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The synthesis and chemistry of 3-diazo-piperidin-2-one

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Abstract—The efficient synthesis of 3-diazo-piperidin-2-one, from L-ornithine, in two steps is reported. The chemistry of this new cyclic α-diazoamide was explored and allows the rapid access to a wide range of 3-substituted piperidin-2-one derivatives.

1. Introduction

Diazo compounds are versatile chemical intermediates that have found a wide range of useful applications in organic synthesis.[1] We recently introduced the nitromethylene moiety as a new stabilizing group for diazo compounds and reported on the chemistry of the new diazo derivative, 3-diazo-2-(nitromethylene)piperidine **1**.[2] As part of that study, we required 3-diazo-piperidin-2-one **2** and were surprised to find that it was not known in the literature (Fig. 1). In fact simple cyclic α-diazoamides, as a class, have received only limited attention in the literature with only a few examples being described.[3]

We now wish to report the synthesis of the novel cyclic α-diazoamide **2** and describe some of its chemistry which allows very rapid access to a wide range of 3-substituted piperidin-2-ones.

2. Results

3-Amino-piperidin-2-one **4** was prepared from L-ornithine **3** in excellent yield by dehydration over alumina in refluxing toluene.[4] Diazotisation of **4** was attempted under a variety of conditions but it was found to occur most efficiently by applying a modification of the method described by Takamura et al. for α-amino-esters.[5] Thus, treatment of **4** with a slight excess of *iso*-amyl nitrite in chloroform with a catalytic amount of acetic acid led to 3-diazo-piperdine-2-one **2**, an orange crystalline solid, isolated in 60% yield (Scheme 1).

Optimisation of the reaction conditions established chloroform to be a better solvent than either DCM or benzene. Compound **2** was found to be very sensitive to the acetic acid used to catalyse the reaction. Thus, if more than 0.15 mol% of acetic acid, or reaction times greater than 15 min, were used then lower overall yields resulted. The

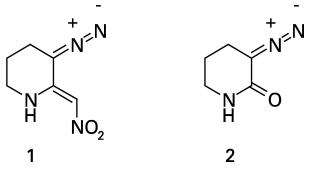
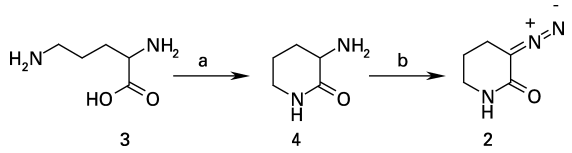
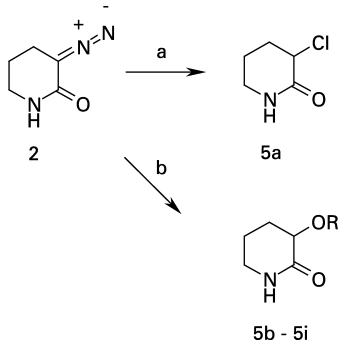


Figure 1.



Scheme 1. (a) Alumina, toluene, reflux, 1.5 h; (b) *iso*-amyl nitrite, $CHCl_3$, AcOH(cat), 15 min.



Scheme 2. (a) HCl, dioxane, reflux, 1 h; (b) ROH, Rh(II) acetate.

Keywords: diazoamide; piperidin-2-one; carbene insertion; cyclopropanation; olefination; pyrazoline.

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Table 1. Metal-catalysed insertion of **2** into O–H bonds

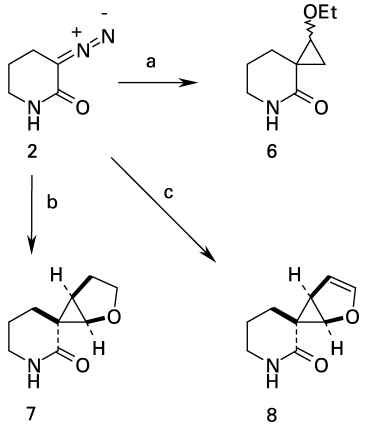
R[a]	Catalyst	Time (h)	*T* (°C)	Yield (%)	Compound
Me	$Rh_2(OAc)_4$	1	25	82	**5b**
Me	$CuSO_4$	0.5	25	30	**5b**
Me	$Cu(acac)_2$	4	55	10	**5b**
Et	$Rh_2(OAc)_4$	2	25	81	**5c**
iso-Pr	$Rh_2(OAc)_4$	4	25	52	**5d**
tert-Bu	$Rh_2(OAc)_4$	1	83	52	**5e**
Bn	$Rh_2(OAc)_4$	5	45	53	**5f**
Ph[b]	$Rh_2(OAc)_4$	5	25	68	**5g**
(*p*-Cl)Bn[b]	$Rh_2(OAc)_4$	8	25	66	**5h**
H[c]	$Rh_2(OAc)_4$	10	35	22	**5i**

[a] Reactions carried out in the alcohol as solvent.
[b] 2 equiv. of alcohol used in DCM as solvent.
[c] Water used in THF as solvent.

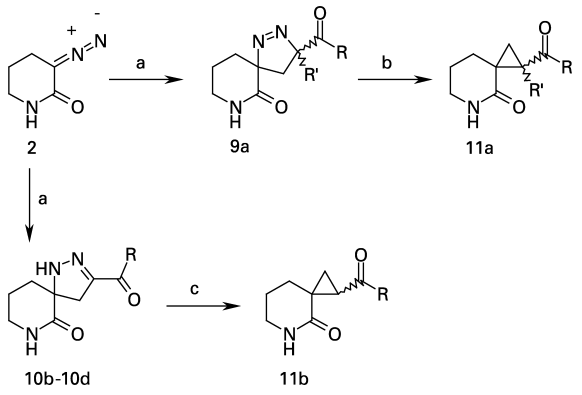
product **2** was stable to purification by silica gel chromatography, was crystallised from cyclohexene and could be stored at 0°C for up to 6 months without significant decomposition. The structure of **2** was confirmed by the usual analytical methods. In particular, IR spectroscopy showed a strong absorbance at 2088 cm^{-1} for the diazo group and CI-MS showed a molecular ion (M+1=126).

The scope and synthetic utility of the chemistry of this new cyclic α-diazoamide was explored. The results of insertion reactions into H–X bonds are summarised above (Scheme 2 and Table 1).

As mentioned above, **2** was found to be very sensitive to acetic acid; however, it reacted cleanly with hydrogen chloride in dioxane to give 3-chloro-piperidin-2-one **5a** in 68% yield.[6] Rhodium-catalysed insertion into the O–H bond of alcohols to give the 3-alkoxy-piperidin-2-ones **5b**–**h** was found to proceed in yields ranging from 52–82%.[7] Catalysis of this reaction by copper(II) salts was also investigated, but was found to afford only low yields of the desired products. The results in Table 1 show that the rhodium-catalysed reactions with methanol and ethanol are both fast and efficient, whereas with the more sterically hindered alcohols, the reactions require longer times and give lower yields.[8] Insertion into water was less efficient



Scheme 3. (a) Ethyl vinyl ether, Rh(II) acetate, room temperature, 1 h; (b) dihydrofuran, Rh(II) acetate, room temperature, 12 h; (c) furan, Rh(II) acetate, room temperature, 40 min.



Scheme 4. (a) Methyl methacrylate, room temperature, 4 h; (b) dioxan, reflux, 20 min; (c) methyl acrylate or methyl vinyl ketone or acrolein, room temperature, 0.5 h; (d) 1,2-dichlorobenzene, reflux, 20 min.

leading to 3-hydroxy-piperidin-2-one **5i** in an isolated yield of only 22%.

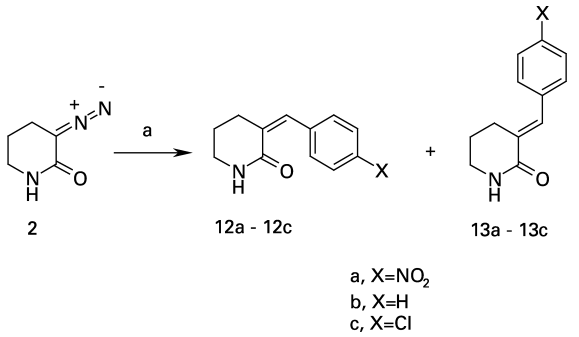
The rhodium-catalysed cyclopropanation of **2** with electron-rich double bonds was found to proceed smoothly and in good isolated yields, with both cyclic and acyclic enol ethers (Scheme 3).

With ethyl vinyl ether, compound **6** was obtained in 66% yield as a mixture of diastereomers, which proved inseparable by silica gel chromatography. However, the reaction with dihydrofuran produced the single diastereisomer **7** in 45% yield. The relative stereochemistry of the product was established by NMR spectroscopy using 2D COSY and nOe experiments. For compound **7** no nOe was observed between the protons at the 4 position of the piperidin-2-one ring and the two protons of the cyclopropyl ring. However, a nOe was observed between the protons at the 4 position of the piperidin-2-one and two of the tetrahydrofuran protons. These observations are consistent with the tetrahydrofuran ring being fused to the cyclopropyl ring in a *trans* relationship to the amide bond. Formation of this product can be rationalised on steric grounds. The reaction of **2** with furan proceeds in an analogues fashion with the single diastereoisomer **8** being isolated in 60% yield.

It is known that the rhodium-catalysed reaction of furan with diazo compounds can lead to dieneals resulting from ring opening of the furan.[9] The crude reaction mixture which led to the formation of **8**, was analysed by proton NMR spectroscopy. This did indeed detect the presence of two minor side products bearing aldehyde protons. However, they made up less than 10% of the reaction mixture and proved unstable to purification by silica gel chromatography and were not isolated and characterised.

Table 2. 1,3-Dipolar additions of **2** to electron-deficient olefins

R	R′	Product **9** (yield)	Product **10** (yield)	Product **11** (yield)
OMe	Me	**9a** (67%)		**11a** (99%)
OMe	–		**10b** (95%)	**11b** (75%)
Me	–		**10c** (91%)	
H	–		**10d** (69%)	



Scheme 5. (a) X–Ph–CHO, $MeReO_3$, $P(Ph)_3$, THF, room temperature, 7–12 h.

The 1,3-dipolar addition of **2** to electron-deficient olefins was found to be a very facile and high yielding process (Scheme 4). The outcome of the reaction was the same irrespective of whether a rhodium catalyst was present in the reaction mixture.

The 1-pyrazoline **9a** was isolated when methyl methacrylate was reacted with **2**. However, the 2-pyrazolines **10b–d** were isolated from the reaction of **2** with methyl acrylate, methyl vinyl ketone and acrolein, respectively. Presumably **10b–d** are formed via 1-pyrazoline intermediates which undergo a facile 1,3 H-transfer. The 1-pyrazoline **9a** extruded nitrogen on heating at 110°C to afford the cyclopropyl derivative **11a** in good yield. 2-Pyrazolines, generally require higher temperatures to undergo this reaction, and indeed **10b** needed to be heated at 180°C to extrude nitrogen and form the cyclopropane **11b** (Table 2).[10]

Recently, the olefination reaction of diazo compounds with aldehydes, catalysed by metals, has been described.[11–13] We investigated the reaction of **2** with both aromatic and alkyl aldehydes catalysed by methyl trioxorhenium.[11] The reaction proceeds smoothly with aromatic aldehydes to form the olefins as a ~3:1 (*E*/*Z*) mixture (Scheme 5). For 4-nitrobenzaldehyde, the two geometric isomers could be separated by chromatography to afford **12a** and **13a** in 15 and 46% isolated yield, respectively. The products using benzaldehyde, **12b** and **13b**, and 4-chlorobenzaldehyde, **12c** and **13c**, could not be separated by chromatography and were isolated as mixtures in moderate combined yields of 30–40%.[14] This reaction failed or gave very low yields, in our hands, when aliphatic aldehydes were used. Other, more recently described catalysts have yet to be tried and may well lead to better yields and stereo-control in this reaction.[12,13]

In summary, 3-diazo-piperidin-2-one **2** has been synthesised and is a new derivative in the rare class of cyclic α-diazo-amides. It is a relatively stable diazo derivative which can be easily handled and conveniently stored at 0°C for long periods. It undergoes a wide range of diazo group chemistry in good to excellent yield and allows rapid access to a number of novel and known 3-substituted piperidin-2-one derivatives. It may prove to be a very versatile intermediate for the synthesis of a wide range of nitrogen-containing heterocycles and some of its applications towards such goals are currently being explored.

3. Experimental

3.1. General

^{1}H NMR spectra were recorded at 250 MHz (Brüker ACF250) or at 400 MHz (Brüker WH400). ^{13}C NMR spectra were recorded at 61.42 MHz (Brüker ACF250). Mass spectra were recorded on a Kratos MS80 spectrometer. Chemical ionisation (CI) mass spectra used ammonia or methane as reagent gas. Infra red were recorded on a Perkin–Elmer 1720X Fourier transform spectrometer. Column chromatography was performed using silica gel 60 (230–400 mesh, Merck).

3.1.1. 3-Amino-piperidin-2-one 4. L-Ornithine hydrochloride **3** (100 g, 0.59 mol) was added to a stirred solution of sodium hydroxide pellets (23.8 g, 0.59 mol) in water (100 ml) at 25°C. After 15 min, this solution was added to a stirred mixture of alumina (300 g) and toluene (1 l) and heated under reflux for 1.5 h. The water produced during the reaction was collected in a Dean–Stark trap. The reaction mixture was allowed to cool and the alumina was filtered off and washed with 10% MeOH/CH_2C1_2 (300 ml). The filtrate and washings were combined and the solvent removed under vacuum to leave **4** as a white crystalline solid, 61.1 g (90%). Mp 35–37°C; IR (nujol) ν_{max} (cm^{-1}) 3340, 3261, 3197, 1646, 1491, 1377, 1349, 1303, 999, 940; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.0 (1H, bs, N–*H*), 3.2 (2H, m, CH_2N), 3.2 (1H, dd, *J*=3.8, 3.9 Hz, C*H*–NH_2), 1.5–2.1 (4H, m, CH_2CH_2), 1.75 (2H, bs, NH_2); MS *m*/*z* (int) 115 (M+1, 100), 99 (10), 70 (96), 58 (30), 42 (42). Anal. found: C 52.51, H 8.66, N 24.25%; calcd for $C_5H_{10}N_2O$: C 52.63, H 8.77, N 24.56%.

3.1.2. 3-Diazo-piperidin-2-one 2. 3-Amino-piperidin-2-one **4** (1.6 g, 14 mmol) was dissolved in chloroform (30 ml). *iso*-Amyl nitrite (2.31 g, 18 mmol) and glacial acetic acid (0.126 g, 2.1 mmol) were added with vigorous stirring. The resulting solution was refluxed for 15 min, cooled in ice and washed with an ice-cold saturated solution of $NaHCO_3$ (10 ml). The organic layer was separated, dried over anhydrous Na_2SO_4 and the solvent removed under vacuum. The red solid was purified by column chromatography (SiO_2: 20% MeOH/CH_2C1_2), crystallised from cyclohexene to give **2** as bright orange needles, 1.07 g (60%). Mp 117–120°C; IR (nujol) ν_{max} (cm^{-1}) 3268, 3172, 2088 (C=N_2), 1635, 1378, 1354, 1320; ^{1}H NMR ($CDC1_3$, 250 MHz) δ 6.5 (1H, bs, N–*H*), 3.25 (2H, m, CH_2N), 2.7 (2H, t, *J*=6.3 Hz, CH_2), 1.9 (2H, m, CH_2); ^{13}C NMR ($CDCl_3$, 60 MHz) δ 167 (*C*=O), 53 (*C*=N_2), 41 (*C*H_2N), 21 (*C*H_2), 20 (*C*H_2); MS *m*/*z* (int) 125 (M+, 85), 96 (12), 68 (90), 53 (41), 41 (100); CI-MS *m*/*z* 126 (M+1). Anal. found: C 47.96, H 5.66, N 33.28%; calcd for $C_5H_7N_3O$: C 48.00, H 5.60, N 33.60%.

3.1.3. 3-Chloro-piperidin-2-one 5a. 3-Diazo-piperidin-2-one **2** (2 g, 0.016 mol) was dissolved in dry dioxan (5 ml) and added dropwise with vigorous stirring to a solution of 4 M HCl in dioxan (50 ml). The yellow colour of the diazo compound faded and after 1 h the solvent was removed under vacuum to leave a pale yellow solid which was recrystallised from diethyl ether to give **5a** as a white crystalline solid, 1.45 g (68%). Mp 116–118°C; IR (nujol) ν_{max} (cm^{-1})

3255, 1648, 1378, 1327, 1177, 812; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.0 (1H, bs, N–*H*), 4.4 (1H, t, *J*=4.95 Hz, C*H*), 3.4 (2H, m, CH_2N), 1.9–2.2 (4H, m, CH_2CH_2); MS *m/z* (int) 135 (M+, 23), 133 (65), 97 (43), 84 (68), 82 (100), 68 (42), 62 (69), 58 (68), 55 (89), 43 (34), 41 (45); CIMS *m/z* 134 (M+1). Anal. found: C 44.87, H 6.11, N 10.38, Cl 26.86%; calcd for C_5H_8NOCl: C 44.94, H 5.99, N 10.49, Cl 26.69%.

3.2. Procedure A. Rhodium-catalysed insertion into the O–H bond of alcohols used as reaction solvent (Table 1)

Rhodium(II) acetate (10 mg) was added to a stirred solution of 3-diazo-piperidin-2-one **2** (2 mmol) in the alcohol (15 ml) at 25°C and the mixture left to stand for 1–4 h. When the evolution of nitrogen had ceased, the solvent was removed under vacuum and the residue dissolved in $CC1_4$ (20 ml). The rhodium catalyst was filtered from the solution, the solvent was removed under vacuum and the residue crystallised from diethyl ether.

3.2.1. 3-Methoxy-piperidin-2-one 5b. White waxy solid, yield: 82%. Mp 35–37°C; IR (nujol) ν_{max} (cm^{-1}) 3272, 1670, 1335, 1204, 1102; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.7 (1H, bs, N–*H*), 3.75 (1H, dd, *J*=7.3, 4.9 Hz, OC*H*), 3.6 (3H, s, OCH_3), 3.35 (2H, m, CH_2N), 1.7–2.2 (4H, m, CH_2CH_2); MS *m/z* (int) 99 (100), 70 (61), 58 (57), 43 (46), 41 (53); CI-MS *m/z* 130 (M+1). Anal. found: C 55.89, H 8.74, N 10.64%; calcd for $C_6H_{11}NO_2$: C 55.81, H 8.53, N 10.85%.

3.2.2. 3-Ethoxy-piperidin-2-one 5c. White solid, yield: 81%. Mp 57–59°C; IR (nujol) ν_{max} (cm^{-1}) 3198, 3083, 1680, 1336, 1312, 1116; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 6.2 (1H, bs, N–*H*), 3.8 (1H, dd, *J*=4.8, 7.2 Hz, OC*H*), 3.65 (2H, q, *J*=7 Hz, OCH_2), 3.3 (2H, m, CH_2N), 1.7–2.1 (4H, m, CH_2CH_2), 1.2 (3H, t, *J*=7 Hz, CH_3); MS *m/z* (int) 99 (100), 98 (72), 84 (13), 70 (57), 57 (21), 43 (18), 41 (13); CI-MS *m/z* 144 (M+1). Anal. found: C 58.74, H 9.32, N 9.57%; calcd for $C_7H_{13}NO_2$: C 58.74, H 9.09, N 9.79%.

3.2.3. 3-*iso*Propoxy-piperidin-2-one 5d. Pale yellow waxy solid, yield: 52%. Mp 46–49°C; IR (nujol) ν_{max} (cm^{-1}) 3202, 3079, 1669, 1495, 1375, 1322, 1312, 1268, 1146, 1089; ^{1}H NMR ($CDCl_3$, 220 MHz) δ 7.1 (1H, bs, N–*H*), 4.1 (1H, septet, *J*=7.8 Hz, C*H*(CH_3)$_2$), 3.9 (1H, dd, *J*=6.8, 4.4 Hz, OC*H*), 3.35 (2H, m, CH_2N), 1.7–2.1 (4H, m, CH_2CH_2), 1.25 (6H, d, *J*=7.8 Hz, CH(CH_3)$_2$); MS *m/z* (int) 99 (62), 98 (27), 70 (30), 55 (35), 43 (100), 41 (35); CI-MS *m/z* 158 (M+1). Anal. found: C 61.54, H 9.64, N 8.53%; calcd for $C_9H_{15}NO_2$: C 61.15, H 9.55, N 8.92%.

3.2.4. 3-*tert*-Butoxy-piperidin-2-one 5e. Reaction carried out at reflux to give a white crystalline solid, yield: 52%. Mp 105–110°C; IR (nujol) ν_{max} cm^{-1} 3202, 3085, 1675, 1366, 1328, 1178, 1108, 1025; ^{1}H NMR ($CDCl_3$, 220 MHz) δ 6.7 (1H, bs, N–*H*), 3.95 (1H, dd, *J*=6.3, 5.9 Hz, OC*H*), 3.3 (2H, m, CH_2N), 1.6–2.0 (4H, m, CH_2CH_2), 1.25 (9H, s, C(CH_3)$_3$); MS *m/z* (int) 156 (30), 143 (19), 116 (100), 98 (40), 71 (42), 57 (90), 41 (32); CI-MS *m/z* 172 (M+1). Anal. found: C 63.41, H 9.96, N 8.02%; calcd for $C_9H_{17}NO_2$: C 63.16, H 9.94, N 8.19%.

3.2.5. 3-Benzyloxy-piperidin-2-one 5f. White needles, yield: 53%. Mp 88–91°C; IR (nujol) ν_{max} (cm^{-1}) 3272, 1661, 1496, 1454, 1334, 1102, 1028; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.2–7.4 (5H, m, *Ph*), 6.9 (1H, bs, N–*H*), 4.8 (2H, 2×d, *J*=11.8 Hz, OCH_2), 3.8 (1H, t, *J*=6.5 Hz, OC*H*), 3.2–3.35 (2H, m, CH_2N), 1.7–2.0 (4H, m, CH_2CH_2); MS *m/z* (int) 99 (100), 91 (97), 84 (11), 71 (11), 51 (14), 43 (36), 41 (32); CI-MS *m/z* 206 (M+1). Anal. found: C 70.51, H 7.38, N 6.42%; calcd for $C_{12}H_{15}NO_2$: C 70.24, H 7.32, N 6.83%.

3.3. Procedure B. Rhodium-catalysed insertion into the O–H bond of alcohols with DCM as reaction solvent or into O–H bond of water with THF as solvent (Table 1)

Rhodium(II) acetate (10 mg) was added to a stirred solution of 3-diazo-piperidin-2-one **2** (2 mmol) and the alcohol (or water) (10 mmol) in methylene chloride (or THF) (15 ml). The solution was stirred at 25–45°C for 5–10 h. The reaction mixture was loaded onto a silica gel column and eluted with CH_2Cl_2, to remove excess alcohol. The product was isolated by elution with 20–50% MeCN/CH_2C1_2 and crystallised.

3.3.1. 3-Phenoxy-piperidin-2-one 5g. Crystallised from acetone to give white needles, yield: 68%. Mp 156–158°C; IR (nujol) ν_{max} (cm^{-1}) 3286, 1665, 1635, 1334, 1318, 1237, 1202, 1072; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.3 (2H, dd, *J*=7.3, 8.7 Hz, arom), 7.1 (1H, bs, N–*H*), 7.0 (2H, dd, *J*=8.7, 1 Hz, arom), 6.95 (1H, t, *J*=7.3 Hz, arom), 4.7 (1H, dd, *J*=5.3, 7.5 Hz, OC*H*), 3.25–3.4 (2H, m, CH_2N), 1.8–2.2 (4H, m, CH_2CH_2); MS *m/z* (int) 191 (17), 98 (28), 94 (67), 77 (40), 70 (100), 55 (61), 51 (37), 43 (78), 41 (62); CI-MS *m/z* 192 (M+1). Anal. found: C 69.40, H 6.83, N 7.02%; calcd for $C_{11}H_{13}NO_2$: C 69.11, H 6.81, N 7.33%.

3.3.2. 3-(*p*-Chlorobenzyloxy)-piperidin-2-one 5h. White solid, yield: 66%. Mp 104–106°C; IR (nujol) ν_{max} (cm^{-1}) 3191, 1674, 1467, 1377, 1309, 1183, 1109, 810; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.3 (4H, m, *Ph*), 6.0 (1H, bs, N–*H*), 4.8 (2H, 2×d, *J*=12.1 Hz, OCH_2), 3.8 (1H, dd, *J*=6.7, 5.0 Hz, OC*H*), 3.3 (2H, m, CH_2N), 1.9–2.1 (4H, m, CH_2CH_2); ^{13}C NMR ($CDCl_3$, 60 MHz) δ 172 (*C*=O), 138 (*C*quat), 133 (*C*–Cl), 129 (*C*arom), 128 (*C*arom), 74 (*C*H), 72 (*C*H_2O), 42 (*C*H_2N), 28 (*C*H_2), 19 (*C*H_2); MS *m/z* (int) 125 (65), 99 (100), 98 (70), 89 (26), 84 (16), 71 (12), 43 (29), 41 (19); CI-MS *m/z* 240 (M+1). Anal. found: C 60.48, H 5.69, N 5.73%; calcd for $C_{12}H_{14}ClNO_2$: C 60.25, H 5.86, N 5.86%.

3.3.3. 3-Hydroxy-piperidin-2-one 5i. White needles, yield: 22%. Mp 134–136°C; IR (nujol) ν_{max} (cm^{-1}) 3308, 3206, 1652, 1456, 1319, 1261, 1118, 1096; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 6.7 (1H, bs, N–*H*), 4.1 (1H, dd, *J*=6.3, 9.3 Hz, OC*H*), 4.0 (1H, bs, O–*H*), 3.3 (2H, m, CH_2N), 1.6–2.3 (4H, m, CH_2CH_2); MS *m/z* (int) 99 (7), 87 (17), 57 (43), 55 (26), 44 (100), 43 (62), 41 (60); CI-MS *m/z* 116 (M+1). Anal. found: C 52.6, H 8.1, N 12.6%; calcd for $C_5H_9NO_2$: requires C 52.17, H 7.83, N 12.17%.

3.3.4. 5-Aza-1-ethoxy-4-oxo-spiro[2.5]octane 6. A solution of 3-diazo-piperidin-2-one **2** (0.2 g, 1.6 mmol) in ethyl vinyl ether (20 ml) was treated with rhodium(II) acetate (10 mg). The reaction was stirred at 25°C for 1 h,

then the solvent was removed under vacuum and the residue was purified by silica gel column chromatography eluted with acetonitrile to give the product as a white crystalline solid 0.18 g (66%). Mp 106–108°C; IR (nujol) ν_{max} (cm^{-1}) 3182, 1660, 1435, 1336, 1194, 1129, 1082, 821; ^1H NMR ($CDCl_3$, 250 MHz) δ 6.8 (1H, bs, N–*H*), 3.65 (1H, dd, *J*=4.4, 7 Hz, C*H*–O), 3.6 (2H, q, *J*=7 Hz, OCH_2), 3.4 (2H, m, CH_2N), 1.8–2.0 (4H, m, CH_2CH_2), 1.5 (1H, t, *J*=7 Hz, C*H*), 1.2 (3H, t, *J*=7 Hz, CH_3), 0.7 (1H, t, *J*=4.4 Hz, C*H*); ^{13}C NMR ($CDCl_3$, 60 MHz) δ 174 (*C*=O), 67 (O*C*H_2), 64 (O*C*H), 42 (*C*H_2N), 25 (*C*spiro), 24 (*C*H_2), 23 (*C*H_2), 21 (*C*H_2), 15 (*C*H_3); MS *m/z* (int) 169 (M+, 8), 140 (100), 112 (72), 84 (16), 77 (9), 69 (31), 55 (19), 41 (56); CI-MS *m/z* 170 (M+1). Anal. found: C 64.11, H 9.03, N 8.32%; calcd for $C_9H_{15}NO_2$: C 63.88, H 8.93, N 8.28%.

3.3.5. 3′-Aza-2-oxa-2′-oxo-spiro[bicyclo[3.1.0]hexane-6,1′-cyclohexane] 7. Rhodium(II) acetate (10 mg) was added to a solution of 3-diazo-piperidin-2-one **2** (0.25 g, 2 mmol) in dihydrofuran (10 ml) and the reaction was stirred for 12 h at 25°C. The solvent was then removed under vacuum and the residue was passed down a silica gel column eluted with 5% hexane/THF to afford the product. This was recrystallised from diethyl ether/pentane to give a white crystalline solid 0.15 g (45%). Mp 135–140°C; IR (nujol) ν_{max} (cm^{-1}) 3228, 3187, 1651, 1485, 1417, 1366, 1335, 1253, 1148, 1122, 1096, 1048, 820; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.0 (1H, bs, N–*H*), 4.2 (1H, dd, *J*=8.4, 18 Hz, OC*H*), 4.1 (1H, d, *J*=6 Hz, C*H*), 3.9 (1H, dt, *J*=8.9, 4.4 Hz, OC*H*), 3.35 (2H, m, CH_2N), 2.45 (1H, dd, *J*=1.24, 7.3 Hz, OC*H*), 2.25 (1H, m, C*H*), 1.8–2.0 (3H, m, CH_2, C*H*), 1.65 (2H, m, CH_2); ^{13}C NMR ($CDCl_3$, 60 MHz) δ 172 (*C*=O), 75 (O*C*H_2), 69 (O*C*H), 42 (CH_2N), 30 (*C*spiro), 29 (*C*H), 24 (*C*H_2), 22 (*C*H_2), 19 (*C*H_2); MS *m/z* (int) 167 (M+, 47), 152 (14), 138 (28), 124 (19), 110 (42), 83 (100), 67 (28), 41 (35); CI-MS 168 (M+1). Anal. found: C 64.52, H 7.93, N 8.14%; calcd for $C_9H_{13}NO_2$: C 64.67, H 7.78, N 8.38%.

3.3.6. 3′-Aza-2-oxa-2′-oxo-spiro[bicyclo[3.1.0]hexane-6,1′-cylohex-3-ene] 8. Rhodium(II) acetate (15 mg) was added to a solution of 3-diazo-piperidin-2-one **2** (0.27 g, 2.1 mmol) in furan (25 ml). The reaction mixture was stirred at 25°C for 40 min and then the solvent removed under vacuum. The residue was purified by silica gel column chromatography eluted with 5% IPA/MeCN to afford the product as an orange crystalline solid 0.25 g (60%). Mp 132°C dec; IR (nujol) ν_{max} (cm^{-1}) 3183, 3037, 1643, 1594, 1488, 1421, 1332, 1257, 1146, 960; ^1H NMR ($CDCl_3$, 250 MHz) δ 6.9 (1H, bs, N–*H*), 6.4 (1H, d, *J*=2.5 Hz, OC*H*), 5.2 (1H, t, *J*=2.6 Hz, C*H*), 4.8 (1H, d, *J*=5.7 Hz, OC*H*), 3.35 (2H, m, CH_2N), 2.9 (1H, dd, *J*=5.7, 2.7 Hz, C*H*), 1.8 (2H, m, CH_2), 1.4 (2H, m, CH_2); ^{13}C NMR ($CDCl_3$, 60 MHz) δ 174 (*C*=O), 148 (O*C*H), 102 (C=*C*H), 71 (O*C*H), 42 (*C*H_2N), 36 (*C*H), 22 (*C*H_2), 17 (*C*H_2), 16 (*C*spiro); CI-MS *m/z* 166 (M+1). Anal. found: C 65.61, H 6.63, N 8.24%; calcd for $C_9H_{11}NO_2$: C 65.43, H 6.71, N 8.48%.

3.3.7. 1,2,7-Triaza-3-methoxycarbonyl-3-methyl-6-oxo-spiro[4.5]dec-1-ene 9a. 3-Diazo-piperidin-2-one **2** (1.9 g, 15.2 mmol) was dissolved in methyl methacrylate (20 ml) and stirred for 4 h at 25°C. When the yellow solution had turned colourless, the solvent was removed under vacuum and the residue recrystallised from diethyl ether/pentane to give white needles, 2.3 g (67%). Mp 94–97°C; IR (nujol) ν_{max} (cm^{-1}) 3198, 3058, 1733, 1658, 1445, 1373, 1346, 1302, 1274, 1170, 1143, 840; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.0 (1H, bs, N–*H*), 3.8 (3H, s, OCH_3), 3.3–3.5 (2H, m, CH_2N), 1.8–2.2 (4H, m, CH_2CH_2), 2.05 (1H, d, *J*=12.9 Hz, CH_2), 1.9 (1H, d, *J*=12.9 Hz, CH_2), 1.5 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 60 MHz) δ 171 (*C*=O), 169 (*C*=O), 98 (*C*quat), 98 (*C*spiro), 53 (OCH_3), 43 (*C*H_2N), 38 (*C*H_2), 33 (*C*H_2), 23 (*C*H_3), 20 (*C*H_2); MS *m/z* (int) 197 (M−28, 31), 165 (46), 137 (100), 109 (24), 79 (16), 67 (20), 41 (20); CI-MS *m/z* 198 (M−28+1). Anal. found: C 53.39, H 6.75, N 18.46%; calcd for $C_{10}H_{15}N_3O_3$: C 53.33, H 6.66, N 18.67%.

3.3.8. 1,2,7-Triaza-3-methoxycarbonyl-6-oxo-spiro[4.5]-dec-2-ene 10b. 3-Diazo-piperidin-2-one **2** (1 g, 8 mmol) was dissolved in methyl acrylate (50 ml) and stirred at 25°C for 30 min. The product crystallised out of the reaction mixture, was filtered and washed with chloroform (15 ml) to afford a white solid, 1.6 g (95%). Mp 160–161°C; IR (nujol) ν_{max} (cm^{-1}) 3212, 3046, 1730, 1644, 1581, 1493, 1342, 1328, 1285, 1261, 1138, 1099, 789; ^1H NMR (DMSO-$_{d6}$, 250 MHz) δ 8.8 (1H, bs, N–*H*), 7.7 (1H, bs, N–*H*), 3.7 (3H, s, OCH_3), 3.3 (1H, d, *J*=16.8 Hz, CH_2), 3.2 (2H, m, CH_2N), 2.65 (1H, d, *J*=16.8 Hz, CH_2), 1.6–1.9 (4H, m, CH_2CH_2); ^{13}C NMR (DMSO-$_{d6}$, 60 MHz) δ 171 (*C*=O), 163 (*C*=O), 136 (*C*=N), 68 (*C*spiro), 51 (OCH_3), 41 (*C*H_2N), 41 (*C*H_2), 34 (*C*H_2), 19 (*C*H_2); MS *m/z* (int) 183 (M−28, 34), 153 (100), 140 (78), 121 (92), 108 (78), 96 (35), 81 (32), 43 (42); CI-MS *m/z* 212 (M+1). Anal. found: C 51.00, H 6.24, N 19.72%; calcd for $C_9H_{13}N_3O_3$: C 51.18, H 6.20, N 19.89%.

3.3.9. 1,2,7-Triaza-3-methylcarbonyl-6-oxo-spiro[4.5]-dec-2-ene 10c. 3-Diazo-piperidin-2-one **2** (0.11 g, 0.88 mmol) was dissolved in DCM (2 ml) and added, with stirring, to methyl vinyl ketone (10 ml) at 25°C. After 30 min the product crystallised from the reaction mixture, was filtered and washed with methylene chloride (5 ml) to give white crystals, 0.157 g (91%). Mp 200–201°C; IR (nujol) ν_{max} (cm^{-1}) 3227, 1659, 1634, 1557, 1429, 1385, 1342, 1286, 1256, 1103, 996, 632; ^1H NMR (DMSO-$_{d6}$, 250 MHz) δ 9.1 (1H, bs, N–*H*), 7.7 (1H, bs, N–*H*), 3.2 (2H, m, CH_2N), 3.18 (1H, d, *J*=16.7 Hz, CH_2), 2.55 (1H, d, *J*=16.7 Hz, CH_2), 2.25 (3H, s, CH_3), 1.75–1.9 (4H, m, CH_2CH_2); ^{13}C NMR (DMSO-$_{d6}$, 60 MHz) δ 193 (*C*=O), 171 (*C*=O), 145 (*C*=N), 68 (*C*spiro), 41 (*C*H_2N), 40 (*C*H_2), 32 (*C*H_2), 25 (*C*H_3), 19 (*C*H_2); MS *m/z* (int) 137 (82), 124 (65), 78 (82), 63 (100), 43 (49); CI-MS *m/z* 196 (M+1). Anal. found: C 55.35, H 6.64, N 21.48%; calcd for $C_9H_{13}N_3O_2$: C 55.38, H 6.67, N 21.54%.

3.3.10. 1,2,7-Triaza-3-formyl-6-oxo-spiro[4.5]dec-2-ene 10d. 3-Diazo-piperidin-2-one **2** (0.19 g, 1.52 mmol) was dissolved in acrolein (10 ml) and stirred for 20 min at 25°C. The product crystallised from the reaction mixture, was filtered and washed with chloroform (5 ml) to give a white crystalline solid, 0.19 g (69%). Mp 178–182°C; IR (nujol) ν_{max} (cm^{-1}) 3164, 1668, 1550, 1491, 1343, 1284, 1246, 1127, 1114, 1003, 850; ^1H NMR (DMSO-$_{d6}$, 250 MHz) δ 9.8 (1H, bs, N–*H*), 9.5 (1H, s, C*H*O) 7.8 (1H, bs, N–*H*), 3.2 (2H, m, CH_2N), 3.15 (1H, d, *J*=16.7 Hz, CH_2), 2.65 (1H, d, *J*=16.7 Hz, CH_2), 1.6–1.9

(4H, m, CH_2CH_2); ^{13}C NMR (DMSO-$_{d6}$, 60 MHz) δ 185 (*C*=O), 170 (*C*=O), 146 (*C*=N), 69 (*C*spiro), 41 (*C*H_2N), 38 (*C*H_2), 34 (*C*H_2), 19 (*C*H_2); FAB-MS *m/z* (int) 182 (M+1, 94), 154 (20), 93 (100), 75 (41), 44 (36). Anal. found: C 52.89, H 6.15, N 22.98%; calcd for $C_8H_{11}N_3O_2$: C 53.04, H 6.08, N 23.20%.

3.3.11. 5-Aza-1-methoxycarbonyl-1-methyl-4-oxo-spiro-[2.5] octane 11a. 1,2,7-Triaza-3-methoxycarbonyl-3-methyl-6-oxo-spiro[4.5]dec-1-ene **9a** (2.25 g, 0.01 mol) was dissolved in dioxan (70 ml) and heated under reflux for 20 min. The solvent was removed under vacuum and the residue recrystallised from diethyl ether/pentane to give the product as white needles, 1.95 g (99%). Mp 112–113°C; IR (nujol) ν_{max} (cm^{-1}) 3193, 3077, 1715, 1669, 1457, 1445, 1315, 1298, 1148, 848; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.2 (1H, bs, N–*H*), 3.7 (3H, s, OCH_3), 3.35 (2H, m, CH_2N), 1.7–2.0 (4H, m, CH_2CH_2), 1.6 (1H, d, *J*=4.8 Hz, CH_2), 1.45 (1H, d, *J*=4.8 Hz, CH_2), 1.4 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 60 MHz) δ 173 (*C*=O), 171 (*C*=O), 52 (OCH_3), 41 (*C*H_2N), 33 (*C*spiro), 32 (*C*quat), 26 (*C*H_2), 22 (*C*H_2), 20 (*C*H_2), 15 (*C*H_3); MS *m/z* (int) 197 (M+, 24), 165 (38), 137 (84), 98 (18), 79 (18), 57 (36), 41 (29); CI-MS *m/z* 198 (M+1). Anal. found: C 60.80, H 7.60, N 6.95%; calcd for $C_{10}H_{15}NO_3$: C 60.91, H 7.61, N 7.11%.

3.3.12. 5-Aza-1-methoxycarbonyl-4-oxo-spiro[2.5]octane 11b. 1,2,7-Triaza-3-methoxycarbonyl-6-oxo-spiro[4.5]dec-2-ene **10b** (0.2 g, 0.95 mmol) was suspended in dichlorobenzene (5 ml) and heated under reflux for 20 min. Most of the solvent was removed under vacuum and the remaining oil subjected to silica gel column chromatography eluted with 25% MeOH/DCM to give the product as an off-white solid, 0.13 g (75%). Mp 70–72°C; IR (nujol) ν_{max} (cm^{-1}) 3191, 3050, l737, 1657, 1493, 1381, 1356, 1335, 1203, 1177, 953; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 6.7 (1H, bs, N–*H*), 3.7 (3H, s, OCH_3), 3.35 (2H, m, CH_2N), 2.4 (1H, dd, *J*=6.7, 8.7 Hz, C*H*), 1.8–2.0 (4H, m, CH_2CH_2), 1.6 (1H, dd, *J*=3.8, 8.7 Hz, CH_2), 1.2 (1H, dd, *J*=3.8, 6.7 Hz, CH_2); ^{13}C NMR ($CDCl_3$, 60 MHz) δ 171 (*C*=O), 171 (*C*=O), 52 (OCH_3), 43 (*C*H_2N), 29 (*C*spiro), 27 (*C*H), 25 (*C*H2), 22 (*C*H_2), 21 (*C*H_2); MS *m/z* (int) 183 (M+, 18), 151 (36), 123 (100), 96 (25), 83 (44), 67 (16), 41 (25); CI-MS *m/z* 184 (M+1). Anal. found: C 59.41, H 7.20, N 7.51%; calcd for $C_9H_{13}NO_3$: C 59.02, H 7.10, N 7.65%.

3.3.13. 3-(4-Nitro-benzylidene)-piperidin-2-one 12a and 13a. 3-Diazo-piperidin-2-one **2** (0.25 g, 2 mmol) was dissolved in THF (15 ml) and added dropwise to a solution of 4-nitrobenzaldehyde (0.3 g, 2 mmol), triphenylphosphine (0.52 g, 2 mmol) and methyl trioxorhenium (18 mg, 3.6 mol%) in THF (20 ml). The reaction mixture was stirred at room temperature for 7 h and then the solvent removed under vacuum. The residue was passed down a silica gel column eluted with 50% MeCN/DCM. The first compound eluted off the column was the (*Z*)-isomer of the title compound **12a**, isolated as a pale yellow crystalline solid, 0.072 g (15.5%). Mp 120–122°C; IR (nujol) ν_{max} (cm^{-1}) 3199, 1669, 1632, 1513, 1463, 1421, 1343, 1312, 1107; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.1 (2H, d, *J*=8.6 Hz, *H* arom), 7.55 (2H, d, *J*=8.6 Hz, *H* arom), 6.7 (1H, s, =C*H*), 6.4 (1H, bs, N–*H*), 3.4 (2H, t, *J*=5.95 Hz, CH_2N), 2.65 (2H, t, *J*=6.3 Hz, CH_2), 2.0 (2H, m, CH_2); ^{13}C NMR ($CDCl_3$, 60 MHz) δ 165 (*C*=O), 146 (*C*–NO_2), 143 (*C*arom), 134 (*C*arom), 133 (*C*arom), 129 (*C*=C), 122 (*C*=C), 42 (*C*H_2), 32 (*C*H_2), 23 (*C*H_2); MS *m/z* (int) 232 (M+, 52), 231 (98), 185 (27), 128 (17), 97 (25), 85 (46), 71 (57), 57 (100), 43 (69); CI-MS *m/z* 233 (M+1). Anal. found: C 61.90, H 5.33, N 11.89%; calcd for $C_{12}H_{12}N_2O_3$: C 62.06, H 5.21, N 12.06%.

The second compound eluted off the column was the (*E*)-isomer of the title compound **13a**, which was isolated as a pale yellow solid, 0.215 g (46%). Mp 125–126°C; IR (nujol) ν_{max} (cm^{-1}) 3382, 3190, 1668, 1622, 1510, 1421, 1340, 1107, 993; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.2 (2H, d, *J*=8.55 Hz, *H* arom), 7.8 (1H, s, =C*H*), 7.5 (2H, d, *J*=8.55 Hz, *H* arom), 6.3 (1H, bs, N–*H*), 3.4 (2H, m, CH_2N), 2.8 (2H, m, CH_2), 1.9 (2H, m, CH_2); MS *m/z* (int) 232 (M+, 40), 231 (80), 202 (19), 185 (23), 97 (30), 71 (62), 43 (81); CI-MS *m/z* 233 (M+1). Anal. found: C 61.72, H 5.20, N 11.82%; calcd for $C_{12}H_{12}N_2O_3$: C 62.06, H 5.21, N 12.06%.

3.3.14. 3-Benzylidene-piperidin-2-one 12b and 13b. 3-Diazo-piperidin-2-one **2** (0.25 g, 2 mmol) was dissolved in THF (15 ml) and added dropwise to a solution of benzaldehyde (0.212 g, 2 mmol), triphenylphosphine (0.52 g, 2 mmol) and methyl trioxorhenium (15 mg, 3 mol%) in THF (20 ml). The reaction mixture was stirred at room temperature for 12 h and then the solvent removed under vacuum. The residue was purified by preparative tlc (SiO_2: 50% MeCN/CHC1$_3$) to afford the product as a mixture of (*E*) and (*Z*) isomers as a pale yellow waxy solid, 0.13 g (34%). Mp 71–75°C; IR (nujol) ν_{max} (cm^{-1}) 3270, 3182, 1668, 1635, 1461, 1414, 1321, 1109, 909; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.2–7.8 (6H, m, 5*H* arom, =C*H*), 6.3 (1H, bs, N–*H*), 3.2 (2H, m, CH_2N), 2.72 (2H, t, *J*=6.4 Hz, CH_2), 1.85 (2H, m, CH_2); MS *m/z* (int) 187 (M+, 13), 97 (54), 83 (46), 68 (83), 41 (89); CI-MS *m/z* 188 (M+1). Anal. found: C 77.30, H 6.87, N 7.30%; calcd for $C_{12}H_{13}NO$: C 77.01, H 6.95, N 7.49%.

3.3.15. 3-(4-Chloro-benzylidene)-piperidin-2-one 12c and 13c. 3-Diazo-piperidin-2-one **2** (0.25 g, 2 mmol) was dissolved in THF (15 ml) and added dropwise to a solution of 4-chlorobenzaldehyde (0.3 g, 2 mmol), triphenylphosphine (0.52 g, 2 mmol) and methyl trioxorhenium (25 mg, 5 mol%) in THF (20 ml). The reaction mixture was stirred at room temperature for 10 h and the solvent removed under vacuum. The residue was purified by preparative tlc (SiO_2: 20% $CHCl_3$/MeCN) to afford the title compound, a mixture of (*E*) and (*Z*) isomers, as a pale yellow waxy solid, 0.17 g (38%). Mp 58–60°C; IR (nujol) ν_{max} (cm^{-1}) 3185, 1670, 1630, 1481, 1439, 1321, 1222, 1109, 910; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.7 (2H, d, *J*=8.5 Hz, *H* arom), 7.5 (2H, d, *J*=8.5 Hz, *H* arom), 7.2 (1H, s, =C*H*), 6.3 (1H, bs, N–*H*), 3.3 (2H, m, CH_2N), 2.6 (2H, t, *J*=6.2 Hz, CH_2), 1.9 (2H, m, CH_2); MS *m/z* (int) 222 (M+, 12), 186 (15), 158 (11), 125 (82), 97 (68), 68 (15), 43 (9); CI-MS *m/z* 223 (M+1). Anal. found: C 65.21, H 5.42, N 5.99%; calcd for $C_{12}H_{12}ClNO$: C 65.01, H 5.45, N 6.32%.

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References

1. (a) Doyle, M. P.; Anthony, M.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo compounds: From Cyclopropane to Ylides*; Wiley: New York, 1998. (b) Zollinger, H. *Diazo Chemistry II. Aliphatic, Inorganic and Organometallic Compounds*; VCH: Weinheim, Germany, 1995.
2. Hutchinson, I. S.; Matlin, S. A.; Mete, A. *Tetrahedron Lett.* **2001**, *42*, 1773–1776.
3. (a) Matlin, S. A.; Chan, L. *J. Chem. Soc., Chem. Commun.* **1981**, 10–11. (b) Lydon, K. M.; McKee, V.; McKervey, M. A. *Acta Crystallogr. Sect. C: Cryst. Struct. Commun.* **1997**, *C53*, 1675–1676.
4. Blade-Font, A. *Tetrahedron Lett.* **1980**, *21*, 2443–2446.
5. Takamura, N.; Mizoguchi, T.; Koga, K.; Yamada, S. *Tetrahedron* **1975**, *31*, 227–230.
6. Romers, C.; Rutten, E. W. M.; Van Driel, C. A. A.; Sanders, W. W. *Acta Crystallogr.* **1967**, *22*, 893–899.
7. Miller, D. J.; Moody, C. J. *Tetrahedron* **1995**, *51*, 10811–10843.
8. Paulissen, R.; Reimlinger, H.; Hayez, E.; Hubert, A. J.; Teyssie, P. *Tetrahedron Lett.* **1973**, *14*, 2233–2236.
9. Matlin, S. A.; Chan, L.; Catherwood, B. *J. Chem. Soc., Perkin Trans. 1* **1990**, 89–96.
10. Jones, W. M.; Tai, W-T. *J. Org. Chem.* **1962**, *27*, 1030–1031. (b) Jones, W. M.; Tai, W-T. *J. Org. Chem.* **1962**, *27*, 1324–1328.
11. Herrmann, W. A.; Wang, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1641–1643.
12. Ledford, B. E.; Carreira, E. M. *Tetrahedron Lett.* **1997**, *38*, 8125–8128.
13. Fujimura, O.; Honma, T. *Tetrahedron Lett.* **1998**, *39*, 625–626.
14. Campi, E. M.; Chong, J. M.; Jackson, W. R.; Van der Schoot, M. *Tetrahedron* **1994**, *50*, 2533–2542.