ORGANIC LETTERS

2005
Vol. 7, No. 9
1809−1812

Formation of Disubstituted β-Lactones Using Bifunctional Catalysis

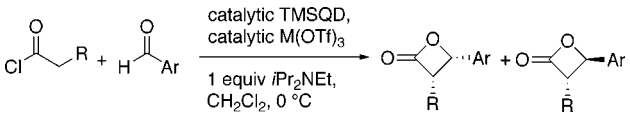
Michael A. Calter,*,† Olexandr A. Tretyak,† and Christine Flaschenriem‡

Department of Chemistry, Wesleyan University, Middletown, Connecticut 06459-0180, and Department of Chemistry, University of Rochester, Rochester, New York 14627-0216

mcalter@wesleyan.edu

Received February 24, 2005

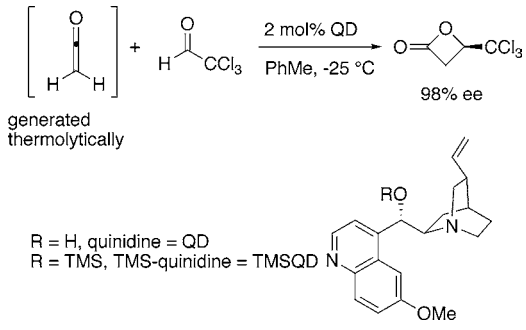
ABSTRACT



Acid chlorides and aromatic aldehydes react in the presence of a stoichiometric amount of a tertiary amine and catalytic amounts of a cinchona alkaloid derivative and a Lewis acid to produce β-lactones in high diastereo- and enantioselectivity. The sense of the diastereoselectivity depends on the substitution of the acid chloride, with the reactions of aliphatic acid chlorides giving predominantly the *trans*-isomer and those of alkoxyacetyl chlorides favoring formation of the *cis*-isomer.

Wynberg and Staring reported in 1982 that cinchona alkaloids function as very effective asymmetric catalysts for the addition of ketene to di- and trichloroaldehydes and ketones (Scheme 1).[1] This report offered the first evidence that the alkaloids could control the electrophile facial selectivity in the reaction of acylammonium enolates.

Scheme 1



Numerous reports have described the ability of the alkaloids to also determine nucleophile facial selectivity;[2] however, the development of a version of the Wynberg reaction employing substituted ketenes has been hampered by the tendency of these ketenes to dimerize under nucleophilic catalysis. Furthermore, the extension of the Wynberg reaction to less highly activated carbonyl electrophiles has also been complicated by rapid ketene dimerization. However, Lectka et al. discovered that a number of Lewis acids are compatible with the generation and cinchona alkaloid-catalyzed reactions of ketenes with imine electrophiles.[3] Furthermore, Nelson and co-workers have recently reported that the combination of a cinchona alkaloid with a Lewis acid, lithium perchlorate, catalyzes the reaction of substituted ketenes with unactivated aldehydes to give the *cis*-β-lactones.[4] We report here that lanthanide and pseudolanthanide triflates also co-catalyze the addition of substituted ketenes to unactivated arylaldehydes but in some cases afford the *trans*-isomer in high diastereo-

† Wesleyan University.
‡ University of Rochester.

(1) (a) Wynberg, H.; Staring, E. G. *J. Am. Chem. Soc.* **1982**, *104*, 166−168. (b) Wynberg, H.; Staring, E. G. J. *J. Org. Chem.* **1985**, *50*, 1977−1979. (c) Wynberg, H. *Top. Stereochem.* **1986**, *16*, 87−129.

(2) (a) Pracejus, H.; Mätje, H. *J. Prakt. Chem.* **1964**, *24*, 195−205. (b) Calter, M. A.; Orr, R. K.; Song, W. *Org. Lett.* **2003**, *5*, 4745−4748. (c) Cortez, G. S.; Tennyson, R. L.; Romo, D. *J. Am. Chem. Soc.* **2001**, *122*, 7831−7832.

(3) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Ferraris, D.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 6626−6635.

(4) Nelson, S. G.; Zhu, C.; Shen, X. *J. Am. Chem. Soc.* **2004**, *126*, 14−15. For a noncinchona alkaloid-based method for the synthesis of disubstituted β-lactones, see: Wilson, J. E.; Fu, G. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 6358−6360.

10.1021/ol050411q CCC: $30.25
Published on Web 03/26/2005

selectivity. This diastereomer has not been previously available from ketene/aldehyde additions, and we present evidence that the lanthanide and pseudolanthanide triflate-catalyzed reactions are mechanistically distinct from other Lewis acid-catalyzed ketene/aldehyde additions. Furthermore, the conditions reported here allow the formation of α-alkoxy-β-lactones, the functional equivalent of glycolate aldol products.

The key observations came from exploring the reactions of phenoxyacetyl chloride in the presence of Hünig's base and the cinchona alkaloid derivative, TMSQD (Scheme 2,

Scheme 2

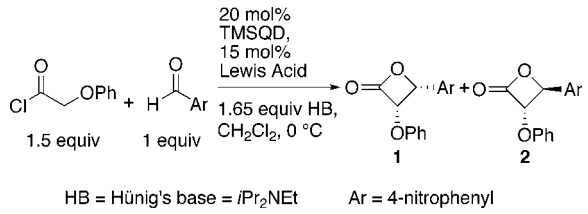


Table 1). These conditions likely result in the generation of phenoxyketene, but we had previously observed that this

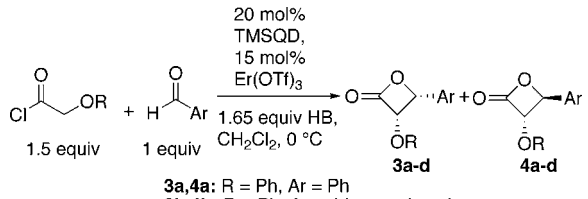
Table 1. Yields and Selectivities for the Formation of **1** and **2**

Lewis acid	**1**/**2**[a]	% yield of **1**[b] (% ee)[c]	% yield of **2**[b] (% ee)[c]
	51:49	3 (nd[d])	3 (nd)
$BF_3{\cdot}OEt_2$		0	0
$Mg(OTf)_2$	38:63	2 (nd)	4 (70)
$Zn(OTf)_2$	87:13	24 (99)	4 (74)
$Sc(OTf)_3$	71:29	52 (>99)	18 (93)
$Yb(OTf)_3$	91:9	82 (>99)	5 (92)
$Er(OTf)_3$	92:8	89 (>99)	5 (92)
$Y(OTf)_3$	50:50	nd	nd
$Gd(OTf)_3$	83:17	38 (92)	7 (38)
$Er(OTf)_3$	93:7	87 (>99)[e]	nd

[a] Determined by ^{1}H NMR analysis of the unpurified reaction mixture. [b] Yield of purified compound. [c] Determined by HPLC analysis of purified isomer. [d] nd = not determined. [e] Reaction performed with TMS-quinine as catalyst; the enantiomer of **1** was the major product.

ketene fails to dimerize under conditions that result in the dimerization of alkylketenes.[2b] Inclusion of an aromatic

Scheme 3



3a,4a: R = Ph, Ar = Ph
3b,4b: R = Ph, Ar = 4-bromophenyl
3c,4c: R = Ph, Ar = 3-chlorophenyl
3d,4d: R = Bn, Ar = 4-cyanophenyl

aldehyde into the reaction failed to produce any lactone product until a Lewis acid was also included in the reaction mixture. Lanthanide and pseudolanthanide triflates afford the highest reaction rates and conversions. The efficiency and diastereoselectivity of the reaction depends highly on the size of the Lewis acid. The use of triflates of the smaller lanthanides, such as ytterbium and erbium, gives the highest selectivity for the *cis*-isomer, while the use of either larger or smaller metals, such as gadolinium or scandium, leads to relatively larger proportions of the *trans*-isomer.

Table 2. Yields and Selectivities for the Formation of **3a**−**d**

products	**3**/**4**[a]	% yield of **3**[b] (% ee)[c]	% yield of **4**[b] (% ee)[c]
3a, **4a**	88:12	58 (>99)	nd
3b, **4b**	88:12	55 (>99)	nd
3c, **4c**	92:8	88 (>99)	5 (nd)
3d, **4d**	87:13	68 (>99)[e]	nd

[a] Determined by ^{1}H NMR analysis of the unpurified reaction mixture. [b] Yield of purified compound. [c] Determined by HPLC analysis of purified isomer. [d] Determined by ^{1}H NMR analysis of the purified product in the presence of a chiral shift reagent. [e] Reaction performed with TMS-quinine as catalyst; the enantiomer of **3d** was the major product.

Other electron-withdrawing group-substituted benzaldehydes also yield the *cis*-β-lactones in high diastereo- and enantioselectivities, as does benzaldehyde itself (Scheme 3,

Scheme 4

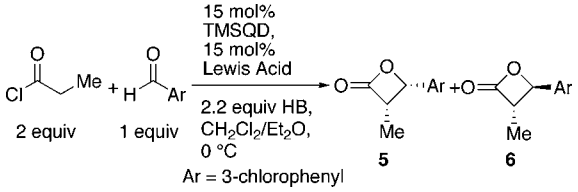


Table 2). Lactones **3a** and **3b** partially decarboxylate to the styrene derivatives under the reaction conditions, leading to lower yields for these compounds.

Table 3. Yields and Selectivities for the Formation of **5**

Lewis acid	**5**/**6**[a]	% yield of **5**[b]	% ee of **5**[c]	% ee of **6**[c]
		0		
$BF_3{\cdot}OEt_2$		0		
$MgBr_2$	52:48	8	nd	nd
$Zn(OTf)_2$	50:50	7	nd	nd
$Sc(OTf)_3$	8:92	85	98	90
$Yb(OTf)_3$	20:80	76	96	92
$Nd(OTf)_3$		0		

[a] Determined by H^1 NMR analysis of the unpurified reaction mixture. [b] Yield of purified compound. [c] Determined by HPLC analysis of purified isomer.

We next attempted the formation of β-lactones with alkyl substituents in the α-position. We screened a number of

Scheme 5

Lewis acids for the reaction of propionyl chloride and 3-chlorobenzaldehyde (Scheme 4, Table 3). Several Lewis acids favored the addition, and all of the reactions produced a higher percentage of the *trans*-isomer than observed with alkoxy-substituted acetyl chlorides. The optical activities of both the *cis*- and *trans*-isomers were uniformly excellent. Scandium triflate was selected as the optimal Lewis acid catalyst for substrate screening based on its ability to furnish synthetically useful diastereoselectivity for the *trans*-isomer.

The aliphatic acid chloride reactions proceeded effectively with a set of aromatic aldehydes similar to those that were effective substrates in the reaction of alkoxy acid chlorides (Scheme 5, Table 4). The diastereo- and enantioselectivities

Table 4. Yields and Selectivities for the Formation of **7a**−**d**

product	R	Ar	*trans*/*cis*[a]	% yield of **7**[b]	% ee of **7**[c]
7a	Me	phenyl	91:9	75	92
7b	Me	4-nitrophenyl	91:9	82	96
7c	Me	4-cyanophenyl	92:8	80	99
7d	Et	4-cyanophenyl	95:5	80	99

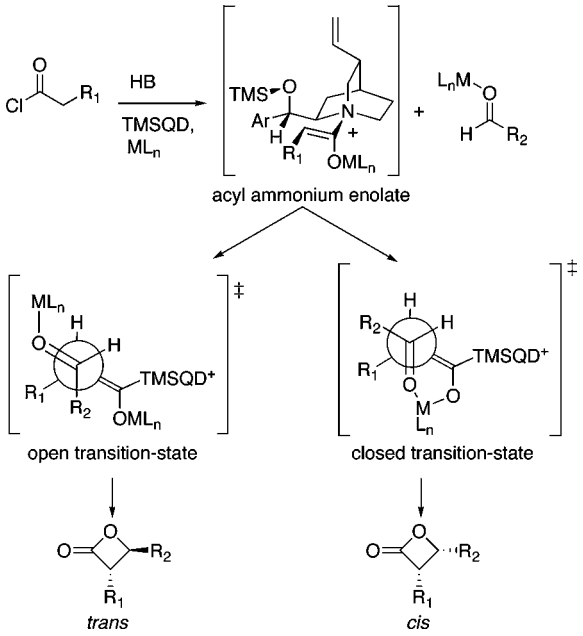
[a] Determined by ^{1}H NMR analysis of the unpurified reaction mixture. [b] Yield of purified compound. [c] Determined by HPLC analysis of purified isomer.

were relatively unaffected by changes in the electronic nature of the aldehyde.

An examination of the results suggests a rationale for stereochemical induction realized with the aliphatic acid chlorides and also a modification of the model proposed by Wynberg. The Lewis acid apparently activates the aldehyde and allows the ketene/aldehyde addition to predominate over ketene dimerization. The stereochemistry of the reaction is most likely set in the reaction of the *Z*-acylammonium enolate intermediates (Scheme 6). Considerable precedence suggests that the *syn*-aldol product, and therefore *cis*-*β*-lactone, results from a closed transition-state aldol reaction of the *Z*-enolate. Therefore, we believe that the *trans*-lactone forms through an open transition-state process. An *anti*-periplanar arrangement between the enolate and the carbonyl in such a transition-state, and minimization of nonbonded interactions, correctly predicts formation of the *trans*-isomer. The open transition-state model also predicts the observed enantiomer in Wynberg's cases, where R_1 = H and the aldehyde is sufficiently electrophilic to react without Lewis acid activation.[1c]

Higher concentrations of Lewis acid favor formation of the *trans*-isomer from the aliphatic acid chlorides, indicating

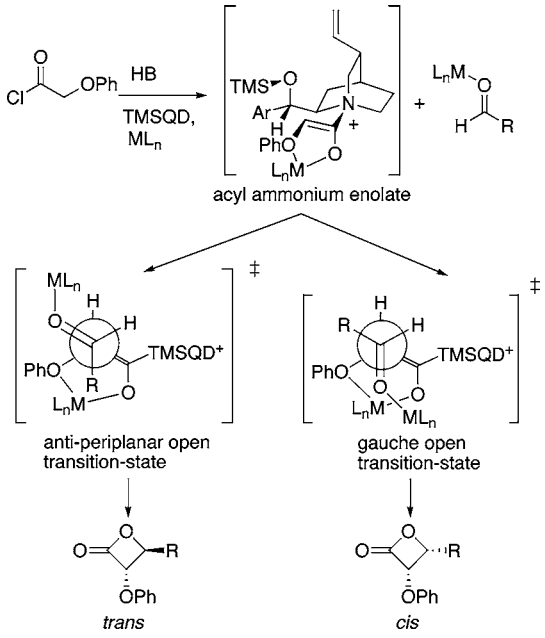
Scheme 6



that the transition-state leading to this isomer includes two molecules of Lewis acid. For example, the *trans*/*cis* ratio in the formation of **7c** changes from 56:44 with 7.5 mol % of $Sc(OTf)_3$ to 92:8 with 15 mol %. This result indicates that the aldehyde and the ammonium enolate both bind to separate molecules of Lewis acid in the transition state leading to the *trans*-isomer.

The *cis*-isomer formed in the reactions of phenoxyacetyl chloride could result from a closed transition-state aldol reaction or an alternative open transition-state process

Scheme 7



(Scheme 7). The phenoxy group most likely forms a chelate with the Lewis acid bound to the acylammonium enolate. The interaction between the R group and the metal ligands would disfavor the antiperiplanar, open transition state, leading to a relative preference for a gauche, open transition state.

In conclusion, we have shown that the combination of a chiral nucleophile and an achiral Lewis acid catalyzes the asymmetric condensation of acid chlorides with aromatic aldehydes, presumably by way of acylammonium enolate intermediates. This catalyst system allows an expansion in the scope of the Wynberg reaction and also the first direct access to *trans*-β-lactones.

Acknowledgment. We acknowledge the Chemistry Departments of the University of Rochester and Wesleyan University for support of this work.

Supporting Information Available: General experimental procedures and characterization data for compounds **1**, **3a**−**d**, **5**, and **7a**−**d** and details of stereochemical proofs, including results of a single-crystal X-ray diffraction structure of **3c**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050411Q