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Discovery of chiral catalysts by asymmetric activation for highly enantioselective diethylzinc addition to imines: using racemic and achiral diimines as effective activators

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Abstract—A library of chiral zinc complexes formed in situ by the combination of achiral and racemic diimines with 3,3′-di(3,5-ditrifluoromethylphenyl)-BINOL and diethylzinc were evaluated in the asymmetric addition of diethylzinc to *N*-acylimines. In the presence of 10 mol % of chiral ligand **4** and racemic diimine **5**, high enantioselectivities of up to 97% ee and yields of up to 96% were achieved for a wide range of aromatic imines in dichloromethane at −30 °C.

1. Introduction

The synthetic usefulness of enantiomerically pure amines in the preparation of biologically active compounds,[1] and as resolving reagents and auxiliaries for asymmetric synthesis[2] has stimulated great interest in the development of efficient methods for preparing such molecules asymmetrically.[3] The catalytic asymmetric addition of organometallic reagents to C=N bonds is amongst the most important reactions for the synthesis of optically active amines. The enantioselective addition of simple diorganozinc reagents to imines has recently received much attention,[4–8] because of the good tolerance of various functionalities with respect to organolithiums and Grignard reagents. Although considerable effort has been focused on this approach, stoichiometric amounts of chiral ligands were usually required to obtain high conversion and enantioselectivity[4] until a small number of chiral catalysts or ligands were recently discovered for the catalytic asymmetric addition of simple diorganozincs to *N*-sulfonylimines,[5] *N*-arylimines,[6] *N*-acylimines,[7] and *N*-diphenylphosphinoylimines.[8] Of these catalytic processes, the zinc complex of [2.2]-paracyclophane-based *N*,*O*-ligand-catalyzed addition of diorganozinc to *N*-acylimines is the only case, which does not require an additional transition metal besides zinc, and gives high enantioselectivity (up to 95% ee).[7] In sharp contrast, a large number of *N*,*O*-ligands, in particular amino alcohols, have been used in the catalytic asymmetric addition of dialkylzincs to C=O bonds.[9] Thus, the design of new efficient catalysts for catalytic asymmetric dialkylzinc additions to imines is of fundamental importance. Asymmetric activation has become an important platform for engineering chiral catalysts to activate carbonyl substrates, however, this concept has rarely been applied to the development of chiral catalysts for asymmetric nucleophilic additions to imines.[10] Recently, we found a zinc complex that was generated in situ by the combination of 3,3′-di(3,5-ditrifluoromethylphenyl)-BINOL **2** and enantiomerically pure diimines **1a** with diethylzinc, which catalyzed the addition of diethylzinc to acylimines in high enantioselectivities (up to 94% ee) (Fig. 1).[11] The major drawback of this process is the use of an enantiomerically pure diimine as the activator. We also observed that the use of **1b**, the enantiomer of **1a**, to activate the zinc complex of **2** gave the same enantioselectivity as **1a**, indicating that the enantiomeric excess or the configuration of the diimine might be unnecessary for

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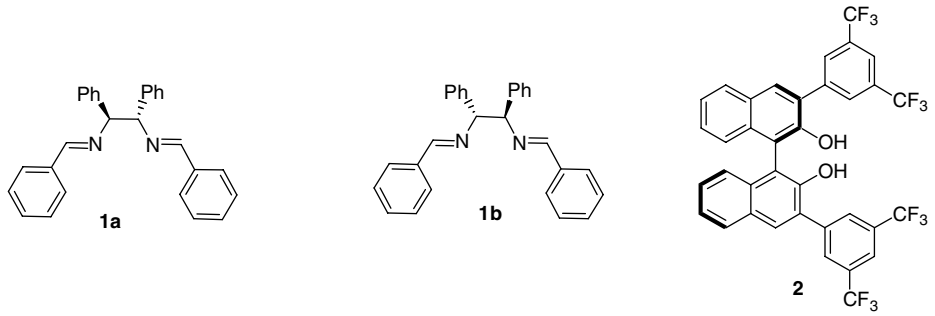


Figure 1. The previously reported enantiomerically pure diimines and a BINOL derivative for building up combined zinc catalysts.[11]

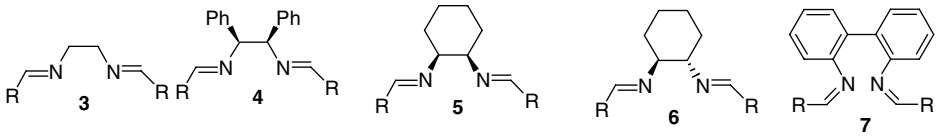


Figure 2. Achiral and racemic diimines evaluated as activators in this study.

controlling the enantioselectivity. Thus, we further speculated that racemic and achiral imines might activate the zinc complex of **2** as efficiently as enantiomerically pure diimines. Walsh et al. have used a similar strategy to engineer catalysts for the addition of diethylzinc to aldehydes.[12] To advance our speculation, and inspired by Walsh's work,[12] we report herein, the evaluation of combined zinc catalysts of racemic and achiral imines **3**–**7** (Fig. 2) with 3,3′-di(trifluoromethylphenyl)-BINOL **2** for the catalytic asymmetric addition of diethylzinc to imines. As a result, we discovered a new efficient catalyst, which promotes the reaction with excellent enantioselectivities of up to 97% ee.

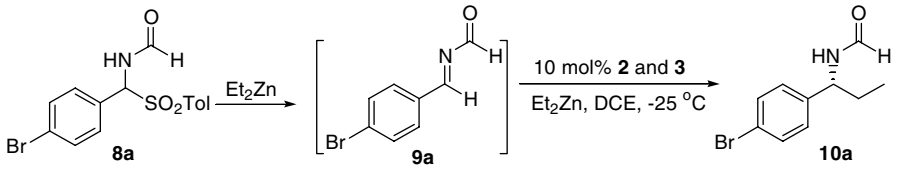
2. Results and discussion

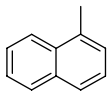
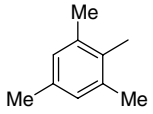
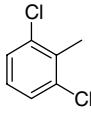
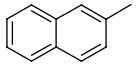
Achiral diimies **3**–**7** were prepared in high yields by the condensation of the corresponding diamines with aldehydes following a reported procedure.[12] Initially, we screened simple achiral ligands **3** for activating the zinc complex of **2**. The resulting combined zinc complexes were used to catalyze the asymmetric addition of diethylzinc to 4-bromophenylacylimine **9a** in 1,2-dichloroethane at −25 °C.[11] As shown in Table 1, the achiral ligands are highly efficient at activating the zinc complex of **2**. Thus, product **10a** was obtained in high yields with the zinc complex of **2** by adding achiral diimines **3a**–**e**. The size of the substituent on the diimine ligands dramatically affects the enantioselectivity. The use of a diimine with bulky substituents resulted in both a comparably low yield and enantioselectivity (entry 2, 61% yield, 38% ee). Among this series of achiral diimine activators **3a**–**e**, **3e** can be considered a better ligand, which in combination with diethylzinc and **2**, catalyzed the model reaction in high yield and enantioselectivity (entry 5, 82% yield, 92% ee). However, a very low enantioselectivity of 21% ee was obtained with the zinc complex of **2** in the absence of any diimine activator (entry 6).

The *meso*-diimines **4** and **5a** derived, respectively, from (1*R*,2*S*)-1,2-diphenyl-ethane-1,2-diamine and *cis*-cyclohexane-1,2-diamine are fundamentally different from achiral imines **3** since they have stereocenters, but as seen in Table 2, they activated the zinc complex of **2** as effectively as achiral diimines **3**. The combined zinc complexes of **2** with *meso*-diimines **4a**–**c** showed a substituent effect with regard to the enantioselectivity, similar to the findings with simple achiral diimines **3a**–**e** as activators. Diimine **4b**, which bears a bulky 2,4,6-trimethylphenyl group, in combination with diethylzinc and ligand **2** led to a zinc complex, which catalyzed the model reaction with lower enantioselectivity (entry 2, 82% ee) relative to the results with its structural analogues **4a** and **4c**. With ligand **4c** derived from benzaldehyde, a high enantioselectivity of 92% ee similar to that reported previously with **1a**, an enantiomerically pure diastereomer of **4c**,[11] was observed. Thus, as we speculated, neither the enantiomeric purity nor configuration of the diimine activator is very important for the stereocontrol of the combined catalyst. In the presence of diimine **5a** derived from *cis*-cyclohexane-1,2-diamine and 2,6-dichlorobenzaldehyde the enantioselectivity is 93% ee (entry 4).

Racemic diimines **6a**–**d**, which were derived from racemic *trans*-cyclohexane-1,2-diamine, were also used for the activation of the chiral zinc complex of **2** (Table 2, entries 5–9). The substituent-effects on both catalytic activity and enantioselectivity are similar to those with achiral ligands **3** and **4** based on the experimental data shown in Table 2, entries 5–8. With diimine **6b**, which bears a bulkier substituent, a lower enantioselectivity (entry 6, 87% ee) was seen than with its structural analogues **6a** and **6c**–**d** (entries 5, 7 and 8, 91–94% ee). The best catalyst among those with diimines **4**–**6** as activators was the zinc complex of **2** combined with diimine **6d**, which was derived from racemic *trans*-cyclohexane-1,2-diamine and naphthalene-2-carbaldehyde. An ee value of as high as 94% was observed with this catalyst

Table 1. Screening simple achiral diimine activators **3a**–**e**[a]



Entry	Activators	R	Yield[b] (%)	ee[c] (%)
1	**3a**		71	75
2	**3b**		61	38
3	**3c**		81	90
4	**3d**		73	84
5	**3e**		82	92
6	—	—	66	21

[a] Unless otherwise specified, the reaction was performed on a 0.1 mmol scale with 3 equiv diethylzinc (1.0 M in hexane) in 1,2-dichloroethane at −25 °C for 36 h.
[b] Isolated yield based on the imine precursor **8a**.
[c] Determined by GC.

(entry 8). The best enantioselectivity of 96% ee was obtained at −30 °C in dichloromethane (entry 9).

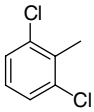
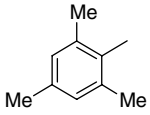
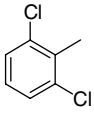
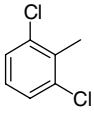
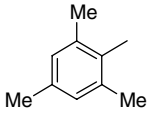
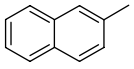
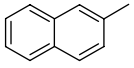
Biphenyl-2,2′-diamine-based achiral diimines **7a**–**d** were also examined. These achiral diimines, in which the axial chirality is generated when they coordinate with chiral transition metal complexes,[12,13] are distinct from simple achiral ligands **3**. As shown in Table 3, this class of achiral ligands shows different trends in the substituent effect on the enantioselectivity from the achiral diimines **3**–**5a** and racemic diimines **6**. The lowest enantioselectivity (27% ee) was obtained with the diimine derived from naphthalene-2-carbaldehyde (entry 3). A high enantioselectivity of 91% ee was also induced in the presence of diimine **7b**, which is derived from 2,6-dichlorobenzaldehyde (entry 2).

The results obtained with diimines **4**–**7** confirm that a chiral backbone is unnecessary for the enantioselectivity; in contrast, an appropriate substituent is crucial for the catalytic performance of the combined zinc complexes. For example, the catalysts derived from **3e**, **4c**, **5a**, **6d**, and **7b**, which contain a distinct backbone, all promoted the model reaction with high enantioselectivities (91–94% ee). These observations are apparently different from those for the asymmetric addition of diethylzinc to aldehydes catalyzed by similar combined zinc complexes.[12] In those cases, diimines based on *meso*-diamines and biphenyl-2,2′-diamine with a flexible chirality are more enantioselective than the simple diimines. In terms of the yield and enantioselectivity, diimines **5a** and **6d** can be considered better ligands.

The combined catalyst of diethylzinc, 3,3′-di(3,5-bistrifluoromethylphenyl)-BINOL and either **5a** or **6d** was subsequently extended to a range of imine precursors bearing either electron-donating or electron-withdrawing groups with 10 mol % loading under optimal conditions. The results are summarized in Table 4. These catalysts generally show high enantioselectivity for the imines tested regardless of the electronic-nature and steric hindrance of the substituent. With the exception of *N*-benzylidene-formamide **9d**, ee values of 90–97% were obtained with the remaining imines. Interestingly, these catalysts are more enantioselective than those with enantiomerically pure diimine **1a** as the activator.[11]

In summary, the combined catalysts of diethylzinc, 3,3′-di(3,5-bistrifluoromethylphenyl)-BINOL **2** and diimines derived from achiral and racemic diamines were for the first time screened for their ability to catalyze the asymmetric catalytic addition of diethylzinc to *N*-acylimines. *meso*-Diimine **5a** and racemic diimine **6d** are two of better ligands for activating the zinc complex of **2**. High

Table 2. Screening *meso* and racemic diimine activators **4–6**[a]

Entry	Activators	R	Yield[b] (%)	ee[c] (%)
1	**4a**		78	88
2	**4b**		63	82
3	**4c**		82	92
4	**5a**		83	93
5	**6a**		88	92
6	**6b**		73	87
7	**6c**		88	91
8	**6d**		83	94
9	**6d**		**89**	**96**[d]

[a] Unless otherwise specified, the reaction is the same as that illustrated in Table 1.
[b] Isolated yield based on the imine precursor **8a**.
[c] Determined by GC.
[d] The reaction was performed at −30 °C in dichloromethane.

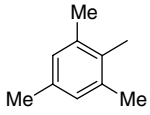
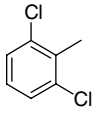
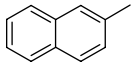
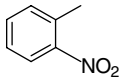
enantioselectivities of up to 97% ee and high yields of up to 96% were obtained for a wide range of aromatic imines. These results confirm that the enantiomeric purity of the diimines is unnecessary for the catalytic performance of the combined catalysts. Thus, our finding may provide some insight into the development of new catalysts for asymmetric addition to imines.

3. Experimental

3.1. General methods

^{1}H and ^{13}C NMR spectra were recorded on a Brucker-300 (300/75 MHz) spectrometer. Optical rotations were measured with a Perkin–Elmer 341 Polarimeter in a 10 cm cell with the solvent indicated. Melting points were measured on an electrothermal digital melting point apparatus. IR spectra were recorded on a NICOLET MX-1E FT-IR. Mass spectra were recorded on a Brucker BioTOF Q. Elemental analyses were carried out using Carlo Erba-1106 Analyzer. Chiral GC analyses were performed on a VARIAN CP-3380 using a CP-Chirasil Dex column.

Table 3. Screening the diimine activators **7** with flexibly axial chirality[a]

Entry	Activators	R	Yield[b] (%)	ee[c] (%)
1	**7a**		77	84
2	**7b**		82	91
3	**7c**		65	27
4	**7d**		70	53

[a] Unless otherwise specified, the reaction is the same as that illustrated in Table 1.
[b] Isolated yield based on the imine precursor **8a**.
[c] Determined by GC.

All reactions were conducted in a flame-dried glassware under an atmosphere of dry argon. All chemicals and solvents were used as received unless otherwise stated. THF (Na, benzophenone), toluene (Na, benzophenone), CH_2Cl_2(CaH_2), $ClCH_2CH_2Cl$(CaH_2) were distilled under argon from the drying agent indicated. The *N*-formyl-α-(*p*-tolylsulfonyl)-benzylamines were prepared according to the literature procedures.[14] The absolute configurations of amides **10** were assigned by the comparison of specific rotations with the literature values.[7a]

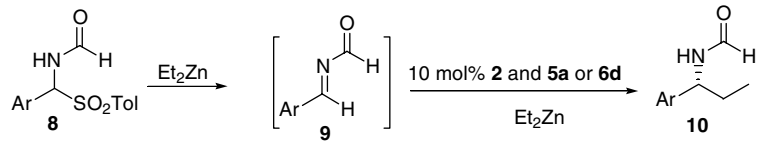
3.2. Synthesis of new achiral diimines 3a–e, 4a–c, 5, 7a–c[12b] and 6a–d

3.2.1. General procedure. The diamine (1.00 mmol) and the corresponding aldehyde (2.00 mmol) were dissolved in methanol (10 mL) and stirred under reflux for 5 h to produce a precipitate. The reaction mixture was cooled down to room temperature and the Schiff base isolated by filtration and purified by recrystallization from a solvent mixture of dichloromethane and hexane.

3.2.2. *N*,*N*′-Bis(2,6-dichlorobenzylidiene)-(±)-*trans*-1,2-diaminocyclohexane 6a. Yield: 87%; white solid, mp133–136 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.53 (m, 4H), 1.88 (m, 6H), 3.60 (m, 2H), 7.16 (t, $J = 7.0$ Hz, 2H), 7.29 (d, $J = 7.9$ Hz, 2H), 8.47 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 24.20, 32.83, 74.89, 128.56, 129.91, 132.85, 134.80, 156.53.

3.2.3. *N*,*N*′-Bis(2,4,6-trimethylbenzylidiene)-(±)-*trans*-1,2-diaminocyclohexane 6b. Yield: 85%; white solid, mp 142–145 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.50 (m, 2H), 1.83 (m, 8H), 2.23 (s, 6H), 2.24 (s, 12H),

Table 4. Asymmetric addition of diethylzinc to imines[a]



Entry	Imines **9** (Ar)	Method[b]	Yield[c] (%)	ee[d] (%)
1	4-BrC_6H_4 **9a**	A	89	96
2	3-BrC_6H_4 **9b**	A	91	97
3	3-ClC_6H_4 **9c**	A	91	95
4	C_6H_5 **9d**	B	90	88
5	4-ClC_6H_4 **9e**	A	96	94
6	4-MeC_6H_4 **9f**	B	90	91
7	4-$MeOC_6H_4$ **9g**	B	91	90
8	4-CNC_6H_4 **9h**	A	84	92
9	4-$CF_3C_6H_4$ **9i**	A	93	94
10	4-$MeO_2CC_6H_4$ **9j**	A	71	93

[a] Unless otherwise specified, the reaction was performed on a 0.2 mmol scale with 3 equiv diethylzinc (1.0 M in hexane).
[b] Method A: The reaction was performed with diimine **6d** as an activator in dichloromethane at −30 °C; Method B: The reaction was performed with diimine **5a** as an activator in 1,2-dichloroethane at −25 °C.
[c] Isolated yield based on products **10** and imine precursors **8**.
[d] Determined by GC and the absolute configuration is assigned as *R* by comparison of the specific rotations with those in the literature.[7]

3.42 (m, 2H), 6.77 (s, 4H), 8.54 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 20.58, 21.04, 24.52, 33.56, 75.61, 129.11, 132.24, 137.32, 138.18, 160.22.

3.2.4. *N*,*N*′-Bis(benzylidiene)-(±)-*trans*-1,2-diaminocyclohexane 6c. Yield: 81%; white solid, mp 141–143 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.50 (m, 4H), 1.87 (m, 6H), 3.41 (m, 2H), 7.31 (m, 6H), 7.58 (m, 4H), 8.21 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 24.44, 32.91, 73.76, 127.86, 128.32, 130.16, 136.31, 160.98.

3.2.5. *N*,*N*′-Bis(2-naphthylidiene)-(±)-*trans*-1,2-diaminocyclohexane 6d. Yield: 90%; white solid, mp 196–200 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.55 (m, 4H), 1.93 (m, 6H), 3.51 (m, 2H), 7.41 (m, 4H), 7.73 (m, 6H), 7.86 (m, 4H), 8.37 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 24.51, 33.00, 73.93, 123.87, 126.16, 126.77, 127.65, 128.15, 128.45, 129.39, 132.95, 133.91, 134.41, 161.15.

3.3. General procedure for the asymmetric diethylzinc addition to imines

A flame-dried vial (10 mL) was charged with ligand **2** (14.2 mg, 0.02 mmol), activator **6d** (7.8 mg, 0.02 mmol) and *N*-[4-bromophenylbenzyl(toluene-4-sulfonyl)methyl]formamide **8a** (74 mg, 0.2 mmol). After the vial was flushed with argon, CH_2Cl_2 (1.0 mL) was added. After the mixture was stirred at −30 °C for 30 min, diethylzinc (0.7 mL, 0.7 mmol, 1 M in hexane) was added. After being stirred at −30 °C for 36 h, the reaction was quenched with HCl (2.0 M, 2 mL). The organic layer was washed with 2.0 M HCl, brine and dried over Na_2SO_4. After removal of the solvent in vacuo, the residue was purified by column chromatography on silica gel (PE–acetone = 5:1) to give the analytically pure *N*-[1-(4-Bromophenyl)propyl]formamide **10a**. Yield: 89%; white solid, mp 97–100 °C; $[\alpha]_D^{20} = +144.3$ (*c* 0.26 $CHCl_3$); The ^{1}H NMR shows a 6.6:1 mixture of two rotamers (rotation of the *N*-formyl group in solution), major rotamer: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.95 (t, $J = 7.4$ Hz, 3H, CH_3), 1.77–1.89 (m, 2H, CH_2), 4.97 (q, $J = 7.4$ Hz, 1H, CH), 6.09 (br s, 1H, NH), 7.39 (d, $J = 8.3$ Hz, 2H, H_{Ar}), 7.59 (d, $J = 8.3$ Hz, 2H, H_{Ar}), 8.21 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 10.73, 29.04, 53.38, 112.11, 127.48, 131.98, 140.21, 160.56; HRESI-MS (positive ion) $C_{10}H_{12}BrNO$ ($[M+H]^+$) requires 263.9994. Found 263.9988; IR (KBr): $\nu = 3322$ (s), 1661 (s), 1520 (s) cm^{-1}. Anal. Calcd for $C_{10}H_{12}BrNO$: C 49.61, H 5.00, N 5.79. Found: C, 49.30; H, 4.94; N, 5.66. Enantiomeric excess: 96%, determined by GC (CP-Chirasil Dex column, $T_c = 180$ °C, $H_2 = 12$ Psi, *S*-isomer, $t_R = 8.68$ min and *R*-isomer, $t_R = 8.92$ min).

3.3.1. *N*-[1-(3-Bromophenyl)propyl]formamide 10b. Yield: 91%; colorless oil; $[\alpha]_D^{20} = +109.8$ (*c* 1.33, $CHCl_3$); ^{1}H NMR shows a 4.9:1 mixture of two rotamers (rotation of the *N*-formyl group in solution), major rotamer: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.92 (t, $J = 7.4$ Hz, 3H, CH_3), 1.76–1.90 (m, 2H, CH_2), 4.91 (q, $J = 7.4$ Hz, 1H, CH), 6.00 (br s, 1H, NH), 7.12–7.42 (m, 4H, H_{Ar}), 8.19 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 10.72, 29.14, 53.39, 122.91, 125.56, 129.55, 130.40, 130.71, 144.16, 160.63; HRESI-MS (positive ion) $C_{10}H_{12}BrNO$ ($[M+H]^+$) requires 263.9994. Found 263.9985; IR (KBr): $\nu = 3276$ (s), 1660 (s), 1534 (s) cm^{-1}. Enantiomeric excess: 97%, determined by GC (CP-Chirasil Dex column, $T_c = 180$ °C, $H_2 = 12$ Psi, *S*-isomer, $t_R = 6.93$ min and *R*-isomer, $t_R = 7.15$ min).

3.3.2. *N*-[1-(3-Chlorophenyl)propyl]formamide 10c. Yield: 91%; colorless oil; $[\alpha]_D^{20} = +114.8$ (*c* 1.46, $CHCl_3$); ^{1}H NMR shows a 4.4:1 mixture of two rotamers

(rotation of the *N*-formyl group in solution), major rotamer: ^{1}HNMR (300 MHz $CDCl_3$): δ (ppm) 0.92 (t, $J = 7.4$ Hz, 3H, CH_3), 1.74–1.91 (m, 2H, CH_2), 4.93 (q, $J = 7.7$ Hz, 1H, CH), 5.88 (br s, 1H, NH), 7.11–7.32 (m, 4H, H_{Ar}), 8.27 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 10.72, 29.12, 53.42, 125.07, 126.74, 127.80, 130.11, 134.70, 143.83, 160.60; IR (KBr): $v = 3276$ (s), 1660 (s), 1534 (s) cm^{-1}. Enantiomeric excess: 95%, determined by GC (CP-Chirasil Dex column, $T_c = 180$ °C, $H_2 = 12$ Psi, *S*-isomer, $t_R =$ 4.61 min and *R*-isomer, $t_R = 4.73$ min).

3.3.3. *N*-(1-Phenylpropyl)formamide 10d.[7a] Yield: 90%; colorless oil; $[\alpha]_D^{20} = +126.2$ (*c* 0.48, $CHCl_3$); ^{1}H NMR shows a 3.2:1 mixture of two rotamers (rotation of the *N*-formyl group in solution), major rotamer: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.04 (t, $J = 7.4$ Hz, 3H, CH_3), 1.91–2.04 (m, 2H, CH_2), 5.08 (q, $J = 7.4$ Hz, 1H, CH), 6.13 (br s, 1H, NH), 7.35–7.49 (m, 5H, H_{Ar}), 8.31 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 10.79, 29.18, 53.85, 126.70, 127.62, 128.82, 141.67, 160.59; Minor rotamer: ^{1}HNMR (300 MHz, $CDCl_3$): δ (ppm) 1.07 (t, $J = 7.4$ Hz, 3H, CH_3), 1.91–2.04 (m, 2H, CH_2), 4.48 (q, $J = 7.4$ Hz, 1H, CH), 6.55 (br s, 1H, NH), 7.35–7.49 (m, 5H, H_{Ar}), 8.24 (d, $J = 11.9$ Hz, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 10.79, 30.42, 58.21, 126.30, 127.86, 129.00, 141.67, 164.60. Enantiomeric excess: 88%, determined by GC (CP-Chirasil Dex column, $T_c = 160$ °C, $H_2 = 12$ Psi, *S*-isomer, $t_R = 4.77$ min and *R*-isomer, $t_R = 4.89$ min).

3.3.4. *N*-[1-(4-Chlorophenyl)propyl]formamide 10e. Yield: 96%; white solid, mp 97–100 °C; $[\alpha]_D^{20} = +130.6$ (*c* 0.68, $CHCl_3$); ^{1}H NMR shows a 3.9:1 mixture of two rotamers (rotation of the *N*-formyl group in solution), major rotamer: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.93 (t, $J = 7.4$ Hz, 3H, CH_3), 1.78–1.90 (m, 2H, CH_2), 4.93 (q, $J = 7.4$ Hz, 1H, CH), 5.76 (br s, 1H, NH), 7.21–7.24 (d, $J = 6.7$ Hz, 2H, H_{Ar}), 7.30–7.32 (d, $J = 6.7$ Hz, 2H, H_{Ar}), 8.21 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 10.70, 29.09, 53.37 (t, CH), 128.13, 129.03, 133.43, 140.17, 160.71. Anal. Calcd for $C_{10}H_{12}ClNO$: C, 60.76; H, 6.12; N, 7.09. Found C, 60.58; H, 6.08; N, 7.06. Enantiomeric excess: 94%, determined by GC (CP-Chirasil Dex column, $T_c = 180$ °C, $H_2 = 12$ Psi, *S*-isomer, $t_R = 5.82$ min and *R*-isomer, $t_R = 5.95$ min).

3.3.5. *N*-[1-*p*-Tolypropyl]formamide 10f.[7a] Yield: 90%; colorless oil; $[\alpha]_D^{20} = +122.3$ (*c* 0.54, $CHCl_3$); ^{1}HNMR shows a 3.3:1 mixture of two rotamers (rotation of the *N*-formyl group in solution), major rotamer: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.91 (t, $J = 7.4$ Hz, 3H, CH_3), 1.73–1.87 (m, 2H, CH_2), 2.33 (s, 3H, $ArCH_3$), 4.93 (q, $J = 7.7$ Hz, 1H, CH), 5.84 (br s, 1H, NH), 7.10–7.19 (m, 4H, H_{Ar}), 8.18 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 10.78, 21.19, 29.12, 53.60, 126.64, 129.52, 137.34, 138.64, 160.50. Enantiomeric excess: 91%, determined by GC (CP-Chirasil Dex column, $T_c = 160$ °C, $H_2 = 12$ Psi, *S*-isomer, $t_R = 6.45$ min and *R*-isomer, $t_R = 6.60$ min).

3.3.6. *N*-[1-(4-Methoxyphenyl)propyl]formamide 10g.[7a] Yield: 91%; colorless oil; $[\alpha]_D^{20} = +132.6$ (*c* 0.39, $CHCl_3$); ^{1}H NMR shows a 3.1: 1 mixture of two rotamers (rotation of the *N*-formyl group in solution), major rotamer: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.91 (t, $J = 7.4$ Hz, 3H, CH_3), 1.74–1.90 (m, 2H, CH_2), 3.79 (s, 3H, OCH_3), 4.92 (q, $J = 7.8$ Hz, 1H, CH), 5.85 (br s, 1H, NH), 6.88 (d, $J = 8.7$ Hz, 2H, H_{Ar}), 7.22 (d, $J = 8.7$ Hz, 2H, H_{Ar}), 8.17 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 10.78, 29.07, 53.12, 55.41, 114.20, 127.89, 133.89, 159.04, 160.49. Enantiomeric excess: 90%, determined by GC (CP-Chirasil Dex column, $T_c = 175$ °C, $H_2 = 12$ Psi, *S*-isomer, $t_R = 8.67$, *R*-isomer, $t_R = 8.88$ min).

3.3.7. *N*-[1-(4-Cyanophenyl)propyl]formamide 10h. Yield: 84%; colorless oil; $[\alpha]_D^{22} = +49.3$ (*c* 1.75, $CHCl_3$); ^{1}H NMR shows a 6.5:1 mixture of two rotamers (rotation of the *N*-formyl group in solution), major rotamer: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.90 (t, $J = 7.4$ Hz, 3H, CH_3), 1.77–1.87 (m, 2H, CH_2), 4.97 (q, $J = 7.4$ Hz, 1H, CH), 5.97 (br s, 1H, NH), 7.37–7.40 (d, $J = 8.3$ Hz, 2H, H_{Ar}), 7.60–7.64 (d, $J = 8.3$ Hz, 2H, H_{Ar}), 8.22 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 10.66, 29.01, 53.70, 118.77, 127.44, 132.66, 147.28, 160.71; HRESI-MS (positive ion) $C_{11}H_{12}N_2O$ ($[M+H]^+$) requires 211.0842. Found 211.0849; IR (KBr): $v = 3250$ (s), 2227 (s), 1665 (s), 1550 (s) cm^{-1}. Enantiomeric excess: 92%, determined by GC (CP-Chirasil Dex column, $T_c = 180$ °C, $H_2 =$ 12 Psi, *S*-isomer, $t_R = 23.31$, *R*-isomer, $t_R = 23.74$ min).

3.3.8. *N*-[1-(4-(Trifluoromethyl)phenyl)propyl]formamide 10i. Yield: 93%; white solid, mp 85–88 °C; $[\alpha]_D^{20} = +91.5$ (*c* 0.82, $CHCl_3$); ^{1}H NMR shows a 4.8:1 mixture of two rotamers (rotation of the *N*-formyl group in solution), major rotamer: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.90 (t, $J = 7.4$ Hz, 3H, CH_3), 1.80–1.89 (m, 2H, CH_2), 5.00 (q, $J = 7.4$ Hz, 1H, CH), 5.92 (br s, 1H, NH), 7.38–7.40 (d, $J = 8.3$ Hz, 2H, H_{Ar}), 7.58–7.60 (d, $J = 8.3$ Hz, 2H, H_{Ar}), 8.21 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 10.37, 28.81, 53.26, 125.57, 126.40, 126.71, 145.47, 160.35; HRESI-MS (positive ion) $C_{11}H_{12}F_3NO$ ($[M+H]^+$) requires 254.0763. Found 254.0787; IR (KBr): $v = 3323$ (s), 1662 (s), 1523 (s) cm^{-1}. Enantiomeric excess: 94%, determined by GC (CP-Chirasil Dex column, $T_c = 175$ °C, $H_2 = 12$ Psi, *S*-isomer, $t_R = 3.24$, *R*-isomer, $t_R = 3.39$ min).

3.3.9. 4-(1-Formylaminopropyl)benzoic acid methyl ester 10j.[7a] 71%; white solid, mp 139–141 °C; $[\alpha]_D^{20} = +41$ (*c* 0.57, $CHCl_3$); ^{1}H NMR shows a 5.1:1 mixture of two rotamers (rotation of the *N*-formyl group in solution), major rotamer: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.92 (t, $J = 7.1$ Hz, 3H, CH_3), 1.80–1.90 (p, $J = 7.3$ Hz, 2H, CH_2), 3.91 (s, 3H, CO_2CH_3), 5.00 (q, $J = 7.6$ Hz, 1H, CH), 5.91 (br s, 1H, NH), 7.34 (d, $J = 8.5$ Hz, 2H, H_{Ar}), 7.99 (d, $J = 8.3$ Hz, 2H, H_{Ar}), 8.23 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 10.68, 29.15, 52.34, 53.65, 126.70, 130.10, 130.18, 146.87, 160.63, 166.92. Enantiomeric excess:

93%, determined by GC (CP-Chirasil Dex column, $T_c = 175$ °C, $H_2 = 12$ Psi, *S*-isomer, $t_R = 15.28$, *R*-isomer, $t_R = 15.94$ min).

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