Organocatalytic asymmetric destruction of 1-benzylated Reissert compounds catalysed by quaternary cinchona alkaloids†

Kim Frisch and Karl Anker Jørgensen*

Received 10th July 2007, Accepted 12th July 2007
First published as an Advance Article on the web 6th August 2007
DOI: 10.1039/b710494d

The enantiomeric enrichment of racemic 1-benzylated Reissert compounds under organocatalytic biphasic conditions is presented. The enrichment is the consequence of an asymmetric destruction of the racemic compounds resulting in the formation of the corresponding 1-benzylated isoquinolines. The highest selectivity has been achieved using quaternary cinchona alkaloids as phase-transfer catalysts. The resolution of a number of racemic 1-benzylated Reissert compounds reveals a significant substrate dependence and a proposal for the mechanism of the reaction is presented.

Introduction

Heterocycles derived from isoquinoline have a special focus in organic chemistry;[1] this being due to their abundance in nature[2] and the fact that many display biological activity.[3] Often these compounds are optically active and contain a chiral center in the C-1 position of the isoquinoline ring system.

Reissert compounds, derived from isoquinolines (*i.e.* 2-acyl-1,2-dihydroisoquinoline-1-carbonitriles **1**), are classical examples of synthetic isoquinoline derivatives bearing a C-1 chiral carbon atom. Since the first synthesis of these compounds in 1905 (by the reaction now known as the Reissert reaction),[4] a number of studies on the addition of electrophiles to the C-1 position have appeared in the literature.[5]

In particular, racemic alkylations of Reissert compounds, resulting in products containing a quaternary stereocenter, have appeared frequently.[6] However, it was not until recently that an enantioselective alkylation was reported by Rozwadowska *et al.*[7,8] Under liquid–liquid phase-transfer conditions (*e.g.* 50% aq. NaOH–toluene), they reported on the enantioselective alkylation of racemic Reissert compounds, derived from various chloroformates (*i.e.* R^1 = O-alkyl, OBn, OPh in structure **1**). In the presence of benzyl bromide, the compounds were benzylated with moderate to high yield (68–98%) and low to moderate enantiomeric excess (20–65%) using *N*-benzylcinchoninium bromide as phase-transfer catalyst.

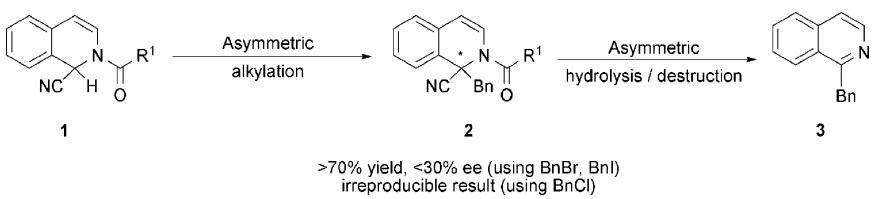
We wondered whether higher enantioselectivities could be obtained with compounds **1** derived from acid chlorides (*i.e.* R^1 = alkyl, Ar) rather than chloroformates due to proximity effects of the R^1 substituent. However, with benzyl bromide or iodide as alkylating agent, high yields (>70%), but low enantiomeric excesses (<30% ee) were obtained for all chiral phase-transfer catalysts and reaction conditions tested (Scheme 1). The low selectivities proved to be the result of racemic background reactions.

Benzyl chloride was tested as well, but with this alkylating agent, only irreproducible results were obtained. To explain this, we examined the reaction more closely and found that the varying results were caused by hydrolysis of the formed products **2**.[9] This reaction, leading to formation of the corresponding 1-substituted isoquinoline **3**, is well-known.[10] However, our investigations revealed that the enantiomers of **2** were hydrolysed at different rates due to the presence of the chiral phase-transfer catalyst; thus giving rise to an enantiomeric enrichment of **2**.

Intrigued by this observation, we set out to investigate, in detail, this novel asymmetric destruction, or in other words kinetic resolution, of 1-benzylated Reissert compounds. In this paper, the results of our investigations are presented.

Results and discussion

We initiated our study of the asymmetric destruction of 1-benzylated Reissert compounds by examining the hydrolysis of

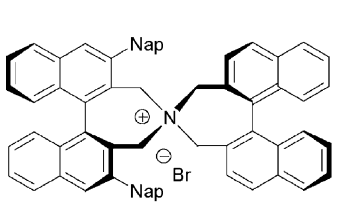


Scheme 1 Asymmetric alkylation of Reissert compounds derived from acid chlorides (R^1 = alkyl, Ar) under alkaline biphasic conditions.

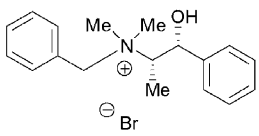
Danish National Research Foundation: Center for Catalysis, Department of Chemistry, Aarhus University, DK-8000, Aarhus C, Denmark. E-mail: kaj@chem.au.dk; Fax: +45 86196199; Tel: +45 89423910

† Electronic supplementary information (ESI) available: Derivation of eqn (2) and the equation (for er *vs.* time) used in Fig. 1a, determination of conversion and *s*-values by HPLC and copies of ^{1}H and ^{13}C NMR spectra for compounds **2a–2k** and **3a–3f**. See DOI: 10.1039/b710494d

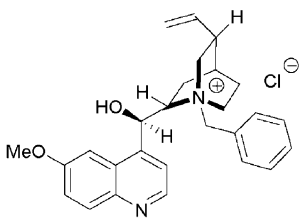
Table 1 Screening of phase-transfer catalysts for the asymmetric destruction of **2a**[a]



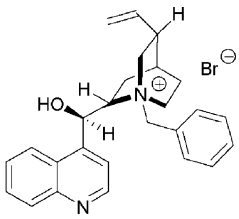
4



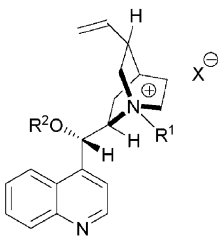
5



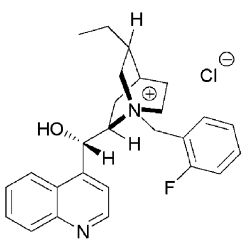
6a



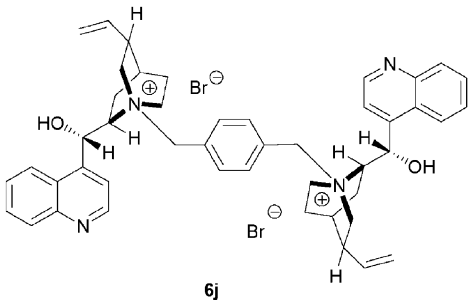
6b



6c-h



6i

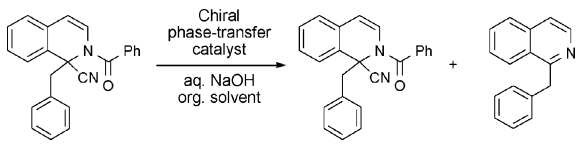


6j

Entry	Catalyst	R^1	R^2	X	Time/h	Conversion[b] (%)	ee[c](%)	*s*[d]
1	None	—	—	—	70	0	0	—
2	**4**	—	—	—	0.2	79	10	1.1
3	**5**	—	—	—	4	47	(−) 4	1.1
4	**6a**	—	—	—	1.5	53	(−) 25	2.0
5	**6b**	—	—	—	3.5	70	(−) 37	1.9
6	**6c**	Bn	H	Cl	4	62	(+) 68	4.7
7	**6d**	Bn	Allyl	Br	42	27	(+) 6	1.5
8	**6e**	Anthracenylmethyl	H	Br	44	27	(+) 6	1.4
9	**6f**	4-OMe-Bn	H	Br	4.5	51	(+) 51	5.0
10	**6g**	4-CF_3-Bn	H	Br	5	52	(+) 60	6.3
11	**6h**	4-NO_2-Bn	H	Cl	9	63	(+) 79	6.2
12	**6i**	—	—	—	5	34	(+) 32	5.7
13	**6j**	—	—	—	4	27	(+) 17	3.1

[a] Reactions were performed with 0.10 mmol **2a** and with 10 mol% phase-transfer catalyst in a mixture of 10 N aq. NaOH and CH_2Cl_2 (1 : 1) at rt. [b] Determined by HPLC. [c] Enantiomeric excess of recovered **2a** determined by chiral HPLC. The parentheses enclose the sign of the optical rotation. [d] Calculated using eqn (2).

racemic **2a** in the presence of a number of chiral phase-transfer catalysts (eqn (1) and Table 1).



2a (racemic) **2a** (non-racemic) **3a** (1)

The selectivities of the catalysts are reported as the stereoselectivity factor $s = k_{fast}^{app}/k_{slow}^{app}$, where k_{fast}^{app} and k_{slow}^{app} are the apparent rate constants for the fastest and the slowest reacting enantiomer of **2a**, respectively. The ratio $k_{fast}^{app}/k_{slow}^{app}$ is determined by the expression given in eqn (2), where "conv" is the conversion of the hydrolysis and ee is the enantiomeric excess of the enriched Reissert compound.

It should be noted that, although the mechanism in this case is considered to be more complex (see mechanistic discussion below), the expression appears similar to the one derived for kinetic resolutions based on simple first order kinetics.[11] Similar *s*-values have been obtained using eqn (2) for different sets of conversion and enantiomeric excess, which indicate that the equation is valid throughout the reaction. This test has been carried out for a number of catalysts and in Fig. 1b, three examples are presented. The figure illustrates the good correlation between the experimental data (dots) and theoretical data (curves) obtained from eqn (2). In fact, the *s*-values calculated from each of the experimental data points varied with no more than ±0.2 within the time-interval studied.

$$s = \frac{k_{fast}^{app}}{k_{slow}^{app}} = \frac{\ln((1-\text{conv})(1-\text{ee}))}{\ln((1-\text{conv})(1+\text{ee}))} \quad (2)$$

Some representative results from the screening of catalysts are reported in Table 1. The screening revealed that derivatives of binaphthyl **4** and ephedrine **5** were less selective than catalysts derived from cinchona alkaloids **6a–j** (entries 2 and 3 *vs.* 4–6).[12] For the latter class, catalysts derived from quinine and cinchonidine were observed to be less selective than catalysts derived from cinchonine (entries 4 and 5 *vs.* 6). For the cinchonine derivatives, the hydroxy-group proved to be essential. For example,

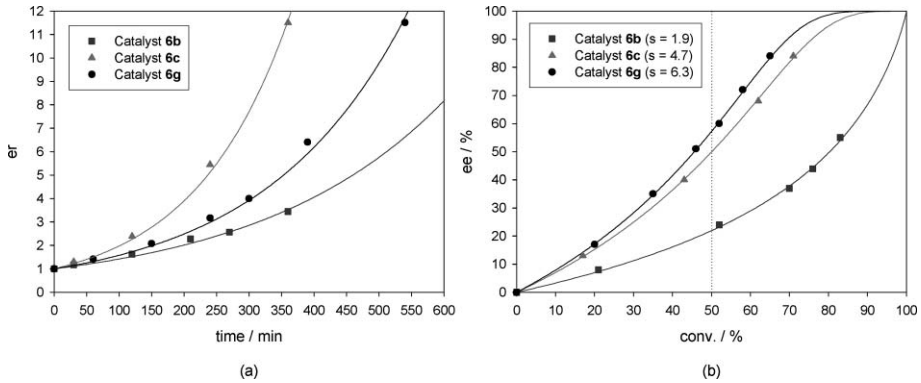


Fig. 1 (a) Plots of enantiomeric ratio (er) *vs.* time and (b) enantiomeric excess (ee) *vs.* conversion for the asymmetric destruction of **2a** in the presence of phase-transfer catalyst **6b**, **6c** or **6g**. Reactions were performed with 0.10 mmol **2a** and with 10 mol% catalyst in a mixture of 10 N aq. NaOH and CH_2Cl_2 (1 : 1) at rt. The dots represent experimental data, while the full lines are obtained from calculations. The er, ee and conversion were measured by chiral HPLC.

significantly higher selectivity was observed for catalyst **6c**, having an unsubstituted oxygen atom, compared to the *O*-allylated **6d** (entry 6 *vs.* 7). For the substituent on the quaternary nitrogen atom, higher selectivity was observed for cinchoninium catalysts quaternised by benzyl rather than anthracenylmethyl (entry 6 *vs.* 8). It was also observed that monomeric catalysts were more selective than dimeric ones (entry 6 *vs.* 13). An increase in the electron density of the *N*-benzyl substituent was not observed to have any effect on the selectivity (entry 6 *vs.* 9). On the other hand, a decrease in the electron density resulted in a higher selectivity (entry 6 *vs.* 10 and 11). This effect was observed to reach a maximum with a CF_3-group in the *para*-position of the aromatic *N*-substituent (entry 10 *vs.* 11).

Thus, the most selective catalyst for the asymmetric hydrolysis of **2a** proved to be the commercially available *N*-(4-trifluoromethylbenzyl)-cinchoninium bromide **6g**, providing a selectivity of $s = 6.3$. This catalyst was selected for further investigations.

In the presence of catalyst **6g**, we monitored the asymmetric hydrolysis of racemic **2a** over time at room temperature (Fig. 1). The results are plotted as the enantiomeric ratio (er) of recovered **2a** *vs.* time in Fig. 1a, and as the enantiomeric excess (ee) *vs.* conversion in Fig. 1b. The plots illustrate, for example, that **2a** is enriched to 11.5 er (*i.e.* 84% ee) within 9 h under the applied conditions (Fig. 1a). At this point, the reaction has proceeded with *ca.* 66% conversion and thus *ca.* 34% enriched **2a** remains (Fig. 1b). As for any non-dynamic kinetic resolution, the maximum possible yield of enantiopure compound is 50% when starting from a racemate. For comparison, the results obtained for the less selective catalysts **6b** and **6c** are included.

In line with Fig. 1b, the plots in Fig. 1a illustrate a good correlation ($R^2 \geq 0.986$) between the experimental data and the expected theoretical change in enantiomeric ratio.[13]

A screening of reaction conditions and additives was carried out as well and a number of results are presented in Table 2. For the solvent screening, significantly lower reactivity and selectivity were observed for solvents such as Et_2O and toluene compared to $ClCH_2CH_2Cl$ and CH_2Cl_2 (entries 1 and 2 *vs.* 3 and 4). This observation was attributed a lower solubility of the phase-transfer catalyst in the former solvents. A lowering of the concentration of the applied aq. NaOH from 10 to 3 N was not observed to have any effect on the selectivity. Only the rate of the hydrolysis was affected (entry 4 *vs.* 5). With a solid-liquid phase-transfer system (KOH–organic solvent), the reaction was significantly slower and unidentified by-products were formed. Addition of a surfactant such as Triton X-405 for micelle formation proved to have a negative effect on the selectivity (entry 4 *vs.* 6). On the other hand, a decrease in the temperature was observed to have a significant effect. Thus, lowering the temperature from room temperature to

Table 2 Screening of reaction conditions and additives for the asymmetric destruction of **2a** catalysed by **6g**[a]

Entry	Organic solvent	Temp./°C	Time/h	Conversion[b](%)	ee[c](%)	s[d]
1	Et_2O	rt	5	13	(+) 4	1.8
2	Toluene	rt	5	23	(+) 14	3.2
3	$ClCH_2CH_2Cl$	rt	5	47	(+) 51	6.1
4	CH_2Cl_2	rt	5	52	(+) 60	6.3
5[e]	CH_2Cl_2	rt	5	21	(+) 18	6.2
6[f]	CH_2Cl_2	rt	4	52	(+) 51	4.5
7	CH_2Cl_2	5	26	43	(+) 54	10.3
8	CH_2Cl_2	−20	118	33	(+) 37	10.1

[a] Reactions were performed with 0.10 mmol **2a** and with 10 mol% phase-transfer catalyst **6g** in a mixture of 10 N aq. NaOH (unless otherwise stated) and an organic solvent (1 : 1). [b] Determined by HPLC. [c] Enantiomeric excess of recovered **2a** determined by chiral HPLC. The parentheses enclose the sign of the optical rotation. [d] Calculated using eqn (2). [e] 3 N aq. NaOH was applied instead of 10 N. [f] The surfactant Triton X-405 (0.3 eq.) was used as additive.

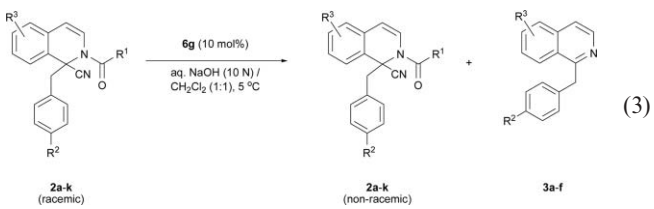
Table 3 Asymmetric destruction of 1-benzylated Reissert compounds in the presence of phase-transfer catalyst **6g**[a]

Entry	Substrate	Product	R^1	R^2	R^3	Time/h	Conversion[b](%)	ee[c](%)	s[d]
1	**2a**	**3a**	Phenyl	H	H	26	43 (56)	(+) 54	9.9
2[e]	**2a**	**3a**	Phenyl	H	H	26	52 (n.d.)	(+) 67	8.8
3	**2b**	**3a**	4-OMe-phenyl	H	H	24	33 (67)	(+) 31	6.0
4	**2c**	**3a**	3,5-DiOMe-phenyl	H	H	72	33 (64)	(+) 35	7.9
5	**2d**	**3a**	4-Br-phenyl	H	H	5	40 (49)	(+) 48	9.7
6	**2e**	**3a**	Me	H	H	24	44 (50)	(+) 46	5.8
7	**2f**	**3a**	iPr	H	H	145	n.d.[f](46)	(+) 6	—
8	**2g**	**3b**	Phenyl	4-OMe	H	24	46 (53)	(+) 53	7.5
9	**2h**	**3c**	Phenyl	4-CN	H	18	80 (20)	(+) 95	4.9
10	**2i**	**3d**	Phenyl	H	5-OMe	24	51 (49)	(+) 69	9.7
11	**2j**	**3e**	Phenyl	H	5-Br	1	44 (48)	(+) 8	1.2
12	**2k**	**3f**	Phenyl	H	4-Br	0.2	34 (66)	(−) 25	3.8

[a] Reactions were performed with 0.10 mmol **2a–k** and with 10 mol% phase-transfer catalyst **6g** in a mixture of 10 N aq. NaOH and CH_2Cl_2 (1 : 1) at 5 °C. All data is for a particular run except the stereoselectivity factor s which is the average of two runs (±0.4). [b] Determined by HPLC. The number in parentheses is the amount of non-racemic **2a–k** recovered by chromatography. [c] Enantiomeric excess of recovered **2a–k** determined by chiral HPLC. The parentheses enclose the sign of the optical rotation. [d] Calculated using eqn (2). [e] The reaction was performed with 0.40 mmol **2a**. The concentrations were maintained. [f] Conversion could not be determined due to the formation of several (unidentifiable) by-products.

5 °C led to an increase in selectivity from $s = 6.3$ to $s = 10.3$ (entry 4 *vs.* 7). An additional decrease in the temperature to −20 °C did not improve the selectivity further (entry 7 *vs.* 8).

With the reaction conditions providing the highest selectivity for compound **2a**, a number of 1-benzylated Reissert compounds were investigated (eqn (3)). The results are presented in Table 3. All reactions were carried out on a 0.10 mmol scale. For reactions of larger scale (*e.g.* 0.40 mmol with maintained concentrations), lower selectivity was observed (entry 1 *vs.* 2). In most cases, all of the non-reacted enantiomerically enriched Reissert compound could be recovered after quenching (see column 8 in the table). With the exception of compound **2k**, all substrates investigated were enriched in their (+)-enantiomer (see column 9 in the table) in the presence of catalyst **6g**.



(3)

The first variation in substitution of the substrates was for the *N*-protecting group (R^1). Compared to substrate **2a**, lower selectivity was observed for substrates having electron-rich benzoyl-groups, such as **2b** and **2c** (entries 3 and 4 *vs.* 1). On the other hand, the electron-poor **2d** was resolved with selectivity similar to that of **2a** (entry 5 *vs.* 1). This compound reacted significantly faster than compounds **2a–c** most likely due to the electron-withdrawing bromine increasing the electrophilicity of the carbonyl-group. Substrates with *N*-alkylcarbonyl groups were also tested. The *N*-acetyl compound **2e** displayed reactivity similar to that of **2a**, but was resolved with lower selectivity (entry 6 *vs.* 1). Compound **2f**, having the more bulky isopropyl group adjacent to the carbonyl group, was observed to hydrolyse significantly slower than the methyl analogue **2e** (entry 7 *vs.* 6). Moreover, the reaction of this substrate proceeded with formation of several by-products and because not all of these products could be identified, a value for the stereoselectivity factor could not be determined. However, from the enantiomeric excess and the amount of recovered substrate, the selectivity was expected to be low.

Next, the substitution on the 1-benzyl substituent (R^2) was varied. Substrate **2g**, having the electron-donating methoxy-group in the *para*-position of the benzyl-substitutent, was resolved with an average *s*-value of 7.5 (entry 8), while the corresponding substrate substituted with the electron-withdrawing cyano-group (**2h**) was resolved with an average *s*-value of 4.9 (entry 9).

Finally, the substitution on the isoquinoline moiety (R^3) was varied. In this case, it is interesting to note the large difference in reaction rate observed for the similar compounds **2a**, **2i** and **2j**. Although the R^3 substituent (*i.e.* H, OMe, Br) is in a position remote to the carbonyl group, compound **2j** reacts significantly faster than **2a** and **2i** (compare entries 1, 10 and 11). Moreover, lower selectivity is observed for the electron-poor substrates **2j** and **2k** compared to the less reactive **2a** and the electron-rich **2i** (compare entries 1 and 10–12). A similar trend is observed for compounds **2g** and **2h** (entries 8 and 9). However, an overall simple reactivity–selectivity relationship does not seem to exist for the reaction (compare *e.g.* entries 1, 5 and 11).

Since the lowest selectivities were obtained for the electron-deficient substrates using the electron-poor catalyst **6g** (with the exception of substrate **2d**), a number of alternative catalysts were tested for these substrates (Table 4). For example, the electron-rich catalyst **6f** was applied for the hydrolysis of substrates **2h**, **2j** and **2k** (entries 2, 4 and 6). All reacted faster than in the presence of **6g**, but with similar or lower selectivity. Interestingly, compound **2j** was enriched in opposite enantiomers using catalyst **6f** and **6g** (compare Table 3; entry 11 and Table 4; entry 4). Since the two catalysts are both derived from cinchonine, differing only in the substitution of the *N*-benzyl group, this observation indicates a sensitive interaction between substrate and catalyst.

A further testing of catalysts also revealed that a significant increase in selectivity was obtained, when substrates **2j** and **2k** were resolved in the presence of the cinchonidine derived **6b** (Table 4; entries 3 and 5). In the presence of this catalyst, **2j** and **2k** reacted fast and were resolved with stereoselectivity factors of 3.5 and 5.7, respectively. On the other hand, compound **2h** also reacted fast in the presence of **6b**, but with a low selectivity of 1.4 (entry 1).

Table 4 Asymmetric destruction of compounds **2h**, **2j**, **2k** in the presence of phase-transfer catalyst **6f** or **6b**[a]

Entry	Substrate	Catalyst	Time/min	Conversion[b](%)	ee[c](%)	s[d]
1	**2h**	**6b**	60	42	(−) 9	1.4
2	**2h**	**6f**	240	68	(+) 59	3.0
3	**2j**	**6b**	30	70	(+) 69	3.5
4	**2j**	**6f**	60	81	(−) 21	1.3
5	**2k**	**6b**	2	60	(+) 71	5.7
6	**2k**	**6f**	2	40	(−) 31	3.7

[a] Reactions were performed with 0.10 mmol substrate and with 10 mol% catalyst in a mixture of 10 N aq. NaOH and CH_2Cl_2 (1 : 1) at 5 °C. [b] Determined by HPLC. [c] Enantiomeric excess of recovered **2** determined by chiral HPLC. The parentheses enclose the sign of the optical rotation. [d] Calculated using eqn (2).

Our mechanistic proposal for this novel asymmetric destruction of 1-benzylated Reissert compounds is outlined in Scheme 2 and Scheme 3. The proposal is illustrated for compound **2a**.

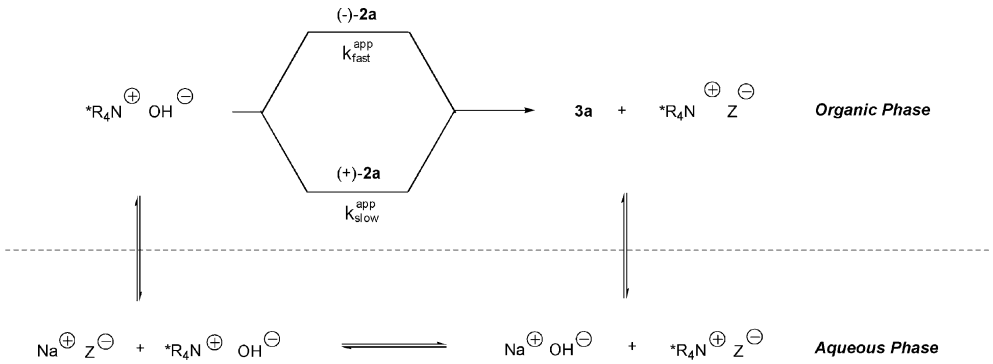
Initially, the racemic Reissert compounds (±)-**2a** and the chiral phase-transfer catalyst (*R_4NZ, Z = halide) are present in the organic phase, while hydroxide ions reside in the aqueous phase (Scheme 2). At the interface between the organic and aqueous phase, an ion-exchange occurs to give a sodium salt (NaZ) and a chiral ion-pair consisting of the catalyst cation and hydroxide (*R_4NOH). While NaZ diffuses to the aqueous phase, the lipophilic *R_4NOH diffuses to the organic phase. In this phase, *R_4NOH reacts with the carbonyl group of (±)-**2a** to give intermediate **7**, which subsequently loses benzoate yielding α-amino nitrile **8** and ensures regeneration of the catalyst (Scheme 3). The reaction step **2a** → **7** is expected to be fast and reversible, and the step **7** → **8** irreversible and rate determining. Thus, the overall the reaction is expected to follow Michaelis–Menten kinetics.[11a]

The reaction between the enantiopure *R_4NOH and **2a**, resulting in four possible diastereomers of **7**, gives rise to a complex match/mismatch situation. Besides configurations, we expect the matching of the two chiral ions of **7** to be influenced by hydrogen-bonding and aromatic interactions.

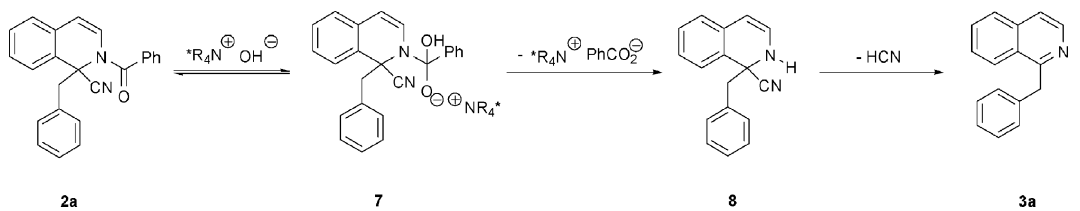
Kinetic considerations reveal that the selectivity s is dictated by both the stability and the reactivity of **7**. That is, the ratio $k_{fast}^{app}/k_{slow}^{app}$ is expressed by the equilibrium constants for the formation and the rate constants for the decomposition of each of the diastereomers of **7**.[14] The involvement of both factors may explain the significant substrate dependence observed. Also, it might explain the relatively low selectivities obtained (*e.g.* one of the diastereomers, derived from (+)-**2a**, may be just as stable/reactive as one derived from (−)-**2a**).

The further reaction of **8** is expected to be a fast retro-Strecker reaction (*i.e.* loss of HCN and formation of the imine **3a**).[15] In fact, α-amino nitriles are known to undergo retro-Strecker reaction under both acidic and basic conditions.[16] However, heating is often required to afford the elimination of HCN with high conversion. We believe that the aromatisation, associated with the formation of **3a**, provides the driving force for the loss of HCN from **8** at the low temperature applied.

It has also been reported that *N*-formylation is an effective way to protect α-amino nitriles otherwise prone to retro-Strecker



Scheme 2 Mechanistic proposal for the asymmetric destruction of 1-benzylated Reissert compounds exemplified by substrate **2a** (Z = halide, cyanide or benzoate).



Scheme 3 Proposed reaction between **2a** and *R_4NOH.

reaction.[16a,16b,16f] Again, the formation of the aromatic **3a** may explain why **2a** undergoes an overall retro-Strecker reaction despite the presence of the *N*-benzoyl group.

Conclusions

In conclusion, we have reported on the asymmetric destruction of 1-benzylated Reissert compounds under phase-transfer conditions. This novel reaction was studied in detail in the presence of various phase-transfer catalysts and under different reaction conditions. Catalysts derived from cinchona alkaloids resulted in the highest selectivity. The most selective proved to be the commercially available *N*-(4-trifluoromethyl-benzyl)-cinchoninium bromide **6g**, which provided a stereoselectivity factor *s* of 10 for model substrate **2a**. In general, however, the reaction was observed to be very substrate dependent and a mechanistic proposal suggesting a complex match/mismatch between substrate and catalyst has been presented.

Finally, we believe that further development of the reaction may result in an approach, alternative to the existing,[7,8] for the synthesis of optically active 1-alkylated Reissert compounds. Additionally, this work adds to a short list of reported kinetic resolutions catalysed by quaternary cinchona alkaloids.[17]

Experimental

General methods

NMR spectra were acquired on a Varian AS 400 spectrometer, running at 400 and 100 MHz for ^{1}H and ^{13}C, respectively. Chemical shifts (δ) are reported in ppm relative to $CDCl_3$ (δ = 7.26) or acetone-d_6 (δ = 2.05) for ^{1}H NMR and relative to the central resonance of $CDCl_3$ (δ = 77.0) or acetone-d_6 (δ = 29.84) for ^{13}C NMR. ^{13}C NMR spectra were acquired on a broad band decoupled mode. Mass spectra were recorded on a micromass LCT spectrometer using electrospray (ES^+) ionization techniques. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. For compounds **2a–k**, **3c** and **3e**, flash column chromatography (FC) was carried out using a Flashmaster II from Jones Chromatography. The enantiomeric excess (ee) of the Reissert compounds and the conversions of the asymmetric destructions were determined by chiral stationary phase HPLC (Daicel Chiralpak AD/AS or Daicel Chiralcel OD columns).

Materials

Analytical grade solvents were used as received. For FC, silica gel from Iatron Laboratories Inc. (Iatrobeads 6RS-8060) or silica gel 60, 230–400 mesh was used. The racemic 1-benzylated Reissert compounds **2a–k** were synthesized using literature procedures (all were purified by recrystallization from EtOH; except compounds **2d** and **2i**, which were purified by FC).[18] 5-Methoxyisoquinoline (used for the preparation of substrate **2i**) was prepared (NaH then MeI in DMF at 0–5 °C) from commercially available 5-hydroxyisoquinoline.[19] Phase-transfer catalysts **6f**,[20] **6h**,[20] **6i**[21] and **6j**[22] were prepared from commercially available cinchonine according to literature procedures. All other compounds were obtained from commercial sources and used as received.

Asymmetric destruction of 2-benzoyl-1-benzyl-1,2-dihydroisoquinoline-1-carbonitrile (2a) (typical procedure). Racemic **2a** (35.0 mg, 0.10 mmol) was dissolved in CH_2Cl_2 (0.5 mL) in a small glass vial with stirring and *N*-(4-(trifluoromethyl)-benzyl)cinchoninium bromide **6g** (5.3 mg, 0.01 mmol) was added. The vial was closed and the mixture was cooled to 5 °C before cold (5 °C) 10 N aqueous NaOH (0.5 mL) was added. The heterogeneous mixture was stirred vigorously at 5 °C for 26 h. The two layers were separated using more CH_2Cl_2 and H_2O (*ca.* 1 mL each) and the aqueous layer was extracted three times with CH_2Cl_2 (*ca.* 1 mL). The combined organic layers were eluted through a short pad of SiO_2 using Et_2O as the eluent, then washed with H_2O and finally with brine. After drying ($MgSO_4$) and filtering the organic layers, a small sample was collected for HPLC analysis (43% conv., 54% ee, s = 10.3). The solvents were then evaporated to obtain an oily mixture of **2a** and **3a**. The mixture was separated by FC on SiO_2 (eluent: gradual polarity change from hexane to 80% Et_2O in hexane) to give the enantiomerically enriched 2-benzoyl-1-benzyl-1,2-dihydroisoquinoline-1-carbonitrile **2a** as an oil, which turned into a white solid when dried under vacuum overnight (19.5 mg, 56%). ^{1}H NMR ($CDCl_3$) δ 7.64 (d, J = 7.4 Hz, 2H), 7.55 (t, J = 7.2 Hz, 1H), 7.44–7.51 (m, 2H), 7.31 (d, J = 7.2 Hz, 1H), 7.11–7.25 (m, 5H), 7.02 (d, J = 7.5 Hz, 1H), 6.83 (d, J = 7.4 Hz, 2H), 6.36 (d, J = 7.9 Hz, 1H), 5.54 (d, J = 8.0 Hz, 1H), 3.73 (d, J = 13.0 Hz, 1H), 3.53 (d, J = 12.9 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 169.4, 133.1, 133.0, 131.9, 130.9, 129.4, 129.3, 129.0, 128.6, 127.9, 127.7, 127.6, 127.4, 127.3, 126.4, 124.7, 117.6, 106.6, 61.3, 43.3. HRMS: $C_{24}H_{18}N_2O$ $[M + Na]^+$ calcd.: 373.1311, found: 373.1316. $[\alpha]_D^{23}$ +100.3 (13 mg mL^{-1} $CHCl_3$, 57% ee). HPLC: Daicel Chiralpak AD column [hexane–iPrOH (95 : 5)]; flow rate 1.0 mL min^{-1} ($\tau_{\mathbf{3a}}$ = 12.1 min; $\tau_{\mathbf{2a},\mathrm{minor}}$ = 25.4 min; $\tau_{\mathbf{2a},\mathrm{major}}$ = 27.5 min).

1-Benzyl-2-(4-methoxybenzoyl)-1,2-dihydroisoquinoline-1-carbonitrile (2b). The title compound was asymmetrically destroyed according to the procedure described for compound **2a**. Reaction time: 24 h. HPLC-analysis: 33% conv., 31% ee, s = 5.6. FC conditions: SiO_2, eluent: gradual polarity change from CH_2Cl_2 to 4% Et_2O in CH_2Cl_2. Recovered enantiomerically enriched **2b**: 67%. Appearance: white solid. ^{1}H NMR ($CDCl_3$) δ 7.64 (d, J = 8.6 Hz, 2H), 7.30 (m, 1H), 7.21 (t, J = 7.3 Hz, 1H), 7.09–7.17 (m, 4H), 7.03 (d, J = 7.2 Hz, 1H), 6.95 (d, J = 8.9 Hz, 2H), 6.82 (d, J = 7.5 Hz, 2H), 6.43 (d, J = 7.9 Hz, 1H), 5.59 (d, J = 8.0 Hz, 1H), 3.88 (s, 3H), 3.67 (d, J = 12.8 Hz, 1H), 3.55 (d, J = 12.9 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 169.0, 162.6, 133.1, 131.8, 130.9, 129.3, 129.2, 127.8, 127.7, 127.4, 127.1, 126.9, 125.1, 124.6, 117.6, 113.9, 106.3, 61.6, 55.5, 42.9. HRMS: $C_{25}H_{20}N_2O_2$ $[M + Na]^+$ calcd.: 403.1417, found: 403.1414. $[\alpha]_D^{23}$ +62.0 (10 mg mL^{-1} $CHCl_3$, 31% ee). HPLC: Daicel Chiralcel OD column [hexane–iPrOH (90 : 10)]; flow rate 1.0 mL min^{-1} ($\tau_{\mathbf{3a}}$ = 9.3 min; $\tau_{\mathbf{2b},\mathrm{minor}}$ = 14.2 min; $\tau_{\mathbf{2b},\mathrm{major}}$ = 19.6 min).

1-Benzyl-2-(3,5-dimethoxybenzoyl)-1,2-dihydroisoquinoline-1-carbonitrile (2c). The title compound was asymmetrically destroyed according to the procedure described for compound **2a**. Reaction time: 72 h. HPLC-analysis: 33% conv., 35% ee, s = 7.9. FC conditions: SiO_2, eluent: gradual polarity change from CH_2Cl_2 to 4% Et_2O in CH_2Cl_2. Recovered enantiomerically enriched **2c**: 64%. Appearance: pale yellow solid. ^{1}H NMR ($CDCl_3$) δ 7.20 (t, J = 7.4 Hz, 1H), 7.02–7.15 (m, 5H), 6.92 (d, J = 7.5 Hz, 1H),

6.73 (d, J = 7.3 Hz, 2H), 6.62 (d, J = 2.2 Hz, 2H), 6.50 (t, J = 2.2 Hz, 1H), 6.27 (d, J = 8.0 Hz, 1H), 5.44 (d, J = 8.0 Hz, 1H), 3.71 (s, 6H), 3.63 (d, J = 13.0 Hz, 1H), 3.42 (d, J = 12.9 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 169.2, 160.8, 135.0, 132.9, 130.9, 129.4, 129.0, 127.9, 127.7, 127.6, 127.5, 127.3, 126.3, 124.8, 117.6, 106.8, 106.5, 104.0, 61.3, 55.60, 55.58, 43.3. HRMS: $C_{26}H_{22}N_2O_3$ [M + Na]$^+$ calcd.: 433.1523, found: 433.1548. $[\alpha]_D^{23}$ +55.3 (12 mg mL^{-1} $CHCl_3$, 35% ee). HPLC: Daicel Chiralpak AS column [hexane–iPrOH (90 : 10)]; flow rate 1.0 mL min^{-1} ($\tau_{\mathbf{3a}}$ = 6.3 min; $\tau_{\mathbf{2c},\text{minor}}$ = 22.3 min; $\tau_{\mathbf{2c},\text{major}}$ = 27.8 min).

1-Benzyl-2-(4-bromobenzoyl)-1,2-dihydroisoquinoline-1-carbonitrile (2d). The title compound was asymmetrically destroyed according to the procedure described for compound **2a**. Reaction time: 5 h. HPLC-analysis: 40% conv., 48% ee, s = 10.0. FC conditions: iatrobeads, eluent: gradual polarity change from hexane to 10% acetone in hexane. Recovered enantiomerically enriched **2d**: 49%. Appearance: white solid. ^{1}H NMR ($CDCl_3$) δ 7.62 (d, J = 8.6 Hz, 2H), 7.51 (d, J = 8.6 Hz, 2H), 7.31 (ddd, J = 2.1, 6.6, 7.5 Hz, 1H), 7.22 (d, J = 7.4 Hz, 1H), 7.10–7.19 (m, 4H), 7.03 (d, J = 7.3 Hz, 1H), 6.82 (d, J = 6.9 Hz, 2H), 6.3 (d, J = 7.9 Hz, 1H), 5.59 (d, J = 7.9 Hz, 1H), 3.70 (d, J = 12.9 Hz, 1H), 3.52 (d, J = 12.9 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 168.4, 132.8, 131.9, 130.9, 130.8, 129.5, 128.8, 127.9, 127.70, 127.66, 127.54, 127.51, 126.8, 125.9, 124.9, 117.5, 107.2, 61.4, 43.2. HRMS: $C_{24}H_{17}BrN_2O$ [M + Na$^+$] calcd.: 451.0416, found: 451.0424. $[\alpha]_D^{23}$ +154.5 (10 mg mL^{-1} $CHCl_3$, 48% ee). HPLC: Daicel Chiralcel OD column [hexane–iPrOH (98 : 2)]; flow rate 1.0 mL min^{-1} ($\tau_{\mathbf{3a}}$ = 16.9 min; $\tau_{\mathbf{2d},\text{major}}$ = 26.3 min; $\tau_{\mathbf{2d},\text{minor}}$ = 31.1 min).

2-Acetyl-1-benzyl-1,2-dihydroisoquinoline-1-carbonitrile (2e). The title compound was asymmetrically destroyed according to the procedure described for compound **2a**. Reaction time: 24 h. HPLC-analysis: 44% conv., 46% ee, s = 6.0. FC conditions: SiO_2, eluent: gradual polarity change from hexane to Et_2O. Recovered enantiomerically enriched **2e**: 50%. Appearance: pale yellow solid. ^{1}H NMR ($CDCl_3$) δ 7.32 (d, J = 7.8 Hz, 1H), 7.26 (t, J = 7.5 Hz, 1H), 7.14–7.23 (m, 2H), 7.10 (t, J = 7.2 Hz, 2H), 6.92 (d, J = 7.5 Hz, 1H), 6.70 (d, J = 7.9 Hz, 2H), 6.33 (d, J = 8.1 Hz, 1H), 5.43 (d, J = 8.1 Hz, 1H), 3.76 (d, J = 13.0 Hz, 1H), 3.26 (d, J = 13.1 Hz. 1H), 2.32 (s, 3H). ^{13}C NMR (acetone-d_6) δ 169.9, 134.2, 131.5, 130.3, 130.2, 129.1, 128.6, 128.3, 128.1, 127.9, 126.2, 125.6, 119.2, 106.2, 60.7, 45.0, 23.0. HRMS: $C_{19}H_{16}N_2O$ [M + Na]$^+$ calcd.: 311.1155, found: 311.1165. $[\alpha]_D^{23}$ +43.7 (14 mg mL^{-1} $CHCl_3$, 46% ee). HPLC: Daicel Chiralcel OD column [hexane–iPrOH (90 : 10)]; flow rate 1.0 mL min^{-1} ($\tau_{\mathbf{3a}}$ = 9.6 min; $\tau_{\mathbf{2e},\text{minor}}$ = 18.0 min; $\tau_{\mathbf{2e},\text{major}}$ = 22.0 min).

1-Benzyl-2-isobutyryl-1,2-dihydroisoquinoline-1-carbonitrile (2f). The title compound was asymmetrically destroyed according to the procedure described for compound **2a**. Reaction time: 145 h. HPLC-analysis: conversion was not determined, 6% ee. FC conditions: SiO_2, eluent: gradual polarity change from hexane to Et_2O. Recovered enantiomerically enriched **2f**: 46%. Appearance: white solid. ^{1}H NMR ($CDCl_3$) δ 7.32 (d, J = 8.3 Hz, 1H), 7.28 (dt, J = 1.2, 7.5 Hz, 1H), 7.15–7.23 (m, 2H), 7.11 (t, J = 7.7 Hz, 2H), 6.95 (dd, J = 1.2, 7.5 Hz, 1H), 6.71 (d, J = 7.1 Hz, 2H), 6.45 (d, J = 8.2 Hz, 1H), 5.47 (d, J = 8.1 Hz, 1H), 3.73 (d, J = 13.0 Hz, 1H), 3.28 (d, J = 13.0 Hz, 1H), 2.92 (septet, J = 6.8 Hz, 1H), 1.28 (d, J = 6.7 Hz, 3H), 1.25 (d, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 175.3, 133.0, 130.7, 129.3, 128.9, 128.4, 127.8, 127.6, 127.44, 127.41, 124.6, 123.5, 118.4, 106.7, 60.3, 44.7, 31.8, 19.3, 18.8. HRMS: $C_{21}H_{20}N_2O$ [M + Na]$^+$ calcd.: 339.1468, found: 339.1453. $[\alpha]_D^{23}$ +9.3 (10 mg mL^{-1} $CHCl_3$, 6% ee). HPLC: Daicel Chiralcel OD + Chiralpak AD column [hexane–iPrOH (98 : 2)]; flow rate 1.0 mL min^{-1} ($\tau_{\mathbf{2f},\text{major}}$ = 38.2 min; $\tau_{\mathbf{2f},\text{minor}}$ = 42.5 min).

2-Benzoyl-1-(4-methoxybenzyl)-1,2-dihydroisoquinoline-1-carbonitrile (2g). The title compound was asymmetrically destroyed according to the procedure described for compound **2a**. Reaction time: 24 h. HPLC-analysis: 46% conv., 53% ee, s = 7.5. FC conditions: SiO_2, eluent: gradual polarity change from CH_2Cl_2 to 4% Et_2O in CH_2Cl_2. Recovered enantiomerically enriched **2g**: 53%. Appearance: pale yellow solid. ^{1}H NMR ($CDCl_3$) δ 7.64 (d, J = 7.5 Hz, 2H), 7.55 (t, J = 7.2 Hz, 1H), 7.47 (m, 2H), 7.30 (dt, J = 1.9, 7.4 Hz, 1H), 7.11–7.23 (m, 2H), 7.02 (d, J = 7.4 Hz, 1H), 6.73 (d, J = 8.6 Hz, 2H), 6.68 (d, J = 8.5 Hz, 2H), 6.36 (d, J = 8.0 Hz, 1H), 5.56 (d, J = 8.0 Hz, 1H), 3.76 (s, 3H), 3.65 (d, J = 13.1 Hz, 1H), 3.48 (d, J = 13.1 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 169.4, 159.0, 133.2, 131.90, 131.87, 129.4, 129.3, 129.0, 128.6, 127.8, 127.7, 127.3, 126.4, 125.0, 124.7, 117.7, 113.3, 106.6, 61.5, 55.1, 42.4. HRMS: $C_{25}H_{20}N_2O_2$ [M + Na]$^+$ calcd.: 403.1417, found: 403.1400. $[\alpha]_D^{23}$ +70.8 (8 mg mL^{-1} $CHCl_3$, 53% ee). HPLC: Daicel Chiralpak AD column [hexane–iPrOH (90 : 10)]; flow rate 1.0 mL min^{-1} ($\tau_{\mathbf{3b}}$ = 13.3 min; $\tau_{\mathbf{2g},\text{minor}}$ = 23.5 min; $\tau_{\mathbf{2g},\text{major}}$ = 27.8 min).

2-Benzoyl-1-(4-cyanobenzyl)-1,2-dihydroisoquinoline-1-carbonitrile (2h). The title compound was asymmetrically destroyed according to the procedure described for compound **2a**. Reaction time: 18 h. HPLC-analysis: 80% conv., 95% ee, s = 4.8. FC conditions: SiO_2, eluent: gradual polarity change from CH_2Cl_2 to 3% Et_2O in CH_2Cl_2. Recovered enantiomerically enriched **2h**: 20%. Appearance: white solid. ^{1}H NMR ($CDCl_3$) δ 7.63 (d, J = 7.1 Hz, 2H), 7.57 (t, J = 7.4 Hz, 1H), 7.42–7.51 (m, 4H), 7.34 (dt, J = 1.8, 7.1 Hz, 1H), 7.11–7.20 (m, 2H), 7.07 (d, J = 7.5 Hz, 1H), 6.94 (d, J = 8.2 Hz, 2H), 6.39 (d, J = 7.9 Hz, 1H), 5.62 (d, J = 7.9 Hz, 1H), 3.73 (d, J = 12.8 Hz, 1H), 3.59 (d, J = 12.7 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 169.5, 138.5, 132.6, 132.3, 131.61, 131.58, 129.9, 129.4, 128.9, 128.7, 127.5, 127.4, 126.8, 126.4, 125.1, 118.6, 116.9, 111.5, 106.8, 61.0, 42.9. HRMS $C_{25}H_{17}N_3O_2$ [M + Na]$^+$: calcd.: 398.1264, found: 398.1278. $[\alpha]_D^{23}$ +123.7 (11 mg mL^{-1} $CHCl_3$, 85% ee). HPLC: Daicel Chiralpak AD column [hexane–iPrOH (85 : 15)]; flow rate 1.0 mL min^{-1} ($\tau_{\mathbf{3c}}$ = 16.0 min; $\tau_{\mathbf{2h},\text{minor}}$ = 27.9 min; $\tau_{\mathbf{2h},\text{major}}$ = 36.9 min).

2-Benzoyl-1-benzyl-5-methoxy-1,2-dihydroisoquinoline-1-carbonitrile (2i). The title compound was asymmetrically destroyed according to the procedure described for compound **2a**. Reaction time: 24 h. HPLC-analysis: 51% conv., 69% ee, s = 9.5. FC conditions: SiO_2, eluent: gradual polarity change from hexane to 20% acetone in hexane. Recovered enantiomerically enriched **2i**: 49%. Appearance: white solid. ^{1}H NMR ($CDCl_3$) δ 7.63 (d, J = 7.0 Hz, 2H), 7.54 (t, J = 7.4 Hz, 1H), 7.46 (d, J = 7.7 Hz, 2H), 7.22 (m, 1H), 7.07–7.18 (m, 3H), 6.79–6.91 (m, 4H), 6.34 (d, J = 8.1 Hz, 1H), 5.97 (d, J = 8.1 Hz, 1H), 3.86 (s, 3H), 3.68 (d, J = 12.9 Hz, 1H), 3.53 (d, J = 12.9 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 169.4, 153.3, 133.2, 133.1, 131.9, 130.9, 129.4, 128.8, 128.5, 127.9, 127.8,

127.4, 125.5, 119.9, 118.4, 117.6, 110.9, 101.2, 61.3, 55.7, 42.8. HRMS: $C_{25}H_{20}N_2O_2$ $[M + Na]^+$ calcd.: 403.1417, found: 403.1425. $[\alpha]_D^{23}$ +109.7 (13 mg mL^{-1} $CHCl_3$, 68% ee). HPLC: Daicel Chiralpak AD column [hexane–iPrOH (95 : 5)]; flow rate 1.0 mL min^{-1} ($\tau_{\mathbf{3d}} = 18.9$ min; $\tau_{\mathbf{2i},minor} = 40.1$ min; $\tau_{\mathbf{2i},major} = 45.2$ min).

2-Benzoyl-1-benzyl-5-bromo-1,2-dihydroisoquinoline-1-carbonitrile (2j). The title compound was asymmetrically destroyed according to the procedure described for compound **2a**. Reaction time: 1 h. HPLC-analysis: 44% conv., 8% ee, $s = 1.3$. FC conditions: SiO_2, eluent: gradual polarity change from CH_2Cl_2 to 4% Et_2O in CH_2Cl_2. Recovered enantiomerically enriched **2j**: 48%. Appearance: white solid. ^{1}H NMR ($CDCl_3$) δ 7.64 (d, J = 7.7 Hz, 2H), 7.44–7.59 (m, 4H), 7.23 (t, J = 5.4 Hz, 1H), 7.15 (t, J = 7.7 Hz, 2H), 7.06 (d, J = 7.6 Hz, 1H), 6.95 (t, J = 8.0 Hz, 1H), 6.84 (d, J = 7.5 Hz, 2H), 6.46 (d, J = 8.2 Hz, 1H), 5.98 (d, J = 8.2 Hz, 1H), 3.61 (d, J = 12.9 Hz, 1H), 3.54 (d, J = 12.9 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 169.4, 133.5, 132.6, 132.5, 132.3, 130.9, 129.5, 129.4, 128.71, 128.68, 128.1, 128.0, 127.9, 127.7, 127.0, 120.1, 117.1, 105.2, 61.6, 42.7. HRMS: $C_{24}H_{17}BrN_2O$ $[M + Na]^+$ calcd.: 451.0398, found: 451.0416. $[\alpha]_D^{23}$ +9.7 (8 mg mL^{-1} $CHCl_3$, 8% ee). HPLC: Daicel Chiralpak AD column [hexane–iPrOH (95 : 5)]; flow rate 1.0 mL min^{-1} ($\tau_{\mathbf{3e}} = 12.2$ min; $\tau_{\mathbf{2j},minor} = 21.8$ min; $\tau_{\mathbf{2j},major} = 23.1$ min).

2-Benzoyl-1-benzyl-4-bromo-1,2-dihydroisoquinoline-1-carbonitrile (2k). The title compound was asymmetrically destroyed according to the procedure described for compound **2a**. Reaction time: 10 min. HPLC-analysis: 34% conv., 25% ee, $s = 3.7$. FC conditions: SiO_2, eluent: gradual polarity change from hexane to 50% Et_2O in hexane. Recovered enantiomerically enriched **2k**: 66%. Appearance: pale yellow solid. ^{1}H NMR ($CDCl_3$) δ 7.67 (dd, J = 1.4, 7.0 Hz, 2H), 7.60 (m, 1H), 7.40–7.56 (m, 4H), 7.21–7.30 (m, 3H), 7.16 (t, J = 7.5 Hz, 2H), 6.81 (d, 7.0 Hz, 2H), 6.69 (s, 1H), 3.74 (d, J = 13.0 Hz, 1H), 3.53 (d, J = 13.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 168.6, 132.5, 132.40, 132.35, 130.6, 129.8, 129.4, 128.8, 128.6, 128.3, 128.0, 127.9, 127.7, 127.4, 126.9, 125.0, 117.2, 101.6, 61.6, 43.8. HRMS: $C_{24}H_{17}BrN_2O$ $[M + K]^+$ calcd.: 451.0416, found: 451.0410. $[\alpha]_D^{23}$ −205.0 (10 mg mL^{-1} $CHCl_3$, 93% ee). HPLC: Daicel Chiralcel OD column [hexane–iPrOH (98 : 2)]; flow rate 1.0 mL min^{-1} ($\tau_{\mathbf{3f}} = 9.2$ min; $\tau_{\mathbf{2k},minor} = 21.4$ min; $\tau_{\mathbf{2k},major} = 25.6$ min).

Preparation of isoquinolines 3a–f. The isoquinolines **3a–f** were isolated from asymmetric destruction of the corresponding 1-benzylated Reissert compounds performed as described above.

1-Benzylisoquinoline (3a). The title compound was isolated from the asymmetric destruction of Reissert compound **2a**. FC conditions: SiO_2, eluent: 20% EtOAc in hexane. Appearance: pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 8.50 (d, J = 5.7 Hz, 1H), 8.14 (d, J = 8.6 Hz, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.62 (t, J = 7.0 Hz, 1H), 7.47–7.58 (m, 2H), 7.21–7.32 (m, 4H), 7.17 (t, J = 7.0 Hz, 1H), 4.67 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 160.1, 142.0, 139.4, 136.5, 129.8, 128.6, 128.55, 128.47, 127.3, 127.2, 126.2, 125.8, 119.8, 42.1. HRMS: $C_{16}H_{13}N$ $[M + H]^+$ calcd.: 220.1121, found: 220.1129.

1-(4-Methoxy)benzylisoquinoline (3b). The title compound was isolated from the asymmetric destruction of Reissert compound **2g**. FC conditions: SiO_2, eluent: 5% Et_2O–CH_2Cl_2. Appearance: white solid. ^{1}H NMR ($CDCl_3$) δ 8.49 (d, J = 5.7 Hz, 1H), 8.16 (d, J = 8.5 Hz, 1H), 7.80 (d, J = 8.2 Hz, 1H), 7.63 (ddd, J = 1.2, 6.9, 8.1 Hz, 1H), 7.49–7.58 (m, 2H), 7.20 (d, J = 8.2 Hz, 2H), 6.80 (d, J = 8.7 Hz, 2H), 4.61 (s, 2H), 3.74 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 160.4, 157.9, 142.0, 136.5, 131.5, 129.8, 129.5, 127.3, 127.13, 127.06, 125.8, 120.0, 113.9, 55.1, 41.2. HRMS: $C_{17}H_{15}NO$ $[M + H]^+$ calcd.: 250.1226, found: 250.1221.

1-(4-Cyano)benzylisoquinoline (3c). The title compound was isolated from the asymmetric destruction of Reissert compound **2h**. FC conditions: SiO_2, eluent: gradual polarity change from CH_2Cl_2 to 15% Et_2O in CH_2Cl_2. Appearance: white solid. ^{1}H NMR ($CDCl_3$) δ 8.49 (d, J = 5.7 Hz, 1H), 8.04 (d, J = 8.5 Hz, 1H), 7.83 (d, J = 8.2 Hz, 1H), 7.66 (t, J = 7.1 Hz, 1H), 7.50–7.59 (m, 4H), 7.37 (d, J = 8.3 Hz, 2H), 4.71 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 158.5, 144.9, 142.1, 136.5, 132.3, 130.1, 129.4, 127.6, 127.0, 125.1, 120.2, 118.9, 110.2, 41.8. HRMS: $C_{17}H_{12}N_2$ $[M + Na]^+$ calcd.: 267.0893, found: 267.0891.

1-Benzyl-5-methoxyisoquinoline (3d). The title compound was isolated from the asymmetric destruction of Reissert compound **2i**. FC conditions: SiO_2, eluent: 10% Et_2O–DCM. Appearance: white solid. ^{1}H NMR ($CDCl_3$) δ 8.51 (d, J = 5.97 Hz, 1H), 7.96 (d, J = 5.9 Hz, 1H), 7.70 (d, J = 8.5 Hz, 1H), 7.43 (t, J = 8.4 Hz, 1H), 7.21–7.30 (m, 4H), 7.13–7–20 (m, 1H), 6.94 (d, J = 7.8 Hz, 1H), 4.65 (s, 2H), 3.99 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 159.4, 154.9, 141.7, 139.5, 129.2, 128.5, 128.4, 127.9, 127.1, 126.1, 117.6, 114.0, 107.1, 55.6, 42.3. HRMS: $C_{17}H_{15}NO$ $[M + Na]^+$ calcd.: 272.1046, found: 272.1048.

1-Benzyl-5-bromoisoquinoline (3e). The title compound was isolated from the asymmetric destruction of Reissert compound **2j**. FC conditions: SiO_2, eluent: gradual polarity change from CH_2Cl_2 to 10% Et_2O in CH_2Cl_2. Appearance: white solid. ^{1}H NMR ($CDCl_3$) δ 8.62 (d, J = 6.0 Hz, 1H), 8.14 (d, J = 8.5 Hz, 1H), 7.95 (d, J = 6.0 Hz, 1H), 7.93 (d, J = 7.5 Hz, 1H), 7.39 (t, J = 7.8 Hz, 1H), 7.23–7.31 (m, 4H), 7.16–7.23 (m, 1H), 4.71 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 160.5, 143.4, 139.1, 135.7, 133.6, 128.6, 128.5, 128.2, 127.5, 126.4, 125.6, 122.4, 118.7, 42.2. HRMS: $C_{16}H_{12}BrN$ $[M + H]^+$ calcd.: 298.0226, found: 298.0228.

1-Benzyl-4-bromoisoquinoline (3f). The title compound was isolated from the asymmetric destruction of Reissert compound **2k**. FC conditions: SiO_2, eluent: 15% Et_2O in hexane. Appearance: white solid. ^{1}H NMR ($CDCl_3$): δ 8.69 (s, 1H), 8.18 (d, J = 8.5 Hz, 1H), 8.14 (d, J = 8.5 Hz, 1H), 7.75 (ddd, J = 1.1, 6.9, 8.2 Hz, 1H), 7.58 (ddd, J = 1.1, 7.0, 8.2 Hz, 1H), 7.22–7.30 (m, 4H), 7.18 (m, 1H), 4.63 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 159.7, 143.7, 138.9, 135.1, 131.1, 128.6, 128.5, 128.3, 128.1, 126.7, 126.4, 126.2, 118.5, 41.8. HRMS: $C_{16}H_{12}BrN$ $[M + H]^+$ calcd.: 298.0226, found: 298.0219.

Acknowledgements

This work was made possible by a grant from The Danish National Research Foundation.

References

1 (*a*) A. I. Meyers, D. A. Dickman and M. Boes, *Tetrahedron*, 1987, **43**, 5095; (*b*) A. R. Katritzky, S. Rachwal and B. Rachwal, *Tetrahedron*, 1996, **52**, 15031; (*c*) J. Royer, M. Bonin and L. Micouin, *Chem. Rev.*, 2004, **104**, 2311; (*d*) M. Chrzanowska and M. D. Rozwadowska, *Chem. Rev.*, 2004, **104**, 3341.

2 (*a*) K. W. Bentley, in *The Isoquinoline Alkaloids*, Pergamon Press, London, 1st edn, 1965; (*b*) K. W. Bentley, *Nat. Prod. Rep.*, 2001, **18**, 148; (*c*) K. W. Bentley, *Nat. Prod. Rep.*, 2004, **21**, 395; (*d*) J. D. Scott and R. M. Williams, *Chem. Rev.*, 2002, **102**, 1669; (*e*) *Comprehensive Medicinal Chemistry*, ed. C. Hansch, P. G. Sammes and J. B. Taylor, Pergamon Press, Oxford, 1st edn, 1990, vol. 3.

3 (*a*) B. E. Maryanoff, D. F. McComsey, J. F. Gardocki, R. P. Shank, M. J. Costanzo, S. O. Nortey, C. R. Schneider and P. E. Setler, *J. Med. Chem.*, 1987, **30**, 1433; (*b*) M. Fujita, H. Egawa, T. Miyamoto, J. Nakano and J. Matsumoto, *Eur. J. Med. Chem.*, 1996, **31**, 981; (*c*) E. Lukevics, I. Segal, A. Zablotskaya and S. Germane, *Molecules*, 1997, **2**, 180; (*d*) Q. Xu and M. Lin, *J. Nat. Prod.*, 1999, **62**, 1025; (*e*) S. Mahmoud, M. Sheha, T. Aboul-Fadl and H. Farag, *Arch. Pharm. (Weinheim, Ger.)*, 2003, **336**, 258; (*f*) S. Mahmoud, T. Aboul-Fadl, H. Farag and A.-M. I. Mouhamed, *Arch. Pharm. (Weinheim, Ger.)*, 2003, **336**, 573; (*g*) E. Reimann, F. Grasberger and K. Polborn, *Monatsh. Chem.*, 2003, **134**, 991 and references therein; (*h*) H.-J. Knölker and S. Agarwal, *Tetrahedron Lett.*, 2005, **46**, 1173 and references therein; (*i*) L. F. Tietze, N. Rackehmann and I. Müller, *Chem.–Eur. J.*, 2004, **10**, 2722 and references therein.

4 A. Reissert, *Ber. Dtsch. Chem. Ges.*, 1905, **38**, 3415.

5 For examples on racemic addition of electrophiles to Reissert compounds see: (*a*) W. E. McEwen and R. L. Cobb, *Chem. Rev.*, 1957, **55**, 511; (*b*) L. R. Walters, E. G. Podrebarac and W. E. McEven, *J. Org. Chem.*, 1961, **26**, 1161; (*c*) J. M. Wefer and F. D. Popp, *J. Org. Chem.*, 1967, **32**, 1999; (*d*) M. Makosza, *Tetrahedron Lett.*, 1969, **9**, 677; (*e*) R. Piccirilli and F. D. Popp, *Can. J. Chem.*, 19690, **47**, 3261; (*f*) J. L. Neumeyer, K. H. Oh, K. K. Weinhardt and B. R. Neustadt, *J. Org. Chem.*, 1969, **34**, 3786; (*g*) F. D. Popp and D. H. Purcell, Jr, *Synthesis*, 1970, **11**, 591; (*h*) H. W. Gibson and F. C. Bailey, *Macromolecules*, 1976, **9**, 221; (*i*) M. D. Rozwadowska, *Can. J. Chem.*, 1977, **55**, 164; (*j*) J. Ezquerra and J. Alvarez-Builla, *J. Heterocycl. Chem.*, 1988, **25**, 917; (*k*) H. W. Gibson and B. Guilani, *J. Org. Chem.*, 1990, **55**, 4226; (*l*) J.-T. Hahn, J. Kant and F. D. Popp, *J. Heterocycl. Chem.*, 1992, **29**, 1165; (*m*) Y. H. R. Jois and H. W. Gibson, *Macromolecules*, 1993, **26**, 6151; (*n*) B. A. Lorsbach, J. T. Bagdanoff, R. B. Miller and M. J. Kurth, *J. Org. Chem.*, 1998, **63**, 2244. See also reference3*g*.

6 See references: 3*g*,5*a*,5*d*,5*f–h*,5*j*,5*m*,5*n*; see also: (*a*) M. S. Taylor and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2004, **126**, 10558; (*b*) J. Seayad, A. M. Seayad and B. List, *J. Am. Chem. Soc.*, 2006, **128**, 1086; (*c*) H. W. Gibson, M. A. G. Berg, J. C. Dickson, P. R. Lecavalier, H. Wang and J. S. Merola, *J. Org. Chem.*, 2007, ASAP.

7 D. Brózda, K. Hoffman and M. D. Rozwadowska, *Heterocycles*, 2006, **67**, 119.

8 Alternative approaches to non-racemic 1-substituted Reissert compounds have previously been reported. For an enantioselective Reissert reaction involving 1-substituted isoquinolines see: (*a*) K. Funabashi, H. Ratni, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.*, 2001, **123**, 10784. For a diastereoselective alkylation of Reissert compounds see:; (*b*) O. Sieck, S. Schaller, S. Grimme and J. Liebscher, *Synlett*, 2003, 337.

9 Although only to a minor extent, decomposition of substrate **1** (R^1 = alkyl, Ar) to give 1-cyanoisoquinoline was also observed under the applied alkaline conditions and in the presence of air. See: (*a*) M. D. Rozwadowska and D. Brózda, *Can. J. Chem.*, 1980, **58**, 1239; (*b*) B. C. Uff, R. S. Budhram, G. Ghaem-Maghami, A. S. Mallard, V. Harutunian, S. Calinghen, N. Choudhury, J. Kant and F. D. Popp, *J. Chem. Res., Miniprint*, 1986, 1901.

10 (*a*) V. Boekelheide and J. Weinstock, *J. Am. Chem. Soc.*, 1952, **74**, 660; (*b*) M. A. G. Berg and H. W. Gibson, *J. Org. Chem.*, 1992, **57**, 748; (*c*) E. Reimann and H. Benend, *Monatsh. Chem.*, 1992, **123**, 939. See also references 5*a*,5*j* and 5*n*.

11 For the derivation of eqn (2) see ESI.† See also: (*a*) D. G. Blackmond, *J. Am. Chem. Soc.*, 2001, **123**, 545; (*b*) H. B. Kagan and J. C. Fiaud, in *Topics in Stereochemistry*, ed. E. L. Eliel and S. H. Wilen, Interscience, New York, 1988, vol. 18, p. 249. See also: (*c*) J. M. Keith, J. F. Larrow and E. N. Jacobsen, *Adv. Synth. Catal.*, 2001, **343**, 5 (*d*) E. Vedejs and M. Jure, *Angew. Chem., Int. Ed.*, 2005, **44**, 3974.

12 For reviews on enantioselective phase-transfer reactions see: (*a*) K. Maruoka and T. Ooi, *Chem. Rev.*, 2003, **103**, 3013; (*b*) M. J. O'Donnell, *Acc. Chem. Res.*, 2004, **37**, 506; (*c*) B. Lygo and B. I. Andrews, *Acc. Chem. Res.*, 2004, **37**, 518. See also: (*d*) E. J. Corey, F. Xu and M. C. Noe, *J. Am. Chem. Soc.*, 1997, **119**, 12414 (*e*) K. Kacprzak and J. Gawroński, *Synthesis*, 2001, **7**, 961.

13 The enantiomeric ratio (er) is expected to change as: er = $\exp((k^{app}_{fast} - k^{app}_{slow})$ [C]t), where [C] is the concentration of the phase-transfer catalyst in the organic phase and t is time. For the derivation of this expressionsee ESI.† See also the mechanistic discussion below.

14 $k^{app}_{fast} = (k'_1K_1 + k'_2K_2)$ and $k^{app}_{slow} = (k'_3K_3 + k'_4K_4)$, where k'_y are the rate constants for the reaction **7** → **8** and K_y are the equilibrium constants for the reaction **2a** → **7** (y = 1–4). See also ESI.

15 The decomposition of **7** by a simultaneous loss of benzoate and HCN (*i.e.* by a one step mechanism) cannot be ruled out as a possible pathway.

16 (*a*) P. Vachal and E. N. Jacobsen, *Org. Lett.*, 2000, **2**, 867; (*b*) M. S. Sigman, P. Vachal and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2000, **39**, 1279; (*c*) J. Dalmolen, M. van der Sluis, J. W. Nieuwenhuijzen, A. Meetsma, B. de Lange, B. Kaptein, R. M. Kellogg and Q. B. Broxterman, *Eur. J. Org. Chem.*, 2004, 1544; (*d*) C. Kison, N. Meyer and T. Opatz, *Angew. Chem., Int. Ed.*, 2005, **44**, 5662; (*e*) N. Girard, L. Pouchain, J.-P. Hurvois and C. Moinet, *Synlett*, 2006, 1679; (*f*) H. Vogt and S. Bräse, *Org. Biomol. Chem.*, 2007, **5**, 406.

17 For kinetic resolutions involving quaternary cinchona alkaloids see: (*a*) R. Annunziata, M. Cinquini and S. Colonna, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2422; (*b*) S. Arai, Y. Shirai, T. Ishida and T. Shioiri, *Tetrahedron*, 1999, **55**, 6375; (*c*) W. Adam, P. B. Rao, H.-G. Degen, A. Leval, T. Patonay and C. R. Saha-Möller, *J. Org. Chem.*, 2002, **67**, 259; (*d*) S. Arai, S. Hamaguchi and T. Shioiri, *Tetrahedron Lett.*, 1998, **39**, 2997. For dynamic kinetic resolutions see: (*e*) K. Szőri, G. Szöllősi and M. Bartók, *Adv. Synth. Catal.*, 2006, **348**, 515.

18 (*a*) A. W. Bridge, M. B. Hursthouse, C. W. Lehmann, D. J. Lythgoe and C. G. Newton, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1839; (*b*) E. Reimann and H. Benend, *Monatsh. Chem.*, 1992, **123**, 939.

19 Y. Yoshida, D. Barrett, H. Azami, C. Morinaga, S. Matsumoto, Y. Matsumoto and H. Takasugi, *Bioorg. Med. Chem.*, 1999, **7**, 2647.

20 S. Arai, H. Tsuge, M. Oku, M. Miura and T. Shioiri, *Tetrahedron*, 2002, **58**, 1623.

21 S.-s. Jew, M.-S. Yoo, B.-S. Jeong, I. Y. Park and H.-g. Park, *Org. Lett.*, 2002, **4**, 4245.

22 S.-s. Jew, B.-S. Jeong, M.-S. Yoo, H. Huh and H.-g. Park, *Chem. Commun.*, 2001, 1244.

