Communications

Activation of sp³ Carbon–Hydrogen Bonds by a Ruthenium(II) Complex and Subsequent Metal-Mediated C−C and C−N Bond Formation**

Nicholas A. Foley, T. Brent Gunnoe,* Thomas R. Cundari,* Paul D. Boyle, and Jeffrey L. Petersen

Catalytic activation and functionalization of C−H bonds remains one of the foremost challenges in the field of homogeneous catalysis.[1–5] Although many transition-metal systems that initiate stoichiometric C−H activation are known, complexes capable of both C−H activation and subsequent transformations that functionalize the substrate are relatively rare.[1,2] This is especially true for substrates with sp³ C−H bonds. We have recently reported that [TpRu(L)(NCMe)R] complexes (Tp = hydrotris(pyrazolyl)-borate, R = Me or Ph, L = CO or PMe₃) catalytically activate aromatic and olefinic sp²-hybridized C−H bonds in combination with C−C bond-forming steps.[6–9] Extension of these reactions to substrates that possess sp³ C−H bonds could be of utility, but the activation of sp³ C−H bonds can be challenging, owing to the weakly coordinating nature of aliphatic moieties. While a functional group can provide a method to pre-coordinate the substrate, the presence of heterogroups or halides can also prevent C−H activation, because such moieties might either coordinate too strongly or provide a thermodynamically or kinetically more accessible site for metal-mediated bond activation.[10,11] Herein, we report initial fundamental studies of stoichiometric sp³ C−H bond activation by [TpRu(PMe₃)(NCR)Me] (R = Me or C₆F₅).

Mechanistic studies suggest that aromatic C−H activations by [TpRu(L)(NCMe)Me] (L = CO or PMe₃) to release methane and produce [TpRu(L)(NCMe)Ar] (Ar = aryl) involve dissociation of NCMe, coordination of the aromatic substrate, and subsequent C−H activation of the substrate.[6,7,9,12] Heating [TpRu(PMe₃)(NCMe)Me] (1) at 60°C in CH₃CN results in C−H activation of acetonitrile to release methane and produce [TpRu(PMe₃)(NCMe)(CH₂CN)] [2, Eq. (1) and Figure 1a]. The formation of 2 is quantitative as
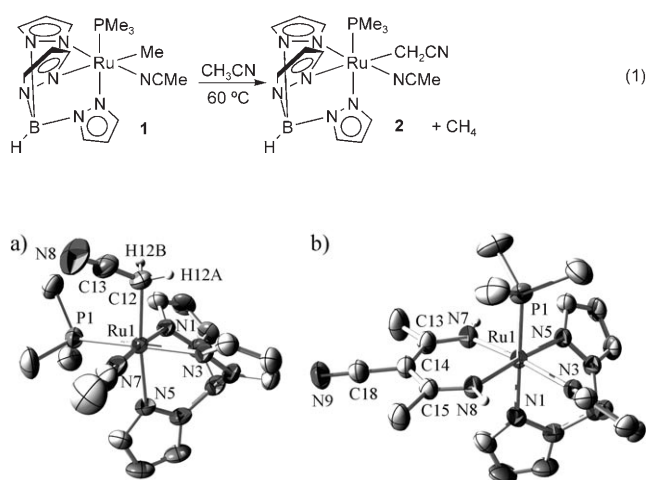
(1)

Figure 1. a) ORTEP of [TpRu(PMe₃)(NCMe)(CH₂CN)] (2, thermal ellipsoids set at 30% probability). Selected bond lengths [Å]: Ru1–C12 2.139(3), C12–C13 1.427(5), N8–C13 1.140(5). b) ORTEP of [TpRu-(PMe₃){κ²-*N,N*-{NHC(CH₃)}₂C(CN)}] (3, thermal ellipsoids set at 30% probability). Selected bond lengths [Å] and angels [°]: Ru1–N8 2.020(2), Ru1–N7 2.034(2), N7–C13 1.293(3), C13–C14 1.434(3), C14–C15 1.430(3), N8–C15 1.299(3); N8-Ru1-N7 88.49(8).

determined by ¹H NMR spectroscopy (greater than 95% yield relative to internal standard). Reactions with CD₃CN in sealed NMR tubes reveal the formation of CH₃D (1:1:1 triplet at approximately 0.15 ppm).

In multiple experiments, complex 1 was heated at 70°C in NCCD₃, and conversion of 1 to [TpRu(PMe₃)(NCCD₃)-(CD₂CN)] ([D₅]2) was monitored by ¹H NMR spectroscopy, yielding an average first-order rate constant $k_{obs} = 1.82(3) \times 10^{-5}$ s⁻¹. On the basis of studies of benzene C−H activation,[7,8] the rate-determining step for the conversion of 1 to 2 is expected to be the C−H activation event. Consistent with this hypothesis, heating 1 in a 1:1 mixture of NCCD₃ and NCCH₃ results in the formation of CH₃D and CH₄. Integration of the two corresponding resonances in the ¹H NMR spectrum reveals a primary kinetic isotope effect (KIE) with $k_H/k_D =$

[*] N. A. Foley, Dr. T. B. Gunnoe, P. D. Boyle
Department of Chemistry, North Carolina State University
Raleigh, NC 27695-8204 (USA)
Fax: (+1) 919-515-8909
E-mail: brent_gunnoe@ncsu.edu

Dr. T. R. Cundari
Center for Advanced Scientific Computing and Modeling (CASCaM)
Department of Chemistry, University of North Texas
Box 305070, Denton, TX 76203 (USA)
Fax: (+1) 940-565-4318
E-mail: tomc@unt.edu

Dr. J. L. Petersen
C. Eugene Bennett Department of Chemistry
West Virginia University
Morgantown, WV 26506-6045 (USA)

2.0(2). The approximately two-fold faster rate of C−H versus C−D activation is similar to the previously reported KIE for benzene C−H/D activation by **1** ($k_H/k_D = 2.7(1)$).[7]

The quantitative formation of **2** is a relatively rare example of alkylnitrile C−H activation.[13,14] Similar to the challenges encountered in the N−H activation of amines,[15] competition between κ^1-nitrogen coordination and the weak coordination of the acetonitrile C−H bond is expected to inhibit C−H activation. In a recent report that focused on successful rhodium-based C−H activation of nitriles, Jones and co-workers note the challenge of selectively cleaving C−H bonds in the presence of functional groups, including cyano groups.[10]

Even though the nitrile ligand of **2** is labile, attempts to observe benzene C−H(D) activation by **2** in C_6D_6 at 60°C resulted in decomposition to multiple undetermined complexes after 20 h. Neither the previously reported [TpRu-$(PMe_3)(NCMe)([D_5]Ph)$] complex nor H/D exchange between benzene and the cyanomethyl ligand was observed,[16] which is consistent with Jones and co-workers' report that the presence of a cyano group may provide ground-state stabilization relative to alkyl ligands.[10] Furthermore, attempts at degenerate C−H(D) activation of NCCD$_3$ by [TpRu(PMe$_3$)(NCMe)(CH$_2$CN)] (**2**) to yield [TpRu-(PMe$_3$)(NCCD$_3$)(CD$_2$CN)] ([D$_5$]**2**) resulted in no observable reaction by ^1H NMR spectroscopy after 15 h at 100°C. These results suggest that replacing the methyl ligand of **1** with the less basic cyanomethyl ligand of **2** increases the free energy of the transition state, $\Delta G^{\pm}$, for C−H activation.

Heating **2** at 180°C for 20 h in NCMe leads to the formation of [TpRu(PMe$_3$){κ^2-N,N-{NHC(CH$_3$)}$_2$C(CN)}] (**3**), which can be isolated in 51% yield. The structure of **3** was verified by a single crystal X-ray diffraction study [Eq. (2) and Figure 1b]. The hexanuclear backbone of the {NHC-

(2)
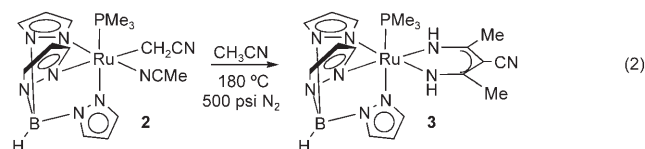
(CH$_3$)}$_2$C(CN) ligand exhibits C−C bond lengths of 1.434(3) and 1.430(3) Å and C−N bond lengths 1.293(3) and 1.299(3) Å, which are suggestive of an electron-delocalized six-membered metallacycle and similar to other transition-metal systems with this ligand.[17,18] The formation of **3** results from the net insertion of two equivalents of NCMe into the Ru−CH$_2$CN bond and tautomerization of the cyanomethylene protons. Heating **2** to 180°C in NCCD$_3$ forms [TpRu-(PMe$_3$){κ^2-N,N-{NDC(CD$_3$)}$_2$C(CN)}] ([D$_8$]**3**), as revealed by the absence of the metallacycle methyl and NH resonances at $\delta = 2.02$ and 6.13 ppm, respectively, in the ^1H NMR spectrum. Conversely, heating [D$_5$]**2** in NCCH$_3$ at 180°C yields all-protio **3**. Heating [D$_8$]**3** in NCCH$_3$ at 180°C results in selective H/D exchange to form [TpRu(PMe$_3$){κ^2-N,N-{NHC-(CD$_3$)}$_2$C(CN)}] ([D$_6$]**3**), making it difficult to monitor the original source of the various fragments in the metallacycle of **3**.

Heating **1** in nitromethane for 3 h results in the formation of [TpRu(PMe$_3$){κ^2-O,N-N(O)C(H)(NO$_2$)}] (**4**), which can be isolated in 64% yield, and the stoichiometric formation of propionamide (Scheme 1). A single crystal X-ray diffraction
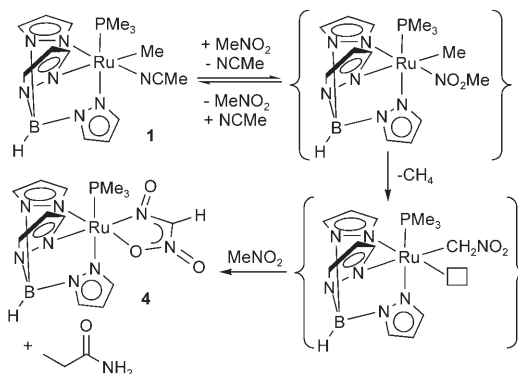
Scheme 1. Proposed pathway for formation of complex **4**.

study of **4** has provided geometric details (Figure 2a). The planarity of the N$_2$O$_3$CH ligand, bond lengths of the N8-C10-N7-O1 backbone (1.370(3), 1.344(3), and 1.313(2) Å) and Ru1-N8-C10-N7-O1-Ru1 ligand bond angles (114.7(1)°, 115.8(2)°, 118.5(2)°, and 111.2(1)°, respectively) are consistent with a conjugated five-membered metallacycle.
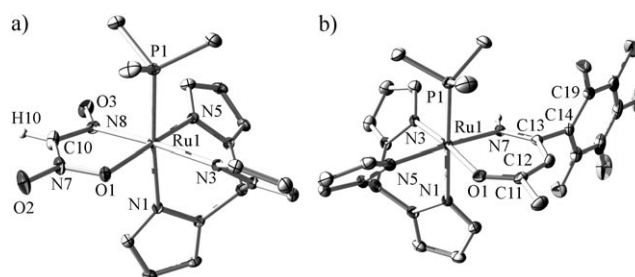
Figure 2. a) ORTEP of [TpRu(PMe$_3$){κ^2-O,N-N(O)C(H)(NO$_2$)}] (**4**, thermal ellipsoids set at 50% probability). Selected bond lengths [Å]: Ru1−N8 1.941(2), Ru1−O1 2.068(1), N7−O1 1.313(2), N7−O2 1.255(2), N7−C10 1.344(3), N8−C10 1.370(3), N8−O3 1.262(2). b) ORTEP of [TpRu-(PMe$_3$){κ^2-O,N-OC(Me)C(H)C(C$_6$F$_5$)NH}] (**8**, thermal ellipsoids set at 50% probability). Selected bond lengths [Å] and torsion angles [°]: Ru1−N7 2.014(1), Ru1−O1 2.057(1), N7−C13 1.308(2), C13−C12 1.405(3), C13−C14 1.502(2), C12−C11 1.397(3), C11−O1 1.275(2); C12-C13-C14-C19 90.2(3).

The formation of **4** likely proceeds by initial dissociative loss of the NCMe ligand and subsequent coordination and metal-mediated C−H activation of nitromethane to release methane and form unsaturated [TpRu(PMe$_3$)(CH$_2$NO$_2$)], followed by reaction with additional MeNO$_2$ to produce **4** and propionamide (Scheme 1). Monitoring the conversion of **1** to **4** by ^1H NMR spectroscopy in [D$_3$]MeNO$_2$ reveals the formation of **4**, CH$_3$D, and one equivalent (based on **1**) of free NCMe, with no observation of intermediates. Futhermore, resonances arising from propionamide are absent, suggesting that it is formed from MeNO$_2$. Release of one equivalent of

NCMe suggests that the nitrile is not incorporated into **4**, and the observation of CH_3D is consistent with the proposed initial C−H(D) activation of nitromethane to form the unobserved complex [TpRu(PMe₃)(CH₂NO₂)]. Formation of **4** and propionamide requires the consumption of three additional equivalents (resulting in four total equivalents of MeNO₂) of nitromethane molecules to give a final atom balance of complex **1** reacting with 4 equivalents of nitromethane to produce complex **1**, propionamide, and net H_3NO_4 in unidentified products. We have been unable to identify the production of free organics other than propionamide and NCMe. Whether propionamide formation is a result of a concomitant extrusion process during the formation of **4** or is due to a separate metal-mediated pathway is unknown; however, stoichiometric production of propionamide relative to the formation of **4** (determined by ¹H NMR spectroscopy) is suggestive of the former. Limited examples of well-defined nitromethane C−H activation mediated by transition metals have been reported.[19]

Heating **1** at 80 °C for 24 h in acetone in the presence of five equivalents of NCMe results in the formation of [TpRu-(PMe₃){κ²-*O,N*-OC(Me)C(H)C(Me)NH}] (**5**), which is isolated in 61 % yield (Scheme 2). Monitoring the formation of **5**
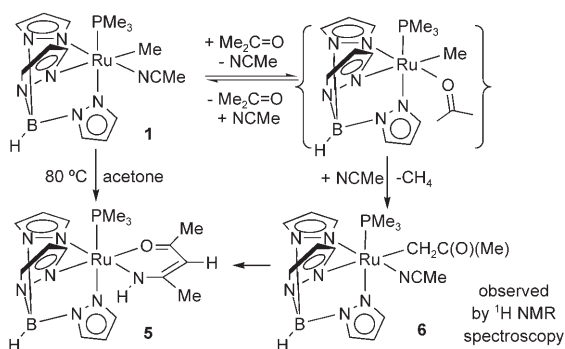

Scheme 2. Proposed pathway for formation of [TpRu(PMe₃){κ²-*O,N*-OC(Me)C(H)C(Me)NH}] (**5**).

by ¹H NMR spectroscopy at 60 °C in (CD₃)₂CO reveals the emergence and disappearance of a ruthenium intermediate and the production of CH_3D simultaneous to the formation of the intermediate. We propose that the most likely pathway for the formation of **5** involves initial C−H activation of coordinated acetone to release methane and produce the unsaturated complex [TpRu(PMe₃)(CH₂C(O)CH₃)], which likely coordinates NCMe to form [TpRu(PMe₃)(NCMe)-{CH₂C(O)CH₃}] (**6**, Scheme 2). Complex **6** has been neither isolated nor fully characterized and is proposed as a viable (albeit unconfirmed) intermediate.

Having established that **1** can mediate sp³ C−H activation of functionalized substrates as well as subsequent C−C or C−N bond formation, we sought to demonstrate the release of a functionalized organic compound from the metal center as an indication of possible opportunities for catalyst development. The addition of one equivalent of pyridinium chloride to a solution of **5** in NCCD₃ immediately produces a new complex (as determined by ¹H NMR spectroscopy), which is presumed

to be [TpRu(PMe₃)(Cl){κ¹-*N*-OC(Me)C(H)C(Me)NH₂}]. Heating the reaction mixture at 60 °C results in the formation of free acetylacetonamine in 86 % yield (verified by ¹H NMR spectroscopy and GC–MS), free pyridine, [TpRu(PMe₃)-(NCCD₃)Cl],[7] and a second complex, which is assigned as [TpRu(PMe₃)(pyridine)Cl] (Scheme 3). The overall transformation from **1** and acetone is a metal-mediated aldol-type reaction between acetone and acetonitrile.
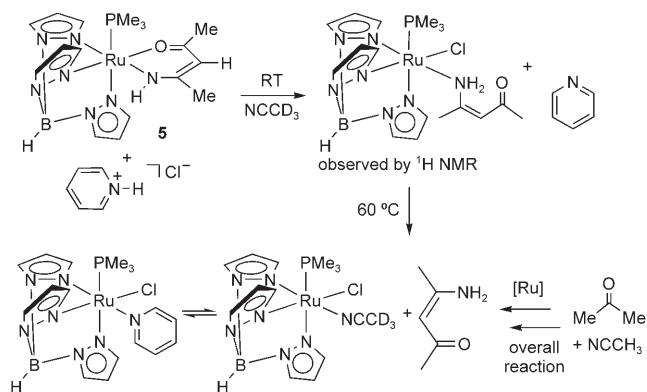
Scheme 3. Observed reactivity between pyridinium chloride and **5** to form free acetylacetonamine.

[TpRu(PMe₃)(NCC₆F₅)Me] (**7**) was synthesized to determine whether the acetone C−H activation and subsequent C−C coupling could be extended to other nitriles. Similar to **1**, heating **7** in neat acetone at 100 °C results in the quantitative formation of [TpRu(PMe₃){κ²-*O,N*-OC(Me)C(H)C-(C₆F₅)NH}] (**8**) in 20 h [Eq. (3)]. Figure 2b shows a crystal
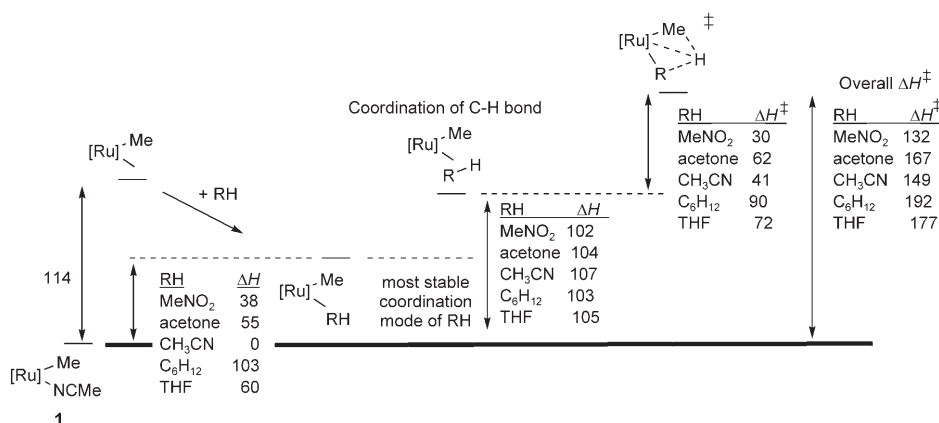

(3)
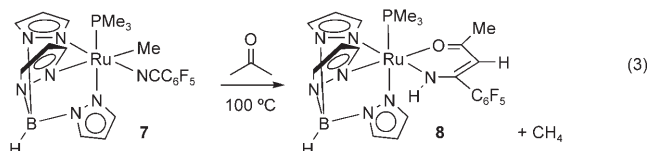
structure obtained from a single crystal X-ray diffraction study of **8**, which reveals a planar six-membered metallacycle composed of the anionic enamido ligand with the perfluorophenyl substituent oriented approximately perpendicular to the metallacycle plane. Heating **7** in (CD₃)₂CO at 100 °C results in the formation of CH_3D and clean conversion to **8** without observation of reaction intermediates. The lack of observation of [TpRu(PMe₃)(NCC₆F₅){CD₂C(O)CD₃}] could result from more rapid intramolecular cyclization (compared with the NCMe system), owing to the strong electron-withdrawing ability of the C₆F₅ moiety.

Attempted C−H activation of [D₈]THF by **1** results in decomposition to multiple Ru-containing products without formation of CH_3D after 25 h at 60 °C. Hydrocarbon C−H activation was also attempted without success. For example, heating **1** in [D₁₂]cyclohexane up to 60 °C results in decom-

position to multiple intractable products without observation of CH₃D. In contrast to the presence of cyano, acyl, and nitro functional groups, which appear to facilitate Ru-mediated C−H activation, the incorporation of chloride prevents C−H activation. For example, heating **1** at 60 °C in either [D₂]dicholoromethane or [D]chloroform results in quantitative formation of [TpRu(PMe₃)(NCMe)Cl].[7]

Compound **1** initiates C−H activation of aromatic C−H bonds, olefin C−H bonds, as well as sp³ C−H bonds of acetonitrile, acetone, and nitromethane. There are likely two key events in the overall C−H activation reactions: 1) coordination of the substrate activated by ligand exchange with NCMe and 2) the C−H bond scission step. More specifically, the failure of **1** to cleanly activate cyclohexane and THF could be due to its inability to sufficiently coordinate these compounds (in competition with NCMe) or to inherently high activation barriers for the C−H activation step for substrates that do not possess electron-withdrawing groups (e.g. nitro, cyano, or acyl). To assess the source of the substrate selectivity, we performed a density functional theory study for several representative substrates.

Scheme 4 depicts the results of calculations beginning with complex **1**. The calculated enthalpies (ΔH) for the

is more pronounced for cyclohexane than for THF, against coordination of these substrates relative to MeNO₂, acetone, and MeCN.

The decreased $\Delta H^{\ddagger}$ values for C−H bond scission for relatively acidic C−H bonds fit into an emerging picture of C−H activation by {TpRu(L)R} fragments as an intramolecular proton transfer (IPT, Scheme 5).[20,21] Goddard, Periana, and co-workers have studied related systems for iridium(III) and labeled the transformation an internal electrophilic substitution.[22] Consistent with these models, previous computational studies suggested that the basicity of X in Scheme 5 greatly impacts the extent to which Ru interacts with the activated proton in the transition state.[20] For example, we have recently determined that when the ligand receiving the activated hydrogen atom possesses a lone pair (e.g. hydroxo or amido ligands), the calculated Ru−H distance in the transition state is increased relative to when X = Me. In this model, it is anticipated that increasing the acidity of the C−H bond or increasing the basicity of the receiving ligand X should facilitate the Ru-mediated C−H activation and vice versa. For [TpRu(PMe₃)(NCMe)X], when X = Me the C−H(D) activation of acetonitrile proceeds smoothly at 60 °C [Eq. (1)]; however, for X = CH₂CN, which is less basic than Me, no evidence of degenerate C−H(D) activation of NCCD₃ could be found up to 100 °C.

The results reported herein demonstrate that {TpRu-(PMe₃)R} can activate sp³ C−H bonds and mediate subsequent C−C and C−N bond-forming reactions, including one example of release of a new organic compound. From a fundamental perspective, the combined experimental and computational studies suggest that a valid model for C−H activation is enhanced C−H acidity upon coordination to Ru^{II} and subsequent delivery of a proton to a basic receiving ligand. In the transition state, Ru can stabilize the protic hydro-

Scheme 4. Calculated energetics (enthalpy, kJ mol⁻¹) for overall C−H activation by **1** ([Ru] = TpRu-(PMe₃)).

overall reactions are positive, suggesting that loss of methane and recoordination of NCMe after C−H activation drive the transformations (see the Supporting Information). In addressing the source of substrate selectivity for C−H activation (i.e. coordination vs. activation energy for the discrete C−H activation step), we have focused on two sets of data: 1) the calculated enthalpy (ΔH) values for substrate coordination through displacement of NCMe and 2) the calculated $\Delta H^{\ddagger}$ values from the C−H adducts to the transition state for C−H activation. The computational results suggest that ground- and transition-state factors contribute to substrate selectivity by **1**. The values for the discrete C−H activation step indicate that the more acidic C−H bonds of MeNO₂, MeCN, and acetone possess lower $\Delta H^{\ddagger}$ values than cyclohexane and THF. Also, calculated ΔH values for competitive coordination of cyclohexane and THF (vs. NCMe) reveal a bias, which
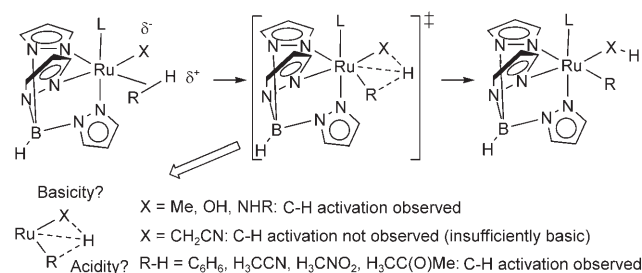
gen atom by an oxidative bonding interaction, which depends on the nature of the substrate being activated and the receiving ligand.

Scheme 5. Model C−H activation pathway by {TpRu(L)(X)} fragments (X = hydrocarbyl, OR, NHR, or CH₂CN).

Communications

See the Supporting Information for full experimental and computational details. CCDC-662853, 662854, 662855, 662856 (for **2**, **3**, **4**, and **8**, respectively) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[1] V. Ritleng, C. Sirlin, M. Pfeffer, *Chem. Rev.* **2002**, *102*, 1731.
[2] L. A. Goj, T. B. Gunnoe, *Curr. Org. Chem.* **2005**, *9*, 671.
[3] R. H. Crabtree, *J. Chem. Soc. Dalton Trans.* **2001**, 2437.
[4] K. I. Goldberg, A. S. Goldman, *ACS Symp. Ser.* **2004**, *885*.
[5] J. A. Labinger, J. E. Bercaw, *Nature* **2002**, *417*, 507.
[6] M. Lail, B. N. Arrowood, T. B. Gunnoe, *J. Am. Chem. Soc.* **2003**, *125*, 7506.
[7] N. A. Foley, M. Lail, J. P. Lee, T. B. Gunnoe, T. R. Cundari, J. L. Petersen, *J. Am. Chem. Soc.* **2007**, *129*, 6765.
[8] M. Lail, C. M. Bell, D. Conner, T. R. Cundari, T. B. Gunnoe, J. L. Petersen, *Organometallics* **2004**, *23*, 5007.
[9] K. A. Pittard, J. P. Lee, T. R. Cundari, T. B. Gunnoe, J. L. Petersen, *Organometallics* **2004**, *23*, 5514.
[10] A. J. Vetter, R. D. Rieth, W. D. Jones, *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 6957.
[11] L. Fan, S. Parkin, O. V. Ozerov, *J. Am. Chem. Soc.* **2005**, *127*, 16772; see selected examples from reference [6].
[12] K. A. Pittard, T. R. Cundari, T. B. Gunnoe, C. S. Day, J. L. Petersen, *Organometallics* **2005**, *24*, 5015.
[13] S. D. Ittel, C. A. Tolman, A. D. English, J. P. Jesson, *J. Am. Chem. Soc.* **1978**, *100*, 7577.
[14] D. Churchill, J. H. Shin, T. Hascall, J. M. Hahn, B. M. Bridgewater, G. Parkin, *Organometallics* **1999**, *18*, 2403.
[15] J. Zhao, A. S. Goldman, J. F. Hartwig, *Science* **2005**, *307*, 1080.
[16] Y. Feng, M. Lail, N. A. Foley, T. B. Gunnoe, K. A. Barakat, T. R. Cundari, J. L. Petersen, *J. Am. Chem. Soc.* **2006**, *128*, 7982.
[17] M. L. Durán, J. A. Garcia-Vazquez, C. Gomez, A. Sousa-Pedrares, J. Romero, A. Sousa, *Eur. J. Inorg. Chem.* **2002**, 2348.
[18] J. Nishijo, N. Nishi, *Eur. J. Inorg. Chem.* **2006**, 3022.
[19] X. W. Zhang, T. J. Emge, R. Ghosh, K. Krogh-Jespersen, A. S. Goldman, *Organometallics* **2006**, *25*, 1303, and references therein.
[20] T. R. Cundari, T. Grimes, T. B. Gunnoe, *J. Am. Chem. Soc.* **2007**, *129*, 13172
[21] D. J. Yonker, N. A. Foley, T. R. Cundari, T. B. Gunnoe, J. L. Petersen, *Organometallics* **2007**, ASAP.
[22] J. Oxgaard, W. J. Tenn, R. J. Nielsen, R. A. Periana, W. A. Goddard, *Organometallics* **2007**, *26*, 1565.