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Rhodium-Catalyzed Enantioselective Addition of Organoaluminum Reagents to *N*-Tosyl Ketimines

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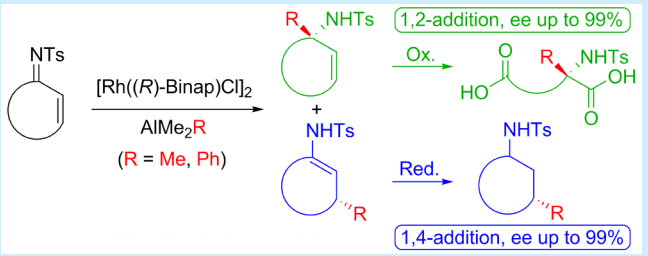
Supporting Information

ABSTRACT: Rhodium(I)/Binap complexes catalyze highly enantioselective additions of methyl- and arylaluminum reagents to cyclic α,β-unsaturated *N*-tosyl ketimines. Depending on the solvent and substituents at the ring, the reaction occurs either in a 1,2-manner to deliver α-tertiary allylic amines or in a 1,4-manner to yield, after subsequent reduction, 3-substituted cycloalkyl amines. Well known in the case of the respective cycloalkenones, these first transformations of the aza-analogues enable the synthesis of amine structures of pharmaceutical and biochemical interest.



Amines with an α-tetrasubstituted carbon (tertiary carbinamines) are important structures due to their occurrence in natural and artificial biologically active molecules.[1] Yet the enantioselective construction of quaternary carbon centers represents a synthetic challenge, and there are only a few methods available to prepare such amines.[2] The catalytic enantioselective addition of carbon nucleophiles to ketimines is one of the most efficient approaches;[3] however, this transformation poses even more problems than the related addition to ketones: with both types of substrates, the differentiation of enantiotopic faces is more demanding than in the case of aldehydes and aldimines. In addition, ketimines usually exist as mixtures of *E*- and *Z*-isomers. Finally, the lower electrophilicity of ketimines is generally a major problem, requiring the use of strong nucleophiles, which can cause deprotonation and thus enamide formation and lead to even higher requirements for stereodifferentiation by the chiral catalyst. During the past decade, considerable efforts have been made to develop novel protocols, mainly based on asymmetric modifications of the Strecker reaction[3b,d] and Mannich-type additions.[3d] Only a few examples of the catalytic asymmetric addition of nonstabilized carbon nucleophiles to ketimines have been published, namely dialkylzinc additions to imines derived from trifluoromethyl ketones and α-ketoesters,[4] allylations[5] and alkynylations,[6] and rhodium- or palladium-catalyzed additions of aryl- and alkenylboron reagents to aromatic *N*-sulfonyl and *N*-carbonyl ketimines.[7,8] Similar reactions on imines derived from cyclic aliphatic ketones, however, have not been reported to date, even though a direct access to optically pure α-tertiary cycloalkylamines would be of high interest. This is true especially for six-membered rings, since they occur in a large number of biologically active compounds, including important antagonists of the *N*-methyl-D-aspartate (NMDA) receptor such as ketamine and gacyclidine.[9] We have developed the first enantioselective 1,2-addition of readily available methyl- and arylaluminum reagents to cycloalkenones.[10,11] This Rh(I)/Binap-catalyzed transformation delivers cyclic tertiary allylic alcohols,[10c] enables kinetic resolution of racemic, substituted cycloalkenones,[10b] and can also be used as an efficient strategy for natural product synthesis.[10a] We anticipated that a similar addition to C,N-double bonds would result in the synthesis of enantiopure α-tertiary amines, and we recently reported the first synthesis of cycloalk-2-enone-derived imines which are activated by *N*-sulfonyl groups toward nucleophilic attack.[12] This paper now describes the first enantioselective additions to this type of substrates.

For a model reaction, *N*-tosyl imine **1a** was chosen which can be prepared in 66% yield by condensing cyclohex-2-enone with tosyl amide.[12] Under conditions optimized for the 1,2-addition to cyclic enones, that is, with in situ prepared $[Rh((R)\text{-Binap})Cl]_2$ and $AlMe_3$ in THF,[10c] the desired product **2a** was obtained with excellent enantioselectivity, albeit in low yield (Table 1, entry 1).[13] The (*S*)-configuration was determined by X-ray crystallographic analysis, demonstrating that the facial selectivity of the catalyst is identical for both enones and their respective *N*-tosyl imines. Furthermore, substantial amounts of enamide **3a** and its tautomeric imine were obtained from a Rh(I)/Binap-catalyzed 1,4-addition. Hydrolysis of these products afforded (*R*)-3-methylcyclohexanone with 98% ee as proven by GC. This represents the first example of a catalytic enantioselective conjugate addition to a cyclic α,β-unsaturated ketimine.[14] Catalysis by $[Rh(cod)Cl]_2$ in the absence of Binap led[10c] to an exclusive 1,4-addition, analogously to the corresponding enone, and racemic **3a** was formed almost quantitatively (entry 2). Attempts to optimize the 1,2-addition

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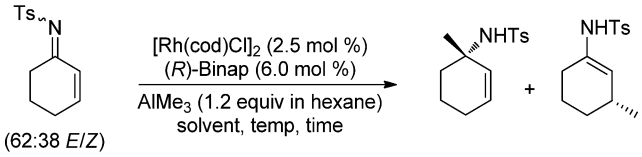
Table 1. Rh(I)/Binap-Catalyzed Addition of $AlMe_3$ to Ketimine 1a



(62:38 *E*/*Z*)

1a **2a** **3a**

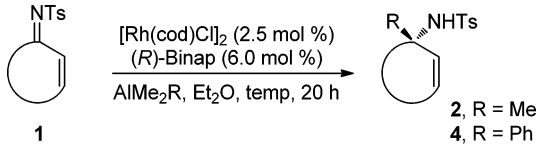
entry	solvent	temp (°C)	time (h)	1,2/1,4 ratio[a]	**2a**, yield (%)[a]	**2a**, ee (%)[b]
1	THF	rt	20	1:1	29	>99
2[c]	THF	rt	1	0:1	0	–
3	toluene	rt	1.5	1:6	<10	99
4	dioxane	rt	20	1:1	26	>99
5	DME	rt	20	4:1	56	99
6	Et_2O	rt	1.5	4:1	53	98
7	Et_2O	0	20	6:1	60 (58)[d]	>99
8[e]	Et_2O	0	20	1:1	30	99
9[f]	Et_2O	0	20	5:1	43	>99
10[g]	Et_2O	0	20	8:1	75 (74)[d]	99

[a]Determined by ^1H NMR analysis of the crude product. [b]Determined by HPLC. [c]Without Binap. [d]Numbers in parentheses are isolated yields after chromatography. [e]$[Rh(cod)OMe]_2$ was used. [f]$[Rh(cod)OH]_2$ was used. [g]1.5 equiv of neat $AlMe_3$ was used.

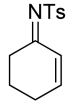
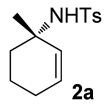
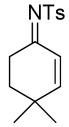
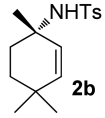
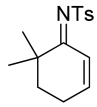
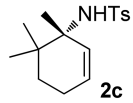
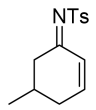
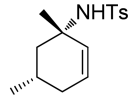
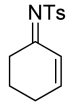
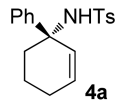
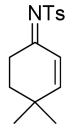
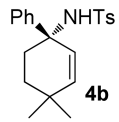
revealed the importance of the solvent: while toluene and dioxane resulted in poor yields of **2a** (entries 3,4), DME and Et_2O led to much higher ratios of 1,2-addition, though with slightly decreased enantioselectivity (entries 5,6). While an increased yield and perfect stereocontrol were achieved at 0 °C (entry 7), varying the rhodium precatalyst did not result in any further improvement (entries 8,9). Finally, a 74% isolated yield was obtained when using neat $AlMe_3$ rather than a solution of this reagent in hexanes (entry 10).[15] Since this yield is higher than the amount of *E*-configured starting material **1a**, an *E*/*Z*-isomerization may have occurred during the reaction. This protocol for enantioselective 1,2-addition of $AlMe_3$ was then applied to various *N*-tosyl ketimines **1** (Table 2).[16]

Substrates with geminal methyl groups at C-4 or C-6 of the six-membered ring were transformed with a similar efficiency as the unsubstituted **1a** (entries 1−3). However, substituents at C-4 significantly lowered the reactivity and required a higher temperature (entry 2). With the tosyl imine derived from 5,5-dimethylcyclohex-2-enone, no 1,2-addition occurred, pointing to a severe steric interaction between the substrate and the catalyst.[10b] Indeed, in the case of the racemic 5-monosubstituted ketimine **1d**, only the (*S*)-enantiomer underwent a 1,2-addition, and (1*S*,5*S*)-**2d**[17] was obtained in a 42% yield (entry 4). Similarly to the respective enones,[10c] methyl groups at C-2 or C-3 prevented 1,2-addition, and the respective ketimines were reisolated. Regarding five-membered rings, the tosyl imine derived from cyclopent-2-enone gradually decomposed under the reaction conditions, while the 3-methyl and the 5,5-dimethyl derivatives did not undergo any transformation. The enantioselective 1,2-addition of aryl groups was attempted using the mixed alane $AlMe_2Ph$, which was prepared from $AlMe_2Cl$ and PhMgBr. This once again revealed the very subtle effects of reagents on regioselectivity: employing the standard catalyst, ketimine **1a** yielded a 2:3 mixture of the 1,2- and 1,4-adduct.[18] The chiral phosphane ligand could be used to influence this ratio, and the highest yield (33%) of 1,2-adduct **4a**[17] was obtained with (*R*)-2,2′-bis[di(3,5-xylyl)phosphino]-1,1′-binaphthyl (Xyl-Binap, entry 5). The 1,4-adduct was also obtained, and upon hydrolysis, it furnished (*R*)-3-phenylcyclohexanone in a 31% yield with 89% ee. Substituents at C-4 of the six-membered ring suppressed the conjugate aryl addition, and 1,2-adduct **4b** was obtained as the sole product in a 48% yield (67% yield brsm, entry 6).

Table 2. Asymmetric Addition of Alanes to Ketimines



1

entry	ketimine	temp	product	yield (%)[a]	ee (%)[b]
1	 **1a**	0 °C	 **2a**	74	99
2	 **1b**	reflux	 **2b**	71	98
3	 **1c**	0 °C	 **2c**	78	>99
4	 *rac*-**1d**	0 °C	 (1*S*,5*S*)-**2d**	42	99
5[c]	 **1a**	0 °C	 **4a**	33	>99
6	 **1b**	rt	 **4b**	48[d]	>99

[a]Isolated yield. [b]Determined by HPLC prior to recrystallization. [c](*R*)-Xyl-Binap as chiral ligand. [d]71% conversion (67% yield brsm).

To gain insight into the steric effects of substituents at C-5, enantiomerically pure (*R*)-**1d** was prepared from the respective ketone and reacted separately with the catalysts containing (*R*)- and (*S*)-Binap (Scheme 1). As expected based on the transformation with *rac*-**1d** (Table 2, entry 4), 1,2-adduct (1*R*,5*R*)-**2d** was obtained as the sole product using (*S*)-Binap and $AlMe_3$. Surprisingly, the same substrate underwent selective 1,4-addition with the (*R*)-Binap complex to furnish enamide *trans*-**3d**, which was isolated as cyclohexylamide **5d** after subsequent reduction with $NaBH_4$. Obviously, the 1,2-addition pathway is sterically blocked in this setting, making the 1,4-addition pathway the only viable reaction.[19] In addition, the discrimination of the 1,4-addition with (*S*)-Binap was also revealed by transformation with $AlMe_2Ph$, since a 5:1 ratio of 1,2- and 1,4-addition was detected and product **4d** was obtained in a 59% yield. In the case of ketimine **1e**, 1,2-

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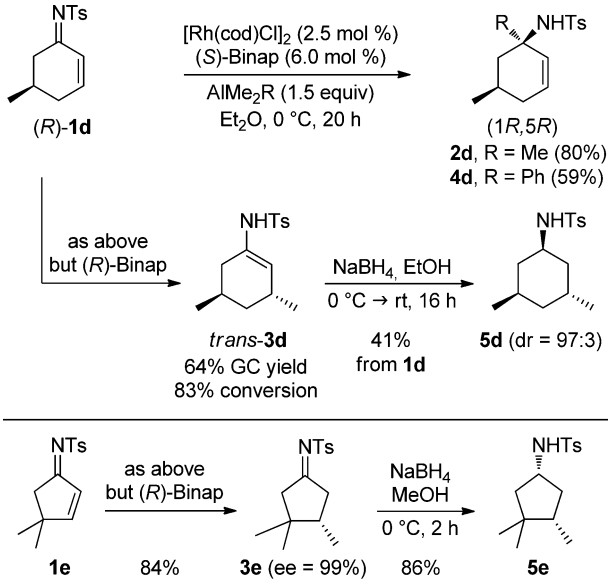
Scheme 1. Regiodivergent Reaction on Ketimine (*R*)-1d and 1,4-Addition to Ketimine 1e



addition was hindered, resulting in an enantioselective 1,4-addition. The imine **3e** thus obtained was diastereoselectively reduced with $NaBH_4$ to afford cyclopentylamide **5e**[17] in a high yield (Scheme 1). This sequence of 1,4-addition and subsequent reduction should be applicable to the stereoselective synthesis of a variety of 3-substituted cycloalkylamines, which are constituents of several pharmaceutically active compounds.[20]

As observed in the transformations of ketimine **1a**, the facial selectivity is the same for the addition of both methyl and phenyl groups, which points to similar catalytic cycles. However, the facial selectivities of the 1,2- and the 1,4-addition are reversed; the selectivity of the latter corresponds to that of a standard Hayashi–Miyaura reaction with arylboronic acids and Binap as a chiral ligand.[21] Thus, the 1,4-addition of aluminum reagents may proceed through a similar mechanism comprising transmetalation of the carbon nucleophile to rhodium and involving, in the case of imine (*R*)-**1d** and (*R*)-Binap, the transition state **A** (Figure 1). The 1,2-addition, observed with (*S*)-Binap using the same substrate, may also proceed through transmetalation, but may involve the transition state **B**, which allows for addition of the group R to C-1 and explains the reversed facial selectivity. The regiodivergence observed in the transformation of (*R*)-**1d** might then stem from unfavorable steric interactions of the methyl group at the substrate and the Binap ligand in the transitions states **C** and **D**. However, alanes are strong Lewis acids and may be bound to the tosyl groups in these structures **A**–**D**, which should also influence the regio- and stereoselectivity.

To show the synthetic applicability of the 1,2-addition, detosylation of amide **2a** was performed with sodium naphthalide, and the highly volatile amine **6** was isolated as carbamate **7** (Scheme 2). Alternatively, magnesium in methanol can be used for this purpose after prior allylation of **2a**. 1,2-Adducts **2** can also be used to synthesize quaternary α-methyl α-amino acids. In the fields of biochemistry and medicine, these compounds are attracting increasing interest for the preparation of modified peptides, which, due to their higher conformational rigidity, have improved pharmacological properties and

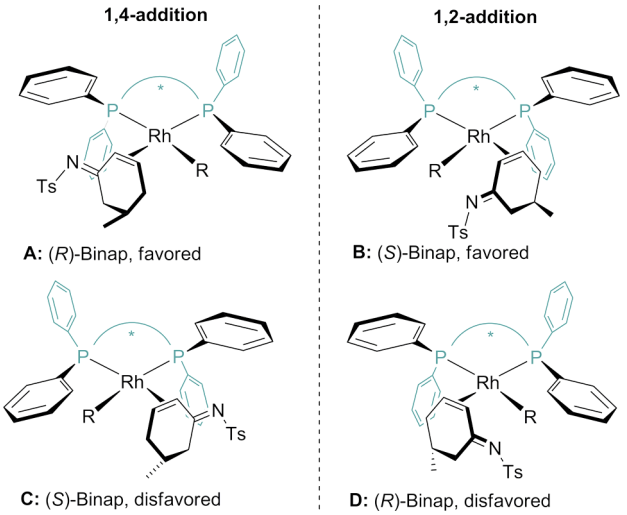
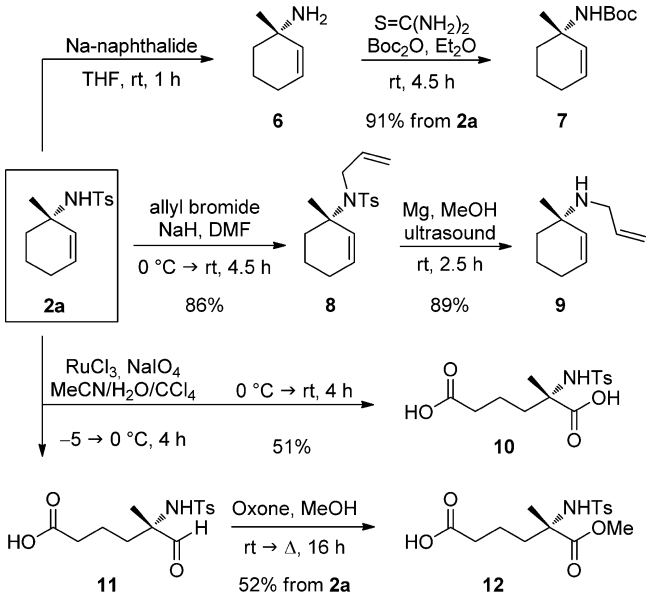


Figure 1. Proposed transition states involved in 1,4- and 1,2-additions to imine (*R*)-**1d** (R = Me, Ph).

enhanced resistance to enzymatic degradation.[22] Treatment of amide **2a** with $RuCl_3/NaIO_4$ at room temperature yielded the desired amino diacid **10**, while at 0 °C incomplete oxidation occurred and α-amino aldehyde **11** was isolated (Scheme 2). This made it easy to differentiate the carboxy groups: aldehyde **11** was converted into methyl ester **12** by treating it with oxone in methanol.[23] Similar α-methyl α-amino acids with carboxyalkyl side chains have been used to synthesize highly active Grb2-SH2 peptide inhibitors.[24]

Scheme 2. Detosylation of Amide 2a and Synthesis of a Quaternary α-Amino Diacid



In conclusion, we have developed the first enantioselective 1,2-addition of methyl- and arylaluminum reagents to cycloalkenone-derived *N*-tosyl imines, yielding α-tertiary allylamides. The applied Rh(I)/Binap catalyst can also result in enantioselective 1,4-additions to these substrates, and both 1,2- and 1,4-adducts are interesting building blocks for biologically important targets. Moreover, the reversed facial selectivity and the regiodivergence observed with ketimine (*R*)-

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1d provide insight into the mechanisms of both addition modes. We are now working on gaining a better understanding of the catalytic cycles and on optimizing the asymmetric conjugate addition of alkyl and aryl groups.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analytical data for all compounds; crystallographic data for compounds (*S*)-**2a**, (1*S*,5*S*)-**2d**, (*S*)-**4a**, and (1*R*,4*S*)-**5e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(15) **Caution**: neat $AlMe_3$ is highly pyrophoric; thus, we recommend use of commercially available solutions of $AlMe_3$ in hexanes if not familiar with the handling of pyrophoric compounds.

(16) The *N*-*tert*-butylsulfonyl imine of cyclohex-2-enone underwent 1,2-addition of $AlMe_3$ in a 32% yield with >99% ee while the respective *N*-diphenylphosphinoyl imine was deprotonated by $AlMe_3$. Use of $AlEt_3$ led to reduction of *N*-tosyl ketimine **1a**, presumably due to *β*-hydride elimination.

(17) Configuration determined by X-ray crystallographic analysis.

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