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Palladium-Mediated Remote Functionalization in γ- and ε-Arylations and Alkenylations of Unblocked Cyclic Enones

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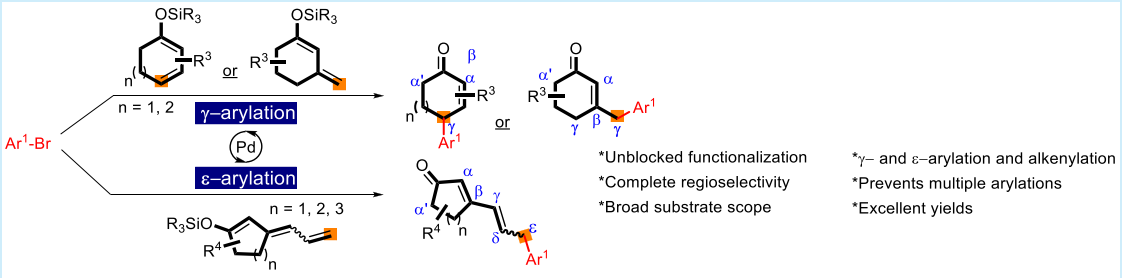
Supporting Information



ABSTRACT: We report herein an extensive investigation of simple and regioselective *endo*- as well as *exo*-γ-arylations of silyl-dienol ethers of unblocked cyclic enones with the utilization of palladium-catalyzed, modified Kuwajima−Urabe conditions. We have also successfully explored a new *exo*-ε-arylation of silyl-trienol ethers of π-extended cyclic enones. In addition, we also report, herein, exclusive γ- and ε-alkenylation of silyl-dienol and silyl-trienol ethers of cyclic enones.

Remote functionalization via the formation of a carbon−carbon bond is one of the most challenging aspects of synthetic organic chemistry.[1] Biologically relevant molecules or pharmaceutical drugs can be derived from commercially available sources by C−C bond formation via remote functionalization.[2] Difficulties in achieving such transformations led to the emergence of innovative metal-catalyzed methodologies involving cross-coupling reactions[3] or C−H functionalizations.[4]

Enones, in particular, cyclic ones, are the core building blocks in numerous alkaloids, especially amaryllidaceae alkaloids and natural products containing carbazole moieties. The assembly of the core structures of such compounds are often achieved by organic transformations of these enones (Figure 1).[5−7] Remote functionalization, particularly at the γ-positions of dienolates and ε-positions of trienolates, is rather inefficient due to the reduced nucleophilicity at these positions when compared to α-enolates.[8]

Challenges for installing an aryl group at sp^3 γ-carbon of enones include the formation of other regioisomeric products at α′-, α-, and β-sites. Similarly, possibilities of regioisomers at α′-, α-, β-, and δ-positions during ε-arylation of vinylogous enones exhibit a problem. Other problems exist in the form of facile multiple arylations that occur at the remote sp^3 positions of enones.[9] Another drawback of dienolates is that they are highly prone toward self-condensation.[10]

Despite these challenges, there have been seminal works in this area by various research groups. Buchwald and co-workers reported γ-arylations on γ-substituted cyclic enones to generate quaternary carbon centers.[8] Similarly, the groups of Maier[11] and Imahori[12] attempted to achieve tertiary γ-arylations on α-substituted and as well as unsubstituted cyclic enones and achieved aromatized γ-arylated products. Research groups of Yamamoto,[13] Hartwig,[14] and Buchwald[15] achieved γ-arylations on β- and γ-substituted conjugated esters, respectively. Research groups of Miura[16] and Mazet[17] reported γ-arylations on α-monosubstituted and α,γ-disubstituted unsaturated terminal aldehydes, respectively. Li, Zhang and co-workers[18] reported γ-arylations on β-substituted amides involving an olefin shift when using *ortho*-substituted aromatic halides.

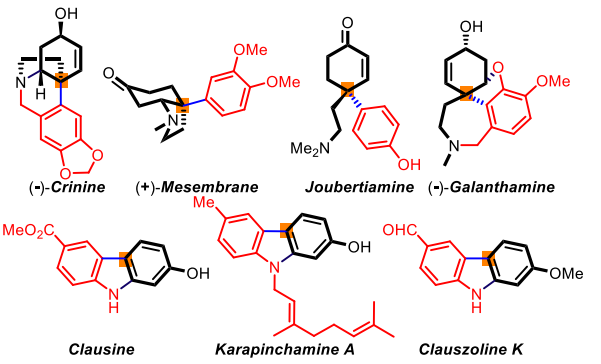


Figure 1. Representative γ-arylated natural products.

Despite this progress, there has been no advancement made toward the controlled γ- and ε-arylations with simple enones as the coupling partners. To solve this unaddressed problem, we

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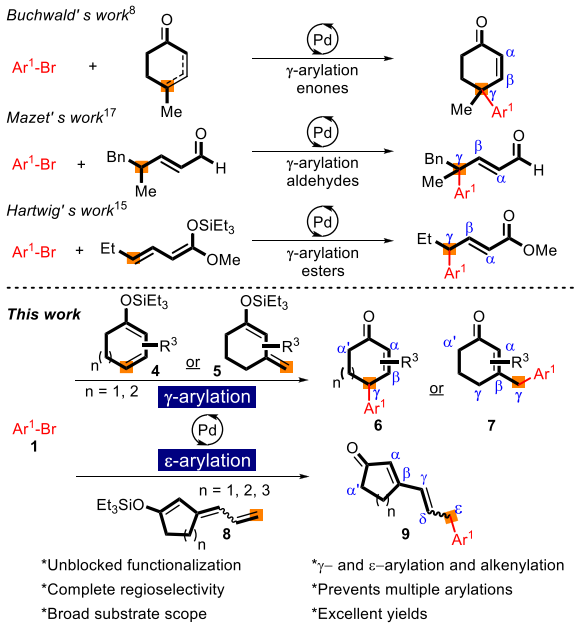
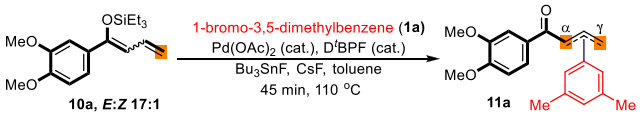
designed a remote functionalization utilizing palladium-catalyzed γ- and ε-arylations with silyl-dienol and trienol ethers of unblocked enones and π-extended enones while other competing nucleophilic sites in the system remain unaffected (Scheme 1). Our work commenced with the initial screening

Scheme 1. γ- and ε-Arylation of Dienol- and Trienol-Ethers of Enones



on the coupling of silyl-dienol ether of unblocked acyclic enone **10a** with aryl bromide by employing modified Kuwajima–Urabe conditions[19,20] to synthesize an exclusively γ-arylated product (Scheme 2). To our disappointment, an

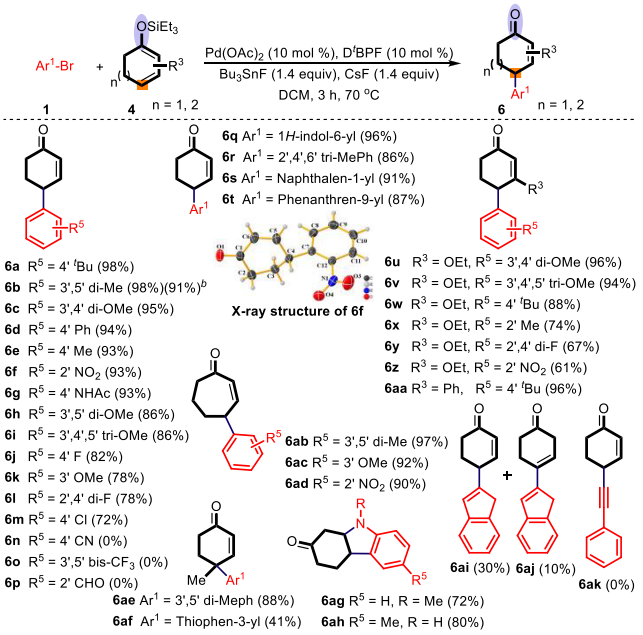
Scheme 2. Initial Attempts towards γ-Arylation of Acyclic Enones



inseparable complex mixture of regioisomers was observed in rather low yield along with the decomposition of the silyl-dienol ether. Despite extensive efforts to optimize this transformation, success eluded us and an inseparable mixture of regioisomeric arylation products was obtained in each attempt. This led us to switch over to cyclic enones, and after a careful optimization study (see the Supporting Information for details), a regioselective γ-arylation of unblocked α,β-unsaturated cyclic enones was successfully achieved (Scheme 3).

The initial optimization was carried out with palladium catalysts. Later nickel complexes were also scanned for this transformation but without any success. The absence of the palladium catalyst expectedly led only to the cleavage of the silylenol ether, and no coupling product was detected. The fluoride source was necessary for the transformation as was the requirement of the cesium fluoride as well as the tributyltin fluoride. The synergistic effect of this system has been well-documented by Hartwig and co-workers.[19b] The D^{t}BPF ligand

Scheme 3. Substrate Scope of Endocyclic sp^3 γ-Arylation of Enones[a]



[a]Unless otherwise mentioned, all reactions were performed with **1** (0.3 mmol), **4** (0.84 mmol), in 3.0 mL of degassed solvent, in a sealed tube. All reagents were added in a glovebox. [b]Reaction performed on 1 mmol scale.

was found to be the most efficient one for this transformation, with some other phosphine ligands also performing decently well. With the optimized reaction conditions in hand, the generality of the regioselective γ-arylations was investigated with various aryl bromides **1** and silyl-dienol ethers of enones **4** (Scheme 3). Initially, variation in substitution on the aryl bromides was examined with silyl-dienol ether of 2-cyclohexen-1-one, and the γ-arylated products **6a**–**6m** were obtained in excellent yield. X-ray crystallographic analysis of **6f** confirmed the structure of the γ-arylated product (CCDC 1884281). Notable failures were **6n**–**6p**, where no product was obtained in the coupling reaction.

Interestingly, the heteroaryl bromide bearing a free N–H group was also found to be a suitable coupling partner for the reaction, resulting in **6q** in high yield. Substrates bearing sterically bulky mesityl, naphthyl, and phenanthrene groups were well-tolerated and furnished the corresponding products (**6r**–**6t**, Scheme 3) in very good yields. Both electronic and steric factors had the least impact on the process. The scope of the reaction was further explored with a diverse set of substituents on 2-cyclohexen-1-one. Electron-donating as well as electron-neutral substituents on the cyclic enones performed well with a variety of bromides to yield the γ-arylated products **6u**–**6aa** (Scheme 3). The methodology was further expanded to the seven-membered cyclic enone 2-cyclohepten-1-one to achieve the γ-arylated products **6ab**–**6ad** in excellent yields. We also performed the reaction of dienol ether of 4-methyl-2-cyclohexen-1-one with aryl and heteroaryl bromides to give **6ae**, **6af** which are essential frameworks in the synthesis of natural products. This also indicated that substitution at the γ-position was also tolerated and the arylation occurred at the desired position. We also successfully synthesized ketoindoline skeletons **6ag**, **6ah** in a one-pot transformation by reaction

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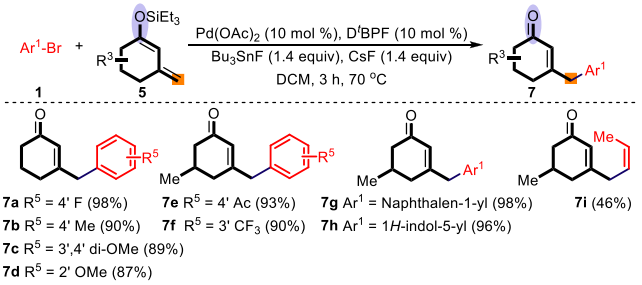
with simple 2-bromoaniline derivatives in which the 1,4-conjugate addition occurred after the γ-arylation.[8] In addition, γ-alkenylation was performed with a cyclic alkenyl bromide (**6ai**, Scheme 3), but the γ-alkenylation was not as efficient as the γ-arylation and the minor isomerization product **6aj** was also isolated in this case. In the same fashion, γ-alkynlation was also attempted but the reaction failed to yield the desired product (**6ak**, Scheme 3).

To further explore the utility of this strategy, we attempted the reaction of 3-methyl substituted cyclic enones which have two enolizable carbons at the γ-positions (Scheme 4). The

Scheme 4. Substrate Scope of Exocyclic sp^3 γ-Arylation of Enones[a]

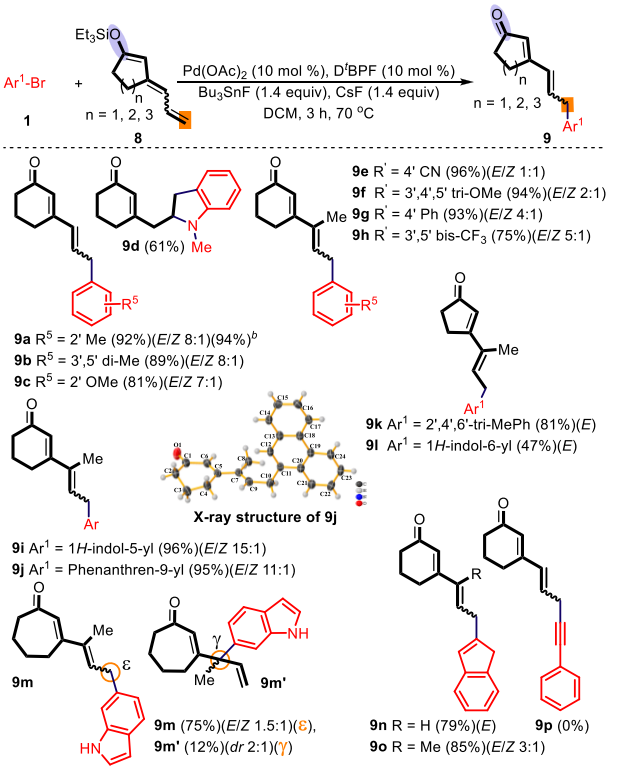


[a]Unless otherwise mentioned, all reactions were performed with **1** (0.3 mmol), **5** (0.84 mmol), in 3.0 mL of degassed solvent, in a sealed tube. All reagents were added in a glovebox.

silyl-dienol ethers formed on the exo sp^3 carbon instead of the *endo* sp^3 carbon. The silyl-dienol ethers of 3-methyl and 3,5-dimethyl-2-cyclohexen-1-one (**5a**, **5b** respectively) reacted with electron-rich as well as electron-deficient aryl bromides to provide the products **7a**–**7h** in excellent yields with exclusive regioselectivity. We were thus able to demonstrate a single reaction condition needed to produce exclusive *exo*-γ-monoarylated products. Similarly, γ-alkenylation was also performed on the exocyclic system by reaction with a vinyl bromide (**7i**, Scheme 4).

We then turned our attention to further remote functionalizations at the sp^3 ε-carbon of silyl-trienol ether of vinylogous enones (Scheme 5). To the best of our knowledge, to date, there is no report on the site-selective ε-arylation of unblocked or blocked side chains of cyclic enones. The silyl-trienol ether of π-extended 2-cyclohexen-1-one **8a** reacted without any need for substituents on the parent chain to yield the cross-coupling products **9a**–**9c** (Scheme 5) with exclusive ε-regioselectivity. The tetrahydroindole moiety **9d** was successfully synthesized in a one-pot fashion from 2-bromo-*N*-methylaniline in which the 1,6-conjugate addition occurred after the ε-arylation. The generality of the reaction was demonstrated by the highly efficient transformations of six-membered enones to **9e**–**9j** (Scheme 5). X-ray crystallographic analysis of **9j** confirmed the ε-selectivity (CCDC 1922702). ε-Arylations in cyclic enones of varied ring sizes were equally effective and yielded **9k**–**9m** in an efficient manner. In seven-membered systems, however, γ-arylation **9m′** was also observed in a minor amount. A highly efficient ε-alkenylation was also achieved on the exocyclic six-membered vinylogous enones by reaction with 2-bromoindene (**9n**, **9o**, Scheme 5). In the same fashion, ε-alkynlation was also attempted but the reaction failed to yield the desired product (**9p**, Scheme 5).

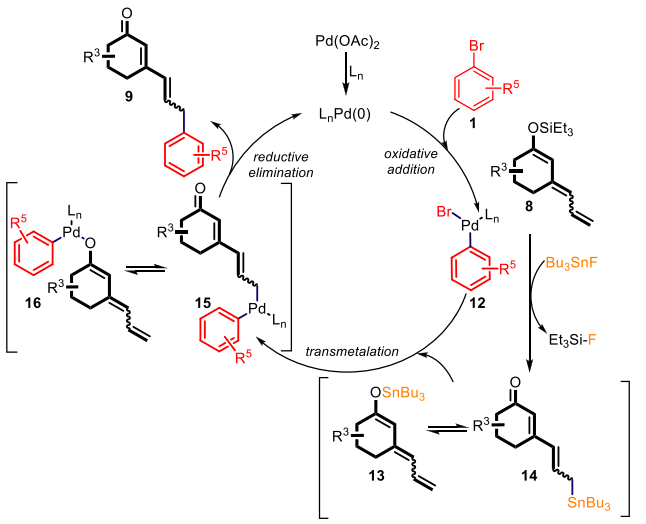
Scheme 5. Substrate Scope of Exocyclic sp^3 ε-Arylation of Enones[a]



[a]Unless otherwise mentioned, all reactions were performed with **1** (0.3 mmol), **8** (0.84 mmol), in 3.0 mL of degassed solvent, in a sealed tube. The *E*/*Z* ratio was determined by ^{1}H NMR of the crude reaction mixture. All reagents were added in a glovebox. [b]Reaction performed on 1 mmol scale.

A plausible mechanism for the transformation is depicted in Scheme 6.[19,21] The Pd(0) generated in situ undergoes an oxidative addition with aryl bromide **1** followed by transmetalation with the reactive stannyl-enol ether of the enone **13** to give organopalladium species **15**. Finally, reductive elimination affords the ε-arylation **9**.

Scheme 6. Plausible Mechanism for ε-Arylation



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In summary, we have developed a new methodology for the *endo* as well as *exo* γ-arylations of various unblocked cyclic enones using a variety of aryl and heteroaryl bromides. Modified Kuwajima−Urabe conditions were utilized to resolve the long-standing problem of remote functionalization on unblocked enone systems. We have also successfully developed a unique and controlled ε-arylation of a variety of cyclic enones with varied substitutions. The site selectivity was exclusive in the γ- and ε-alkenylation of silyl-dienol and silyl-trienol ethers of cyclic enones. The application of this methodology in the synthesis of several alkaloids, especially those of the amaryllidaceae family, is currently in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03462.

Experimental details and spectral characterization of all new compounds (PDF)

Accession Codes

CCDC 1884281 and 1922702 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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