Tetrahedron Letters 50 (2009) 1188–1192

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Diastereocontrol in [4+4]-photocycloadditions of pyran-2-ones: effect of ring substituents and chiral ketal

Lei Li[a], John A. Bender[b,†], F. G. West[a,b,*]

[a] Department of Chemistry, University of Alberta, E3-43 Gunning-Lemieux Chemistry Centre, Edmonton, AB, Canada T6G 2G2
[b] Department of Chemistry, University of Utah, 315 S. 1400 East, Rm 2020, Salt Lake City, UT 84112-0850, USA

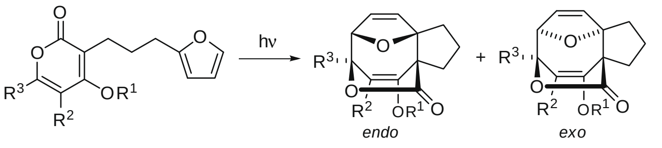
ARTICLE INFO

Article history:
Received 22 September 2008
Revised 16 December 2008
Accepted 22 December 2008
Available online 10 January 2009

ABSTRACT

4-Mesyloxypyran-2-ones joined to furan by a three-carbon linker undergo intramolecular-crossed [4+4]-photocycloaddition with high or complete selectivity for the *exo* cycloadduct. When a C_2-symmetric ketal was present on the tether adjacent to the pyranone ring, moderate levels of asymmetric induction were obtained.

The prevalence of cyclooctane rings in nature has inspired a plethora of methods for their construction.[1] [4+4]-Cycloaddition approaches to the cyclooctanoid system offer several appealing features, including convergent assembly of the eight-membered ring from two relatively simpler four-carbon fragments, formation of two new carbon-carbon bonds, and the potential for introduction of up to four new stereocenters in one step.[2] The seminal work of de Mayo demonstrated that the readily available heterocycle 4,6-dimethylpyran-2-one undergoes photochemical dimerization to a mixture of [2+2]- and [4+4]-cycloadducts.[3] More recently, we have developed a crossed [4+4]-photocycloaddition process, using pyran-2-ones linked to furans by a three-atom tether (Eq. 1).[4] This method can furnish densely functionalized cyclooctadienes or triquinanes[5] in good yields, and in some cases with moderate *endo*/*exo* selectivity. On the other hand, control over the configuration at the newly established bridgehead centers by use of preexisting stereocenters has been largely unsuccessful, apart from one rather specialized example.[6]



(1)

Use of stereochemical control elements within the chain linking the two heterocyclic units was of particular interest.[7] While placement of methyl-substituted branch points on the tether failed to achieve substantial diastereocontrol,[4a,c] we were hopeful that cyclic C_2-symmetric ketals might exert a greater influence.[8] These auxiliaries have been used with some success in Diels–Alder cycloadditions on the 1,3-diene partner,[9] or (in ring-opened form) on the dienophile.[10] In one especially pertinent study, Fukumoto, Kametani, and co-workers demonstrated that moderate levels of diastereoselectivity could be achieved in intramolecular Diels–Alder cycloadditions of *ortho*-quinodimethanes bearing chiral ketals on the tether adjacent to the dienonphile.[11] Here, we describe preliminary studies utilizing C_2-symmetric ketals as chiral auxiliaries in the [4+4]-photocycloaddition reactions of pyran-2-ones.

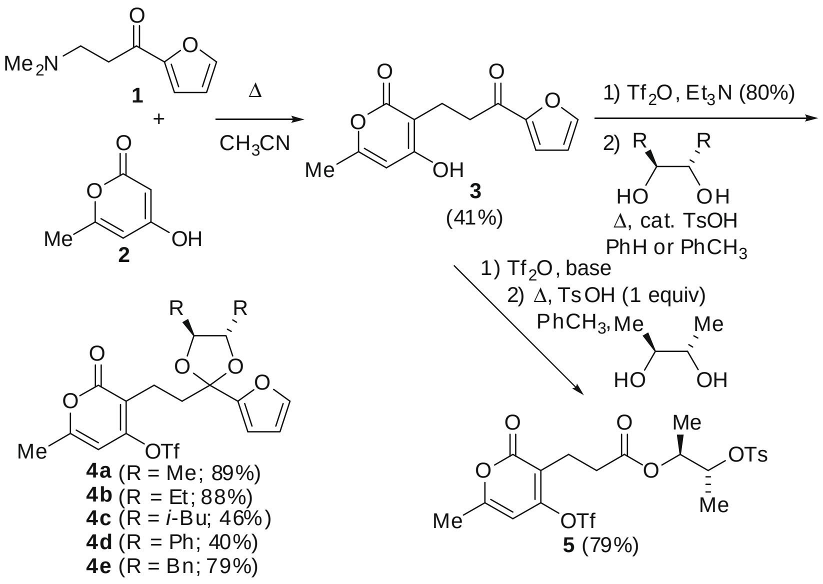
Our initial plan sought to exploit the ready availability of furoyl substrates, formed via Michael addition of 4-hydroxypyran-2-ones to acryloylfuran (Scheme 1).[12] Mannich base **1** can be prepared from acetyl furan in the presence of paraformaldehyde and $Me_2NH{\cdot}HCl$.[13] Upon heating with pyran-2-one **2** in acetonitrile, adduct **3** was obtained in moderate yield. With this material in hand, the C-4 hydroxyl was capped as a triflate, and several C_2-symmetric ketals were prepared under standard conditions (catalytic TsOH in PhH or $PhCH_3$ at reflux), furnishing **4a**–**e**. Due to the extended heating required to drive these reactions to completion, use of stoichiometric quantities of TsOH was investigated with (*R*,*R*)-butanediol. However, under these conditions the furan ring was lost, giving glycol monoester tosylate **5** as the sole product.[14] This process is believed to proceed through protiodefuranation of the desired ketal **4a**, followed by opening of the resulting dioxolanium ion by tosylate.

With **4a**–**e** in hand, we now set out to probe the ability of the ketal unit to impact the stereochemical course of the photocycloaddition reaction (Table 1). Under standard conditions (aq MeOH, rt), ketals **4a**–**c** were converted to roughly equal quantities of *endo* and *exo* cycloadducts **6a**–**c** and **7a**–**c**. The low *endo*/*exo* selectivity was surprising, in comparison to examples with unfunctionalized tethers.[4b] However, poor *endo*/*exo* selectivity was also seen in a number of cases employing a simple ethylene ketal next to the furan.[6] In each successful case of the present study, the *endo* and *exo* adducts were obtained as inseparable mixtures of diastereomers,

---

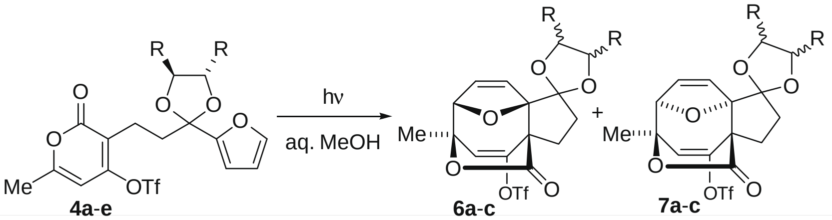
[*] Corresponding author. Tel.: +1 780 492 8187; fax: +1 780 482 8231.
E-mail address: frederick.west@ualberta.ca (F.G. West).
[†] Present address: Bristol-Myers Squibb, 5 Research Parkway, Wallingford, CT 06492, USA.

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.12.117



Scheme 1.

Table 1
Photocycloaddition reactions of furyl ketals **4**[a]



Entry	Substrate	% Yield cycloadducts (*endo*:*exo*)[b]	dr for **6**[c]	dr for **7**[c]
1	**4a**	66 (1:1)	1.8:1	1.4:1
2	**4b**	62 (1:1)	1.5:1	1.8:1
3	**4c**	60 (1.5:1)	1.7:1	nd[d]
4	**4d**	–[e]	–	–
5	**4e**	Trace	nd[d]	nd[d]

[a] Standard procedure: ketal substrate **4** was dissolved in aq MeOH (ca. 60% v/v; ca. 6 mM) in a Pyrex tube, and the resulting solution degassed with a slow stream of dry N_2 gas. The tube was clamped ca. 10 cm from a Hannovia 450 W medium pressure Hg lamp and irradiated until consumption of **4** (2–5.5 h).

[b] All yields given are for homogeneous isolated product following chromatographic purification.

[c] Diastereomeric ratios were determined by ^1H NMR integration of dihydrofuran alkenyl protons, except in the case of **7b**, where integrals of upfield methyl doublets were measured.

[d] Diastereomeric ratios could not be determined in the case of **7c** due to spectral overlap, and in the case of **6e**/**7e** due to insufficient quantities.

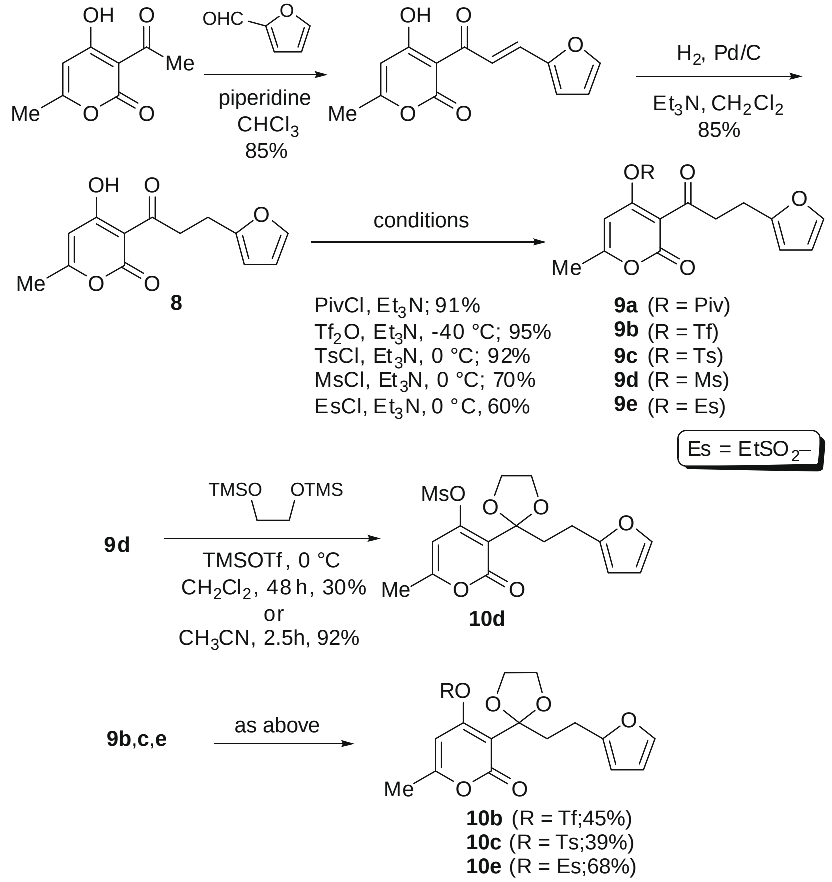
[e] Only uncharacterizable polar materials were formed.

differing in relative configuration between the newly formed bridgehead stereocenters and the chiral ketals. Ratios were measured via integration of downfield alkenyl protons of the dihydrofuran, which were well resolved in all but two cases.

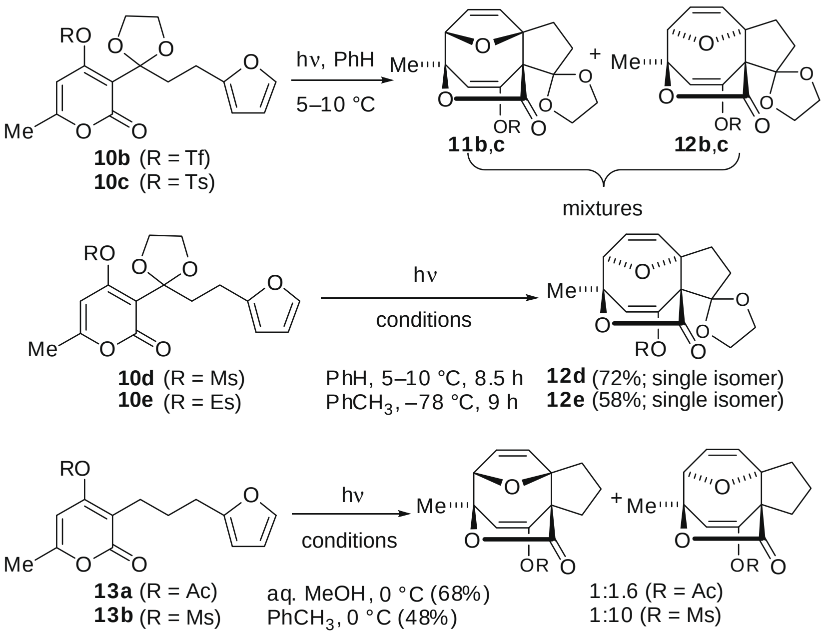
Diphenyl ketal **4d** and dibenzyl ketal **4e** furnished little or no [4+4]-cycloadduct upon irradiation; instead, a complex mixture of polar products was formed, presumably the result of alternative pyran-2-one photochemical pathways.[15] Notably, among the examples that did undergo the desired cycloaddition, the steric bulk of the ketal substituents had little effect on the selectivity, with all cases falling in a range of 1.5–1.8:1 dr, suggesting a relatively small energetic difference between the diastereomeric photocycloaddition transition states.

Given the disappointing levels of diastereoselectivity seen with furyl ketals **4**, we turned our attention to an alternative substitution pattern, with the ketal adjacent to the pyran-2-one ring. Coupling of the heterocyclic reactants was accomplished through aldol condensation of dehydroacetic acid and furfural,[16] and the resulting enone was subjected to catalytic hydrogenation to give **8** (Scheme 2). A variety of protecting groups for the pyranone hydroxyl were examined. Pivalate **9a** could readily be prepared, but was found to be labile during the subsequent ketalization. Sulfonates **9b**–**e** were also prepared in good to excellent yield, and proved to be much more robust to the ketalization conditions.

Ketalization of **9b**–**e** was then examined, using achiral ethylene glycol to optimize conditions. Standard conditions ($HOCH_2CH_2OH$, cat. acid, benzene or toluene, reflux) caused extensive decomposition. However, under the Noyori conditions,[17] moderate amounts of ketal **10d** were obtained. Reaction rates were greatly increased when acetonitrile was used as solvent, providing **10d** in >90% yield. These conditions were applied to **9b**,**c**,**e** and furnished **10b**,**c**,**e** in moderate yields.

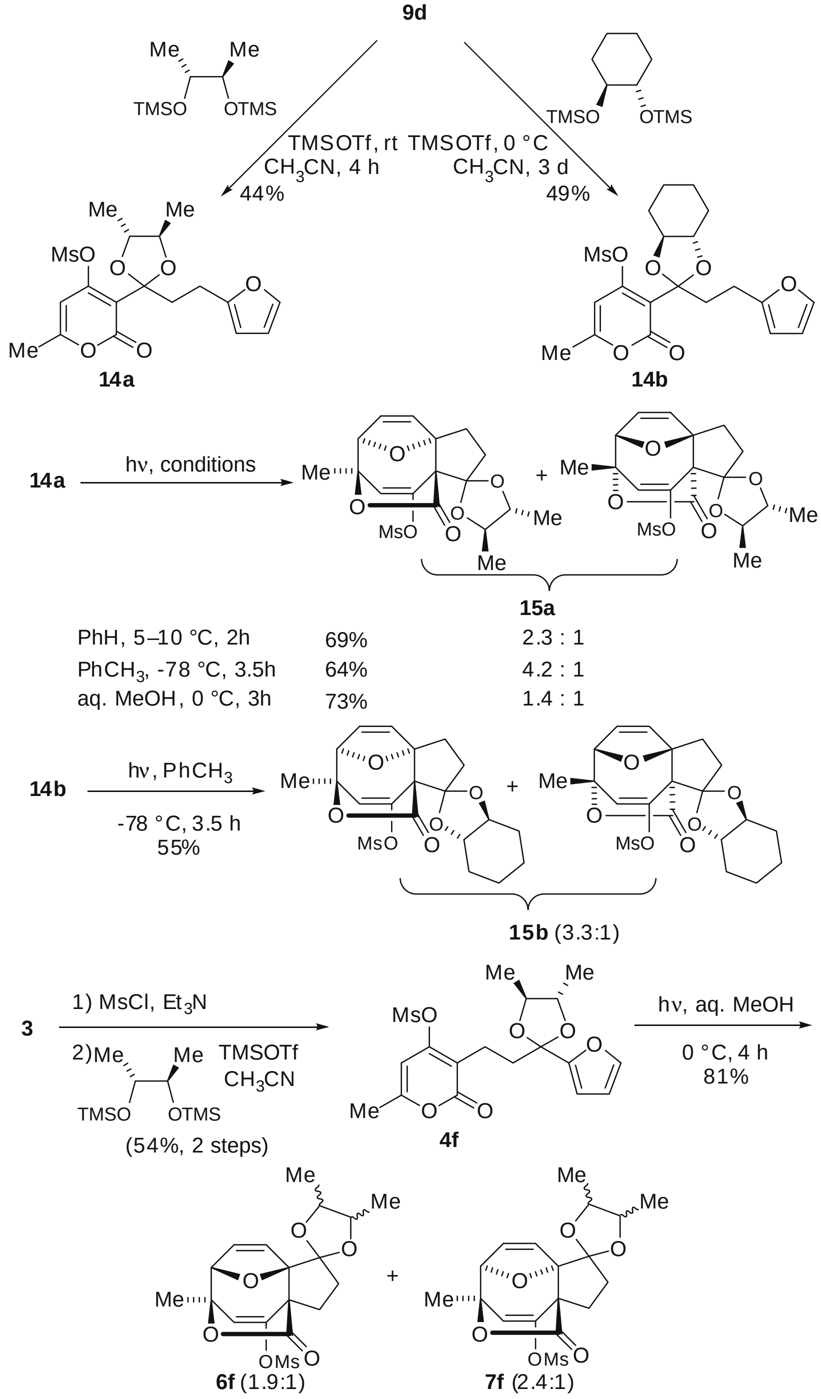


Scheme 2.



Scheme 3.

Next, the photochemical behavior of **10b–e** was examined (Scheme 3). Unlike **4a–c**, these ketals were not stable under the standard conditions (aq MeOH, rt), necessitating the use of aprotic solvents. Upon irradiation in benzene, triflate **10b** underwent [4+4]-photocycloaddition to give a mixture of *endo* **11b** and *exo* **12b**, while tosylate **10c** furnished a complex mixture of products that included some of the expected **11c** and **12c**. *However, under the same conditions, mesylate* ***10d*** *provided exo adduct* ***12d*** *in good yield as a single isomer.* The origin of this remarkable diastereoselectivity is not apparent, but the presence of a small alkanesulfonate at the pyrone

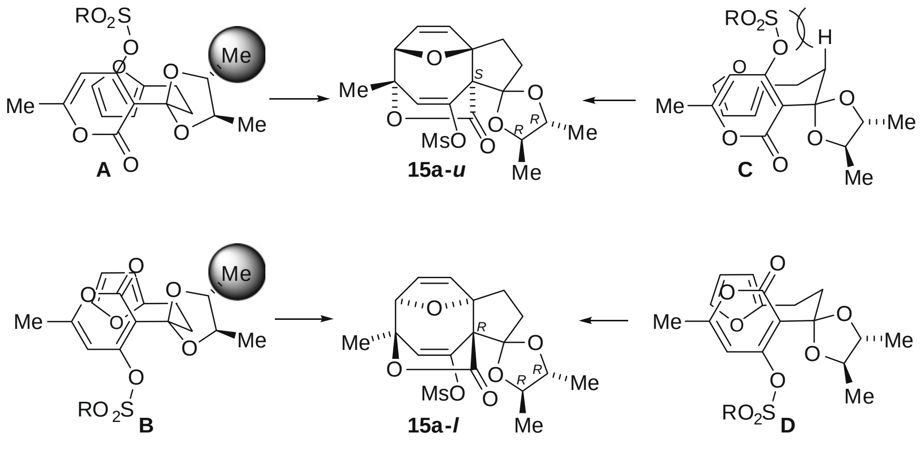


Scheme 4.

C-4 position seems to be essential. For example, ethanesulfonate **10e** also furnished *exo* adduct **12e** as the only detectable photoproduct. Further evidence for this substituent effect can be seen with substrates **13a**,**b**. Acetate **13a** was previously shown to give a 1:1.6 mixture of *endo* and *exo* cycloadducts,[4c] but the corresponding mesylate **13b** furnished a 10:1 *exo*/*endo* ratio of adducts.

The complete *exo* selectivity obtained with **10d** was unexpected, and it offered a clear advantage relative to the earlier cases (**4a**–**c**) with regard to asymmetric induction studies with chiral ketals: with the formation of only the *exo* cycloadduct, stereochemical analysis would be greatly simplified, as only two components would be expected in the product mixture. Thus, ketone **9d** was used for all subsequent experiments.[18] In the event, preparation of branched ketals was found to be substantially slower than for the simple, unsubstituted case (Scheme 4). However, upon extended stirring with TMSOTf and the bis(silyl ether) of racemic butane-2,3-diol or cyclohexane-1,2-diol, ketals **14a** and **14b** were obtained in moderate yields. Irradiation of **14a** in benzene at 5 °C afforded *exo* [4+4]-cycloadduct **15a** in 69% yield and 2.3:1 dr.[19] At −78 °C in toluene, the dr was improved to 4.2:1 with little diminution of chemical yield. These latter conditions were also applied to **14b**, providing **15b** in 55% yield and 3.3:1 dr.

The improvement in diastereoselectivity seen for **14a**,**b** was gratifying, but it was unclear whether it derived from the presence of mesylate, the position of the ketal on the tether, the conditions



Scheme 5.

of irradiation, or some combination of these factors. In contrast to **10d**, **14a** tolerated the conditions that had been used for ketals **4a**–**c**, and irradiation in aq MeOH furnished **15a** in 73% and only 1.4:1 dr, indicating the importance of low temperature and aprotic solvent. To further clarify this issue, we also prepared **4f** (analogous to **4a**, but with mesylate in place of triflate). Unfortunately, this substrate was unreactive to extended irradiation in toluene at −78 °C, or even at rt. Reaction in aq MeOH furnished a nearly equal ratio of *endo* and *exo* cycloadducts **6f** and **7f**, each formed in only moderate diastereoselectivity (1.9–2.4:1 dr). From these results, we conclude that all of the factors mentioned above affect the selectivity of the cycloaddition process.

It was not possible to obtain the major diastereomers of **6**, **7**, or **15** in homogeneous crystalline form, precluding the rigorous assignment of relative configuration. A working model for the most selective case (**14a**) is shown above (Scheme 5). Of the four possible *exo* transition states in which the tether adopts a chair-like conformation (**A**–**D**), **A** and **B** are considered less favorable due to steric interaction between the ketal methyl group adjacent to the pseudoaxial oxygen and the rest of the tether. Likewise **C** is expected to experience unfavorable nonbonded interactions between the sulfonate group and the pseudoaxial hydrogen, while **D** seems to be largely devoid of such issues. This model predicts isomer **15a**–***l***, in which the bridgehead stereocenter adjacent to the ketal has the same relative configuration as the ketal stereocenters, to be the major product. However, pending access to a sample suitable for single crystal X-ray diffraction analysis, this stereochemical assignment must remain tentative.

Pyran-2-ones linked to furans and possessing a keto group in the three-carbon tether are easily prepared. Chiral ketals can be installed adjacent to either heterocycle, and impose poor to moderate levels of diastereoselectivity in the photochemical [4+4]-cycloaddition reactions of these substrates. Notably, derivatization of the 4-hydroxyl on the pyrone ring with a methanesulfonyl group leads to high or complete selectivity for the *exo* cycloadduct in most cases. Improved selectivity and a more detailed understanding of the mechanism of asymmetric induction may be possible through further optimization of the ketal moiety and the photocycloaddition conditions, and the results of these continuing studies will be described in due course.

Acknowledgements

The authors wish to thank NIGMS, NSF, and NSERC (Canada) for generous support of this work.

References and notes

1. (a) Evans, P. A.; Baum, E. W.; Fazal, A. N.; Pink, M. *Chem. Commun.* **2005**, 63; (b) Murakami, M.; Ashida, S.; Matsuda, T. *J. Am. Chem. Soc.* **2006**, *128*, 2166; (c) Clark, J. S.; Walls, S. B.; Wilson, C.; East, S. P.; Drysdale, M. J. *Eur. J. Org. Chem.* **2006**, 323; (d) Murphy, G. K.; Marmsäter, F. P.; West, F. G. *Can. J. Chem.* **2006**, *84*, 1470; (e) Krishnan, K. S.; Smitha, M.; Suresh, E.; Radhakrishnan, K. V. *Tetrahedron* **2006**, *62*, 12345; (f) DeBoef, B.; Counts, W. R.; Gilbertson, S. R. *J. Org. Chem.* **2007**, *72*, 799; (g) Zhang, Y.-D.; Ren, W.-W.; Lan, Y.; Xiao, Q.; Wang, K.; Xu, J.; Chen, J.-H.; Yang, Z. *Org. Lett.* **2008**, *10*, 665; (h) Jiao, L.; Yuan, C.; Yu, Z.-X. *J. Am. Chem. Soc.* **2008**, *130*, 4421; Reviews: (i) Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881; (j) Michaut, A.; Rodriguez, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 5740; (k) López, F.; Mazcareñas, J. L. *Chem. Eur. J.* **2007**, *13*, 2172.
2. (a) Zhu, M.; Qiu, Z. L.; Hiel, G. P.; Sieburth, S. McN. *J. Org. Chem.* **2002**, *67*, 3487; (b) Wang, Y.; Schill, B. D.; Arif, A. M.; West, F. G. *Org. Lett.* **2003**, *5*, 2747; (c) Wender, P. A.; Croatt, M. P.; Witulski, B. *Tetrahedron* **2006**, *62*, 7505; (d) Harmata, M.; Rashatasakhon, P.; Barnes, C. L. *Can. J. Chem.* **2006**, *84*, 1456.
3. (a) de Mayo, P.; Yip, R. W. *Proc. Chem. Soc. London* **1964**, 84; (b) de Mayo, P.; McIntosh, C. L.; Yip, R. W.. In *Organic Photochemical Synthesis*; Srinivasan, R., Roberts, T. D., Eds.; Wiley-Interscience: New York, 1971; Vol. 1, pp 99–100.
4. (a) West, F. G.; Chase, C. E.; Arif, A. M. *J. Org. Chem.* **1993**, *58*, 3794; (b) Chase, C. E.; Bender, J. A.; West, F. G. *Synlett* **1996**, 1173; (c) Li, L.; Chase, C. E.; West, F. G. *Chem. Commun.* **2008**, 4025.
5. Li, L.; McDonald, R.; West, F. G. *Org. Lett.* **2008**, *10*, 3733.
6. Song, D.; McDonald, R.; West, F. G. *Org. Lett.* **2006**, *8*, 4075.
7. For examples of diastereoselectivity in related metal-catalyzed or photochemical [4+4]-cycloadditions using tether-based control elements, see: (a) Wender, P. A.; Nuss, J. M.; Smith, D. B.; Suárez-Sobrino, A.; Vågberg, J.; Decosta, D.; Bordner, J. *J. Org. Chem.* **1997**, *62*, 4908; (b) Sieburth, S. McN.; McGee, K. F., Jr.; Al-Tel, T. H. *J. Am. Chem. Soc.* **1998**, *120*, 587; (c) McGee, K. F., Jr.; Al-Tel, T. H.; Sieburth, S. McN. *Synthesis* **2001**, 1185.
8. (a) Mash, E. A.; Hemperly, S. B.; Nelson, K. A.; Heidt, P. C.; Van Deusen, S. *J. Org. Chem.* **1990**, *55*, 2045; Review: (b) Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 477.
9. Boehler, M. A.; Konopelski, J. P. *Tetrahedron* **1991**, *47*, 4519.
10. (a) Sammakia, T.; Berliner, M. A. *J. Org. Chem.* **1994**, *59*, 6890; (b) Anderson, J. C.; Blake, A. J.; Graham, J. P.; Wilson, C. *Org. Biomol. Chem.* **2003**, *1*, 2877.
11. Nemoto, H.; Nagai, M.; Kohzuki, K.; Fukumoto, K.; Kametani, T. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2835.
12. Bravo, P.; Resnati, G.; Viani, F.; Cavicchio, G. *J. Chem. Res. (S)* **1986**, 374.
13. Joshi, M. V.; Hemler, C.; Cava, M. P.; Cain, J. L.; Bakker, M. G.; McKinley, A. J.; Metzger, R. M. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1081.
14. For an early report on the scope of this unexpected process, see: Bender, J. A.; Daves, S.; West, F. G. *Tetrahedron Lett.* **1998**, *39*, 2051.
15. (a) Corey, E. J.; Streith, J. *J. Am. Chem. Soc.* **1964**, *86*, 950; (b) Chapman, O. L.; McIntosh, C. L.; Pacanshy, J. *J. Am. Chem. Soc.* **1973**, *95*, 244; (c) Huang, B.-S.; Pong, R. G. S.; Laureni, J.; Krantz, A. *J. Am. Chem. Soc.* **1977**, *99*, 4154; (d) Arnold, B. R.; Brown, C. E.; Lusztyk, J. *J. Am. Chem. Soc.* **1993**, *115*, 1576; (e) Chase, C. E.; Jarstfer, M. B.; Arif, A. M.; West, F. G. *Tetrahedron Lett.* **1995**, *36*, 8531.
16. Wiley, R. H.; Jarboe, C. H.; Ellert, H. G. *J. Am. Chem. Soc.* **1955**, *77*, 5102.
17. Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357.
18. Although ethanesulfonate **10e** also demonstrated complete *exo* selectivity, its precursor **9e** was not used in subsequent studies due to extremely slow rates of ketalization.
19. Diastereomer ratios for **15a** and **15b** were measured by integration of the enol mesylate alkene protons, which were well resolved in both cases.