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Origin of Enantioselectivity in the Organocatalytic Reductive Amination of α-Branched Aldehydes

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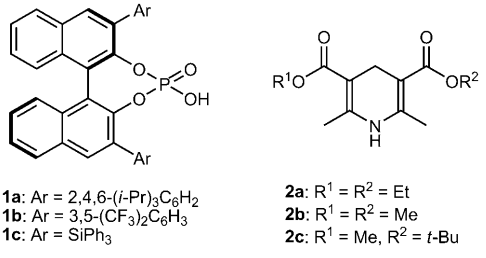
Abstract: The reason for enantioselectivity in the reductive amination of α-branched aldehydes was investigated. The relative energies of all the diastereomeric transition states for hydride transfer of a suitable computational model were calculated at the B3LYP/6-311+G(2d,2p) level of theory. Our calculations successfully reproduce and rationalize the experimentally observed stereochemical outcome of the reaction.

Keywords: density functional theory; dynamic kinetic resolution; Hantzsch esters; organocatalysis; reduction

The enantioselective reduction of C=N double bonds using dihydropyridines as hydrogen donors[1] in combination with axially chiral phosphoric acid catalysts[2] is among the most remarkable achievements in organocatalysis (Figure 1). Initially optimized and developed for *N*-arylketimines,[3] this approach to metal-free hydrogenation has been successively applied to the reduction of imino esters[4] and heterocycles[5] as well as reductive tandem reactions.[6] In all these processes, the catalyst controls the stereochemistry of a chiral center which is formed in the hydride transfer step. We recently reported a density functional theory study on the mode of action of diarylphosphoric acid organocatalysts in the transfer hydrogenation of ketimines using Hantzsch esters as hydrogen donors.[7] Our results showed that diarylphosphoric acids act as bifunctional Lewis base/Brønsted acid (LBBA) catalysts.[8] Moreover, we showed that both *E* and *Z* iminium (presumably in equilibrium under the reaction conditions) species are competent substrates for the hydride transfer. Following imine protonation, the resulting phosphate engages in two hydrogen bonds, one with the iminium and one with the N–H group of the dihydropyridine. Hydride transfer and phosphate protonation releases the *N*-arylamine and the Hantzsch pyridine and regenerates the phosphoric acid, hence closing the catalytic cycle. We also investigated the origins of enantioselection for two substrates displaying a reversed sense of stereoinduction, namely the N-PMP imine derived from acetophenone and 2-phenylquinoline. In both cases, our model succesfully reproduced the sense of enantioselection and we could rationalize the results in terms of the geometry of the C=N double bond in the reacting iminium ion.



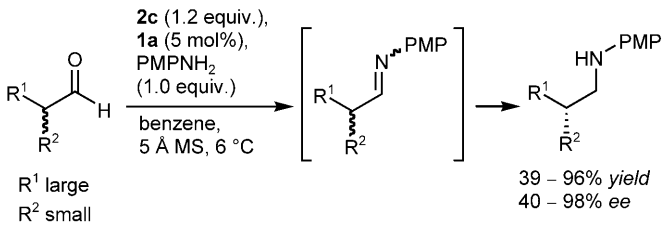
1a: Ar = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$
1b: Ar = 3,5-(CF$_3$)$_2$C$_6$H$_3$
1c: Ar = SiPh$_3$

2a: R^1 = R^2 = Et
2b: R^1 = R^2 = Me
2c: R^1 = Me, R^2 = *t*-Bu

Figure 1. Axially chiral phosphoric acid organocatalysts and Hantzsch esters employed for asymmetric imine reduction.

List and co-workers recently reported a highly efficient dynamic kinetic resolution (DKR) of α-branched aldehydes *via* reductive amination with *p*-anisidine, giving β-branched PMP-protected amines in mostly excellent yields and enantiomeric excesses (Scheme 1).[9]

In this protocol, imines are prepared *in situ* by mixing an aldehyde with *p*-anisidine and molecular sieves. In the presence of a phosphoric acid catalyst, imines undergo fast tautomerization and, therefore, racemize. The efficiency of this process is based on selective hydride transfer to one of the enantiomers of the resulting iminium ion. Unlike all the other aforementioned cases, in the DKR of aldehydes *via* reduc-



Scheme 1. Reductive amination of α-branched aldehydes *via* dynamic kinetic resolution (PMP = *p*-methoxyphenyl).[9]

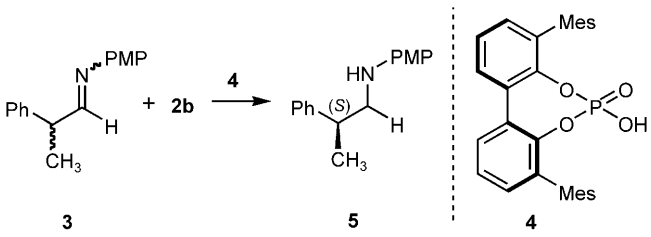
tive amination, hydride transfer does not create a new chiral center.

In this communication we present a theoretical study aimed at the elucidation of the reason for enantioselection in this synthetically relevant transfer hydrogenation.

We employed the same computational methods that were used in our previous study on the transfer hydrogenation of ketimines and quinolines.[7] The computational approach used here has been extensively shown to be appropriate for studying enantioselectivity in a variety of organocatalytic processes.[10]

We considered the transfer hydrogenation of imine **3**, whose reaction with Hantzsch ester **2c** in the presence of catalyst **1a** leads to the corresponding amine **5** in 87% yield and 96% enantiomeric excess.[11] In line with our computational approach to investigate ketimine and quinoline reduction,[7] we employed compound **4** as a model for the bulky BINOL derived phosphoric acid **1a**, with a biphenyl instead of the binaphthyl backbone and bulky mesityl substituents instead of triisopropylphenyl groups in the 3 and 3′ positions. The dihydropyridine used in this study is dimethyl Hantzsch ester **2b** (Scheme 2). It is worth noting that in the case of the DKR, the nature of the esters in the dihydropyridine was shown to have some influence on the enantiomeric excess of the resulting product, with Hantzch ester **2c** giving the best results.[9]

As mentioned above, in the presence of a Brønsted acid, substrate racemization can take place through a rapid imine/enamine tautomerization. Likewise, the tautomerism can also be responsible for *E*/*Z* imine isomerization. Although we did not perform a detailed study of the mechanism of the tautomerization, it is a safe assumption that, in the presence of a Brønsted acid, the barrier for the proton transfer is considerably lower than the approximately 20 kcal mol^{-1} found for the hydride transfer to the iminium. For instance, in our previous study we calculated that protonation of a PMP ketimine has a barrier smaller than 2 kcal mol^{-1}.[7] Therefore, the barrier for enamine protonation should not be much higher. The enantioselectivity is thus determined in the hydride transfer step. Although nucleophilic addition to an aldimine does not create a new stereogenic center, attack on the *Re* and *Si* faces of a chiral substrate are two stereochemically distinct events which need to be considered separately (Figure 2).



Scheme 2. The considered reaction (Mes = 2,4,6-trimethylphenyl).

We have calculated the eight transition states (TSs) for hydride transfer accounting for all combinations of *R* and *S* stereochemistry at the α-carbon, *E* and *Z* iminium geometry and *Re* and *Si* facial attack of the transferring hydride. Relative energies and selected interatomic distances for the optimized TSs are summarized in Table 1. Inspection of the interatomic distances revealed no apparent correlation with the energies of the TSs. In our previous study on ketimine reduction we observed that low-energy TSs tended to

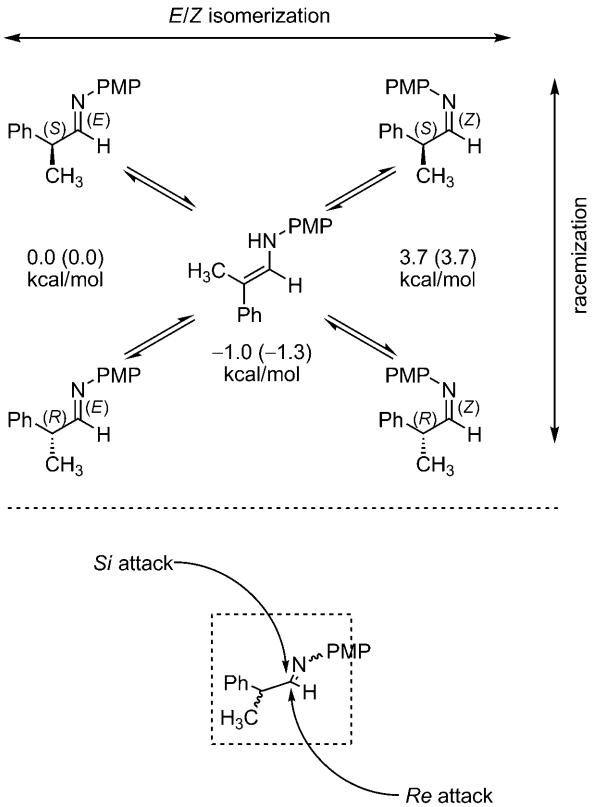
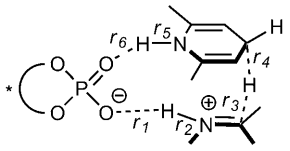


Figure 2. Stereochemical possibilities for the hydride transfer to imine **3**. The calculated energies for the two isomers of imine **3** as well as for the corresponding *E*-enamine are given, both in benzene and in gas phase (in parentheses).

Table 1. Calculated relative energies and selected distances[a] for the hydride transfer transition states.[b]



TS	ΔE_{gas}	ΔE_{solv}	r_1	r_2	r_3	r_4	r_5	r_6
S-Si-E	0.0	0.0	1.83	1.04	1.46	1.27	1.05	1.67
S-Re-E	5.4	5.4	1.81	1.04	1.50	1.27	1.05	1.68
S-Si-Z	8.2	8.4	1.72	1.04	1.43	1.33	1.05	1.67
S-Re-Z	0.0	0.9	1.69	1.04	1.43	1.30	1.05	1.63
R-Si-E	2.8	3.3	1.84	1.04	1.53	1.26	1.05	1.63
R-Re-E	1.2	1.8	1.82	1.04	1.44	1.28	1.05	1.66
R-Si-Z	9.5	10.2	1.73	1.04	1.40	1.32	1.05	1.66
R-Re-Z	3.9	4.4	1.67	1.04	1.44	1.28	1.05	1.64

[a] Energies are in kcal mol^{-1}, distances are in Angstroms.
[b] For simplicity, the schematic representation of the transition state does not include iminium and dihydropyridine substituents.

have a short iminium/phosphate hydrogen bond (r_1). Another difference between the reduction of ketimines and α-branched aldimines is that here all TSs for hydride transfer are somewhat early, with the moving hydride being closer to the C-4 of Hantzsch ester **2b** than to the iminium carbon of substrate **3**.

We note that the two transition states with the lowest energy leading to the formation of each *R* and *S* enantiomers of amine **5** (*R-Re-E* and *S-Si-E*, Figure 3) have an *E* geometry of the C=N double bond. In these two TSs, the relative arrangement of iminium and Hantzsch ester is enantiomeric (which means that without the phosphoric acid catalyst the two TSs would be enantiomers).

S-Si-E, the TS with the overall lowest energy, has an optimal binding geometry between substrates and catalyst as well as a good relative arrangement of dihydropyridine and iminium ion (Figure 3).

More specifically, the phenyl ring on the α-carbon of imine **3** points away from the phosphate, therefore minimizing steric interactions with the mesityl substituent of catalyst **4**. The PMP group on the iminium nitrogen lies parallel with one ester group of dihydropyridine **2b** at a distance of roughly 3.5 Å. Furthermore, one *ortho*-proton of the PMP group engages in a weak interaction with one phosphate oxygen

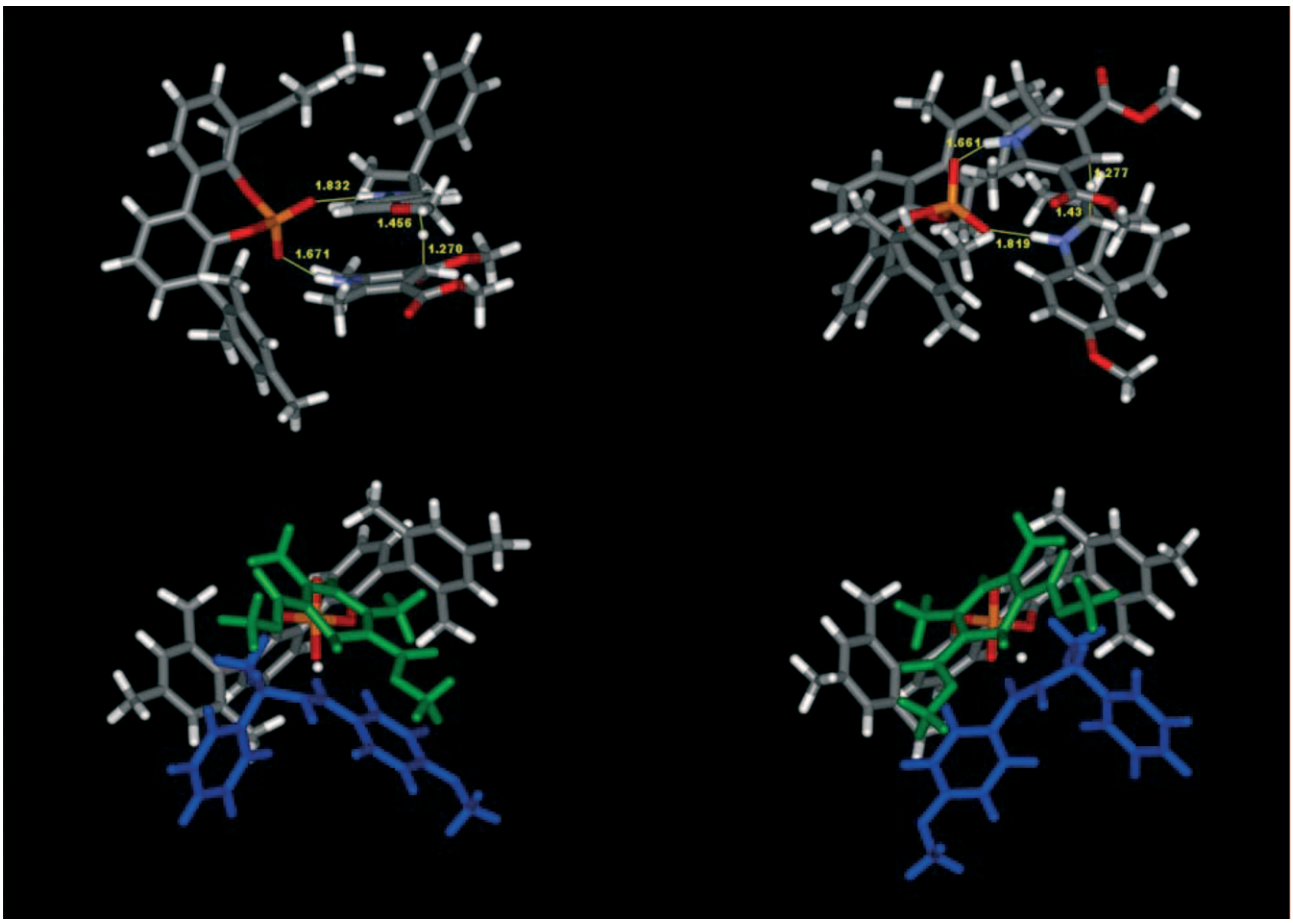


Figure 3. Lowest energy transition states leading to the *S* (*left*) and *R* (*right*) enantiomer of amine **5**. In order to better display the steric interactions, in the bottom view the Hantzsch ester is coloured in green and the imine in blue.

(2.27 Å). On the other hand, in *R-Re-E* the PMP group is considerably closer to the mesityl substituent of phosphoric acid **4** (2.26 Å for the shortest $H_{mesityl}$–H_{PMP} distance), while the substituents on the α-carbon of the substrate do not experience severe steric repulsion with either Hantzsch ester or catalyst. The unfavourable interaction of the imine protecting group with the catalyst is hence responsible for the energy difference of 1.8 kcal mol^{-1} between *R-Re-E* and *S-Si-E*, which is in good agreement with the experimentally observed enantiomeric excess.

All other transition states experience variable degrees of unfavourable steric interactions (for three-dimensional representations, see Supporting Information). For instance, in the two energetically lowest-lying TSs with a *Z* geometry at the C=N double bond (*S-Re-Z* and *R-Re-Z*), the phenyl substituent on the α-carbon of the iminium clashes with one mesityl group and, to a minor extent, with the PMP group. In the case of acetophenone ketimine reduction, the *Z* isomer of the iminium adopts a hairpin shape which allows it to achieve a better fit in the catalyst binding pocket.[7] In the case of imine **3**, instead, the presence of a tetrahedral α-carbon with a bulky phenyl substituent renders the complex between *Z* iminium, Hantzsch ester and phosphoric acid sterically more crowded. In both *R-Si-E* and *S-Re-E*, the relative orientation of substrates and catalyst imposes unfavourable interactions between both mesityl substituents of catalyst **4** and the PMP and Ph groups of imine **3**. Consequently, the energies of these TSs are 3.3 and 5.4 kcal mol^{-1} higher than *S-Si-E*, respectively. The repulsion between one methyl ester of dihydropyridine **2b** and both aryl groups of substrate **3** results in the high energy of both *R-Si-Z* and *S-Si-Z* (+10.2 and +8.4 kcal mol^{-1}, respectively).

In conclusion, we investigated the reason for enantioselection in the reductive amination of α-branched aldehydes. Our calculations successfully reproduce the observed stereoselectivity. Unlike in the case of ketimine reduction, hydride transfer to the *E*-iminium is energetically more accessible. The origin of enantioselectivity closely resembles what we observed for the 3,4-dihydroquinolinium reduction. More specifically, in the energetically-favoured transition state, both Hantzsch ester and iminium ion are placed between the bulky mesityl substituents in a sandwich-like structure that minimizes steric interactions, especially the one between the phenyl group of the substrate and the aryl groups of the catalyst. The results reported here will aid the further development of organocatalytic transfer hydrogenations using bifunctional LBBA catalysis.

Experimental Section

Computational Details

All calculations were performed using the B3LYP density functional method[12] as implemented in the *Gaussian03* package.[13] Stationary points were fully optimized using the 6–31G(d,p) basis set. Gas-phase energies were calculated using the larger 6–311+G(2d,2p) basis set. The effect of solvation was calculated using the CPCM model for benzene (ε=2.247).[14] Due to the size of the model (130 atoms), the computational cost for vibrational analysis was considered prohibitive. The nature of the calculated transition states was instead confirmed by careful inspection of the corresponding eigenvectors.

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