ORGANIC
LETTERS

2009
Vol. 11, No. 3
621−624

Design of a Bisamidinium Claisen Rearrangement Catalyst for Monodentate Substrates

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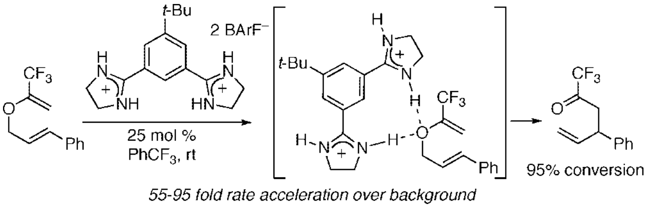
Received November 21, 2008

ABSTRACT



A bisamidinium catalyst has been designed for the Claisen rearrangement. The primary design feature is a dual hydrogen bonding array that can coordinate a singular oxygen atom of the substrate. The ability to function as a dual hydrogen donor is key as the bisamidinium accelerates the Claisen rearrangement to a greater extent than Brønsted acids with lower pK_a values.

The Claisen rearrangement, discovered in 1912 by Ludwig von Claisen, is the thermal isomerization of an allyl vinyl ether or the corresponding nitrogen or sulfur analogues to afford a bifunctionalized molecule in a [$\pi^2s + \sigma^2s + \pi^2s$] process.[1] Subsequently, the power of the Claisen rearrangement has been recognized as indicated by its widespread application.[2]

In spite of extensive study of this reaction,[2] the lack of general catalytic, enantioselective variants of the Claisen rearrangement is striking with only three highly selective examples presently reported,[3−5] all of which require a two-point interaction with the catalyst. For catalysts which interact with a single Lewis basic moiety in the Claisen rearrangement substrate, enantioselective vaiants of the Claisen rearrangement require stoichiometric amounts of chiral Lewis acids.[6,7] This requirement prompted us to examine the use of hydrogen bond (H-bond) donors as catalysts in this important reaction with the goal of identifying modular templates that allow turnover for monodentate substrates.

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10.1021/ol8026945 CCC: $40.75

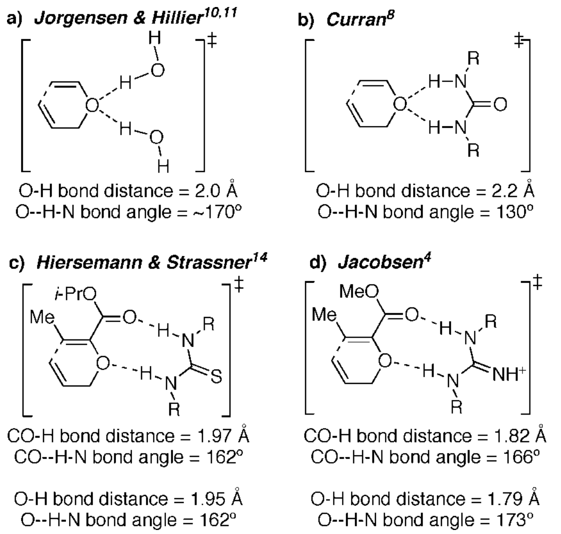

Figure 1. Hydrogen bonding structures in Claisen rearrangements.

Our interest was spurred by an earlier report of the Claisen rearrangement of allyl vinyl ethers with a C6-methoxy group being catalyzed by ureas and thioureas, although elevated temperatures were needed.[8] This work was, in turn, inspired by reports of Claisen rearrangement acceleration by water which was proposed to arise from hydrogen bonding.[9] Subsequent calculations by Jorgensen[10] and Hillier[11] provided further support for this hypothesis and identified two hydrogen bonds with water in the transition state (Figure 1a). For the urea system, it was hypothesized[8] that the urea forms a dual hydrogen bond through the lone pairs on the oxygen of the allyl vinyl ether (Figure 1b). We found that MM2* calculations[12] of a minimized structure between the allyl vinyl ether and the urea indicated that the orientation of the urea hydrogen bond donors were not optimal compared to the water accelerated system (Figure 1b); rather, an OHN bond angle of 130° was observed (Figure 1b). We theorized that the rate of the Claisen rearrangement could be increased if the hydrogen bond donors were optimized to form an OHN bond angle of 180°.[13]

This assertion finds further support in recent work on the Claisen rearrangement with 2-alkoxycarbonyl-substituted allyl vinyl ethers. For thioureas, Hiersemann and co-workers make a compelling argument that the optimal hydrogen bonding association afforded by a urea favors a two-point interaction to optimize the desirable angle (see Figure 1c).[14] Subsequent studies by Jacobsen and coowokers with the guanidiniums revealed a similar hydrogen bonding network that nears the ideal 180° hydrogen bond angles.[4]

To devise a catalyst capable of undergoing a two-point interaction with substrates containing a single Lewis basic atom, we began by identifying the optimal orientation and distance of an amide N−H bond with an ether. Thus, the positions for the hydrogen bond donors were obtained by using Spartan to model the complex between dimethyl ether and two molecules of acetamide (Figure 2).[15]

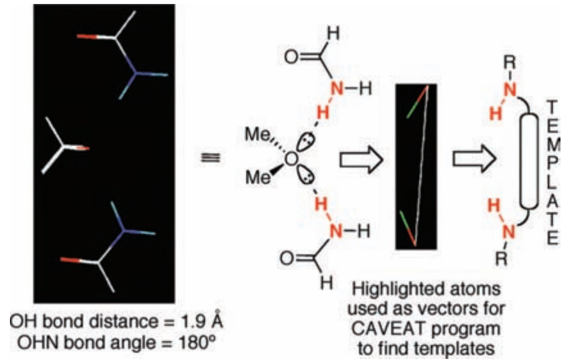

Figure 2. Optimal positions for hydrogen bond donors.

The bond lengths and bond angles of the acetamide molecules with dimethyl ether correspond to two moderate hydrogen bonds comparable to those observed in most catalysis involving hydrogen bonding (Figure 2).[13] The bonds between atoms highlighted in red in Figure 2 were then used as vectors for the database mining program CAVEAT. Using the Cambridge Crystal Database, several templating substructures that contain these vectors were found (Figure 3).[16]

A number of crystal structures were obtained that satisfied the vectors in Figure 2 to provide both hydrogen bonds in the optimal positions, but crystal structure **3** was the most promising candidate (Figure 3). In particular, structure **3** inspired the design of bisamidine **4**. Such compounds avoid self-hydrogen bonding and the rotation about the aryl substituent bond leads to degenerate conformations. The modular nature combined with the fact that it could easily be synthesized made this structural type particularly appealing. Furthermore, calculations of the bisamidine and bisa-

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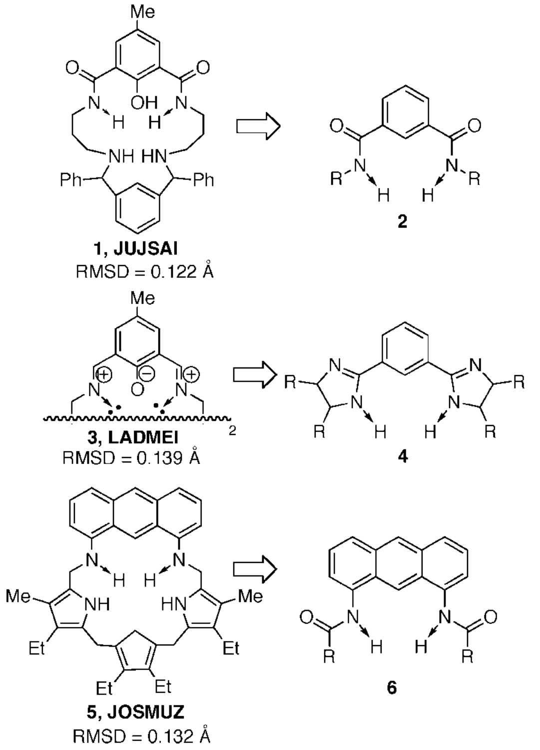


Figure 3. Substructure obtained from the CAVEAT search (arrows in structures match the input vectors from Figure 2; rmsd = root-mean-square deviation of vectors in crystal structures compared to input vectors).

midinium (Figure 4) with allyl vinyl ether revealed formation of a dual hydrogen bonding adduct with bond angles (172°) approaching an ideal linear hydrogen bond.

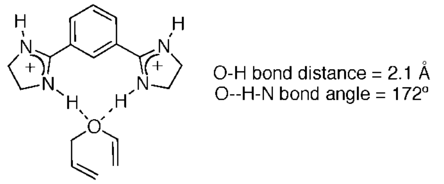
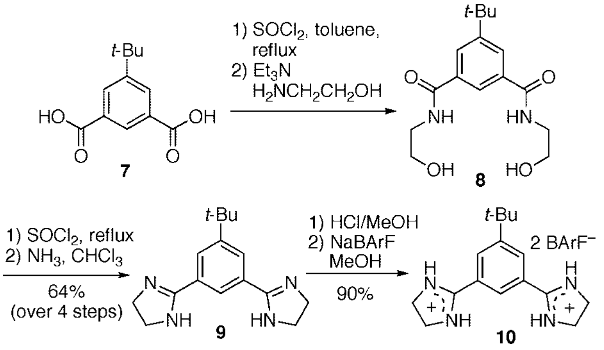


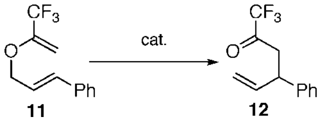
Figure 4. Hydrogen bonding of the bisamidinium of **4** (R = H) with allyl vinyl ether.

To test the applicability of a bisamidine in catalysis of the Claisen rearrangement, we synthesized **9** in a straightforward manner (Scheme 1). Due to the poor solubility of bisamidine **9**, bisamidinium **10** was synthesized by forming the chloride salt in quantitative yield. Anion exchange with sodium barfate[17] then provided **10** in 90% yield. In addition to increasing solubility, the doubly cationic nature of **10** also provides a superior set of hydrogen bond donors.[18]

Scheme 1. Synthesis of Bis-amidinium **10**



Allylvinyl ether **11** (eq 1) was selected to preclude the >formation of a [1,3] sigmatropic product.[19] The Claisen rearrangement of **11** occurs via a nonpolarized transition state[19] which should prevent formation of the enolate/allylic cation pair and favor only the concerted Claisen rearrangement pathway leading to [3,3] sigmatropic product **12**.



(1)

With bisamidinium catalyst **10** in hand, the reaction of **11** was screened with various solvents. Very little to no background reaction was observed without catalyst in a range of solvents. As expected for a catalyst that interacts via

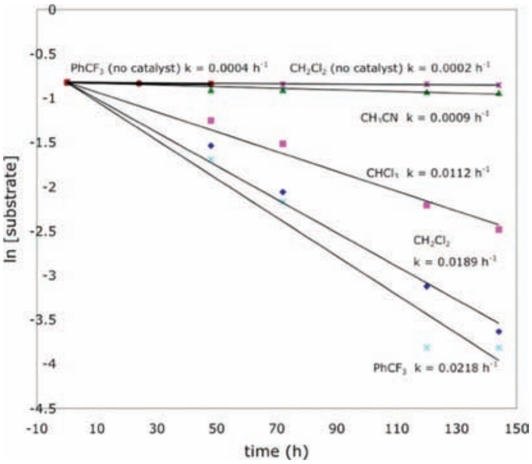


Figure 5. Effect of solvent in the bisamidinium catalyzed Claisen rearrangement (eq 1). Reaction conditions: [**11**] = 0.44 M, rt, 25 mol % **10** when employed.

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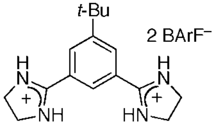
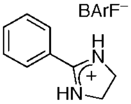
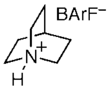
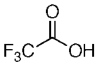
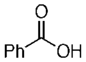
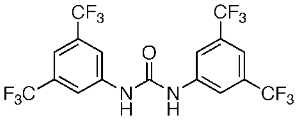
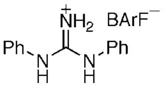
Table 1. Use of Brønsted Acids to Catalyze the Claisen Rearrangement of **11** (eq 1)[a]

cat.		pK_a[b]	loading (mol %)	conv. (%)[c]
	**10**	11.6	25	95[d]
	**13**	11.6	50	33
	**14**	11	50	36
	**15**	-0.25	50	27
	**16**	4.2	50	3
	**17**	27 (DMSO)	25	4
	**18**	10.7	50	43

[a] Reaction conditions: 72 h at rt in $PhCF_3$. [b] Smith, M. B.; March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structures*, 6th ed.; Wiley-Interscience: New Jersey, 2007. Jenks, W. P.; Regenstein, J. Ionization Constants of Acids and Bases. In *Handbook of Biochemistry and Molecular Biology*, 3rd ed.; Fasman, G. D., Ed.; CRC Press: Ohio, 1975; Vol. 1, pp 305−351. [c] Determined by ^1H NMR spectroscopy (see Supporting Information). [d] Obtained 70% isolated yield of the volatile product.

hydrogen-bonding, ethereal solvents strongly inhibited the catalyst. Among nonpolar solvents, $PhCF_3$ and CH_2Cl_2 were optimal; rate accelerations for catalyst **10** with respect to the uncatalyzed processes were 55- and 95-fold, respectively (Figure 5). These values approach those estimated between the reaction of allyl vinyl ether in organic solvents vs water (∼60−100−fold).[10,20]

To illustrate the effectiveness of bisamidinium catalyst **10**, a comparison with other hydrogen bonding catalysts was undertaken. As such, bisamidinium **10**, monoamidinium **13**, ammonium salt **14**, trifluoroacetic acid (**15**), benzoic acid (**16**), urea **17**, and guanidinium **18** were examined in the Claisen rearrangement of **11** (Table 1). Interestingly, bisamidinium **10** catalyzed the Claisen rearrangement more rapidly than stronger Brønsted acids **15** and **16**. The dual hydrogen bond donating nature of **10** is crucial for optimal reactivity as twice the amount of comparable monohydrogen bond donors (**13** and **14**) were not as reactive. Bisamidinium **10** is also much more effective than urea **17** which was used by Curran in his studies of the Claisen rearrangement.[8]

In conclusion, we have discovered that bisamidinium **10** can catalyze the Claisen rearrangement of allyl vinyl ether **11**. The reactivity of **10** is superior to higher catalyst loadings of stronger Brønsted acids indicating that hydrogen bonding potential is not solely a function of acidity. Further support for the designed dual hydrogen bonding motif was found in the lower reactivity of the corresponding monoamidinium. The reaction has been optimized to take place in a reasonable amount of time, and studies toward an enantioselective variant are currently under way. Experiments to expand the use of **10** to other reactions of interest are being undertaken.

Acknowledgment. We thank the NIH (GM59945) and the NSF (CHE-0616885) for financial support.

Supporting Information Available: Experimental details and characterization of all new compounds is provided. This material is available free of charge via the Internet at http://pubs.acs.org.

OL8026945

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