

Highly Enantioselective Synthesis of Pipercolic Acid Derivatives *via* an Asymmetric Aza-Diels–Alder Reaction

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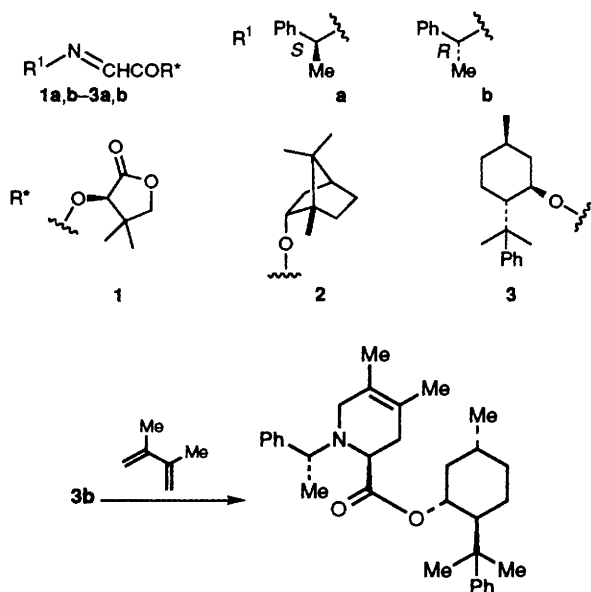
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Very high asymmetric induction is observed in the aza-Diels–Alder reaction between dienes and the imine (*R*)-PhMeCH=N=CHCO₂PhMen* (where PhMen* = 8-phenylmenthyl), which bears matched auxiliaries on nitrogen and on the ester; reactions in trifluoroethanol, in the presence of trifluoroacetic acid (1 equiv.), give substituted pipercolic acid derivatives in *ca* 50% isolated yield, with only a single regio- and diastereo-isomer of the cycloadduct detectable in all cases (d.e. >95%).

The aza-Diels–Alder reaction is potentially one of the most versatile and rapid routes to substituted piperidines.¹ Of the possible [2π + 4π] combinations for generating such heterocycles, the reaction between an imine and a diene is perhaps the most attractive, considering the accessibility and diversity of these two classes of reactant. In general, the use of strongly electron-deficient imines seems to be a prerequisite. This requirement can be partially met by the use of imino-acetate esters (RN=CHCO₂R'), with the added advantage that the ester group in the adduct can be readily modified to afford a range of 2-substituted piperidines (a sub-structure present in many natural products). Nevertheless, an additional electron-withdrawing group has usually been considered necessary, as exemplified by the use of *N*-acyl² and *N*-tosyl^{3–5} imines. However, there has been only limited success with asymmetric versions of these reactions, although Holmes *et al.*⁶ have used *N*-tosyl imines of the type Ts–N=CHCO₂R* bearing a chiral ester auxiliary, and found Lewis acid catalysed conditions under which the reaction with cyclopentadiene gives the *exo* adduct with about 75% asymmetric induction.

Bailey *et al.*^{7,8} have utilised simple imino-acetate esters bearing the 1-phenylethyl auxiliary on nitrogen.⁹ By using DMF in the presence of TFA (1 equiv.) and water (catalytic), the Diels–Alder reaction with cyclopentadiene gives the *exo* adduct in 80% yield, and with 94% asymmetric induction; with acyclic dienes (*e.g.* 2-methylbutadiene), asymmetric induction is about 70%, but removal of the unwanted diastereoisomer is difficult, so that homochiral products are hard to obtain.



Scheme 1 Reagents and conditions: Method A, DMF, TFA (1 equiv.), H₂O (cat.);^{7,8} Method B, CF₃CH₂OH, TFA (1 equiv.). † The imine **3b** and its protonated iminium ion are believed to exist predominantly as the *E*-isomers.⁸

In a combination of these two approaches, the use of double auxiliaries has now been explored, and we report these results herein. Initially, the glyoxylate esters of pantolactone, borneol, and 8-phenylmenthol (prepared by ozonolysis of the corresponding fumarate di-esters) were treated with (*S*)- and (*R*)-1-phenylethylamine, giving six imino-acetates bearing two chiral auxiliaries (*i.e.* 3 diastereoisomeric pairs, **1a/b**, **2a/b**, **3a/b**). These were treated with 2,3-dimethylbutadiene under the cycloaddition conditions developed by Bailey

Table 1 Results from the aza-Diels–Alder reaction of the *N*-1-phenylethyl (*R**) 8-phenylmenthyl ester (PhMen*) dienophiles **3a/b** with a range of dienes

Diene	Adduct	Mismatched auxiliaries ^a		Matched auxiliaries ^a	
		D.e. ^b (%)	Yield ^c (%)	D.e. ^b (%)	Yield ^c (%)
		23 (1.6:1)	54	>95	54 ^d
		82 (10:1)	49	>95	53 ^e
		49 (2.9:1)	61	>95	48 ^d
		<49 (1.7:1.2:1)	48	>95	69 ^d
		0 (1:1)	38	>95	51 ^d
				>95	40 ^d

^a 'Matched' used the (*R*) auxiliary on nitrogen and 'mismatched' used the (*S*) auxiliary. ^b d.e. is a measure of the asymmetric induction, given as a % (and also as a diastereoisomeric ratio); for the cyclopentadiene adduct, three diastereoisomers were formed in the 'mismatched' case—in all other reactions, a single diastereoisomer within the piperidine ring was produced. ^c Isolated yield of the cycloadduct(s) after flash chromatography; single regioisomers were observed in all cases. ^d Assignment of configuration of the major diastereoisomer was made by analogy with previous results (refs. 7 and 8). ^e Stereochemical assignment by conversion to a previously assigned derivative.⁸

et al.^{7,8}. For five of these reactions, only modest asymmetric induction was observed. However, with *N*-(*R*)-phenylethyl and 8-phenylmenthyl ester auxiliaries, only a single diastereoisomeric Diels–Alder adduct could be detected. The yield and reproducibility of the reactions were enhanced by conducting them in trifluoroethanol as solvent (obviating the need for catalytic water)⁸ and, with these conditions in hand, a range of dienes were treated with matched and mismatched auxiliaries, as summarised in Table 1.†

The complexity of the ¹H NMR spectra necessitated the use of ¹³C NMR for analysis of the diastereoisomeric ratios, for which a lower detection limit of 2.5% was determined. In all cases, only a single diastereoisomeric Diels–Alder adduct could be detected. Detachment of the ester auxiliary can be achieved by saponification,⁶ whilst removal of the 1-phenylethyl auxiliary can be achieved by catalytic hydrogenation.^{7,8}

In summary, we have demonstrated that the iminoacetate (*R*)-PhMeCH=N=CHCO₂PhMen* **3b** can be used in asymmetric aza-Diels–Alder reactions with cyclic or acyclic dienes. The cycloadditions with acyclic dienes proceed in about 50% yield, with complete control of regio- and stereo-chemistry *via* an *endo* transition state, and yielding pipercolic acid derivatives of known absolute stereochemistry in a single step. The corresponding cycloadditions to cyclic dienes proceed *via* an *exo* transition state, and this chemistry offers very promising approaches to a variety of bicyclic precursors of alkaloid natural products.

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Footnote

† *Typical experimental procedure.* The imine **3b** (0.1 g, 0.26 mmol) was dissolved in trifluoroethanol (1 ml) containing 4 Å molecular sieves, under nitrogen. To this was added TFA (21 µl, 0.26 mmol) and, after stirring for 5 min, cyclohexadiene (50 µl, 0.52 mmol). Stirring was continued at room temp. for 24 h and, after work up (removal of solvent and simple base washes), the reaction mixture was purified by flash chromatography using ethyl acetate–hexane (1 : 9). The cycloadduct was the first component to elute (*R*_f = 0.35), and was isolated in 51% yield based on **3b**; the by-products had considerably lower *R*_fs, and were presumably polymeric or acyclic.

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