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Ligand-Induced Control of C−H versus Aliphatic C−C Migration Reactions of Rh Carbenoids

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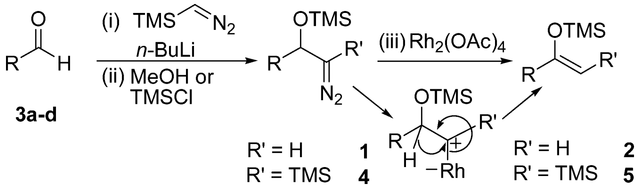
Dirhodium carboxylates and carboximidates have emerged as powerful and selective catalysts for many metal carbene transformations. They not only are highly efficient but also show exceptional versatility; by simply changing the ligands on rhodium, one can tune the reactivity of metal carbenes to favor either X−H insertion, C═C addition, or ylide formation.[1] One reaction that cannot be controlled by ligand tuning is the promotion of aliphatic 1,2-C−C migration over 1,2-C−H migration because, until now, C−H migration has always been the favored pathway.[2] We have now discovered the first examples where, by simply changing ligands on rhodium, the normally favored α-C−H migration pathway can be completely reversed and unprecedented α-C−C migration dominates instead.[3]

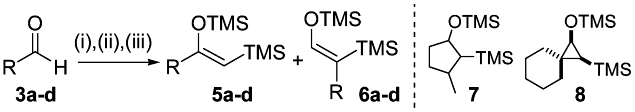
Our discovery emanated from our interest in the reaction of trimethylsilyldiazomethane with aldehydes. We recently reported a novel one-pot procedure for the synthesis of silyl enol ethers from aldehydes using lithiated trimethylsilyldiazomethane (LTMSD).[4] In this process, after addition of LTMSD and quenching with MeOH, an intermediate diazocompound **1** is generated, which upon treatment with $Rh_2(OAc)_4$ undergoes an α-C−H migration reaction to furnish the silyl enol ether **2** (Scheme 1). It occurred to us that, if we substituted MeOH with TMSCl, this would generate a silylated diazocompound **4**, which could, in principle, undergo the related 1,2-C−H migration reaction upon treatment with a suitable metal catalyst and furnish α-silyl silyl enol ethers **5**, a potentially very useful class of compounds.[5]

Scheme 1. One-Pot Procedure for the Synthesis of Silyl Enol Ethers

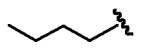
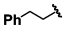
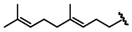
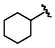


We began our investigations with dihydrocinnamaldehyde **3b**. However, reaction with LTMSD followed by quenching with TMSCl and treatment with $Rh_2(OAc)_4$ only furnished the diazocompound **4b**. Clearly, the α-silylated diazocompound **4b** generated was substantially more stable than **1** and therefore required more vigorous conditions for its decomposition.[6] After some experimentation, two protocols, A and B, were established to effect metal carbene formation followed by rearrangement. Method A involved replacement of THF by toluene and heating to 110 °C,[7] while method B involved using $Rh_2(tfa)_4$ at room temperature in place of $Rh_2(OAc)_4$. These two protocols were applied to four representative aldehydes **3a**−**d**,[8] and the results are summarized in Table 1. The use of $Rh_2(OAc)_4$ gave the expected 1,2-C−H migration reaction almost exclusively in the case of aldehydes **3a**−**c**, furnishing the silyl enol ether **5a**−**c** with high *Z* selectivity together with a small amount of 1,2-C−C migration product **6a**−**c** (entry 1). In the case of cyclohexanecarboxaldehyde **3d**, the 1,2-C−H insertion still dominated but now was accompanied by competitive 1,3-C−H insertion (entry 3).[9]

Table 1. Alkyl versus Hydride Migration in Rh-Catalyzed Decomposition of α-Silylated Diazocompounds



Conditions: (i) LTMSD, THF, -78 °C; (ii) TMSCl, -78 °C; (iii) Method A: $Rh_2(OAc)_4$, toluene, reflux.; Method B: $Rh_2(tfa)_4$, toluene, RT.

entry	R	method	products[a] 1,2-C-H (Z/E)[c]	 1,2-C-C (Z/E)[c]	 1,3-C-H /1,5-C-H	yield[b]
			**5a**	**6a**	**7**[d]	
1	**(3a)**	A	69 (93/7)	18 (81/19)	13	70
2		B	–	95 (82/18)	5	52
			5b	**6b**		
3		A	91 (97/3)	9 (84/16)	–	72
4	**(3b)**	B	–	100 (90/10)	–	56
			**5c**	**6c**		
5		A	93 (93/7)	7 (*Z* only)	–	69
6	**(3c)**	B	–	100 (85/15)	–	66
			**5d**	**6d**	**8**	
7		A	69 (94/6)	6 (86/14)	25	74
8	**(3d)**	B	–	44 (88/12)	56	57

[a] Ratios calculated by ^1H NMR of the crude reaction mixture. [b] Isolated yield after Kugelrohr distillation. [c] Assignment based on NOESY experiments on **5b** and **6b**. [d] Mixture of two diastereoisomers.

Using $Rh_2(tfa)_4$ in place of $Rh_2(OAc)_4$ resulted in a *dramatic and complete switch over from C−H migration to C−C migration* in all cases. These are the first examples of aliphatic C−C migration reaction competing and actually dominating over the normally facile C−H migration. Even in the case of substrates with the potential for facile 1,5-C−H insertion (**3a**) or facile C═C addition (**3c**), *the aliphatic C−C migration reaction completely dominated when using* $Rh_2(tfa)_4$. Cyclohexanecarboxaldehyde **3d** also gave no 1,2-C−H migration products at all; the products were wholly derived from 1,2-C−C migration and 1,3-C−H insertion (entry 4).

The distribution of products obtained from the different substrates and catalysts can be understood by considering the possible stereoelectronically required conformations for migration of the intermediate metal carbenes (Scheme 2).[10] We will initially consider reactions of the primary aliphatic aldehydes (e.g., **3a**) with $Rh_2(OAc)_4$. The ratio of products formed is dependent on the equilibrium populations of conformers **A**−**D** and the intrinsic rate constants for 1,2-C−H (large)/1,2-C−R (small)/1,3-C−H (small) migration/insertion reactions from the cognate conformer (Curtin−Hammett). Conformer **C** is likely to be the most populated as it suffers the least steric and electronic repulsions, but it is also the

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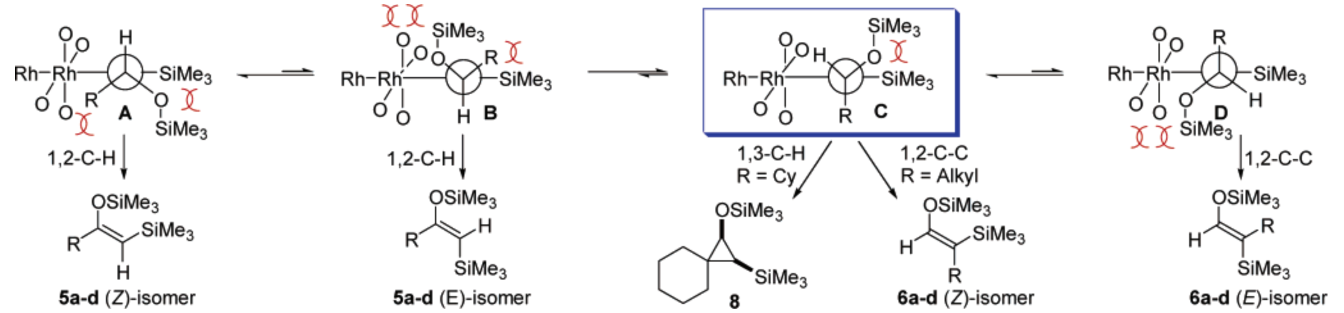
Scheme 2. Product Distribution in Rh-Catalyzed Decomposition of α-Silylated Diazocompounds



least reactive. In contrast, conformers **A** and **B** are the most reactive and can undergo very fast 1,2-C−H migration leading to *Z* and *E* silyl enol ethers **5a**, respectively. The high selectivity in favor of the *Z* isomer is because conformer **B** suffers combined steric and electronic repulsion (between the acetate ligands attached to rhodium and the oxygen of the silyl ether). In the case of the secondary substituted aldehyde **3d**, the increased bulk of the R group disfavors conformers **A** and **B** further, leading to increased populations of conformers **C** and **D**, of which **C** will dominate. The only pathways available to conformer **C** are 1,3-C−H insertion or 1,2-C−C migration, and now 1,3-C−H insertion, furnishing the cyclopropane **7**, begins to compete with the fast 1,2-C−H migration from the very minor conformer **A** giving **5d**.

The change in selectivity on going from $Rh_2(OAc)_4$ to $Rh_2(tfa)_4$ can be rationalized based on the increased electrophilicity of the Rh carbenoid,[11] which will lead to lower barriers for migration. If the barriers to migration are now lower than the barriers that interconvert conformations **A**−**D**, the product ratio will reflect the nascent population of the carbenoids (Curtin−Hammett principle not applicable). It can be reasonably expected that the most stable conformers of the carbenoid (**C** then **D**) are also those that are formed most easily, and these lead to the observed silyl enol ethers **6a**−**c** as *Z* (major)/*E* mixtures.

Interestingly, treatment of the diazocompound **1** ($R = Ph(CH_2)_2$) with either $Rh_2(OAc)_4$ or $Rh_2(tfa)_4$ at room temperature furnished silyl enol ether **2** derived wholly from C−H migration; no competing C−C migration was observed. Thus, it seems that the silyl group attached to the rhodium carbene exerts a profound effect on the chemoselectivity of the migration. The effect is most likely due to (i) the increased steric hindrance around the metal carbene, which affects the populations and barriers to their interconversion, of the stereoelectronically required conformations for migration, (ii) destabilization of the rhodium carbene by the silyl group (it stabilizes the diazocompounds but destabilizes the metal carbene as the carbon center of the carbene is strongly electrophilic[12]), promoting an earlier transition state, and (iii) the extent to which the product distribution is dominated by rates of migration/insertion reactions versus nascent conformer populations of the Rh carbenoids, a factor controlled by ligands on rhodium. With acetate ligands on rhodium, product distribution is controlled by rates of migration/insertion (late transition state), while with trifluoroacetate ligands, product distribution is controlled by conformer populations[13] (early transition state).

In summary, we have developed a new and convenient synthesis of α-silyl silyl enol ethers from aldehydes and trimethylsilyldiazomethane in good yield and high stereoselectivity. More importantly, we have shown that, by tuning the ligands on rhodium, the normally favored C−H migration process can be completely reversed to favor C−C migration instead. This discovery adds to the rich history associated with tuning chemoselectivity of rhodium carbenoid reactions through choice of ligands on Rh.

Acknowledgment. We gratefully thank the EPSRC and GlaxoSmithKline for a CASE Award to C.G.S., and we thank Merck and Pfizer for unrestricted support. We thank Prof. Guy Lloyd-Jones and Dr. Jeremy Harvey for useful discussions.

Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Doyle, M. P.; Loh, K.-L.; DeVries, K.; Chinn, M. S. *Tetrahedron Lett.* **1987**, *28*, 833. (b) Padwa, A.; Austin, D. J.; Hornbuckle, S. F.; Semones, M. A.; Doyle, M. P.; Protopova, M. N. *J. Am. Chem. Soc.* **1992**, *114*, 1874. (c) Padwa, A.; Austin, D. J.; Price, A. T.; Semones, M. A.; Doyle, M. P.; Protopova, M. N.; Winchester, W. R.; Tran, A. *J. Am. Chem. Soc.* **1993**, *115*, 8669. For reviews see: (d) Padwa, A.; Austin, D. J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1797. (e) Doyle, M. P.; Ren, T. In *Progress in Inorganic Chemistry*; Karlin, K. D., Ed.; John Wiley & Sons: New York, 2001; Vol. 49, p 113. (f) Merlic, C. A.; Zechman, A. L *Synthesis* **2003**, 1137.

(2) (a) Pellicciari, R.; Fringuelli, R.; Ceccherelli, R.; Sisani, E. *J. Chem. Soc., Chem. Commun.* **1979**, 959. (b) Miyauchi, K.; Hori, K.; Hirai, T.; Takebayashi, M.; Ibata, T. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2142. (c) Hudlicky, T.; Olivo, H. F.; Natchus, M. G.; Umpierrez, E. F.; Pandolfi, E.; Volonterio, C. *J. Org. Chem.* **1990**, *55*, 4767. (d) Taber, D. F.; Herr, R. J.; Pack, S. K.; Geremia, J. M. *J. Org. Chem.* **1996**, *61*, 2908. Small amounts of α-C−C migration (3−17%) have been reported with metal-free isopropylcarbene: (e) Mansoor, A. M.; Stevens, I. D. R. *Tetrahedron Lett.* **1966**, *7*, 1733.

(3) The 1,2-C−C migrations of metal carbenes have been observed when no other competing processes are possible: (a) Padwa, A.; Hornbuckle, S. F.; Zhang, Z.; Zhi, L. *J. Org. Chem.* **1990**, *55*, 5297. (b) Ye, T.; McKervey, A. *Tetrahedron* **1992**, *48*, 8007.

(4) (a) Aggarwal, V. K.; Sheldon, C. G.; Macdonald, G. J.; Martin, W. P. *J. Am. Chem. Soc.* **2002**, *124*, 10300. (b) Reactions with commercial TMSD were very much lower yielding than TMSD made by us using the procedure described by Shioiri: Shioiri, T.; Aoyama, T.; Mori, S. *Org. Synth.* **1990**, *68*, 1.

(5) (a) Hosomi, A.; Hayashida, H.; Tominaga, Y. *J. Org. Chem.* **1989**, *54*, 3254. (b) Duhamel, L.; Gralak, J.; Bouyanzer, A. *Tetrahedron Lett.* **1993**, *34*, 7745.

(6) (a) Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1989**, *37*, 2261. (b) Mardsen, S. P.; Pang, W.-K. *Tetrahedron Lett.* **1998**, *39*, 6077.

(7) The $Rh_2(OAc)_4$-catalyzed decomposition of **4b** at room temperature in either THF or toluene only gave recovery of starting material.

(8) Pivaldehyde was also examined, but the intermediate diazocompound related to **4** was too stable and did not decompose under either protocol A or B.

(9) The formation of cyclopropanes via 1,3-C−H insertion when competitive 1,2-C−H migration is also possible has recently been reported: Shi, W.; Zhang, B.; Zhang, J.; Liu, B.; Zhang, S.; Wang, J. *Org. Lett.* **2005**, *7*, 3103−3106.

(10) Nickon, A. *Acc. Chem. Res.* **1993**, *26*, 84.

(11) For a discussion of early/late TS with different ligands on Rh, see: (a) Taber, D. F.; Hennessy, M. J.; Louey, J. P. *J. Org. Chem.* **1992**, *57*, 436−441. (b) Taber, D. F.; Joshi, P. V. *J. Org. Chem.* **2004**, *69*, 4276−4278.

(12) Nakamura, E.; Yoshikai, N.; Yamanaka, M. *J. Am. Chem. Soc.* **2002**, *124*, 7181−7192.

(13) For an example of where substrate comformation dominates over electronic effects of ligands on Rh in primary/secondary C−H insertion, see: Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Person, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958.

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