Enantioselective intramolecular 1,3-dipolar cycloadditions of diazocarbonyl-derived oxidopyryliums

David M. Hodgson,*[a] Paul A. Stupple,[a] and Craig Johnstone[b]

[a] *Dyson Perrins Laboratory, Department of Chemistry, University of Oxford, South Parks Road, Oxford, OX1 3QY, UK*

[b] *AstraZeneca, Mereside, Alderly Park, Macclesfield, Cheshire, SK10 4TG, UK*

E-mail: david.hodgson@chem.ox.ac.uk

Dedicated to Professor A. McKervey on his retirement from Queen's University, Ireland

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Abstract

Catalytic enantioselective tandem oxidopyrylium formation - intramolecular 1,3-dipolar cycloaddition reactions of phthalic anhydride-derived unsaturated diazocarbonyl compounds in up to 19% *ee* are described.

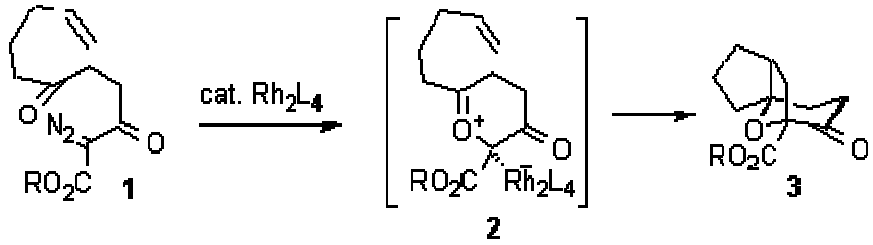
Keywords: Asymmetric catalysis, oxidopyryliums, cycloadditions, diazo compounds, rhodium

Introduction

Compared with enantioselective Diels-Alder and hetero Diels-Alder processes, enantioselective 1,3-dipolar cycloadditions are relatively underdeveloped.[1] Nevertheless, the latter reaction class holds considerable potential for the asymmetric synthesis of heterocycles.[2] Studies by Padwa *et al.* established Rh(II)-catalysed tandem carbonyl ylide formation-1,3-dipolar cycloaddition of diazocarbonyl compounds as an excellent method for the synthesis of oxapolycycles.[3] In 1997, using this latter method, we reported the first examples of enantioselective carbonyl ylide cycloadditions: unsaturated 2-diazo-3,6-diketoesters underwent intramolecular cycloaddition catalysed by Davies' prolinate catalyst Rh_2(*S*-DOSP)$_4$[4] in up to 52% *ee* (Scheme 1, Fig. 1).[5] Rh_2(*S*-DOSP)$_4$ is a fully hydrocarbon soluble version of a prolinate catalyst originally reported during pioneering studies by McKervey on enantioselective transformations of diazocarbonyl compounds using rhodium catalysts.[6]

Cascade reactions such as the example shown in Scheme 1 are of interest because of the rapid generation of molecular complexity,[3] and because of the demands which it places upon a catalyst – which should both efficiently decompose the diazo precursor and form a catalyst-associated ylide (eg, **2**),[7] from which highly (ideally) enantioenriched cycloadduct ensues. The

latter likely requires that cycloaddition occurs prior to, or simultaneously with, catalyst dissociation from the ylide. Detailed catalyst studies using ester **1** eventually led to higher *ee*s of intramolecular cycloadduct **3** using phosphate catalysts,[8] such as Pirrung's Rh_2(*R*-BNP)$_4$;[9] high levels of asymmetric induction have also been reported by Hashimoto and co-workers in intermolecular carbonyl ylide cycloadditions using 1-diazo-2,5-diketones with DMAD, catalysed by Rh(II) carboxylates such as Rh(*S*-PTPA)$_4$ (Fig. 1).[10] Enantioselective carbonyl ylide type intermolecular cycloadditions of (aromatic) oxidopyryliums derived from methyl 2-(diazoacetyl)benzoate [**4**, O(CH$_2$)$_2$CH=CH$_2$ = OMe] have also been disclosed,[11] and in the present paper we report some preliminary studies on enantioselective intramolecular cycloadditions of unsaturated oxidopyryliums.



Scheme 1

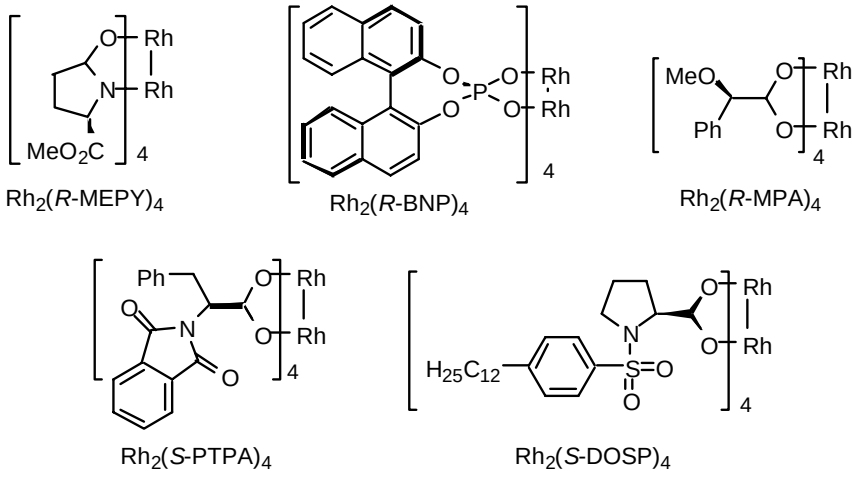
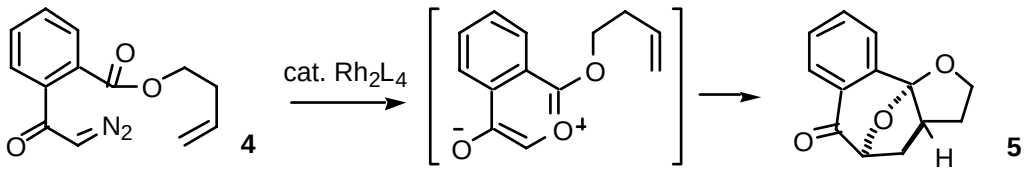


Figure 1. Chiral Rh(II) catalysts used in the current study.

Results and Discussion



Scheme 2

Our initial studies focused on cycloaddition precursor **4** as Padwa had already shown that this diazo compound was a viable substrate for tandem oxidopyrylium formation - intramolecular 1,3-dipolar cycloaddition (Scheme 2).[12] The diazoketoester **4** was screened with representatives of the known classes of chiral rhodium(II) catalysts (Fig. 1), selected for their varying electronic and steric properties and ability to induce enantioselectivity in other diazocarbonyl transformations.[3] The reactions were carried out in a parallel fashion with purification being simplified by the use of disposable Bond-Elut® prepacked silica cartridges. The isolated cycloadduct **5** was analysed using automated ^{1}H NMR and HPLC systems. These techniques facilitated rapid acquisition of the data set presented in Table 1.

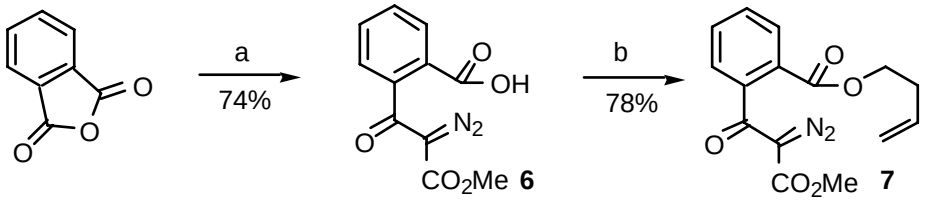
Table 1. Cycloadditions of diazoketoester **4**

Entry	Catalyst	Solvent	Temp.	Yield	*Ee*[a]
1	$Rh_2(OAc)_4$	CH_2Cl_2	25 °C	78%	-
2	Rh_2(*R*-MEPY)$_4$	CH_2Cl_2	25 °C	60%	~0%
3	Rh_2(*R*-BNP)$_4$	CH_2Cl_2	25 °C	73%	~0%
4	Rh_2(*R*-MPA)$_4$	CH_2Cl_2	25 °C	80%	~0%
5	Rh_2(*R*-PTPA)$_4$	CH_2Cl_2	25 °C	79%	~0%
6	Rh_2(*S*-DOSP)$_4$	CH_2Cl_2	25 °C	85%	6% (B)
7	Rh_2(*R*-MEPY)$_4$	hexane	25 °C	9%[b]	-
8	Rh_2(*R*-BNP)$_4$	hexane	25 °C	16%[b]	-
9	Rh_2(*R*-MPA)$_4$	hexane	25 °C	30%[b]	-
10	Rh_2(*R*-PTPA)$_4$	hexane	25 °C	43%[b]	-
11	Rh_2(*S*-DOSP)$_4$	hexane	25 °C	32%	11% (B)
12	Rh_2(*R*-MEPY)$_4$	C_6H_6	25 °C	31%	2% (A)
13	Rh_2(*R*-BNP)$_4$	C_6H_6	25 °C	50%	5% (B)
14	Rh_2(*R*-MPA)$_4$	C_6H_6	25 °C	93%	4% (B)
15	Rh_2(*R*-PTPA)$_4$	C_6H_6	25 °C	95%	9% (B)
16	Rh_2(*S*-DOSP)$_4$	C_6H_6	25 °C	96%	16% (B)
17	Rh_2(*R*-MEPY)$_4$	C_6H_6	40 °C	64%	7% (A)
18	Rh_2(*R*-BNP)$_4$	C_6H_6	40 °C	65%	7% (B)
19	Rh_2(*R*-MPA)$_4$	C_6H_6	40 °C	93%	2% (B)
20	Rh_2(*R*-PTPA)$_4$	C_6H_6	40 °C	95%	2% (A)
21	Rh_2(*S*-DOSP)$_4$	C_6H_6	40 °C	90%	7% (B)
22	Rh_2(*R*-MEPY)$_4$	C_6H_6	7 °C	23%	4% (A)
23	Rh_2(*R*-BNP)$_4$	C_6H_6	7 °C	44%	15% (B)
24	Rh_2(*R*-MPA)$_4$	C_6H_6	7 °C	50%	3% (A)
25	Rh_2(*R*-PTPA)$_4$	C_6H_6	7 °C	70%	2% (A)
26	Rh_2(*S*-DOSP)$_4$	C_6H_6	7 °C	76%	19% (B)

[a] "A" refers to the major peak being that which elutes first from Chiralpak AD; "B" refers to the major peak being that which elutes second.
[b] Impurities were present which prevented accurate determination of *ee*. All *ee*s appear to be less than 10% as judged by HPLC.

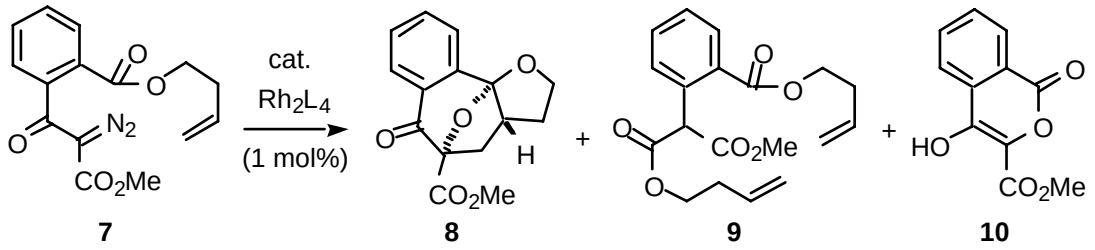
CH_2Cl_2 was initially used as the solvent, which with each catalyst was found to furnish cycloadduct **5** in good yield, but with no enantioselectivity, aside from Rh_2(*S*-DOSP)$_4$ (Table 1, entry 6, 6% *ee*). The cycloaddition precursor **4** was found to have only limited solubility in hexane at room temperature, which may account for the low yields of **5** that were obtained in this solvent (entries 7-10). Also, complete purification was not possible in these latter cases, which therefore prevented accurate determination of enantioselectivities by HPLC analysis, although the *ee*s appeared to be below 10%. Using C_6H_6 as the solvent at room temperature, cycloadduct **5** was isolated in moderate to excellent yields, although once again the level of enantiocontrol was low. The highest level of enantioselectivity in the formation of cycloadduct **5** at room temperature was provided by Rh_2(*S*-DOSP)$_4$ (entry 16, 16% *ee*). Neither increasing the reaction temperature to 40 °C, nor cooling to 7 °C had a significant effect on the asymmetric induction (the *ee* with Rh_2(*S*-DOSP)$_4$ at 7 °C was 19%, entry 26); however, the yields generally improved as the reaction temperature was increased.

As we had earlier observed good asymmetric induction in intramolecular cycloaddition with tethered alkenes when using an α-diazo-β-ketoester substrate (*cf*, Scheme 1) we decided to examine oxidopyrylium formation - cycloaddition using a diazoketodiester (Scheme 3). Methyl ester **7** was studied, as this facilitated *ee* analysis by chiral shift agents.[13] Methyl ester **7** was efficiently prepared by addition of lithiated methyl diazoacetate to phthalic anhydride[14] (74%), followed by esterification of the resulting diazoacid **6** with 3-buten-1-ol using DCC (78%).



Scheme 3. Reagents and conditions: (a) Methyl diazoacetate, LDA, THF, -78 °C, 140 min; (b) CH_2=CH$(CH_2)_2$OH, DMAP, DCC, THF, 25 °C, 15 h.

The tandem cyclisation-cycloaddition of **7** was next investigated using three solvents and using two catalysts, Rh_2(*S*-DOSP)$_4$ and Rh_2(*R*-BNP)$_4$. The results of this survey are presented in Table 2. Reaction of **7** under Rh_2(*S*-DOSP)$_4$ catalysis gave cycloadduct **8** (Scheme 4) in good yield using hexane, CH_2Cl_2 or C_6H_6 as the solvent. However, the enantioselectivity, determined by using the chiral shift agent Pr(hfc)$_3$ (15 mol%), was found to be small in each case.



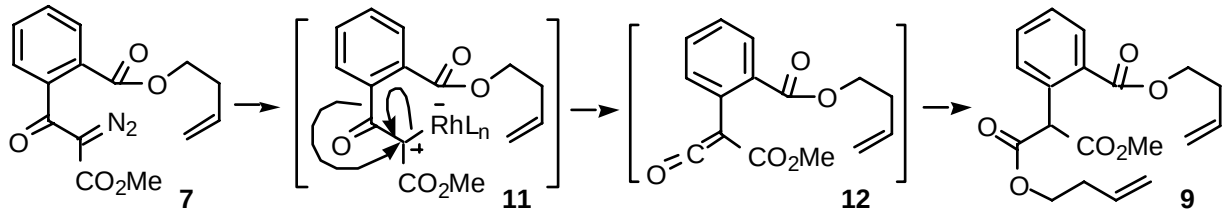
Scheme 4

Table 2. Cycloadditions of diazoketodiester **7**

Entry	Catalyst	Solvent	Temp	Isolated Yields			*Ee*[a]
				8	9	10	of 8
1	Rh_2(*S*-DOSP)$_4$	hexane	25 °C	88%	0%	0%	2%
2	Rh_2(*S*-DOSP)$_4$	CH_2Cl_2	25 °C	78%	0%	0%	6%
3	Rh_2(*S*-DOSP)$_4$	C_6H_6	25 °C	82%	0%	0%	6%
4	Rh_2(*R*-BNP)$_4$	hexane	25 °C	0%	25%	26%	-
5	Rh_2(*R*-BNP)$_4$	CH_2Cl_2	25 °C	41%	0%	31%	0%
6	Rh_2(*R*-BNP)$_4$	C_6H_6	25 °C	79%	0%	0%	0%

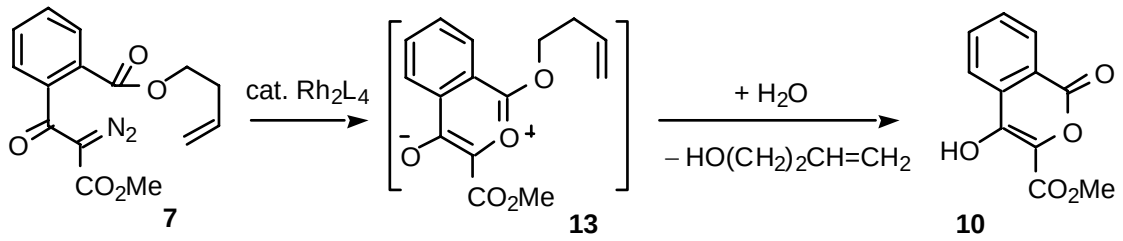
[a] Determined by ^{1}H NMR using (+)-Pr(hfc)$_3$; the major peak was at higher ppm.

When Rh_2(*R*-BNP)$_4$ was used as the catalyst the chemoselectivity was found to be less predictable. In hexane, cycloadduct **8** was not formed, however, triester **9** and enol **10** were isolated (Scheme 4). Triester **9** could result from Wolff rearrangement of the putative intermediate metallocarbene **11** arising from diazoketodiester **7** (Scheme 5), followed by addition to the resulting ketene **12** of 3-buten-1-ol which is released during the formation of enol **10**.



Scheme 5

Enol **10** may originate from addition of traces of water present in the reaction mixture to the intermediate oxidopyrylium **13** formed from **7**, followed by loss of 3-buten-1-ol (Scheme 6).



Scheme 6

Using either CH_2Cl_2 or C_6H_6 as the solvent with Rh_2(*R*-BNP)$_4$ afforded cycloadduct **8**, however, both samples were found to be racemic. The remarkably different product profile observed using hexane may originate from the low level of solubility of Rh_2(*R*-BNP)$_4$ in this solvent. In both CH_2Cl_2 and C_6H_6 the catalyst was found to be particularly soluble as indicated by the formation of green solutions after addition of the Rh(II) complex, rather than the suspension that was observed in hexane.

In conclusion, this paper reports the first studies on asymmetric intramolecular cycloadditions of unsaturated oxidopyryliums. The low levels of enantioinduction obtained show that such cycloadditions are possible in an enantioselective manner, although the extent of their potential remains to be established. Comparison with Hashimoto's studies of intermolecular oxidopyrylium cycloadditions with highly electron deficient dipolarophiles such as DMAD[11] suggests the nature of the dipolarophile plays a crucial role in enantioselectivity.

Experimental Section

General Procedures. Reactions were carried out under an argon atmosphere in oven dried apparatus, where appropriate. Syringes and needles were oven dried and cooled in a desiccator over self-indicating silica gel or P_2O_5 prior to use. Anhydrous THF was obtained by distillation from sodium benzophenone ketyl under argon. Anhydrous C_6H_6 and CH_2Cl_2 were obtained by distillation from CaH_2 under argon. Hexane was stored over molecular sieves for at least 24 h prior to use. 'Petrol' refers to that fraction of light petroleum ether boiling in the range 40-60 °C. Reaction temperatures are reported as internal, unless otherwise stated. Thin layer chromatography (TLC) was carried out on glass backed plates precoated with 0.25 mm Merck silica gel 60 F-254 and were visualised by the quenching of UV fluorescence (254 nm) and staining with $KMnO_4$, vanillin or 5% (w/v) dodeca-molybdophosphoric acid in EtOH followed by heat. Column chromatography was carried out on Kieselgel 60 (40-63 μm), Sorbsil C60 40/60 silica or Bond-Elut® cartridges (silica, 10 g). Solvents were removed using a Büchi rotary evaporator under reduced pressure, remaining solvent residues were removed using a static oil pump (~1 mmHg), where appropriate. ^{1}H NMR (δ_H) and ^{13}C NMR (δ_C) spectra were recorded using a Bruker AC 200, a Varian Gemini 200, or a Bruker DPX 400 spectrometer in $CDCl_3$,

unless otherwise stated. Chemical shifts are reported in parts per million (ppm) relative to the internal $CDCl_3$ lock. Coupling constants (*J*) are reported in Hz. A combination of DEPT 135, DEPT 90, DEPT 45, HMQC, HMBC and COSY experiments were used to aid spectral interpretation. IR spectra (ν_{max}) were recorded as thin films using NaCl plates or KBr discs using a Perkin-Elmer 1750 FT-IR spectrometer or a Perkin-Elmer Paragon 1000 FT-IR spectrometer. Peak intensities are specified as strong (s), medium (m), weak (w) or shoulder (sh). Melting points are uncorrected and were obtained using a Griffin Melting Point Apparatus, recrystallisation solvents (where appropriate) are indicated in parentheses. Mass spectra were recorded on a VG Micromass ZAB 1F, a Masslab 20-250, a VG TRIO-1 or a VG Platform 1 machine. High resolution mass spectra were obtained from the EPSRC Mass Spectrometry Service Centre, Swansea. *m/z* values are reported in Daltons and are followed by their percentage abundancies in parentheses. Microanalyses were performed by the Analytical Services Department at the Inorganic Chemistry Laboratory, Oxford, using an elemental analyser Vario EL. Enantiomeric excess was determined by ^{1}H NMR with the addition of the chiral shift agent (+)-Pr(hfc)$_3$. Alternatively, chiral stationary phase HPLC was performed using a Daicel Chiralpak AD column (4.6 mm x 250 mm) on a Gilson system with 712 Controller Software and a 118 UV/vis detector set at 254 nm. Retention times for major (t_R mj) and minor (t_R mn) enantiomers are given in minutes.

9,10-Benzo-2,11-dioxa-tricyclo[5.3.1.0^{1,5}] undecan-8-one (5).[12] General procedure: To a stirred solution of the diazoketone **4**[12] (approx. 100 mg, 0.46 mmol) in solvent (10 ml) at the desired temperature was added a Rh(II) catalyst (1 mol%). When TLC analysis indicated complete consumption of starting material, the reaction mixture was either concentrated *in vacuo* (CH_2Cl_2) or transferred directly (C_6H_6 and hexane) onto a silica Bond Elut® (10 g; 5:1 petrol:Et_2O) to give the title compound as a white solid. R_f 0.25 (1:1 petrol:Et_2O); ν_{max}/cm^{-1} (KBr) 2964w (CH), 1698s (C=O), 1600m, 1288s, 1041s, 1004m; δ_H (200 MHz) 1.90-2.12 (1 H, m), 2.16 (1 H, m), 2.28-2.50 (2 H, m), 2.60-2.70 (1 H, m), 4.35-4.60 (2 H, m, C(3)H_2), 4.91 (1 H, d, *J* 8.0, C(7)H), 7.42-7.52 (1 H, m, C(Ar)H), 7.57-7.62 (2 H, m, 2 x C(Ar)H), 7.99 (1H, dd, *J* = 7.5, 1.5 Hz, C(Ar)H). Ee determined by HPLC (Chiralpak AD, 60:40 hexane:EtOH, 0.5 ml/min, 0.5 mg/ml), $t_R$mn, 12.9; $t_R$mj, 19.0 (obtained from reaction using Rh_2(*S*-DOSP)$_4$ in C_6H_6).

Methyl 3-(2-carboxyphenyl)-2-diazo-3-oxopropanoate (6). A stirred solution of (Pr^i)$_2$NH (6.04 ml, 4.31 mmol) in THF (120 ml) was cooled to −78°C before dropwise addition of Bu^nLi (17.8 ml of a 2.3 M solution in hexanes). After 0.5 h the LDA was added dropwise over 20 min, *via* cannula, to a solution of methyl diazoacetate (4.41 g of 93% (w/w) mixture with CH_2Cl_2, 4.10 mmol, CAUTION: chilled glassware and blast shields were used in the preparation of methyl diazoacetate,[15] due to the reported potential for explosions) and recrystallised ($CHCl_3$) phthalic anhydride (5.51 g, 37.2 mmol) in THF (150 ml) at −78 °C. After 2 h glacial acetic acid (2.6 ml) was added and the reaction mixture allowed to warm to room temperature. The solution was concentrated *in vacuo* until the volume was approx. 50 ml before 2 M HCl (5 ml) and H_2O

(45 ml) were added. The aqueous phase was separated and extracted with Et_2O (3 x 50 ml). The combined organic layers were extracted with sat. aq. $NaHCO_3$ (50 ml) and H_2O (10 ml). The combined aqueous layers were acidified with 2 M HCl, extracted with CH_2Cl_2 (3 x 100 ml) and concentrated *in vacuo*. The residue was purified by column chromatography (19:1 CH_2Cl_2:MeOH) to give the title compound as a pale yellow foam (6.85 g, 74%). R_f 0.42 (9:1 CH_2Cl_2:MeOH); mp 71-72 °C; ν_{max}/cm^{-1} (KBr) 2960w,br (OH), 2136m (CN_2), 1725s (C=O), 1637w (C=C), 1340m, 1263m; δ_H (200 MHz) 3.70 (3 H, s, CH_3), 7.28 (1 H, d, *J* 2.0, C(Ar)H), 7.32-7.66 (2 H, m, 2 x C(Ar)H), 8.13 (1 H, d, *J* 7.5, C(Ar)H), 10.52 (1 H, s, br, CO_2H); δ_C (50.3 MHz) 52.2 (CH_3), 76.8 (CN_2), 126.4, 129.7, 130.5 and 133.2 (4 x CH), 127.0 and 141.2 (2 x quat.), 161.1 (CO_2CH_3), 170.3 (CO_2H), 188.7 (C=O); *m/z* (CI+) 266 (MNH_4^+, 30%), 249 (MH^+, 12), 240 (100), 238 (70), 166 (83), 152 (70), 121 (71), 105 (90) (Found MH^+, 249.0509. $C_{11}H_9N_2O_5$ requires 249.05115).

Methyl 3-[(but-3-enyl) 2-phenylcarboxylate]-2-diazo-3-oxopropanoate (7). To a stirred solution of diazoacid **6** (2.59 g, 10.44 mmol), 3-buten-1-ol (0.89 ml, 10.44 mmol) and DMAP (180 mg, 1.48 mmol) in THF (50 ml) at room temperature was added DCC (2.37 g, 11.48 mmol). After 15 h the precipitate was filtered off, washed with Et_2O (10 ml) and the filtrate diluted with a second portion of Et_2O (50 ml). The combined organic layers were washed with sat. aq. $NaHCO_3$ (30 ml) and concentrated *in vacuo*. The residue was purified by column chromatography (5:1 petrol:Et_2O) to give the title compound as a yellow oil (2.47 g, 78%). R_f 0.46 (1:1 petrol:Et_2O); ν_{max}/cm^{-1} (thin film) 2133m (CN_2), 1724s (C=O), 1642m, 1337m, 1278m, 1127m; δ_H (200 MHz) 2.43-2.53 (2 H, m, CH_2CH=CH_2), 3.68 (3 H, s, CH_3), 4.32 (2 H, t, *J* 6.5, OCH_2), 5.08-5.20 (2 H, m, CH=CH_2), 5.83 (1 H, ddt, *J* 17.0, 10.5 and 6.5, CH=CH_2), 7.26 (1 H, d, *J* 2.0, C(Ar)H), 7.29-7.64 (2 H, m, 2 x C(Ar)H), 8.03 (1 H, d, *J* 7.5, C(Ar)H); δ_C (50.3 MHz) 32.7 (CH_2CH=CH_2), 52.0 (CH_3), 64.4 (CO_2CH_2), 76.4 (CN_2), 117.4 (CH=CH_2), 126.4, 129.7, 129.9, 132.6 and 134.0 (5 x CH), 128.2 and 141.1 (2 x quat.), 161.2 and 165.8 (2 x CO_2), 188.7 (C=O); *m/z* (CI+) 320 (MNH_4^+, 100%), 303 (MH^+, 31), 294 (42), 292 (31), 275 (68), 70 (60) (Found MH^+, 303.0975. $C_{15}H_{15}N_2O_5$ requires 303.09810).

9,10-Benzo-7-carbomethoxy-2,11-dioxa-tricyclo[5.3.1.0^{1,5}]undecan-8-one (8).

General procedure: To a stirred solution of the diazoketodiester **7** (approx. 100 mg, 0.33 mmol) in solvent (10 ml) at the desired temperature was added a Rh(II) catalyst (0.5-1.0 mol%). When TLC analysis indicated complete consumption of starting material the reaction mixture was either concentrated *in vacuo* (CH_2Cl_2) or transferred directly (C_6H_6 or hexane) onto a silica Bond-Elut® (10 g; 5:1 petrol:Et_2O). The title compound **8** was isolated as a white solid, which could be further purified by recrystallisation from cyclohexane. R_f 0.28 (1:1 petrol:Et_2O); mp 109-110 °C (cyclohexane); (Found: C, 65.61; H, 5.17. $C_{15}H_{14}O_5$ requires C, 65.69; H, 5.14%); ν_{max}/cm^{-1} (KBr) 1749s (C=O), 1700s (C=O), 1601w, 1324w, 1285w, 1080s; δ_H (400 MHz) 1.97-2.06 (1 H, m, C(4)H_aH$_b$), 2.42 (1 H, dd, *J* 14.2 and 8.6, C(6)H_aH$_b$), 2.41-2.48 (1 H, m, C(4)H$_a$$H_b$), 2.64 (1 H, dd, *J* 14.2 and 3.8, C(6)H$_a$$H_b$), 2.68-2.76 (1 H, m, C(5)H), 3.88 (3 H, s, OCH_3), 4.39-4.45 (1 H, m, C(3)H_aH$_b$), 4.58 (1 H, ddd, *J* 14.0, 8.6 and5.4, C(3)H$_a$$H_b$), 7.47-7.51 (1 H, m, C(Ar)H), 7.59-7.66 (2 H, m, 2 x C(Ar)H), 8.01 (1 H, d, *J* 7.7, CHCC(O)); δ_C (100

MHz) 33.1 (C(4)H_2), 35.4 (C(6)H_2), 47.3 (C(5)H), 53.0 (OCH_3), 72.3 (C(3)H_2), 90.4 and 114.8 (2 x quat.), 122.1, 127.7, 129.0 and 134.5 (4 x C(Ar)H), 128.8 and 143.9 (2 x quat.(Ar)), 167.3 (CO_2), 191.5 (C=O); *m/z* (APCI+) 297 ($M+Na^+$, 11%), 275 (MH^+, 100), 257 (10). Ee determined by comparison of split singlet (δ 3.88) integrals in 200 MHz ^{1}H NMR spectrum using 0.10 equiv. Pr(hfc)$_3$.

(But-3-enyl) methyl 2-((but-3-enyl) 2-phenylcarboxylate)-malonate (9) was isolated as a colourless oil. R_f 0.42 (1:1 petrol:Et_2O); ν_{max}/cm^{-1} (thin film) 2956w (CH), 1750s (C=O), 1735s (C=O), 1714s (C=O), 1256m, 1143m; δ_H (400 MHz) 2.44 (2 H, q, *J* 6.7, C*H*$_2$CH=CH_2), 2.56 (2 H, q, *J* 6.7, C*H*$_2$CH=CH_2), 3.82 (3 H, s, CH_3), 4.26-4.31 (2 H, m, OCH_2), 4.40 (2 H, t, *J* 6.7, OCH_2), 5.08-5.24 (4 H, m, 2 x CH=C*H*$_2$), 5.78 (1 H, ddt, *J* 17.0, 10.3 and 6.7, C*H*=CH_2), 5.82 (1 H, s, C(=O)CH), 5.90 (1 H, ddt, *J* 17.0, 10.3 and 6.7, C*H*=CH_2), 7.44-7.49 (2 H, m, 2 x C(Ar)H), 7.57-7.61 (1 H, m, C(Ar)H), 8.06 (1 H, dd, *J* 7.8 and 1.1, C(Ar)H); δ_C (100 MHz) 32.8 and 33.0 (2 x *C*H_2CH=CH_2), 52.7 (CH_3), 54.8 (*C*HC(=O)), 64.3 and 64.8 (2 x OCH_2), 117.3 and 117.5 (2 x CH=*C*H_2), 128.0 (C(Ar)H), 129.6 (quat.(Ar), 130.0, 131.0 and 132.4 (3 x C(Ar)H), 129.6 (quat.(Ar)), 133.6 and 133.9 (2 x *C*H=CH_2), 166.8, 168.4 and 169.0 (3 x CO_2); *m/z* (CI+) 364 (MNH_4^+, 42%), 347 (MH^+, 69), 118 (43), 72 (98), 70 (100) (Found M^+, 346.1415. $C_{19}H_{22}O_6$ requires 346.14164).

Methyl 4-hydroxy-1-oxo-1H-isochromene-3-carboxylate (10) was isolated as a white solid. R_f 0.37 (1:1 petrol:Et_2O); mp 153-155 °C; ν_{max}/cm^{-1} (KBr) 1732s (C=O), 1668m, 1652m, 1463m, 1298m; δ_H (400 MHz) 4.01 (3 H, s, CH_3), 7.73-7.77 (1 H, m, CH), 7.87-7.91 (1 H, m, CH), 8.08 (1 H, dd, *J* 8.0 and 0.6, CH), 8.36 (1 H, dd, *J* 8.0 and 0.5, CH), 10.55 (1 H, s, OH); δ_C (100 MHz) 52.9 (CH_3), 123.4, 130.1, 131.8, 134.9 (4 x CH), 123.9, 124.0, 131.5, 148.1 (4 x quat.), 158.9 and 166.0 (2 x CO_2); *m/z* (APCI-) 219 ($M-H^+$, 100%), 161 (20), 160 (13) (Found M^+, 220.0373. $C_{11}H_8O_5$ requires 220.03717).

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References

1. Kobayashi, S.; Jørgensen, K. A., Eds.; *Cycloaddition Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2002.

2. Padwa, A.; Pearson, W. H., Eds.; *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; John Wiley & Sons: New York, 2002.
3. (a) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223. (b) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; John Wiley & Sons: New York, 1998; Ch. 7. (c) Clark, J. S. *Nitrogen, Oxygen and Sulfur lide Chemistry*; Oxford University Press: Oxford, 2002. (d) Mehta, G.; Muthusamy, S. *Tetrahedron* **2002**, *58*, 9477.
4. Davies, H. M. L. *Eur. J. Org. Chem.* **1999**, 2459.
5. Hodgson, D. M.; Stupple, P. A.; Johnstone, C. *Tetrahedron Lett*. **1997**, *38*, 6471.
6. Kennedy, M.; McKervey, M. A.; Maguire A. R.; Roos, G. H. P. *J. Chem. Soc. Chem. Commun.* **1990**, 361.
7. (a) Hodgson, D. M.; Pierard, F. Y. T. M.; Stupple, P. A. *Chem. Soc. Rev*. **2001**, *30*, 50. (b) Hodgson, D. M.; Stupple, P. A.; Forbes, D. C. In *Rodd's Chemistry of Carbon Compounds, Topical Volume, Asymmetric Catalysis*; Sainsbury, M., Ed.; Elsevier: Oxford, 2001; p 65. (c) Kitagaki, S.; Hashimoto, S. *J. Synth. Org. Chem. Jpn.* **2001**, *59*, 1157.
8. Hodgson, D. M.; Stupple, P. A.; Pierard, F. Y. T. M.; Labande, A. H.; Johnstone, C. *Chem. Eur. J.* **2001**, *7*, 4465. See also: Hodgson, D. M.; Labande, A. H.; Pierard, F. Y. T. M. *Synlett* **2003**, 59.
9. Pirrung, M. C.; Zhang, J. *Tetrahedron Lett.* **1992**, *33*, 5987. For a related chiral Rh(II) phosphate catalyst reported contemporaneously by McKervey, see: McCarthy, N.; McKervey, M. A.; Ye, T.; McCann, M.; Murphy, E.; Doyle, M. P. *Tetrahedron Lett.* **1992**, *33*, 5983.
10. Kitagaki, S.; Masahiro, A.; Kataoka, O.; Matsuno, K.; Umeda, C.; Watanabe, N.; Hashimoto, S. *J. Am. Chem. Soc.* **1999**, *121*, 1417.
11. Kitagaki, S.; Yasugahira, M.; Anada, M.; Nakajima, M.; Hashimoto, S. *Tetrahedron Lett.* **2000**, *41*, 5931 (up to 93% *ee* using DMAD); Suga, H.; Inoue, K.; Inoue, S.; Kakehi, A. *J. Am. Chem. Soc.* **2002**, *124*, 14836 (up to 98% *ee* using an 3-acryloyl-2-oxazolidinone with a chiral Lewis acid–Rh catalyst combination).
12. Padwa, A.; Carter, S. P.; Nimmesgern, H.; Stull, P. D. *J. Am. Chem. Soc.* **1988**, *110*, 2894.
13. No satisfactory analytical method could be found for resolving the cycloadduct from corresponding ethyl ester.
14. Moody, C. J.; Taylor, R. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 721.
15. Searle, N. E. *Org. Synth.* **1963**, *Coll. Vol. IV*, 424.

