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Diastereoselective Intermolecular Pauson–Khand Reactions of Chiral Cyclopropenes

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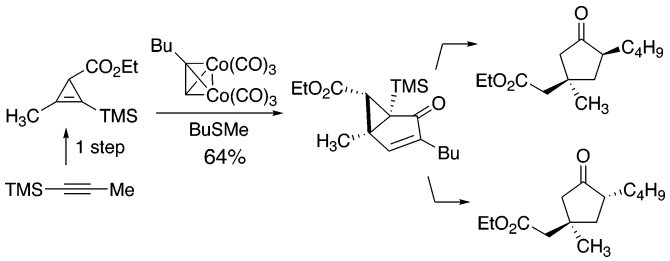
ABSTRACT



In this Letter, it is demonstrated that the unusual reactivity of cyclopropenes can increase the scope and utility of intermolecular Pauson–Khand reactions. The well-defined chiral environment of cyclopropenes has a powerful influence on the diastereoselectivity of the reactions and leads to the production of a single cyclopentenone in each of the described cases. The cyclopropane ring strongly influences the stereochemistry of reactions at the enone, and the three-membered ring can subsequently be cleaved under mild conditions.

The Pauson−Khand cyclocarbonylation is one of the most powerful reactions of the past century,[1] and since its discovery[2] it has been recognized that strained alkenes are usually the "best substrates" for the reaction.[3] Since the original report,[2] there has been a tremendous effort to improve the scope of the reaction and to develop catalytic[1b,4] and asymmetric variants.[1a,d,5] Although the scope of the intramolecular Pauson−Khand reaction has increased dramatically,[1] improving intermolecular protocols to include unstrained alkenes has presented a greater challenge.[1b] A notable exception is the elegant "directed Pauson−Khand" reaction pioneered by Krafft,[6] in which a ligand for cobalt is tethered to the alkene.[1a,b,5b,6] That advance increased the scope of the intermolecular to include mono- and disubstituted alkenes. Still, the development of alternative approaches (e.g., traceless tethers from intramolecular Pauson−Khand reactions)[7] is an active area of investigation because of the clear need to increase the scope of the intermolecular protocol.

A philosophically different approach to improving the intermolecular Pauson−Khand reaction is to embrace the

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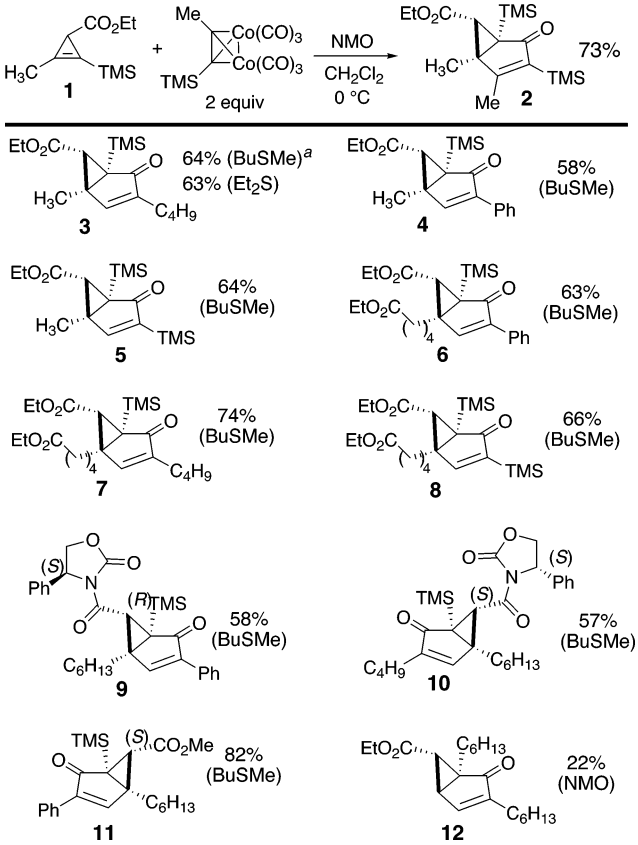
unusual reactivity of strained molecules. The most developed of such approaches is the allenic Pauson−Khand reaction,[1a,d,8] which uses the strain that is inherent to allenes (∼10 kcal/mol) to drive reactivity. This stereospecific[8a] approach has been especially effective for increasing the scope of intramolecular Pauson−Khand reactions. Methylenecyclopropanes[9] and cyclobutenes[10] are further examples of strained alkenes that serve as useful coupling partners in Pauson−Khand-type reactions.

Cyclopropenes are intriguing substrates for synthesis[11] because they are easily prepared and handled but at the same time possess remarkable strain energy (∼55 kcal/mol)[12] and unusual reactivity. Because the chiral environment is compact and well defined, it is particularly suitable for diastereoselective transformations.[11a] In recent years, the synthetic utility of cyclopropenes has been augmented by efficient preparations of enantiomerically enriched derivatives[13] and by the development of facially selective reactions of chiral cyclopropenes.[14] Although it would seem that cyclopropenes would also be excellent substrates for intermolecular Pauson−Khand reactions, there are few examples in the literature.[15]

Percias and co-workers have elegantly demonstrated that cyclopropene itself is a good substrate for intermolecular Pauson−Khand reactions.[15b] Pauson−Khand reactions of chiral cyclopropenes have been addressed in a single study by Smit, Nefedov, and co-workers.[15a] In that work, the methyl ester of cyclopropene **1** was reported to react with dicobalthexacarbonyl complexes of alkynes on dry silica gel. Reactions carried out in hexane were inferior. However, the reported yields were low,[16] the protocol calls for an excess (2 equiv) of the cyclopropene, and the diastereoselectivity of the reaction was unclear.[16] We decided to thoroughly investigate the reactivity of cyclopropene Pauson−Khand reactions and report here that such reactions can proceed with exceptional efficiency in the presence of sulfide[17a] or *N*-oxide[17b,c] promoters. The well-defined chiral environment of cyclopropenes has a powerful influence on diastereoselectivity: a single cyclopentenone was isolated in each of the reactions described in Scheme 1. *exo*-Diastereoselectivity

Scheme 1. Pauson−Khand Reactions of Chiral Cyclopropenes



[a] Alternate conditions: BuSMe or Et_2S, 100 °C, dioxane. All yields are the average of two runs.

was rigorously assigned by X-ray crystallography for a derivative of **9** and by NOE studies for **4**. 2-Silyl-3-alkylcyclopropene-1-carboxylates are particularly good substrates for the Pauson−Khand chemistry. Ethyl 2-hexylcyclopropene-1-carboxylate gives the complementary regioisomer, but the reaction was less efficient and gave **12** in only 22% isolated yield. Although a number of uncharacterized materi-

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(16) Kireev et al.[15a] assigned endo selectivity for adducts prepared on silica. In solvent, we observe exo adducts. Also, the highest yield reported in the paper does not agree with the amounts given in the experimental section.

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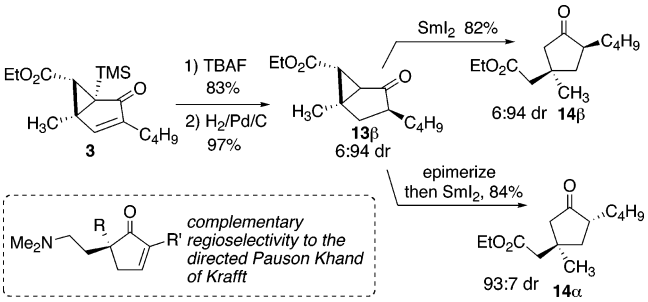
als accompanied the formation of **12**, it was free from isomeric Pauson−Khand adducts. As the cyclopropene is the more valuable of the two reaction partners, all protocols in Scheme 1 use it as the limiting reagent. The best results were obtained when a large excess of promoter was utilized, and while BuSEt was the promoter used for most studies, we demonstrated that inexpensive Et_2S was equally effective for the synthesis of **3**. While most of the reactions in Scheme 1 were carried out with racemic materials, enones **9**−**11** were prepared in enantiomerically enriched form from readily available, resolved starting materials.

The bicyclic enones that are reported here are significant in their own right, as a number of drug candidates share the core structure.[18] Furthermore, cyclopropene Pauson−Khand reactions provide straightforward access to complex cyclopentanones: the three-membered ring strongly influences the stereochemistry of reactions at the enone, and the three-membered ring can be cleaved under mild conditions. For example, Scheme 2 shows that desilylation and hydrogenation provides **13*β*** with high diastereoselectivity, Reductive ring cleavage[15b] gives cyclopentanone **14*β***, which bears all carbon-quaternary and -tertiary stereocenters. The complementary diastereomer **14α** can be obtained by epimerizing **13*β*** to **13α** prior to SmI_2 reduction. Notably, the types of products that are accessible via cyclopropene Pauson−Khand/reductive cleavage complement those that can be formed using directed Pauson−Khand methodology.[6]

In summary, cyclopropenes are a powerful tool for promoting regio- and stereoselective intermolecular Pauson−Khand reactions, and we believe that they will find applications in a host of cycloaddition processes. In future studies, the many opportunities for stereocontrolled synthesis (e.g., stereoselective cuprate additions; specific enolate trapping upon cyclopropane cleavage) will be explored. Further work will also be focused on target directed synthesis and mechanistic understanding of the origin of regio- and stereoselectivity in the cyclopropene Pauson−Khand reaction.

Scheme 2. Diastereoselective Synthesis of Cyclopentanones



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Supporting Information Available: Full experimental and characterization details and ^1H and ^{13}C NMR spectra; X-ray data in CIF format, 2D-NMR and NOE data are provided for stereochemical assignments. This material is available free of charge via the Internet at http://pubs.acs.org.

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