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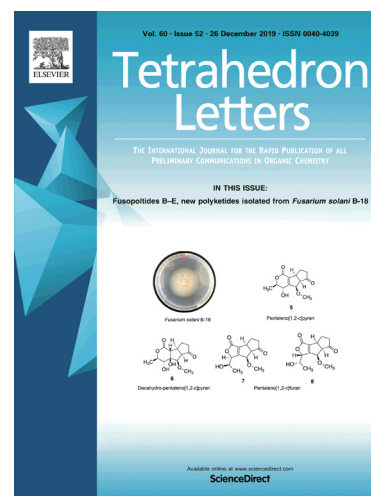
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Nickel-Catalyzed Deoxygenation of Oxiranes: Conversion of Epoxides to Alkenes

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ABSTRACT

Deoxygenation of epoxides takes place under the catalysis of nickel in the presence of diethylzinc as a deoxygenation agent to yield alkenes. Epoxides with a wide variety of substitution patterns are deoxygenated in this catalytic system to give terminal, 1,1-disubstituted, 1,2-disubstituted, trisubstituted, and tetrasubstituted alkenes in high yields. Reactions of 1,2-disubstituted epoxides we examined proceeded in an *E*-stereoselective manner. High compatibility with other functional groups through this transformation was also observed.

Keywords:

Deoxygenation reaction; Epoxide; Nickel catalyst; Diethylzinc

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1. Introduction

Deoxygenation of oxiranes, namely conversion of epoxides to alkenes, is important and fundamental synthetic transformation in organic chemistry, and some of efficient reactions have been utilized for “deprotection” of masked alkenes as their epoxides. Phosphorus betaine method is known as a useful protocol for isomerization of *trans*-alkenes to their *cis*-isomers throughout stereospecific epoxidation-deoxygenation sequence.¹⁻² Non-catalyzed deoxygenation reactions are generally carried out using a stoichiometric amount of heavy metals, phosphines, or iodines,³ and these reactions yield voluminous chemical waste. In such a context, efficient catalytic process is desirable from a viewpoint of green chemistry. So far, reactions with a catalyst based on transition metals, such as Rh, Re, Au, Ag, Mo, and Cu have been developed.⁴⁻⁹ Some of these reactions are stereospecific, while deoxygenation of multi-substituted oxiranes is, in general, not so efficient, and to the best of our knowledge, that of tetra-substituted oxirane is not successful.

Nickel is advantageous to use as a catalyst, in light of low toxicity, earth-abundance, and inexpensiveness, and we have explored chemistry of nickel-catalyzed reactions, especially those thought to proceed *via* oxanickelacycle as a catalytic intermediate.¹⁰⁻¹² We describe herein the nickel-catalyzed deoxygenation of epoxide, as the first nickel-catalyzed variant.

2. Results and discussion

First of all, we screened catalysts and organometallic reagents in the deoxygenation reaction of epoxide **1a** in THF at 50 °C for 24 h under argon as a probe reaction (eq. 1). Organometallic reagent was expected to behave a deoxygenation agent and/or reductant. Results are compiled in Table 1.

When 2.4 equivalents of Et₂Zn was used as an organometallic reagent, desirable deoxygenated alkene **2a** was obtained selectively in 93% yield, in the presence of 10 mol% of Ni(acac)₂ (Table 1, entry 2), while palladium-catalyst exhibited almost no catalytic activity (entry 1), and Co(acac)₂ showed moderate activity to give the expected product **2a** in 70% yield (entry 3). A reaction with iron catalyst gave an intractable mixture (entry 4). Next, we examined organometallic reagents other than Et₂Zn. In the presence of 10 mol% of Ni(acac)₂, Et₃Al gave a reductive ring opening product **3a** in 97% yield (entry 5), and no products were detected, and starting **1a** was recovered, using the Et₃B, Zn dust and EtZnOEt¹³ (entries 6-8). EtZnCl¹⁴ was not so effective in this reaction (entry 9). When Me₂Zn was used instead of Et₂Zn, the deoxygenation reaction of **1a** smoothly proceeded to form **2a** in 90% yield (entry 10).

For the present nickel-catalyzed deoxygenation of epoxide **1a**, we attempted further optimization of the reaction conditions, regarding reaction temperature, solvents, and ligands to be used (eq. 2). The results are summarized in Table 2. The yield of expected alkene **2a** decreased to 53% when the reaction was conducted at room temperature (Table 2, entry 1), and was somewhat lower at reflux temperature (entry 3). As for the solvent, reactions in ethereal solvent such as THF and dimethoxyethane (DME), gave alkene **2a** in high yields (entries 2 and 4), and moderate yields in toluene, DMF and DMA (entries 5-7).

Nickel-catalyst without any ligands gave the best yield of **2a**, when the reaction was carried out in THF. Among phosphine ligands we examined, PPh₃, PBu₃, bidentate dppf and Xantphos, were not effective in the present deoxygenation reaction (Table 2, entries 8, 10-12), and with PCy₃ ligand, **3a** was obtained as a main product (Table 2, entry 9). When isolated **3a** was subjected to the optimized conditions (similar to the conditions in entry 2), **3a** was not converted to **2a**.

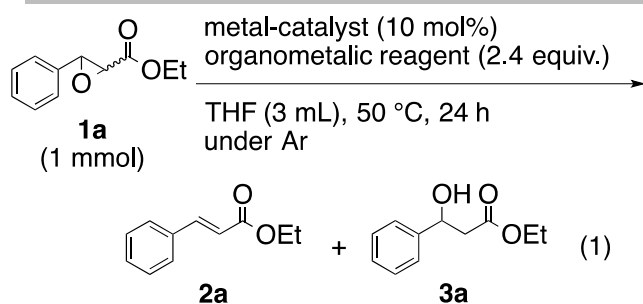
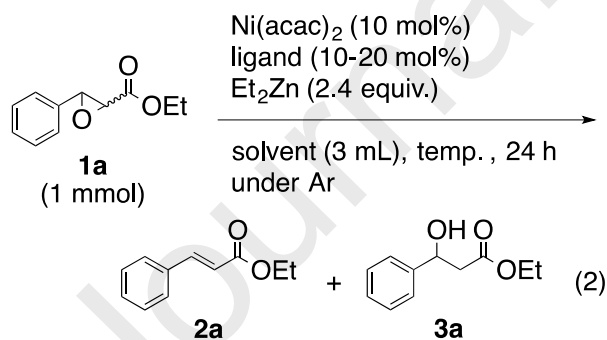


Table 1. Screening of catalysts and organometallic reagents for deoxygenation of oxirane **1a**^a

entry	metal-catalyst	organometallic reagent	yield % ^b		
			1a	2a	3a
1	Pd(OAc) ₂	Et ₂ Zn	90	4	0
2	Ni(acac) ₂	Et ₂ Zn	0	93	0
3	Co(acac) ₂	Et ₂ Zn	9	70	0
4	Fe(OAc) ₂	Et ₂ Zn	complex mixture		
5	Ni(acac) ₂	Et ₃ Al	2	0	97
6	Ni(acac) ₂	Et ₃ B	93	0	0
7	Ni(acac) ₂	Zn dust	99	0	0
8	Ni(acac) ₂	EtZnOEt	99	0	0
9	Ni(acac) ₂	EtZnCl	0	11	0
10	Ni(acac) ₂	Me ₂ Zn	0	90	0

^a A reaction of epoxide **1a** (1.0 mmol) was undertaken in the presence of transition-metal catalyst (0.1 mmol) and organometallic reagent (2.4 mmol, in 1 M hexane solution) in THF (3 mL) at 50 °C for 24 h under argon. ^b Isolated yield.

Table 2. Optimization of the reaction conditions for nickel-catalyzed deoxygenation of oxirane **1a**^a

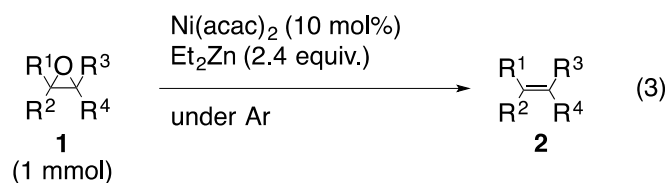


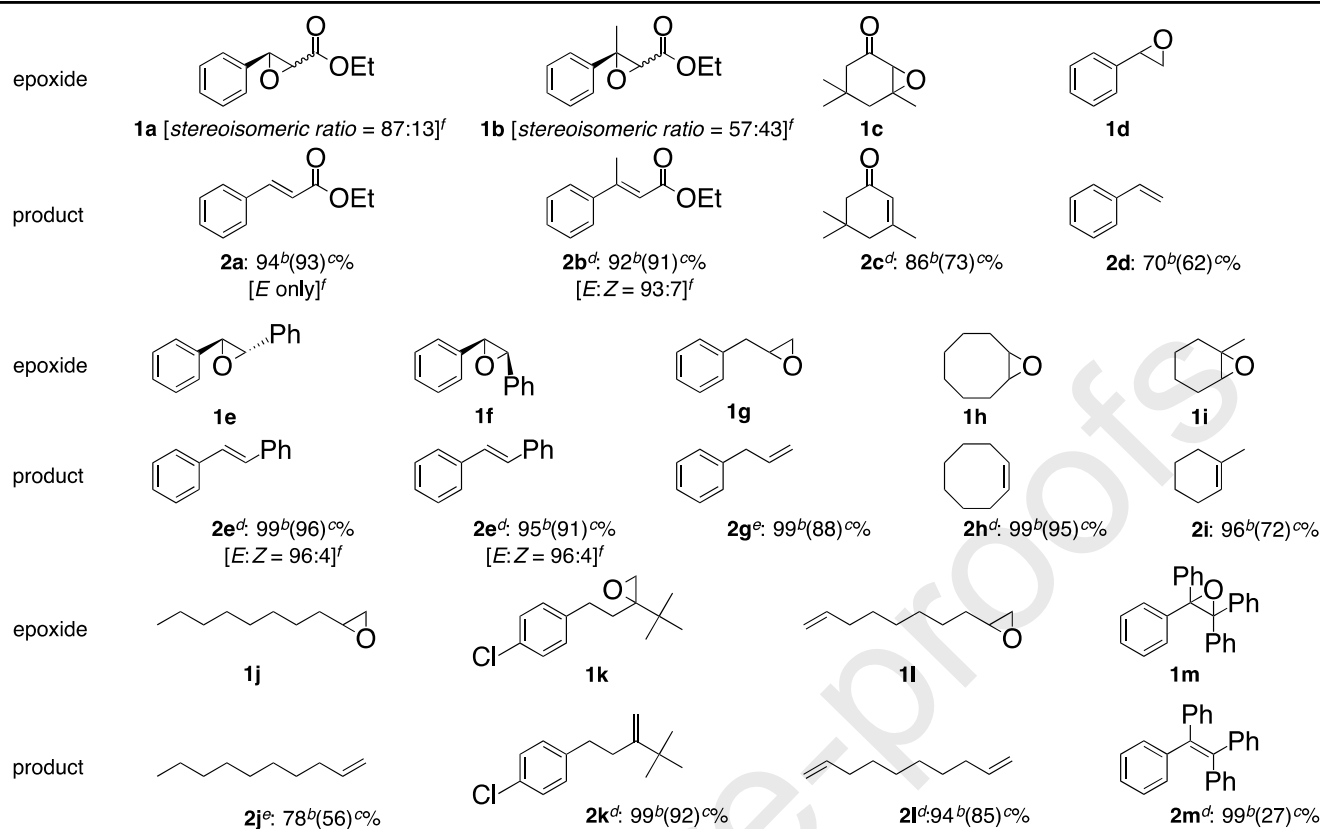
entry	solvent	conditions	ligand ^b	yield % ^d
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entry	solvent	conditions	ligand ^b	yield % ^d	
1	THF	rt	-	53	0
2	THF	50 °C	-	93	0
3	THF	80 °C, reflux	-	84	0
4	DME	50 °C	-	91	0
5	toluene	50 °C	-	47	0
6	DMF	50 °C	-	74	0
7	DMA	50 °C	-	41	0
8	THF	50 °C	PPh ₃ ^b	11	0
9	THF	50 °C	PCy ₃ ^b	7	87
10	THF	50 °C	P(<i>n</i> -Bu) ₃ ^b	9	0
11	THF	50 °C	DPPF ^c	22	0
12	THF	50 °C	Xantphos ^c	23	0

^a A reaction of epoxide **1a** (1.0 mmol) was undertaken in the presence of Ni(acac)₂ (0.1 mmol) and Et₂Zn (2.4 mmol, in 1 M hexane solution) in solvent (3 mL) shown in a column for 24 h under argon. ^b 20 mol% of ligand was used. ^c 10 mol% of ligand was used. ^d Isolated yield.

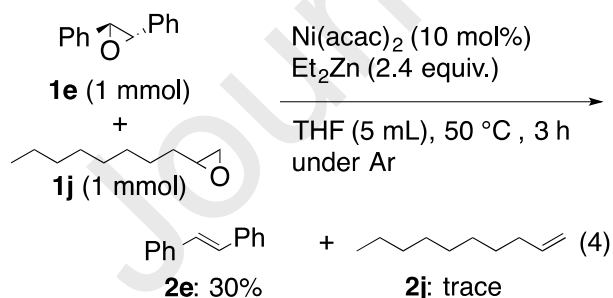
Under the optimized conditions, we examined the substrate-scope of the present nickel-catalyzed deoxygenation of epoxides **1** (eq. 3). The results are summarized in Table 3. Deoxygenation of epoxides **1a**, **1b** and **1c**, which were derived from α,β -unsaturated carbonyl compounds, smoothly proceeded to give the corresponding alkenes **2a**, **2b** and **2c** in good to excellent yields. Interestingly, in the case of **1a** and **1b**, a mixture of stereoisomers was subjected to the reaction conditions, and produced alkene **2a** was only *E*-isomer (94% yield) and *E/Z* of **2b** was 93/7 (92% yield). Styrene oxide, *trans*-stilbene oxide and *cis*-stilbene oxide were also deoxygenated to give the corresponding alkenes. In the reactions of these oxiranes with a phenyl group, *E*-selectivity, just as in the cases of **2a** and **2b**, was observed; reactions of both *trans*-stilbene oxide **1e** and *cis*-stilbene oxide **1f** gave the same product **2e**. Deoxygenation of “unactivated” epoxides derived from aliphatic and alicyclic alkenes, including 1,1-disubstituted oxirane also took place, and deoxygenated alkenes **2g**, **2h**, **2i**, **2j**, and **2k** were obtained in high yields without any double bond isomerization. In the case of epoxide bearing an alkenyl moiety, the “additional” carbon-carbon double bond was intact throughout the reaction, and the corresponding 1,9-diene **2l** was produced in 94% yield. Successful deoxygenation of tetrasubstituted epoxide **1m** is also noteworthy.





^a A reaction of epoxide **1** (1.0 mmol) was undertaken in the presence of Ni(acac)₂ (0.1 mmol) and Et₂Zn (2.4 mmol, in 1 M hexane solution) in THF (3 mL) at 50 °C for 24 h under argon. ^b The number shows estimated %yield that was determined by ¹H NMR analysis with ferrocene as an internal standard based on the epoxide **1** consumed. ^c The number in parentheses shows isolated %yield. ^d A reaction was undertaken in toluene (3 mL) at 110 °C for 48 h under argon. ^e A reaction was undertaken in DME (3 mL) at 80 °C for 48 h under argon. ^f Stereoisomeric ratio was determined by ¹H NMR.

Competitive reaction of aliphatic and aromatic epoxides, **1e** and **1j**, in the initial period of reaction at low conversion of substrates was examined (eq. 4). After the competitive reaction was conducted in THF at 50 °C for 3 h, 30% of aromatic alkene **2e** was produced, while aliphatic epoxide **1j** was almost intact, suggesting faster cleavage of C-O bond at benzyl position (eq. 4).

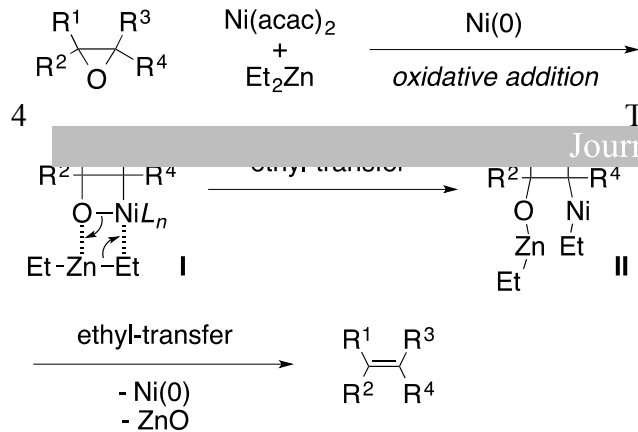


A plausible mechanism for the present deoxygenation reaction of epoxide is shown in Scheme 1. Ni(acac)₂ will be reduced to nickel(0) species by organozinc reagent *via* dialkylnickel.¹⁵ It is known that epoxide readily undergoes oxidative addition toward nickel(0) species to form 4-membered oxanickelacycles.¹⁶ Thus formed intermediate **I** would react with diethylzinc to afford intermediate **II** through ethyl-transfer from zinc to the nickel-metal center, leading to Zn-O and Ni-C bond formation.^{10a-c, 16c,e} The second ethyl-transfer from zinc to nickel of the intermediate **II** might cause expelling zinc as its oxide, generation of diethylnickel, and formation of alkene. In the reaction of **1a**,

formation of **3a** was observed in some cases. In such a case, the second ethyl-transfer would be possibly slow, and β -hydride elimination followed by reductive elimination would be preferable, leading to generation of zinc aldolate of **3a**. In the present deoxygenation of oxiranes, *E*-selectivity is also interesting. As for nickel-catalyzed stereoselective reactions, it was previously reported that single electron transfer was thought to be involved in a step of oxidative addition of organic halides to nickel(0).^{17, 18} At the moment, we assume that single electron transfer from nickel(0) to oxirane would take place to generate alkoxide and benzyl radical or carbon-radical α to carbonyl group, and the generated radical, which is stereochemically labile, changes its configuration to more stable one, and finally the second one-electron reduction from transient nickel(I) would give formal oxidative addition intermediate **I**. This configurational change of radical is possibly in relation to stereoselectivity.

Scheme 1. A plausible mechanism for the present deoxygenation reaction

In conclusion, we found nickel-catalyzed deoxygenation reaction of epoxides by constitution of novel catalytic system with the use of diethylzinc. In this reaction, epoxides with a wide structural variety were successfully deoxygenated without any side reactions to afford the corresponding alkenes in good to excellent yields. Mechanistic study and further application of



this catalytic system to other transformation of organic molecules are now in progress.

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Supplementary Material

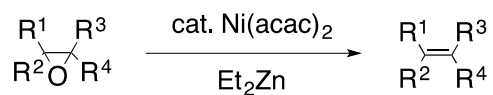
The supplementary data (¹H NMR and ¹³C NMR spectra of products) to this article can be found online at Elsevier website.

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