

Contact Ion Pair Directed Lewis Acid Catalysis: Asymmetric Synthesis of *trans*-Configured β -Lactones**

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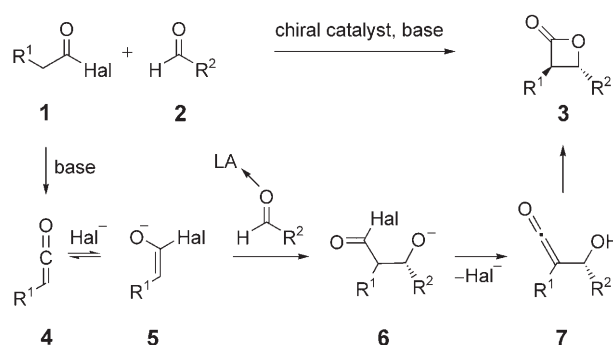
Dedicated to Professor Sir Jack Baldwin

β -Lactones readily undergo nucleophilic ring-opening reactions as a result of their intrinsic ring strain and thus behave as activated aldol equivalents.^[1] Various hard nucleophiles such as metal alcoholates, amines, and C nucleophiles can regioselectively cleave the acyl–oxygen bond providing the corresponding aldol adducts.^[1,2] Consequently, the development of catalytic asymmetric [2+2] cycloadditions of ketenes^[3] and aldehydes^[4–7] offers an alternative to catalytic asymmetric ester and amide aldol reactions, which in most cases require the preformation and isolation of enolate equivalents such as silyl ketene acetals.^[8]

β -Lactones are not only very useful building blocks, but also represent a structural motif in a number of important natural and synthetic bioactive products such as the anti-obesity drug tetrahydrolipstatin (Xenical, F. Hoffmann-La Roche). The majority of these bioactive compounds have a *trans* configuration about the heterocyclic system.^[9] Unfortunately, almost all of the known catalytic asymmetric [2+2] cycloadditions using substituted ketene substrates provide preferentially the *cis* isomers. To our knowledge, there is only one [2+2] cycloaddition available for the catalytic enantioselective formation of *trans*-configured β -lactones.^[7b] This conversion is limited though to the use of aromatic aldehydes, whereas most bioactive systems such as Xenical contain an aliphatic chain at the 4-position of the 3,4-disubstituted oxetanone.^[10–13]

The aim of the present work was to develop a *trans*-selective catalytic asymmetric [2+2] cyclocondensation of acyl halides **1** and aliphatic aldehydes **2** which would thus represent a surrogate for the rare type of catalytic enantioselective *anti*-aldol additions.^[14] The development of this

process was based upon the initial idea that if enolate **5**, and not ketene **4**, represents the reactive intermediate, the *trans*-configured product would be expected to be formed in preference (Scheme 1). The enolate would undergo an



Scheme 1. Initial working hypothesis for the *trans*-selective catalytic asymmetric formation of β -lactones (LA = Lewis acid).

enantioselective aldol addition to the aldehyde, which is activated by coordination to a chiral Lewis acid. The resulting acyl halide alcoholate **6** would subsequently experience a dehydrohalogenation to give the hydroxyalkyl-substituted ketene **7**, which in turn could cyclize to form the thermodynamically more stable *trans*-configured product. The key aspect is then that the enolate, which should be present at least in small quantities in equilibrium with ketene **4**,^[15] would have to react faster than the ketene intermediate **4** itself. Since this preference is usually not observed, the enolate would have to be further activated and/or generated by the catalyst.

To realize this idea, the anionic nucleophile might be directed by the formation of a contact ion pair (CIP) with a positively charged aprotic functionality within the ligand system, for example, by a quaternary ammonium moiety (Figure 1). In contrast, protic cations might quench either the anionic nucleophile or the Lewis acid after deprotonation by a base, which is required to generate the enolate intermediate.^[16] The new concept would thus have the principal

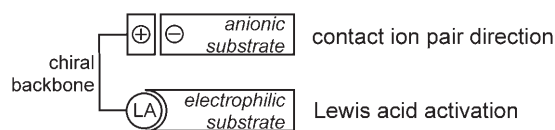


Figure 1. The concept of contact ion pair directed Lewis acid catalysis.

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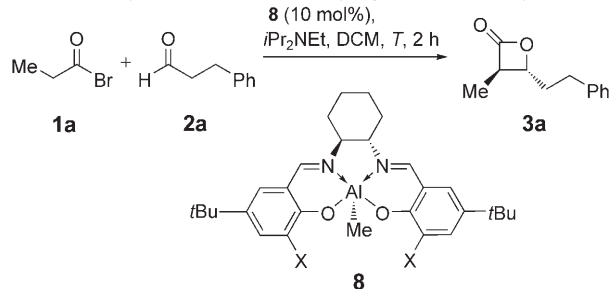
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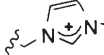
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advantage—over bifunctional Lewis acid/Lewis base catalysis^[17]—that the cationic functionality does not deactivate the Lewis acid by a self-quenching process, and the strategy would implement a cooperative combination of the two concepts of phase-transfer catalysis^[18] and Lewis acid catalysis.

To establish proof of principle, we selected readily available enantiopure aluminum–salen complexes^[19,20] **8** differing in the substituent X at the 6-position of the phenol ring (Table 1).^[21] The transformation of propionyl bromide with dihydrocinnamaldehyde was investigated as model reaction.

Table 1: Development of a contact ion pair/Lewis acid catalyst.^[a]



Entry	8	X	T [°C]	Yield [%] ^[b]	e.r. ^[c]	trans/cis ^[d]
1	8a	H	−20	42	56:44	21:79
2	8b	<i>i</i> Bu	−20	28	38.5:61.5	25:75
3	8c	<i>t</i> Bu	−20	0	—	—
4	8d		−20	59	79.5:20.5	91:9
5	8e		−20	68	70:30	85:15
6	8f		−20	69	75:25	92:8
7	8g		−20	65	83:17	90:10
8	8h		−20	51	80:20	86:14
9	8g		−50	72 ^[f]	90:10	92:8
10 ^[e]	8g		−70	82 ^[g]	94:6	97:3

[a] The catalyst was prepared in situ if not mentioned otherwise; reaction time 2 h. [b] Yield determined by ^1H NMR spectroscopy using acetophenone as an internal standard. [c] Enantiomer ratios determined by HPLC on a chiral support. [d] Ratio determined by ^1H NMR spectroscopy. [e] Preformed catalyst was used. [f] Reaction time 5 h. [g] Reaction time 24 h.

The most simple catalyst system **8a** (X = H) produced β -lactone **3a** with moderate *cis* selectivity in almost racemic form (entry 1, Table 1). For the more bulky salen **8b** carrying isobutyl substituents, both reduced reactivity and *cis* selectivity were noted, while *tert*-butyl substituents in **8c** completely impeded any product formation, presumably for steric reasons.

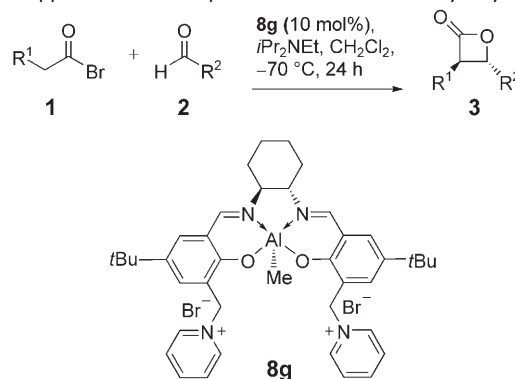
In contrast, all catalysts **8d–h** possessing a positively charged substituent at the phenol 6-position led to enhanced

reactivity. Moreover, the enantioselectivity was significantly improved, and the major enantiomer displays an inverted absolute configuration. Most strikingly, the cationic ammonium or heterocyclic functionalities provided high *trans* selectivities (entries 4–8, Table 1). As a general trend, the enantioselectivity was slightly reduced with increased steric bulk of the cationic moiety. The planar pyridinium system **8g** possessing an sp²-hybridized N atom was the most selective catalyst so far. One explanation may be that formation of the contact ion pair with **8g** might be more efficient than with ammonium functionalities. Imidazolium derivative **8h**, in which the positive charge is delocalized over two N atoms, led to significantly lower enantio- and diastereoselectivity as a consequence of a less stable contact ion pair.

To attain synthetically useful enantioselectivities, the reaction temperature had to be further decreased. While the reaction catalyzed by trimethylammonium system **8d** was extremely slow at -50°C as a result of poor catalyst solubility, the pyridinium catalyst **8g**, prepared in four steps from 2-hydroxy-5-*tert*-butylbenzaldehyde with an overall yield of 87% (see the Supporting Information), was significantly more reactive (entry 10, Table 1) and gave high enantioselectivity and *trans* selectivity and good yield at -70°C .

The reaction generally provided high *trans* selectivities with aliphatic aldehydes (Table 2). The enantioselectivity did not significantly depend on the aldehyde, and almost identical

Table 2: Application of the optimized bifunctional catalyst system **8g**.



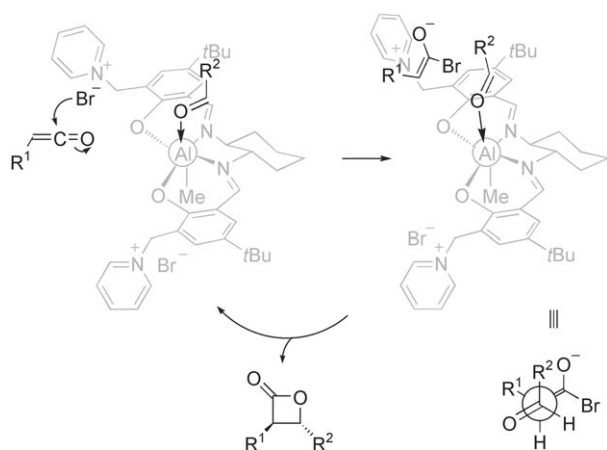
Entry	3	R ¹	R ²	Yield [%] ^[a]	<i>ee</i> [%] ^[b]	<i>trans/cis</i> ^[c]
1	3a	Me	(CH ₂) ₂ Ph	82 ^[d]	88	97:3
2	3b	Me	<i>n</i> Hept	77	87	96:4
3	3c	Me	(CH ₂) ₃ CH=CH ₂	74 ^[d]	88	96:4
4	3d	Me	(CH ₂) ₈ CH=CH ₂	62	87	94:6
5	3e	Me	Et	76 ^[d]	87	95:5
6	3f	Me	<i>n</i> Pr	67	93	97:3
7	3g	Me	<i>n</i> Bu	64	89	97:3
8	3h	Me	<i>i</i> Bu	76 ^[d]	87	94:6
9	3i	<i>n</i> Pr	(CH ₂) ₂ Ph	91	94	98:2
10	3j	<i>n</i> Pr	(CH ₂) ₃ CH=CH ₂	96	95	98:2
11	3k	<i>n</i> Pr	Et	63	94	97:3
12	3l	<i>n</i> Pr	<i>n</i> Pr	93	95	98:2
13	3m	<i>n</i> Pr	<i>n</i> Bu	92	93	96:4
14	3n	<i>n</i> Pr	<i>i</i> Bu	76	94	96:4

[a] Yield of isolated product if not indicated otherwise. [b] Determined by HPLC or GC on a chiral support (see the Supporting Information). [c] Ratio determined by ^1H NMR spectroscopy. [d] Determined by ^1H NMR spectroscopy.

results were obtained with substrates possessing long aliphatic side chains (entries 2–4, and 10, Table 2) with or without a C=C bond, with β -branched aldehydes such as isovaleraldehyde (entries 8 and 14, Table 2),^[22] and with sterically undemanding aldehydes like propanal, butanal or pentanal (entries 5–7, 11–13, Table 2). In particular these latter results are remarkable, since high enantioselectivities have previously never been reported for very small aliphatic aldehydes in other catalytic asymmetric cycloadditions with acyl halides or ketenes.

Both yields and enantioselectivities were further increased when valeroyl bromide was used instead of propionyl bromide (entries 9–14, Table 2). It is expected that the corresponding ketene with a bulkier substituent is less reactive and hence a background reaction, in which the pyridinium moiety is not involved, should be less favorable when a larger acyl bromide is used.

The proposed reaction mechanism is depicted in Scheme 2. The aldehyde is assumed to bind with its sterically more accessible lone pair to the free Al coordination site to



Scheme 2. Working model for the action of the catalyst.

form an octahedral complex. Since the unstable acyl bromide enolate is expected to be present in only minute concentrations, it is likely that the reacting intermediate is generated directly in the catalyst sphere by attack of the catalyst's bromide counteranion to the ketene. This attack would be expected to occur selectively *trans* to the residue R^1 to minimize repulsive interactions, thus selectively forming the *E*-configured enolate contact ion pair. This reactive species should nucleophilically attack the aldehyde via an open transition state in a staggered conformation, which would already explain the observed *trans* selectivity without the necessity for the initially proposed formation of an additional ketene intermediate **7** (Scheme 1). Our model is in agreement with the products' *R,R* configurations.^[23] The suggested mode of action is supported furthermore by the fact that acid chlorides do not provide the targeted products at -70°C , probably because chloride is less nucleophilic than bromide.

In conclusion, we have introduced a novel concept within the context of dual-activation catalysis that combines the

cooperative action of aprotic contact ion pair and Lewis acid catalysis. This concept has allowed us to develop the first *trans*-selective catalytic asymmetric [2+2] cyclocondensation of acyl bromides with aliphatic aldehydes, furnishing 3,4-disubstituted β -lactones; thus it represents an alternative to asymmetric *anti*-aldol additions. The described and related catalyst systems should also be attractive for alternative reactions that rely on contact ion pair catalysis. Studies directed towards developing our catalyst systems further in this direction are underway.

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