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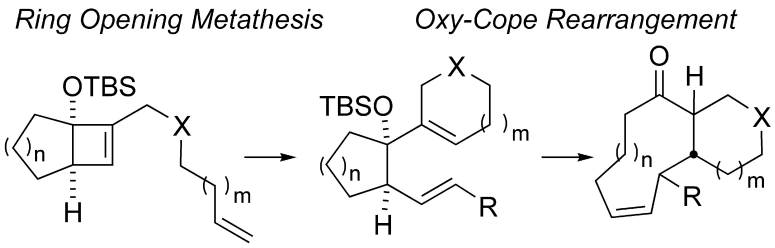
Brian H. White, and Marc L. Snapper

J. Am. Chem. Soc., **2003**, 125 (48), 14901-14904• DOI: 10.1021/ja037656n • Publication Date (Web): 07 November 2003



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Ring-Opening Metathesis/Oxy-Cope Rearrangement: A New Strategy for the Synthesis of Bicyclic Medium Ring-Containing Compounds

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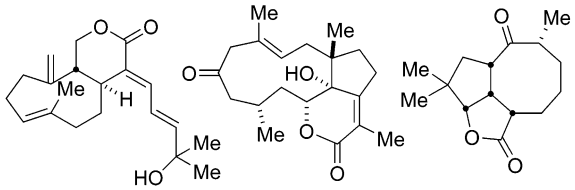
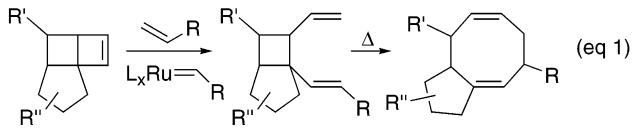
Abstract: Ring-opening/ring-closing metathesis on cyclobutene-containing substrates with angular oxygen functionality provides a stereospecific introduction of 1,5-bis-dienes required for an anion-accelerated oxy-Cope rearrangement. The reaction sequence offers generally a stereocontrolled preparation of a variety of medium ring-containing bicyclic ring systems, while rearrangement to the bicyclo[7,3,0]dodecane (9-5) system leads to a mixture of olefin isomers.

Introduction

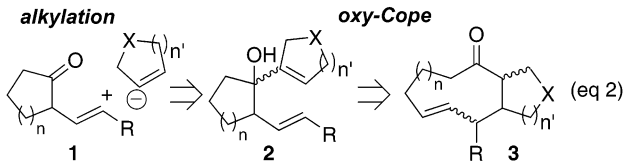
The development of new strategies for the efficient construction of medium-sized rings continues to be important for accessing natural products and their structural variants,[1] as well as for generating novel scaffolds toward applications in chemical biology and pharmaceutical research.[2] We recently described a ring-opening metathesis/Cope rearrangement strategy for the rapid construction of bicyclo[5.3.0]undecadienes (i.e., 5-8 ring system, eq 1)[3] which included a concise, stereocontrolled synthesis of asteriscanolide.[4] Herein, we extend the strategy to



provide a general ring-opening metathesis/Cope protocol, allowing for the preparation of a range of polycyclic, medium ring-containing compounds (i.e., 5-9, 5-10, 5-11, 6-9... ring systems).



Whereas release of ring strain can drive the formation of eight-membered rings (eq 1), [3,3]-sigmatropic rearrangements into larger ring-containing targets, such as those represented by 9-deoxyxeniolide[5] and clavirolide A,[6] require an alternative driving force. In this regard, anion-accelerated oxy-Cope rearrangements have been demonstrated as an attractive and proven solution for achieving these rearrangements (eq 2).[7]



Typically, the oxy-Cope precursors are accessed through the addition of a vinyl or allyl group into the appropriate unsaturated

(1) For example, see: (a) Yet, L. *Chem. Rev.* **2000**, *100*, 2963. (b) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073. (c) Furstner, A. *Top. Catal.* **1998**, *4*, 285. (d) Molander, G. A. *Acc. Chem. Res.* **1998**, *31*, 603. (e) Nubbemeyer, U. *Top. Curr. Chem.* **2001**, *216*, 125. (f) Trost, B. M. *Pure Appl. Chem.* **1992**, *64*, 315.

(2) For recent examples, see: (a) Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Ninkovic, S.; Sarabia, F.; He Y.; Vourloumis, D.; Yang, Z.; Li, T.; Giannakakou, P.; Hamel, E. *Nature* **1997**, *387*, 268. (b) Spring, D. R.; Krishnan, S.; Blackwell, H. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1354. (c) Souers, A. J.; Virgilio, A. A.; Rosenquist, S. A.; Fenuik, W.; Ellman, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 1817. (d) Spatola, A. F.; Darlak, K.; Romanovskis, P. *Tetrahedron Lett.* **1996**, *37*, 591. (e) Kohli, R. M.; Burke, M. D.; Tao, J.; Walsh, C. T. *J. Am. Chem. Soc.* **2003**, *125*, 7160. (f) Otto, S.; Furlan, R. L. E.; Sanders, J. K. M. *Science* **2002**, *297*, 590. (g) Jefferson, E. A.; Arakawa, S.; Blyn, L. B.; Miyaji, A.; Osgood, S. A.; Ranken, R.; Risen, L. M.; Swayze, E. E. *J. Med. Chem.* **2002**, *45*, 3430.

(3) Snapper, M. L.; Tallarico, J. A.; Randall, M. L. *J. Am. Chem. Soc.* **1997**, *119*, 1478.

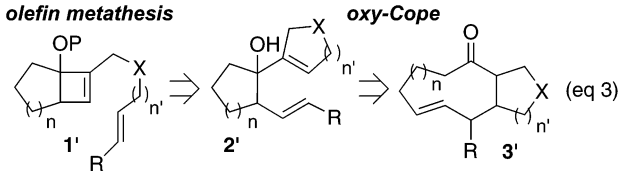
(4) Limanto, J.; Snapper, M. L. *J. Am. Chem. Soc.* **2000**, *122*, 8071.

(5) Vervoort, H. C.; Fenical, W. *Nat. Prod. Lett.* **1995**, *6*, 49.

(6) Su, J.; Zhong, Y.; Shi, K.; Cheng, Q.; Snyder, J. K.; Hu, S.; Huang, Y. *J. Org. Chem.* **1991**, *56*, 2337.

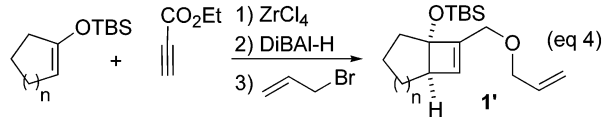
(7) For recent reviews on the oxy-Cope rearrangement, see: (a) Paquette, L. A. *Tetrahedron* **1997**, *53*, 13971. (b) Paquette, L. A. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 609. (c) Hill, R. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, Chapter 7.1. (d) Wilson, S. R. *Org. React.* **1993**, *43*, 93. For recent applications in medium-ring syntheses, see: (e) Gentric, L.; Hanna, I.; Ricard, L. *Org. Lett.* **2003**, *5*, 1139. (f) Yang, J.; Long, Y. O.; Paquette, L. A. *J. Am. Chem. Soc.* **2003**, *125*, 1567. (g) Banwell, M. G.; Hockless, D. C. R.; McLeod, M. D. *New J. Chem.* **2003**, *27*, 50. (h) Hashimoto, H.; Jin, T.; Karikomi, M.; Seki, K.; Haga, K.; Uyehara, T. *Tetrahedron Lett.* **2002**, *43*, 3633. (i) Banwell, M. G.; McRae, K. J.; Willis, A. C. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2194. (j) Njardarson, J. T.; Wood, J. L. *Org. Lett.* **2001**, *3*, 2431. (k) Chu, Y.; White, J. B.; Duclos, B. A. *Tetrahedron Lett.* **2001**, *42*, 3815.

carbonyl precursor (→**2**). This approach, however, can lead to diastereomers where it is difficult to obtain *cis*-dialkenylcycloalkanols in high yield, and the diastereomers can lead to different oxy-Cope products (**3**).[8] Instead, we envisioned a Lewis acid-mediated [2+2] cycloaddition,[9] intramolecular ring-opening metathesis sequence,[10] to provide stereospecific access to the *cis*-1,5-dienes (**2′**) fitted with the appropriate functionality for the oxy-Cope rearrangement (eq 3). The realization and scope of strategy is demonstrated through the preparation of a range of medium ring-containing polycyclic compounds (i.e., 5-9, 5-10, 5-11, and 6-9 ring systems).



Results and Discussion

The requisite cyclobutenes (**1′**) can be prepared through a Lewis acid-mediated [2+2] cycloaddition between cyclic silyl enol ethers and ethyl propiolate (eq 4),[9] followed by reduction and alkylation of the resulting cyclobutene esters to provide substrates ready for an intramolecular ring-opening metathesis. Our preliminary efforts toward generating the desired *cis*-1,5-dienes from these cyclobutene-containing adducts are summarized in Table 1.



Treatment of the cyclobutenes with Grubbs' second-generation olefin metathesis catalyst[11] **4** (or Hoveyda−Grubbs catalyst[12] **5**) provides cleanly the desired *cis*-1,5-dienes in 82−95% yields (Table 1). The allylated substrates generate dihydrofurans (entries 1−3) and dihydropyrroles (entry 5), while the butenylated precursor (**12**) provides the dihydropyran-containing product (**13**, entry 4). Under these reaction conditions, side reactions, such as dimerization of the cyclobutene substrates or secondary metatheses of the ring-opened products, are not observed.

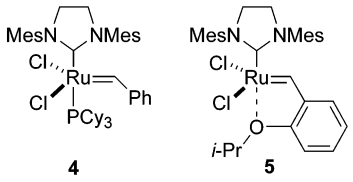
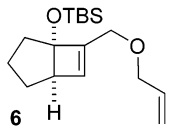
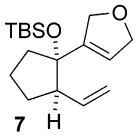
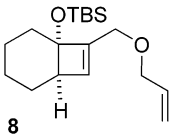
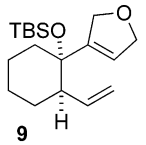
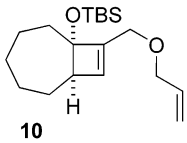
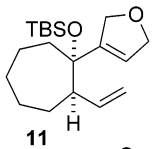
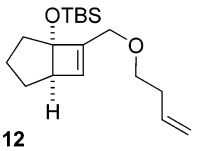
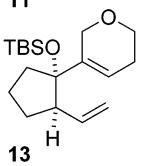
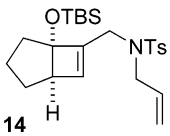
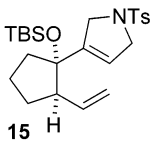


Table 1. Ring-Opening Metathesis of Cyclobutenes

entry	cyclobutene	metathesis product[a]	yield
(1)	 **6**	 **7**	89%
(2)	 **8**	 **9**	82%
(3)	 **10**	 **11**	82%
(4)	 **12**	 **13**	83%
(5)	 **14**	 **15**	95%

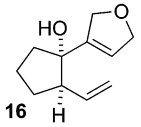
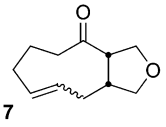
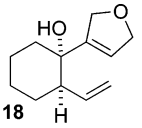
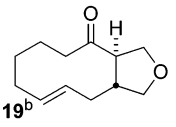
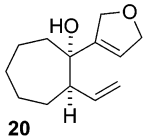
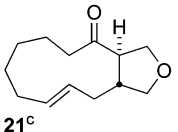
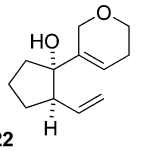
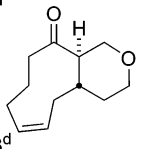
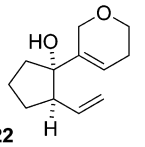
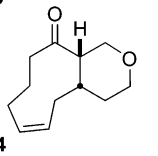
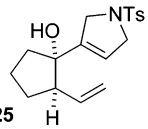
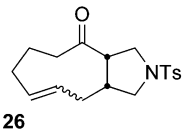
[a] Reaction conditions: 2 mol % **4**, C_6H_6, 60 °C, 1 h.

With the appropriately functionalized 1,5-dienes in hand, conditions for an effective [3,3]-sigmatropic rearrangement were explored. While in some cases a direct, thermal rearrangement of the metathesis product was viable, a more general solution was to remove the silyl-protecting group with TBAF and then deprotonate the resulting alcohol with KHMDS and 18-crown-6 to give the desired ring-expanded products under relatively mild conditions. The rearrangement results are summarized in Table 2. After the reaction was quenched, the 6-9, 5-10, and 5-11 ring systems were obtained as single olefin isomers (entries 2−4); the larger 10- and 11-membered ring products possessed the *trans*-olefin stereochemistry (e.g., **19** and **21**), whereas the 6-9 ring system was generated as the *cis*-olefin isomer (**23** and **24**). Rearrangements to the 5-9 systems (entries 1 and 5) lead to mixtures of olefin isomers (**17** and **26**) with the major products favoring the *cis*-stereochemistry.

While quenching of the enolates generated through the oxy-Cope in the 5-9 ring systems (entries 1 and 6) under "equilibrating" reaction conditions (MeOH, room temperature, 24 h) gave a mixture of ring fusion isomers, a "nonequilibrating" or "kinetic" quench (1 N HCl, −40 to −78 °C) yielded the *cis*-ring junction stereochemistry exclusively.[13] Kinetic quenches of the 5-10 and 5-11 systems (entries 2 and 3) yielded some of the *cis*-ring fused product, whereas addition of methanol allowed the *cis*-diastereomer to equilibrate completely to the *trans*-ring fusion isomers. Interestingly, the 6-9 ring system (entry 4) could provide either the *cis*- or the *trans*-ring fusion stereochemistry

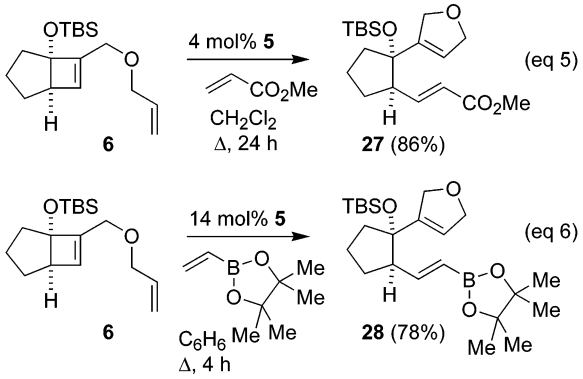
(8) (a) Kato, T.; Kondo, H.; Nishino, M.; Tanaka, M.; Hata, G.; Miyake, A. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2958. (b) Sworin, M.; Lin, K.-C. *J. Am. Chem. Soc.* **1989**, *111*, 1815. (c) Paquette, L. A.; Shi, Y.-J. *J. Am. Chem. Soc.* **1990**, *112*, 8478. (d) Jisheng, L.; Gallardo, T.; White, J. B. *J. Org. Chem.* **1990**, *55*, 5426.
(9) Clark, R. D.; Untch, K. G. *J. Org. Chem.* **1979**, *44*, 248.
(10) (a) Zuercher, W. J.; Hashimoto, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 6634. (b) Usher, L. C.; Estrella-Jimenez, M.; Ghiviriga, I.; Wright, D. L. *Angew. Chem., Int. Ed.* **2002**, *41(23)*, 4560. (c) Buschmann, N.; Rückert, A.; Blechert, S. *J. Org. Chem.* **2002**, *67*, 4325. (d) Ovaa, H.; Stapper, C.; van der Marel, G. A.; Overkleeft, H. S.; van Boom, J. H.; Blechert, S. *Tetrahedron* **2002**, *58*, 7503.
(11) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.
(12) Garber, S. B.; Kingbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.
(13) See Experimental Section and Supporting Information for details.

Table 2. Anion-Accelerated Oxy-Cope Rearrangement

entry	metathesis product	Cope product[a]	yield
(1)	 **16**	 **17**	80% 2.1:1 *cis*:*trans*
(2)	 **18**	 **19**[b]	82%
(3)	 **20**	 **21**[c]	82%
(4)	 **22**	 **23**[d]	64%
(5)	 **22**	 **24**	59%
(6)	 **25**	 **26**	72% 3.2:1 *cis*:*trans*

[a] Reaction conditions: (a) KHMDS, 18-crown-6, −40 °C, acid (1 N HCl or AcOH) quench. (b) Reaction run at 0 °C, MeOH quench. (c) Reaction run at −15 °C, MeOH quench. (d) Reaction quenched with MeOH.

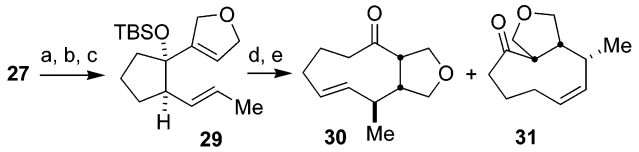
selectively (**23** or **24**) depending on the quench conditions employed.



To extend the utility of the methodology, as well as to obtain additional insight into the stereochemical course of the rearrangement, additional functionality was introduced through a tandem olefin metathesis sequence (eqs 5 and 6).[14] Cyclobutene **6** can undergo a stereoselective ring-opening/cross metathesis with monosubstituted, electron-poor olefins to provide *cis*-1,5-dienes where the newly formed disubstituted olefin is of the *E*-configuration (**27** and **28**).[15] Hoveyda−Grubbs' catalyst **5** was found to be superior for this transformation, as the longer reaction times at elevated temperatures lead to greater decomposition of catalyst **4**.

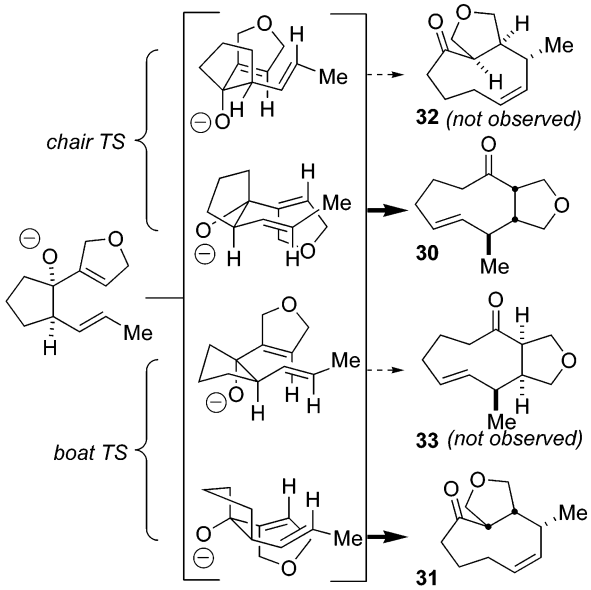
(14) Stragies, R.; Blechert, S. *Synlett* **1998**, 169.

Scheme 1 [a]



[a] Reaction conditions: (a) DIBAL−H, THF, −78 °C, 82%; (b) Ph_3PBr_2, pyr., CH_2Cl_2, 0 °C, 89%; (c) $NaBH_4$, DMSO, 79%; (d) TBAF, THF (96%); (e) KHMDS, 18-C-6, THF, −15 °C, 71% (1.8:1 **30**:**31**).

Scheme 2



With the additional functionality on the 1,5-dienes, an opportunity to examine in greater detail the stereochemical course of the oxy-Cope rearrangement becomes possible. To minimize interference from other reasonable reaction pathways, methyl ester **27** was reduced to diene **29** (Scheme 1). Hydroxyl deprotection, followed by oxy-Cope rearrangement, generates a 1.8:1 mixture of 5-9 isomers **30** and **31**, differing in both their olefin geometry and their relative stereochemistry of the newly introduced methyl substituent.

These results provide insight into the origins of the *cis*/*trans*-olefin stereochemistry observed in entries 1 and 5 in Table 2. As illustrated in Scheme 2, the major rearrangement adduct **30**, with a *trans*-olefin and the methyl group cis to the ring fusion hydrogens, could be formed through a chair transition state, whereas the minor isomer **31**, with a *cis*-olefin and the methyl group trans to the ring junction hydrogens, is likely to be accessed through a boat transition state.[16] In both cases, the oxygen anion appears to prefer the pseudoequatorial orientation. Products **32** and **33**, which would originate from an axial alkoxide, in either the boat or the chair transition state, are not observed. Interestingly, where rearrangements to the nine-

(15) (a) Ulman, M.; Belderrain, T. R.; Grubbs, R. H. *Tetrahedron Lett.* **2000**, *41*, 4689. (b) Morrill, C.; Grubbs, R. H. *J. Org. Chem.* **2003**, *68*, 6031.

(16) For previous examples of oxy-Cope rearrangements which may proceed through a mixture of boat and chair transition states, see: (a) Evans, D. A.; Nelson, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 774. (b) Paquette, L. A.; Guevel, R.; Sauer, D. R. *Tetrahedron Lett.* **1992**, *33*, 923. (c) Chu, Y.; Colclough, D.; Hotchkin, D.; Tuazon, M.; White, J. B. *Tetrahedron* **1997**, *53*, 14235.

membered ring with a pendant dihydrofuran ring lead to olefin isomers (entries 1 and 5, Table 2), the rearrangement with a dihydropyran substrate proceeds exclusively to the *cis*-olefin-containing product (entries 4 and 5, Table 2), this reaction occurring presumably through a boat transition state with an equatorial alkoxide. The reason for the difference in selectivity in the rearrangements to the nine-membered ring between the furanyl and pyranyl substrates is unclear at this point. On the other hand, the *trans*-olefin selectivity observed for substrates **19** and **21** (entries 2 and 3, Table 2) suggests that the larger rings rearrange exclusively though a chair transition state with an equatorially positioned oxyanion.[8d,17]

Conclusion

The sequence represents a flexible means of preparing medium ring-containing polycyclic compounds. The ring-opening/cross metathesis allows for substantial control over substrate architecture, as well as functionality. Moreover, the understanding of stereochemical issues in the key rearrangements allows for utility in applications requiring sensitive stereochemical control. Further extensions of the methodology, as well as applications in synthesis, are underway.

Experimental Section

General Procedure for Ring-Opening/Ring-Closing Metathesis. A flask was charged with Grubbs' catalyst (**4**) (2 mol %), fitted with a condenser, and put under a N_2 atmosphere. Benzene (60 mM) was added to dissolve the catalyst, and the cyclobutene (1 equiv) was added by syringe, either neat or as a solution in benzene. The reaction was heated to 60 °C and allowed to stir for 1 h. The reaction was then cooled to room temperature, ethyl vinyl ether (1 equiv) was added to the reaction, and the solution was concentrated in vacuo. The resulting oil was purified through silica gel chromatography.

General Procedure for TBS Deprotections. A flask was charged with the silyl ether (1 equiv) and dissolved in THF (0.13 M). TBAF (3 equiv) was added as a solid, and the reaction was stirred until no more starting material remained by TLC (generally 18−24 h). The reaction was poured into HCl (1 N) and extracted with ethyl acetate. The combined organic extracts were dried with $MgSO_4$ and concentrated in vacuo. The resulting alcohol was purified by chromatography on silica gel.

General Procedure of Cope Rearrangement. A flask was charged with 18-crown-6 (1.6 equiv) and alcohol (1 equiv). Both were dissolved in THF (0.05 M), and the reaction was cooled to −40 °C. KHMDS (1.38 equiv) was added dropwise, and the reaction was stirred for 1 h. The reaction was quenched by adding either methanol or HCl (see kinetic and thermodynamic quenches below, for details).

Kinetic Quench. The cold THF reaction mixture (−40 to −78 °C) is added via cannula to a solution of HCl (1 N). The desired product(s) is extracted from the aqueous THF with ethyl acetate.

Thermodynamic Quench. The reaction is quenched with MeOH and allowed to stir for 12−24 h while being warmed to room temperature. The reaction mixture is then acidified with HCl before the desired product(s) is isolated by extraction with ethyl acetate.

Acknowledgment. We are grateful to the National Science Foundation for financial support (CHE-0132221). In addition, we would also like to thank Jarred T. Blank for substantial assistance with X-ray crystallographic studies.

Supporting Information Available: Experimental procedures, compound characterizations, and crystallographic data (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA037656N

(17) Clive, D. L. J.; Russell, C. G.; Suri, S. C. *J. Org. Chem.* **1982**, *47*, 1632.