

Nickel-catalyzed [3 + 2] Cycloaddition of α,β -Unsaturated Ketones with Vinyl Oxiranes

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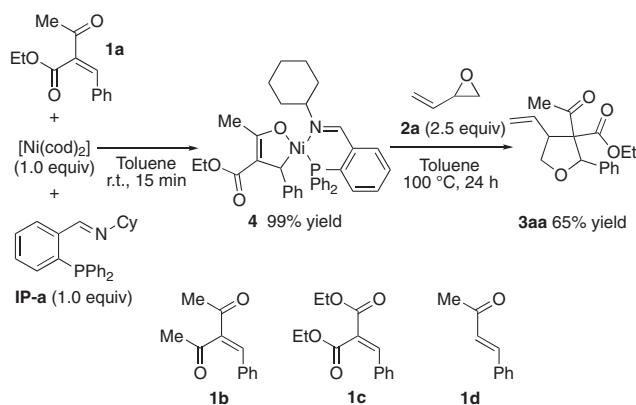
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A nickel-catalyzed cycloaddition of α,β -unsaturated ketones with vinyl oxiranes to afford polysubstituted tetrahydrofurans has been developed. The key intermediate is a five-membered nickelacycle, which is formed by oxidative cyclization of nickel(0) to α,β -unsaturated ketones.

Transition-metal-catalyzed cycloadditions represent a powerful strategy of assembling complex heterocyclic compounds from readily available starting materials. Thus, the development of new formal reaction patterns still constitutes an important ongoing challenge.¹ Among these, a formal [3 + 2] cycloaddition of oxiranes with olefins seems to be an attractive strategy to construct tetrahydrofuran frameworks in a single operation. However, these types of cycloaddition are rarely reported.² We recently developed a series of nickel-catalyzed cycloaddition using α -ester-substituted α,β -unsaturated ketones as a key component.³ During the course of our study, we found that α -ester-substituted α,β -unsaturated ketones **1** reacted with vinyl oxiranes **2** to furnish polysubstituted tetrahydrofuran **3** via a formal [3 + 2] cycloaddition; the reaction process included oxidative cyclization of α -ester-substituted α,β -unsaturated ketones to nickel(0).

We first examined the stoichiometric reaction. The reaction of α -ester-substituted α,β -unsaturated ketone **1a** was treated with $[\text{Ni}(\text{cod})_2]$ and iminophosphine ligand⁴ **IP-a** in toluene at ambient temperature for 15 min (Scheme 1). *Oxa*-nickelacycle **4** was obtained in quantitative yield.^{3,5} Neither benzylidene-substituted pentane-2,4-dione **1b**, diethyl malonate **1c**, nor enone **1d** participated in oxidative cyclization with $[\text{Ni}(\text{cod})_2]/\text{IP-a}$, and each was recovered unchanged quantitatively. Treatment of **4** with vinyl oxirane (**2a**) in toluene at 100 °C for 24 h afforded tetrahydrofuran **3aa** in 65% yield. The results prompted us to investigate the possibilities of the catalytic reactions of **1a** with **2a**. Indeed, the reaction of **1a** with **2a** in the presence of 10 mol % of $[\text{Ni}(\text{cod})_2]$ and 20 mol % of **IP-a** in toluene at 100 °C for 24 h furnished the tetrahydrofuran **3aa** in 56% yield (Table 1, Entry 1). Not even trace amounts of cycloadduct **3aa** were obtained in the absence of nickel. Further examination of reaction conditions revealed that the cycloaddition proceeds at lower reaction temperature (60 °C), providing a higher yield of desired cycloadduct **3aa** (75% yield, Entry 2). It was also found that the reaction furnished **3aa** in 98% yield at 30 °C (Entry 3). In other reaction media, the yields of **3aa** were decreased (Entries 4–6). Among the iminophosphines examined, cyclohexylamine-derived ligand **IP-a** gave the best result (Entries 3 and 7–9). With other phosphine ligands, such as PMe_3 , PMe_2Ph , and PPh_3 , the reaction afforded even lower amounts of desired cycloadduct **3aa** (Entries 10–12).

The scope of α,β -unsaturated ketones **1** and vinyl oxiranes **2** in the cycloaddition is summarized in Table 2. It was found



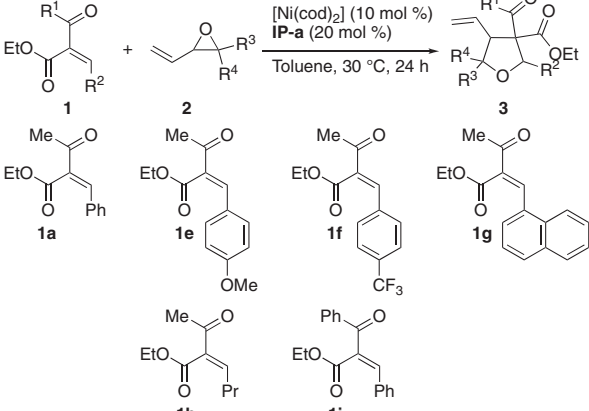
Scheme 1. Stoichiometric reaction.

Table 1. [3 + 2] Cycloaddition of α,β -unsaturated ketone **1a** with vinyl oxirane **2a** with nickel catalyst^a

Entry	Ligand	Solvent	Temperature/°C	Yield/% ^b
1	IP-a	Toluene	100	56
2	IP-a	Toluene	60	75
3	IP-a	Toluene	30	98
4	IP-a	THF	30	77
5	IP-a	MeCN	30	37
6	IP-a	Pyridine	30	18
7	IP-b	Toluene	30	34
8	IP-c	Toluene	30	11
9	IP-d	Toluene	30	59
10	PMe_3	Toluene	30	<1
11	PMe_2Ph	Toluene	30	<1
12	PPh_3	Toluene	30	9

^aReactions were carried out using $[\text{Ni}(\text{cod})_2]$ (10 mol %), ligand (20 mol %), **1a** (0.5 mmol), and **2** (1.25 mmol) for 24 h. ^bReactions afford tetrahydrofurans **3** as a mixture of inseparable diastereoisomers.

that vinyl oxirane **2b** possessing pentyl substituent on the oxirane ring also reacted with α,β -unsaturated ketone **1a** to furnish the corresponding tetrahydrofuran derivative **3ab** in 71% yield (Entry 2). However, the reaction of **1a** with vinyl oxirane **2c** possessing *gem*-dimethyl substituents on the oxirane ring did

Table 2. Nickel-catalyzed [3 + 2] cycloaddition of α,β -unsaturated ketones **1** with vinyl oxiranes **2**^a


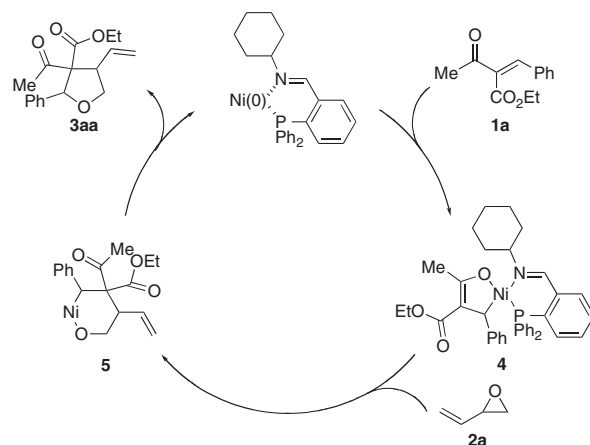
Entry	1	2	R ³	R ⁴	3	Yield/% ^b
1	1a	2a	H	H	3aa	98
2	1a	2b	C ₅ H ₁₁	H	3ab	71
3	1a	2c	Me	Me	3ac	<1
4	1e	2a	H	H	3ea	81
5	1f	2a	H	H	3fa	76
6	1g	2a	H	H	3ga	63
7	1h	2a	H	H	3ha	71
8	1i	2a	H	H	3ia	51

^aReactions were carried out using [Ni(cod)₂] (10 mol %), **IP-a** (20 mol %), **1** (0.5 mmol), and **2** (1.25 mmol) in toluene at 30 °C for 24 h. ^bReactions afford tetrahydrofurans **3** as a mixture of inseparable diastereoisomers.

not afford the desired cycloadduct (Entry 3). A range of α,β -unsaturated ketones **1** was also tested in the reaction with **2a**. β -Aryl-substituted enones possessing an electron-donating or -withdrawing group on the phenyl ring also provided corresponding cycloadducts **3ea** and **3fa** in 81% and 76% yields respectively (Entries 4 and 5). β -Naphthyl-substituted enone **1g** also participated in the reaction with **2a** to give tetrahydrofuran **3ga** in 63% yield (Entry 6). The reaction of β -alkyl-substituted enone **1h** provided the cycloadduct **3ha** in 71% yield (Entry 7). Enone **1i** reacted with **2a** to furnish tetrahydrofuran **3ia** in 51% yield (Entry 8).⁶

The formation of polysubstituted tetrahydrofuran **3aa** can be rationalized as arising from oxidative cyclization of nickel(0) to an enone **1a** to form *oxa*-nickelacycle **4** (Scheme 2). Subsequent coordination of vinyl oxirane **2a** and nucleophilic addition of nickel enolate to vinyl oxirane **2a** take place to afford six-membered *oxa*-nickelacycle **5**,^{5d,7} which undergoes reductive elimination to give **3aa**; the starting nickel(0) complex is regenerated.

In conclusion, we have developed a new nickel-catalyzed [3 + 2] cycloaddition of α,β -unsaturated ketones with vinyl oxiranes to provide polysubstituted tetrahydrofurans. We manifested that the reaction is initiated by oxidative cyclization of α,β -unsaturated ketones with nickel(0). Further efforts to control the diastereoselectivity of the reaction are now in progress.⁸

**Scheme 2.** Plausible reaction mechanism.

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- For some selected examples of six-membered *oxa*-nickelacycle intermediate formation, see: a) C. Molinaro, T. F. Jamison, *J. Am. Chem. Soc.* **2003**, *125*, 8076. b) T. Mori, T. Nakamura, M. Kimura, *Org. Lett.* **2011**, *13*, 2266.
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