

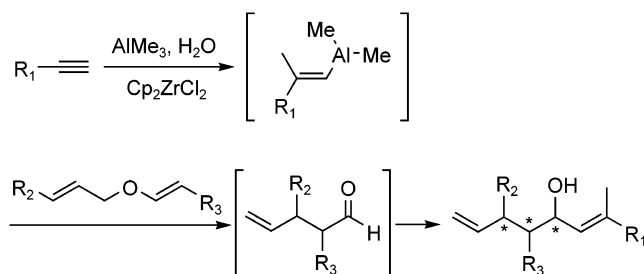
Transition-Metal-Mediated Cascade Reactions: The Water-Accelerated Carboalumination–Claisen Rearrangement–Carbonyl Addition Reaction

Peter Wipf,* David L. Waller, and Jonathan T. Reeves

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

pwipf+@pitt.edu

Received June 14, 2005



A three-step cascade reaction involving a water-accelerated catalytic carboalumination, a Claisen rearrangement, and a nucleophilic carbonyl addition converts terminal alkynes and allyl vinyl ethers into allylic alcohols containing up to three contiguous asymmetric carbon centers. Stoichiometric quantities of water as an additive increase the rate of the [3,3] sigmatropic rearrangement as well as the diastereoselectivity of the carbonyl addition process. Reaction products contain 1,6-diene functionalities that are readily cyclized to substituted cyclopentenones. An extension of this methodology to a sequence involving a [1,3] sigmatropic shift was feasible with a cyclopropylmethyl vinyl ether substrate.

Introduction

The development of multicomponent, domino, and cascade reaction technology has dramatically increased the level of molecular complexity that can be introduced during a single synthetic operation.^{1–3} Cascade reactions often integrate modern synthetic methods, such as metal-based catalysis, with classical synthetic bond constructions.⁴ The ability to create new synthetic manifolds by merging compatible methodologies offers significant opportunities for optimizing synthetic efficiency.

We have previously reported several cascade reactions leading to diverse functionality, including allylic⁵ and homoallylic⁶ amines, *C*-cyclopropyl alkylamines,⁵ bicy-

clobutanes,⁷ oxazolines, and thiazolines.⁸ Many of these methods utilize alkenylzirconocenes, derived from in situ hydrozirconation⁹ of alkynes, for subsequent C,C-bond formation.¹⁰ In addition, we have reported other cascade processes in connection with our studies of water-accelerated zirconium-catalyzed carboalumination,^{5,11} including water-accelerated aromatic Claisen rearrangements,¹² and a cascade aromatic Claisen rearrangement–asym-

(1) (a) Ramon, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602. (b) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471. (c) Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekanth, A. R.; Mathen, J. S.; Balagopal, L. *Acc. Chem. Res.* **2003**, *36*, 899. (d) Weber, L. *Curr. Med. Chem.* **2002**, *9*, 2085. (e) Mayer, S. F.; Kroutil, W.; Faber, K. *Chem. Soc. Rev.* **2001**, *30*, 332.

(2) (a) Pulici, M.; Cervi, G.; Martina, K.; Quartieri, F. *Comb. Chem. High Throughput Screen.* **2003**, *6*, 693. (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (c) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168.

(3) For a review of recent applications of cascade reactions to natural product synthesis, see: Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551.

(4) For recent examples, see: (a) Suffert, J.; Salem, B.; Klotz, P. *J. Am. Chem. Soc.* **2001**, *123*, 12107. (b) MacMillan, D. W. C.; Dong, V. M. *J. Am. Chem. Soc.* **2001**, *123*, 2448. (c) May, J. A.; Stoltz, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 12426. (d) Lampropoulou, M.; Herrmann, R.; Wagner, G. *Tetrahedron* **2004**, *60*, 4635. (e) Wipf, P.; Coleman, C. M.; Janjic, J. M.; Iyer, P. S.; Fodor, M. D.; Shafer, Y. A.; Stephenson, C. R. J.; Kendall, C.; Day, B. W. *J. Comb. Chem.* **2005**, *7*, 322.

(5) (a) Wipf, P.; Kendall, C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2001**, *123*, 5122. (b) Wipf, P.; Nunes, R. L.; Ribe, S. *Helv. Chim. Acta* **2002**, *85*, 3478. (c) Wipf, P.; Kendall, C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2003**, *125*, 761.

(6) Wipf, P.; Kendall, C. *Org. Lett.* **2001**, *3*, 2773.

(7) Wipf, P.; Stephenson, C. R. J.; Okumura, K. *J. Am. Chem. Soc.* **2003**, *125*, 14964.

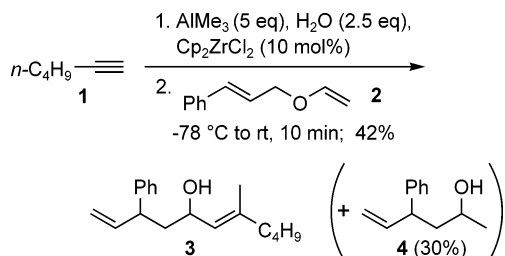
(8) Wipf, P.; Wang, X. *J. Comb. Chem.* **2002**, *4*, 656.

(9) (a) Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853. (b) Wipf, P.; Kendall, C. In *Topics in Organometallic Chemistry. Metalloenes in Regio- and Stereoselective Synthesis*; Takahashi, T., Ed.; Springer-Verlag: Heidelberg, 2004; Vol. 8, Chapter 1, p 1–25.

(10) For a review of carbon–carbon bond formation with alkenylzirconocenes, see: Wipf, P.; Nunes, R. *Tetrahedron* **2004**, *60*, 1269.

TABLE 1. Optimization of Reaction Conditions for the Conversion of **1** to **3**

entry	AlMe ₃ (equiv)	H ₂ O (equiv)	solvent	yield of 3 (%)
1	2.2	1.1	CH ₂ Cl ₂	56
2	2.05	1.0	CH ₂ Cl ₂	60
3	1.5	0.75	CH ₂ Cl ₂	0
4	1.0	0.5	CH ₂ Cl ₂	0
5	2.5	1.25	CH ₂ Cl ₂	60
6	2.2	2.25	CH ₂ Cl ₂	25
7	2.25	0.56	CH ₂ Cl ₂	61
8	2.0	1.0	ClCH ₂ CH ₂ Cl	60
9	2.25	1.2	toluene	48

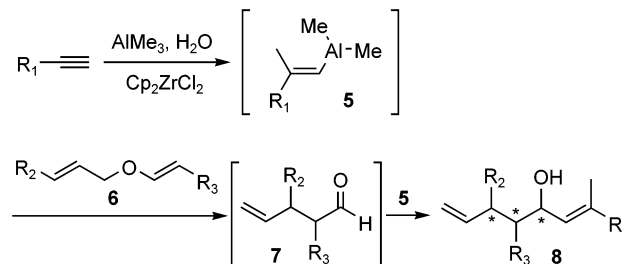
SCHEME 1. Cascade Process with Cinnamyl Vinyl Ether **2**

metric carboalumination leading to branched alkanols in high enantiomeric excess.¹³ We now report an aliphatic Claisen rearrangement-based methodology encompassing a three-step cascade process with allyl vinyl ethers.¹⁴

Results and Discussion

Optimization of Cascade Alkyne Carboalumination–Claisen Rearrangement–Carbonyl Addition.

Treatment of a solution of 1-hexyne (**1**) with AlMe₃ (5 equiv), H₂O (2.5 equiv), and Cp₂ZrCl₂ (10 mol %) in CH₂Cl₂ followed by addition of cinnamyl vinyl ether **2** provided allylic alcohol **3** in 42% yield as a 1:1 mixture of diastereomers after only 10 min reaction time as the reaction mixture was warmed from -78 to +25 °C (Scheme 1). In addition to the desired **3**, a major side product (~30%) was formed and subsequently identified as the secondary alcohol **4**. Suppressing the formation of this methyl transfer product was our primary goal in optimizing this model reaction (Table 1). Reduction of the equivalents of both AlMe₃ and H₂O to 2.2 and 1.1, respectively (entry 1), suppressed the undesired methyl addition to nearly undetectable levels. Further variation in the stoichiometry to 2 equiv of AlMe₃ and 1 equiv of H₂O (entry 2) furnished the desired product **3** in 60% yield with no evidence of the methyl transfer byproduct **4**; however, some hydrolysis of the starting vinyl ether was observed. Reduction of the amount of AlMe₃ to levels below 2 equiv resulted in no reaction or only a trace of product (entries 3 and 4). An increase in the amount of AlMe₃ to 2.5 equiv and of H₂O to 1.25 equiv had little effect on the yield (entry 5). Equimolar amounts of AlMe₃ and H₂O resulted in a very slow reaction and lowered

SCHEME 2. Cascade Conversion of Alkyne to Allylic Alcohol

the yield substantially (entry 6). Interestingly, good yields were obtained with substoichiometric amounts of H₂O (entry 7); however, this was unique to simple unfunctionalized allylic vinyl ethers. The optimum stoichiometry was found to be 2 equiv of AlMe₃ and 1 equiv of H₂O, yielding approximately 60% of the desired material. The reaction was also sensitive to the choice of solvent. Conducting the entire process in dichloroethane showed no benefit over dichloromethane (entry 8). When toluene was used as a solvent, the rearrangement/addition step was very slow and gave a yield of only 48% (entry 9). Therefore, dichloromethane was chosen as the preferred solvent for this transformation.

Mechanistically, 1,6-diene **8** arises from an initial water-accelerated zirconium-assisted alkyne carboalumination^{11–13} (Scheme 2).¹⁵ The intermediate vinylalane **5** can act as a Lewis acid^{12,16} to promote the [3,3] sigmatropic rearrangement of the allylic vinyl ether **6** to the aldehyde **7**, which undergoes rapid attack by the vinylalane to generate the final allylic alcohol **8** bearing up to three contiguous stereocenters. It is possible that in the presence of water partially hydrolyzed alane acts as bidentate or oligodentate Lewis¹⁷ or Brønsted¹² acid and enhances the rate of all three distinctive C,C-bond-forming steps in this sequence.

Preparation of Allyl Vinyl Ethers. To explore the scope and limitations of this new cascade reaction, a straightforward access to allyl vinyl ethers had to be identified.¹⁸ Hg(II)-catalyzed alcohol exchange of cinnamyl alcohol with 2-methoxypropene generated isopropenyl ether **9**¹⁹ in 45% yield (Scheme 3). The *n*-butyl-substituted vinyl ether **11** was synthesized using Buchwald's coupling protocol (CuI, Cs₂CO₃, and phenanthroline **14**)²⁰ with vinyl iodide **10**.²¹ After a 24 h reaction time, only a low 17% yield of the (*E,E*)-vinyl ether **11** was obtained. Alternatively, we considered Frauenrath's allylic ether isomerization methodology for the preparation of a (*Z*)-

(15) Negishi, E.-I. *Dalton Trans.* **2005**, 827.

(16) (a) Schneider, C.; Brauner, J. *Eur. J. Org. Chem.* **2001**, 4445. (b) Abe, N.; Hanawa, H.; Maruoka, K.; Sasaki, M.; Miyashita, M. *Tetrahedron Lett.* **1999**, 40, 5369. (c) Hanawa, H.; Abe, N.; Maruoka, K. *Tetrahedron Lett.* **1999**, 40, 5365.

(17) (a) Ooi, T.; Takahashi, M.; Yamada, M.; Tayama, E.; Omoto, K.; Maruoka, K. *J. Am. Chem. Soc.* **2004**, 126, 1150. (b) Maruoka, K.; Banno, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, 112, 7791. (c) Takai, K.; Mori, I.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1984**, 57, 446.

(18) Wipf, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 827–874.

(19) Yamamoto, H.; Banno, H.; Maruoka, K. *Tetrahedron: Asymmetry* **1991**, 2, 647.

(20) Buchwald, S. L.; Nordmann, G. *J. Am. Chem. Soc.* **2003**, 125, 4978.

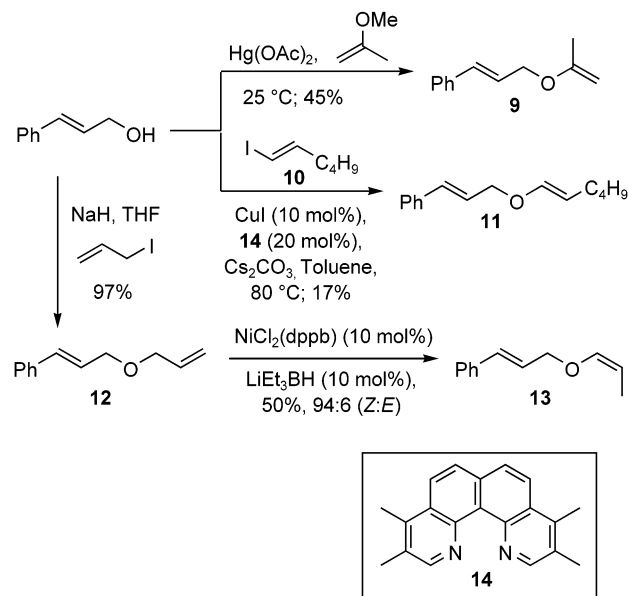
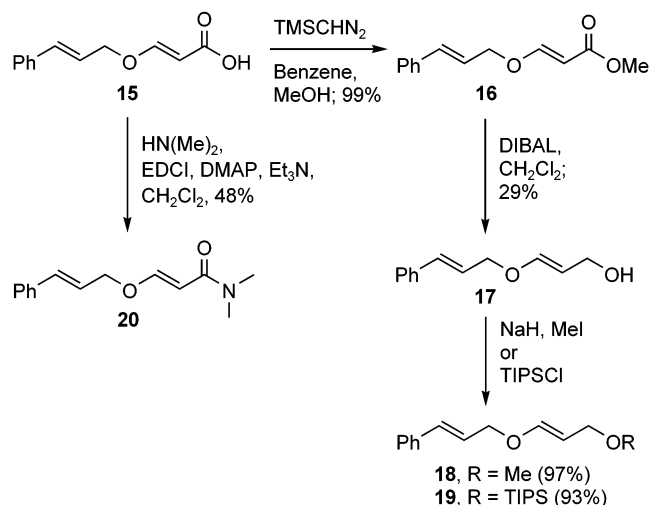
(21) Whitney, G. C.; Zweifel, G. *J. Am. Chem. Soc.* **1967**, 89, 2753.

(11) (a) Wipf, P.; Lim, S. *Angew. Chem., Int. Ed. Engl.* **1993**, 32, 1068. (b) Wipf, P.; Ribe, S. *Org. Lett.* **2000**, 2, 1713. (c) Ribe, S.; Kondru, R. K.; Beratan, B. N.; Wipf, P. *J. Am. Chem. Soc.* **2000**, 122, 4608.

(12) Rodriguez, S.; Wipf, P. *Adv. Synth. Catal.* **2002**, 344, 434.

(13) Wipf, P.; Ribe, S. *Org. Lett.* **2001**, 3, 1503.

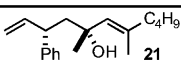
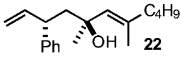
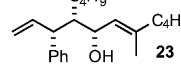
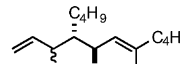
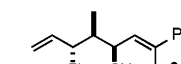
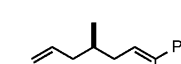
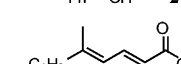
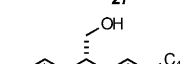
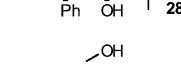
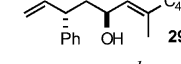
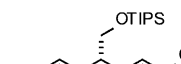
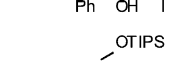
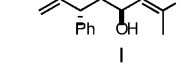
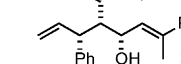
(14) For an example of a Lewis acid mediated Claisen rearrangement–aldehyde methylation, see: Ooi, T.; Takahashi, M.; Maruoka, K. *J. Am. Chem. Soc.* **1996**, 118, 11307.

SCHEME 3. Synthetic Routes to Allyl Vinyl Ethers

SCHEME 4. Synthesis of Cinnamyl Alcohol Derived Vinyl Ethers


vinyl ether.²² Bisallyl ether **12**²³ was obtained by alkylation of the sodium salt of cinnamyl alcohol with allyl iodide. Treatment of catalytic NiCl₂(dppb) with Li(Et)₃BH generated the Ni–H catalyst necessary to effect terminal olefin isomerization of **12**, furnishing vinyl ether **13** in 50% yield as a 94:6 ratio of alkenes favoring the desired (Z)-isomer.

More highly substituted allyl vinyl ethers were accessible from acrylic acid **15**.²⁴ Esterification of **15** with TMSCHN₂ proceeded in excellent yield to generate **16** (Scheme 4).²⁵ Reduction of this ester to the primary alcohol proved difficult, since conjugate addition with concomitant loss of cinnamyl alcohol predominated under a range of reducing conditions. Nevertheless, DIBAL

TABLE 2. Reaction Scope with Cinnamyl Derivatives

Entry	Substrates	Products (major/minor) ^a	Yield [%] (dr) ^b
1 ^c	9 , 1-hexyne	 21  22	75 (10:6:7)
2 ^d	11 , 1-hexyne	 23  24	90 (10:1:0.8)
3	13 , phenylacetylene	 25  26	65 (10:1)
4	16 , 1-hexyne	 27  28	37 (-)
5	17 , 1-hexyne	 29  30	30 (10:1)
6	18 , 1-hexyne	dec.	n/a
7	19 , 1-hexyne	 31  32	60 (10:1)
8	20 , phenylacetylene	 33  34	10 (10:2)

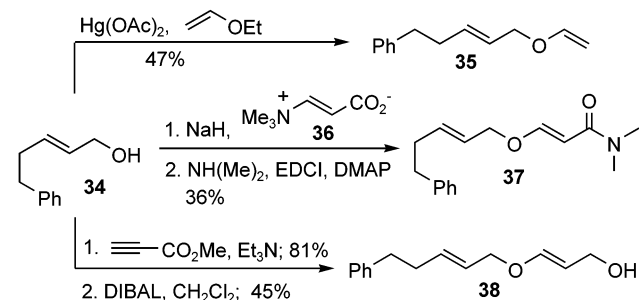
^a Shown as major (top)/minor (bottom). ^b Determined by integration of the ¹H NMR spectrum of the product mixture; dr = diastereomeric ratio. ^c Major and minor diastereomers are unassigned. ^d Minor diastereomers are unassigned as indicated.

reduction provided a 29% yield of allylic alcohol **17**, which could be easily converted in excellent yield to the corresponding methyl or TIPS ethers **18** or **19**, respectively. Conversely, amide coupling of dimethylamine to **15** with EDCI²⁶ furnished dimethyl amide **20** in 48% yield.

Reaction Scope. Most cinnamyl vinyl ether substrates were converted in variable yield but in good diastereoselectivity to the corresponding allylic alcohols under the optimized cascade reaction conditions (Table 2).

(26) Sheehan, J. C.; Cruickshank, P. A.; Boshart, G. L. *J. Org. Chem.* **1961**, 26, 2525.

(22) Wille, A.; Tomm, S.; Frauenrath, H. *Synthesis* **1998**, 305.
 (23) Serra, A. C.; da Silva Correa, C. M. M.; do Vale, M. L. C. *Tetrahedron* **1991**, 47, 9463.
 (24) Büchi, G. H.; Vogel, D. E. *Org. Synth.* **1988**, 66, 29.
 (25) Shioiri, T. *J. Pharm. Soc. Jpn.* **1993**, 113, 760.

SCHEME 5. Synthesis of Phenethyl Alcohol Derived, Alkyl-Substituted Vinyl Ethers

Isopropenyl ether **9** furnished the tertiary allylic alcohols **21** and **22** in 75% yield as a 10:6.7 mixture of diastereomers. A higher yield and an improved diastereoselectivity were accomplished with butyl-substituted vinyl ether **11**, which provided the stereochemical triad in allylic alcohols **23** and **24** as a 10:1:0.8 mixture of diastereomers. The (*Z*)-vinyl ether **13** led to allylic alcohols *anti,syn*-**25** and *anti,anti*-**26** in 65% yield as a 10:1 mixture of diastereomers (entry 3). Not unexpectedly, the presence of an ester functionality in the Claisen precursors was problematic. Rapid conjugate addition of vinyl aluminoxane to **16** led to the fragmentation product **27** (37%) and cinnamyl alcohol (47%, entry 4). The dienophile **27** is likely derived from a conjugate addition of the vinyl organometallic to the α,β -unsaturated ester **16**, followed by β -elimination of cinnamyl alcohol. Allylic alcohol **17** was better suited for the desired conversion and produced diols **28** and **29** in a modest 30% yield but in excellent diastereoselectivity (10:1, entry 5). Methyl ether **18** decomposed via elimination pathways, giving only trace amounts of byproducts (entry 6). In contrast, the more strongly shielded TIPS ether **19** rearranged smoothly to give *syn,syn*-**30** and *syn,anti*-**31** in 60% yield and 10:1 diastereoselectivity (entry 7). The relative stereochemistry of **30** and **31** was confirmed to be identical to **28** and **29** by desilylation (TBAF, THF) of the monoprotected substrates. Amide **20** proved most resistant to rearrangement, requiring 10 equiv of water-activated alane to generate a low yield of hydroxyl amides **32** and **33** (10:2, entry 8). Most likely, coordination of the Lewis acidic alanes to the amide group interferes with the desired rearrangement.

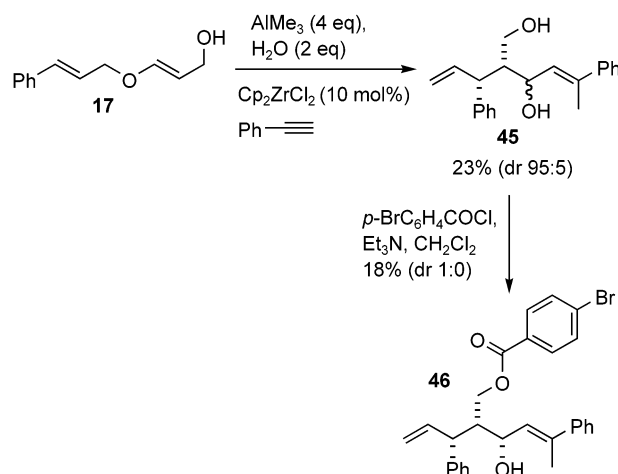
The cascade reaction is not limited to conjugated allylic ethers. In addition to the cinnamyl alcohol derived substrates, a series of alkyl-substituted allyl vinyl ethers were prepared from allylic alcohol **34** (Scheme 5).²⁷ These substrates gave very similar results to their phenyl-substituted counterparts (Table 3). Again, absence of additional heteroatoms in the Claisen precursor provided a higher yield of allylic alcohols (entry 1), whereas amide **37** and allylic alcohol **38** led to low yields but higher diastereomeric ratios in the cascade conversion (entries 2 and 3).

To assign the relative configuration of the major diastereomers, diol **45**, the product of the cascade reaction of **17** with phenylacetylene, was derivatized to its mono-*p*-bromobenzoyl ester **46** and analyzed by X-ray diffrac-

TABLE 3. Reaction Scope with Phenethyl Alcohol Derived Allyl Vinyl Ethers³²

Entry	Substrates	Products (major/minor) ^a	Yield [%] (dr) ^b
1 ^c	35 , phenylacetylene		78 (10:6)
2 ^d	37 , phenylacetylene		34 (10:4:1)
3	38 , phenylacetylene		17 (10:0.8:0.5)

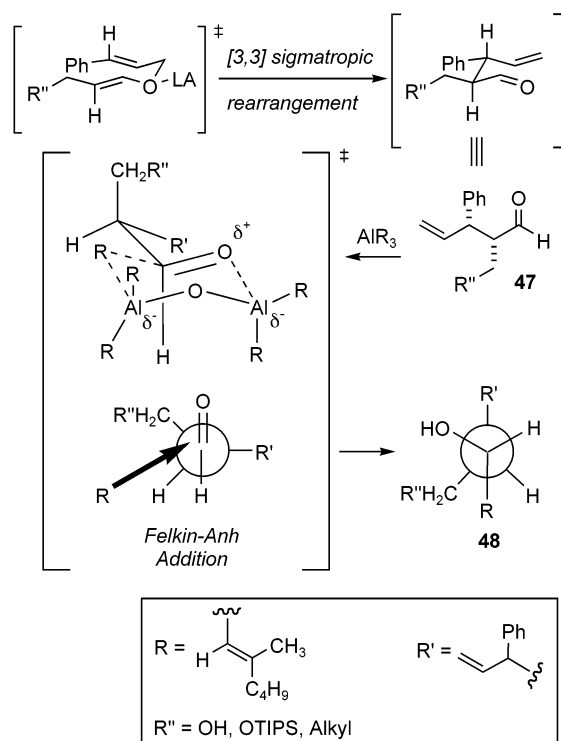
^a Shown as major (top)/minor (bottom). ^b Determined by integration of the ¹H NMR spectrum of the product mixture. ^c Major and minor diastereomers are unassigned. ^d Minor diastereomers are unassigned as indicated.

SCHEME 6. X-ray Analysis of Ester 46 Confirmed the *Syn,Syn*-Configuration for the Major Diastereomer

tion (Scheme 6). In addition to monobenzoate **46**, a 75% yield of the bis-benzoate was also obtained, but the latter was not diastereomerically pure and therefore unsuitable for analysis. The configuration of the major diastereomer formed in the cascade process can be explained by a chairlike transition state for the accelerated Claisen rearrangement (Scheme 7).^{18,28,29} The resulting aldehyde (or ketone) is then subjected to a highly selective Felkin–

(27) Charette, A. B.; Molinaro, C.; Brochu, C. *J. Am. Chem. Soc.* **2001**, *123*, 12168.

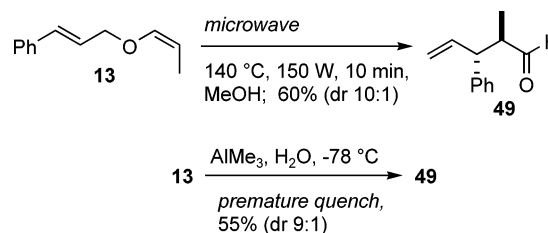
SCHEME 7. Proposed Mechanism



Anh addition³⁰ of the vinylalane, directed by the α -stereocenter. After aldehyde **47** is formed, addition takes place with the most bulky substituent orthogonal to the carbonyl π -bond. This conformation follows the Felkin–Anh model and allows the nucleophile to assume a Bürgi–Dunitz trajectory³¹ for attack onto the carbonyl group.

In the addition of alkylaluminum reagents to aldehydes, a six-membered transition state is generally preferred over a four-membered transition state when more than 1 equiv of AlR_3 is employed.³³ In our case, chelation control in the addition can be ruled out since substrates **17** and **19** gave identical diastereomers (vide supra). The stereodirecting effect of the newly formed aldehyde α -stereocenter, in combination with the steric demand of the oligomeric alane nucleophile,³⁴ leads to a high overall induction in the carbonyl addition step. Further support for the significance of steric effects is provided by the poor diastereoselectivity of substrates that lack an α -stereocenter or, as in the case of **9**, if the

SCHEME 8. Control Reactions for Test of Stereochemical Integrity of the Aldehyde Intermediate



intermediate is a ketone, which is known to exhibit diminished, substituent dependent complexation to aluminum Lewis acids compared to aldehydes.³⁵

We were concerned that the intermediate aldehyde **47** might epimerize under the reaction conditions, leading to decreased product diastereomeric ratio (dr); therefore, we attempted to isolate this intermediate and compare it to the product of a thermal Claisen rearrangement with a substrate of known configuration. Allyl vinyl ether **13**, when subjected to microwave heating,³⁶ underwent a [3,3] sigmatropic rearrangement in 10 min to yield aldehyde **49** in 60% yield as a 10:1 mixture of diastereomers (Scheme 8).³⁷ Conversely, attempts to quench a cascade carboalumination–Claisen rearrangement–vinylalane addition reaction before the allyl vinyl ether was consumed resulted only in recovered starting material and final cascade reaction products. Presumably, nucleophilic addition to the intermediate aldehyde was too rapid for preparative isolation. However, the addition of alkylalanes to carbonyl groups is slower than vinyl transfer, and when the reaction with an *alkyl* aluminoxane was quenched prematurely, we were able to isolate aldehyde **49** in 55% yield. A 9:1 diastereoselectivity was observed in this reaction, and the configuration of **49** was identical to the aldehyde obtained by thermal rearrangement, thus indicating that α -epimerization during the cascade reaction was unlikely.

Since the addition of water to mixtures of alane and zirconocene leads to a significant rate increase in the alkyne carboalumination,^{11a} we also probed the potential accelerating effect of water in the aldehyde addition.^{11c} Treatment of aldehyde **49** at -78°C with vinylalane **50**, prepared via Negishi carboalumination³⁸ in the absence of water, led in less than 1 min to addition product **25** as a modest 3:1 mixture of diastereomers. In the presence of stoichiometric quantities of water, the vinylalane also rapidly added to this aldehyde, but now in 8:1 diastereoselectivity (Scheme 9). These results indicate that, while

(28) (a) Wunderli, A.; Zsindely, J.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1973**, *56*, 989. (b) Vance, R. L.; Rondan, N. G.; Houk, K. N.; Jensen, F.; Borden, W. T.; Komomicki, A.; Wimmer, E. *J. Am. Chem. Soc.* **1988**, *110*, 2314. (c) Ireland, R. E.; Wipf, P.; Xiang, J. N. *J. Org. Chem.* **1991**, *56*, 3572. (d) Khaledy, M. M.; Kalani, M. Y. S.; Khuong, K. S.; Houk, K. N.; Aviyente, V.; Neier, R.; Soldermann, N.; Velker, J. *J. Org. Chem.* **2003**, *68*, 572–577.

(29) Sterically hindered Lewis acids tend to increase the dr in Claisen rearrangements. See, for example: Boeckman, R. K., Jr.; Neeb, M. J.; Gaul, M. D. *Tetrahedron Lett.* **1995**, *36*, 803.

(30) Anh, N. T.; Maurel, F.; Lefour, J.-M. *New J. Chem.* **1995**, *19*, 353.

(31) Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipf, G. *Tetrahedron* **1974**, *30*, 1563.

(32) Resubjecting a mixture of **41** and **42**, or **43** and **44**, to the reaction conditions for 2 h did not lead to any change in the diastereomeric ratio or the yield of recovered material. Therefore, we conclude that the dr is not influenced by selective destruction of the minor isomer.

(33) (a) Ashby, E. C.; Smith, R. S. *J. Org. Chem.* **1977**, *42*, 425. (b) Evans, D. A. *Science* **1988**, *240*, 420.

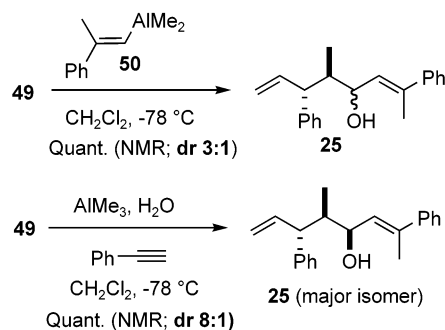
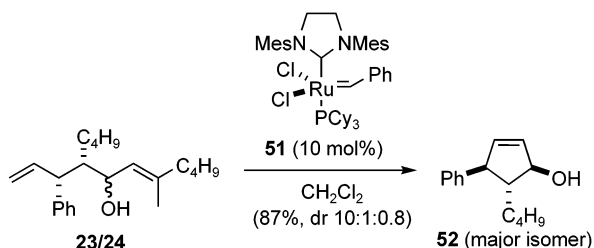
(34) It is well-accepted that aluminoxanes are highly aggregated species, forming clusters which have average molecular weights of about 1100 amu (in the case of methyl aluminoxane). Additionally, some of these clusters have been observed by X-ray crystallography. For reviews on this general topic, see: (a) Chen, E. Y.-X.; Marks, T. J. *Chem. Rev.* **2000**, *100*, 1391. (b) Roesky, H. W.; Walawalkar, M. G.; Murugavel, R. *Acc. Chem. Res.* **2001**, *34*, 201.

(35) Maruoka, K.; Nagahara, S.; Yamamoto, H. *Tetrahedron Lett.* **1990**, *31*, 5475.

(36) (a) Martinez, I.; Alford, P. E.; Ovaska, T. V. *Org. Lett.* **2005**, *7*, 1133. (b) Giguere, R. J.; Bray, T. L.; Duncan, S. M.; Majetich, G. *Tetrahedron Lett.* **1986**, *27*, 4945.

(37) Configuration is based on a chairlike transition state: (a) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423. (b) Reference 18. (c) Reference 28.

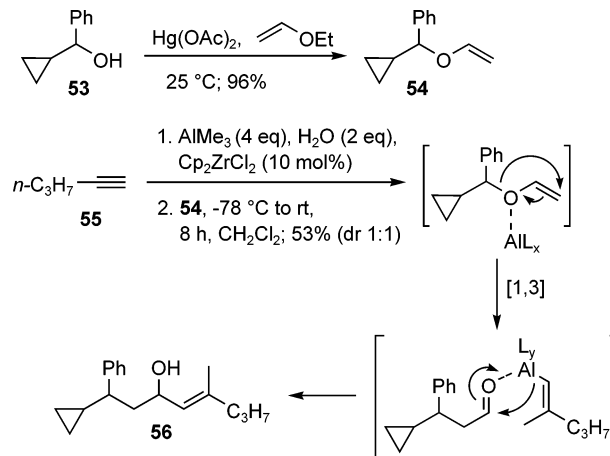
(38) Negishi, E.; Van Horn, D. E.; King, A. O.; Okukado, N. *Synthesis* **1979**, 501.

SCHEME 9. Control Experiments Establish the Beneficial Effect of Water on the Diastereoselectivity of the Addition Process**SCHEME 10. Preparation of Cyclopentenes by Ring-Closing Metathesis**

no measurable rate enhancement in the already fast 1,2-addition is gained at -78°C from the addition of water, the larger aluminoxane cluster acting as a bulky nucleophile in the 1,2-addition or a tighter transition state leads indeed to improved facial selectivity in the carbonyl addition step.

Conversion of 1,6-Diene to Cyclopentene. As a practical demonstration of the synthetic potential of this new cascade reaction, we converted a 10:1:0.8 mixture of the 1,6-dienes **23** and **24** in the presence of ruthenium catalyst **51**³⁹ to the cyclopentenols **52** (Scheme 10). These substituted cyclopentenols have found use in the preparation of carbocyclic nucleosides, some of which are potent antiviral agents lacking the labile anomeric linkage that increases susceptibility to degradative enzymes such as phosphorylases.^{40,41}

[1,3] vs [3,3] Rearrangement. The [1,3] sigmatropic rearrangement of allyl vinyl ethers can compete with the [3,3] sigmatropic shift,¹⁸ especially in the presence of strong Lewis acids and with substrates that favor allyl cation intermediates.⁴² While we have not specifically observed reaction products in our cascade processes that are derived from [1,3] rearrangements, this process is feasible under our typical reaction conditions, as demonstrated by the facile conversion of cyclopropylmethyl vinyl ether **54** into the allylic alcohol **56** (Scheme 11). The

SCHEME 11. [1,3] Rearrangement of Cyclopropylmethyl Vinyl Ether

conversion of **54** to **56** appears to be the first case of a [1,3] sigmatropic rearrangement of a cyclopropane analogue of an allyl vinyl ether.⁴³ Starting material **54** was prepared in high yield from alcohol **53** by a Hg(II)-mediated vinyl ether exchange.

Conclusions

We have developed a rapid diastereoselective three-step cascade carboalumination–Claisen rearrangement–carbonyl addition process leading to 1,6-diene functionalities containing allylic alcohols with up to three contiguous stereocenters. The stoichiometric quantities of water that are used as an additive increase the rate of the [3,3] sigmatropic rearrangement as well as the diastereoselectivity of the carbonyl addition. The resulting products are readily converted to substituted cyclopentenols. The cascade reaction strategy can also be extended to a sequence involving a [1,3] sigmatropic shift, as demonstrated with cyclopropane containing substrate **54**.

Experimental Section

(E)-7-Methyl-3-phenylundeca-1,6-dien-5-ol (3). **General Protocol A.** To a -30°C solution of AlMe_3 (540 mg, 7.35 mmol) and Cp_2ZrCl_2 (85.8 mg, 0.294 mmol) in CH_2Cl_2 (6 mL) was added H_2O (66.1 μL , 3.67 mmol) dropwise. The reaction mixture was warmed to ambient temperature and then cooled to 0°C and treated with 1-hexyne (676 μL , 5.88 mmol). The mixture was stirred for 30 min, cooled to -78°C , and treated with vinyl ether **2** (470 mg, 2.94 mmol) in CH_2Cl_2 (1.5 mL). The mixture was warmed to ambient temperature over 10 min and quenched with 1 M Rochelle's salt (3 mL). The aqueous layer was extracted with CH_2Cl_2 ($3 \times 5 \text{ mL}$), and the combined organic layers were washed with brine, dried (MgSO_4), and concentrated. The residue was purified by chromatography on SiO_2 (hexanes/ EtOAc , 5:1) to furnish alcohol **3** as a colorless oil which was a 1:1 mixture of inseparable diastereomers as indicated by ^1H NMR analysis: IR (neat) 3334, 2956, 2929, 1452, 996, 913, 700 cm^{-1} ; ^1H NMR δ 7.34–7.18 (m, 5 H), 6.03–5.92 (m, 1 H), 5.22–5.17 (m, 1 H), 5.11–5.02 (m, 2 H), 4.31–4.26 (m, 1 H), 3.49–3.39 (m, 1 H), 2.09–1.96 (m, 3 H), 1.88–1.74 (m, 1 H), 1.54 (2 br s, 3 H), 1.42–1.20 (m, 4 H), 0.94 (t,

(39) Grubbs, R. H.; Scholl, M.; Ding, S.; Lee, C. W. *Org. Lett.* **1999**, 1, 953.

(40) (a) Marquez, V.; Lim, M. *Med. Res. Rev.* **1986**, 6, 1. (b) Roberts, S.; Biggadike, K.; Borthwick, A.; Kirk, B. In *Topics in Medicinal Chemistry*; Leeming, P. R., Ed.; Royal Society of Chemistry: London, 1988; p 172.

(41) Crimmins, M. T.; King, B. W.; Zuercher, W. J.; Choy, A. L. *J. Org. Chem.* **2000**, 65, 8499.

(42) (a) Nasveschuk, C. G.; Rovis, T. *Org. Lett.* **2005**, 7, 2173. (b) Gansaeuer, A.; Fielenbach, D.; Stock, C.; Geich-Gimbel, D. *Adv. Synth. Catal.* **2003**, 345, 1017. (c) Grieco, P. A.; Clark, J. D.; Jagoe, C. T. *J. Am. Chem. Soc.* **1991**, 113, 5488. (d) Nonoshita, K.; Banno, H.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, 112, 316.

(43) For the [1,3] sigmatropic rearrangement of the corresponding allyl vinyl ether, see: Maruoka, K.; Nonoshita, K.; Banno, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, 110, 7922.

1.5 H, $J = 4.7$ Hz), 0.91 (t, 1.5 H, $J = 4.5$ Hz); ^{13}C NMR δ 143.8 (2 C), 142.3, 141.9, 139.5, 139.0, 128.4 (4 C), 127.6 (5 C), 127.2, 126.2 (2 C), 114.2, 114.0, 66.6, 66.4, 46.2, 46.1, 43.0, 42.9, 39.2 (2 C), 29.9 (2 C), 22.3 (2 C), 16.5 (2 C), 13.9 (2 C); MS (EI) m/z (rel intensity) 240 ($[\text{M} - \text{H}_2\text{O}]^+$, 34), 201 (30), 183 (62), 155 (16), 117 (100); HRMS (EI) m/z calcd for $\text{C}_{18}\text{H}_{26}\text{O}$ 258.1984, found 258.1982.

Acknowledgment. This work has been supported by the National Science Foundation (CHE-0315205) and

Merck Research Laboratories. We thank Dr. Steve Geib (University of Pittsburgh) for X-ray crystallographic analysis of **46**.

Supporting Information Available: Experimental procedures, ^1H and ^{13}C NMR spectra for all new compounds, and crystallographic data (CIF) for **46**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO051211V