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Palladium-Catalyzed Cascade Arylation of Vinylogous Esters Enabled by Tris(1-adamantyl)phosphine

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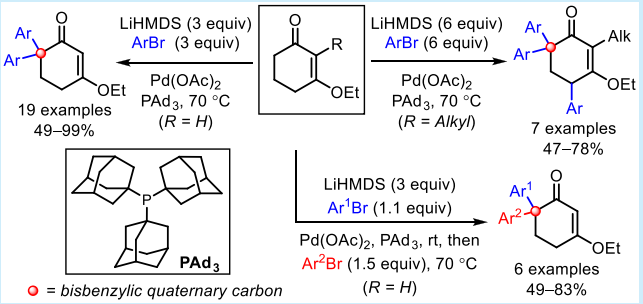
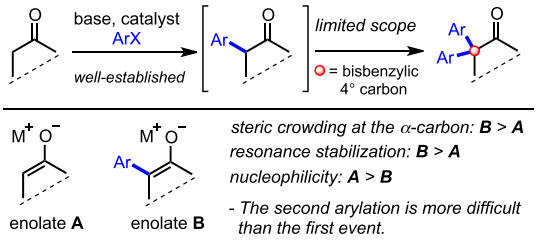
Supporting Information

ABSTRACT: Described is a method for the transformation of a cyclic vinylogous ester to the corresponding polyarylated product. We found a catalytic system comprising palladium diacetate and tris(1-adamantyl)phosphine is quite effective in promoting a set of controlled cascade arylations. As a result, a range of novel (hetero)aryl-containing scaffolds was synthesized with a high level of efficiency.



The prevalence of (hetero)aryl motifs in biologically active compounds and organic electronic materials has spurred considerable research efforts on the development of efficient C−H arylation methods.[1] In this context, direct arylation of C(sp^2)−H bonds in arenes has been widely applied for the assembly of conjugated aromatic frameworks.[2] Advancements on transition-metal catalysis have notably expanded the capacity of aliphatic C−H functionalization with aryl electrophiles.[3] A subgroup of these leading arylative transformations involves deprotonative cross-coupling processes of C(sp^3)−H bonds adjacent to a carbanion-stabilizing group, collectively referred to as α-arylation reactions.[4] Building on the seminal works of Buchwald,[5] Miura,[6] and Hartwig,[7] the palladium-catalyzed α-arylation of carbonyl derivatives has been refined as an indispensible tool in the arsenal of synthetic chemists.[8] Despite progress, only a handful of reaction systems have been identified that could enable the successive incorporation of aryl groups at the α-carbon.[9] In particular, forging a polyarylated quaternary center via α-arylation cascade remains a formidable challenge.[10−13] It is presumed that the nucleophilicity of enolate **B** derived from the monoarylation product is compromised by both stabilizing resonance effects and steric hindrance posed by the α-aryl group (Scheme 1); hence, the installation of the second aryl group becomes more difficult due to the lower reactivity (**A** vs **B**).[14] As an initial foray to tackle such a challenge, we herein present novel deprotonative arylations of cyclic vinylogous esters, facilitated by the combination of palladium catalysis and tris(1-adamantyl)-phosphine (PAd_3).

Scheme 1. Synthesis of Bisbenzylic Quaternary Carbons by Catalytic Cascade α-Arylation



Previous works by Zhang,[15] Lautens,[16] and Wu[17] have revealed that α-alkyl and α-unsubstituted vinylogous esters are amenable to catalytic α-monoarylation reactions. From their comprehensive survey, however, Lautens and co-workers found that the established arylation conditions were not compatible with a vinylogous ester substrate already bearing an α-aryl substituent (i.e., **2b**, vide infra); this observation echoes with the presumption summarized in Scheme 1.[16] As part of our ongoing studies toward the synthesis of *Amaryllidaceae* alkaloids, we have been optimizing the catalytic arylation of 3-ethoxy-2-cyclohexenone (**1a**) with 1-bromo-3,4-(methylenedioxy)benzene. In this context, we sought to leverage the unique electronic and steric properties of tris(1-adamantyl)phosphine[18] for improving the α-arylation reaction. In the event, monoarylated product **2a** could be synthesized in relatively high yield in the presence of $Pd(dba)_2$ (3 mol %) and PAd_3 (3.4 mol %) (Table 1, entries 1−4). With $Pd(OAc)_2$ as the palladium source, we observed that, compared with less sterically bulky or less electron-releasing ligands, using PAd_3 as the ligand furnished more diarylated product **3a** (cf. entries 5−8). This finding enlightened us about the prospect of developing synthetically useful cascade α-arylations; hence, we undertook further variation of reaction parameters. Increasing the loadings of both $Pd(OAc)_2$ and PAd_3 caused a great improvement in yields of **3a** (entries 9 and 10). When more equivalents of the bromoarene and lithium bis-

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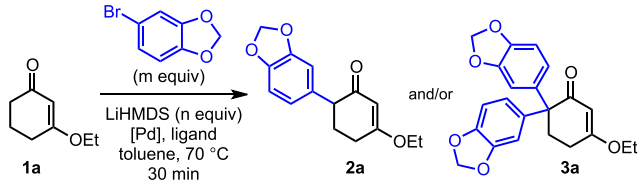
Table 1. Evaluation of Conditions[a]



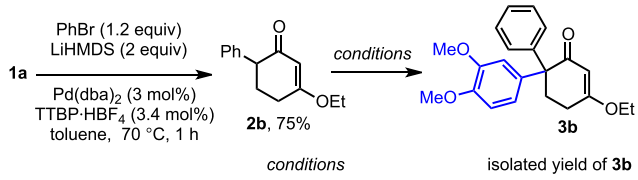
entry	*m*:*n*	[Pd] (mol %)	ligand (mol %)	yield% of **2a**[b]	yield% of **3a**[b]
1	1.2:2	$Pd(dba)_2$ (3)	TTBP·HBF_4 (3.4)	52	trace
2	1.2:2	$Pd(dba)_2$ (3)	BINAP (3.4)	16	trace
3	1.2:2	$Pd(dba)_2$ (3)	xantphos (3.4)	56	<5
4	1.2:2	$Pd(dba)_2$ (3)	PAd_3 (3.4)	72	<5
5	1.2:2	$Pd(OAc)_2$ (3)	PAd_3 (3.4)	23	42
6	3:3	$Pd(OAc)_2$ (3)	PAd_3 (3.4)	trace	47
7	3:3	$Pd(OAc)_2$ (3)	TTBP·HBF_4 (3.4)	21	17
8	3:3	$Pd(OAc)_2$ (3)	PPh_3 (3.4)	35	trace
9	3:3	$Pd(OAc)_2$ (5)	PAd_3 (6)	trace	45
10	3:3	$Pd(OAc)_2$ (10)	PAd_3 (12)	trace	76
11	6:6	$Pd(OAc)_2$ (10)	PAd_3 (12)	trace	81
12[c]	3:3	$Pd(OAc)_2$ (10)	PAd_3 (12)	trace	40
13[d]	3:3	$Pd(OAc)_2$ (10)	PAd_3 (12)	trace	71
14[e]	3:3	$Pd(OAc)_2$ (10)	PAd_3 (12)	18	17
15[f]	3:3	$Pd(OAc)_2$ (10)	PAd_3 (12)	51	<5

[a]Reactions were evaluated using 1.0 mmol of **1a**. For detailed procedures, see the Supporting Information. [b]Isolated yield. [c]With NaHMDS as the base. [d]With 1,4-dioxane as the solvent. [e]Reaction was conducted at 50 °C. [f]Reaction was conducted at room temperature. TTBP·HBF_4: tri-*tert*-butylphosphonium tetrafluoroborate. BINAP: (±)-2,2′-bis(diphenylphosphino)-1,1′-binaphthalene. Xantphos: 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.

(trimethylsilyl)amide (LiHMDS) were employed, **3a** was obtained in a slightly higher yield (cf. entries 10 and 11). The reaction performed with a sodium base (sodium bis(trimethylsilyl)amide (NaHMDS)) was less favorable than that employing LiHMDS (entry 12). Changing the solvent to 1,4-dioxane caused no marked effects in the process (entry 13). Additional experiments indicated that reaction temperature (70 °C) is another crucial factor for attaining high efficiency (entries 14 and 15). To validate that the arylation events occurred in sequence, we prepared monoarylated product **2b** independently and then examined its conversion to **3b** (Scheme 2). Not unexpectedly, the $Pd(OAc)_2/PAd_3$ system was proven highly competent in this previously elusive arylation,[16] thus delivering **3b** in 84% yield.

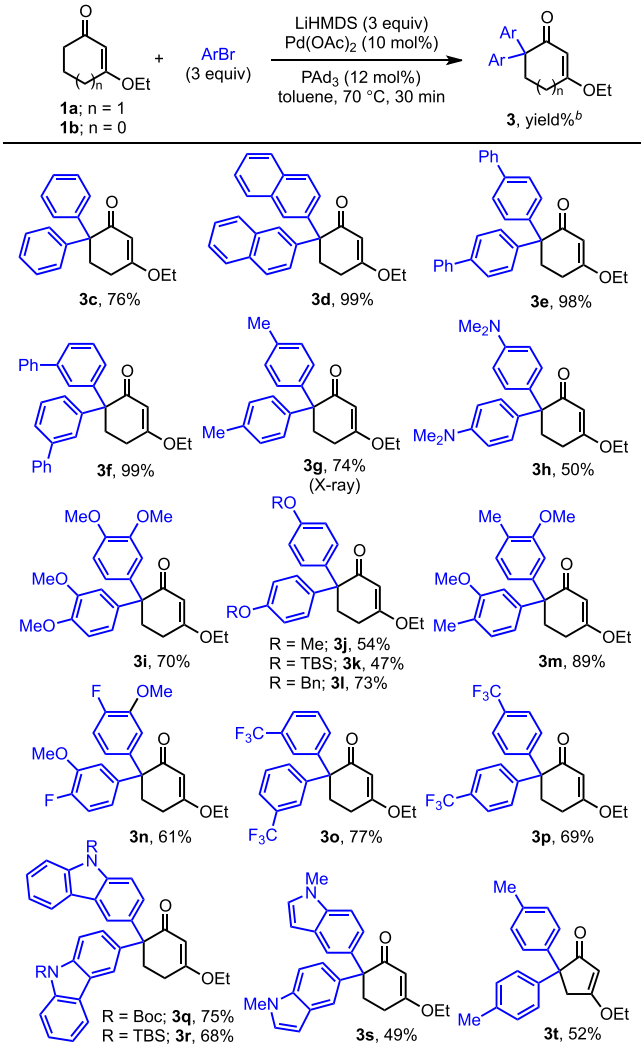
We decided to apply conditions employing 3 equiv of bromoarenes to examine the scope of the cascade diarylation (Scheme 3). Synthesis of *α*,*α*-bis(phenyl), *α*,*α*-bis(2-naphthyl), and *α*,*α*-bis(biphenyl) products (see **3c**–**f**) could be readily achieved with high efficiency. Aryl bromides that bear electron-donating groups (−OMe, −OTBS, −OBn, $-NMe_2$, etc.) coupled uneventfully with **1a** to afford the corresponding diarylated products **3g**–**m**. Fluoro and trifluoromethyl

Scheme 2. Comparison of Two Reaction Conditions



	conditions	isolated yield of **3b**
Data taken from ref. 16	LiHMDS (1.3 equiv), Pd-P(*t*-Bu)$_3$-G2 (2 mol%) 4-bromoveratrole (1.2 equiv), toluene, rt, 4 h	0%
This work	LiHMDS (1.5 equiv), $Pd(OAc)_2$ (10 mol%) PAd_3 (12 mol%), 4-bromoveratrole (1.5 equiv), toluene, 70 °C, 30 min	84%

Scheme 3. Scope of the Cascade Diarylation of 1a[a]



[a]Reactions were evaluated using 0.5 mmol of **1a**. [b]Isolated yield.

substituents are compatible with the reaction conditions (see **3n**–**p**). At this stage, we found no apparent correlations between the product yields and electronic properties of the aryl bromides. The method also permitted successive installation of bis(carbazolyl) and bis(indolyl) moieties at the *α*-carbon (see **3q**–**s**). A five-membered-ring precursor **1b** was amenable to the diarylative protocol giving **3t** in 52% yield.

Subsequently, we found that the arylation reaction of a *α*′-methyl-substituted congener **1c** took an interesting twist. When **1c** was subjected to the standard conditions with 4-

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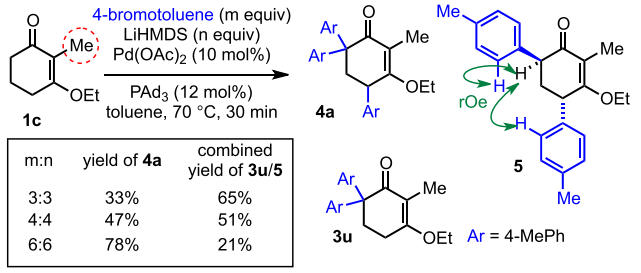
bromotoluene, three polyarylated products were identified (Scheme 4). The structure of the major component was fully

Scheme 4. Cascade Triarylation of 1c

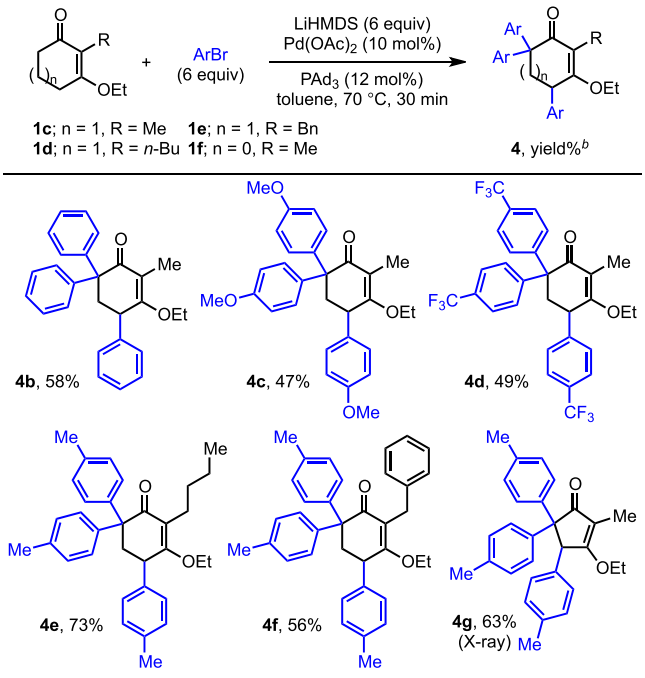


m:n	yield of **4a**	combined yield of **3u**/**5**
3:3	33%	65%
4:4	47%	51%
6:6	78%	21%

characterized and assigned as α,α,γ-triaryl vinylogous ester **4a**. An inseparable mixture of the expected product **3u** and a constitutional isomer **5** was also collected, which implied the regioselectivity of the second arylative event with **1c** is low. While the distinct reactivity induced by the seemingly remote methyl group (cf. **1a** and **1c**) could not be fully accounted, this result constitutes a rare case in accessing γ-reactivity for the direct arylation of conjugated carbonyls.[19] To our delight, we were able to increase yields of **4a** by simply adding more equivalents of LiHMDS and 4-bromotoluene. When the reaction was conducted at room temperature (rt), mono-arylated compound **2c** was generated as the sole product in 76% yield (see Supporting Information).

With viable conditions in hand for the cascade triarylation, we investigated the scope of this one-step triarylative transformation (Scheme 5). Representative bromoarenes with different electronic properties all reacted with **1c** to afford the corresponding triarylated products **4b**–**d** in moderate yields. Cyclic vinylogous esters bearing *n*-butyl or benzyl group also

Scheme 5. Scope of the Cascade Triarylation of α'-Substituted Substrates[a]

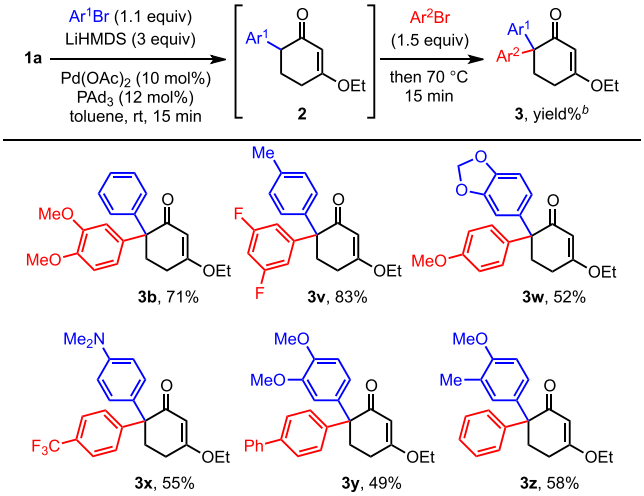


[a]Reactions were evaluated using 0.5 mmol of **1**. [b]Isolated yield.

worked well in this reaction system (see **4e** and **4f**). In the case with **1f**, a vicinal triarylation proceeded smoothly to furnish a densely functionalized cyclopentenone derivative **4g**, whose structural assignment was unambiguously determined by X-ray diffraction analysis. It would be difficult to prepare these triarylated products in one step by currently existing methods.

Mindful of the optimization study (cf. entries 10 and 15 in Table 1), we noted that the kinetic barrier of the first arylation reaction is lower than the second event. Taking advantage of this phenomenon, we were able to achieve a one-pot sequential introduction of two distinct aryl moieties at the α-carbon by adding corresponding bromoarenes at different temperatures. This modular sequence allows a facile construction of bisbenzylic α-quaternary stereocenters, and its generality is showcased in Scheme 6. The corresponding dihomo-arylated

Scheme 6. Scope of the One-Pot Sequential Diarylation of 1a[a]

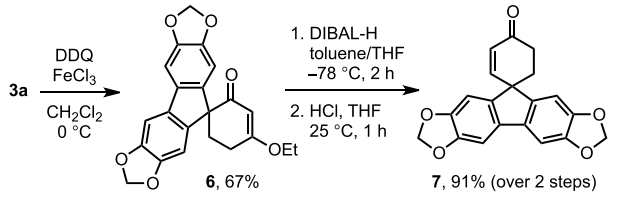


[a]Reactions were evaluated using 0.5 mmol of **1a**. [b]Isolated yield.

products were not observed in these transformations. Analogously, we studied the one-pot sequential threefold arylation of **1c** by introducing 4-bromotoluene and 4-bromoveratrole at different stages, through which a pair of separable diastereomers **4h** and **4h′** was generated in a combined yield of 45% (see Supporting Information).

To showcase the utility of the method, compound **3a** was subjected to an oxidative aromatic coupling reaction, thereby providing cyclized product **6** in 67% yield (Scheme 7). Synthesis of enone **7** was accomplished via a standard Stork-Danheiser transposition.[20] Overall, by integrating the cascade arylations and selected strategic transformations, we demonstrated a rapid route to functionalized spiro-fluorene derivatives of potential interests to organic material science.

Scheme 7. A Concise Synthesis of Spiro-Fluorenes



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In summary, we developed a series of new arylative transformations pertaining to cyclic vinylogous esters. The ability of these protocols to efficiently construct bisbenzylic α-quaternary center from synthetically versatile precursors provides a useful tactic for the synthesis of novel aromatic architectures. We believe that the introduction of tris(1-adamantyl)phosphine[18] to the field of catalytic α-arylation reactions presents a promising direction for the discovery of new bond-forming reactions.[21] Further studies aiming to establish new types of α-arylation reactions by applying the [Pd]/PAd_3 system are currently under investigation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03071.

Experimental procedures and characterization data (PDF)

Accession Codes

CCDC 1943073−1943074 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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(21) A preliminary study indicated the coupling reaction between γ-butyrolactone and 4-bromotoluene under the standard conditions (Table 1, entry 8) gave α,α-bis(tolyl) product **8** in an unoptimized yield of 33% (see the Supporting Information). Under the same conditions, the reactions of other substrates such as 2-cyclohexen-1-one, 4,4-dimethyl-2-cyclohexen-1-one, and acetophenone resulted in the partial recovery of starting materials, and none of the corresponding diarylated products were observed.

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