Generation of Heteroatom-Substituted Carbene Complexes of Iridium by Double C–H Activation of Ether and Amine Substrates[**]

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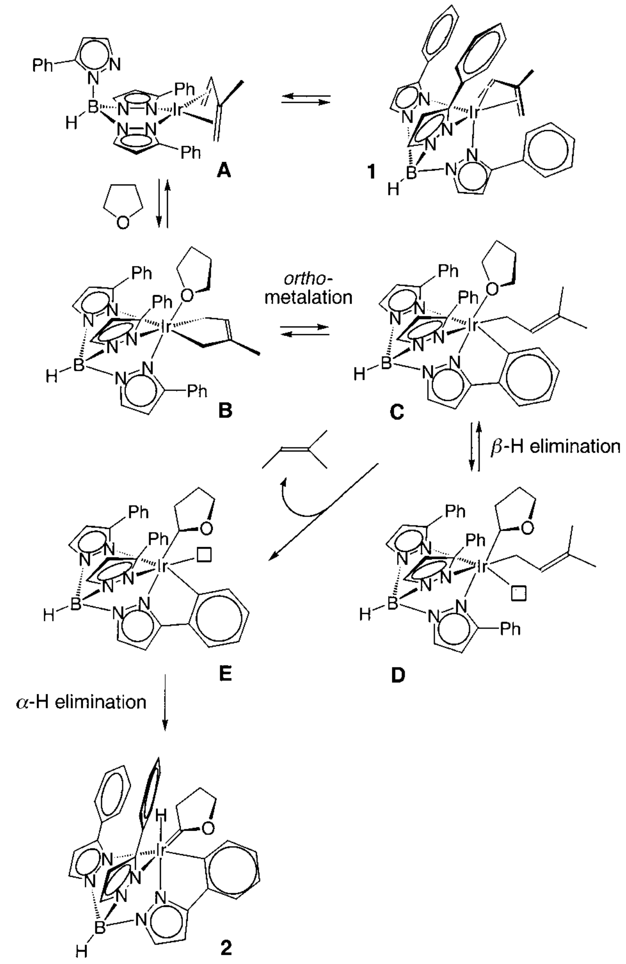
Dedicated to Professor José Barluenga
on the occasion of his 60th birthday

The selective activation of C–H bonds of hydrocarbons and other common organic substrates (such as ethers, amines, and nitriles) is a far-reaching objective of current research in organometallic chemistry.[1] A very valuable reaction is the regioselective activation of two α-C–H bonds of an ether or amine functionality, RCH_2X ($X = OR'$, NR_2'), since it constitutes an unused synthetic route to Fischer-type carbenes, $M = C(R)X$.[2] Despite its potential applications, this double C–H activation[3, 4] is still a rarely observed process. Herein, we wish to report that $[Ir(\kappa^3\text{-}Tp^{Ph})(\eta^4\text{-isoprene})]$ (**1**; Tp^{Ph} = hydridotris(3-phenylpyrazol-1-yl)borate), when treated with substrates such as anisole (MeOPh), *N,N*-dimethylaniline (Me_2NPh), tetrahydrofuran (C_4H_8O), ethyl phenyl ether (EtOPh), or even diethyl ether (Et_2O), generates heteroatom-substituted carbene complexes.[4–7] Most significantly, and at variance with somewhat related Cp*Ir systems ($Cp^* = \eta^5\text{-}Me_5C_5$),[7] α-elimination from the activated ether or amine substrate takes place for every case investigated, even if β-hydrogen atoms are available.

Recently, it has been shown that $[IrTp^{Me_2}(\eta^4\text{-}H_2C{=}C(R){-}C(R){=}CH_2)]$ compounds (R = H, Me; Tp^{Me_2} = hydridotris(3-methylpyrazol-1-yl)borate) give Ir^{III} adducts of composition $[IrTp^{Me_2}(\sigma^2\text{-}CH_2{-}C(R){=}C(R){-}CH_2)(L)]$ when treated with a Lewis base L.[8] Taking advantage of the possibility of precoordination of a substrate and, having additionally demonstrated that $[IrTp^x(R)(R')]$ centers (R, R′ = H, alkyl, aryl; x = Me, Ph) activate two α-C–H bonds of THF,[4b, c, 9] **1** was heated in the presence of THF (80 °C, 4 h).[10] High yields (about 90 %) of a cyclic carbene **2** derived from a molecule of THF were obtained. As can be seen, not only were two α-C–H bonds of THF cleaved but also one of the Tp^{Ph}-phenyl substituents underwent cyclometalation (see Supporting Information for characterization). One of the THF hydrogen atoms formed the hydride functionality of **2** (Scheme 1; the reaction pathway is discussed in full later), the other two activated hydrogens formally added in a 1,4-fashion to the original η^4-diene moiety of **1**, which therefore acted as a sacrificial hydrogen-atom acceptor and leaving group[11] (evolved as 2-methyl-2-butene according to NMR evidence).



Scheme 1. Proposed reaction pathway to **2**.

As a further test for the applicability of **1** in this C–H bond activation chemistry, its reactions with MeOPh and Me_2NPh (both 80 °C, 4 h) were investigated. As shown in Scheme 2, the former led to the formation of another cyclic carbene complex **3** (97 % yield by NMR), whereas the second provided a mixture of two N-substituted carbene derivatives, **4a** and **4b**, in an approximately 2:1 ratio (NMR). This proportion did not vary upon prolonged heating (toluene, 120 °C, 24 h). It is worth noting that the preferential formation of **4a** and the seemingly exclusive one of **3** hints that, in terms of phenyl group activation, the putative less-strained metalation of the ring attached to the carbene prevails over that of the Tp^{Ph}-phenyl substituent.[9]

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[**] This work was supported by the “Fonds zur Förderung der wissenschaftlichen Forschung” with a Schrödinger Stipendium for C.S. (J1756-CHE), the Spanish Ministry of Education (DGES, Project PB97-0733), and the Junta de Andalucía.

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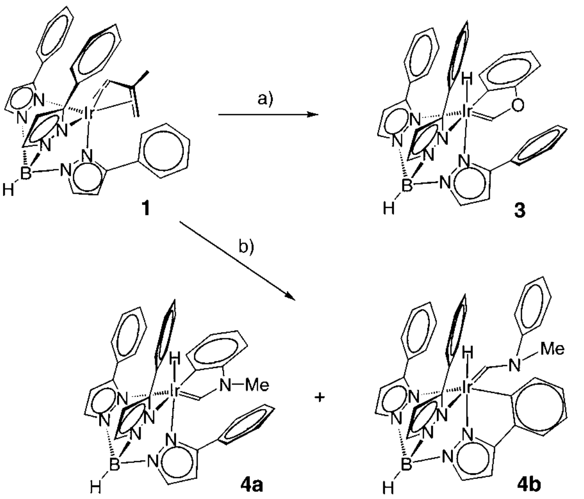


Scheme 2. Reaction conditions: a) MeOPh, 4 h, 80 °C, toluene; b) Me_2NPh, 4 h, 80 °C, toluene. The isoprene ligand is liberated as 2-methyl-2-butene.

Characterization of **3**, **4a**, and **4b** was made by elemental analysis, NMR- and IR spectroscopies (see Supporting Information) and was confirmed in the case of **4a** by a single crystal structure determination (Figure 1).[12] Some relevant bonding parameters included in the Figure legend compare well with related data reported in the literature.[4c, 7b, 13] Compound **4b** was identified as the isomer featuring a κ^4-Tp^{Ph} ligand and a nonmetalated =C(H)NMePh fragment, as detected by ^{13}C NMR spectroscopy (the two characteristic peaks for 3-phenylpyrazol-1-yl metalation at 122.4 and 120.8 ppm were observed).[9] Because of a slow rotation around the carbene carbon–nitrogen bond, the ^1H NMR data show broadened signals for the hydride and for all hydrogen atoms of the carbene ligand. Low temperature NMR resulted in resolution of the signals associated with the hydride, methyl, and carbene moieties into two peaks in the corresponding region (500 MHz, $T_c = 27 \pm 1$ °C), so that the possibility of a reversible α-H migration reaction[7b] responsible for the broadening of the signals can be excluded.

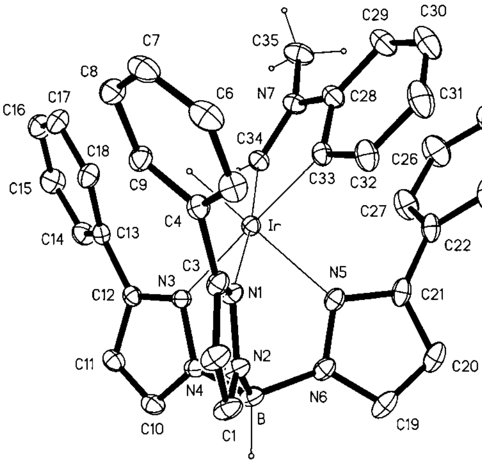
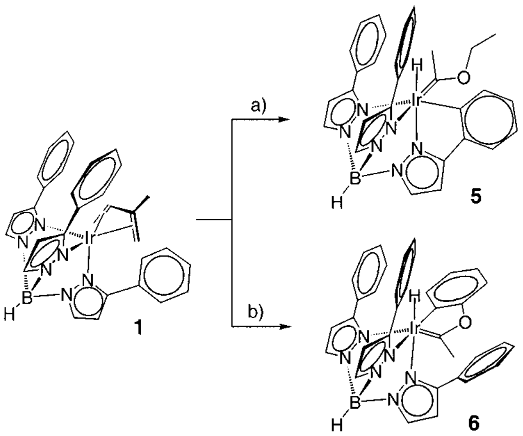


Figure 1. ORTEP plot of **4a** (most hydrogen atoms are omitted for clarity; thermal ellipsoids are at the 20 % probability level). Selected bond lengths [Å] and angles [°]: Ir-H 1.63(3), Ir-C33 2.015(3), Ir-C34 1.930(3), Ir-N1 2.169(2), Ir-N3 2.177(2), Ir-N5 2.200(2), N7-C34 1.320(4), N7-C35 1.475(4); C34-Ir-C33 79.2(1), C34-Ir-N1 171.9(1), C33-Ir-N1 98.4(1), C34-Ir-N3 98.0(1), C33-Ir-N3 176.3(1), N1-Ir-N3 84.8(1), N1-Ir-N5 87.5(1), N3-Ir-N5 85.8(1).

In view of the complexity of this system which, as has already been pointed out, comprises three C–H activation steps, rationalizing the formation of **2**–**4** is not a simple task. Perusal of the literature[8, 14] suggests that the reaction presumably proceeds initially by opening one pyrazolyl arm to give the tetracoordinated, 16-electron species **A** (Scheme 1), which is subsequently trapped by THF and rearranges to the formally Ir^{III} species **B**. Metalation of a Tp^{Ph}-phenyl substituent (to give **C**) could precede reversible β-C–H activation from the ether,[15] until eventually the **C**/**D** equilibrium mixture would eliminate 2-methyl-2-butene irreversibly to give **E**, which, by α-H elimination, forms the product **2**.

In agreement with the assumptions implied in Scheme 1, treatment of **1** with $[D_8]$THF gives $[D_{8.2}]$**2**, in which the hydride NMR signal is absent in the ^1H spectrum but apparent in the ^2H spectrum (signal intensity = 1 relative to the functionalized THF-deuterium atoms; that is, about 1.2 equivalents of deuterium became incorporated into one Tp^{Ph}-phenyl ring). That means, the final step in the formation of **2** is the α-C–H activation, specifically, an α-H elimination reaction. For the analogous transformations of **1** to produce **3** and **4** (assuming that this conclusion can be extended to these systems) there exists no alternative to the β-elimination pathway, whereas in the case of **2**, α-H elimination prevails over β-H elimination.[6] To ascertain whether the rigid, cyclic nature of the ether has any influence on this result, reactions with the more flexible Et_2O molecule were investigated.

Heating a solution of **1** in Et_2O (60 °C, 12 h) gave the hydride ethoxy carbene complex **5** (Scheme 3), which displays a ^1H NMR signal at $\delta = -22.8$ (hydride) and a ^{13}C signal at $\delta = 274.8$ (carbene; see Supporting Information). It is evident that α-H elimination also competes favorably with β-H elimination in this system. A comparable activation of Et_2O has been reported recently for platinum.[16] However, the somewhat related compound $[IrCp^*(Me)(OTf)(PMe_3)]$ ($Tf = SO_2CF_3$), whilst activating THF in a manner similar to **1**, reacts with Et_2O to give $[IrCp^*(H)(\eta^2\text{-}H_2C{=}C(H)\text{-}OEt)]^+$



Scheme 3. Reaction conditions: a) neat Et_2O, 12 h, 60 °C; b) EtOPh, 10 h, 60 °C, toluene; or EtOPh, 2 h, 110 °C, toluene.

instead, presumably by means of β-H elimination.[7] As shown also in Scheme 3, activation of EtOPh by **1** (toluene, 110 °C, 2 h) gave compound **6** (see Supporting Information). It thus appears that the very important steric demands of the Tp^x ligand (as compared with the somewhat less bulky cyclopentadienyl ligand, Cp^x) and its rigid nature, which tends to enforce six-fold coordination to the metal center, favors α-H elimination over β-H elimination in the transformations studied here.

In summary, we have shown that the Ir^I compound **1** effects the regioselective, double C–H activation of a variety of ether and amine substrates by allowing their precoordination to the metal center. The formation of Fischer-type carbenes in this cascade activation (cyclometalation-β-elimination (or vice versa)-α-elimination) is made possible by the presence of an adequate hydrogen-accepting leaving group. The Tp^x- and Cp^x-Ir systems reported herein include O and N heteroatoms. Comparative studies on the facility of these fundamental organometallic reactions (α- and β-eliminations) on closely related Tp^x- and Cp^x-Ir systems without these heteroatoms that could alter the relative energies of the transition states and intermediates,[17] are presently in progress and will be reported in due course.

Experimental Section

1: To a suspension of [(IrCl(coe)$_2$)$_2$] (175 mg, 0.20 mmol) in CH$_2$Cl$_2$ (6 mL), 2-methylbutadiene (0.3 mL, excess) was added at room temperature to give a colorless solution. A solution of TlTp^{Ph} (253 mg, 0.40 mmol) in CH$_2$Cl$_2$ (6 mL) was then added. Stirring the reaction mixture for 4 h at room temperature resulted in the precipitation of TlCl. After filtration, the clear solution was evaporated to dryness. The crude product (orange powder) was purified via column chromatography (neutral aluminum oxide 90% activated, eluents PE (petroleumether):Et$_2$O = 15:1, eluted as a pale violet band). Compound **1** was obtained upon changing the eluents to PE:Et$_2$O = 4:1 and it eluted as a yellow band. Removing the solvent and drying in vacuum gave pure **1**. Yield: 198 mg (71%). Elemental analysis: calcd for C$_{32}$H$_{30}$BIrN$_6$ (%): C 54.8, H 4.3, N 12.0; found: C 54.4, H 4.1, N 12.2.

Compounds **2**–**6** can be prepared similarly by treating **1** with an excess of the corresponding ether or amine. As a representative example the synthesis of **5** is given: A solution of **1** (70 mg, 0.10 mmol) in Et$_2$O was heated at 60 °C for 12 h. The solution was evaporated to dryness. Purification by flash chromatography (neutral aluminum oxide 90% activated, eluents PE:Et$_2$O = 2:1, eluted as a yellow band) resulted in pure **5**. Yield: 58 mg (82%). Elemental analysis: calcd for C$_{31}$H$_{30}$BIrN$_6$O (%): C 52.8, H 4.3, N 11.9; found: C 53.0, H 4.6, N 11.7.

Received: January 28, 2000 [Z14616]

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[10] The related compound [Ir(κ^4(N,N',N'',C^{Ph})-Tp^{Ph})(Et)(η^2-C$_2$H$_4$)] activates THF to give **2** but with the other ether or amine substrates employed in this work the reaction failed due to the formation of [Ir(κ^5($N,N',N'',C^{Ph},C^{Ph'}$)-Tp^{Ph})(η^2-C$_2$H$_4$)].[9]

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[12] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC- 139166. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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DesVI: A New Member of the Sugar *N,N*-Dimethyltransferase Family Involved in the Biosynthesis of Desosamine[**]

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Methylation catalyzed by *S*-adenosylmethionine (AdoMet) dependent enzymes is one of the most common reactions occurring in biological systems. While a large number of methyltransferases which catalyze methylation at carbon,

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[**] The authors gratefully acknowledge financial support provided by the National Institutes of Health (GM 54346). H.-w.L. also thanks the National Institute of General Medical Sciences for a MERIT Award. L.Z. is the recipient of a Graduate School Dissertation Fellowship from the University of Minnesota.