DOI: 10.1002/anie.201104073

Methylene Transfer

Methyltransferase Activity of an Iridium Center with Methylpyridinium as Methylene Source**

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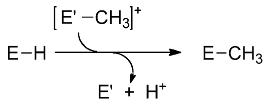
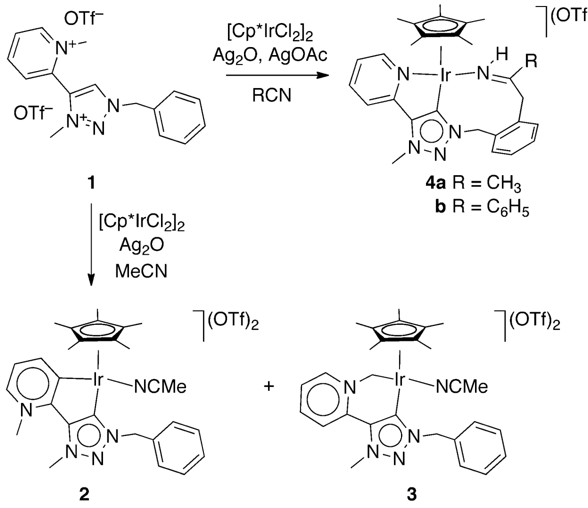
The selective transfer of a methyl or alkyl group to an unactivated carbon center is of prevalent synthetic and biochemical interest.[1] In biological systems, methylation typically involves transferring a CH_3 group from a sulfide carrier, such as S-adenosylmethionine (AdoMet) which is a mild methylating agent,[2] using a cobalamin cofactor as a CH_3 donor.[3] While most AdoMet-type transferases deliver a methyl group, recent work showed that certain enzymes utilize a methylene unit (CH_2) for substrate alkylation.[4]

Synthetic mimics of methyltransferases have been developed for the transfer of a methyl group from sulfonium or iminium salts to a heteroatom receptor (E = N, O, P, S; Scheme 1).[5] Non-enzymatic mimicking of alkyl-group transfer from sulfur or nitrogen to carbon and formation of a new C–C bond, as observed, for example in DNA methylation,[6] is very rare.[7] A key challenge is the $E'-C_{Me}$ bond cleavage from the carrier system (E′ = S, N), which is required to activate the transferable group.[8] Notably, selective C–N bond cleavage has been observed using an imidazolium-type source for alkyl-group release under mild conditions in N-heterocyclic carbene (NHC) ruthenium complexes,[9] though no controlled transfer to a substrate was noticed. Herein we report an iridium complex that facilitates the selective transfer of a methylene group from a pyridinium fragment to an aryl unit with concomitant activation of a nitrile solvent molecule. This process involves C–N bond cleavage and formation of two $C(sp^2)-C(sp^3)$ bonds within the iridium coordination sphere. This complex thus represents a unique functional analogue of methyltransferases and enables new synthetic transformations.



Scheme 1. Generic methyl transfer, E′ = S, N for unactivated methyl sources, E′ = O, halide, for activated methyl sources.

In previous studies we have shown that $[\{Ir(Cp^*)Cl_2\}_2]$ ($Cp^* = C_5Me_5$) reacts in the presence of Ag_2O with the pyridinium triazolium salt **1** either by pyridinium $C(sp^2)-H$ bond activation or by exocyclic C–H bond activation to give **2** and **3**, respectively (Scheme 2).[10] If acetate is added to the reaction mixture either as AgOAc or NaOAc, **1** undergoes a $N_{py}-CH_3$ bond activation process instead and affords complex **4a** comprising a tridentate triazolylidene ligand with a chelating pyridine and imine donor group.[11] Formally, complex **4a** is the product of a methylene shift from the pyridinium fragment to the benzyl group, and subsequent insertion of a MeCN molecule. Support for solvent activation[12] was obtained by carrying out the reaction in benzonitrile (PhCN) instead of MeCN, which yielded complex **4b**.



Scheme 2. Synthesis of complex **4** by methylene transfer and RCN activation.

The solution NMR spectra of complexes **4a** and **4b** each display two characteristic AB resonance patterns for the two pairs of benzylic protons ($^2J_{HH}$ 14.1 and 12.9 Hz, in **4a**), which are in a rigidly fixed geometry due to the tridentate bonding of the ligand. The signal for the imine-bound proton appears slightly more downfield in **4a** ($\delta_H = 10.58$ ppm) than in **4b** ($\delta_H = 9.85$ ppm). In the ^{13}C NMR spectrum, the signal for the N_{imine}-bound carbon atom is at $\delta = 190$ ppm. Most diagnostically, IR spectroscopy revealed a stretch vibration at $\nu_{C=N} = (1635 \pm 1)\ cm^{-1}$.

The connectivity pattern was confirmed by single-crystal X-ray diffraction studies on **4a** and **4b** (Figure 1). The NCN-

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[**] We thank J. Muldoon and Y. Ortin for NMR measurements. This work has been financially supported by the European Research Council (ERC-StG 208561) and by Science Foundation Ireland.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201104073.

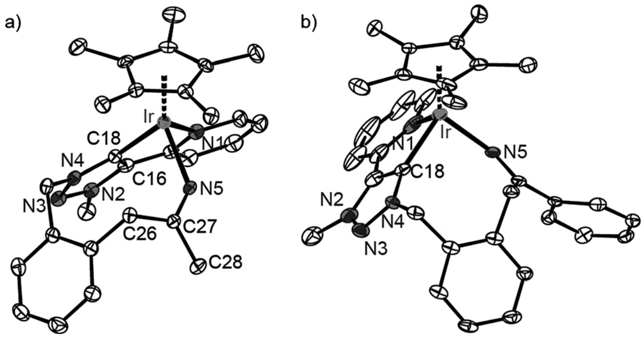


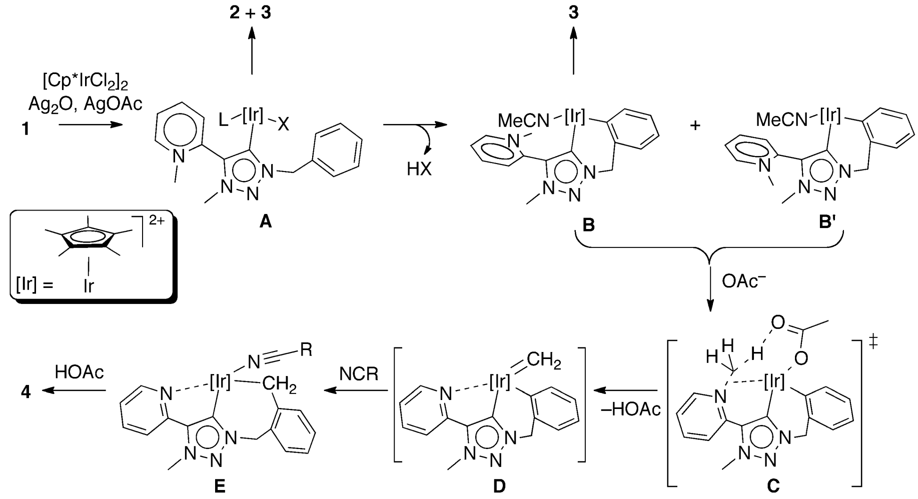
Figure 1. ORTEP representations of complexes **4a** (a; thermal ellipsoids set at 50% probability) and **4b** (b; thermal ellipsoids set at 30% probability). Solvent molecules, OTf$^-$ ions, and hydrogen atoms omitted for clarity; selected bond lengths [Å] and angles [°] for complexes **4a**/**4b**: Ir–C18 2.044(2)/2.01(7), Ir–N1 2.151(2)/2.159(7), Ir–N5 2.085(2)/2.067(6); C18-Ir-N1 76.34(9)/75.5(3), C18-Ir-N5 84.82(9)/89.6(2), N1-Ir-N5 84.05(8)/85.5(2).

tridentate ligand may be considered as a facially coordinating pincer ligand.[13] The bond angle of the five-membered metallacycle comprising the pyridine and the triazolylidene unit is acute and indicates some strain (C$_{\text{trz}}$-Ir-N$_{\text{py}}$ 75°), while the nine-membered metallacycle is considerably more flexible and adopts a coordination mode close to ideal for pseudo-octahedral iridium(III) complexes (C$_{\text{trz}}$-Ir-N$_{\text{imine}}$ 85–90°). The higher strain is also reflected in the Ir–N$_{\text{py}}$ bond of both complexes which is 0.07–0.09 Å longer than the corresponding Ir–N$_{\text{imine}}$ bond.

Mechanistic details of this C–N bond breaking and multiple C–C bond making process were investigated by isotope labeling studies. When using compound **1** with a ^{13}C-labeled methyl group at N$_{\text{py}}$ (**1***)[11] under standard reaction conditions, complex **4a*** was produced, which contained the ^{13}C nucleus exclusively in the benzylic position between the aryl and the imine unit. Selective ^{13}C labeling of **4a*** was confirmed by the split of the resonance arising from the two benzylic protons into two doublets of doublets ($\delta_H = 4.27$ ppm, $^1J_{CH} = 128$ Hz, $^2J_{HH} = 12.9$ Hz), and by the doublet resonance for the NH proton ($^3J_{CH} = 9$ Hz). Similarly, all the ^{13}C NMR signals for the phenyl group and the C=N moiety appear as doublets as a consequence of their coupling to the benzylic ^{13}C nucleus (e.g., $\delta_{C=N} = 192.05$ ppm with $^1J_{CC} = 43.1$ Hz). No traces of unlabeled benzylic carbon were detected, indicating a selective transfer of the N$_{\text{py}}$-bound carbon to the phenyl ring of the benzyl substituent.

Deuterium labeling of **1** at both N$_{\text{py}}$ and N$_{\text{trz}}$ by using CD$_3$OTf as methylating agent gave **1-D$_6$**. Reaction of this partially deuterated precursor with [{Ir(Cp*)Cl$_2$}$_2$] in CH$_3$CN under standard conditions gave **4a** with only little D incorporation. The ^{2}H NMR spectrum revealed 17% deuterium in the benzylic position as compared to the triazole-bound N$_{\text{trz}}$–CD$_3$ group, yet no deuterium incorporation in the terminal CH$_3$ group attached to the imine. The corresponding ^{1}H NMR spectrum confirmed these measurements, indicating no N$_{\text{trz}}$–CH$_3$ residues and a benzylic proton integration of approximately 80%. The inverse labeling, that is, starting from the protio ligand precursor **1** and performing the reaction in CD$_3$CN gave complex **4a-D$_5$** with essentially complete deuteration at the terminal methyl group bound to the imine, and approximately (60 ± 10)% deuterium incorporation into the benzylic position. While these results do not allow for determining whether a methyl or a methylene group is transferred, they clearly indicate solvent-mediated isotope scrambling during the transfer process. No such scrambling at the methylene group linking the aryl and the triazole heterocycle or at the N$_{\text{trz}}$-bound methyl group was observed.[14] Hence, isotope exchange in the starting material seems unlikely. Similarly, exchange processes after the formation of **4** at only one of the two available benzylic positions are not supported.

When the reaction was stopped before completion, a variety of intermediates were detected. Thus after 2 h, signals for a hydride-containing intermediate were observed ($\delta_H = -14.28$ ppm, Cp* protons appear as doublet with $J_{HH} = 0.8$ Hz). Separation of the product mixture at this stage failed to give the hydride species in pure form. However, two species were isolated that were assigned **B** and **B′** along with minor quantities of **4a** (Scheme 3). These products are present in a 1:0.7 ratio, irrespective of the reaction time (2–16 h) or the reaction temperature (25–85 °C), pointing to a thermodynamically controlled distribution. The two species are similar according to their ^{1}H NMR spectra, which both contain four pyridyl signals, two methyl resonances (for N$_{\text{py}}$-CH$_3$ and N$_{\text{trz}}$-CH$_3$), and the benzylic protons split into an AB signal.[15] Most diagnostically, both compounds contain only four phenyl protons appearing as two doublets and two



Scheme 3. Proposed mechanism for the iridium-mediated methylene transfer (X probably OTf, NCMe with non-coordinating OTf, or Cl).

doublets of doublets, which suggests orthometalation by C_{phenyl}–H bond activation of the benzyl group. The major difference between the two species consists in the chemical shift of the N_{py}–CH_3 group ($\delta_H = 4.37$ versus 3.92 ppm) and the pyridinium proton in the *meta* position (C3–H at $\delta_H = 8.08$ versus 8.33 ppm). These differences concur with the presence of two rotamers comprising the N_{py}–CH_3 group either pointing towards (**B**) or away from the monodentate NCMe ligand at iridium (**B′**). Nuclear Overhauser experiments indicate an *anti* conformation of the two N–CH_3 groups for the major isomer.[16] These cyclometalated products were also obtained from **1** and $[\{IrCp^*Cl_2\}_2]$ with AgOAc only, that is, in the absence of Ag_2O. In CH_2Cl_2 or in the solid state these rotamers **B** and **B′** smoothly and spontaneously interconvert at room temperature to the ylide **3** exclusively. In MeCN, the stability of the intermediates **B** and **B′** is greatly enhanced as C–H bond activation and ylide formation is only induced after several days under reflux, indicating that NCMe displacement from **B** is essential to form complex **3**. The ylide complex **3** is stable when heated in MeCN in the presence of OAc^-. In contrast, the carbene intermediate **B** and complex **2** undergo methylene transfer under these conditions, gradually generating **4a**.

A tentative mechanism that is in agreement with these observations is depicted in Scheme 3. Intermediate **A** has been detected previously[10] and may be formed by in-situ transmetalation or by iridium-mediated C–H activation, which would rationalize the traces of iridium-hydride species observed. Subsequent cyclometalation, probably OAc^- assisted[17] or by oxidative addition,[18] generates a mixture of the C,C-bidentate chelates **B** and **B′**. Upon exchange of the MeCN ligand in **B** by acetate, concerted and presumably rate-limiting activation of the C–H bond and cleavage of the N_{py}–C bond ensues (**C**),[9] producing a carbene species (speculatively represented as **D**) which may be susceptible to protonation and solvent-mediated H/D exchange.[19] The interplay of acetate and iridium in mediating the proton abstraction and N_{py}–C bond activation seems most critical to this methyl transfer process. Methylene insertion into the Ir–C_{aryl} bond, followed by activation of a coordinated solvent molecule through nucleophilic addition of the anionic benzyl group is postulated to generate the nine-membered metallacycle in **4**. Although tentative, this mechanism takes into consideration that acetate is essential for the reaction to occur, and it allows the formation of the ylide **3** from the intermediates **B** and **B′** to be rationalized in the absence of acetate. The transfer of the carbon is selective, while H/D scrambling with the solvent may occur either at the carbene intermediate **D** or before protonation of the imide ligand in the conversion of **E** into **4**. Owing to the fast proton exchange at acetate, the mechanism also provides a rationale for the fact that none of the deuterium labeling experiments resulted in D incorporation at the imine position.

In agreement with the proposed model, the methylene transfer is suppressed when the precursor **1** contains a fluorinated benzyl group ($CH_2C_6F_5$). No products similar to **4** were observed, and instead, only pyridinium C–H bond activation took place to give C_6F_5-containing analogues of **2** and **3**. Likewise, substitution of the benzylic group in **1** with a phenyl unit suppressed the methylene group transfer and afforded a bidentate cyclometalated product resulting from C_{phenyl}–H bond activation reminiscent of **B**.[20] Apparently, the steric flexibility of the benzyl group promotes the carbon transfer while phenyl coordination induces sufficient constraints to prevent the pyridinium ring from approaching the iridium center. Attempts to expand the reaction towards the transfer of different alkyl groups were unsuccessful. When using the ethyl pyridinium analogue of **1**, a complicated mixture of products formed that was inseparable in our hands, yet the crude product mixture showed no NMR signals that might indicate the migration of the ethyl group from the pyridinium fragment.

Complex **4a** is stable under neutral conditions and undergoes only incomplete N–H to N–D exchange in the presence of D_2O even after several days. In acidic media (methanolic HCl), rapid dissociation of the imine donor group and Schiff base reactivity was observed, resulting in the formation of complex **5** featuring a non-coordinated ketone (Figure 2). No trace of H_2 formation was observed. Complex **5** is characterized by a diagnostic IR absorption at $\nu_{C=O} = 1715\ cm^{-1}$ for the non-coordinating carbonyl group. In the ^1H NMR spectrum the benzylic group adjacent to the triazolylidene ligand appears as a singlet while the CH_2 protons α to the carbonyl unit are split into an AB pattern ($^2J_{HH}$ 17.5 Hz).[21]

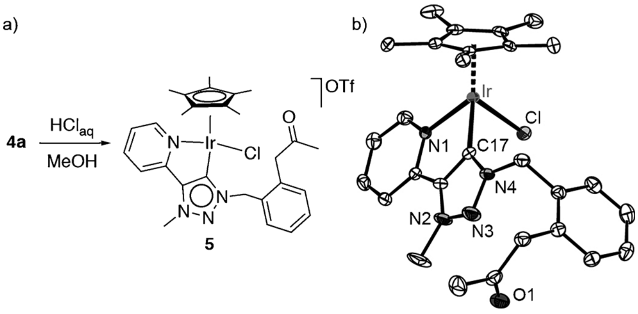


Figure 2. Synthesis (a) and ORTEP representation of **5** (b; thermal ellipsoids set at 50% probability, OTf^- ion, and hydrogen atoms omitted for clarity); Selected bond lengths [Å] and angles [°]: Ir–C17 2.021(3), Ir–N1 2.130(2), Ir–Cl 2.4089(7); C17-Ir-N1 76.45(11).

In conclusion, we have observed an iridium-mediated, selective methylene transfer from a pyridinium unit to an unfunctionalized aryl carbon. Pyridinium demethylation is of great relevance, for example in the regeneration of mutated carcinogenic DNA. Most of the elementary steps of the observed transfer reaction have precedents: the N–C bond activation in N-heterocyclic carbene ruthenium complexes,[9] the C_{aryl}–H bond activation and subsequent $C(sp^2)$–$C(sp^3)$ bond formation in the metal-catalyzed cross-coupling of unfunctionalized arenes,[1e,f] and nitrile activation in recent metal-mediated reactions.[12] Combining these processes in a single transformation provides a first functional model of methyltransferase and opens new avenues for organic functionalizations.

Received: June 14, 2011

Keywords: functional analogues · iridium · methyl transferase · methylene transfer · pyridinium

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[15] The AB sets are centered at $\delta = 5.66$ and 5.09 ppm for **B** ($^2J_{HH} = 17.8$ Hz) and at $\delta = 5.66$ and 5.13 ppm for **B′** ($^2J_{HH} = 14.6$ Hz).

[16] Saturation of the major N_{py}-CH_3 resonance at $\delta = 3.92$ ppm revealed a through-space interaction only with the pyridine *ortho* proton. The minor component **B′** featured a positive nuclear Overhauser effect (nOe) upon saturation at the N_{py}-CH_3 frequency ($\delta_H = 4.37$ ppm) with the N_{trz}-CH_3 group ($\delta_H = 4.04$ ppm) and with the *ortho* C_{py}-H ($\delta_H = 9.13$ ppm), indicating a pseudo-*syn* arrangement of the two N-CH_3 groups. Variable temperature NMR spectroscopy between −30 and +70 °C did not provide any evidence for interconversion of the two species.

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