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Highly diastereoselective radical addition to glyoxylate imines of chiral amines without additional heteroatoms

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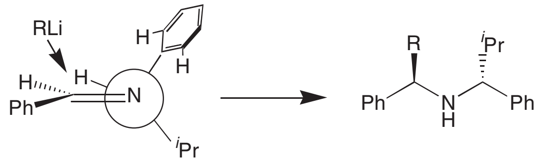
Abstract—The diastereoselective addition of alkyl radicals to glyoxylate imines of α-alkylbenzylamines has been investigated and it was found that diastereoselectivity improved as the size of the alkyl group increased.

The synthesis of nonproteinogenic α-amino acids is an important objective in organic synthesis. Among the many methods developed,[1] triethylborane or diethylzinc mediated radical addition to glyoxylate imines of chiral nonracemic amines is very attractive because it gives the desired addition products under mild conditions (Scheme 1).[2] However, under these conditions, open-chain flexible systems give poor diastereoselectivity and so conformationally constrained auxiliaries were designed to give products with high diastereoselectivity.[2] Recently, we have developed a model for the diastereoselective addition of alkyllithiums to Schiff bases of chiral amines (Scheme 2).[3] This system is also flexible in the sense that there is no additional heteroatom for complexation to make the transition state rigid. It was shown that the chiral centre adopts a preferred conformation, which is governed by 1,3-allylic strain[4] and the phenyl group orients in such a way that it acts as a smaller group than any alkyl residue.[3,5] The observed diastereoselectivity is due to differential steric interaction of the incoming reagent with the phenyl group and alkyl group (Scheme 2). These results suggested that by choosing an appropriate chiral auxiliary and conditions one could achieve high diastereoselectivity for various reactions. Herein, we disclose our results for the diastereoselective addition of alkyl radicals to Schiff bases of ethyl glyoxylate.



Scheme 2.

Schiff bases **1**–**7** of ethyl glyoxylate with various chiral α-alkylbenzylamines were prepared (Fig. 1). The alkyl and aryl moieties of the amine were varied to increase their steric effects. These Schiff bases were treated with triethylborane or diethylzinc in the presence of air at −78 °C under the reported conditions (see Table 1). It was found that toluene was the better solvent for diethylzinc mediated reactions while dichloromethane was superior for triethylborane mediated reactions. The

Scheme 1.

Keywords: Diastereoselective; Radical addition; Schiff bases.

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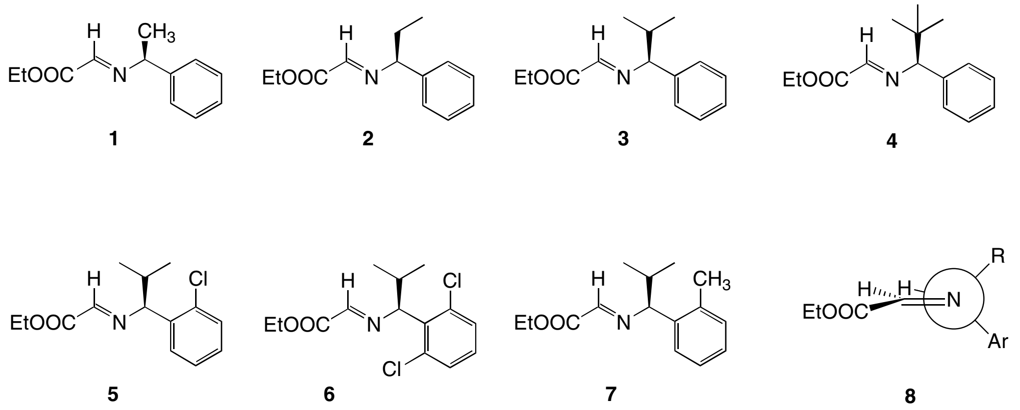
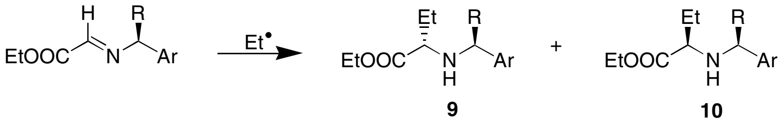


1 2 3 4 5 6 7 8

Figure 1.

Table 1. Diastereoselective addition of ethyl radicals to various Schiff bases[a,b]



9 10

Entry	R	Ar	Radicals[c] initiator	Diastereomeric ratio (9:10)[d]	Yield (%)
1	Me	Ph	Et_3B	53:47	80
2	Et	Ph	Et_3B	70:30	76
3	*i*Pr	Ph	Et_3B	82:18	79
4	*t*Bu	Ph	Et_3B	85:15	54
5	*i*Pr	2-Cl-C_6H_4	Et_3B	73:27	60
6	*i*Pr	2,6-$Cl_2C_6H_3$	Et_3B	37:63	60
7	*i*Pr	2-Me-C_6H_4	Et_3B	70:30	60
8	Me	Ph	Et_2Zn	67:33	80
9	Et	Ph	Et_2Zn	74:26	75
10	*i*Pr	Ph	Et_2Zn	85:15	70
11	*t*Bu	Ph	Et_2Zn	92:08	89
12	*i*Pr	2-Cl-C_6H_4	Et_2Zn	82:18	70
13	*i*Pr	2,6-$Cl_2C_6H_3$	Et_2Zn	47:53	75
14	*i*Pr	2-Me-C_6H_4	Et_2Zn	82:18	65

[a] All reactions were carried out at −78 °C using 6 equiv of ethyl iodide in the presence of 10 mL of air for each millimole of Schiff base.

[b] Reactions using diethylzinc were carried out in toluene and triethylborane in dichloromethane.

[c] Three equivalent of triethylborane and 2 equiv of diethylzinc were used.

[d] Diastereoselectivity was determined by 400 MHz ^{1}H NMR analysis and the structure of the major diastereomer was determined using literature precedents.[1,2]

results are compiled in Table 1. In analogy to alkyllithium addition to Schiff bases,[3] diastereoselectivity for the radical addition reaction also increased as the R group was changed from methyl to ethyl to isopropyl and further to *tert*-butyl in the Schiff bases **1**–**4** (Table 1, entries 1–4 and 8–11). Any increase in the steric size of the aryl group resulted in a decrease in diastereoselectivity and even reversal of diastereoselectivity was observed in the case of the 2,6-dichlorophenyl group (Table 1, compare entries 3 with 5–7 and 10 with 12–14). It is interesting to note that there was no reversal of diastereoselectivity when diethylzinc was used in place of triethylborane as the chain transfer reagent.[2d] These results indicate that diethylzinc may not be complexing simultaneously with nitrogen and oxygen in the Schiff base.

These results indicate that the model proposed for the addition of alkyllithium reagents to Schiff bases also holds true for radical addition. The diastereoselectivity observed can be rationalized on the basis of the difference in the steric interaction between the incoming radical and the alkyl or aryl moieties in conformation **8**.

Schiff bases **3** and **4** gave maximum diastereoselectivity and were evaluated further using optically pure amines[3,6] and the results are complied in Tables 2 and 3. When triethylborane was used as a radical initiator, Schiff base **3** gave the product with better diastereoselectivity but in the case of diethylzinc mediated reactions Schiff base **4** gave the product with better diastereoselectivity, albeit in modest yield. As expected from the model, diastereoselectivity increased with an

Table 2. Et_3B mediated addition of various alkyl radicals to Schiff bases **3** and **4**

Entry	Schiff base	RI	Diastereomeric ratio	Yield (%)
1	**3**	Ethyl iodide	82:18	79
2	**3**	*iso*-Propyl iodide	85:15	80
3	**3**	*tert*-Butyl iodide	93:07	80
4	**3**	Cyclohexyl iodide	92:08	75
5	**4**	Ethyl iodide	85:15	54
6	**4**	*iso*-Propyl iodide	87:13	35
7	**4**	*tert*-Butyl iodide	88:12	21
8	**4**	Cyclohexyl iodide	86:14	40

Table 3. Et_2Zn mediated addition of various alkyl radicals to Schiff bases **3** and **4**

Entry	Schiff base	RI	Diastereomeric ratio	Yield (%)
1	**3**	Ethyl iodide	85:15	70
2	**3**	*iso*-Propyl iodide	97:03	63
3	**3**	*tert*-Butyl iodide	81:19	60
4	**3**	Cyclohexyl iodide	87:13	49
5	**4**	Ethyl iodide	92:08	89
6	**4**	*iso*-Propyl iodide	97:03	45
7	**4**	*tert*-Butyl iodide	86:14	40
8	**4**	Cyclohexyl iodide	92:08	20

increase in the size of the radical. However, in the case of diethylzinc there was some decrease in diastereoselectivity when the *tert*-butyl radical was used. We observed a small amount of ethyl addition product in all cases and were not able to prevent this addition completely even by using a large amount of air or alkyl halide. Any reduction in the amount of diethylzinc or triethylborane had a significant impact on the yield. The diastereoselectivity obtained in all cases is either superior to or comparable with reported diastereoselectivities for known Schiff bases of alkyl glyoxylates of amines having additional heteroatoms or a more rigid structure.

In conclusion, these results demonstrate that without resorting to a conformationally constrained auxiliary or Schiff bases of amines with additional heteroatoms to rigidify the transition state, high diastereoselectivities can be achieved.

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