Asymmetric Preparation of New *N*,*N*-Dialkyl-2-amino-1,1,2-triphenylethanol Catalysts and a Kinetic Resolution in the Addition of Diethylzinc to Flavene-3-carbaldehydes

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Abstract: Enantiopure *N*,*N*-dialkyl-(*S*)-2-amino-1,1,2-triphenylethanols were prepared using a new synthetic methodology and tested for their ability to catalyze the enantioselective addition of diethylzinc to aldehydes. The structural modification of N-substituents of the catalysts led us to identify *N*-methyl-*N*-(*S*)-1-phenylethyl-substituted **4d** as an effective catalyst for the addition. Also disclosed is a kinetic resolution of racemic flavene-3-carbaldehydes with the chiral catalyst.

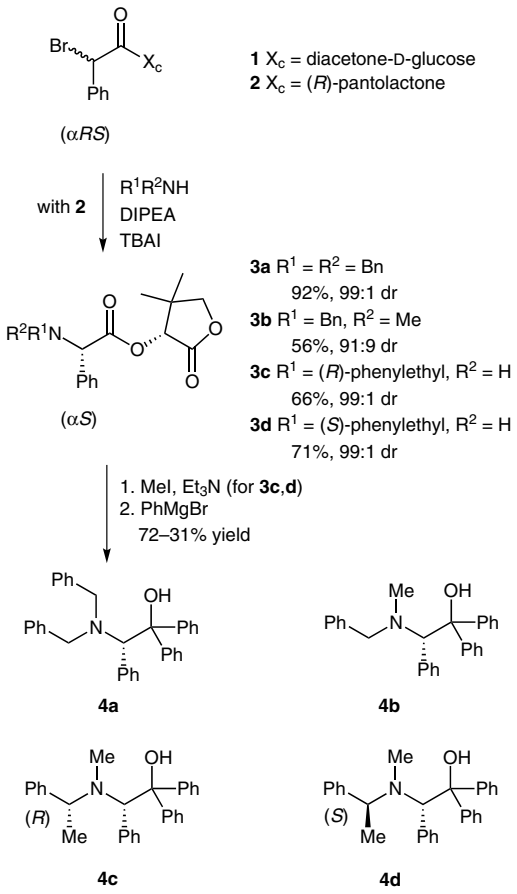
Key words: addition, asymmetric catalysis, chirality, enantioselectivity, kinetic resolution

A great deal of effort has been devoted to the development of efficient chiral catalysts for catalytic asymmetric reactions. Among the various types of chiral catalysts explored, β-amino alcohols have proven to be especially efficient for the addition of organometallic reagents to carbonyl compounds.[1] In particular, 2-amino-1,1,2-trisubstituted ethanols are known as some of the most efficient chiral catalysts for the addition of dialkylzinc to aldehydes.[2] However, the preparation of the optically pure catalysts is not a trivial task, and fine-tuning of their structures for optimal catalytic behavior requires carefully controlled synthetic strategies. Thus, it is of interest to develop a practical synthesis of new catalysts, based on processes that are compatible with structural diversity.

Herein, we report the asymmetric syntheses of new *N*,*N*-dialkyl-2-amino-1,1,2-triphenylethanols using a dynamic resolution mediated by a chiral auxiliary in the nucleophilic substitution of α-bromo esters. The application of the synthesized catalysts to the addition of diethylzinc to aldehydes, a typical catalytic asymmetric benchmark reaction, is also discussed. Furthermore, we present a successful example of kinetic resolution of racemic flavene-3-carbaldehyde by addition of diethylzinc.

Our strategy for the synthesis of enantiopure *N*,*N*-dialkyl-2-amino-1,1,2-triphenylethanols involves an asymmetric nucleophilic substitution of α-bromo esters with an amine nucleophile followed by Grignard addition as shown in Scheme 1. In the nucleophilic substitution with amine nucleophiles, the chiral information of a chiral auxiliary is efficiently transferred to the new C–N bond formation at the α-bromo carbon center via dynamic resolution of two diastereomeric α-bromo-α-phenyl acetates **1** and **2**.[3] This nucleophilic substitution readily enabled us to fine-tune N-substitution through the use of various amine nucleophiles.

The previous studies by Pericàs et al. have revealed that 2-piperidino-1,1,2-triphenylethanol provides excellent enantioselectivity in the addition of dialkylzinc to aldehydes and structural changes in the *N*,*N*-dialkyl substituents have important chemical consequences.[2c–f] In order to further understand the influence of the *N*-alkyl substituents on the catalytic properties, we have prepared four different chiral catalysts **4a**–**d** having different *N*-benzyl substituents.



Scheme 1 Asymmetric preparation of chiral catalysts **4a**–**d**

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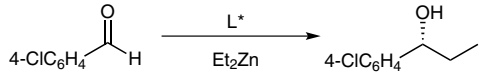
We first used diacetone-D-glucose as a chiral auxiliary for the asymmetric syntheses of N-substituted amino esters via dynamic kinetic resolution of α-bromo esters.[4] The treatment of a 1:1 diastereomeric mixture of α-bromo-α-phenyl acetate **1** with dibenzylamine, benzylmethylamine, (*R*)-1-phenylethylamine, and (*S*)-1-phenylethylamine in the presence of tetrabutyl ammonium iodide (TBAI) and diisopropyl ethylamine (DIPEA) gave the substitution products in diastereomeric ratios (dr) of 92:8, 92:8, 94:6, and 94:6, respectively. In an effort to improve the stereoselectivity, we also examined a series of substitution reactions of (*R*)-pantolactone-derived α-bromo-α-phenyl acetate **2**.[5] Nucleophilic substitutions of **2** were conducted under the same reaction conditions as those used for α-bromo ester **1**. Much higher stereoselectivities were observed with dibenzylamine, (*R*)-1-phenylethylamine, and (*S*)-1-phenylethylamine to produce **3a**, **3c**, and **3d** in a diasteromeric ratio of 99:1 in 92–66% yields as shown in Scheme 1. Meanwhile, no substantial difference in stereoselectivity was found in the reaction with benzylmethylamine to afford **3b** (91:9 dr). The subsequent reduction of **3a** and **3b** using an excess of PhMgBr in THF furnished the expected β-dialkylamino alcohols **4a** and **4b**. Enantiopure chiral catalyst (*S*)-**4a** was easily isolated in 72% yields by flash column chromatography, and enantiopure (*S*)-**4b** was obtained in 31% yield by recrystallization. Chiral HPLC analysis of catalysts **4a**,**b** confirmed that no racemization had taken place in the reaction with excess PhMgBr. The N-methylation of **3c** and **3d** with methyl iodide was efficiently carried out in DMF using triethylamine as the base. Subsequent treatment with excess PhMgBr completed the synthesis of enantiopure chiral catalysts (*R*,*S*)-**4c** and (*S*,*S*)-**4d** in 34% and 41% overall yields.[6]

Chiral catalysts **4a**–**d** were initially tested in the enantioselective addition of diethylzinc to 4-chlorobenzaldehyde as shown in Table 1. Reactions were performed with two equivalents of diethylzinc and 5 mol% of the catalyst in *t*-BuOMe at room temperature for five hours. When 4-chlorobenzaldehyde was added to the mixture of diethylzinc and *N*,*N*-dibenzyl-substituted chiral catalyst **4a**, 1-(4-chlorophenyl)-1-propanol was obtained with an enantiomeric excess (ee) of 6% and low conversion after five hours[7] (Table 1, entry 1). In contrast, the reaction of chiral catalyst **4b** having *N*-benzyl and *N*-methyl groups showed promising results, in which the aldehyde was completely consumed after five hours with a much higher enantiomeric excess of 92% (Table 1, entry2). It is speculated, based on previous studies of β-amino alcohol–ethylzinc complexes,[2,8] that the success of chiral catalyst **4b** might rely on the steric difference between the *N*-methyl and *N*-benzyl groups. When more sterically demanding *N*-1-phenylethyl-substituted chiral catalysts **4c** and **4d** were subjected to the same reaction conditions, the additional stereogenic center of the *N*-1-phenylethyl substituents had a remarkable effect on the enantioselectivity (Table 1, entries 3 and 4). It was found that *N*-(*S*)-1-phenylethyl-substituted catalyst **4d** was more effective to give the *R* product with an ee of 96%, while *N*-(*R*)-1-phenylethyl-substituted catalyst **4c** led to low conversion and poor enantioselectivity. Simple structural modifications of the *N*-alkyl substituents of **4a**–**d** had a significant impact on the stereochemical outcome of the addition.

Table 1 Enantioselective Addition of 4-Chlorobenzaldehyde



Entry[a]	Solvent	Catalyst (mol%)	Temp	Conv. (%)[b]	ee (%)[c,d]
1	*t*-BuOMe	**4a** (5)	r.t.	13	6
2	*t*-BuOMe	**4b** (5)	r.t.	98	92
3	*t*-BuOMe	**4c** (5)	r.t.	20	32
4	*t*-BuOMe	**4d** (5)	r.t.	100	96
5	toluene	**4d** (5)	r.t.	100	94
6	*n*-hexane	**4d** (5)	r.t.	100	96
7	THF	**4d** (5)	r.t.	27	26
8	Et_2O	**4d** (5)	r.t.	100	94
9	*t*-BuOMe	**4d** (3)	r.t.	90	93
10	*t*-BuOMe	**4d** (2)	r.t.	93	89
11	*t*-BuOMe	**4d** (1)	r.t.	92	86
12	*t*-BuOMe	**4d** (5)	0 °C	36	94

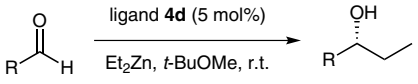
[a] Reactions run for 5 h.
[b] Conversion (%) was determined by ^{1}H NMR analysis of the reaction mixture.
[c] Determined by CSP-HPLC (Chiralcel OJ-H).
[d] Absolute configuration (*R*) assigned by comparison with known elution order reported in the literature.[2]

To obtain optimal conditions for the reaction of *N*-methyl-*N*-(*S*)-1-phenylethyl-substituted catalyst **4d**, we examined experimental parameters such as solvent, molar ratio of the catalyst, and reaction temperature as shown in entries 5–12 (Table 1). Among the solvents examined, *n*-hexane was found to give the same enantioselectivity as *t*-BuOMe for chiral catalyst **4d**, and the reaction in THF gave the lowest enantioselectivity (26% ee) with 5 mol% catalyst loading (Table 1, entries 6 and 7). Decreasing the catalyst loading to 3 mol% was not satisfactory and gave a slightly lower ee of 93% (Table 1, entry 9). Significant decrease in enantioselectivity was observed in the reactions with 2 mol% and 1 mol% of **4d** (Table 1, entries 10 and 11). We found that the reaction at 0 °C took place slowly with a slightly abated enantioselectivity (Table 1, entry 12). Thus, the use of two equivalents of diethylzinc in *t*-BuOMe at room temperature with 5 mol% catalyst loading was taken as the optimal conditions for the addition with **4d**.

With the identification of chiral catalyst **4d** as an effective catalyst for the stereoselective addition of diethylzinc to

4-chlorobenzaldehyde, the substrate scope of the enantioselective reaction was examined as shown in Table 2. The reactions of 4-bromobenzaldehyde, 4-fluorobenzaldehyde, 4-cyanobenzaldehyde, 4-trifluoromethylbenzaldehyde, and 4-methylbenzaldehyde provided the corresponding (*R*)-propanols with almost the same enantioselectivity as the reaction with 4-chlorobenzaldehyde (Table 2, entries 1–5). However, the reaction of 4-methoxybenzaldehyde resulted in the decreased enantioselectivity of 80% ee (Table 2, entry 6). Among the reactions of 2- or 3-substituted benzaldehydes, high stereoselectivities were observed in the reactions with 2-methoxy-, 3-methoxy-, and 3-bromobenzaldehydes, whereas mild drops in stereoselectivity were seen with 2-bromobenzaldehyde, 3-methylbenzaldehyde, 1-naphthaldehyde, and 2-naphthaldehyde (Table 2, entries 7–13). Also, lower enantioselectivities of 80% ee and 79% ee were observed in the reactions of both cinnamaldehyde and α-methylcinnamaldehyde (Table 2, entries 14 and 15). Curiously, a much lower enantioselectivity was observed in the reaction with benzaldehyde (Table 2, entry 16).

Table 2 Reactions of Various Aldehydes with Chiral Catalyst **4d**



Entry[a]	R	Conv. (%)[b]	ee (%)[c,d]
1	4-BrC_6H_4	92	94
2	4-FC_6H_4	100	90
3	4-NCC_6H_4	100	94
4	4-$F_3CC_6H_4$	89	93
5	4-MeC_6H_4	52	91
6	4-$MeOC_6H_4$	80	80
7	2-$MeOC_6H_4$	70	91
8	3-$MeOC_6H_4$	95	95
9	3-BrC_6H_4	81	92
10	2-BrC_6H_4	99	86
11	3-MeC_6H_4	53	88
12	1-Naph	84	85
13	2-Naph	90	87
14	(*E*)-PhCH=CH	95	80
15	(*E*)-PhCH=C(Me)	72	79
16	Ph	40	55

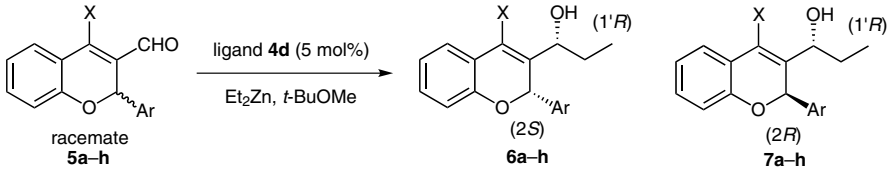
[a] Reactions run for 5 h.
[b] Conversion (%) was determined by ^{1}H NMR analysis of the reaction mixture.
[c] Determined by CSP-HPLC (Chiralcel OB-H or OJ-H).
[d] Absolute configuration (*R*) assigned by comparison with known elution order reported in the literature.[2]

Given the high levels of enantioselectivity attained in the asymmetric addition of diethylzinc to various aldehydes with chiral catalyst **4d**, we examined whether racemic flavene-3-carbaldehydes **5a**–**h** bearing an additional chiral center at the 2-position might be good substrates for kinetic resolution (Table 3). To the best of our knowledge, there is no successful example of kinetic resolution of racemic aldehydes by addition with dialkylzinc.[9] The flavene (2-phenyl-2*H*-chromene) structural core is a widespread element in natural flavonoids, and the development of asymmetric synthetic strategies for highly functionalized flavenes is of considerable interest.[10,11] Efficient kinetic resolution in the addition to flavene-3-carbaldehydes can allow both the unconverted aldehydes **5** and flavenyl alcohols **6** and **7** to be obtained in highly enantioenriched forms.

When racemic flavene-3-carbaldehyde **5a** was treated with diethylzinc and chiral catalyst **4d** for three hours, the addition proceeded in 51% conversion to provide a diastereomeric mixture (79:21 dr) of 3-flavenyl-substituted propanols **6a** and **7a** with 93% ee and 95% ee, respectively. Kinetic resolution in the asymmetric addition favoring (*S*)-**5a** proceeded with a selectivity factor (*s*) of 5, where the unreacted (*R*)-flavene-3-carbaldehyde **5a** was recovered with 52% ee as shown in Table 3 (entry 1).[11,12] Based on the *R*-configuration of the recovered aldehyde and the assumption that the *re*-face of flavene-3-carbaldehyde is preferentially attacked to form the (*R*)-propanol, the absolute configurations of the major enantiomers of **6a** and **7a** are provisionally assigned as (2*S*,1′*R*) and (2*R*,1′*R*), respectively.[13]

We then probed the influence of the substituent on the flavene scaffold. When the kinetic resolution of flavenes **5b**–**d** having different 2-aryl groups was explored using chiral catalyst **4d**, similar results to those of the reaction of **5a** were obtained with selectivities of 4–6 (Table 3, entries 2–4). The high enantioselectivity and relatively low diastereoselectivity indicates that the stereocontrol is mainly governed by the chirality of the catalyst and that the stereogenic center at the 2-position of the flavene scaffold plays only a minor role in the reactions of **5a**–**d**.[14] In addition, the same experimental procedure was applied to the kinetic resolution of flavenes **5e**–**h** having 4-chloro substituent. The reaction of **5e** for three hours showed 46% conversion with chiral catalyst **4d** and produced a diastereomeric mixture (98:2 dr) of **6e** and **7e** with 72% ee and 83% ee, respectively (Table 3, entry 5). The analogous reactions of 4-chloro-substituted flavene carbaldehydes **5f**–**h** gave similar results as shown in entries 6–8 (Table 3), in which higher diastereoselectivity was obtained, but with lower enantioselectivity in comparison with the reactions of **5a**–**d**. Notably high efficiency in kinetic resolution was obtained with 4-chloro substituted flavenes **5e**–**h**, affording selectivity values ranging from 12 to 9.[15] Limited results indicate that the 4-chloro substituent exerts some impact on the stereoselectivity, and the substrate-controlled addition is more operative in the reactions of **5e**–**h**,

Table 3 Kinetic Resolution of Flavene-3-carbaldehydes **5a–h**



Entry[a]	Aldehyde	Conv. (%)[b]	ee (%) of recovered (*R*)-**5**[c]	Selectivity factor *s*[d]	dr of **6**/**7**[b]	ee (%)[c]
1	**5a** Ar = Ph, X = H	51	52	5	79:21	**6a** 93 **7a** 95
2	**5b** Ar = 4′-MeOC$_6$H$_4$, X = H	61	63	4	77:23	**6b** 94 **7b** 96
3	**5c** Ar = 2′-MeOC$_6$H$_4$, X = H	54	48	4	72:28	**6c** 96 **7c** 97
4	**5d** Ar = 4′-ClC$_6$H$_4$, X = H	40	40	6	84:16	**6d** 89 **7d** 89
5	**5e** Ar = Ph, X = Cl	46	60	9	98:2	**6e** 72 **7e** 83
6	**5f** Ar = 4′-MeOC$_6$H$_4$, X = Cl	64	95	12	95:5	**6f** 75 **7f** 76
7	**5g** Ar = 2′-MeOC$_6$H$_4$, X = Cl	46	61	12	98:2	**6g** 87 **7g** 74
8	**5h** Ar = 4′-ClC$_6$H$_4$, X = Cl	47	61	11	97:3	**6h** 79 **7h** 99

[a] Reactions run for 3 h at r.t. with 2 equiv of diethylzinc.
[b] Conversion (%) was determined by direct ^{1}H NMR analysis of the crude mixture.
[c] The ee values were determined by CSP-HPLC.
[d] Selectivity (*s*) values represent an average of at least two experiments, while conversion and ee are for specific cases.

contrary to the strong catalyst-controlled enantiodifferentiation observed in the reactions of **5a–d**.

In summary, we have reported a novel synthetic method for *N*,*N*-dialkyl 2-amino-1,1,2-triphenyl ethanol catalysts and developed a new efficient chiral catalyst **4d** for the additions of diethylzinc to aldehydes. In addition, we presented the first example of catalytic kinetic resolution of racemic aldehydes in the reaction with dialkylzinc. The interesting kinetic resolution affords densely functionalized flavene derivatives that can be transformed into more complex molecules. Further investigation of the extension of the kinetic resolution to various racemic aldehydes and its application to the syntheses of biologically interesting molecules is under way.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett. Included are detailed experimental procedures and characterization data (NMR spectra and HPLC chromatogram).

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(6) **Preparation of Chiral Catalyst 4d**
To a solution of 1:1 diastereomeric mixture of 2-bromo-2-phenylacetic acid (*R*)-pantolactone ester **2** in dry CH_2Cl_2 (0.1 M) at r.t. was added (*S*)-1-phenylethylamine (1.2 equiv), TBAI (1.0 equiv), and DIPEA (1.0 equiv). After the resulting reaction mixture was stirred at r.t. for 12 h, the solvent was evaporated, and the crude material was purified by column chromatography on silica gel to give **3d** in 71% yield with 99:1 dr. To a solution of **3d** in DMF at r.t., MeI (2.0 equiv) and DIPEA (1.2 equiv) were added slowly. The resulting reaction mixture was stirred at r.t. for 24 h. After the mixture was concentrated, the crude product was dissolved in anhyd THF. To the solution of the product was added a solution of PhMgBr (4.0 equiv). The reaction was then allowed to proceed at r.t. for 24 h. The reaction was quenched by the addition of 1 M aq HCl and extracted with EtOAc. The combined organic extracts were dried with anhyd $MgSO_4$, filtered, and concentrated in vacuo. Chromatographic separation on silica gel afforded the chiral catalyst **4d** with 41% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–6.87 (m, 20 H), 5.68 (s, 1 H), 4.98 (s, 1 H), 3.49 (q, *J* = 6.8 Hz, 1 H), 1.88 (s, 3 H), 1.15 (d, *J* = 6.8 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.7, 146.1, 142.6, 138.4, 131.0, 128.2, 128.1, 127.9, 127.5, 127.3, 127.0, 126.8, 126.4, 126.3, 125.4, 125.3, 79.1, 74.0, 59.8, 35.3, 15.5. HRMS: *m/z* calcd for $C_{29}H_{30}NO$ [M^+ + 1]: 408.2327; found: 408.2329..

(7) **General Procedure for the Addition of Diethylzinc to Aldehydes**
Diethylzinc (1.0 M in toluene, 2.0 equiv) was added to a solution of chiral catalyst (0.05 equiv) and aldehyde (1.0 equiv) in *t*-BuOMe at 0 °C. The homogeneous solution was stirred at r.t. for 5 h (3 h for kinetic resolution). The reaction was quenched by addition of 1 M aq HCl and extracted with $CHCl_3$. The combined organic extracts were dried with anhyd $MgSO_4$, filtered, and concentrated in vacuo. Chromatographic separation on silica gel (eluent hexane–EtOAc) afforded the enantioenriched ethanols, and the enantioselectivity of the products was measured by HPLC with chiral columns using racemic material as a standard (eluent: *i*-PrOH in hexane; 0.5 mL/min, 217 nm UV detector).

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(12) The selectivity factor (*s*) was estimated using the equation, $s = k_S/k_R = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$, where ee is the enantiomeric excess of unconverted aldehyde **5** and the conversion (*C*) determined by ^{1}H NMR of reaction mixture.

(13) The absolute configuration at the 2-position of major enantiomers of **6a** and **7a** was confirmed by the reaction of highly enantioenriched (*R*)-**5a** with diethylzinc.

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(15) The use of commercially available (*S*)-2-piperidino-1,1,2-triphenylethanol for the kinetic resolution of flavenes **5e**–**h** gave selectivity values ranging from 4 to 6.

