ORGANOMETALLICS

Communication

pubs.acs.org/Organometallics

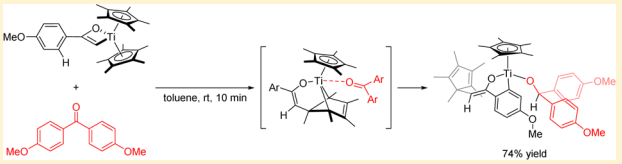
Facile C–H, C–F, C–Cl, and C–C Activation by Oxatitanacyclobutene Complexes

Trang T. Nguyen, Jeffery A. Bertke, Danielle L. Gray, and Kami L. Hull*

Department of Chemistry, University of Illinois at Urbana-Champaign, 600 South Mathews Avenue, Urbana, Illinois 61801, United States

Supporting Information

ABSTRACT: Aryl ketones react readily with oxatitanacyclobutenes bearing pentamethylcyclopentadienyl ligands to form unique titanocene complexes resulting from Cp* modification and C–H activation. An intermediate in this reaction is intercepted with various functional groups to form carbonyl insertion, C–F activation, and cyclopropane ring-opening products.



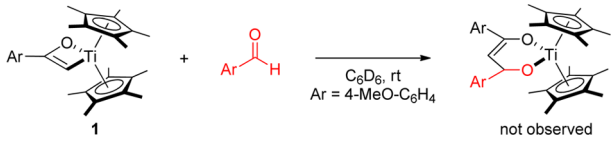
Downloaded by STOCKHOLM UNIV on September 8, 2015 | http://pubs.acs.org
Publication Date (Web): August 26, 2015 | doi: 10.1021/acs.organomet.5b00470

Oxa- and azametallacycles of group IV metals are important intermediates in a number of metal-mediated reactions, including hydroamination,[1,2] reductive cyclization,[3,4] vinyl cyclopropane ring opening,[5] aldehyde–alkyne coupling,[6] and aldehyde–imine coupling.[7] The key step in many of these reactions involves insertion of the substrate's unsaturated bond into the metal–carbon bond of the metallacycles. This reactivity has been extensively studied in the cases of azametallacycles, generated from titanium and zirconium imido complexes, and more recently with oxazirconacyclobutenes.[6] On the other hand, the reactivity of analogous oxatitanacyclobutenes toward unsaturated organic substrates has not been reported. In order to develop analogous catalytic cycles with Ti–oxo complexes, it is key to understand their fundamental reactivity and probe the decomposition pathways for these compounds. The results described herein probe the reaction between oxatitanacyclobutenes and carbonyl-containing compounds.

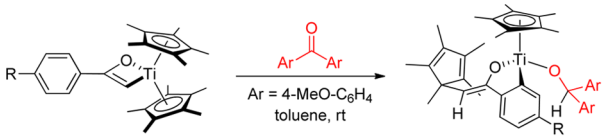
It is known that aldehydes and aldimines insert into the [M]–C bond of azazirconacyclobutenes,[7a,b,8] oxazirconacyclobutenes,[6,9] and azatitanacyclobutenes;[7c,d] however, the insertion of aldehydes into oxatitanacyclobutenes has not been reported. Treatment of titanocene complex **1** with aldehyde resulted in rapid consumption of the starting materials. The aldehyde insertion product was not detected by ^{1}H NMR spectroscopy (Scheme 1); rather, a complex mixture of products was observed.[10]

To gain insight into the reactions of **1** with carbonyl compounds, the less reactive benzophenone was chosen to probe its reactivity. Interestingly, addition of 1 equiv of 4,4′-bismethoxybenzophenone to a solution of **1a** in C_6D_6 resulted in an immediate color change, from green to dark red, and complete conversion to a new complex was observed after 10 min at room temperature (Scheme 2). Analysis of the crude reaction mixture by ^{1}H NMR spectroscopy revealed that a single product was formed in near-quantitative yields. The ^{1}H NMR spectrum had an interesting pattern in the Cp* methyl region, with a singlet integrating to 15 hydrogen atoms and 5 singlets each integrating to 3 hydrogen atoms, indicating desymmetrization of one of the Cp* ligands. Additionally, a singlet, corresponding to the vinylic proton, had moved from 7.60 to 4.62 ppm. These observations were consistent with reductive elimination between a Cp* ligand and the Ti–C bond of the oxatitanacyclobutene; a related reaction was recently reported by Chirik for reductive elimination from complexes bearing the 2,3,4,5-tetramethyl-1-(trimethylsilyl)cyclopentadienyl ligand.[11] Further, the AA′BB′ spin system of the (*p*-methoxy)phenyl of the aryl ring in **1a** became a ABC spin system and a new singlet at 6.56 ppm was observed. On the basis of the ^{1}H and ^{13}C NMR spectra the structure was proposed to be titanacycle **2a**. The new [Ti]–C bond is between the aryl from **1a** and the [Ti]; the hydride has transferred to the ketone, resulting in the formation of an alkoxide ligand.

Scheme 1. Proposed Aldehyde Insertion into a Ti–C Bond



Scheme 2. Reaction of Oxatitanacyclobutenes with Benzophenone



1a: R = OMe
1b: R = H

2a: R = OMe, 74% isolated yield
2b: R = H, 51% isolated yield

Received: June 3, 2015

© XXXX American Chemical Society

DOI: 10.1021/acs.organomet.5b00470
Organometallics XXXX, XXX, XXX–XXX

To confirm the structural assignment, X-ray-quality crystals were grown by slow diffusion of pentane into a THF solution of **2a**. The structure of **2a**·THF is shown in Figure 1. The titanium is

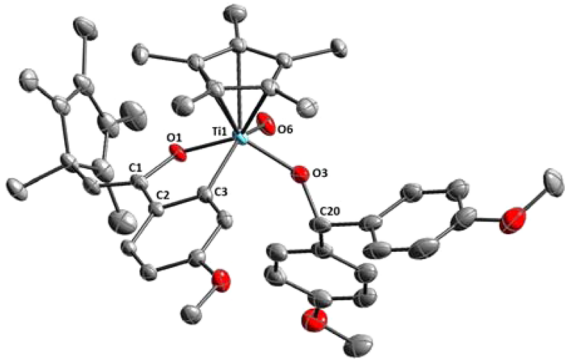


Figure 1. X-ray crystal structure of **2a**·THF. Hydrogen atoms and THF carbons are omitted for clarity. Oxygen O6 is from THF. Ellipsoids are drawn at the 50% probability level.

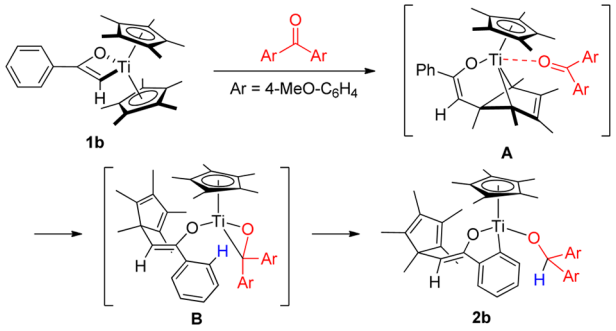
in a pseudo-square-pyramidal environment, and all of the atoms of the titanacycle are coplanar. The acyclic Ti−alkoxide (Ti1−O3) bond length of 1.8351(12) Å is shorter than the cyclic Ti−alkoxide (Ti1−O1) bond length of 1.9273(11) Å, consistent with a larger Ti−O3−C20 bond angle of 143.86(11)° in comparison to the Ti−O1−C1 bond angle of 123.33(10)°.

Carbonyl compounds are known to insert into the metal−carbon bond of titanacyclobutenes bearing the unsubstituted Cp ligand to form six-membered metallacycles in good yields.[12] The difference in reactivity between those complexes and titanacycles **1** is explained by the increased steric interactions at the metal center. Interestingly, benzophenone imine undergoes a similar reductive elimination reaction, while no reaction was observed when other Lewis basic groups, including triphenylphosphine, tributylphosphine, triphenylphosphine oxide, 4-dimethylaminopyridine, benzonitrile, ethyl benzoate, and *N*,*N*-dimethylbenzamide, were added to a solution of **1** in C_6D_6 by ^{1}H NMR.[10] Analogous oxazirconacyclobutenes bearing a Cp* ligand have a larger Cp*−Ti−Cp* bond angle[9] in comparison to that of **1**,[13] suggesting a less crowded metal center. These complexes form six-membered metallacycle insertion products[6,9] and have been reported to undergo C−H activation to form a five-membered metallacycle similar to **2**;[14] however, this transformation is only affected at temperatures exceeding 150 °C. The details of such conversion are not known, but various intermediates, including zwitterion, diradical, and free zirconium−oxo, have been invoked.

In Chirik's recent report, it was concluded that the silyl group was essential to the transformation, as an oxatitanacyclobutene complex with all-alkyl-substituted Cp ring did not exhibit the same reactivity.[11] While complexes **1a**,**b** are stable for extended times in solution at up to 60 °C, the addition of the ketones is important to trigger this transformation.

A tentative mechanism for this transformation is illustrated in Scheme 3. In the first step, due to the high oxophilicity of titanium, coordination of the carbonyl oxygen to **1b** promotes the reductive elimination between the Cp* ring and the Ti−C bond, to afford intermediate **A**. Reductive elimination of the unsubstituted Cp ligand in titanocene complexes has also been previously reported.[15] The presence of a Ti−vinyl linkage may be crucial for this reactivity, as a Ti−vinyl bond is slower to insert into hindered carbonyls, relative to a Ti−alkyl bond.[16] From **A**,

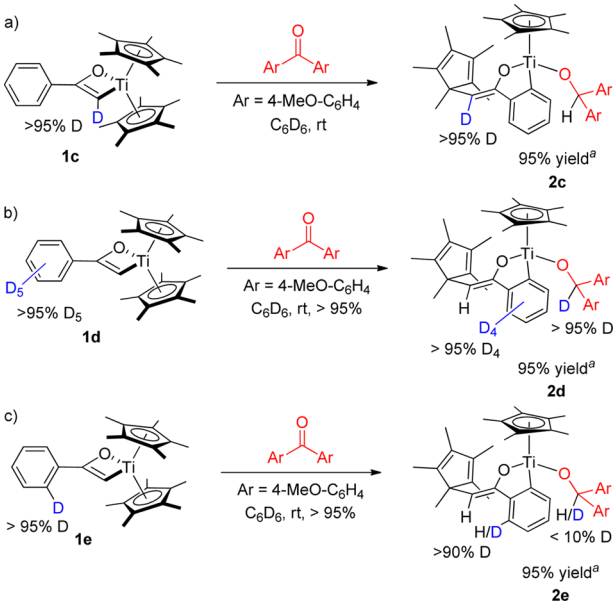
Scheme 3. Proposed Mechanism for C−H Activation



titanium inserts into the carbonyl C═O bond and the modified Cp* ligand dissociates from the metal, forming the proposed intermediate **B**. Titanium−ketone intermediates have been proposed in the reaction of bis(cyclopentadienyl)-titanacyclobutane with tetrakis(trifluoromethyl)-cyclopentadienone[17] and the cyclization reaction of enones.[3a] With the phenyl ring now proximal, C−H activation occurs to form a stable five-membered metallacycle and an alkoxide ligand, generating product **2b**.

The proposed mechanism is supported by deuterium labeling experiments. Three isotopically labeled isomers of **1b**, prepared from Cp*$_2$Ti═O(pyr) and the corresponding alkynes, were combined with 4,4′-bismethoxybenzophenone in C_6D_6 (Scheme 4). Deuteration at the alkene carbon in metallacycle **1c** (Scheme

Scheme 4. Labeling Study[a]



[a]In situ yield determined by ^{1}H NMR spectroscopy and comparison to an internal standard.

4a) results in labeling of the alkene proton in **2c**, supporting the direct reductive elimination between one Cp* ligand and a Ti−C bond. Further, as Scheme 4b illustrates, one of the ortho C−D bonds is transferred selectively to form the new Ti−OCD(Ph)$_2$ bond of **1d**. Interestingly, when only one ortho position was deuterated, as in **1e** (Scheme 4c), a very large intramolecular KIE of >9 was observed, as determined by integration in the ^{1}H NMR spectrum.[10]

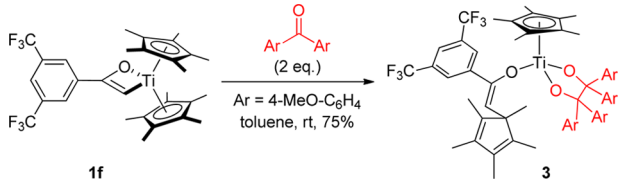
Downloaded by STOCKHOLM UNIV on September 8, 2015 | http://pubs.acs.org
Publication Date (Web): August 26, 2015 | doi: 10.1021/acs.organomet.5b00470

DOI: 10.1021/acs.organomet.5b00470
Organometallics XXXX, XXX, XXX−XXX

Downloaded by STOCKHOLM UNIV on September 8, 2015 | http://pubs.acs.org
Publication Date (Web): August 26, 2015 | doi: 10.1021/acs.organomet.5b00470

It was hypothesized that blocking the ortho positions in oxametallacycle **1** would inhibit C−H activation and allow for the direct observation of intermediate **B**. However, reactions of titanocene−oxo with 2,6-difluorophenylacetylene and 2,4,6-trimethoxyphenylacetylene generated hydroxyacetylide complexes instead of the desired titanacycles. The selective formation of the hydroxyacetylides over oxatitanacyclobutenes is attributed to the increased steric repulsion between the Cp* and the ortho substituents.[13] Meta substituents are also known to slow the rate of C−H activation;[18] **1f** was synthesized and treated with 4,4′-bismethoxybenzophenone (Scheme 5). Excitingly, 50% conversion to reductive elimination was seen by ^{1}H NMR spectroscopy; the metallacycle and Ti−alkoxide resulting from C−H activation were not observed. When 2 equiv of the benzophenone was added to a solution of **1f** in C_6D_6, quantitative conversion to product **3** was observed by ^{1}H NMR spectroscopy. The proposed mechanism for the formation of **3** is that, upon the formation of intermediate **B**, another 1 equiv of the ketone undergoes rapid insertion into the Ti−C bond, as the C−H activation is slowed by the proximal CF_3 groups.

Scheme 5. Formation of Double-Insertion Product



X-ray-quality crystals of **3** were obtained from a toluene solution layered with pentane. As seen in Figure 2, the solid-state structure of **3** shows a five-membered metallacycle with two molecules of ketone having undergone a pinacol coupling. The metal is in a three-legged piano-stool geometry, with a slightly puckered metallacycle. The acyclic alkoxide oxygen has an almost linear geometry, with the Ti−O7−C31 angle of 171.44(11)° suggesting a four-electron alkoxide ligand. Complex **2a**, in comparison, has a bent alkoxide with a Ti−O3−C20 angle of 143.86(11)°.

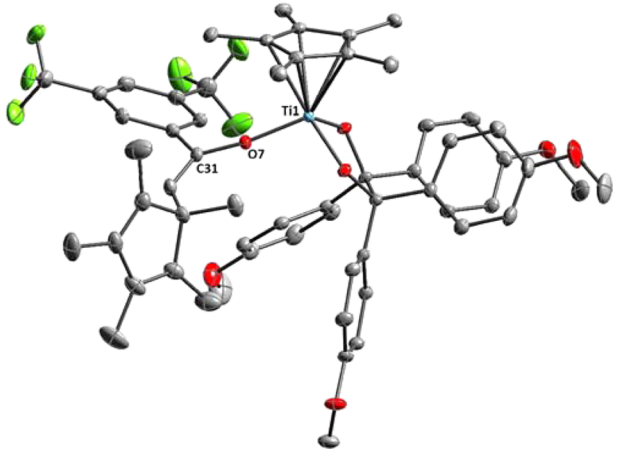
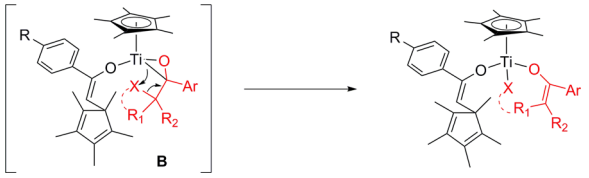


Figure 2. X-ray crystal structure of **3**. Hydrogen atoms are omitted for clarity. Ellipsoids are drawn at the 50% probability level.

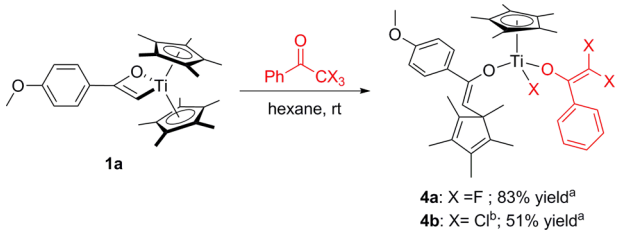
Formation of complexes **2** demonstrates the ability of titanocenes **1** to undergo C−H activation. When C−H activation is slow, as with **1f**, intermediate **B** reacts with a second ketone to form pinacol-type product **3**. These intriguing results suggested the possibility of a more general C−X activation (Scheme 6),

Scheme 6. Intramolecular Trapping of B with an Adjacent Reactive C−X Bond



providing that the C−X bond activation from **B** is faster than C−H activation and carbonyl insertion. Trifluoromethyls are known to undergo C−F activation with titanocene complexes via an intermediate similar to **B**.[17] Reaction of **1a** with 1 equiv of trifluoroacetophenone (Scheme 7) resulted in an immediate color change from green to yellow. ^{1}H NMR spectroscopy reveals the same pattern expected from reductive elimination of Cp*, as observed in Scheme 1; however, the phenyl ring bearing the methoxy group remains symmetric, suggesting that C−H activation did not occur. In addition, ^{19}F NMR spectroscopy shows two doublets at −99.96 and −116.07 ppm, suggesting the presence of an olefinic CF_2 group. Analogous reactivity was observed with 2,2,2-trichloroacetophenone, which afforded **4b** in 51% isolated yield. The formation of **4a**,**b** is consistent with the mechanism outlined in Scheme 6. The driving force for this process could be the formation of a strong Ti−X bond. The ketone plays an important role, as treatment of **1a** with ethyl trifluoroacetate or octafluorotoluene[19] resulted in no reaction.

Scheme 7. Reaction of Oxatitanacyclobutene with CX_3COPh[a,b]



[a]Isolated yield. [b]Reaction run in pentane.

Single crystals suitable for X-ray crystallography were grown by slow diffusion of pentane into a toluene solution of **4a**. As depicted in Figure 3, **4a** has a piano-stool geometry, with the three leg positions occupied by one fluorine and two alkoxide ligands. One of the alkoxides results from reductive elimination of Cp* and the ring carbon from **1a**; the other results from C−F activation of the reactive trifluoromethyl. Both of these ligands show strong deviation from sp^2 geometry with Ti−O1−C11 and Ti−O2−C19 angles of 156.06(14) and 167.36(14)°, respectively, suggesting the multiple-bonding nature of the Ti−O linkages.

Next, the ability of **B** to undergo C−C bond activation was studied with phenyl cyclopropyl ketone. The proposed transformation in Scheme 6 would result in the formation of an oxatitanacyclohexene complex. Related oxatitanacyclohexenes generated via carbonyl insertion into the Ti−C bonds of titanacyclobutenes are known to be stable.[12,16b] Indeed, treatment of **1a** with 4-methoxyphenyl cyclopropyl ketone

DOI: 10.1021/acs.organomet.5b00470
Organometallics XXXX, XXX, XXX−XXX

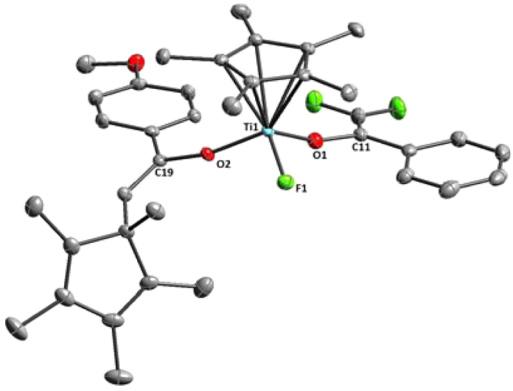
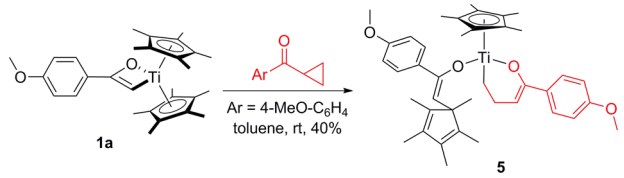


Figure 3. X-ray crystal structure of **4a**. Hydrogen atoms are omitted for clarity. Ellipsoids are drawn at the 50% probability level.

resulted in the formation of titanacycle **5** (Scheme 8). When cyclobutyl phenyl ketone was used, an immediate color change

Scheme 8. Formation of Cyclopropane-Opened Product



from green to bright red was observed. The ^{1}H NMR spectrum indicated consumption of starting materials and formation of an intractable mixture of products; the C−C activation product was not observed.

In summary, aryl ketones promote facile reductive elimination of the usually inert Cp* ligand, providing a rare example of this reactivity in all-alkyl-substituted Cp-based ligands. Reactions proceed with the formation of a highly reactive Ti−ketone complex, capable of C−X activation (X = H, F, Cl, C). These transformations proceed readily at room temperature to generate a number of novel titanium complexes. In addition, these results indicate potential catalyst decomposition pathways in titanocene-catalyzed reactions; coordination of a Lewis basic group, e.g., a ketone, aldehyde, or imine, to the metal center could promote the reductive elimination and thus catalyst deactivation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.5b00470.

Experimental procedures, characterization data, and crystallographic data (PDF)

Crystallographic data for **2a**, **3**, and **4a** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail for K.L.H.: kamihull@illinois.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the University of Illinois, Urbana−Champaign, and the Petroleum Research Fund for their generous support.

■ REFERENCES

(1) (a) Walsh, P. J.; Baranger, A. M.; Bergman, R. G. *J. Am. Chem. Soc.* **1992**, *114*, 1708. (b) McGrane, P. L.; Livinghouse, T. *J. Org. Chem.* **1992**, *57*, 1323. (c) Haak, E.; Bytschkov, I.; Doye, S. *Angew. Chem., Int. Ed.* **1999**, *38*, 3389. (d) Johnson, J. S.; Bergman, R. G. *J. Am. Chem. Soc.* **2001**, *123*, 2923. (e) Cao, C.; Ciszewski, J. T.; Odom, A. T. *Organometallics* **2001**, *20*, 5011. (f) Tillack, A.; Castro, I. G.; Hartung, C. G.; Beller, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 2541. (g) Ong, T.-G.; Yap, G. P. A.; Richeson, D. S. *Organometallics* **2002**, *21*, 2839. (h) Bytschkov, T.; Doye, S. *Tetrahedron Lett.* **2002**, *43*, 3715. (i) Li, C.; Thomson, R. K.; Gillon, B.; Patrick, B. O.; Schafer, L. L. *Chem. Commun.* **2003**, 2462. For recent reviews see: (j) Severin, R.; Doye, S. *Chem. Soc. Rev.* **2007**, *36*, 1407−1420. (k) Bytschkov, I.; Doye, S. *Eur. J. Org. Chem.* **2003**, *2003*, 935−946. (l) Hazari, N.; Mountford, P. *Acc. Chem. Res.* **2005**, *38*, 839−849. (m) Odom, A. L. *Dalton Trans.* **2005**, 225−233.

(2) For other amino functionalization reactions, see: (a) Fairfax, D.; Stein, M.; Livinghouse, T.; Jensen, M. *Organometallics* **1997**, *16*, 1523−1525. (b) Kablaoui, N. M.; Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 5818−5819. Duncan, D.; Livinghouse, T. *Organometallics* **1999**, *18*, 4421−4428.

(3) (a) Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 3182−3191. (b) Sturla, S. J.; Buchwald, S. L. *Organometallics* **2002**, *21*, 739−748.

(4) For a recent review see: Micalizio, G. C. Early Transition Metal Mediated Reductive Coupling Reactions. In *Comprehensive Organic Synthesis II*, 2nd ed.; Knochel, P., Ed.; Elsevier: Amsterdam, 2014; pp 1660−1737.

(5) Macklin, T. K.; Micalizio, G. C. *Nat. Chem.* **2010**, *2*, 638−643.

(6) Kortman, G. D.; Orr, M. J.; Hull, K. L. *Organometallics* **2015**, *34*, 1013−1016.

(7) (a) Ruck, R. T.; Bergman, R. G. *Organometallics* **2004**, *23*, 2231−2233. (b) Ruck, R.; Zuckerman, R. L.; Krska, S. W.; Bergman, R. G. *Angew. Chem., Int. Ed.* **2004**, *43*, 5372−5374. (c) Basuli, F.; Aneetha, H.; Huffman, J. C.; Mindiola, D. J. *J. Am. Chem. Soc.* **2005**, *127*, 17992−17993. (d) Aneetha, H.; Basuli, F.; Bollinger, J.; Huffman, J. C.; Mindiola, D. J. *Organometallics* **2006**, *25*, 2402−2404.

(8) (a) Hanna, T. A.; Baranger, A. M.; Walsh, P. J.; Bergman, R. G. J. *J. Am. Chem. Soc.* **1995**, *117*, 3292−3293. (b) Hanna, T. A.; Baranger, A. M.; Bergman, R. G. *J. Org. Chem.* **1996**, *61*, 4532−4541.

(9) Vaughan, G. A.; Hillhouse, I. P. G. L.; Rheingold, A. L. *J. Am. Chem. Soc.* **1990**, *112*, 7994−8001.

(10) See the Supporting Information.

(11) Pappas, I.; Chirik, P. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 6241−6244.

(12) Meinhart, J. D.; Grubbs, R. H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 171−180.

(13) Polse, J. L.; Andemen, R. A.; Bergman, R. G. *J. Am. Chem. Soc.* **1995**, *117*, 5393−5394.

(14) Carney, M. J.; Walsh, P. J.; Hollander, F. J.; Bergman, R. G. *J. Am. Chem. Soc.* **1989**, *111*, 8751−8753.

(15) (a) Rosenthal, U.; Lefeber, C.; Arndt, P.; Tillack, A.; Baumann, W.; Kempe, R.; Burlakov, V. V. *J. Organomet. Chem.* **1995**, *503*, 221−223. (b) Tillack, A.; Baumann, W.; Ohff, A.; Lefeber, C.; Spannenberg, A.; Kempe, R.; Rosenthal, U. *J. Organomet. Chem.* **1996**, *520*, 187−193.

(16) (a) Doxsee, K. M.; Mouser, J. K. M. *Organometallics* **1990**, *9*, 3012−3014. (b) Doxsee, K. M.; Mouser, J. K. M. *Tetrahedron Lett.* **1991**, *32*, 1687−1690. (c) Pappas, I.; Chirik, P. J. *Polyhedron* **2014**, *84*, 67−73.

(17) Burk, M. J.; Staley, D. L.; Tumas, W. *J. Chem. Soc., Chem. Commun.* **1990**, *11*, 809.

(18) Kalyani, D.; Sanford, M. S. *Org. Lett.* **2005**, *7*, 4149−4152.

(19) Bailey, B. C.; Huffman, J. C.; Mindiola, D. J. *J. Am. Chem. Soc.* **2007**, *129*, 5302−5303.

Downloaded by STOCKHOLM UNIV on September 8, 2015 | http://pubs.acs.org
Publication Date (Web): August 26, 2015 | doi: 10.1021/acs.organomet.5b00470

DOI: 10.1021/acs.organomet.5b00470
Organometallics XXXX, XXX, XXX−XXX