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Catalytic Asymmetric Formation of δ-Lactones from Unsaturated Acyl Halides

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Dedicated to Professor Franz Effenberger on the occasion of his 80th birthday

Abstract: Previously unexplored enantiopure zwitterionic ammonium dienolates have been utilized in this work as reactive intermediates that act as diene components in hetero-Diels–Alder reactions (HDAs) with aldehydes to produce optically active δ-lactones, subunits of numerous bioactive products. The dienolates were generated in situ from *E*/*Z* mixtures of α,β-unsaturated acid chlorides by use of a nucleophilic quinidine derivative and $Sn(OTf)_2$ as co-catalyst. The latter component was not directly involved in the cycloaddition step with aldehydes and simply facilitated the formation of the reactive dienolate species. The scope of the cycloaddition was considerably improved by use of a complex formed from $Er(OTf)_3$ and a simple commercially available norephedrine-derived ligand that tolerated a broad range of aromatic and heteroaromatic aldehydes for a cooperative bifunctional Lewis-acid-/Lewis-base-catalyzed reaction, providing α,β-unsaturated δ-lactones with excellent enantioselectivities. Mechanistic studies confirmed the formation of the dienolate intermediates for both catalytic systems. The active Er^{III} complex is most likely a monomeric species. Interestingly, all lanthanides can catalyze the title reaction, but the efficiency in terms of yield and enantioselectivity depends directly on the radius of the Ln^{III} ion. Similarly, use of the pseudo-lanthanides Sc^{III} and Y^{III} also resulted in product formation, whereas the larger La^{III} and other transition metal salts, as well as main group metal salts, proved to be inefficient. In addition, various synthetic transformations of 6-CCl_3- or 4-silyl-substituted α,β-unsaturated δ-lactones, giving access to a number of valuable δ-lactone building blocks, were investigated.

Keywords: bifunctional catalysis · cycloaddition · hetero-Diels–Alder reaction · lactones · lanthanides

Introduction

The quest for operationally simple catalytic methodologies that permit the diversity-oriented asymmetric synthesis of densely functionalized molecules from simple precursors is a considerable challenge for modern synthetic chemistry. In this regard, the discovery and application of new reactive intermediates in association with chiral catalyst systems represents an attractive tool with which to overcome the need for over-engineered, sensitive substrates that are tedious and expensive to prepare.

The Diels–Alder reaction is recognized as one of the most useful and powerful synthetic transformations, because its application not only leads to great increases in molecular complexity, but can also result in structures that lend themselves to additional amplification of complexity. Of the different versions of this methodology, the hetero-Diels–Alder reaction (HDA) has found considerable relevance.[1] The application of chiral Lewis acids has been the most frequently employed strategy to achieve stereocontrol in HDA reactions with carbonyl derivatives. In particular, the [4+2] cycloaddition of Danishefsky-type dienes with different aldehydes to prepare enantioenriched pyran-4-one derivatives has been widely investigated.[2–9]

The structurally related Brassard-type dienes [Brassard's diene: 1,3-dimethoxy-1-(trimethylsilyloxy)buta-1,3-diene[10]] provide direct access to β-methoxy-substituted α,β-unsaturated δ-lactones. δ-Lactones constitute an exceptionally widespread structural motif in natural and synthetic com-

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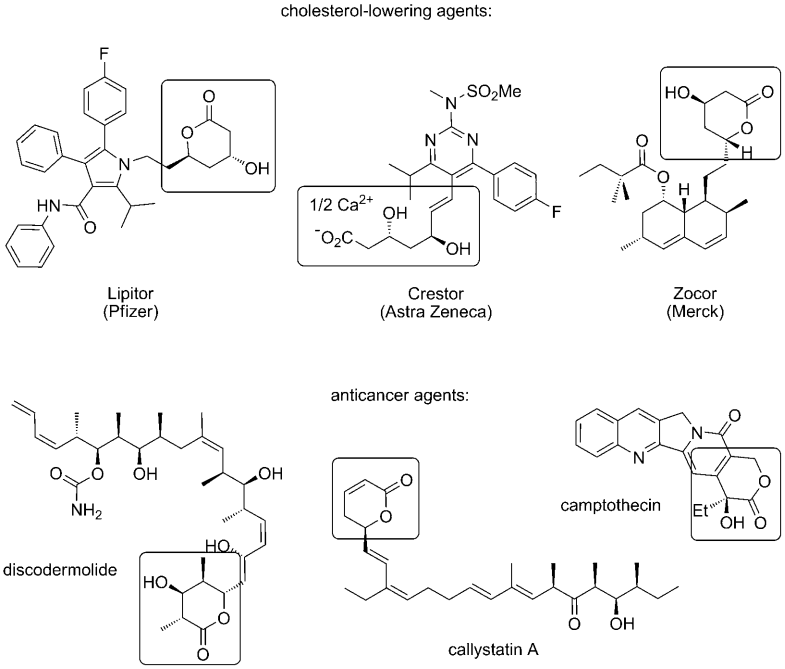
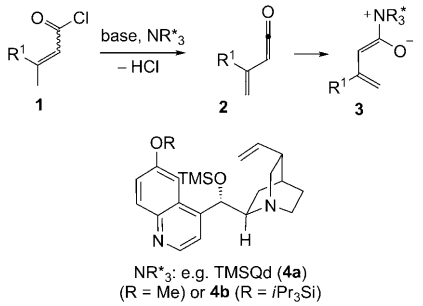
pounds displaying a wide range of biological activity. In many cases they show high efficacy as antibacterial,[11] antiviral (e.g. HIV protease inhibitors),[12] anticancer,[13] immunosuppressive,[14] or cholesterol-lowering (HMGR inhibitors) agents.[15] The majority of statin drugs—such as Lipitor and Zocor, for example—contain either a β-hydroxy-δ-lactone moiety or the corresponding open-chain δ-hydroxy carboxylate form.[16] In addition, δ-lactones are very useful building blocks for the synthesis of bioactive compounds.[17]

Unfortunately, the synthesis, isolation, purification, and application of Brassard-type dienes is complicated by their moisture- and acid-sensitive natures, which has limited their utility in synthetic transformations. In addition, so far only a few examples of the use of vinylketene acetals as diene components in highly enantioselective HDA reactions[18–19] have been reported, because these dienes are prone to be destroyed by Lewis acids. All reported HDA examples have, to the best of our knowledge, been restricted to the use of Brassard-type dienes and require extended reaction times to provide useful yields.



Here we present a different HDA concept for the synthesis of δ-lactones **6**, circumventing the use of vinylketene acetals. Our work was based on the hypothesis that vinylketenes **2**, which are formed in situ by dehydrohalogenation from α,β-unsaturated acid chlorides **1** (Scheme 1),[20] might be trapped and at the same time activated as diene components for Diels–Alder reactions by enantiopure tertiary amines, thus forming enantiomerically pure zwitterionic dienolates of type **3**.[21] It was believed that a species of this type should be reactive enough, when adopting an *s-cis* conformation, to undergo [4+2] cycloadditions with aldehydes. Our investigations were inspired by the tertiary-amine-catalyzed asymmetric synthesis of β-lactones from ketenes through the intermediate formation of zwitterionic enolates.[22]



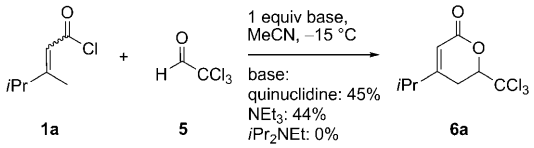
Scheme 1. Proposed formation of zwitterionic dienolate intermediates for [4+2] cycloaddition with aldehydes.

Vinylketenes had previously not been useful for catalytic asymmetric Diels–Alder reactions, as a result of their variable tendency to undergo [2+2] cycloadditions[23] and due to their inherent and (in comparison with non-conjugated ketenes) significantly increased instability (rapid dimerization and polymerization, sensitivity towards moisture, air, acids, and bases).[24–25] However, because of the considerable homology of **3** to vinylketene acetals, it was anticipated that the intermediate and rapid formation of these dienolates should overcome these problems. Early studies had shown that vinylketenes are rapidly trapped by various nucleophiles.[26]

Asymmetric ammonium enolates, generated in situ through the reaction between a chiral tertiary amine catalyst and ketene or a ketene equivalent,[27] have been widely exploited as reactive intermediates for the synthesis of optically active compounds. The first studies in this direction date back to the early 1960s, when Pracejus reported that enantiomerically enriched esters can be obtained by addition of alcohols to ketenes in the presence of brucine as a chiral catalyst.[28]

Results and Discussion

At the outset, the model reaction between 3,4-dimethylpent-2-enoyl chloride (**1a**) and the highly electron-deficient aldehyde chloral (**5**) was investigated (Scheme 2). Initial experiments in acetonitrile at −15 °C with stoichiometric amounts of quinuclidine or triethylamine, acting both as a base and as an achiral nucleophilic catalyst, provided the racemic δ-lactone **6a** in moderate yield.

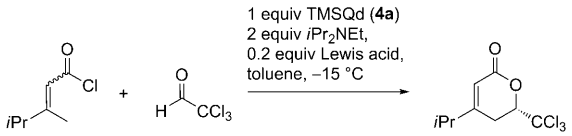


1a 5 6a

Scheme 2. Proof of concept.

The combination of trimethylsilylquinidine (TMSQd, **4a**, 1.0 equiv) and iPr$_2$NEt (Hünig's base, 2.0 equiv) in toluene at −15 °C gave the product with an *ee* value of 82%, albeit in very low yield (18%, Table 1, entry 1), which was ascribed to incomplete conversion of **1a** (^{1}H NMR monitoring). In order to facilitate the deprotonation process and to activate the aldehyde substrate, various metal triflate salts M(OTf)$_n$ were investigated as Lewis acid co-catalysts (entries 2–18). The deprotonation process—visible through the formation of a precipitate of [iPr$_2$NHEt]Cl in toluene—was significantly improved with all investigated Lewis acids,[29] and the yield of **6a** increased to >70% in the presence of 20 mol% variously of Er(OTf)$_3$ (76%), Sn(OTf)$_2$ (75%), Sc(OTf)$_3$ (74%), or Nd(OTf)$_3$ (72%) when the acid chloride was slowly added by syringe pump over a period of 30 min.

Table 1. Investigation of the effects of various Lewis acids in the TMSQd-catalyzed model reaction between **1a** and **5**.



1a 5 6a

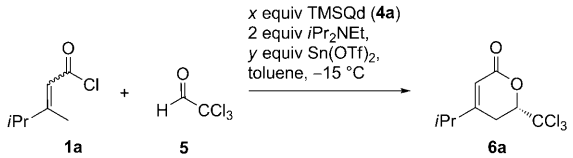
Entry	Lewis acid	Yield[a] [%]	*ee*[b] [%]
1	–	18	82
2	Sn(OTf)$_2$	75	81
3	LiOTf	66	83
4	Mg(OTf)$_2$	62	82
5	Al(OTf)$_3$	62	81
6	In(OTf)$_3$	68	81
7	Bi(OTf)$_3$	61	81
8	Zr(OTf)$_4$	63	81
9	Cu(OTf)$_2$	68	81
10	Zn(OTf)$_2$	56	81
11	Sc(OTf)$_3$	74	81
12	Y(OTf)$_3$	55	82
13	Nd(OTf)$_3$	72	82
14	Sm(OTf)$_3$	65	82
15	Eu(OTf)$_3$	57	82
16	Gd(OTf)$_3$	61	82
17	Er(OTf)$_3$	76	82
18	Yb(OTf)$_3$	68	82

[a] Yield determined from the mass of the crude product in combination with ^{1}H NMR with DMSO as internal standard. [b] *ee* determined by HPLC.

The enantiomeric excesses were determined to be 82(±1)% in all experiments regardless of the nature of the Lewis acid co-catalyst. Because the enantioselectivity does not depend upon the presence or absence of the metal triflate salt, we assume that the Lewis acid is not directly involved in the cycloaddition step and simply facilitates the dehydrochlorination of **1**. Increasing the temperature to 0 °C gave similar results [70% yield with Er(OTf)$_3$, *ee* = 80%], whereas decreasing the temperature to −40 °C resulted in a dramatic decrease in yield (22% with Er(OTf)$_3$, *ee* 84%).

Investigation of the co-catalyst loadings (Table 2) showed that reducing the amount of the Lewis acid to 10 mol% had almost no negative effect in the case of Sn(OTf)$_2$ (entries 1 and 2), and even with as little as 1.4 mol% the reaction was still relatively efficient (entry 4). Decreasing the amount of TMSQd (**4a**) necessitated a slower addition of the acid chloride in order to avoid massive polymerization (entries 6 and 7). Through the action of **4a** (20 mol%) and Sn(OTf)$_2$ (10 mol%) with addition of **1a** to the reaction mixture over 110 min, **6a** was obtained in 78% isolated yield.

Table 2. Investigation of catalyst and Lewis acid loadings for the model reaction between **1a** and **5**.



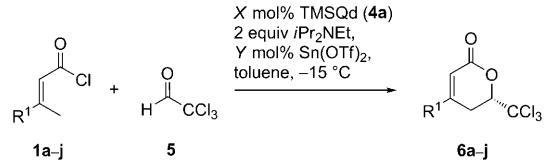
1a 5 6a

Entry	TMSQd (*x* equiv)	Sn(OTf)$_2$ (*y* equiv)	Yield[a] [%]	*ee*[b] [%]
1	1	0.2	75	81
2	1	0.1	72	82
3	1	0.05	65	82
4	1	0.014	60	82
5	0.4	0.1	72	81
6	0.2	0.1	65	81
7[c]	0.2	0.1	78[d]	82
8[c]	0.1	0.1	70	81

[a] Yield determined from the mass of the crude product in combination with ^{1}H NMR with DMSO as internal standard. [b] *ee* determined by HPLC. [c] Compound **1a** was added by syringe pump over 110 min. [d] Isolated yield after column chromatography.

Similar reaction conditions were applied to several alternative substrates **1b–f**, bearing different branched or unbranched aliphatic, alicyclic, or aromatic groups R^1 (Table 3). The δ-lactones **6a–f** were formed in good yields and with *ee*s of up to 95% (entries 1–7). Both the enantioselectivities and the degrees of conversion of the acid chlorides depended primarily upon the steric bulk of R^1. Whereas with the unbranched Et substituent the *ee* was only moderate (entry 2), the values were significantly higher and preparatively useful with branched or aromatic substituents (en-

Table 3. Preparation of α,β-unsaturated δ-lactones **6**.



Entry	**1**	R^1	*X*	*Y*	Yield[a] [%]	*ee*[b] [%]
1	**1a**	*i*Pr	20	10	78	82
2	**1b**	Et	20	10	60	54
3[c]	**1c**	*i*Bu	40	20	73	70
4	**1d**	*c*Hex	20	10	75	83
5	**1e**	*t*Bu	20	10	58	95
6	**1e**	*t*Bu	40	20	80	95
7	**1f**	Ph	20	10	73	81
8	**1g**	Et_3Si	100	30	54	96
9[d]	**1g**	Et_3Si	40	20	43	96
10	**1h**	$BnMe_2Si$	100	30	47	92
11	**1i**	nPr_3Si	100	30	51	97
12	**1j**	nBu_3Si	100	30	61	97

[a] Isolated yields. [b] *ee* determined by HPLC. [c] Catalyst **4b**, bearing an $OSi(iPr)_3$ group instead of the OMe group on the quinoline part, was used (see Scheme 1 for the catalyst structure). [d] Compound **1g** was added by syringe pump over 220 min.

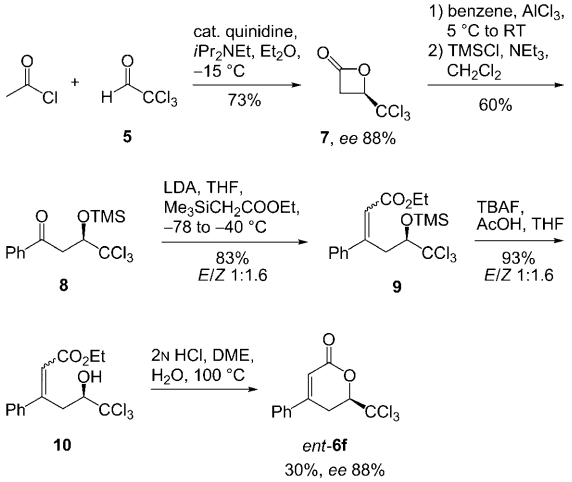
tries 3–7). Notably, even in the case of **1b** (R^1 = Et) the C–C bond formation occurred with complete regioselectivity. With the more bulky *i*Bu or *t*Bu substituents, higher catalyst and co-catalyst loadings were required in order to obtain high conversions (entries 3 and 6).

Both a 1.5:1 mixture of (*Z*)- and (*E*)-3-phenylbut-2-enoyl chloride (**1f**) and the geometrically pure *E*-configured substrate afforded nearly identical yields and *ee* values [TMSQd (0.4 equiv), $Sn(OTf)_2$ (20 mol%); (*E*)-**1f**: 68% yield, 81% *ee*; (*Z*/*E*)-**1f**: 71% yield, 81% *ee*], showing that the configuration of the double bond does not have any significant impact on the reaction outcome.

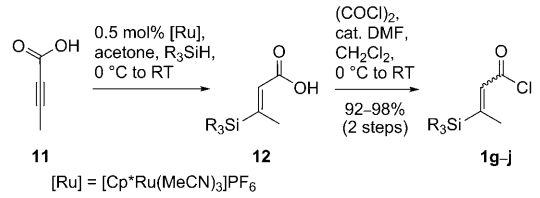
To determine the absolute configuration of the generated stereocenter by chemical correlation, *ent*-**6f** was prepared by an alternative reaction pathway (Scheme 3).

The *R*-configured β-lactone **7** was obtained with 88% *ee* by a reported procedure[30] and subsequently ring-opened under Friedel–Crafts conditions to provide a β-hydroxyketone.[31] Peterson olefination of the TMS-protected derivative **8** afforded **9** as a mixture of two geometrical isomers. After removal of the silyl group the *E* isomer cyclized under acidic conditions to yield the targeted lactone *ent*-**6f**, whereas the *Z* isomer remained in the acyclic form. HPLC analysis showed that this lactone *ent*-**6f** had the opposite configuration to the product obtained through the TMSQd/$Sn(OTf)_2$-catalyzed [4+2] cycloaddition between the acid chloride **1f** and chloral (**5**), which was thus assigned as the *S* enantiomer.

To extend the synthetic value of the methodology it was also applied to substrates **1g–j** bearing trialkylsilyl moieties (Table 3, entries 8–12). The required carboxylic acids were easily prepared by Ru-catalyzed hydrosilylation of tetrolic acid by a procedure developed by Trost et al. (Scheme 4).[32]



Scheme 3. Determination of the absolute configuration by chemical correlation: synthesis of *ent*-**6f** via the known β-lactone **7**.



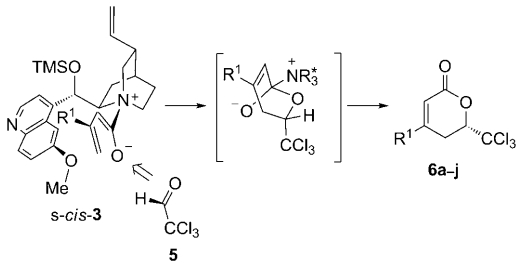
Scheme 4. Preparation of α,β-unsaturated acid chlorides **1g–j** bearing silyl substituents at their β-positions.

The carboxylic acid functionalities were subsequently smoothly converted into the corresponding acid chlorides.

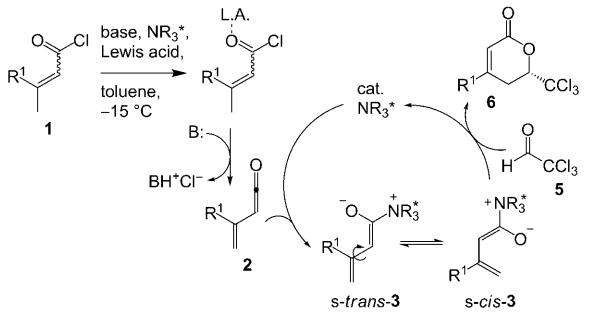
To provide acceptable yields in the cycloaddition step, stoichiometric quantities of the tertiary amine catalyst had to be used in order to overcome incomplete conversion of the acid chlorides. Presumably the bulky trialkylsilyl substituents hamper the deprotonation of the reactive methyl group. Nonetheless, the obtained enantioselectivities were excellent.

As a general trend, the remote control of the enantioselectivity for the reactions presented in Table 3 depends largely on the steric bulk of R^1. A working hypothesis to explain the enantioselectivity was developed with the aid of MMFF calculations performed to figure out the preferred conformations of the *cisoid* zwitterionic dienolates (Scheme 5). Because the *re* face (with regard to the C1-enolate atom) is shielded by the quinoline and the OTMS moieties, the aldehyde will attack from the better accessible *si* face, by either a concerted or a stepwise pathway.[33] In the preferred orientation of the aldehyde in the transition state the residue R^1 and the CCl_3 group should point away from each other to avoid unfavorable steric interactions, thus explaining the large influence of R^1.

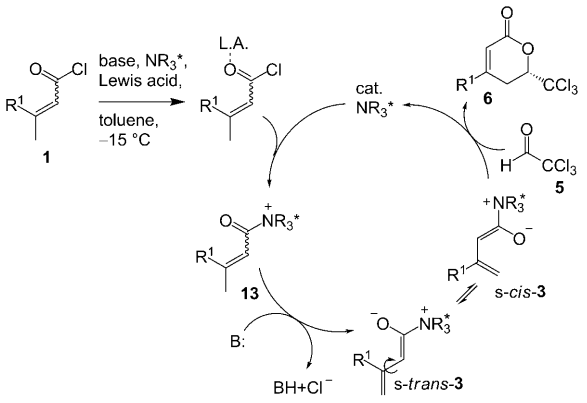
At least two similar mechanisms may be envisaged for the formation of the reactive intermediate **3**. The first one involves Lewis acid activation of the acid chloride for an attack of the nucleophilic catalyst, thus forming the acylammonium species **13** (Scheme 6), which would be less Lewis



Scheme 5. Proposed explanation of the remote stereocontrol.



Scheme 7. Alternative II for the reaction mechanism, involving a vinylketene intermediate (L.A. = Lewis acid).



Scheme 6. Alternative I for the reaction mechanism, involving an acylammonium intermediate (L.A. = Lewis acid).

basic than the acid chloride. The Lewis acid might hence be released. Subsequently iPr$_2$NEt would deprotonate the γ-position, generating the zwitterionic dienolate **3**, which would undergo a cycloaddition with the dienophile when adopting the *s-cis* conformation. Because the Lewis acid does not display any influence on the selectivity of the reaction, it is most probably not coordinated to the zwitterionic intermediate.

The second alternative (Scheme 7) involves dehydrohalogenation of the acid chloride, initiated by the stoichiometric base and assisted by the Lewis acid, thus forming the vinylketene derivative **2**. This species is again less Lewis basic than the acid chloride, thus releasing the Lewis acid. After attack of the nucleophilic catalyst on the ketene, the zwitterionic dienolate intermediate **3** is formed.

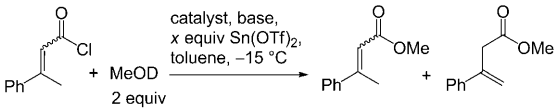
To provide more information about the reaction mechanism, deuteration experiments with monodeuterated methanol (MeOD) were carried out. Related studies directed towards investigation of the alcoholysis of α,β-unsaturated acid chlorides in the presence of triethylamine have been reported.[26c]

An experiment with NEt$_3$ in toluene in the absence of a Lewis acid (Table 4, entry 1), affording a 20:80 mixture of the α,β-unsaturated ester **14** and the β,γ-unsaturated isomer **15**, served as a reference in our studies. Contrary to the previous results by Truce and Bailey, MS analysis of the crude material indicated that the α,β-unsaturated compound was also partially deuterated (16% of monodeuterated ester [D$_1$]-**14**), whereas the β,γ-unsaturated ester **15** was mainly monodeuterated ([D$_1$]-**15**, 61%). Small amounts of the bisdeuterated esters [D$_2$]-**14** and [D$_2$]-**15** were also detected.

Under the elaborated conditions of the catalytic asymmetric cycloaddition [TMSQd (**4a**, 0.2 equiv) and Sn(OTf)$_2$ (0.1 equiv), entry 2], the amount of α,β-unsaturated isomer was increased to 31%. MS analysis showed that the α,β-unsaturated ester **14** contained a larger proportion of the monodeuterated compound [D$_1$]-**14** (30 vs. 16%), whereas in the case of **15** only a slight increase in the degree of deuteration was observed.

As a further control experiment, a mixture of undeuterated esters **14** and **15** was subjected to the reaction conditions [TMSQd (0.2 equiv), Sn(OTf)$_2$ (0.1 equiv), DIEA (2 equiv)] in the presence of MeOD (2 equiv). The esters were recovered undeuterated, showing that no deuterium incorporation occurs through H/D exchange after product formation.

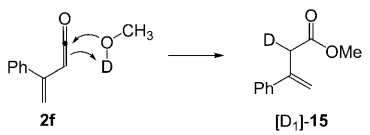
Table 4. Deuteration experiments for the esterification of the α,β-unsaturated acid chloride **1f**.



	X	Catalyst (equiv)	Base (equiv)	**14**/**15**[a]	[D$_0$]-**14**[b]	[D$_1$]-**14**[b]	[D$_2$]-**14**[b]	[D$_0$]-**15**[b]	[D$_1$]-**15**[b]	[D$_2$]-**15**[b]
1	–	NEt$_3$ (2)	–	20:80	82	16	2	31	61	8
2	0.1	**4a** (0.2)	iPr$_2$NEt (2)	31:69	67	30	3	24	67	9

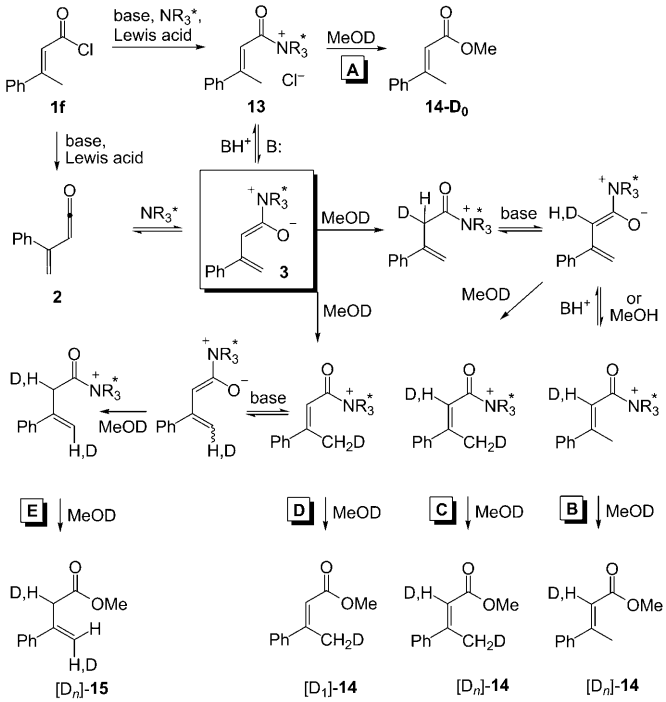
[a] Determined by ^{1}H NMR. [b] The percentages of nondeuterated (D$_0$), monodeuterated (D$_1$), and bisdeuterated (D$_2$) ester in **14** and **15** were determined by GC-MS.

The generation mainly of the α-monodeuterated β,γ-unsaturated ester [D_1]-**15** can be readily explained in terms of a vinylketene intermediate as depicted in Scheme 8.



Scheme 8. Generation of monodeuterated ester [D_1]-**15** via a vinylketene intermediate.

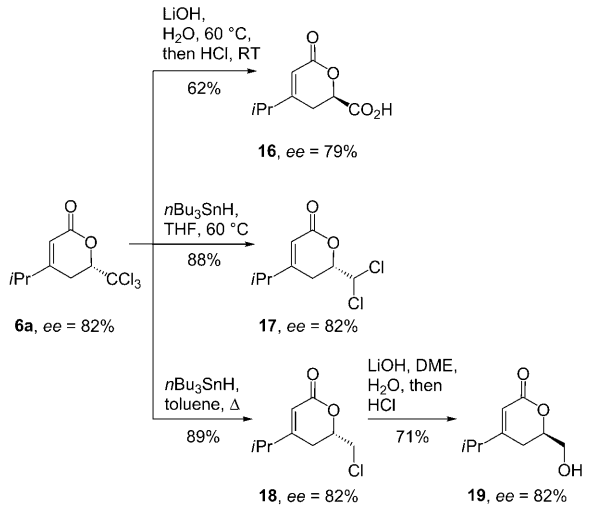
The formation of the monodeuterated α,β-unsaturated ester [D_1]-**14**, however, as well as the observation of bisdeuterated species for both isomers, is consistent with a parallel mechanism involving a series of acid/base equilibria based on an acylammonium/zwitterionic dienolate couple (Scheme 9).



Scheme 9. General mechanistic picture of the equilibria involving the acylammonium/dienolate couple.

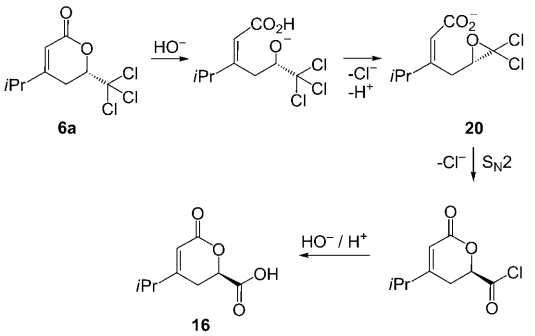
Whereas the formation of the undeuterated α,β-unsaturated ester [D_0]-**14** should mainly occur through the acylammonium salt **13** (reaction pathway **A**), the generation of the monodeuterated [D_1]-**14** and the bisdeuterated compounds provides compelling evidence for the existence of the common zwitterionic dienolate intermediate **3**, which could be generated either by deprotonation of **13** or by attack of the nucleophilic catalyst on a vinylketene. The equilibration between **3** and **13** allows the incorporation of a variable number of deuterium atoms. Upon trapping of **3** by MeOD a range of α,β- and β,γ-unsaturated deuterated esters are thus generated (pathways **B**–**E**). In addition, deuterated methanol is not the only D^+ source in the acid/base equilibria, because a considerable amount of protonated Hünig's base is formed during the reaction and can undergo H/D exchange with MeOD. From the experimental data it is difficult to draw a definite conclusion about the intermediate formation of a vinylketene species. However, the existence of a zwitterionic dienolate intermediate has been established.

The trichloromethyl moiety in lactones **6** is a synthetically versatile functional group that can be readily modified into several valuable functionalities. Basic hydrolysis of **6a** with LiOH in water at 60 °C gave the carboxylic acid **16** without significant racemization (Scheme 10).



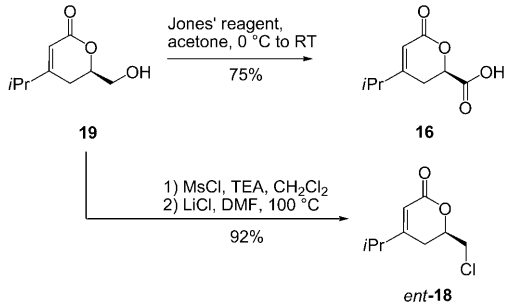
Scheme 10. Synthetic modification of the trichloromethyl group.

The hydrolysis occurred with inversion of the stereocenter, in close analogy to literature precedence for the hydrolysis of CCl_3-substituted β-lactones and trichloromethylcarbinols,[34] due to the intermediate formation of the dichloroepoxide **20**, which is ring-opened through an S_N2 mechanism (Scheme 11).



Scheme 11. Inversion of the configuration during the hydrolysis of **6a**.

Selective partial reductive removal of the chlorine atoms of the trichloromethyl group was achieved by treatment with tributyltin hydride (Scheme 10).[35] Performing the reduction in THF at 60 °C afforded the dichloro derivative **17**,[36] whereas in toluene at reflux the monochloro derivative **18** was obtained. The latter was smoothly hydrolyzed to give the primary alcohol **19**. The configuration of the stereocenter was also inverted in that case, as verified by direct oxidation of compound **19** to carboxylic acid **16** with Jones' reagent (CrO_3 in H_2SO_4, 8 N, Scheme 12). The final confirmation of the inversion was obtained by conversion of **19** into *ent*-**18**, with the opposite configuration to the material obtained by radical reduction of **6a** (Scheme 12).

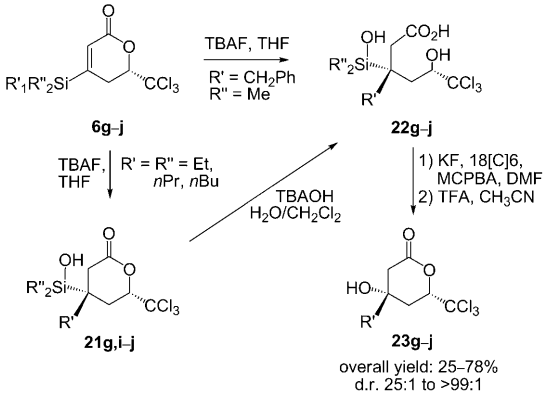


Scheme 12. Determination of the absolute configuration of the stereocenter by chemical correlation.

Additional derivatization at the 4-position is possible through modification of the silyl moieties in **6g–j**. Fleming et al.[37] reported that a fluoride-triggered 1,2-migration of a phenyl substituent on silicon to an adjacent electrophilic carbon can be induced by TBAF (tetrabutylammonium fluoride) treatment of an α,β-disilyl enone. Migration of allyl groups was first reported by Jung and Piizzi, who used an *E*-configured β-silyl enone as substrate.[38] The C–Si bond could be oxidatively cleaved under Tamao conditions to yield a homoallylic alcohol. Similarly, Salvatori et al. investigated β-silyl-substituted α,β-unsaturated aldehydes.[39] Recently, Trost and co-workers[32] reported related 1,2-migrations for *Z*-configured β-silyl-substituted α,β-unsaturated ketones or esters. The migration reactions were found to be selective for aromatic, benzylic, and allylic residues, with simple alkyl groups not being transferred.[40]

For the β-silyl-substituted δ-lactones **6g–j** it was envisaged that analogous migration reactions might be performed stereoselectively, taking advantage of the sterically demanding CCl_3 residues in their δ-positions, thus leading to the diastereoselective formation of O-substituted quaternary stereocenters (Table 5). Treatment with TBAF (2.0 equiv) triggered the migration of benzyl or simple alkyl substituents. Silanols **22** were subsequently oxidized to provide the almost diastereomerically pure tertiary alcohols **23** by slightly modified Tamao oxidation conditions. To accomplish this transformation, the lactone moiety in **21** first had to be hydrolyzed, presumably because the free carboxylate moiety intramolecularly activates the silyl group.[32]

Table 5. Diastereoselective preparation of β-hydroxy δ-lactones **23** by alkyl migration/oxidation.



Entry	Substrate	R′	R″	Yield **22**[a] [%]	Yield **23**[a] [%]	d.r.[b] [%]
1[c]	**6g**	Et	Et	44	70	>99:1
2	**6h**	Bn	Me	92	85	25:1[c]
3	**6i**	*n*Pr	*n*Pr	38	65	>99:1
4	**6j**	*n*Bu	*n*Bu	41	61	>99:1

[a] Isolated yield. [b] Determined by ^{1}H NMR of isolated **23**. [c] d.r. of crude **22h** and crude **23h** = 7:1.

Different migration behavior was observed for the benzyl- and alkyl-substituted δ-lactones **6g–j**: whereas the benzyl-substituted compound **6h** directly afforded the ring-opened product **22h**, in the alkyl migration the products **21** were converted into the *seco*-acids **22** only slowly under the reaction conditions. For that reason, an additional hydrolysis step was required to accomplish the subsequent oxidation (Table 5).

The configurations were unambiguously determined by NOE experiments (Figure 1) and are consistent with the mechanism depicted in Scheme 13.

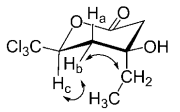
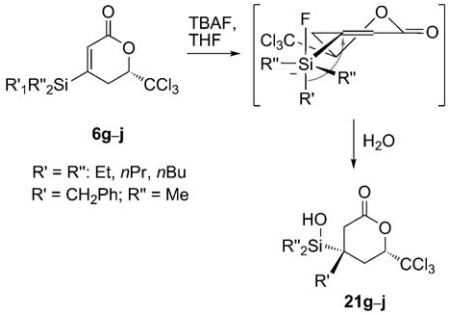


Figure 1. NOE connectivities for **23g**.

Because the *si* face of the C=C double bond is shielded by

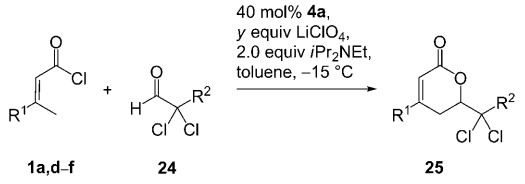


Scheme 13. Proposed explanation for the diastereoselectivity.

the bulky trichloromethyl group, the addition occurs mainly from the opposite face, generating the new stereocenter with the *S* configuration (Scheme 13). It is likely that the accelerated ring-opening step in the case of the benzyl substrate **6h** might compete with the fluoride-triggered migration, thus explaining the lower stereoselectivity in that case (*dr* of the crude product 7:1), because the migration at the acyclic stage would be expected to proceed without efficient stereocontrol.

The formation of δ-lactones can also be accomplished in the case of α,α-dichlorinated aldehydes, as exemplified for 2,2-dichloropropanal[41] (**24a**). Although the use of metal triflate co-catalysts did not lead to high levels of conversion of **24a**, use of an excess of $LiClO_4$ resulted in smooth reactions (Table 6, entries 1–4).[42]

Table 6. Preparation of α,β-unsaturated δ-lactones **25** from dichlorinated aldehydes **24**.



1a,d–f **24** **25**

Entry	**1**	R^1	R^2	Y	Yield[a] [%]	*ee*[b] [%]
1	**1a**	*i*Pr	Me	2.0	67	74
2	**1d**	*c*Hex	Me	1.5	56	76
3	**1e**	*t*Bu	Me	1.5	79	71
4	**1f**	Ph	Me	1.5	57	72
5	**1a**	*i*Pr	Et	3.0	35	60
6	**1a**	*i*Pr	*n*Pr	3.0	29	32

[a] Isolated yields. [b] *ee* determined by HPLC.

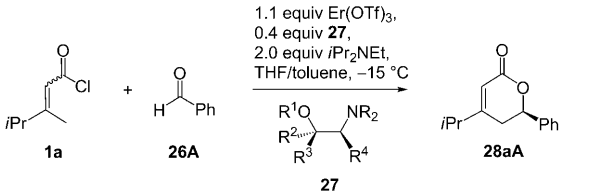
Non-activated or less activated aldehydes such as benzaldehyde or *p*-nitrobenzaldehyde did not furnish the target products. The development of bifunctional Lewis acid/Lewis base catalysts through which the reactivities of the dienolate and of the aldehyde could be controlled simultaneously thus appeared to be required.[43] The combination of a Lewis acid and a Lewis base successfully united in one catalytic system has recently found numerous applications in asymmetric catalysis, due to synergistic activation of both the electrophilic and the nucleophilic substrates, often allowing high reaction rates and excellent chirality transfer.[44]

Our studies were based upon the hypothesis that a lanthanide Lewis acid, offering an exceptionally high number of coordination sites, should be advantageous for binding both of the aldehyde and the dienolate, plus additional ligands to control reactivity and stereoselectivity.[45–46]

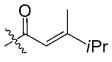
To create a cycloaddition transition state with a high level of organization the nucleophilic catalyst should be directly connected to the Lewis acid template. We envisaged that an oxophilic lanthanide should bind strongly to an alkoxide moiety whereas a tertiary amino group should enter into hemilabile coordination, still permitting sufficient reactivity for nucleophilic trapping of a vinylketene intermediate.[47]

Although Er^{III} complexes with aliphatic β- or γ-amino alcohols possessing tertiary amino groups have to the best of our knowledge never previously been described in the literature, $Er(OTf)_3$ was initially chosen as the lanthanide source for these investigations, owing to the combination of: a) the comparatively low price of Er, which is linked to its importance for the telecommunications industry,[48] and b) its relatively small ionic radius (as a consequence of the lanthanide contraction),[49] which was regarded as advantageous for achieving 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 abolish the nucleophilicity of pyridine in the model reaction in THF/toluene depicted in Table 7 (entry 1), whereas no reaction took place in the absence either of nucleophile or of Lewis acid.

Table 7. Screening of 1,2-amino alcohol derivatives for the Lewis-acid-/Lewis-base-catalyzed formation of the α,β-unsaturated δ-lactone **28aA**.[a]



1a **26A** **27** **28aA**

	27	NR_2	R^1	R^2	R^3	R^4	Yield[b] [%]	*ee*[c] [%]
1	pyr	–	–	–	–	–	87	–
2	**27a**	NMe_2	H	H	Ph	Me	27	74
3	**27b**	$N(CH_2)_4$	H	H	Ph	Me	35	95
4	**27c**	$N(CH_2)_5$	H	H	Ph	Me	32	96
5	**27d**	$N(CH_2)_3$	H	H	Ph	Me	27	57
6	**27e**		H	H	Ph	Me	14	44
7	**27f**		H	H	Ph	Ph	0	–
8	**27g**	$N(CH_2)_4$	H	Ph	Ph	Me	<5	6
9	**27h**	$N(CH_2)_4$	H	H	H	Me	0	–
10	**27i**	$N(CH_2)_4$	H	H	Ph	H	10	32
11	**27j**	$N(CH_2)_4$	Me	H	Ph	Me	24	−34
12	**27k**	$N(CH_2)_4$	TMS	H	Ph	Me	0	–
13	**27l**	$N(CH_2)_4$		H	Ph	Me	11	−33

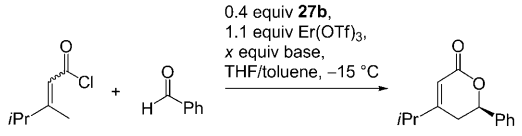
[a] Compound **1a** was slowly added by syringe pump over 120 min (1:1 stoichiometry of both substrates). Stirring was continued for an additional 150 min. [b] Yield determined from the mass of the crude product in combination with ^1H NMR with $MeNO_2$ as internal standard. [c] *ee* determined by HPLC. Negative values indicate that the *S*-configured product was preferentially formed.

With *N*-methylephedrine (**27a**), the δ-lactone **28aA** was formed with a promising *ee* of 74% (entry 2), although the yield was low. Replacement of the NMe_2 group by a pyrrolidine unit (**27b**) not only enhanced the reactivity (yield = 35%), but also resulted in an *ee* value of 95% (entry 3). A piperidine ring (ligand **27c**) provided similar results, where-

as the azetidine **27d** was far less selective (entries 4–5). The nucleophilicity of the tertiary amino group is essential, as it was demonstrated in entries 6 and 7, in which the steric accessibility and the electron density of the amino group are diminished with the consequence of reduced or no reactivity. For ligands containing a tertiary or primary alcohol moiety the title reaction was retarded (entries 8 and 9), in the latter case presumably due to ligand O-acylation. An N-substituted stereocenter is required for high stereocontrol and, surprisingly, also for sufficient reactivity (entry 10). A methyl-protected hydroxy group in the ligand impeded high enantioselectivity (entry 11), whereas TMS protection gave no product at all (entry 12). Entry 13 demonstrates that O-acylated amino alcohols, such as in **27l**, cannot be significantly involved in the catalytic cycle. Compound **27l** was also never detected in the reaction mixture or the crude product with **27b** as ligand. This indicates: a) that the oxygen atom binds strongly to the Er^{III} ion, and b) that this bond must be inert under the reaction conditions.

Different bases were investigated as alternatives to iPr$_2$NEt (Table 8). Although with the more bulky PMP (1,2,2,6,6-pentamethylpiperidine) only minute amounts of

Table 8. Investigation of different bases for the model reaction between **1a** and **26A**.



1a **26A** **28aA**

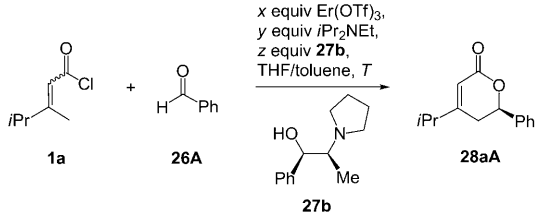
Entry	Base (x equiv)	Yield[a] [%]	ee[b] [%]
1	iPr$_2$NEt (2.5)	35	95
2	PMP (2.5)	traces	95
3	MDC (2.5)	33	89
4	DMC (2.5)	59	2
5	NaH (1.3)	0	–
6	NaHMDS (2.5)	0	–

[a] Yield determined from the mass of the crude product in combination with ^{1}H NMR with MeNO$_2$ as internal standard. [b] ee determined by HPLC.

product were obtained (entry 2), methyl dicyclohexyl amine (MDC) provided the desired product in comparable yield and with slightly lower selectivity than obtained with iPr$_2$NEt (entry 3). In the case of the sterically less hindered dimethyl cyclohexyl amine (DMC, entry 4) the reactivity was considerably improved, but with complete loss of enantioselectivity, indicating that DMC is nucleophilic enough to catalyze a non-enantioselective background reaction. Strong bases such as NaH or NaHMDS did not afford any targeted product (entries 5&6).

To enhance the yield to a synthetically useful level, it was necessary to decrease the addition time of **1a** from 120 to 30 min (Table 9, entries 1 and 2)[50] and to raise the reaction temperature from −15 to −10 °C (entry 3), the amount of

Table 9. Optimization of the model reaction between **1a** and **26A**.



1a **26A** **27b** **28aA**

	t [min]	T [°C]	X	Y	Z	Yield[a] [%]	ee[b] [%]
1	120	−15	1.1	2.0	0.4		
2	30	−15	1.1	2.0	0.4	38	95
3	30	−10	1.1	2.0	0.4	42	95
4	30	−10	1.5	2.0	0.4	52	95
5	30	−10	1.5	2.5	0.4	58	95
6	**30**	**−10**	**1.5**	**2.5**	**0.2**	**56**	**95**
7	30	−10	1.5	2.5	0.1	49	91
8	30	−10	1.5	2.5	0.05	30	84

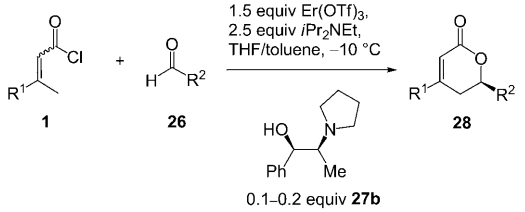
[a] Yield determined from the mass of the crude product in combination with ^{1}H NMR with MeNO$_2$ as internal standard. [b] ee determined by HPLC.

Er(OTf)$_3$ from 1.1 to 1.5 equiv (entry 4), and the amount of iPr$_2$NEt from 2.0 to 2.5 equiv (entry 5), whereas the amount of the chiral nucleophilic ligand could be decreased to 10–20 mol% without seriously affecting the reaction outcome (entries 6 and 7). Amino alcohol loadings lower than 10 mol% resulted in reduced yields and enantioselectivities (entry 8).

In contrast with the catalyst system described above, the second-generation Lewis acid/Lewis base catalyst system provided excellent enantioselectivities irrespective of the size of the substituent R^1 at the 3-position in the acid chloride **1** (Table 10, entries 1–6). Unbranched alkyl groups such as Me or Et, α- or β-branched alkyls such as iPr and iBu, alicyclic substituents such as cyclohexyl, or aromatic groups such as Ph all furnished ee values of ≥94% with PhCHO as test substrate. Although the yield was low with 3-methylbut-2-enoyl chloride **1l**, which is notoriously highly sensitive towards polymerization under basic reaction conditions, in all other cases in which **26A** was employed as heterodienophile the yields were synthetically useful.

The reactions generally provided excellent enantioselectivities with all kinds of aromatic aldehydes regardless of their electronic or steric natures (entries 7–21, ee 88–96%).[51] Whereas 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) relative to PhCHO and also permitted the use of α,β-unsaturated enals (entry 18). The substitution pattern of the aldehyde is less important; o-, m-, or p-substituted systems were all well tolerated. Even the employment of electron-rich heterocycles such as furan- or thiophenecarbaldehydes (entries 19–21) provided the desired products highly enantioselectively, albeit in low yields. In contrast, neither enolizable nor non-enolizable aliphatic aldehydes, nor non-activated α,β-unsaturated enals, were tolerated by the catalyst system.[52]

Table 10. Scope and limitations of the title reaction.[a]



	28	R^1	R^2	27b [equiv]	Yield[b] [%]	ee[c] [%]
1	**aA**	*i*Pr	Ph	0.2	56	95
2	**kA**	Me	Ph	0.2	24	95
3	**bA**	Et	Ph	0.2	62	95
4	**cA**	*i*Bu	Ph	0.2	54	98
5	**dA**	*c*Hex	Ph	0.2	65	96
6	**fA**	Ph	Ph	0.1	64	94
7	**fB**	Ph	*o*-$MeOC_6H_4$	0.2	26	94
8	**fC**	Ph	*p*-MeC_6H_4	0.2	30	94
9	**fD**	Ph	2-naphthyl	0.2	55	95
10	**fE**	Ph	*o*-ClC_6H_4	0.1	77	88
11	**fF**	Ph	*m*-ClC_6H_4	0.2	78	93
12	**fG**	Ph	*p*-ClC_6H_4	0.1	71	92
13	**fH**	Ph	*m*-BrC_6H_4	0.2	77	95
14	**fI**	Ph	*p*-BrC_6H_4	0.1	70	93
15	**fJ**	Ph	*o*-$O_2NC_6H_4$	0.2	91	91
16	**fK**	Ph	*p*-$O_2NC_6H_4$	0.2	72	88
17	**fL**	Ph	*m*-$F_3CC_6H_4$	0.1	87	93
18	**fM**	Ph	*p*-$O_2NC_6H_4CH{=}CH$	0.2	62	92
19	**fN**	Ph	2-furyl	0.1	23	94
20	**fO**	Ph	2-thiophenyl	0.2	40	95
21	**fP**	Ph	2-(3-Br)-thiophenyl	0.2	46	96

[a] The acid chlorides were 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] *ee* determined by HPLC.

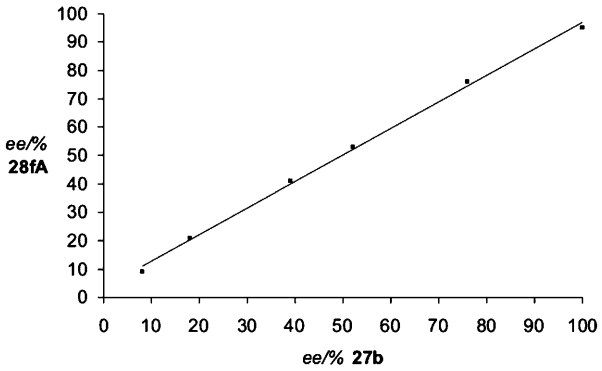
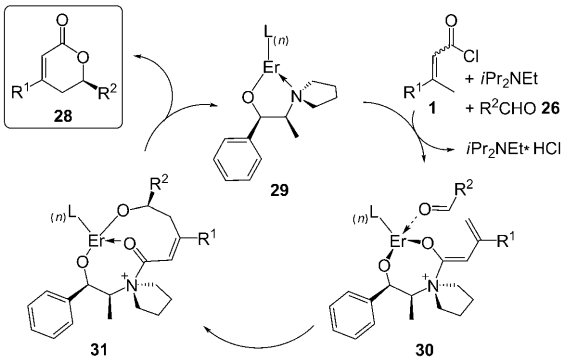


Figure 2. Investigation of a potential nonlinear effect for the formation of **28 fA** under the conditions of Table 10, entry 6.



L = R^2CHO **26**, acid chloride **1**, iPr_2NEt, OTf^-, Cl^-, product **28**

Scheme 14. Proposed catalytic cycle for the Er^{III}-/amino-alcohol-catalyzed formation of δ-lactones from α,β-unsaturated acid chlorides **1** and aldehydes **26**.

The complexation of **27b** seems to proceed very rapidly, because identical results were obtained by either preformation of the catalyst for 15 or 150 min at RT or by addition of the ligand to the reaction mixture without any precoordination. Even if the alcohol moiety was first deprotonated with NaH at RT for 1 h the outcome was identical in terms both of yield and of enantioselectivity. Limited data relating to the Er catalyst structure are available because Er^{III} complexes are paramagnetic, thus precluding NMR investigations, and attempts to obtain X-ray quality crystals have failed. ESI-MS experiments were performed with different $Er(OTf)_3$/ligand mixtures in THF/toluene, but no significant species could be identified from the MS spectra.

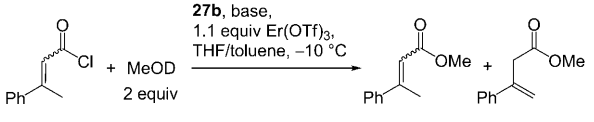
Er^{III} is known to prefer high coordination numbers, typically seven to 10.[53] We therefore assume that the ligand and both substrates all bind to the same metal center. The absence of a nonlinear effect (Figure 2) indicates that higher aggregates are most likely not involved.

The results presented in Table 10 are in accordance with a mechanism in which the reversibly binding Lewis basic amino site forms a nucleophilic dienolate that strongly binds to the metal ion in **30**, resulting in a highly organized transition state for a vinylogous aldol addition reaction (Scheme 14).[54] A concerted [4+2] cycloaddition pathway as suggested in Scheme 5 appears to be less likely in this case because it would have to proceed through a strained tricyclic intermediate. Turnover is achieved by an intramolecular acylation leading to **29**. Cl^- ions generated from **1** are assumed to be the reason for the need for stoichiometric amounts of $Er(OTf)_3$, because 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, whereas use of mixtures of $Er(OTf)_3$ and $ErCl_3$ results in considerably decreased reactivity.

As discussed above, compelling evidence for the existence of a zwitterionic dienolate intermediate in the case of the TMSQd (**4a**)/$Sn(OTf)_2$ catalyst system could be obtained by deuteration experiments with MeOD. The formation of the monodeuterated α,β-unsaturated ester [D_1]-**14** and the bisdeuterated α,β- and β,γ-unsaturated esters [D_2]-**14** and [D_2]-**15** was interpreted in terms of an equilibrium between a dienolate and an acylammonium species, allowing the incorporation of a variable number of deuterium atoms. Analogous experiments were carried out with the bifunctional ligand **27b**/$Er(OTf)_3$ system (Table 11).

The reference experiment with Er^{III}/NEt_3 (entry 1) furnished isomer **15** in large excess. MS analysis of the crude material showed the presence of mono- and polydeuterated

Table 11. Deuteration experiments for the esterification of the α,β-unsaturated acid chloride **1f**.



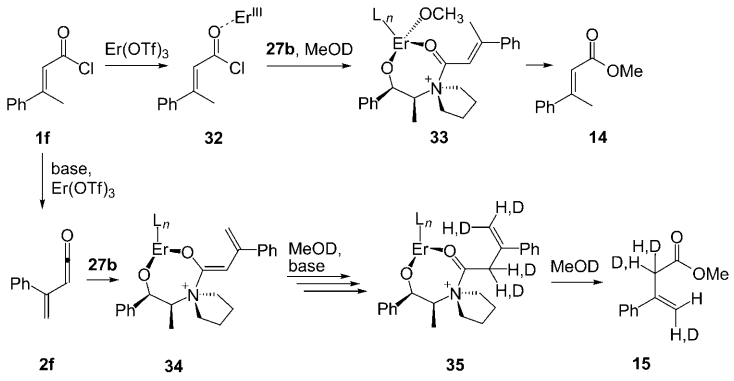
1f **14** **15**

	27b (equiv)	Base (equiv)	**14**/**15**[a]	[D_0]-**14**[b]	[D_1]-**14**[b]	[D_2]-**14**[b]	[D_3]-**14**[b]	[D_0]-**15**[b]	[D_1]-**15**[b]	[D_2]-**15**[b]	[D_3]-**15**[b]
1	–	TEA (3)	7:93	68	24	5	3	39	44	14	3
2	0.2	DIEA (4)	81:19	98	2	0	0	32	59	7	2

[a] Determined by ^{1}H NMR. [b] The percentages of nondeuterated ([D_0]), monodeuterated ([D_1]), bisdeuterated ([D_2]), and trisdeuterated ([D_3]) ester in **14** and **15** were determined by GC-MS.

esters for both **14** and **15**. The results obtained with ligand **27b** (0.2 equiv) and Er(OTf)$_3$ (1.1 equiv) differ considerably (entry 2). The α,β-unsaturated ester **14** was formed in excess, but the deuterium incorporation was negligible. With regard to isomer **15**, the percentage of monodeuterated ester was increased relative to the NEt_3 experiment. Significant amounts of the dideuterated compound and small amounts of the trideuterated compound were also detected in the crude material. As a control experiment, a mixture of undeuterated esters **14** and **15** was subjected to the reaction conditions [ligand **27b** (0.2 equiv), Er(OTf)$_3$ (1.1 equiv), *i*Pr$_2$NEt (4 equiv)] in the presence of MeOD (2 equiv). The esters were recovered undeuterated, showing that no deuterium incorporation occurs through H/D exchange after product formation.

Because the nondeuterated α,β-unsaturated ester **14** is formed preferentially, the reaction presumably occurs to some degree via an acylammonium intermediate, generated upon attack of the tertiary amine moiety of the ligand on the Lewis-acid-activated acid chloride **32** (Scheme 15).



1f **32** **33** **14**

2f **34** **35** **15**

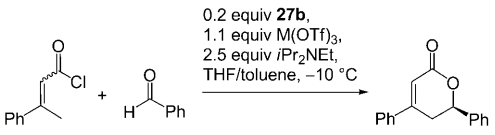
Scheme 15. General mechanistic alternatives, either through an acylammonium intermediate or through a vinylketene.

The acylammonium salt might be trapped either by MeOD or, more likely, by methoxide linked to the oxophilic Er (intermediate **33**). The significant amount of bisdeuterated isomer [D_2]-**15** can only be explained by formation of dienolate **34**.

A correlation between the ionic radius of the lanthanide cation and the reaction outcome was found (Table 12).

For lanthanides the ionic radii decrease linearly with increasing atomic numbers ("lanthanide contraction").[45] Lanthanide cations with smaller ionic radii than Er and Ho (entries 1–3) following Er in the Periodic Table of the elements

Table 12. Dependence of the reaction outcome on the ionic radius of the lanthanide(III) cation.



1f **26A** **28fA**

	M	Effective ionic radius[a] [Å]	Yield[b] [%]	*ee*[c] [%]
1	Lu	0.977	64	95
2	Yb	0.985	63	96
3	Tm	0.994	62	96
4	Er	1.004	62	95
5	Ho	1.015	62	94
6	Dy	1.027	46	88
7	Tb	1.040	30	77
8	Gd	1.053	24	70
9	Eu	1.066	25	66
10	Sm	1.079	26	55
11	Nd	1.109	13	34
12	Pr	1.126	11	34
13	Ce	1.143	15	34

[a] For M^{3+} with coordination number 8. [b] Yield determined from the mass of the crude product in combination with ^{1}H NMR with $MeNO_2$ as internal standard. [c] *ee* determined by HPLC.

all displayed catalytic activity similar to that of Er(OTf)$_3$, affording the δ-lactone **28fA** with comparable yields and enantioselectivities. In contrast, starting from Dy (entries 6–13), as the ionic radius of the metal center increased, a dramatic reduction in the reaction's efficiency and the *ee* values was observed, until a plateau was reached with Nd^{III} triflate (entries 11–13). The tendency is illustrated in Figure 3.

The results with the pseudolanthanide triflates of the group III elements Sc, Y, and La (Table 13) are in agreement with these observations. The relatively small Sc^{III} furnished the desired product with low yield and enantioselectivity (entry 1), whereas Y^{III} performed similarly to Dy^{III} (entry 2), which has a comparable ionic radius. In contrast, the larger La^{III} failed to afford any product (entry 3).

Presumably, a relatively small ionic radius of the lanthanide is required for the formation of a rigid transition state in which both reaction components (aldehyde and dienolate in **30**; Scheme 14) are arranged in close proximity. Looser transition states are probably obtained with the larger lanthanides, resulting in lower stereocontrol and disfavoring

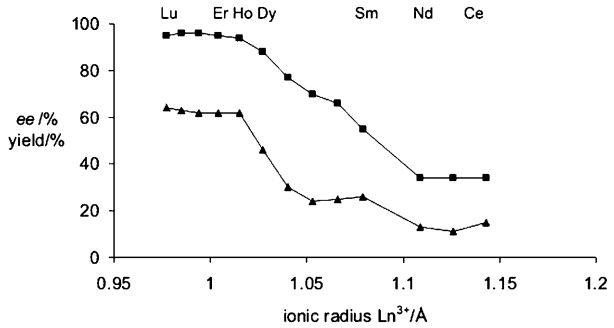
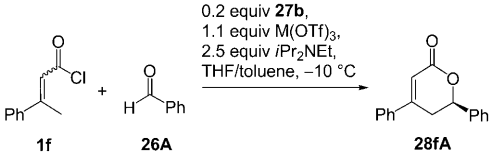


Figure 3. Influence of the ionic radius of Ln^{III} on the title reaction [data from Table 12; square: *ee* (%), triangle: yield (%)].

Table 13. Dependence of the reaction outcome on the ionic radii of pseudolanthanide(III) cations.



	M	Effective ionic radius[a] [Å]	Yield[b] [%]	*ee*[c] [%]
1	Sc	0.870	33	51
2	Y	1.019	46	92
3	La	1.160	0	–

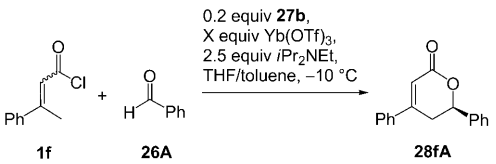
[a] For M^{3+} with coordination number 8. [b] Yield determined from the mass of the crude product in combination with ^{1}H NMR with $MeNO_2$ as internal standard. [c] *ee* determined by HPLC.

the product formation. Another parameter associated with the ionic radius is the coordination number (CN) of the metal. It might be expected that fewer ligands should be packed around the central metal ion as the ionic radius decreases. In fact, such a tendency is indeed observed for some classes of lanthanide complexes (e.g. the hydrated Ln^{3+} ions), but several exceptions to this rule are known and the difference in the CN across the series of lanthanide complexes is usually small (8 vs. 9 or 10).[55]

NMR complexation studies were performed with the diamagnetic Lu^{3+} (Figure 4). Addition of the triflate salt (1 equiv) to the amino alcohol resulted in a shift of the ligand signals and broadened peaks. Upon addition of Hünig's base (1 equiv) the signals became sharp again and protonation of base was observed. The two signals for the diastereotopic ligand NCH_2 protons were split and the new signals were significantly shifted, indicating the coordination both of the alkoxide moiety and of the tertiary amino group, whereas in the absence of base coordination is presumably relatively labile. Addition of benzaldehyde does not change the ligand and aldehyde spectrum, showing that the lifetime of the corresponding Lu/aldehyde complex is most likely very brief on the NMR timescale. However, complexation of benzaldehyde was established in the case of the paramagnetic Er^{III}, resulting under the same conditions in a shift from 9.97 to 9.27 ppm at −20 °C in $CDCl_3$.

An obvious limitation of the bifunctional Er^{III}/Lewis base catalyst system is the need for stoichiometric amounts of the Lewis acid in order to obtain preparatively useful yields. Of the investigated alternative lanthanides, ytterbium[56] showed a peculiar activity, as shown in Table 14.

Table 14. Effect of the amount of $Yb(OTf)_3$.



	X	Yield[a] [%]	*ee*[b] [%]
1	1.5	65	96
2	1.1	63	96
3	0.8	62	95
4	0.6	62	93
5	0.4	54	87
6	0.2	19	73

[a] Yield determined from the mass of the crude product in combination with ^{1}H NMR with $MeNO_2$ as internal standard. [b] *ee* determined by HPLC.

The amount of metal triflate could be reduced to 0.6 equiv without loss of catalytic activity (entries 1–4),

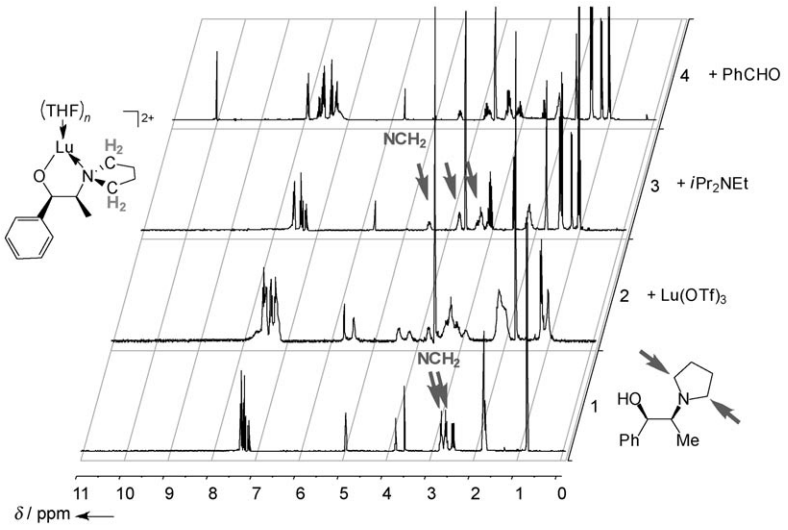


Figure 4. ^{1}H NMR complexation studies in [D_8]THF at RT. Spectrum 1: ligand **27b**. Spectrum 2: ligand **27b**+Lu^{III} triflate (1:1). Spectrum 3: ligand **27b**+Lu^{III} triflate+iPr$_2$NEt (1:1:1). Spectrum 4: ligand **27b**+Lu^{III} triflate+iPr$_2$NEt+PhCHO (1:1:1:1).

whereas use of 0.4 equiv resulted in a somewhat lower yield and enantioselectivity (entry 5).[57–58] Use of lower amounts resulted in poor yields and moderate *ee* values (entry 6).

The new reaction seems to be specific for metal(III) triflates of the (pseudo)lanthanide series. For instance, the corresponding salts of Sr^{2+}, Ba^{2+}, Hf^{4+} (also having noble gas configuration and capable of adopting high coordination numbers), Al^{3+}, In^{3+}, Sn^{2+}, Cu^{2+}, or Zn^{2+} failed to give any δ-lactone product in combination with ligand **27b**.

Conclusion

We have developed tertiary-amine-catalyzed enantioselective [4+2] cycloadditions of α,β-unsaturated acid chlorides **1** and the electron-poor aldehyde chloral (**5**), which proceeded through the formation of previously unexplored enantiopure zwitterionic ammonium dienolates. The substituent at the β-position in compounds **1** could be varied to a large degree, and the trichloromethyl group allowed several useful functional groups to be installed at the δ-position. β-Hydroxy-δ-lactones possessing O-substituted quaternary stereocenters[59] at the β-position were diastereoselectively synthesized through 1,2-migration reactions starting from the δ-lactones **6g–j** containing trialkylsilyl substituents at the β-position. The scope of the cycloadditions was considerably improved by use of a novel Er^{III}/Lewis base catalyst system that tolerated a broad range of aromatic and heteroaromatic aldehydes, providing direct access to δ-lactone building blocks with generally excellent enantioselectivities. Our results show that: a) Er^{III} and the amino alcohol ligand form an inert Er–O bond precluding O-acylation, b) both the Lewis acid and the nucleophilic amino moiety are essential for product formation, and c) the catalyst is most likely a monomeric species. Mechanistic studies confirmed the formation of the dienolate intermediates for both catalytic systems. Interestingly, all lanthanides were found to be capable of promoting the title reaction, but the efficiency in terms of yield and enantioselectivity was directly dependent on the radius of the Ln^{III} ion. Similarly, use of the pseudolanthanides Sc^{III} and Y^{III} resulted in product formation, whereas that of the larger La^{III} and other transition metal salts, as well as main group metal salts, proved to be inefficient. A key characteristic of the new bifunctional catalyst system is its simplicity, because the commercially available nucleophilic amino alcohol ligand can be prepared from inexpensive norephedrine[60] in a single step.[61]

Experimental Section

General information, additional procedures, NMR spectra, and HPLC chromatograms are given in the Supporting Information.

General procedure for the formation of the chloral-derived α,β-unsaturated δ-lactones 6: Dry $Sn(OTf)_2$ (41.7 mg, 0.1 mmol) was placed in the reaction flask in a glove-box. Subsequently, toluene (3.6 mL), a solution of trimethylsilylquinidine (TMSQd, **4a**, 79.3 mg, 0.2 mmol) in toluene (2.4 mL), and iPr$_2$NEt (331 μL, 2.0 mmol) were successively added. After the system had been cooled to −15 °C, a solution of chloral (**5**, 97 μL, 1 mmol) in toluene (2 mL) was added. After an additional 10 min a solution of the corresponding acid chloride **1** (1 mmol) in toluene (2 mL) was added by syringe pump over 120 min. The reaction mixture was allowed to stir for an additional 3 h, and aqueous HCl (1 N, 6 mL) was then added to quench the reaction. MTBE (20 mL) was added and the organic phase was washed with aqueous HCl (1 N, 2×10 mL) and with brine (10 mL). After drying over $MgSO_4$ and filtration, the solvent was removed under reduced pressure.

General procedure for the formation of the α,β-unsaturated δ-lactones 28 from aldehydes 26: Dry $Er(OTf)_3$ (0.51 mmol) was placed in the reaction flask in a glove-box. THF (0.9 mL), toluene (0.8 mL), and a solution of (1*R*,2*S*)-1-phenyl-2-(pyrrolidin-1-yl)propan-1-ol (**27b**, 0.034–0.068 mmol) in THF (0.3 mL) were added and the mixture was stirred for 15 min at room temperature. After the system had been cooled to −10 °C, iPr$_2$NEt (0.85 mmol) and the corresponding aldehyde (0.34 mmol) were successively added. A solution of the corresponding acid chloride **1** (0.34 mmol) in toluene (0.5 mL) was then added by syringe pump over 30 min. After stirring for an additional 2 h at −10 °C, the reaction mixture was filtered through a short plug of silica gel (2 cm, hexanes/ethyl acetate 1:1). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (hexanes/ethyl acetate).

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