Cross-Coupling

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Single-Flask Multicomponent Palladium-Catalyzed α,γ-Coupling of Ketone Enolates: Facile Preparation of Complex Carbon Scaffolds

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Abstract: *A three-component palladium-catalyzed reaction sequence has been developed in which γ-substituted α,β-unsaturated products are obtained in a single flask by an α-alkenylation with either a subsequent γ-alkenylation or γ-arylation of a ketone enolate. Coupling of a variety of electronically and structurally different components was achieved in the presence of a Pd/Q-Phos catalyst (2 mol%), usually at 22°C with yields of up to 85%. Most importantly, access to these products is obtained in one simple operation in place of employing multiple reactions.*

Sequential multicomponent reactions have long been recognized as an efficient approach to the synthesis of complex molecules, especially when they can be conducted as single-flask (one-pot) operations. The first reaction of a multicomponent sequence serves to generate a substrate that enters into the next step or steps of the sequence. Among the implementations of this concept are the sequential addition of reactants to a single flask or tandem reactions in which all components may be present simultaneously.[1] Overall transformations are accomplished more efficiently than would be the case through use of individual reactions. In recent years, this concept has been developed extensively through use of metal-promoted reaction sequences,[2] with carbon–carbon bond-forming reactions playing especially important roles. Potentially amenable to multicomponent sequences are transition-metal-catalyzed α-alkenylation of enolates[3] (Figure 1a) and the related γ-arylation and γ-alkenylation of dienolates generated from either α,β- or β,γ-unsaturated carbonyl compounds (Figure 1b and c).[4] Individually, these reactions provide access to β,γ-unsaturated and γ-substituted, α,β-unsaturated carbonyl compounds, respectively. Facile access to both of these classes of scaffolds is desirable because of their appearance in biologically important compounds and their versatility in further synthetic transformations.[3a,5] Greater synthetic efficiency could be achieved if the α- and γ-coupling reactions were employed in single-flask sequences (Figure 1d).

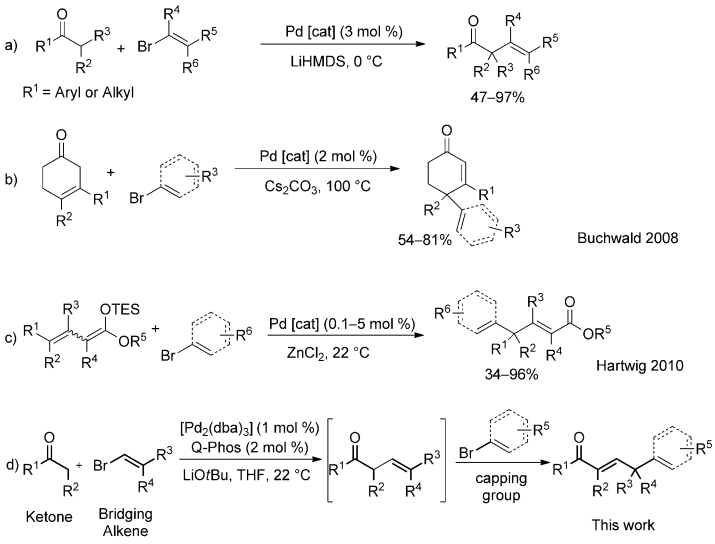

Figure 1. a) Palladium-catalyzed α-alkenylation of enolates. b, c) Palladium-catalyzed γ-arylation and γ-alkenylation of dienolates. d) Palladium-catalyzed sequential α,γ-coupling. dba = dibenzylideneacetone, TES = triethylsilyl, THF = tetrahydrofuran, Q-Phos = 1-di-*tert*-butylphosphino-1′,2′,3′,4′,5′-pentaphenylferrocene.

Previous studies of palladium-catalyzed coupling reactions of dienolates have demonstrated ligand-dependent selectivity for achieving γ-coupling as opposed to either α- or β-coupling. Work by Miura and co-workers led to a procedure for coupling α,β-unsaturated aldehydes and ketones with aryl bromides at 120°C to afford γ-arylated tertiary products.[6] Later, Hyde and Buchwald employed both α,β- and β,γ-unsaturated ketones to form γ-arylated and γ-alkenylated quaternary products at 100°C (Figure 1b).[7] More recently, Huang and Hartwig reported a procedure using milder reaction conditions for the γ-arylation and γ-alkenylation of silyl ketene acetals at 22°C (Figure 1c).[8] While good yields have been achieved utilizing these procedures, there is ample room for improvement because of drawbacks which include high temperatures or the need to prepare, in separate steps, the required unsaturated carbonyl or their ketene acetal derivatives. Also, the scope of γ-alkenylation has been much more limited than for γ-arylation.[5d,7–9]

To overcome the need for the separate synthesis of the dienolate precursor, we envisioned a palladium-catalyzed α-

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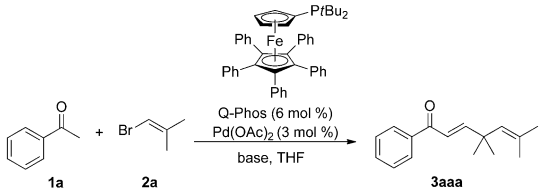
alkenylation and subsequent γ-arylation or γ-alkenylation sequence that would generate a γ-substituted α,β-unsaturated scaffold more directly in a single operation (Figure 1 d). This sequence would employ a ketone, an alkenyl halide to generate a bridging alkene unit, and either an aryl halide or an alkenyl halide as a capping group. Herein, we report a mild palladium-catalyzed procedure to effect this type of sequential α,γ-coupling in one flask with excellent regioselectivity and control of the sequence of incorporation of components for the rapid construction of complex carbon scaffolds, thus providing facile access to molecular diversity.

Initial success was achieved upon the isolation of an α,γ-alkenylated product (**3aaa**) when acetophenone (**1a**) and a small excess of **2a** were subjected to our recently published α-alkenylation conditions (Table 1, entry 1).[3b] To optimize

Table 1: Optimization of the reaction conditions for the formation of **3aaa**.[a]



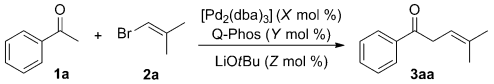
Entry[b]	**2a**[c]	Base[c]	*T* [°C]	Yield [%][d]	*t* [h]
1	130	LiHMDS (110)	0	35	2
2	250	LiHMDS (250)	22	0	12
3	250	LiO*t*Bu (250)	22	99	12

[a] Here and in subsequent figures, the multiple letter designations in the compound numbering refer to the ketone, bridging, and capping groups in that order. [b] Reactions were conducted on a 0.5 mmol scale. [c] Reported in mol%. [d] Yield of isolated products. HMDS = hexamethyldisilazide.

the formation of **3aaa**, the amount of LiHMDS and alkenyl halide were both increased to 250 mol%. However, neither an α-alkenylated nor an α,γ-alkenylated product was detected (entry 2). A screening of bases identified LiO*t*Bu as a suitable base, thus resulting in a quantitative yield of **3aaa** as a single regioisomer (entry 3). The crude product was remarkably pure as shown by the ^{1}H NMR spectrum of the material obtained after a simple work-up procedure without further purification. While **3aa** could be obtained very efficiently under these optimized reaction conditions, a sequential coupling employing two different electrophiles (bridging alkene and capping group) would allow a greater variation in scope.

To employ two different electrophiles as bridging alkene and capping groups, the use of the reactants must proceed with a good level of control in their order of incorporation. The formation of the initial α-alkenylated intermediate must result in a high yield before the incorporation of a second electrophilic component and must avoid further reaction of this intermediate with the first electrophile to give the previously observed α,γ-alkenylated product **3aaa**. A facile way to overcome the formation of **3aaa** is to employ excess ketone, but this tactic is wasteful because of the large excess of the second electrophile (capping group) needed because of the presence of unreacted starting ketone enolate. We therefore focused on developing reaction conditions that utilize a 1:1 ratio of **1a** and **2a** to afford high conversion into the initial coupling product **3aa** with minimal side product formation (Table 2). The reaction parameters examined

Table 2: Optimization of the reaction conditions for the formation of **3aa**.



Entry[a]	*X*[b]	*Y*[b]	*Z*[b]	Solvent (M)	*T* [°C]	Yield [%][c]
1	1	2	220	toluene (0.25)	22	16
2	1	2	220	THF (0.25)	22	79
3	1	2	220	THF (0.50)	22	66
4	1	2	220	THF (0.13)	22	83
5	1	2	220	THF (0.06)	22	89
6	1	2	220	THF (0.25)	0	29
7	2	4	220	THF (0.25)	0	72
8	1	2	280	THF (0.25)	22	89
9	1	2	340	THF (0.25)	22	95
10	1	2	400	THF (0.25)	22	96

[a] Reactions were conducted on a 0.25 mmol scale. [b] Reported in mol%. [c] Determined by NMR spectroscopy using an internal standard.

included the choice of solvent, molarity, temperature, and base loading. The use of a large excess of LiO*t*Bu was the most beneficial reaction component examined, thus affording 96% yield of **3aa** (entry 10). Optimized reaction conditions employed [$Pd_2(dba)_3$] (1 mol%), Q-Phos (2 mol%), and LiO*t*Bu (400 mol%) in THF (0.25 M) at 22°C, and they were employed for the subsequent study of the desired sequential α,γ-couplings.

For the sequential couplings, an alkenyl bromide (100 mol%) was added as a bridging alkene to a solution of the starting ketone enolate, base, and catalyst in THF at 22°C. After 45 minutes, either an alkenyl bromide or an aryl halide (110 mol%) was added as a capping group and reacted for 16 hours at either 22°C or 45°C. The scope of ketones was explored by employing **2a** as a bridging alkene and either **2b** or **2c** as a capping group (Figure 2). For most examples, employing either **2b** or **2c** as a capping group led to similar yields of the isolated products unless otherwise stated. Electron-neutral and electron-rich methyl ketones afforded high yields of the desired products (**3aab**, **3aac**, **3bab**, **3bac**), while an electron-deficient ketone was not as reactive and resulted in moderate yields at 45°C with **2c** as a capping group (**3cac**). Attempts to synthesize **3cab** resulted in substantially lower yields than **3cac** under similar reaction conditions. An *ortho*-substituted methyl aryl ketone afforded high yields at 45°C (**3dab**, **3dac**). Aliphatic ketones were not as effective as aryl ketones for the subsequent γ-coupling and resulted in a low yield of the desired α,γ-coupled product **3eab**. An acyclic α-substituted ketone resulted in moderate yields at 45°C (**3fab**, **3fac**). When α-tetralone was subjected to our reaction conditions at 45°C, the desired products were obtained in moderate yields without any detection of

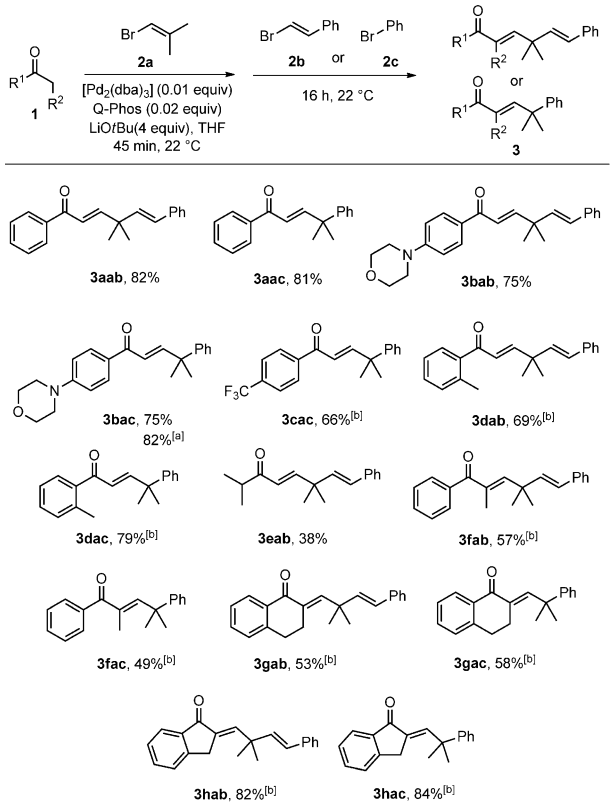


Figure 2. Reaction scope of ketones. Yields are those of the isolated products. Reactions were conducted on a 0.25 mmol scale relative to **1**. [a] Conducted on a 5 mmol scale. [b] Reaction was run at 45 °C in THF (0.125 M).

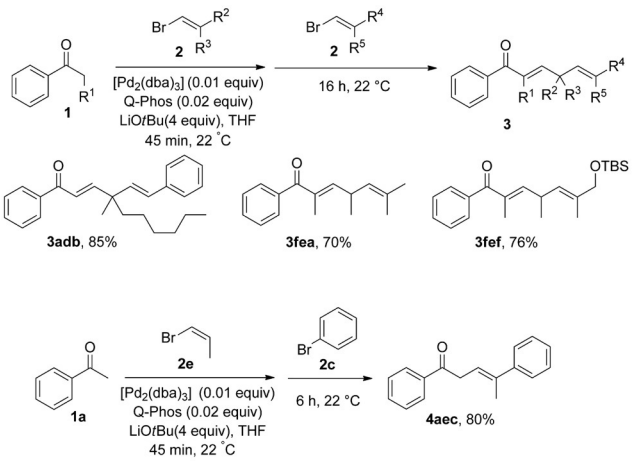


Figure 3. Reaction scope of bridging alkene. Yields are those of the isolated products. Reactions were conducted on a 0.25 mmol scale relative to **1**. TBS = *tert*-butyldimethylsilyl.

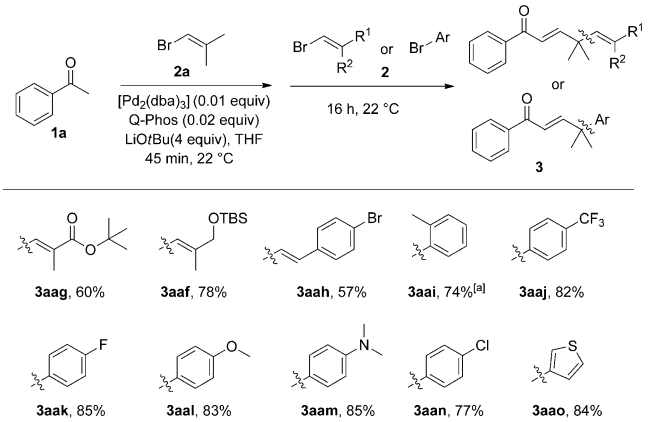


Figure 4. Reaction scope of capping group. Yields are those of the isolated products. Reactions were conducted on a 0.25 mmol scale relative to **1**. [a] Reaction was run at 45 °C in THF (0.125 M).

aromatized naphthol products (**3gab**–**3gac**). Employing indanone at 45 °C resulted in high yields with both styryl and phenyl capping groups (**3hab**, **3hac**). Our protocol was applicable to scale-up, thus producing 1.38 grams (82 % yield) of **3bac**.

Next, the scope of the bridging alkenyl halide was examined (Figure 3). A high yield of a γ-quaternary product (**3adb**) was obtained when R^2 is an extended alkyl chain. Products with tertiary γ-carbon atoms could be generated in high yields (**3fea**, **3fef**) by employing propiophenone, *cis*-1-bromopropene, and an alkenyl capping group with *cis* substitution. An altered outcome was observed when an α-unsubstituted ketone was employed and *cis*-1-bromopropene was utilized as a bridging alkene. With bromobenzene as the capping group, a nonconjugated ketone product **4aec** was produced in contrast with the normally obtained conjugated ketones.[10] α-Bromostyrene and 2-bromo-3-methyl-2-butene did not result in significant product formation when employed as bridging alkenes.

Finally, the scope with respect to the capping group to form a quaternary γ-center was examined with **1a** as the ketone and **2a** as the bridging alkene (Figure 4). An activated ester alkenyl bromide capping group resulted in moderate yields (**3aag**) and was the only example in which a competing α,α-coupling product was observed, but still favored the usual α,γ-coupling product by a factor of 2:1. When the ester group was replaced by a silyl-protected alcohol, complete selectivity for the α,γ-coupled product was observed in good yield without desilylation (**3aaf**). Employing a capping group containing an alkenyl bromide and an aryl bromide moiety afforded a moderate yield of **3aah** with 3:1 chemoselectivity favoring the γ-alkenylation over the arylation product. A more sterically hindered *ortho*-substituted aryl bromide afforded a good yield at 45 °C (**3aai**). A range of *para*-substituted electron-deficient and electron-rich aryl bromides all coupled in high yields (**3aaj**–**aam**). Employing chlorobenzene as a capping group resulted in an insignificant yield at 22 °C, and led to the use of 4-chloro-1-bromobenzene as a capping group to afford a high yield of **3aan**. A thiophene capping group was tolerated and gave a high yield of **3aao**. Employing 3-bromopyridine, 2-bromoaniline, 5-bromoindole, and α-bromostyrene as capping groups resulted in low yields of the desired products.

A final preliminary observation suggests that this approach to α,γ-coupling may not be limited to the use of

palladium as a catalyst. When the β,γ-unsaturated ketone **3 fa**, obtained by our previously reported nickel- or palladium-catalyzed ketone alkenylation,[3b,c] was subjected to further coupling with (*E*)-β-bromostyrene with a nickel catalyst, **3 fab** was obtained in 83% yield as an overall α,γ-coupling product (Figure 5). The same product was obtained above in 57% yield from the palladium-catalyzed sequential procedure (Figure 2). We are unaware of previously reported nickel-catalyzed γ-alkenylations or γ-arylations.

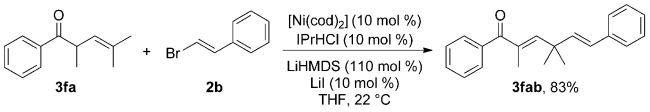


Figure 5. Nickel-catalyzed γ-alkenylation. cod = 1,5-cyclooctadiene.

In conclusion, we have described the development of a novel palladium-catalyzed reaction sequence that operates by α-alkenylation of a ketone with an alkenyl bromide (bridging group) and subsequent γ-coupling of an alkenyl bromide or aryl bromide (capping group) for rapid construction of α,β-unsaturated ketones with complex carbon scaffolds. The large number of examples in Figures 2–4 illustrates the broad scope of this α,γ-coupling reaction. A variety of electronically and structurally different ketones, bridging alkenyl bromides, and capping alkenyl bromides or aryl bromides provide moderate to high yields with excellent regioselectivity for γ-coupling under relatively mild reaction conditions (22–45 °C). The procedure avoids the use of large excesses of any of the three components, thus facilitating the isolation of the final products. In some cases, the crude product is sufficiently pure and further purification is not necessary. Most importantly, the overall products are obtained in a single-flask sequence in place of employing separate reactions for facile access to molecular diversity. Points for further study of this reaction sequence include identifying additional factors which affect the reaction outcome, choice of catalysts, mechanistic details, enantioselective versions, and applications in synthesis.

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