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Exploring Structural Diversity in Ligand Design: The Aminoindanol Case

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Abstract: A series of enantiopure ligands based on the aminoindanol scaffold, but differing in regio- and stereochemistry has been synthesized. These ligands have been conveniently derivatized and their catalytic efficiency in different enantioselective reactions has been screened to determine privileged candidates with respect to regio- and stereochemistry for each considered process. The nature of the amino substituent has been optimized for specific applications and this has led to the development of an efficient method for the preparation of bulky bicyclic amines by reductive amination.

Keywords: addition to carbonyl compounds; allylic substitution; amino alcohols; asymmetric catalysis; N,O ligands; reductive amination

Introduction

The ever growing field of enantioselective catalysis is in permanent search for new chiral ligands. However, the quest for these ligands is sometimes restricted to molecules obtained from the chiral pool, either directly or after derivatization. While this strategy has clear advantages in terms of price and enantiomeric purity, the obvious drawbacks are that the choice is limited and often only one of the enantiomers is readily available. Thus, there is an interest for developing new methods for the preparation of optically pure ligands in both enantiomeric forms. One of the most practical approaches to fulfill this goal consists in the preparation of the target ligands or their precursors through catalytic highly enantioselective processes that can afford products of both enantiomeric series. Within this approach, enantiomerically pure epoxides are ideal *relays* for the preparation of modular 1,2-difunctional compounds suitable for catalytic application through ring-opening processes. Over a decade ago, we and others started the exploration of this strategy.[1]

Indene oxide is probably one of the most readily available enantiopure epoxides. On this basis, we became interested in the preparation of aminoindanol-derived ligands to be used in asymmetric catalysis by regioselective ring-opening of this epoxide with nitrogen nucleophiles.[2] From the point of view of structural diversity, a recent analysis of chemical databases[3] has shown a repetitive pattern in the scaffolds more commonly found in organic molecules. According to the results reported in this study, half of the indexed compounds (more than 24 million) can be described by as little as 143 frameworks, and the indane scaffold represents one of the most widespread. Nevertheless, despite the prevalence of its corresponding framework and the application of some chiral aminoindanols as ligands in asymmetric catalysis, the full potential of this substructure has been usually neglected, as efforts in this field have been mostly restricted to *cis*-1-amino-2-indanol (**1a**).[4]

While this compound is commercially available in both enantiomeric forms, the aminoindanol scaffold offers a wider range of possibilities based on the simple variation of the regio- and stereochemistry of the two functional groups. As depicted in Figure 1, the aminoindanol family encompasses four different members, each one of them with its corresponding enantiomer. It must be mentioned that, in the present work, the letters **a**, **b**, **c** or **d** used in Figure 1 refer to each one of these isomers or their derivatives.

The rigidity associated with the indane scaffold limits the set of conformers accessible to these struc-

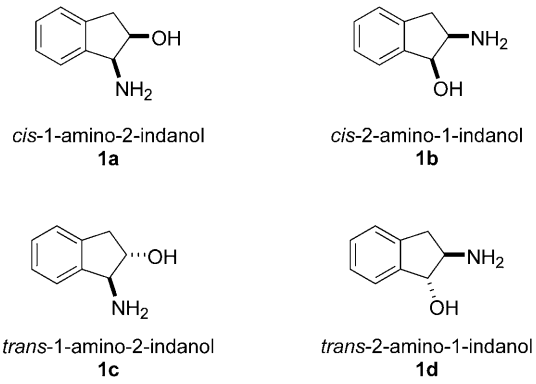


Figure 1. Structural diversity of the aminoindanol isomers.

tures with respect to their acyclic analogues. When the chelated metal complexes usually involved in catalysis are considered, it can be seen that this fact generates a rather flat geometry for the *trans* regioisomers and a bent disposition for their *cis* counterparts (Figure 2). Needless to say, these changes are expected to have a significant impact on the catalytic profile of the considered amino alcohols or of their derivatives. Thus, it can be expected *a priori* that the *cis* derivatives will present a more marked facial preference for the coordination of substrates and reagents and, hence, that they will induce higher degrees of enantioselectivity. However, it is important to recall that rather flat species derived from *trans* disubstituted scaffolds, like those involved in the Jacobsen epoxidation,[5] are able to induce very high levels of enantioselectivity. An additional point to take into account refers to the availability of the five-membered chelates derived from *trans* structures. Thus, when long metal–O,N bonds are involved in the chelate, like in the methylzinc alkoxides represented in Figure 2, a *trans* stereochemistry in the indane skeleton introduces an affordable level of strain (some 11.3 kcal mol^{-1} according to PM3 calculations on the 2-amino-1-indanol system). On the other hand, the energetic cost associated to the formation of a *trans* chelate could be unaffordable when short element–O,N bonds are involved in the process (some 29 kcal mol^{-1}, according to PM3 calculations, for each diastereomeric pair of the regioisomeric 2-methyl-1,3,2-oxazaborolidines that can be constructed on the indane structure). Finally, it is important to recall that the pair of atoms metal,O or metal,N involved in the catalytic event varies from one process to another (see Figure 2, structures **b** and **c**) so that, according to steric considerations, the optimal ligand regioisomer can also vary from one process to another.

According to this, we decided to study the use in catalysis of the four possible derivatives bearing in common the aminoindanol structure, which would eventually allow us to find the ideal candidate for each reaction studied. In the cases where strain considerations make unlikely the participation of *trans* diastereomers, this study will be restricted to the *cis* ones.

It is also worth noting that 1- and 2-aminoindanols can be considered as constrained surrogates of phenylglycinol and the members of the ephedrine family,

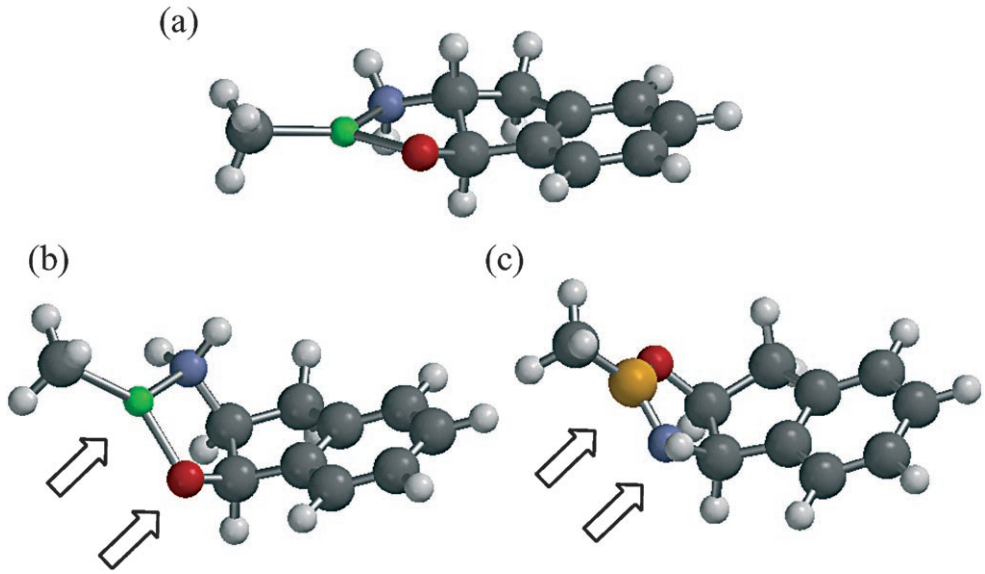


Figure 2. PM3 optimized molecular structures of metal chelates [methylzinc (green) and methylboron (golden)] of aminoindanols showing the flat structure of *trans* derivatives (**a**) and the bent nature of the *cis* ones (**b** and **c**). Arrows in structures **b** and **c** indicate both the preferred face for substrate and reagent coordination and the atoms in the metal chelates involved in reference catalytic processes (aldehyde alkylation and ketone reduction with borane).

respectively. Indeed, the stereochemical diversity of the latter has been explored in several studies[6] concerning, for instance, CBS reduction,[6a] Et_2Zn addition to aldehydes[6b] or asymmetric transfer hydrogenation,[6c] to name but a few.

Results and Discussion

Preparation of a Family of Aminoindanol-Derived Ligands

As previously mentioned, *cis*-1-amino-2-indanol (**1a**) is commercially available. As for the rest of the ligands, they were prepared in a few steps either by chemical resolution of racemates or by *de novo* synthesis starting from achiral compounds.[7] The amino alcohols obtained in this manner were transformed into their dimethylamino or piperidino[8] derivatives to ensure sufficient steric diversity in the amino moiety.

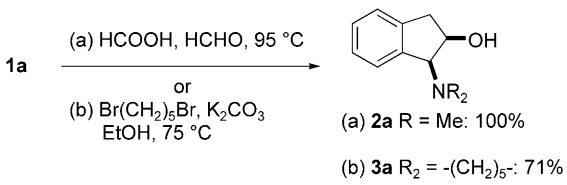
Preparation of Derivatives of 1a

The dialkylamino derivatives were obtained from commercially available **1a** following methods described in the literature. Reductive amination with formaldehyde[9] or nucleophilic substitution with 1,5-dibromopentane[10] afforded the dialkylamino derivatives in a straightforward manner (Scheme 1).

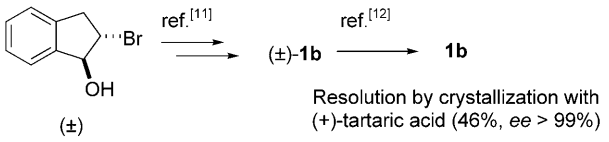
Preparation of 1b and Derivatives

Racemic *cis*-2-Amino-1-indanol (**1b**)[11] was obtained from the commercially available bromohydrin by conversion of the bromide into an azide and subsequent reduction to the amine. Resolution of the racemic mixture by crystallization of the corresponding tartrate allowed access to optically pure **1b** in both enantiomeric forms (Scheme 2).[12]

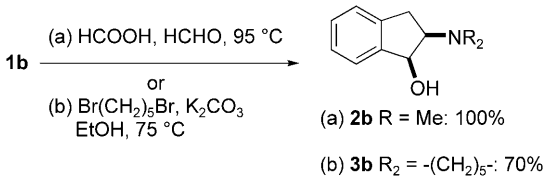
The procedures described for the dialkylation of **1a** were applied to **1b** as depicted in Scheme 3, which allowed us to isolate the dimethylamino and piperidino derivatives in 100% and 70% yields, respectively.



Scheme 1. Preparation of dialkyl derivatives of **1a**.



Scheme 2. Preparation of **1b** by resolution of a racemate.



Scheme 3. Preparation of dialkyl derivatives of **1b**.

Preparation of 1c and Derivatives

The preparation of **1c** (*trans*-1-amino-2-indanol, Scheme 4) started with the asymmetric epoxidation of indene[13] using Jacobsen's method.[5] The corresponding indene oxide was obtained in 93% *ee*, and after several trials the best method found to attain optical purity consisted in the transformation of this scalemic indene oxide into the corresponding hydroxycarbamate by regioselective ring-opening with ammonia and protection of the amine as a carbamate.[14] This intermediate could be recrystallized to attain 100% enantiomeric purity, after which acid hydrolysis of the carbamate afforded **1c** in quantitative yield. Again, the dialkylamino derivatives **2c** and **3c** were synthesized without any problem.

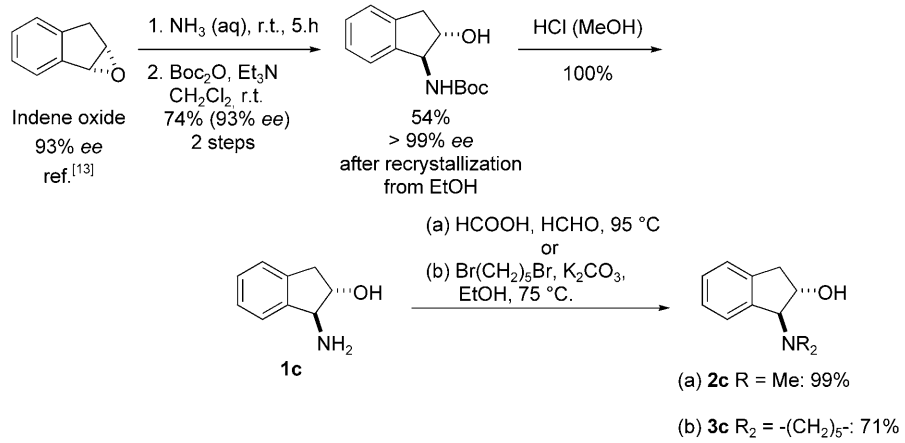
Preparation of 1d and Derivatives

Finally, **2d** and **3d** were prepared from **2c** and **3c** through the intermediacy of an aziridinium ion,[15] which was regioselectively ring-opened at the benzylic position with sodium *p*-nitrobenzoate. The corresponding ester was reduced with DIBALH to furnish the desired *trans*-2-dialkylamino-1-indanols (Scheme 5).

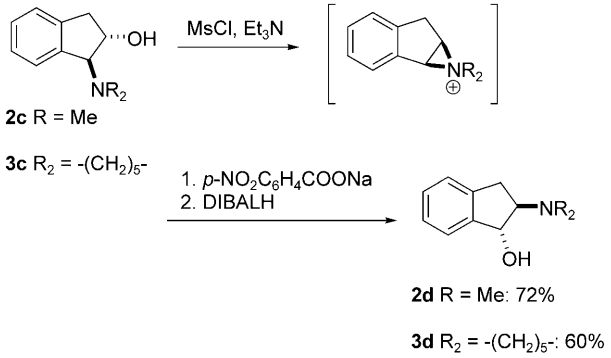
With this whole set of molecules sharing the aminoindanol scaffold in hand (**2a–d**, **3a–d**) the stage was set to analyze their performance as ligands in a series of catalytic enantioselective reactions.

Enantioselective Ethylation of Benzaldehyde

Given the successful application of modular amino alcohols in the alkyl- and arylzinc additions to aldehydes,[1a–c,16,17] we decided to use these reactions as benchmarks to test the catalytic profile of the synthesized aminoindanol ligands. It is worth noting that



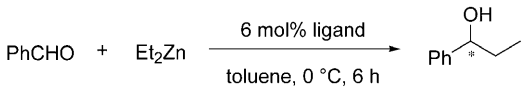
Scheme 4. Preparation of dialkyl derivatives of **1c** from scalemic indene oxide.



Scheme 5. Preparation of dialkyl derivatives of **1d** from **2**–**3c**.

Umani-Ronchi et al. had described the catalytic activity of aminoindanol ligands in this reaction with the dibutyl and diallyl derivatives of **1a**,[18] but their *ee*s did not exceed 50%. The results obtained using 6 mol% ligand in toluene at 0 °C are summarized in Table 1.

Table 1. Catalytic profile displayed by ligands **2a–d** and **3a–d** in the Et_2Zn addition to benzaldehyde.

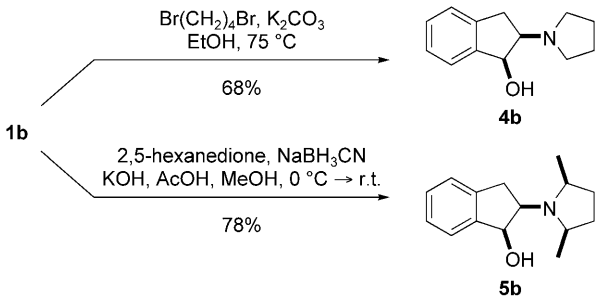


Entry	Ligand	Conversion [%]	*ee* [%]	Configuration
1	**2a**	91	15	*R*
2	**3a**	95	19	*R*
3	**2b**	56	38	*S*
4	**3b**	99	85	*S*
5	**2c**	45	47	*R*
6	**3c**	98	33	*R*
7	**2d**	12	11	*S*
8	**3d**	91	44	*S*

In nearly all cases the ligands containing the piperidino subunit (**3a–d**) displayed superior catalytic activity than their dimethylamino counterparts (**2a–d**) both in terms of conversion and enantioselectivity. Among ligands **3**, the *cis*-2-piperidino derivative **3b** exhibited the best activity/selectivity profile (entry 4). These results corroborated our working hypothesis that changes in the regio- and stereochemistry of the aminoindanol scaffold, as well as the steric hindrance around the amino group, can have a dramatic effect on the outcome of a given reaction.

Based on our results[1a–b] and Umani-Ronchi's,[18] there seemed to be a clear correlation between the bulkiness of the amino substituent and the enantioselectivity of the addition process. Consequently, we decided to carry out a fine-tuning involving this substructure, focusing on the array that had proven to provide better results: the *cis*-2-amino series. Hence, different ligands derived from **1b** with structural diversity in the dialkylamino moiety were synthesized by nucleophilic substitution or reductive amination. The pyrrolidino (**4b**)[10] and α,α′-dimethylpyrrolidino (**5b**)[19] derivatives were prepared as shown in Scheme 6.

Attempts to generate the dimethylpiperidino analogue of **5b** resulted in a mixture of diastereomers which could not be separated. Finally, we set our



Scheme 6. Synthesis of bicyclic amines by alkyaltion of **1b**.

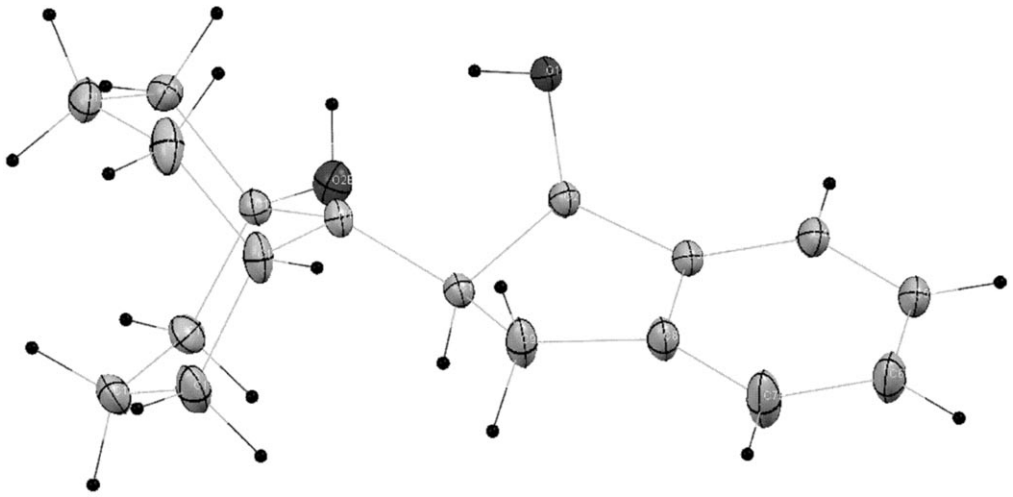
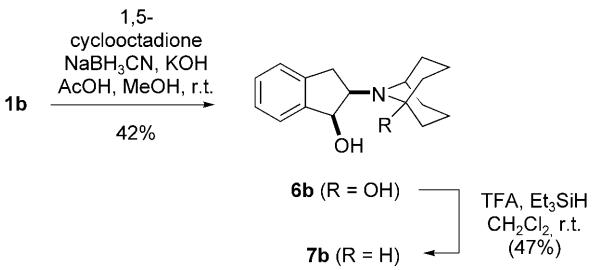


Figure 3. X-ray structure of hemiaminal **6b**.

sights on the bulkier bicyclic amine **7b**, which we tried to prepare by reductive amination of **1b** with 1,5-cyclooctanedione. However, under the standard conditions a compound which was identified as the hemiaminal **6b** was obtained. This assignment was confirmed by single-crystal X-ray diffraction (Figure 3).[20]

After several trials, we succeeded in reducing the hemiaminal to the desired amine **7b** upon treatment with triethylsilane in the presence of trifluoroacetic acid (Scheme 7).[21] In the scarce precedents involving construction of bulky amines by reductive amination, the hemiaminal intermediate was reduced by a two-step procedure consisting in conversion of the alcohol into a chloride followed by reduction with $LiAlH_4$[22] or radical-involving methods (Bu_3SnH/AIBN).[23] Interestingly, in the last case the authors report that reduction of a bicyclic hemiaminal with the Et_3SiH/TFA combination is sluggish, which they attribute to the inability to form the bridgehead iminium intermediate[23] (Bredt's rule). However, in our system this reaction worked well and the amine was generated from the hemiaminal in a single step with moderate yields. This approach represents a novel and efficient alternative to the protocols described so far for the preparation of bulky tertiary amines involving the 9-azabicyclo[3.3.1]nonane system.



Scheme 7. Synthesis of bicyclic amine **7b** by reductive amination of **1b**.

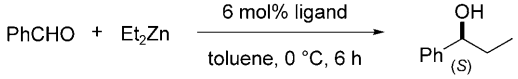
The catalytic activity of these bulky amines, together with that of the hemiaminal **6b**, was then tested in the same reaction and the results (displayed in Table 2) were compared with the best candidate arising from the first screening: **3b**.

Somewhat surprisingly, as illustrated in this table, variations on the amine leading to increased steric bulk (entries 3 and 5) did not have a positive impact on the outcome of the reaction, and **3b** remained the best catalyst for this particular reaction.

Next, we turned our attention to the enantioselective methylation of benzaldehyde. This time, the screening was limited to the best ligands as regards ethylation of aldehydes, along with **2b** as an example of acyclic amine. The results clearly show that increasing the steric bulk of the amino substituent leads to an important improvement of the enantioselectivity of the methylation, although this is accompanied with some decrease in the catalytic activity (Table 3).

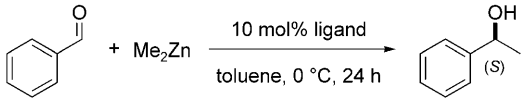
In light of these results, **2b** was ruled out as a candidate for screening the catalytic activity of the aminoindanols in the phenylation of *p*-tolualdehyde. This

Table 2. Catalytic activity of ligands **3**–**7b** in the Et_2Zn addition to benzaldehyde.



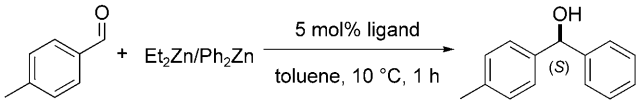
Entry	Ligand	Conversion [%]	*ee* [%]
1	**3b**	>99	85
2	**4b**	93	73
3	**5b**	>99	79
4	**6b**	4	–
5	**7b**	61	81

Table 3. Catalytic activity of ligands **2–3b** and **7b** in the Me_2Zn addition to benzaldehyde.



Entry	Ligand	Conversion [%]	*ee* [%]
1	**2b**	74	27
2	**3b**	73	70
3	**7b**	45	87

Table 4. Enantioselective addition of PhZnEt catalyzed by **3b** and **7b**.



Entry	Ligand	Conversion [%]	*ee* [%]
1	**3b**	>99	60
2	**7b**	>99	86

time **7b** matched complete conversion with a high enantioselectivity, much better than the one obtained with **3b** (Table 4). Clearly, in this case steric factors were crucial to achieve high enantioselectivity and this tends to indicate that, under the studied reaction conditions, the higher reactivity towards the carbonyl group of the ethylphenylzinc species[24,25] compensates any possible decrease in catalytic activity of the bulky **7b** ligand.

So far we have seen that the catalytic performance of aminoindanol ligands in diorganylzinc additions to aldehydes critically depends on the regio- and the stereochemistry of the ligands, and that simple modification of the steric environment of the amino group can also lead to very significant improvements in enantioselectivity. Not surprisingly if the nature of the atoms involved in the catalytic process is considered (see structures **b** and **c** in Figure 2), the optimal aminoindanol ligands for this process derive from the *cis*-2-amino-1-indanol isomer rather than from its more commonly used regioisomer, i.e., *cis*-1-amino-2-indanol.

A high number of catalytic systems use ligands which are not amino alcohols, but that can be readily prepared from this class of molecules. To explore the behaviour of the indane scaffold in processes of these types, we decided to extend the study of the regioisomeric and diastereomeric aminoindanols to reactions catalyzed by their derivatives.

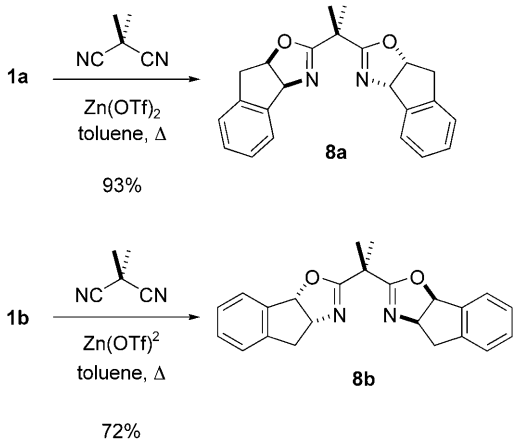
Palladium-Catalyzed Asymmetric Allylic Alkylation

Our efforts to expand the scope of the comparison began by preparing the bis(oxazoline) (BOX) derivatives of the aminoindanol scaffold. Since their introduction in 1989 based on Pfaltz's preliminary studies with the semicorrin platform,[27] BOX have been found to successfully catalyze several metal-mediated processes such as asymmetric allylic alkylation,[27] allylic oxidation, aziridination of olefins and imines, cyclopropanation and Mukaiyama aldol reactions, just to quote a few.[28]

The synthesis of the aminoindanol-derived BOX ligands was carried out following a reported protocol[29] which furnished **8a** and **8b** in good to excellent yields (Scheme 8). Worthy of note is the profound effect on the shape of the bis(oxazoline) exerted by the regiochemistry of the aminoindanol building block. It must be mentioned that although the preparation of bis(oxazoline) **8a** has been reported,[30] its use in asymmetric catalysis remains virtually unexplored.[31]

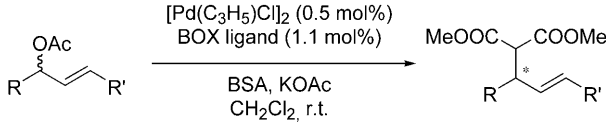
With these bis(oxazolines) in hand, we were ready to perform a comparison of their activity in asymmetric allylic alkylation. Several allylic acetates were alkylated with dimethyl malonate using 1.1 mol% of ligand, and the results are presented in Table 5.

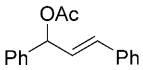
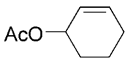
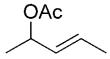
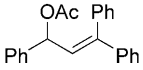
It is interesting to observe (entries 1 and 2) that both BOX ligands are able to induce the alkylation of 1-acetoxy-1,3-diphenyl-2-propene with high enantioselectivity. In this reaction, the U-shaped bis(oxazoline) **8a** behaves slightly better than the less sterically demanding **8b**. Noteworthy, with less bulky substrates (entries 3, 4 and 5, 6) **8b** is more enantioselective than **8a**, although the performance of both ligands with these substrates is far from optimal.



Scheme 8. Preparation of the bis(oxazoline) derivatives **8a**, **b** from **1a**, **b**.

Table 5. Pd-catalyzed asymmetric allylic alkylation mediated by ligands **8a** and **8b** [BSA = *N*,*O*-bis(trimethylsilyl)acetamide].



Entry	Ligand	Substrate	Time [h]	Conversion [%]	*ee* [%]	Configuration
1	**8a**		20	>99%	98	*S*
2	**8b**		20	>99%	93	*R*
3	**8a**		48	19	<1	–
4	**8b**		48	17	9	–
5	**8a**		48	16	8	*S*
6	**8b**		48	18	47	*R*
7	**8a**		48	–	–	–
8	**8b**		48	–	–	–

Trimethylsilyl Cyanide Addition to Aldehydes

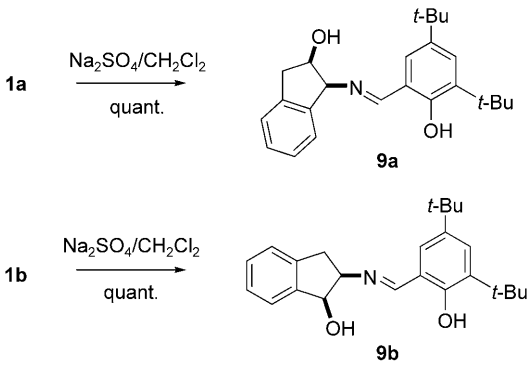
The formation of cyanohydrins is a classical transformation in organic synthesis. However, the development of catalytic enantioselective variants using chiral Lewis acids[32] and the versatility of the nitrile group have given this reaction a second youth.

In particular, imines have become a very interesting group of modular ligands to perform this reaction. In 1991, Oguni et al.[33] reported the use of an imino alcohol as the chiral ligand for the titanium-catalyzed silylcyanation of aldehydes. More recently, Walsh et al.[34] reported the use of imines derived from commercially available **1a** in combination with titanium tetraisopropoxide with moderate yields and enantioselectivities. Thus, we decided to extend this study to other aminoindanols with the aim of finding the best candidate isomer for this application.[35] In view of the results recorded in the addition of diorganozinc species to aldehydes, only the *cis* type regioisomers were studied.

Both imines were prepared quantitatively by simply treating a solution of the aminoindanol and salicylaldehyde with anhydrous sodium sulfate (Scheme 9). This method allowed the isolation of Walsh's imine **9a**[34] and of its analogue derived from *cis*-2-amino-1-indanol: **9b**.

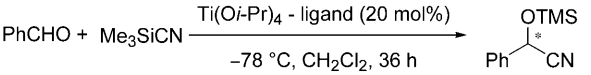
The study of the behaviour of **9a** and **9b** was carried out using the same conditions as described by Walsh et al.[34] These involved a 20 mol% loading of ligand and Ti(O-*i*-Pr)$_4$ in CH_2Cl_2 at −78 °C and the results are summarized in Table 6.

As exemplified in this table, and according to the results described by Walsh, the results were only moderate for **9a**. As for the new ligand **9b**, it performed poorly. It is thus clear that, for this particular process, the discriminating effect of the phenyl substituent is more efficiently transmitted to the diastereomeric transition states when imines derived from *cis*-1-amino-2-indanol are employed in the reaction.



Scheme 9. Preparation of imines **9a** and **9b**.

Table 6. Silylcyanation of benzaldehyde catalyzed by **9a**, **b**.



Entry	Ligand	Conversion [%]	*ee* [%]	Configuration
1	**9a**	69	70	*S*
2	**9b**	27	16	*R*

Asymmetric Borane Reduction of Prochiral Ketones

Another interesting field where chiral amino alcohols have found applicability is as the precursors of oxazaborolidines. These species have proven to be an excellent option in the enantioselective reduction of ketones with borane for the production of enantioenriched secondary alcohols. The use of oxazaborolidines in asymmetric ketone reduction was introduced by Itsuno et al.[36] although it was Corey who pro-

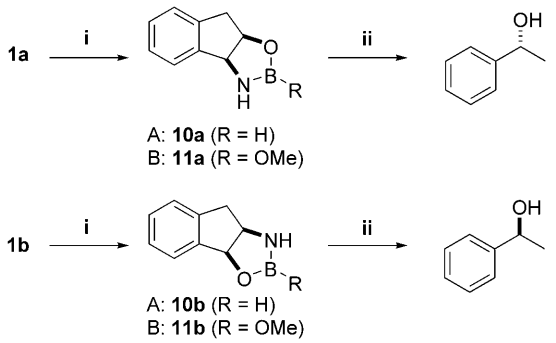
posed the mechanism, which allowed for a rational development of the catalytic system.[37]

Since their use was first described by Didier's group for the borane reduction of ketones,[38] the aminoindanol scaffold has been employed by other authors[18,39] in this reaction, either as the B–H, the B–Me or B–OMe derivative. Nevertheless, this work has been restricted to derivatives of **1a**. Therefore, our aim was to compare the results obtained for the commercially available aminoindanol with those of its regioisomer. According to the strain considerations set up above (Figure 2), the use of the *trans* diastereomers **1c** and **d** was not considered for this application. Thus, the B–H and the B–OMe oxazaborolidines derived from **1a** and **1b** were prepared by Methods A and B (Table 7) and tested in the reaction. In Method A, the B–H oxazaborolidine was generated *in situ* by reaction between the amino alcohol and borane, while Method B involved pre-formation of the B–OMe derivative and subsequent addition of the borane and the ketone to be reduced.

Since it is well known that oxazaborolidine-mediated reductions tend to be very sensitive to reaction temperature,[40] the reactions were performed at several temperatures in order to establish the optimal conditions for the process with this set of ligands. The results obtained for the catalytic asymmetric reduction of acetophenone using **10a**, **b** and **11a**, **b** are illustrated in Table 7.

These results show that B–OMe oxazaborolidines (**11**) perform slightly better than their B–H counterparts (**10**). As for the regiochemistry, the *cis*-1-amino-2-indanol (**a** series) tends to provide better *ee*s than its 2-amino regioisomer (**b**) and this observation stands for both methods.

Table 7. Asymmetric reduction of acetophenone by *in situ* generation of oxazaborolidines.



Method A: **(i)** $BH_3{\cdot}SMe_2$ (1.2 equiv.), THF; **(ii)** acetophenone (1.0 equiv.)
Method B: **(i)** $B(OMe)_3$ (0.12 equiv.), THF; **(ii)** $BH_3{\cdot}SMe_2$ (1.0 equiv.), then acetophenone (1.0 equiv.)

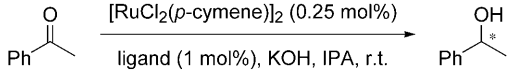
Entry	Ligand	*T*	Conversion [%]	*ee* [%]
1	**10b**	0 °C	74	68
2	**10a**	r.t.	>99	94
3	**10b**	r.t.	>99	84
4	**10b**	40 °C	>99	81
5	**11a**	0 °C	>99	92
6	**11b**	0 °C	93	78
7	**11a**	r.t.	>99	93
8	**11b**	r.t.	>99	82
9	**11a**	40 °C	>99	92
10	**11b**	40 °C	>99	81

Asymmetric Transfer Hydrogenation

The reduction of ketones by hydrogen transfer has emerged as a powerful alternative to the use of molecular hydrogen. In this method, alternative hydrogen sources (usually isopropyl alcohol – IPA – or formic acid/triethylamine) involving less potential risks are used. The process is normally mediated by ruthenium catalysts, enantiocontrol being secured through the use of enantiopure monotosylated 1,2-diamines as ligands.[41] Enantiopure amino alcohols have also found regular application as ligands for this process,[42] and we have shown that when these molecules are modularly constructed it is possible to optimize their structures for high enantiocontrol.[43] According to these facts, we thought it would be interesting to apply the aminoindanols to this reduction as an alternative to oxazaborolidines. The use of **1a** in this field was pioneered by Wills et al. in 1997.[44] The same authors have described the comparative use of **1a**, **1c** and several *N*-alkyl derivatives in this reaction.[14] Therefore, the effect of the stereochemistry had been studied, but the consequences of a change in the regiochemistry remained unexplored, so we decided to undertake the comparative study of the catalytic activity of **1a** and **1b** in the asymmetric reduction of acetophenone with a ruthenium catalyst. The results are summarized in Table 8.

Table 8 clearly indicates that when **1b** is used the reaction is slowed down, and its enantioselectivity drops, so that **1a** proved to be the best option. It is also worth mentioning that, with the studied ligands, the application of longer reaction times can be trou-

Table 8. Transfer hydrogenation of acetophenone employing **1a**, **b** as ligands.



Entry	Ligand	*t* [h]	Conversion [%]	*ee* [%]	Configuration
1	**1a**	2	90	84	*R*
2	**1b**	2	33	77	*S*
3	**1a**	4	91	76	*R*
4	**1b**	4	36	76	*S*

blesome due to the reversibility of the reaction which can gradually erode the enantiomeric purity of the product as verified when comparing entries 1–3 and 2–4.

Conclusions

A systematic study of the catalytic profile of the regio- and stereoisomers of the aminoindanol structure has been carried out for the first time, and the isomers depicting optimal properties as ligands for a variety of important catalytic enantioselective processes have been identified. The results have demonstrated that, whilst for most reactions commercially available *cis*-1-amino-2-indanol **1a** and/or its derivatives represent the best possible option, that is more a general tendency than a rule, as demonstrated in the addition of diorganozinc reagents to aldehydes, where this tendency is completely reversed and cycloalkylated derivatives of *cis*-2-amino-1-indanol **1a** bearing bulky amino substituents afford the highest enantioselectivities. According to the results recorded for the reactions involving cyclic chelates studied here, it appears that internal delivery of the reagent from the heteroatom occupying the benzylic position in a *cis*-aminoindanol structure (see structures **b** and **c** in Figure 2) fulfills the requirements for highest enantioselectivity. From a synthetic point of view, we have shown that very bulky tertiary amines, involving the 9-azabicyclo[3.3.1]nonane system can be readily prepared by a two-step procedure consisting in the formation of an intermediate hemiaminal and its subsequent reduction under acidic conditions.

Experimental Section

Synthesis of 5b by Reductive Amination[19]

(1*S*,2*R*)-2-Amino-1-indanol **1b** (298 mg, 2.0 mmol) was dissolved under argon in 2 mL of MeOH. An aliquot of 0.13 mL of a methanolic solution containing KOH (33 mg, 0.5 mmol) and acetic acid (0.125 mL, 2.2 mmol) were added. Afterwards, at 0 °C, 2,5-hexanedione (0.2 mL, 2.0 mmol), followed by $NaBH_3CN$ (127 mg, 2.0 mmol) dissolved in MeOH (1.0 mL) were successively added. The temperature rose spontaneously to room temperature and the miyture was stirred overnight (20 h). The reaction was monitored by TLC and quenched with 4 N HCl (5 mL). MeOH was removed under vacuum and the remaining solution was washed with CH_2Cl_2. The aqueous solution was basified by careful addition of K_2CO_3 until pH 9–10, and extracted with CH_2Cl_2 (3×10 mL). The xtract was then dried with Na_2SO_4 and solvent evaporated under vacuum to yield a white solid, which was further purified by column chromatography (hexanes/EtOAc from 1:1 to 1:3) to afford **5b** as a white solid; yield: 325 mg (71%); mp 75 °C; $[\alpha]_D^{23}$: −47.3 (*c* 0.85, $CHCl_3$); IR (neat, ATR): ν = 3245, 3065, 2972, 2927, 2869, 1456, 1328, 1211, 1059, 1018, 975, 760, 739, 670 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.55–7.42 (1H, m, Ar*H*), 7.30–7.15 (3H, m, Ar*H*), 4.74 (1H, d, *J* = 5.5 Hz, C*H*OH), 3.47 (1H, ddd, *J* = 4.9 Hz, *J* = 7.1 Hz, *J* = 12.3 Hz, C*H*NR_2), 3.2–2.9 (4H, m, C*H*HCHN, CH*H*CHN, 2C*H*CH_3), 1.93 (2H, m, CH_2), 1.53 (2H, m, CH_2), 1.24 (3H, d, *J* = 6.4 Hz, CH_3), 1.02 (3H, d, *J* = 6.4 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 143.5 (C), 141.5 (C), 128.4 (CH), 126.8 (CH), 125.4 (CH), 124.5 (CH), 73.5 (CH), 67.9 (CH), 63.0 (CH), 56.4 (CH), 33.8 (CH_2), 32.9 (CH_2), 32.5 (CH_2), 25.3 (CH_3), 22.7 (CH_3); HR-MS (ESI+): *m*/*z* = 232.1693, calcd. for $C_{15}H_{22}NO$ $[M+H]^+$: 232.1696.

Preparation of Hemiaminal 6b

The experimental procedure was the same as for **5b** with the following quantities: (1*S*,2*R*)-2-amino-1-indanol **1b** (298 mg, 2.0 mmol) in MeOH (2 mL), 0.13 mL from a methanolic solution containing KOH (33 mg, 0.5 mmol) and acetic acid (0.125 mL, 2.2 mmol), 1,5-cyclooctanedione (280 mg, 2.0 mmol) in MeOH (1 mL), and $NaBH_3CN$ (127 mg, 2.0 mmol) in MeOH (1 mL). The viscous oil obtained was purified by column chromatography (from hexanes/EtOAc 1:1 to 1:3) to afford 9-[(1*S*,2*R*)-1-hydroxy-2,3-dihydro-1*H*-inden-2-yl]-9-azabicyclo[3.3.1]nonan-1-ol (**6b**); yield: 227 mg (42%); $[\alpha]_D^{23}$: −61.4 (*c* 1.02, $CHCl_3$); IR (neat, ATR): ν = 3385, 2917, 2873, 1432, 1371, 1175, 1034, 974, 876, 832, 743, 714 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.40–7.48 (1H, m, Ar*H*), 7.18–7.27 (3H, m, Ar*H*), 4.83 (1H, d, *J* = 5.5 Hz, C*H*OH), 3.56 (1H, dd, *J* = 7.1 Hz, *J* = 13.3 Hz, C*H*NR_2), 3.04 (1H, dd, *J* = 7.1 Hz, *J* = 15.5 Hz, C*H*H), 2.86 (1H, dd, *J* = 7.5 Hz, *J* = 15.5 Hz, CH*H*), 2.80 (1H, m, C*H*NCH_2CH_2), 2.50 (1H, br s, O*H*), 2.42 [1H, m, C*H*HC(OH)N], 2.26 [2H, m, CH_2C(OH)N], 2.12 [1H, m, CH*H*C(OH)N], 1.94 [4H, m, 2CH_2(CH_2)CH_2], 1.70 [4H, m, 2CH_2(CH)CH_2CH_2]; ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 143.4 (C), 140.7 (C), 128.5 (CH), 127.0 (CH), 125.6 (CH), 124.8 (CH), 73.9 (CH), 59.8 (CH), 55.0 (CH), 42.4 (2 CH_2), 36.5 (CH_2), 34.2 (2 CH_2), 23.1 (2 CH_2); HR-MS (ESI+): *m*/*z* = 274.1795, calcd. for $C_{17}H_{24}NO_2$ $[M+H]^+$: 274.1802.

Reduction of Hemiaminal 6b to (1*S*,2*R*)-2-(9-Azabicyclo[3.3.1]nonan-9-yl)-2,3-dihydro-1*H*-inden-1-ol (7b)

Hemiaminal **6b** (112 mg, 0.41 mmol) was dissolved in anhydrous CH_2Cl_2 (3 mL) under argon. Triethylsilane (1.15 mL, 7.0 mmol) and TFA (0.83 mL, 6.6 mmol) (dried over 4 Å activated MS for 1 h before using it) were added dropwise, and the mixture was stirred at room temperature for 60 h. Then, the reaction was quenched with 10 mL of a saturated solution of $NaHCO_3$ and basified to pH 11–12 with 30% aqueous NaOH. It was extracted with CH_2Cl_2 (3×15 mL) and allowed to stir over $MgSO_4$. An orange spot appeared in the TLC when stained with ninhydrin, which evolved throughout 8 h. After that, it was filtered off and purified by column chromatography in neutral alumina with hexane/EtOAc (from 9:1 to 1:3) to afford the desired product; yield: 49 mg (47%). mp 95 °C; $[\alpha]_D^{23}$: +64.8 (*c* 1.04, $CHCl_3$); IR (neat, ATR): ν = 3238, 2923, 2849, 1735, 1561, 1477, 1308, 1274, 1178, 1139, 1072, 1034, 942, 834, 724 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.50–7.42 (1H, m, Ar*H*), 7.17–7.30

(3H, m, Ar*H*), 4.78 (1H, d, $J=4.9$ Hz, C*H*OH), 3.75 (1H, ddd, $J=4.9$ Hz, $J=7.1$ Hz, $J=12.3$ Hz, C*H*NR_2), 3.10 (2H, bs, C*H*NCH_2CH_2), 2.99 (1H, dd, $J=11.6$ Hz, $J=14.6$ Hz, C*H*H), 2.89 (1H, dd, $J=7.1$ Hz, $J=14.6$ Hz, CH*H*), 2.07 (6H, m, 3 CH_2), 1.64 (6H, m, 3 CH_2), 1.6 (1H, br s, O*H*); ^{13}C NMR ($CDCl_3$, 100.6 MHz): $\delta=142.9$ (C), 141.9 (C), 128.8 (CH), 126.9 (CH), 125.9 (CH), 124.8 (CH), 71.5 (CH), 62.5 (CH), 49.3 (CH), 33.8 (CH_2), 28.5 (CH_2), 27.0 (CH_2), 20.5 (4 CH_2); HR-MS (ESI+): $m/z=258.1863$, calcd. for $C_{17}H_{24}NO$ $[M+H]^+$: 258.1852.

Supporting Information

Detailed experimental procedures for the preparation of the enantiopure aminoindanol precursors and ligands derived from them, as well as the application of these compounds in asymmetric catalysis are available in the Supporting Information.

Acknowledgements

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[20] Crystals of **6b** could be obtained by slow evaporation of a solution of the compound in a mixture of ethanol and ethyl acetate. Crystal data for **6b** at 100 K: $2\cdot(C_{17}H_{23}NO_2)$, 546.73 g mol^{-1}, orthorhombic, $P2_12_12_1$, $a=6.7084(3)$ Å, $b=19.3348(9)$ Å, $c=22.5361(10)$ Å, $V=2923.1(2$ Å^3, $Z=4$, $\rho_{calcd.}=1.242$ Mg/m^3, $R_1=0.0420$ (0.0470), $wR2=0.1144$ (0.1196), for 16172 reflections with $I>2\sigma(I)$ (for 17104 reflections [R_{int}: 0.0250] with a

total measured of 59257 reflections), goodness-of-fit on $F^2 = 1.194$, largest diff. peak (hole) = 0.72 (−0.61) e Å^{-3}. CCDC 693931 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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