

Palladium-Catalyzed β -Arylation of Silyl Ketene Acetals and Application to the Synthesis of Benzo-Fused δ -Lactones

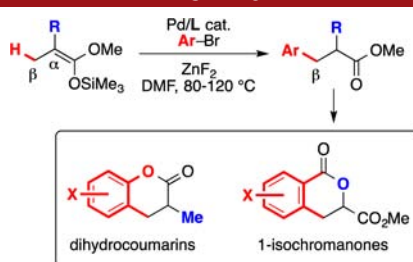
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ABSTRACT



Silyl ketene acetals are shown to be competent nucleophiles in Pd-catalyzed migrative $\text{C}(\text{sp}^3)\text{--H}$ arylations. Compared to the parent ester lithium enolates, they possess decreased reactivity but enhanced chemoselectivity. This behavior was exploited through the synthesis of valuable benzo-fused δ -lactones such as 1-isochromanones and dihydrocoumarins.

The metal-catalyzed functionalization of nonacidic $\text{C}(\text{sp}^3)\text{--H}$ bonds in alkane fragments of organic molecules is both a topic of current great interest and a very challenging problem.¹ In this context, a number of methods relying on the introduction of a powerful directing group have been successfully introduced for the intermolecular arylation of unactivated $\text{C}(\text{sp}^3)\text{--H}$ bonds.² We recently reported the intermolecular palladium(0)-catalyzed migrative C--H arylation of ester lithium enolates as a mechanistically distinct alternative to directed $\text{C}(\text{sp}^3)\text{--H}$

arylations (Scheme 1a).³ This reaction was shown to occur via initial formation of a palladium enolate, rearrangement to the less hindered Pd homoenolate (via $\beta\text{--H}$ elimination, rotation, and insertion), and reductive elimination.^{3b,4} Although this method offers a number of advantages compared to directed arylations, including the use of simple esters, mild reaction temperatures, and the absence of polyarylated products, we were aware that the generation of a relatively basic and nucleophilic lithium enolate was

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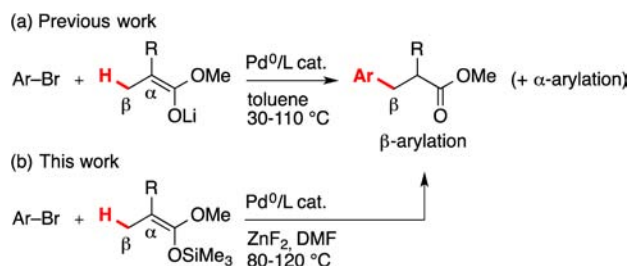
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detrimental to chemoselectivity with sensitive aryl halides. To tackle this issue, we turned our attention to silyl ketene acetals (SKAs), initially employed in Pd-catalyzed α -arylations by Musco, Santi, and co-workers, as milder surrogates for ester enolates (Scheme 1b).⁵ Herein, we report that SKAs show diminished reactivity but enhanced chemoselectivity compared to lithium enolates in the β -arylation of esters. The newly developed method was applied to the synthesis of valuable heterocycles such as 1-isochromanones and dihydrocoumarins.

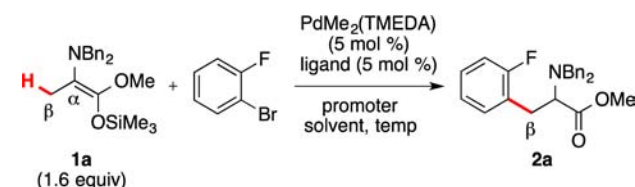
Scheme 1. β -Arylation of Ester Lithium Enolates and SKAs



We started to investigate the β -arylation of (*E*) α -amino SKA **1a** obtained from bis-benzyl-protected alanine methyl ester,⁶ with 2-fluorobromobenzene by extension of our work on the corresponding lithium enolate.^{3c} Reaction parameters were screened extensively, and some representative examples are presented in Table 1. We first used conditions adapted from Hartwig and co-workers with ZnF_2 as a promoter in DMF ^{5f,g} and tested ligands **L**¹–**L**³, which previously gave comparable results with lithium enolates (with a slightly enhanced reactivity for **L**³), in combination with $\text{PdMe}_2(\text{TMEDA})$ (5 mol %) as the Pd source (entries 1–3).^{3c} In the present case, the ligand effect was much more pronounced since only ligand **L**³ showed significant reactivity. In light of this result, we synthesized novel analogues of phosphine **L**³ (**L**⁴–**L**⁹) and studied the effect of substituents at key positions on their reactivity (entries 4–9). We found that slight modifications of the imidazole ring (**L**⁴–**L**⁵, entries 4 and 5), phosphorus substituents R^1 (**L**⁶, entry 6), and *ortho* substituent R^2 (**L**⁷–**L**⁹) were detrimental to the reaction efficiency to variable extents, and thus the initial imidazolylphosphine **L**³ could not be outperformed.

Next, the effect of other promoters, which have been previously employed in α -arylations of SKAs,⁵ was analyzed (entries 10–13). Zinc fluoride turned out to be by far the most efficient promoter, and both its zinc and fluoride components were found to be important (entries 10–12). DMF was found to be the best solvent (entries 14 and 15), and the optimal temperature was found to be 120 °C (entries 16–18). Finally, increasing the amount of ZnF_2

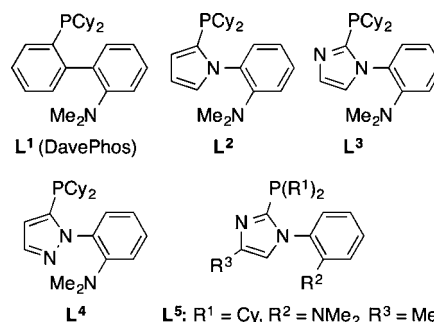
Table 1. Optimization of the β -Arylation of Amino SKA **1a**



entry ligand promoter (equiv) solvent temp (°C) NMR yield (%)^a

1	L ¹	ZnF_2 (0.5)	DMF	120	0
2	L ²	ZnF_2 (0.5)	DMF	120	0
3	L ³	ZnF_2 (0.5)	DMF	120	56
4	L ⁴	ZnF_2 (0.5)	DMF	120	0
5	L ⁵	ZnF_2 (0.5)	DMF	120	24
6	L ⁶	ZnF_2 (0.5)	DMF	120	48
7	L ⁷	ZnF_2 (0.5)	DMF	120	41
8	L ⁸	ZnF_2 (0.5)	DMF	120	17
9	L ⁹	ZnF_2 (0.5)	DMF	120	26
10	L ³	CsF (0.5)	DMF	120	16
11	L ³	CuF_2 (0.5)	DMF	120	0
12	L ³	ZnCl_2 (0.5)	DMF	120	14
13	L ³	LiOAc (0.5)	DMF	120	6
14	L ³	ZnF_2 (0.5)	dioxane	100	0
15	L ³	ZnF_2 (0.5)	NMP	120	0
16	L ³	ZnF_2 (0.5)	DMF	80	44
17	L ³	ZnF_2 (0.5)	DMF	100	50
18	L ³	ZnF_2 (0.5)	DMF	130	48
19	L ³	ZnF₂ (1.0)	DMF	120	58 (59)^b

^a Determined by ¹H NMR analysis of the crude mixture using 3-fluorophenylacetonitrile as a standard. ^b With 10 mol % of **L**³. Yield of the isolated product in parentheses.



L⁵: $\text{R}^1 = \text{Cy}$, $\text{R}^2 = \text{NMe}_2$, $\text{R}^3 = \text{Me}$
L⁶: $\text{R}^1 = \text{iPr}$, $\text{R}^2 = \text{NMe}_2$, $\text{R}^3 = \text{H}$
L⁷: $\text{R}^1 = \text{Cy}$, $\text{R}^2 = \text{OMe}$, $\text{R}^3 = \text{H}$
L⁸: $\text{R}^1 = \text{Cy}$, $\text{R}^2 = \text{iPr}$, $\text{R}^3 = \text{H}$
L⁹: $\text{R}^1 = \text{Cy}$, $\text{R}^2 = \text{CF}_3$, $\text{R}^3 = \text{H}$

to 1 equiv and the ligand loading to 10 mol % slightly improved the yield, which reached an optimal value of 59% for the isolated product **2a** (entry 19). The hydrolyzed SKA and the unreacted aryl bromide constituted most of the remaining mass balance. No trace of α -arylated product was observed with SKA **1a**, similar to the corresponding lithium enolate.^{3c}

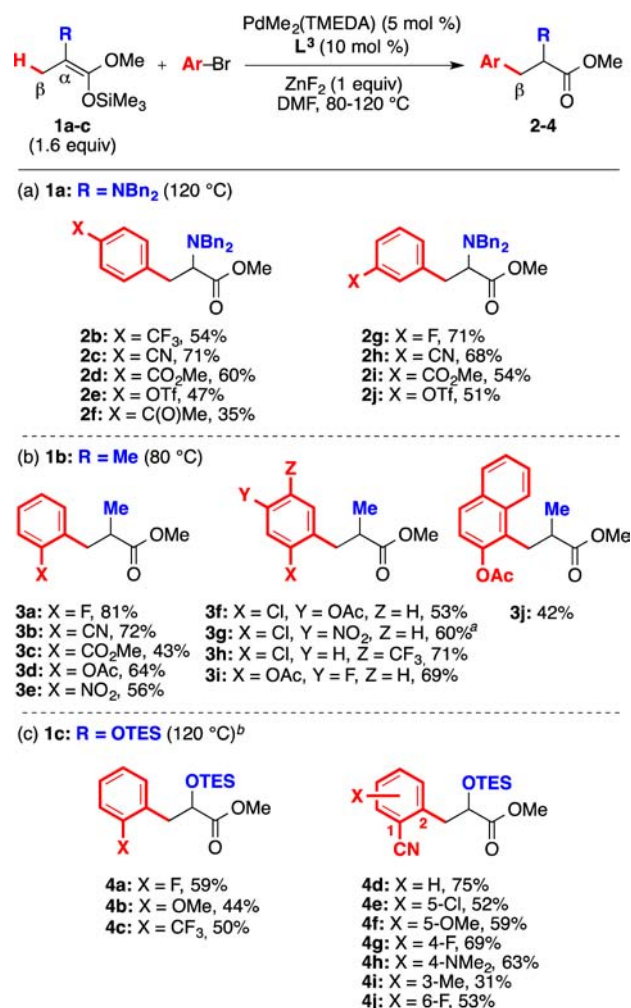
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Scheme 2. Scope of the β -Arylation of SKAs



^a At 120 °C. ^b TES = triethylsilyl.

The optimal conditions were applied to other aryl bromides, giving rise to valuable precursors of phenylalanine analogues (Scheme 2a).⁸ Moderate to good yields were obtained with a variety of electron-withdrawing substituents, including methyl esters (**2d**, **2i**) and triflates (**2e**, **2j**) which were previously found to be incompatible with lithium enolates.^{3c} Sensitive acetophenone **2f** was also obtained, albeit in lower yield. More sensitive functional groups such as OH, NO₂, and CHO were found to be incompatible with these reaction conditions. In addition, aryl bromides containing electron-donating substituents such as OMe, NMe₂, and OSi(*i*Pr)₃ were found to be essentially unreactive. This behavior indicates that, with bulky SKA **1a**, transmetalation to form the intermediate Pd enolate is rate-limiting and requires a very reactive organopalladium ArPd(L)X species with an electron-deficient Ar group to proceed. In addition, the conversion dropped dramatically at temperatures lower than 80 °C, whereas the reaction of the corresponding lithium enolate performed efficiently at 70 °C, thereby pointing also at a rate-limiting transmetalation with SKA **1a**.

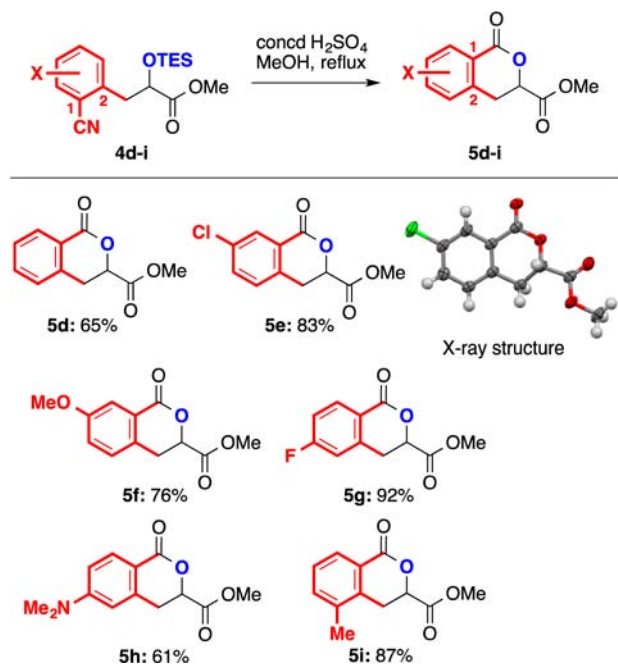
Next, the β -arylation of commercially available SKA **1b** (R = Me) was examined, by extension of previous work with the corresponding lithium enolate (Scheme 2b).^{3a,b} We deliberately chose to employ aryl bromides with an *ortho* electronegative group like in previous studies since unproductive mixtures of β - and α -arylated products are obtained in other cases. It was found that the use of SKA **1b** greatly expanded the scope of the reaction compared to the corresponding lithium enolate. Indeed, more sensitive *ortho* substituents such as a nitrile (**3b**), methyl ester (**3c**), acetate (**3d**), and nitro group (**3e**) can now be employed with satisfying results, in addition to more inert substituents like F (**3a**) which were previously used with the lithium enolate.^{3a,b} Aryl bromides with multiple substituents also underwent β -arylation successfully and in a completely β -selective manner (**3f–i**), in addition to a naphthyl bromide (**3j**). SKA **1b** was found to be more reactive than the more hindered SKA **1a**. This allowed the reaction to be run at 80 °C and to increase functional group tolerance. Indeed, acetate and nitro groups were found to be compatible under these milder conditions. SKA **1b** showed enhanced chemoselectivity but lower reactivity than the corresponding lithium enolate which reacts with 2-fluorobromobenzene as low as 30 °C. This is a further indication that transmetalation is the rate-limiting step of the current process.

The reaction of TES-protected SKA **1c** (mixture of *E* and *Z* isomers), readily available from methyl lactate, was next studied (Scheme 2c). Of note, the reaction of the corresponding lithium enolate would be compromised by the known propensity of such species to decompose at room temperature.^{5g,9} Compound **1c** successfully underwent β -arylation; however, similarly as above for SKA **1b** (and contrary to α -amino SKA **1a**), an *ortho* electronegative group on the aryl bromide was required to achieve a complete β -selectivity. The reaction was again performed at 120 °C similar to **1a**, presumably due to the bulkiness of SKA **1c**. In addition to inert *ortho* substituents (**4a–c**), the reaction was successfully performed with an *ortho* cyano group (**4d**), furnishing aryl lactates **4a–d** in moderate to good yields. It is noteworthy that the triethylsilyl group was not cleaved under these reaction conditions. This method was also applied successfully to differently substituted *o*-bromobenzonitriles (**4e–j**), which were subsequently converted to 1-isochromanones (vide infra).

Some of the above β -arylated products contain reactive *ortho* substituents which can be utilized to build original heterocyclic compounds. As a first application, we were able to convert aryl lactates **4d–i** (Scheme 2c) to 1-isochromanones **5d–i** in good yields upon standard treatment with concentrated sulfuric acid in methanol (Scheme 3). Overall, this method represents a straightforward and efficient access to this important class of heterocycles

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Scheme 3. Application to the Synthesis of 1-Isochromanones

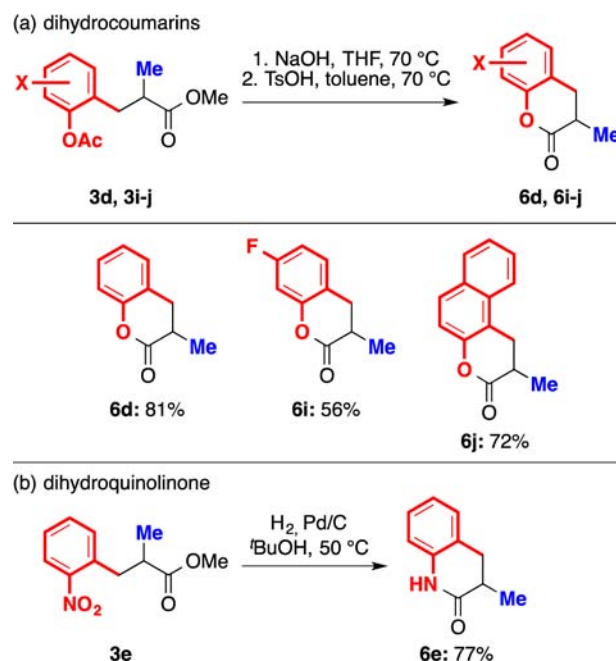


relevant to medicinal chemistry and natural product synthesis.¹⁰

In addition, we envisioned that *o*-acetoxyated β -arylated products obtained as shown in Scheme 2b might lead to valuable dihydrocoumarins upon basic hydrolysis of the acetate and cyclization of the corresponding phenol onto the methyl ester (Scheme 4a). After a short optimization of this protocol, dihydrocoumarins **6d**, **6i**, and **6j** were indeed obtained efficiently.¹¹ Dihydroquinolinones are similarly interesting compounds for drug discovery.¹² From *o*-nitro-substituted β -arylated product **3e**, a standard hydrogenation in the presence of Pd/C directly afforded dihydroquinolinone **6e** in good yield (Scheme 4b).

In conclusion, we have shown that SKAs are competent nucleophiles in Pd-catalyzed migrative $\text{C}(\text{sp}^3)\text{--H}$ arylations. Compared to the parent ester lithium enolates, they

Scheme 4. Application to the Synthesis of Dihydrocoumarins and a Dihydroquinolinone



show decreased reactivity but enhanced chemoselectivity. This behavior was exploited through the synthesis of valuable benzo-fused lactones (and one lactam) such as 1-isochromanones and dihydrocoumarins.

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Supporting Information Available. Full characterization of all new compounds, detailed experimental procedures, copies of NMR spectra for target molecules, and X-ray crystal structure data (CIF) for compound **5e**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.

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