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Development of a Formal [4 + 1] Cycloaddition: $Pd(OAc)_2$-Catalyzed Intramolecular Cyclopropanation of 1,3-Dienyl β-Keto Esters and MgI_2-Promoted Vinylcyclopropane−Cyclopentene Rearrangement

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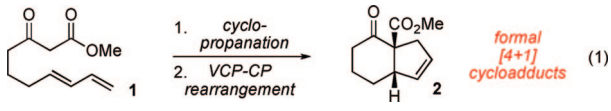
Cycloaddition reactions are unrivaled in their power to rapidly construct complex molecular architectures. While classic cycloadditions such as the Diels−Alder reaction have long been a mainstay of organic synthesis, the use of transition metal reagents has served to greatly increase the scope of cycloaddition chemistry.[1] Indeed, otherwise inaccessible modalities such as [4+4],[2] [5+2],[3] and [2+2+2][4] cycloadditions among many others have been achieved by way of metal catalysis. Remarkably, however, examples of [4+1] cycloadditions remain relatively underdeveloped, despite the obvious synthetic advantages that accompany their realization.[5] To be sure, given the conceptual analogy to [4+2] reactions and the prevalence of five-membered rings in biologically relevant organic architectures, the development of new [4+1] cycloadditions has the potential for a significant impact in the area of complex molecule synthesis.

The value of [4+1] cycloadditions has not escaped the attention of synthetic chemists, and several strategies have been disclosed over the past 30 years aimed at realizing this important goal. Included in this number are direct carbene−diene cycloadditions,[5a−c] stepwise carbenoid−ketene annulations,[5de] and transition metal-catalyzed carbonyl−diene insertions.[5f−m] Perhaps the most versatile strategies to produce [4+1] cycloadducts have been advanced by Hudlicky[5n−p] and Danheiser,[5q−s] whereby 1,3-dienes are subjected to cyclopropanation followed by vinylcyclopropane−cyclopentene (VCP−CP) rearrangement. This ingenious strategy allows for the leverage of powerful cyclopropanation technologies while circumventing the mechanistic difficulties associated with direct [4+1] reaction. Still, both the Hudlicky and Danheiser approaches require the use of α-diazocarbonyls or the generation of reactive carbenes; require harsh conditions for rearrangement; and are not easily lent to broad generality. There thus remains a strong need for more practical and comprehensive solutions to the [4+1] cycloaddition problem.

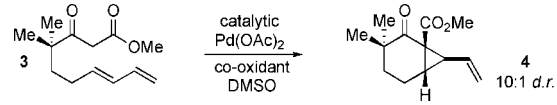
Our group is pursuing the development of an alternative [4+1] protocol based on the cyclopropanation/rearrangement paradigm (eq 1). Specifically, we are interested in the development of oxidative coupling[6] between acidic methylene moieties (e.g., β-keto esters) and 1,3-dienes to produce vinylcyclopropanes directly. In conjunction with VCP−CP rearrangement, this oxidative strategy could serve as a powerful platform for the development of a broad range of [4+1] cycloadditions. Inspired by the work of Bäckvall,[7] who has pioneered oxidative nucleophilic additions to 1,3-dienes, we decided to explore the use of Pd(II)-catalysis to achieve this goal.[8] Herein we describe the development of the first direct metal-catalyzed cyclopropanation of 1,3-dienes and its application to a formal [4+1] cycloaddition protocol.



(1)

The salient points of our cyclopropanation development studies are shown in Table 1. To begin, we found that the use of substrates bearing *gem*-dimethyl substitution in the 4-position was necessary for optimal results due to the propensity of unsubstituted substrates to undergo Saegusa-Ito type oxidation.[9] In our first experiments, treatment of β-keto ester **3** with 40 mol% $Pd(OAc)_2$ and $Cu(OAc)_2/O_2$ co-oxidant in DMSO at elevated temperatures did not produce any of the desired cyclopropane **4** (entry 1). Hypothesizing that the concentration of the nucleophilic enol tautomer of **3** was insufficiently low under these conditions, we attempted to employ base additives, but without success (entry 2).

Table 1. Optimization Studies for Intramolecular Cyclopropanation of 1,3-Dienyl β-Keto Esters



entry	mol % $Pd(OAc)_2$	co-oxidant (equiv)	additive (equiv)	temp (°C)	time (h)	yield (%)
1	40	$Cu(OAc)_2$ (0.2)/O_2	−	65	48	−
2	40	$Cu(OAc)_2$ (0.2)/O_2	K_2CO_3 (2)	65	48	−
3	40	$Cu(OAc)_2$ (0.2)/O_2	$Mg(ClO_4)_2$ (1)	rt	18	35
4	20	$Cu(OAc)_2$ (0.2)/O_2	$Mg(ClO_4)_2$ (1)	rt	48	25
5	20	$Cu(OAc)_2$ (0.2)/O_2	$Mg(ClO_4)_2$ (1)	40	18	39
6	10	$Cu(OAc)_2$ (0.1)/O_2	$Mg(ClO_4)_2$ (1)	65	12	50
7	10	$Cu(OAc)_2$ (2.5)	$Mg(ClO_4)_2$ (1)	65	8	52
8	**10**	**$Cu(O_2CiPr)_2$ (2.5)**	**$Mg(ClO_4)_2$ (1)**	**65**	**12**	**92**

[a] Diastereomeric ratios were determined by GC or ^{1}H NMR analysis.

On the other hand, with the addition of 1 equiv of $Mg(ClO_4)_2$,[10] we observed the formation of the desired vinylcyclopropane **4** in 35% yield after 18 h at room temperature (entry 3). Decreasing the loading of $Pd(OAc)_2$ to 20 mol% resulted in increased reaction time and decreased yield (entry 4), which could be remedied by raising the reaction temperature to 40 °C (entry 5). A further increase of temperature to 65 °C allowed for lowering of the Pd catalyst loading to 10 mol% (with either sub- or superstoichiometric copper co-oxidant) while shortening the reaction time and increasing the yield to ∼50% (entries 6 and 7). Finally, by simply changing the co-oxidant from $Cu(OAc)_2$ to 2.5 equiv of $Cu(O_2CiPr)_2$, we were able to achieve highly efficient formation of **4** in 92% yield with greater than 10:1 diastereoselectivity (entry 8).[11] In this case, substoichiometric $Cu(O_2CiPr)_2/O_2$ was less efficient.

The dramatic improvement in yield that followed from alteration of the carboxylate ligands was due to suppression of formation of a significant (≥20% yield) side product identified to be dienyl acetate **8** (Figure 1). Our rationale for the formation of **8** is shown as part of our overall mechanistic hypothesis.[12] Thus we propose that keto ester substrate **3** coordinates to both the Pd(II) catalyst and $Mg(ClO_4)_2$ to generate intermediate **5**. Intramolecular attack

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of the enol moiety to the Pd-bound diene would then, with loss of RCO_2H, produce π-allyl intermediate **6**. A second nucleophilic attack of the enol function to the π-allyl moiety produces the desired **4**, with concomitant reduction of Pd (thus requiring reoxidation to complete the catalytic cycle). When the carboxylate ligand of intermediate **6** is acetate, reductive elimination to form allyl ester **7** is a competitive process and leads to formation of the diene **8** upon further oxidation. On the other hand, when the carboxylate ligand of **6** is isobutyrate, the reductive elimination pathway is inhibited, allowing for exclusive formation of the desired **4**. The reason for the divergent behavior of these two ligands is at present unclear.

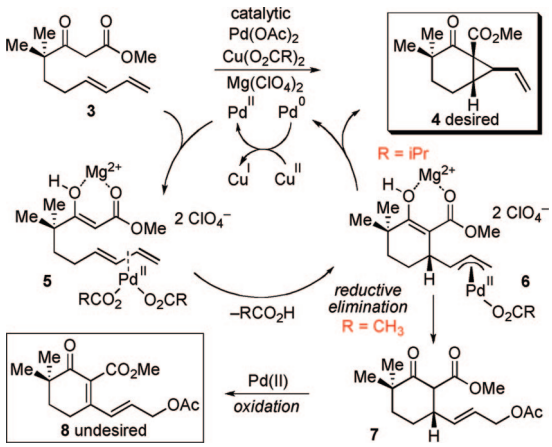


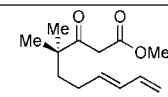
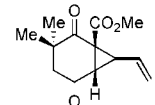
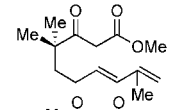
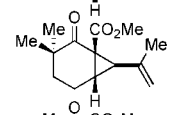
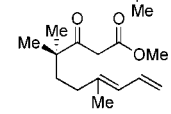
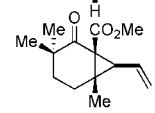
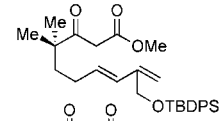
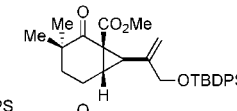
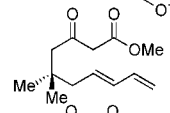
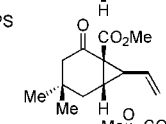
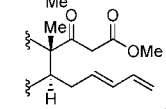
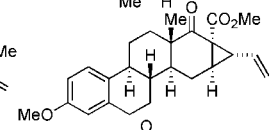
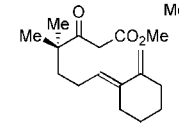
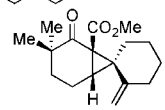
Figure 1. Pd(OAc)$_2$-Catalyzed Intramolecular Cyclopropanation of 1,3-Dienyl β-Keto Esters

In anticipation of our [4+1] process, we have probed the scope of this intramolecular cyclopropanation method (Table 2). In addition to monosubstituted dienyl substrate **3** (entry 1), we have found that substitution at the 2 or 4 position of the diene is readily accommodated, and the corresponding cyclopropyl adducts can be prepared in high yields and with excellent diastereoselectivities (entries 2 and 3). The facile production of the cyclopropane product in entry 3 is especially noteworthy given that two of the three cyclopropyl carbons are quaternary. Notably, we have found that incorporation of a useful functional handle in the form of a silyloxymethyl substituent could be achieved in high yield and with excellent stereoselectivity (entry 4). Furthermore, cyclopropanation could be effected in reasonable yield with *gem*-dimethyl substitution in the δ-position to block undesired substrate oxidation (entry 5). We suggest the lower efficiency of this substrate is due to 1,3-diaxial strain between a methyl substituent and the π-allyl Pd group in the transition state for the cyclopropane-forming event. Interestingly, efficient cyclization could be achieved even in a relatively complex setting, such as with a substrate derived from estrone (entry 6), although the diastereoselectivity in this case was relatively poor. Finally, we found that our method was viable for the production of even highly congested cyclopropanes such as that shown in entry 7, albeit with a yield significantly lower than that with other substrates. The poor efficiency of this cyclization is perhaps not surprising, considering the steric strain experienced by the tricyclic product.

With cyclopropanation conditions in hand, we next sought to transform our vinylcyclopropanes into the corresponding formal [4+1] cycloadducts. To our dismay, none of the standard conditions[13] (pyrolysis, transition metal reagents, or Lewis acids) for vinylcyclopropane−cyclopentene rearrangement were effective for our substrates. We thus sought to identify a workable new protocol.

Because of the mildness and simplicity such a protocol would offer, we were especially intrigued by the notion of employing metal

Table 2. Scope Studies of Pd(OAc)$_2$-Catalyzed Intramolecular Cyclopropanation of 1,3-Dienyl β-Keto Esters[a]

Entry	Substrate	Product	% yield	d.r.[b]
1			92	10:1
2			93	>100:1
3			85	15:1
4			87	20:1
5			52	50:1
6[c]			59	3:1
7[d]			40 (BRSM)	13:1

[a] See Supporting Information for details on substrate synthesis. Reactions were run in the presence of 10 mol% Pd(OAc)$_2$, 2.5 equiv of Cu(O$_2$CiPr)$_2$, and 1 equiv of Mg(ClO$_4$)$_2$ at 0.1 M in DMSO at 65 °C. [b] Diastereomeric ratios were determined by GC. [c] Diastereomeric ratio determined by ^{1}H NMR analysis; the minor diastereomer is epimeric at all cyclopropyl carbons. [d] 50% conversion.

iodide reagents to effect VCP−CP rearrangement.[14] A screen of metal iodide salts under various conditions revealed that MgI_2 in CH_3CN at 40 °C efficiently promoted the rearrangement of a number of our vinylcyclopropane adducts (Table 3).[15] Despite the potential sensitivity to the iodide ion, these conditions were sufficiently mild so as to leave the β-keto ester moiety intact (entries 1−5). Vinyl substitution was well tolerated (entries 2 and 4), as was an allylic silyl ether moiety (entry 4). This protocol was also effective at promoting rearrangement of the complex estrone-derived substrate (entry 5). It should be noted that these conditions were not productive for the rearrangement of the products shown in entries 3 and 7 in Table 2, indicating further development of this protocol is required.

The mechanism by which we presume magnesium iodide effects VCP−CP rearrangement is shown in eq 2. Thus the iodide ion undergoes homoconjugate addition to the vinylcyclopropane substrate **9**, producing an allyl iodide enolate intermediate **10**. The only alkylative pathway available to the (*E*)-**10** isomer would be that of the S$_N$2′ reaction, reforming the starting vinylcyclopropane. To the extent that (*Z*)-**10** is formed, however, this isomer can undergo intramolecular S$_N$2 alkylation to produce the cyclopentene [4+1] cycloadduct **11**.

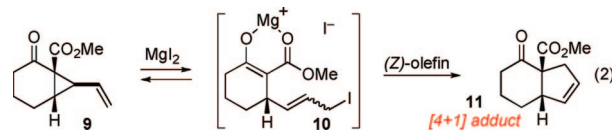
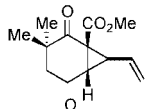
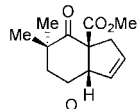
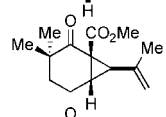
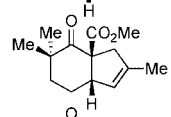
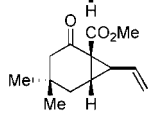
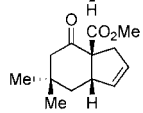
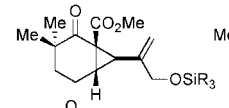
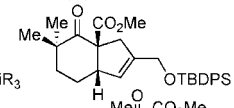
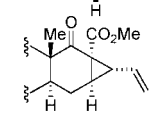
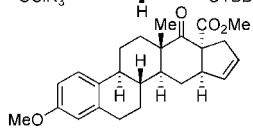


Table 3. Formal [4 + 1] Products via MgI_2-Promoted Vinylcyclopropane−Cyclopentene Rearrangement[a]

Entry	Substrate	Product	time (h)	% yield
1			4	86
2			6	75
3			6	80
4			8	74
5			8	78

[a] Reactions were run in the presence of 150 mol% MgI_2 at 0.2 M in CH_3CN at 40 °C.

Importantly, although the MgI_2 promoted VCP−CP rearrangement is not compatible with DMSO as solvent, the vinylcyclopropanation is operative in acetonitrile, thus raising the hope that this two-step [4+1] protocol can be rendered into a one-pot procedure. This possibility has not yet been confirmed experimentally.

In conclusion, we have developed a new formal [4+1] cycloaddition protocol for the conversion of 1,3-dienyl β-keto esters to bicyclic cyclopentene products. The key components of this strategy are the development of a Pd(II)-catalyzed intramolecular cyclopropanation reaction and a new mild VCP−CP rearrangement promoted by MgI_2. Currently, we are working to (1) extend this strategy to include other nucleophilic moieties, (2) remove the need for a *gem*-dimethyl blocking group, and (3) render this sequence into a one-pot protocol.

Acknowledgment. We thank the Parkin Group for obtaining a crystal structure, and the NSF (CHE-0619638) is thanked for acquisition of an X-ray diffractometer.

Supporting Information Available: Experimental procedures and product characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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