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

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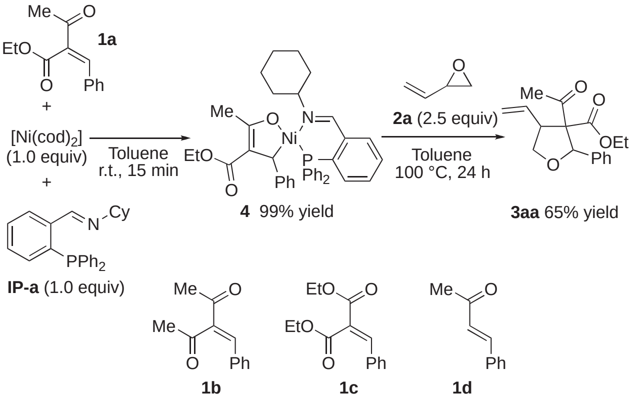
A nickel-catalyzed cycloaddition of α,β-unsaturated ketones with vinyl oxiranes to afford polysubstituted tetrahydrofurans has been developed. The key intermediate is a five-membered nickelacycle, which is formed by oxidative cyclization of nickel(0) to α,β-unsaturated ketones.

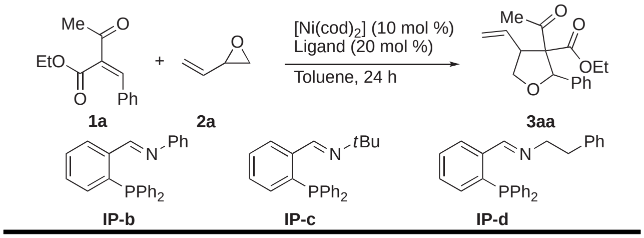
Transition-metal-catalyzed cycloadditions represent a powerful strategy of assembling complex heterocyclic compounds from readily available starting materials. Thus, the development of new formal reaction patterns still constitutes an important ongoing challenge.[1] Among these, a formal [3 + 2] cycloaddition 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 [Ni(cod)$_2$] and iminophosphine ligand[4] **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 [Ni(cod)$_2$]/**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 [Ni(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$_2$Ph, and PPh$_3$, the reaction afforded even lower amounts of desired cycloadduct **3aa** (Entries 10–12).



Scheme 1. Stoichiometric reaction.

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

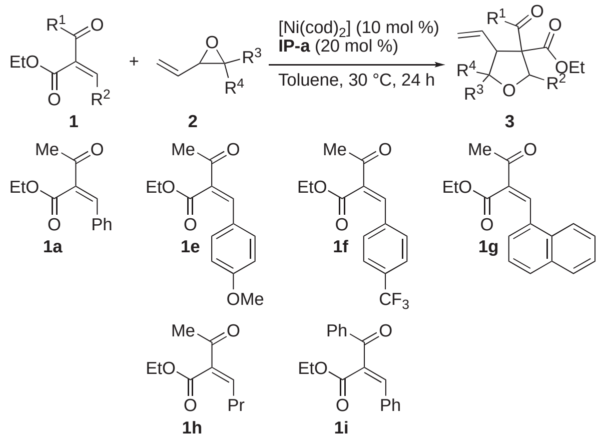


Entry	Ligand	Solvent	Temperature/°C	Yield/%[b]
1	**IP-a**	Toluene	100	56
2	**IP-a**	Toluene	60	75
3	**IP-a**	Toluene	30	98
4	**IP-a**	THF	30	77
5	**IP-a**	MeCN	30	37
6	**IP-a**	Pyridine	30	18
7	**IP-b**	Toluene	30	34
8	**IP-c**	Toluene	30	11
9	**IP-d**	Toluene	30	59
10	PMe$_3$	Toluene	30	<1
11	PMe$_2$Ph	Toluene	30	<1
12	PPh$_3$	Toluene	30	9

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

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



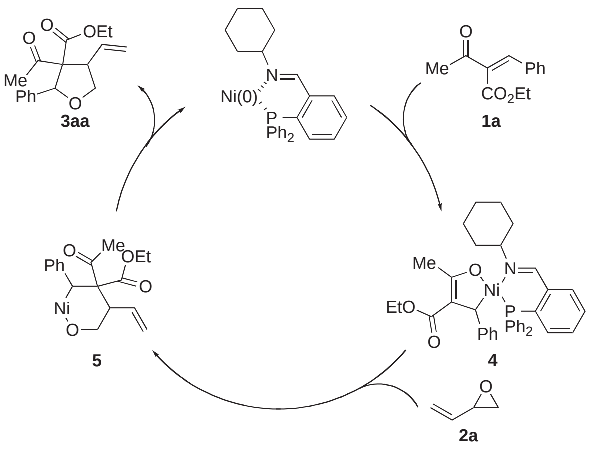
Entry	1	2	R^3	R^4	3	Yield/%[b]
1	**1a**	**2a**	H	H	**3aa**	98
2	**1a**	**2b**	C_5H_{11}	H	**3ab**	71
3	**1a**	**2c**	Me	Me	**3ac**	<1
4	**1e**	**2a**	H	H	**3ea**	81
5	**1f**	**2a**	H	H	**3fa**	76
6	**1g**	**2a**	H	H	**3ga**	63
7	**1h**	**2a**	H	H	**3ha**	71
8	**1i**	**2a**	H	H	**3ia**	51

[a] Reactions 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. [b] Reactions 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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8 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.