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# Lewis Acid−Lewis Base Catalyzed Enantioselective Hetero-Diels−Alder Reaction for Direct Access to δ-Lactones

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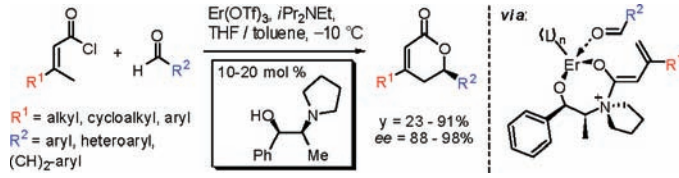
## ABSTRACT




**A complex formed in situ from $Er(OTf)_3$ and a simple commercially available norephedrine ligand promotes an unprecedented [4 + 2] cycloaddition of α,β-unsaturated acid chlorides with a broad range of aromatic and heteroaromatic aldehydes by a cooperative bifunctional Lewis acid−Lewis base catalytic mode of action providing valuable δ-lactone building blocks with excellent enantioselectivity.**

δ-Lactone moieties constitute an exceptionally widespread structural motif in natural and synthetic compounds which display high efficacy, e.g., as anticancer[1] or cholesterol-lowering agents. For instance, the majority of statin drugs such as Lipitor and Zocor, the world's biggest selling drugs in the last years, contain a β-hydroxy-δ-lactone moiety or the corresponding open-chain carboxylate form.[2]

Hetero-Diels−Alder (HDA) reactions[3] of Brassard's diene (1,3-dimethoxy-1-(trimethylsilyloxy)butadiene) and aldehydes have been developed to synthesize β-methoxy-substituted α,β-unsaturated δ-lactones.[4,5] Recently, we have reported a direct concept using α,β-unsaturated acid chlorides as substrates which is based on the in situ formation of vinylketenes.[6] These intermediates were previously not useful for catalytic asymmetric Diels−Alder reactions as a result of their tendency to preferentially undergo [2 + 2] cycloadditions and due to their inherent instability (rapid dimerization and polymerization).[7,8] However, in our preceding studies we demonstrated that these species can be trapped in situ and at the same time activated as diene components for [4 + 2] cycloadditions by an enantiopure nucleophilic tertiary amine, thus forming zwitterionic dienolates **1** (Figure 1) which are able to undergo an enantioselective HDA reaction with the highly activated aldehyde chloral.

Nonactivated aldehydes, e.g. benzaldehyde or even *p*-nitrobenzaldehyde, did not furnish the targeted products due

(1) Shaw, S. J.; Sundermann, K. F.; Burlingame, M. A.; Myles, D. C.; Freeze, B. S.; Xian, M.; Brouard, I.; Smith, A. B., III *J. Am. Chem. Soc.* **2005**, *127*, 6532.

(2) Istvan, E. S.; Deisenhofer, J. *Science* **2001**, *292*, 1160.

(3) General review on HDA reactions: Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558.

(4) (a) Fan, Q.; Lin, L.; Liu, J.; Huang, Y.; Feng, X. *Eur. J. Org. Chem.* **2005**, 3542. (b) Lin, L.; Fan, Q.; Qin, B.; Feng, X. *J. Org. Chem.* **2006**, *71*, 4141. (c) Du, H.; Zhao, D.; Ding, K. *Chem. Eur. J.* **2004**, *10*, 5964. (d) Lin, L.; Chen, Z.; Yang, X.; Liu, X.; Feng, X. *Org. Lett.* **2008**, *10*, 1311. For an alternative enantioselective concept using allenic esters, see: (e) Oisaki, K.; Zhao, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 7439.

(5) (a) Reviews about δ-lactones: Collins, I. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1377. (b) Boucard, V.; Broustal, G.; Campagne, J. M. *Eur. J. Org. Chem.* **2007**, 225.

(6) Tiseni, P. S.; Peters, R. *Angew. Chem., Int. Ed.* **2007**, *46*, 5325.

(7) Tidwell, T. T. *Ketenes*; John Wiley & Sons: Hoboken, NJ, **2006.**

(8) 2-(Trimethylsilyl)vinylketene has been reported to be a remarkably stable vinylketene and has been used for non-enantioselective HDA reactions: Bennett, D. M.; Okamoto, I.; Danheiser, R. L. *Org. Lett.* **1999**, *1*, 641.

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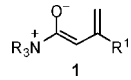


**Figure 1.** Zwitterionic dienolates **1** as reactive dienes for enantioselective HDA reactions.

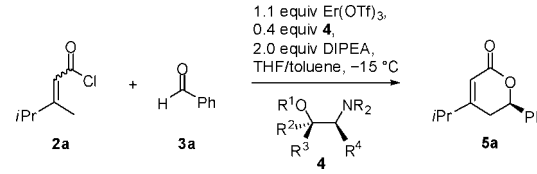
to poor reactivity of the organocatalysts. A bifunctional Lewis acid−Lewis base catalyst by which the reactivity of both the dienolate and aldehyde could be controlled was therefore required.[9,10] The combination of Lewis acids and Lewis bases successfully united in one catalytic system has recently found numerous applications in asymmetric catalysis due to synergistic activation of both the electrophilic and nucleophilic substrates, often allowing high reaction rates and excellent chirality transfer.[11]

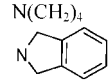
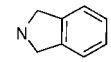
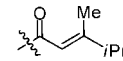
The present studies were based upon the hypothesis that a Lewis acid such as a lanthanide salt, which offers an exceptionally high number of coordination sites, would be advantageous to bind both aldehyde and dienolate plus additional ligands to control reactivity and stereoselectivity.[12] The development of lanthanide complexes acting as bifunctional catalysts was pioneered by the seminal work of Shibasaki et al.[13]

To implement a cycloaddition transition state with a high level of organization the nucleophilic catalyst should be directly connected to the Lewis acid template. We envisaged that an oxophilic lanthanide would tightly bind to an alcoholate moiety while a tertiary amino group would undergo a hemilabile coordination still permitting a sufficient reactivity to nucleophilically trap a vinylketene intermediate.

Although Er(III) complexes with aliphatic $\beta$- or $\gamma$-amino alcohols possessing a tertiary amino group have to our knowledge never been previously described in the literature, $Er(OTf)_3$ was chosen for these investigations as lanthanide source owing to the combination of (a) a comparatively low price of Er which is linked to its importance for telecommunication industry[14] and (b) a relatively small ionic radius (as a consequence of the lanthanide contraction)[15] which should be advantageous to achieve a rigid cycloaddition transition state. The assumption of a cooperative bifunctional Lewis acid−Lewis base activation mechanism was initially supported by the observation that $Er(OTf)_3$ did not destroy the nucleophilicity of pyridine in the model reaction presented in Table 1 (entry 1), while no reaction took place in the absence of either nucleophile or Lewis acid.

**Table 1.** Development of the Title Reaction[a]




| no. | 4 | $NR_2$ | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Yield / %[b] | *ee* / %[c] |
|---|---|---|---|---|---|---|---|---|
| 1 | pyr | - | - | - | - | - | 87 | - |
| 2 | **4a** | $NMe_2$ | H | H | Ph | Me | 27 | 74 |
| 3 | **4b** | $N(CH_2)_4$ | H | H | Ph | Me | 35 | 95 |
| 4 | **4c** |  | H | H | Ph | Me | 14 | 44 |
| 5 | **4d** |  | H | H | Ph | Ph | 0 | - |
| 6 | **4e** | $N(CH_2)_4$ | H | Ph | Ph | Me | < 5 | 6 |
| 7 | **4f** | $N(CH_2)_4$ | H | H | H | Me | 0 | - |
| 8 | **4g** | $N(CH_2)_4$ | Me | H | Ph | Me | 24 | –34 |
| 9 | **4h** | $N(CH_2)_4$ |  | H | Ph | Me | 11 | –33 |
| 10[d] | **4b** | $N(CH_2)_4$ | H | H | Ph | Me | 38 | 95 |
| 11[d-e] | **4b** | $N(CH_2)_4$ | H | H | Ph | Me | 42 | 95 |
| 12[d-f] | **4b** | $N(CH_2)_4$ | H | H | Ph | Me | 52 | 95 |
| 13[d-g] | **4b** | $N(CH_2)_4$ | H | H | Ph | Me | 58 | 95 |
| 14[d-h] | **4b** | $N(CH_2)_4$ | H | H | Ph | Me | **56** | **95** |
| 15[d-g,i] | **4b** | $N(CH_2)_4$ | H | H | Ph | Me | 49 | 91 |
| 16[d-g,j] | **4b** | $N(CH_2)_4$ | H | H | Ph | Me | 30 | 84 |

[a] Compound **2a** was slowly added by syringe pump over 120 min (1:1 stoichiometry of both substrates). Stirring was continued for an additional 150 min. [b] NMR yields using $MeNO_2$ as internal standard. [c] Determined by chiral column HPLC. [d] Compound **2a** was added over 30 min. [e] $T = -10$ °C. [f] 1.5 equiv of $Er(OTf)_3$. [g] 2.5 equiv of DIPEA. [h] 0.2 equiv of **4b**. [i] 0.1 equiv of **4b**. [j] 0.05 equiv of **4b**.

With *N*-methylephedrine **4a**, $\delta$-lactone **5a** was formed with a promising ee of 74% (entry 2), yet the yield was low. Replacing the $NMe_2$ group by a pyrrolidine unit not only enhanced the reactivity (yield = 35%) but also resulted in an ee value of 95% (entry 3). The nucleophilicity of the tertiary amino group is essential as entries 4 and 5 demonstrate, in which the steric accessibility and the electron density of the amino group are diminished with the consequence of reduced or no reactivity. Whereas in the case of a tertiary or primary alcohol moiety the title reaction was retarded (entries 6 and 7), a methyl-protected hydroxyl impeded high enantioselectivity (entry 8), while TMS protection gave no product at all. Entry 9 demonstrates that

(9) In our previous work, $Sn(OTf)_2$ was used as cocatalyst but was not directly involved in the cycloaddition step itself, see ref 6.

(10) For the application of bifunctional catalysts in [2 + 2] cycloadditions of ketenes, see, e.g.: (a) $LiClO_4$ in combination with O-protected cinchona alkaloids: Zhu, C.; Shen, X.; Nelson, S. G. *J. Am. Chem. Soc.* **2004**, *126*, 5352. (b) Metal triflates including $Er(OTf)_3$ in combination with O-protected cinchona alkaloids: Calter, M. A.; Tretyak, O. A.; Flaschenriem, C. *Org. Lett.* **2005**, *7*, 1809. (c) $In(OTf)_3$ in combination with O-protected cinchona alkaloids: France, S.; Shah, M. H.; Weatherwax, A.; Wack, H.; Roth, J. P.; Lectka, T. *J. Am. Chem. Soc.* **2005**, *127*, 1206. (d) Oxazaborolidine catalyst: Gnanadesikan, V.; Corey, E. J. *Org. Lett.* **2006**, *8*, 4943. (e) A hybrid cinchona alkaloid/salene−Co complex: Lin, Y.-M.; Boucau, J.; Li, Z.; Casarotto, V.; Lin, J.; Nguyen, A. N.; Ehrmantraut, J. *Org. Lett.* **2007**, *9*, 567.

(11) Dual activation catalysis review: Ma, J.-A.; Cahard, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 4566.

(12) Review about the use of lanthanides in asymmetric catalysis: Mikami, K.; Terada, M.; Matsuzawa, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3554.

(13) (a) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1236. (b) Shibasaki, M.; Kanai, M.; Funabashi, K. *Chem. Commun.* **2002**, 1989. (c) Kanai, M.; Kato, N.; Ichikawa, E.; Shibasaki, M. *Synlett* **2005**, 1491. (d) Shibasaki, M.; Matsunaga, S. *Chem. Soc. Rev.* **2006**, *35*, 269.

(14) Bellemare, A. *Prog. Quant. Electron.* **2003**, *27*, 211. $Er(OTf)_3$ is, e.g., ca. 4−5 times less expensive than $Yb(OTf)_3$.

(15) Shannon, R. D. *Acta Crystallogr.* **1976**, *A32*, 751.

O-acylated amino alcohols as in **4h** cannot be significantly involved in the catalytic cycle. Compound **4h** has also never been detected in the reaction mixture or crude product using **4b** as ligand. This indicates that (a) the oxygen atom binds to the Er(III) ion and (b) that this bond must be inert under the reaction conditions. The complexation of **4b** proceeds very rapidly since identical results were obtained by either preformation of the catalyst for 15 or 150 min at rt or by adding the ligand to the reaction mixture without any precoordination time. Even if the alcohol moiety is first deprotonated by NaH at rt for 1 h the outcome is identical in terms of both yield and enantioselectivity.

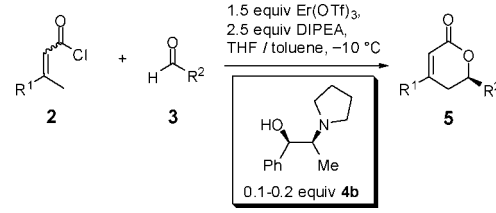
To enhance the yield to a synthetically useful level, it was necessary to decrease the addition time of **2a** from 150 to 30 min (entry 10)[16] to raise the reaction temperature from −15 to −10 °C (entry 11), the amount of $Er(OTf)_3$ from 1.1 to 1.5 equiv (entry 12) and the amount of DIPEA from 2.0 to 2.5 equiv (entry 13), while the amount of the chiral nucleophilic ligand could be decreased to 10−20 mol % without seriously impacting the reaction outcome (entries 14−15). Amino alcohol loadings lower than 10 mol % resulted in reduced yield and enantioselectivity (entry 16).

In contrast to the organocatalyst of our previous studies,[6] the novel Lewis acid−Lewis base catalyst system provided excellent enantioselectivities irrespective of the size of the substituent $R^1$ at the 3-position of acid chloride **2** (Table 2, entries 1−6). Unbranched alkyl groups such as Me or Et, α- or *β*-branched alkyls as in *i*-Pr and *i*-Bu, alicyclic substituents like cyclohexyl or aromatic groups such as Ph all furnished ee values ≥94% using PhCHO as test substrate. While the yield was low with 3,3-dimethylacryloyl chloride **2b**, which is notoriously highly sensitive toward polymerization under basic reaction conditions, the yields were synthetically useful in all other cases employing **3a** as dienophile.

The reaction generally provided excellent enantioselectivities with all kinds of aromatic aldehydes regardless of their electronic or steric nature (entries 7−21, ee = 88−96%).[17] While electron donors such as *o*-OMe or *p*-Me resulted in lower yields (entries 7 and 8), electron-withdrawing substituents such as Cl, Br, $NO_2$, or $CF_3$ enhanced the reactivity (entries 10−17) as compared to PhCHO and also promoted the use of α,*β*-unsaturated enals (entry 18). The substitution pattern of the aldehyde is less important, since all ortho-, meta-, or para-substituted systems were well tolerated. Even employing electron-rich heterocycles such as furan or thiophene (entries 19−21) was successful while the catalyst system is not yet amenable to aliphatic aldehydes.[18]

Er(III) is known to prefer high coordination numbers, typically 7−10.[19] We therefore assume that the ligand and both substrates all bind to the same metal center (Scheme 1), which is further supported by the absence of a nonlinear effect indicating that higher aggregates are most likely not involved. The results presented in Table 1 are in accordance with a mechanism in which the reversibly binding Lewis basic site forms a nucleophilic dienolate which strongly binds to the metal ion in **7**,[20] resulting in a highly organized

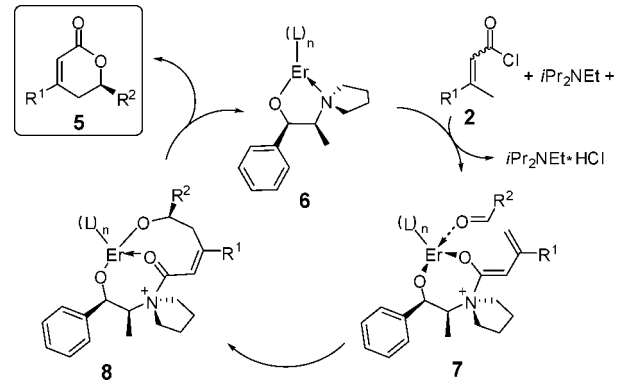
**Table 2.** Scope and Limitations of the Title Reaction[a]




| no. | 5 | $R^1$ | $R^2$ | 4b/equiv | yield[b]/% | ee[c]/% |
|---|---|---|---|---|---|---|
| 1 | **a** | *i*Pr | Ph | 0.2 | 56 | 95 |
| 2 | **b** | Me | Ph | 0.2 | 24 | 95 |
| 3 | **c** | Et | Ph | 0.2 | 62 | 95 |
| 4 | **d** | *i*Bu | Ph | 0.2 | 54 | 98 |
| 5 | **e** | *c*Hex | Ph | 0.2 | 65 | 96 |
| 6 | **f** | Ph | Ph | 0.1 | 64 | 94 |
| 7 | **g** | Ph | *o*-$MeOC_6H_4$ | 0.2 | 26 | 94 |
| 8 | **h** | Ph | *p*-$MeC_6H_4$ | 0.2 | 30 | 94 |
| 9 | **i** | Ph | 2-naphthyl | 0.2 | 55 | 95 |
| 10 | **j** | Ph | *o*-$ClC_6H_4$ | 0.1 | 77 | 88 |
| 11 | **k** | Ph | *m*-$ClC_6H_4$ | 0.2 | 78 | 93 |
| 12 | **l** | Ph | *p*-$ClC_6H_4$ | 0.1 | 71 | 92 |
| 13 | **m** | Ph | *m*-$BrC_6H_4$ | 0.2 | 77 | 95 |
| 14 | **n** | Ph | *p*-$BrC_6H_4$ | 0.1 | 70 | 93 |
| 15 | **o** | Ph | *o*-$O_2NC_6H_4$ | 0.2 | 91 | 91 |
| 16 | **p** | Ph | *p*-$O_2NC_6H_4$ | 0.2 | 72 | 88 |
| 17 | **q** | Ph | *m*-$F_3CC_6H_4$ | 0.1 | 87 | 93 |
| 18 | **r** | Ph | *p*-$O_2NC_6H_4CH{=}CH$ | 0.2 | 62 | 92 |
| 19 | **s** | Ph | 2-furyl | 0.1 | 23 | 94 |
| 20 | **t** | Ph | 2-thiophenyl | 0.2 | 40 | 95 |
| 21 | **u** | Ph | 2-(3-Br)thiophenyl | 0.2 | 46 | 96 |

[a] Compound **2** was slowly added by syringe pump over 30 min (1:1 stoichiometry of both substrates). Stirring was continued for an additional 120 min. [b] Isolated yield. [c] Determined by chiral column HPLC.

**Scheme 1.** Proposed Catalytic Cycle




(16) Slow addition of the acid chloride substrates over 30 min is recommended to maintain a low vinylketene concentration so as to minimize di- and oligomerization.

(17) The absolute configuration was determined by chemical correlation (see the Supporting Information).

(18) The enolizable dihydrocinnamaldehyde and cyclohexylcarbaldehyde as well as the nonenolizable pivaldehyde resulted in complete aldehyde decomposition.

transition state for a vinylogous aldol addition reaction.[21] Turnover is achieved by an intramolecular acylation.

Cl ions generated from **2** are assumed to be the reason for the required use of stoichiometric amounts of $Er(OTf)_3$, since the coordination of $Cl^-$ might deactivate the catalyst species and additional Er(III) might be necessary as a $Cl^-$ trap. This is supported by the fact that $ErCl_3$ cannot catalyze the title reaction, while mixtures of $Er(OTf)_3$ and $ErCl_3$ result in considerably decreased reactivity. To render the process catalytic in the lanthanide, an alternative $Cl^-$ trap or an alternative leaving group would be required.

In conclusion, we have developed a novel bifunctional Lewis acid−Lewis base catalyst system which enables the [4 + 2] cycloaddition of α,β-unsaturated acid chlorides and a broad range of aromatic and heteroaromatic aldehydes, providing direct access to δ-lactone building blocks with generally excellent enantioselectivity. Our results show that (a) Er(III) and the amino alcohol ligand form an inert Er−O bond precluding O-acylation, (b) the Lewis acid[22] as well as the nucleophilic amino moiety are essential for product formation, and (c) the catalyst is most likely a monomeric species. A key characteristic of the catalyst system is its simplicity, since the commercially available nucleophilic amino alcohol ligand can be prepared from inexpensive norephedrine[23] in a single step.[24] This catalyst should also be attractive for alternative reactions which rely on a synergistic activation mechanism. Studies along these lines are underway.

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**Supporting Information Available:** Experimental procedures, full characterization data for all new products, $^1H/^{13}C$ NMR spectra, and HPLC data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL800742D

(19) (a) Selected examples: Ren, Y.; Chen, S.; Xie, G.; Gao, S.; Shi, Q. *Inorg. Chim. Acta* **2006**, *359*, 2047. (b) Freire, R. O.; do Monte, E. V.; Rocha, G. B.; Simas, A. M. *J. Organomet. Chem.* **2006**, *691*, 2584.

(20) Er(III) complexes are paramagnetic thus precluding NMR investigations. Unfortunately, mass spectroscopic investigations did not lead to the identification of significant catalyst species, and attempts to get X-ray quality crystals have failed so far.

(21) Denmark, S. E.; Heemstra, J. R., Jr.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4682.

(22) Similar results as with $Er(OTf)_3$ were also obtained with $Yb(OTf)_3$ possessing a similar ionic radius ($R^1$, $R^2$ = Ph: yield = 63%; ee = 96%), while the larger Ce(III) (yield = 22%; ee = 34%) and Pr(III) (yield = 11%; ee = 34%) gave significantly lower reactivity and enantioselectivity.

(23) Both enantiomers of norephedrine or **4b** are commercially available at a comparable price.

(24) (a) Kang, J.; Lee, J. W.; Kim, J. I. *J. Chem. Soc., Chem. Commun.* **1994**, *17*, 2009. (b) Zhao, D.; Chen, C.-Y.; Xu, F.; Tan, L.; Tillyer, R.; Pierce, M. E.; Moore, J. R. *Org. Synth.* **2000**, *77*, 12.