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Catalytic Asymmetric Synthesis of *trans*-Configured β-Lactones: Cooperation of Lewis Acid and Ion Pair Catalysis

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Abstract: The development of the first *trans*-selective catalytic asymmetric [2+2] cyclocondensation of acyl halides with aliphatic aldehydes furnishing 3,4-disubstituted β-lactones is described. This work made use of a new strategy within the context of asymmetric dual activation catalysis: it combines the concepts of Lewis acid and organic aprotic ion pair catalysis in a single catalyst system. The methodology could also be applied to aromatic aldehydes and offers broad applicability (29 examples). The utility was further demonstrated by nucleophilic ring-opening reactions that provide highly enantiomerically enriched *anti*-aldol products.

Keywords: *anti*-aldol · catalysis · enolates · ketenes · pyridinium

Introduction

Although β-lactones are fairly reactive four-membered heterocyclic ring systems, they were already described in 1883.[1,2] β-Lactones offer rich potential as synthetic intermediates[3] and, most importantly, they can be viewed as masked and activated aldol products because they readily undergo nucleophilic ring-opening reactions as a result of their intrinsic ring strain, which is similar to that of epoxides (β-lactones: ca. 23 kcal mol^{1}; epoxides: ca. 27 kcal mol).[4] Various hard nucleophiles, such as metal alkoxides, amines, or C-nucleophiles can regioselectively cleave the acyl–oxygen bond providing the corresponding aldol adducts in a divergent manner.[3,5] Accordingly, the development of catalytic, asymmetric [2+2] cycloadditions of ketenes[6] and aldehydes[7–9] offers the possibility of replacing catalytic asymmetric aldol reactions, which often require the preformation and isolation of enolate equivalents such as silyl ketene acetals.[10]

Various bioactive natural and synthetic products possessing a β-lactone structural motif can act as specific enzyme inhibitors.[11,12] Among the derivatives of natural products, tetrahydrolipstatin (orlistat, Xenical) has been identified as an anti-obesity agent and is available as over-the-counter weight-loss medication in a number of countries. Of late, *trans*-configured β-lactones such as tetrahydrolipstatin have generated renewed interest due to the recent findings that they can serve as specific inhibitors of fatty acid synthase (FAS-TE), which is an approved drug target for cancer treatment.[13] Owing to the significant activity of *trans*-configured β-lactones, a number of approaches have been reported for their synthesis.[12b,14] Unfortunately, the [2+2] cycloaddition approach using ketenes and aldehydes provides, in general, *cis* isomers as the major products. To the best of our knowledge, there is only one [2+2] cycloaddition available for the catalytic enantioselective formation of *trans*-configured β-lactones,[9b] which appears to be limited to the use of aromatic aldehydes, whereas many bioactive systems, such as tetrahydrolipstatin, carry an aliphatic chain at the 4-position of the 3,4-disubstituted 2-oxetanone.[15–18]

The aim of the present work was to develop a *trans*-selective catalytic asymmetric [2+2] cyclocondensation of acyl halides **1** and aliphatic or aromatic aldehydes **2**.[19] A solution to this problem would provide a protocol for the challenging catalytic enantioselective *anti*-aldol addition reactions.[20] The development of such a methodology was based upon the idea that if an enolate such as **5**, and not a ketene such as **4**, represented the reactive intermediate, the *trans*-configured product would be expected to be formed in preference by activation of the aldehyde with a mono-coordinat-

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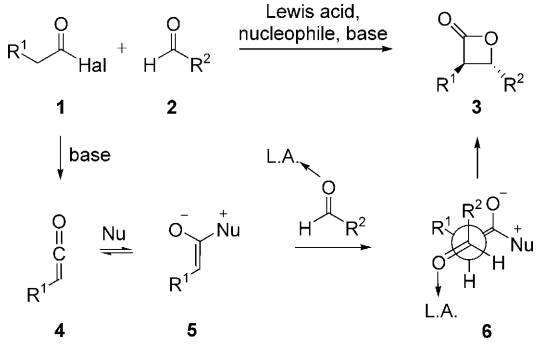
ing Lewis acid (Scheme 1). The choice of a Lewis acid with only one available coordination site was expected to be essential to avoid a cyclic transition state leading to the *cis*-

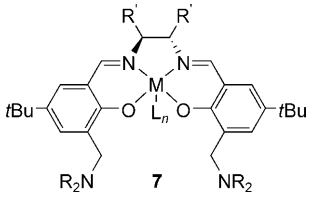


Scheme 1. Concept for the asymmetric formation of *trans*-configured β-lactones **3** (L.A. = Lewis acid with only one available coordination site).

configured product through a Zimmerman–Traxler-type transition state. The catalyst could thus combine the cooperative action of a Lewis acid and a nucleophilic moiety to generate and direct the enolate to the aldehyde through the open transition state **6**. In this state, a staggered conformation around the generated C–C bond[9b,15] could be adopted in which the nucleophilic function should be oriented *gauche* to the aldehyde H for steric reasons. The initial aldol adduct could then cyclize to form the heterocyclic product.

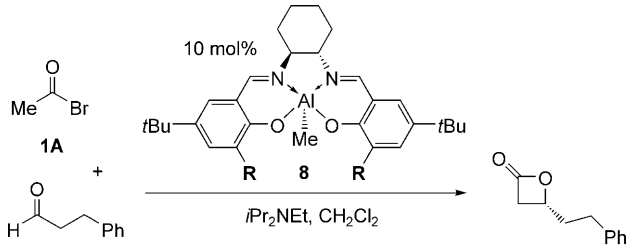
Results and Discussion

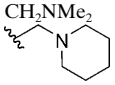
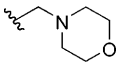
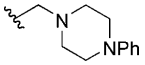
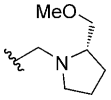
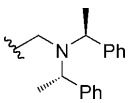
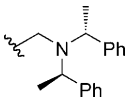
N,*N*′-Bis(salicylidene)ethylenediamine (salen) ligands were chosen because of their modular nature and their ready availability.[21] Kozlowski and co-workers first described catalyst systems with the general structure **7** that incorporate basic amino moieties into the structurally well-defined salen complex.[22]



To evaluate the role of the amino functionalities, ligands lacking the nucleophilic or basic groups were studied as control systems. With the standard salen complex **8a** (R = *t*Bu), the desired product was not formed in the simple model reaction of acetyl bromide (**1A**) and dihydrocinnamaldehyde (**2a**) in CH_2Cl_2 at −20 °C (Table 1, entry 1). With R = H or

Table 1. Investigation of the influence of nonbasic and Lewis/Brönsted basic substituents R on salen–Al complexes **8** for the formation of β-lactone **3Aa**.



Entry	8	R	T [°C]	t [h]	Yield [%][a]	ee [%][b] (isomer)
1	**8a**	*t*Bu	−20	29	0	–
2	**8b**	H	−20	45	73[c]	2 (*R*)
3	**8c**	*i*Bu	−50→−20	48	95[c]	6 (*R*)
4	**8d**	CH_2NMe_2	−50→−20	48	65	50 (*R*)
5	**8e**		−50→−20	48	49	44 (*R*)
6	**8f**		−50→−20	48	54	44 (*R*)
7	**8g**		−50→−20	48	51	40 (*R*)
8	**8h**		−50→−20	48	47	32 (*R*)
9	**8i**		−50→−20	48	69	10 (*R*)
10	**8j**		−50→−20	48	62	10 (*R*)
11	**8k**	CH_2SMe	−50	3	79	46 (*R*)

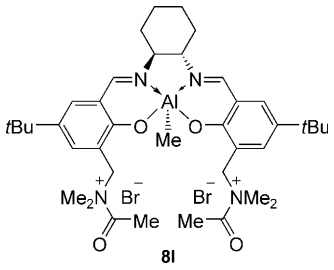
[a] Yield determined by ^{1}H NMR spectroscopy using acetophenone as internal standard. [b] Enantiomeric excess (*ee*) determined by HPLC. [c] Conversion of aldehyde determined by ^{1}H NMR spectroscopic analysis.

*i*Bu, good conversion into the nearly racemic cycloaddition product was found (Table 1, entries 2 and 3). In contrast, with complex **8d**, which carries dimethylaminomethylene donors, a promising enantiomeric excess of 50 % was attained.

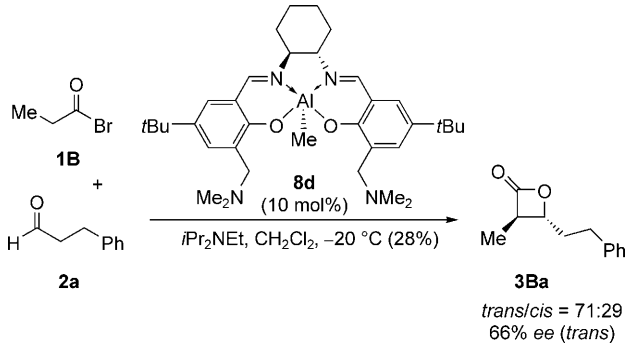
Slightly lower enantioselectivities were observed with piperidine (44 % *ee*; Table 1, entry 5), morpholine (44 % *ee*; Table 1, entry 6), or *N*-phenyl piperazine donors (40 % *ee*; Table 1, entry 7). Catalysts containing α-branched amino functions were less selective (Table 1, entries 8–10). These results show that the efficiency of the basic group decreases with increasing steric hindrance. Catalyst **8k** (Table 1, entry 11), carrying a nucleophilic thioether moiety, was found to be more reactive but less enantioselective than **8d**.

For the reactivity of catalysts **8d–j**, the ratio and addition order of acetyl bromide and the auxiliary base iPr_2NEt is crucial. For the investigations summarized in Table 1, an

excess of acetyl bromide was used relative to iPr$_2$NEt (3 equiv of acetyl bromide, 2.5 equiv iPr$_2$NEt), the latter being added as the last component to the reaction mixture. With an increased amount of base, less product formation was observed. An equal amount of base and acetyl bromide significantly impeded the reaction, whereas with an inverse order of addition, that is, first the base, then acetyl bromide, no reaction at all took place. Furthermore, when an excess of iPr$_2$NEt was used, the catalyst was completely inhibited. Under these conditions the catalyst is apparently deactivated by coordination of the base. In contrast, under the conditions detailed in Table 1, the amino groups of **8d–j** might be partly protonated, which could disturb the formation of a reactive enolate. On the other hand, the amino functions might be acylated as in the case of **8l**, but there would not be enough base remaining for efficient enolate formation.

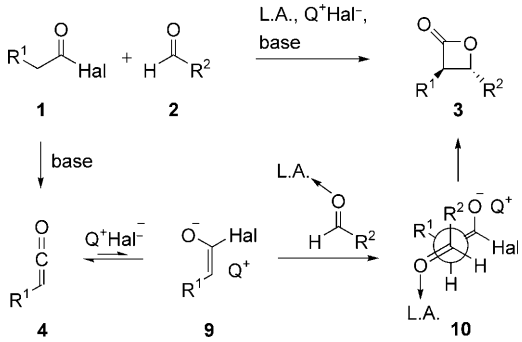


Nevertheless, with propionyl bromide (**1B**) as methylketene source, *trans*-configured β-lactone **3Ba** was preferentially formed at −20 °C (*trans*/*cis* = 71:29) with a promising *ee* value of 66 %, albeit in a low yield of 28 % (Scheme 2).



Scheme 2. Formation of α,β-disubstituted β-lactone **3Ba** catalyzed by **8d**.

Different catalyst species possessing either acylated or protonated amino functionalities were expected to be present that might exhibit different selectivity profiles. The influence of structurally well-defined, positively charged aprotic ammonium moieties was subsequently investigated because the development of a *trans*-selective catalytic asymmetric [2+2] cyclocondensation might also be achieved if acyl halide enolates **9** represent the reactive intermediates (Scheme 3). A possible approach involved the use of a catalyst that included a Lewis acid moiety working in concert



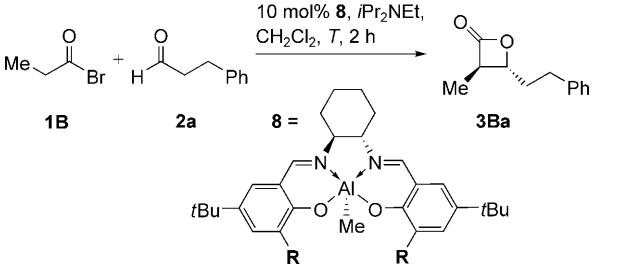
Scheme 3. Modified concept for the asymmetric formation of *trans*-configured β-lactones **3** (L.A. = Lewis acid with only one available coordination side, Q$^+$ = cationic aprotic organic functionality).

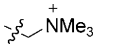
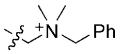
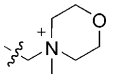
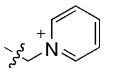
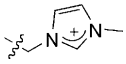
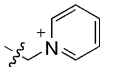
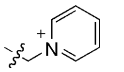
with a positively charged aprotic organic functionality (Q$^+$) within the ligand system that could direct the enolate through formation of an ion pair. The enolate could then undergo an enantioselective aldol addition to the aldehyde, which is activated by the mono-coordinating Lewis acid; a key aspect being that the acyl halide enolate would have to react faster than the ketene intermediate. Because this preference is usually not observed,[23] the unstable enolate[24,25] would have to be generated within the catalyst sphere by attack of the halide counterion on the ketene intermediate, and be stabilized by ion pair formation with the organic cationic functionality Q$^+$.[26] Compared with conventional bifunctional Lewis acid/Lewis base catalysts,[27] this cooperative catalysis concept would have the principal advantage that the cationic aprotic organic functionality does not deactivate the Lewis acid by a self-quenching process.

To establish proof of principle, a range of enantiopure Al–salen complexes **8**, which differed in the substituents R at the 6-position of the phenol rings, were applied to the transformation of propionyl bromide (**1B**) with dihydrocinnamaldehyde (**2a**) as a model reaction (Table 2). To compare the effect of the substituents R, the reactions presented in Table 2 were all performed at −20 °C and stopped after 2 h, unless indicated otherwise. The most simple catalyst system **8b** (X = H) produced β-lactone **3Ba** with moderate *cis*-selectivity in almost racemic form (Table 2, entry 1). For the more bulky salen **8c**, carrying isobutyl substituents, both reduced reactivity and *cis*-selectivity were noted, whereas *tert*-butyl substituents in **8a** again completely prevented all product formation, presumably for steric reasons.

In contrast, catalysts **8m–q** possessing positively charged substituents at the phenol 6-position led to enhanced reactivity. Moreover, the enantioselectivity was significantly improved. Most strikingly, the cationic ammonium or heterocy-

Table 2. Optimization of a cooperative organic ion pair/Lewis acid catalyst.[a]

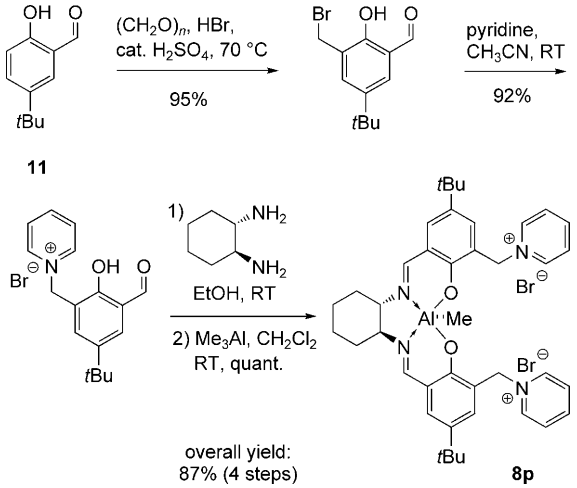


Entry	8	R	T [°C]	Yield [%][b]	ee [%][c]	trans/cis[d]
1	**8b**	H	−20	42	12[e]	21:79
2	**8c**	*i*Bu	−20	28	0[f]	25:75
3	**8a**	*t*Bu	−20	0	–	–
4	**8m**		−20	59	59	91:09
5	**8n**		−20	68	40	85:15
6	**8o**		−20	69	50	92:08
7	**8p**		−20	65	66	90:10
8	**8q**		−20	51	60	86:14
9	**8p**		−50	72[g]	80	92:08
10[h]	**8p**		−70	82[i]	88	97:03

[a] The catalyst was prepared in situ if not mentioned otherwise. [b] Yield determined by ^{1}H NMR analysis using acetophenone as internal standard. [c] Enantiomeric excess of the *trans*-isomer determined by chiral column HPLC. [d] Ratio determined by ^{1}H NMR spectroscopic analysis. [e] 21% *ee* for the *cis* isomer. [f] 23% *ee* for the *cis* isomer. [g] Reaction time 5 h. [h] Use of preformed catalyst. [i] Reaction time 24 h.

clic functionalities provided high *trans*-selectivities (Table 2, entries 4–8). As a general trend, the enantioselectivity was slightly reduced with increased steric bulk of the cationic moieties. The planar pyridinium system **8p** was the most selective catalyst, which might be explained by a more efficient contact ion pair formation as a result of the planar sp^2-nitrogen atom compared with the tetrahedral ammonium functionalities. Imidazolium derivative **8q**, in which the positive charge is delocalized over two nitrogen atoms, led to lower enantio- and diastereoselectivity.

To attain a higher level of enantioselectivity, the reaction temperature had to be further decreased and the catalyst was isolated prior to use; in previous experiments it was prepared in situ. Whereas the reaction catalyzed by the trimethylammonium system **8m** was extremely slow at −50°C as a result of poor catalyst solubility, the pyridinium catalyst **8p** was significantly more reactive (Table 2, entry 9) and rendered high enantio- and *trans*-selectivity as well as providing a good yield at −70°C (Table 2, entry 10). Compound **8p** was readily prepared in four steps from 2-hydroxy-5-*tert*-butylbenzaldehyde (**11**) with an overall yield of 87% (Scheme 4).



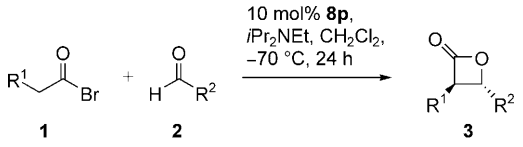
Scheme 4. Synthesis of catalyst **8p** in four steps from aldehyde **11**.

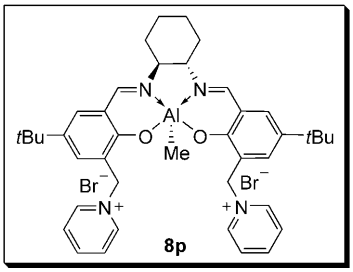
The β-lactone formation triggered by **8p** generally provided high *trans*-selectivities with all the aliphatic aldehydes tested (Table 3). The enantioselectivities did not significantly depend on the aldehyde, and almost identical results were obtained with substrates possessing long aliphatic side chains (Table 3, entries 4–6), with or without a C=C double bond, β-branched isovaleraldehyde (Table 3, entry 10) or sterically undemanding aldehydes such as propanal, butanal, or pentanal (Table 3, entries 7–9). In particular, these last results are remarkable because high enantioselectivities have previously never been reported for these sterically undemanding aliphatic aldehydes in alternative catalytic asymmetric cycloadditions with acyl halides. Both yields and enantioselectivities were higher in the case of valeroyl bromide (**1C**; Table 3, entries 13–18) compared with propionyl bromide (**1B**). Again, the enantioselectivity was found to be almost independent of the aldehyde used.

In contrast to the aldehydes described above, the α-branched cyclohexylcarboxaldehyde gave very little conversion at −70°C. Therefore, the temperature had to be increased to −40°C to provide the product with useful selectivity (80% *ee*, *trans*/*cis* = 87:13) and yield (78%; Table 3, entry 11). With acetyl bromide (**1A**) the reaction with cyclohexylcarboxaldehyde could again be performed at −70°C, providing an enantiomeric excess of 88% (Table 3, entry 12), whereas with acetyl bromide/dihydrocinnamaldehyde the *ee* dropped to 70% (Table 3, entry 3). The method is apparently less general for the formation of 4-monosubstituted β-lactones. Although 10 mol% of catalyst **8p** was commonly used for the experiments in Table 3, a similar result was also achieved with just 2.5 mol% (entry 2).

trans-Configured β-aryl-substituted β-lactones are considerably less stable than their β-alkyl-substituted counterparts due to a marked sensitivity towards elimination, which is ac-

Table 3. Application of the dual activation catalyst **8p** to the reaction of aliphatic aldehydes.

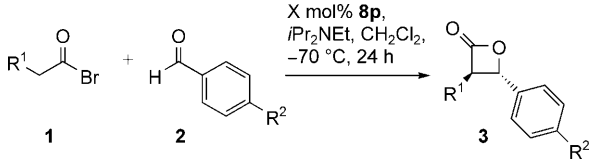




Entry	3	R^1	R^2	8p [mol%]	Yield [%][a]	*ee* [%][b]	*trans*/*cis*[c]
1	**3Ba**	Me	$(CH_2)_2Ph$	10	82[d]	88	97:03
2	**3Ba**	Me	$(CH_2)_2Ph$	2.5	73	85	97:03
3	**3Aa**	H	$(CH_2)_2Ph$	10	76	70	–
4	**3Bb**	Me	*n*Hept	10	77	87	96:04
5	**3Bc**	Me	$(CH_2)_3CH{=}CH_2$	10	74[d]	88	96:04
6	**3Bd**	Me	$(CH_2)_8CH{=}CH_2$	10	62	87	94:06
7	**3Be**	Me	Et	10	76[d]	87	95:05
8	**3Bf**	Me	*n*Pr	10	67	93	97:03
9	**3Bg**	Me	*n*Bu	10	64	89	97:03
10	**3Bh**	Me	*i*Bu	10	76[d]	87	94:06
11	**3Bi**	Me	*c*Hex	10	78[e]	80	87:13
12	**3Ai**	H	*c*Hex	10	82	88	–
13	**3Ca**	*n*Pr	$(CH_2)_2Ph$	10	91	94	98:02
14	**3Cc**	*n*Pr	$(CH_2)_3CH{=}CH_2$	10	96	95	98:02
15	**3Ce**	*n*Pr	Et	10	63	94	97:03
16	**3Cf**	*n*Pr	*n*Pr	10	93	95	98:02
17	**3Cg**	*n*Pr	*n*Bu	10	92	93	96:04
18	**3Ch**	*n*Pr	*i*Bu	10	76	94	96:04

[a] Yield of isolated product. [b] Enantiomeric excess of the *trans* isomer determined by chiral column HPLC or GC (see the Supporting Information). [c] Ratio determined by ^{1}H NMR analysis. [d] Determined by ^{1}H NMR spectroscopic analysis. [e] Reaction performed at −40 °C.

Table 4. Application of **8p** to the reaction of aromatic aldehydes.



Entry	3	R^1	R^2	X 8p [mol%]	Yield [%][a]	*ee* [%][b]	*trans*/*cis*[c]
1	**3Bj**	Me	H	2.5	70	93	96:04
2	**3Bj**	Me	H	10	80	91	94:06
3	**3Bk**	Me	CF_3	2.5	84	75	97:03
4	**3Bl**	Me	Cl	2.5	75	77	96:04
5	**3Bm**	Me	CN	2.5	87	70	98:02
6	**3Bn**	Me	NO_2	2.5	90	78	97:03
7	**3Bo**	Me	Br	2.5	81	71	96:04
8	**3Cj**	*n*Pr	H	10	46	94	97:03
9	**3Ck**	*n*Pr	CF_3	10	93	80	96:04
10	**3Cl**	*n*Pr	Cl	10	62	83	95:05
11	**3Cm**	*n*Pr	CN	10	90	81	98:02
12	**3Cn**	*n*Pr	NO_2	10	88	80	97:03
13	**3Co**	*n*Pr	Br	10	70	88	98:02

[a] Yield determined by ^{1}H NMR spectroscopic analysis using acetophenone as internal standard. [b] Enantiomeric excess of the *trans*-isomer determined by chiral column HPLC. [c] Ratio determined by ^{1}H NMR spectroscopic analysis.

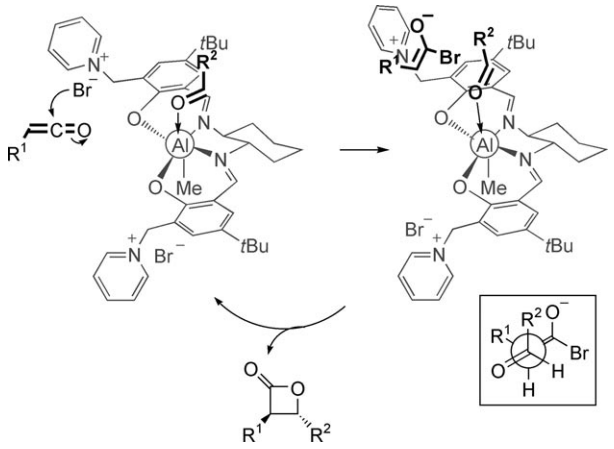
celerated by electron donors on the aromatic ring.[28] As a consequence, alternative workup conditions were necessary in the present study for product isolation. The transformation of propionyl bromide (**1B**) with benzaldehyde (**2j**) was investigated as a model reaction. All attempts at aqueous workup (acidic, basic, or neutral) led to either complete or partial decomposition of the product. However, by catalyst quenching with an excess of *i*Pr$_2$NEt at low temperature and filtration through a plug of deactivated silica gel (followed by column chromatography) it was possible to isolate the targeted β-lactone **3Bj** (Table 4, entries 1 and 2).

For reactions of propionyl bromide with different aromatic aldehydes, 2.5 mol% of **8p** was usually sufficient (Table 4). With benzaldehyde, an *ee* value of 93% was attained (Table 4, entry 1). In the case of electron-poor aryl groups, the products were formed with good yield but the enantioselectivity was decreased to 70–78% *ee* although high *trans* selectivity was maintained (Table 4, entries 3–7). On the other hand, no product could be isolated with 4-methylbenzaldehyde or 4-methoxybenzaldehyde; in the first case due to decomposition of the product during workup and, in the second case, maybe because of low substrate reactivity.

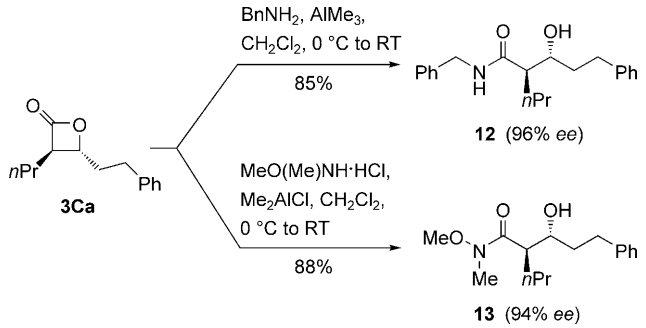
Reactions between a range of aromatic aldehydes and *n*-valeroyl bromide required a catalyst loading of 10 mol% to achieve useful yields (Table 4, entries 8–13). In this case, again, higher enantioselectivities (80–94% *ee*) were generally attained than with propionyl bromide.

The proposed mode of operation is depicted in Scheme 5. The aldehyde is assumed to bind with its sterically more accessible lone pair to the only free Al coordination site, to form an octahedral complex. Because the unstable, highly reactive acyl bromide enolate[23–25] is expected to be present in only minute concentrations and could therefore not be spectroscopically detected in our studies despite intensive attempts (NMR and IR spectroscopy, mass spectrometry), it is likely that the short-living reactive intermediate is generated directly in the catalyst sphere by reaction of the catalyst's bromide counterion with the ketene.[29] This attack is expected to occur selectively *trans* to the residue R^1 to minimize repulsive interactions, thus selectively forming the *E*-configured enolate. This reactive species should nucleophilically attack the aldehyde through an open transition state that adopts a staggered conformation with the enolate C1 atom *gauche* to the aldehyde H atom. Our model is in agreement with the products' configuration.[30]

The synthetic utility of the *trans*-configured products was finally showcased by conducting nucleophilic ring-opening reactions with a primary amine and with Weinreb amine (Scheme 6), giving access to the *anti*-aldol products in good yield and with high enantiomeric excess.



Scheme 5. Working model for the cooperative action of the ion pair and Lewis acid catalysis.



Scheme 6. Formation of enantioenriched *anti*-aldol products by nucleophilic ring-opening reactions.

Conclusion

This work has explored a new strategy within the context of asymmetric cooperative catalysis.[31] It combines the concepts of Lewis acid and aprotic organic ion pair catalysis in a single catalyst system (Figure 1).[32]

This mode of activation has allowed us to develop the first *trans*-selective catalytic asymmetric [2+2] cycloondensation of acyl halides with aliphatic aldehydes, furnishing 3,4-disubstituted β-lactones. Despite the high sensitivity of the 4-aryl-substituted β-lactones towards elimination, the methodology could also be applied to aromatic aldehydes by making use of a different workup procedure. In general, this new methodology offers broad applicability and represents an alternative to asymmetric *anti*-aldol additions.

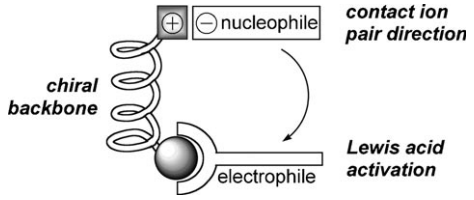


Figure 1. The concept of ion pair directed Lewis acid catalysis.

Experimental Section

General procedure for the formation of catalysts 8a–k and 8m–q in situ: A solution of Me_3Al in toluene (2 M, 0.10 mL, 0.21 mmol, 1 equiv) was added to a solution of the corresponding salen ligand (0.21 mmol, 1 equiv) in CH_2Cl_2 (3.5 mL). The mixture was stirred for 3 h at ambient temperature.

General procedure for the formation of *trans*-configured β-lactones 3 with aliphatic substituents at the β-position: Aldehyde **2** (0.75 mmol, 1 equiv), acyl bromide **1** (4.5 mmol, 6 equiv), and diisopropylethylamine (1.875 mmol, 2.5 equiv) were successively added at −70 °C to a mixture of complex **8p** (0.075 mmol, 0.1 equiv) in CH_2Cl_2 (3 mL). The resulting heterogeneous mixture was stirred at −70 °C for 24 h then poured into aqueous 1 M HCl (30 mL) and extracted with CH_2Cl_2 (2×20 mL). The combined organic phase was dried over $MgSO_4$ and filtered through a short plug of silica gel. CH_2Cl_2 was subsequently removed in vacuo and the crude product mixture was purified by flash chromatography if not indicated otherwise.

General procedure for the formation of *trans*-configured β-lactones 3 with an aryl substituent in the β-position: Aldehyde **2** (0.75 mmol, 1 equiv), acyl bromide **1** (4.5 mmol, 6 equiv), and diisopropylethylamine (1.875 mmol, 2.5 equiv) were successively added at −70 °C to a mixture of complex **8p** (0.0188 mmol, 0.025 equiv) in CH_2Cl_2 (3 mL). The resulting heterogeneous mixture was stirred at −70 °C for 24 h, then the reaction mixture was quenched with diisopropylethylamine (4 mL) and filtered through a short plug of Et_3N-deactivated silica gel. CH_2Cl_2 was subsequently removed in vacuo and the crude product mixture of the *trans*-configured β-aryl-substituted β-lactones **3** was purified by rapid flash chromatography using Et_3N-deactivated silica gel.

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[1] A. Einhorn, *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2208.
[2] For [2+2] cycloaddition of carbonyl moieties with a ketene, see: H. Staudinger, S. Bereza, *Liebigs Ann.* **1911**, *380*, 243.
[3] a) H. W. Yang, D. Romo, *Tetrahedron* **1999**, *55*, 6403; b) Y. Wang, R. L. Tennyson, D. Romo, *Heterocycles* **2004**, *64*, 605.
[4] A. Greenberg, J. F. Liebmann, *Strained Organic Molecules*, Academic Press, New York, **1978**, Vol. 38, Chapter 5.
[5] a) S. G. Nelson, Z. Wan, *Org. Lett.* **2000**, *2*, 1883; b) G. G. Zipp, M. A. Hilfiker, S. G. Nelson, *Org. Lett.* **2002**, *4*, 1823; c) S. G. Nelson, W. S. Cheung, A. J. Kassick, M. A. Hilfiker, *J. Am. Chem. Soc.* **2002**, *124*, 13654. Soft nucleophiles are known to preferentially cleave the alkyl–O bond. β-Lactones are therefore also masked β-substituted carboxylic acids, see reference [3].
[6] For comprehensive reviews on ketene chemistry, see: a) T. T. Tidwell, *Ketenes*, Wiley, New York, **2006**; b) T. T. Tidwell, *Eur. J. Org. Chem.* **2006**, 563; c) For ketene history, see: T. T. Tidwell, *Angew. Chem.* **2005**, *117*, 5926; *Angew. Chem. Int. Ed.* **2005**, *44*, 5778; d) D. H. Paull, A. Weatherwax, T. Lectka, *Tetrahedron* **2009**, *65*, 6771; e) R. K. Orr, M. A. Calter, *Tetrahedron* **2003**, *59*, 3545.
[7] Lewis base catalyzed asymmetric processes: a) D. Borrmann, R. Wegler, *Chem. Ber.* **1967**, *100*, 1575; b) H. Wynberg, E. G. J. Staring, *J. Am. Chem. Soc.* **1982**, *104*, 166; c) H. Wynberg, E. G. J. Staring, *J.*

Org. Chem. **1985**, *50*, 1977; d) G. S. Cortez, R. L. Tennyson, D. Romo, *J. Am. Chem. Soc.* **2001**, *123*, 7945; e) J. E. Wilson, G. C. Fu, *Angew. Chem.* **2004**, *116*, 6518; *Angew. Chem. Int. Ed.* **2004**, *43*, 6358; f) S. H. Oh, G. S. Cortez, D. Romo, *J. Org. Chem.* **2005**, *70*, 2835; g) H. Henry-Riyad, C. Lee, V. C. Purohit, D. Romo, *Org. Lett.* **2006**, *8*, 4363; h) M. Mondal, A. A. Ibrahim, K. A. Wheeler, N. J. Kerrigan, *Org. Lett.* **2010**, *12*, 1664.

[8] Lewis acid catalyzed reactions: a) Y. Tamai, H. Yoshiwara, M. Someya, J. Fukumoto, S. Miyano, *J. Chem. Soc. Chem. Commun.* **1994**, 2281; b) B. W. Dymock, P. J. Kocienski, J.-M. Pons, *Chem. Commun.* **1996**, 1053; c) H. W. Yang, D. Romo, *Tetrahedron Lett.* **1998**, *39*, 2877; d) S. G. Nelson, T. J. Peelen, Z. Wan, *J. Am. Chem. Soc.* **1999**, *121*, 9742; e) see reference [5a]; g) S. G. Nelson, C. Zhu, X. Shen, *J. Am. Chem. Soc.* **2004**, *126*, 14; h) R. E. Forslund, J. Cain, J. Colyer, M. P. Doyle, *Adv. Synth. Catal.* **2005**, *347*, 87; i) T. Kull, R. Peters, *Adv. Synth. Catal.* **2007**, *349*, 1647; j) highlight article: C. Schneider, *Angew. Chem.* **2002**, *114*, 771; *Angew. Chem. Int. Ed.* **2002**, *41*, 744.

[9] Lewis acid–Lewis base catalyzed asymmetric processes: a) C. Zhu, X. Shen, S. G. Nelson, *J. Am. Chem. Soc.* **2004**, *126*, 5352; b) M. A. Calter, O. A. Tretyak, C. Flaschenriem, *Org. Lett.* **2005**, *7*, 1809; c) V. Gnanadesikan, E. J. Corey, *Org. Lett.* **2006**, *8*, 4943; d) Y.-M. Lin, J. Boucau, Z. Li, V. Casarotto, J. Lin, A. N. Nguyen, J. Ehrmantraut, *Org. Lett.* **2007**, *9*, 567.

[10] For a review, see: C. Palomo, M. Oiarbide, J. M. Garcia, *Chem. Soc. Rev.* **2004**, *33*, 65.

[11] a) C. Lowe, J. C. Vederas, *Org. Prep. Proced.* **1995**, *27*, 305; b) A. Pommier, J.-M. Pons, *Synthesis* **1995**, 729.

[12] a) R. H. Feling, G. O. Buchanan, T. J. Mincer, C. A. Kauffman, P. R. Jensen, W. Fenical, *Angew. Chem.* **2003**, *115*, 369; *Angew. Chem. Int. Ed.* **2003**, *42*, 355; b) C. Masse, J. Morgan, J. Adams, J. Panek, *Eur. J. Org. Chem.* **2000**, 2513.

[13] a) S. J. Kridel, F. Axelrod, N. Rosenkrantz, J. W. Smith, *Cancer Res.* **2004**, *64*, 2070; b) L. M. Knowles, F. Axelrod, C. D. Browne, J. W. Smith, *J. Biol. Chem.* **2004**, *279*, 30540; c) P.-Y. Yang, K. Liu, M. Hong Ngai, M. J. Lear, M. R. Wenk, S. Q. Yao, *J. Am. Chem. Soc.* **2010**, *132*, 656.

[14] a) P. Barbier, F. Schneider, U. Widmer, *Helv. Chim. Acta* **1987**, *70*, 1412; b) P. Barbier, F. Schneider, *Helv. Chim. Acta* **1987**, *70*, 196; c) P. Barbier, F. Schneider, *J. Org. Chem.* **1988**, *53*, 1218; d) O. Dirat, C. Kouklovsky, Y. Langlois, *Org. Lett.* **1999**, *1*, 753; e) A. K. Ghosh, C. Liu, *Chem. Commun.* **1999**, 1743; f) I. Paterson, V. A. Doughty, *Tetrahedron Lett.* **1999**, *40*, 393; g) C. Wedler, B. Costisella, H. Schick, *J. Org. Chem.* **1999**, *64*, 5301; h) P. J. Parsons, J. K. Cowell, *Synlett* **2000**, 107; i) A. K. Ghosh, S. Fidanze, *Org. Lett.* **2000**, *2*, 2405; j) J. A. Bodkin, E. J. Humphries, M. D. McLeod, *Aust. J. Chem.* **2003**, *56*, 795; k) J. A. Bodkin, E. J. Humphries, M. D. McLeod, *Tetrahedron Lett.* **2003**, *44*, 2869; l) A. N. Thadani, R. A. Batey, *Tetrahedron Lett.* **2003**, *44*, 8051; m) J. Polkowska, E. Lukaszewicz, J. Kiegiel, J. Jurczak, *Tetrahedron Lett.* **2004**, *45*, 3873; n) J. S. Yadav, K. Vishweahwar Rao, M. Sridhar Reddy, A. R. Prasad, *Tetrahedron Lett.* **2006**, *47*, 4393; o) J. S. Yadav, K. Vishweahwar Rao, A. R. Prasad, *Synthesis* **2006**, 3888; p) J. S. Yadav, M. Sridhar Reddy, A. R. Prasad, *Tetrahedron Lett.* **2006**, *47*, 4995; q) G. Kumaraswamy, B. Markondaiah, *Tetrahedron Lett.* **2008**, *49*, 327.

[15] For a *trans*-diastereoselective Lewis acid–Lewis base catalyzed procedure that uses chiral enantiopure aldehydes, see: X. Shen, A. S. Wasmuth, J. Zhao, C. Zhu, S. G. Nelson, *J. Am. Chem. Soc.* **2006**, *128*, 7438.

[16] For *trans*-diastereoselective catalytic nonenantioselective formation of β-lactams by ketenes, see, for example: A. Weatherwax, C. J. Abraham, T. Lectka, *Org. Lett.* **2005**, *7*, 3461, and references cited therein.

[17] For selected theoretical studies on the *cis*/*trans* diastereoselectivity of the formation of 1,2-disubstituted β-lactones by ketenes, see: a) B. Lecea, A. Arrieta, X. Lopez, J. M. Ugalde, F. P. Cossio, *J. Am. Chem. Soc.* **1995**, *117*, 12314; b) J.-M. Pons, M. Oblin, A. Pommier, M. Rajzmann, D. Liotard, *J. Am. Chem. Soc.* **1997**, *119*, 3333; c) D. A. Singleton, Y. Wang, H. W. Yang, D. Romo, *Angew. Chem.* **2002**, *114*, 1642; *Angew. Chem. Int. Ed.* **2002**, *41*, 1572.

[18] For *trans*-selective alkylation of β-lactones, see, for example: a) J. Mulzer, T. Kerkmann, *J. Am. Chem. Soc.* **1980**, *102*, 3620; b) J. Mulzer, A. Chucholowski, O. Lammer, I. Ibrill, G. Huttner, *J. Chem. Soc. Chem. Commun.* **1983**, 869; c) A. Griesbeck, D. Seebach, *Helv. Chim. Acta* **1987**, *70*, 1320.

[19] Preliminary results were reported as a communication, see: a) T. Kull, R. Peters, *Angew. Chem.* **2008**, *120*, 5541; *Angew. Chem. Int. Ed.* **2008**, *47*, 5461; for other studies by our group utilizing ketenes or related species for cycloadditions, see: b) J. Cabrera, T. Hellmuth, R. Peters, *J. Org. Chem.* **2010**, *75*, 4326; c) P. S. Tiseni, R. Peters, *Chem. Eur. J.* **2010**, *16*, 2503; d) M. Zajac, R. Peters, *Chem. Eur. J.* **2009**, *15*, 8204; e) P. S. Tiseni, R. Peters, *Org. Lett.* **2008**, *10*, 2019; f) P. S. Tiseni, R. Peters, *Angew. Chem.* **2007**, *119*, 5419; *Angew. Chem. Int. Ed.* **2007**, *46*, 5325; g) F. M. Koch, R. Peters, *Angew. Chem.* **2007**, *119*, 2739; *Angew. Chem. Int. Ed.* **2007**, *46*, 2685; h) M. Zajac, R. Peters, *Org. Lett.* **2007**, *9*, 2007.

[20] a) S. E. Denmark, T. Wynn, G. L. Beutner, *J. Am. Chem. Soc.* **2002**, *124*, 13405; b) H. Ishitani, Y. Yamashita, H. Shimizu, S. Kobayashi, *J. Am. Chem. Soc.* **2000**, *122*, 5403; c) S. E. Denmark, W.-J. Chung, *Angew. Chem.* **2008**, *120*, 1916; *Angew. Chem. Int. Ed.* **2008**, *47*, 1890; d) N. Yoshikawa, N. Kumagai, S. Matsunaga, G. Moll, T. Ohshima, T. Suzuki, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, *123*, 2466.

[21] a) T. P. Yoon, E. N. Jacobsen, *Science* **2003**, *299*, 1691; b) T. Katsuki, *Synlett* **2003**, 281; c) K. Matsumoto, B. Saito, T. Katsuki, *Chem. Commun.* **2007**, 3619; d) C. Mazet, E. N. Jacobsen, *Angew. Chem.* **2008**, *120*, 1786; *Angew. Chem. Int. Ed.* **2008**, *47*, 1762; e) G. M. Sammis, E. N. Jacobsen, *J. Am. Chem. Soc.* **2003**, *125*, 4442; f) M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 5315; g) J. K. Myers, E. N. Jacobsen, *J. Am. Chem. Soc.* **1999**, *121*, 8959; h) S.-X. Wang, M.-X. Wang, D.-X. Wang, J. Zhu, *Org. Lett.* **2007**, *9*, 3615.

[22] For Lewis acid–Lewis base bifunctional salen Zn or Ti catalysts, see: a) E. F. DiMauro, M. C. Kozlowski, *J. Am. Chem. Soc.* **2002**, *124*, 12668; b) M. W. Fennie, E. F. DiMauro, E. M. O'Brien, V. Annamalai, M. C. Kozlowski, *Tetrahedron* **2005**, *61*, 6249.

[23] Mechanistic studies by Nelson et al. supported a ketene–aldehyde reaction pathway as the operative mechanism in Al^{III}-catalyzed acid chloride/aldehyde cyclocondensations. In contrast, for Ti^{IV}-catalyzed reactions providing racemic dioxanones, acyl halide enolates were suggested as reactive intermediates: S. G. Nelson, T. J Peelen, Z. Wan, *Tetrahedron Lett.* **1999**, *40*, 6541.

[24] Species such as $H_2C{=}C(O^-)Cl$ proved computationally unstable relative to ketene and Cl^-, see: R. E. Rosenberg, *J. Org. Chem.* **1998**, *63*, 5562.

[25] Ammonium salts of acid chloride enolates can be isolated if the electron density of the enolate C atom is stabilized by an electron-withdrawing group such as a Cl atom. Studies by Brady and Scherubel have shown that the enolate-forming step is reversible. In contrast, in the absence of an electron-withdrawing substituent, the enolate salts could neither be isolated nor detected spectroscopically, as a result of their instability: a) W. T. Brady, G. A. Scherubel, *J. Am. Chem. Soc.* **1973**, *95*, 7447; b) W. T. Brady, G. A. Scherubel, *J. Org. Chem.* **1974**, *39*, 3790.

[26] For recent reviews on organic ion pair catalysis, see: a) T. Ooi, K. Maruoka, *Angew. Chem.* **2007**, *119*, 4300; *Angew. Chem. Int. Ed.* **2007**, *46*, 4222; b) T. Hashimoto, K. Maruoka, *Chem. Rev.* **2007**, *107*, 5656.

[27] a) For a review on dual activation catalysis, see: J.-A. Ma, D. Cahard, *Angew. Chem.* **2004**, *116*, 4666; *Angew. Chem. Int. Ed.* **2004**, *43*, 4566; b) M. Shibasaki, M. Kanai, K. Funabashi, *Chem. Commun.* **2002**, 1989.

[28] a) A. Pommier, J. M. Pons, *Synthesis* **1993**, 441–459; b) J. Mulzer, M. Zippel, G. Brüntrup, *Angew. Chem.* **1980**, *92*, 469–470; *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 465–466.

[29] Acid chlorides did not provide the targeted products at −70 °C.

[30] The absolute configuration was determined for **3Bf** by comparison of the specific optical rotation with literature data (N. Sakai, S. Ageishi, H. Isobe, Y. Hayashi, Y. Yamamoto, *J. Chem. Soc. Perkin*

Trans. 1 **2000**, 71). Since a uniform reaction pathway can be assumed, the configuration has been assigned to all disubstituted β-lactones **3** derived from aliphatic aldehydes. The absolute configuration of the monosubstituted β-lactones **3Aa** and **3Ai** was determined by HPLC analysis based on our previous work (see ref. [8i]). The absolute configuration of β-lactones **3** derived from aromatic aldehydes was determined by comparison of the specific optical rotation of **3Bj**, **3Bm** and **3Bn** with data reported by Calter et al. (see ref. [9b]).

[31] For other approaches used by our group in this field, see for example, reference [19c–g] and: S. Jautze, R. Peters, *Angew. Chem.* **2008**, *120*, 9424; *Angew. Chem. Int. Ed.* **2008**, *47*, 9284.

[32] For a pioneering work on the combination of Lewis acid and ion pair catalysis utilizing alkali metal crown ether complexes for anion direction, see: M. Sawamura, H. Nagata, H. Sakamoto, Y. Ito, *J. Am. Chem. Soc.* **1992**, *114*, 2586.

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