Synthetic Methods

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Synthesis and Application of β-Substituted Pauson–Khand Adducts: Trifluoromethyl as a Removable Steering Group**

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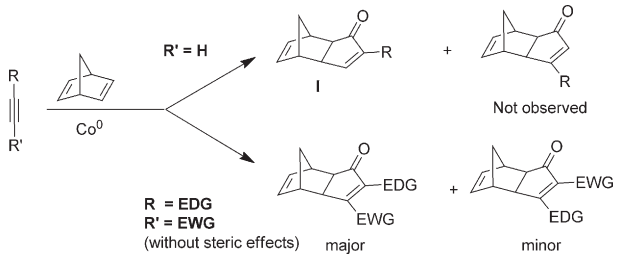
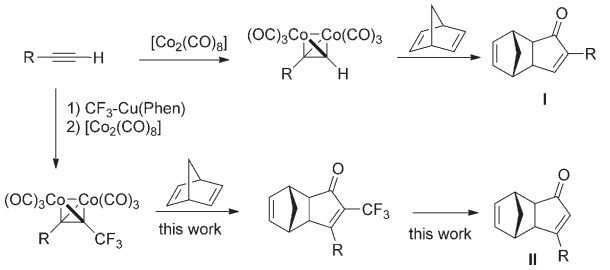
The Pauson–Khand reaction (PKR) is a well-established methodology for the construction of cyclic and polycyclic structures containing five-membered rings.[1,2] Since its discovery in 1973 this reaction has been widely used in organic synthesis. The intramolecular PKR has been extensively applied to build polycyclic compounds. In this case, both the stereo- and regioselectivity are controlled by the substrate. The intermolecular version of the reaction has been less exploited because of its smaller range of reactive alkenes,[3] although it has the advantage that in many cases the stereochemistry can be controlled by the presence of either chiral auxiliaries[4] (bound to the alkyne or the alkene) or chiral ligands[5] (bound to the intermediate cobalt complex). However, one of the difficulties encountered with the intermolecular PKR is the control of the regiochemical outcome.[6–10] While this control is achieved when dealing with terminal alkynes (in this case only the α-substituted cyclopentenone **I** is formed[8]), with internal nonsymmetric alkynes the regiochemistry of the PK adducts depends on a combination of steric and electronic effects, which are difficult to predict (Scheme 1).[7–10] In the absence of steric effects, electron-donating groups (EDGs) show preference for the α-position, whereas electron-withdrawing groups (EWGs) tend to displace to the β-position.[9] However, recent studies have shown that the electronic effects are much less significant than previously described and can, therefore, be overcome by the steric effects.[10]

In previous studies of the intermolecular PKR of nonsymmetric fluorinated alkynes we observed that the electron-withdrawing effect of the fluorinated substituents had little impact on the regioselectivity.[11] Unexpectedly, these fragments ended up in the α-position of the PK adduct. To ascertain whether this was a purely steric effect, herein we studied the regioselectivity of the PKR of a family of trifluoromethylacetylenes. In all cases the regioselectivity was complete, being the PK adduct with the trifluoromethyl in α-position the only one observed. The subsequent study of the reactivity of these adducts allowed us to find an efficient procedure to remove the trifluoromethyl group. Therefore we uncovered a new procedure, outlined in Scheme 2, to prepare the previously unknown β-substituted PK adducts **II**. Here we describe the first synthesis of the regioisomeric PK adducts of terminal alkynes **II** and their practical application to the formal synthesis of α-cuparenone.



Scheme 1. General trends of the regioselectivity of intermolecular PKR.



Scheme 2. Standard intermolecular PKR for internal alkynes affording adducts **I** and the sequence for the synthesis of the regioisomers **II** described here. The trifluoromethylation Cu reagent CF_3-Cu(Phen) was prepared as described in the Experimental Section.

We chose *p*-methoxyphenylacetylene **1a** as a model substrate to explore our synthetic proposal, since the electron-donating nature of the *p*-methoxyphenyl group and its medium size should favor to end up at the α-position. The trifluoromethylated alkyne was synthesized from **1a** by following the procedure described by F.-L. Qing and coworkers.[12] This alkyne was difficult to purify, because of its volatility and highly lipophilic character. These features

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