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Transition-Metal-Free α-Vinylation of Enolizable Ketones with β-Bromostyrenes

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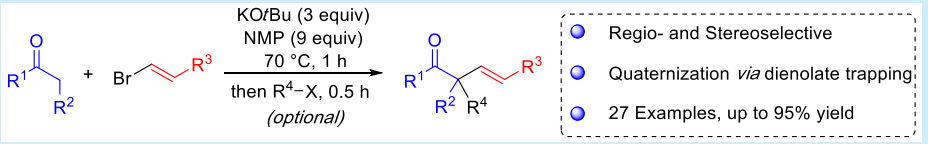
Supporting Information



ABSTRACT: An α-vinylation of enolizable ketones has been developed by using β-bromostyrenes and a KO*t*Bu/NMP system. β,γ-Unsaturated ketones of *E* configuration were obtained in excellent yield and selectivity. Further synthetic possibilities are highlighted by one-pot functionalization via trapping of intermediate dienolates with alkyl, allyl, benzyl, and propargyl halides to generate quaternary centers. The reported transformation is believed to involve phenylacetylene and propargylic alcohol derivatives.

The regio- and stereoselective synthesis of β,γ-unsaturated carbonyl compounds is an important transformation in organic chemistry since these units are present in many natural products and serve as building blocks to access complex structures.[1] The search for efficient and selective methods to yield allylic carbonyl compounds has a long history. With an objective of alleviating the intrinsic limitation of prototropic rearrangement of β,γ-unsaturated carbonyl compounds into their α,β-unsaturated counterparts,[2] many syntheses have been developed based on the use of organometallic reagents,[3] metal-mediated coupling reactions,[4] and transition-metal catalyzed α-vinylation reactions of enolates.[5] In contrast, there have been few reports for the synthesis of allylic carbonyl compounds that do not require transition metals.[6] In early investigations on radical-chain transformations, Bunnett reported the photo-stimulated reaction between potassium acetonate and vinyl halides.[7] An observation made by Galli in 1993 showed that a competing elimination−addition pathway via acetylene intermediates was involved under certain conditions.[8] The presence of propargylic alcohols hinted at an ionic mechanism involving Favorsky-type reactions. Multiple contributions by Galli, Rappoport, and Rossi later hinted that an unequivocal $S_{RN}1$ ketone α-vinylation reaction occurred only for triphenylvinyl bromide, highlighting the rich mechanistic world of vinylic substitution reactions. Recently, Trofimov developed on Galli's initial observation by developing a general base-mediated synthesis of β,γ-unsaturated ketones by the reaction of enolizable ketones and arylacetylenes at temperatures ≥80 °C.[9] The reactions proceed in the presence of either KOH or KO*t*Bu in DMSO to provide β,γ-unsaturated ketones in good selectivities; however, isomerization into their α,β-unsaturated ketones derivatives could not be avoided (minimally 5−10%). We recently developed a transition-metal-free protocol for the α-arylation of enolizable ketones with aryl halides using a mixture of KO*t*Bu and DMF.[10] Since the reactions of aryl iodides proceed at room temperature under these conditions, we believed that the development of a very mild α-vinylation of enolizable ketones was feasible. Our main goal was to achieve complete selectivity for β,γ-unsaturated ketone isomers of *E* configuration at low temperatures.

To start our investigation, we reacted propiophenone **1a** with β-bromostyrene **2a**[11] in DMF for 1 h at 70 °C in the presence of KO*t*Bu as base (Table 1). Under these conditions, addition of 3 equiv of the latter gave the expected β,γ-unsaturated ketone **3a** in 66% yield, along with 16% of enone **4a** (entry 1). Switching the solvent to DMSO or NMP furnished **3a** in 72% and 93% yields, respectively, along with trace amounts of the isomerized enone **4a** when NMP was employed (entries 2 and 3). The yields of **3a** decreased to 61% and 22% by using only 2 and 1 equiv of KO*t*Bu (entries 4 and 5). The use of NaO*t*Bu gave a low yield (entry 6), while LiO*t*Bu proved to be totally unsuitable since phenylacetylene **5a** and propargylic alcohol **6a** were generated in 11% and 72% yields, respectively (entry 7). Other potassium bases, such as KOH or K_2CO_3, also gave disappointing results (entries 8, 9), and reactions at room temperature only led to 39% and 52% yields, after 1 and 24 h, respectively (entry 10). Moreover,

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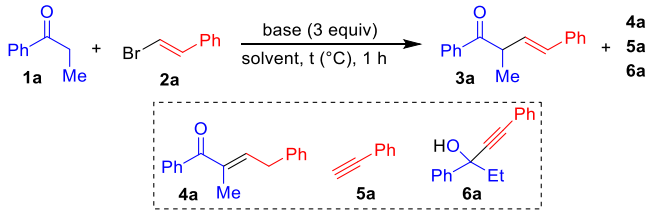
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. α-Styrylation of Propiophenone 1a with β-Bromostyrene 2a: Reaction Conditions[a]



entry	base	solvent	temp (°C)	3a (%)	4a (%)	5a (%)	6a (%)
1	KO*t*Bu	DMF	70	66	16	0	0
2	KO*t*Bu	DMSO	70	72	23	0	0
3	KO*t*Bu	NMP	70	93[b]	2	0	0
4	KO*t*Bu[c]	NMP	70	61	2	2	0
5	KO*t*Bu[d]	NMP	70	22	5	6	0
6	NaO*t*Bu	NMP	70	46	5	0	0
7	LiO*t*Bu	NMP	70	4	0	11	72
8	KOH	NMP	70	8	4	4	0
9	K_2CO_3	NMP	70	0	0	0	0
10	KO*t*Bu	NMP	25	39 (52)	7 (8)	6 (5)	38 (36)

[a]Reaction conditions: propiophenone **1a** (2 mmol), β-bromostyrene **2a** (1 mmol), base (3 mmol), solvent (9 mmol). Yields calculated by ^{1}H NMR using hexamethylbenzene as an internal standard. Yields in parentheses were calculated after 24 h. [b]70% from the β-iodostyrene and 28% for the β-chlorostyrene. [c]2 mmol. [d]1 mmol.

lower **3a**/**4a** ratios were obtained at 25 °C than at 70 °C. Under the optimal conditions, ketones were thus reacted with β-bromostyrenes in the presence of 3 equiv of KO*t*Bu in NMP at 70 °C for 1 h (entry 3).

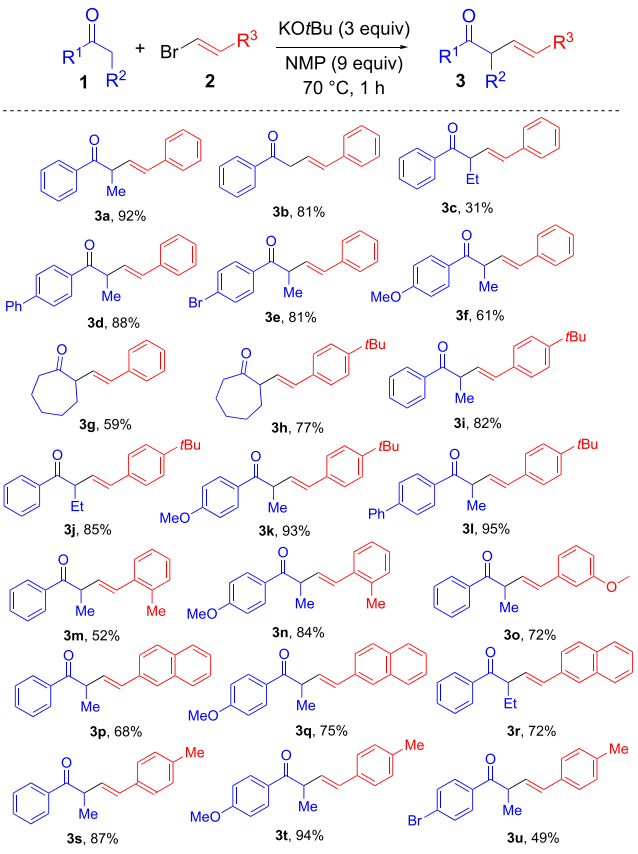
We subsequently turned our attention to the scope of the reaction (Scheme 1). In addition to propiophenone, acetophenone undergoes vinylation to give **3b** in a very good 81% yield without the double vinylation product being detected. In contrast, butyrophenone only led to a low 31% yield of **3c**. Electron-withdrawing and -donating substituents are well tolerated at the *para* position of propiophenones, giving **3d**−**3f** in good to excellent yields. Cycloheptanone also undergoes vinylation to give **3g** in 59% yield and the reaction also tolerated a *p*-*tert*-butyl substituent on the styrene partner, yielding 77% of α-vinylketone **3h**. Reactions of electron-rich or -poor aryl ketones with various β-bromostyrenes substituted at all positions (*o*, *m*, *p*) with methyl, *tert*-butyl, methoxy, and naphthyl groups provided the desired compounds **3i**−**3u** in yields ranging from 49% to 95% (Scheme 1). Selectivity for β,γ- vs α,β-unsaturated ketones is almost complete in all cases, the lower yields being caused by incomplete conversions. In all cases, β,γ-unsaturated ketones were obtained with complete selectivity for *E* stereoisomers.

To further highlight the synthetic potential of this base-mediated α-vinylation of ketones, we performed one-pot trapping of intermediate dienolates with carbon-based electrophiles (Scheme 2). As expected, β,γ-unsaturated ketones **7** bearing all-carbon quaternary centers at the α-position could be isolated in good 60−71% yields, except for **7b** leading to a low 35% yield (Scheme 2).

Beyond iodoalkanes, this method enables efficient one-pot procedures using allyl, benzyl, and propargyl bromides. However, the use of iodobenzene did not lead to the corresponding α-arylated ketone, probably due to steric hindrance.

In order to gain insight into the reaction mechanism, we reacted β-bromostyrene **2a** with 1 equiv of KO*t*Bu and observed an 86% yield of phenylacetylene **5a** in only 10 min at 50 °C (Scheme 3, path a). Under the same reaction conditions,

Scheme 1. Substrate Scope of the α-Vinylation of Ketones[a]



[a]Reaction conditions: ketone **1** (2 mmol), β-bromostyrene **2** (1 mmol), KO*t*Bu (3 mmol), NMP (0.9 mL), 70 °C, 1 h; isolated yields.

propargylic alcohol **6a** is obtained in 58% yield and β,γ-unsaturated ketone **3a** (*E* configuration) in 40% yield when 2 equiv of KO*t*Bu are used and 1 equiv of propiophenone **1a** is added after 10 min in a Favorsky-type reaction (Scheme 3, path b).[12] Both **5a** and **6a**, which were observed as byproducts

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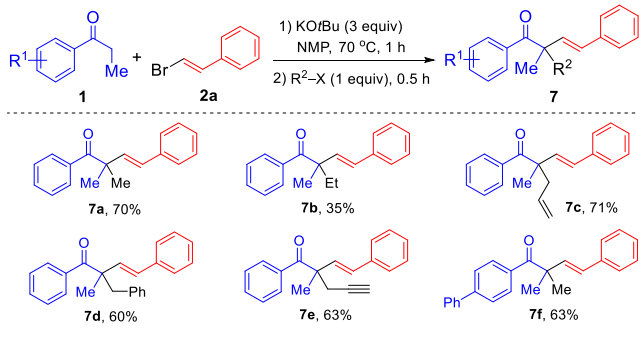
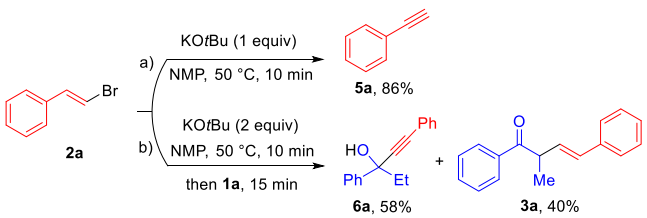
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. One-Pot Trapping of Dienolate Intermediates for the Generation of Quaternary Carbon Centers[a]



[a]Reaction conditions: ketone **1** (2 mmol), β-bromostyrene **2a** (1 mmol), KO*t*Bu (3 mmol), NMP (9 mmol), 70 °C, 1 h, then R^2–X (1 mmol), 0.5 h; isolated yields.

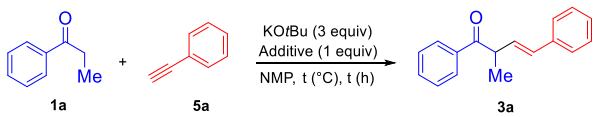
Scheme 3. Generation of Phenylacetylene 5a and Propargylic Alcohol 6a from β-Bromostyrene 2a



during optimization (see Table 1), are likely reaction intermediates or side reaction products.

It was then observed that, in the reaction conditions disclosed herein, the reaction of propiophenone **1a** and phenylacetylene **5a** to give **3a** is efficient at low temperatures (Table 2). While a low 7% yield of the latter is observed after 5 min at 50 °C, accompanied by 81% of intermediate **6a**, prolonging the reaction time to 4 h leads to an excellent 90% yield in **3a** (*E* isomer) (entries 1 and 2). The reaction gives the same yield after 24 h at room temperature (entry 3). To the best of our knowledge, the selective formation of β,γ-unsaturated ketones of *E* configuration from simple ketones and arylacetylenes has never been reported at temperatures lower than 80 °C.[9] It is worth noting that reactions performed in the presence of stoichiometric amounts of hydroquinone (entry 4) and galvinoxyl (entry 5) as potential radical scavengers lowered the yields to 22% and 39%, respectively. While an effect is observed, one cannot conclude that the process involves radical intermediates.

Table 2. α-Styrylation of Propiophenone 1a with Phenylacetylene 5a[a]

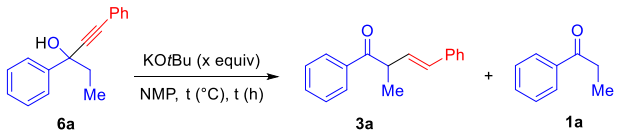


entry	additive	*t* (h)	temp (°C)	**3a** (%)
1	–	0.09	50	7[b]
2	–	4	50	90
3	–	24	25	91
4	hydroquinone	4	50	22
5	galvinoxyl	4	50	39

[a]Reaction conditions: propiophenone **1a** (2 mmol), phenylacetylene **5a** (1 mmol), additive (1 mmol), KO*t*Bu (3 mmol), NMP (0.9 mL). Yields calculated by ^{1}H NMR using hexamethylbenzene as an internal standard. [b]**6a** is obtained in 81% yield as a byproduct.

We next investigated the conditions for the transformation of propargyl alcohol **6a**, as another potential intermediate of the reaction (Scheme 3), into β,γ-unsaturated ketone **3a** (Table 3). In the absence of a base at 100 °C for 24 h, **6a** is recovered quantitatively (entry 1), but the presence of 1 equiv of KO*t*Bu already leads to 2% of **3a** and 36% of **1a** *via* a retro-Favorsky reaction[13] at only room temperature (entry 2). By increasing the temperature up to 50 °C, **3a** was obtained in 35% and 40% yields after 0.5 and 4 h, respectively (entries 3–4). Complete rearrangement of **6a** to **3a** was obtained only *via* the addition of 2 equiv of KO*t*Bu at 50 °C, leading to 72% of the desired compound **3a** (entry 5). Interestingly, the use of a catalytic amount of KO*t*Bu (20 mol %) only led to a slight rearrangement of **6a** into **1a** without formation of **3a**, even at 100 °C (entry 6).

Table 3. Base-Mediated Rearrangement of Propargylic Alcohol 6a to β,γ-Unsaturated Ketone 3a[a]

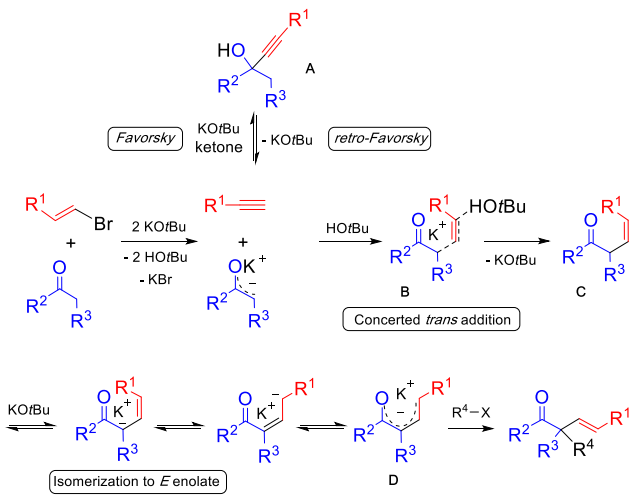


entry	*x*	*t* (h)	temp (°C)	**6a** (%)	**3a** (%)	**1a** (%)
1	–	24	100	100	0	0
2	1	0.5	25	50	2	36
3	1	0.5	50	16	35	42
4	1	4	50	18	40	26
5	2	4	50	0	72	7
6	0.2	4	100	76	0	24

[a]Reaction conditions: propargylic alcohol **6a** (1 mmol), KO*t*Bu (*x* mmol), NMP (0.9 mL). Yields calculated by ^{1}H NMR using hexamethylbenzene as an internal standard.

In light of these results, we propose an ionic mechanism based on the one postulated by Trofimov for the base-mediated addition of arylacetylenes to ketones (Scheme 4).[9a−c] The arylacetylene and the enolate, in situ generated by β-

Scheme 4. Plausible Reaction Mechanism



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Org. Lett. XXXX, XXX, XXX−XXX

elimination reaction of the bromostyrene and deprotonation of the ketone, respectively, would react together by a concerted *trans* addition with the assistance of HO*t*Bu to provide the *E* dienolate **D** after base-mediated isomerization of the intermediate *Z* allylic ketone **C**. A Favorsky reaction could also be envisioned from the attack of the corresponding acetylide on the ketone.[12] A retro-Favorsky reaction from the corresponding propargylic alcohol **A**[13] could then explain the results obtained in Scheme 3 and Table 3.

In summary, we have developed a highly regio- and stereoselective synthesis of *β*,*γ*-unsaturated ketones of *E* configuration from enolizable ketones and *β*-bromostyrenes under transition-metal-free conditions. The reactions can be performed with KO*t*Bu at room temperature for 24 h in moderate yields or up to 70 °C for only 1 h without isomerization into the thermodynamically favored enones. The observation that radical scavengers did not completely suppress the transformation, coupled with the successful trapping of intermediates with carbon-based electrophiles to generate all-carbon quaternary centers, rather points toward an ionic mechanism.[14]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b04004.

Experimental procedures, compound characterization, and copies of ^{1}H NMR and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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Org. Lett. XXXX, XXX, XXX−XXX