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A short stereoselective synthesis of (+)- and (−)-2-oxabicyclo[3.3.0]oct-6-en-3-one by intramolecular carbon–hydrogen insertion catalyzed by chiral dirhodium(II) carboxamidates

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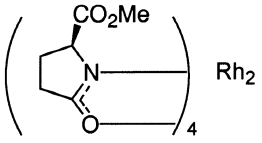
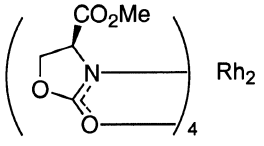
Abstract—The synthesis of (1*S*,5*R*)-(−)-2-oxabicyclo[3.3.0]oct-6-en-3-one, a useful synthetic precursor en route to various prostaglandins, from divinylcarbinol via catalytic metathesis and C–H insertion of 3-cyclopentenyl diazoacetate is described. Enantioselectivities of 90±1% have been achieved in the insertion process.

1. Introduction

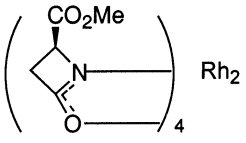
Enantioselective intramolecular C–H insertion reactions of diazoacetates catalyzed by chiral dirhodium(II) carboxamidates **1**–**4** are exceptionally versatile.[1,2] Generally favoring the formation of five-membered lactones,[3] these reactions occur with high enantiocontrol in good yield. However, certain functional groups, including a vinyl substituent,[4,5] inhibit insertion, and this consideration has limited investigations where such restrictions would be a factor. This was certainly the case in our consideration of metal carbene C–H insertion as a route to the known prostaglandin precursor **5**,[6] which requires intramolecular insertion of a carbene into an allylic position.



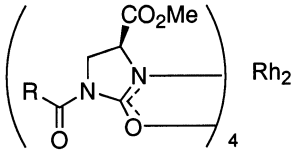
1 Rh_2(5*S*-MEPY)$_4$



2 Rh_2(4*S*-MEOX)$_4$



3 Rh_2(*S*-MEAZ)$_4$



4 Rh_2(*S*-MPPIM)$_4$
R = CH_2CH_2Ph

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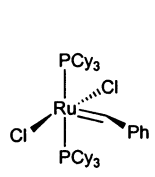
2. Results and discussion

Our initial strategy to prepare 3-cyclopentenyl diazoacetate **6** came from diazoacetylation of 3-cyclopentenol (Scheme 1).



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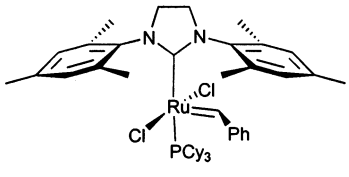

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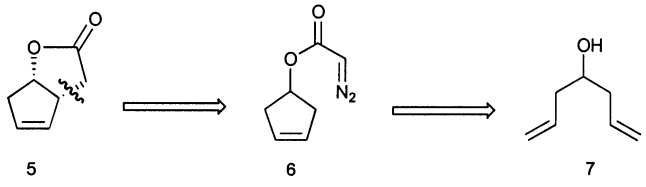

5 **6** **7**

Scheme 1.

Although 3-cyclopentenol has been prepared from cyclopentadiene,[7] we found the synthesis was cumbersome and resulted in a low yield of product. We therefore devised a strategy starting from 1,6-heptadien-4-ol (Scheme 2), which is commercially available or can be prepared in one step from allyl bromide.[8]

To this end, acetoacetic ester **8** was prepared from 1,6-heptadien-4-ol by reaction with diketene, followed by smooth ring closure with Grubb's catalyst **11**[9] to give **9**.

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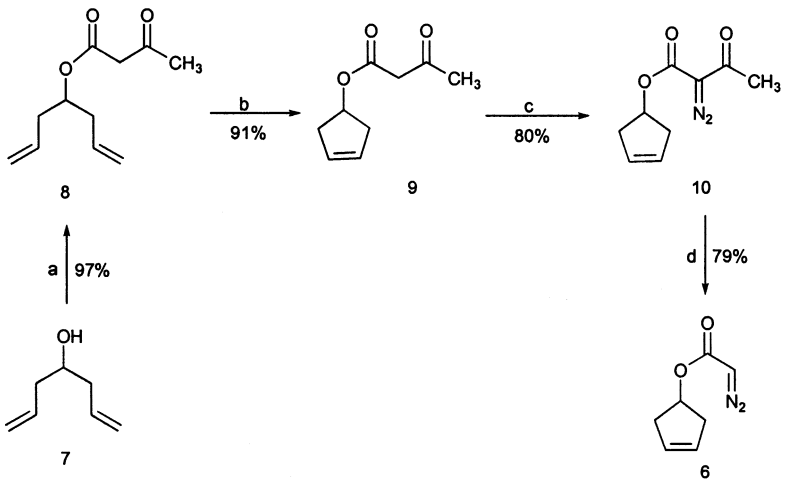
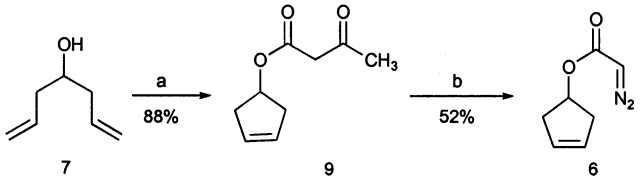


Scheme 2. *Reagents and conditions*: (a) diketene, Et_3N, DMAP, THF, rt; (b) Grubb's catalyst **11** (1 mol%) CH_2Cl_2 rt; (c) MsN_3, Et_3N, rt; (d) LiOH, H_2O, THF, rt.

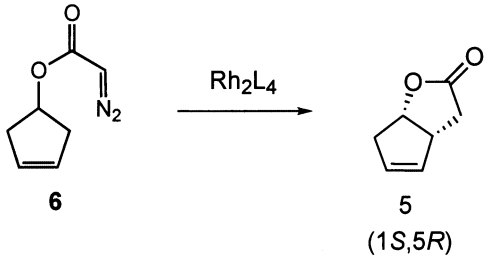
Treatment of **9** with methanesulfonyl azide (MsN_3) and subsequent deacetylation with LiOH then yielded 3-cyclopentenyl diazoacetate.

Alternatively, acetoacetate **9** can be prepared in one-pot from alcohol **7** via the action of Grubb's catalyst **12**[10,11] followed by the addition of diketene in 88% isolated yield (Scheme 3). Grubb's second generation catalyst **12** is considerably more functional group tolerant, as evidenced by the rapid ring closure of **7** which was unsuccessful with the first generation catalyst **11**. Furthermore, diazoacetate **6** can be prepared in one-pot from carbinol **7** in yields comparable to those obtained from the three-pot process.



Scheme 3. *Reagents and conditions*: (a) Grubb's catalyst **12** (1 mol%) THF 40°C, 1 h then diketene, NEt_3 cat DMAP rt; (b) MsN_3, Et_3N, rt THF then LiOH, H_2O, rt.

Diazoacetate **6** was subjected to catalytic conditions for C–H insertion (Eq. (1)). Reaction with $Rh_2(OAc)_4$ failed to produce the desired racemic C–H insertion product. Reaction with $Rh_2[(4S)\text{-MEAZ}]_4$ **3** gave dimer **14**[3] (Table 1). Further reactions with $Rh_2(5S\text{-MEPY})_4$ **1** and $Rh_2[(4S)\text{-MEOX})]_4$ **2** yielded C–H insertion product, but with low yields and enantiomeric excesses. However, reaction with $Rh_2[(4S)\text{-MPPIM}]_4$ **4** led to a considerable improvement in yield and enantiomeric excess (73%, 91% ee). In addition, $Rh_2[(4R)\text{-MPPIM}]_4$ produced the opposite oxabicyclic antipode (59%, 89% ee).



(1)

The racemic lactone **5** has been prepared from cyclopentadiene via cycloaddition with ketene and subsequent Baeyer–Villiger oxidation,[12] and resolution has been accomplished with either the cycloadduct[13] or the lactone.[14] More recently, efforts have been undertaken to perform asymmetric Baeyer–Villiger oxidation, but with mixed results.[15] Consequently, the methodology presented here is a viable and convenient alternative to the standard process.

Table 1. Selectivity for enantioselective C–H insertion[a]

Catalyst	Yield **5** (%)[b]	Yield **13** (%)	Ee (%)[c]
$Rh_2(OAc)_4$	–	–	
$Rh_2[(S)\text{-MEAZ}]_4$	–	53	
$Rh_2[(S)\text{-MEPY}]_4$	8	15	34
$Rh_2[(S)\text{-MEOX}]_4$	35	–	76
$Rh_2[(S)\text{-MPPIM}]_4$	73	–	91
$Rh_2[(R)\text{-MPPIM}]_4$	59[d]	–	89

[a] All reactions were carried out using 1 mol% catalyst with controlled addition of diazoacetate **6** in CH_2Cl_2 at 40°C.

[b] Absolute configuration was determined by co-injection with enantiomerically pure material commercially obtained. Only isolated yields are reported.

[c] Ee (%) of **5** was determined by analysis with a Chiraldex B-DM column (beta-cyclodextrindimethyl, 30 m×0.25 mm ID).

[d] Absolute configuration is (1*R*,5*S*).

3. Experimental

3.1. General

^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were obtained as solutions in $CDCl_3$; chemical shifts are reported in parts per million (ppm, δ) downfield from Me_4Si (TMS). Mass spectra were obtained using electron ionization on a quadrupole instrument. Infrared spectra were recorded using NaCl plates with absorptions recorded in wavenumbers (cm^{-1}). Enantiomeric excess (% ee) was measured with a Chiraldex B-DM column programmed initially at 85°C for 10 min then 1°C/min to 140°C. All reagents were commercially obtained unless otherwise noted. Chromatographic purification was performed using silica gel. Anhydrous THF was distilled over Na/benzophenone ketyl, and CH_2Cl_2 was distilled over CaH_2 prior to use. Methanesulfonyl azide was prepared by reaction with methanesulfonyl chloride with sodium azide and was not distilled.[16] The preparation of enantiomeric forms of $Rh_2(MEPY)_4$,[17] $Rh_2(MEOX)_4$,[18] $Rh_2(MEAZ)_4$,[19] and $Rh_4(MPPIM)_4$[20] have been previously reported.

3.2. 1,6-Heptadien-4-yl acetoacetate, 8

To a stirred solution of 1,6-heptadien-4-ol **7** (1.73 g, 15.4 mmol), triethylamine (0.156 g, 1.54 mmol) and a catalytic amount of DMAP ($\sim$2 mg) in anhydrous THF (15 mL) at rt was added a solution of diketene (1.48 g, 17.7 mmol) in THF (30 mL) via addition funnel. The resulting solution was stirred for 8 h after which the solvent was evaporated. The residue was dissolved in CH_2Cl_2 (50 mL), filtered through a pad of SiO_2, and evaporated to give a clear yellow liquid which was distilled (78°C, 0.5 Torr) yielding a clear liquid (2.94 g, 97%): TLC R_f=0.42 (5:1 hexanes:EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.76–5.62 (comp, 2H), 5.06–4.91 (comp, 4H), 3.36 (s, 2H), 2.32–2.23 (comp, 5H), 2.19 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.3, 166.5, 133.1, 118.0, 73.5, 50.2, 37.8, 30.0; HRMS (EI) calcd for $C_{11}H_{17}O_3$ 197.1178, found 197.1176 $(M+H)^+$.

3.3. 1-Cyclopentene-4-yl acetoacetate, 9

3.3.1. Procedure A. To a solution of 1,6-heptadien-4-yl acetoacetate **8** (686 mg, 3.50 mmol) in 35 mL of anhydrous CH_2Cl_2 under argon was added benzylidine(bistricyclohexylphosphine)ruthenium(II) dichloride (29 mg, 0.035 mmol). The resulting brown solution was stirred for 30 min (reaction complete as shown by tlc). Air was then bubbled through the solution for 3 h to oxidize the catalyst. Evaporation of the solvent, purification by flash chromatography on silica gel (6:1 hexanes:EtOAc), followed by distillation to remove trace catalyst (82°C, 0.5 Torr) gave a clear liquid (0.537 g, 91%): TLC R_f=0.30 (6:1 hexanes:EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.67 (s, 2H), 5.37 (tt, J=6.9, 2.1 Hz, 1H), 3.37 (s, 2H), 2.70 (dd, J=16.8, 6.9 Hz, 2H), 2.37 (dd, J=16.8, 2.1 Hz, 2H), 2.19 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.5, 166.9, 128.1, 75.2, 50.1, 39.5, 30.0; HRMS (EI) calcd for $C_9H_{13}O_3$ 169.0865, found 169.0869 $(M+H)^+$.

3.3.2. Procedure B. To a solution of 1,6-heptadien-4-ol **7** (259 mg, 2.31 mmol) in 20 mL of anhydrous THF under argon at 40°C was added [1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(phenylmethylene)-(tricyclohexylphosphine)ruthenium] (30 mg, 0.035 mmol). The resulting brown solution was stirred for 30 min (reaction completion shown by tlc). The solution was then allowed to cool to rt and air was bubbled through the solution for 1 h to oxidize the catalyst. To this solution was added triethylamine (0.024 g, 0.231 mmol), a catalytic amount of DMAP ($\sim$2 mg), and diketene (0.224 g, 2.66 mmol); stirring was continued for 8 h. Evaporation of the solvent, followed by purification by flash chromatography on silica gel (6:1 hexanes:EtOAc), gave a clear liquid (0.334 g, 88%). Data consistent with Procedure A.

3.4. 1-Cyclopentene-4-yl diazoacetoacetate, 10

To a solution of 1-cyclopentene-4-yl acetoacetate **9** (0.600 g, 3.57 mmol) and triethylamine (404 mg, 3.93 mmol) in 4 mL of anhydrous THF was added methanesulfonyl azide (475 mg, 3.93 mmol) in 8 mL of THF. The reaction was stirred for 8 h at rt. Evaporation of the solvent and purification by chromatography on silica gel (6:1 hexanes:EtOAc) gave a light yellow oil which slowly solidified on standing (0.566 g, 80%): TLC R_f=0.32 (6:1 hexanes:EtOAc); mp=44–46°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.69 (s, 2H), 5.48 (tt, J=6.9, 2.4 Hz, 1H), 2,77 (dd, J=16.8, 6.9 Hz, 2H), 2.46–2.40 (comp, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.2, 161.3, 128.1, 75.7, 39.7, 28.2; IR (thin film) ν 3068, 2919, 2833, 2141 (C=N_2), 1709, 1654, 1363, 1314 cm^{-1}; HRMS (EI) calcd for $C_9H_{11}N_2O_3$ 195.0770, found 195.0777 $(M+H)^+$.

3.5. 1-Cyclopentene-4-yl diazoacetate, 6

3.5.1. Procedure A. To a solution 1-cyclopentene-4-yl diazoacetoacetate **10** (0.400 g, 2.06 mmol) in 2 mL of THF was added LiOH in H_2O (8.24 mL, 1 M). The reaction was stirred for 1 h at rt, diluted with EtOAc (50 mL), and extracted with H_2O (50 mL) and brine (50 mL). Evaporation of the EtOAc and purification by chromatography on silica gel (9:1 hexanes:EtOAc) gave a bright yellow liquid (0.251 g, 79%): TLC R_f=0.31 (9:1 hexanes:EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.62 (s, 2H), 5.36 (tt, J=6.9, 2.1 Hz, 1H), 4.67 (br s, 1H), 2,77 (dd, J=16.5, 6.9 Hz, 2H), 2.33 (dd, J=16.5, 2.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.5, 128.0, 74.5, 46.1, 39.5; IR (thin film) ν 3111, 2944, 2907, 2839, 2123 (C=N_2), 1691, 1387 cm^{-1}; HRMS (EI) calcd for $C_7H_7N_2O_2$ 151.0508, found 151.0512 $(M-H)^+$.

3.5.2. Procedure B. To a solution of 1-cyclopentene-4-yl acetoacetate **5** (340 mg, 2.02 mmol) and triethylamine (225 mg, 2.22 mmol) in 2 mL of anhydrous THF was added methanesulfonyl azide (269 mg, 2.22 mmol) in 2 mL of THF. The reaction was stirred for 8 h at rt. A solution of LiOH in H_2O (8.08 mL, 1 M) was then added. The reaction was stirred for 1 h at rt, diluted

with EtOAc (25 mL), and extracted with H_2O (25 mL) and brine (25 mL). Evaporation of the EtOAc and purification by chromatography on silica gel (9:1 hexanes:EtOAc) gave a bright yellow liquid (161 mg, 53%): Data consistent with Procedure A.

3.6. (1*S*,5*R*)-(−)-2-Oxabicyclo[3.3.0]oct-6-en-3-one, 5

To a stirred solution of Rh_2[(4*S*)-MPPIM]$_4$ (16 mg, 0.0115 mmol, 1.0 mol%) in dry CH_2Cl_2 (11.5 mL) was added via syringe pump (0.8 mL/h) a solution of 1-cyclopentene-4-yl diazoacetate (178 mg, 1.15 mmol) in dry CH_2Cl_2 (7.7 mL). The initial purple color of the reaction solution turned olive green by the end of the substrate addition; refluxing was continued for 3 h. The solution was cooled to rt, filtered over a short plug of silica to remove the catalyst, and evaporated. Purification of the residue by silica gel chromatography (3:1 hexane:EtOAc) yielded a light yellow oil which slowly solidified (105 mg, 73%, 91% ee): TLC R_f=0.36 (3:1 hexanes:EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.74–5.70 (m, 1H), 5.54–5.50 (m, 1H), 5.08–5.04 (m. 1H), 3.49–3.42 (m, 1H), 2.75–2.66 (comp, 3H), 2.36 (dd, J=18, 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.6, 131.1, 129.5, 82.9, 45.4, 39.3, 33.1; HRMS (EI) calcd for $C_7H_8O_2$ 124.0524, found 124.0518 $(M)^+$. For (1*R*, 5*S*)-(+)-2-oxabicyclo[3.3.0]oct-6-en-3-one, Rh_2(4*R*-MPPIM)$_4$ was used under the same conditions (59%, 89% *ee*). All data (NMR, tlc, HRMS) is consistent with the authentic sample commercially obtained.

3.7. *trans*-Dicyclopent-1-ene-4-yl ethylene dicarboxylate, 14

TLC R_f=0.40 (9:1 hexanes:EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.16 (s, 1H), 5.70 (s, 2H), 5.45 (m, 1H), 2.73 (dd, J=16.5, 6.9 Hz, 2H), 2.45 (comp, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.0, 129.8, 128.2, 75.2, 39.4; HRMS (EI) calcd for $C_{14}H_{17}O_4$ 249.1127, found 249.1129 $(M+H)^+$.

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