

Nickel-catalyzed Tishchenko reaction *via* hetero-nickelacycles by oxidative cyclization of aldehydes with nickel(0) complex†

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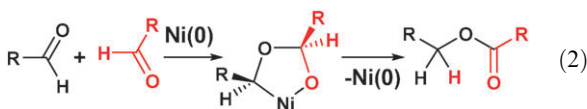
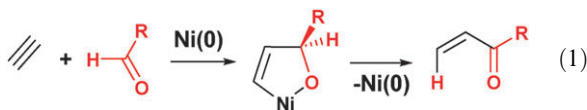
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A Ni(0)-catalyzed Tishchenko reaction which can be applied to a variety of aliphatic aldehydes (1°, 2°, 3°) and aromatic aldehydes was developed. The reaction might proceed *via* a hetero-nickelacycle intermediate.

The Tishchenko reaction was discovered more than one hundred years ago, and its use continues to this day. The Tishchenko reaction is an atom-efficient method for the synthesis of homo-dimer esters of simple aldehydes that have numerous applications in the food and perfume industries. The reported catalysts of the Tishchenko reaction could be classified into three categories based on the reaction mechanism:¹ Lewis acid catalysts, metal alkoxide catalysts and late transition metal catalysts.^{1b} However, unfavorable common side reactions have been reported: the aldol reaction for Lewis acid catalysts, benzoin condensation for metal alkoxide catalysts,^{1a} and decarbonylation for late transition metal catalysts. In general, decarbonylation is an unfavorable side reaction of hydroacylation that proceeds *via* an acyl metal intermediate. The Tishchenko reaction can be regarded as the hydroacylation of aldehydes.² In the course of our research on hetero-nickelacycles,³ we found that nickel-catalyzed hydroacylation of alkynes with aldehydes might proceed *via* oxidative cyclization of an alkyne and an aldehyde with nickel(0) followed by β -H elimination and reductive elimination (eqn (1)).^{3f} In this reaction, decarbonylation can be circumvented because no acylnickel intermediate is generated during the reaction. Moreover, Stone reported the formation of the corresponding nickelacycle by oxidative cyclization of (CF₃)₂C=O with nickel(0).⁴ Thus, it is logical that a nickel complex might act as a catalyst for the Tishchenko reaction *via* oxidative cyclization (eqn (2)). Herein, we report a highly efficient, nickel-catalyzed homo-dimerization of aldehydes.



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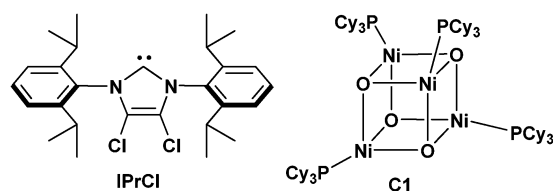
As a ligand for the Tishchenko reaction of PhCHO, PCy₃ was examined, because PCy₃ can form an η^2 -aldehyde nickel complex⁵ and can promote oxidative cyclization with alkenes, alkynes and dienes.^{3a,d,f} Although the reaction occurred to give benzylbenzoate (**1**) in 90% yield, at the end of the reaction, a red crystal had precipitated (Table 1, **C1**).⁶

The reaction of **1** with Ni(cod)₂ and PCy₃ did not give **C1** at all. Thus, **C1** might be generated by the reaction of PhCHO with Ni(cod)₂ and PCy₃, which suggests that PCy₃ is not an efficient ligand for the Tishchenko reaction.⁷ In the presence of 2 mol% of Ni(cod)₂/IPr at 60 °C for 6 h, the reaction proceeded to give **1** quantitatively. IPrCl was more effective for the reaction. Even in the presence of 1 mol% of Ni(cod)₂ and IPrCl, **1** was obtained quantitatively.

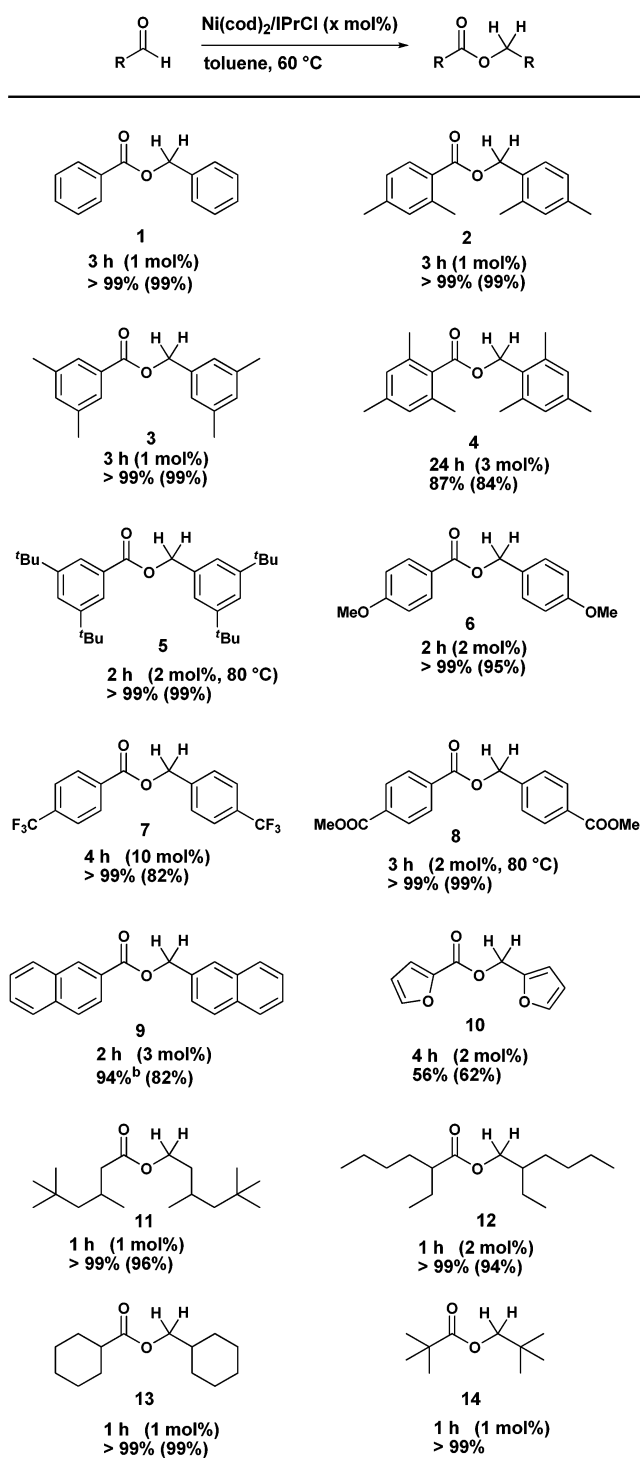
The reaction was applied to various aryl aldehydes to give the corresponding esters in excellent yields (Table 2, **2–8**).[‡] Both 2-naphthaldehyde and 2-furaldehyde also underwent the Tishchenko reaction to give the expected esters (**9** and **10**). However, aryl aldehydes having either a sterically hindered group or an electron-withdrawing group required a higher reaction temperature or a larger amount of catalyst (**4**, **5** and **7**). Primary, secondary and tertiary aliphatic aldehydes were available for this reaction (**11**, **12**, **13** and **14**). The reaction product of the primary aldehyde **11** is an industrial chemical used for antiperspirant and perfume.⁸ To date, a variety of catalysts of the Tishchenko reaction have been reported. However, few catalysts are effective for both aliphatic aldehydes and aryl aldehydes. Moreover, this reaction can catalyze the

Table 1 Ni-catalyzed Tishchenko reaction of PhCHO

| L | Ni/L (mol%) | T/°C | Time/h | Yield (%) |
|------------------|-------------|------|--------|-----------------|
| PCy ₃ | 10/20 | 100 | 24 | 90 ^a |
| IPr | 2/2 | 60 | 6 | > 99 |
| IPrCl | 2/2 | 60 | 1.5 | > 99 |
| | 1/1 | 60 | 3 | > 99 |



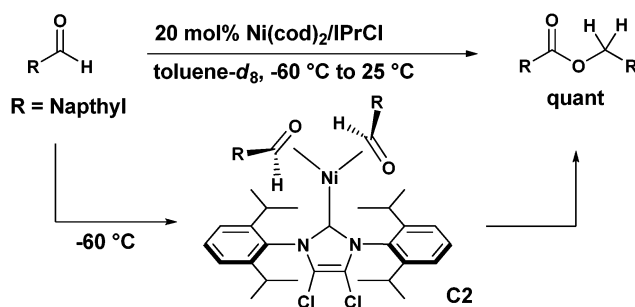
^a A red crystal of **C1** precipitated.

Table 2 Ni(0)/IPrCl-catalyzed Tishchenko reaction^a

^a GC yield, isolated yields are in parenthesis. ^b NMR yield.

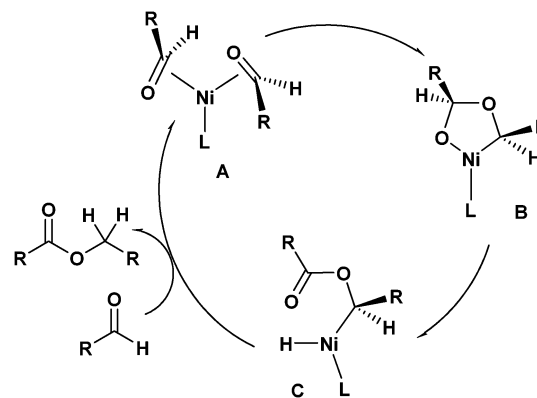
dimerization of enolizable aldehydes that, in general, readily undergo aldol reaction under the Tishchenko reaction conditions.⁹

In the presence of 20 mol% of Ni(cod)₂ and IPrCl, the Tishchenko reaction of 2-naphthaldehyde (2-C₁₀H₇CHO) was monitored by NMR (Scheme 1). At -60 °C, the resonances of the carbonyl hydrogen and the carbon of the aldehyde ligated

**Scheme 1** Ni-catalyzed Tishchenko reaction of 2-C₁₀H₇CHO.

to nickel(0) were observed at δ 4.7 in ¹H NMR and δ 109.3 in ¹³C NMR, which indicates that 2-C₁₀H₇CHO coordinates to the nickel(0) center in η^2 -mode.^{3a,10} Moreover, the resonance at δ 4.7 disappeared in ¹H NMR spectra of the reaction with 2-naphthaldehyde-*d*₁ (2-C₁₀H₇CDO) at -60 °C. The ratio of the integration of the aldehyde hydrogen toward the isopropyl group of IPrCl indicates that two aldehyde molecules coordinate to nickel(0). The reaction mixture was allowed to warm to 25 °C to give **9** quantitatively. Moreover, the reaction rate constant was zero order in [2-C₁₀H₇CHO]. These observations suggest that the rate-determining step is either oxidative cyclization, β -H elimination or reductive elimination. In order to gain more information about the rate-determining step of this reaction, the labeling experimental of 2-C₁₀H₇CHO and 2-C₁₀H₇CDO was conducted. In the presence of 3 mol% of Ni(cod)₂/IPrCl, the reaction of 2-C₁₀H₇CHO (or 2-C₁₀H₇CDO) was monitored at 60 °C by means of ¹H NMR spectroscopy.¹¹ The rate constants of disappearance of 2-C₁₀H₇CHO (*k*_H) and 2-C₁₀H₇CDO (*k*_D) are 3.55(3) × 10⁻⁴ and 1.87(1) × 10⁻⁴ mol m⁻³ s⁻¹, respectively, showing a primary kinetic isotope effect (*k*_H/*k*_D = 1.9). This indicates that either β -hydrogen elimination or reductive elimination is the rate-determining step because no primary kinetic isotope effect is expected during oxidative cyclization.¹²

A plausible mechanism is shown in Scheme 2. The coordination of an aldehyde to nickel(0) occurs very rapidly to give a bis(η^2 -aldehyde)Ni(L) (A), which corresponds to **C2** in Scheme 1, followed by oxidative cyclization to give an oxa-nickelacycle intermediate (B). β -H elimination followed by reductive elimination might give an ester with simultaneous coordination of an aldehyde to nickel(0) to regenerate A.

**Scheme 2** A plausible mechanism.

In conclusion, we demonstrated the Tishchenko reaction catalyzed by a nickel(0) complex, in which the oxidative cyclization of two aldehyde molecules with nickel(0) is an important key reaction step. The reaction can be applied to a variety of aliphatic aldehydes (1°, 2°, 3°) and aromatic aldehydes. The reaction rate constant is zero-order in the aldehyde concentration. The observed primary kinetic isotope effect suggests that the rate-determining step is β -hydrogen elimination or reductive elimination. Thus, this reaction shows the high potential of the nickel catalyst for the Tishchenko reaction.

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Notes and references

‡ General experimental procedures of Ni(0)/IPrCl-catalyzed Tishchenko reaction (Table 2): to a solution of Ni(cod)₂ (11.0 mg, 0.040 mmol) and IPrCl (18.3 mg, 0.040 mmol) in 2 mL of toluene was added the aldehyde (4 mmol) under an inert atmosphere at 23 °C. The reaction mixture was heated at 60 °C or 80 °C for 1–24 h. The reaction was monitored by GC analysis. GC yields were determined using pentadecane as an internal standard. The product was isolated by a silica gel chromatography.

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- The molecular structure of **C1** was assumed to be a cubic tetrameric structure as shown in Scheme 1 by X-ray crystallography. However, we could not accurately obtain its structure due to the disorder of the positions of oxygen and nickel and the disorder of the PCy₃ moiety.
- The formation of **C1** in nickel-catalyzed reactions employing carbonyl compounds or alcohols was observed. Thus, the complex **C1** would be a dead-end complex in catalytic reactions of carbonyl compounds or alcohols.
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