J|A|C|S
COMMUNICATIONS

Published on Web 10/01/2002

Non-Carbonyl-Stabilized Metallocarbenoids in Synthesis: The Development of a Tandem Rhodium-Catalyzed Bamford−Stevens/Thermal Aliphatic Claisen Rearrangement Sequence

Jeremy A. May and Brian M. Stoltz*

Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125

Received August 5, 2002

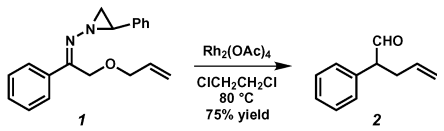
Of the transformations available to synthetic chemists, the Claisen rearrangement arguably stands alongside the Diels−Alder and aldol reactions as one of the most powerful, well-characterized, and elegant protocols for the construction of carbon−carbon bonds.[1] The ability to control and predict stereochemical issues in these reactions, and the acceleration of all three reactions with Lewis acid catalysis, has led to significant accomplishments in the area of asymmetric synthesis.[2] Although numerous modifications to the Claisen rearrangement exist, the classic allylic enol ether variant is often overlooked due to the difficulty associated with the stereoselective preparation of allylic enol ethers as a single stereoisomer. In particular, the (*Z*)-isomer has proven exceptionally challenging to access reliably. In conjunction with a general program aimed toward the preparation and utilization of non-carbonyl-stabilized diazo compounds,[3] we have discovered a novel generation of such acyclic (*Z*)-enol ethers via rhodium-catalyzed elimination of diazo alkanes prepared in situ from *N*-aziridinyl imines.[4] Additionally, we have found that in the case of allylic enol ethers, a subsequent thermal Claisen rearrangement occurs in good yield and with high levels of diastereoselectivity. The result is the development of a highly stereoselective tandem rhodium-catalyzed Bamford−Stevens/Claisen reaction (Scheme 1).[5,6]

As a general method to prepare non-carbonyl-stabilized diazo compounds in situ, we chose to investigate the decomposition of *N*-aziridinyl imines (also known as Eschenmoser hydrazones) in the presence of standard rhodium(II) catalysts.[7,8] This overall transformation would potentially render any ketone as a carbenoid precursor.[9] To test for the influence of Rh(II) catalysts on the in situ generated non-carbonyl-stabilized diazo compound, we carried out a control experiment on hydrazone **3a**. As illustrated in Scheme 2, discrete reaction pathways were observed in the presence or absence of the $Rh_2(OAc)_4$ catalyst. Without catalyst, multiple decomposition products resulted from what would be considered highly reactive *carbene* chemistry. Alternatively, in the presence of $Rh_2(OAc)_4$, catalyst-mediated de-diazotization most likely produces a rhodium-carbenoid intermediate, which attenuates the reactivity of the species and results in a more selective *carbenoid* type reaction. In the particular case of hydrazone **3a**, a 1,2-hydride migration occurs to form enol ether **6a** in high yield and excellent stereoselectivity. These results are in full accord with previous examples of carbene and metallocarbenoid hydride migrations, wherein high levels of (*Z*)-olefin selectivity are also found.[10] Interestingly, it appears that the stereoselectivity observed is general across a range of substrates, including those that generate acyclic trisubstituted enol ethers (e.g., **6b**).

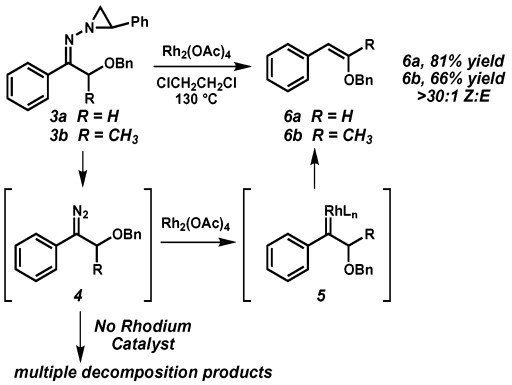
Having established the carbenoid reactivity profile of our in situ prepared diazo compounds, as well as the catalytic Bamford−Stevens elimination reaction, we turned our attention to the development of a conceptually novel tandem process. We reasoned that rhodium-mediated stereoselective hydride migration of the derived diazoalkane from an allyloxy hydrazone such as **1** would produce a 1,5-diene poised for Claisen rearrangement. To our delight, treatment of hydrazone **1** with $Rh_2(OAc)_4$ in 1,2-dichloroethane at 80 °C resulted in a tandem process proceeding via (A) thermal decomposition of the aziridine, (B) rhodium-mediated de-diazotization, (C) stereoselective 1,2-hydride migration (>20:1 *Z:E* selectivity), and finally (D) thermal aliphatic Claisen rearrangement (i.e., Scheme 1, **1** → **2**).[11]

With this new tandem process in hand, we have examined the scope of the rearrangement and found that the reaction is quite general (see Tables 1 and 2). The tandem sequence tolerates aromatic, alkyl, and alkenyl substitution adjacent to the hydrazone functionality. The allylic portion can be modified with numerous substituents that produce a wide range of Claisen products. In relevant cases, high levels of diastereoselectivity are generally observed, and the sense of stereoinduction is consistent with the intermediacy of a (*Z*)-enol ether proceeding through a chairlike transition state. For example, rearrangement of hydrazone **7** results in the formation of aldehyde **8** in greater than 20:1 anti:syn diastereoselectivity (Table 1, entry 1). In some cases (i.e., Table 1, entries 5 and 7), thermal Claisen rearrangement of the intermediate enol ether was sluggish; however, the rearrangement could be accelerated at low temperature (−40 °C) by addition of Me_2AlCl to the cooled reaction mixture.[12]

Scheme 1



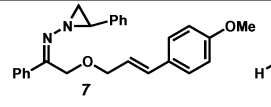
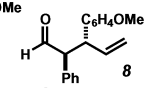
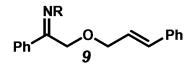
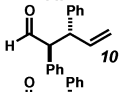
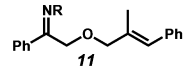
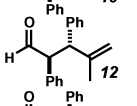
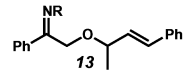
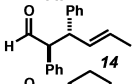
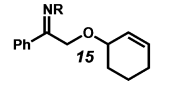
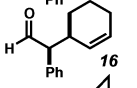
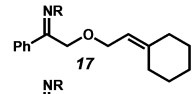
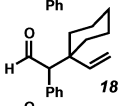
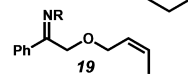
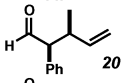
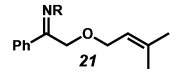
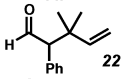
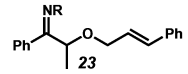
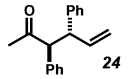
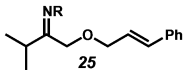
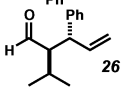
Scheme 2



* To whom correspondence should be addressed. E-mail: stoltz@caltech.edu.

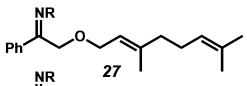
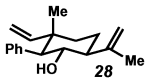
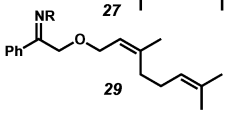
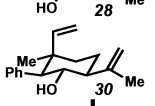
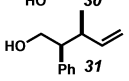
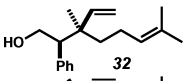
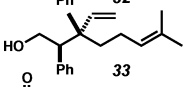
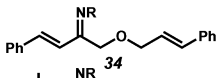
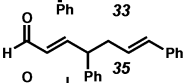
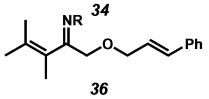
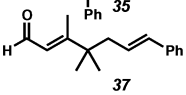
10.1021/ja028020j CCC: $22.00

Table 1. The Tandem Bamford−Stevens/Claisen Reaction[a]

entry	Substrate[b]	Product	Yield(dr)[c]
1	 **7**	 **8**	82% (>20:1)
2	 **9**	 **10**	87% (>20:1)
3	 **11**	 **12**	76% (3:1)
4	 **13**	 **14**	79% (>20:1)
5	 **15**	 **16**	72% (6:1)[d]
6	 **17**	 **18**	86%
7	 **19**	 **20**	63% (7:1)[d]
8	 **21**	 **22**	71%
9	 **23**	 **24**	72% (8:1)
10	 **25**	 **26**	73% (7:1)[e]

[a] $Rh_2(OAc)_4$ (1 mol %), $ClCH_2CH_2Cl$, 130 °C, 2−4 h. [b] R = NCH_2CHPh. [c] Diastereomer ratios determined by ^1H NMR of the crude reaction mixture. [d] Subsequent treatment with Me_2AlCl at −40 °C. [e] $Rh_2(OAc)_4$, NMP, 200 °C, 1 h.

Table 2. Cascade Reactions[a]

entry	Substrate[b]	Product	Yield(dr)[c]
1	 **27**	 **28**	68% (>20:1)[d]
2	 **29**	 **30**	63% (>20:1)[d]
3	**19**	 **31**	64% (9:1)[e]
4	**27**	 **32**	88% (>20:1)[e]
5	**29**	 **33**	78% (>20:1)[e]
6	 **34**	 **35**	62%
7	 **36**	 **37**	68%

[a] $Rh_2(OAc)_4$ (1 mol %), $ClCH_2CH_2Cl$, 130 °C, 2−8 h. [b] R = NCH_2CHPh. [c] Diastereomer ratios determined by ^1H NMR of the crude reaction mixture. [d] Subsequent treatment with Me_2AlCl at −40 °C. [e] Subsequent treatment with DIBAL at −40 °C.

In addition to the Bamford−Stevens/Claisen sequence, we have investigated a number of cascade reactions, wherein a third chemical step occurs after the initial tandem process. For instance, Lewis acid promotion of neryl and geranyl ethers **27** and **29** induces a cascade terminating in a carbonyl-ene reaction to produce the cyclohexanols **28** and **30** with excellent diastereoselectivity.[13] Alternatively, using reductive conditions (DIBAL, −40 °C) for the rearrangement of the intermediate (*Z*)-enol ethers furnished the corresponding unsaturated alcohol as the major product (Table 2, entries 3−5). Notably, α,β-unsaturated hydrazones **34** and **36** undergo a Bamford−Stevens/Claisen/Cope rearrangement cascade (entries 6 and 7) with excellent stereoselectivity observed for each example.[14]

In summary, we have developed a tandem rhodium-catalyzed Bamford−Stevens/Claisen rearrangement sequence. The method relies on the in situ generation and presumed catalytic interception of non-carbonyl-stabilized diazoalkanes to form (*Z*)-enol ethers with nearly complete stereoselectivity, thereby establishing a general route to the (*Z*)-isomer of simple acyclic Claisen enol ethers. Additionally, this work further establishes the utility and feasibility of generating rhodium carbenoids from ketones. We are currently investigating the scope and generality of such in situ generated non-carbonyl-stabilized rhodium carbenoids for other reactions including those involving asymmetric catalysis and chemically triggered Eschenmoser hydrazone equivalents.

Acknowledgment. The authors wish to thank the NSF (CHE-0135056), the Dreyfus Foundation, Merck Research Laboratories, and Abbott Laboratories for financial support.

Supporting Information Available: Experimental details and characterization data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Wipf, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, Chapter 7.2; p 827. (b) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423.
(2) Santelli, M.; Pons, J.-M. *Lewis Acids and Selectivity in Organic Synthesis*; CRC Press: New York, 1996.
(3) For alternative approaches, see: (a) Aggarwal, V. K.; Vicente, J.; Bonnert, R. V. *Org. Lett.* **2001**, *3*, 2785. (b) Doyle, M. P.; High, K. G.; Su-Min, O.; Osborn, A. K. *Tetrahedron Lett.* **1989**, *30*, 3049.
(4) (a) Felix, D.; Müller, R. K.; Horn, U.; Joos, R.; Schreiber, J.; Eschenmoser, A. *Helv. Chim. Acta* **1972**, *55*, 1276. For a recent review, see: (b) Kirmse, W. *Eur. J. Org. Chem.* **1998**, *2*, 201.
(5) (a) Bamford, W. R.; Stevens, T. S. *J. Chem. Soc.* **1952**, 4735. (b) Ojima, I.; Kondo, K. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1539.
(6) (a) For a thermal Bamford−Stevens reaction using an aziridinyl imine, see: Mohamadi, F.; Collum, D. B. *Tetrahedron Lett.* **1984**, *25*, 271. For Shapiro reactions of aziridinyl imines, see: (b) Maruoka, K.; Oishi, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 2289. (c) Evans, D. A.; Nelson, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 774.
(7) For an excellent monograph on the preparation and use of diazo carbonyl compounds, see: Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; Wiley & Sons: New York, 1998.
(8) *N*-aziridinyl imines in combination with catalysis have seen limited use. For examples, see: (a) Padwa, A.; Austin, D. J.; Gareau, Y.; Kassir, J. M.; Xu, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 2637. (b) Sarkar, T. K.; Ghorai, B. K. *J. Chem. Soc., Chem. Commun.* **1992**, 1184. (c) Fang, F. G.; Maier, M. E.; Danishefsky, S. J.; Schulte, G. *J. Org. Chem.* **1990**, *55*, 831.
(9) All hydrazones were prepared from the corresponding ketones. See the Supporting Information.
(10) (a) Taber, D. F.; Herr, R. J.; Pack, S. K.; Geremia, J. M. *J. Org. Chem.* **1996**, *61*, 2908. (b) Pirrung, M. C.; Hwu, J. R. *Tetrahedron Lett.* **1983**, *24*, 565. (c) See refs 3b and 8b.
(11) For an alternative rhodium carbenoid-initiated Claisen rearrangement, see: Wood, J. L.; Moniz, G. A.; Pflum, D. A.; Stoltz, B. M.; Holubec, A. A.; Dietrich, H.-J. *J. Am. Chem. Soc.* **1999**, *121*, 1748.
(12) (a) Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205. (b) Nonoshita, K.; Banno, H.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, *112*, 316. (c) Takai, K.; Mori, I.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 446.
(13) For a similar ene reaction, see: Corey, E. J.; Roberts, B. E.; Dixon, B. R. *J. Am. Chem. Soc.* **1995**, *117*, 193.
(14) For the Tandem Claisen Cope reaction, see: Ziegler, F. E.; Piwinski, J. J. *J. Am. Chem. Soc.* **1982**, *104*, 7181.

JA028020J