ORGANIC LETTERS

2009
Vol. 11, No. 15
3274−3277

A New Route to Acyclic Diaminocarbenes via Lithium−Halogen Exchange

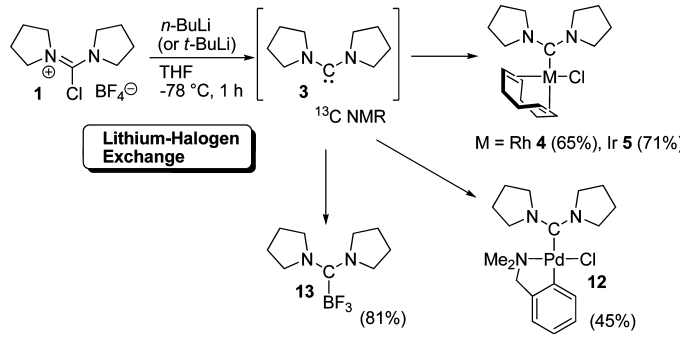
David R. Snead, Ion Ghiviriga, Khalil A. Abboud, and Sukwon Hong*

Department of Chemistry, University of Florida, P. O. Box 117200, Gainesville, Florida 32611-7200

sukwon@ufl.edu

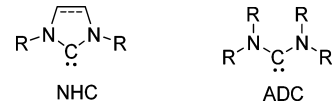
Received April 17, 2009

ABSTRACT



A lithium−halogen exchange route has been developed to generate acyclic diaminocarbenes (ADC) from chloroamidinium salts. Convenient access to various ADC complexes (B, Rh, Ir, Pd) stems from a one-pot transmetalation protocol. Formation of a carbenoid species is suggested by 1D and 2D NMR studies with a ^{13}C-labeled chloroamidinium precursor and also by X-ray structures of transition metal−carbene complexes. Rh-ADC complex 4 is an effective catalyst for the 1,2-addition of aryl boronic acids to aryl aldehydes.

N-Heterocyclic carbenes (NHCs) have emerged as important ancillary ligands[1] as well as nucleophilic organocatalysts[2] as a result of their highly σ-donating capacity. In contrast, acyclic diaminocarbenes (ADCs) have received much less attention despite several interesting properties.[3−7] ADCs are more electron-donating than NHCs,[4] and furthermore they impose greater steric demands owing to substantially larger N−C−N bond angles (121.0° vs 104.7°).[3c]



The paucity of ADCs may be attributed to the more challenging preparation of acyclic carbenes and ADC-metal complexes (Figure 1A).[3−6] For example, intermolecular formamidinium ion formation often gives low yield along with byproduct,[3b] and stronger bases such as LDA are required to deprotonate a less acidic formamidinium proton.[3,4,7] Therefore, new alternative routes have been developed to prepare ADC-metal complexes. Slaughter reported formation of bidentate, Chugaev-type ADC-metal complexes

(1) (a) Hahn, F. E.; Jahnke, M. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 3122–3172. (b) Glorius, F. *Top. Organomet. Chem.* **2007**, *21*, 1–20. (c) Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Angew. Chem., Int. Ed.* **2007**, *46*, 2768–2813. (d) *N-heterocyclic Carbenes in Synthesis*; Nolan, S. P., Ed.; Wiley-VCH: Weinheim, Germany, 2006. (e) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290–1309.

(2) (a) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988–3000. (b) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606–5655.

(3) (a) Alder, R. W.; Blake, M. E.; Chaker, L.; Harvey, J. N.; Paolini, F.; Schütz, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 5896–5911. (b) Alder, R. W.; Blake, M. E.; Bufali, S.; Butts, C. P.; Orpen, A. G.; Schütz, J.; Williams, S. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1586–1593. (c) Alder, R. W.; Allen, P. R.; Murray, M.; Orpen, A. G. *Angew. Chem., Int. Ed.* **1996**, *35*, 1121–1123. Recent review: (d) Vignolle, J.; Cattoën, X.; Bourissou, D. *Chem. Rev.* Published ASAP (DOI: 10.1021/cr800549j).

10.1021/ol9013156 CCC: $40.75
Published on Web 07/08/2009

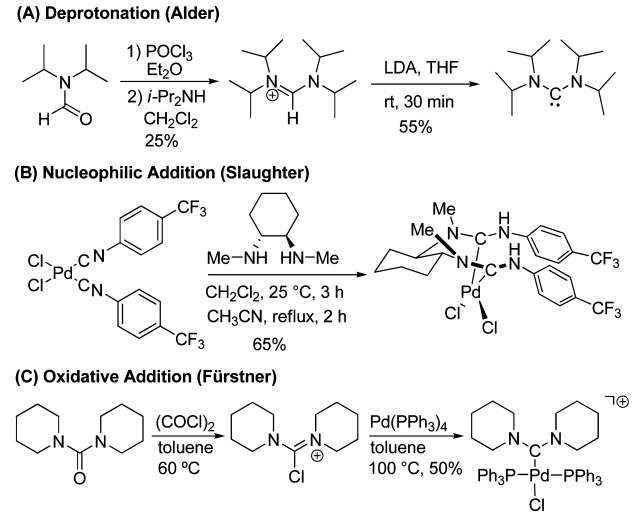
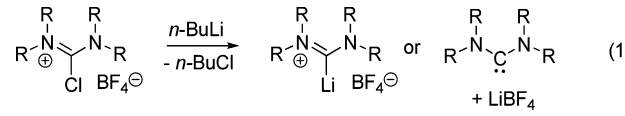


Figure 1. Routes to acyclic diaminocarbenes.

by nucleophilic addition of either hydrazines or amines to metal-bound isocyanides (Figure 1B),[5] and Fürstner demonstrated that monodentate ADC-Pd complexes can be prepared via oxidative addition of $(Ph_3P)_4Pd$ into the C−Cl bond of chloroamidinium ion precursors (Figure 1C).[6] However, this route to carbenes requires the use and incorporation of phosphine into metal catalyst, limiting the applicability.

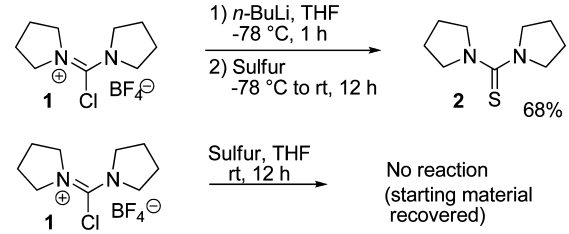
We envisioned that, when applied to chloroamidinium precursors, lithium−halogen exchange might provide a new and general route to diaminocarbenes (eq 1). Organolithium reagents have played an important role in organic synthesis,[8] and the formation of these reagents proceeds through a number of routes including reduction with metallic lithium,[9] deprotonation with a lithiated base,[10] lithium−halogen exchange,[11] and transmetalation.[12] It is important to note that lithiation has been speculated to generate carbenoid intermediates in reaction with R_2CBr_2[13] and in the Fritsch−Buttenberg−Wiechell rearrangement.[14] Nevertheless, to the best of our knowledge, there have been no examples using lithium−halogen exchange to form diaminocarbenes from chloroamidiniums. Recently, our group discovered that ADC-Cu complexes can be generated in situ from chloroamidinium **1** and Cu(I)-thiophenecarboxylate in the presence of Grignard reagents.[15] Herein, we report a more general lithium−halogen exchange route to acylic diaminocarbenes and convenient one-pot transmetalation to various metal-ADC species.



(1)

First, access to the carbene intermediate through lithium−halogen exchange was probed. Intercept of a carbene intermediate with sulfur to form a thiourea can be taken as simple proof of carbene generation (Scheme 1).[16] We were

Scheme 1. Proof of Carbene Intermediacy



pleased to isolate thiourea **2** in 68% yield when the organolithium intermediate was treated with elemental sulfur. Without lithium−halogen exchange no thiourea was formed.

In addition, the carbene intermediacy is further supported by low-temperature ^{13}C NMR studies with ^{13}C-labeled chloroamidinium precursor **1′**. After treatment of chloroamidinium **1′** with *n*-BuLi at −78 °C in THF-d_8, a characteristic ADC resonance at 233 ppm[17] was observed at −30 °C, suggesting the generation of a carbene species.[18] In the 2D gHMBC spectrum, the carbene carbon (232.9 ppm) displayed couplings with two protons at 3.47 and 3.66 ppm (Figure 2). The gDQCOSY spectrum

(4) (a) Frey, G. D.; Herdtweck, E.; Herrmann, W. A. *J. Organomet. Chem.* **2006**, *691*, 2465–2478. (b) Frey, G. D.; Herrmann, W. A. *J. Organomet. Chem.* **2005**, *690*, 5876–5880. (c) Herrmann, W. A.; Öfele, K.; Preysing, D. V.; Herdtweck, E. *J. Organomet. Chem.* **2003**, *684*, 235–248. (d) Denk, K.; Sirsch, P.; Herrmann, W. A. *J. Organomet. Chem.* **2002**, *649*, 219–224.

(5) (a) Wanniarachchi, Y. A.; Kogiso, Y.; Slaughter, L. M. *Organometallics* **2008**, *27*, 21–24. (b) Wanniarachchi, Y. A.; Slaughter, L. M. *Chem. Commun.* **2007**, 3294–3296. (c) Moncada, A. I.; Manne, S.; Tanski, J. M.; Slaughter, L. M. *Organometallics* **2006**, *25*, 491–505.

(6) (a) Kremzow, D.; Seidel, G.; Lehmann, C. W.; Fürstner, A. *Chem.−Eur. J.* **2005**, *11*, 1833–1853. (b) Arduengo, A. J., III.; Tapu, D.; Marshall, W. J. *J. Am. Chem. Soc.* **2005**, *127*, 16400–16401. (c) Fürstner, A.; Seidel, G.; Kremzow, D.; Lehmann, C. W. *Organometallics* **2003**, *22*, 907–909. (d) McGuinness, D. S.; Cavell, K. J.; Yates, B. F.; Skelton, B. W.; White, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 8317–8328.

(7) (a) Rosen, E. L.; Sanderson, M. D.; Saravanakumar, S.; Bielawski, C. W. *Organometallics* **2007**, *26*, 5774–5777. (b) Dhudshia, B.; Thadani, A. N. *Chem. Commun.* **2006**, 668–670.

(8) *The Chemistry of Organolithium Compounds*; Rappoport, Z.; Marek, I., Eds.; John Wiley and Sons Ltd.: Chichester, England, 2004; Parts 1 and 2 of Vol. 2.

(9) (a) Najera, C.; Sansano, J. M.; Yus, M. *Tetrahedron* **2003**, *59*, 9255–9303. (b) Yus, M. *Chem. Soc. Rev.* **1996**, 155–161.

(10) (a) Anctil, E. J.; Snieckus, V. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., DiederichF., Eds.; Wiley-VCH: Weinheim, Germany 2004; pp 761−813. (b) Beak, P.; Johnson, T. A.; Kim, D. D.; Lim, S. H. *Top. Organomet. Chem.* **2003**, *5*, 139–176.

(11) (a) Bailey, W. F.; Patricia, J. J. *J. Organomet. Chem.* **1988**, *352*, 1–46. (b) Jones, R. G.; Gilman, H. In *Organic Reactions*; Adams, R., Ed.; Wiley: New York, 1951; Vol. 6, pp 339−366.

(12) Pereyre, M.; Quintard, J.-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworths: Stoneham, 1986.

(13) (a) Köbrich, G.; Fischer, R. H. *Tetrahedron* **1968**, *24*, 4343–4346. (b) Dilling, W. L.; Edamura, F. Y. *J. Org. Chem.* **1967**, *32*, 3492–3499.

(14) (a) Luu, T.; Morisaki, Y.; Cunningham, N.; Tykwinski, R. R. *J. Org. Chem.* **2007**, *72*, 9622–9629. (b) Fritsch, P. *Liebigs Ann. Chem.* **1894**, *279*, 319–323. (c) Buttenberg, W. P. *Liebigs Ann. Chem.* **1894**, *279*, 324–337. (d) Wiechell, H. *Liebigs Ann. Chem.* **1894**, *279*, 337–344.

(15) Hirsch-Weil, D.; Snead, D. R.; Inagaki, S.; Seo, H.; Abboud, K. A.; Hong, S. *Chem. Commun.* **2009**, 2475–2477.

(16) Arduengo, A. J., III. *Acc. Chem. Res.* **1999**, *32*, 913–921.

(17) Tapu, D.; Dixon, D. A.; Roe, C. *Chem. Rev.* **2009**, Published ASAP (DOI: 10.1021.cr800521g).

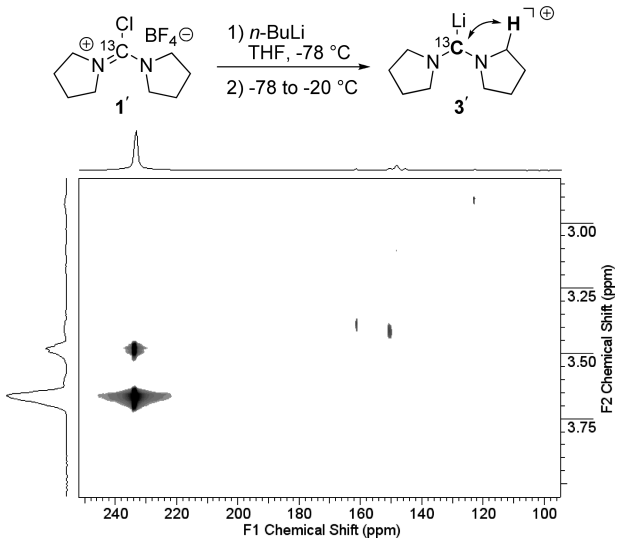


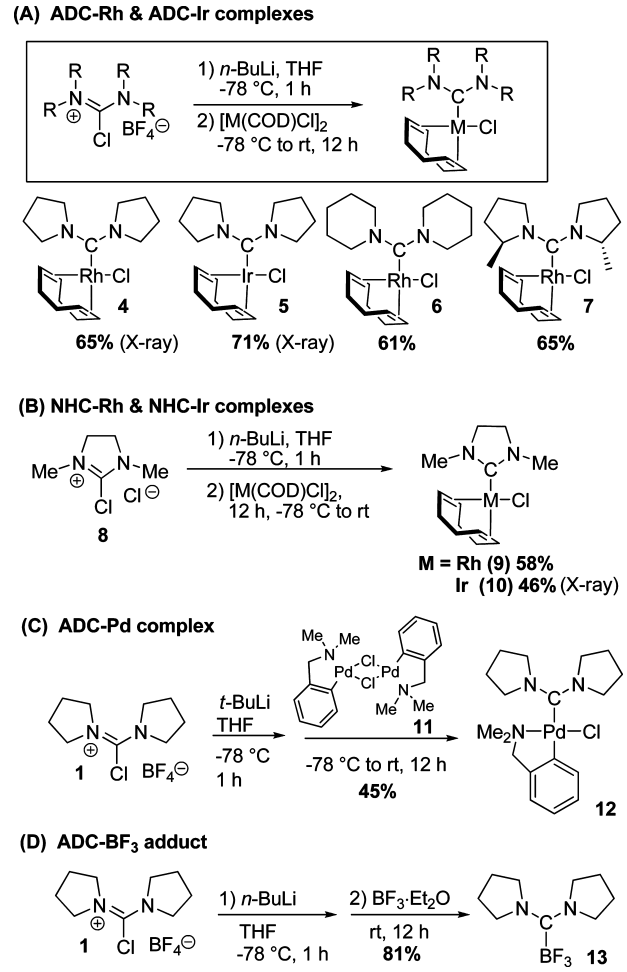
Figure 2. 2D gHMBC spectrum.

revealed the sequence 3.47−1.89−1.76−3.66. The carbons carrying these protons were detected in the gHMQC spectrum at 48.4, 26.5, 24.5, and 55.8 ppm, respectively.[19] Therefore, the two proton resonances at 3.47 and 3.66 ppm can be assigned to the two protons at the C2 position of pyrrolidine, and this gHMBC spectrum is consistent with the proposed carbene intermediate structure.

Encouraged by these results, we turned our attention to a potential transfer of the lithiocarbene to ADC-metal complexes. To our delight, various metal-carbene complexes were prepared in good yields through lithium−halogen exchange followed by one-pot transmetalation (Scheme 2). ADC ligands stemming from pyrrolidine and piperidine, as well as 2-methylpyrrolidine, were successfully introduced to Rh and Ir metal centers. When cyclic chloroimidazolidinium precursor **8** was used, NHC-Rh **9** and NHC-Ir **10** were isolated in reasonable yields. In addition, an ADC-Pd complex was prepared in 45% yield using palladacycle **11**[20] with *t*-BuLi. Interestingly, this carbene intermediate can also be trapped with a main group electrophile, BF_3, to form a highly stable Lewis acid-base adduct.[21] It is important to note that the lithium−halogen exchange protocol has allowed access to a variety of transition metal-carbene complexes as well as a main group adduct and does not necessitate the use of electron-rich metal precursors or the inclusion of phosphine ligands.

X-ray structures of ADC-Rh(COD)Cl **4** (Figure 3), ADC-Ir(COD)Cl **5**,[18] and NHC-Ir(COD)Cl **10**[18] provided unambiguous proof of the aforementioned methodology for

Scheme 2. Synthesis of Diaminocarbene−Metal Complexes via One-Pot Transmetalation



diaminocarbene-metal complexes. ADC-Rh(COD)Cl **4** exhibits a N−C−N carbene bond angle of 117.90°, whereas NHC-Ir(COD)Cl **10** has an angle of 108.6°. The pyrrolidine rings of the ADC exhibit a torsion angle of approximately 26°, which contrasts the flat nature of the heterocyclic ring in the NHC complex **10**. Ir-ADC complex **5** exhibits a longer carbene−Ir bond length of 2.045(5) Å as compared to a length of 2.028(7) Å for NHC-Ir **10**, which suggests the ADC is more sterically demanding.

Rh-ADC complex **4** proved effective in the 1,2-addition of aryl boronic acids to aryl aldehydes (Table 1).[22] Notably, ADC complex **4** gave yields higher than those of both an NHC complex and a diene complex (entries 1−3), indicating the potential of ADCs as an alternative to phosphine[23] or NHC[24] ligands. The reaction works well with various boronic acids (entries 3−7), if *ortho*-substituted aldehydes (entries 3−8) or electron-deficient aldehydes (entries 9 and 10) are used.

(18) See Supporting Information for details.
(19) The non-equivalence of the α positions in the pyrrolidine moiety indicates restricted rotation about the carbene C−N bond.
(20) Cope, A. C.; Friedrich, E. C. *J. Am. Chem. Soc.* **1968**, *90*, 909–913.
(21) Arduengo, A. J., III.; Davidson, F.; Krafczyk, R.; Marshall, W. J.; Schmutzler, R. *Monatsh. Chem.* **2000**, *131*, 251–265.
(22) (a) Miyaura, N. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 1535–1553. (b) Darses, S.; Genet, J.-P. *Chem. Rev.* **2008**, *108*, 288–325. (c) Schmidt, F.; Stemmler, R. T.; Rudolph, J.; Bolm, C. *Chem. Soc. Rev.* **2006**, *35*, 454–470.

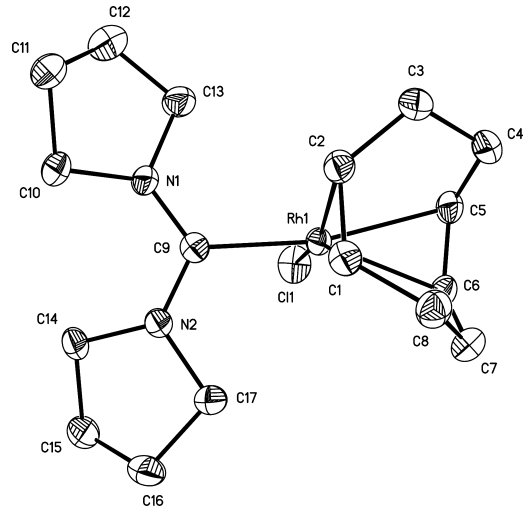


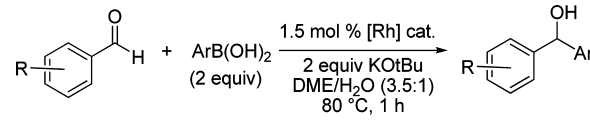
Figure 3. Molecular structure of complex **4**. Thermal ellipsoids are drawn at the 50% probability level. Selected bond lengths (Å) and angles (deg): Rh1−C9, 2.022(2); Rh1−Cl1, 2.3855(6); Rh1−C1, 2.110(2); Rh1−C2, 2.104(2); Rh1−C5, 2.241(2); Rh1−C6, 2.197(2); N1−C9−N2,117.90(18);N2−C9−N1−C10,25.68(32);N1−C9−N2−C14, 26.69(30).

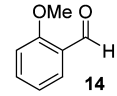
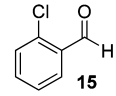
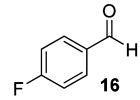
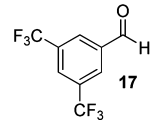
In summary, a lithium−halogen exchange route has been developed to generate acyclic diaminocarbenes from chloroamidinium salts. The one-pot transmetalation allows convenient access to various metal-ADC complexes. Generation of a lithiated carbene intermediate is suggested by NMR studies. The metal-carbene complexes were confirmed by X-ray. Rh-ADC complex **4** is an efficient catalyst for the 1,2-addition of aryl boronic acids to aryl aldehydes. Currently, further elaboration of this methodology to access other transition metal-carbene complexes as well as development of chiral ADC ligands are in progress in our laboratory.

(23) (a) Jagt, R. B. C.; Toullec, P. Y.; de Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *Org. Biomol. Chem.* **2006**, *4*, 773–775. (b) Duan, H.-F.; X., J.-H.; Shi, W.-J.; Zhang, Q.; Zhou, Q.-L. *Org. Lett.* **2006**, *8*, 1479–1481. (c) Pucheault, M.; Darses, S.; Genet, J.-P. *Chem. Commun.* **2005**, 4714–4716. (d) Sakai, M.; Ueda, M.; Miyaura, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 3279–3281.

(24) (a) Trindade, A. F.; Gois, P. M. P.; Veiros, L. F.; André, V.; Duarte, M. T.; Afonso, C. A. M.; Caddick, S.; Cloke, F. G. N. *J. Org. Chem.* **2008**, *73*, 4076–4086. (b) Imlinger, N.; Wurst, K.; Buchmeiser, M. R. *J. Organomet. Chem.* **2005**, *690*, 4433–4440. (c) Focken, T.; Rudolph, J.; Bolm, C. *Synlett* **2005**, 429–436. (d) Imlinger, N.; Mayr, M.; Wang, D.; Wurst, K.; Buchmeiser, M. R. *Adv. Synth. Catal.* **2004**, *346*, 1836–1843. (e) Fürstner, A.; Krause, H. *Adv. Synth. Catal.* **2001**, *343*, 343–350.

Table 1. ADC-Rh Catalyzed 1,2-Addition of Boronic Acids[a]



entry	aldehyde	$ArB(OH)_2$	[Rh] cat.	yield (%)[b]
1	 **14**	Ph	$[Rh(COD)Cl]_2$	62
2		Ph	**IMes-Rh**	80
3		Ph	**4**	92
4		1-Naphthyl	**4**	96
5		2-MeC_6H_4	**4**	92
6		4-FC_6H_4	**4**	83
7		4-$MeOC_6H_4$	**4**	83
8	 **15**	Ph	**4**	95
9	 **16**	Ph	**4**	87[c]
10	 **17**	Ph	**4**	41

[a] The reaction was conducted with 1.5 mol % of [Rh] (0.0075 mmol), KO*t*Bu (1 mmol), aldehyde (0.5 mmol), and boronic acid (1 mmol) in 1.95 mL of DME and 0.55 mL of H_2O. [b] Yield was taken as the average of multiple runs. [c] Reation time of 7 h. IMes-Rh = IMesRh(COD)Cl.

Acknowledgment. We thank the James & Esther King Biomedical Research Program and Florida Department of Health (08KN-04) for support of this research.

Supporting Information Available: Detailed synthetic procedures, analytical data for new compounds, and X-ray crystallographic data for **4**, **5**, and **10** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9013156