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Palladium-Catalyzed α-Arylation of Vinylogous Esters for the Synthesis of γ,γ-Disubstituted Cyclohexenones

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Supporting Information

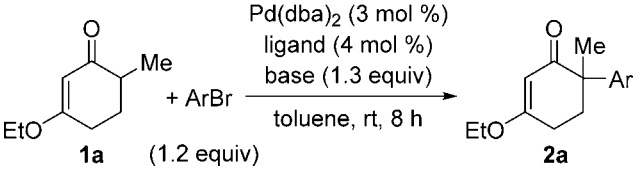
ABSTRACT: A palladium-catalyzed α-arylation of cyclic vinylogous esters to form products that are converted in one step to γ-alkyl-γ-aryl-substituted cyclohexenones is reported. This Pd-catalyzed reaction proceeds at room temperature, is generally high-yielding, and uses an amount of a commercially available catalyst as low as 0.25 mol %. The scope of aryl bromides is particularly broad, and alkenyl bromides can also be used. This two-step protocol, comprising α-arylation and reductive transposition, can be performed in one pot and is applicable to gram-scale synthesis.

γ,γ-Disubstituted cyclohexenones are versatile synthetic intermediates, and they or their derivatives are found in a variety of molecules with therapeutic value.[1] The potential of these six-membered rings resides in both the enone functional group and the fact that the stereocenter at the γ-position can be used for substrate-controlled diastereoselective transformations. It is well known that enones can take part in a variety of reactions, such as 1,2- and 1,4-additions, epoxidation, Diels–Alder reaction, etc. Consequently, a number of methods for the preparation of cyclohexenones have been reported. Of particular interest herein are methods leading to γ-alkyl-γ-aryl-substituted cyclohexenones. These structures have classically been accessed by a variant of the Robinson annulation.[2] While this method remains useful, the synthesis of the required α-aryl aldehyde substrate is not always straightforward and makes the method less suitable for the preparation of a library of products. A notable advance was Meyers' use of chiral bicyclic lactams as a template for stereoselective alkylation, yielding products that can be transformed to the target cyclohexenones.[3] This sequence contains at least five steps.

In the field of transition metal catalysis, Buchwald reported a few examples of γ-arylation of cyclic enones, leading to γ-alkyl-γ-aryl-substituted cyclohexenones.[4] In this case, the substrates are prepared by Birch reduction of anisoles. Unsubstituted vinylogous esters have been used in a Pd-catalyzed α-arylation for the formation of *tertiary* centers, but the method suffers from a very limited substrate scope (i.e., only electron-rich aryl bromides give good yields), a high catalyst loading (10 mol % Pd), and a high reaction temperature (100 °C).[5] Recently, a Rh-catalyzed desymmetrative hydrosilylation of cyclohexa-2,5-dienones was disclosed.[6] We also reported the Rh-catalyzed redox isomerization of cyclohexa-2,5-dienols for the synthesis of the corresponding γ,γ-dialkyl-substituted cyclohexenones.[7] We were then prompted to study the α-arylation of α-alkyl-substituted vinylogous esters, which would act as precursors to γ-alkyl-γ-aryl-substituted cyclohexenones. Establishing mild reaction conditions and a broad substrate and aryl bromide scope were important considerations in this study.[8,9]

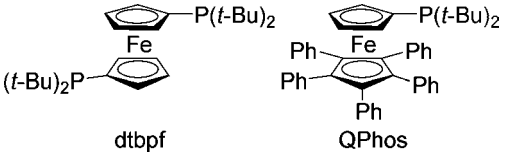
An initial screen of reaction conditions revealed that $Pd(dba)_2$, along with one of a few bulky, electron-rich ligands, was capable of promoting the reaction of the lithium enolate of **1a** with 3,4-dimethoxybromobenzene at room temperature (Table 1). The highest yield was obtained with $P(t\text{-}Bu)_3$ as the ligand (Table 1, entry 3), which was introduced to the field of α-arylation by Hartwig.[10]

Table 1. Evaluation of the Reaction Conditions[a]



entry	ligand	base	yield (%)[b]
1	dtbpf	LiHMDS	60
2	QPhos	LiHMDS	60
3	$P(t\text{-}Bu)_3{\cdot}HBF_4$	LiHMDS	80
4	$P(t\text{-}Bu)_3{\cdot}HBF_4$	NaHMDS	0

[a]Ar = $3,4\text{-}(MeO)_2C_6H_3$ [b]Isolated yields after flash chromatography.



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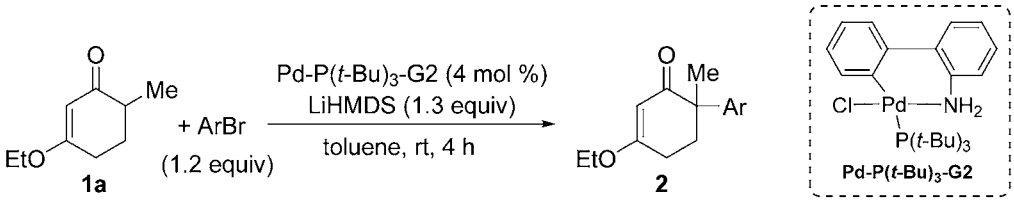
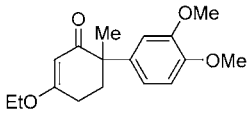
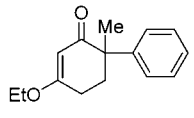
Scheme 1. Scope of Aryl and Alkenyl Bromides Reacting with Substrate 1a[a]

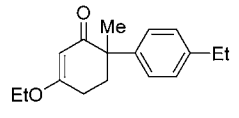




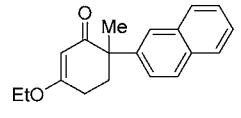
2a, 83% yield



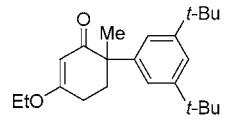
2b, 86% yield



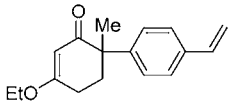
2c, 83% yield



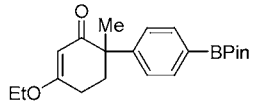
2d, 72% yield



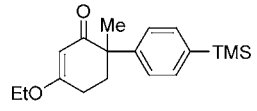
2e, 93% yield



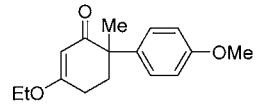
2f, 65% yield



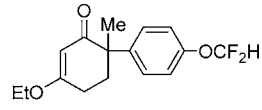
2g, 75% yield



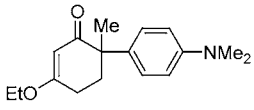
2h, 92% yield



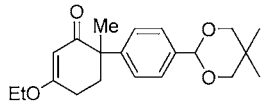
2i, 79% yield



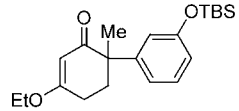
2j, 79% yield



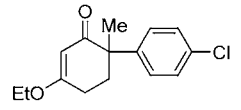
2k, 90% yield



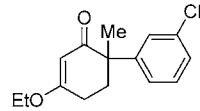
2l, 95% yield



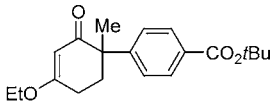
2m, 95% yield



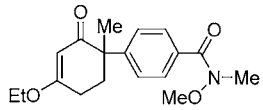
2n, 84% yield



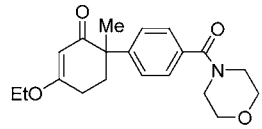
2o, 65% yield



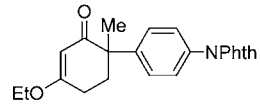
2p, 86% yield



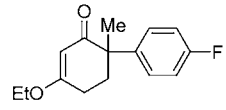
2q, 62% yield



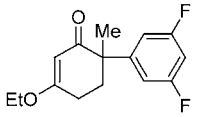
2r, 55% yield



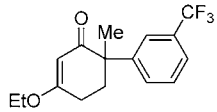
2s, 72% yield



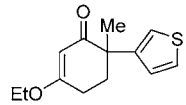
2t, 90% yield



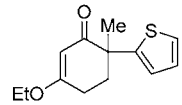
2u, 80% yield



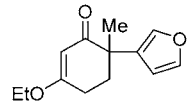
2v, 83% yield



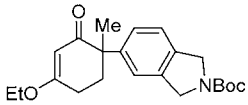
2w, 83% yield



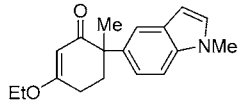
2x, 50% yield



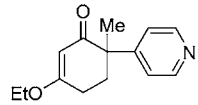
2y, 74% yield



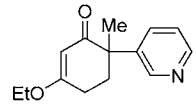
2z, 64% yield



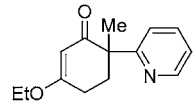
2aa, 77% yield



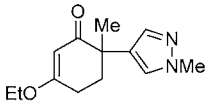
2ab, 39% yield[b]



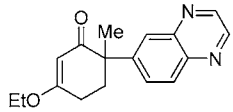
2ac, 40% yield[b]



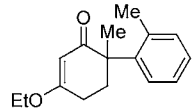
2ad, 50% yield[b]



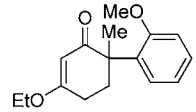
2ae, 25% yield[b]



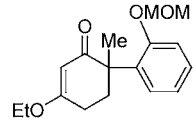
2af, 62% yield



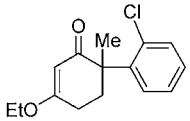
2ag, 65% yield[c]



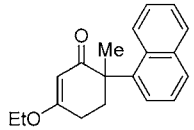
2ah, 72% yield[c]



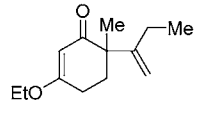
2ai, 58% yield[c]



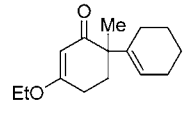
2aj, 40% yield[c,d]



2ak, 63% yield[c]



2al, 71% yield



2am, 88% yield

3, 80% yield[e]

[a]Using 0.7 mmol of **1a**. See the Supporting Information for details. [b]With $Pd(OAc)_2$ (4 mol %) and P(*t*-Bu)$_3$·HBF_4 (8 mol %). [c]For 16 h. [d]40% yield of **2aj**, isolated admixed with 8% of unreacted starting material. [e]With 2.2 equiv of LiHMDS.

After these initial optimization studies had been completed, it became apparent that the conditions under which the enolate was formed had an impact on the reaction outcome. More specifically, forming the enolate at −20 °C and introducing it to

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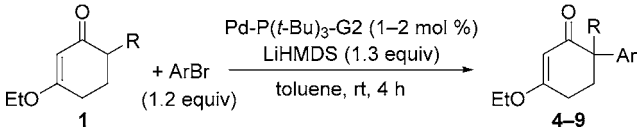
the palladium catalyst and aryl bromide at the same temperature proved beneficial. In addition, we found that the commercially available catalyst Pd-P(t-Bu)$_3$-G2 could be used with analogous or better results than those seen using Pd(dba)$_2$ and the phosphine salt. These conditions are represented in Scheme 1 and were used to study the scope of the reaction. A wide range of aryl and alkenyl bromides with various steric and electronic parameters were reactive. The model product **2a** was formed in 83% yield. Vinylogous esters **2b–f** bearing electron-neutral or moderately electron-rich aryl groups were formed in good to excellent yields. Bpin and TMS groups were tolerated in **2g** and **2h**, which were formed in 75 and 92% yield. The more electron-donating substituents −OMe, −OCF$_2$H, and −NMe$_2$, found in **2i–k**, were equally compatible with the reaction. Alcohols and aldehydes had to be protected as their respective silyl ether and acetal derivatives, forming **2l** and **2m**, both in 95% yield. Chloro groups in **2n** and **2o** were tolerated, allowing further cross-coupling of the products. Electron-deficient aryl groups bearing an ester or an amide could also be present, as seen in **2p–r**. While a free amine was not tolerated, its phthalimide derivative delivered **2s** in 72% yield. In addition to different fluorinated aromatics **2t–v**, a range of heterocycles were employed in this reaction, including thiophene (**2w**, **2x**), furan (**2y**), indoline (**2z**), indole (**2aa**),[11] pyridine (**2ab–ad**), pyrazole (**2ae**), and quinaxoline (**2af**). Most of them were formed in relatively good yields, considering the more challenging nature of these coupling partners. In the pyridine and pyrazole cases, it was necessary to use Pd(OAc)$_2$ and P(t-Bu)$_3$·HBF$_4$ instead of the palladacycle, presumably because of catalyst deactivation by the heterocycle. The reaction is also compatible with *ortho*-substituted aryl bromides, as exemplified by products **2ag–ak**, formed in 40–72% yield. Di-*ortho*-substituted aryl bromines were not reactive.[12] Finally, two different alkenyl bromides were successfully engaged, further illustrating the versatility of this protocol (**2al**, **2am**).[13] It is noteworthy that tertiary centers can be formed, as seen in **3** (80% yield). The same product was formed in 14% yield by the previous method.[5]

With respect to substrate **1**, a variety of alkyl substituents can be introduced at the α position. The results are shown in Table 2. The reaction can accommodate ethyl (**4**) and *n*-propyl (**5**) chains with a 1 or 2 mol % catalyst loading. A bulkier benzyl group (**6**) is also tolerated. When an allyl chain was introduced, we observed an isomerized (E) internal alkene in product **7**. The presence of a primary alkyl chloride was found not to interfere, with **8** being isolated in 61% yield. A congested quaternary center bearing an isopropyl group can also be formed in 33% yield (**9**).[14] However, the reaction could not be applied to a substrate already bearing an α-aryl group (Table 2, entry 7).

Table 2. Scope of Six-Membered Vinylogous Esters[a]

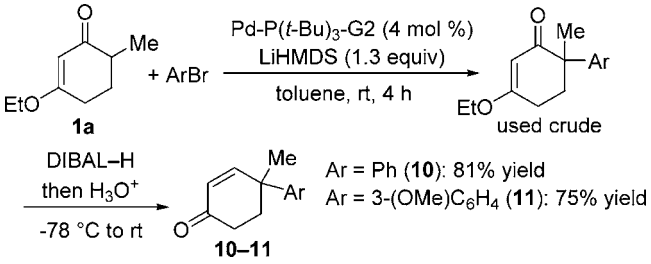


entry	R	mol % Pd	yield (%)
1	Et (**1b**)	2	73 (**4**)
2	*n*-Pr (**1c**)	1	88 (**5**)
3	Bn (**1d**)	2	76 (**6**)
4	allyl[b] (**1e**)	2	53[b] (**7**)
5	−(CH$_2$)$_3$Cl (**1f**)	2	61 (**8**)
6	*i*-Pr (**1g**)	1	33 (**9**)
7	Ph (**1h**)	2	0

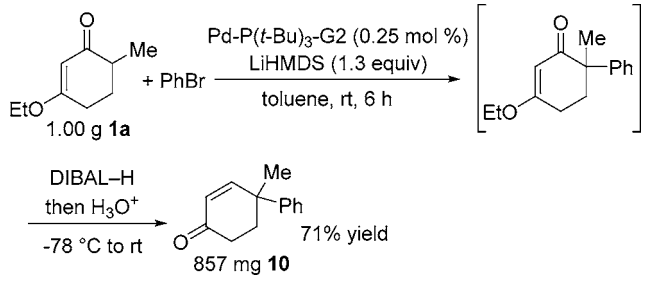
[a]Ar = 3,4-(OMe)$_2$C$_6$H$_3$. See the Supporting Information for details. [b]Isomerized to the (E) internal alkene in the product.

With the scope of the reaction now established, we turned our attention to converting the products into the desired γ,γ-disubstituted cyclohexenones using a reductive transposition.[15] This sequence can conveniently be executed from the crude arylation mixture (i.e., after quench, filtration, and removal of the solvents) (Scheme 2) or even in a one-pot protocol where DIBAL-H is introduced directly at the end of the Pd-catalyzed reaction (Scheme 3). The one-pot reaction could be performed on a 1.00 g scale of **1a**, using a catalyst loading as low as 0.25 mol %, in an overall yield of 71% (Scheme 3).

Scheme 2. Arylation–Reductive Transposition Sequence



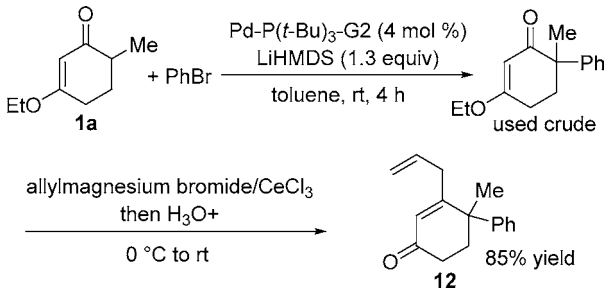
Scheme 3. Gram-Scale One-Pot Synthesis of a γ,γ-Disubstituted Cyclohexenone



A Grignard reagent could also be used in place of DIBAL-H in a near-quantitative second step to deliver cyclohexenone **12** with added functionality in 85% overall yield (Scheme 4).[16]

Finally, in order to further probe the generality of the method, it was tested on five- and seven-membered-ring vinylogous esters. Yields comparable to those obtained for our six-membered products were observed in the arylation step (Figure 1).

Scheme 4. Arylation–Grignard Addition Sequence



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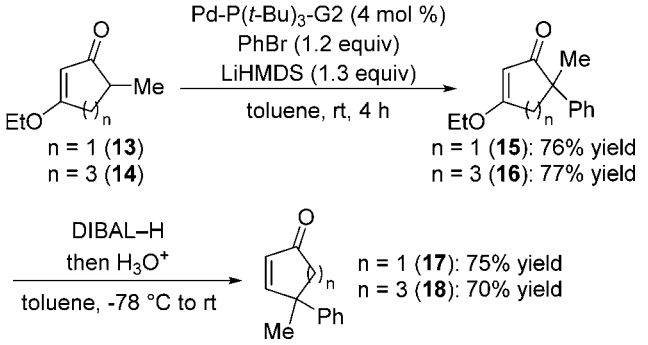

Figure 1. Synthesis of five- and seven-membered γ,γ-disubstituted cycloalkenones.

In summary, we have developed a palladium-catalyzed α-arylation protocol for the synthesis of vinylogous esters bearing a quaternary carbon center, which can readily be converted to γ-alkyl-γ-aryl-substituted cyclohexenones. The method is modular, and the scope of aryl bromides is particularly broad, with a range of functional groups and heterocycles being tolerated. Efforts are underway to extend this method to the synthesis of more complex molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03394.

Detailed experimental procedures and characterization data (PDF)

X-ray crystallographic data for **2aa** (CIF)

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Notes

The authors declare no competing financial interest.

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