# Diastereoselectivity in the O–H Insertion Reactions of Rhodium Carbenoids Derived from Phenyldiazoacetates of Homochiral Alcohols

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Abstract: Rhodium(II) acetate catalysed decomposition of the phenyldiazoacetates 3 in the presence of alcohols (methanol, propan-2-ol, tert-butanol) led to the O–H insertion products 4 - 6 in varying yields; the diastereomeric excess of the product ranged from 5-53%.

The ready availability, relative stability and facile decomposition (under thermal, photochemical, and transition-metal catalysed conditions) of diazocarbonyl compounds makes them useful intermediates for synthesis. Of the three methods mentioned for the decomposition of diazocarbonyl compounds, the transition-metal catalysed procedure is often the method of choice because it takes place under relatively mild conditions, the preferred catalysts being rhodium(II) carboxylates. The reaction is believed to involve a metallo-carbenoid intermediate, e.g. $L_nRh=CR^1Z$, but whatever the exact nature of the species, it retains the reactivity of a "free" carbene. Thus cyclopropanation, C–H insertion, addition to aromatic rings, and ylide formation are all well described reactions of rhodium carbenoids.[1-6] Our own interest in rhodium carbenoid mediated processes centres on the so-called X–H insertion reaction (X = heteroatom; N, O, S),[7-9] which despite its potential in synthesis (as illustrated in general in Scheme 1), has been much less widely studied. The utility of this reaction would be significantly enhanced if an 'asymmetric version' could be developed, and therefore we were intrigued by the possibility of using chiral auxiliaries (in the Z-group) to control the stereochemistry of the newly formed tertiary centre.
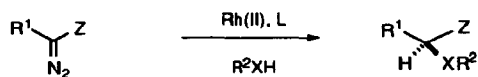
Scheme 1. R^1, R^2 = alkyl, aryl, heteroaryl; Z = COR, CO_2R, SO_2R, $PO(OR)_2$; X = O, NR, S

Diazocarbonyl compounds containing chiral auxiliaries are known, and although they have been used in asymmetric cyclopropanations,[10-12] there are no reports of their use in carbenoid O–H insertion reactions. The diazocarbonyl compounds selected for study were the phenyldiazoacetates 3a-3d of (−)-borneol, (+)-menthol, (−)-*trans*-2-phenylcyclohexanol and (−)-8-phenylmenthol. Initial

attempts to prepare these diazoesters by diazo-transfer to the corresponding phenylacetates, PhCH$_2$COOR*, using the *in situ* formylation method (NaH, HCO$_2$Et; MsN$_3$),[13] resulted in low yields of products. Therefore they were prepared from the corresponding α-ketoesters 1[14] using the Bamford-Stevens reaction.[13] Thus reaction with tosylhydrazide give the tosylhydrazones 2 (75 - 92%), which were readily converted into the diazoesters 3 (90 - 100%) by treatment with triethylamine in dichloromethane at room temperature (Scheme 2).
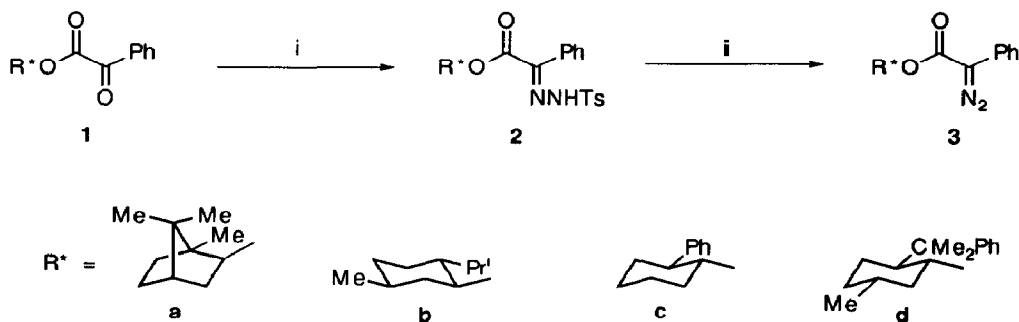
Scheme 2. *Reagents*: i, TsNHNH$_2$, toluene, reflux; ii, Et$_3$N, CH$_2$Cl$_2$, r.t.

Rhodium(II) acetate (2 mole%) catalysed decomposition of the diazoesters 3 in dichloromethane in the presence of the alcohol, ROH (2 equiv), resulted in rapid evolution of nitrogen, and the formation of the carbenoid O–H insertion products 4-6 in, with the exception of *tert*-butanol, good yield (Table). The insertion products 4-6 were formed as mixtures of diastereomers, the ratio of which could be determined from the ^{1}H NMR spectrum of the mixture. In the case of 4b, 4d, 5b, 5d, and 6d the two diastereomers were separable by chromatography. Interestingly in many cases, the starting α-ketoester 1 (which was *not* present in 3) was a by-product of the reaction.

The (−)-borneol derived diazoester 3a gave uniformly poor results. In the case of the diazoesters 3b and 3c, 2-propanol provided products with the best diastereomeric excesses. However, for the 8-phenylmenthol derived diazoester 3d, the best results were obtained for insertion into *tert*-butanol.

In the case of the methanol derived products 4b, 4c and 4d the stereochemistry of the major diastereomer was established by preparing authentic samples from commercially available α-methoxyphenylacetic acid. Thus esterification of the (S)-(+)-acid with (+)-menthol, or with (−)-8-phenylmenthol, or of the (S)-(+)- and (R)-(−)-acids with (−)-*trans*-2-phenylcyclohexanol gave the corresponding α-methoxyesters which retained the configuration of the starting α-methoxyphenylacetic acid at the α-carbon. This confirmed that the stereochemistry at the new chiral centre of the major diastereomer formed in the carbenoid O–H insertion reaction of the diazoesters 3b and 3c with methanol was (S), and of diazoester 3d was (R). The stereochemistry of the major diastereomers produced by the insertion reactions of 2-propanol was also proved by independent synthesis. Reaction of the homochiral alcohol with a single enantiomer of mandelic acid, was followed by silver(I) oxide mediated alkylation with 2-iodopropane to give the authentic products 5b, 5c and 5d as single diastereomers, confirming that the stereochemistry at the new chiral centre of the major diastereomer formed in the 2-propanol O–H insertion reactions of the diazoester 3b was (S), and of diazoesters 3c and 3d was (R). The stereochemistry of the α-*tert*-butoxyesters 6b - 6d is inferred by comparison of their NMR spectra with the isopropoxy esters 5.

Table. O–H Insertion reactions of rhodium carbenoids derived from diazoesters **3**.

3

Rh₂(OAc)₄
————————→
ROH, CH₂Cl₂

4 R = Me
5 R = iPr
6 R = tBu

| Diazo ester	R*	ROH	Product	Yield(%)	d.e.(%)	Major isomer[a]
3a		MeOH	**4a**	95	5[b]	n.d.
		iPrOH	**5a**	95	5[b]	n.d.
		tBuOH	**6a**	70	5[b]	n.d.
3b		MeOH	**4b**	75	8	S
		iPrOH	**5b**	82	24	S
		tBuOH	**6b**	36	14	(S)
3c		MeOH	**4c**	88	10	S
		iPrOH	**5c**	71	42	R
		tBuOH	**6c**	48	16	(R)
3d		MeOH	**4d**	63	44	R
		iPrOH	**5d**	85	36	R
		tBuOH	**6d**	40	53	(R)

a   Where the stereochemistry at the α-carbon of the major diastereomer is given in brackets this is inferred by analogy with that resulting from the other nucleophiles used.

b   Accurate d.e. difficult to obtain from ¹H NMR of mixture of diastereomers due to overlapping peaks.

n.d.   not determined.

In order to check that the products were configurationally stable under the reaction conditions, the diastereomeric mixture **5c** was resubjected to the reaction conditions, and the diastereomeric ratio remained unchanged. Therefore we assume that observed diastereoselectivity arises during the carbenoid O–H insertion reaction. Although the mechanism of such processes is unknown, we assume that, by analogy with the reduction of the corresponding α-ketoesters,[15] the diastereoselectivity arises from nucleophilic attack on the electrophilic rhodium carbenoid from the face opposite the large group, A, on the auxiliary as shown schematically below, leading to the observed configurations at the α-carbon in the major diastereomer. The conformation of the carbenoid is, of

course, unknown, but we assume it retains the preferred *trans*-arrangement about the ester O-CO bond and the s-*trans* conformation of its diazocarbonyl precursor. On this basis the model predicts that the menthol based diazoester **3b** should lead to the (S)-configuration at the new chiral centre, whereas both the diazoesters **3c** and **3d** should have the (R)-configuration at the newly formed chiral centre. The reason why the 2-phenylcyclohexanol based diazoester **3c** should give different diastereoselectivities according to the nature of the alcohol is not clear, but presumably reflects the different steric demands for insertion into the O–H bond of methanol vs. 2-propanol.
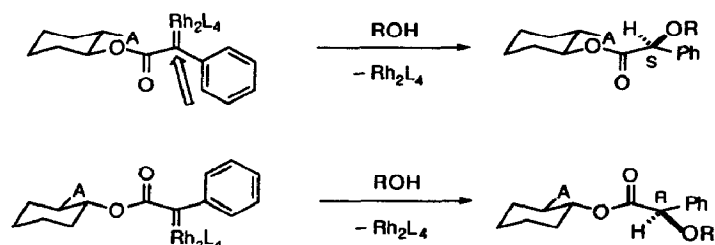
Acknowledgements

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