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

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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]

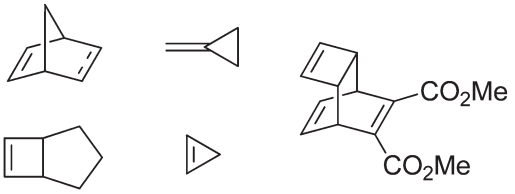
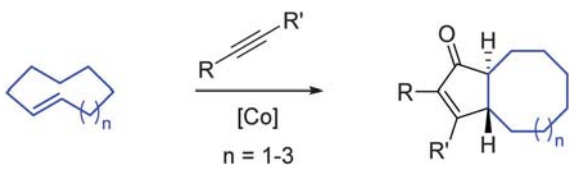


Fig. 1 Reactive alkenes for the intermolecular PKR.

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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