Enantioselective catalytic syntheses of α-branched chiral amines

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Chiral amines play a pivotal role in fine chemical and natural product syntheses and the design of novel materials.

Introduction

The synthesis of α-branched amines continues to be a highly attractive field, as these compounds are valuable building blocks found in many modern active pharmaceutical ingredients and drug candidates. In several of our ongoing projects involving the synthesis of biologically active compounds, we required access to α-branched chiral amines.

α-Branched amines can be prepared by various routes, all of which can be performed in an asymmetric fashion (Scheme 1). Enzymatic and chemical separation of racemic α-branched amines, as well diastereoselective methods,[1,2] certainly still play a major role on an industrial scale.[3] However, poor separation of nearly symmetrical substrates and economic reasons nowadays call for catalytic approaches to this class of compounds. In this Feature Article we would like to present two different major approaches for the synthesis of chiral amines that have been successfully accomplished in our research group.

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Stefan Bräse, born in Kiel, Germany in 1967, studied chemistry in Göttingen, Bangor (UK) and Marseille and received his PhD in 1995 in Göttingen (Armin de Meijere). After postdoctoral appointments in Uppsala (Jan Bäckvall) and La Jolla (K. C. Nicolaou), he began his independent research career at the RWTH Aachen (Germany) in 1997. He accepted a call to Bonn in 2001 and moved to Karlsruhe in 2003. His research interests include the synthesis of biologically active compounds using combinatorial chemistry and asymmetric metal-catalyzed processes.

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Thomas Baumann was born in Bayreuth, Germany in 1977. After receiving his diploma in chemistry from the University of Bayreuth in 2003, he joined the Bräse research group at the University of Karlsruhe for his postgraduate studies. The main topics of his research interests include organo-catalytic strategies towards the synthesis of α,α-disubstituted amino acid derivatives.

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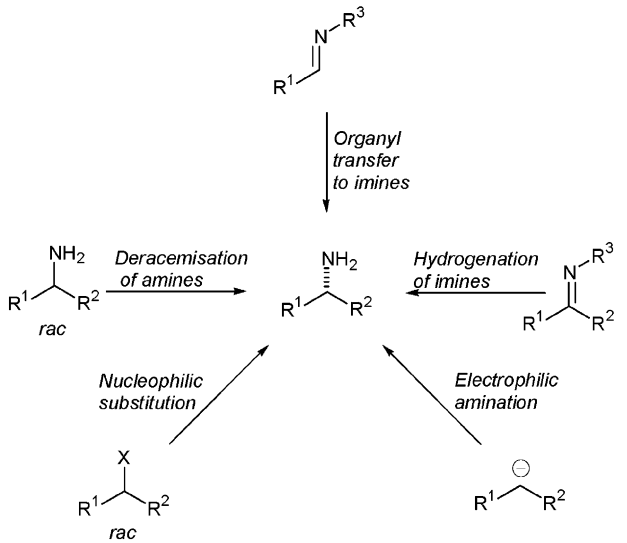


Scheme 1 Asymmetric syntheses of α-branched amines.

In general, imines can serve as valuable starting materials since organyl groups or hydrogen can be delivered stereoselectively to the C=N double bond. The catalytic hydrogenation of ketoimines using chiral catalysts has been studied extensively, an exceptional example being the synthesis of the herbicide metolachlor.[4] In certain cases, the well-established CBS reduction is also met with success.[5] In contrast, our effort was directed towards the catalytic organyl transfer to *in situ*-generated aldimines.

The examples known for the electrophilic or nucleophilic addition of nitrogen sources to carbon nucleophiles and electrophiles, respectively, are rather limited. However, the functionalisation of alkenes by hydroamination or aminohydroxylation has found increased attention in organic synthesis. Quite recently, interesting organo-catalytic approaches were disclosed by the groups of Rueping,[6] List,[7] and others. Our research in this context has been focussed on the asymmetric α-amination of disubstituted aldehydes using various nitrogen electrophiles under L-proline catalysis.

Asymmetric 1,2-additions to imines

The catalytic asymmetric preparation of α-chiral amines by addition of organometallic reagents to C=N bonds is a field of considerable importance to homogeneous catalysis.[8]

While there have been numerous efforts to control the stereoselectivity of this reaction by chiral auxiliaries or (stoichiometric amounts of) chiral ligands, the catalytic asymmetric addition of simple alkylmetals has only been achieved in recent years. In this context, the enantioselective addition of alkylzinc reagents to imines has attracted considerable interest.[9]

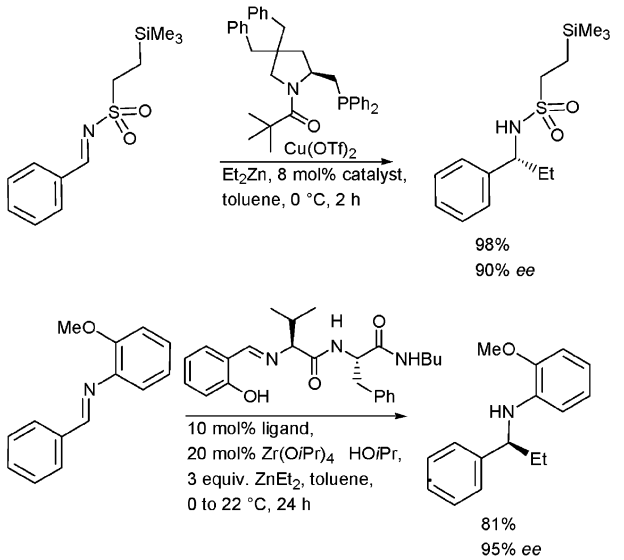
When we entered this field, Tomioka and co-workers had just described the dialkylzinc addition to *N*-sulfonyl imines in the presence of chiral amidophosphine copper(II) complexes, producing high levels of enantioselectivity.[10] At the same time, Hoveyda, Snapper and co-workers reported a zirconium-catalysed variant using peptidic Schiff-base ligands, the catalytic properties of which were optimised in a combinatorial fashion (Scheme 2).[11]

The Tomioka method comprises the features of a 1,4-addition reaction due to the use of a copper-catalyst and an *N*-sulfonyl imine substrate. The zirconium-based variant by Hoveyda/Snapper suggests a classical Lewis-acid-catalyzed reaction pathway. However, at the time no catalytic addition was known comparable to the classic dialkylzinc addition to aldehydes which is a Lewis-acid/Lewis-base-catalysed process.[12]

The lack of a simple method employing only a sub-stoichiometric amount of an *N*,*O*-ligand without any additional metal centre (other than zinc itself) could not simply be ascribed to selectivity problems in the addition reaction, but rather to the low reactivity of many imine substrates or precursors towards alkylzinc reagents. Additionally, reactive imine derivatives or their addition products tend to coordinate to the catalytically active zinc complexes, therefore preventing the formation of a catalytic cycle.

Hence, at the outset of our study, a novel source for imines had to be found. Among other substrates, we examined the reactivity of *N*-(*tert*-butyloxycarbonyl)-α-(*p*-tolylsulfonyl)-benzylamine (**4a**), which, today, has successfully been applied as *N*-acyl imine precursor for a variety of catalyses and is readily available in a one-pot-synthesis from benzaldehyde, *tert*-butyl carbamate, and *p*-tolylsulfinic acid.[13,14] The reaction with zinc reagents proceeds *via* deprotonation of the carbamate **4a**, upon which elimination of the sulfinate takes place to form the *N*-acyl imine **5a**.[15] Although these compounds showed some reactivity in the reaction with dialkylzinc, only complex mixtures of products could be obtained. Some of the products could be identified by GC-MS analysis, indicating that addition to the imine bond had indeed occurred, whereas the formation of by-products was triggered by the attack of dialkylzinc on the carbonyl group of the carbamate.

We reasoned that replacing the carbamate for an amide would prevent the complexation of zinc species by the



Scheme 2 The Tomioka (top) and Hoveyda/Snapper (below) method for the synthesis of α-branched amines.

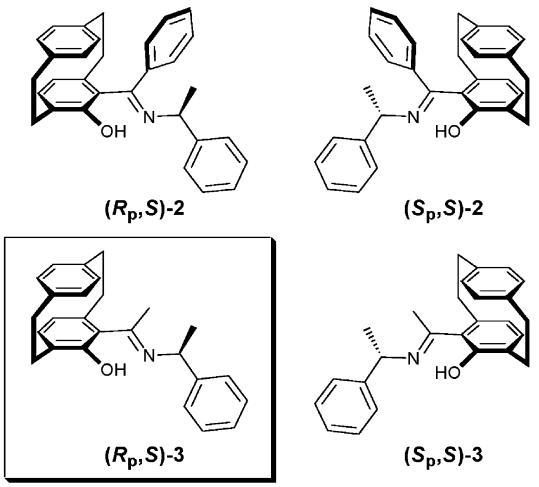


Fig. 1 [2.2]Paracyclophane–based ketimine ligands.

protecting group, thus avoiding attack on the carbonyl group. Therefore, we examined the applicability of the *N*-acetyl derivative **4b**.[14]

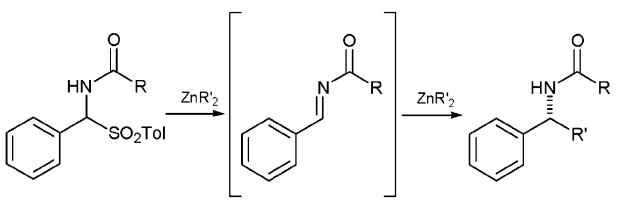
With this substrate, the addition reaction proceeded cleanly to give the alkylated *N*-acetyl amine **6b** as the only product. As ligands, we chose to employ the [2.2]paracyclophane-based *N*,*O*-ketimines **2** and **3** (Fig. 1).[16–18] A solvent screening indicated that hexane was the solvent of choice, giving up to 79% ee in the presence of 6 mol% of (R_p,*S*)-**3** (Table 1, entries 1–4). More polar solvents improved the yield while diminishing the enantioselectivity. In THF, only racemic product was obtained. By employing 3 equivalents of diethylzinc at 10 °C, the product was formed in 80% ee (entry 5).

To further improve the reaction conditions, we used the *N*-formyl derivative **4c** and subjected it to a ligand screening employing the four [2.2]paracyclophane-based *N*,*O*-ligands depicted in Fig. 1. Although we had expected an attack of the zinc species on the formyl group to a certain extent, the reaction proceeded smoothly to give the *N*-(1-phenylpropyl)-formamide **6c** in 61 to 95% ee in the presence of 1 mol% of the ligand (entries 7–10). We chose (R_p,*S*)-**3** for further investigation, as its broader substrate tolerance was known from previous work.

Functionalised substrates are generally well tolerated in dialkylzinc additions. Electron rich (Table 2, entry 5) and electron poor (entries 3, 4, 6, 7) substrates gave comparably high enantiomeric excesses of 90 to 95% ee. *Ortho*- and *para*-substituents did not influence the selectivity of the catalysis, (exception: entry 8), and even hindered imines were recognized with a very high level of enantioselectivity (entry 7). For *meta*-substituted substrates, however, ligand (R_p,*S*)-**2** gave superior results (entries 11, 13). A tenfold scale-up to 5 mmol of substrate (entry 2) gave identical results to the ones obtained on a 0.5 mmol scale.

Although the substrate tolerance was broad, each precursor had a relatively small temperature window for optimal enantioselectivity. As the solubility of the starting materials in hexane is very low, the deprotonation of the α-amido sulfone **7** to give the *N*-formyl imine is apparently the rate limiting step. The addition reaction itself was fast and proceeded even in the absence of a catalyst. The amount of available imine was thus controlled by careful choice of the temperature. Higher temperatures liberated the imine too fast, and thus, decrease the enantioselectivity due to the fast uncatalysed background reaction. Lower temperatures "froze"

Table 1 Substrate screening and optimisation of reaction conditions



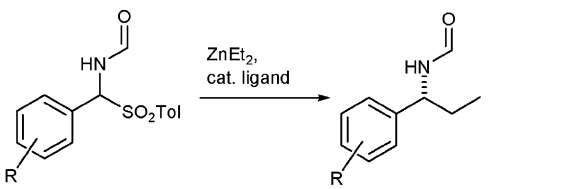
4a R = O*t*Bu
b R = Me
c R = H

5a-c **6a-c**

Entry	R′	Ligand (mol%)	Reaction conditions[a]	Yield (%)[b] (ee [%][c])
1	Me	(R_p,*S*)-**3** (6)	$ZnMe_2$, hexane, 0 → 20 °C	**6b** 57 (79)[d]
2	Me	(R_p,*S*)-**3** (6)	$ZnMe_2$, toluene, 0 → 20 °C	**6b** 99 (47)[d]
3	Me	(R_p,*S*)-**3** (6)	$ZnMe_2$, CH_2Cl_2, 0 → 20 °C	**6b** 95 (34)[d]
4	Me	(R_p,*S*)-**3** (6)	$ZnMe_2$, THF, 0 → 20 °C	**6b** 77 (0)[d]
5	Me	(R_p,*S*)-**3** (2)	$ZnEt_2$, hexane, 10 °C	**6b** 50 (80, *R*)[e]
6	Me	(R_p,*S*)-**3** (2)	$ZnEt_2$, hexane, 20 °C	**6b** 92 (63, *R*)[e]
7	H	(R_p,*S*)-**2** (1)	$ZnEt_2$, hexane, 10 °C, 36 h	**6c** 92 (95, *R*)[e]
8	H	(S_p,*S*)-**2** (1)	$ZnEt_2$, hexane, 10 °C, 36 h	**6c** 90 (92, *R*)[e]
9	H	(R_p,*S*)-**3** (1)	$ZnEt_2$, hexane, 10 °C, 36 h	**6c** 93 (93, *R*)[e]
10	H	(S_p,*S*)-**3** (1)	$ZnEt_2$, hexane, 10 °C, 36 h	**6c** 92 (61, *S*)[e]

[a] Reaction time 16 h unless stated otherwise. [b] Determined by GC analysis of the crude reaction mixture. [c] Determined by GC_{CSP} or HPLC. [d] 2 equiv. of $ZnMe_2$ as a 1 M solution in toluene. [e] 3 equiv. of $ZnEt_2$ as a 1 M solution in hexane.

Table 2 Scope and limitation. Substrate spectrum of the diethylzinc addition to imines[a]



7 **8**

Entry	R	Ligand (mol%)	*T*/°C	*t*/h	Yield[b] (%)	ee[c] (%)
1	H	(R_p,*S*)-**3** (2)	10	36	>99	95 (*R*)
2	H	(R_p,*S*)-**3** (2)	20	16	>99	93 (*R*)[d]
3	4-Cl	(R_p,*S*)-**3** (2)	20	3	>99	89 (*R*)
4	4-Cl	(R_p,*S*)-**3** (5)	20	1	97	90 (*R*)
5	4-OMe	(R_p,*S*)-**3** (2)	20	16	97	95 (*R*)
6	4-CO_2Me	(R_p,*S*)-**3** (2)	0	36	90	94 (*R*)
7	2,6-Cl_2	(R_p,*S*)-**3** (2)	0	36	98	95 (*R*)
8	4-*t*Bu	(R_p,*S*)-**3** (2)	0	24	>99	75 (*R*)
9	4-Me	(R_p,*S*)-**3** (2)	10	24	>99	95 (*R*)
10	3-Cl	(R_p,*S*)-**3** (2)	0	24	94	84 (*R*)
11	3-Cl	(R_p,*S*)-**2** (5)	0	24	99	93 (*R*)
12	3-Me	(R_p,*S*)-**3** (2)	−10	24	>99	70 (*R*)
13	3-Me	(R_p,*S*)-**2** (5)	−15	24	97	91 (*R*)

[a] 0.5 mmol imine precursor **7**, 3 equiv. $ZnEt_2$, hexane. [b] Determined by GC analysis of the crude reaction mixture. [c] Determined by GC_{CSP} or HPLC. [d] 5 mmol scale.

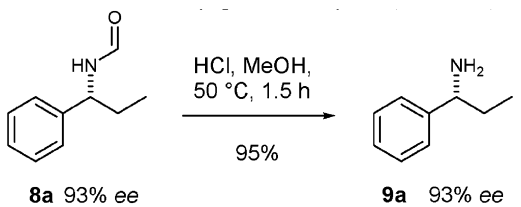
the reaction due to the diminished solubility of the starting material.

The deprotection of *N*-formyl amine product **8a** proceeded smoothly and furnished the (*R*)-phenylpropylamine **9a** free of racemisation and in nearly quantitative yield (Scheme 3).

Enantiomerically pure diarylmethylamines are also important intermediates in the synthesis of biologically active compounds (Fig. 2).[19] Among several drug candidates, Cetirizine hydrochloride (**11**) stands out as a commercially important non-sedating antihistamine agent. Binding studies indicate that the pure (*R*)-enantiomer displays a better pharmacological profile than the racemate. Despite the importance of enantiopure diarylmethylamines, synthetic access and notably asymmetric (catalytic) variants are rather limited.[8] While there are several synthetic routes to *e.g.* enantiopure Cetirizine employing either resolution techniques, stoichiometric amounts of chromium complexes,[20] or diastereoselective approaches *via* chiral auxiliaries, there have been only few reports on the asymmetric catalytic addition of an organometallic arylation agent to an imine derivative, most of which are very recent.[21,22] When we started our work on diarylmethylamines, Hayashi and Ishigedani had described a highly enantioselective rhodium-catalysed process for the arylation of *N*-sulfonylimines with aryl stannanes in up to 96% ee (Scheme 4).[23] This method gave rise to diarylmethylamines **10** in high enantioselectivities but required the use of 5 equivalents of the stannane in order to obtain the products in high yield.

Although phenyl zinc addition to aldehydes was a well established process at that time, its transfer to imines had proved to be difficult. This is mostly due to the much higher reactivity of diphenylzinc as compared to dialkylzinc and thus the concomitant rapid uncatalysed background reaction.[24]

The catalytic procedure for the enantioselective addition of organozinc to masked *N*-formyl imines using catalytic amounts of [2.2]paracyclophane-based ketimines was



Scheme 3 Deprotection of *N*-formyl amines.

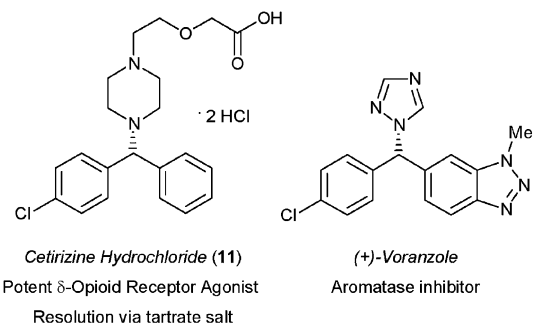
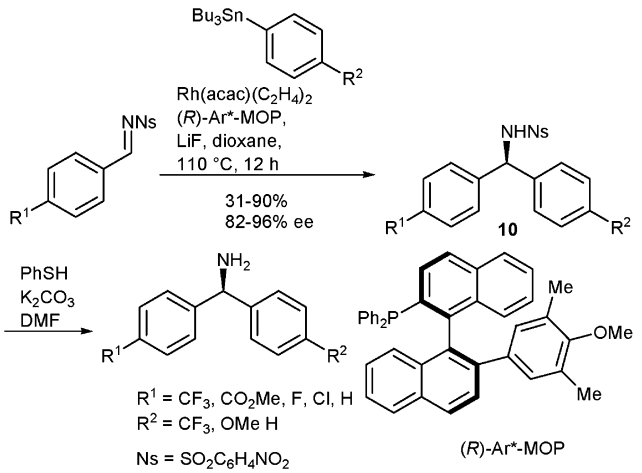


Fig. 2 Biologically active diarylmethylamines.



Scheme 4 Enantioselective arylation of *N*-sulfonylimines with aryl stannanes.[23]

nevertheless investigated with aryl zinc reagents. In a fruitful cooperation with the Bolm group at the RWTH Aachen, we were able to develop the first highly enantioselective phenylzinc addition to imines, giving rise to optically active diarylmethylamines in very high enantiomeric excess.[25]

At the outset of this study, a range of different *N*,*O*-ligands (Fig. 1 and 3) was examined in the phenylation of *N*-formyl-α-(*p*-tolylsulfonyl)-*p*-methylbenzylamine (**14a**, Table 3). We started out by using the reaction conditions developed for the enantioselective phenyl transfer to aldehydes, using a mixed zinc reagent formed *in situ* from diphenylzinc and diethylzinc. This reagent selectively transferred only the phenyl moiety to the substrate, affording *N*-formyl amine **16a** in very high yield, and without formation of the corresponding ethylation product.

A ligand screening showed that ferrocene (R_p,*S*)-**12** and cyrhetrene **13**, which at that time represented the best ligands for the enantioselective phenyl transfer to aldehydes (up to 99% ee), gave only moderate enantioselectivities in the addition to imine precursor **14a**. In contrast, the use of [2.2]paracyclophane-based ketimines **2** and **3** gave rise to

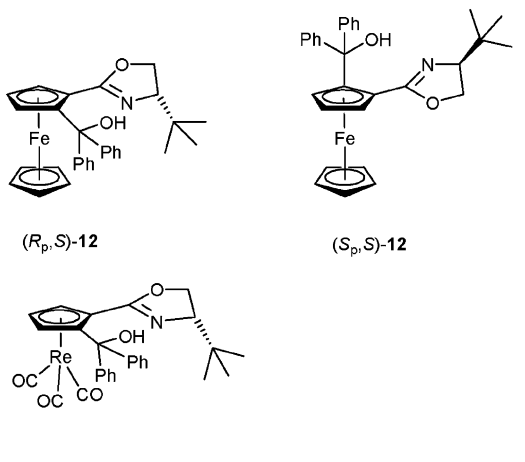


Fig. 3 *N*,*O*-Ligands used in the arylation of imines.

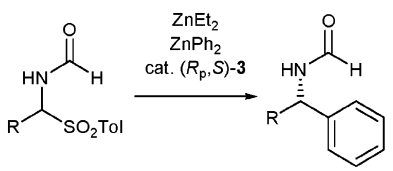
N-formyldiarylmethylamines in good to excellent enantioselectivities (up to 97% ee). Ketimine (R_p,*S*)-**3**, producing the best results in the ligand screening, was chosen for further optimisation studies.

Toluene proved to be the solvent of choice, while in hexane only moderate yields were obtained. The amount and ratio of zinc reagents was varied and found to be optimal with respect to yield and enantioselectivity when two equivalents of both diphenylzinc and diethylzinc were applied. When diphenylzinc was used alone, the enantiomeric excess was slightly lower as compared to the application of the mixture. This can be explained by a faster and therefore more competitive uncatalysed background reaction of diphenylzinc in contrast to the modified reagent formed from diphenylzinc and diethylzinc.

In analogy to the addition of dialkylzinc to imines the reaction temperature had a significant impact on the stereochemical outcome of the process. For *N*-formyl-α-(*p*-tolylsulfonyl)-*p*-methylbenzylamine (**14a**) as the substrate, the highest enantiomeric excess of 97% ee was obtained at −20 °C. At −40 °C not only the ee dropped significantly, but also the yield was diminished.

In order to demonstrate the broad applicability of the method, a wider range of substrates was applied in the title reaction (Table 3). The results revealed that aromatic imine precursors with different electronic properties as well as different substitution patterns were equally well tolerated. The substrates can be electron-rich or electron-poor, and even sterically hindered imines with a double *ortho*-substitution gave excellent results (95% ee, entry 8). Only *meta*-substituted starting material gave a product with a slightly lower ee-value (89% ee, entry 7). Interestingly, the same effect was observed in the diethylzinc addition to imines using (R_p,*S*)-**2** and (R_p,*S*)-**3**.[18] A decrease of catalyst loading resulted in the formation of products with slightly or significantly lower enantiomeric excess, depending on the substrate (entries 2, 4, 5).

Table 3 Substrate spectrum for the phenyl transfer to imines[a]



14a-g **15a-g**

Entry	R	Product	(R_p,*S*)-**3** (mol%)	Yield[b] (%)	ee[c] (%)
1	4-MeC_6H_4	**16a**	10	99 (85)	97 (+)
2	4-MeC_6H_4	**16a**	5	99	94 (+)
3	4-ClC_6H_4	**16b**	10	99 (82)	94 (+)-(*R*)
4	4-ClC_6H_4	**16b**	5	99	81 (+)-(*R*)
5	4-ClC_6H_4	**16b**	1	98	69 (+)-(*R*)
6	4-MeOC_6H_4	**16c**	10	99 (75)	97 (+)
7	3-MeC_6H_4	**16d**	10	98	89 (+)
8	2,6-$Cl_2C_6H_4$	**16e**	10	99 (89)	95 (+)
9	4-*t*BuC_6H_4	**16f**	10	98 (81)	96 (+)
10	4-COOMeC_6H_4	**16g**	10	99 (80)	95 (−)

[a] Reactions were carried out in toluene at −20 °C for 12 h, 2 equiv. $ZnPh_2$, 2 equiv. $ZnEt_2$, with 0.25 mmol of imine precursors **14a–g**. [b] Determined by ^{1}H NMR. Yields in parenthesis refer to yields after column chromatography. [c] Determined by HPLC using a chiral stationary phase.

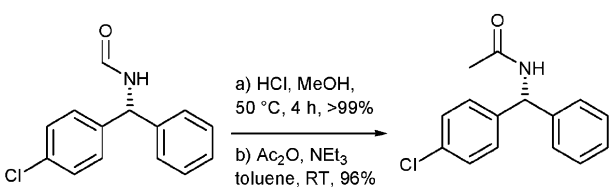
The deprotection of *N*-formyl amines **15** to the free amines can again easily be achieved by acidic methanolysis (Scheme 5). For *N*-formyl amine **15b** it was shown that the deprotection proceeds quantitatively and without racemisation. The absolute configuration of **15b** was assigned to be (*R*) by comparison of the specific optical rotation of free amine (−)-**16b** with the literature value. This is consistent with the asymmetric induction observed in the diethylzinc addition to imines in the presence of (R_p,*S*)-**2** and (R_p,*S*)-**3**.[18] The enantiomeric excess of *C*-(4-chlorophenyl)-*C*-phenylmethylamine was determined by HPLC analysis of *N*-[(4-chlorophenyl)phenylmethyl] acetamide (**16b**), obtained by treatment of the amine with acetic anhydride and triethylamine.

Compared to aldehyde substrates, imines were attacked by the zinc reagents on the opposite enantiotopic face when the same ketimine ligands were used. Thus (R_p,*S*)-**2** gave the *R*-configured amines, while, in the case of comparable aldehydes, usually the *S*-configured alcohols were produced. We assume that the transition state for the organyl transfer is much different for imines and aldehydes. Although the mechanism is not yet fully understood, the experimental results and preliminary DFT studies indicate a coordination of the imine to the active zinc catalyst *via* the carbonyl oxygen atom in the transition state.

Asymmetric amination of α,α-disubstituted aldehydes

Fully substituted stereogenic centres with an adjoined amine functionality were still not accessible by the aforementioned routes, since simple ketimines were not viable substrates for asymmetric 1,2-additions. Since we required α-alkylated phenylglycines for various projects, we envisaged the organocatalytic modification of aldehydes. Although by the time we started our work in 2003, a large variety of organo-catalytic reactions was already known,[26] there was no information available, whether α,α-disubstituted aldehydes were suitable substrates in enamine catalysis.

Encouraged by the successful utilisation of azodicarboxylates as nitrogen electrophiles in the asymmetric α-amination of carbonyl compounds using catalytic chiral copper(II)-bisoxazoline complexes,[27] both Jørgensen and List almost simultaneously examined the possibilities of proline as a catalyst for the asymmetric reaction of aldehydes with azodicarboxylates.[28] Shortly thereafter, Jørgensen and co-workers also reported on the proline-catalysed asymmetric α-amination of ketones.[29]



15b (94% *ee*) **16b** (94% *ee*)

Scheme 5 Deprotection and protection of *N*-formyl amines.

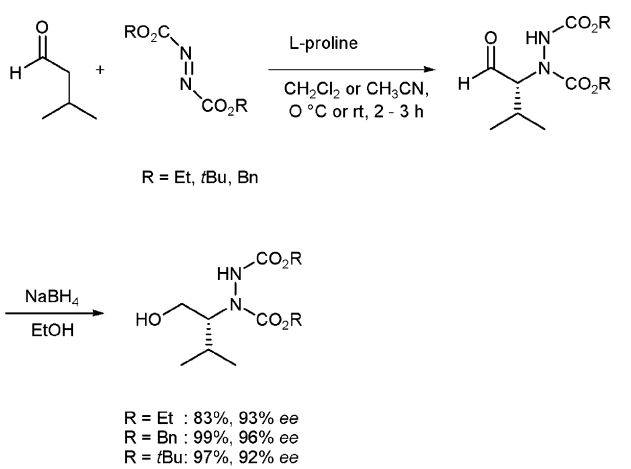
The procedure is remarkably simple: 1.5 equivalents of aldehyde or ketone are added at room temperature to a stirred solution of 1 equivalent of the azodicarboxylate and substoichiometric amounts of the catalyst in acetonitrile or dichloromethane.

A range of α-unbranched aldehydes and ketones was thus aminated in excellent enantioselectivities.[28,29] For the ketones, high regioselectivity can be observed, resulting in the amination of the higher substituted α-carbon. While no tendency in terms of stereoselectivity can be extracted from the experiments carried out with aldehydes, the enantiomeric excess of the ketones seems to increase with the size of the substituent adjacent to the α-carbon taking part in the reaction. This, on the other hand, appears to happen at the expense of regioselectivity, which is decreased slightly at the same time. Among the azodicarboxylates tested were diethyl azodicarboxylate (DEAD), diisopropyl azodicarboxylate, and dibenzyl azodicarboxylate (DBAD), but no unique preference for one or the other in terms of stereoselectivity can be noted (Scheme 6).

Intrigued by these results and driven by the need for a smooth synthetic route towards α-substituted arylglycines, we decided to investigate into the α-amination of α,α-disubstituted aldehydes.[30,31] This route leads to an interesting class of compounds. Especially the α-alkyl-α-aryl-substituted species exhibit particular biological activity, such as α-methyl-4-carboxyphenylglycine, which acts as a metabotropic group I/group II glutamate receptor antagonist.

Furthermore, it opens access to a completely new set of Evans-type oxazolidinones and chiral *N*-amino oxazolidinones, which could be used as chiral auxiliaries in asymmetric reactions.[32,33]

The required α,α-disubstituted aldehydes can be either purchased from commercial suppliers or, in the case of α-aryl-substituted aldehydes, be obtained in a convenient two-step synthesis from the corresponding acetophenones *via* Wittig reaction with (methoxymethyl)triphenylphosphonium chloride, followed by acidic cleavage of the resulting enol ether.[31] Alternatively, the acetophenone can be converted to the corresponding epoxide in a Corey–Chaikovsky procedure,[31] followed by an indium(III)-catalysed rearrangement to give the desired aldehyde.[31]



Scheme 6 The proline-catalysed α-amination of α-unbranched aldehydes.[28,29]

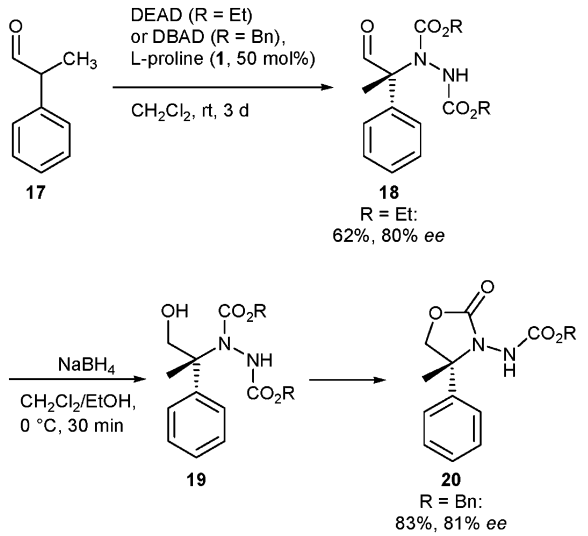
These α-branched racemic aldehydes can be aminated in moderate to good yield and enantiomeric excess of up to 86% ee following the aforementioned procedure by List and Jørgensen (Scheme 7).[30] The resulting products contain a fully substituted carbon centre in the α-position. This was the first example for the application of α-branched aldehydes in a proline-catalysed process.

In contrast to the α-hydrazino-aldehydes synthesised by List and Jørgensen, the product **18**, arising from the amination of hydratropaldehyde (**17**) with DEAD or DBAD, possesses configurational stability due to the absence of an acidic α-proton, and thus can be isolated without racemisation. If, on the other hand, reduction of the carbonyl group was carried out using sodium borohydride, the resulting alcohol **19** would spontaneously undergo intramolecular substitution to form chiral oxazolidinone **20**, provided that DBAD was employed in the amination step.

Of the different solvents tested in the reaction of hydratropaldehyde with DEAD in the presence of L-proline, dichloromethane produced the best results in terms of enantioselectivity and was therefore used in the following studies.

The α-amination of aliphatic α,α-disubstituted aldehydes such as 2-methylbutyraldehyde only produced a moderate enantiomeric excess of 28% ee, with the stereoselectivity even decreasing with increasing length of the alkyl chains. However, a remarkable improvement in terms of enantioselectivity was observed when the reaction was applied to α-alkyl-α-aryl substituted aldehydes. These substrates were found to result in 81% ee in the case of α-methyl-α-phenyl substituted hydratropaldehyde and even 86% ee in the case of the 2-naphthyl substituted analogues (Fig. 4).

The reaction tolerates a wide range of substitution patterns for the aryl-substituent, accepting electron-releasing methoxy-groups in *para* and *meta* position. as well as an electron



Scheme 7 Proline-catalysed α-amination of α-branched hydratropaldehyde **17** and subsequent reduction of the hydrazino aldehyde **18** to form oxazolidinones **20** by intramolecular substitution.[30]

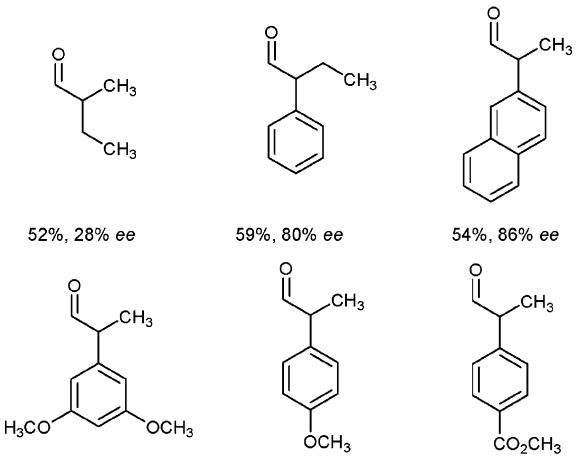


Fig. 4 A selection of α,α-disubstituted aldehydes successfully converted in the proline-catalysed α-amination with diethyl azodicarboxylate (DEAD).[30]

withdrawing methoxycarbonyl group in *para* position, with only slight deviation in stereoselectivity. Above that, no significant change of the enantiomeric excess was observed when the α-methyl group was exchanged for an ethyl group.

To elucidate the role of the azodicarboxylate, both DEAD and DBAD were reacted with hydratropaldehyde. But again, the reaction proved to be rather indifferent to the type of azodicarboxylate involved. The much bulkier di-*tert*-butylazodicarboxylate did not lead to a successful conversion of hydratropaldehyde. The central role of L-proline as a catalyst for this process was shown by exchange for the four-membered ring analogue, L-azetidinecarboxylic acid. In all cases, the detected ee's were significantly lower than in the reactions carried out with L-proline. This was most probably due to a different set of geometrical parameters, leading to an impairment in the coordination of the azodicarboxylate by the enamine in the transition state. Based on extensive studies into the mechanism of proline-catalysed aldol and Mannich reactions,[34,35] it was postulated that in this reaction type the formation of an *E*-enamine between the aldehyde and proline – with the enamine bond *anti* to the carboxylic moiety – is followed by the addition of the electrophile. Facial selectivity is induced by the carboxylic acid transferring its proton to the azodicarboxylate to compensate for the negative charge. This transition state model is consistent with the experimentally determined configuration of the amination products.[28,30]

Blackmond *et al.* had observed an accelerating reaction rate and a positive non-linear effect for the proline-catalysed α-amination of α-unbranched aldehydes with azodicarboxylates, as well as the α-aminoxylation with nitroso benzene.[36] Since the reaction times for the proline-catalysed α-amination of α,α-disubstituted aldehydes are considerably elongated in comparison to α-unbranched species (within several days in contrast to a few hours), it can be concluded that the aforementioned acceleration does not occur in the latter case.

The conversion of the amination product into Evans-type oxazolidinones can be effected in several ways. The removal of the *N*-protecting group and cleavage of the hydrazine-bond can be achieved by hydrogenation of the open benzyloxycarbonyl (= Cbz)-protected product over Raney nickel in methanol/acetic acid, followed by ring closure with phosgene and triethylamine in dichloromethane.[28a] Alternatively, the Cbz-group in the *N*-protected oxazolidinone **20** can be removed by hydrogenation using palladium/charcoal in acetic acid/methanol at ambient pressure to give the *N*-aminooxazolidinone **21**. The hydrazine bond can then be cleaved by treatment with either Zn/acetone in acetic acid or with sodium nitrite in acetic acid/HCl (Scheme 8).[28b,30]

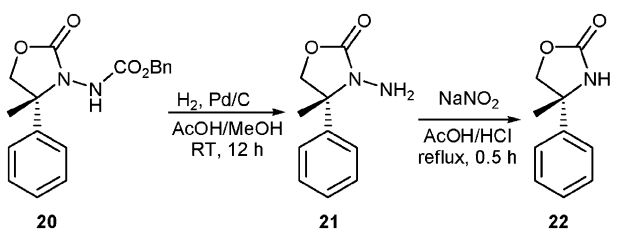
Access to the corresponding *N*-protected amino acid esters is given by mild oxidation of the *N*-Boc-protected amination product with sodium chlorite, followed by esterification with trimethylsilyl diazomethane. Cleavage of the protective groups with trifluoroacetic acid (TFA) and samarium iodide then affords the free amino acid ester, which can be protected in the α-amino position with Boc-anhydride and 4-dimethylaminopyridine (DMAP).[37]

The scope of the organo-catalysed α-amination of α,α-disubstituted aldehydes with azodicarboxylates was extended by Barbas and co-workers, who used the reaction in the synthesis of two metabotropic glutamate receptor antagonists, AIDA and APICA.[38] In these reactions, indane carbaldehyde and analogous compounds having an ester functionality, leading to AIDA, or a bromo-substitutent, which was later converted to a phosphate in the case of APICA, were reacted with DBAD in the presence of L-proline as the catalyst. The products, possessing fully substituted stereogenic centres, were obtained in excellent enantioselectivities (99% ee).

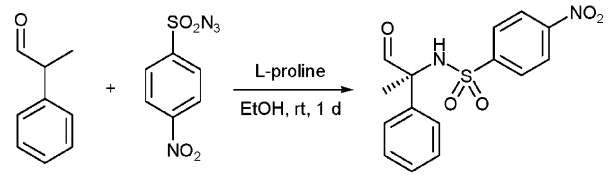
For the preparation of the cell adhesion inhibitor BIRT-377, the direct α-amination of a 2-methylpropanal derivative with dibenzyl azodicarboxylate was accomplished using a L-proline-derived tetrazole catalyst, providing the desired aldehyde in excellent yield and stereoselectivity.[37]

Since the methods available for deprotection of the hydrazides obtained by the α-amination with azodicarboxylates were at that point rather unsatisfactory, the search for other nitrogen electrophiles allowing for easier deprotection of the aminated product culminated in the application of sulfonyl azides.[39] To our surprise, reaction with α,α-disubstituted aldehydes in the presence of L-proline did not result in the corresponding triazenes but, even more conveniently, in α-sulfamidated products. Thus, the reaction of hydratropaldehyde **17** with 4-nitrobenzenesulfonyl azide (4-nosyl azide, **23a**) delivered the product **24a** in 52% yield and 82% ee (Scheme 9).[40]

A screening of different solvents revealed that alcohols deliver the best results in terms of both yields and enantioselectivity. An interesting solvent-effect was observed in the



Scheme 8 Conversion of amination product to Evans-type oxazolidinones.[30]



Scheme 9 Proline-catalysed α-sulfamidation of hydratropaldehyde with 4-nosyl azide.

reaction of hydratropaldehyde with 2-nitrobenzenesulfonyl azide (2-nosyl azide). Thus, reaction in technical ethanol, denatured with 1% petroleum ether, delivered products in significantly higher enantiomeric excess (67% ee) than reaction in absolute ethanol (55% ee). The role of the alkane additive in the observed stereochemical enhancement was confirmed in a series of reactions involving different alkane additives (pentane to decane) in combination with absolute ethanol.

Interestingly, a likewise effect was not observed, when 4-toluenesulfonyl azide (tosyl azide) was applied in the reaction. In this case however, reaction in *N*-butyl-*N*′-methylimidazolium tetrafluoroborate ([bmim][BF_4]), an ionic liquid, resulted in an increase in stereoselectivity in comparison to ethanol (72% ee compared to 59% ee). Different ionic liquids were tested for their potency in improving efficiency and selectivity of the reaction. However, none was superior to [bmim][BF_4] or even ethanol.

Although a number of different organo-catalysts proved to be capable of catalysing the reaction of hydratropaldehyde with tosyl azide or 2-nosyl azide, L-proline was found to be the best choice, when regarding the combination of yield and stereoselectivity. In this context, an important observation was made for a deeper understanding of the reaction details. Thus, *all* catalysts tested in the reaction, including **25** and **26** (Fig. 5), delivered products with the same absolute configuration for the major enantiomer. This is in contradiction to results reported by Jørgensen *et al.* for the application of catalysts related to **26**. In a number of different enamine catalysis reactions, this class of catalysts resulted in opposite stereochemistry, when compared to products obtained by application of L-proline. This was explained by different modes of stereoinduction: while proline actively directs the incoming electrophile to one enamine face by hydrogen-transfer from the carboxylic group to the β-position of the forming product, catalysts of type **26** effect the shielding of the corresponding enamine face, thus forcing the electrophile to react at the opposite face. The results for the α-sulfamidation thus suggest, that stereoinduction in this reaction is *generally* exerted by shielding of one enamine face, regardless of the catalyst involved.

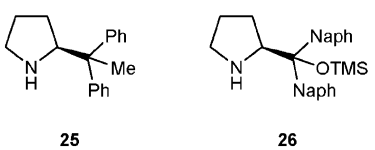


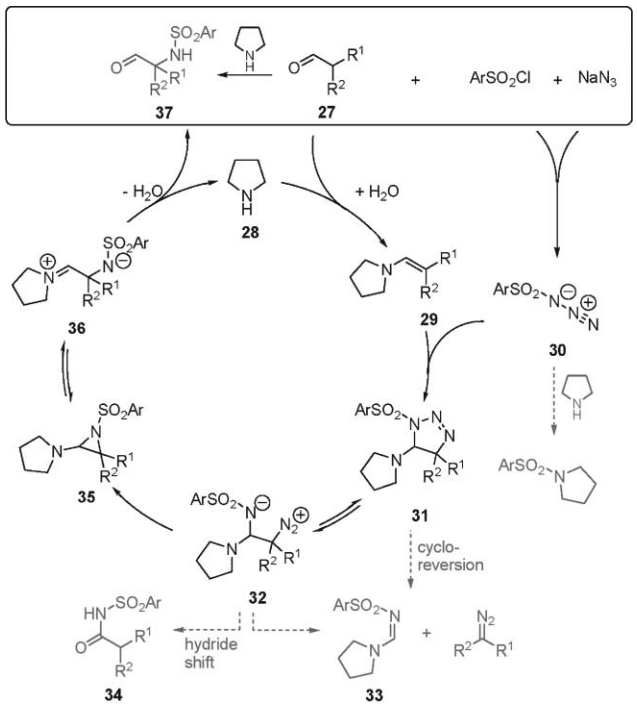
Fig. 5 Organocatalysts used in the α-sulfamidation of hydratropaldehyde with 2-nosyl azide.

The influence of the azide species on the outcome of the reaction proved to be difficult to evaluate. A number of divergent influences seem to determine the dependence of electronic and steric properties on stereoselectivity and efficiency. Thus, electron deficient 4-nosyl azide delivered the highest enantiomeric excess (82% ee), followed by more electron rich 3,4-dimethoxybenzenesulfonyl azide (67% ee), 1- and 2-naphthalenesulfonyl azide (65 and 63% ee, respectively), tosyl azide (59% ee), and then electron deficient 2-nosyl azide (56% ee). The most electron deficient perfluorobutanesulfonyl azide displayed high reactivity (reaction completed within 1 h), nevertheless, both yield and stereoselectivity remained rather low (24% yield, 29% ee). In contrast, electron deficient methanesulfonyl azide resulted in comparatively high stereoselectivity (71% ee) but low yield (33%).

A somewhat more consistent picture arises, when comparing the yields obtained from different aldehydes. All-aliphatic aldehydes delivered the products in comparatively high yield (around 50%), but low enantiomeric excess (between 5 and 28% ee). In contrast, the presence of the α-phenyl-substituent in hydratropaldehyde seemed to effect a slight decrease in reactivity (38% yield), but a considerable increase in stereoselectivity (56 to 86% ee, depending on the azide species employed). Upon increasing the electron density of the aromatic system by introduction of a methoxy-substituent, the enantioselectivity of the reaction with 2-nosyl azide was further increased to 72–86% ee. However, the position of the methoxy-substituent seemed to play a vital role for both efficiency and selectivity. Thus the reaction of the *ortho*-methoxy-substituted species with 2- or 4-nosyl azide delivered the products in less than 30% yield, as well as the lowest enantiomeric excess in the series of monomethoxy-substituted arylpropionaldehydes. When a second methoxy-substituent was added, the negative effect of *ortho*-substitution on the yields seemed to be partly compensated by the increase in electron density; this was however at the expense of stereoselectivity.

Crystal structures were obtained from several products by X-ray analysis. In all the cases, in which enantiopure crystals were obtained, (*S*)-configuration was assigned to the product. The findings described above can not be satisfactorily explained by the pathway usually ascribed to enamine catalysis reactions.[26] Based on the nature of main and by-products isolated in the reaction of hydratropaldehyde with tosyl azide catalyzed by pyrrolidine, and in accordance with literature published earlier in this field,[41] we therefore proposed a mechanism including as a central step the regioselective 1,3-dipolar cycloaddition of the sulfonyl azide **30** to the enamine **29**,[42] formed *in situ* between aldehyde **27** and amine catalyst **28**.[43] This reaction step can be characterised as a Sustmann type III cycloaddition, with predominant interactions between the dipole's LUMO and the dipolarophile's HOMO,[44] leading to the regioselectivity displayed in Scheme 10. The configuration, as well as the conformation of the enamine should be decisive for the stereochemical outcome of the reaction.

The triazoline intermediate **31**, resulting from the cycloaddition step, opens spontaneously to form betaine **32**, which is a widely accepted intermediate in a number of rearrangement reactions involving triazolines. The opening of triazoline **31** is

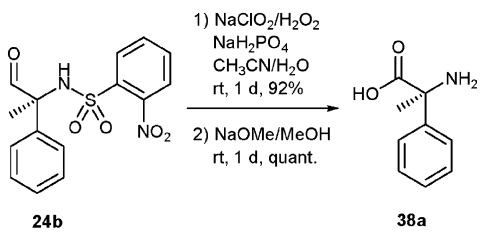


Scheme 10 Proposed mechanism for the pyrrolidine-catalysed α-sulfamidation of α-branched aldehydes with sulfonyl azides.

followed by the loss of dinitrogen under formation of aziridine **35**, which in turn opens to form the α-amidated iminium compound **36**. Hydrolysis finally furnishes the α-sulfamidation product **37**.

Since unprotected α-amino aldehydes are usually not chemically stable,[45] the carbonyl group of the sulfamidated product has to be transformed prior to deprotection of the amino group. This can be achieved either by treatment of the ethanolic reaction mixture with sodium borohydride after the reaction is completed, to yield the corresponding α-amino alcohol, or by oxidation of the isolated product **24b** with sodium chlorite and hydrogen peroxide to yield the corresponding α-amino acid **38a**.[46] *N*-Deprotection of the latter was achieved by treatment with methanolic sodium methylate solution (Scheme 11).[47]

Recently, we discovered that chloroamine-T is a potent reagent to yield sulfamidated aldehydes **24** and ketones in good to excellent yields.[48] However, the asymmetric version of this process has yet to be explored. Initial studies with quaternary ammonium salts gave selectivities up to 25% ee.[49]



Scheme 11 Deprotection of the α-sulfamidation products after oxidation.

In conclusion, we have presented asymmetric metal-catalysed and organo-catalytic approaches towards the synthesis of chiral, α-branched amines. Currently we are using these methods for the generation of biogenic structures.

Acknowledgements

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