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Regiocontrolled Oxidative C−C Coupling of Dienol Ethers and 1,3-Dicarbonyl Compounds

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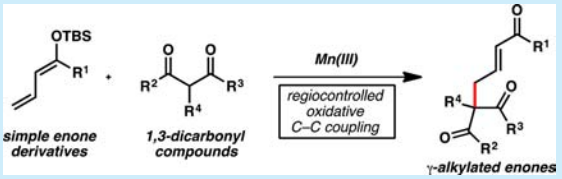
Supporting Information

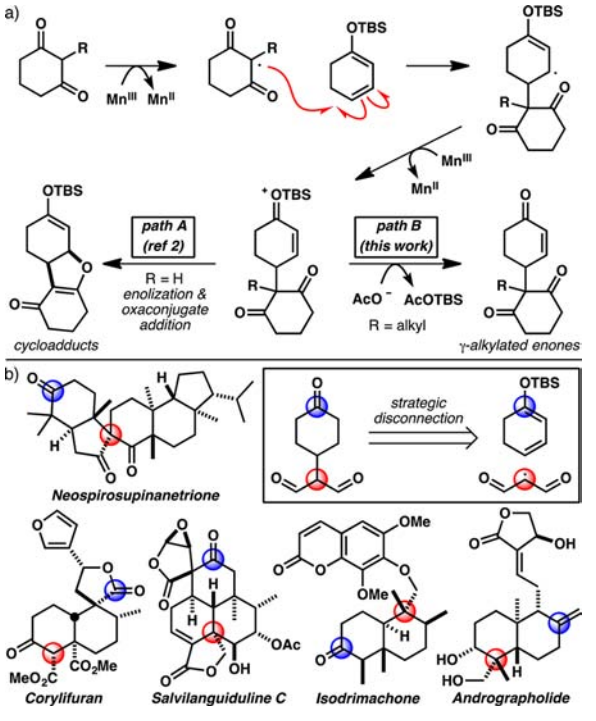
ABSTRACT: A strategy for synthesis of γ-alkylated enones through oxidative coupling of siloxydienes and 1,3-dicarbonyl compounds is reported. This method is an interrupted form of our formal [3 + 2] cycloaddition method reported previously. The present work excels in generating all-carbon quaternary centers via C−C bond formation at the remote γ-site which is traditionally challenging to functionalize. Stereoselectivity and functional group tolerance are examined in complex systems. Double alkylation reactions are also described.



Carbonyl chemistry is a cornerstone of organic synthesis owing to the wide variety of transformations based on the reactivity of this functional group. Reactions such as carbonyl additions, enolate alkylations, and conjugate additions to enones are among the most prominent carbonyl transformations and generate new bonds at the carbonyl carbon, the adjacent α-carbon, or the β-carbon, respectively. Methods for functionalization of the γ-carbon are considerably less common, however.[1] As a result, the synthesis of target molecules bearing elements of complexity at this more remote site remain a substantial challenge.

We recently reported the use of Mn(III) salts to mediate the efficient, regiocontrolled formal [3 + 2] cycloaddition of dienol ethers and β-dicarbonyl compounds.[2−4] This oxidative strategy represents a formal umpolung of reactivity[5] with several distinct advantages, including the fact that the radical precursor requires no prefunctionalization with reactive groups such as halogens. Our methodology enables the stereoselective synthesis of substituted tetrahydrofuran derivatives from readily available precursors. A core component of this transformation is the selective generation of a new C−C bond at the terminus of a conjugated π-system (Scheme 1a, path A).[6] We reasoned that the complete regiocontrol in the C−C bond formation process is due to the formation a doubly stabilized alkoxyallyl radical intermediate. Further oxidation of this radical could generate a cationic silylated enone that is susceptible to oxaconjugate addition to furnish the cycloadduct.[7] We hypothesized that if the cyclization step were interrupted then the regio- and stereocontrol inherent in the C−C coupling could be leveraged toward the synthesis of valuable γ-alkylated enone compounds that are poised for further manipulations (path B).[8] We recognized the power of this hypothetical method to construct key strategic bonds in complex natural products (Scheme 1b) with a retron indicated by an acceptor-type carbonyl or carbonyl derivative (highlighted in blue) situated four bonds away from a donor atom (highlighted in red) flanked by oxygenated carbons. Herein, we describe our successful implementation of the interrupted cycloaddition strategy to achieve the efficient synthesis of enone compounds bearing remote all-carbon quaternary centers in high yield.[9]

Scheme 1. Strategy for γ-Alkylation and Relevant Natural Products



The feasibility of achieving an interrupted cyclization first became apparent when we attempted our [3 + 2] cycloaddition reaction using the isophorone-derived dienol ether **1a** with diketone **2a** (eq 1). We observed none of the desired tetrahydrofuran product, but a small amount of the C−C

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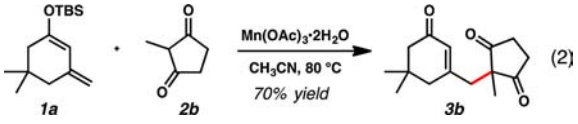
coupling product **3a** was isolated.[10] We reasoned that the presence of two substituents at the β-carbon of the enone likely hinders the oxaconjugate addition step of the putative mechanism. Based on our mechanistic hypothesis for the process, we predicted that a diketone incapable of enolization would completely prevent cyclization and allow the evidently slow desilylation process to predominate (Scheme 1, path B). Indeed, when substituted diketone **2b** was employed in an analogous reaction the yield of the C−C coupling product (**3b**) increased substantially (eq 2).

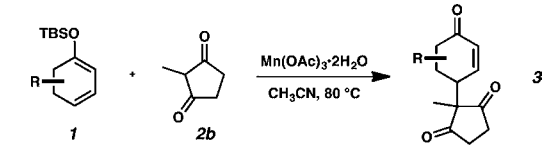


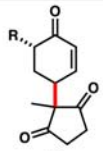
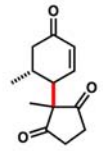
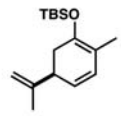
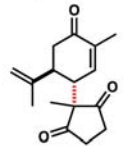
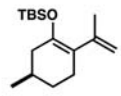
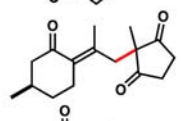
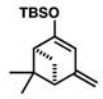
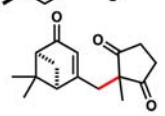
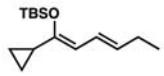
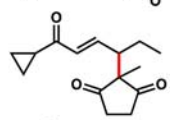
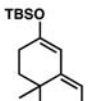
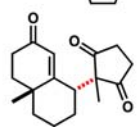
With this validation of our novel strategy for γ-alkylation, we next examined the scope of the coupling using a variety of dienol ether substrates and diketone **2b** (Table 1). The siloxydienes are readily prepared from the parent enone compounds through thermodynamically controlled enolization and silylation,[11] or via soft enolization.[2,8b,e] 1,3-Stereoinduction is significant, but somewhat less than expected from the corresponding cyclization reactions (entries 1−3).[2] Diastereoselectivity was very high, however, when the existing stereocenter was located near the reaction site (entries 4 and 5). Dienol ethers derived from the terpenes carvone (**1f**), pulegone (**1g**), and verbenone (**1h**) demonstrate the tolerance of isolated alkenes and strained rings near the reactive group (entries 5−7). The synthesis of carvone derivative **3g** highlights the ability to synthesize all-carbon quaternary centers at sterically congested sites under mild conditions. The high yield of pulegone derivative **3h** indicates that constrained dienes are not required for reactivity. This was further verified by alkylation of linear diene **1i** (entry 8). Stereoselectivity in a decalin system was excellent, with a single diastereomer of triketone **3k** observed.

Variation of the dicarbonyl coupling partner revealed that a number of functionalized compounds bearing quaternary centers could be generated readily under our standard reactions conditions (Table 2). In terms of yield and stereoselectivity, the six-membered ring diketone **2c** performs almost identically to the five-membered ring diketone (entries 1−3). Acyclic diketone **2d** is also viable in the alkylation reaction (entry 4). Ketolactones and ketoesters are excellent substrate classes, although diastereoselectivity in the formation of the all-carbon quaternary center is modest (entries 5−8). In our earlier work malonate esters did not react,[2] perhaps due to a higher barrier to oxidation. We have since discovered that Meldrum's acid[12] derivatives function as surrogates for malonates, thereby further expanding the scope of viable coupling partners (entry 9).

In the course of our prior studies of the related [3 + 2] cycloaddition reaction we observed that substrates derived from β,β-disubstituted enones did not deliver the tetrahydrofuran products (see eq 1). This observation could be explained by a sluggish oxaconjugate addition step or perhaps a thermodynamic preference for the enone form. We recognized this as an opportunity to explore formation of 2:1 adducts through

Table 1. Scope of Dienol Ether Coupling Partner[a]



entry	dienol ether			product		yield (%)
1		R = H	1b		3c	76
2		R = Me	1c		6.6:1 dr 3d	72
3		R = Allyl	1d		6.2:1 dr 3e	59
4			1e		>20:1 dr 3f	53
5			1f		>20:1 dr 3g	35
6[b]			1g		3h	86
7[c]			1h		3i	69
8[c]			1i		3j	62
9[c]			1j		3k	45

[a]Isolated yield (average of two runs) from reaction of dienol ether **1** (0.25 mmol), diketone **2b** (1.1 equiv), and $Mn(OAc)_3\cdot 2H_2O$ (2.25 equiv) in CH_3CN (7.5 mL) at 80 °C for 2−4 h. [b]1:1 mixture of E/Z isomers. [c]Yield calculated over two steps from the corresponding ketone using crude dienol ether.

sequential double oxidation of an unsubstituted dicarbonyl compound.[13] To test this idea, we reexamined the coupling isophorone-derived siloxydiene **1a** and dione **2a** in a 2:1 molar ratio. We were delighted to find that the double alkylation product **3u** could be isolated in 80% yield under these conditions (Table 3, entry 1).[10] The verbenone-derived siloxydiene behaved similarly (entry 2). Meldrum's acid (**2j**) undergoes double alkylation with dienol ether **1b** to generate contiguous tertiary−quaternary−tertiary centers in a single step, although no diastereoselectivity was observed. 1,3-Indanedione also furnished the 2:1 addition product with no evidence of competing oxaconjugate addition. The pseudoantiaromatic character of the enol form of this diketone likely negates the alternative pathway.

We were surprised to discover that ethyl benzoylacetate (**2l**, eq 3) delivered a 1:1 adduct in modest yield with no detectable double addition or oxaconjugate addition products.[14] The keto form is likely stabilized in this case due to electron releasing substituents affixed to each carbonyl, although the steric contribution is uncertain. We also found that 2,2-dimethyl-3,5-

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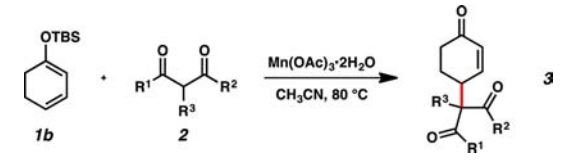
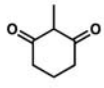
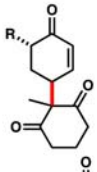
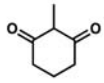
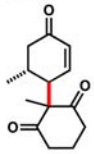
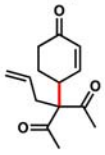
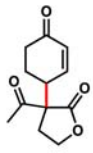
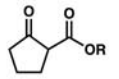
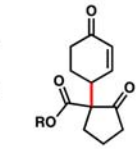
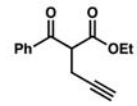
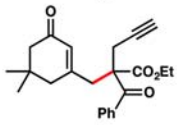
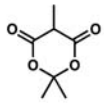
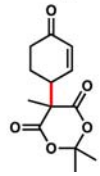
Table 2. Scope of Dicarbonyl Coupling Partner[a]



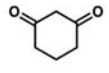
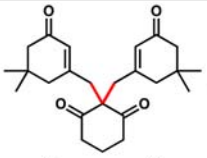
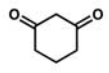
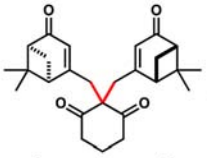
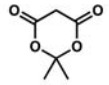
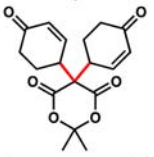
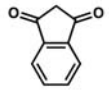
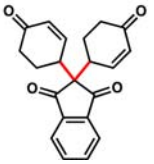
entry	dicarbonyl compound		product			yield (%)
1		2c		R = H	3l	80
2[b]		2c		R = Me 6.6:1 dr	3m	74
3[c]		2c		>20:1 dr	3n	54
4		2d			3o	65
5		2e		2:1 dr	3p	86
6		R = Me 2f		1.7:1 dr	3q	78
7		R = Allyl 2g		1.8:1 dr	3r	70
8[d]		2h			3s	61
9		2i			3t	56

[a]Isolated yield (average of two runs) from reaction of dienol ether **1b** (0.25 mmol), diketone **2** (1.1 equiv), and $Mn(OAc)_3{\cdot}2H_2O$ (2.25 equiv) in CH_3CN (7.5 mL) at 80 °C for 2–4 h. [b]Reaction with dienol ether **1c**. [c]Reaction with dienol ether **1e**. [d]Reaction with crude dienol ether **1a**. Yield calculated over two steps from the corresponding ketone using crude dienol ether.

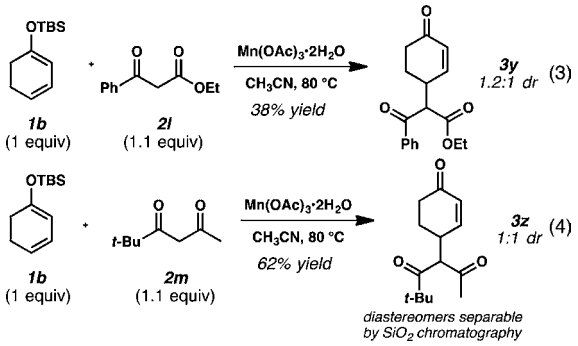
hexanedione (**2m**) furnished the 1:1 adduct and, remarkably, the two product diastereomers were separable by silica gel chromatography (eq 4). The evident stability of the keto form suggests that significant allylic strain in the enol form likely precludes further reaction in this case.

To further explore the synthetic utility of our Mn-mediated coupling, we envisioned utilizing chlorinated acetoacetate **2n** to access products in a higher oxidation state (Scheme 2a). The coupling proceeded in 65% yield, and upon exposure of the product to DBU, elimination and isomerization proceeded to furnish the formal α-arylation product **4** in excellent isolated yield. Encouraged by our success with sensitive functional

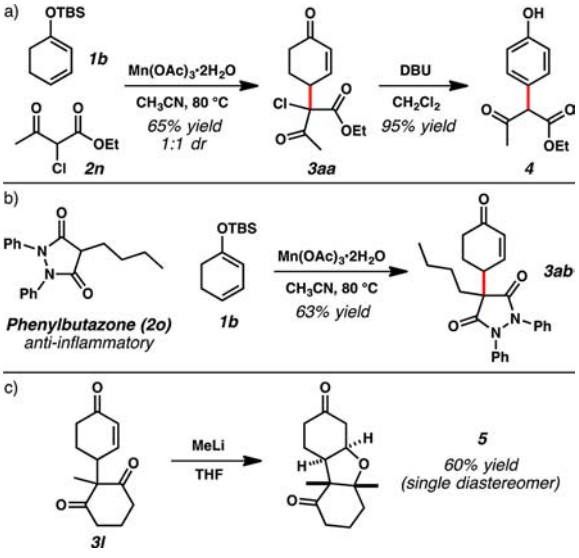
Table 3. Double Alkylation Reactions[a]

entry	dicarbonyl compound	dienol ether	product		yield (%)
1	 2a	 1a		3u	80
2	 2a	 1h		3v	78
3	 2j	 1b		3w 1:1 dr	64
4	 2k	 1b		3x 2.6:1 dr	70

[a]Isolated yield (average of two runs) from reaction of diketone **2** (0.125 mmol), dienol ether **1** (2 equiv), and $Mn(OAc)_3{\cdot}2H_2O$ (4.48 equiv) in CH_3CN (7.5 mL) at 80 °C for 2–4 h.



Scheme 2. Synthetic Applications of Oxidative Coupling



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groups, we examined coupling of the commercially available anti-inflammatory compound phenylbutazone (**2o**) and found good results under our standard coupling conditions (Scheme 2b). Finally, exposure of coupling product **3l** to MeLi led to a remarkable chemo- and stereoselective carbonyl addition/cyclization cascade, yielding tetrahydrofuran derivative **5** as a single isolated diastereomer. This transformation supplements our prior formal cycloaddition methodology[2] and enables the synthesis of derivatives bearing vicinal fully substituted carbon centers through a simple, versatile protocol.

In summary, we have developed an efficient means of C−C bond formation in enone systems using readily available silyl dienol ethers and dicarbonyl compounds. This transformation is a formal umpolung of carbonyl reactivity and does not require prefunctionalization of the radical precursor with halogens. Our method excels in the formation of challenging all-carbon quaternary centers under mild conditions that permit excellent functional group compatibility. This work complements our prior [3 + 2] cycloaddition methodology and provides access to versatile enone products that are attractive building blocks for complex molecule synthesis. We anticipate that this enabling technology will permit exploration of new chemical space and contribute to the design of efficient synthetic strategies.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01397.

Experimental procedures, characterization data (PDF)
Copies of NMR specta (PDF)

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Notes

The authors declare no competing financial interest.

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