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Communication

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Cu-Catalyzed Stereoselective γ-Alkylation of Enones

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Supporting Information

ABSTRACT: A general regio- and stereoselective γ-C−C bond formation is achieved using α-halocarbonyl compounds and dienol ethers via Cu(II) catalysis. This method constitutes a novel approach to the challenging 1,6-dioxygenation motif. A range of γ-substituted enones, including many bearing all-carbon quaternary centers, are available through a simple protocol under mild reaction conditions with superb functional group compatibility. Excellent stereoinduction is observed providing controlled access to challenging stereochemical arrays.

The carbonyl group is arguably the most important and versatile functional group in synthetic chemistry. This moiety is valuable not only for the useful electrophilic character of the carbonyl carbon but also due to the ability to manipulate the surrounding atoms to construct new bonds.[1] Utilizing these features of carbonyl reactivity in combination, powerful strategies for synthesizing dicarbonyl compounds have been developed. Claisen condensation, enolate alkylation with α-halocarbonyl electrophiles, and Michael addition protocols are robust classical platforms for generating 1,3-, 1,4-, and 1,5-dicarbonyl compounds. The homologous 1,6-dicarbonyl motif is considerably more challenging, however. Dienolate derivatives of enones posit a potential solution,[2] but such hypothetical reactions are often complicated by the decreased electron density at the distant γ-site, and most electrophiles are found to react preferentially at the more nucleophilic α-C (Scheme 1, path A).[3] As a result, it has been necessary to rely on antithetical disconnections such as oxidative cleavage of cyclohexenes, but these methods have substantial scope limitations (path B). The need for a direct γ-C−C bond formation technique is therefore quite significant.

Our research program has aimed to develop robust systems for bond formation at γ-sites that are directly applicable to the synthesis of valuable target molecules bearing substitutions at this location.[4] One potential strategy involves the addition of radical intermediates to dienol ethers which are, in turn, readily available enone derivatives (Scheme 1, path C).[4b,c] This design is based on the hypothesis that site selectivity in bond formation will be controlled through a preference for the stabilized oxyallyl radical that is only accessible through the γ-addition pathway. Seminal reports by Kim and co-workers suggested the viability of this design using specialized substrates such as hydroxamic acids, but a general application of this strategy to common ketone synthesis has not been reported.[3h,i] We have therefore sought a system to resolve the significant and long-standing problem of γ-C−C bond formation in simple enone systems. In this communication we disclose the first regio- and stereoselective γ-alkylation protocol that enables direct synthesis of 1,6-dicarbonyl compounds from simple enones and readily available α-halocarbonyl compounds using Cu catalysis.

At the outset, we were attracted to recent reports of Cu catalysts capable of activating α-haloesters toward addition to π-

Scheme 1. Strategies for 1,6-Dicarbonyl Synthesis

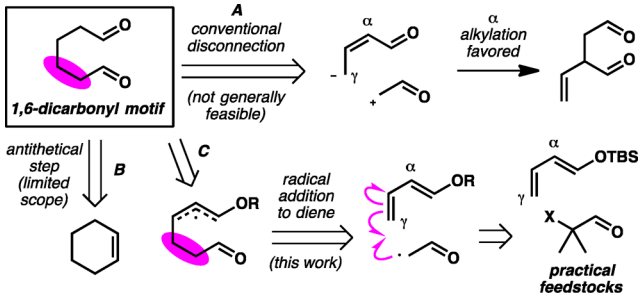
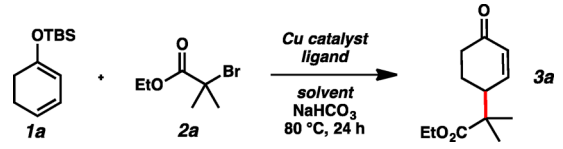


Table 1. Optimization of Radical Coupling Conditions[a]



entry	Cu catalyst (mol %)	ligand (mol %)	solvent	% yield
1	none	none	toluene	0
2	$Cu(OTf)_2$ (10)	none	toluene	0
3	$Cu(OTf)_2$ (10)	bipy (20)	toluene	0
4	$Cu(OTf)_2$ (10)	TMEDA (20)	toluene	16
5	$Cu(OTf)_2$ (10)	PMDTA (20)	toluene	58
6	CuI (10)	PMDTA (20)	toluene	16
7	$CuCl_2$ (10)	PMDTA (20)	toluene	12
8	$CuBr{\cdot}SMe_2$ (10)	PMDTA (20)	toluene	49
9	$CuCO_3$ (10)	PMDTA (20)	toluene	42
10	none	PMDTA (20)	toluene	0
11	$Cu(OTf)_2$ (10)	PMDTA (20)	CH_3CN	73
12	$Cu(OTf)_2$ (10)	PMDTA (20)	THF	77
13	$Cu(OTf)_2$ (10)	PMDTA (20)	1,4-dioxane	86
14	$Cu(OTf)_2$ (10)	PMDTA (20)	DCE	92
15	***$Cu(OTf)_2$ (7.5)***	***PMDTA (15)***	***DCE***	***94***

[a]Isolated yield from reaction of dienol ether **1a** (0.25 mmol), α-haloester **2a** (1.5 equiv), $NaHCO_3$ (1.0 equiv), Cu catalyst, and ligand in 1 mL of solvent at 80 °C for 24 h.

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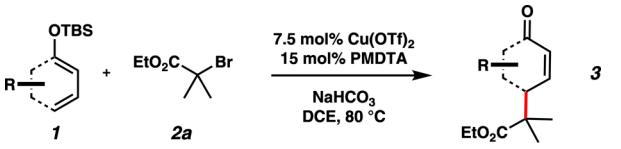
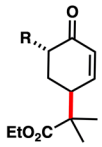
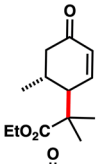
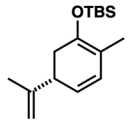
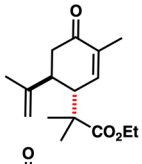
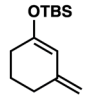
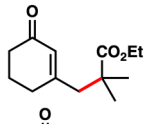
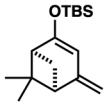
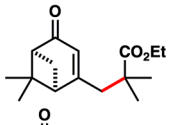
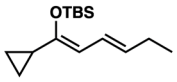
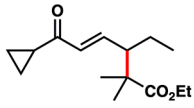
Table 2. Scope of Siloxydiene Coupling Partner[a]



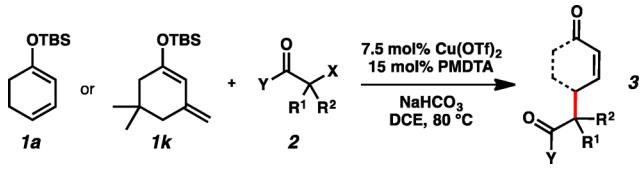
entry	siloxydiene		product		% yield
1		**1a** R = H		**3a**	94
2		**1b** R = Me		**3b** >20:1 dr	82
3		**1c** R = Bn		**3c** >20:1 dr	88
4		**1d** R = Allyl		**3d** >20:1 dr	64
5		**1e** R = CH_2CO_2t-Bu		**3e** >20:1 dr	72
6		**1f**		**3f** >20:1 dr	68
7		**1g**		**3g** >20:1 dr	76
8[b]		**1h**		**3h**	75
9[b]		**1i**		**3i**	71
10[b]		**1j**		**3j**	64

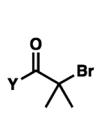
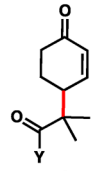
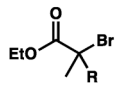
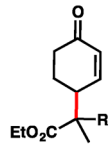
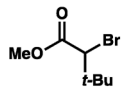
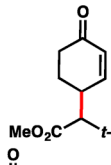
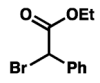
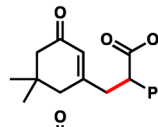
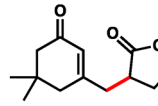
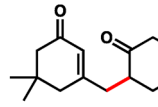
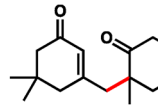
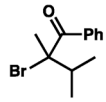
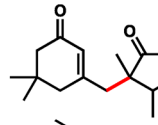
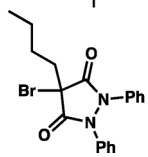
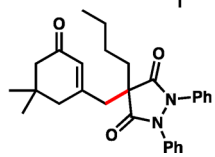
[a]Isolated yield (average of two runs) from reaction of dienol ether **1a** (0.25 mmol), α-haloester **2a** (1.5 equiv), $NaHCO_3$ (1.0 equiv), 7.5 mol % $Cu(OTf)_2$, and 15 mol % PMDTA in 1 mL of DCE at 80 °C for 24 h. [b]Isolated yield over two steps from the corresponding enone.

systems.[5] Although the mechanism of these transformations has not been rigorously supported, we hypothesized that a C-centered radical may be a key intermediate that is potentially useful in our proposed coupling.[6] We selected readily available, stable TBS dienol ether **1a**[4b,c] and commercially available α-haloester **2a** to examine the γ-alkylation with a range of Cu catalysts in toluene solvent with a heterogeneous base (Table 1).[7] We quickly learned that the supporting ligand is critical to reactivity: unligated Cu(II) and the bipy complex each fail to catalyze the coupling. Tertiary amine Cu complexes are catalytically active, and commercially available pentamethyldiethylenetriamine (PMDTA) is particularly effective (entries 1−5).[5] Other Cu salts were inferior to $Cu(OTf)_2$, and Cu is necessary for the reaction to occur (entries 6−10). A solvent survey found 1,2-dichloroethane (DCE) to be the optimal solvent (entries 11−14). Reduction of the catalyst loading to 7.5 mol % resulted in isolation of the γ-alkylation product **3a** in 94% yield.[8]

We have observed that a variety of dienol ethers are viable substrates for the γ-alkylation reaction (Table 2). These dienol ethers are prepared by straightforward enolization/silylation under basic conditions or through soft enolization techniques.[4b,c] When the enone precursor contained an α-substituent, we observed exceptional stereoselectivity in the alkylation reaction, delivering the 1,6-dicarbonyl products in high yield as a single detectable diastereomer (entries 2−5). This stereoinduction was maintained with β-substituted enones as well, delivering the *anti* stereodiads as a single isolated diastereomer (entries 6−7). Dienols containing an exocyclic reactive site also proved to be very good substrates for the coupling reaction (entries 8−10).

Table 3. Scope of α-Halo Coupling Partner[a]



entry	siloxydiene	halocarbonyl		product		% yield
1	**1a**		**2b** Y = OAllyl		**3k**	80
2	**1a**		**2c** Y = OPropargyl		**3l**	84
3	**1a**		**2d** Y = OCH_2CH_2OH		**3m**	93
4	**1a**		**2e** Y = NEt_2		**3n**	77
5[b]	**1a**		**2f** Y = $SC_{18}H_{37}$		**3o**	97
6	**1a**		**2g** Y = H		**3p**	85
7	**1a**		**2h** R = CO_2Et		**3q**	93
8[c]	**1a**		**2i** R = H		**3r**	90
9[d]	**1a**		**2j**		**3s**	82
10[e]	**1k**		**2k**		**3t**	74
11[e]	**1k**		**2l**		**3u**	65
12[e]	**1k**		**2m**		**3v**	83
13[e]	**1k**		**2n**		**3w**	57
14[e]	**1k**		**2o**		**3x**	72
15[e,f]	**1k**		**2p**		**3y**	85

[a]Isolated yields. See Table 2 for reaction conditions. [b]Reaction in EtOH solvent. [c]1:1 dr. [d]1.4:1 dr. [e]Isolated yield over two steps from the corresponding enone. [f]Reaction at 22 °C.

Modification of the α-halocarbonyl coupling partner provided a test of functional group tolerance (Table 3). We were delighted to discover that alkenes, alkynes, unprotected hydroxyl groups, amides, thioesters, and even aldehydes are compatible with our protocol (entries 1−6). Use of an α-

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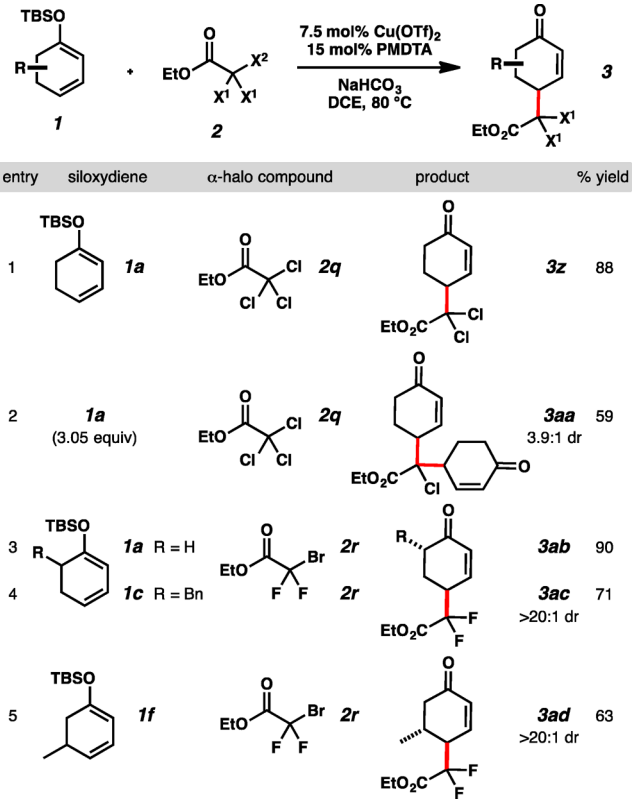
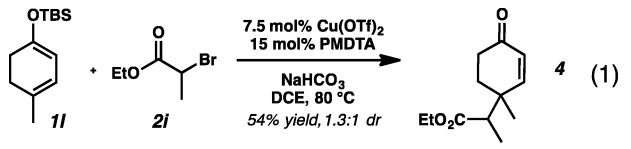
Table 4. α-Polyhalo Coupling Partners[a]



[a]Isolated yields. See Table 2 for reaction conditions.

bromomalonate, an α-bromopropionate, a neopentyl bromide, or a benzylic bromide each provided excellent results, indicating both steric and electronic flexibility in the halide component (entries 7−10). Isophorone-derived dienol ether **1k** was readily alkylated with either cyclic or acyclic α-halocarbonyls to generate tertiary or all-carbon quaternary centers in high isolated yields (entries 10−15). Notably, α-chlorocyclohexanone (**2m**) performed well under our standard conditions and the use of a brominated derivative of the commercialized antiinflammatory agent phenylbutazone (**2p**) delivered the coupling product in very good yield when the reaction was conducted at 22 °C.

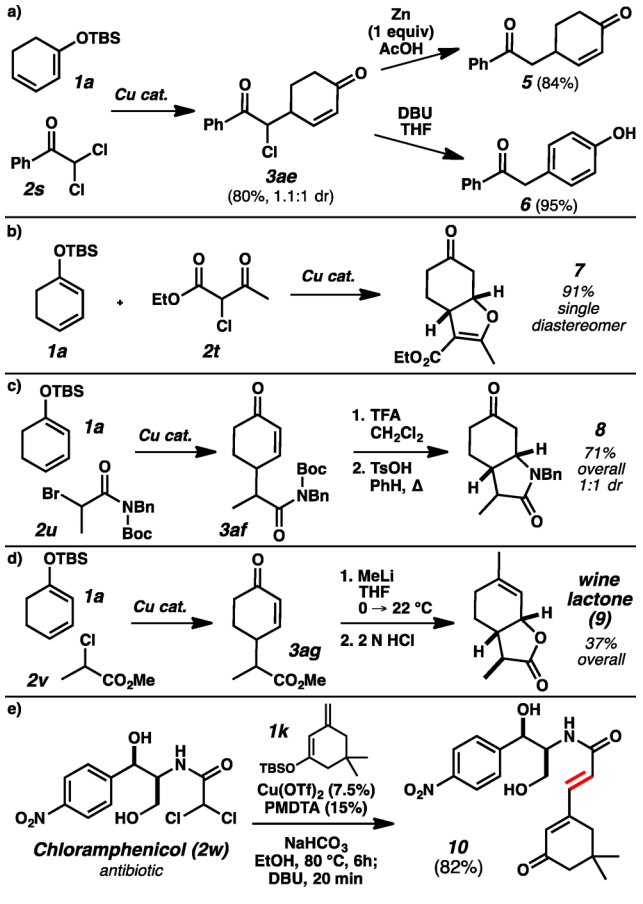
Seeking to test the limits of our method for preparing sterically congested systems, we examined γ-alkylated dienol ether **1l** (eq 1).



Although this substrate was unreactive with tertiary α-halo esters (e.g., **2a**), vicinal quaternary and tertiary carbon centers could be accessed using ethyl 2-bromopropionate (**2i**) under our standard conditions, thereby demonstrating the ability to generate sterically challenging C−C bonds with relative ease.

In further examining the scope of the halocarbonyl component, we observed that ethyl trichloroacetate (**2q**, Table 4, entry 1) furnished the coupled product **3z** in excellent yield. Adjustment of reagent stoichiometry led to formation of the 2:1 coupling product **3aa** as the major product, although the final chloride proved reluctant to couple further even under

Scheme 2. Synthetic Applications of Coupling Products



forcing conditions (entry 2). In addition to chlorinated compounds, ethyl bromodifluoroacetate (**2r**) was found to provide desirable difluoroacetate derivatives efficiently (entries 3−5). The exceptional diastereoselectivity was maintained with these less sterically demanding substrates.

Although primary α-halo compounds were unreactive under our standard reaction conditions, we discovered that dihalocarbonyl compounds served as viable synthons for the parent coupling partners. α,α-Dichloroacetophenone (**2s**) coupled with dienol ether **1a** in 80% yield, and the initial coupling product was readily reduced with Zn^0 in AcOH to enone **5** in 84% yield (Scheme 2a). Alternatively, the initial coupling product (**3ae**) eliminates under basic conditions to furnish the formal α-arylation product **6** in 95% yield.

To explore the prospect of heterocycle synthesis, we employed haloacetoacetate **2t** in our transformation and obtained hexahydrobenzofuran **7**, the product of a formal [3 + 2] cycloaddition, in excellent yield (Scheme 2b).[4c] Toward *N*-heterocycles, we employed propionimide **2u** in our coupling, and after cleavage of the Boc group and acid-catalyzed conjugate addition, lactam **8** was formed in 71% overall yield (Scheme 2c). Through a similar strategy, dienol ether **1a** was coupled with propionate **2v**, and after subsequent chemoselective addition of MeLi and acid treatment, the natural product wine lactone (**9**) was isolated in 37% overall yield (Scheme 2d). As a final application, the unprotected broad-spectrum antibiotic chloramphenicol (**2w**) was coupled to dienol ether **1k** with concomitant elimination to acrylamide **10** in high overall yield (Scheme 2e).

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To conclude, we have developed a robust, general, Cu-catalyzed technology for γ-alkylation of enones via readily available dienol ether derivatives and α-halo compounds. The transformation proceeds in excellent yield, exhibits complete regiocontrol, tolerates sterically demanding coupling partners, and is highly diastereoselective. This method enables the synthesis of 1,6-dicarbonyl compounds that have largely eluded conventional bond formation strategies. The excellent functional group compatibility of this transformation ensures broad applicability to a variety of highly functionalized target molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b02565.

Experimental procedures and characterization data (PDF)

Copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(7) The base is important to overall reactivity, although several bases were found to be competent. See the Supporting Information for details.

(8) The reaction proceeds with lower catalyst loadings, but achieving high yield requires a long reaction time. A reaction with 1 mol % $Cu(OTf)_2$ for 48 h delivered a 77% yield although conversion was incomplete.

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