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

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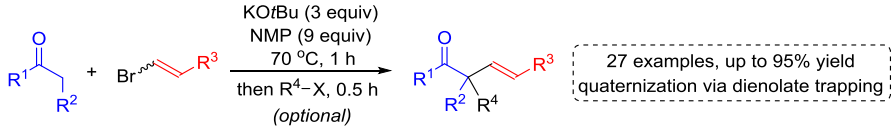
Supporting Information Placeholder



ABSTRACT: An intermolecular α-vinylation of enolizables 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 functionalizations *via* trapping of intermediate dienolates with alkyl, allyl, benzyl, and propargyl halides to generate quaternary centers. The reported transformation is believed to proceed *via* phenylacetylene and propargylic alcohol intermediates.

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 to 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]

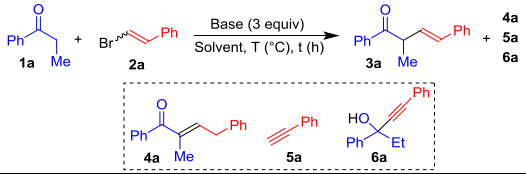
In early investigations on radical-chain transformations, Bunnett reported the photostimulated reaction between potassium acetonate and vinyl halides.[7] An observation made by Galli in 1993 showed that a competing elimination-addition pathway *via* acetylene intermediates was involved under certain conditions.[8] The presence of propargylic alcohols hinted at an ionic mechanism involving Favorsky-type reactions. Multiple contributions [9] by Galli, Rappoport, and Rossi later hinted that an unequivocal $S_{RN}1$ ketone α-vinylation reaction occurred only for triphenylvinyl bromide,[10] highlighting the rich mechanistic world of vinylic substitution reactions. Recently, Trofimov expanded on Galli's initial observation by developing a general base-mediated synthesis of β,γ-unsaturated ketones by the reaction of enolizables ketones and arylacetylenes at temperatures ≥ 80 °C.[11] 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 to 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 based on a mixture of KO*t*Bu and DMF.[12] 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 enolizables 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** [13] in DMF at 70 °C in the absence of base. Under these conditions, reagents are recovered quantitatively (Table 1, entry 1). Addition of 3 equiv of KO*t*Bu gave the expected β,γ-unstaturated ketone **3a** in 66% yield, along with 16% of enone **4a** (entry 2). Switching solvents to DMSO and NMP furnished **3a** in 72% and 93% yields, respectively, along with trace amounts of the isomerized enone **4a** when NMP is employed (entries 3 and 4). The yields of **3a** decreased to 61% and 22% by using only 2 and 1 equiv of KO*t*Bu (entries 5 and 6). The use of NaO*t*Bu gave a low yield (entry 7), while LiO*t*Bu proved to be totally unsuitable since phenylacetylene **5a** and propargylic alcohol **6b** were generated in 11% and 72% yields, respectively (entry 8). Other potassium bases, such as KOH and K_2CO_3, also gave disappointing

results (entries 9 and 10). Unfortunately, reactions at room temperature only lead to 39% and 52% yields, after 1 h and 24 h, respectively (entry 11). Moreover, lower **3a**/**4a** ratios are obtained at 25 °C than at 70 °C. Under the optimal conditions, ketones are thus reacted with β-bromostyrenes in the presence of 3 equiv of KO*t*Bu in NMP at 70 °C for 1 h (entry 4).

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

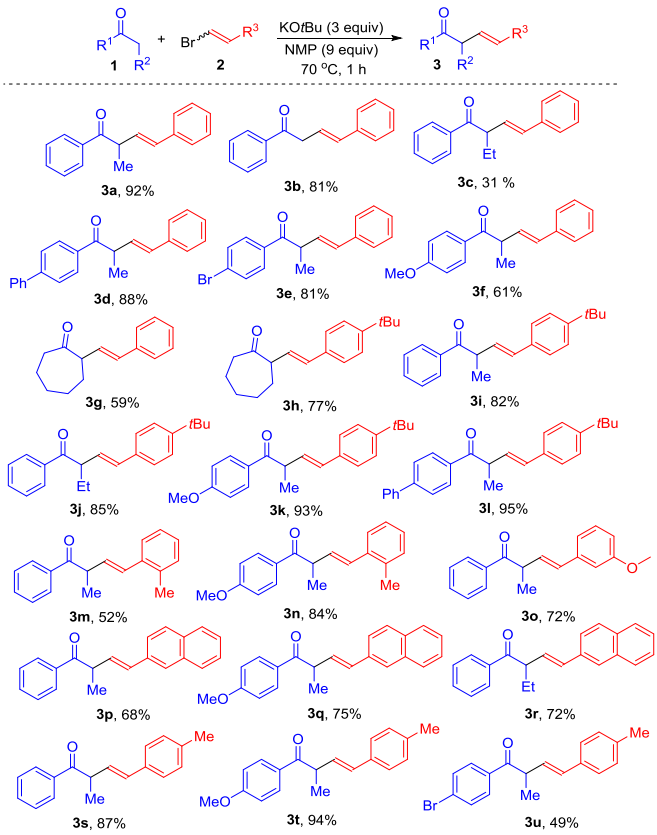


entry	base	solvent	temp (°C)	**3a** (%)	**4a** (%)	**5a** (%)	**6a** (%)
1	–	DMF	70	0	0	0	0
2	KO*t*Bu	DMF	70	66	16	0	0
3	KO*t*Bu	DMSO	70	72	23	0	0
4	KO*t*Bu	NMP	70	93	2	0	0
5	KO*t*Bu[b]	NMP	70	61	2	2	0
6	KO*t*Bu[c]	NMP	70	22	5	6	0
7	NaO*t*Bu	NMP	70	46	5	0	0
8	LiO*t*Bu	NMP	70	4	0	11	72
9	KOH	NMP	70	8	4	4	0
10	K_2CO_3	NMP	70	0	0	0	0
11	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 internal standard. Yields in parentheses were calculated after 24 h. [b] 2 mmol. [c] 1 mmol.

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. On the contrary, butyrophenone only led to a low 31% of **3c**. Electron-withdrawing and -donating substituents are well tolerated at the *para* position of propiophenones, giving **3d–3f** in very 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 and -poor aryl ketones with 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%. 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.

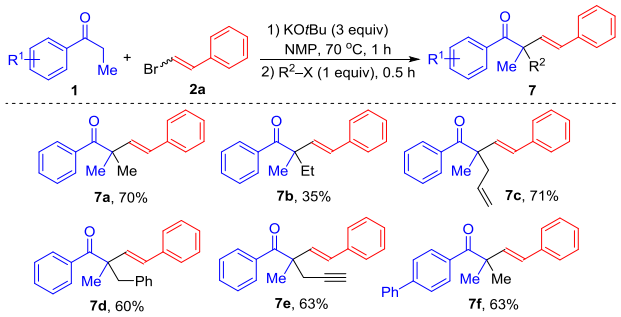
Scheme 1. Substrate Scope of the α-Vinylation of Ketones[a]



[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.

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. As expected, β,γ-unsatured ketones **7** bearing all-carbon quaternary centers at the α position could be isolated in very 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.

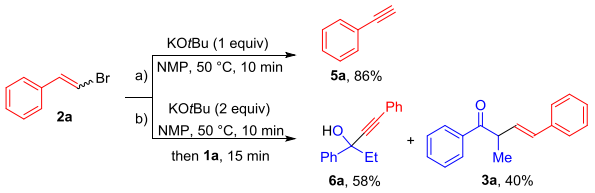
Scheme 2. One-Pot Trapping of Dienolate Intermediates for the Generation of Quaternary Carbon Centers[a]



[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.

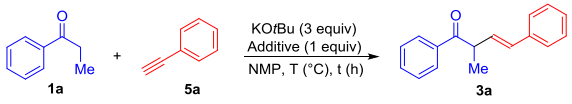
In order to gain insight into the reaction mechanism, we reacted β-bromostyrene **2a** with 1 equiv of KO*t*Bu and observed 86% yield of phenylacetylene **5a** in only 10 minutes at 50 °C (Scheme 3, path a). Under the same reaction conditions, propargylic alcohol **6a** is obtained in 58% yield and β,γ-unsaturated ketone **3a** in 40% yield when 2 equiv of KO*t*Bu are used and 1 equiv of propiophenone **1a** is added after 10 minutes in a Favorsky-type reaction (Scheme 3, path b).[14] Both **5a** and **6a**, which were observed as by-products during optimization, are likely reaction intermediates.

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



To the best of our knowledge, Trofimov never reported the formation of β,γ-unsaturated ketones from ketones and arylacetylenes at temperatures lower than 80 °C.[11] In the reaction conditions disclosed herein, the reaction of propiophenone **1a** and phenylacetylene **5a** is efficient at low temperatures (Table 2). While a low 7% yield of **3a** is observed after 5 minutes at 50 °C, accompanied by 81% of intermediate **6a**, prolonging the reaction time to 4 h leads to an excellent 90% (entries 1–2). The reaction gives the same yield after 24 h at room temperature (entry 3), which is a clear departure from Trofimov's results. Reactions 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]

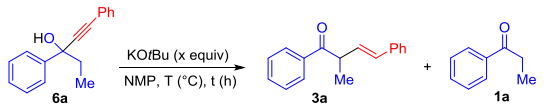


entry	additive	t (h)	temp (°C)	**3a**
1	-	0.09	50	7[b]
2	-	4	50	90
3	-	24	25	91
4	hydroquinone	4	50	22
5	galvinoxyl	4	50	39

[a] Reaction conditions: propiophenone **1a** (2 mmol), phenylacetylene **5a** (1 mmol), additive (1 mmol), KO*t*Bu (3 mmol), NMP (9 mmol), yields calculated by ^{1}H NMR using hexamethylbenzene as internal standard. [b] **6a** is obtained in 81% as by-product.

We next investigated the conditions for an efficient transformation of propargyl alcohol **6a** to β,γ-unsaturated ketone **3a** (Table 3). In the absence of 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 [15] at only room temperature (entry 2). By increasing the temperature to 50 °C, **3a** was obtained in 35% and 40% yields after 0.5 h 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 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** to **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]

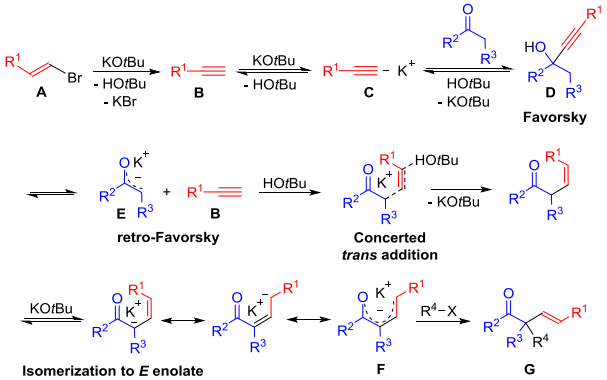


entry	x	t (h)	temp (°C)	**6a**	**3a**	**1a**
1	-	24	100	100	0	0
2	1	0.5	25	50	2	36
3	1	0.5	50	16	35	42
4	1	4	50	18	40	26
5	2	4	50	0	72	7
6	0.2	4	100	76	0	24

[a] Reaction conditions: propargylic alcohol **6a** (1 mmol), KO*t*Bu (x mmol), NMP (9 mmol), yields calculated by ^{1}H NMR using hexamethylbenzene as internal standard.

In light of these results, we propose an ionic mechanism similar to the one postulated by Trofimov for the base-mediated addition of arylacetylenes to ketones (Scheme 4).[11a-c] After an initial β-elimination reaction of **A** to give arylacetylene **B**, which then undergoes deprotonation to give the acetylide anion **C**, a nucleophilic attack to the ketone yields propargylic alcohol **D** via a Favorsky reaction.[14] This intermediate undergoes a retro-Favorsky reaction [15] followed by a concerted *trans* addition of enolate **E** on arylacetylene **B** with the assistance of HO*t*Bu to provide the *E* dienolate **F** after base-mediated isomerization of the intermediate *Z* allylic ketone. Given that β,γ-unsaturated ketones of *E* configuration are the only reaction products, it is clear that the dienolate **F** of *E* configuration is more stable and that ketone **G** is the kinetic product.

Scheme 4. Plausible Reaction Mechanism



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 per-

formed with KO*t*Bu at room temperature for 24 h in moderate yields or up to 70 °C for only 1 h without isomerization to the thermodynamically favored enones. The observation that radical scanvengers did not completely suppress the transformation, coupled with the successful trapping of intermediates with carbon-based electrophiles to generate all-carbon quaternary centers, point toward an ionic mechanism involving sequential Favorsky and retro-Favorsky reactions.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and compound characterization (^{1}H, ^{13}C, HRMS).

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Author Contributions

§ M.P.D. and Y.Z. contributed equally to this manuscript.

Notes

The authors declare no competing financial interest.

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