Nucleophilic β-alkenylation of *N*-alkoxyenamines: An umpolung strategy for the preparation of β,γ-unsaturated ketones

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Nucleophilic β-alkenylation of *N*-alkoxyenamines: an umpolung strategy for the preparation of β,γ-unsaturated ketones

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ABSTRACT

An umpolung strategy has been developed for the synthesis of β,γ-unsaturated ketones utilizing nucleophilic β-alkenylation of *N*-alkoxyenamines, which are prepared *in situ* from ketones and isoxazolidine, with alkenyl aluminum reagents. Various β,γ-unsaturated ketones have been prepared following this simple procedure under mild conditions.

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β,γ-Unsaturated ketones are an important molecular scaffold because of their presence in biologically active and natural compounds, including histone deacetylase (HDAC) inhibitor trichostatin A,[1] antitumor agent lactimidomycin,[2] antifungal agent khafrefungin,[3] and anticancer drug taxol.[4] In addition, β,γ-unsaturated ketones also serve as versatile intermediates in organic synthesis because of the well-studied chemistry of carbonyls and olefins.[5] Therefore, synthesis of β,γ-unsaturated ketone scaffold has received considerable attention over the past two decades.

A reliable method for the synthesis of β,γ-unsaturated ketones is widely known as a three-step synthesis and consists of a cross-aldol reaction of different aldehydes, Wittig olefination of β-hydroxy aldehyde, and oxidation of homoallylic alcohol.[1d] Several other methods have been developed for a convenient straightforward synthesis of β,γ-unsaturated ketones from simple ketones or α-haloketones; these include: (i) Pd- or Ni-catalyzed cross-coupling of ketone enolate with alkenyl halide under basic conditions,[6] (ii) nickel-catalyzed cross-coupling of α-haloketone with alkenyl zirconium reagent,[7]

Scheme 1. α-Alkenylation of ketones via enamines.

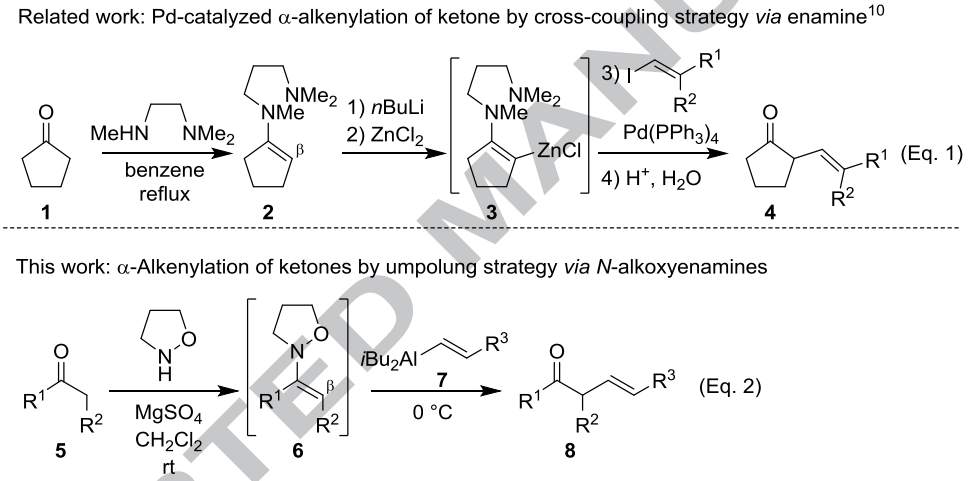
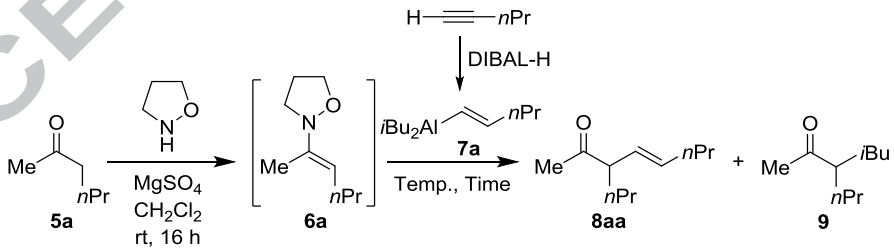


Table 1. Optimization for nucleophilic β-alkenylation using *N*-alkoxyenamine.

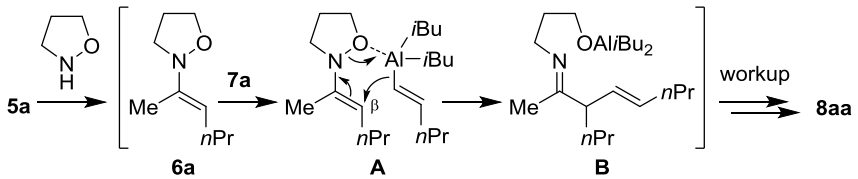


Entry	Alkenyl aluminum reagent **7a** (equiv.)	Temperature (°C)	Time (h)	Yield of **8aa** (%)[a]	Yield of **9** (%)[a]
1	3	0	1	62	ND[b]
2	2	0	2	36	ND[b]
3	1	0	2	17	ND[b]
4	3	−40	5	ND[b]	ND[b]
5	3	rt	1	24	28

[a] Yield after purification by preparative TLC.

[b] Not detected.

Scheme 2. Proposed reaction pathway.



(iii) copper-catalyzed 1,2-addition of α-haloketone to alkyne at elevated temperature,[8] and (iv) base-promoted α-alkenylation of ketone with terminal alkyne at high temperature.[9] In contrast, less is known about the α-alkenylation of ketones via enamine[10] and their derivative[11] although the chemistry of enamine has widely studied. There is an example for α-alkenylation of simple ketones via an enamine, where enamine **2** was converted to β,γ-unsaturated ketone **4** via β-lithiation of **2**, Li/Zn transmetalation, Negishi cross-coupling of **3** with alkenyl iodide, and protonolysis (Scheme 1; Eq. 1).[10] The scope and overall utility of this reaction, however, are limited by the level of care required to conduct such a complex and sequential procedure.

We are interested in developing alternative methods for the efficient formation of β,γ-unsaturated ketones that would provide facial access to these compounds and allow them to be used in further synthetic applications. We recently reported the development of a procedure for the umpolung α-arylation of carbonyls (aldehydes and ketones), which was triggered by the reaction of *N*-alkoxyenamines with triarylaluminum reagents.[12] As part of our program investigating the introduction of other nucleophiles in the umpolung chemistry of *N*-alkoxyenamines, we herein report our umpolung strategy for the synthesis of β,γ-unsaturated ketones **8** utilizing nucleophilic β-alkenylation of *N*-alkoxyenamines **6**, which were prepared from readily available ketones **5** and isoxazolidine (Scheme 1; Eq. 2).

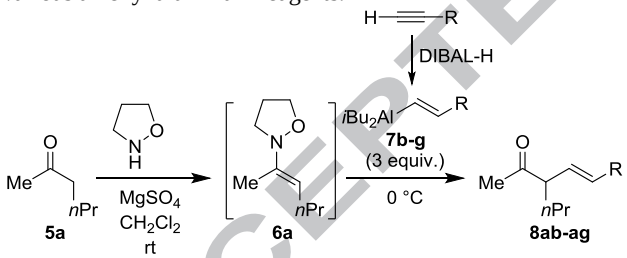
We first optimized the umpolung β-alkenylation of *N*-alkoxyenamine **6a** with regards to the amount of alkenyl aluminum reagent **7a** and the reaction temperature (Table 1), where **6a** was prepared *in situ* from 2-hexanone (**5a**) and isoxazolidine. Alkenyl aluminum reagent **7a** was prepared *in situ* by hydroalumination of 1-pentyne with DIBAL-H.[13] According to our previous report,[12a] we first selected the stepwise operation to form the *N*-alkoxyenamine **6a**. After the formation of **6a** from **5a** and isoxazolidine in the presence of $MgSO_4$, the reaction of **6a** with alkenyl aluminum reagent **7a** (3 equiv.) proceeded smoothly at 0 °C to afford α-alkenyl ketone **8aa** in 62% yield (Table 1, entry 1).[14] Interestingly, none of α-isobutyl ketone **9** was obtained under above reaction conditions. Either reduced amount of alkenyl aluminum reagent or cooled reaction temperature (−40 °C) led to a significant decrease in the yield of α-alkenyl ketone **8aa** (Table 1, entries 2–4). When the reaction was carried out at room temperature, desired **8aa** was obtained in 24% yield, along with α-isobutyl ketone **9** in 28% yield (Table 1, entry 5). This result indicated that temperature control was important for this reaction to suppress the formation of α-isobutyl ketone **9**. On the basis on these results, the use of alkenyl aluminum reagent 7**a** (3 equiv.) at 0 °C was considered necessary to achieve good conversion and yield for this reaction.[15]

The plausible reaction pathway for the formation of β,γ-unsaturated ketone **8aa** from 2-hexanone (**5a**) can be rationalized by the nucleophilic β-alkenylation of *N*-alkoxyenamine **6a**, which is generated *in situ* by the condensation reaction of **5a** and isoxazolidine (Scheme 2). This umpolung reaction of **6a** could generate imine intermediate **B** by coordination with the alknenyl aluminum reagent **7a**, followed by N-O bond cleavage and simultaneous nucleophilic attack of alkenyl aluminum reagent **7a** (C_β-position). Upon aqueous work-up, imine intermediate **B** affords the β,γ-unsaturated ketone **8aa**.

Having optimized the reaction conditions for the umpolung reaction, we proceeded to evaluate the scope of this reaction by investigating the introduction of various alkenyl aluminum reagents to *N*-alkoxyenamine **6a** (Table 2). Requisite alkenyl aluminum reagents **7b–g** were prepared *in situ* by hydroalumination of commercially available terminal alkynes with DIBAL-H according to literature procedures.[13] The umpolung reaction of **6a** with sterically hindered (*tert*-butyl group) alkenyl aluminum reagent **7b** also proceeded to afford β,γ-unsaturated ketone **8ab** in 59% yield (Table 2, entry 1). Alkenyl aluminum reagents **7c** (R = cPropyl) and **7d** (R = cHexyl), prepared by hydroalumination of cyclic alkyl alkynes with DIBAL-H, gave the corresponding α-alkenylated products **8ac** and **8ad** in moderate yields (Table 2, entries 2 and 3). The use of alkenyl aluminum reagent **7e** bearing a benzyl group (R = CH_2Ph) gave β,γ-unsaturated ketone **8ae** in moderate yield (Table 2, entry 4). For the alkenyl aluminum reagents **7f** and **7g** carrying extended alkyl chains, α-alkenylated products **8af** and **8ag** were obtained in low yield (Table 2, entries 5 and 6).[16]

The scope of different ketones in the synthetic protocol was then explored using several alkenyl aluminum reagents (Table 3). The reaction of acyclic ketones **5b** and **5c**, carrying terminal alkene and nitrile, with **7a** proceeded smoothly to afford the corresponding β,γ-unsaturated ketones **8ba** and **8ca** in yields of 71% and 55%, respectively (Table 3, entries 1 and 2). Cyclic ketones such as cyclohexanone (**5d**) and cyclododecanone (**5e**) also gave the corresponding α-alkenylated products **8da** and **8ea** in moderate to good yields (Table 3, entries 3 and 4). We also

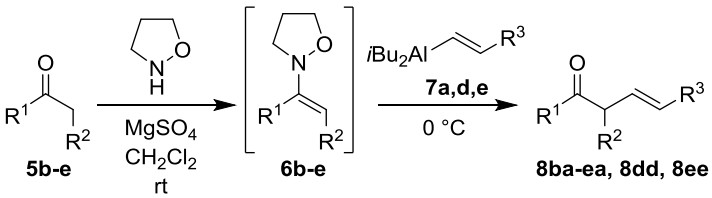
Table 2 Nucleophilic β-alkenylation of *N*-alkoxyenamine using various alkenyl aluminum reagents.[a]

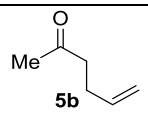
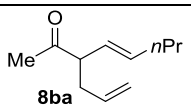
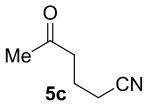
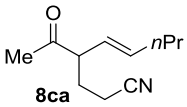
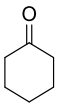
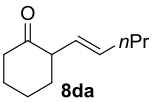
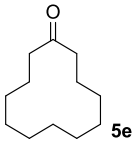
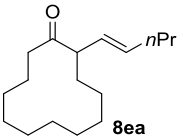
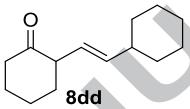
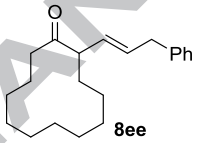


Entry	R	Product	Yield (%)[b]
1	*t*Bu (**7b**)	**8ab**	59
2	cPr (**7c**)	**8ac**	44
3	cHexyl (**7d**)	**8ad**	51
4	CH_2Ph (**7e**)	**8ae**	56
5	CH_2CH_2Ph (**7f**)	**8af**	28
6	$CH_2CH_2CH_2CH_2Cl$ (**7g**)	**8ag**	30

[a] Reaction conditions: 2-hexanone (1 equiv.), isoxazolidine (2 equiv.), $MgSO_4$ (250 mg), CH_2Cl_2 (5 mL), room temp., 16 h, then alkenyl aluminum reagent (3 equiv.), 0 °C, 1–2 h.
[b] Yield after purification by preparative TLC.

Table 3 Nucleophilic β-alkenylation of various *N*-alkoxyenamines using alkenyl aluminum reagents.[a]



Entry	Substrate	R^3	Product	Yield (%)[b]
1	 **5b**	*n*Pr (**7a**)	 **8ba**	71
2	 **5c**	*n*Pr (**7a**)	 **8ca**	55
3	 **5d**	*n*Pr (**7a**)	 **8da**	53
4	 **5e**	*n*Pr (**7a**)	 **8ea**	65
5	**5d**	cHexyl (**7d**)	 **8dd**	58
6	**5e**	CH_2Ph (**7e**)	 **8ee**	60

[a] Reaction conditions: ketone (1 equiv.), isoxazolidine (2 equiv.), $MgSO_4$ (250 mg), CH_2Cl_2 (5 mL), room temp., 16 h, then alkenyl aluminum reagent (3 equiv.), 0 °C, 1–2 h.

[b] Yield after purification by preparative TLC.

examined the use of cyclic ketones with two different alkenyl aluminum reagents, which also afforded the corresponding expected products **8dd** and **8ee** in moderate to good yields (Table 3, entries 5 and 6).

We have developed a procedure for nucleophilic β-alkenylation of *N*-alkoxyenamines with alkenyl aluminum reagents under mild conditions that allowed the formation of β,γ-unsaturated products without isomerization to α,β-unsaturated ketones. The advantages of this novel protocol include a simplified procedure and milder reaction conditions when compared with other α-alkenylations of ketones. Efforts to further expand the scope of this reaction and demonstrate the synthetic utility of products are currently underway in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://---

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14. *Experimental procedure*: To a solution of anhydrous $MgSO_4$ (250 mg) in dry CH_2Cl_2 (5.0 mL) were added isoxazolidine (73.0 mg, 1.0 mmol) and 2-hexanone **5a** (50.1 mg, 0.50 mmol) at room temperature. After stirring at room temperature for 16 h, the reaction mixture was filtered under Ar atmosphere. Alkenyl aluminum reagent **7a**[13] (0.60 M in *n*-hexane, 3.0 mL, 1.5 mmol) was added dropwise to the filtrate at 0 °C. After stirring at 0 °C for 1 h, the reaction was quenched with aqueous Rochelle's salt (1.3 M). The resulting suspension was extracted with $CHCl_3$. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography (*n*-hexane/Et_2O = 20:1) to give the β,γ-unsaturated ketone **8aa** (52.2 mg, 62%) as a colorless oil. IR (neat) ν_{max} cm^{-1}: 1716 (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (br t, *J* = 7.5 Hz, 6H), 1.14-1.50 (m, 5H), 1.62-1.72 (m, 1H), 1.88-2.12 (m, 2H), 2.13 (s, 3H), 3.02 (br dd, *J* = 15.0, 8.5 Hz, 1H), 5.28 (ddt, *J* = 15.0, 8.5, 1.0 Hz, 1H), 5.57 (br dt, *J* = 15.0, 7.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.6, 13.9, 20.3, 22.4, 28.3, 3 3.1, 34.6, 57.2, 128.0, 134.4, 210.4. HRMS (ESI): calcd for $C_{11}H_{21}O$ $[M+H]^+$ 169.1586, found 169.1587.

15. The reaction of **5a** with **7a** (3 equiv.) in the presence of isoxazolidine (2 equiv.) at 0 °C for 1 h gave β,γ-unsaturated ketone **8aa** in 21% yield (one-pot procedure).

16. For the umpolung β-alkenylation of *N*-alkoxyenamine **6a** with diisobutyl(styryl)aluminum [prepared *in situ* by Ni-catalyzed β-hydroalumination of phenylacetylene with DIBAL-H], α-alkenylated product carrying styryl group was obtained in 11% yield. When other alkenyl aluminum reagent [prepared *in situ* by hydroalumination of 1-phenyl-2-(trimethylsilyl)acetylene with DIBAL-H] was used, a trace amount of α-alkenylated product was detected.

<Highlights>

- The synthesis of β,γ-unsaturated ketones by an umpolung strategy.
- A nucleophilic β-alkenylation of *N*-alkoxyenamines.
- The reaction features simple procedure.