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A novel approach to bicyclic fused cyclopentenone derivatives

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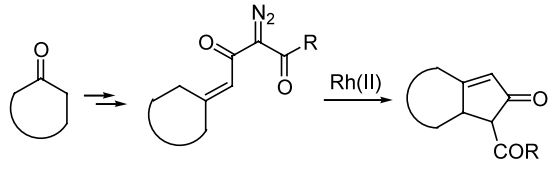
Abstract—A new four-step reaction sequence leading to bicyclic fused cyclopentenone derivatives starting from cyclic ketones has been developed.

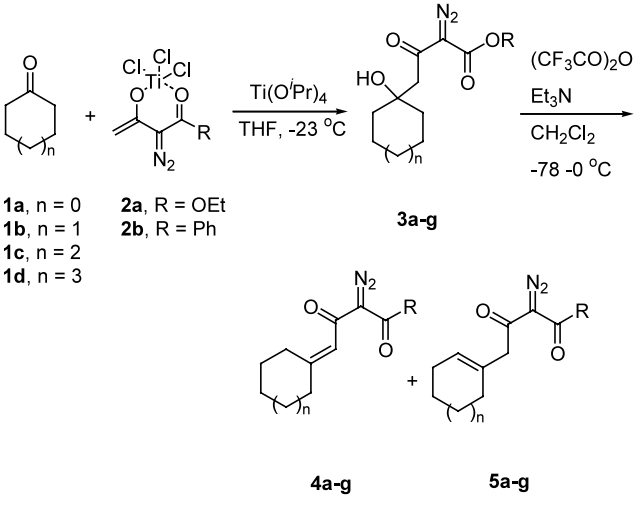
Bicyclic fused cyclopentenone derivatives are important structural units in natural product synthesis. Therefore, these types of bicyclic compounds have attracted attention from synthetic organic chemists over decades and various approaches have been developed.[1] For example, the Pauson–Khand reaction recently emerged as a powerful tool to construct bicyclic cyclopentenone structures.[2] In connection with research in the application of α-diazo carbonyl compounds in organic synthesis,[3] we have developed a new method for synthesizing bicyclic fused cyclopentenone derivatives based on an intramolecular C–H bond insertion by Rh(II) carbene (Scheme 1).

Thus, the nucleophilic addition to cyclic ketones **1a**–**d** by Ti(IV) enolates **2a**–**b** derived from an α-diazo-β-keto ester or a ketone is expected to give alcohols **3a**–**g** (Scheme 2). Although the similar aldol condensation of an α-diazo-β-ketoester with aldehydes has been developed by Calter et al.,[4] the corresponding reaction with ketones has not been reported.[5] When Calter's reaction conditions ($TiCl_4/Et_3N$, −78°C/CH_2Cl_2) were applied to the condensation of ethyl 2-diazoacetoacetate with cyclohexanone **1b**, the reaction was found to proceed very slowly. Obviously, the carbonyl group of a ketone is less reactive than that of aldehydes. To improve the reactivity, the cyclohexanone was activated with 1 equiv. of $Ti(O^iPr)_4$ before adding to the Ti(IV) enolate. Moreover, the reaction temperature was raised to −23°C with dry ice/CCl_4. Under these conditions, the nucleophilic addition occurred at an acceptable rate to give the expected alcohols in reasonable yields (Table 1).[6]

Next, we proceeded to convert the alcohols **3a**–**g** to α,β-unsaturated carbonyl compounds **4a**–**g**. However, because of the steric hindrance, the tertiary hydroxyl



Scheme 1.



a, n = 0, R = OEt; b, n = 1, R = OEt; c, n = 2, R = OEt
d, n = 3, R = OEt; e, n = 0, R = Ph; f, n = 1, R = Ph
g, n = 2, R = Ph

Scheme 2.

Keywords: Ti(IV) enolate; nucleophilic addition; Rh(II) carbene; intramolecular C–H insertion.

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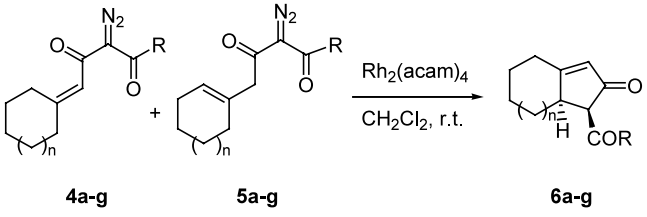
Table 1. Nucleophilic condensation of **1a–d** with **2a–b** and dehydration of **3a–g**

Entry	**1a–b**	**2a–b**	Reaction time (h)	Yield (%) of **3a–g**[a]	**3a–g**	Reaction time (h)	Ratio **4**:**5**[b]	Yield (%) (**4**+**5**)[a]
1	**1a**	**2a**	9	84	**3a**	17	3.5:1	85
2	**1b**	**2a**	9.5	85	**3b**	23	100:0	84
3	**1c**	**2a**	5.3	64	**3c**	23	3:1	74
4	**1d**	**2a**	8.5	58	**3d**	16	2:1	66
5	**1a**	**2b**	9	40	**3e**	15	7:1	56
6	**1b**	**2b**	8	56	**3f**	17	100:0	62
7	**1c**	**2b**	7	58	**3g**	17	6:1	67

[a] Yields after silica gel column chromatography.
[b] Ratio was determined by ^{1}H NMR (200 MHz) of the crude product.

group was found to be inert to many reagents. After examining the dehydration of the alcohol under various conditions, we finally found that $(CF_3CO)_2O/Et_3N$ can effectively dehydrate the alcohols at room temperature in CH_2Cl_2. An inseparable mixture of **4a–g** and **5a–g** was obtained in moderate to good yields. Similar results were obtained with other substrates (Table 1).[7] The ratios of **4a–g** to **5a–g** vary according to the ring size of the cyclic alkane moiety, but the compounds **4a–g** dominate in all cases. For the alcohols **3b** and **3f**, **4b** and **4f** were the only products (entries 2 and 6, Table 1).

Since the mixtures of **4a–g** and **5a–g** were not separable by silica gel column chromatography, they were subjected to the Rh(II)-mediated diazo decomposition without further purification. The diazo decomposition with $Rh_2(OAc)_4$ gave a complex mixture. As it is known that the ligands of the Rh(II) catalyst can dramatically affect the diazo decomposition reaction,[8] we decided to examine other Rh(II) catalysts. To our delight, the diazo decomposition of a mixture of **4a** and **5a** with $Rh_2(NHCOCH_3)_4$ cleanly gave a major product, which was separated in 72% yield. The structure of this product was shown to be *cis*-1-carboethoxy bicyclo[4,3,0]-non-3-en-2-one **6a** (Scheme 3).[9] For other diazo substrates, similar results were obtained (Table 2).[10]

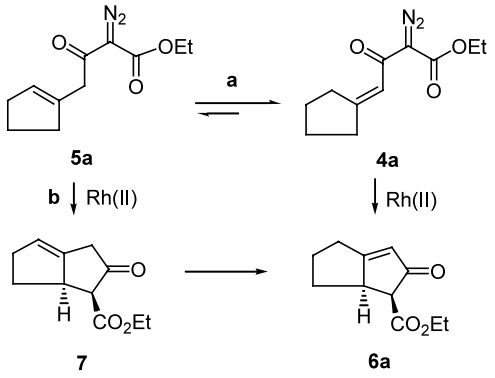


Scheme 3.

Table 2. $Rh_2(NHCOCH_3)_4$-catalyzed intramolecular C–H insertion

Entry	**4a–g** and **5a–g**[a]	Reaction time (h)	Products	Yield (%)[b]
1	**a**	2	**6a**	72
2	**b**	2	**6b**	76
3	**c**	3	**6c**	62
4	**d**	2	**6d**	72
5	**g**	5	**6g**	60

[a] For Entry 5, 5 mol% of $Rh_2(NHCOCH_3)_4$ was used; in all the other cases, 1 mol% catalyst was used.
[b] Yields after silica gel column chromatography.



Scheme 4.

It is interesting to note that the $Rh_2(NHCOCH_3)_4$-catalyzed reaction of the mixtures of **4a**,**c**,**d**,**g** and **5a**,**c**,**d**,**g** gave **6a**,**c**,**d**,**g** as the main isolated products. Two possible reaction pathways are conceivable for the transformation of **5a**,**c**,**d**,**g** to **6a**,**c**,**d**,**g** (Scheme 4). In pathway a, there is an equilibrium between **4a** and **5a**. Diazo compound **4a** reacts faster under the catalytic conditions to give **6a**, thus driving the equilibrium to the right. In pathway b, diazo compound **5a** reacts with $Rh_2(NHCOCH_3)_4$ to give **7**, which isomerizes to generate **6a**.

In summary, we have developed a novel approach to the two-ring fused cyclopentenone derivatives based on $Rh_2(NHCOCH_3)_4$-catalyzed diazo decomposition. This novel reaction sequence has the advantages of high efficiency, readily available starting materials and mild reaction conditions. This approach should also be applicable to the synthesis of other cyclopentenone derivatives.

Acknowledgements

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7. General procedure for the dehydration of the alcohols **3a**–**g**. Under N_2, **3b** (254 mg, 1 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL) and the solution was cooled to −78°C. While stirring, $(CF_3CO)_2O$ (420 mg, 2 mmol) and Et_3N (202 mg, 2 mmol) were added and the reaction temperature was allowed to rise to rt within 2 h. Another 5 mL Et_3N was added and the reaction mixture was stirred at rt for 23 h. Volatile fractions were removed by rotovap to leave a crude residue, which was purified by silica gel column chromatography to give **4b** (198 mg, 84%). IR (CCl_4) 2134, 1717, 1645, 1444, 1362 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.33 (t, $J=7.2$ Hz, 3H), 1.62–1.72 (m, 6H), 2.23–2.39 (m, 2H), 2.81–2.87 (m, 2H), 4.29 (q, $J=7.2$ Hz, 2H), 6.81 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.3, 26.2, 27.9, 28.8, 30.7, 38.4, 61.2, 117.8, 161.5, 163.9, 182.6; MS (FAB) m/z 237 [$(M+H)^+$, 22], 163 (9), 135 (10), 123 (19), 95 (41), 69 (64), 43 (100).
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9. The *cis* configuration of the product was assigned by comparison with the ^1H NMR data of the *trans* isomer reported in Ref. 1c.
10. Typical procedure for the $Rh_2(NHCOCH_3)_4$-catalyzed reaction of diazo compounds **4a**–**g** and **5a**–**g**. To a solution of **4b** (118 mg, 0.5 mmol) in anhydrous CH_2Cl_2 (10 mL) was added $Rh_2(NHCOCH_3)_4$ (0.5 mg, 0.025 mmol). The solution was stirred under N_2 for 48 h. The solvent was removed under reduced pressure to give a crude residue, which was purified by column chromatography to yield **6b** (79 mg, 76%) as an oil. IR (CCl_4) 1719, 1636, 1552, 1253 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.18 (dq, $J=13$, 3.2 Hz, 1H), 1.31 (t, $J=7.1$ Hz, 3H), 1.40 (tq, $J=13$, 3.8 Hz, 1H), 1.54 (tq, $J=13$, 3.2 Hz, 1H), 1.88 (d, $J=13$ Hz, 1H), 2.02–2.07 (m, 1H), 2.25–2.29 (m, 1H), 2.33 (dt, $J=13$, 5 Hz, 1H), 2.86 (d, $J=13.9$ Hz, 1H), 3.02 (s, 1H), 3.05 (d, $J=3.8$ Hz, 1H), 4.22 (q, $J=7.1$ Hz, 2H), 5.82 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.1, 25.0, 26.5, 30.8, 33.9, 45.8, 59.3, 61.4, 124.9, 169.2, 184.1, 201.3; MS (EI) m/z 208 (M^+, 28), 162 (32), 134 (100), 107 (15), 106 (20), 79 (22), 53 (8), 39 (22).