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Water-Accelerated Tandem Claisen Rearrangement–Catalytic Asymmetric Carboalumination

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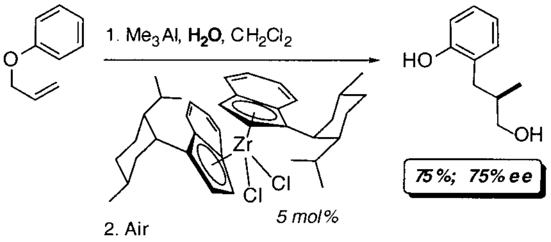
ABSTRACT

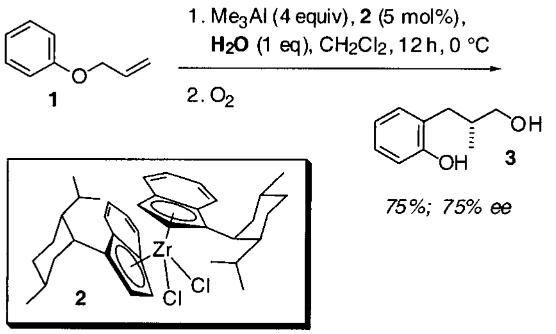


The addition of stoichiometric quantities of water accelerates both the trimethylaluminum-mediated aromatic Claisen reaction and the chiral zirconocene-catalyzed asymmetric carboalumination of terminal alkenes. The two reactions occur in a tandem sequence resulting in the selective formation of two new C–C and one C–O bond after oxidative quench of the intermediate trialkylalane.

Recently, we have found that additives such as methylaluminoxane (MAO) and, especially, water provide considerable acceleration and increased functional group tolerance for the catalytic asymmetric carboalumination of α-olefins.[1,2] Furthermore, the general synthetic utility of this transformation has been demonstrated in the preparation of a key segment for the total synthesis of the marine natural product pitiamide A.[3] While the addition of water to organometallic reaction mixtures is quite counterintuitive, its rate-enhancing effects have also been demonstrated in the zirconocene dichloride catalyzed carboalumination of alkynes,[4] as well as in an increasing number of unrelated synthetic processes.[5] We now report a novel tandem process in which water accelerates both a sigmatropic rearrangement and a subsequent carbometalation reaction, providing enantioenriched and polyfunctionalized building blocks for organic synthesis. In addition to its rate-accelerating function, water as an additive is crucial for extending the functional group tolerance of the zirconocene-catalyzed carbometalation step to include such Lewis-basic moieties as phenoxide anions.

Addition of allyl phenyl ether **1** to a mixture of 4 equiv of Me_3Al, 5 mol % of Erker's catalyst **2**,[6] and 1 equiv of H_2O in CH_2Cl_2 at 0 °C followed by oxidative workup afforded the tandem Claisen rearrangement−methylalumination product **3** in 75% yield and 75% ee (Scheme 1).[7] No

Scheme 1



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[1] Wipf, P.; Ribe, S. *Org. Lett.* **2000**, *2*, 1713.

[2] (a) Kondakov, D. Y.; Negishi, E. *J. Am. Chem. Soc.* **1995**, *117*, 10771. (b) Kondakov, D. Y.; Negishi, E.-I. *J. Am. Chem. Soc.* **1996**, *118*, 1577.

[3] Ribe, S.; Kondru, R. K.; Beratan, B. N.; Wipf, P. *J. Am. Chem. Soc.* **2000**, *122*, 4608.

[4] Wipf, P.; Lim, S. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1068.

[5] For a review, see: Wipf, P.; Ribe, S. *Chem. Commun.* **2001**, 299.

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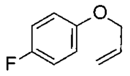
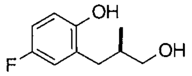
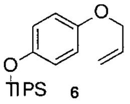
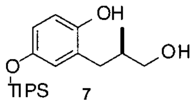
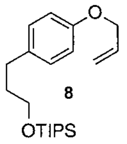
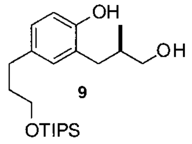
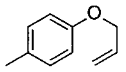
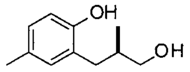
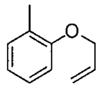
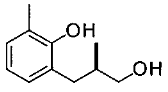
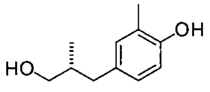
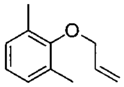
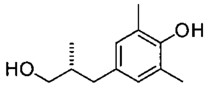
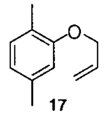
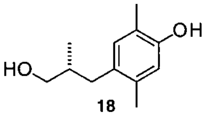
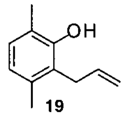
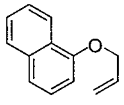
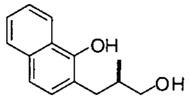
product was formed in the absence of water as an additive. The scope of this new cascade transformation is summarized in Table 1.

Table 1. H_2O-Accelerated Tandem Claisen Rearrangement−Methylalumination

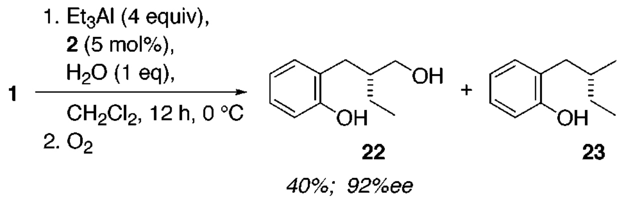
entry	substrate	product	yield (*ee*)[a]
1	 **4**	 **5**	78% (*78%*)
2	 **6**	 **7**	51% (*74%*)
3	 **8**	 **9**	60% (*73%*)
4	 **10**	 **11**	74% (*76%*)
5	 **12**	 **13**	51% (*74%*)
		+  **14**	29% (*70%*)
6	 **15**	 **16**	78% (*75%*)
7	 **17**	 **18**	39% (*60%*)
		+  **19**	55%
8	 **20**	 **21**	75% (*80%*)

[a] Determined by Mosher ester analysis (^1H NMR).

Both strongly electron-withdrawing and electron-donating functional groups on the benzene ring appear to be tolerated in the rearrangement (entries 1 and 2). Bulky silyl ethers such as TIPS are suitable alcohol protective groups (entries 2 and 3). *ortho*-Substitution partially directs the rearrangement step toward the *para*-position (entry 5); as expected, the *para*-Claisen[8] product **16** is formed exclusively with 2,6-disubstituted allyl phenyl ether **15** (entry 6). While all *para*-Claisen products underwent smooth asymmetric carbometalation, the sterically slightly more hindered *ortho*-allyl phenol **19** derived from the trisubstituted ether **17** resisted this transformation (entry 7). This subtle steric effect is surprising in light of the facile carbometalation of the alkene precursor of **11** (entry 4) and serves as an illustration of the likely considerable congestion in the transition state involving the bulky precatalyst **2**. In both **12** and **17**, the ratio of *ortho*- to *para*-Claisen products was ca. 1.5:1. Finally, the tandem process is not limited to phenyl derivatives, as the rearrangement of naphthol **20** demonstrates (entry 8). Yields varied in all examples from 50% to 80%, with the more highly functionalized derivatives that underwent alkene carbometalation more slowly ranging at the lower end of this scale. In general, the enantioselectivities observed for the alkene functionalization step were analogous to results reported earlier for nonconjugated α-olefins.[1,2] Further improvements in % ee will depend on the development of more effective zirconocene catalysts.

The reaction is not limited to methyl transfer to the alkene. Treatment of **1** with Et_3Al under otherwise identical conditions provided the ethylated diol **22** in 92% ee (Scheme 2).

Scheme 2



The yield of **22** was modest (40%), since oxidative cleavage of the Al−C bond was more sluggish in this case, and significant quantities of the hydrolysis product **23** were detected after workup.

In our earlier studies,[1] we observed that the popular metallocene polymerization additive MAO[9] was capable of reproducing the rate-enhancing effects of water in the catalytic asymmetric carboalumination of α-olefins, albeit at reduced efficiency. For preparative scale applications, MAO is nonetheless superior to H_2O as an additive, because in contrast to H_2O, addition of commercially available MAO

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(6) Erker, G.; Aulbach, M.; Knickmeier, M.; Wingbermühle, D., Krüger, C.; Nolte, M.; Werner, S. *J. Am. Chem. Soc.* **1993**, *115*, 4590.

(7) The enantiomeric excess was determined by conversion to the corresponding bis-Mosher ester derivatives. The absolute configuration was assigned in analogy to refs 1−3.

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

(9) Chen, E. Y.-X.; Marks, T. J. *Chem. Rev.* **2000**, *100*, 1391.

solutions to the reaction mixture does not lead to exothermic gas evolution. Since several Al(III) derivatives have been used for catalysis of the Claisen rearrangement,[8,10] we expected MAO to be a suitable promoter for both steps in our tandem reaction sequence.

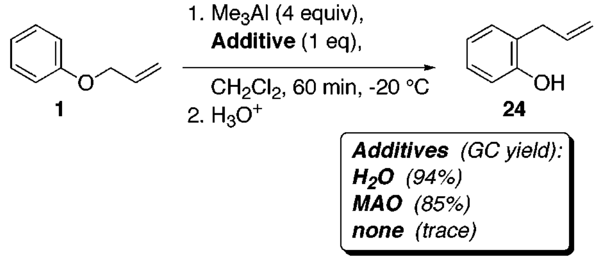
Addition of **1** to a solution of 4 equiv of Me_3Al, 1 equiv of MAO (used as a 10% solution in toluene), and 2−5 mol % of ***ent*-2** in CH_2Cl_2 provided 71% of ***ent*-3** in 75% ee after 12 h at 0 °C (entry 1, Table 2). Fluorobenzene **4** required the use of 2 equiv of MAO; a reduction of the amount of MAO additive to 1 equiv dramatically reduced the yield of ***ent*-5** to 31%. In general, however, all other substrates were converted to diols with 1 equiv of MAO in yields and enantioselectivities that were closely comparable to the H_2O-mediated reactions. Interestingly, the selectivity between *ortho*- and *para*-Claisen pathways for substrates **12** and **17** increased slightly from an average of ca. 1.5:1 for the H_2O-mediated process to ca. 2:1 in the MAO environment. This experimental result suggests that the species responsible for the acceleration of the aromatic Claisen rearrangement is not **2** or a common derivative of **2** but the combination of Me_3Al and the additive, e.g., H_2O or MAO, respectively. Indeed, treatment of **1** with either H_2O or MAO led to a fast sigmatropic shift even at −20 °C, and high yields of *ortho*-allyl phenol **24** were detected by GC analysis (Scheme 3).[11] Me_3Al alone was not a significant accelerator under these reaction conditions. Claisen rearrangement is much faster than the additive-accelerated alkene carboalumination, which explains the lack of any side products derived from premature carbometalation of the allylic ether moiety.

Table 2. MAO-Accelerated Tandem Claisen Rearrangement−Methylalumination

entry	substrate	product	yield, % (ee, %)[a]
1	**1**	***ent*−3**	71 (75)
2	**4**	***ent*−5**	80 (76)
3	**6**	***ent*−7**	58 (75)
4	**8**	***ent*−9**	55 (74)
5	**10**	***ent*−11**	75 (74)
6	**12**	***ent*−13**	60 (77)
		***ent*−14**	25 (73)
7	**15**	***ent*−16**	78 (72)
8	**17**	***ent*−18**	34 (69)
		19	59
9	**20**	***ent*−21**	74 (76)

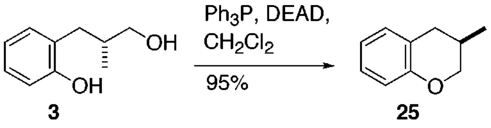
[a] Determined by Mosher ester analysis (^1H NMR).

Scheme 3



In conclusion, a new tandem Claisen rearrangement−catalytic asymmetric carbometalation of allyl aryl ethers has been developed. In this process, two new C−C bonds and one C−O bond (after oxidative cleavage of the C−Al bond) are formed with high regio- and stereocontrol under mild reaction conditions. The rates of both the sigmatropic rearrangement and the alkene functionalization are effectively enhanced by the unconventional additives H_2O and MAO, which allow the process to occur at low temperatures and provide for the necessary functional group tolerance. Our preliminary investigations regarding the mechanisms of these transformations have not yet yielded conclusive information about actual structures of reactive intermediates. Upon addition of H_2O to the reaction mixture, an exothermic reaction with alane leads to gas evolution and formation of an alanoxide with “super Lewis acid” properties that readily coordinates to the ether oxygen of the organic substrate and abstracts σ-bound ligands from the zirconocene complex. The former process catalyzes the [3.3]sigmatropic rearrangement,[8] while the ligand transfer provides the reactive cationic zirconocene complex for the carbometalation of the alkene.[12] In general, the Lewis acid complexes that catalyze the Claisen rearrangement as well as the alkene carbometalation are readily deactivated by the presence of either ether or phenoxide functions in the substrate, but the more reactive transient species obtained in the presence of MAO and, especially, H_2O are apparently capable of partially overcoming this deficiency. The resulting functionalized phenols are useful intermediates for organic synthesis. For example, diol **3** is readily cyclized under Mitsunobu conditions to give the chroman **25** in excellent yield (Scheme 4). Further investigations of water/MAO-accelerated carbometalation processes will be reported in due course.

Scheme 4



Acknowledgment. We are grateful to the National Science Foundation (CHE-9453461) for support of this research.

Supporting Information Available: Experimental procedures and spectral data for compounds **3**−**25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[10] (a) Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205. (b) Maruoka, K.; Saito, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1995**, *117*, 1165. (c) Sharma, G. V. M.; Ilangovan, A.; Sreenivas, P.; Mahalingam, A. K. *Synlett* **2000**, 615.

[11] In our studies, $EtAlCl_2$ demonstrated the highest acceleration in this rearrangement, but only reduced alkane was isolated. See also: Beholz, L. G.; Stille, J. R. *J. Org. Chem.* **1993**, *58*, 5095.

[12] Yang, X. M.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc.* **1994**, *116*, 10015.