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A Complementary Process to Pauson–Khand-type Annulation Reactions for the Construction of Fully Substituted Cyclopentenones

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Abstract

A complementary process to the Pauson–Khand annulation is described that is well suited to forging densely substituted/oxygenated cyclopentenone products (including fully substituted variants). The reaction is thought to proceed through a sequence of metallacycle-mediated bond-forming events that engages an internal alkyne and a β -keto ester in an annulation process that forges two C–C bonds. A variant of this annulation process has also been established that delivers deoxygenated cyclopentenones that lack the allylic tertiary alcohol.

TOC Graphic:

Carbocyclic systems bearing dense patterns of oxygenation present lingering challenges for efficient chemical synthesis.¹ While diverse polycyclic systems can be forged with a great variety of available ring-forming processes, even the most powerful of modern methods are not well equipped to *simultaneously* establish numerous and/or contiguous fully substituted sp^3 centers (quaternary centers and tertiary alcohols) within the newly formed ring. This widely appreciated characteristic of available methods has resulted in the conception of synthesis strategies to highly substituted and oxygenated carbocycles that proceed in two distinct phases, where ring formation is strategically decoupled from the challenge of establishing densely substituted and/or highly oxygenated motifs.^{1d} Despite impressive innovations that enable hydrocarbon functionalization after ring-formation,² carbocyclic systems that contain numerous/contiguous fully substituted sp^3 carbons remain quite difficult to prepare. Of the many annulation processes routinely employed in target-oriented

SUPPORTING INFORMATION PARAGRAPH:

Experimental procedures and tabulated spectroscopic data for new compounds (PDF) are available free of charge via the Internet at <http://pubs.acs.org/page/jacsat/submission/authors.html>. This includes the preparation of each substrate for the Ti-mediated annulation reactions described.

synthesis campaigns, Pauson–Khand and Pauson–Khand-like reactions³ stand out as particularly powerful for establishing cyclopentenones, especially when conducted in an intramolecular fashion (Figure 1A). Despite the great history of successfully harnessing the power of such annulation processes in complex molecule synthesis,⁴ this class of reactions is most effective with sparsely substituted alkenes (Figure 1B).³ Here, we describe a mode of reactivity that can be employed for the formation of densely substituted cyclopentenones that are not directly accessible with Pauson–Khand-type reactions, enabling direct formation of fully substituted five-membered ring-containing products (Figure 1C).

As illustrated in Figure 2A, we have recently described a metallacycle-mediated annulation reaction that proceeds through intramolecular reaction of an alkyne with a β -diketone,⁵ and have been investigating the potential value of this annulation process in studies targeting a total synthesis of ryanodol.⁶ This previous success served as a foundation to the current investigations that are based on the recognition that a related process may be quite useful for generating densely substituted cyclopentenones that are not accessible with Pauson–Khand-like annulation reactions. Proceeding through unique bond-forming events (Figure 2B), it was anticipated that formation of a metallacyclopentene⁷ (**A**) would be followed by intramolecular reaction with the proximal ketone to generate an oxametallacyclopentene intermediate (**B**). Subsequent engagement of the metal–carbon σ -bond of this intermediate in an intramolecular addition reaction to the tethered ester could result in formation of a bridged polycyclic metal-alkoxide (**C**), the rearrangement and hydrolysis of which would deliver a fully substituted and oxygenated cyclopentenone product.

Investigations began as illustrated in eqs. 1–3 of Figure 3, and demonstrate that the planned annulation process was feasible. These initial experiments revealed that treatment of simple unsaturated β -keto ester substrates with the combination of $\text{Ti}(\text{O}i\text{-Pr})_4$ (2 equiv) and $c\text{-C}_5\text{H}_9\text{MgCl}$ (4 equiv) results in formation of the expected cyclopentenone product in good yield (up to 77%),⁸ noting that the nature of the ester has some impact on efficiency of the process. Perhaps not surprisingly, the *t*-Bu ester **3** was less effective in the annulation reaction, delivering the product **4** in a depressed yield of 50% – it is believed that this decreased efficiency is due primarily to steric effects imposed by the *t*-Bu substituent. Moving on, minor modification of the quaternary center between the two reactive carbonyls had little impact on the efficiency of the process. As depicted in eqs. 4 and 5, substrates **5** and **7** were smoothly converted to the tricyclic products **6** and **8** in 71 and 83% yield, respectively.

The substitution on the alkynyl carbon distal to the β -keto ester appeared to have a significant impact on efficiency of the annulation process. Moving from substrates that contain a methyl group at this position to others that contain a phenyl (eq. 6), substituted allyl (eq. 7), and trimethylsilyl substituent (eq. 8), all resulted in more complex reaction mixtures from which only modest quantities of the expected products could be obtained (45, 42, and 37%, respectively).

Disappointingly, the effectiveness of this organometallic transformation was also negatively impacted by tether length (eq. 9). It is certainly appreciated that tether length plays an important role in the efficiency and viability of all intramolecular Pauson–Khand-like

reactions, and it is indeed typical that substrates with tethers that result in the formation of a five-membered ring are most effective in a great variety of intramolecular reactions.⁹ While it was understood that strategic substitution of the tether in **15** may certainly result in enhanced efficiency for cyclization due to the impact of conformation on rate of cyclization (i.e. Thorpe-Ingold effect),¹⁰ attention was directed to other concerns regarding the potential utility of this new annulation reaction in stereoselective synthesis.¹¹

As illustrated in Figure 3B, the annulation process can be conducted in a highly diastereoselective manner. Notably, with a substrate containing an α -chiral center (**17**), the annulation process proceeds with exquisite levels of stereoselection. Here, the bicyclic product **18** was isolated in 62% yield and with 20:1 dr. When the stereocenter is relocated to the β -position (symmetrically disposed about the alkyne and the ketone), as in **19** (eq. 11), the annulation reaction also proceeds with acceptable efficiency (68%), albeit without observable levels of diastereoselection. In more conformationally constrained systems (i.e. **21** and **23**, eqs 12–13), the annulation also proceeds to deliver fused tricyclic products **22** and **24** as single isomers.¹²

While these latter annulation reactions proceeded in a manner that indicates the great stereocontrol possible in this new carbocycle-forming reaction, the diminished efficiencies (43% and 40%, respectively) were concerning. As illustrated in Figure 4, additional studies have revealed that the initial products of this metallacycle-mediated annulation process are not stable to the reaction conditions. For example, treatment of the tricyclic enone **22** with the combination of $\text{Ti}(\text{O}i\text{-Pr})_4$ and $c\text{-C}_5\text{H}_9\text{MgCl}$, resulted in a relatively clean conversion to the deoxygenated product **25**. As such, competing rates of initial cyclization and subsequent deoxygenation can complicate efforts to utilize this annulation process in diverse molecular environments. If the deoxygenated product is desired, it is possible to conduct a tandem annulation/deoxygenation with synthetically useful efficiency. As illustrated in eqs. 15 and 16, the β -keto ester substrates **2** and **21** are converted directly to the deoxygenated bi- and tricyclic products **26** and **25** in 47% and 43% yield, simply by employing additional quantities of $\text{Ti}(\text{O}i\text{-Pr})_4$ (~4 equiv.) and Grignard reagent (~8 equiv.).

While providing direct access to densely substituted cyclopentenones not readily available from other annulation methods, it was discovered that the products of this annulation process are rather resistant to otherwise straightforward functional group manipulations. That said, redox manipulations that engage the alkene of the enone were straightforward, and provided a means to generate additional stereodefined carbocyclic systems. As illustrated in Figure 5, directed epoxidation, conjugate reduction, and heterogeneous hydrogenation were all effective for stereoselectively generating the bicyclic cyclopentanones **27**, **28**, and **30** (in all cases, no evidence was found for the production of stereoisomeric products).

In conclusion, we report a general annulation process for the synthesis of densely functionalized and highly oxygenated carbocycles that proceeds through the union of alkynes with β -keto esters. The reactions that have emerged through these studies are complementary to classic carbocycle-forming processes in organic chemistry, delivering products not readily available from Pauson–Khand and Pauson–Khand-like annulation reactions. The reactivity realized is thought to proceed through a metallacycle-centered

reaction cascade that engages each metal–carbon bond of a metallacyclopropene in reactions with two different carbonyl systems. In addition to establishing the basic coupling process and reporting preliminary scope substitution (ester and alkyne) and tether length, our studies have also shed light on structural features that lead to stereoselection and led to the discovery of a competing reaction process that results in the formation of deoxygenated products. While complex, and certainly appearing to be sensitive to substrate structure, we look forward to exploring key features of this annulation reaction in ongoing methods development projects and target-oriented synthesis campaigns.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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- (11). Substrates explored for this annulation uniformly contained a quaternary center between the two ketones due to anticipated problems associated with competitive enolization under the reaction conditions. Attempts to employ an α -monosubstituted β -keto imide were unsuccessful. For an interesting selective enolization of such a β -keto imide, see: Evans DA; Clark JS; Metternich R; Novack VJ; Sheppard GS J. Am. Chem. Soc 1990, 112, 866–868.
- (12). Switching the nature of the ethereal solvent used for these annulation reactions was not found to have a significant impact on efficiency (Et₂O vs. THF). Also, the competing process of deoxygenation, as seen in Figure 4, represents an ever-present obstacle for optimization of the annulation reaction to deliver tertiary alcohol-containing products due to what appears to be substrate-dependent variable rates of reaction for the subsequent deoxygenation. Over the course of our initial study, benefits were sometimes observed by minor modification of the reaction conditions or experimental setup (see Supporting Information for experimental details).

A. Examples of natural product synthesis featuring intramolecular “Pauson–Khand”-type annulation reactions:

B. Limitations of Pauson–Khand-type annulation chemistry:

C. Intramolecular alkyne– β -keto ester coupling.

Figure 1.
Introduction.

A. Intramolecular alkyne- β -diketone annulation.

B. Reaction design:

Figure 2.

An approach to cyclopentenone synthesis by intramolecular metallacycle-mediated coupling of an alkyne to a β -keto ester.

Figure 3.
Intramolecular annulation reactions between alkynes and β -keto esters: *initial exploration*.

Figure 4. Products of the annulation are not stable under the reaction conditions; modified reaction conditions realize sequential cyclization and deoxygenation.

Figure 5.
Some stereoselective transformations of the cyclopentenone products.