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The Pauson–Khand reaction of medium sized *trans*-cycloalkenes†

Cite this: *Chem. Commun.*, 2013, **49**, 3055

Received 5th February 2013,
Accepted 26th February 2013

DOI: 10.1039/c3cc41005f

www.rsc.org/chemcomm

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Medium sized *trans*-cycloalkenes are unusually reactive in the intermolecular Pauson–Khand reaction (PKR) with regard to typical monocyclic alkenes. This is due to the ring strain imparted by the *E* stereochemistry. The PKR of these alkenes offers a modular, regioselective and straightforward entry to *trans* fused [*n*.3.0] bicyclic scaffolds (*n* = 6–8).

The Pauson–Khand reaction (PKR) is the method of choice for a straightforward assembly of cyclopentenone fragments from an alkene and an alkyne.[1] When executed in an intramolecular fashion, this cobalt(0) mediated co-cyclization is an extremely efficient way to build up complexity and ring strain in a single synthetic step from relatively simple precursors. Its continued use in the total synthesis of complex organic molecules speaks for its reliability.[2] Conversely, the intermolecular version of the PKR has not found widespread use despite its potential for bringing together readily available building blocks (alkenes, alkynes) into an elaborated cyclopentanic scaffold in a single step.[3,4] This is basically due to limitations in the substrate scope, particularly concerning the alkene counterpart. Accordingly, much effort has been devoted to unveiling suitable reaction partners beyond the classical norbornene derivatives that the pioneering work of Pauson and co-workers focused on.[5] A key feature of reactive *unfunctionalized* alkenes—not purposely decorated with coordinating groups—[6] is that they contain considerable ring strain embedded in the form of a polycyclic structure or a small ring[7] (Fig. 1). Because of such restraints, general and successful examples of intermolecular PKRs inevitably yield *cis* fused adducts.[8] During our efforts for finding synthetically useful substrates for the intermolecular PKR,[9] we hypothesized whether we could capitalize on ring strain arising from a *trans* linkage in medium sized cycloalkenes such as (*E*)-cyclooctene. This transformation would enable a direct and modular access to a *trans* fused bicyclo[6.3.0]undecane scaffold, which is a common motif among terpenes (Scheme 1).[10]

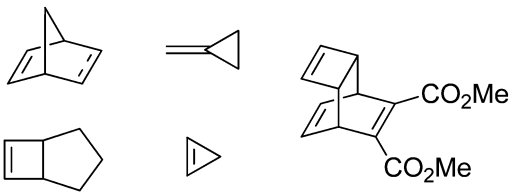
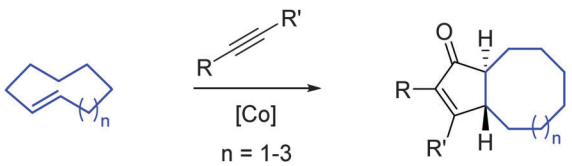


Fig. 1 Reactive alkenes for the intermolecular PKR.

There is a burgeoning interest in the use of (*E*)-cyclooctene derivatives – which easily engage in cycloaddition reactions – as tools for bioconjugation,[11] radiolabelling[12] and other biotechnological applications. Although metal-mediated transformations of (*E*)-cyclooctene are scarce in the literature,[13] several efficient methods for its preparation are available, including flow processes based on the photosensitized isomerization of (*Z*)-cyclooctene.[14] For our purpose, we chose to prepare (*E*)-cyclooctene by a more conventional two-step route from cyclooctene oxide.[15]

Initial attempts to perform the PKR of (*E*)-cyclooctene under thermal activation were unsuccessful. For most alkyne hexacarbonyl cobalt complexes the cycloaddition reaction does not occur significantly below 50 °C, temperature at which (*E*)-cyclooctene already isomerizes back to (*Z*)-cyclooctene at a reasonable rate. The reactivity of (*Z*)-cyclooctene is, in turn, very sluggish: when subjected to reaction with complex **1a**, it does not furnish any product.

To avoid alkene isomerization processes we centered our efforts on the *N*-oxide promoted reactions.[16] Gratifyingly, we found that the trimethylsilylacetylene hexacarbonyl dicobalt complex **1a** smoothly reacted with an excess of the alkene under the presence



Scheme 1 Intermolecular PKR with *trans*-cycloalkenes.

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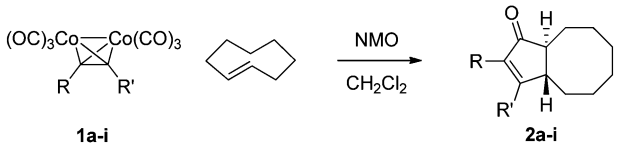
† Electronic supplementary information (ESI) available: Experimental procedures and characterization data for new compounds; 2D NOESY spectrum of **2a**. See DOI: 10.1039/c3cc41005f



Scheme 2 *N*-Oxide promoted PKRs of (*E*)-cyclooctene.

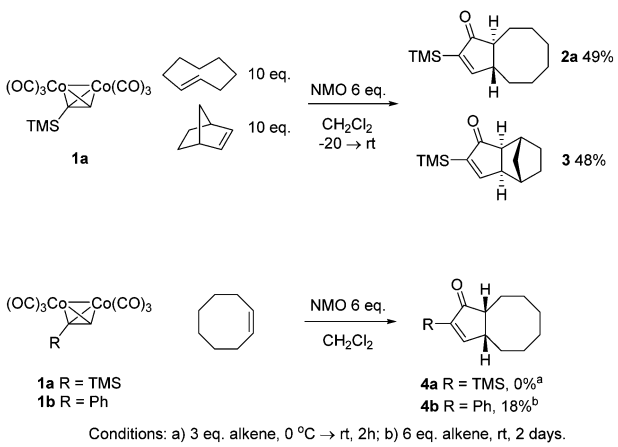
Table 1 Scope of the PKR of (*E*)-cyclooctene[a]

Complex	R	R′	*T*	Product	Yield[b] (%)
1a	TMS	H	0 °C → r.t.	**2a**	84
1b	Ph	H	−20 °C → r.t.	**2b**	69
1c	*n*-Bu	H	−20 °C → r.t.	**2c**	79
1d	CH_2CH_2Ph	H	−25 °C → r.t.	**2d**	92
1e	*n*-Pr	*n*-Pr	−20 °C → r.t.	**2e**	78
1f	CH_2NHBoc	H	−45 °C → r.t.	**2f**	98
1g	CMe_2OH	H	−50 °C → r.t.	**2g**	80
1h	CH_2OTBS	H	0 °C → r.t.	**2h**	38
1i	CH_2OTIPS	CH_2OTIPS	−30 °C → r.t.	**2i**	86

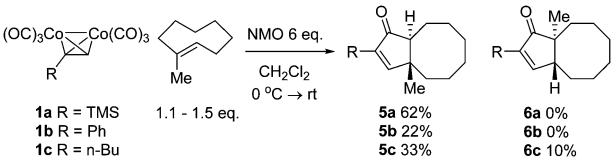
[a] Conditions: 3 eq. alkene, 6 eq. *N*-methylmorpholine *N*-oxide (NMO). [b] Isolated yield.

of *N*-methylmorpholine *N*-oxide (NMO) to yield the corresponding cyclopentenone in excellent yield (Scheme 2). The *trans* stereochemistry at the ring fusion of the adduct was corroborated by a 2D NOESY experiment (see ESI†). We then extended this chemistry to a series of alkyne hexacarbonyl dicobalt complexes with varying degrees of substitution and stereoelectronic properties (Table 1). Good yields of the desired compounds were obtained with most of the substrates, including aliphatic alkynes, alcohols and protected amines. In some instances lowering the reaction temperature resulted in improved yields of the cyclopentenone. For the propargyl derivative **1h**, a particularly challenging substrate for the PKR, we were able to isolate the desired cyclopentenone, albeit in much diminished yields. Lower temperatures did not lead to any improvement in this case.

In an attempt to ascertain the relative reactivity of (*E*)-cyclooctene in a qualitative manner, we then performed a competition experiment (Scheme 3, top). Complex **1a** was subjected to reaction with an equimolar mixture of competing alkenes in large excess with respect to the complex. The results show that (*E*)-cyclooctene is similar in reactivity to norbornene, one of the best alkenes for the PKR. In sharp contrast, (*Z*)-cyclooctene furnishes the corresponding cyclopentenone only in combination with the more reactive phenylacetylene complex **1b**, after an extended reaction time and in low yield (Scheme 3, bottom).



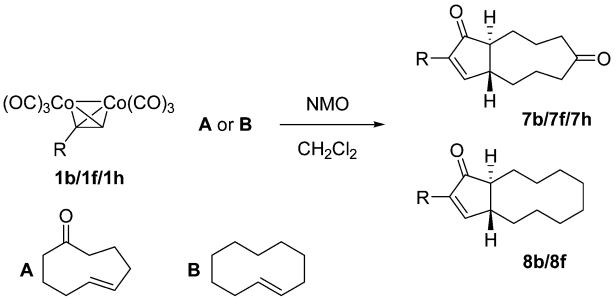
Scheme 3 Relative reactivities of *trans*- and *cis*-cycloalkenes.



Scheme 4 PKRs of (*E*)-1-methylcyclooctene.

Next, we sought to explore the scope of this approach with regard to the alkene counterpart. We were pleased to find that the PKR of (*E*)-1-methylcyclooctene with terminal alkynes (Scheme 4) occurs in a regioselective manner, something which is very rare.[17] When we treated complexes **1a** and **1b** with (*E*)-1-methylcyclooctene, we could only isolate one regioisomer from the crude, corresponding to the 1-methyl substituted bicyclo[6.3.0]undec-10-en-9-one (**5a and 5b**). In the case of complex **1c** a 77 : 23 mixture of regioisomers was obtained, favoring again the γ substituted cyclopentenone **5c**. The lower yields obtained here are due to the slim excess of alkene used in these experiments.

Gratifyingly, larger *trans*-cycloalkenes also participate in the reaction, although significant erosion in the yields is observed as the ring strain diminishes. We subjected (*E*)-cyclonon-5-en-1-one (**A**, prepared in two steps from 2-chlorocyclopentanone)[18] to reaction with various alkyne hexacarbonyl dicobalt complexes under our standard set of conditions (Scheme 5). Whereas no product formation was observed for the less reactive complexes (bearing internal and/or electron rich alkynes), those derived from terminal alkynes with a phenyl or an electron withdrawing substituent furnished the expected cycloalkenediones **7** in moderate yields (Table 2). In a rather anticipated outcome, the even less strained (*E*)-cyclodecene (**B**) only furnished the desired Pauson–Khand adduct **8** with *N*-Boc-propargylamine complex **1f**, under the same set of conditions used for (*E*)-cyclooctene (Table 1). For these less reactive alkenes we reasoned that decomposition of the unsaturated cobalt complex occurring from amine *N*-oxide mediated decarbonylation might effectively compete with the Pauson–Khand reaction manifold, thus leading to significant yield erosion. To overcome this shortcoming we assessed



Scheme 5 PKRs of 9- and 10-membered *trans*-cycloalkenes.

Table 2 Scope of the PKR with larger ring cycloalkenes[a]

Complex	R	Alkene	*T*	Product	Yield[b] (%)
1b	Ph	**A**	−20 °C → r.t.	**7b**	43
1f	CH_2NHBoc	**A**	−45 °C → r.t.	**7f**	49
1f	CH_2NHBoc	**A**	−20 °C	**7f**	67[c]
1h	CH_2OTBS	**A**	−30 °C → r.t.	**7h**	43
1h	CH_2OTBS	**A**	−20 °C	**7h**	61[c]
1f	CH_2NHBoc	**B**	−45 °C → r.t.	**8f**	38
1f	CH_2NHBoc	**B**	−20 °C	**8f**	65[c]
1b	Ph	**B**	−20 °C	**8b**	19[c]

[a] Conditions: 3 eq. alkene, 6 eq. *N*-methylmorpholine *N*-oxide (NMO). [b] Isolated yield. [c] Slow addition of NMO (see ESI).

qualitatively – by TLC monitoring – the lowest temperature at which product formation was taking place significantly. For complex **1f** this turned out to be around −20 °C. Subsequently, we performed the reaction again, but adding the *N*-oxide solution slowly by means of a syringe pump while keeping the reaction at −20 °C, in order to minimize the accumulation of the unsaturated cobalt complex in solution. Employing this methodology, useful yields could be obtained with both **A** and **B** (Table 2). Even the less reactive complex of this series, **1b**, furnished the corresponding adduct with (*E*)-cyclodecene, albeit in low yield.

In conclusion, we have shown that the ring strain contained in medium sized *trans*-cycloalkenes can be exploited in the intermolecular Pauson–Khand reaction to access functionalized bicyclic structures in a stereo- and regioselective manner. Given the fact that 8-, 9-, and 10-membered *trans*-cycloalkenes can be accessed with certain ease (in comparison with norbornene derivatives for instance), this transformation contributes significantly to expand the synthetic utility of the intermolecular PKR.

We are grateful to MINECO (CTQ2011-23620), *Generalitat de Catalunya* (2009SGR 00901) and IRB Barcelona for financial support. A.L. acknowledges MINECO (*Juan de la Cierva* contract) and EU (PEOPLE-2011-CIG-294045) for funding.

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