ORGANIC LETTERS

2007
Vol. 9, No. 12
2325−2328

Stereoselective Olefin Isomerization Leading to Asymmetric Quaternary Carbon Construction

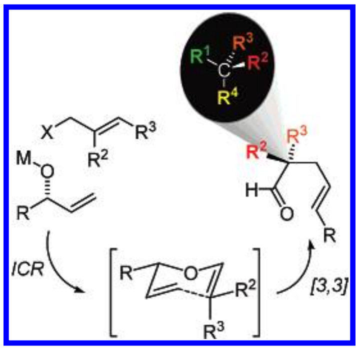
Kan Wang, Christopher J. Bungard, and Scott G. Nelson*

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

sgnelson@pitt.edu

Received March 21, 2007

ABSTRACT



Chemo- and stereoselective Ir(I)-catalyzed isomerization of 1,1-disubstituted and trisubstituted allylic ethers and in situ [3,3] sigmatropic rearrangement of the resulting allyl vinyl ethers provide for the highly stereoselective construction of quaternary carbon stereocenters. The olefin isomerization–Claisen rearrangement (ICR) sequence allows adjacent quaternary–tertiary stereocenter relationships to be established with excellent diastereoselection. Several complementary strategies for enantioselective quaternary carbon synthesis derive directly from the ICR reaction design.

Asymmetric construction of quaternary carbon stereocenters continues to pose a special challenge in organic synthesis.[1] [3,3] Sigmatropic rearrangements are among the well-established methods affording general access to all-carbon stereocenters even in architecturally complex settings.[2,3] Ireland enolate−Claisen rearrangements, the most versatile and widely utilized variant of the [3,3] sigmatropic rearrangements, therefore provide an especially attractive strategy for introducing sterically congested quaternary carbon stereocenters.[4,5] However, extending the Ireland−Claisen methodology to acyclic substrates is complicated by the poor control of enolate geometry accompanying enolization of α-disubstituted esters and the resulting errosion of Claisen diastereoselection (Figure 1).[6] This analysis led us to examine olefin isomerization−Claisen rearrangement (ICR) reactions as a strategy for achieving asymmetric

---

[1] Recent reviews: (a) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105−10146. (b) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363−5367. (c) *Quaternary Stereocenters*; Christoffers, J., Baro, A., Eds.; Wiley-VCH: Weinheim, 2005. (d) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369−396.

[2] Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423−1452 and references therein.

[3] For selected examples: (a) Ziegler, F. E.; Klein, S. I.; Pati, U. K.; Wang, T.-F. *J. Am. Chem. Soc.* **1985**, *107*, 2730−2737. (b) Ziegler, F. E.; Nangia, A.; Schulte, G. *J. Am. Chem. Soc.* **1987**, *109*, 3987−3991. (c) Lemieux, R. N.; Meyers, A. I. *J. Am. Chem. Soc.* **1998**, *120*, 5453−5457. (d) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388−401. (e) Boeckman, R. K., Jr.; del Rosario Rico Ferreira, M.; Mitchell, L. H.; Shao, P. *J. Am. Chem. Soc.* **2002**, *124*, 190−191.

[4] Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897−5898.

[5] Chelate-organized and/or cyclic enolates can provide good control of enolate geometry for α,α-disubstituted esters in advance of Ireland−Claisen rearrangements. (a) For a review, see ref 1c, pp 120−131. For other selected examples, see: (b) Ireland, R. E.; Wipf, P.; Armstrong, J. D., III *J. Org. Chem.* **1991**, *56*, 650−657. (c) Echavarren, A. M.; de Mendoza, J.; Prados, P.; Zapata, A. *Tetrahedron Lett.* **1991**, *32*, 6421−6424. (d) Devine, P. N.; Meyers, A. I. *J. Am. Chem. Soc.* **1994**, *116*, 2633−2634. (e) Gilbert, J. C.; Selliah, R. D. *Tetrahedron* **1994**, *50*, 1651−1664. (f) Enders, D.; Knopp, M. *Tetrahedron* **1996**, *52*, 5805−5818. (g) Calad, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 2046−2047.

10.1021/ol0706511 CCC: $37.00

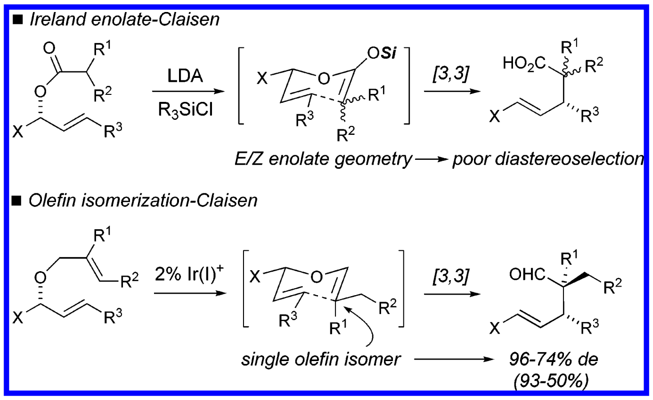


Figure 1. ICR-based strategy for quaternary carbon construction.

Claisen-based chiral quaternary carbon construction that would share the operational simplicity and reliability characterizing the Ireland−Claisen process.[7,8] This account describes the highly stereoselective construction of quaternary carbon stereocenters via chemo- and stereoselective Ir(I)-catalyzed isomerization of 1,1-disubstituted and trisubstituted allylic ethers and in situ [3,3] sigmatropic rearrangement of the resulting allyl vinyl ethers. These investigations reveal several complementary strategies for the enantioselective construction of all-carbon quaternary stereocenters based on the ICR technology.

Achieving rigorous stereocontrol in the ICR-based Claisen rearrangements is predicated on controlling vinyl ether geometry during the initial olefin isomerization event. During isomerization of 1,1-disubstituted or trisubstituted allyl ethers, the limited energetic differentiation of the resulting *E*- or *Z*-vinyl ethers raises concerns for controlling olefin geometry and, ultimately, Claisen stereoselectivity. As a result, documenting the capacity of metal-catalyzed isomerization of 1,1-disubstituted or trisubstituted allylic ethers to deliver stereodefined trisubstituted vinyl ethers was an essential component of these investigations. Moreover, enantioselective reaction variants would be predicated on the 2,2-disubstituted vinyl ether moieties causing limited disruption of chairlike transition states responsible for efficient transfer of substrate chirality during bond reorganization.

Preliminary efforts addressing these issues employed ethers **1** and **2** as representative test substrates for assaying olefin isomerization and Claisen stereoselectivity. Reacting **1** with 2 mol % of Ir(PCy_3)$_3$BPh$_4$ (**3**) at 75 °C elicited highly *Z*-selective isomerization and concomitant sigmatropic rearrangement to directly generate the 2,2-disubstituted pentenal derivative *anti*-**4** (anti/syn = 97:3, 60%) (Figure 2).

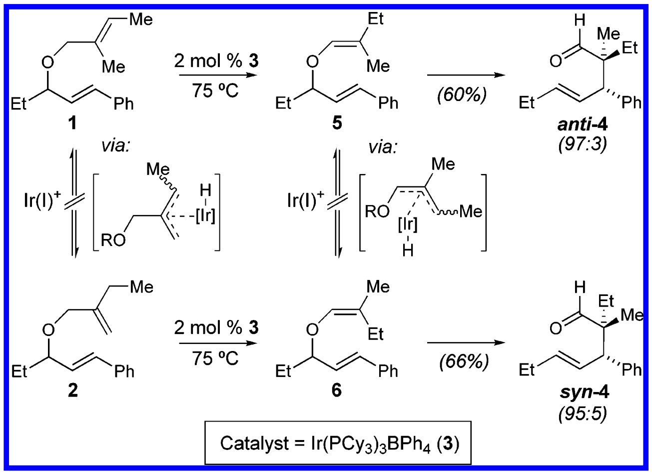


Figure 2. Correlating ICR substrate regiochemistry and Claisen diastereoselectivity.

The trisubstituted allyl ether **2** participated in similarly stereoselective ICR reorganization to provide the *syn*-2,2,3-trisubstituted pentenal *syn*-**4** in 66% yield (syn/anti = 95:5). These preliminary investigations suggested that oxidative insertion at allylic C−H bonds other than those adjacent to oxygen was not operative in these reactions. Thus, the regioisomeric di(allyl) ethers **1** and **2** are not subject to Ir(I)-catalyzed interconversion prior to vinyl ether formation, and once generated, the unique vinyl ether isomers **5** and **6** are immune to scrambling of olefin geometry that would accompany random allylic C−H insertion. This observation correlates olefin *regiochemistry*, rather than olefin *stereochemistry*, with the stereochemical outcome of the [3,3] sigmatropic rearrangement.

Analyzing the data presented in Table 1 reveals the general access to quaternary carbon stereocenters afforded by the ICR methodology. A variety of 1,1-disubstituted allylic ethers (e.g., **7**) possessing aliphatic alkyl, branched alkyl, and protected oxygen substituents undergo highly diastereoselective ICR reorganization to generate the stereodefined α,α-disubstituted pentenals **8a**−**e** (dr = 97:3−87:13) (entries a−e).[9] Claisen rearrangement of the benzyl-substituted allylic ethers **7c** and **7d** serves to highlight that olefin isomerization is highly regioselective even when resonance-stabilized styrene formation is a possible competing pathway. Trisubstituted allyl ethers **7g** and **7h** also afford efficient conduits to all-carbon stereocenters, delivering Claisen adducts **8g** and **8h** with excellent syn stereocontrol of the vicinal quaternary−

---

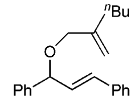
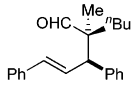
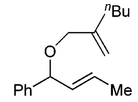
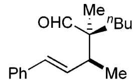
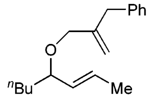
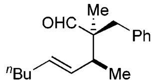
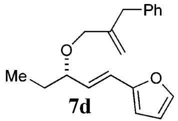
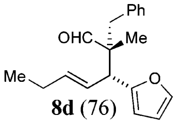
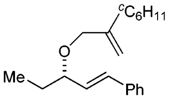
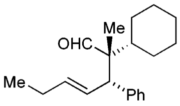
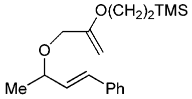
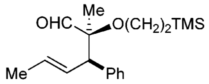
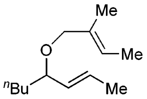
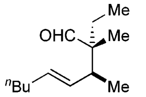
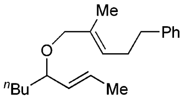
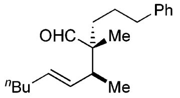
(6) Selected recent examples of stereoselective quaternary carbon construction via [3,3] sigmatropic rearrangement of allyl vinyl ethers: (a) May, J. H.; Stoltz, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 12426−12427. (b) Nordmann, G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 4978−4979. (c) Miyamoto, H.; Okawa, Y.; Nakazaki, A.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 2274−2277.

(7) (a) Nelson, S. G.; Bungard, C. J.; Wang, K. *J. Am. Chem. Soc.* **2003**, *125*, 13000−13001. (b) Nelson, S. G.; Wang, K. *J. Am. Chem. Soc.* **2006**, *128*, 4232−4233.

(8) Other examples of olefin isomerization−Claisen rearrangements: (a) Reuter, J. M.; Salomon, R. G. *J. Org. Chem.* **1977**, *42*, 3360−3364. (b) Wille, A.; Tomm, S.; Frauenrath, H. *Synthesis* **1998**, 305−308. (c) Higashino, T.; Sakaguchi, S.; Ishii, Y. *Org. Lett.* **2000**, *2*, 4193−4195. (d) Ben Ammar, H.; Le Nôtre, J.; Salem, M.; Kaddachi, M. T.; Dixneuf, P. H. *J. Organomet. Chem.* **2002**, *662*, 63−69. (e) Le Nôtre, J.; Brissieux, L.; Sémeril, D.; Bruneau, C.; Dixneuf, P. H. *Chem. Commun.* **2002**, 1772−1773. (f) Schmidt, B. *Synlett* **2004**, 1541−1544. (g) Nevado, C.; Echavarren, A. M. *Tetrahedron* **2004**, *60*, 9735−9744.

(9) The relative stereochemistry for **8a** was established by X-ray diffraction analysis of the corresponding semicarbazide derivative; data are provided in the Supporting Information.

Table 1. Olefin Isomerization−Claisen Rearrangement of 1,1-Disubstituted and Trisubstituted Allyl Ethers^{a-c}

entry	ICR substrate **7**	% yield **8**	dr
a	 **7a**	 **8a** (90)	97:3
b	 **7b**	 **8b** (93)	93:7
c	 **7c**	 **8c** (75)	93:4 (3)
d	 **7d** (95% ee)	 **8d** (76)	96:4 (95% ee)
e	 **7e** (95% ee)	 **8e** (70)	87:13 (92% ee)
f	 **7f**	 **8f** (58)	94:6
g	 **7g**	 **8g** (75)	95:5
h	 **7h**	 **8h** (71)	95:5

[a] Diastereomer ratios (dr) determined by 500 MHz ^{1}H NMR or HPLC analysis. [b]Product enantiomeric purity reported in parentheses for reactions employing enantioenriched di(allyl) ethers **7**. [c]Percentage of z_{C4-C5} olefin isomer in parentheses.

tertiary stereocenter relationships. Certain substrates bearing aliphatic C_2 alkyl substituents can yield minor amounts of the C_4-C_5 *cis*-olefin isomer (Table 1, entry c); quenching the Ir(I) catalyst (3 mol % of PPh_3) prior to thermolysis prevents post-rearrangement olefin isomerization (entries d and e).[7a]

Vinyl ether stereochemistry is dictated by the energetic differentiation of the η^1 organoiridium species **9** and **10** that immediately precede vinyl ether formation (Figure 3). Oxidative C−H insertion at C_1 in **11** can generate either of two isomeric η^3−Ir(III) complexes, **12** or **13**. Isomerization of these intermediates to the corresponding η^1 complexes **9** and **10** must precede reductive elimination of the vinyl ether. Destabilization of **10** due to the $A^{1,3}$ interaction incurred between the ether and the Ir(III)−phosphine moieties results in reductive elimination proceeding via **9** to selectively generate *E*- or *Z*-enol ethers from 1,1-disubstituted or trisubstituted allyl ethers, respectively.

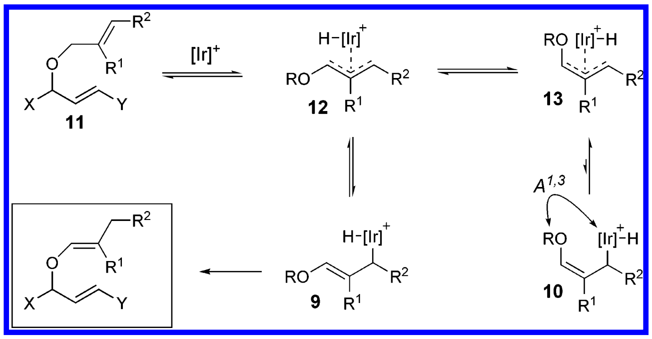
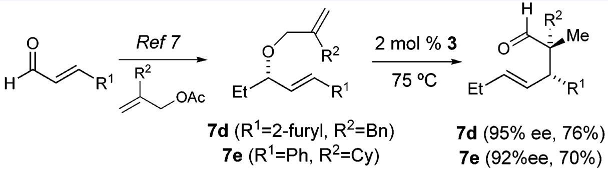


Figure 3. Mechanism for olefin isomerization stereoselectivity.

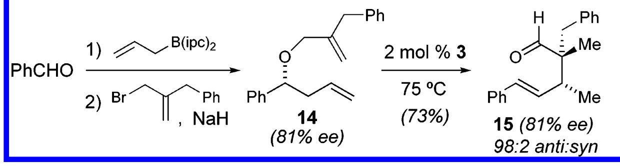
Among the defining characteristics of these ICR reactions is the flexibility they offer in devising enantioselective reaction variants. First, enantioenriched ICR substrates were prepared in a single step by catalytic asymmetric Et_2Zn−aldehyde addition and in situ zinc alkoxide allylation under Pd(0) catalysis (eq 1).[10] Under the ICR reaction conditions, the enantioenriched 1,1-disubstituted allylic ethers **7d**/**e** afforded the 2,2-disubstituted-4-pentenals **8d** and **8e** with near perfect chirality transfer. Alternatively, enantioenriched ICR substrates could be prepared by asymmetric aldehyde allylation followed by O-alkylation (81% ee) (eq 2).[11,12] Allyl homoallyl ether **14** participated in stereoselective tandem olefin isomerization to the corresponding (*E*,*Z*)-allyl vinyl ether and in situ [3,3] sigmatropic rearrangement to afford the 2,3-*anti*-pentenal derivative **15** (81% ee).



7d (R^1=2-furyl, R^2=Bn)
7e (R^1=Ph, R^2=Cy)

7d (95% ee, 76%)
7e (92%ee, 70%)

(1)



14
(81% ee)

15 *(81% ee)*
98:2 anti:syn

(2)

Ring-bearing Claisen substrates often exhibit attenuated diastereoselection due to limited energetic differentiation of the competing boat and chair transition states.[13] The cyclohexenol-derived di(allyl) ethers **16a** and **16b**, therefore,

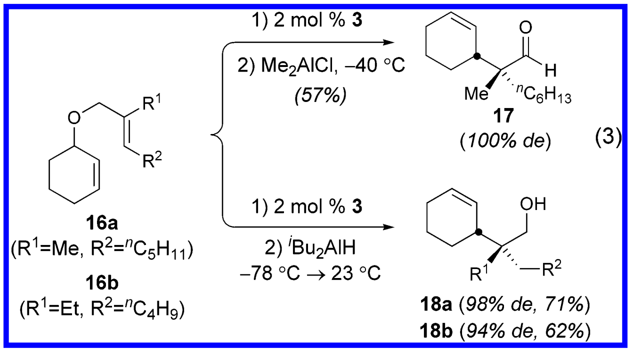
---

(10) (a) Kim, H.; Lee, C. *Org. Lett.* **2002**, *4*, 4369−4371. (b) Stevens, B. D.; Nelson, S. G. *J. Org. Chem.* **2005**, *70*, 4375−4379. (c) Ref 6b.

(11) Brown, H. C.; Randad, R. S.; Bhat, K. S.; Zaidlewicz, M.; Racherla, U. S. *J. Am. Chem. Soc.* **1990**, *112*, 2389−2392.

(12) The enantioselectivity obtained in preparing **14** was not optimized.

provided an especially stringent test for the stereocontrol available from the ICR-based Claisen rearrangements. Attempted ICR reorganization of these substrates under typical thermal reaction conditions afforded poor conversion or decomposition at more elevated temperatures (eq 3). Alternatively, following Ir(I)-catalyzed isomerization, reacting the crude allyl vinyl ether with Me_2AlCl (1.0 equiv, −40 °C) afforded the Claisen-derived aldehyde **17** as a single diastereomer (57% yield).[14] Diisobutylaluminum hydride proved to be an equally efficient Lewis acid promoter, generating the neopentyl alcohols **18a**/**b** as single diastereomers (71 and 62% yield, respectively), thereby affording direct entry to alcohol-containing Claisen adducts without resorting to a separate aldehyde reduction step.[15]



(3)

Olefin isomerization−Claisen rearrangement reactions provide convenient access to stereodefined all-carbon stereocenters and vicinal quaternary−tertiary stereocenter relationships. The success of these reactions enables a variety of easily accessed strategies for achieving enantioselective quaternary carbon installation.

Acknowledgment. Support from the National Science Foundation (CHE 0316000), the National Institutes of Health (P50 GM067082) for the University of Pittsburgh Center for Chemical Methodologies and Library Development (UPCMLD), the Bristol-Myers Squibb Foundation, and the Merck Research Laboratories is gratefully acknowledged.

Supporting Information Available: Experimental procedures and representative ^1H and ^{13}C spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0706511

---

(13) (a) Ireland, R. E.; Daub, J. P. *J. Org. Chem.* **1981**, *46*, 479−485. (b) Bartlett, P. A.; Pizzo, C. F. *J. Org. Chem.* **1981**, *46*, 3896−3900.

(14) Tayama, E.; Saito, A.; Ooi, T.; Maruoka, K. *Tetrahedron* **2002**, *58*, 8307−8312 and references therein.

(15) For the use of diisobutylaluminum hydride as a promoter for Claisen rearrangements, see ref 6a.