

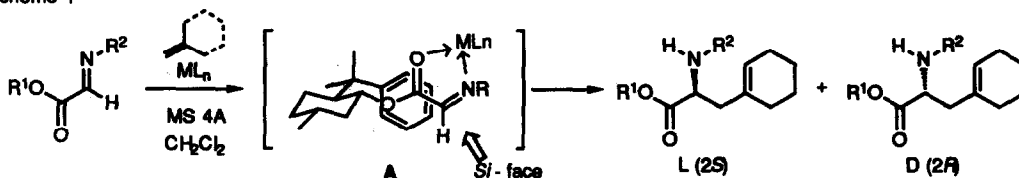
## Asymmetric Imine-Ene Reactions with Chiral Glyoxylate-Derived $\alpha$ -Imino Esters: An Efficient Route to Asymmetric Synthesis of $\alpha$ -Amino Acids

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**Abstract:** The asymmetric ene reactions with  $\alpha$ -imino esters, prepared from (-)-8-phenylmenthyl glyoxylate, are shown to provide an efficient entry to the asymmetric synthesis of  $\alpha$ -amino acids.

The asymmetric synthesis of (non)proteinogenic  $\alpha$ -amino acids has become an area of great interest because of the advent of peptide-derived chemotherapeutics.<sup>1,2</sup> The asymmetric ene reaction with  $\alpha$ -imino ester as a glycine equivalent should constitute a direct and versatile entry to the asymmetric synthesis of  $\alpha$ -amino acids, if the C-C bond formation takes place regioselectively at the imino carbon.<sup>3</sup> We now wish to report the first example of the asymmetric "imine-ene" reactions with chiral  $\alpha$ -imino esters (Scheme 1, Table 1).

Scheme 1




First, the reactions of isobutene with  $\alpha$ -imino esters, prepared in the presence of molecular sieves (MS 4A) from achiral glyoxylates and *R*-arylethylamine, were found to give indeed the imine-ene products with formation of C-C bonds, using an appropriate Lewis acid such as  $SnCl_4$  or  $TiCl_4$ . All the ene reactions preferentially afforded *D(R)*- $\alpha$ -amino esters (entries 1 ~ 4),<sup>4</sup> except with  $EtAlCl_2$  to provide *N*-ethyl product. Of interest is *R*-naphthylethylimine to provide higher *D(R)*-selectivity but lower chemical yield (entry 5).

Next, the reactions with imines derived from *S*- $\alpha$ -amino esters afforded higher (but still insufficient) level of diastereofacial selectivity along with better chemical yield (entries 6 ~ 8). The *L(S)*-stereochemistry of the major diastereomer was determined after hydrogenation through comparison with an authentic *L(S)*-leucine derivative obtained with 2*S*-triflyloxyisovalerate.<sup>5</sup> Thus, the sense of asymmetric induction is exactly the same as reported for the reaction of allylic metals<sup>6</sup> where the *S*-amino esters produce the *L(S)*-chiralities.

Finally, (-)-8-phenylmenthol<sup>7</sup>-derived esters were found to exhibit remarkably high diastereofacial selectivity along with high chemical yield (entries 11 ~ 12). The *L(S)*-stereochemistry of the major diastereomer was determined through comparison with an authentic *D(R)*-diastereomer obtained from (-)-8-phenylmenthyl (*S*)-triflyloxyester.<sup>5,7d</sup> Induction of *L(S)*-chirality indicates that the *syn*-chelation (A) is also favorable with  $\alpha$ -imino esters. Thus, olefins presumably attack the imine carbon from the *si*-face, since the phenyl group blocks the attack from the *re*-face (A).<sup>7</sup>

Table 1. Asymmetric Imine-Ene Reaction with Glyoxylate-derived  $\alpha$ -Imino Esters.<sup>a</sup>

Entry	R <sup>1</sup>	R <sup>2</sup>	ML <sub>n</sub>	Temp (°C)	% Yield	L (S)	: D (R)
1	Me	(R)-CH(Ph)CH <sub>3</sub>	MeAlCl <sub>2</sub>	20	22	45	: 55
2			MeAl(OTf) <sub>2</sub>	20	33	35	: 65
3			SnCl <sub>4</sub>	20	61	30	: 70
4			TiCl <sub>4</sub>	-78	21	20	: 80
5		(R)-CH(Np)CH <sub>3</sub>			13	15	: 85
6		(S)-CH(Pr <sup>i</sup> )CO <sub>2</sub> Me		-30	76	80	: 20
7				-78	40	85	: 15
8		(S)-CH(Ph)CO <sub>2</sub> Me		-30	82	72	: 28
9 <sup>b</sup>		Bn	TiCl <sub>4</sub>	20	21	88	: 12
10 <sup>b</sup>			SnCl <sub>4</sub>	20	32	90	: 10
11 <sup>c</sup>				20	76	97	: 3
12 <sup>d</sup>		Ts		0	60	>98	: <2

<sup>a</sup> Unless otherwise marked, the ene reaction was carried out using the isolated imine and an excess (ca. 2 eq) of isobutene. <sup>b</sup> Via the *in situ* preparation of imine. <sup>c</sup> Via the *in situ* preparation of imine in the presence of SnCl<sub>4</sub> (1 eq). <sup>d</sup> Methylene cyclohexane was used instead of isobutene. For the preparation of imine see: *Synlett* 1991, 561.

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