Asymmetric catalysis of intramolecular N–H insertion reactions of α-diazocarbonyls

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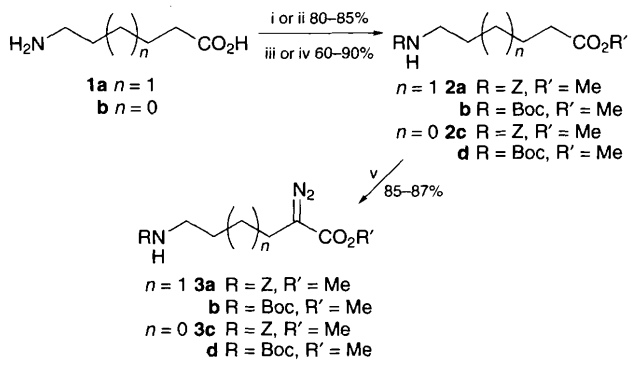
Intramolecular N–H insertion reactions of α-diazocarbonyl substrates are catalysed by rhodium(II) carboxylates with catalyst-dependent competition with C–H insertion and β-elimination; asymmetric N–H insertion leading to a pipecolic acid derivative with ee up to 45% is achieved using chiral catalysts.

Among the many reactions of α-diazocarbonyl compounds with great potential in enantioselective synthesis are X–H insertions, both inter- and intra-molecular, where X is a carbon, nitrogen, oxygen or sulfur atom.[1] Although all four processes are known, only C–H insertion has reached the stage of development where there are now several chiral catalysts available, all based on rhodium, capable of producing high enantioselectivities in intramolecular C–C bond formation.[2] Several examples of inter- and intra-molecular O–H insertion of rhodium carbenoids with alcohols and water are known.[3] A recent study of α-diazoesters containing chiral auxiliaries shows that α-hydroxy and α-alkoxy esters are accessible with moderate diastereoselectivities.[4] An early attempt by Nicoud and Kagan to exploit the chiral auxiliary approach to N–H insertion through the use of chiral amines did not produce significant levels of diastereoselection.[5] There are as yet no examples of the use of chiral catalysts in asymmetric N–H insertion despite the fact that the process with achiral catalysts is now a well established route to four, five and six-membered heterocycles including numerous bicyclic β-lactams, the Merck industrial synthesis of thienamycin representing an outstanding example of the power of the process.[1]

We have examined several aspects of intramolecular N–H insertion, including the chiral catalyst option, as a route to natural and unnatural heterocyclic amino acids. Substrate structures were chosen so as to reveal the influence of catalyst on two potentially significant competing side-reactions, namely C–H insertion and β-elimination. In previous studies of N–H insertion the substrates used were such that β-elimination was not possible.[6] In our preliminary studies therefore it was important to determine whether alkene formation *via* β-elimination would compete with N–H insertion. Although metal-catalysed decomposition of diazocarbonyl compounds containing β-hydrogen atoms can lead rapidly to alkene formation. Taber's work[7] indicates that the extent of this reaction can be influenced by the nature of the ligands on the metal.

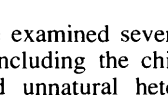
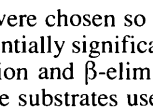
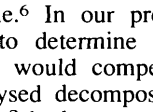
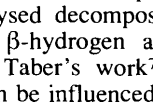
Suitable substrates were constructed from amino acids **1a** and **1b** by conversion to Z- or Boc-protected amino acid esters **2a–d** (Scheme 1) and thence to diazo esters **3a–d** *via* diazo transfer using mesyl azide.[8,†]

Several rhodium(II) derivatives (Table 1) were employed as catalysts for the decomposition of the α-diazo ester **3a** (Scheme 2). The reactions were carried out by adding a solution of the substrate in CH_2Cl_2 to the catalyst (5 mol%) in CH_2Cl_2 (*ca.* 0.005 mol dm^{-3}) under N_2 either at reflux, room temperature or 0 °C. Reaction yields after work up were consistently >90%. Up to three products could be isolated and identified as those of N–H insertion product **4**, C–H insertion **5** and β-hydride elimination **6** (Scheme 2),‡ in proportions which revealed a marked catalyst dependency. The C–H insertion product

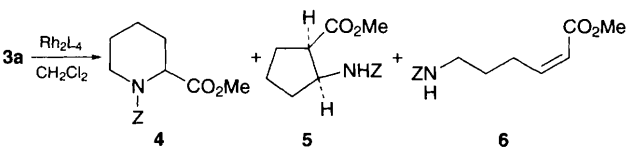


Scheme 1 *Reagents and conditions*: i, ROCOCl, Na_2CO_3, H_2O, room temp., R = Bn; ii, $(Bu^tO)_2CO$, NaOH, Bu^tOH, H_2O; iii, MeOH, H_2SO_4, cat. R = Bn; iv, (*a*) Cs_2CO_3, pH = 7; (*b*) MeI, DMF; v, (*a*) LiHMDS, THF, −78 to −40 °C; (*b*) $CF_3CO_2CH_2CF_3$, −78 °C; (*c*) MsN_3, Et_3N, MeCN, room temp.

Table 1 Competing N–H, C–H insertion reactions and β-elimination. Asymmetric induction

			Product ratio[b]			ee (%)[c]	
Entry	Ligand	Temperature[a]	4	5	6	4	5
1	(*S*)- 	reflux	0	4	1	—	5
		room temp.	2.4	1	2.4	<5	5
2	(*S,S,S*)- 	room temp.	3.2	1	1.9	7	24
3	(*S*)- 	reflux	5	1.2	1	10	18
		room temp.	2.5	1	1.8	3	14
4	(*S*)- 	reflux	7	2.6	1	27	28
		room temp.	9	3	1	40	24
		0 °C	2.6	1	1.3	45	20

[a] Addition of the α-diazo ester at the reaction temperature. [b] Product ratios were determined by ^1H NMR. [c] ee (%) were measured by ^1H NMR using the chiral shift reagent, Eu(hfc)$_3$.



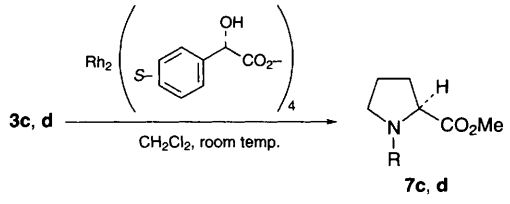
Scheme 2

cyclopentane **5** was produced with the *cis*-geometry of the substituents, as revealed by NOE measurements, and this was also the geometry of the elimination product **6**.

The use of rhodium(II) acetate as catalyst favoured N–H insertion exclusively, furnishing (±)-NZ-pipecolic acid methyl ester **4** in excellent yield. In contrast, Doyle's dirhodium(II) tetrakis[methyl 1-(3-phenylpropanoyl)imidazolidin-2-one-(*S*)-carboxylate], Rh_2[4(*R*)-MPPIM]$_4$, catalyst[2] favoured β-elimination exclusively, even though in other substrates this catalyst is among the most effective for asymmetric intramolecular C–H insertion. The entries in Table 1 reveal a broad spectrum of temperature dependent and ligand dependent catalytic activity. The effect of change of temperature on product type was most noticeable with the pyroglutamic acid derived catalyst in entry 1. Whereas the predominant product at reflux was that of C–H insertion with no detectable amounts of N–H insertion, when the reaction was performed at room temperature the major products were those of N–H and β-elimination. With the remaining catalyst (entries 2, 3 and 4) although all three modes of reaction were observed, it is significant that N–H insertion did compete successfully with the other two. However, the *N*-protecting group on **3** also plays a role. When a parallel series of reactions was conducted with the NBoc precursor **3b** the product distribution changed dramatically: C–H insertion was now the dominant reaction followed by β-elimination and finally N–H insertion.

Nevertheless, the performance of the NZ precursor **3a** (Table 1) shows that catalyst-dependent asymmetric N–H insertion is attainable. All of these catalysts have been used before by us in C–H insertion with moderate to good enantioselectivities[9a]–diastereoselectivities.[9b] This is the first report of asymmetric synthesis in N–H insertion with chiral catalysts. The highest ee values (entry 4) were observed with Rh_2[(*S*)-mandelate]$_4$. Although the values are modest in these preliminary studies, it is noteworthy that changing the temperature alone can produce an increase from 27 to 45% in ee for N–H insertion leading to a pipecolic acid derivative.

As a further illustration of this approach to asymmetric synthesis of amino acids we prepared diazoesters **3c** and **3d** as precursors for proline derivatives (Scheme 3). Here C–H insertion should be disfavoured as it will result in cyclobutane formation. In the event, both precursors with rhodium(II) mandelate furnished N–H insertion products **7c** and **7d** exclusively, though the extent of asymmetric synthesis was less (15% ee for **7d** in CH_2Cl_2 at 20 °C) than that observed with pipecolic acid.



Scheme 3

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Footnotes

† All new compounds exhibited consistent spectral data.

‡ *Selected data* for **3a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.55 [m, 4 H, $(CH_2)_2$], 2.33 (m, 2 H, CH_2CN_2), 3.22 (m, 2 H, CH_2NHZ), 4.80 (m, 1 H, NH), 5.09 [s, 2 H, CH_2 (Z)], 7.34 [s, 5 H, Ph]. IR ν/cm^{-1} 3360 (NH), 2100 (N_2), 1730–1680 (CO). MS (*m*/*z*, %) 306 (M$^+$, 9), 277 (14), 262 (30), 142 (20), 108 (19), 91 (100). For **4**[10]: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (mixture of two conformers) 1.27 (m, 1 H), 1.44 (m, 1 H), 1.70 (m, 3 H), 2.22 (m, 1 H), 3.00 (m, 1 H), 3.68, 3.74 (s, 3 H), 4.09 (m, 1 H), 4.85, 4.96 (bs, 1 H), 5.16 (s, 2 H), 7.37–7.30 (comp. 5 H). Identical with a sample prepared from authentic pipecolic acid. For **5**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.65 (m, 2 H, CH_2), 1.81 (m, 1 H, CHH), 1.97 (m, 3 H, CH_2CH*H*), 3.01 (m, 1 H, CHNHZ), 3.62 (s, 3 H, $COOCH_3$), 4.27 (m, 1 H, CHCO), 5.10 [s, 2 H, CH_2 (Z)], 5.23 (m, 1 H, NH), 7.34 (s, 5 H, Ph). 6.1% NOE between C*H*COOCH$_3$ and C*H*NHZ. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.80, 156.65, 137.10, 128.47, 128.12, 120.08, 66.62, 54.12, 46.55, 32.09, 27.82, 22.07. IR ν/cm^{-1} 3350 (NH), 1719 (CO). MS (*m*/*z*, %) 277 (M$^+$, 16), 245 (11), 218 (5), 186 (12), 174 (11), 108 (29), 91 (100). For **6**: *cis*: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.74 [m, 4 H, $(CH_2)_2$], 2.68 (m, 2 H, CH_2C=C), 3.21 (m, 2 H, CH_2-NHZ), 3.71 (s, 3 H, $COOCH_3$), 5.10 [s, 2 H, CH_2 (Z)], 5.20 (m, 1 H, NH), 5.83 (d, 1 H, *J* 11 Hz, CH=C), 6.21 (m, 1 H, C=CH), 7.33 (s, 5 H, Ph). MS (*m*/*z*, %) 277 (M$^+$, 8), 245 (3), 186 (4), 170 (5), 142 (7), 108 (10), 91 (100), 84 (5), 65 (9), 49 (8).

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