C–H Activation

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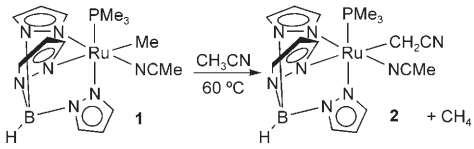
Activation of sp^3 Carbon–Hydrogen Bonds by a Ruthenium(II) Complex and Subsequent Metal-Mediated C–C and C–N Bond Formation**

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 sp^3 C–H bonds. We have recently reported that [TpRu(L)(NCMe)R] complexes (Tp = hydrotris(pyrazolyl)-borate, R = Me or Ph, L = CO or PMe_3) catalytically activate aromatic and olefinic sp^2-hybridized C–H bonds in combination with C–C bond-forming steps.[6–9] Extension of these reactions to substrates that possess sp^3 C–H bonds could be of utility, but the activation of sp^3 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 sp^3 C–H bond activation by [TpRu(PMe_3)(NCR)Me] (R = Me or C_6F_5).

Mechanistic studies suggest that aromatic C–H activations by [TpRu(L)(NCMe)Me] (L = CO or PMe_3) 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(PMe_3)(NCMe)Me] (**1**) at 60 °C in CH_3CN results in C–H activation of acetonitrile to release methane and produce [TpRu(PMe_3)(NCMe)(CH_2CN)] [**2**, Eq. (1) and Figure 1a]. The formation of **2** is quantitative as



(1)

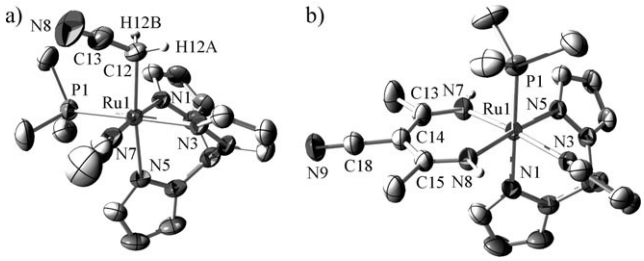


Figure 1. a) ORTEP of [TpRu(PMe_3)(NCMe)(CH_2CN)] (**2**, thermal ellipsoids set at 30% probability). Selected bond lengths [Å]: Ru1–C12 2.139(3), C12–C13 1.427(5), N8–C13 1.140(5). b) ORTEP of [TpRu(PMe_3){κ^2-*N*,*N*-{NHC(CH_3)}$_2$C(CN)}] (**3**, thermal ellipsoids set at 30% probability). Selected 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 ^{1}H NMR spectroscopy (greater than 95% yield relative to internal standard). Reactions with CD_3CN in sealed NMR tubes reveal the formation of CH_3D (1:1:1 triplet at approximately 0.15 ppm).

In multiple experiments, complex **1** was heated at 70 °C in $NCCD_3$, and conversion of **1** to [TpRu(PMe_3)($NCCD_3$)(CD_2CN)] ([D_5]**2**) was monitored by ^{1}H 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 $NCCD_3$ and $NCCH_3$ results in the formation of CH_3D and CH_4. Integration of the two corresponding resonances in the ^{1}H 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)

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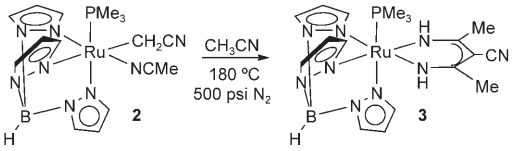
2.0(2). The approximately two-fold faster rate of C–H versus C–D activation is similar to the previously reported KIE for benzene C–H/D activation by **1** ($k_H/k_D = 2.7(1)$).[7]

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 ^{1}H 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, $\Delta G^{\ddagger}$, for C–H activation.

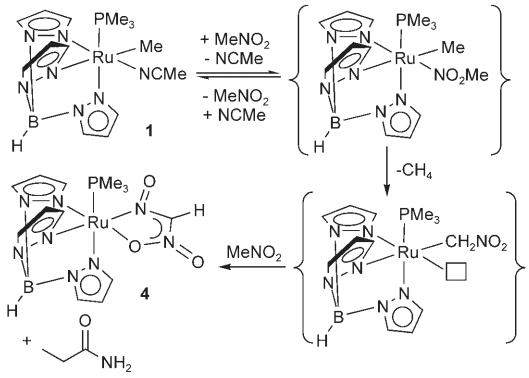
Heating **2** at 180 °C for 20 h in NCMe leads to the formation of [TpRu(PMe$_3$){κ^2-*N*,*N*-{NHC(CH$_3$)}$_2$C(CN)}] (**3**), which can be isolated in 51 % yield. The structure of **3** was verified by a single crystal X-ray diffraction study [Eq. (2) and Figure 1 b]. The hexanuclear backbone of the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

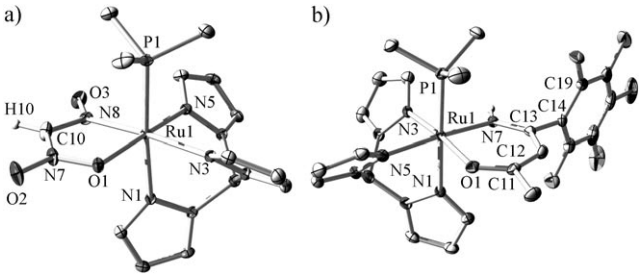
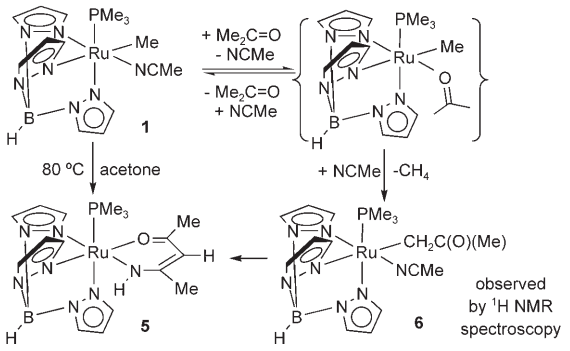


Figure 2. a) ORTEP of [TpRu(PMe$_3$){κ^2-*O*,*N*-N(O)C(H)(NO$_2$)}] (**4**, thermal ellipsoids set at 50 % probability). Selected bond lengths [Å]: Ru1–N8 1.941(2), Ru1–O1 2.068(1), N7–O1 1.313(2), N7–O2 1.255(2), N7–C10 1.344(3), N8–C10 1.370(3), N8–O3 1.262(2). b) ORTEP of [TpRu(PMe$_3$){κ^2-*O*,*N*-OC(Me)C(H)C(C$_6$F$_5$)NH}] (**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 ^{1}H NMR spectroscopy in [D$_3$]$MeNO_2$ reveals the formation of **4**, CH_3D, 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(PMe_3)(CH_2NO_2)]. Formation of **4** and propionamide requires the consumption of three additional equivalents (resulting in four total equivalents of $MeNO_2$) 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 ^{1}H NMR spectroscopy) is suggestive of the former. Limited examples of well-defined nitromethane C–H activation mediated by transition metals have been reported.[19]

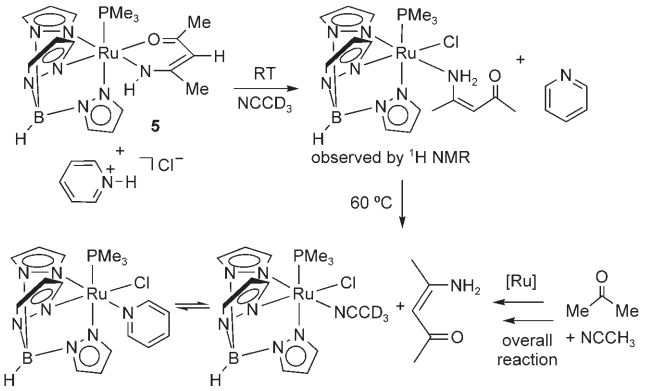
Heating **1** at 80 °C for 24 h in acetone in the presence of five equivalents of NCMe results in the formation of [TpRu(PMe_3){κ^2-*O*,*N*-OC(Me)C(H)C(Me)NH}] (**5**), which is isolated in 61 % yield (Scheme 2). Monitoring the formation of **5**



Scheme 2. Proposed pathway for formation of [TpRu(PMe_3){κ^2-*O*,*N*-OC(Me)C(H)C(Me)NH}] (**5**).

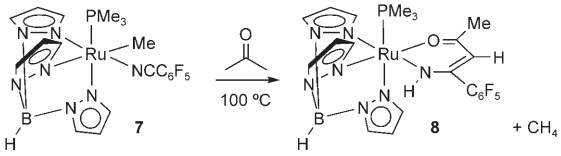
by ^{1}H NMR spectroscopy at 60 °C in $(CD_3)_2CO$ reveals the emergence and disappearance of a ruthenium intermediate and the production of CH_3D simultaneous to the formation of the intermediate. We propose that the most likely pathway for the formation of **5** involves initial C–H activation of coordinated acetone to release methane and produce the unsaturated complex [TpRu(PMe_3)($CH_2C(O)CH_3$)], which likely coordinates NCMe to form [TpRu(PMe_3)(NCMe){$CH_2C(O)CH_3$}] (**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 sp^3 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 $NCCD_3$ immediately produces a new complex (as determined by ^{1}H NMR spectroscopy), which is presumed to be [TpRu(PMe_3)(Cl){κ^1-*N*-OC(Me)C(H)C(Me)NH_2}]. Heating the reaction mixture at 60 °C results in the formation of free acetylacetonamine in 86 % yield (verified by ^{1}H NMR spectroscopy and GC–MS), free pyridine, [TpRu(PMe_3)($NCCD_3$)Cl],[7] and a second complex, which is assigned as [TpRu(PMe_3)(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(PMe_3)(NCC_6F_5)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(PMe_3){κ^2-*O*,*N*-OC(Me)C(H)C-(C_6F_5)NH}] (**8**) in 20 h [Eq. (3)]. Figure 2b shows a crystal



(3)

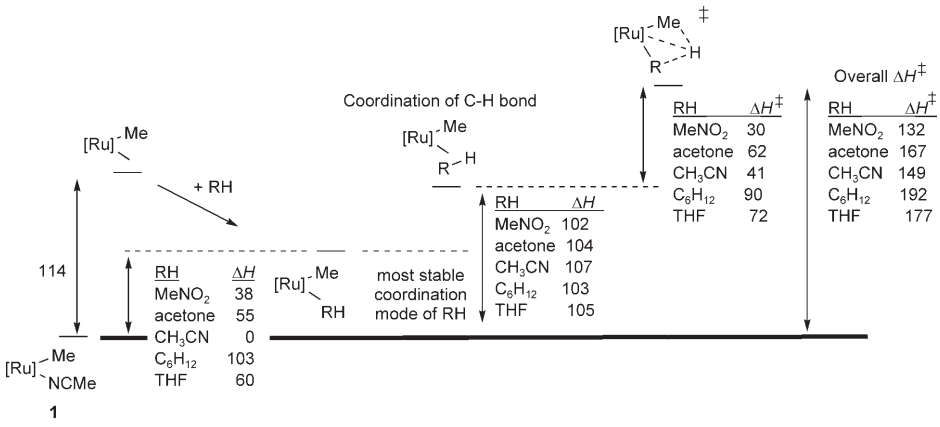
structure obtained from a single crystal X-ray diffraction study of **8**, which reveals a planar six-membered metallacycle composed of the anionic enamido ligand with the perfluorophenyl substituent oriented approximately perpendicular to the metallacycle plane. Heating **7** in $(CD_3)_2CO$ at 100 °C results in the formation of CH_3D and clean conversion to **8** without observation of reaction intermediates. The lack of observation of [TpRu(PMe_3)(NCC_6F_5){$CD_2C(O)CD_3$}] could result from more rapid intramolecular cyclization (compared with the NCMe system), owing to the strong electron-withdrawing ability of the C_6F_5 moiety.

Attempted C–H activation of [D_8]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 [D_{12}]cyclohexane up to 60 °C results in decom-

position to multiple intractable products without observation of CH_3D. 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 $[D_2]$dicholoromethane or [D]chloroform results in quantitative formation of $[TpRu(PMe_3)(NCMe)Cl]$.[7]

Compound **1** initiates C–H activation of aromatic C–H bonds, olefin C–H bonds, as well as sp^3 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.

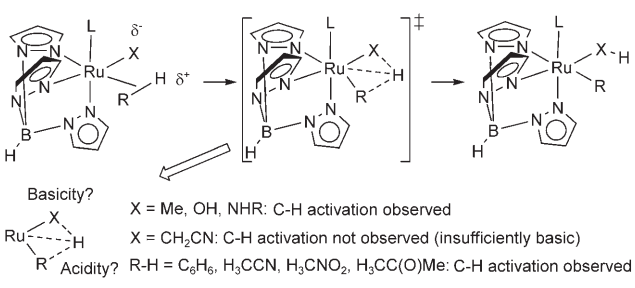
Scheme 4 depicts the results of calculations beginning with complex **1**. The calculated enthalpies (ΔH) for the overall reactions are positive, suggesting that loss of methane and recoordination of NCMe after C–H activation drive the transformations (see the Supporting Information). In addressing the 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 $MeNO_2$, 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 is more pronounced for cyclohexane than for THF, against coordination of these substrates relative to $MeNO_2$, acetone, and MeCN.



Scheme 4. Calculated energetics (enthalpy, kJ mol^{-1}) for overall C–H activation by **1** ([Ru] = TpRu(PMe$_3$)).

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 $[TpRu(PMe_3)(NCMe)X]$, when X = Me the C–H(D) activation of acetonitrile proceeds smoothly at 60 °C [Eq. (1)]; however, for $X = CH_2CN$, which is less basic than Me, no evidence of degenerate C–H(D) activation of $NCCD_3$ could be found up to 100 °C.

The results reported herein demonstrate that {TpRu(PMe$_3$)R} can activate sp^3 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 hydrogen 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 CH_2CN).

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.

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Keywords: acetonitrile · C—C coupling · C—H activation · C—N bond formation · ruthenium

[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.

