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Tandem Enyne Metathesis and Claisen Rearrangement: A Versatile Approach to Conjugated Dienes of Variable Substitution Patterns

Daniel A. Clark, Amol A. Kulkarni, Kyle Kalbarczyk, Bryan Schertzer, and Steven T. Diver*

Contribution from the Department of Chemistry, University at Buffalo, the State University of New York, Buffalo, New York 14260-3000

Received May 10, 2006; E-mail: diver@buffalo.edu

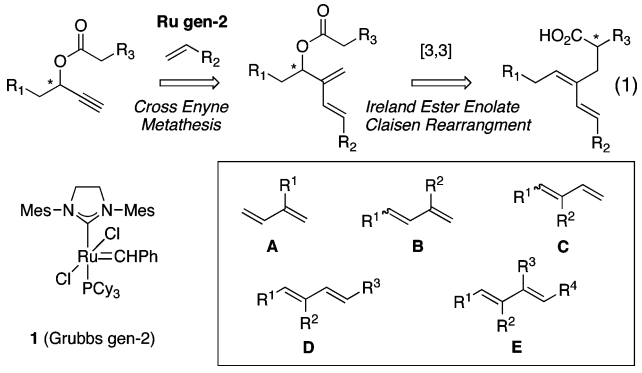
Abstract: To extend the versatility of the ruthenium carbene-promoted enyne metathesis, it was combined with an Ireland ester enolate Claisen rearrangement. This reaction sequence provided conjugated dienes of higher substitution pattern than that obtained through a cross-enyne metathesis alone. The Ireland−Claisen was conducted across both acyclic and cyclic dienes produced from cross-metathesis and methylene-free enyne metathesis, respectively. In the case of cyclodienes, the Ireland−Claisen rearrangement produced *s-trans* locked dienes which underwent mode-selective ene reaction. The tandem, sequential use of the Ireland−Claisen rearrangement also proved suitable for chirality transfer originating from chiral propargylic alcohols. Last, the tandem metathesis/Ireland−Claisen was utilized to access 4-substituted-3,5-cyclohexadiene diol derivatives, which are valuable chiral intermediates for natural product synthesis. The combination of this pericyclic reaction with a catalytic metathesis reaction extends the versatility of cross-metathesis since additional diene motifs can be accessed.

Introduction

Tandem reactions offer a simple way of extending the complexity-building potential of a catalytic reaction.[1] Tandem reactions refer to two reactions operating in succession in the same reaction vessel. Sequential tandem reactions are a second class of successive reactions run in two separate reaction steps. The first category of tandem reactions are well-suited to complexity building and have been used due to their efficiency for making carbon−carbon bonds. The tandem use of sequential reactions offers the advantage of a unique combination of the two reactions. The use of combined, sequential tandem reactions to overcome weaknesses in a catalytic reaction represents a new and potentially useful way to extend the versatility of the catalytic reaction. This may include improved reaction scope or allow access to structural motifs not possible through the catalytic reaction working alone.

Enyne metathesis has emerged as an important synthetic method for conjugated diene synthesis.[2] Perhaps the most synthetically useful version of catalytic enyne metathesis is the intermolecular reaction between alkene and alkynes, producing conjugated diene products (eq 1, first step). The synthetic appeal of intermolecular (cross) metathesis is that it offers direct, catalytic access to conjugated dienes, which have broad utility in synthesis. Moreover, use of Grubbs' ruthenium carbenes permits chemoselectivity (functional group tolerance), providing wide substrate scope with respect to the unsaturated reactants. Yet an unresolved weakness of the cross-enyne metathesis is that only a limited number of diene substitution patterns can be accessed directly (inset, Scheme 1).

Scheme 1. Dienes by Enyne Metathesis with Consecutive Claisen Rearrangement



The enyne cross-metathesis is limited to particular substitution patterns. The basic reaction between 1-alkenes and 1-alkynes

(1) General reviews on tandem reactions: (a) Ho, T. L. *Tandem Organic Reactions*; Wiley: New York, 1992. (b) Tietze, L. F.; Beifuss, U. *Angew. Chem.* **1993**, *105*, 137−170. (c) Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103−13159. (c) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115−136. (d) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195−206. (e) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551−564. (f) Wasilke, J. C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001−1020. Tandem reactions involving metathesis steps: (g) Sutton, A. E.; Seigal, B. A.; Finnegan, D. F.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 13390−13391. (h) White, B. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2003**, *125*, 14901−14904. (i) Peppers, B. P.; Diver, S. T. *J. Am. Chem. Soc.* **2004**, *126*, 9524−9525. (j) Seigal, B. A.; Fajardo, C.; Snapper, M. L. *J. Am. Chem. Soc.* **2005**, *127*, 16329−16332. (k) Kim, B. G.; Snapper, M. L. *J. Am. Chem. Soc.* **2006**, *128*, 52−53.

(2) Recent reviews: (a) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317−1382. (b) Poulsen, C. S.; Madsen, R. *Synthesis* **2003**, 1−18. First examples of cross-enyne metathesis: (c) Blechert, S.; Stragies, R.; Schuster, M. *Angew. Chem., Int. Ed.* **1997**, *36*, 2518−2520. (d) Kinoshita, A.; Sakakibara, N.; Mori, M. *J. Am. Chem. Soc.* **1997**, *119*, 12388−12389.

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(terminal alkynes) produces a conjugated diene bearing the 1,3-disubstitution pattern (e.g., **B**). The high regioselectivity of the cross-metathesis results in **B** such that **C** is not formed (featuring 1,2-disubstitution). Currently this limits the diene structural motifs accessible by intermolecular enyne metathesis. The simplest 2-substituted butadiene **A** comes from ethylene−alkyne cross-metathesis.[1d] Higher diene substitution patterns as represented in **D** and **E** cannot be accessed. Though tandem reactions have been applied to metathesis processes,[1a−e] they have not been utilized to address a deficiency of the parent reaction. In this article we combined the diene synthesis with a consecutive Ireland ester enolate Claisen rearrangement (Ireland−Claisen) to form acyclic and cyclic dienes with high substitution patterns not approachable through catalytic enyne metathesis alone (eq 1). We also demonstrate that the Ireland−Claisen rearrangement can be performed across dienes without difficulty, that chirality transfer is observed, and that the tandem method is suitable for enantiospecific synthesis of a chiral cyclohexadiene diol derivative.

Results and Discussion

The tandem sequential enyne metathesis/Ireland−Claisen rearrangement was first evaluated in acyclic dienes. In all of these cases, the enyne metathesis was conducted first between alkyne and alkene reactants to give the conjugated dienes. The conjugated dienes were isolated and reacted in a second reaction to obtain the Ireland−Claisen products. The Ireland−Claisen reaction consisted of enolization, trapping to form the silyl ketene acetals, and subsequent in situ [3,3] sigmatropic rearrangement on warming to ambient temperature. To the best of our knowledge, the Ireland−Claisen reaction has not employed conjugated dienes directly in the pericyclic process.[3]

Acyclic Dienes. The results of the tandem enyne metathesis/Claisen reaction are illustrated in Table 1. In these cases, the intermediate dienes are produced by cross-metathesis with ethylene,[4] enol ethers, or 1-alkenes. The yields in the third column represent that of purified dienes. The Ireland−Claisen rearrangement[5] results in acyclic dienes featuring a translocated diene with distal carboxylic acid functionality (last column, Table 1). The workup conditions were chosen to obtain either the carboxylic acid or the corresponding ester (entries 1 and 2).[5b] The [3,3] sigmatropic rearrangement occurs across one alkene of the conjugated diene without difficulty (entries 1−4). 2,3-Disubstituted butadiene **6B**[4d] gave rearrangement to a 1,2,3-trisubstituted butadiene **6C** in good yield (entry 5). In this single example a mixture of stereoisomers was produced in the Claisen step. In the minor isomer of **6C** an NOE enhancement of the allylic methyl group at δ 2.05 was observed on irradiation of the benzylic methine proton appearing at δ 6.71, thereby supporting the *E* geometry of the trisubstituted alkene in the diene moiety. It is unlikely that the refluxing conditions alone are responsible for the partial erosion of stereochemistry since similar conditions were used with **2B** in entry 1. It is possible that the silyl ketene acetal of **6B** experiences a *syn*-pentane interaction in the Claisen chair transition state occurring between the equatorial phenyl and the axial isopropenyl group, resulting in partial loss of stereochemical information transfer. The dienol ether **7B**,[4e] produced as a 1:1 mixture in the metathesis step, underwent Claisen rearrangement without perturbing the enol ether (entry 6). The produced diene **7C** was produced as a 1.3:1 mixture of diastereomers.

Table 1. Tandem Enyne Metathesis/Claisen for Acyclic Dienes

entry	alkyne	metathesis product[a]	Ireland-Claisen product[b]
1	**2A** (n=0)	**2B** (n=0, 68%)	**2C** (n=0, R=H, 82%)[c]
2	**2A** (n=0)	**2B**	**3C** (n=0, R=Me, 52%)[d]
3	**4A** (n=1)	**4B** (n=1, 99%)[e]	**4C** (n=1, R =H, 82%)[c]
4	**5A** (n=2)	**5B** (n=2, 99%)[e]	**5C** (n=2, R =H, 58%)
5	**6A**	**6B**[e]	**6C** (85%, 5:1 *Z*/*E*)[c]
6	**4A**	**7B** (1:1 *E*/*Z*)[e]	**7C** (60%. 1.3:1 *E*/*Z*)
7	**8A**	**8B** (82%, >95% *E*)	**8C** (61%, >95% *E*)
8	**2A** (n=0)	**9B** (R = *n*-C_4H_9, 68%)	**9C** (R = *n*-C_4H_9, 80%)
9	**4A** (n=1)	**10B** (R = *n*-C_4H_9, 93%)	**10C** (R = *n*-C_4H_9, 85%)
10	**5A** (n=2)	**11B** (R = *n*-C_4H_9, 71%)	**11C** (R = *n*-C_4H_9, 57%)

[a] Metathesis conditions: **Ru gen-2** (5 mol %), 9 equiv of alkene, CH_2Cl_2, reflux, 12−24 h. [b] Ireland−Claisen conditions: LiHMDS/HMPA/TBSCl, −78 °C; warm to rt, 12 h. [c] Refluxed 2 h. [d] Workup with KF (2 equiv), $KHCO_3$ (2 equiv), and MeI (5 equiv) in THF, 15 h. [e] Compound previously reported; see Supporting Information for details.

Cross-metathesis between simple alkenes and terminal alkynes generally gives mixtures of *E*/*Z* isomers. There are few instances where even modest *E* selectivity is obtained.[6] In earlier work, we found that kinetically formed *E*/*Z* diene mixtures underwent equilibration via subsequent cross-metathesis (diene−alkene metathesis) to give predominantly the *E* isomer.[6b] 1,3-Disubstituted dienes obtained from cross-metathesis with 1-hexene were formed with high *E* selectivity using extended reaction times (12−24 h). As expected, the *E* geometry at the alkene not involved in the sigmatropic shift was preserved (entries 7−10). The final products feature dienes substituted at both ends with a high degree of sterocontrol: in one case due to the metathesis step; in the other due to the Claisen rearrangement.

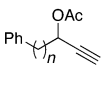
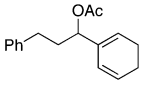
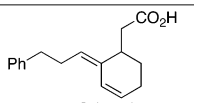
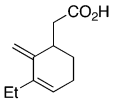
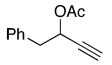
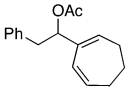
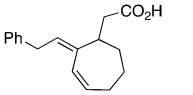
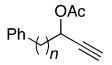
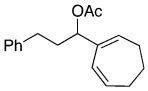
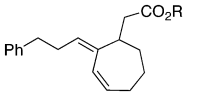
(3) The Ireland−Claisen has been used to transform nonconjugated dienes to conjugated dienes, see: (a) Wender, P. A.; Ihle, N. C.; Correia, C. R. D. *J. Am. Chem. Soc.* **1988**, *110*, 5904−5906. (b) Parker, K. A.; Farmar, J. G. *J. Org. Chem.* **1986**, *51*, 4023−4028.

(4) Ethylene cross-metathesis: (a) Kinoshita, A.; Sakakibara, N.; Mori, M. *J. Am. Chem. Soc.* **1997**, *119*, 12388−12389. (b) Kinoshita, A.; Sakakibara, N.; Mori, M. *Tetrahedron* **1999**, *55*, 8155−8167. (c) Smulik, J. A.; Diver, S. T. *J. Org. Chem.* **2000**, *65*, 1788−1792. (d) Smulik, J. A.; Diver, S. T. *Org. Lett.* **2000**, *2*, 2271−2274. Enol ether cross-metathesis: (e) Giessert, A. J.; Snyder, L.; Markham, J.; Diver, S. T. *Org. Lett.* **2003**, *5*, 1793−1796.

(5) (a) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897−8. (b) Ireland, R. E.; Wipf, P.; Armstrong, J. D., III *J. Org. Chem.* **1991**, *56*, 650−7. (c) Ireland, R. E.; Wipf, P.; Xiang, J. N. *J. Org. Chem.* **1991**, *56*, 3572−82.

(6) (a) Lee, H. Y.; Kim, B. G.; Snapper, M. A. *Org. Lett.* **2003**, *5*, 1855−1858. (b) Giessert, A. J.; Diver, S. T. *J. Org. Chem.* **2005**, *70*, 1046−1049.

Table 2. Tandem Enyne Metathesis/Claisen for Cyclic Dienes

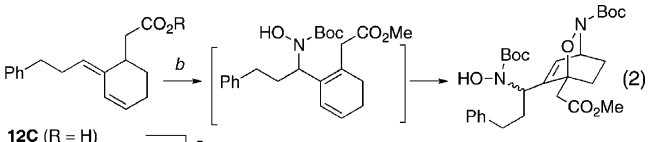
entry	alkyne	metathesis product[a]	Ireland-Claisen product[b]
1	 **5A** (n=2)	 **12B** (64%)	 **12C** (68%)
2	 **13A**	 **13B** (72%)	 **13C** (61%)
3	 **4A**	 **14B** (62%)	 **14C** (63%)
4 5	 **5A** (n=2) **5A** (n=2)	 **15B** (65%)	 **15C** (R=H, 68%) **16C** (R=Me, 63%)[c]

[a] Metathesis conditions: **Ru gen-2** (5 mol %), 8 equiv of polybutadiene (entries 1−2) or 4 equiv of cyclopentene (entries 3−5), CH_2Cl_2, 40 °C. [b] Ireland−Claisen conditions: LiHMDS/HMPA, −78 [deg]C; TBSCI, rt, 12 h. [c] Workup with KF (2 equiv), KHCO3 (2 equiv), and MeI (5 equiv) in THF, 15 h.

Cyclodienes. The consecutive Claisen rearrangement was also applied to cyclodienes obtained using the 'methylene-free' ring synthesis.[7] The methylene-free ring synthesis can be used for the synthesis of 2-substituted-1,3-cyclohexadienes or 1,3-cycloheptadienes using either a four-carbon or five-carbon source, respectively. In the cyclohexadiene synthesis, 1,5-cyclooctadiene or polybutadiene can be used as the four-carbon source. The 1,3-cycloheptadiene synthesis utilizes ring expansion of cyclopentene. These two methylene-free procedures were employed in the first metathesis steps of Table 2.

Unlike the acyclic examples in Table 1, the alkene participating in the pericyclic process (see **12B**, Table 2) is substituted at the diene terminus. None of the examples in Table 1 show this substitution pattern; all of those cases involve acyl rearrangement to a methylene position. In the higher substitution found in cyclodienes of Table 2 diene substitution could potentially thwart the Claisen step of the tandem reaction sequence. Despite this concern, rearrangement into the cyclohexadiene system proved uneventful, providing the *s-trans* alkylidene cyclohexenes under the standard conditions used above (entry 1, Table 2). The internal alkyne-derived cyclohexadiene **13B** underwent rearrangement efficiently, giving diene **13C**, featuring a 1,2,3-trisubstitution pattern (entry 2). The ring expansion of cyclopentene provided cycloheptadienes[7a] **14B** and **15B**, which underwent Ireland−Claisen rearrangement to give the corresponding *exo*-alkylidenes in comparable yields (entries 3−5).

The *s-trans* dienes can be used in a mode-selective reaction. Normally, concerted cycloadditions to conjugated dienes proceed through the *s-cis* conformation. Dienophiles react with *dienes* in cycloaddition or with an *alkene*-portion of the diene as enophiles, giving the ene reaction. Since the diene products of tandem metathesis/Claisen rearrangement in Table 2 (last column) are locked into an *s-trans* conformation, we reasoned that concerted cycloaddition would not be possible, offering a unique venue to illustrate this reactivity profile. The restricted conformation would permit a competitive ene reaction to occur selectively over cycloaddition. Though mode selectivity seemed to be a plausible expectation, diene **12D** has three different sets of allylic hydrogens that could engage with the enophile, possibly leading to three different constitutional isomers.[8]



Conditions: (a) $TMSCHN_2$, CH_2Cl_2/MeOH; (b) BocNHOH (4 equiv), Pr_4NIO_4 (4 equiv), CH_2Cl_2, 0 °C, 2 h.

Mode-selective ene reaction was evaluated using an acyl nitroso generated under oxidative conditions in situ. Acyl nitroso species are synthetically useful due to their potential to form both C−N and C−O bonds from conjugated dienes (1,4-*N*,*O*-difunctionalization). The acyl nitroso can serve dually as dienophile and/or enophile.[9] In the event, **12D** underwent a position-selective ene reaction, subsequently trapped by an in situ hetero [4+2], giving adduct **18** in good isolated yield as a 1.7:1.0 mixture of separable diastereomers (eq 2). The ene reaction occurred first, producing an intermediate *cis*-endocyclic diene **17**. Remarkably, the ene reaction displayed position selectivity, reacting preferentially with the single endocyclic allylic hydrogen. Stopping the reaction at the ene product **17** using fewer equivalents of hydroxamic acid and oxidant (1.2−2.0 equiv) proved unsuccessful. With less reagent, partial consumption of the *s-trans* diene **12D** was observed along with adducts **18**. Presumably the nitroso cycloaddition is faster than the initial ene reaction. This may be explained by the observation of Keck that acyl nitroso species give qualitatively faster cycloaddition vs ene reaction.[9h]

The regiochemistry of the major diastereomer of cycloadduct **18** was assigned based on the COSY spectrum showing coupling between the distal bridgehead proton (m, δ 4.75 ppm) and both the vinylic proton (δ 6.32 ppm) and one of the bicyclic CH_2 protons (δ 1.82 ppm). Also, a weak NOE to the upfield Boc group (δ 1.48 ppm) was observed upon irradiation of the bridgehead methine resonance (δ 4.75 ppm). The diastereomers of **18** gave NOE spectra reflecting differences in local chirality around the exocyclic α-amino methine proton.[10]

Chirality Transfer. The Ireland−Claisen reaction provides a means to produce a remote asymmetric center. Chirality transfer from a chiral center bearing the propionyl group to the remote α-chiral center of the carboxyl group was observed. In this case, chirality originated from the chiral propargyl alcohol **19**, obtained through enantioselective enzymatic ester hydrolysis[4c] (eq 3). Esterification and ethylene metathesis gave the butadiene

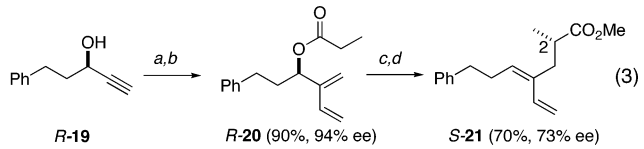
(7) (a) Kulkarni, A. A.; Diver, S. T. *Org. Lett.* **2003**, *5*, 3463−6. (b) Kulkarni, A. A.; Diver, S. T. *J. Am. Chem. Soc.* **2004**, *126*, 8110−8111.

(8) For an excellent discussion of the regiochemistry of nitroso ene reactions, see: Adam, W.; Krebs, O. *Chem. Rev.* **2003**, *103*, 4131−4146.

(9) Nitroso dienophiles: (a) Kirby, G. W. *Chem. Soc. Rev.* **1977**, *6*, 1−24. (b) Miller, M. J. *Tetrahedron* **1998**, *54*, 1317−1348. Early examples: (c) Keck, G. E.; Fleming, S. A. *Tetrahedron Lett.* **1978**, 4763−6. (d) Keck, G. E.; Nickell, D. G. *J. Am. Chem. Soc.* **1980**, *102*, 3632−3634. (e) Boger, D. L.; Patel, M.; Takusagawa, F. *J. Org. Chem.* **1985**, *50*, 1911−1916. (f) Sato, T.; Aoyagi, S.; Kibayashi, C. *Org. Lett.* **2003**, *5*, 3839−3842. Acylnitroso ene reactions in synthesis: (g) Keck, G. E.; Webb, R. *Tetrahedron Lett.* **1979**, 1185−6. (h) Keck, G. E.; Webb, R. R.; Yates, J. B. *Tetrahedron* **1981**, 4007−4016. (i) Matsumura, Y.; Aoyagi, S.; Kibayashi, C. *Org. Lett.* **2003**, *5*, 3249−3252.

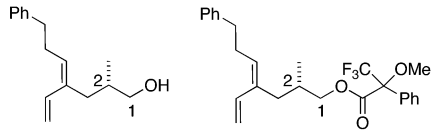
(10) See Supporting Information for details.

Scheme 2. Chirality Transfer in Claisen Rearrangement and Assignment of Absolute Stereochemistry



R-**19** *R*-**20** (90%, 94% ee) *S*-**21** (70%, 73% ee)

Conditions: (a) propionyl chloride, Et_3N, DMAP (cat.),CH_2Cl_2, 96%; (b) **1** (5 mol %), ethylene (80 psig), CH_2Cl_2, rt, 94%; (c) KHMDS/TMSCl, Et_2O, -78 °C to rt, 82%; (d) $TMSCHN_2$, CH_2Cl_2/MeOH, 86%



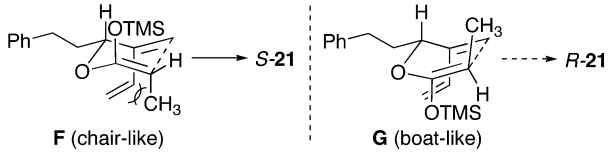
22 (2*S*,*R**)-**23A** (2*S*,*S**)-**23B**

20 in 94% ee. In propionates **20**, silyl ketene acetal formation under standard conditions (LiHMDS, TBSCl THF/HMPA, −78 °C) was problematic and resulted in poor conversions. We overcame these difficulties using the conditions described by McIntosh (KHMDS/TMSCl, toluene, −78 °C)[11] to give more efficient silyl ketene acetal generation, thereby obtaining the Claisen product in 82% yield. Esterification using $TMSCHN_2$ gave the methyl ester *S*-**21**, which was used for analysis. Enantiomeric excess determination was performed on **21**, which showed 73% ee (hplc), indicating 78% chirality transfer.[12]

The absolute stereochemistry of the Claisen product *S*-**21** was determined on the basis of a Mosher method. Reduction of the ester to primary alcohol **22** ($LiAlH_4$, Et_2O, 96% yield) was followed by Mosher ester synthesis. The alcohol **22** was reacted separately with the *R**-MTPA and *S**-MTPA to provide the *2S*,*R**-diastereomer **23A** and the *2S*,*S**-diastereomer **23B**, respectively (Scheme 2).[13] Using the method devised by Kobayashi,[14] the diastereotopic C1 methylene protons (adjacent to the C_2 stereocenter under scrutiny) are influenced differentially by the Mosher ester chiral center. The empirical model predicts that if the compound has *S* stereochemistry, then the *2S*,*S** diastereomer will show a larger separation of the chemical shift ($\Delta\delta$) of the protons H_a and H_b comprising the AB system whereas the *2S*,*R** diastereomer will not show a major difference in the chemical shift of H_a,H_b. This was observed: the AB quartet for *S**,*S*-**22B** solved for H_a at δ 4.16 and H_b at δ 4.00 with $\Delta\delta$ = 0.16 ppm, whereas the diastereomer *R**,*S*-**22A** showed H_a at δ 4.09 and H_b at δ 4.05 (J_{AB}= 10.7 Hz) with $\Delta\delta$ = 0.03 ppm.[15]

The origin of the modest chirality transfer in the Ireland−Claisen step was examined next. First, high diastereoselectivity of the enolization step was established in a model ester enolate using menthyl propionate. Under similar enolization/trapping conditions to that used in eq 3, the *E*-silyl ketene acetal was formed under kinetic control in >95:5 ratio. This assignment was made based on proton NMR determination observing the quartet at δ 3.78 ppm, similar to that observed by Ireland et al. in their comprehensive study.[5b] Having verified high diastereoselectivity in the enolization step, we considered that the slight erosion of chirality transfer may be due to destabilizing 1,3-diaxial interaction in the dominant chairlike transition state **F**. Ireland et al.[5c] suggest that the energy differences between favored chair- and boat-like transition states can be very small depending on substitution and the electronic nature of the alkene. As a result, a competing boat transition state **G** may become energetically accessible (Scheme 3). Leakage through the boat-like transition state would result in formation of the enantiomer *R*-**21**, thereby eroding the enantiomeric excess of *S*-**21** arising through the chairlike transition state. This explains the modest chirality transfer, which is unusual for the Ireland−Claisen rearrangement.

Scheme 3. Possible Transition States in Ireland−Claisen Step



Application. Chiral cyclohexadiene diol derivatives are versatile intermediates used in the synthesis of many natural products.[11] Enantioselective oxidation of monosubstituted benzenes using *P. putidia* are very powerful, providing access to 3-substituted-3,5-cyclohexadiene-1,2-diols (see **J**).[16] While highly useful to produce the 3-substitution pattern, the enzymatic method is not well-suited to the direct synthesis of 4-substituted-3,5-cyclohexadiene-1,2-diols. The 4-substitution pattern can be found in a number of natural products including the epoxyquinoids.[17] Because of our interest in synthesizing ambewelamide A, we sought a metathesis route to 4-substituted cyclohexadiene diols. Initial experiments focused on cross-metathesis to make the cyclohexadiene ring similar to the methylene-free metathesis, but the allylic oxygen atoms inhibited this process. For example, direct enyne metathesis between 3,4-dialkoxy-1,5-hexadienes **H** and alkynes failed to give the desired 1,3-cyclohexadienes. The tandem sequence of cross-enyne metathesis and Ireland−Claisen reaction was used tactically to assemble the unsaturated elements to set the stage for a final ring-closing metathesis. The intramolecular nature of the metathesis step was expected to overcome the difficulties encountered in cross-metathesis with allylic ethers present in the alkene substrate.

The tandem metathesis/Claisen sequence was used to access chiral cyclohexadiene diol **27** (Scheme 4). In this case, the tandem sequence was followed by a ring-closing metathesis to form the cyclohexadiene ring system. The starting material, erythronolactol **24**, is readily available in two steps from isoascorbic acid.[18] A series of routine transformations were

(11) (a) Hong, S.; Lindsay, H. A.; Yaramatsu, T.; Zhang, X.; McIntosh, M. C. *J. Org. Chem.* **2002**, *67*, 2042−2055. (b) Hutchinson, J. M.; Hong, S.; McIntosh, M. C. *J. Org. Chem.* **2004**, *69*, 4185−4191.

(12) Similar to that observed: Höck, S.; Koch, F.; Borschberg, H. J. *Tetrahedron: Asymmetry* **2004**, *15*, 1801−1808.

(13) In these stereochemical descriptors, the asterisk denotes the known chirality from the Mosher ester.

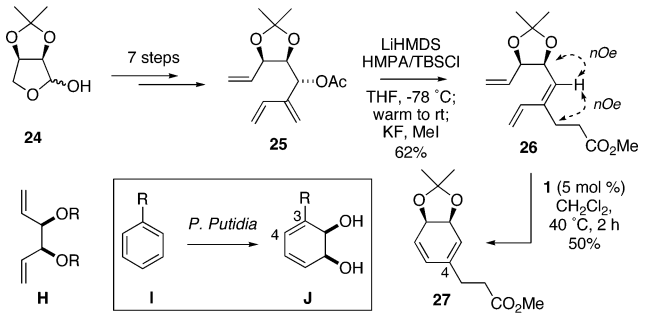
(14) Tsuda, M.; Toriyabe, Y.; Endo, T.; Kobayashi, J. *Chem. Pharm. Bull.* **2003**, *51*, 448−451.

(15) In the few instances where the Mosher method is unsuccessful (see ref 14), poor separation ($\Delta\delta$ = 0.00−0.05 ppm) in both diastereomers was observed. In the case of **23A**,**B**, this was not the case as there was found to be greater chemical shift dispersion in one diastereomeric Mosher ester (expected range is $\Delta\delta$ = 0.14−0.20 ppm) and almost none in the other.

(16) (a) Boyd, D. R.; Bugg, T. D. H. *Org. Biomol. Chem.* **2006**, *4*, 181−192. (b) Johnson, R. A. *Org. React.* (New York) **2004**, *63*, 117−264. (c) Hudlicky, T.; Gonzalez, D.; Gibson, D. T. *Aldrichim. Acta.* **1999**, *32*, 35−62. (d) Hudlicky, T.; Thorpe, A. J. *Chem. Commun.* **1996**, *17*, 1993−2000.

(17) (a) Kakeya, H.; Onose, R.; Yoshida, A.; Koshino, H.; Osada, H. *J. Antibiot.* **2002**, *55*, 829−831. (b) Williams, D. E.; Bombuwala, K.; Lobkovsky, E.; De Silva, E. D.; Veranja, K.; Allen, T. M.; Clardy, J.; Andersen, R. J. *Tetrahedron Lett.* **1998**, *39*, 9579−9582. (c) Ernst-Russel, M. A.; Chai, C. L. L.; Hurne, A. M.; Waring, P.; Hockless, D. C. R.; Elix, J. A. *Aust. J. Chem.* **1999**, *52*, 279.

Scheme 4. Enantiospecific Synthesis of Cyclohexadiene **27**



needed to install the unsaturated elements in **25** (7 steps, 25% overall yield). Butadiene **25** was then subject to the standard Ireland−Claisen conditions with basic workup to limit isomerization of the triene. In this way, triene **26** was obtained as the methyl ester in good yield. The triene **26** was isolated as an inseparable 10:1 mixture of stereoisomers. The major diastereomer was assigned structure **26** on the basis of an observed NOE and due to the facile subsequent ring-closing metathesis to give desired diene **27**. [19] Irradiation of the vinylic proton at δ 5.37 ppm produced NOE enhancements of both the methine proton at δ 5.07 ppm and the allylic methylene group appearing at δ 2.55 ppm.

Completion of the synthesis was achieved through ring-closing metathesis using Grubbs' complex **1** (5 mol %), which provided desired cyclodiene **27** in 50% yield. The optically active product showed characteristic vinyl resonances with the expected multiplicities. The ring-closing metathesis took longer than expected; complete consumption of triene was observed after 2 h. Given that dienes of type **H** failed to give cross-enyne metathesis, it is likely that initiation occurs on triene **26** at the unsubstituted end of the diene moiety. Since 4-substitution can be accessed, this sequence provides a complementary method to enzymatic oxidation of substituted benzenes.

Conclusion

We expanded the versatility of enyne cross-metathesis through sequential combination with the Ireland−Claisen rearrangement. This tandem sequence provides access to a variety of conjugated diene substitution patterns previously inaccessible by direct intermolecular enyne metathesis. This study shows that an alkene moiety of a conjugated diene can be used effectively in the Ireland−Claisen rearrangement. In the case of tandem Claisen rearrangement conducted on cyclodienes, an *s-trans* conjugated diene is produced. Chirality transfer also proved possible. Combination of enyne metathesis with Ireland−Claisen rearrangement was also successfully employed for the synthesis of 4-substituted cyclohexadienes, offering a strategy complementary to enzymatic oxidation of monosubstituted benzenes. The Ireland−Claisen reaction, when combined in a sequential manner with enyne metathesis, helps surmount a shortcoming of the catalytic process. This work demonstrates a potentially general concept in tandem sequential reactions where the combination of reactions is used to redress the deficiencies of a catalytic method.

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Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) The triene **26** proved stable in $CDCl_3$ under heating for a 2 h period.