J|A|C|S
COMMUNICATIONS

Published on Web 11/09/2004

Expanding the Scope of C−H Amination through Catalyst Design

Christine G. Espino, Kristin Williams Fiori, Mihyong Kim, and J. Du Bois*

Department of Chemistry, Stanford University, Stanford, California 94305-5080

Received September 3, 2004; E-mail: jdubois@stanford.edu

Catalytic methods for intramolecular C−H bond amination are finding increased application in synthesis owing to their efficiency, predictable selectivity, and the value of the heterocycles produced (Figure 1).[1−3] To add further to the versatility of such processes, we have endeavored to gain mechanistic knowledge that could aid with the invention of new, robust catalyst systems. These efforts have culminated in the design and synthesis of $Rh_2(esp)_2$, a tethered dicarboxylate-derived complex that shows superior catalytic activity for intramolecular C−H oxidation with sulfamate, sulfamide, and urea substrates. Of added note, the marked performance of $Rh_2(esp)_2$ has allowed us to delineate effective protocols for the intermolecular conversion of C−H bonds to C−N centers. Collectively, such findings advance C−H amination as a general tool for the construction of nitrogen-containing structures.

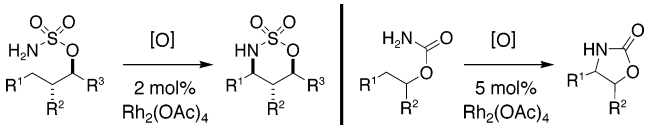


Figure 1. Rh-catalyzed oxidation of sulfamate and carbamate esters.

An understanding of the reaction mechanism for Rh-promoted nitrene insertion is of principal importance for further development of such processes. Our investigation thus far has provided direct evidence that the dinuclear Rh catalyst undergoes structural changes within minutes of initiating the reaction.[4] The inclusion of MgO or other soluble bases (e.g., 2,6-di-*tert*-butylpyridine) seemed to have little effect in preventing speciation of the Rh complex. Tetracarboxylate Rh dimers, while stable to many conditions, including strong acid, participate freely in ligand exchange reactions.[5] We hypothesized that carboxylate detachment from the dinuclear Rh core was responsible for catalyst degradation. Accordingly, the joining of two carboxylate ligands through an appropriately spaced linker would confer added stability to these complexes.[6] In the event that carboxylate shifts were to occur, the chelate effect would disfavor complete ligand dissociation from the metal centers.[7] Such strategies for catalyst design are inspired by the inventive work of Taber and Davies for Rh-mediated diazodecomposition reactions.[8,9]

m-Benzenedipropionic acid **1** was selected for exploratory studies as this ligand had been shown to exchange with $Rh_2(O_2CCF_3)_4$ to give $Rh_2(mbdp)(O_2CCF_3)_2$ **2** (Scheme 1).[8,10] In our hands, however, **2** proved catalytically inactive for C−H amination with sulfamates. Attempts to replace the two trifluoroacetate groups in the Taber complex with a second *m*-benzenedipropionate were unsuccessful, affording only intractable polymeric materials. We reasoned that substitution of the methylene groups in **1** would confer some degree of preorganization to an otherwise conformationally unconstrained ligand.[6] The tetramethylated *m*-benzenedipropionic acid **4** was identified and could be conveniently accessed in gram quantities from the commercial xylene dichloride **3**. Substitution of this dicarboxylate onto $Rh_2(O_2CCF_3)_4$ proceeded with remarkable facility and afforded the desired $Rh_2(esp)_2$ complex in 64% yield

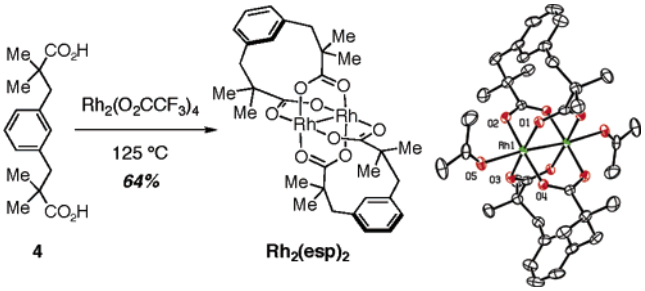
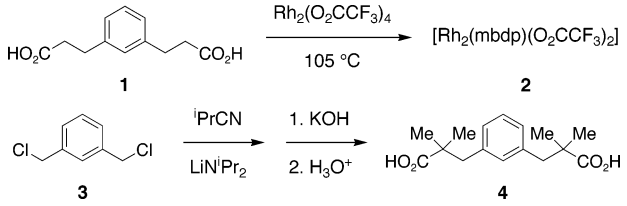


Figure 2. Preparation and X-ray analysis of $[Rh_2(esp)_2 \cdot (acetone)_2]$.

Scheme 1



(Figure 2).[11] Ligand metathesis has been conducted routinely on 300 mg of the starting trifluoroacetate dimer, and the desired complex is readily isolated by chromatography on silica gel. Single-crystal X-ray analysis of $Rh_2(esp)_2$ confirmed an initial structural assignment based on ^1H NMR and mass spectrometry. The ORTEP diagram shows the *m*-xylene spacer to be an optimal bridge for the two carboxylate moieties. Additionally, two acetone solvent molecules are coordinated in axial positions along the Rh−Rh vector, the site at which it is assumed substrate binding and oxidation occur.

$Rh_2(esp)_2$ has proven to be an exceptionally effective and general catalyst for C−H amination. Nitrene insertion of substrates possessing 3° C−H bonds (e.g., **5**) may be conducted at catalyst loadings as low as 0.15 mol %; quantitative conversion of starting material to product is observed (Figure 3). By contrast, reaction of sulfamate **5** using the isosteric $Rh_2(O_2C^tBu)_4$ complex (0.15 mol %) furnishes only 20% of the desired heterocycle. Considerable benefit is gained from $Rh_2(esp)_2$ for oxidation of substrates having unactivated methylene units. In one such example, a 1 mol % charge of $Rh_2(esp)_2$ is sufficient for the complete reaction of *n*-butylsulfamate **7**. It should be noted that sulfamates exemplified by **7** offer perhaps the most stringent test for new catalysts as such compounds have proven to be among the most difficult for efficient oxidation.[1a,b,12] Accordingly, five times as much $Rh_2(O_2C^tBu)_4$ must be used with **7** to reach only moderate levels of oxathiazinane formation (∼75%).[13]

The dramatic improvement in catalyst activity witnessed with $Rh_2(esp)_2$ and sulfamates extends to alternative substrate types. For the first time, we are able to effect high yields of heterocyclic product formation with urea **9** and sulfamide **11** starting materials (Figure 4).[14] Such reactions afford a direct synthesis of 1,2- and 1,3-diamine derivatives from easily accessible starting materials.[15]

10.1021/ja0446294 CCC: $27.50

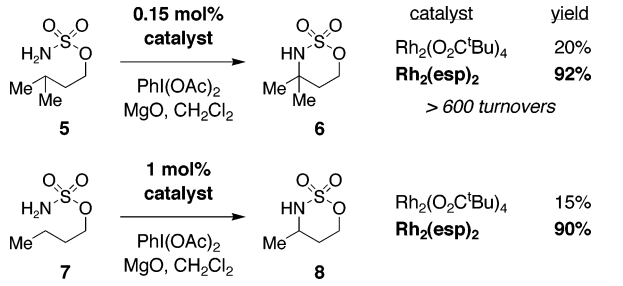


Figure 3. Comparative data of $Rh_2(esp)_2$ and $Rh_2(O_2C^tBu)_4$ as catalysts for intramolecular C−H amination with sulfamates.

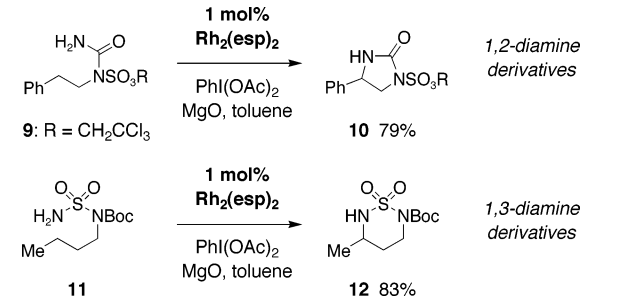


Figure 4. Oxidative cyclization of urea and sulfamide substrates.

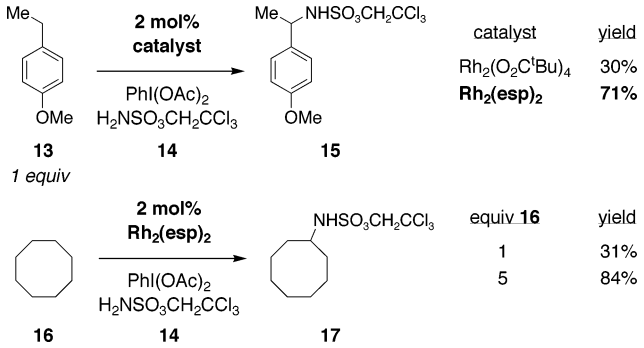


Figure 5. Intermolecular C−H insertion with catalytic $Rh_2(esp)_2$.

Encouraged by the performance of $Rh_2(esp)_2$ for intramolecular C−H amination, a preliminary examination was made of the corresponding intermolecular oxidation reaction (Figure 5). Prior reports of such processes using Mn, Fe, Ru, Rh, and Cu complexes suffer from low product conversions and/or a requirement for excess substrate (5−100 equiv).[1,3,16] By employing trichloroethylsulfamate **14** as the N-atom source,[17] we have found that 2 mol % $Rh_2(esp)_2$ is sufficient to convert 1 equiv of ethylanisole **13** to the aminated product **15** in 71% yield. Higher yields of **15** (84%) may be obtained with 2 equiv of substrate. Similar findings have been recorded for C−H insertion with cyclooctane **16**. These results stand in contrast to intermolecular experiments performed with 2 mol % $Rh_2(O_2C^tBu)_4$, which gives at best 20% yield of insertion product **17** when 5 equiv of cyclooctane is employed.

Guided by mechanistic postulates and prior art, we have prepared and characterized $Rh_2(esp)_2$, a novel catalyst for C−H amination reactions that operates with uncommon activity. Despite the nonrigid nature of the tethered dicarboxylate ligand, $Rh_2(esp)_2$ assembles in high yield and is considerably more resilient as a catalyst than its mono-carboxylate counterpart. The invention of dimeric Rh structures based on analogous ligand designs should further enable methods for both intra- and intermolecular C−H amination.

Acknowledgment. The authors thank X. Ottenwaelder and X. Xie for performing the X-ray crystallographic analysis. C.G.E. and K.W.F. gratefully acknowledge the National Science Foundation for pre-doctoral awards. C.G.E. is also the recipient of graduate fellowships from Pfizer and the ACS Division of Organic Chemistry, sponsored by Merck Research Laboratories. This work has been supported by a grant from the NSF (CHE-0110362) and through generous gifts from Abbott, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Glaxo-SmithKline, Merck, Pfizer, and Roche.

Supporting Information Available: Experimental protocols for the preparation of $Rh_2(esp)_2$ and all reactions performed with this catalyst are included along with analytical and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For recent reviews on C−H amination, see: (a) Dauban, P.; Dodd, R. H. *Synlett* **2003**, 1571−1586. (b) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, and 2905−2920.
(2) (a) Espino, C. G.; Du Bois, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 598−600. (b) Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935−6936. (c) Wehn, P. M.; Du Bois, J. *J. Am. Chem. Soc.* **2002**, *124*, 12950−12951. (d) Wehn, P. M.; Lee, J.; Du Bois, J. *Org. Lett.* **2003**, *5*, 4823−4826. (e) Hinman, A.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510−11511. (f) Fiori, K. W.; Fleming, J. J.; Du Bois, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 4349−4352.
(3) (a) Yu, X.-Q.; Huang, J.-S.; Zhou, X.-G.; Che, C.-M. *Org. Lett.* **2000**, *2*, 2233−2236. (b) Au, S.-M.; Huang, J.-S.; Che, C.-M.; Yu, W.-Y. *J. Org. Chem.* **2000**, *65*, 7858−7864. (c) Liang, J.-L.; Huang, J.-S.; Yu, X.-Q.; Zhu, N.; Che, C.-M. *Chem.—Eur. J.* **2002**, *8*, 1563−1572. (d) Liang, J.-L.; Yuan, S.-X.; Huang, J.-S.; Che, C.-M. *J. Org. Chem.* **2004**, *69*, 3610−3619.
(4) Espino, C. G.; Brodsky, B. H.; Kim, M.; Du Bois, J. Manuscript in preparation.
(5) Doyle, M. P.; Ren, T. *Prog. Inorg. Chem.* **2001**, *49*, 113−168 and references therein.
(6) For a discussion on the kinetic stability of tethered dicarboxylate ligands for Rh^{2+} dimers, see: (a) Bickley, J.; Bonar-Law, R.; McGrath, T.; Singh, N.; Steiner, A. *New J. Chem.* **2004**, *28*, 425−433. Also see: (b) Gallagher, J. F.; Ferguson, G.; McAlees, A. J. *Acta Crystallogr.* **1997**, *C53*, 576−579. (c) Bonar-Law, R. P.; McGrath, T. D.; Singh, N.; Bickley, J. F.; Femoni, C.; Steiner, A. *J. Chem. Soc., Dalton Trans.* **2000**, 4343−4347.
(7) The effectiveness of the tethered dicarboxylate Rh dimers for carbene and nitrene transfer is consistent with a carboxylate shift mechanism recently suggested by Corey: Lou, Y.; Horikawa, M.; Kloster, R. A.; Hawryluk, N. A.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 8916−8918.
(8) Taber, D. F.; Meagley, R. P.; Louey, J. P.; Rheingold, A. L. *Inorg. Chim. Acta* **1995**, *239*, 25−28.
(9) (a) Davies, H. M. L. *Eur. J. Org. Chem.* **1999**, 2459−2469. (b) Davies, H. M. L.; Venkataramani, C. *Org. Lett.* **2003**, *5*, 1403−1406.
(10) This ligand has been shown to bridge a diferric complex: Beer, R. H.; Tolman, W. B.; Bott, S. G.; Lippard, S. J. *Inorg. Chem.* **1989**, *28*, 4557−4559.
(11) See Supporting Information for details.
(12) Cui, Y.; He, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 4210−4212.
(13) Espino, C. G. Ph.D. Thesis, Stanford University, Stanford, CA, 2004.
(14) Analogous reactions performed using $Rh_2(oct)_4$ or $Rh_2(O_2CCPh_3)_4$ afforded product yields below 40%. A full account of studies with urea and sulfamide substrates will be forthcoming.
(15) For alternative methods to cyclic sulfamides and applications thereof, see: (a) Nicolaou, K. C.; Longbottom, D. A.; Snyder, S. A.; Nalbanadian, A. Z.; Huang, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 3866−3870 and references therein. (b) Régaïnia, Z.; Winum, J.-Y.; Smaine, F.-Z.; Toupet, L.; Aouf, N.-E.; Montero, J.-L. *Tetrahedron* **2003**, *59*, 6051−6056.
(16) For representative papers, see: (a) Mahy, J. P.; Bedi, G.; Battioni, P.; Mansuy, D. *Tetrahedron Lett.* **1988**, *29*, 1927−1930. (b) Nägeli, I.; Baud, C.; Bernardinelli, G.; Jacquier, Y.; Moran, M.; Müller, P. *Helv. Chim. Acta* **1997**, *80*, 1087−1105. (c) Liang, J.-L.; Yuan, S.-X.; Chan, P. W. H.; Che, C.-M. *Org. Lett.* **2002**, *4*, 4507−4510. (d) Díaz-Requejo, M. M.; Belderraín, T. R.; Nicasio, M. C.; Trofimenko, S.; Pérez, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 12078−12079.
(17) We have employed **14** previously for intermolecular olefin aziridination reactions. For a convenient preparation, see: Guthikonda, K.; Du Bois, J. *J. Am. Chem. Soc.* **2002**, *124*, 13672−13673.

JA0446294