Enantioselective Claisen Rearrangements: Development of a First Generation Asymmetric Acyl-Claisen Reaction

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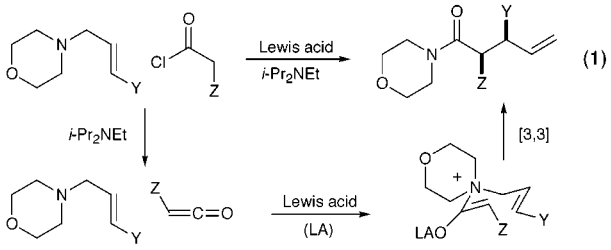
The development of an enantioselective catalytic Claisen rearrangement[1] remains an important yet elusive goal in chemical synthesis.[2] With this objective in mind, we recently reported the acyl-Claisen rearrangement, a Lewis acid-catalyzed variant of the Bellus reaction[3] that utilizes acid chlorides and allylic amines in the stereoselective synthesis of α,β-disubstituted-γ,δ-unsaturated carbonyls (eq 1).[4] In this communication, we demonstrate that



(1)

Lewis acid architecture can play an important role in the design of an enantioselective variant of this new [3,3]-sigmatropic bond reorganization. Specifically, the Lewis acidic complexes **2** derived from MgI_2 and bis(oxazolinyl)aryl (Arbox) ligands provide a highly effective asymmetric environment for a broad range of acyl-Claisen rearrangements that employ chelating substrates. To our knowledge, these studies collectively represent the first example of an enantioselective acyl-Claisen reaction.

Our initial efforts toward an enantioselective Claisen process were focused on the addition-rearrangement of benzyloxyacetyl chloride with *N*-allylmorpholine in the presence of a variety of chiral Lewis acids (eq 2). Given the demonstrated utility of chelation as an organizational control element in asymmetric catalysis,[5] it was assumed that two-point coordination between the chiral complex and an α-heteroatom-substituted allyl vinylammonium would engender a stereoselective process. A preliminary survey of "privileged ligand"−metal salt combinations[6] revealed that the [Mg((*R*,*R*)-Ph-pybox)](I)$_2$ complex **1** (200 mol %, −20 °C, 24 h) was most successful in providing the Claisen adduct (*S*)-**3** in 87% yield and 56% ee (Table 1). Subsequent optimization of ligand architecture for a series of magnesium iodide derived complexes demonstrated that the (*R*,*R*)-Arbox framework **2a** was effective in affording (*S*)-**3** in 88% yield and 83% ee (entry 2). Significantly, a number of 1,2-bis(oxazolinyl)-aryl complexes have previously been reported;[7] however, we believe this study represents the first enantioselective transformation that successfully employs this class of ligand framework.

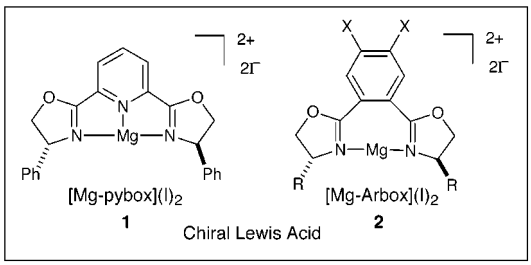
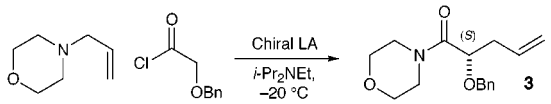


Table 1. The Effect of Chiral Lewis Acid Structure on the Enantioselective Acyl-Claisen Rearrangement



(2)

entry	chiral Lewis acid complex	R	X	mol % LA	time (h)	% yield	% ee[a]
1	**1**	−	−	200	24	87	56
2	**2a**	Ph	H	200	24	88	83
3	**2b**	Ph	Cl	200	24	65	86
4	**2c**	*p*-MeOPh	Cl	50	24	81	42
5	**2c**	*p*-MeOPh	Cl	100	24	63	81
6	**2c**	*p*-MeOPh	Cl	200	24	80	91
7	−	−	−	−	24	42	

[a] Enantiomeric excess was determined by chiral GLC.

From an investigation of ligand substituent effects on reaction efficiency, we determined that complexes that possess chlorine moieties on the aryl backbone and methoxy substituents on the phenyl oxazoline provide higher levels of enantiocontrol (entry 6, 91% ee). These substituent effects appear cumulative as incorporation of only the chlorine moieties renders a less selective process (cf. entries 3 and 6). It is important to note that substoichiometric quantities of (*R*,*R*)-**2c** afford lower enantioselectivities (entry 4). We tentatively conclude that diminished stereocontrol in this case arises from a competing nonmetal-mediated rearrangement pathway. Indeed, control experiments reveal that Claisen adduct **3** is formed with moderate efficiency in the absence of Lewis acid (entry 7).[8] The superior levels of enantioselectivity exhibited by complex **2c** (200 mol %) to afford (*S*)-**3** in 91% ee and 80% yield (entry 6) prompted us to select this Lewis acid for further exploration.

The effect of acid chloride structure on enantioselectivity was next evaluated. From the results summarized in Table 2, it is evident that the capacity of the acid chloride to participate in metal chelation is related to the enantiofacial discrimination of the [3,3]-isomerization event. As expected, poorly chelating substrates such as acetoxyacetyl and (*tert*-butyldimethylsilyloxy)acetyl chloride

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(8) As reported in our initial acyl-Claisen survey, we have not observed a nonmetal-mediated process with alkyl-substituted acid chlorides (e.g. propionyl chloride).[4]

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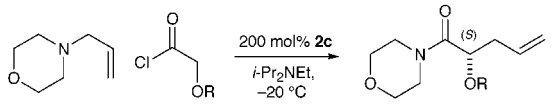
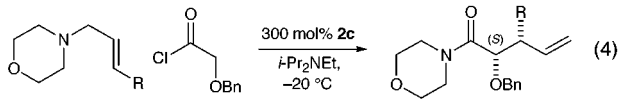
Table 2. The Effect of Acid Chloride Structure on the Enantioselective Acyl-Claisen Rearrangement

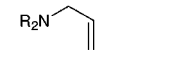
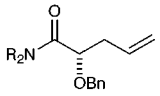
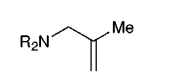
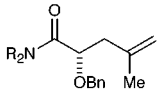
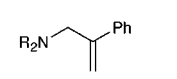
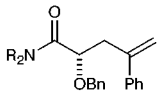
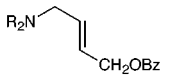
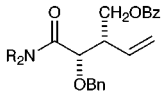
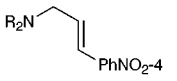
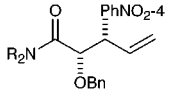
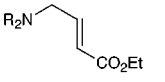
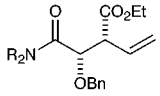
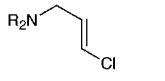
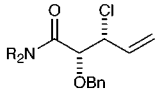
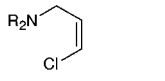
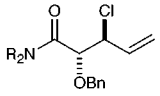


entry	OR	time (h)	% yield	% ee[a]
1	OAc	20	44	37
2	OTBS	20	67	38
3	OPhCl-4	20	59	71
4	OPh	20	48	78
5	OMe	24	28	80
6	OBn	24	80	91

[a] Enantiomeric excess was determined by chiral GLC or HPLC.

Table 3. Enantioselective Acyl-Claisen Rearrangement with Representative Allyl Morpholines



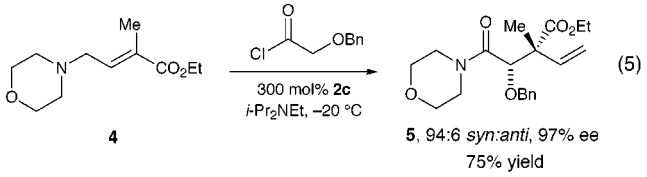
entry	amine[a]	product[a]	% yield	*syn:anti*[b]	% ee[b]
1			80	--	91[c]
2			78	--	91[c]
3			79	--	90
4			86	92:8	86[c]
5			82	99:1	97
6			84	97:3	96
7			95	98:2	91
8			74	3:97	91

[a] NR_2 = *N*-morpholine. [b] Ratios determined by chiral GLC or HPLC. Absolute stereochemistry determined by chemical correlation or by analogy. [c] Reaction performed with 200 mol % **2c**.

(entries 1 and 2) exhibit only modest levels of stereocontrol (≤38% ee), while optimal levels of asymmetric induction were obtained with ketene surrogates that contain Lewis basic α-alkoxy substituents (entry 5, R = Me, 80% ee; entry 6, R = Bn, 91% ee).

Experiments that probe the scope of the allyl morpholine reaction component are summarized in Table 3. Significant structural variation in the C(3)-allyl substituent is possible to afford a diverse range of α,β-disubstituted-γ,δ-unsaturated carbonyls with excellent levels of diastereo- and enantioselectivity (entries 4−8, 74−95% yield, 92:8 to 99:1 *syn:anti*, 86−97% ee).[9] Incorporation of alkyl and aryl substituents at the C(2)-olefin position is also readily tolerated without significant loss in enantioselectivity (entry 2, 78% yield, 91% ee; entry 3, 79% yield, 90% ee). In accord with established Claisen methodology,[1b] complementary diastereomers can be accessed in enantioenriched form by the appropriate selection of double bond geometry on the allyl component. Thus, while (*E*)-(3-chloro-2-butenyl)morpholine yields predominantly the syn Claisen product (entry 7, 95% yield, 98:2 syn:anti, 91% ee), the (*Z*) isomer affords the corresponding anti product with similar levels of stereocontrol (entry 8, 74% yield, 3:97 syn:anti, 91% ee). Importantly, formation of the α,β-unsaturated amide resulting from β-elimination of the chloride substituent is not observed in either case, illustrating the mild reaction conditions employed in this asymmetric Claisen process.

Finally, a demonstration of the utility of this new reaction to provide enantioselective access to elusive acyclic structural motifs is presented in the addition-rearrangement of 3,3-disubstituted allyl morpholine **4** (eq 5). The central issue in this reaction is that of



Lewis acid controlled asymmetric construction of quaternary carbon centers on an acyclic framework. As outlined in eq 5, complex (*R,R*)-**2c** effectively translates the methyl-carboethoxy substitution pattern on allylamine **4** with high levels of enantiocontrol and stereospecificity to furnish the quaternary carbon bearing Claisen adduct (*S*)-**5** in 97% ee and 94:6 syn:anti selectivity.[10]

In conclusion, we have developed the first enantioselective acyl-Claisen rearrangement. Studies toward a catalytic variant of this reaction are underway and will be reported in due course.

Acknowledgment. This paper is dedicated to Professor David A. Evans on the occasion of his 60th birthday. T.P.Y. is grateful for an NSF predoctoral fellowship. Financial support was provided by the NIH (R01 GM61214-01), the UC AIDS Research Program, and kind gifts from Boehringer-Ingelheim, Dupont, Johnson and Johnson, and Merck.

Supporting Information Available: Experimental procedures and spectral data for all compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) In a representative procedure, the allylic morpholine (0.10 mmol, 0.025 M in CH_2Cl_2) and *i*-Pr_2NEt (0.15 mmol) were added sequentially to a catalyst solution (0.2 mmol) in CH_2Cl_2 at 23 °C. The resulting solution was cooled to −20 °C before benzyloxyacetyl chloride (0.12 mmol, 1.0 M in CH_2Cl_2) was added over 12 h. After an additional 12 h, the resulting solution was treated with 1 N NaOH and extracted into EtOAc. The organics were dried ($MgSO_4$) and concentrated, and the ligand was precipitated with EtOH. The supernatant was filtered, concentrated, and then purified by flash chromatography.

(10) Although one of the most common structural motifs found in organic architecture, quaternary carbon stereogenicity remains a formidable challenge to asymmetric synthesis. For an excellent review of enantioselective quaternary carbon construction, see: Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 388.