Synthesis of 2-amino-apopinan-3-ol and applications of its derivatives in asymmetric reduction of ketones

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Abstract

Monoterpenes are optically active compounds which occur in nature. This fact makes them interesting precursors for the synthesis of optically active ligands, which can be applied in various asymmetric reactions.

In this work, we present the synthesis of optically pure 2-amino-apopinan-3-ol from (–)-α-pinene. The obtained amino alcohol was used as a precursor of oxazaborolidine, which was used as catalyst in the asymmetric reduction of aryl-alkyl ketones with borane. In the second part, we transformed 2-amino-apopinan-3-ol into PHOX ligand in a three-step reaction. The complex of ruthenium precursor with PHOX ligand was used as a catalyst in the asymmetric transfer hydrogenation of aryl-alkyl ketones. Alcohols with enantiomeric excesses of up to 97% were isolated using both reduction methods.

Keywords

asymmetric reduction; PHOX; oxazaborolidine; monoterpene

Optically active monoterpenes widely occur in nature, consequently they are readily used in organic synthesis as a valuable chiral platform. β-Pinene, α-pinene, 2-carene, and 3-carene are chiral bicyclic compounds that can be easily modified by generating new stereogenic centers. The bicyclic framework of these compounds makes them rigid structures with well defined steric hindrance. These properties induce applications of monoterpene derivatives as chiral ligands in catalytic asymmetric synthesis, which is an important part of organic synthesis. Catalytic activity of metal complexes results from the metal used, while stereoselectivity is induced by a chiral organic ligand. Ligands, which are the chiral backbones of the catalysts, control the binding of substrates and further reaction stages through steric and electron interactions. Commonly used ligands contain nitrogen, phosphorus, oxygen and sulfur as donor atoms. The use of phosphorus and nitrogen as donor atoms has created a group of P,N-ligands currently widely used. [1, 2]

Among the P,N-ligands, several types of molecular structures can be distinguished. One of the most developed is the group of amine N-donor and phosphine P-donor ligands. The nitrogen atom with sp^3 hybridization occurs both in the form of NH_2, N-alkyl or aryl

substituted and cyclic structures (Figure 1, A). These ligands were used in iridium-catalyzed asymmetric reduction of α,β-unsaturated ketones [3] and α-substituted derivatives of acrylic acid [4], copper-catalyzed addition of diethylzinc to imines [5], and palladium-catalyzed asymmetric allylic substitution reactions [6].

The second important type of P,N-ligands are imine N-donor and phosphine P-donor ligands. The nitrogen donor is in the acyclic or cyclic part of the molecule (Figure 1, B). Acyclic ligands were used in palladium-catalyzed asymmetric allylic addition to compounds with both alkyl and aryl substituents [7], which was studied using various types of carbon and nitrogen nucleophiles [8]. This type of ligands has also found application in iridium-catalyzed enantioselective hydrogenation of tri- and tetra-substituted alkenes. [9] A very large group of ligands with sp2 hybridized nitrogen atom are PHOX ligands. The donor nitrogen is in the oxazoline ring. The first chiral phosphine oxazoline ligands were obtained in the early 1990s. [10-12] They form a class of ligands containing a C1 symmetry axis. [13] PHOX ligands have found use in palladium-catalyzed asymmetric allylic substitution [14], iridium-catalyzed reduction of carbon-carbon [15] and carbon-nitrogen double bonds [16], or palladium-catalyzed asymmetric Heck reactions [17].

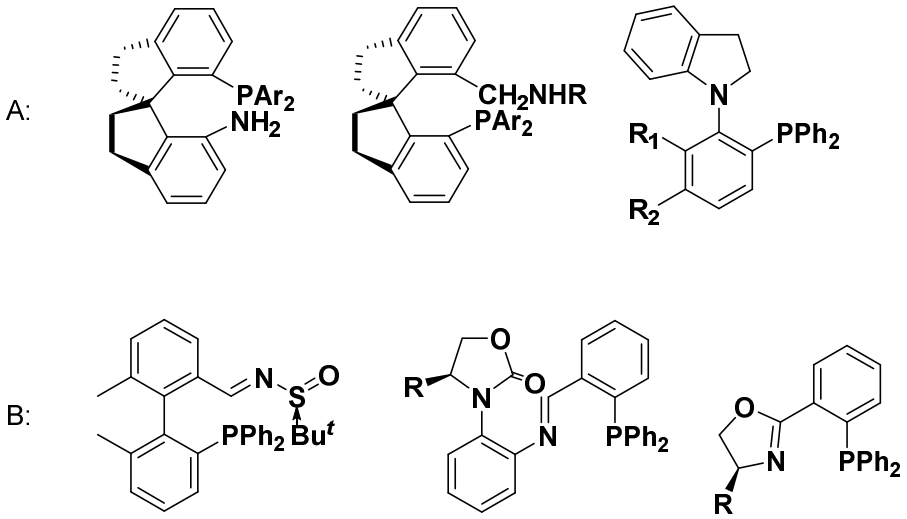


Figure 1 Examples of P,N-donor ligands

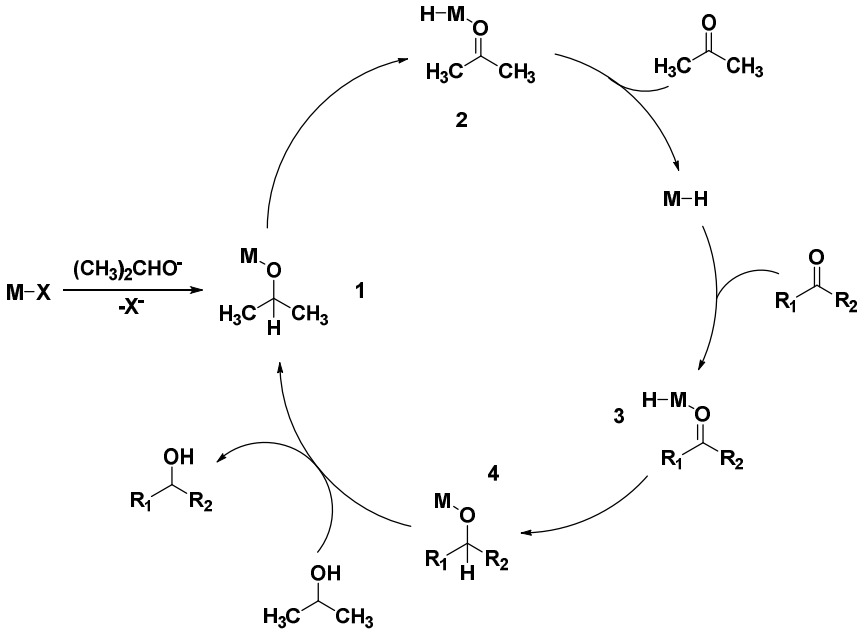
Asymmetric transfer hydrogenation (ATH) of prochiral ketones is one of the asymmetric reduction methods. ATH uses organic molecules as a hydrogen source instead of hydrogen gas. The reaction, due to its simplicity, can be carried out on both a small and medium scale. The stereoselectivity of the reaction depends on the functional groups in the substrate and on the appropriate transition metal complex with the chiral ligand.

The method of ATH involves the formation of metal hydride by the interaction of a hydrogen donor with a catalyst, which then transfers hydrogen to the substrate. [18] This mechanism is characteristic for the catalysts containing transition metals such as ruthenium (II), rhodium (I), or iridium (I), which may form mono or dihydride complexes depending on the metal. The most popular hydrogen sources are isopropanol and a mixture of formic acid and triethylamine. During the hydrogen transfer process from isopropanol, isopropanol is

oxidized to acetone, which competes for hydrogen with the reaction substrate. [19] This makes the reaction reversible. However, the reaction equilibrium is shifted towards the product by using isopropanol as the solvent and conducting the reaction under diluted conditions.

ATH reactions may occur according to two different mechanisms. Hydrogen can be transferred directly from the donor to the substrate or can be supplied gradually, first by forming an intermediate metal hydride followed by the substrate reduction. [20] The reaction proceeds via direct hydrogen transfer when main group metal complexes are used as the catalysts, whereas in the case of transition metal complexes the reaction occurs through the formation of an intermediate metal hydride. [21]

The mechanism of the reaction catalyzed by the transition metal complex begins with the formation of the compound **1** between the transition metal complex and isopropanol (Scheme 1). In turn, hydrogen is transferred from the isopropanol to the metal **2**. Further, as a result of reductive elimination, acetone is released and the active metal hydride complex is formed, which in oxidative addition reacts with ketone to form complex **3**. Next, the hydride is transferred from the metal to the carbonyl carbon atom (**4**). The final stage is the cleavage of the alcohol product by exchanging the proton with isopropanol. [22]



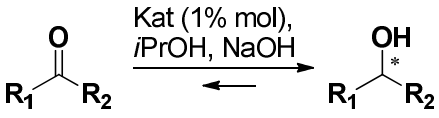
Scheme 1 The classic mechanism of transfer ketone hydrogenation with isopropanol catalyzed by a transition metal complex

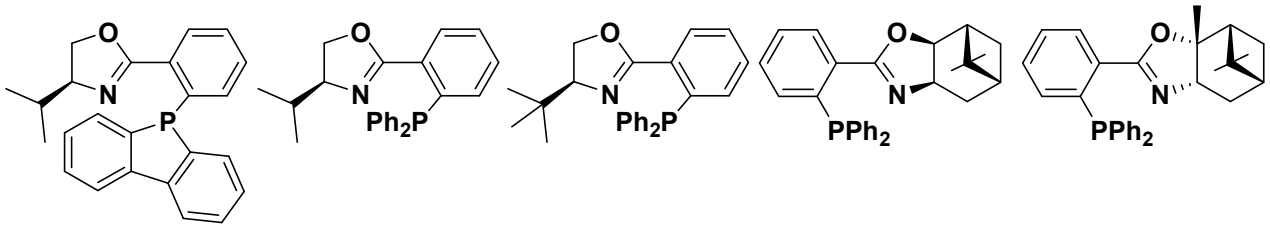
PHOX ligands were used in asymmetric transfer hydrogenation of ketones with ruthenium catalysts and isopropanol as the source of hydrogen. The reaction can be carried out with ruthenium complexes, which are obtained prior to the reaction, as well as generated in situ. The resulting complexes [$RuCl_2L(PPh_3)$] were activated with sodium hydroxide and reduced alkyl aryl ketones with very good yields and enantiomeric excesses. The enantioselectivity of the reaction increases with the spatial crowding of the alkyl substituent in the substrate and in the ligand's oxazoline ring (Table 1). In the case of

isopropyl phenyl ketone, alcohol was obtained with an excess of 92% ee and, despite the prolonged reaction time, it was not possible to increase it, and the reaction after this time proceeded with 87% conversion. This indicates that the reaction is an equilibrium process and its shift towards alcohol reoxidation is relatively slow. [23]

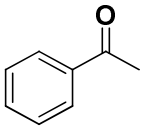
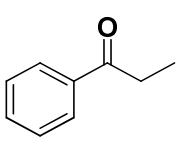
In 2017, we published the synthesis and application of pinene derived PHOX ligands in ruthenium catalyzed asymmetric transfer hydrogenation of ketones (Table 1). [24] We reduced ketones using 0.05 mol % of the catalyst with ligand **8**. Product alcohols were isolated with very good yields (up to 98%) and very good enantiomeric excesses (up to 90%). When we applied ligand **9**, we obtained alcohols with lower yields and enantiomeric excesses. Most likely this is due to the *trans* position of the oxazoline ring in ligand **9** relative to the *gem*-dimethyl bridge in the pinane system.[24]

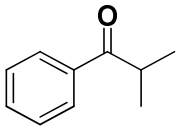
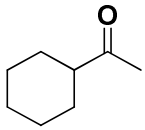
Table 1 Asymmetric transfer hydrogenation of ketones catalyzed by Ru-PHOX





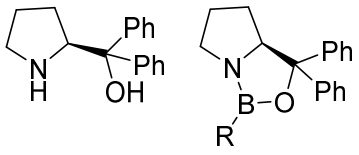
5 **6** **7** **8** **9**

Substrate	Ligand	Time [min.]	Conv. [%}	Ee [%]	Ref.
	[$RuCl_2$**5**(PPh_3)]	1	71	87 (*R*)	23
		3	80	78 (*R*)	23
	[$RuCl_2(PPh_3)_3$]+**5**	1	9	91 (*R*)	23
		30	37	88 (*R*)	23
		60	49	86 (*R*)	23
	[$RuCl_2(PPh_3)_3$]+**6**	5	24	94 (*R*)	23
		30	74	86 (*R*)	23
		60	83	73 (*R*)	23
	[$RuCl_2(PPh_3)_3$]+**7**	30	81	85 (*R*)	23
		60	84	79 (*R*)	23
	[$RuCl_2(PPh_3)_3$]+**8**	30	98	90 (*S*)	24
	[$RuCl_2(PPh_3)_3$]+**9**	30	72	37 (*R*)	24
	[$RuCl_2$**5**(PPh_3)]	4	50	91 (*R*)	23
		10	85	87 (*R*)	23
	[$RuCl_2(PPh_3)_3$]+**8**	30	88	90 (*S*)	24
	[$RuCl_2(PPh_3)_3$]+**9**	30	93	51 (*R*)	24

	[RuCl$_2$**5**(PPh$_3$)]	4	56	93 (*R)*	23
		10	74	93 (*R*)	23
		30	87	92 (*R*)	23
	[RuCl$_2$**5**(PPh$_3$)]	2	70	60 (*S*)	23
	[RuCl$_2$(PPh$_3$)$_3$]+**6**	60	88	58 *(S)*	5

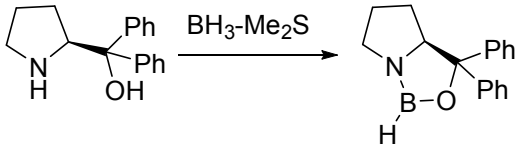
Another way to reduce prochiral ketones to chiral secondary alcohols is enantioselective reduction with borane catalyzed by chiral oxazaborolidines. Before oxazaborolidine was used catalytically, Itsuno et al. presented enantioselective reduction of ketones with borane using stoichiometric quantities of oxazabobolidines prepared *in situ* from borane and β-amino alcohols. [25-27] The catalytic versions of reaction were reported by Corey et al. [28]

(*S*)-α,α-Diphenyl-2-pyrrolidinomethanol **10**, derived from (*S*)-proline, was widely used as the best chiral promotor enabling the synthesis of chiral secondary alcohols with high yield and predictable absolute stereochemistry (Figure 2). However, the production of oxazaborolidine **10a** requires heating of the amino alcohol at the boiling point of tetrahydrofuran with an excess of BH_3 [29]. In turn, Quallich et al. showed that the same synthesis of oxazaborolidine **10a** can be carried out with an excess of borane-dimethyl sulfide adduct (BH_3-SMe_2) in THF at room temperature for 8-10 hours (Scheme 2) [32]. The breakthrough was the synthesis of B-Me oxazaborolidine **10b** formed in reaction of **10** with methylboronic acid forming a catalyst more resistant to air and moisture, which catalyzes the reduction of ketones with an excellent enantioselectivity [33], but the reaction requires complete removal of water to avoid undesirable effects [34].



10 **10a** R=H
10b R=Me

Figure 2 Various chiral catalysts and precatalysts

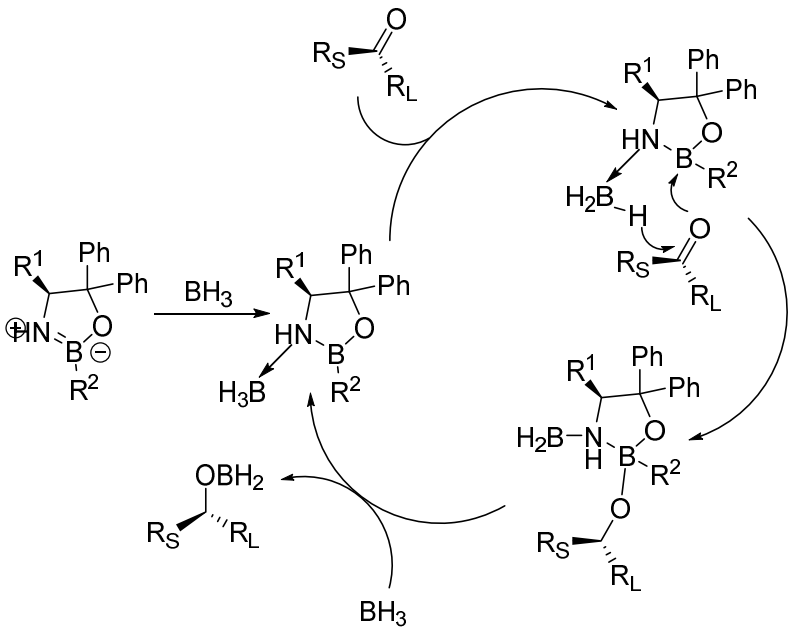


10 **10a**

Scheme 2 Generation of oxazaborolidine 10a *in situ* from 10 and borane

In reductions catalyzed by oxazaborolidines, high enantioselectivities result from complexing both borane and ketone to the oxazaborolidine molecule (Scheme 3). In the

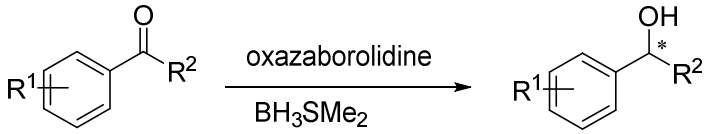
three-molecule complex thus formed, selective hydride transfer to the carbonyl group takes place. The catalytic cycle begins with the complexation of borane to the nitrogen atom. Then, the oxygen atom of the ketone is complexed to the endocyclic boron in such a way to minimize steric effects of substituents. With this arrangement of the ketone and complexed borane, the hydride ion is transferred through a six-membered transition state. Under the influence of another borane molecule, the reduction product is released and the catalyst restored. The six-membered transition also explains the configuration of product alcohols. [35]

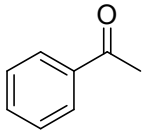
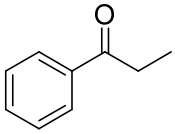
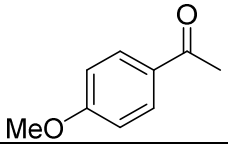
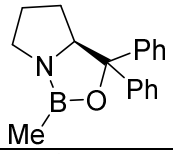
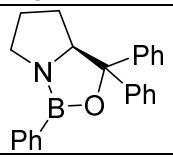
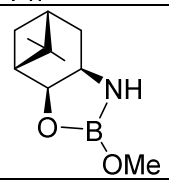


Scheme 3 Mechanism of oxazaborolidine-catalyzed borane reduction reactions

Oxazoborolidines obtained from amino alcohols proved to be effective catalysts in highly enantioselective reduction of ketones with borane. Using both proline and β-pinene derived amino alcohols as oxazaborolidine catalysts, ketones were reduced with high enantiomeric excesses (up to 99%) and with virtually quantitative yield (Table 2). [29-31]

Table 2 Oxazaborolidine-catalyzed asymmetric reduction of ketones with borane

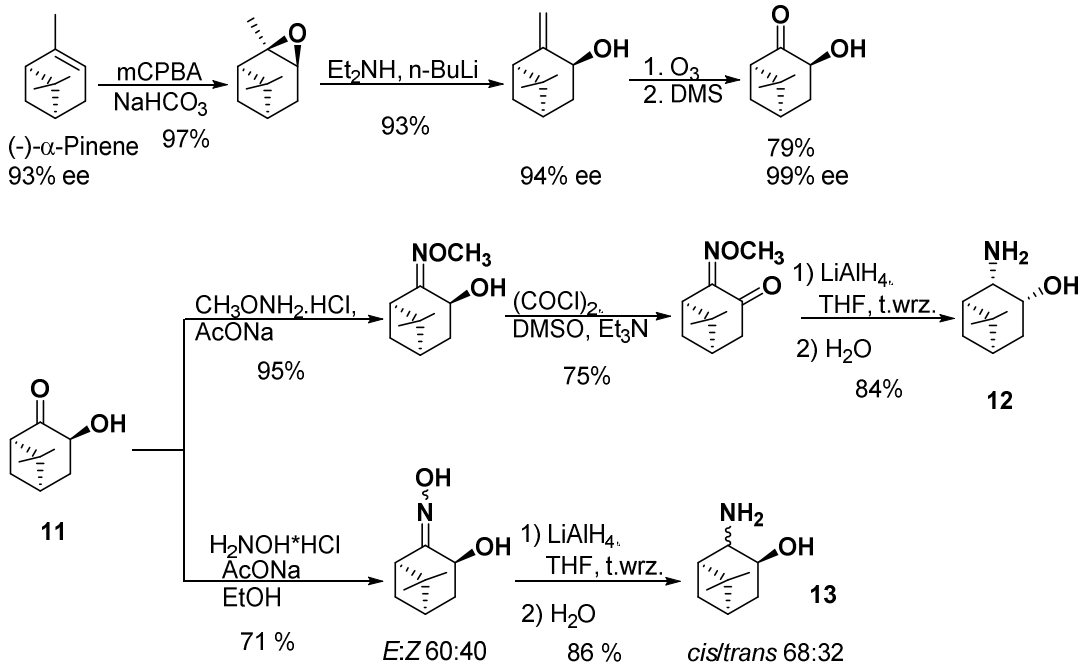


Oxazaborolidine	Ketone						Ref.
							
	% ee	Conv. [%[	%ee	Conv. [%[	%ee	Conv. [%[	
	96.5	100%	96.7	100%	99	100%	29
	97	100	98	100	98	100	30
	98	98	93	99	97	97	31

In this paper, we present our work on application of β-amino alcohols synthesized from the (–)-α-pinene in enantioselective reduction of ketones by ATH method and using oxazaborolidine.

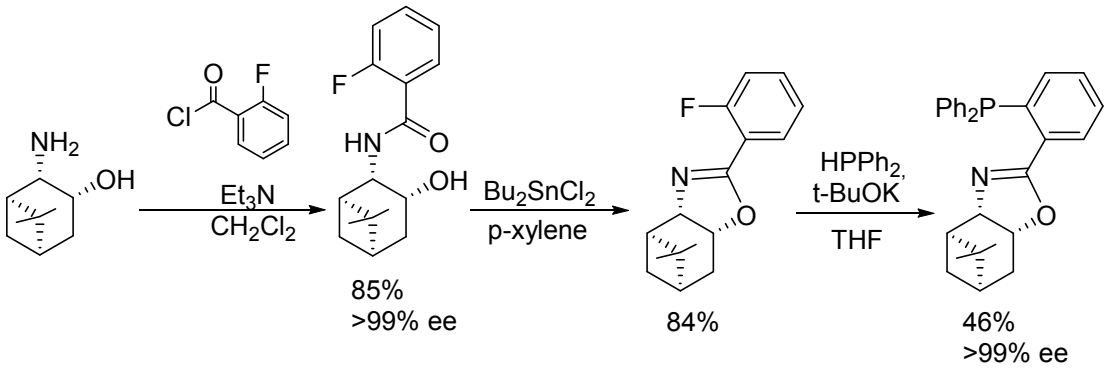
Synthesis of β-amino alcohols

The synthesis of β-amino alcohols from (–)-α-pinene is shown on Scheme 44. α-Pinene was converted to 3-hydroxynopinone (**11**) according to the procedures previously described in the literature. [36,37] 3-Hydroxynopinone was obtained in an enantiomeric pure form after crystallization. Next, hydroxyketone was transformed into β-amino alcohols by two ways. In the first method, carbonyl group from hydroxyketone reacted with methoxyamine to give oxime methyl ether. Then, hydroxyl group was oxidized to the carbonyl group using Swern method. After reduction of α-keto-oxime ether with lithium aluminum hydride β-amino alcohol **12** was obtained. In the second method, we obtained amino alcohol **13** as a mixture of *cis/trans* isomers. 3-Hydroxynopinone (**11**) reacted with hydroxylamine to give oxime as a mixture of *E*/*Z* isomers. This mixture was reduced with lithium aluminum hydride producing **13** as a mixture of *cis/trans* isomers in the ration of 68:32. The position of amino group was determined in relation to the hydroxyl group because the configuration of the hydroxyl group was defined since the synthesis of *trans*-pinocarveol. The *cis*-**13** means that both amine and hydroxyl groups are *cis* to each other.



Scheme 4 Synthesis of 2-amino-apopinan-3-ol

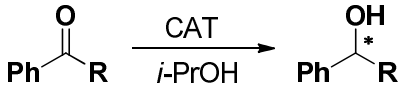
Then, we used amino alcohol **12** for the synthesis of PHOX ligand. (Scheme 5) In the first step, amino alcohol **12** was converted to the amide by the reaction with 2-fluorobenzoyl chloride. Next, we used Masamune protocol for cyclization with a catalytic amount of dibutyl tin dichloride and we isolated oxazoline. In the last step, fluorine atom was substituted by diphenylphosphine group giving PHOX ligand.

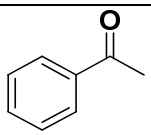
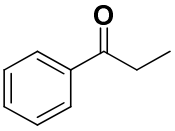
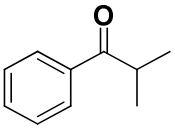


Scheme 5 Synthesis of PHOX ligand

The obtained ligand was used in the asymmetric transfer hydrogenation of ketones. Complexation of PHOX ligand with $RuCl_2(PPh_3)_3$ in isopropanol gave the solution of catalyst **CAT**, which was used in transfer hydrogenation of acetophenone and its derivatives (Table 3). We used isopropanol as the hydrogen source and sodium hydroxide or potassium *tert*-butoxide solution in isopropanol (0.125M)as a base. The reaction was carried out in an inert gas atmosphere. Products alcohols were obtained with good yields (up to 75%) and enantiomeric excesses (up to 96%).

Table 3 Transfer hydrogenation of acetophenone derivatives

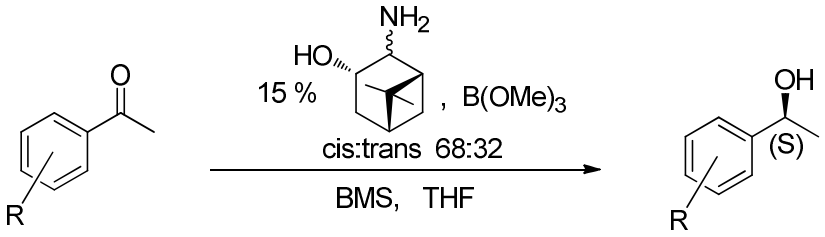


Ketone	CAT [% mol]	BASE	Time [h]	Yield [%]	Ee [%]	Conf.
	0,1	NaOH	1	75	87	*R*
	0,1	*t*-BuOK	1	73	93	
	0,1	NaOH	1	64	92	*R*
	0,1	*t*-BuOK	1	69	96	
	0,1	NaOH	1,5	8	58	*R*
	0,1	*t*-BuOK	1,5	22	86	

Asymmetric reduction of aryl-alkyl ketones with borane

We used commercially available trimethyl borate for the in situ generation of the active catalyst. Amino alcohol was treated with borate and the corresponding B-methoxy-oxazaborolidine was used without isolation from the reaction mixture to catalyze the reduction of ketones with borane at room temperature and at 0˚C. Experiments with 15 mol % of amino alcohol **13** and 12 mol % of $B(OMe)_3$ gave (*S*)-1-phenylethanol of 96% ee in 94% yield. The reaction conditions were applied for the reduction of other substituted acetophenones. As the results in Table 4 indicate, all the ketones were reduced with high enantioselectivities regardless of the substituent position.

Table 4 Asymmetric reduction of ketones with borane adduct of amino alcohols



R	Product	
	Yield, %	Ee, %
H	94	96
2-OCH_3	95	94

3-OCH_3	89	97
4-OCH_3	89	97

Conclusion

β-Amino alcohols synthesized from (-)-α-pinene were transformed to PHOX ligand and oxazaborolidine catalyst and they were successfully applied in asymmetric reductions of aryl-alkyl ketones. Products of these reactions, secondary alcohols were obtained with high enantiomeric excesses (up to 97%).

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