Advanced Synthesis & Catalysis

DOI: 10.1002/adsc.201400824

Enantioselective Preparation of 3-Arylcycloalkylamines by Rhodium-Catalyzed 1,4-Addition and Subsequent Stereodivergent Reduction

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Received: August 19, 2014; Revised: October 10, 2014; Published online: ■■ ■■, 0000

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201400824.

Abstract: *N*-Sulfonylimines of cycloalk-2-enones are well-suited for the enantioselective rhodium(I)/binap-catalyzed 1,4-additions of arylzinc halides. The cyclic enamides, obtained after quenching, are sensitive towards chromatography, but can undergo diastereoselective reductions to furnish *cis*- or *trans*-3-arylcycloalkylamines with five- to seven-membered rings. The 1,4-addition is not influenced by a methyl group at C-5 of six-membered rings, providing further configurational options. 3-Arylcycloalkylamines are subunits in a number of bioactive substances and can also be oxidatively transformed into cyclic γ-amino acids.

Keywords: asymmetric catalysis; conjugate addition; rhodium; sulfonamides; zinc

Introduction

The conjugate addition of non-stabilized carbon nucleophiles to α,β-unsaturated carbonyls belongs to the fundamental reactions in organic chemistry.[1] On the one hand, it leads to C,C bond formation, on the other hand, the saturated ketones thus obtained – or the enolates initially formed – can be used for various subsequent transformations.[2] Even 17 years after publication of the first highly enantioselective protocol for such 1,4-additions,[3] much effort is still being spent on further improvements and broadening of the synthetic applicability.[4] Besides enones, asymmetric catalysis has frequently been performed on substrates activated by cyano, sulfonyl, phosphonyl, or nitro groups,[1b,5] but only rarely using α,β-unsaturated imines.[6–9] This is surprising in view of the high relevance of nitrogen-containing moieties in nature, as especially amino groups occur ubiquitously in natural and artificial bioactive compounds. Enantiopure amines, however, ought to be efficiently prepared from the products of such conjugate additions to α,β-unsaturated imines. The reported examples of this transformation comprise Cu-catalyzed enantioselective 1,4-additions of dialkylzinc to acyclic *N*-sulfonylimines[6a,b] or to acyclic *N*-aryl-α-imino esters,[6c] but enantioselectivities do not exceed 91% *ee*. Moreover, the initially formed saturated imines – or their tautomeric enamines – were either hydrolyzed to the respective carbonyls or transformed by oxidative cleavage of the C,C double bonds of the enamines. Subsequent transformation to amines was reported in only one single example by hydrogenation over Pd/C to furnish an 82:18 mixture of diastereomers.[6c]

Recently, we reported the first preparation of cycloalk-2-enone-derived *N*-sulfonylimines[10] as well as their transformation in highly enantioselective Rh(I)/binap-catalyzed additions of methyl- and arylaluminum reagents.[11] The 1,2- *versus* 1,4-selectivity of this reaction is influenced by several factors, and we have initially performed optimization towards 1,2-addition to deliver valuable α-tertiary cycloalk-2-enylamides, which can be applied to the preparation of α-quaternary α-amino acids. However, the products of 1,4-addition are interesting compounds in their own right because subsequent diastereoselective reductions could deliver 3-substituted cycloalkylamines with *cis*- or *trans*-configuration at the ring. This structure, especially in the case of six-membered rings, is commonly found in pharmaceutically active compounds.[12,13] We now report on the highly regio- and enantioselective Rh-catalyzed conjugate additions of various aryl groups to *N*-sulfonyl ketimines with subsequent stereodivergent reduction.[14]

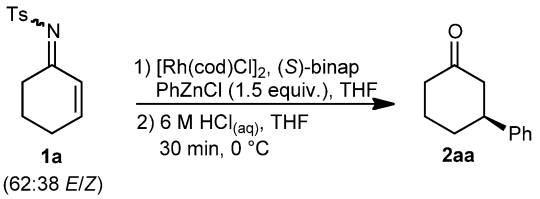
In our previous study, we had observed that the Rh(I)/binap-catalyzed addition of $PhAlMe_2$ to the cyclohex-2-enone-derived *N*-tosylimine occurs with poor regioselectivity and yields a 2:3 mixture of the 1,2- and the 1,4-adducts.[11] In contrast, the Hayashi–Miyaura reaction, i.e., the Rh-catalyzed enantioselective addition of aryl nucleophiles to α,β-unsaturated ketones, proceeds with complete 1,4-selectivity when using boron-, titanium-, zinc-, silicon-, or tin-based reagents.[15] For conjugate addition to the respective imines, the use of arylzinc halides[16] appeared to be most attractive due to their smooth and efficient preparation, their functional group tolerance which is paired with high reactivity, and their application in aprotic media which precludes the risk of the *N*-tosylimines being hydrolyzed under the reaction conditions.

Results and Discussion

As a starting point, we studied the Rh(I)/binap-catalyzed addition of PhZnCl to ketimine **1a** which is obtained in a 66% yield by condensing cyclohex-2-enone and *p*-$TsNH_2$.[10] The zinc reagent was prepared from the respective aryl bromide by sequential treatment with *n*-BuLi or *t*-BuLi and then $ZnCl_2$ in THF,[17] and after the addition reaction, the crude mixtures were immediately hydrolyzed under acidic conditions to enable convenient GC analysis of ketone **2aa** (Table 1). With 5 mol% of rhodium, i.e., 2.5 mol% of the dimeric pre-catalyst $[Rh(cod)Cl]_2$, a fast reaction was observed at 0 °C, and (*S*)-**2aa** was obtained in excellent yield and *ee* (entry 1). Thus, tosylimine **1a** appears to be more reactive towards this transformation than the corresponding enone, but the facial selectivity is the same for both substrates.[16a] Moreover, both (*E*)- and (*Z*)-**1a** reacted equally well. Performing the reaction at room temperature, the catalyst loading could be reduced to 2 mol% rhodium without any deterioration (entry 2), while a slightly lower chemoselectivity was observed with 1 mol% (entry 3). Slow addition of PhZnCl did not lead to an improvement (entry 4), and formation of the phenylzinc halide from the respective Grignard reagent rather than from phenyllithium caused a substantially lower enantioselectivity (entries 5 and 6). The presence of magnesium salts may lead to some background reactivity;[18] in contrast, no 1,4-addition was observed in the absence of the rhodium catalyst when the zinc reagent was prepared from phenyllithium.

Quenching of the reaction mixture under slightly alkaline conditions led to the isolation of the respective enamide **3aa** as the sole product, however, it could not be purified due to decomposition upon column chromatography (Table 2). For the preparation of cycloalkylamines, the crude enamide was therefore directly subjected to reduction, but $NaBH_4$ led to an unselective hydride addition (entry 1). Similar observations have been noted by Hutchins et al. when reducing the *N*-(diphenyl)phosphinylimine derived from 3-methylcyclohexanone, while high *cis*- or *trans*-selectivity was reported with *t*-$BuNH_2{\cdot}BH_3$ or L-Selectride®, respectively.[19] Indeed, the former reagent led to a 13:87 *dr*, and *cis*-**4aa** was obtained in

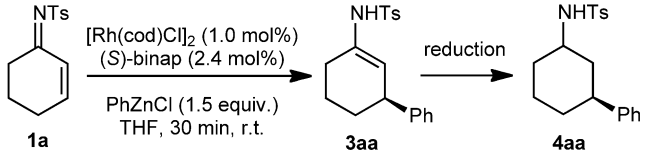
Table 1. Optimization of the 1,4-addition.



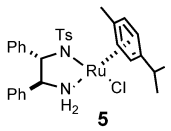
Entry	$[Rh(cod)Cl]_2$ [mol%]	*t* [min]/ *T* [°C]	Conversion [%][a]	Yield/ *ee* [%][a]
1	2.5	30/0	98	93/99
2	1.0	30/r.t.	98	>97/99
3	0.5	30/r.t.	95	84/98
4[b]	0.5	30/r.t.	87	75/95
5[c]	2.5	60/r.t.	98	89/63
6[b,c]	2.5	30/r.t.	98	82/86

[a] Determined by GC.
[b] Slow addition of PhZnCl within 12 min.
[c] PhZnCl prepared from PhMgBr instead of PhLi.

Table 2. 1,4-Addition and subsequent stereodivergent reduction.



reduction
– $NaBH_4$ (5.0 equiv.), EtOH, 0 °C to r.t., 68 h
– *t*-$BuNH_2{\cdot}BH_3$ (2.1 equiv.), CH_2Cl_2, 16 h, 0 °C
– RuCl(*p*-cymene)[Ts-DPEN] (**5**, 5.0 mol%)
HCOOH/NEt_3 (5/2, 1.5 equiv.), CH_3CN, 16 h, r.t.



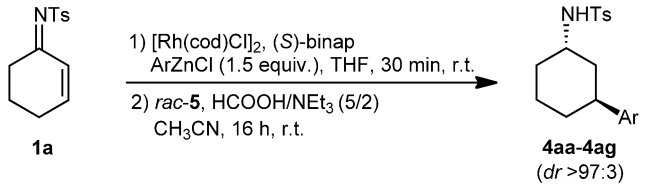
Entry	Reduction	*dr*[a] (*trans*/*cis*)	Yield [%][b]	*ee*[c] [%]
1	$NaBH_4$	52:48	88[d]	–[d]
2	*t*-$BuNH_2{\cdot}BH_3$	13:87	62	99
3	*rac*-**5**, HCOOH	>97:3	83	99
4	(*S*,*S*)-**5**, HCOOH	>97:3	78	99
5[e]	(*S*,*S*)-**5**, HCOOH	>97:3	93	99

[a] Determined by ^1H NMR analysis of the crude product.
[b] Isolated yield of the major diastereomer over 2 steps.
[c] Determined by HPLC.
[d] Combined yield of diastereomers, *ee* not determined.
[e] (*R*)-binap was used to furnish *ent*-**3aa**/*ent*-**4aa**.

a 62% yield (entry 2). For preparation of the *trans*-diastereomer, L-selectride® could not be used, causing only deprotonation of the enamide.[20] However, the transfer hydrogenation catalyst RuCl(*p*-cymene)[Ts-DPEN] (**5**),[21] which our group has already employed for enantioselective C,N double bond reductions,[22] furnished pure *trans*-**4aa** in very good yields (entries 3–5).[23] This *trans*-selectivity must be due to prevailing substrate control since the diastereomeric ratio was the same when using either *rac*-**5** (entry 3) or its (*S*,*S*)-enantiomer (entry 4) for reduction of the enamide from 1,4-additions with (*S*)-binap. Even when performing the 1,4-addition with (*R*)-binap and reducing *ent*-**3aa** with (*S*,*S*)-**5** (entry 5), the same diastereoselectivity was observed. Drawn from the significantly increased yield of *ent*-**4aa**, however, this latter combination ought to be the matched pair.

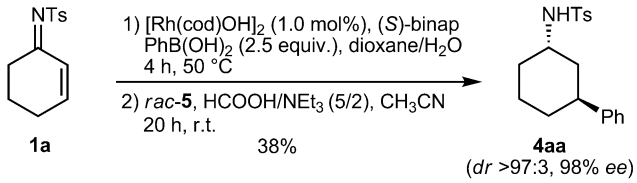
This protocol was then applied to the 1,4-addition of various aromatic residues (Table 3). Compared to the phenyl group (entry 1), most aryl groups required a higher catalyst loading for achieving high yields, while the enantioselectivity was always excellent. Both electron-rich (entry 2) as well as electron-deficient aryl groups (entries 3 and 4) could be introduced, slightly longer reaction times being needed for the latter. Steric constraints were stated with the 2-tolyl reagent, yet a moderate yield was achieved (entry 5), and good results were obtained with 3,5-xylyl or 2-naphthyl groups (entries 6–8). In some of these transformations, the *ee* was significantly decreased if the crude products of the 1,4-addition were not filtered over activated charcoal prior to reduction. Traces of remaining rhodium may then lead to C,C

Table 3. 1,4-Addition of various aryl groups.



Entry	Ar	$[Rh(cod)Cl]_2$ [mol%]	Yield [%][a]	*ee* [%][b]
1	C_6H_5 (**a**)	1.0	83	99
2	4-$MeOC_6H_4$ (**b**)	2.5	91	99
3[c]	4-FC_6H_4 (**c**)	2.5	68	99
4[c]	4-$CF_3C_6H_4$ (**d**)	2.5	89	>99
5	2-MeC_6H_4 (**e**)	2.5	53	99
6	3,5-xylyl (**f**)	2.5	quant.	99
7	3,5-xylyl (**f**)	1.0	82	99
8	2-naphthyl (**g**)	1.0	70	99

[a] Isolated yield.
[b] Determined by HPLC.
[c] 1,4-Addition performed for 1 h.



Scheme 1. 1,4-Addition of phenylboronic acid.

double bond migration in the respective enamides **3** and, thus, partial racemization.[24]

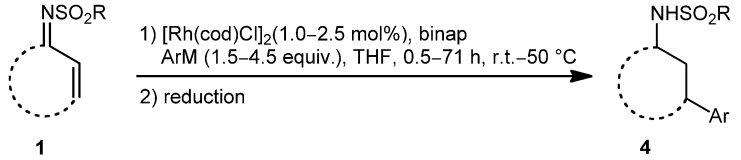
Besides arylzinc halides, the 1,4-addition was also performed using phenylboronic acid under classical conditions (Scheme 1).[15b] The aqueous reaction medium, however, caused partial hydrolysis and the yield of *trans*-**4aa** was significantly lowered. Nevertheless, utilization of organoboron reagents should further enlarge the scope of transferable functionalized aryl groups.

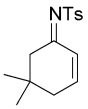
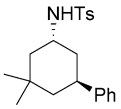
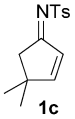
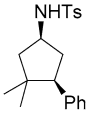
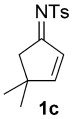
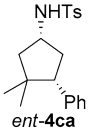
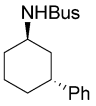
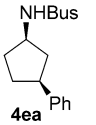
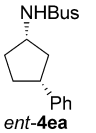
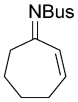
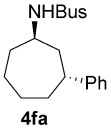
In order to evaluate the substrate scope, the 1,4-addition–reduction sequence was applied to the 5,5-disubstitued imine **1b**, leading to an even better yield compared with the unsubstituted imine **1a** (Table 4, entry 1 *vs.* Table 3, entry 1).[25,26] While the *N*-tosylimine from cyclopent-2-enone is so far not available in reasonable yield,[10] its 4,4-disubstituted derivative **1c** could be transformed into *cis*-**4ca**, however, the conversion was incomplete after 71 h at 50 °C even with increased amounts of catalyst and PhZnCl (entry 2). In contrast, this substrate readily undergoes 1,4-addition of $AlMe_3$,[11] and accordingly, use of $PhAlMe_2$ led to complete conversion after 19 h at room temperature (entry 3). In the case of this substrate, a reduction with $NaBH_4$ was favourable, since a transfer hydrogenation with *rac*-**5** also led to *cis*-**4ca** but with a lower diastereoselectivity of 84:16.

In addition to *N*-tosylimines, *N*-*tert*-butylsulfonylimines (Bus-imines)[10] were also suitable, albeit slightly less reactive, requiring increased amounts of catalyst and a reaction temperature of 40 °C. Moreover, the yield was significantly lower in the case of the six-membered ring **1d** even when using the matched pair of catalysts (Table 4, entry 4 *vs.* Table 2, entry 5). With the cyclopent-2-enone derived imine **1e**, the transfer hydrogenation with (*S*,*S*)-**5** furnished preferentially the *cis*-diastereomer of **4ea**, and both a higher yield and diastereoselectivity were achieved in the matched pair with (*R*)-binap (entries 5 and 6). In the case of the cycloheptenone-derived imine **1f**, the *trans*-diastereomer was formed as the major product in a high yield (entry 7). A special feature of the cycloalkylamides **4da**–**4fa** is the possibility to cleave the Bus group by acidic hydrolysis[27] in contrast to the tosyl group which is usually removed under reductive conditions (see below).

As an acyclic substrate, the chalcone-derived imine **1g** was subjected to a 1,4-addition of 3,5-xylylZnCl,

Table 4. 1,4-Addition to various α,β-unsaturated imines.



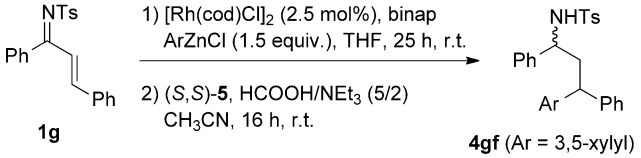
Entry	Imine	[Rh(cod)Cl]$_2$/ligand	Reagent	t/T	Reduction	dr[a] (*trans*/*cis*)	Product	Yield/*ee* [%][b]
1	 **1b**	1.0 mol%/(*S*)-binap	PhZnCl (1.5 equiv.)	3 h/r.t.	*rac*-**5**, HCOOH	>97:3	 **4ba**	95/>99
2	 **1c**	2.5 mol%/(*S*)-binap	PhZnCl (4.5 equiv.)	71 h/50 °C	$NaBH_4$	3:97	 **4ca**	71/96
3	 **1c**	1.0 mol%/(*R*)-binap	$PhAlMe_2$ (1.5 equiv.)	19 h/r.t.	$NaBH_4$	4:96	 *ent*-**4ca**	92/97
4	 **1d**	2.5 mol%/(*R*)-binap	PhZnCl (1.5 equiv.)	0.5 h/40 °C	(*S*,*S*)-**5**, HCOOH	>97:3	 **4da**	58/98
5	 **1e**	2.5 mol%/(*S*)-binap	PhZnCl(1.5 equiv.)	1.5 h/40 °C	(*S*,*S*)-**5**, HCOOH	21:79	 **4ea**	50[c]/99
6	 **1e**	2.5 mol%/(*R*)-binap	PhZnCl (1.5 equiv.)	1.5 h/40 °C	(*S*,*S*)-**5**, HCOOH	13:87	 *ent*-**4ea**	63[c]/99
7	 **1f**	2.5 mol%/(*R*)-binap	PhZnCl (1.5 equiv.)	1.5 h/40 °C	(*S*,*S*)-**5**, HCOOH	94:6	 **4fa**	85/97

[a] Determined by ^{1}H NMR analysis of the crude product.
[b] Isolated yield; *ee* determined by HPLC.
[c] Diastereomeric mixture.

and hydrolysis of the 1,4-adduct furnished the respective ketone with 56% *ee* (Table 5, entry 1).[28] Performing a racemic 1,4-addition with subsequent reduction with (*S*,*S*)-**5** led to a 62:38 *dr* and about 70% *ee* for both diastereomers of **4gf** (entry 2). The sequence was then repeated with (*R*)- and (*S*)-binap furnishing a 70:30 and a 42:58 *dr*, respectively (entries 3 and 4). In both pairs, the major diastereomer was obtained with 92% *ee*, thus, the combination of two reactions of moderate enantioselectivity altogether results in a strong enhancement of the enantiopurity.

The smooth 1,4-addition to the 5,5-dimethyl-substituted imine **1b** (Table 4, entry 1) led to the assumption that – similar to the respective enones[25] – catalyst control would outpace substrate control in the case of 5-monosubstituted derivatives making it possible to override a stereocenter at C-5 of the ring. Combined with the stereodivergent reductions, this ought

Table 5. 1,4-Addition to the imine derived from chalcone.



Entry	binap	*dr*[a] crude/purified	Yield [%][b]	*ee* [%][c]
1	(*R*)	–[d]	53[d]	56[d]
2	*rac*	62:38/54:46	52	69/71
3	(*R*)	70:30/70:30	95	92/15
4	(*S*)	42:58/31:69	57	1/92

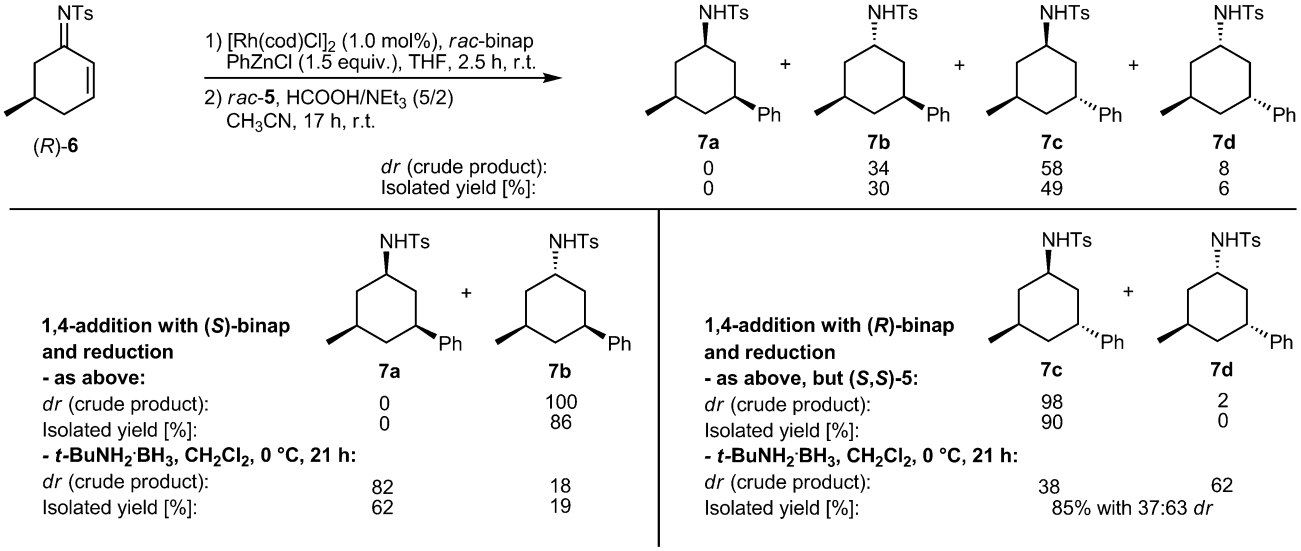
[a] Determined by ^{1}H NMR analysis, relative configuration not determined.
[b] Isolated yield of purified diastereomeric mixture.
[c] Determined by HPLC and stated for both diastereomers.
[d] The 1,4-adduct was not reduced, but hydrolyzed with 6 M HCl; yield and *ee* refer to the respective ketone.

to lead to a selective synthesis of all stereoisomers of 3,5-disubstituted cyclohexylamines. This assumption was studied using imine (*R*)-**6** which was prepared from (*R*)-5-methylcyclohexenone (Scheme 2). Transformation with the racemic catalysts in both steps revealed that the 1,4-addition occurs with a poor 2:1 *trans*/*cis*-selectivity (upper section, ratio of **7c**+**7d** *vs.* **7b**) and, concerning the reduction, that the *trans*-directing influence of the phenyl group is stronger than that of the methyl group (**7c** *vs.* **7d**). With (*S*)-binap, the 1,4-addition occurred with complete *cis*-selectivity, and only diastereomer **7b** was obtained after a *trans*-selective reduction with *rac*-**5** (left column, first entry). Applying (*S*)-binap but a subsequent reaction with *t*-BuNH$_2$·BH$_3$, a good 4.6:1 *cis*/*trans*-selectivity was observed in the reduction, and the all-*cis*-diastereomer **7a** was obtained in a 62% isolated yield (left column, second entry).[29]

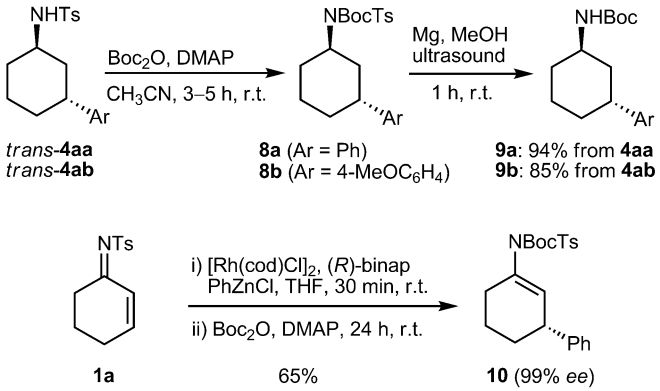
In contrast, (*R*)-binap led to a *trans*-selective 1,4-addition of the phenyl group and, with respect to this substituent, the reduction occurred with increased *trans*-selectivity when using (*S*,*S*)-**5** instead of *rac*-**5** (right column, first entry). This afforded diastereomer **7c** in a very high yield. With *t*-BuNH$_2$·BH$_3$ as reductant, the directing influence of the phenyl group was again predominant leading to a 1:1.6 mixture of **7c** and **7d** which could not be separated by column chromatography (right column, second entry). Altogether, formation of diastereomer **7d** occurs with the lowest selectivity, but calculated from the isolated diastereomeric mixture, it is still formed in a synthetically useful 54% yield.

An inherent property of the tosyl group is its chemical robustness, frequently requiring harsh conditions for its removal.[30] After carbamate protection, however, detosylation can smoothly be accomplished with magnesium in MeOH under ultrasonication.[31] Accordingly, tosylamides *trans*-**4aa** and *trans*-**4ab** were transformed into their Boc derivatives **9a** and **9b** in very high yields (Scheme 3). The Boc protection also proceeded well with the zinc aza-enolate initially obtained from 1,4-addition of PhZnCl to imine **1a**, i.e., when performing a one-pot sequence. In contrast, this reaction was very slow if applied to the enamide **3aa** obtained after aqueous quenching of the 1,4-addition. The carbamate group stabilizes enamide **10** towards chromatography on silica gel and enables isolation and purification. Thus, this is a first alternative employment of the aza-enolates from the 1,4-addition than just protonation.

The *cis*-diastereomer of 3-aminocyclohexanecarboxylic acid has attracted some interest in recent years as



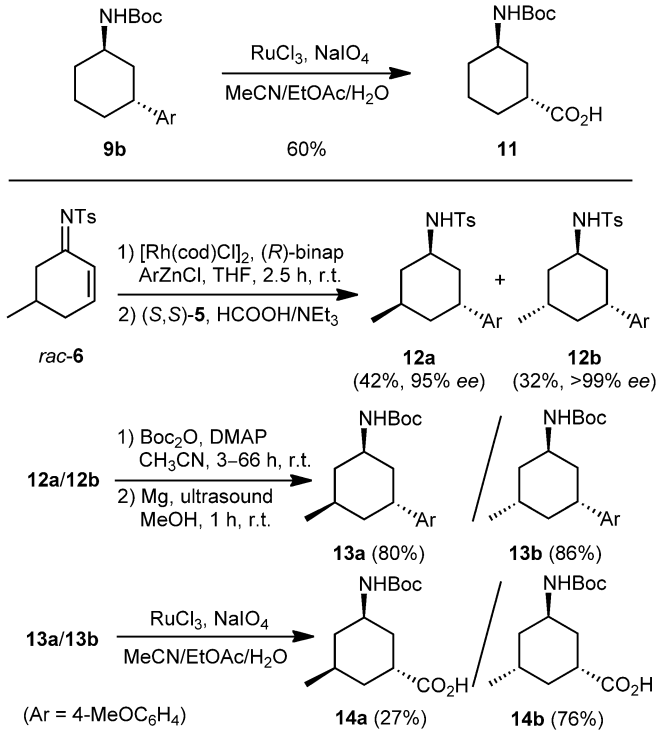
Scheme 2. Stereodivergent transformation of imine (*R*)-**6**.



Scheme 3. Synthesis of Boc-protected cyclohexyl- and cyclohexenylamines.

an inhibitor of GABA uptake[32] and as a structural motif in modified peptides.[33] It is easily accessible by hydrogenation of 3-aminobenzoic acid which can be succeeded by chiral resolution to obtain enantiopure material.[34] In contrast, the *trans*-diastereomer is much more difficult to prepare,[35] yet it could also be an interesting structure as one of the substituents must necessarily reside in an axial position. Therefore, an oxidative cleavage of the *para*-anisyl group in carbamate **9b** was performed and the desired γ-amino acid **11** was obtained in a 60% yield (Scheme 4).

This cyclohexane derivative is conformationally flexible, but a third substituent at the ring would control whether the carboxy or the amino group adopts the axial position. To prove this concept, the *para*-anisyl group was added to the racemic ketimine **6**, and after *trans*-selective reduction, the diastereomers **12a** and **12b** were obtained in 42% and 32% yield, respectively. These compounds were then separately transformed into their Boc derivatives **13a**/**13b**, which, after oxidative cleavage, furnished the γ-amino acids **14a**/**14b**.[36]



Scheme 4. Synthesis of 3-aminocyclohexanecarboxylic acids.

Conclusions

α,β-Unsaturated *N*-sulfonylimines react similarly to the corresponding carbonyl compounds in Hayashi–Miyaura-type reactions with arylzinc halides. Combined with a suitable reduction method, this can be utilized for the enantioselective preparation of various 3-arylcycloalkylamines with either *cis*- or *trans*-configuration at the ring. In the case of cyclohexenone-derived imines, stereocontrol by the Rh(I)/binap catalyst prevails over substrate control by a stereocenter at C-5 of the ring; this can be used for the selective synthesis of all four diastereomers of 3-methyl-5-phenylcyclohexylamine. Moreover, the introduced aryl rings can be degraded to carboxy moieties furnishing conformationally rigid cyclic γ-amino acids. We are now working on employing other classes of chiral ligands for less reactive or acyclic substrates and on using the initially formed zinc aza-enolates or the respective enamides for subsequent C,C bond formations.

Experimental Section

Rh-Catalyzed 1,4-Addition of Arylzinc Chloride

A mixture of $[Rh(cod)Cl]_2$, binap, and ketimine (400 μmol) was stirred for 30 min under reduced pressure. THF (2.5 mL) was added, and the resulting solution was stirred for 45 min at room temperature. The arylzinc chloride (solution in THF, 1.5 equiv.) was added in one portion, and the dark red solution was stirred for the given time. The mixture was then poured into a stirred mixture of methyl *tert*-butyl ether (MTBE, 32 mL), $NaHCO_3$ (1.50 g), and H_2O (0.8 mL), stirred for 15 min, and dried over Na_2SO_4. After addition of activated charcoal, the suspension was filtered over Celite®, and the filtrate was concentrated under reduced pressure. The crude product was immediately subjected to the respective subsequent transformation.

Reduction with *t*-$BuNH_2{\cdot}BH_3$

A solution of *t*-$BuNH_2{\cdot}BH_3$ (73.1 mg, 840 μmol) in CH_2Cl_2 (2.0 mL) was added to the crude product of the respective 1,4-addition (400 μmol) at 0 °C and stirred for the given time. The reaction mixture was quenched by addition of H_2O (2.0 mL) and stirred for 0.5 h. More H_2O (10 mL) was

added and the aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel.

Transfer Hydrogenation

RuCl(*p*-cymene)[Ts-DPEN] (**5**, 12.7 mg, 20.0 μmol) and the crude product of the respective 1,4-addition (400 μmol) were dissolved in CH_3CN (4.0 mL), a mixture of HCOOH and Et_3N (5/2, 252 μL, 600 μmol) was added, and the solution was stirred for 16 h at room temperature. The reaction mixture was poured into H_2O (10 mL) and extracted with EtOAc (5×10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography over silica gel.

Acknowledgements

We thank the Konrad-Adenauer-Stiftung, Bonn for a scholarship for J.W., the BASF SE, Ludwigshafen for the generous donation of chemicals, and Lucas Millbrodt, Philipps-Universität Marburg for technical assistance.

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Enantioselective Preparation of 3-Arylcycloalkylamines by Rhodium-Catalyzed 1,4-Addition and Subsequent Stereodivergent Reduction

Adv. Synth. Catal. **2015**, *357*, 1 – 9

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