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Palladium-Catalyzed Alkenylation of Ketone Enolates under Mild Conditions

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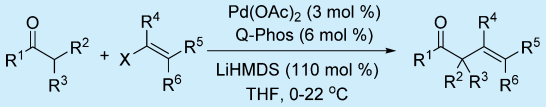
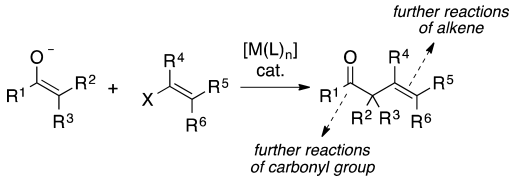
Supporting Information

ABSTRACT: A protocol for a mild, catalytic, intermolecular alkenylation of ketone enolates has been developed using a Pd/Q-Phos catalyst. Efficient intermolecular coupling of a variety of ketones with alkenyl bromides was achieved with a slight excess of LiHMDS and temperatures down to 0 °C.



β,γ-Unsaturated carbonyls are structural features present in a number of important compounds.[1] From a synthetic chemist's perspective, the carbonyl and alkene moieties also provide an attractive platform to access a diverse range of complex structures[2] by further transformations of these two functional groups. Several synthetic approaches have been developed en route to β,γ-unsaturated compounds including transition-metal-catalyzed methods to mediate C−C bond formation between metal enolates and alkenyl halides (Scheme 1).[3] Both inter- and intramolecular versions of these reactions have been reported. However, compared to related arylation reactions with aryl halides,[4] these alkenylations remain at an early stage of development with ample opportunity for improvement.

Scheme 1. Transition-Metal-Catalyzed Alkenylation of Enolates



One potential complication using enolate nucleophiles is that the α-hydrogens of the alkenylation products are more acidic than those of the starting ketones due to allylic resonance in the enolates formed from the products. Consequently, several side reactions can occur due to (1) quenching of the starting ketone enolate by the product, resulting in low conversions, (2) dialkenylations, and/or (3) rearrangement of the initial products to $\alpha\beta$-unsaturated carbonyl compounds.[5] The majority of previously reported ketone enolate alkenylations employ elevated temperatures. As an example, one of the more recently developed procedures of relevance to our studies is performed at 80 °C with a large excess of base (250 mol %),[6] although lower temperatures have been reported in select cases.[3] Here we report a protocol for intermolecular alkenylations that is efficient at lower temperatures with a nearly stoichiometric amount of base. These mild conditions minimize the undesired side reactions discussed above.

Our studies began with a screening of bases together with a palladium catalyst and a bulky ferrocenylphosphine ligand, starting from conditions used in prior work in our laboratory.[7] Several synthetic procedures, including Negishi couplings,[8] Reformatsky reactions,[9] and α-arylations[10] have utilized more mildly basic Zn derivatives as opposed to harsher alkali metal species. With this factor in mind, our initial conditions employed $Zn(TMP)_2$ as the base to couple **1** and **2** in the presence of $Pd(dba)_2$ (2.5 mol %) and Q-Phos (**3a**, 5 mol %) in THF at 22 °C. Compared to the less basic Zn enolates (Table 1, entry 1), further base screenings revealed that Li enolates (entries 2 and 4) reacted faster and resulted in higher yields without observation of unwanted side reactions. Screenings using Na and K bases led to the formation of unidentified precipitates and lower yields (entries 3, 5, and 6). The use of Cs_2CO_3 resulted in no reaction (entry 7). With Li bases performing best, LiHMDS was chosen for use in further studies. An evaluation of solvents showed that both THF and toluene gave comparable results (entries 2 and 8), whereas more polar solvents resulted in lower yields (entries 9 and 10).

During the screening for optimum conditions, two different protocols were employed. Procedure A involved having a base, ligand, and catalyst present, then adding a ketone to generate an enolate, followed by addition of the alkenyl halide. In procedure B, a preformed enolate was added to a solution of

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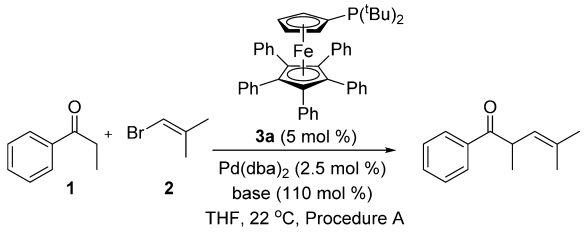
Table 1. Base and Solvent Screen[a]



entry	base	solvent	time (h)	yield[b] (%)
1	$Zn(TMP)_2$	THF	6	47
2	LiHMDS	THF	0.5	85
3	KHMDS	THF	24	50
4	LiOtBu	THF	0.5	87
5	NaOtBu	THF	52	24
6	KOtBu	THF	24	45
7	Cs_2CO_3	THF	24	0
8	LiHMDS	toluene	0.5	88
9	LiHMDS	DMF	24	14
10	LiHMDS	CH_3CN	24	0

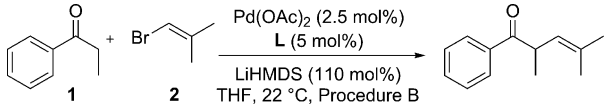
[a]Procedure A: Ketone was added to Pd source, ligand, and base in solution followed by addition of alkenyl halide. [b]Isolated yield.

ligand, catalyst, and alkenyl halide. The reactions proceeded ca. three times faster with procedure B than with procedure A and with similar yields (Table 2, entries 1 and 2). Our choice of procedure B for our further studies is in contrast to the use of conditions that are analogous to procedure A for many prior cases of enolate alkenylations[6,11] and arylations.[12]

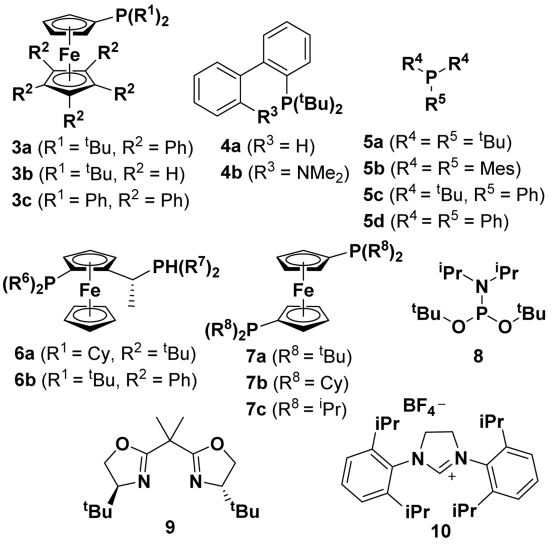
Several ligands varying in electronic and steric properties were screened using $Pd(dba)_2$ (2.5 mol %) and LiHMDS (1.1 equiv) in THF at 22 °C. In these studies, $Pd(dba)_2$ and $Pd(OAc)_2$ performed comparably well as catalysts (Table 2, entries 2 and 3). Triarylphosphines (entries 5, 9, and 11) were inferior to more electron-rich and sterically demanding dialkyl arylphosphines (entries 3, 4, 6, 7, and 10). Among the dialkylarylphosphines, those bearing a ferrocene (entries 3 and 4) gave the highest yields. Dialkylferrocenyl monophosphines outperformed ferrocenyl diphosphines for which a ^{t}Bu substituent led to a modest yield, whereas a cyclohexyl or ^{i}Pr substituent led to no reaction (entries 3, 4, and 14−16). The use of other ligand classes, including a phosphoramidite, a bis(oxazoline) (BOX) ligand, and an *N*-heterocyclic carbene, resulted in low yields (entries 17−19). From the ligand screen, it was concluded that the bulky, electron-rich monophosphine Q-Phos (**3a**) performed best with respect to both yield and reaction time. This ligand has also found use in enolate arylations.[13]

The optimal reagents resulting in fast reaction times permitted the use of lower catalyst loadings and temperatures. Similar yields were achieved with catalyst loadings as low as 0.67 mol % at 22 °C (Table 3, entry 1). Reducing the temperature to 0 °C with 3 mol % catalyst consistently gave high yields and full conversion (entry 4). Upon lowering the temperature, a significant difference was observed between procedure A and procedure B. At 0 °C, procedure B resulted in 100% conversion after 40 min, whereas procedure A achieved only 80% conversion after 10 h (entries 4 and 5). The lower reactivity in procedure A could be rationalized by the strong amide base perhaps interacting with the catalyst. Optimal conditions were achieved using LiHMDS (110 mol %),

Table 2. Ligand Screen*

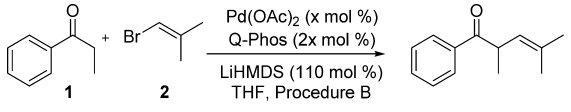


entry	(L)	time (h)	yield[a]	entry	(L)	time (h)	yield[a]
1[b,c]	**3a**	0.5	85	11	**5d**	24	0
2[c]	**3a**	0.15	88	12	**6a**[d]	24	0
3	**3a**	0.15	88	13	**6b**[d]	24	0
4[b,c]	**3b**	3	88	14	**7a**[d]	24	58
5[b,c]	**3c**	24	< 5	15	**7b**[d]	24	0
6	**4a**	24	75	16	**7c**	24	0
7	**4b**	24	50	17	**8**	24	26
8	**5a**	24	25	18	**9**	24	20
9	**5b**	24	0	19[e]	**10**	24	15
10	**5c**	24	68				



*Procedure B: Ketone enolate was generated by adding ketone to a solution of base. The ketone enolate was then added to a Pd source, ligand, and alkenyl halide in solution. [a]Isolated yield. [b]Procedure A (see Table 1). [c]$Pd(dba)_2$ instead of $Pd(OAc)_2$. [d]Ligand (3 mol %). [e]130 mol % of LiHMDS.

Table 3. Optimization of Catalyst Loadings and Temperature[a]



entry	*x* (mol %)	temp (°C)	time (h)	yield[b] (%)	conv[c] (%)
1	0.67	22	3	85	100
2	0.1	22	40	*e*	35
3	2.5	0	1.25	92	98
4	3	0	0.66	97	100
5[d]	3	0	10	*e*	80[e]

[a]Procedure B (see Table2). [b]Isolated yield. [c]Based on starting ketone. [d]Procedure A (see Table1). [e]Not isolated.

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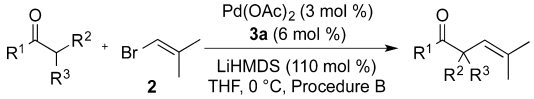
$Pd(OAc)_2$ (3 mol %), and Q-Phos (6 mol %) at 0 °C in THF following procedure B.

With optimum conditions determined, the scope of coupling of ketones to **2** was explored. A range of electron-rich and -deficient secondary aryl ketones reacted rapidly in high yields (70−97%) at 0 °C (Table 4, entries 1−6). The use of 4′-

Table 4. Scope of Ketones[a]



entry	R^1	R^2	R^3	time	yield[b] (%)	conv[c] (%)
1	$p(NMe_2)C_6H_4$	Me	H	10 min	84	100
2	$p(OMe)C_6H_4$	Me	H	10 min	87	100
3	C_6H_5	Me	H	40 min	97	100
4	$p(Cl)C_6H_4$	Me	H	1.5 h	78	90
5	$p(CF_3)C_6H_4$	Me	H	1.5 h	78	93
6[d]	α-tetralone		H	1 h	70	86
7[e]	$p(NMe_2)C_6H_4$	Me	Me	20 h	82	100
8	C_6H_5	H	H	30 min	22	33

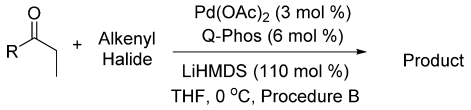
[a]Procedure B (see Table 2). [b]Isolated yield. [c]Based on starting ketone. [d]Toluene as solvent. [e]Run at 22 °C.

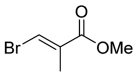
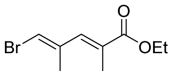
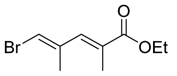
chloropropiophenone led exclusively to the α-alkenylation product without any detectable α-arylation (entry 4). Generation of a quaternary carbon center was possible when the temperature was elevated to 22 °C (entry 7). The use of an α-unsubstituted ketone resulted in the desired α-alkenylation occurring in only 22% yield (entry 8). The highest conversions and yields are obtained using α-mono- or disubstituted ketones that give products containing a tertiary or quaternary α-center without formation of detectable side products.

Next, the scope of alkenyl halides was examined. When different halides were compared, alkenyl bromides were superior to analogous alkenyl iodides and chlorides (Table 5, entries 1−3). Gratifyingly, the conjugated ester-activated derivatives coupled in moderate to high yields (61% and 78%) despite generating products containing α-protons that are presumably more acidic than in the other products (entries 4 and 5). Reactions involving more sterically hindered electrophiles, including use of an alkenyl triflate, resulted in moderate yields (47−71%) (entries 6 and 7). Electrophiles with *trans*-1,2-substitution reacted rapidly to give modest yields in THF. Changing the solvent from THF to toluene in these cases resulted in increased yields (entries 7−9). Coupling of the aliphatic ketone, 3-pentanone, with activated electrophiles resulted in moderate yields (75 and 50%, Table 5, entries 10 and 11).

As mentioned above, a potential concern for both alkenylation and arylation of enolates is the increased acidity of the products' α-hydrogens, which may lead to further reactions. In the case of α-alkenylation, steric factors based on the introduction of a *cis*-substituted alkene may be considered. Subsequent deprotonation of the alkenylation product from an α-substituted ketone may be disfavored due to A-1,3 strain in the resulting enolate. These considerations may be reflected in in a comparison of entries 2 and 9 in Table 5, where lower yields and conversions are observed in the latter case for the product lacking *cis*-substitution. This result may be due to the more facile deprotonation of the non-*cis*-substituted product by the starting ketone enolate, resulting in its quenching. Likewise,

Table 5. Scope of Alkenyl Halides*



entry	R	Alkenyl Halide	time	yield[a]	(conv)[b]
1	Ph		24 h	[c]	(20)
2	Ph		40 min	97	(100)
3[d]	Ph		24 h	26	(37)
4[e]	Ph		10 min	61	(74)
5	Ph		10 min	78	(100)
6[d,e]	Ph		20 h	71	(86)
7[e]	Ph		15 min	47	(57)
8[e]	Ph		10 min	80	(96)
9[e,f]	Ph		40 min	63	(79)
10[e]	Et		1 hour	75	[g]
11[e]	Et		30 min	50	[g]

*Procedure B (see Table 2). [a]Isolated yield. [b]Based on starting ketone. [c]Was not isolated. [d]Run at 22 °C. [e]Toluene as solvent. [f]Alkenyl bromide and product were both a 95:5 *E*:*Z* mixture. [g]Not determined due to volatility of the starting ketone.

when the α-substitution pattern is varied from formation of a tertiary to a secondary product (entries 3 and 8 in Table 4), much lower conversions and yields are observed. This possible effect of A-1,3 strain in inhibiting product deprotonation is consistent with the protocol being most efficient when secondary and tertiary ketones are coupled to form *cis*-substituted products. Of the factors responsible for A-1,3 strain, the absence of a *cis*-alkene substituent is not as unfavorable as using an α-unsubstituted ketone. Another result that may be expected to arise from deprotonation of the α-alkenylation products would be isomerization of the initial products to produce conjugated 2-alkenones. This outcome was not observed in our systems, although it has been observed under previously reported conditions.[5]

In summary, we have developed a procedure for Pd-catalyzed alkenylation of enolates that has been applied to synthesize β,γ-unsaturated ketones under mild conditions. A range of ketones readily undergo coupling with alkenyl bromides varying in steric and electronic properties in good to excellent yields. With this combination of conditions and a variety of substrates now established, we are exploring the mechanistic details and the possibility of developing an enantioselective version of this procedure.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, ^{1}H, ^{13}C, and ^{19}F NMR spectra, and characterization data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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