s in 84% yield. In contrast, 6t and 6u 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 [{Cp*Rh(MeCN)}2][SbF6]2 (8 mol%) was also necessary to isolate 6w in 90% yield. It is noteworthy that the primary alkylation products 6a–w are obtained directly without requiring decarboxylation, and is in contrast to previous group-directed RhlII-catalyzed C–H functionalization reactions with diazo derivatives.[4c,13]

The effect of substitution at the ylide carbon atom was investigated with the compound 17. After 48 h at 90 °C, 85% conversion was reached and 18 was isolated, along with unidentified impurities, in 50% yield as determined by NMR spectroscopy [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 modified conditions deliver the 3-monosubstituted N-methoxylactam 20 after reaction of 19 and 2b [Eq. (4)].[14] Alternatively, the pyrimidine directing group, which enabled the formation of 6u, can be cleaved to give 21 [Eq. (5)]. Moreover, the quinoline 23a was obtained in 77% yield by cross-coupling of 22 and 2b and was then converted into the benz[c]acidine 24a in one step and 60% yield, after treatment with a catalytic amount of [{Cp*IrCl2}] 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 the 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 harsh reaction conditions typically used for the synthesis of benz[c]acidines,[16] a motif frequently explored in drug discovery.[17]

In a preliminary study of the mechanism of the C–H cross-coupling of sulfoxonium ylides, we could verify that using either [{Cp*RhCl2}] (2 mol%), 1 (4 mol%), or 3 (4 mol%) as the rhodium source under the optimized reaction 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. First, we established that the C–H cleavage step is reversible. Thus, the reaction of 5 and 2b under the optimized reaction conditions but in a mixture of 1,2-dichlorobenzene (1,2-DCB) and [D]HFIP ([CF3]2CHOD), led to an extensive incorporation of deuterium in recovered [D]15 and [D]16b at the positions indicated in Figure 3a. Moreover, control experiments using 6b as substrate revealed that 1) the incorporation of deuterium at the b-position in [D]3a can occur under the reaction
conditions, and that 2) stirring 6b in 1,2-DCB/[D]HFIP at 60 °C for 16 hours in the absence of any other reagent or catalyst is sufficient to enable deuterium incorporation in 6b at the enolizable positions. Furthermore, when treating [D₆]5 and 2b under the optimized reaction conditions for 1–2 hours, we observed an important loss of deuterium in recovered [D₆]5n, even at low conversion, whereas the 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_D/k_H) was observed when comparing the reactivity of a mixture of 5 and 2b in the presence of either HFIP or [D]HFIP and a cosolvent [1,2-dichloroethane (1,2-DCE)]. Thus, 6b and [D₆]6b[18] were obtained after 2 hours in 18 and 7% yield, respectively (k_D/k_H = 2.6 by initial conversion rates; Figure 3 c). Similarly, in parallel experiments using the complex 3, the yields of isolated 6a and [D₆]6b[18] were 19 and 10%, respectively, (k_D/k_H = 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). 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]

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[11] CCDC 1557332 (3) and CCDC 1557333 (4) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre.
[12] 7: 2-(3-methoxyphenyl)pyridine; 8: ethyl 3-((pyridin-2-yl)benzoate; 9: 1-(pyridin-2-yl)-1H-indole; 10: 2-(1H-pyrrol-1-yl)pyridine; 11: 2-(furan-3-yl)pyridine; 12: 2H-[1,2-bipyridin]-2-one; 13: 1-phenyl-1H-pyrazole; 14: 1-(pyrimidin-2-yl)-1H-indole; 15: 2-(furan-3-yl)pyrimidine; 16: (E)-1-phenylethan-1-one O-methyl oxime.
[18] See the Supporting Information for the location and amount of deuterium transfer in [D6]6a and [D6]6b in these experiments.

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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).
Figure 2. Rhodium-catalyzed cross-coupling of α-carbonyl oxosulfonium ylides with C(sp^2)–H bonds. All yields given are for isolated products after 17 h from 0.34 mmol of 2 (1.7 equiv) unless otherwise noted. See Ref. [12] for compound names. [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] [Cp*Rh(OAc)_2·H_2O] (8 mol%) was used as rhodium catalyst without AgSbF_6. [j] Yield of recovered 15. [k] [Cp*Rh(MeCN)_3][SbF_6]_2 (8 mol%) was used as rhodium catalyst without AgSbF_6. [l] Trans and cis methyl oximes (3.5:1).
Scheme 1. Reagents and conditions: a) See Figure 2. b) \([\text{Cp}^*\text{IrCl}_2]_2\) (4 mol%), iPrOH/H$_2$O (9.5:0.5), air, 90 °C.

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.
A new alliance: The rhodium-catalyzed cross-coupling of sulfoxonium ylides with carbon–hydrogen bonds, in hexafluoropropanol 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.