ORGANIC LETTERS

2010
Vol. 12, No. 6
1236−1239

Diastereoselective Synthesis of P-Stereogenic Heterocycles via Enyne Ring-Closing Metathesis

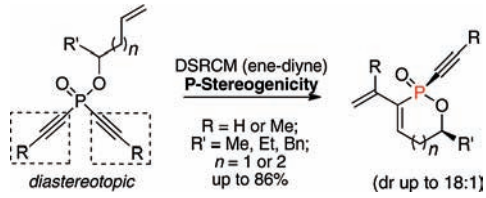
James Stephen Harvey, Guy T. Giuffredi,† and Véronique Gouverneur*

Chemistry Research Laboratory, Department of Chemistry, University of Oxford, Mansfield Road, Oxford OX1 3TA, U.K.

veronique.gouverneur@chem.ox.ac.uk

Received January 14, 2010

ABSTRACT



A range of P-containing ene-diynes suitable for desymmetrization was prepared via a two-step process starting from phosphorus oxychloride. In the presence of the Hoveyda−Grubbs II catalyst, these substrates underwent diastereoselective enyne ring-closing metathesis leading to various synthetically useful P-stereogenic heterocycles featuring an exocyclic alkynyl group. These products are amenable to further functional manipulation.

The rapid growth in the field of asymmetric transition-metal-catalyzed reactions has relied on the availability of a robust synthetic route to chiral ligands.[1] In this context, P-stereogenic phosphines and derivatives are widely recognized as an important class of compounds, especially since they have also found applications in organocatalysis[2] and for drug development.[3] To date, their use remains relatively limited in comparison with chiral phosphines bearing stereogenic carbon centers or possessing axial or planar chirality.[4] This is likely due to the difficulties associated with the development of robust and general methods for the stereocontrolled creation of a P-stereocenter. For many years, several research groups have reported various asymmetric syntheses of P-stereogenic phosphorus compounds by resolution[5] or using chiral auxiliaries,[6] but more recently, the focus is also on generic approaches featuring catalytic asymmetric reactions.[7]

Imamoto et al. have demonstrated that P-stereogenic ligands bearing alkynyl groups induced excellent enantioselectivity in various transition-metal-catalyzed reactions, a result which was accounted for evoking the large steric differentiation at phosphorus.[8] These data indicate that transition metal catalysis would undoubtedly benefit from the availability of an increased range of P-stereogenic ligands bearing an alkynyl group (Figure 1).

In light of literature precedents, which demonstrate that various phosphorus-containing dienes, trienes, and dienynes are suitable substrates for metathesis,[9] we were particularly interested in developing a diastereoselective enyne ring-

† Author to whom correspondence regarding the X-ray crystal structures should be addressed.

(1) (a) Zhang, X. *Tetrahedron: Asymmetry* **2004**, *15*, 2099. (b) Crepy, K. V. L.; Imamoto, T. *Top. Curr. Chem.* **2003**, *111*, 1. (c) Kagan, H. B.; Dang Tuan, P. *J. Am. Chem. Soc.* **1972**, *94*, 6429. (d) Kagan, H. B. *Asymmetric Synth.* **1985**, *5*, 1. (e) Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581.

(2) (a) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal* **2004**, *346*, 1035. (b) Vedejs, E.; Daugulis, O.; Diver, S. T. *J. Org. Chem.* **1996**, *61*, 430. (c) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719. (d) Connon, S. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3909.

(3) (a) Pirat, J.-L.; Virieux, D.; Clarion, L.; Volle, J.-N.; Bakalara, N.; Mersel, M.; Montbrun, J.; Cristau, H.-J. Application WO 2009/004096A1, 2009; p 82. (b) Stoianova, D. S.; Whitehead, A.; Hanson, P. R. *J. Org. Chem.* **2005**, *70*, 5880. (c) Stoianova, D. S.; Hanson, P. R. *Org. Lett.* **2000**, *2*, 1769. (d) Whitehead, A.; Waetzig, J. D.; Thomas, C. D.; Hanson, P. R. *Org. Lett.* **2008**, *10*, 1421. (e) Waetzig, J. D.; Hanson, P. R. *Org. Lett.* **2006**, *8*, 1673.

(4) (a) Shibata, Y.; Tanaka, K. *J. Am. Chem. Soc.* **2009**, *131*, 12552. (b) Chen, I. H.; Yin, L.; Itano, W.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 11664. (c) Ito, H.; Ito, S.; Sasaki, Y.; Matsuura, K.; Sawamura, M. *J. Am. Chem. Soc.* **2007**, *129*, 14856. (d) Taylor, A. M.; Altman, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 9900.

(5) (a) Pietrusiewicz, K. M.; Zablocka, M. *Chem. Rev.* **1994**, *94*, 1375. (b) Meisenheimer, J.; Lichtenstadt, L. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 356. (c) Campbell, I. G. M.; Way, J. K. *J. Chem. Soc.* **1961**, 2133.

(6) (a) Jugé, S. *Phosphorus, Sulfur Silicon Relat. Elem.* **2008**, *183*, 233. (b) Jugé, S.; Genêt, J. P. *Tetrahedron Lett.* **1989**, *30*, 2783. (c) Jugé, S.; Stephan, M.; Laffitte, J. A.; Genêt, J. P. *Tetrahedron Lett.* **1990**, *31*, 6357. (d) Brown, J. M.; Carey, J. V.; Russell, M. J. H. *Tetrahedron* **1990**, *46*, 4877. (e) Carey, J. V.; Barker, M. D.; Brown, J. M.; Russell, M. J. H. *J. Chem. Soc., Perkin Trans. 1* **1993**, 831.

10.1021/ol100098c
Published on Web 02/25/2010

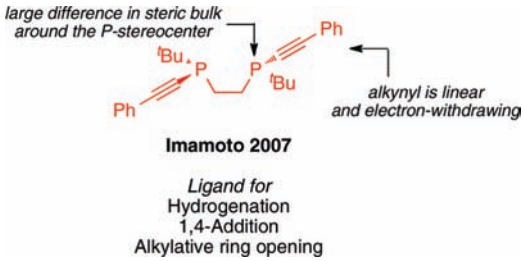
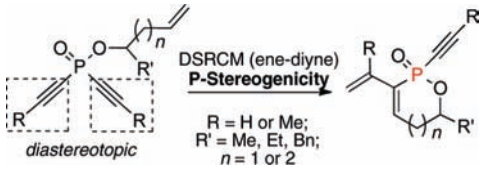


Figure 1. P-Stereogenic ligand with alkynyl groups.

closing metathesis (DSRCM) as a strategically valuable route to P-stereogenic[3c] compounds featuring an exocyclic alkynyl group (Scheme 1). We opted for a catalytic diastereoselective

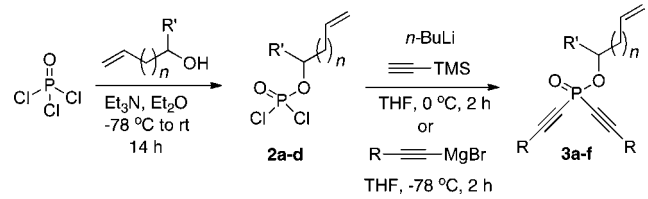
Scheme 1. Metathesis Approach to P-Stereogenic Compounds with Alkynyl Groups: Diastereoselective Ene-Diyne Metathesis



desymmetrization process of ene-diynic P-templates bearing two diastereotopic alkynyl substituents and a secondary alkoxy group that will serve as stereoinductor. The substrates selected for this investigation were designed to undergo 1,3-stereocontrolled ring closure. The products resulting from enyne metathesis are structurally novel P-stereogenic heterocycles bearing the desired exocyclic alkynyl group and a dienic fragment amenable to rich functionalization. Herein we report the first example of catalytic diastereoselective ene-diyne metathesis leading to the formation of various chiral P-stereogenic heterocycles. Diastereoselective enyne metathesis reactions are scarce in the literature[10] and have not been investigated as a strategy to induce carbon or heteroatom stereogenicity. We also demonstrate with two representative transformations that the primary product of metathesis can be further manipulated.

To initiate our investigations, we synthesized a range of P-containing ene-diynes **3a**−**f** designed to yield a single regioisomer upon RCM. On the basis of careful mechanistic work by Lloyd-Jones and co-workers providing evidence for an "ene-then-yne" pathway for the Ru-catalyzed ring-closing metathesis of enynes,[11] we anticipated that initiation would occur on the monosubstituted alkene of **3a**−**f**, followed by cyclization onto one of the two diastereotopic alkynes to afford the desired desymmetrized P-stereogenic heterocycles. The ene-diynes **3a**−**f** were prepared via monoaddition of various chiral unsaturated alcohols to phosphorus oxychloride followed by double addition of either propynyl magnesium bromide or trimethylsilylethynyl lithium. This concise synthetic route allowed for facile diversification of both the ene and diyne fragments (Table 1). In all cases, the desired dichlorophosphinate intermediates **2a**−**d** were obtained in sufficient purity to be engaged directly in the next step. Pleasingly, the addition of the alkynyl groups led successfully to the desired ene-diynes **3a**−**f** with overall chemical yields ranging from 42 to 83%.

Table 1. Synthesis of P-Containing Ene-Diynes **3a**−**f**



entry	R′	*n*	R	product	yield (%)[a]	product	yield (%)[b]
1	Me	1	H	**2a**	72	**3a**	56
2	Et	1	H	**2b**	66	**3b**	47
3	Bn	1	H	**2c**	46	**3c**	42
4	Me	2	H	**2d**	46	**3d**	55
5	Me	2	Me	**2d**	46	**3e**	65
6	Me	1	Me	**2a**	72	**3f**	83

[a] Crude yield after workup. [b] Isolated yield after purification by silica gel column chromatography.

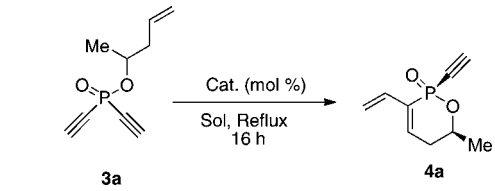
We investigated next the feasibility of the suggested diastereoselective metathesis approach to access alkynyl-substituted P-stereogenic heterocycles. Our initial studies began with ene-diyne **3a** prepared from 1-methylbut-3-enol and possessing two terminal ethynyl groups (Table 2). When the reaction was performed using 2 mol % of the Grubbs catalyst II in DCM at reflux, the desired product **4a** was formed, albeit in low conversion and very modest diastereoselectivity (entry 1). An attempt to increase conversion

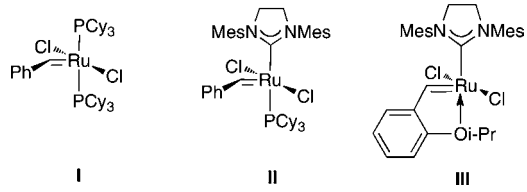
(7) (a) Join, B.; Mimeau, D.; Delacroix, O.; Gaumont, A.-C. *Chem. Commun.* **2006**, 3249. (b) Glueck, D. S. *Chem.—Eur. J.* **2008**, *14*, 7108. (c) Brunker, T. J.; Anderson, B. J.; Blank, N. F.; Glueck, D. S.; Rheingold, A. L. *Org. Lett.* **2007**, *9*, 1109. (d) Scriban, C.; Glueck, D. S. *J. Am. Chem. Soc.* **2006**, *128*, 2788. (e) Moncarz, J. R.; Laritcheva, N. F.; Glueck, D. S. *J. Am. Chem. Soc.* **2002**, *124*, 13356. (f) Blank, N. F.; Moncarz, J. R.; Brunker, T. J.; Scriban, C.; Anderson, B. J.; Amir, O.; Glueck, D. S.; Zakharov, L. N.; Golen, J. A.; Incarvito, C. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **2007**, *129*, 6847. (g) Blank, N. F.; McBroom, K. C.; Glueck, D. S.; Kassel, W. S.; Rheingold, A. L. *Organometallics* **2006**, *25*, 1742. (h) Anderson, B. J.; Glueck, D. S.; DiPasquale, A. G.; Rheingold, A. L. *Organometallics* **2008**, *27*, 4992. (i) Chan, V. S.; Stewart, I. C.; Bergman, R. G.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 2786. (j) Chan, V. S.; Bergman, R. G.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 15122. (k) Genet, C.; Canipa Steven, J.; O'Brien, P.; Taylor, S. *J. Am. Chem. Soc.* **2006**, *128*, 9336. (l) Gammon, J. J.; Canipa, S. J.; O'Brien, P.; Kelly, B.; Taylor, S. *Chem. Commun.* **2008**, 3750. (m) Nishida, G.; Noguchi, K.; Hirano, M.; Tanaka, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3410.

(8) Imamoto, T.; Saitoh, Y.; Koide, A.; Ogura, T.; Yoshida, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 8636.

(9) (a) Timmer, M. S. M.; Ovaa, H.; Filippov, D. V.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **2001**, *42*, 8231. (b) Schuman, M.; Trevitt, M.; Redd, A.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2000**, *39*, 2491. (c) Slinn, C. A.; Redgrave, A. J.; Hind, S. L.; Edlin, C.; Nolan, S. P.; Gouverneur, V. *Org. Biomol. Chem.* **2003**, *1*, 3820. (d) Bisaro, F.; Gouverneur, V. *Tetrahedron* **2005**, *61*, 2395. (e) Dunne, K. S.; Bisaro, F.; Odell, B.; Paris, J.-M.; Gouverneur, V. *J. Org. Chem.* **2005**, *70*, 10803. (f) McReynolds, M. D.; Dougherty, J. M.; Hanson, P. R. *Chem. Rev.* **2004**, *104*, 2239. (g) Harvey, J. S.; Malcolmson, S. J.; Dunne, K. S.; Meek, S. J.; Thompson, A. L.; Schrock, R. R.; Hoveyda, A. H.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2009**, *48*, 762.

Table 2. Optimization Studies for DSRCM of **3a** into **4a**





entry	cat (mol %)	atmosphere	solvent	conv (%)[a]	dr[b]
1	II (2)	Ar	DCM	34	3:1
2	II (2)	ethylene	DCM	40	2:1
3	II (5)	Ar	DCM	75	3:1
4	II (5)	ethylene	DCM	73	3:1
5	II (10)	Ar	DCM	90	4:1
6	I (10)	Ar	toluene	45	3:1
7	II (10)	Ar	toluene	>98	10:1
8	***III (10)***	***Ar***	***toluene***	***>98***	***18:1***

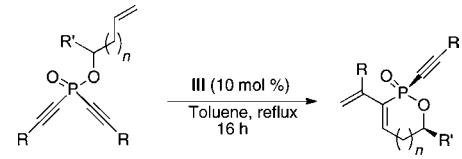
[a] Conversion to desired product measured by 400 MHz ^{1}H NMR. [b] Measured from the crude by 400 MHz ^{1}H NMR. Mes = 2,4,6-*i*-Pr-C_6H_3.

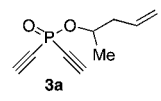
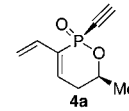
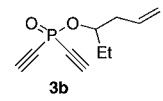
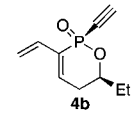
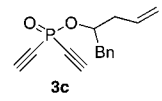
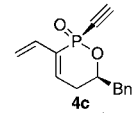
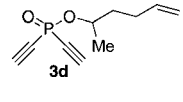
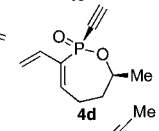
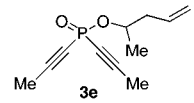
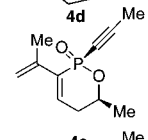
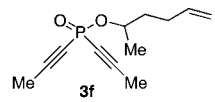
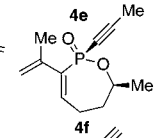
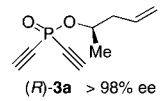
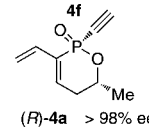
by conducting this reaction under an atmosphere of ethylene (Mori's conditions)[12] led to no improvement of the conversion or diastereomeric ratio. Further optimization work focused on increasing the catalyst loading from 2 to 10 mol %. With 10 mol % of II, almost full conversion to the desired product was observed (entry 5). When using an intermediate catalyst loading of 5 mol %, the reaction stalled at ~75% conversion (entries 3 and 4). In all cases, the level of diastereocontrol remained unsatisfactory. Notably, using the same Grubbs catalyst II in toluene at reflux instead of dichloromethane, we were pleased to observe that the product was formed with a dr of 10:1 (entry 7).[13] The level of diastereocontrol was further improved (dr = 18:1) using 10 mol % of Hoveyda catalyst III in toluene (entry 8). The observation that a change of solvent can impact on the efficiency of a diastereocontrolled ring closure in the context of the metathesis reaction has not been discussed. It is, however, well-documented that the nature of the solvent can modulate catalyst activity or lead to variations in enantioselectivity for asymmetric metathesis reactions.[14]

Having established optimized reaction conditions for the ring closure of **3a**, we extended the scope of the reaction to ene-diynes **3b**−**f** (Table 3). A range of six- and seven-membered P-stereogenic heterocycles was made accessible upon ring-closing metathesis. For ethynyl-substituted substrates, the desired products were obtained with conversion superior to 98% with no trace of oligomer or homodimer byproducts observed by ^{1}H or ^{31}P NMR. The isolated chemical yields were consistently high and independent of the substituent on the stereogenic carbon or the ring size of the product. Decreasing the steric bulk on the stereogenic center from Bn to Et or Me led to an increase in selectivity. The dr dropped significantly for the ring closure of **3d** leading to the seven-membered ethynyl tetrahydro oxaphosphine oxide **4d**. Substitution at the alkynyl motif had a detrimental effect on both conversion and selectivity (entries 5 and 6). As expected, the chemistry was easily transposed to the preparation of enantiopure (*R*)-**4a** from the chiral nonracemic phosphinate (*R*)-**3a**, which was directly accessible from (*R*)-4-penten-1-ol.

The relative *cis* relationship between the alkynyl substituent and the R′ group of the products was unambiguously

Table 3. Scope of Diastereoselective Enyne Ring-Closing Metathesis



entry	ene-diyne	product	convn (%)[a] / yield (%)[b]	dr[c]
1	 **3a**	 **4a**	> 98 / 86	18:1
2	 **3b**	 **4b**	> 98 / 85	10:1
3	 **3c**	 **4c**	> 98 / 80	11:1
4	 **3d**	 **4d**	> 98 / 79	3:1
5	 **3e**	 **4e**	15 / n.d.[d]	4:1
6	 **3f**	 **4f**	0 [e]	-
7	 (*R*)-**3a** > 98% ee	 (*R*)-**4a** > 98% ee	> 98 / 71	18:1

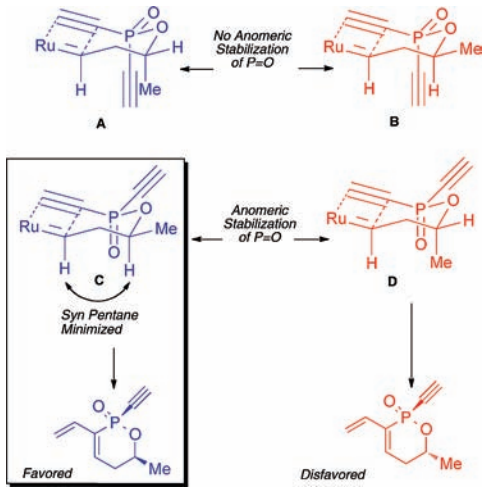
[a] Conversion measured by 400 MHz ^{1}H NMR. [b] Combined isolated yield of both diastereomers. [c] Diasteroselectivity determined by 400 MHz ^{1}H NMR of the unpurified product. [d] Not determined. [e] Only starting material recovered.

(10) For elegant examples, see: (a) Layton, M. E.; Morales, C. A.; Shair, M. D. *J. Am. Chem. Soc.* **2002**, *124*, 773. (b) Porta, M.; Blechert, S. *Abstracts of Papers, ISOM 18*, Aug. 2−7th, **2009**. (c) For enantioselective enyne ring-closing metathesis, see: Lee, Y.-J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 10652. (d) Kim, S.-H.; Zuercher, W. J.; Bowden, N. B.; Grubbs, R. H. *J. Org. Chem.* **1996**, *61*, 1073.

confirmed by single-crystal X-ray analysis of **4a** and **5b** and was assigned by analogy for the other ring-closed products (see Supporting Information for details).

In order to gain more insight into the DSRCM reaction, further experiments were performed to determine whether the products obtained upon ring closure were the result of a kinetically or thermodynamically controlled process. After separation of the two diastereomers of product **4a** both the major *cis* and minor *trans* were subjected separately to the reaction conditions. The results of these experiments showed that no epimerization took place, suggesting that the reactions are under kinetic control. A plausible mechanistic rationale for the observed selectivity is presented in Scheme 2. The donation of the endocyclic oxygen lone pair

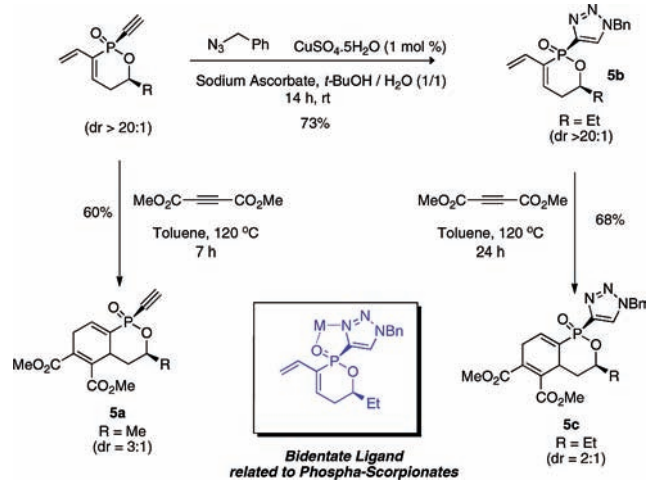
Scheme 2. Rationale for the Observed Selectivity



into the σ^* orbital of the exocyclic P═O bond[15] stabilizes both **C** and **D** with **C** being favored likely due to minimization of *syn*-pentane interaction (Scheme 2).

With the DSRCM products in hand, we investigated next the possibility to engage the diene or the alkyne in postmetathesis transformations (Scheme 3). The dienic motif would be amenable to Diels−Alder chemistry, and the alkyne group could possibly undergo a click-type 1,3-dipolar cycloaddition. Both reactions will increase structural complexity, leading to a new family of P-stereogenic ligands suitable for investigation in the context of catalysis. For these experiments, the ring-closed product was engaged as a single diastereomer. Compound **4a** was reacted with dimethylacetylene dicarboxylate (DMAD) as the reacting dienophile. After 7 h in toluene at reflux, the desired cycloadduct **5a** was obtained in 60% yield as a 3:1 mixture of diastereomers. Upon treatment with benzyl azide and 1 mol %

Scheme 3. Two-Directional Functionalization



of $CuSO_4 \cdot 5H_2O$ and sodium ascorbate, the desired triazole **5b** was isolated in 73% yield. A single diastereomeric product was formed, indicating that no epimerization occurred in this process. The Diels−Alder cycloaddition of **5b** with DMAD was also successful delivering **5c** in 68% yield. Compounds **5b** and **5c** resemble conspicuously the ligands of the phospha-scorpionates family.[16]

In conclusion, we have reported a novel route to P-stereogenic heterocycles bearing an exocyclic alkynyl group, based on a key diastereoselective ene-diyne ring-closing metathesis reaction. This is the first report of diastereoselective enyne metathesis to create stereogenicity at an atom other than carbon. We have shown that the ring-closed products are amenable to postmetathesis functionalization via either Diels−Alder or click chemistry. This work undoubtedly paves the way for the development of an enantioselective ene-diyne ring-closing metathesis process from prochiral templates.

Acknowledgment. We thank the John Fell (062/214) and the EPSRC for very generous funding.

Supporting Information Available: Additional experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

OL100098C

(11) Lloyd-Jones, G. C.; Margue, R. G.; de Vries, J. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 7442.

(12) (a) Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, *63*, 6082. (b) Kinoshita, A.; Sakakibara, N.; Mori, M. *Tetrahedron* **1999**, *55*, 8155.

(13) Evans, P. A.; Cui, J.; Buffone, G. P. *Angew. Chem., Int. Ed.* **2003**, *42*, 1734.

(14) (a) Samojlowicz, C.; Bieniek, M.; Zarecki, A.; Kadyrov, R.; Grela, K. *Chem. Commun.* **2008**, 6282. (b) Funk, T. W.; Berlin, J. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 1840. (c) Grandbois, A.; Collins, S. K. *Chem.—Eur. J.* **2008**, *14*, 9323. (d) Fujimura, O.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 824. (e) Sattely, E. S.; Cortez, G. A.; Moebius, D. C.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 8526. (f) Fujimura, O.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 2499. (g) Lee, A.-L.; Malcolmson, S. J.; Puglisi, A.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 5153. (h) Rost, D.; Porta, M.; Gessler, S.; Blechert, S. *Tetrahedron Lett.* **2008**, *49*, 5968.

(15) (a) Ruben, E. A.; Plumley, J. A.; Chapman, M. S.; Evanseck, J. D. *J. Am. Chem. Soc.* **2008**, *130*, 3349. (b) Gorenstein, D. G. *Chem. Rev.* **1987**, *87*, 1047.

(16) (a) van Assema, S. G. A.; Tazelaar, C. G. J.; de Jong, G. B.; van Maarseveen, J. H.; Schakel, M.; Lutz, M.; Spek, A. L.; Slootweg, J. C.; Lammertsma, K. *Organometallics* **2008**, *27*, 3210. (b) Rheingold, A. L.; Liable-Sands, L. M.; Trofimenko, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 3321.