ORGANIC
LETTERS

2002
Vol. 4, No. 16
2743−2745

Catalytic Diastereoselective Reductive Claisen Rearrangement

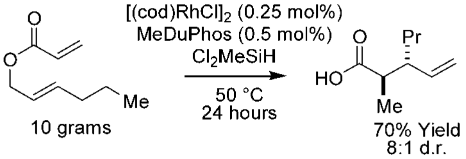
Steven P. Miller and James P. Morken*

Department of Chemistry, Venable and Kenan Laboratories, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-3290

morken@unc.edu

Received May 31, 2002

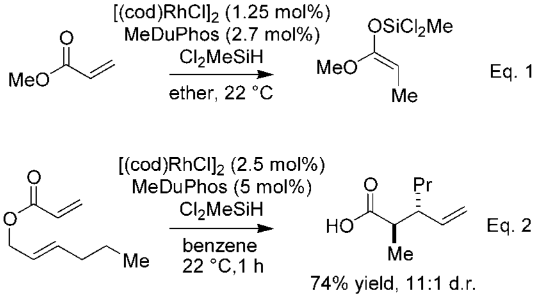
ABSTRACT



A catalytic amount of [(cod)RhCl]$_2$ and MeDuPhos initiates an ester enolate Claisen rearrangement with good yields and diastereocontrol. Reaction conditions are mild and tolerant of base-sensitive functionality.

The ester enolate Claisen rearrangement is a particularly powerful method for stereocontrolled carbon−carbon bond formation from simple achiral materials.[1] The transition state for the reaction is well understood such that prediction of the major product diastereomer is usually straightforward. One of the drawbacks to the ester enolate Claisen rearrangement is the requirement for enolate generation, which often requires treatment with strong base. As an alternative, investigations in our laboratories have centered on catalytic enolate generation techniques for use in carbon−carbon bond-forming reactions, specifically under mild conditions.[2] One example of this is the rhodium-MeDuPhos[3] catalyzed diastereoselective reductive aldol reaction, which we have determined proceeds through the intermediacy of *E*-silylketene acetals (eq 1, Scheme 1).[4b,e] We considered that similar enolate generation techniques might be used to access silylketene acetals that might then participate in an Ireland−

Scheme 1



---

[1] For excellent reviews, see: (a) Chai, Y.; Hong, S.; Linday, H. A.; McFarland, C.; McIntosh, M. C. *Tetrahedron* **2002**, *58*, 2905. (b) Wipf, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 5, p 827. (c) Blechert, S. *Synthesis* **1989**, 71. (d) Ziegler, F. E. *Acc. Chem. Res.* **1977**, 589. For examples of enantioselective ester enolate Claisen rearrangements, see: (e) Corey, E. J.; Lee, D. H. *J. Am. Chem. Soc.* **1991**, *113*, 4026. (f) Kazmaier, U.; Krebs, A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2012. (g) Kazmaier, U.; Mues, H.; Krebs, A. *Chem. Eur. J.* **2002**, *8*, 1850. For an example of an enantioselective acyl-Claisen rearrangement, see: (h) Yoon, T. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 2911. For an example of a catalytic enantioselective Claisen rearrangement, see: (i) Abraham, L.; Czerwonka, R.; Hiersemann, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 4700.

[2] (a) Mascarenhas, C. M.; Duffey, M. O.; Liu, S. Y.; Morken, J. P. *Org. Lett.* **1999**, *1*, 1427. (b) Taylor, S. J.; Morken, J. P. *J. Am. Chem. Soc.* **1999**, *121*, 12202. (c) Taylor, S. J.; Duffey, M. O.; Morken, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 4528. (d) Mascarenhas, C. M.; Miller, S. P.; White, P. S.; Morken, J. P. *Angew. Chem., Int. Ed.* **2001**, *40*, 601. (e) Zhao, C. X.; Taylor, S. J.; Bass, J.; Morken, J. P. *Org. Lett.* **2001**, *3*, 2839. (f) Zhao, C. X.; Duffey, M. O.; Taylor, S. J.; Morken, J. P. *Org. Lett.* **2001**, *3*, 1829.

[3] Me-DuPhos: 1,2-bis(dimethylphospholano)benzene. See: Burk, M. J.; Feaster, J. E.; Harlow, R. L. *Organometallics* **1990**, *9*, 2653.

[4] (a) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897. (b) Ireland, R. E.; Willard, A. K. *Tetrahedron Lett.* **1975**, *46*, 3975. (c) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. (d) Ireland, R. E.; Varney, M. D. *J. Am. Chem. Soc.* **1984**, *106*, 3668. (e) Ireland, R. E.; Wipf, P.; Armstrong, J. D. *J. Org. Chem.* **1991**, *56*, 650. (f) Ireland, R. E.; Wipf, P.; Xiang, J. N. *J. Org. Chem.* **1991**, *56*, 3572.

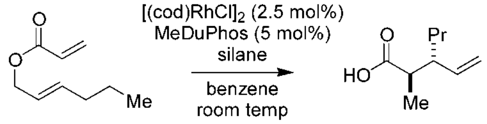
10.1021/ol026273b CCC: $22.00

Claisen ester enolate rearrangement.[4,5] In order for successful reaction outcome, there are two issues of critical concern. First, the rate of hydrosilation of the acrylate must be faster than that of the pendant alkene. Second, control of silylketene acetal geometry is crucial for control of reaction stereoselectivity.

On the basis of the precedent in the reductive aldol reaction described in eq 1, we attempted the reductive Ireland–Claisen rearrangement in eq 2. Our first experiments, using ether as the reaction solvent, were suboptimal, providing 8% yield and 7.3:1 stereoisomer ratio. A survey of reaction solvents found benzene to be superior to ether, CH_2Cl_2 (36%, 5.3:1 dr), THF (45%, 4.4:1 dr), toluene (54%, 9.8:1 dr), and hexanes (no reaction), providing reaction product in 74% isolated yield and 11:1 diastereomer ratio. Standard conditions employ 2.5 mol % $[(cod)RhCl]_2$, 5 mol % MeDuPhos, and 1.25 equiv of silane in each experiment. Notably, while reactions were carried out under nitrogen with rigorously purified reagents and solvents, we have subsequently found that reagents and solvents used as received from commercial vendors provide similar yields and stereoselection. In accord with our observations on reductive aldol reactions, the product configuration is consistent with generation of an *E*-silylketene acetal followed by rearrangement through a chairlike six-membered transition state.[6]

To examine the impact of reaction variables on product outcome, a series of experiments with different silanes were carried out (Table 1). As can be seen from the results of this survey, dichloromethylsilane provides highest product yield (entry 1), although the highest levels of diastereoselection were obtained when diethoxy(methyl)silane (entry 5) was used as reductant. While there are no readily interpretable correlations between reductant structure and reactivity, from inspection of the data it appears that highest reactivity results from silanes with more than one inductively withdrawing group attached.

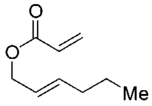
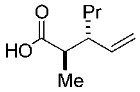
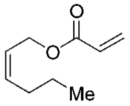
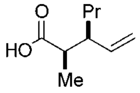
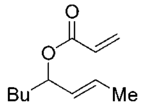
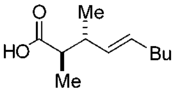
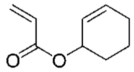
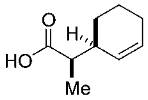
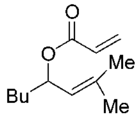
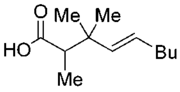
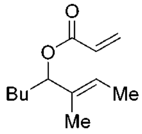
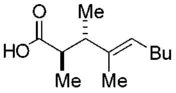
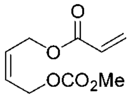
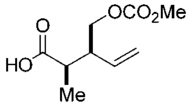
Table 1. Reductive Claisen Rearrangement with 5 mol % Rh-DuPhos and Various Silanes



entry	silane	time (h)	yield	dr
1	Cl_2MeSiH	1	74	11:1
2	Ph(Me)ClSiH	15	8	4.3:1
3	$ClPh_2SiH$	6	nr	na
4	$(EtO)_3SiH$	2	47	21:1
5	$(EtO)_2MeSiH$	2	47	>25:1
6	$(EtO)Me_2SiH$	2	9	10:1
7	Me_2PhSiH	1	nr	na
8	Et_2MeSiH	1	nr	na

Experiments aimed at surveying the reaction substrate scope were examined and employed dichloromethylsilane since it provided the optimal combination of yield and diastereoselection in our initial studies. As described above, *trans*-2-hexenylacrylate (entry 1, Table 2) undergoes reductive Claisen rearrangement to provide the *anti* diastereomer of product in high yield and diastereoselection. The opposite product diastereomer was obtained from *cis*-2-hexenylacrylate (entry 2), in accord with the stereochemical model proposed by Ireland for the ester enolate Ireland–Claisen rearrangement. Substitution at the carbinol position (entry 3) is tolerated and leads to the *trans* alkene in the reaction product in 91% yield and with an exceptional level of stereocontrol. Reaction of the cyclic allylic ester depicted in entry 4 proceeds with low levels of stereoselection and in low yield. This is presumably a consequence of incipient steric interactions in the required cyclic transition structure for rearrangement.[7] Trisubstituted olefins (entries 5 and 6)

Table 2. Reductive Claisen Rearrangement with 5 mol % Rh-DuPhos and Cl_2MeSiH

entry	substrate	product	time	yield	dr
1			1h	74	11:1
2			2h	49	23:1
3			4h	91	>25:1
4			4h	16	3:1
5			15h	74	na
6			15h	76	>25:1
7			15h	45	>25:1

---

(5) For one example of a reductive Claisen rearrangement, see: Cambie, R. C.; Milbank, J. B. J.; Rutledge, P. S. *Org. Prep. Proced. Int.* **1997**, *29*, 367.

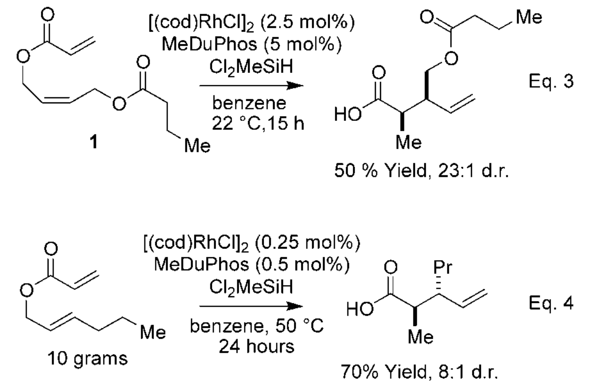
(6) While we have not been able to observe the presumed intermediate silylketene acetal in any of our experiments, the reactions products are racemic.

(7) For a similar Ireland–Claisen rearrangement with a cyclic allylic ester that proceeds in low stereoselection, see: Bartlett, P. A.; Pizzo, C. F. *J. Org. Chem.* **1981**, *46*, 3896.

participate in the reductive Claisen rearrangement. The example in entry 5 also demonstrates the ability to form all-carbon quaternary centers in good yields with this methodology. Allylic carbonate functionality (entry 7) survives the rearrangement, suggesting that silyl ketene acetal formation is faster than formation of the rhodium-π-allyl species documented by Matsuda.[8]

To demonstrate the complementary aspects of the reductive Ireland−Claisen rearrangement relative to base-promoted ester enolate rearrangements, we undertook the experiments described in Scheme 2. The base-mediated ester enolate Claisen rearrangement involving the propionate ester derivative of **1**, instead of the acrylate ester, would yield product mixtures as a result of competitive enolization of both carbonyls.[9] However, the chemoselectivity of the reductive Ireland−Claisen rearrangement allows the acrylate to participate in the rearrangement while the saturated ester remains untouched (eq 3). The success of this transformation is a direct consequence of the reducing nature of enolate generation[10] as opposed to base-promoted enolization under standard conditions. We expect that this difference in reactivity may allow for effective rearrangement with other base-sensitive substrates that are currently difficult under standard ester enolate Claisen conditions.

Scheme 2



The experiment depicted in eq 4 (Scheme 2) indicates that the reductive Ireland−Claisen rearrangement may be accomplished on large scale and requires only 0.5 mol % Rh metal. While higher temperature and extended reaction times were required with lower catalyst loading, the reaction still proceeded in a 70% yield and with 8:1 diastereomer ratio.

In conclusion, we have used a readily available catalyst, prepared from $[(cod)RhCl]_2$ and Me-DuPhos, for the chemo- and stereoselective reduction of allyl acrylates to *E*-silylketene acetals. The intermediate may then participate in an Ireland−Claisen rearrangement providing γ,δ-unsaturated carboxylic acids with a high level of stereocontrol. The chemoselective nature of the transformation may offer a practical complement to base-promoted ester enolate Claisen rearrangements.

Acknowledgment. We thank NIGMS (GM064451), Bristol-Myers Squibb, Dow, DuPont, GlaxoSmithKline, and the David and Lucile Packard Foundation for financial support. We thank Emily Houston for experimental assistance.

Supporting Information Available: Characterization data for all new compounds and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026273B

---

(8) Muraoka, T.; Matsuda, I.; Itoh, K. *J. Am. Chem. Soc.* **2000**, *122*, 9552.

(9) For elegant examples of chemoselective Ireland−Claisen rearrangements involving selective deprotonation, see: (a) Burke, S. D.; Fobare, W. F.; Pacofsky, G. J. *J. Org. Chem.* **1983**, *48*, 5221. (b) Paterson, I.; Hulme, A. N. *J. Org. Chem.* **1995**, *60*, 3288. (c) Pratt, L. M.; Beckett, R. P.; Bellamy, C. L.; Corkill, D. J.; Cossins, J.; Courtney, P. F.; Davies, S. J.; Davidson, A. H.; Drummond, A. H.; Helfrich, K.; Lewis, C. N.; Mangan, M.; Martin, F. M.; Miller, K.; Nayee, P.; Ricketts, M. L.; Thomas, W.; Todd, R. S.; Whittaker, M. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1359.

(10) For reports of presumed catalytic reductive enolate generation followed by C−C bond formation, see: (a) Revis, A.; Hilty, T. K. *Tetrahedron Lett.* **1987**, *28*, 4809. (b) Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 2005. (c) Matsuda, I.; Takahashi, K.; Sato, S. *Tetrahedron Lett.* **1990**, *31*, 5331. (d) Kiyooka, S.; Shimizu, A.; Torii, S. *Tetrahedron Lett.* **1998**, *39*, 5237.