

Origin of 1, 3-induction in the addition of alkyl lithium to imines bearing an N-stereogenic center

Nancy,^a Soma Ghosh,^a Nishan Singh,^a Gurmeet Kaur Nanda,^a P. Venugopalan,^a Prasad V. Bharatam^b and Sanjay Trehan^{*a}

^a Department of Chemistry, Panjab University, Chandigarh-160 014, India. E-mail: trehan_s@yahoo.com

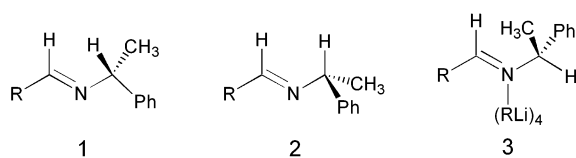
^b Department of Chemistry, Guru Nanak Dev University, Amritsar-143 005, India

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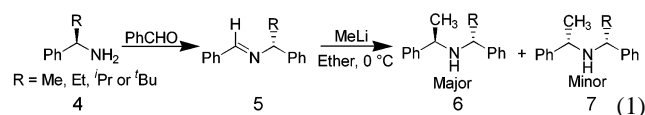
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The origin of diastereoselectivity in the addition of alkyl lithium to chiral Schiff bases has been investigated experimentally and theoretically and the formation of the major diastereomer can be explained from the energy minimized structure of the Schiff base in which the phenyl group has been found to orient in such a manner that it posed lesser steric hindrance to the incoming nucleophile as compared to the alkyl group

Construction of optically active amines by addition of organometallic reagents to imines bearing a stereogenic centre on nitrogen has been investigated in detail.¹ The method simultaneously achieves formation of optically active amine and the construction of carbon framework. Despite all the remarkable achievements synthetically, very few efforts have been directed towards understanding the origin of diastereoselectivity.^{1b} Yamamoto proposed an empirical model to explain the observed diastereoselectivity in their allylation reaction.² The reaction was proposed to proceed *via* conformation **1** and the product formation occurred *via* attack from the side of the hydrogen. Recently, Savoia, based on the NOE studies on the Schiff bases complexed with Lewis acids, proposed an alternate model based on the assumption that the N-chiral centre with conformation **2** undergoes reorientation to an alternate conformation **3** after complexation with alkyl lithium. The product formation occurs by attack of nucleophile from the side of the methyl group.³ Herein we propose a conceptually new model based on experimental and theoretical results. Based on these investigations we also report a chiral amine whose Schiff bases result in high C=N π facial selectivity.



To evaluate the proposed models racemic chiral amines with R being methyl, ethyl, isopropyl and *tert*-butyl were prepared⁴ and were condensed with benzaldehyde to give corresponding Schiff bases. The Schiff bases were treated with methyl lithium at 0 °C in ether. The Schiff base having R as *tert*-butyl group did not undergo any reaction and starting material was recovered. The addition products in other cases were purified *via* flash column chromatography. Due care was taken to avoid separation of the diastereomers. The relative stereochemistry of the major diastereomer, in cases where R is either ethyl or isopropyl, was determined by X-ray crystallographic analysis.[†]



It is interesting to note that the diastereoselectivity increased as the size of the alkyl group increased from methyl to ethyl to isopropyl (Table 1, entries 1–3). A similar trend was also

observed when the nucleophile used was *n*-Butyl lithium in ether at –78 °C. The stereochemistry of the major isomer in other cases was determined by comparison with the methyl lithium addition product. Increase in the steric bulk of R should further facilitate the reorganisation of Schiff base **5** into a conformation similar to **3** to minimize increased 1,2 steric interaction. This should result in decrease in diastereoselectivity as the steric hindrance from the side of methyl increases when it is replaced with ethyl or isopropyl. Thus, these results rule out the possibility of conformation **3** leading to the major diastereomer formation.

Table 1 Addition of alkyl lithium to various Schiff bases **5**

Entry	R	R'Li	Diastereomeric Ratio ^a	Isolated yield (%)
1	Me	MeLi	70 : 30 (2.3 : 1)	63
2	Et	MeLi	86 : 14 (6.1 : 1)	52
3	<i>i</i> Pr	MeLi	92 : 08 (11.5 : 1)	51
4	Me	<i>n</i> -BuLi	73 : 27 (2.7 : 1)	79
5	Et	<i>n</i> -BuLi	74 : 26 (2.8 : 1)	76
6	<i>i</i> Pr	<i>n</i> -BuLi	97 : 03 (32.3 : 1)	82

^a Diastereomeric ratio was determined from 300MHz ¹HNMR.

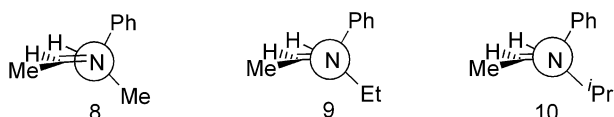
In order to understand the observed diastereoselectivity we have carried out *ab initio* MO and DFT studies on the structure of Schiff bases **8–10**.⁵ The energies of various minima for **8–10** is compiled in Table 2. Theoretical structure of all the Schiff bases showed *syn* arrangement (H–C–N–C–H) to be the most stable as expected according to 1,3-allylic strain model.⁶ The other conformations with phenyl and methyl *syn* were appreciably higher in energy for **8** at all levels of calculation. In the case of **9** the minima for phenyl *syn* and ethyl *syn* were not well defined and they appeared as shoulders at 90° and 240° respectively. In the case of **10** the minima with isopropyl *syn* was also not seen and a shoulder appeared at 240° which is

Table 2 Relative energies (in kcal mol⁻¹) of minima of **8–10**

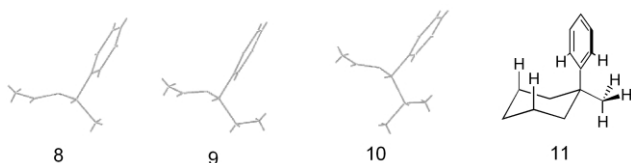
Schiff base	Dihedral Angle	HF/3-21G	HF/6-31+G*	MP2/6-31+G*	B3LYP/6-31+G*
8	0	0	0	0	0
8	120	2.47	2.55	1.57	1.89
8	240	3.72	3.98	3.83	3.33
9	0	0	0	0	0
9	90 ^a	3.59	3.49	2.84	2.74
9	240 ^a	5.94	5.96	5.20	4.94
10	0	0	0	0	0
10	90	2.95	2.96	2.56	2.42
10	150	7.03	5.92	5.44	4.69
10	240 ^a	6.70	6.52	6.07	5.42

^a Appear as shoulder on the potential energy surface

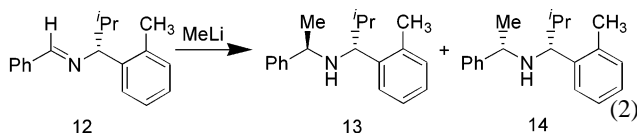
higher in energy by 5.42–6.70 kcal mol⁻¹ at different levels of calculation. Two minima were seen with respect to phenyl *syn* and they appeared at H–C–N–C–Ph dihedral angle of +30° and –30° at +2.42–2.95 kcal mol⁻¹ and 4.69–7.03 kcal mol⁻¹ higher in energy respectively than the H *syn* conformation. The calculated rotational barriers for **8**, **9** and **10** are 4.8, 7.5 and 8.8 kcal mol⁻¹ respectively. It is interesting to note that with an increase in rotational barrier, diastereomeric excess of the product increases.



The phenyl and alkyl in the global minima of Schiff bases **8–10** adopts a preferential conformation which is strikingly similar to 1-methyl-1-phenylcyclohexane **11**.⁷ In **11**, phenyl in axial position is preferred over the equatorial position as compared to methyl because it can adapt a conformation to minimize 1,3-diaxial interaction. The relationship between the incoming nucleophile and phenyl or alkyl of the chiral centre in the Schiff bases **8–10** is 1,3 that can have serious steric implications.⁸ We propose that phenyl poses less steric interaction to the incoming nucleophile in comparison to the alkyl group and as a result the major product is formed by attack from the side of the phenyl. If this is true then preference for attack from the side of the phenyl should increase as the size of alkyl group increases as observed. It is important to note that in the minimized structure of **10**, a methyl group of the isopropyl moiety is positioned in such a way to increase 1,3-steric interaction with the incoming nucleophile.



To substantiate further that attack occurs from the side of the phenyl group it was changed to *ortho*-toluyl keeping R as isopropyl. The resulting product after methyl lithium addition under identical conditions had lower diastereoselectivity (87 : 13, compare with table 1 entry 3) thus corroborating further that the attack of nucleophile occurs from the side of the phenyl group. If conformation **1** proposed by Yamamoto² represents the true conformation leading to the desired product, then there should not be any change in the diastereoselectivity when phenyl is changed to *ortho*-toluyl. In any case the conformation **1** does not correspond to an energy minimum (not even a local minimum) on the potential energy surface of **1**.



Since Schiff base derived from 1-phenyl-2-methylpropylamine gave product in high diastereoselectivity, it was evaluated further from the synthetic point of view. The amine was resolved by converting into (D)-camphorsulfonic acid salt. Optically pure amine was obtained after three crystallizations from water and basification of the recrystallized salt. Amine was obtained in 94–96% optical purity.⁹ The configuration of the chiral centre was determined by comparison with the reported optical rotation.¹⁰ The optically pure 1-phenyl-2-methylpropylamine was condensed with various aldehydes and the resulting Schiff bases were treated with *n*-butyl lithium in ether at –78 °C. The results are compiled in Table 3. The products were obtained in consistently high diastereoselectivity and good yield.

Table 3 Addition of butyl lithium to various Schiff bases of 1-phenyl-2-methylpropylamine

Entry	R	Diastereomeric ratio ^a	Isolated yield (%)
1	<i>o</i> -Me–Ph	93 : 7	81
2	<i>p</i> -Me–Ph	92 : 8	83
3	<i>o</i> -Cl–Ph	98 : 2	83
4	<i>p</i> -Cl–Ph	93 : 7	72
5	Naphthyl	98 : 2	74
6	Cyclohexyl	97 : 3	70
7	<i>tert</i> -Bu	99 : 1	71

^a Diastereomeric ratio was determined from 300 MHz ¹H NMR.

In conclusion, we have proposed a new model to explain diastereoselectivity observed in the alkyl lithium addition reaction to Schiff bases bearing an N-stereogenic centre with no additional heteroatom. During this investigation we have also identified Schiff bases derived from 1-phenyl-2-methylpropylamine show superior C=N π facial selectivity as compared to the Schiff bases derived from the commonly used 1-phenethylamine. Work is in progress in our laboratory to show the superiority of 1-phenyl-2-methylpropylamine over 1-phenethylamine in different systems.

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Notes and references

† In the case of **6** (R = Et) crystals for X-ray crystallography were obtained from corresponding hydrochloride salt C₁₇H₂₂Cl₁N₁, *M* = 275.81, *T* = 293(2) K, Monoclinic, *P*2₁/*n*, *a* = 11.098(4), *b* = 8.006(2), *c* = 18.969(9) Å, β = 101.97(3)°, *V* = 1648.8(11) Å³, *Z* = 4, μ (MoK α) = 0.220 mm⁻¹, 2373 reflections measured, 2251 unique (*R*_{int} = 0.0402), 1510 observed [*I* > 2 σ (*I*)], *R* = 0.0629, *wR* = 0.1598 and *R* = 0.0961, *wR* = 0.1845 for observed and all data respectively. In the case of **6** (R = *i*-Pr) crystals for X-ray analysis were prepared from its salt with *p*-nitrobenzoic acid. C₂₅H₂₈N₂O₄, *M* = 420.49, *T* = 293(2) K, Triclinic, *P*1, *a* = 8.631(1), *b* = 12.435(2), *c* = 12.704(2) Å, α = 117.72(1), β = 101.03(1), γ = 96.19(1)°, *V* = 1153.9(3) Å³, *Z* = 2, μ (MoK α) = 0.082 mm⁻¹, 3692 reflections measured, 3418 unique (*R*_{int} = 0.0167), 2730 observed [*I* > 2 σ (*I*)], *R* = 0.0428, *wR* = 0.1127 and *R* = 0.0560, *wR* = 0.1230 for observed and all data respectively. CCDC 201482 & 201483. See <http://www.rsc.org/suppdata/cc/b3/b300478c/> for crystallographic data in .cif or other electronic format.

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