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Practical Enantioselective Synthesis of β-Lactones Catalyzed by Aluminum Bissulfonamide Complexes

Thomas Kull[a] and René Peters[a,*]

[a] ETH Zürich, Laboratory of Organic Chemistry, Wolfgang-Pauli-Str. 10, Hönggerberg HCI E 111, 8093 Zürich, Switzerland
Fax: (+41)-44-633-1226; e-mail: peters@org.chem.ethz.ch

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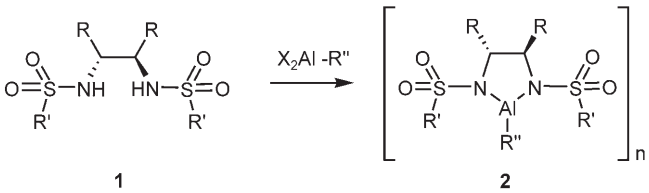
Abstract: The development of an efficient and practical aluminum-bissulfonamide complex catalyzed enantioselective formation of β-lactones by [2+2] cycloaddition of ketene (generated *in situ* from acetyl bromide by dehydrobromination) with various α-unbranched and -branched aliphatic aldehydes is presented. The methodology offers the advantage of operational simplicity not only as the ligand synthesis requires just a single sulfonylation step from commercially available enantiomerically pure diamines. The products are formed in high to excellent yields with *ee* values typically ranging from 78 to 90% using 10 mol% of the bissulfonamide ligand. The key finding of this work was a remarkable rate acceleration by using an aluminum/ligand ratio of 1.5:1.

Keywords: aluminum; catalysis; cycloaddition; ketenes; β-lactones; sulfonamides

β-Lactones can be regarded as activated aldol equivalents, since they readily undergo ring opening reactions due to their intrinsic ring strain.[1] Various hard nucleophiles are able to regioselectively cleave the acyl-oxygen bond thus providing the corresponding β-hydroxy carbonyl derivatives.[2] Accordingly, the development of catalytic asymmetric [2+2] cycloadditions of ketenes[3] and aldehydes offers the possibility to replace catalytic asymmetric ester aldol reactions which in most cases require the preformation, isolation and purification of moisture sensitive silyl ketene acetals. From both a technical and economical point of view, the use of silyl protecting groups is an issue on production scale, not only because SiO_2 being formed during waste combustion processes has the tendency to block the combustors' chimneys.

The main goal of the work presented herein was to develop a widely applicable and practical catalyst system for β-lactone formation by [2+2] cycloaddition of ketene and aldehydes.[4] Previous work by other groups had shown that the asymmetric formation of β-lactones can be catalyzed either nucleophilically, for example, by action of chiral tertiary amines such as brucine[5] or *Cinchona* alkaloids,[6] or by Lewis acid catalysts.[7] The most promising results with regard to the latter strategy were obtained by aluminum-based systems. In the pioneering work by Miyano et al.[8] and Kocienski et al.[9] bissulfonamide ligands derived from chiral C_2 symmetric 1,2-diamino-1,2-diphenylethane (DiPh) were utilized employing either the preformed gaseous parent ketene[8] or the commercially available, yet expensive trimethylsilylketene.[9] However, the induced enantioselectivities were in general moderate. Recently, Nelson et al. could significantly improve both the scope and enantioselectivity by employing Al catalysts prepared from tridentate aminobissulfonamide ligands and trimethylaluminum.[10] Moreover, the ketene substrates could be generated *in situ* from acyl bromides by treatment with ethyldiisopropylamine. Based on these precedents our overall goal was to develop a system with enhanced practicality which should be as simple as possible, but still should provide high enantioselectivities and yields. For that reason we decided to reinvestigate bissulfonamide-derived Al complexes **2** (Scheme 1) which although simple to prepare still



1 2

Scheme 1. Formation of bissulfonamide aluminum complexes **2**.

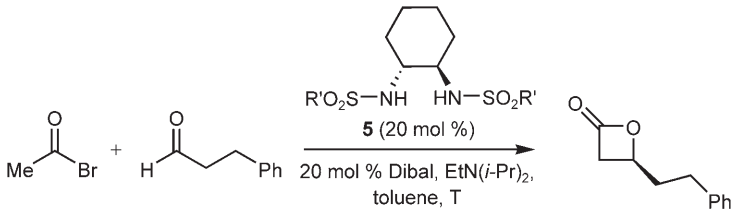
allow a high structural diversity: along these lines the influence of different Al substituents R″, sulfonamide residues R′ and C_2 symmetric diamino backbones can be investigated. Surprisingly, only a single application of this type of Al catalyst possessing a bissulfonylated cyclohexane-1,2-diamino (Cy) ligand backbone has been reported in literature, namely the investigation of Al-catalyzed cyclopropanations,[11] whereas the corresponding 1,2-diphenylaminoethane-derived aluminum catalysts have been frequently applied in catalysis after the pioneering studies by Corey et al. on catalytic enantioselective Diels–Alder reactions.[12]

The cyclocondensation of acetyl bromide (**3**)[13] and dihydrocinnamaldehyde (**4a**) was selected as model reaction. The initial ligand screening using the (*R*,*R*)-cyclohexane-1,2-diamino (Cy) backbone revealed that two *ortho* substituents on an aromatic sulfonyl residue R′ are essential to achieve acceptable enantioselectivities with 20 mol% of the catalyst, but that the *ortho* substituents also slow down the reaction to a large degree (Table 1). Al-complexes missing the *ortho*-substituents on R′ generally catalyzed the model reaction smoothly at −78 °C (half conversion after 0.1 to 0.7 h as determined by ^{1}H NMR monitoring with the exception of entry 9), but the enantioselectivities were far from being preparatively useful (entries 5–8, 10). With methyl or ethyl *ortho*-substituents, the reaction temperature had to be increased to −60 °C to obtain reasonable reaction rates (entries 1 and 2), while in the case of isopropyl residues, the conversion was very slow even at −50 °C (entry 4). The bis-*ortho*-substituted aromatic residues R′ allowed the formation of lactone **6a** with *ee* values >70%, the best results being realized with the Cy-Dmtb ligand **5a** (*ee* = 80%, half conversion after 2.5 h, entry 1). Entries 1 and 2 also revealed, that the *para*-substituents have a substantial influence upon the reaction rate.

The investigation of the influence of the Al substituent R″ showed that the bulky isobutyl moiety permitted a significantly higher enantioselectivity (Cy-Trim **5b**, $T = -60$ °C, *ee* = 80%) than the ethyl (*ee* = 72%) or methyl (*ee* = 53%) residues, but again the higher selectivity was at the expense of a reduced reaction rate.[14]

With a lower catalyst loading of 10 mol% the reaction was not only further decelerated, but proceeded also less enantioselectively (Cy-Trip **5d**, $T = -70$ °C, *ee* = 65%). The catalysts with *ortho*-disubstituted aromatic residues R″ being selected for further investigations were generally prepared *in situ* by stirring a 1:1 mixture of the bulky ligands **5a**, **5b** or **5d** and Dibal at room temperature for 1 h followed by heating the mixture to 80 °C for 4 h.[15] The complex ^{1}H NMR spectra of these mixtures showed that about one third of the ligand was not consumed under these conditions.[16] By rising the Dibal amount to 1.5 equivs. per

Table 1. Initial screening of bissulfonamide ligands **5** derived from (*R*,*R*)-cyclohexyl-1,2-diamine.



3 **4a** **6a**

Entry[a]	Ligand	R′	T [°C]	$\tau_{1/2}$[b] [h]	*ee*[c] [%]
1	Cy-Dmtb **5a**	2,6-$(CH_3)_2$-4-*t*-BuC_6H_2	−60	2.5	80
2	Cy-Trim **5b**	2,4,6-$(CH_3)_3C_6H_2$	−60	8	80
3	Cy-Trie **5c**	2,4,6-$(C_2H_5)_3C_6H_2$	−60	3.3	73
4	Cy-Trip **5d**	2,4,6-(*i*-Pr)$_3C_6H_2$	−50	21	71
5	Cy-1-Naph **5e**	1-naphthyl	−78	0.2	43
6	Cy-2-Naph **5f**	2-naphthyl	−78	0.25	37
7	Cy-BTFM **5g**	3,5-$(CF_3)_2C_6H_3$	−78	0.2	35
8	Cy-Ts **5h**	4-$CH_3C_6H_4$	−78	0.1	30
9	Cy-2-NO_2 **5i**	2-$NO_2C_6H_4$	−78	35	19
10	Cy-PFP **5j**	C_6F_5	−78	0.7	17
11	Cy-Tf **5k**	CF_3	−78	<0.5	2

[a] All reactions were performed at a concentration $c = 0.13$ M. The ketene was preformed in a separate flask by treatment of **3** (3 equivs.) with *i*-Pr_2NEt (2.5 equivs.) in toluene at −78 °C for 4 h. The ketene solution was subsequently transferred *via* canula into the reaction flask.

[b] Determined by ^{1}H NMR monitoring.

[c] *ee* determined by chiral column HPLC (Daicel OD-H, see Supporting Information).

equiv. of ligand, the signals of the free ligand completely disappeared. With 10 mol% of the ligand and 15 mol% of Dibal the reaction is not only dramatically accelerated by the excess of Dibal, but surprisingly also more selective than with a 1:1 stoichiometry of ligand and Al source (Table 2). As demonstrated for

Table 2. Investigation of the effect of the ligand/Al-source ratio for Cy-Trip **5d** and Dibal.

Entry	**5d**/DIBAL [mol%]	Reaction time [h]	Conversion[b] [%]	Yield[c] [%]	*ee*[d] [%]
1	10:10	18	37	32	65
2	10:12.5	18	57	55	70
3	10:15	15	100	87	78
4	10:17.5	15	100	62	77
5	10:20	15	98	66	72

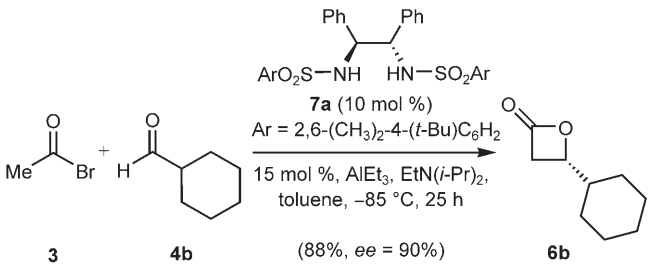
[a] All reactions were performed at −70 °C at a concentration $c = 0.25$ M. The ketene was formed *in situ*.
[b] Determined by ^{1}H NMR.
[c] Yield after aqueous workup determined by ^{1}H NMR using acetophenone as an internal standard.
[d] *ee* determined by chiral column HPLC (Daicel OD-H, see Supporting Information).

5d, the reaction which was very sluggish at −50 °C with 20 mol% of catalyst (half conversion of the aldehyde after 21 h), proceeded within 15 h at −70 °C to completion using 10 mol% of the chiral ligand and 15 mol% of Dibal. A further increase of the amount of Dibal is detrimental to both yield and enantioselectivity.

Due to the markedly enhanced activity the reaction temperature was further reduced. At −85 °C, product **6a** was obtained in 93% yield after 48 h and with 88% *ee* (Table 3, entry 1, compare to the reactions at −60 °C: Cy-Trip **5d**: 99% yield, 75% *ee*; Cy-Dmtb **5a**: 72% yield, 73% *ee*, Cy-Trim **5b**: 62% yield, 70% *ee*).

When the same conditions were applied to cyclohexylcarbaldehyde **4b** chosen as a model substrate for α-branched aldehydes, the product was obtained in disappointing 17% yield after 40 h at −85 °C (20% conversion) and with just 72% *ee*. However, with ligand Cy-Dmtb **5a**, which performed inferiorly for dihydrocinnamaldehyde **4a**, the product was obtained in 87% yield and with 86% *ee* after 40 h at −85 °C (Table 3, entry 12).

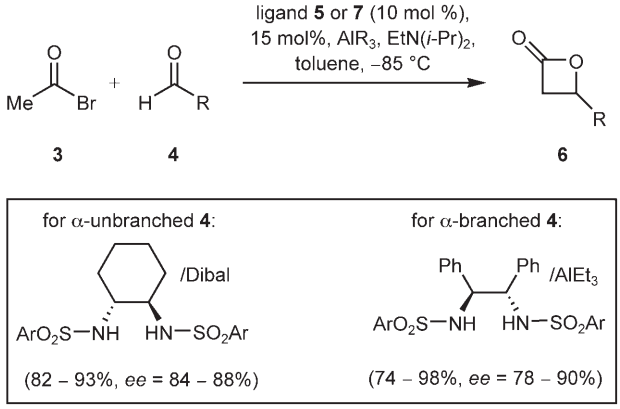
Next the influence of the diamino backbone was investigated. While the cyclohexane-1,2-diamino (Cy) backbone is superior for dihydrocinnamaldehyde (**4a**), ligands derived from 1,2-diphenyl-1,2-diamine (DiPh) are more efficient for the α-branched cyclohexanecarbaldehyde (**4b**, Scheme 2). In the latter case, $AlEt_3$ was superior as Al source. Under these conditions the product was obtained in 88% yield after 25 h and with 90% *ee* (10 mol% DiPh-Dmtb **7a**, 15 mol% $AlEt_3$). The stoichiometry effect for the catalyst formation was also observed in this case, albeit less pronounced: with 10 mol% DiPh-Dmtb **7a** and 10 mol% $AlEt_3$ the reaction gave 87% yield after 45 h with a slightly diminished *ee* of 87%.[17]



Scheme 2.

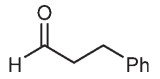
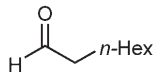
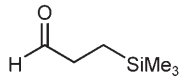
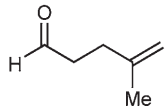
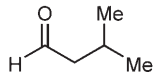
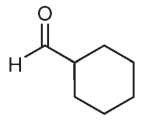
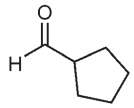
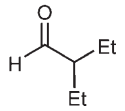
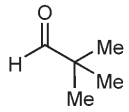
At present we have no direct experimental evidence about the origin of the stoichiometry effect. The ^{1}H NMR spectra of complexes which were formed from various combinations of 1.0 equiv. of the bissulfonamide ligands **5** or **7** and 1.5 equivs. of the Al sources show like in the case of a 1:1 stoichiometry C_1-symmetric dimeric complexes **2** ($n = 2$ in Scheme 1) as the main species.[18] However, in addition to these dimers, the formation of small amounts of unidentified complexes has been detected which might differ from the 1:1 stoichiometry and which might possess a significantly higher activity. The higher activity could finally result from a Lewis acid-assisted Lewis acid activation (LLA concept).[19]

The scope of the methodology is summarized in Scheme 3 and Table 3: in general both α-branched and -unbranched aldehydes are well tolerated and furnish the corresponding β-lactones **6** in high yield and with *ee* values ranging from 78 to 90% using the best combinations (Table 3) of sulfonamide and Al source.[20,21] The results obtained for the two model substrates **4a** and **4b** can be generalized: the (*R*,*R*)-cy-



Scheme 3. Al-bissulfonamide-catalyzed enantioselective formation of β-lactones **6**.

Table 3. Scope of the Al-bissulfonamide-catalyzed enantioselective formation of β-lactones **6**.

Entry[a]	**4**	Ligand	Reaction time [h]	Conversion[b] [%]	Al source	Yield[c] [%]	*ee* [%]	Configuration[g]
1	 **4a**	Cy-Trip **5d**	48	98	Dibal	93	88[d]	(*S*)
2		DiPh-Dmtb **7a**	48	78	Dibal	66	82[d]	(*R*)
3	 **4c**	Cy-Trip **5d**	63	100	Dibal	86	84[e]	(*S*)
4		DiPh-Trip **7b**	144	75	Dibal	44	73[e]	(*R*)
5	 **4d**	Cy-Trip **5d**	62	100	Dibal	82	84[f]	(*R*)
6		DiPh-Dmtb **7a**	88	85	Dibal	71	79[f]	(*S*)
7	 **4e**	Cy-Trip **5d**	140	100	Dibal	92	88[f]	(*S*)
8		DiPh-Dmtb **7a**	140	40	Dibal	34	74[f]	(*R*)
9	 **4f**	DiPh-Trip **7b**	26	100	Dibal	98	85[f]	(*R*)
10		Cy-Trip **5d**	49	100	Dibal	84	84[f]	(*S*)
11	 **4b**	DiPh-Dmtb **7a**	25	100	Et_3Al	88[h]	90[f]	(*S*)
12		Cy-Dmtb **5a**	23	99	Et_3Al	87	86[f]	(*R*)
13	 **4g**	DiPh-Dmtb **7a**	84	100	Et_3Al	90	80[f]	(*S*)
14		Cy-Dmtb **5a**	84	100	Et_3Al	81	80[f]	(*R*)
15	 **4h**	DiPh-Dmtb **7a**	136	95	Et_3Al	94	80[f]	(*S*)
16		Cy-Dmtb **5a**	113	98	Et_3Al	87	68[f]	(*R*)
17	 **4i**	DiPh-Dmtb **7a**	135	100	Et_3Al	83	78[e]	(*S*)
18		Cy-Dmtb **5a**	135	100	Et_3Al	89	75[e]	(*R*)

[a] All reactions were performed at −85 °C at a concentration $c = 0.25$ M. The ketene was formed *in situ*.
[b] Determined by ^{1}H NMR.
[c] Yield determined by ^{1}H NMR using acetophenone as internal standard.
[d] *ee* determined by chiral column HPLC (Daicel OD-H, see Supporting Information).
[e] *ee* determined by chiral column HPLC (Daicel OD-H) after nucleophilic ring opening of the product with (*S*)-1-methylbenzyl amine (see Supporting Information).
[f] *ee* determined by chiral column GC (Supelco Gamma Dex™, see Supporting Information).
[g] The configuration was determined by comparison of the $[\alpha]_D$ values of compounds **6a**, **6b**, **6f** and **6i** with literature data (see Supporting Information). Since a uniform reaction pathway can be assumed, the absolute configuration can be assigned to all cycloaddition products **6**.
[h] The isolated yield on larger scale was 90 % (see Experimental Section).

clohexane-1,2-diamino (Cy) backbone is superior for α-unbranched aldehydes, whereas ligands derived from (*S*,*S*)-1,2-diphenyl-1,2-diamine (DiPh) are more efficient for the α-branched substrates. In Table 3 both standard conditions for α-branched and -unbranched systems, respectively, are given for comparison for each substrate. For the β-branched isovaleraldehyde **4f** enantioselectivities were almost identical using the different ligand backbones, however, DiPh-Trip **7b** led to a considerably higher reactivity (entry 9). Due to the volatility of most of the prepared β-lactones, the yields in Table 3 were determined after aqueous work-up by ^{1}H NMR using acetophenone as internal standard. However, similarly high yields were obtained after isolation by column chromatography using a low-boiling eluent as exemplified for **6a** (87 %), **6b** (90 %) and **6f** (85 % isolated yield).

In summary, we have developed an efficient and practical methodology for the aluminum-catalyzed enantioselective formation of β-lactones. In contrast to Nelson's Al catalyst, the system described herein tolerates also α-branched aldehydes and offers the advantage that it is remarkably simple as the ligand syn-

thesis requires only a simple sulfonylation step of commercially available enantiomerically pure diamines. We believe that due to the simplicity of the reaction system it should also be interesting for technical applications.

Experimental Section

Typical Procedure

To a mixture of ligand **7a** (0.15 mmol, 0.1 equiv.) in absolute toluene (6.0 mL) was slowly added at ambient temperature a solution of $AlEt_3$ (1.0 M in hexane, 0.225 mmol, 0.15 equivs.). The mixture was heated to 80 °C and stirred for 4 h. Subsequently, the solution was stirred for 1 h at ambient temperature. The catalyst solution was then cooled to −85 °C and cyclohexylcarbaldehyde (**4b**, 1.5 mmol), acetyl bromide (**3**, 4.5 mmol, 3 equivs.) and diisopropylethylamine (3.75 mmol, 2.5 equivs.) were successively added. The resulting heterogeneous mixture was stirred at −85 °C for 25 h until complete conversion as monitored by ^{1}H NMR. The reaction mixture was poured into aqueous 1 M HCl (60 mL) and extracted with diethyl ether (3 × 45 mL). The combined organic phase was dried over $MgSO_4$, filtered and diethyl ether was removed under vacuum. The solution of the crude product was directly used for column chromatography (pentane → pentane/diethyl ether, 8:1) without prior removal of toluene giving **6a** as colorless oil; yield: 209 mg (1.35 mmol, 90 %), *ee* = 90 %.

Acknowledgements

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[13] Attempts with acetyl chloride instead failed. This might be ascribed to a blocking of the hard Al ion by coordination of the hard chloride anion which is generated during the ketene formation. The coordination of the softer bromide anion is anticipated to be more labile.
[14] The reactions were less enantioselective with R″ = Cl (e.g., Cy-Trip **5d**, Al source Et_2AlCl, −78 °C, *ee* = 50 %, very slow reaction) or R″ = F (e.g., Cy-Trip **5d**, Al source *i*-Bu_2AlF, −78 °C, *ee* = 28 %, very slow reaction).
[15] Both longer (6 h) and shorter (2 h) heating periods resulted in less enantioselective reactions.
[16] Note that with $AlMe_3$ the signals for free ligand were already disappeared after 30 min.
[17] Similarly, DiPh-Trip **7b**/Dibal gave the following results with (a) cyclohexanecarbaldehyde **4b** (0.25 M, toluene, −85 °C, 45 h): 10 mol % **7b**/10 mol % Dibal: 70 % yield, 70 % *ee*; 10 mol % **7b**/15 mol % Dibal: 75 % yield, 75 % *ee*; (b) dihydrocinnamaldehyde **4a** (0.25 M, toluene, −85 °C, 44 h): 10 mol % **7b**/10 mol % Dibal: 42 % yield, 74 % *ee*; 10 mol % **7b**/15 mol % Dibal: 79 % yield, 78 % *ee*.
[18] Dimeric complexes of this type have been characterized by X-ray structure analysis in earlier studies: E. J. Corey, S. Sarshar, *J. Am. Chem. Soc.* **1992**, *114*, 7938.
[19] H. Yamamoto, K. Futatsugi, *Angew. Chem. Int. Ed.* **2005**, *44*, 1924.
[20] Similar to previous catalytic asymmetric [2+2] cycloadditions of the parent ketene and aldehydes, the catalyst systems reported herein are not applicable to benzaldehyde and α,β-unsaturated aldehydes, since the products decomposed during the isolation/purification proce-

dures presumably due to elimination reactions. The same problem was faced with conjugated ynals.
[21] No clear picture is evident with regard to the reaction times: while in some cases, the conversion is complete after one day even with sterically hindered aldehydes such as cyclohexanecarbaldehyde **4b** or isovaleraldehyde **4f**, for other substrates up to 6 days at −85 °C are necessary to achieve full conversion.

