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Palladium-Catalyzed Allylic Alkylation of 2-Aryl-1,3-dithianes, an Umpolung Synthesis of β,γ-Unsaturated Ketones

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Abstract. Palladium-catalyzed allylic alkylation of 2-aryl-1,3-dithianes at room temperature is described. A variety of cyclic and acyclic electrophiles successfully coupled with *in-situ* generated 2-sodio-1,3-dithiane nucleophiles to afford the allylated products in good to excellent yields (25 examples). Deprotection of these products leads to valuable β,γ-unsaturated ketones. Direct synthesis of such β,γ-unsaturated ketones via a one-pot allylation-oxidation protocol is also presented. Investigation into the stereochemistry of the allylation reaction revealed that the 2-sodio-1,3-dithiane nucleophile behaves as a "soft" nucleophile, which underwent external attack on the π-allyl palladium complex to provide retention of stereochemistry (double inversion pathway). Additionally, the utility of this method was demonstrated through a sequential one-pot allylation-Heck cyclization to produce asterogynin derivatives, which are important bioactive compounds in medicinal chemistry.

Keywords: Allylic Alkylation; Dithiane; Umpolung; β,γ-Unsaturated Ketone; "soft" Nucleophile.

Introduction

β,γ-Unsaturated ketones are important building blocks for the synthesis of bioactive compounds used in the pharmaceutical industry.[1] Some examples include griseofulvin, isopinnatal, nidemone, and trichostatin A (Figure 1). The synthesis of β,γ-unsaturated ketones is challenging, however, due to their facile isomerization to the thermodynamically favored α,β-unsaturated ketones.[2]

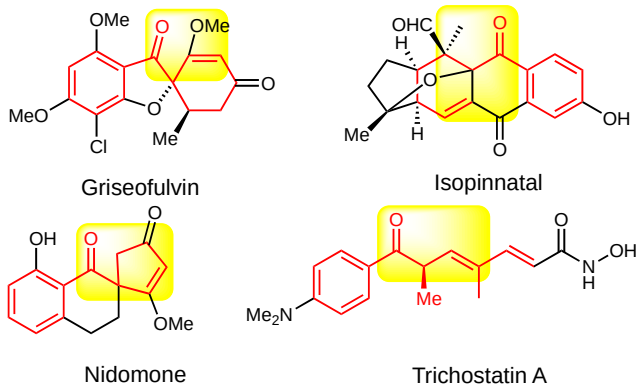

Figure 1. Examples of β,γ-unsaturated ketone motifs in pharmaceuticals.

Although several methods have been reported for the synthesis of β,γ-unsaturated ketones, only a few procedures are practical. The acylation of olefins, for example, is a potentially useful and common procedure to access β,γ-unsaturated ketones, but α,β-unsaturated ketone byproducts are nearly always observed and usually very difficult to separate from the desired products.[3] A variety of allylic organometallics[4] have been used with acyl halides to generate β,γ-unsaturated ketones in moderate to good yields (Scheme 1, a). Unfortunately, these multi-step procedures are time-consuming and complicated by the need to synthesize and purify the intermediates, which limits their application.[4d, 5] In 2012, Nagalakshmi and coworkers demonstrated that copper nano particles could be employed as a heterogeneous catalyst for the allylation of acid chlorides; however, the scope of this reaction is limited to linear allyl halides (Scheme 1, b).[6] Thus, it is clear that new methods to prepare a wide range of

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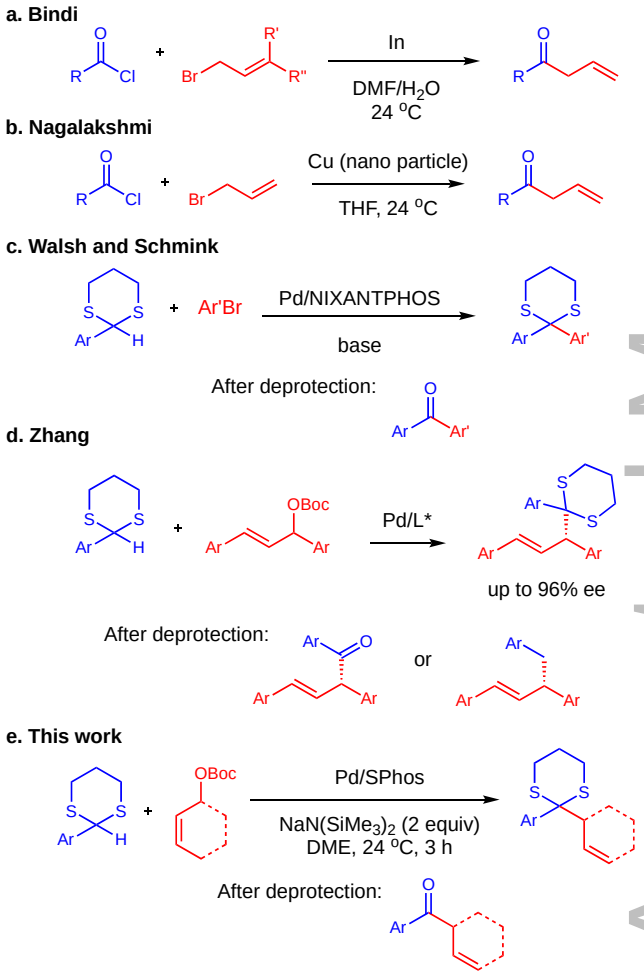
β,γ-unsaturated ketones in high yields are very desirable.

Retrosynthetic analysis of β,γ-unsaturated ketones leads to two possible disconnections, the more traditional acid chloride and allyl anion approach and the less common allyl cation and the acyl anion equivalent (Figure 2). Acyl anion equivalents can be generated by a variety of methods, the most well known of which is the use of 1,3-dithiane nucleophiles.

The concept of umpolung synthesis, or dipole inversion, was demonstrated by Corey and Seebach in 1965 with the introduction of metallated dithianes.[7] It was shown that 1,3-dithianes could be deprotonated with strong bases, such as *n*-butyllithium, and employed as acyl anion equivalents with a variety of electrophiles. Following this breakthrough, metallated 1,3-dithianes became well-established reagents in organic synthesis and are widely used in C–C bond formation.[8] Although the reactivity of metallated 1,3-dithianes has been well-developed over the years, it is surprising that only a handful of publications have reported the use of 1,3-dithianes in transition metal catalyzed reactions. In our effort to develop deprotonative cross-coupling processes (DCCP),[9] we became interested in the coupling of 2-aryl-1,3-dithianes to aryl halides under conditions where the dithianes are reversibly deprotonated in the presence of base. Based on this approach, we developed an arylation of dithianes and demonstrated its application to the synthesis of medicinally relevant benzophenone derivatives (Scheme 1, c).[10] Schmink and coworkers simultaneously reported very similar conditions for this coupling reaction.[11] Since several of the nucleophiles we employed in arylation reactions also found utility in palladium and nickel catalyzed allylic substitution reactions, we decided to investigate metallated 1,3-dithianes in allylic alkylation reactions. During our investigations, Liu, Zhang and coworkers published an enantioselective allylic substitution (up to 96% ee) with Boc activated (*E*)-1,3-diarylprop-2-en-1-ols (Scheme 1, d).[12] There is little overlap between their choices of electrophiles and the ones presented herein.

Herein we report a room-temperature palladium-catalyzed allylic alkylation of 1,3-dithianes to form β,γ-unsaturated ketone equivalents in good to excellent yields (Scheme 1, e) and a one-pot allylic alkylation-deprotection to generate β,γ-unsaturated ketones directly with yields up to 90%. To further demonstrate the utility of this method, a sequential dithiane initiated allylic substitution-Heck cyclization to afford the core structure of asterogynin is presented. Experiments to probe the stereochemistry of the reaction point to a mechanism that involves exo-attack of the metallated 1,3-dithiane on the π-allyl palladium intermediate, indicating that the metallated dithiane behaves as a "soft" nucleophile (double inversion mechanism).



Scheme 1. β,γ-Unsaturated ketone syntheses.

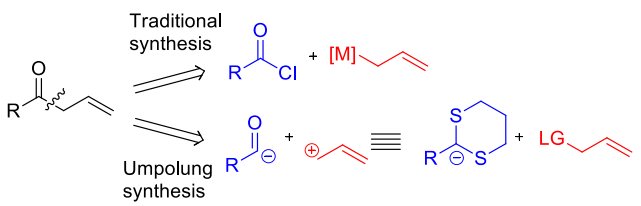


Figure 2. Retrosynthesis of β,γ-unsaturated ketones.

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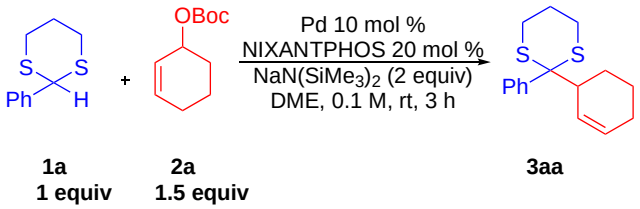
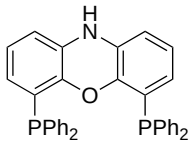
Results and Discussion

We carried out optimization studies using 2-phenyl-1,3-dithiane **1a** as the pronucleophile and *tert*-butyl cyclohex-2-enyl carbonate **2a** as an electrophilic partner. Initially, we conducted the allylic alkylation reaction using conditions similar to those employed in our arylation of 2-aryl-1,3-dithianes and allylic alkylation of diarylmethanes,[13] which are $Pd(OAc)_2$ (10 mol %), van Leeuwen's NIXANTPHOS[14] (20 mol %), $NaN(SiMe_3)_2$ (2 equiv), and DME solvent at room temperature (Scheme 2). After 3 h the allylic substitution product was afforded in 70% assay yield (AY), as determined by ^1H NMR of the crude reaction mixture. We next examined palladium precursors $Pd(dba)_2$, $Cl_2Pd(NCPh)_2$ and $[PdCl(C_3H_5)]_2$. Catalyst prepared from $Cl_2Pd(NCPh)_2$ showed the highest activity, affording product **3aa** in 84% AY.





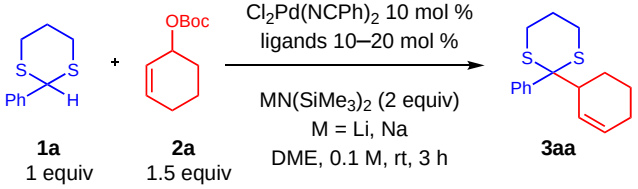
NIXANTPHOS

70% AY, Pd = $Pd(OAc)_2$
50% AY, Pd = $Pd(dba)_2$
84% AY, Pd = $Cl_2Pd(NCPh)_2$
60% AY, Pd = $[PdCl(C_3H_5)]_2$

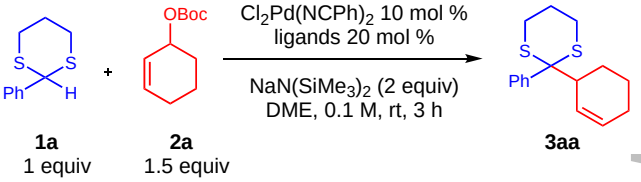
Scheme 2. Initial lab scale (0.1 mmol) optimization using NIXANTPHOS as ligand with different Pd sources.

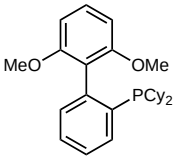
In search of a more efficient catalyst, we then screened 42 diverse mono-dentate (20 mol %) and bidentate (10 mol %) phosphine ligands and 2 bases, Li and $NaN(SiMe)_2$, using microscale (10 μmol) high-throughput experiments (HTE) (see Supporting Information for details). The results revealed that the most promising hits were CataCXium PCy[15] and SPhos.[16] Employing the two top hits on laboratory scale (0.1 mmol) led to product **3aa** in 94% (CataCXium PCy) and 92% (SPhos) AY, respectively. We chose to continue with SPhos, because it is more economical.

a. Microscale screening (10 micromol):

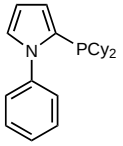


b. Lab-scale (0.1 mmol)





SPhos
92% AY



CataCXium PCy
94% AY

Scheme 3. Ligand identification in the allylic substitution.

With the optimized Pd/ligand combination, we next studied the Pd-phosphine ratio. Decreasing the palladium/ligand ratio from 10/20 mol % to 10/15 mol % did not impact the yield (Table 1, entry 1). However, 10 mol % of each resulted in a drop in the AY of **3aa** to 83% yield (entry 2). We next examined the impact of reducing the palladium and ligand loading. Decreasing the palladium loading from 10 to 2.5 mol % with 3.75 mol % SPhos provided the allylation product in 95% AY (entry 3). Further decreasing catalyst loading to 1.0 mol % Pd and 1.5 mol% SPhos resulted in 60% AY (entry 4). Reaction concentrations also impact the reaction outcome. Reducing the concentration of **1a** from 0.2 to 0.1 M provided AY of 97%, whereas further reduction to 0.05 caused the assay yield to fall to 84% (entries 5–6). Reducing the equivalents of the electrophile from 2 to 1.5 gave 96% AY, but further reduction to 1.2 equiv caused a decrease in AY to 84% (entries 7–8). Heating the reaction mixture to 60 °C caused increased decomposition of the electrophile **2a** and decreased the AY of **3aa** to 87% (entry 9). The optimized conditions in entry 7 were then used to examine the scope of nucleophiles.

Table 1. Optimization of allylic alkylation of **1a**.[a],[b]

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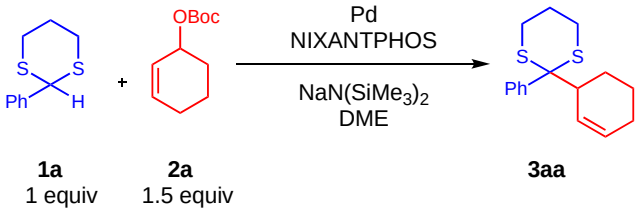


1a 1 equiv | **2a** 1.5 equiv | **3aa**

Entry	X/Y (mol %)	**1a**:**2a**	T °C	Conc. (M)	AY (%)
1	10/15	1:2	rt	0.2	95
2	10/10	1:2	rt	0.2	84
3	2.5/3.75	1:2	rt	0.2	95
4	1/1.5	1:2	rt	0.2	60
5	2.5/3.75	1:2	rt	0.1	97
6	2.5/3.75	1:2	rt	0.05	84
7	2.5/3.75	1:1.5	rt	0.1	96
8	2.5/3.75	1:1.2	rt	0.1	84
9	2.5/3.75	1:1.5	60	0.1	87

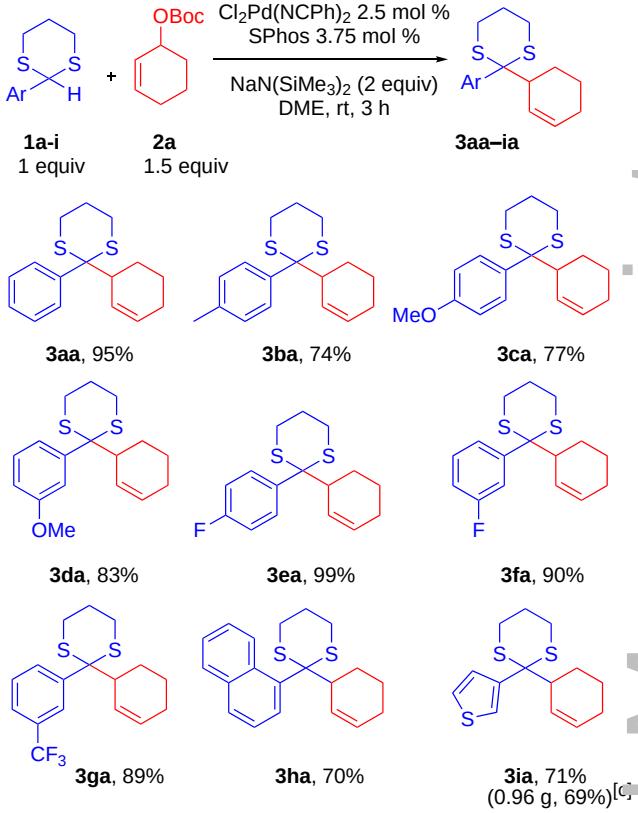
[a]Reactions conducted on 0.1 mmol scale. [b]Assay yields (AY) determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

Scope of Nucleophiles in the Palladium-Catalyzed Allylic Alkylation Reaction.

Having identified the optimal conditions, we explored allylic alkylation with *tert*-butyl cyclohex-2-en-1-yl carbonate **2a** and a variety of 1,3-dithiane pronucleophiles. The parent 2-phenyl-1,3-dithiane furnished the product **3aa** in 95% isolated yield. Pronucleophiles with electron donating groups are less acidic and more challenging to deprotonate. Nonetheless, both 2-(4-tolyl)-1,3-dithiane and 2-(4-methoxyphenyl)-1,3-dithiane gave the corresponding products, **3ba** and **3ca** in 74 and 77% yields, respectively. Pronucleophiles with electron withdrawing groups underwent substitution to give excellent yields. Thus, 2-(3-methoxyphenyl)-, 2-(4-fluorophenyl)-, 2-(3-fluorophenyl)-, and 2-(3-trifluoromethylphenyl)-1,3-dithianes underwent Pd catalyzed allylation with **2a** to afford **3da**, **3ea**, **3fa** and **3ga** in 83, 99, 90 and 89% yields, respectively. A sterically hindered substrate 2-(1-napthalyl)-1,3-dithiane reacted to afford **3ha**[29] in 70% yield; however, 2-(2-tolyl)-1,3-dithiane did not perform well under the established reaction conditions, giving only 8% yield. The heterocyclic substrate 2-(3-thiophenyl)-1,3-dithiane reacted to provide **3ia** in 71% yield, but 2-(3-furyl)-1,3-dithiane was not an effective pronucleophile in this reaction.

In order to be useful, reactions must be scalable. To examine the scalability of our substitution, the allylation of 2-thiophen-1,3-dithiane with **2a** was examined on 4.9 mmol scale (1.0 g), providing the corresponding product **3ia** in 69% yield (0.96 g).

Table 2. Scope of nucleophiles in allylic alkylation with **2a**.[a],[b]



[a]Reactions conducted on 0.1 mmol scale. [b]Isolated yields after chromatographic purification. [c]4.9 mmol **2a**.

Scope of Electrophiles in the Palladium-Catalyzed Allylic Alkylation reaction.

Under optimal conditions, the scope of allylic carbonate derived electrophiles reacting with 2-phenyl-1,3-dithiane **1a** was examined (Table 3). Cyclopentenyl and cycloheptenyl electrophiles reacted to provide the desired products **3ab** and **3ac** in 97 and 87% yields, respectively. The reaction of the 7-membered ring substrate was slower and required a longer reaction time (16 h). In the case of linear allylic carbonate derivatives, CataCXium PCy performed better than SPhos under the optimized conditions. The parent allyl OBoc and 2-Me allyl OBoc delivered **3ad** and **3ae** in 87 and 88% yields after 3 h, respectively. Longer reaction times (16 h) were needed for unsymmetrical η^3-allyl groups. It is known that π-allyl palladium complexes often react

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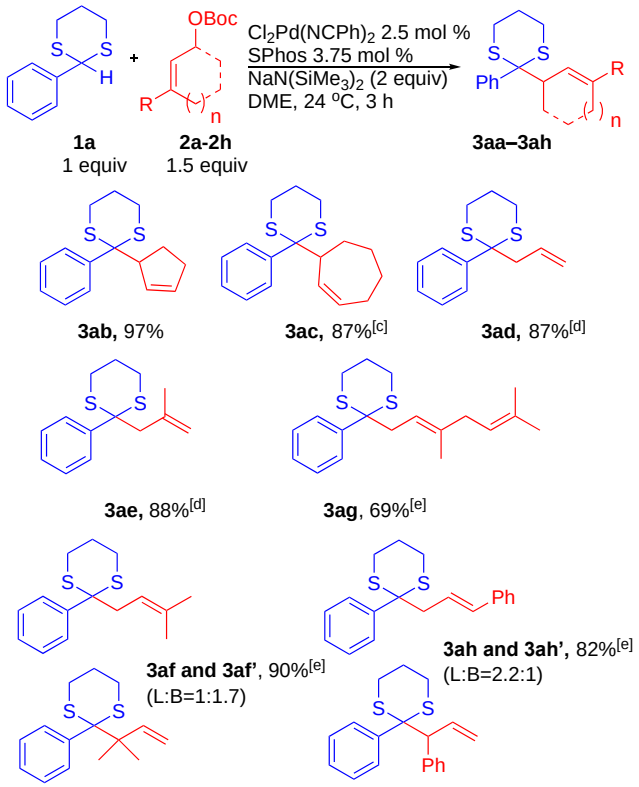
with carbon nucleophiles at the less substituted end of the π-allyl.[17] For Boc-protected prenyl alcohol **2f**, however, the branched isomer **3af'** was slightly favored (linear:branched 1:1.7, 86% yield). The allylation with Boc-protected cinnamyl alcohol **2h** slightly favored the linear product **3ah** (80%) with linear:branched ratio of 2.2:1. Surprisingly the allylation with geranyl alcohol **2g** gave only linear product **3ag** in moderate yield (69%).

Table 3. Scope of electrophiles in allylic alkylation with **1a.**[a],[b]

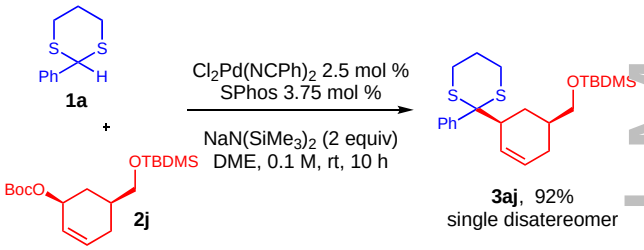


[a]Reactions conducted on 0.1 mmol scale. [b]Isolated yield after chromatographic purification. [c]16 h. [d]3.75 mol% of CataCXium PCy. [e]3.75 mol% of CataCXium PCy, 16 h, ratio of linear:branched (L:B) determined by ^{1}H NMR of purified reaction products.

Probing the stereochemistry of the allylic substitution.

In Tsuji-Trost allylic alkylation reactions, the nucleophiles are divided into two classes based on the pK_a of the pronucleophile: (1) "hard" or unstabilized nucleophiles from pronucleophiles with pK_a values > 25 and (2) "soft" or stabilized nucleophiles from pronucleophiles with pKa's < 25.[18] The difference between these two species is the nature of attack by the nucleophile on the π-allyl intermediate. The "hard" nucleophiles undergo attack on the metal center of the π-allyl palladium complex followed by reductive elimination. This reaction pathway proceeds by a single inversion in the allylic substitution. In contrast, "soft" nucleophiles directly attack the π-allyl, providing net retention of stereochemistry (via double inversion).

To determine which of these two pathways was operative in our allylic substitution, 2-phenyl-1,3-dithiane (pK_a = 31[19]) was coupled with *cis*-disubstituted stereoprobe **2j** to generate the substitution product in 92% yield as a single diastereomer (Scheme 4). Analysis of the ^{1}H NMR spectrum of **3aj** indicated that the structure was consistent with the *cis*-isomer. This result reveals that 2-phenyl-1,3-dithiane behaves as a "soft" nucleophile. This result is consistent with our prior work using diphenylmethane pronucleophiles,[17e, 20] and supports our hypothesis that soft nucleophiles should be classified as those with pronucleophile pK_a's up to at least 32.



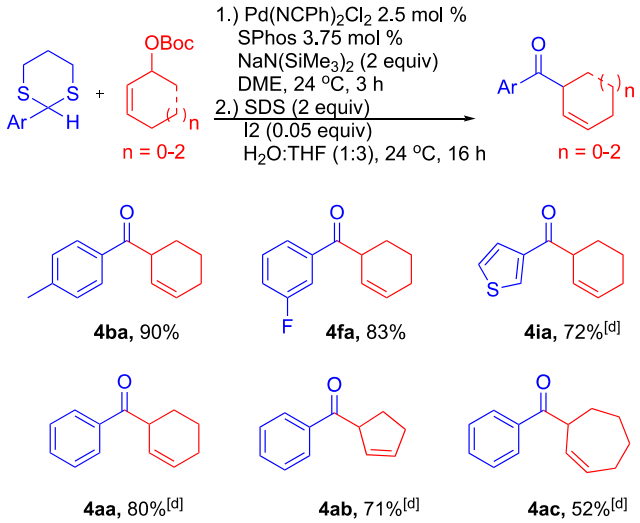
Scheme 4. Stereoprobe study indicating that the allylic substitution reaction proceeds via the double inversion or soft nucleophile pathway.

Development of a sequential one-pot umpolung synthesis of β, γ-unsaturated ketones.

Conversion of the dithiane product to the corresponding ketone can be challenging.[21] With our allylic substitution products, great care must be exercised to avoid the facile isomerization of the alkene into conjugation with the carbonyl group during deprotection. An attractive oxidative approach employs iodine in the conversion of 1,3-dithianes to the corresponding carbonyl compounds.[22] A key advantage of using iodine to remove the dithiane is that it avoids heavy metal reagents, such as mercury,[23] silver,[24] thallium,[25] and cerium,[26] some of which are toxic. In 2008, Barik and

coworkers disclosed an effective protocol for 1,3-dithiane deprotection using a combination of iodine and hydrogen peroxide in the presence of SDS (sodium dodecyl sulfate, proposed to stabilize reactive intermediates).[27] Based on these conditions, we developed a one-pot allylation-deprotection that could be conducted without isolation or purification of the intermediate dithiane. We found that hydrogen peroxide was not necessary when the deprotection was carried out over a longer reaction time (12 h) under air. Thus, after the allylic alkylation step was completed, as judged by TLC, the crude reaction mixture was evaporated to dryness and I_2 was added in a catalytic amount (2 mol %) in THF. A solution of SDS in water was then added to the flask, and the resulting reaction mixture was stirred at rt for 12–16 h. Using the 2-(4-tolyl)-1,3-dithiane **1b**, 2-(2-fluorophenyl)-1,3-dithiane **1f**, and 2-(3-thiophenyl)-1,3-dithiane **1i**, the corresponding β,γ-unsaturated ketones were isolated directly from a single reaction flask in 90 (**4ba**), 83 (**4fa**), and 55% yields (**4ia**), over the two steps (Table 4). The yield of the β,γ-unsaturated ketone **4ia** could be improved to 72% by isolating and purifying dithiane **3ia** prior to submission to the oxidative deprotection conditions. Using the two-step method, allylated products with five, six and seven membered ring **3ab**, **3aa** and **3ac** underwent deprotection to afford the corresponding β,γ-unsaturated ketones **4ab**, **4aa** and **4ac** in 71%, 80% and 52% yields respectively.

Table 4. Sequential one-pot synthesis of β,γ-unsaturated ketones (**4ba** and **4fa**).[a],[b],[c] and two step procedure (**4ia**, **4aa**, **4ab**, **4ac**).[d]



[a]Reactions conducted on 0.1 mmol scale. [b]Isolated yield after chromatographic purification. [c]The oxidation conditions were developed based on Barik's conditions. [d]Allylation product isolated and purified before oxidation (16 h reaction time).

Development of a sequential allylation-Heck cyclization.

Asterogynin derivatives are important bioactive compounds in medicinal chemistry. To further demonstrate the synthetic value of our method, we were interested in pursuing the synthesis of asterogynin derivatives via a tandem allylation-Heck cyclization. Considering the differences between allylic alkylation and Heck cyclization, we explored the reaction conditions separately. Based on the Heck reaction literature,[28] we started investigating the cyclization of the allylated product **3jb** with the combination of $Cl_2Pd(NCPh)_2$ or Pd(OAc)2, PPh_3, and carbonate bases in DME or acetonitrile at 60 or 80 °C, but under these conditions the cyclization product was either not detected or only traces were formed (Table 5, entries 1–5). We next studied different temperatures and found that 5 mol% $Pd(OAc)_2$, 15 mol % PPh_3, and 5 equiv of NEt_3 in acetonitrile at 80 °C were the most promising conditions, which afforded **4jb** in 75% yield (Table 5, entry 7). Based on this result, we began examining a sequential allylation-Heck cyclization of **1j** with different electrophiles (Scheme 5). After completion of the allylation (as determined by TLC), the catalyst was removed from the crude reaction mixture by filtration through a pad of silica. The reaction mixture was dried under vacuum, dissolved in MeCN and transferred to a separate vial containing a premixed solution of $Pd(OAc)_2$ and PPh_3 in MeCN and NEt_3. The reaction mixture was then stirred for 16 h at 80 °C. The cyclopentenyl electrophile **2b** reacted to afford the allylation-Heck cyclization product **4jb** in 67% yield over the two steps, and the acyclic allylic carbonate **2d** yielded the isolated product **4jd** in 75% yield. In the case of the cyclohexenyl electrophile **2a**, the cyclization was more challenging. With this substrate, the reaction was conducted in DMF, and the temperature had to be increased to 120 °C. Under these conditions, the product **4ja** was isolated in 71% yield (Scheme 5) with *cis* isomer confirmed by the crystal structure of **4jb** (Figure 3, obtained by slow evaporation of THF to give colorless crystal; CCDC number is 1854101). The structure crystalized in the orthorhombic space group $Pca2_1$ which showed that

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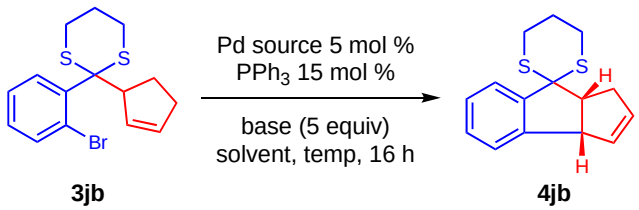
two hydrogen atoms on C8 and C12 are *cis* to each other.

Table 5. Optimization of Heck cyclization of **3jb**.[a]



3jb **4jb**

Entry	Pd	Base	Sol.	T (°C)	AY (%)
1	$Cl_2Pd(NCPh)_2$	Ag_2CO_3	DME	60	0
2	$Cl_2Pd(NCPh)_2$	Na_2CO_3	DME	60	0
3	$Pd(OAc)_2$	Ag_2CO_3	DME	60	0
4	$Pd(OAc)_2$	Na_2CO_3	DME	60	trace
5	$Pd(OAc)_2$	Na_2CO_3	MeCN	80	12
6	$Pd(OAc)_2$	NEt_3	DME	60	30
7	$Pd(OAc)_2$	NEt_3	MeCN	80	75

[a]Assay yields (AY) determined by ^1H NMR spectroscopy of the crude reaction mixtures.

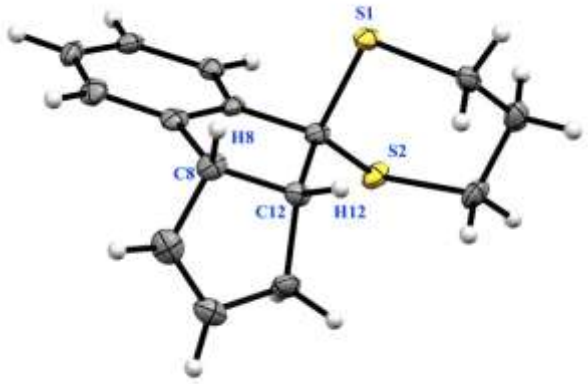
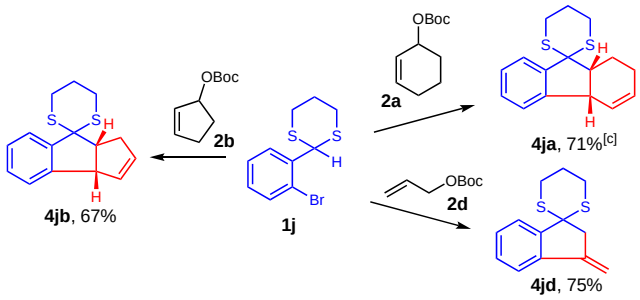
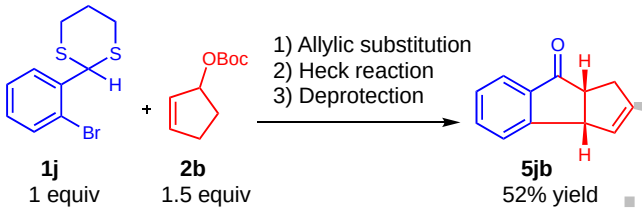


Figure 3.The structure of **4jb** with 50% thermal ellipsoids.



Scheme 5. Sequential Allylation-Heck cyclizations.[a],[b]
[a]Reactions conducted on 0.1 mmol scale. [b]Isolated yield after chromatographic purification. [c]Heck cyclization conducted in DMF at 120 °C. Allylation: $Cl_2Pd(NCPh)_2$ 5 mol %, dppe 7.5 mol %, $NaN(SiMe_3)_2$ (2 equiv) in DME at 24 °C for 36 h. Heck cyclization: $Pd(OAc)_2$ 5 mol %, PPh_3 15 mol %, NEt_3 (5 equiv) in MeCN at 120 °C for 16 h.

Finally, we conducted a one-pot allylation-Heck cyclization-deprotection process using dithiane **1j** and the cyclopentenyl-OBoc **2b** (Scheme 6, see Supporting Information for experimental details). The ketone derivative **5jb** was isolated in 52% overall yield over three steps.



1j 1 equiv **2b** 1.5 equiv **5jb** 52% yield

Scheme 6. A one-pot synthesis of **5jb**.[a],[b]
[a]Reactions conducted on 0.1 mmol scale. [b]Isolated yield after chromatographic purification. Allylation: $Cl_2Pd(NCPh)_2$ 5 mol %, dppe 7.5 mol %, $NaN(SiMe_3)_2$ (2 equiv) in DME at 24 °C for 36 h. Heck cyclization: $Pd(OAc)_2$ 5 mol %, PPh_3 15 mol %, NEt_3 (5 equiv) in MeCN at 120 °C for 16 h. Deprotection: SDS (0.2 equiv), I_2 (0.05 equiv) in THF:H_2O (3:1) at 24 °C for 16 h.

Conclusion

In summary, we have developed the palladium-catalyzed allylic alkylation of 2-aryl-1,3-dithiane derivatives for umpolung synthesis of variously substituted β,γ-unsaturated ketone derivatives. This protocol is easily applicable to various substitution patterns of the 2-aryl-1,3-dithianes and allylic electrophiles (including cyclic derivatives). In addition, allylated dithianes can be effectively transformed in the same reaction flask to the corresponding β,γ-unsaturated ketone derivatives in good yields. Importantly, our conditions successfully avoid isomerization of the β,γ-unsaturated ketone products. We also have employed this method in a sequential synthesis of asterogynin derivatives. Allylated *o*-bromo phenyl substituted dithiane derivatives can undergo Heck-type cyclization by a simple synthetic operation to give oligo cyclic ketones in good overall yields. Moreover, we have presented the first stereochemical investigation of Pd-catalyzed allylic substitution of 2-aryl-1,3-dithianes. The result of this study showed that deprotonated 2-phenyl-1,3-dithiane behaves as a "soft" nucleophile, which undergoes external attack on the π-allyl palladium complex under our reaction conditions.

Experimental Section

General Methods All reactions were performed under nitrogen using oven-dried glassware and standard Schlenk or vacuum line techniques. Air- and moisture-sensitive solutions were handled under nitrogen and transferred via syringe. Anhydrous DME and Acetonitrile were purchased from Sigma-Aldrich and used as solvents without further purification. Unless otherwise stated, reagents were commercially available and used as purchased without further purification. Chemicals were obtained from Sigma-Aldrich, Acros, TCI America or Matrix Scientific. TLC was performed with Merck TLC Silicagel60 F254 plates and detection was under UV light at 220 nm. Silica gel (230–400 mesh, Silicycle) was used for flash chromatography. The ^{1}H NMR and $^{13}C\{^{1}H\}$ NMR spectra were obtained using a Bruker AM-500 Fourier-transform NMR spectrometer at 500 and 125 MHz, respectively. Chemical shifts are reported in units of parts per million (ppm) downfield from tetramethylsilane (TMS), and all coupling constants are reported in hertz. The infrared spectra were obtained with KBr plates using a Perkin-Elmer Spectrum 100 Series FTIR spectrometer. High resolution mass spectrometry (HRMS) data were obtained on a Waters LC-TOF mass spectrometer (model LCT-XE Premier) using chemical ionization (CI) or electrospray ionization (ESI) in positive or negative mode, depending on the analyte. Melting points were determined on a Unimelt Thomas-Hoover melting point apparatus.

General Procedure for the Pd-catalyzed allylic alkylation of 2-aryl-1,3-dithianes. An 8 mL reaction vial equipped with a stir bar was charged with 2-aryl-1,3-dithiane (0.10 mmol, 1.0 equiv). Under a nitrogen atmosphere in the glovebox, a solution (from stock solution) of $Cl_2Pd(NCPh)_2$ (1.0 mg, 0.0025 mmol) and SPhos (1.5 mg, 0.00375 mmol) in 0.5 mL of dry DME was taken up by micropipette (Fisher Scientific, 1 mL tip) and added to the reaction vial. Next, the allylic coupling partner (0.15 mmol, 1.5 equiv) was added to the reaction mixture using a micropipette (Fisher Scientific, 200 μL tip). A solution of $NaN(SiMe_3)_2$ (36.8 mg, 0.20 mmol, 2.0 equiv) in 0.5 mL of dry DME was added to the reaction vial by micropipette (Fisher Scientific, 1 mL tip). The reaction mixture was sealed with a cap, transferred out of the glovebox and was stirred at rt for 3 h. Next, the reaction mixture was quenched with 3 drops of H_2O, diluted with 3 mL of ethyl acetate, and filtered over a pad of silica. The pad was rinsed with 6 mL ethyl acetate (2×3), and the solution was concentrated. The crude material was loaded onto a silica gel column and purified by flash chromatography with 2% ethyl acetate in hexanes.

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[29] X-ray chromatography data was collected to confirm the structure, see more details in supporting information (CCDC number is 1839979).

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Palladium-Catalyzed Allylic Alkylation of 2-Aryl-1,3-dithianes, an Umpolung Synthesis of β,γ-Unsaturated Ketones

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