Observations on the versatility of methylenecyclopropanes as olefinic components in the intramolecular Pauson–Khand reaction

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Cyclopropyl tethered methylenecyclopropanes can function in the intramolecular Pauson–Khand reaction either as simple alkene components, or give rearranged hydroindenones in which neither of the two carbon atoms of the alkyne component form part of the cyclopentenone unit in the product.

Extensive and elegant studies by Binger[1] have established that transition metal mediated reactions of alkylidenecyclopropanes with olefinic and acetylenic acceptors provide a valuable method for cyclopentanoid construction. The essentially contemporaneous introduction of the intramolecular variant by ourselves[2a] and by the Nakamura group[2b] has led, *via* a series of systematic studies using both nickel(0) and palladium(0) catalysts,[2] to greatly improved levels of regiocontrol, and recent detailed stereochemical studies by Lautens[2h] have further enhanced the synthetic potential of this methodology.

Within this framework, it was therefore of interest to extend our studies to encompass the intramolecular variant of the highly useful Pauson–Khand reaction[3] using such substrates. Our primary objective, as encapsulated in Fig. 1(*a*), was to attach the tethering chain to the cyclopropyl unit, and hence to examine the possibility of generating highly strained tricyclic systems. During the course of our own work, a systematic study describing the contrasting tethering connectivity implied in Fig. 1(*b*) has been published.[4] In this latter case, however, as in the similarly precedented concept of using the enhanced reactivity of an allylidene cyclopropane as the diene component in Diels–Alder reactions,[5] a spiro fused cyclopropyl adduct is necessarily formed.

In the first instance, we elected to study the behaviour of the readily prepared[2f,g] methylenecyclopropanes **1a** and **1b** using octacarbonyldicobalt and the mild amine *N*-oxide protocol developed by Schreiber[6] (Scheme 1). The obtention of the

Fig. 1

1a R = H
b R = C_9H_{19}

2a 41%
b 38%

Scheme 1 *Reagents and conditions*: i, $Co_2(CO)_8$ (1.0 equiv.), benzene, room temp., 1 h; ii, NMO (6 equiv.), benzene, reflux, 2 h.

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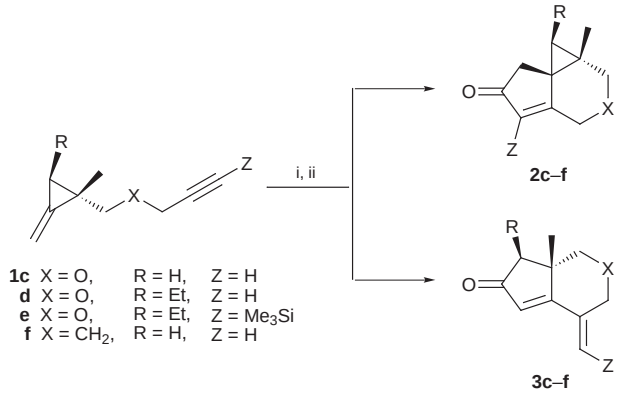
tricyclic adducts **2a** and **2b** confirmed the validity of this approach and the isolation of **2b** as a single diastereoisomer also established, as expected, that the *trans* stereochemistry of the substituents around the methylenecyclopropane was preserved in the cycloaddition product.

We were therefore encouraged to extend the scope of this approach to the methylenecyclopropane **1c**, in which the additional methyl group was expected to lead to the formation of the adducts **2**, containing two contiguous quaternary carbon centres (Table 1). In the event, under the previously described reaction conditions, the anticipated tricyclic product **2c** was not formed, and initial spectral data clearly indicated that cyclopropyl ring opening had occurred to give a bicyclic hydroindenone derivative containing an exocyclic carbon–carbon double bond. The full complexity of this bizarre rearrangement and the precise structures **3** of the rearranged cycloadducts were only revealed however through a careful systematic study of further substrates **1d–f** in which the progressive incorporation of additional substituents on the cyclopropyl ring and on the alkyne provided regio- and stereo-chemical markers to trace the outcome of the reaction in terms of carbon atom connectivity (Table 1, entries 1–4). The relative location and stereochemistry of the substituents in cycloadducts **3c–f** was rigorously established using a combination of 2D NMR, NOESY and

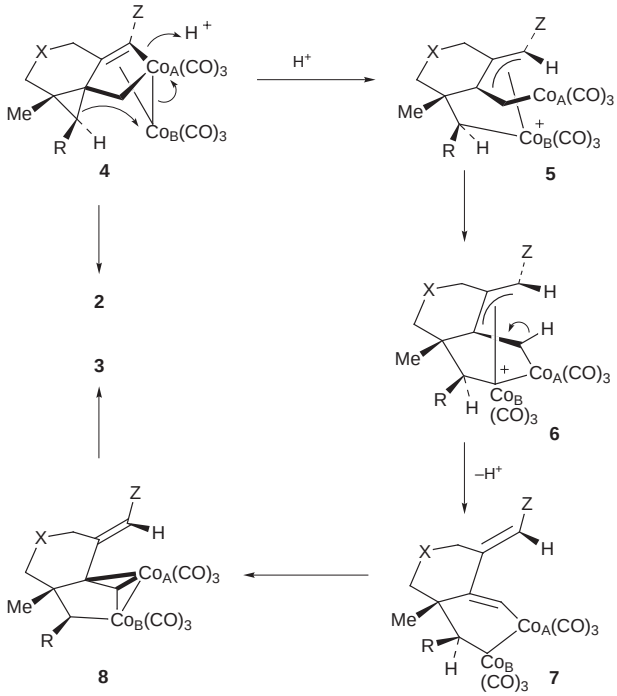
Table 1 Reaction of compounds **1c–f**



1c X = O, R = H, Z = H
d X = O, R = Et, Z = H
e X = O, R = Et, Z = Me_3Si
f X = CH_2, R = H, Z = H

Entry	Substrate	Reaction conditions[a] Solvent	*t*/h	*T*/°C	Products (% yield)
1	**1c**	benzene	1	reflux	**3c** (51)
2	**1d**	benzene	2	reflux	**3d** (47)
3	**1e**	benzene	1.5	reflux	**2e** (10), **3e** (40)
4	**1f**	benzene	1	reflux	**3f** (51)
5	**1c**	THF	10	room temp.	**2c** (44), **3c** (12)
6	**1d**	benzene	24	room temp.	**2d** (20), **3d** (26)
7	**1e**	THF	2	reflux	**2e** (28), **3e** (28)

[a] *Reagents and conditions*: i, $Co_2(CO)_8$ (1.0 equiv.), benzene, room temp., 1 h; ii, NMO (6 equiv.) and reaction conditions above.



Scheme 2

HMBC experiments. Thus, careful scrutiny of structures **3** uncovers the remarkable fact that *neither* of the two carbon atoms of the tethered alkyne have been incorporated into the cyclopentenone unit of the final product in this intramolecular variant of the Pauson–Khand reaction. It was also of interest to note that cyclisation proceeded smoothly using the all-carbon tethering chain in the terminal alkyne **1f**, thereby providing a concise route to the usefully functionalised bicyclo[4.3.0]non-1-en-3-one **3f** (entry 4). From both a mechanistic and preparative standpoint the preservation of the original cisoid geometry of the substituents (R and CH_3) around the cyclopropyl ring in the rearranged adducts is also significant, as is the fact that **3e** was isolated as a single geometrical isomer, most probably of *E* configuration.

Finally, from a preparative standpoint, we have also been able, through a judicious choice of experimental conditions, to suppress the rearrangement pathway, and hence to redirect the course of the reaction towards the formation of our originally desired tricyclic systems, as shown for the prototypical substrates **1c**, **1d** and **1e** (Table 1, entries 5, 6 and 7).

From the foregoing examples, it is clear that the presence of the additional methyl group is necessary in order to isolate the skeletally rearranged products **3**. While detailed mechanistic speculation is premature at this stage, it seems reasonable to postulate that the formation of the standard metallacycle **4** (Scheme 2) occurs in all cases as an early common intermediate. At lower temperatures and preferably in the presence of a more coordinating cosolvent such as THF, the major reaction pathway then follows the normal sequence of events to give products of type **2**. At higher temperatures in refluxing benzene, however, the relief of strain in those substrates possessing the additional methyl group engenders rearrangement. A formal mechanistic rationale involves 'edge' attack[7] on the proximal bond of the cyclopropyl ring by the suitably aligned neighbouring cobalt atom (Co_B) to give a π-allyl complex whose protonolysis on the sp^2 carbon would lead to the cation **5**. Such an opening would proceed with retention of configuration at the migrating terminus. Formation of the metallacycle **6** followed by proton loss to liberate the diene system then leads to **7** which can either rearrange or formally be considered as an equivalent of the necessary metallacyclic framework **8** for insertion of carbon monoxide and reductive elimination to afford products of type **3**.

The inherent reactivity of the methylenecyclopropane unit in the present intramolecular variant of the Pauson–Khand reaction can therefore be harnessed, by virtue of controlling a bifurcated reaction pathway, either for the construction of tricyclic systems with preservation of the cyclopropyl ring, or for the preparation of heavily functionalised and stereochemically complex bicyclo[4.3.0]non-1-en-3-one derivatives.

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