RHODIUM(II)- AND COPPER(I)-CATALYZED INTRAMOLECULAR CARBON–HYDROGEN BOND INSERTIONS WITH METAL CARBENOIDS DERIVED FROM DIAZO KETONES

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The decomposition of diazo ketones in the presence of Rh(II) and Cu(I) catalysts affords products of C–H bond insertion in high yields. The effect of structural variation on intramolecular and transannular C–H insertions of diazo ketones has been investigated. The enantioselectivity of the insertion was examined with 15 chiral catalysts of different structural types. It was low in all cases. The poor enantioselectivity of the insertion of diazo ketones in comparison to that obtained in insertions of diazo esters and diazo amides is attributed to two factors: The oxocarbenes derived from diazo esters and diazo amides are stabilized by resonance of the carbonyl group with the heteroatom. Furthermore, the conformational constraints which must be overcome in order to reach the transition state for intramolecular insertion are lower in the case of carbenes derived from diazo ketones than in those from diazo esters and amides owing to the higher rotational barriers of amides and esters in comparison with that of ketones. This results in an earlier, and therefore less selective transition state for insertion of diazo ketones.

Key words: Carbenoids; Carbenes; Diazo compounds; Enantioselective catalysis; Insertions; Rhodium; Copper; Chelates.

The reaction of diazo compounds with transition metal complexes derived from Cu(I), Rh(II), Ru(II), *etc.* affords metal carbenoids, capable of transferring their carbene moiety to suitable acceptors[1]. The selectivity of the metal carbenoid depends upon the substituent of the carbene, the nature of the metal and upon that of its ligands[2]. If the ligands are chiral, enantioselective carbene transfer may occur. The development of chiral metal complexes serving as catalysts for diazo decomposition and, hence, enantioselective carbenoid reactions has made spectacular progress over the last ten years. Numerous catalyst–carbene combinations are known, and almost

fully enantioselective carbene transfer reactions have been realized[3]. Diazo esters and diazo amides are the most suitable precursors for asymmetric carbene transfer. In contrast, the enantioselectivity of diazo ketones in typical carbenoid reactions is usually low. Except for a few isolated examples of intramolecular cyclopropanations[4] and C–H insertions[5], enantioselective carbenoid reactions of diazo ketones have by far not met the spectacular success encountered with diazo esters and diazo amides, although diazo ketones have found numerous successful applications in racemic synthesis[6]. Some years ago we have reported enantioselective intramolecular C–H insertions of diazoacetate esters in the presence of chiral Rh(II) carboxamidate catalysts, such as $[Rh_2\{(2S)\text{-mepy}\}_4]$, which proceeded with enantioselectivities of up to 95% and better[7] while insertion reactions of structurally analogous diazo ketones were almost totally unselective. A similar lack of enantiocontrol in carbenoid reactions of diazo ketones has been found by other authors[3], but no satisfactory explanation has been proposed, nor have catalysts been designed to overcome this deficiency.

The present investigation deals with intramolecular carbenoid insertion of diazo ketones in the presence of chiral Rh(II) and Cu(I) catalysts. It was expected that, by varying the structures of the diazo ketones, and by screening a series of structurally different catalysts, some leads would emerge, which would contribute to the rational design of more selective chiral Rh(II) catalysts. Diazo ketones with variable structures were synthesized such as to allow the investigation of transannular insertions with diazocycloalkanones, intramolecular and transannular insertions of diazocycloalkenonens, and intramolecular insertions of diazo ketoesters having alcohol moieties with different steric hindrance.

EXPERIMENTAL

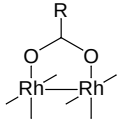
General. See ref.[8]

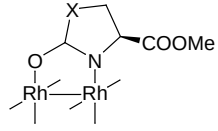
Catalysts. $[Rh_2(OAc)_4]$ (**1a**) and $[Cu(acac)_2]$ (**5a**) were purchased from Fluka or from Pressure Chemical Co. Pittsburgh. The other Rh(II) catalysts were synthesized by ligand exchange from $[Rh_2(OAc)_4]$: $[Rh_2\{(S)\text{-meba}\}_4]$ (**1b**): ref.[9]; $[Rh_2\{(-)\text{-mpmt}\}_4]$ (**1c**): ref.[10]; $[Rh_2\{(S)\text{-}(-)\text{-ptpa}\}_4]$ (**1e**): ref.[11]; $[Rh_2\{(2S)\text{-mepy}\}_4]$ (**2a**): ref.[12]; $[Rh_2\{(4S)\text{-mppim}\}_4]$ (**2b**): ref.[13]; $[Rh_2\{(S)\text{-tbsp}\}_4]$ (**3a**): ref.[14]; $[Rh_2\{(R)\text{-}(-)\text{-bnp}\}_4]$ (**4a**): ref.[15]; $[Rh_2\{(R)\text{-}(-)Me_2\text{bnp}\}_4]$ (**4b**): ref.[16]; [Cu-semicorrin] (**5b**): ref.[17]; [Cu-iPr-pybox] (**5c**): ref.[18]; $[Rh_2\{(+)\text{-dmanth}\}_4]$ (**1d**) and $[Rh_2\{(S)\text{-}(-)\text{-ptleu}\}_4]$ (**1f**): ref.[19] and the prolinate catalysts **3b**–**3d** were provided by M. A. McKervey. Abbreviations of ligands: acac, acetylacetonate; bnhp, bisnaphthol phosphate; dmanth, octahydro-1:4,5:8-dimethano-9-anthroate; meba, 2-methoxyethylbenzoate; Me_2bnhp, 3,3'-dimethylbisnaphthol phosphate; mepy, methyl 2-pyrrolidonecarboxylate; mpmt, 2-carboxymethylbenzoate; mppim, methyl *N*-(3-phenylpropanoyl)imidazolidinone-4-carboxylate; naph-pro, *N*-naphthoyl prolinate; ptle, *N*-phtaloyl *tert*-leucinate; ptpa,

N-phthaloyl phenylalalinate; pybox, 2,4-bis-(3-isopropyloxazoline)pyridine; tbbz-pro, *N*-(4-*tert*-butylbenzoyl) prolinate; tbsp, *N*-(4-*tert*-butylbenzenesulfonyl) prolinate; tipps-pro, *N*-(2,4,6-triisopropylbenzenesulfonyl) prolinate.

Synthesis and Reaction of Diazocycloalkanones **8a**–**8c**

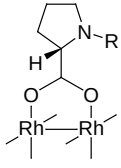
Diazocycloheptan-1-one[20] (**8a**) was synthesized *via* formylation of cycloheptanone[21] (**6**) (61%) followed by deformylating diazo transfer with TsN_3 (ref.[22]; yield 90%; yellow oil, purified by chromatography (silica gel, ether–petroleum ether 33 : 67)). ^{1}H NMR (200 MHz, $CDCl_3$): 1.66–1.77 (m, 6 H); 2.50–2.58 (m, 4 H).

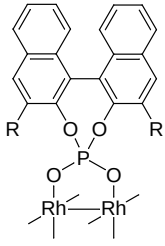




		R
1a	$[Rh_2\{(OAc)_4\}]$	methyl
1b	$[Rh_2\{(S)$-meba$\}_4]$	2-(1*S*)-methoxyethylphenyl
1c	$[Rh_2\{(-)$-mpmt$\}_4]$	2-(-)-carboxymenthylphenyl
1d	$[Rh_2\{(+)$-dmanth$\}_4]$	(+)-1,2,3,4,5,6,7,8-octahydro-1:4,5:8-dimethano-9-anthryl
1e	$[Rh_2\{(S)$-(-)-ptpa$\}_4]$	(*S*)-2-phenyl-1-phthalimidoethyl
1f	$[Rh_2\{(S)$-(-)-ptleu$\}_4]$	(*S*)-2,2-dimethyl-1-phthalimidopropyl

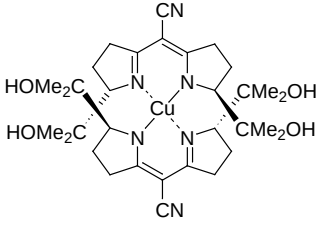
		X
2a	$[Rh_2\{(2S)$-mepy$\}_4]$	CH_2
2b	$[Rh_2\{(4S)$-mppim$\}_4]$	$NC(O)(CH_2)_2Ph$



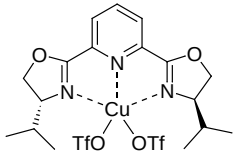


		R
3a	$[Rh_2\{(S)$-tbsp$\}_4]$	4-*tert*-butylbenzenesulfonyl
3b	$[Rh_2\{(S)$-tipps-pro$\}_4]$	2,4,6-triisopropylbenzenesulfonyl
3c	$[Rh_2\{(S)$-tbbz-pro$\}_4]$	4-*tert*-butylbenzoyl
3d	$[Rh_2\{(S)$-naph-pro$\}_4]$	1-naphthoyl

		R
4a	$[Rh_2\{(R)$-(-)-bnhp$\}_4]$	H
4b	$[Rh_2\{(R)$-(-)-Me_2bnhp$\}_4]$	Me



5b [Cu-semicorrin]



5c [Cu-pybox]

Diazotransfer via trifluoroacetylation[23] *(Danheiser procedure).* To LiHMDS (1 M in hexane, 7.14 ml, 1.10 equivalent) in dry THF (18 ml) the ketone **6** (6.50 mmol) in THF (12 ml) was added dropwise at –78 °C during 15 min. After stirring at –78 °C during 30 min, $CF_3CO_2CH_2CF_3$ (1.04 ml, 7.8 mmol) was added with a syringe at once. After 10 min, the temperature was raised to –40 °C and kept for 30 min. The mixture was poured into 5% HCl (35 ml) and Et_2O (45 ml). The aqueous layer was extracted with Et_2O (2 × 30 ml). The organic layers were washed with saturated NaCl (35 ml) and then concentrated under reduced pressure. The resulting crude product was immediately dissolved in CH_3CN (25 ml) under argon, and Et_3N (1.35 ml, 9.7 mmol) and H_2O (0.11 ml, 1.0 equivalent) were added. Methanesulfonyl azide[24] (MsN_3, 1.17 g, 9.70 mmol) in CH_3CN (20 ml) was added dropwise within 20 min. The mixture was stirred at 25 °C for 2.5 h and then concentrated to 15 ml under reduced pressure. It was diluted with Et_2O (45 ml), and washed with 10% NaOH (3 × 30 ml) and with saturated NaCl. After drying ($MgSO_4$), filtration, and concentration, the crude product was purified by flash chromatography.

2-Diazocyclooctanone[11] (**8b**). Yield 70% *via* Danheiser procedure; purification by chromatography (silica gel, petroleum ether–ether–NEt_3 80 : 20 : 1); yellow oil. IR ($CHCl_3$): 3 053 m, 2 985 s, 2 934 s, 2 087 s, 1 612 s. ^{1}H NMR (200 MHz, $CDCl_3$): 1.57–1.80 (m, 8 H); 2.50–2.65 (m, 4 H). ^{13}C NMR (50 MHz): 24.4 (t); 25.7 (t); 25.8 (t); 28.4 (t); 29.7 (t); 37.8 (t); 127.8 (s); 198.8 (s). MS: 124 (M^+), 95 (38), 81 (80), 67 (100), 55 (99).

2-Diazocyclodecanone[11] (**8c**). Yield 27% *via* Danheiser procedure; purification by chromatography (silica gel, hexane–EtOAc 80 : 20); m.p. 54 °C. IR (CH_2Cl_2): 3 053 m, 2 928 s, 2 082 vs, 1 607 s, 1 357 m. ^{1}H NMR (200 MHz, $CDCl_3$): 1.30–1.90 (m, 12 H); 2.45–2.61 (m, 2 H); 2.63–2.80 (m, 2 H). ^{13}C NMR (100 MHz): 21.4 (t); 22.1 (t); 23.4 (t); 25.6 (t); 25.7 (t); 28.3 (t); 29.6 (t); 37.7 (t); 128.5 (s); 190.1 (s); MS: 152 (M^+), 95 (38), 67 (100), 55 (85).

Diazo Decomposition of Diazocycloalkanones **8**. General Procedure

The diazo ketone **8** (1.00 mmol) in dry CH_2Cl_2 (10 ml) was added, with a syringe pump within 15 h, to the previously dried (heat-gun) catalyst (0.02 mmol) in CH_2Cl_2 (5.0 ml) at 25 °C. After the addition, the solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography to afford the bicyclic ketone **10** (from **8b**) or **11** (from **8c**). The enantiomeric excess of the ketones was determined by GC. For results with various catalysts, see Table I.

cis-Bicyclo[3.3.0]octan-2-one[25] (**10**). Chromatography on silica gel with hexane–EtOAc 90 : 10; ee by GC with Betadex, 90 °C or Lipodex D, 70 °C. IR (CH_2Cl_2): 3 053 vs, 2 959 m, 2 870 w, 1 728 vs, 1 459 w, 1 261 m. ^{1}H NMR (200 MHz, $CDCl_3$): 1.20–1.70 (m, 4 H); 1.73–1.98 (m, 3 H); 2.10–2.31 (m, 3 H); 2.47–2.65 (m, 1 H); 2.68–2.85 (m, 1 H). ^{13}C NMR (100 MHz): 26.1 (t); 26.3 (t); 29.8 (t); 33.4 (t); 38.0 (t); 41.0 (d); 52 (d); 223.5 (s). MS: 124 (M^+), 95 (66), 80 (60), 68 (39), 67 (100), 55 (27).

cis-Bicyclo[5.3.0]decan-2-one[26] (**11**). Chromatography on silica gel with hexane–EtOAc 90 : 10; absence of induction determined from optical rotation ($[\alpha]_D$ 0). IR (CH_2Cl_2): 3 054 vs, 2 932 s, 1 696 vs, 1 421 m. ^{1}H NMR (400 MHz, $CDCl_3$): 1.05–2.05 (m, 12 H); 2.26–2.41 (m, 2 H); 2.46–2.54 (m, 1 H); 3.07–3.16 (m, 1 H). ^{13}C NMR (100 MHz): 24.5 (t); 25.4 (t); 26.2 (t); 27.8 (t); 32.5 (t); 35.2 (t); 40.4 (d); 43.3 (t); 54.7 (d); 213.9 (s). MS: 152 (M^+), 123 (22), 111 (100), 95 (94), 67 (98), 55 (50).

Synthesis and Decomposition of 1-Cyclohexylidene-3-diazopropan-2-one (**15**)

Cyclohexylidenepropan-2-one (**14**). This compound was synthesized in 69% yield from cyclohexanone (**6d**) and diethyl (2-oxopropyl)phosphonate (**13**) according to Villeras and Rambaud[27]. ^{1}H NMR (200 MHz, $CDCl_3$): 1.44–1.73 (m, 6 H); 2.08–2.19 (m, 5 H); 2.71–2.82 (m, 2 H); 5.97 (s, 1 H).

Cyclohexylidene-3-diazopropan-2-one (**15**). To sodium hexamethyldisilazane (4.1 ml, 4.00 mmol) in dry THF (5.0 ml) was added dropwise at –78 °C, 1-cyclohexylidenepropan-2-one (**14**; 500 mg, 3.62 mmol) in THF (10 ml) under nitrogen. After 30 min of stirring at –78 °C $CF_3COOCH_2CF_3$ (0.51 ml, 4.3 mmol) was added at once. After 10 min, the temperature was allowed to rise to 0 °C. The mixture was hydrolyzed at –20 °C by addition of 1 M HCl (15 ml) and then extracted with Et_2O (3 × 25 ml). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The resulting oil was dissolved in CH_3CN (12 ml) under argon. Et_3N (0.75 ml, 5.4 mmol), H_2O (0.65 g, 5.4 mmol) and MsN_3 (0.65 g, 5.43 mmol) were added, and the mixture was stirred for 1.0 h. The solvent was partially evaporated, and the remaining solution was dissolved in Et_2O (25 ml) and washed with saturated NaCl (3 × 25 ml). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure and the resulting orange oil was purified by chromatography (silica gel, petroleum ether–Et_2O 80 : 20) to afford **15** (360 mg, 2,19 mmol, 60%). IR ($CHCl_3$): 1 340 s, 1 605 s, 1 642 s, 2 101 vs, 2 935 m. ^{1}H NMR (400 MHz, $CDCl_3$): 1.52–1.74 (m, 6 H); 2.08–2.20 (m, 2 H); 2.79–2.98 (m, 2 H); 5.17 (s br, 1 H); 5.69 (s br, 1 H). ^{13}C NMR (100 MHz): 26.2 (t); 27.9 (t); 28.8 (t); 30.2 (t); 38.0 (t); 118.8 (d); 161.0 (s); 186.0 (s). MS: 164 (12, M^+), 149 (47), 136 (38), 125 (74), 123 (27), 109 (24) 97 (30), 95 (38), 85 (20), 83 (27), 81 (29), 71 (36), 69 (30), 67 (22), 57 (78), 55 (100).

Diazo decomposition of **15**. *1,4,5,6,7,7a-Hexahydro-2H-inden-2-one* (**16**). The reaction was carried out as described above with 100 mg of **15** (0.61 mmol). The catalysts were liberated from the residual solvent by heating under reduced pressure prior to use. The ketone[28] **16** was isolated as colorless liquid after flash chromatography on silica gel with petroleum ether–Et_2O 50 : 50; ee by GC with Lipodex D column, 120 °C, or Betadex 120, 90–150 °C. For yields and ee's, see Table II. IR ($CHCl_3$): 2 936 m, 1 697 s, 1 619 s, 1 220 s. ^{1}H NMR (400 MHz, $CDCl_3$): 1.13 (qd, J = 12.32, 3.44, 1 H); 1.33–1.57 (m, 2 H); 1.82–1.89 (m, 1 H); 1.95–2.07 (m, 2 H); 2.12–2.30 (m, 2 H); 2.53–2.69 (m, 2 H); 2.79–2.86 (m, 1 H); 5.84 (s br, 1 H). ^{13}C NMR (100 MHz): 25.3 (t); 27.1 (t); 31.0 (t); 35.1 (t); 41.8 (t); 42.4 (t); 126.8 (d); 184.6 (s); 209.0 (s).

Synthesis and Decomposition of Alkyl 4-Cyclohexylidene-2-diazo-3-oxobutanoates **24a**–**24e**

Alkyl 4-cyclohexylidene-3-oxobutanoates (**19a**, **19b**). The phosphine oxides **18a**, **18b** were synthesized from ethyl diphenylphosphinite[29] and alkyl 4-bromo-3-oxobutanoate[30] and were condensed with cyclohexanone according to van den Goorbergh[31].

Methyl 4-cyclohexylidene-3-oxobutanoate (**19a**). Yield 67%. IR ($CHCl_3$): 1 731 s, 1 682 m, 1 612 m. ^{1}H NMR (400 MHz, $CDCl_3$): 1.53–1.72 (m, 6 H); 2.17–2.21 (m, 2 H); 2.79–2.85 (m, 2 H); 3.47 (s, 2 H); 3.74 (s, 3 H); 6.01 (s, 1 H). ^{13}C NMR (100 MHz): 15.3 (q); 26.1 (t); 27.9 (t); 28.8 (t); 30.2 (t); 38.2 (t); 65.9 (t); 119.7 (d); 165.6 (s); 168.1 (s); 192.3 (s).

Ethyl 4-cyclohexylidene-3-oxobutanoate (**19b**). Yield 32%. ^{1}H NMR (200 MHz, $CDCl_3$): 1.26 (t, J = 7.1, 3 H); 1.50–1.71 (m, 6 H); 2.13–2.21 (m, 2 H); 2.76–2.84 (m, 2 H); 3.43 (s, 2 H); 4.19 (q, J = 7.1, 2 H); 6.00 (s, 1 H).

Ester Exchange of **18a**. 2,4-Dimethylpentan-3-yl and Dicyclohexylmethyl 4-Cyclohexylidene-3-oxobutanoates **19c** and **19d**

The methyl ester **19a** was heated with the appropriate alcohol in refluxing toluene in the presence of 4-dimethylaminopyridine for 17 and 48 h, respectively[32]. After cooling, the mixture was treated with aqueous NH_4Cl and extracted with EtOAc.

2,4-Dimethylpentan-3-yl 4-cyclohexylidene-3-oxobutanoate (**19c**). Crude **19c** was purified by chromatography (silica gel, petroleum ether–Et_2O 95 : 5). Yield 75%. ^{1}H NMR (400 MHz, $CDCl_3$): 0.87 (d, *J* = 6.9, 6 H); 0.90 (d, *J* = 6.9, 6 H); 1.53–1.71 (m, 6 H); 1.84–2.00 (m, 4 H); 2.01–2.08 (m, 2 H); 3.50 (s, 2 H); 4.63 (t, *J* = 6.4, 1 H); 5.60 (s br, 1 H). ^{13}C NMR (100 MHz): 17.2 (q); 19.5 (q); 21.9 (t); 22.7 (t); 25.4 (t); 28.6 (t); 29.4 (d); 47.9 (t); 52.8 (t); 84.0 (d); 127.2 (d); 131.1 (s); 167.3 (s); 201.5 (s).

Dicyclohexylmethyl 4-cyclohexylidene-3-oxobutanoate (**19d**). Crude **19d** was purified by chromatography (silica gel, hexane–EtOAc 20 : 1). Yield 28%. ^{1}H NMR (200 MHz, $CDCl_3$): 0.81–1.35 (m, 12 H); 1.48–1.81 (m, 18 H); 1.87–2.09 (m, 2 H); 3.14 (s, 2 H); 4.65 (t, *J* = 5.4, 1 H); 5.59 (s br, 1 H).

Alkyl 4-Cyclohexylidene-2-diazo-3-oxobutanoates **20a**–**20d**

Methyl 4-cyclohexylidene-2-diazo-3-oxobutanoate (**20a**). Synthesized *via* trifluoroacetylation (Danheiser procedure) in 86% yield. IR ($CHCl_3$): 3 019 s, 2 138 s, 1 712 m, 1 638 m, 1 438 m. ^{1}H NMR (400 MHz, $CDCl_3$): 1.54–1.75 (m, 6 H); 2.22–2.30 (m, 2 H); 2.83–2.88 (m, 2 H); 3.84 (s, 3 H); 6.81 (s, 1 H). ^{13}C NMR (100 MHz): 26.2 (t); 28.0 (t); 28.9 (t); 30.8 (t); 38.5 (t); 52.1 (q); 117.7 (d); 161.9 (s); 164.1 (s); 182.4 (s). MS: 222 (21, M^+), 162 (58), 135 (23), 134 (92), 133 (30), 123 (89), 107 (24), 106 (56), 105 (45), 95 (31), 94 (24), 93 (22), 92 (42), 91 (96), 81 (30), 79 (71), 78 (58), 77 (38), 67 (52), 65 (27), 59 (27), 55 (100), 53 (57), 51 (27). HR MS: 222.0995 ($C_4H_{14}O_3N_2^+$; calculated 222.1005).

Ethyl 4-cyclohexylidene-2-diazo-3-oxobutanoate (**20b**). Yield 30% (not optimized). IR ($CHCl_3$): 2 933 s, 2 137 s, 1 709 s, 1 638 m, 1 603 w. ^{1}H NMR (400 MHz, $CDCl_3$): 1.31 (t, *J* = 7.1; 3 H); 1.50–1.76 (m, 6 H); 2.19–2.29 (m, 2 H); 2.77–2.89 (m, 2 H); 4.27 (q, *J* = 7.1, 2 H); 6.80 (s, 1 H). ^{13}C NMR (100 MHz): 14.4 (q); 26.3 (t); 28.0 (t); 28.9 (t); 30.8 (t); 38.5 (t); 61.3 (t); 117.9 (d); 161.5 (s);163.9 (s); 182.6 (s). MS: 236 (22, M^+), 162 (58), 135 (21), 134 (83), 133 (29), 123 (100), 107 (25), 106 (47), 105 (36), 95 (28), 94 (22), 93 (29), 92 (37), 91 (70), 81 (30), 79 (56), 78 (43), 77 (28), 67 (43), 55 (83), 53 (47).

(2,4-Dimethylpentan-3-yl) 4-cyclohexylidene-2-diazo-3-oxobutanoate (**20c**). Yield 87% by diazo transfer with MsN_3 (procedure of Taber[13]). IR ($CHCl_3$): 3 020 vs, 2 136 m, 1 708 s, 1 640 m, 1 293 m. ^{1}H NMR (200 MHz, $CDCl_3$): 0.87 (d, *J* = 6.7, 6 H); 0.90 (d, *J* = 6.7, 6 H); 1.45–1.75 (m, 6 H); 1.81–2.05 (m, 6 H); 4.69 (t, *J* = 6.3, 1 H); 5.52 (s br, 1 H).

Dicyclohexylmethyl 4-cyclohexylidene-2-diazo-3-oxobutanoate (**20d**). Yield 89% *via* diazo transfer[13] with MsN_3. IR ($CHCl_3$): 2 932 s, 2 135 s, 1 707 s, 1 640 m, 1 448 m. ^{1}H NMR (200 MHz, $CDCl_3$): 0.85–1.32 (m, 12 H); 1.49–1.81 (m, 18 H); 1.92–2.05 (m, 2 H); 4.73 (t, *J* = 5.4, 1 H); 5.52 (s br, 1 H).

Alkyl 4-Cyclohexylidene-2-diazo-3-oxobutanoates **20a**, **20b**, **20e** *via* **23a**, **23b, 23e**

Alkyl 4-(1-Hydroxycyclohexyl)-3-oxobutanoates **22**. *General Procedure*[33]

The appropriate alkyl acetoacetate (2.70 mmol) was added dropwise at 0 °C to NaH (2.90 mmol) in THF (10 ml). The mixture was stirred for 20 min, and the temperature was allowed to rise to 20 °C. It was again cooled to 0 °C and BuLi (2.8 mmol) was added dropwise, and the mixture was stirred for 15 min. To this solution of alkyl acetoacetate dianion (**21a**, **21b**, **21e**) was added cyclohexanone (**6d**; 3.80 mmol) in THF (10 ml), and the mixture was stirred at 0 °C for 30 min. After stirring for 12 h at 20 °C, the reaction mixture was decomposed with aqueous HCl while cooling. It was extracted (Et_2O), dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was purifed by column chromatography.

Methyl 4-(1-hydroxycyclohexyl)-3-oxobutanoate (**22a**). Yield 66%. Purification on silica gel with petroleum ether–ether 70 : 30. IR ($CHCl_3$): 3 542 br, 3 019 s, 2 861 w, 1 745 s, 1 709 s, 1 653 w, 1 628 w, 1 228 vs. ^{1}H NMR (400 MHz, $CDCl_3$): 1.19–1.73 (m, 10 H); 2.71 (s, 2 H); 3.14 (s br, 1 H); 3.49 (s, 2 H); 3.75 (s, 3 H). ^{13}C NMR (100 MHz): 21.9 (t); 25.6 (t); 37.5 (t); 50.6 (t); 52.4 (t); 52.8 (t); 70.9 (s); 167.3 (s); 204.1 (s). MS: 214 (11, M^+), 196 (20), 171 (28), 139 (36), 126 (21), 123 (26), 122 (51), 116 (100), 101 (45), 99 (88), 98 (26), 97 (28), 95 (20), 84 (42), 81 (84), 74 (21), 70 (25), 69 (49), 59 (41), 57 (25), 56 (21), 55 (74). HR MS: 214.1212 ($C_{11}H_{18}O_4^+$; calculated 214.1205).

Ethyl 4-(1-hydroxycyclohexyl)-3-oxobutanoate (**22b**). Yield 28%. Purification on silica gel with petroleum ether–ether 70 : 30. IR ($CHCl_3$): 3 531 br, 2 921 s, 1 736 s, 1 703 s, 1 650 m. ^{1}H NMR (200 MHz, $CDCl_3$): 1.11–1.18 (m, 10 H); 1.29 (t, J = 7.2, 3 H); 2.69 (s, 2 H); 3.21 (s br, 1 H); 3.45 (s, 2 H); 4.18 (q, J = 7.2, 2 H). ^{13}C NMR (100 MHz): 14.1 (q); 21.9 (t); 25.6 (t); 37.6 (t); 50.9 (t); 52.8 (t); 61.5 (t); 70.9 (s); 166.9 (s); 204.2 (s). MS: 228 (11, M^+), 210 (20), 185 (27), 139 (44), 130 (100), 126 (28), 123 (36), 122 (55), 115 (31), 99 (83), 98 (32), 97 (42), 95 (24), 88 (33), 85 (36), 84 (68), 81 (94), 71 (24), 70 (31), 69 (58), 57 (69), 56 (31), 55 (43), 55 (81).

(–)-Menthyl 4-(1-hydroxycyclohexyl)-3-oxobutanoate (**22e**). Yield 64% from (–)-menthyl 3-oxobutanoate[34]. Purification on silica gel with petroleum ether–ether 95 : 5. ^{1}H NMR (400 MHz, $CDCl_3$): 0.77 (d, J = 6.9, 3 H); 0.90 (d, J = 7.4, 3 H); 0.92 (d, J = 6.9, 3 H); 0.95–1.73 (m, 17 H); 1.81–1.92 (m, 1 H); 1.98–2.06 (m, 1 H); 2.71 (s, 2 H); 3.24 (s br, 1 H); 3.45 (s, 2 H); 4.70 (m, 1 H). ^{13}C NMR (100 MHz): 16.2 (q); 20.7 (q); 21.9 (t); 22.0 (q); 23.3 (t); 25.6 (t); 26.2 (d); 31.4 (d); 34.1 (t); 37.5 (t); 40.7 (t); 46.9 (d); 51.2 (t); 52.8 (t); 70.8 (s); 75.7 (d); 166.5 (s); 204.4 (s).

Alkyl 4-(1-Hydroxycyclohexyl)-2-diazo-3-oxobutanoates **23**

The diazo transfer was effected according to the general procedure of Taber[32].

Methyl 4-(1-hydroxycyclohexyl)-2-diazo-3-oxobutanoate (**23a**). Yield 89%. IR ($CHCl_3$): 3 520 br, 2 936 s, 2 139 s, 1 717 s, 1 638 m. ^{1}H NMR (400 MHz, $CDCl_3$): 1.34–1.55 (m, 6 H); 1.56–1.72 (m, 4 H); 3.03 (s, 2 H); 3.45 (m, 1 H); 3.82 (s, 3 H). ^{13}C NMR (100 MHz): 21.9 (t); 25.6 (t); 37.8 (t); 49.2 (t); 52.2 (q); 71.5 (s); 161.9 (s); 192.9 (s). MS: 240 (3, M^+), 169 (52), 142 (34), 137 (27), 123 (20), 109 (20), 99 (32), 97 (32), 95 (24), 81 (69), 55 (100), 54 (44), 53 (20). HR MS: 240.1107 ($C_{11}H_{16}O_4N_2^+$; calculated 240.1110).

Ethyl 4-(1-hydroxycyclohexyl)-2-diazo-3-oxobutanoate (**23b**). Yield 68%; yellow oil. IR ($CHCl_3$): 3 520 br, 2 936 s, 2 140 s, 1 713 s, 1 637 m. ^{1}H NMR (400 MHz, $CDCl_3$): 1.31 (t, J =

7.2, 3 H); 1.58–1.72 (m, 4 H); 3.03 (s, 2 H); 3.50 (m, 1 H); 4.28 (q, *J* = 7.2, 2 H). ^{13}C NMR (100 MHz): 14.2 (q); 22.0 (t); 25.7 (t); 37.9 (t); 49.3 (t); 61.6 (t); 71.5 (s); 161.6 (s); 193.1 (s). MS: 254 (6, M^+), 183 (47), 156 (34), 137 (41), 123 (29), 99 (49), 97 (42), 95 (37), 81 (100), 71 (20), 69 (25), 67 (26), 57 (24), 55 (86), 54 (54), 53 (23), 45 (24).

(–)-Menthyl 4-(1-hydroxycyclohexyl)-2-diazo-3-propanoate (**23e**). Yield 98%; pale yellow oil. IR ($CHCl_3$): 3 510 br, 2 932 s, 2 139 s, 1 705 s, 1 635 m, 1 456 w. ^{1}H NMR (400 MHz, $CDCl_3$): 0.80 (d, *J* = 6.9, 3 H); 0.91 (d, *J* = 7, 4, 3 H); 0.93 (d, *J* = 6.9, 3 H); 1.01–1.77 (m, 17 H); 1.78–1.92 (m, 1 H); 2.03–2.11 (m, 1 H); 3.06 (AB, n_a = 3.075, n_b = 3.047, *J* = 15.8, 2 H); 3.63 (s, br, 1 H); 4.82 (td, *J* = 10.8, 4.4, 1 H). ^{13}C NMR (100 MHz): 16.5 (q); 20.7 (q); 21.9 (q); 22.0 (t); 23.6 (t); 25.7 (t); 26.6 (q); 31.5 (d); 34.1 (t); 37.9 (t); 41.1 (t); 47.0 (d); 49.3 (t); 71.5 (s); 76.2 (d); 77.6 (s); 161.3 (s); 193.3 (s).

Alkyl 4-Cyclohexylidene-2-diazo-3-oxobutanoates **20a**, **20b**, **20e** *via Dehydration of* **23a**, **23b**, **23e**. *General Procedure*[35]

To the diazo compound **23** (1.50 mmol) in pyridine (10 ml), $POCl_3$ (0.50 ml, 5.5 mmol) was added at 0 °C under argon. After 6 h of stirring at 0 °C, the mixture was stirred during 12 h at 20 °C. It was poured on ice/water (50 ml) and extracted with hexane. The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, petroleum ether–ether 95 : 5). Yield: **20a** 50%; **20b** 68%; yellow oils. For data of **20a**–**20d** see above.

(–)-Menthyl 4-cyclohexylidene-2-diazo-3-oxobutanoate (**20e**). Yield 66%. IR ($CHCl_3$): 2 930 s, 2 136 s, 1 704 s, 1 640 s. ^{1}H NMR (400 MHz, $CDCl_3$): 0.80 (d, *J* = 6.9, 3 H); 0.85–0.99 (m, 6 H); 1.00–1.78 (m, 17 H); 1.81–1.92 (m, 1 H); 1.96–2.12 (m, 1 H); 4.76–4.88 (m, 1 H); 5.56 (s, 1 H). ^{13}C NMR (100 MHz): 16.5 (q); 20.7 (q); 22.0 (q); 22.1 (t); 23.6 (t); 25.4 (t); 26.6 (d); 28.8 (t); 31.5 (d); 34.1 (t); 38.5 (t); 41.2 (t); 47.0 (d); 75.7 (d); 125.7 (d); 131.6 (s); 161.2 (s); 191.0 (s). MS: 346 (1, M^+), 208 (28), 163 (21), 162 (46), 138 (25), 134 (21), 95 (49), 83 (100), 81 (29), 69 (46), 57 (32), 55 (57).

Decomposition of Diazo Ketoesters **20a**–**20e**. Alkyl 2-Oxo-1,4,5,6,7,7a-hexahydro-2*H*-indene-1-carboxylates **24a**–**24e**. General Procedure

For procedure see above: diazo decomposition of diazocycloalkanones **8**. For results with various catalysts, see Table III.

Methyl 2-oxo-1,4,5,6,7,7a-hexahydro-2H-indene-1-carboxylate (**24a**). Yield 50–75%. IR ($CHCl_3$): 2 936 m, 1 710 s, 1 623 w, 1 364 m. ^{1}H NMR (200 MHz, $CDCl_3$): 1.07–1.68 (m, 3 H); 1.80–2.09 (m, 2 H); 2.16–2.42 (m, 2 H); 2.78–2.90 (m, 2 H); 2.98–3.11 (m, 2 H); 3.75 (s, 3 H); 5.80 (s, 1 H). ^{13}C NMR (100 MHz): 24.9 (t); 26.5 (t); 30.8 (t); 34.0 (t), 45.8 (d); 52 5 (q); 59 1 (d); 124.9 (d); 169.5 (s); 184.2 (s); 201.1 (s).

Ethyl 2-oxo-1,4,5,6,7,7a-hexahydro-2H-indene-1-carboxylate[36] (**24b**). ^{1}H NMR (400 MHz, $CDCl_3$): 1.26–1.68 (m, 7 H); 1.84–1.95 (m, 1 H); 1.96–2.11 (m, 1 H); 2.21–2.39 (m, 2 H); 2.81–2.93 (m, 1 H); 2.96–3.05 (m, 2 H); 4.15–4.31 (q, *J* = 7.3, 2 H); 5.82 (s, 1 H). ^{13}C NMR (100 MHz): 14.4 (q); 25.3 (t); 26.8 (t); 31.1 (t); 34.3 (t); 46.1 (d); 59.6 (d); 61.8 (t); 125.2 (d); 169.4 (s); 184.3 (s); 201.5 (s).

(2,4-Dimethylpentan-3-yl) 2-oxo-1,4,5,6,7,7a-hexahydro-2H-indene-1-carboxylate (**24c**). Yield 10–20%. IR ($CHCl_3$): 2 939 m, 1 724 s, 1 701 s, 1 623 s, 1 464 w. ^{1}H NMR (400 MHz, $CDCl_3$): 0.83–0.96 (m, 12 H); 1.15–1.63 (m, 3 H); 1.84–1.98 (m, 3 H); 2.00–2.07 (m, 1 H); 2.21–2.37 (m, 2 H); 2.81–2.88 (m, 1 H); 3.01–3.09 (m, 2 H); 4.60 (t, *J* = 6.2, 1 H); 5.82 (s, 1 H).

^{13}C NMR (100 MHz): 17.1 (q); 17.3 (q); 19.5 (q); 25.1 (t); 25.1 (t); 26.6 (t); 29.4 (d); 30.8 (t); 34.0 (t); 46.3 (d); 59.7 (d); 83.9 (d); 125.2 (d); 183.5 (s); 201.3 (s).

Dicyclohexylmethyl 2-oxo-1,4,5,6,7,7a-hexahydro-2H-indene-1-carboxylate (**24d**). Yield 15–79%. ^{1}H NMR (400 MHz, $CDCl_3$): 0.71–2.08 (m, 27 H); 2.17–2.39 (m, 2 H); 2.80–2.87 (m, 1 H); 2.98–3.03 (m, 2 H); 4.68 (t, *J* = 5.8, 1 H); 5.82 (s, 1 H). ^{13}C NMR (100 MHz): 25.1 (t); 26.0 (t); 26.1 (t); 26.2 (t); 26.3 (t); 26.4 (t); 26.6 (t); 27.2 (t); 27.6 (t); 29.80 (t); 20.82 (t); 30.9 (t); 34.1 (t); 38.3 (d); 38.4 (d); 46.2 (d); 59.6 (d); 82.7 (d); 125.1 (d); 169.2 (s); 183.6 (s); 201.3 (s).

(–)-Menthyl 2-oxo-1,4,5,6,7,7a-hexahydro-2H-indene-1-carboxylate (**24e**). Yield 0–50%. ^{1}H NMR (400 MHz, $CDCl_3$): 0.76 (d, *J* = 6.9, 3 H); 0.79–1.72 (m, 16 H); 1.80–2.14 (m, 4 H); 2.21–2.38 (m, 2 H); 2.81–2.89 (m, 1 H); 2.96–3.06 (m, 2 H); 4.68–4.77 (m, 1 H); 5.80 (s br, 1 H). ^{13}C NMR (100 MHz): 16.2 (q); 20.7 (q); 21.9 (q); 23.4 (t); 25.1 (t); 25.8 (d); 26.6 (t); 30.9 (t); 31.5 (d); 34.0 (t); 34.2 (t); 40.8 (t); 46.0 (d); 46.9 (d); 59.6 (d); 75.5 (d); 125.0 (d); 168.8 (s); 183.6 (s); 201.2 (s).

Synthesis and Decomposition of 8-Diazocyclooct-2-en-1-one[37] (**26**)

Diazocyclooct-2-en-1-one (**26**)

Cyclooct-2-en-1-one[38] (**25**) was converted in 62% yield to **26** by the general procedure of Danheiser (see above). IR ($CHCl_3$): 3 016 s, 2 934 m, 2 085 s, 1 636 w, 1 578 m. ^{1}H NMR (200 MHz, $CDCl_3$): 1.68–1.80 (m, 4 H); 2.26–2.36 (m, 2 H); 2.55–2.62 (m, 2 H); 2.55–2.62 (m, 2 H); 5.76–5.84 (dt, *J* = 12.4, 1.5, 1 H); 6.07–6.20 (dt, *J* = 12.5, 6.3, 1 H). ^{13}C NMR (100 MHz): 22.5 (t); 23.9 (t); 28.2 (t); 29.7 (t); 126.7 (d); 139.4 (d); 190.5 (s).

Diazo Decomposition of **26**.
cis-Bicyclo[3.3.0]oct-3-en-2-one (4,5,6,6a-Tetrahydropentalen-3(3aH)-one (**27**))

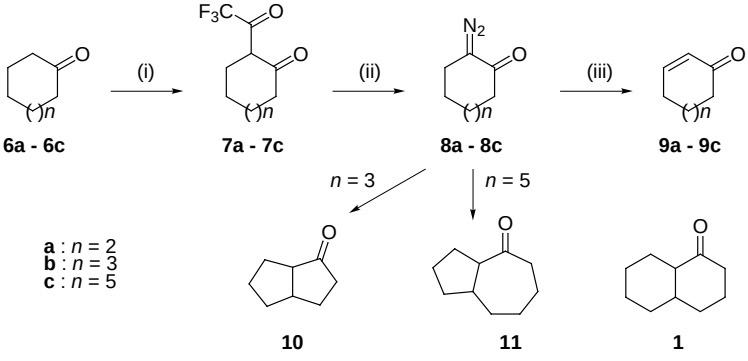
The reactions were carried out under the conditions described above: see diazo decomposition of diazocycloalkanones **8**. For results, see Table IV. The ee was determined by GC with Lipodex E column, 90 °C. Data of **27**: IR ($CHCl_3$): 3 013 m, 2 958 m, 2 870 w, 1 700 s, 1 584 m, 1 450 w, 1 348 m, 1 219 m. ^{1}H NMR (400 MHz, $CDCl_3$): 1.19–1.33 (m, 1 H); 1.57–1.77 (m, 4 H); 1.87–1.94 (m, 1 H); 2.66–2.73 (m, 1 H); 3.32–3.39 (m, 1 H); 6.14 (dd, *J* = 5.3, 1.8, 1 H); 7.53 (dd, *J* = 5.5, 3.1, 1 H);. ^{13}C NMR (100 MHz): 23.5 (t); 29.3 (t); 30.1 (t); 46.6 (d); 49.6 (d); 134.5 (d); 167.4 (d); 213.5 (s).

RESULTS AND DISCUSSION

Transannular Insertion of 2-Diazocycloalkan-1-ones **8**

The 2-diazocycloalkan-1-ones **8a**–**8c** were prepared from the corresponding ketones **6** either *via* formylation followed by deformylating diazo transfer with tosyl azide (TsN_3) in the presence of Et_3N, as described[20–22] or *via* trifluoroacetylation and subsequent diazo transfer with MsN_3 (Scheme 1), without isolation of the intermediates **7** (method of Danheiser[23]). The Danheiser procedure was superior.

The decomposition of 2-diazocycloheptan-1-one (**8a**) with $[Rh_2(OAc)_4]$ or $[Cu(acac)_2]$ afforded an untractable mixture of products in which cyclohept-2-en-1-one (**9a**) could be detected spectroscopically. In contrast, the higher homologue, 2-diazocyclooctan-1-one (**8b**) reacted with $[Rh_2(OAc)_4]$ almost quantitatively *via* transannular insertion to *cis*-bicyclo[3.3.0]octan-2-one (**10**) (Table I). Other Rh(II) catalysts exhibited similar selectivity for transannular C–H insertion, and the potentially competitive 1,2-hydrogen migration leading to **9b** was not observed with **8b**. Even Cu catalysts, which are not particularly prone to promote C–H insertions, provided the bicyclic ketone **10** in appreciable yields. The Cu(I) catalysts were, however, not sufficiently reactive and some unreacted diazoketone **8b** was recovered. Decomposition of **8c** with Cu(I) and Rh(II) catalysts afforded *cis*-bicyclo-[5.3.0]decan-2-one (**11**) in high yield, rather than the expected bicyclo-[4.4.0]decan-2-one (**12**) which is reportedly formed upon decomposition of **8c** with CuO. Note that in the Cu(II)-catalyzed diazo decompositions, the catalytically acive species is a Cu(I) compound which is formed by reduction of Cu(II) by the diazo compound.



(i) LiHMDS (1.1 eq.), $CF_3CO_2CH_2CF_3$ (1.2 eq.), -78 °C; (ii) Et_3N (1.5 eq.), H_2O (1 eq.), MsN_3 (1.5 eq.), 25 °C; (iii) Rh(II), 5%, 25 °C

SCHEME 1

The decomposition of 2-diazocycloalkan-1-ones can proceed either *via* 1,2-hydrogen migration to cycloalkenones or *via* transannular C–H insertion. In free carbenes, 1,2-hydrogen migration is a very fast process with activation energies in the range of *ca* 5 kcal/mol (ref.[39]). With metal carbenoids, however, the selectivity is different, and cyclopropanations as well as intramolecular C–H insertions can be competitive with hydrogen migration. Intramolecular insertions occurring in preference over hydrogen

migration from an adjacent CH_3 group of metal carbenoids have been reported[40]. Olefin formation becomes predominant if the adjacent group is CH_2 (ref.[41]). In our series of diazo ketones hydrogen migration predominates with diazocycloheptanone (**8a**), presumably owing to the strain in the putative transannular insertion product (bicyclo[3.2.0]heptan-2-one), but is virtually absent with **8b** and **8c**. The still higher diazocycloalkanones were not investigated owing to their known tendency to suffer hydrogen migration.

The metal-catalyzed decomposition of 2-diazocycloalkan-1-ones **8** has been investigated in the past[20]. Cycloalkenones **9** were formed with Ag_2O, instead of ring-contracted products derived from the expected Wolff rearrangement. Decomposition with CuO, in turn, resulted in mixtures of products of transannular insertion together with cycloalkenones. Thus 2-diazocyclodecan-1-one (**8c**) afforded *cis*-bicyclo[4.4.0]decan-2-one (**12**; 13%) and cyclodec-2-en-1-one (**9c**; 39%) upon exposure to CuO.

TABLE I
Transannular insertion of 2-diazocycloalkan-1-ones[a] **6**

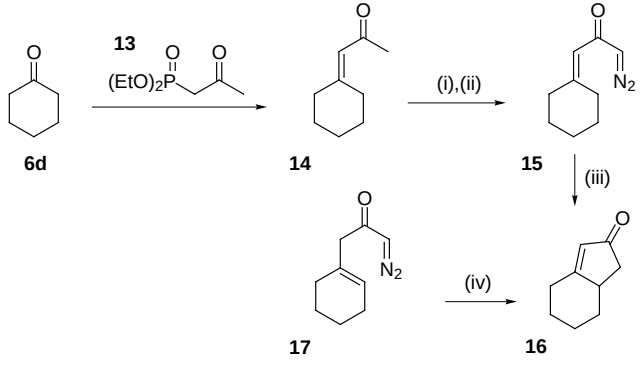
Compound	Catalyst	Solvent	Product	Yield, %	ee, %
8b	$[Rh_2(OAc)_4]$ (**1a**)	CH_2Cl_2	**10**	96	–
8b	$[Rh_2\{(S)\text{-meba}\}_4]$ (**1b**)	CH_2Cl_2	**10**	86	12
8b	$[Rh_2\{(5S)\text{-mepy}\}_4]$ (**2a**)	CH_2Cl_2	**10**	71	0
8b	$[Rh_2\{(5S)\text{-mepy}\}_4]$ (**2a**)	pentane	**10**	40	10
8b	$[Rh_2\{(4R)\text{-mppim}\}_4]$ (**2b**)	CH_2Cl_2	**10**	90	9
8b	$[Rh_2\{(R)\text{-(–)-bnp}\}_4]$ (**4a**)	CH_2Cl_2	**10**	60	9
8b	[Cu-semicorrine] (**5b**)	CH_2Cl_2	**10**	50[b]	7
8b	[Cu{(*R*)-isoPr-pybox}] (**5c**)	CH_2Cl_2	**10**	37[c]	19
8c	$[Cu(acac)_2]$ (**5a**)	CH_2Cl_2	**11**	56	–
8c	$[Rh_2(OAc)_4]$ (**1a**)	CH_2Cl_2	**11**	83	–
8c	$[Rh_2\{(2S)\text{-mepy}\}_4]$ (**1a**)	CH_2Cl_2	**11**	82	0
8c	$[Rh_2\{(4R)\text{-mppim}\}_4]$ (**2b**)	CH_2Cl_2	**11**	60	0
8c	$[Rh_2\{(R)\text{-(–)-bnp}\}_4]$ (**3a**)	CH_2Cl_2	**11**	50	0
8c	[Cu-semicorrine] (**4b**)	DCE[d]	**11**	30	0

[a] Conditions: Syringe pump addition of **8** (1.00 mmol) in CH_2Cl_2 to the catalyst (0.02 mmol) in CH_2Cl_2 at room temperature (23 °C). [b] Determined by GC, Lipodex E column. [c] Unreacted diazo ketone recovered. [d] DCE, dichloroethane, 80 °C.

Diazo decomposition by several chiral Rh(II) catalysts, which have shown exceptional enantioselectivity in CH insertions of diazo esters, afforded satisfactory yields of **10**, but were disappointing with respect to enantioselectivity with ee's around 10%. The chiral Cu(I) catalysts **5b** and **5c** produced enantioselectivities of 7 and 19%, respectively. In addition to the catalysts mentioned in Table I, several other Rh(II) prolinates and some of the Cu(I)–Schiff base complexes of O'Connar[42] were also examined, but no significant improvement could be achieved. A selection of chiral Rh(II) and Cu(I) catalysts was also tested with **8c**. However, these reactions proceeded without enantioselectivity.

Intramolecular Insertion of 1-Cyclohexylidene-3-diazopropan-2-one (**15**) *and 4-Cyclohexylidene-2-diazo-3-oxobutanoates* **23a**–**23e**

1-Cyclohexylidenepropan-2-one (**14**) was synthesized from cyclohexanone (**6d**) and diethyl (2-oxopropyl)phosphonate (**13**) in the presence of K_2CO_3, and transformed to the diazo ketone **15** by the procedure of Danheiser[23]. Reaction of **15** with $[Rh_2(OAc)_4]$ under the usual conditions furnished the cyclized product 1,4,5,6,7,7a-hexahydro-2*H*-inden-2-one (**16**) in 60% yield. This yield is in the range expected for intramolecular insertions of diazo ketones into allylic C–H bonds[43] and compares favorably with that reported for cyclization of the isomeric diazo ketone **17** to **16** with $[Rh_2(OAc)_4]$ (26%) and $[Cu(OTf)_2]$ (59%, ref.[44]) or with $BF_3{\cdot}Et_2O$ (50%, ref.[45]). The yields decreased slightly with the asymmetric catalysts. Asymmetric induction was very modest with all of the catalysts investigated. The highest enantioselecitivty (18%) resulted upon exposure of **15** to $[Rh_2\{(R)\text{-}(-)\text{-bnp}\}_4]$ (**4a**).



(i) NaHMDS (1.1 eq.), $CF_3CO_2CH_2CF_3$ (1.2 eq.), -78 °C; (ii) Et_3N (1.5 eq.), H_2O (1 eq.), MsN_3 (1.5 eq.), 25 °C; (iii) Rh(II), 5%, 25 °C; (iv) $[Rh_2(OAc)_4]$ or $[Cu(OTf)_2]$ or BF_3Et_2O

SCHEME 2

The unsaturated diazo ketoesters **20a**, **20b** were synthesized by condensation of cyclohexanone with the phosphine oxides[29] **18a**, **18b** to afford the unsaturated esters **19a**, **19b** in 67 and 32% yields, respectively[31]. The 2,4-dimethylpentan-3-yl and dicyclohexylmethyl esters **19c**, **19d**, in turn, were synthesized *via* ester exchange of **19a** with the respective alcohols in the presence of DMAP in refluxing toluene[32]. Diazo transfer according to Danheiser[23] proceeded in 80–90% yield to the diazo ketoester **20**. Alternatively, diazo esters **20** were accessible *via* condensation of cyclohexanone (**6d**) with alkyl dilithioacetoacetate (**21**). Since dehydration of the intermediate alcohol **22** to **19** could not be achieved[33,46], the sequence of steps was inverted, *i.e.*, diazo transfer was effected prior to dehydration. Diazo transfer with **22** was carried out according to Taber[47], and dehydration of the diazo alcohol **23** proceeded smoothly to **20** under the conditions reported by Padwa ($POCl_3$/pyridine)[48]. This approach was used for the preparation of **20a**, **20b**, and **20e**.

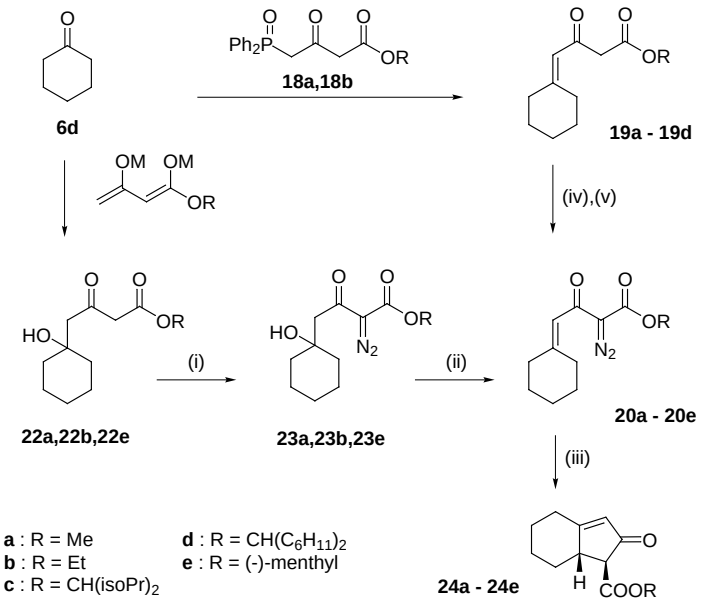
The intramolecular insertion of the methyl and ethyl esters **20a**, **20b** proceeded in 80–85% yield to the known hexahydro-2*H*-indene derivative **24a**, **24b** (*cis*-isomer). The yields with the sterically more crowded esters significantly decreased to 30–50%. These reactions were accompanied by products of carbenoid insertions into the C–H bonds of the alcohol moiety, a well-known phenomenon in reactions of menthyl diazoacetates[49]. Owing to their insufficient activity, the chiral Rh(II) carboxamidate catalysts were not generally used for diazo decomposition in this series, but were replaced by catalysts based on optically active carboxylic acids and binaphthol phosphates. Yields of the desired insertion products were considerably lower

TABLE II
Intramolecular C–H insertion[a] of 1-cyclohexylidene-3-diazopropan-2-one (**15**)

Catalyst	**16**, yield, %	ee, %
$[Rh_2(OAc)_4]$ (**1a**)	60	–
$[Rh_2\{(S)$-(–)-ptpa$\}_4]$ (**1e**)	40	3
$[Rh_2\{(2S)$-mepy$\}_4]$ (**2a**)	24	5
$[Rh_2\{(S)$-tbps$\}_4]$ (**3a**)	48	5
$[Rh_2\{(S)$-naph-pro$\}_4]$ (**3d**)	36	3
$[Rh_2\{(S)$-(–)-bnp$\}_4]$ (**4a**)	42	18

[a] For conditions, see Table I.

than with $[Rh_2(OAc)_4]$ and enantioselectivities varied from 0 to 23%. Representative examples are summarized in Table III.

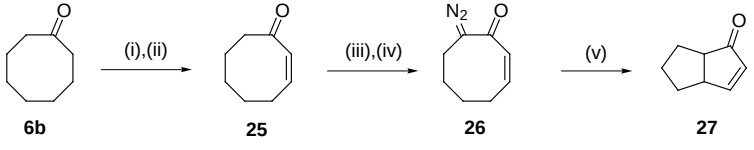


(i) Et_3N (2 eq.), MsN_3 (1.1 eq.), 25 °C; (ii) Pyridine, $POCl_3$ (4 eq.), 0 °C, (iii) Rh(II), 5%, 25 °C; (iv) LiHMDS (1.1 eq.), $CF_3CO_2CH_2CF_3$ (1.2 eq.), -78 °C; (v) Et_3N (1.5 eq.), H_2O (1 eq.), MsN_3 (1.5 eq.), 25 °C

SCHEME 3

Transannular Insertion of 8-Diazocyclooct-2-en-1-one (**26**)

8-Diazocyclooct-2-en-1-one (**26**) was synthesized by diazo transfer with cycloct-2-en-1-one (**25**) according to Danheiser[23]. Exposure of **26** to $[Rh_2(OAc)_4]$ afforded *cis*-bicyclo[3.3.0]oct-3-en-2-one (4,5,6,6a-tetrahydropentalen-3(3a*H*)-one) (**27**) in 60% yield (Table IV). With the chiral Rh(II) carboxamidate catalysts the yields were somewhat lower, but no significant level of enantioselectivity could be achieved.



(i) Br_2 (1 eq.), $HOCH_2CH_2OH$ (1 eq.). 5-10 °C, MeOH (2 eq.), reflux 72 h; (ii) H_2SO_4 5%; (iii) LiHMDS (1.1 eq.), $CF_3CO_2CH_2CF_3$ (1.2 eq.), -78 °C; (iv) Et_3N (1.5 eq.), H_2O (1 eq.), MsN_3 (1.5 eq.), 25 °C; (v) Rh(II) or Cu(I), 5%, 25 °C

SCHEME 4

Enantioselectivity in C–H Insertions of Diazo Ketones

The absence of enantioselectivity in transition metal-catalyzed decompositions of diazo ketones is a well known phenomenon. Doyle has proposed an interpretation for the intramolecular cyclopropanation of diazo esters as compared to that of the analogous diazo ketones in the presence of Rh(II) carboxamidates[4c]: In the diazo esters the carbenoid reaction occurs from a conformation **28a** in which the carbonyl group of the metal-complexed carbene points away from the plane defined by the ligands of the metal. In

TABLE III
Intramolecular insertion[a] of alkyl 4-cyclohexylidene-2-diazo-3-oxobutanoates **19a–19e**

Compound	R	Catalyst	**24**, yield, %	ee, de, %
20a	Me	$[Rh_2(OAc)_4]$ (**1a**)	85	–
20a	Me	$[Rh_2\{(+)\text{-dmanth}\}_4]$ (**1d**)	65	13
20a	Me	$[Rh_2\{(S)\text{-tbps}\}_4]$ (**3a**)	65	13
20a	Me	$[Rh_2\{(S)\text{-tipps-pro}\}_4]$ (**3b**)	81	8
20a	Me	$[Rh_2\{(S)\text{-tbbz-pro}\}_4]$ (**3c**)	95	7
20a	Me	$[Rh_2\{(R)\text{-Me}_2\text{bnhp}\}_4]$ (**4b**)	66	12
20b	Et	$[Rh_2(OAc)_4]$ (**1a**)	80	–
20b	Et	$[Rh_2\{(5S)\text{-mepy}\}_4]$ (**2a**)	20	5
20b	Et	$[Rh_2\{(R)\text{-(–)-bnp}\}_4]$ (**4a**)	70	10
20c	$(isoPr)_2CH$	$[Rh_2(OAc)_4]$ (**1a**)	40	–
20c	$(isoPr)_2CH$	$[Rh_2\{(S)\text{-(–)-ptpa}\}_4]$ (**1e**)	20	0
20c	$(isoPr)_2CH$	$[Rh_2\{(S)\text{-tbps}\}_4]$ (**3a**)	12	2
20d	$(C_6H_{11})_2CH$	$[Rh_2(OAc)_4]$ (**1a**)	31	–
20d	$(C_6H_{11})_2CH$	$[Rh_2(+)\text{-mpmt}\}_4]$ (**1c**)	15	?
20d	$(C_6H_{11})_2CH$	$[Rh_2\{(S)\text{-(–)-ptpa}\}_4]$ (**1e**)	30	3
20d	$(C_6H_{11})_2CH$	$[Rh_2\{(R)\text{-(–)-bnp}\}_4]$ (**4a**)	32	0
20e	(–)-Menthyl	$[Rh_2(OAc)_4]$ (**1a**)	50	–
20e	(–)-Menthyl	$[Rh_2\{(R)\text{-meba}\}_4]$ (**1b**)	40	16
20e	(–)-Menthyl	$[Rh_2\{(S)\text{-ptleu}\}_4]$ (**1f**)	30	8
20e	(–)-Menthyl	$[Rh_2\{(S)\text{-tbps}\}_4]$ (**3a**)	35	0

[a] For conditions, see Table I.

this conformation, the chain containing the double bond is in close proximity of the chiral ligands. In contrast, in the case of diazo ketones, the carbonyl group of the product determining conformation **29b** might be oriented towards the plane of the ligands. In this conformation, the hydrocarbon chain containing the reacting double bond is turned away from the chiral ligands, the interactions with the ligands are reduced and enantiocontrol decreases. A similar situation could prevail for intramolecular insertions. However, it is not clear why carbenoids derived from diazo esters prefer conformation **28a** and carbenoids derived from diazo ketones should occur preferentially in conformation **29b**.

Doyle[50] and Hashimoto[3d,11] have provided models for asymmetric induction for intramolecular insertions of diazo esters and diazo amides with Rh(II) carboxamidate and carboxylate catalysts, respectively. The X-ray structures of their catalysts exhibit some, though limited structural similarities around the coordination site of the carbene. In both cases, two adjacent quadrants are essentially occupied by the chiral ligands. In contrast, the chiral Rh(II) binaphthol phosphate and chiral Cu(I) catalysts have c_2 symmetry and, although all of these catalysts may produce enantioselectivity with diazo esters and diazo amides, they are unselective with diazo ketones. Since catalysts as different as c_2-symmetric Cu(I)–semicorrin complex **5b**, the Cu(I)–pybox catalyst **5c**, the Rh(II) carboxylates, Rh(II) carboxamidates, and Rh(II) binaphthol phosphates fail with respect to enantioselectivity with diazo ketones, it appears that this failure might arise from the diazo ketones or the carbenes derived therefrom rather than from the catalysts. The carbenes derived from diazo ketones differ from the ester and amide counterparts with respect to two properties: resonance interactions between the heteroatoms and the carbonyl group in oxycarbonyl

TABLE IV
Transannular insertion[a] of 8-diazocyclooct-2-en-1-one (**26**)

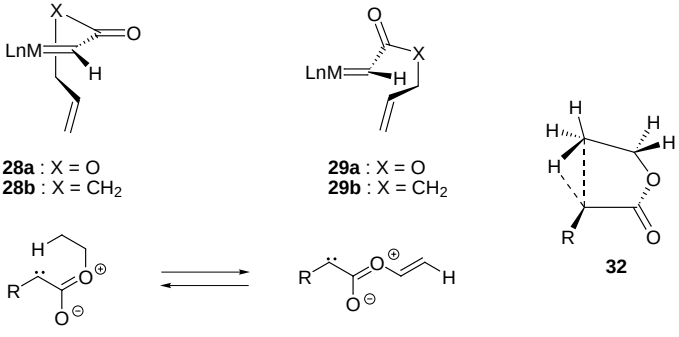
Catalyst	Solvent, *T*, °C	**27**, yield, %	ee, %
$[Rh_2(OAc)_4]$ (**1a**)	CH_2Cl_2, 23	60	–
$[Rh_2\{(2S)$-mepy$\}_4]$ (**2a**)	DCE, 80	30	5
$[Rh_2\{(4R)$-mppim$\}_4]$ (**2b**)	CH_2Cl_2, 23	52	10
$[Rh_2\{(R)$-(–)-bnp$\}_4]$ (**4a**)	CH_2Cl_2, 23	55	5

[a] For conditions, see Table I.

carbenes and amides, respectively, will result in a decrease in positive charge at the carbonyl group and, thereby, render the carbene less electron-deficient. The selectivity of the carbene decreases with increasing electron deficiency. The question has not been investigated systematically with diazo ketones, but it is known that the Hammett ρ-value for intramolecular benzylic insertion of diazo acetoacetates decreases from –1.39 with $[Rh_2(acam)_4]$ (acam = acetamide) to –1.26 with $[Rh_2(OAc)_4]$ and –0.66 with $[Rh_2(pfb)_4]$ (pfb = perfluorobutyrate)[51]. Note that in the above mentioned linear free energy relationships, the electrophilic nature of the carbene was modulated by the electron-attracting nature of the ligands of the catalyst, and not by the substituent of the carbene. A less electron-withdrawing ligand will lead to a later transition state and, hence, to higher selectivity. Pirrung and Morehead have related the selectivity of the Rh-carbenoids with the degree of backbonding from the metal to the vacant p-orbital of the carbene. Backbonding increases the stabilty of the carbene and, hence, its selectivity[52]. These tendencies should apply in analogy to diazo ketones which are expected to produce more electrophilic and, therefore, less selective carbenes in comparison with carbenes derived from diazo esters or amides.

In addition, conformational effects may be of importance in intramolecular and transannular insertions. To our knowledge, no data are available for the preferred conformations and the rotational barriers of oxocarbenes, and therefore we limit the discussion on consequences of the introduction of functionalities adjacent to the carbonyl group. In acyclic aldehydes and ketones, the most stable conformations have very similar energies and the rotational barriers are small, in the range of 0.7–1.2 kcal/mol (ref.[53]). A double bond conjugated with the carbonyl function has only little effect on the conformational mobility. Acrolein exists mainly in the *s-trans* conformation which is more stable by 1.7 kcal/mol than the *s-cis* conformer; the rotational barrier is 5.0–6.4 kcal/mol. Acrylic acid and acrylic esters exhibit small energy differences between the *s-cis* and the *s-trans* conformations, and the rotational barriers are below 4 kcal/mol. Esters occur in two preferred conformations, since the C–O bond has a considerable double bond character. The *Z*- (or *trans*) conformer **30** is more stable by 5–6 kcal/mol than the *E*- (or *cis*) isomer **31** with a rotational barrier of 10–13 kcal/mol. In amides the structures are nearly planar; in *N*-methylacetamide the *Z*-conformer is more stable than *E* by 2.1–2.5 kcal/mol, and the barrier for rotation is 21.3 kcal/mol. Inspection of molecular models shows that in the case of intramolecular C–H insertions, formation of a five-membered ring may not occur from the *Z*-isomer **31**, the

reacting centers being too far apart. The *E*-conformer **30** is more suited; however, in order to allow interaction between the carbenic centre and both atoms of the reacting C–H bond, which is required to reach the three-membered transition state for insertion, the conformation most favorable for insertion has the O–C bond of the alcohol bent out of the plane of the carbonyl group as depicted in **32**. This implies that the rotational barrier must at least partly be overcome in order to reach the transition state for insertion. This results in an increased energy of activation and, therefore, in a later transition state and higher selectivity in comparison with that observed with diazo ketones. An analogous argument should apply to diazo amides.



SCHEME 5

Resonance stabilization of the carbene and conformational effects are interconnected; the consequences of both effects point into the same direction, and they are consistent with the experimental results presently available. It is clear, however, that this hypothesis should be tested by experimental and theoretical methods.

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