

# Diastereoselective Intermolecular Pauson–Khand Reactions of Chiral Cyclopropenes

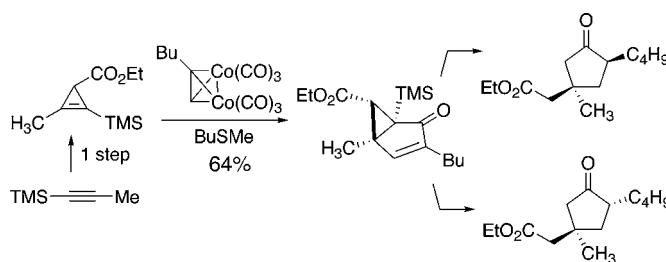
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## ABSTRACT



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,<sup>1</sup> and since its discovery<sup>2</sup> it has been recognized that strained alkenes are usually the “best substrates” for the reaction.<sup>3</sup> Since the original report,<sup>2</sup> there has been a tremendous effort to improve the scope of the reaction and to develop catalytic<sup>1b,4</sup> and asymmetric variants.<sup>1a,d,5</sup> Although the scope of the intramolecular Pauson–Khand reaction has increased dra-

matically,<sup>1</sup> improving intermolecular protocols to include unstrained alkenes has presented a greater challenge.<sup>1b</sup> A notable exception is the elegant “directed Pauson–Khand” reaction pioneered by Krafft,<sup>6</sup> in which a ligand for cobalt is tethered to the alkene.<sup>1a,b,5b,6</sup> 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)<sup>7</sup> 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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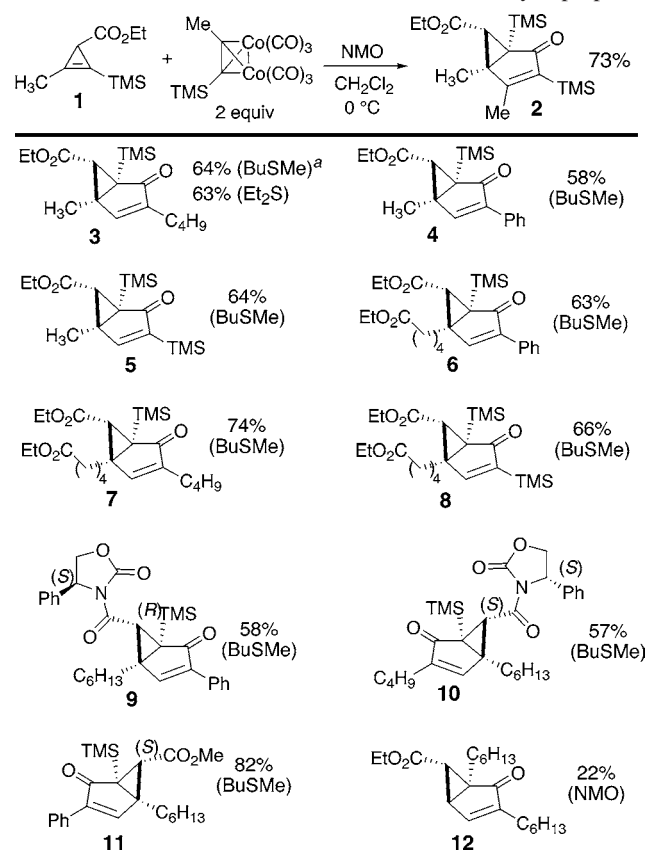
unusual reactivity of strained molecules. The most developed of such approaches is the allenic Pauson–Khand reaction,<sup>1a,d,8</sup> which uses the strain that is inherent to allenes (~10 kcal/mol) to drive reactivity. This stereospecific<sup>8a</sup> approach has been especially effective for increasing the scope of intramolecular Pauson–Khand reactions. Methylenecyclopropanes<sup>9</sup> and cyclobutenes<sup>10</sup> are further examples of strained alkenes that serve as useful coupling partners in Pauson–Khand-type reactions.

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

Percias and co-workers have elegantly demonstrated that cyclopropene itself is a good substrate for intermolecular Pauson–Khand reactions.<sup>15b</sup> Pauson–Khand reactions of chiral cyclopropenes have been addressed in a single study by Smit, Nefedov, and co-workers.<sup>15a</sup> 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,<sup>16</sup> the protocol calls for an excess (2 equiv) of the cyclopropene, and the diastereoselectivity of the reaction was unclear.<sup>16</sup> 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<sup>17a</sup> or *N*-oxide<sup>17b,c</sup> 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



<sup>a</sup> Alternate conditions: BuSMe or Et<sub>2</sub>S, 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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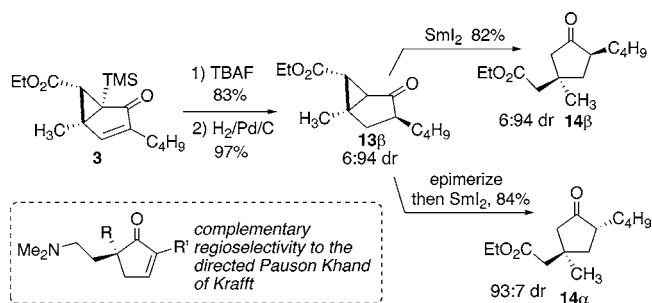
als accompanied the formation of **12**, it was free from isomeric Pauson–Khand adducts. As the cyclopropene is the more valuable of the two reaction partners, all protocols in Scheme 1 use it as the limiting reagent. The best results were obtained when a large excess of promoter was utilized, and while BuSEt was the promoter used for most studies, we demonstrated that inexpensive Et<sub>2</sub>S 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.<sup>18</sup> 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 **13β** with high diastereoselectivity. Reductive ring cleavage<sup>15b</sup> gives cyclopentanone **14β**, which bears all carbon-quaternary and -tertiary stereocenters. The complementary diastereomer **14α** can be obtained by epimerizing **13β** to **13α** prior to SmI<sub>2</sub> 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.<sup>6</sup>

In summary, cyclopropenes are a powerful tool for promoting regio- and stereoselective intermolecular Pauson–Khand reactions, and we believe that they will find applica-

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**Scheme 2.** Diastereoselective Synthesis of Cyclopentanones



tions 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.

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**Supporting Information Available:** Full experimental and characterization details and <sup>1</sup>H and <sup>13</sup>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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