Development of a New Lewis Acid-Catalyzed Claisen Rearrangement

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Since its discovery in 1912,1 the Claisen rearrangement has become one of the most powerful tools for carbon–carbon bond formation in chemical synthesis.2 This [3,3]-sigmatropic rearrangement, which involves the conversion of an allyl vinyl ether to an α,β-disubstituted γ,δ-unsaturated carbonyl, generally proceeds with high levels of stereoselectivity, securing its widespread use in natural product and medicinal agent synthesis.3 Activation of this rearrangement has traditionally been accomplished under thermal control; however, significant rate acceleration can be achieved through the incorporation of cationic3 or anionic4 charge density.5 This activation step has been elegantly demonstrated by Knoechel et al.6 In 1978, Bellus and Malherbe reported the conceptually novel ketene–Claisen reaction.7 In an attempt to perform a [2 + 2] cycloaddition, the authors discovered that treatment of an allyl ether with dichloroketene resulted instead in the formation of a 1,3-dipolar allyl vinyl ether, which subsequently underwent [3,3]-bond reorganization (eq 1). Although the scheme of this reaction was determined to be limited to highly electrophilic ketenes,7 this study further demonstrated the capacity of zwitterionic 1,5-dienes to readily participate in charge-accelerated sigmatropic isomerization. Subsequently, the studies of Edstrom,8 Mariano,9 and TiCl4-benzyl amine complexes (eq 2) have been extended to a broad range of ketenes (1) and with excellent levels of stereocontrol (99:1 anti/syn).10 Notably, this reaction is contingent upon the use of Lewis acid (entry 1); control experiments performed in the presence of metal salt resulted only in the production of ketene dimer. Importantly, this procedure can be performed using only catalytic quantities of Lewis acid (5–10 mol %), an essential criterion for the development of an enantioselective catalytic process. The excellent levels of diastereoselectivity (99:1 anti/syn) and catalyst efficiency (5 mol %) displayed by TiCl4-THF2 afford TiCl4 in 92% yield (entry 5) defined this metal salt as the optimal catalyst for exploration of this new acyl-Claisen rearrangement.

Scheme 1

Experiments that probe the scope of the allyl morpholine reaction component are summarized in Table 2. Significant structural variation in the allyl substituent (R₁ = H, alkyl, aryl, or halogen, entries 1–4) is possible without loss in yield or diastereoselectivity (>76% yield, >99:1 syn/anti). In accord with established Claisen methodology, complementary stereocontrol can be accessed through the appropriate selection of double bond geometry on the allyl component. While excellent levels of syn stereoselection are observed with trans-allyllic morpholines (entries 1–3), the anti Claisen adduct is readily furnished (95:5 anti:syn) using the cis double bond isomer (entry 5).

The reaction is also quite general with respect to the acid chloride structure (Table 3). As highlighted in entry 1, this methodology provides a new strategy for the catalytic production of unnatural β-substituted α-amino acids using α-phthalalhydrinclyl chloride (77% yield, 98:2 syn/anti). This process is also tolerant of oxygen and sulfur substituents on the acyl chloride component (>81% yield, 86:14 to 92:8 syn/anti, entries 2–3). A powerful feature of this new Claisen process is the capacity to build diverse functional and stereochemical arrays that are not readily available using conventional catalytic methods. For example, both the syn and anti α-oxo, β-chloro Claisen isomers 13 and 14 can be accessed in high yield and stereospecificity from chloro-substituted allyl morpholines and α-benzylxacyl chloride (entries 4–5).

A further illustration of the proficiency of this reaction to provide catalytic access to elusive structural motifs is presented in the rearrangement of 3,3-disubstituted allyl morpholines 15 and 16 (eqs 2 and 3). The principal issue in these reactions is that of transition state-controlled π-facial discrimination to selectively build quaternary carbon stereocenters on both cyclic and acyclic architecture. The reaction of propionyl chloride with 1-methyl-3-N-morpholino-cyclohexene (15) provides excellent levels of diastereofacial discrimination (eq 2, 95:5 anti/syn). As illustrated in eq 3, the reaction can also translate the subtle methyl versus ethyl substitution pattern on morpholine 16 to furnish the acyclic framework 18 with complete stereospecificity (>99:1 syn).

Finally, preliminary studies have recently been conducted that establish this new Claisen methodology as a suitable platform for enantioselective catalysis. Details of this work along with a full account of this survey will be forthcoming.

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Supporting Information Available: Experimental procedures, spectral data for all compounds, stereochemical proofs, and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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