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Nickel-Catalyzed Selective Conversion of Two Different Aldehydes to Cross-Coupled Esters

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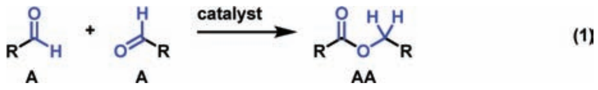
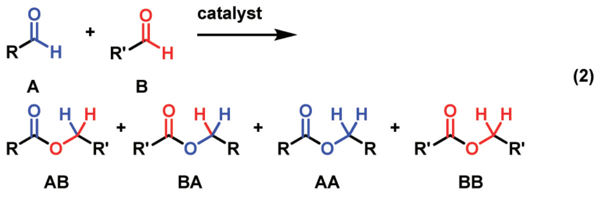
Ⓢ *Supporting Information*

ABSTRACT: In the presence of a Ni(0)/NHC catalyst, an equimolar mixture of aliphatic and aryl aldehydes can be employed to selectively yield a single cross-coupled ester. This reaction can be applied to a variety of aliphatic (1°, 2°, *cyc*-2°, and 3°) and aryl aldehyde combinations. The reaction represents 100% atom efficiency and generates no waste. Mechanistic studies have revealed that the striking feature of the reaction is the simultaneous coordination of two aldehydes to Ni(0).

Ester compounds are a fact of daily life, and the need for them will never lessen. Thus, it is worthwhile to provide an environmentally benign method to synthesize esters.[1] One of the most promising methods is the Tishchenko reaction, which is a direct catalytic conversion of simple aldehydes to esters (eq 1).[2] Since its discovery in 1887, a variety of catalysts, such as Lewis acid and transition-metal catalysts, have been elaborated to develop the reaction. Nevertheless, this reaction has not been accepted as a common method for ester synthesis because of a crucial limitation: *there is no selective crossed Tishchenko reaction* that can prepare a single cross-coupled ester selectively from among the four possible esters that could be formed from two different aldehydes (eq 2). In fact, some groups have attempted to prepare a single cross-coupled ester from among the four possible esters, but it has never been accomplished.[3,4] The highest selectivity reported to date has been 0.71,[3g] where the selectivity is defined as **AB**/(**AB** + **BA** + **AA** + **BB**) using the labels in eq 2. For the development of a selective crossed Tishchenko reaction, a new catalyst that can discriminate between two different aldehydes must be discovered and developed.



(1)



(2)

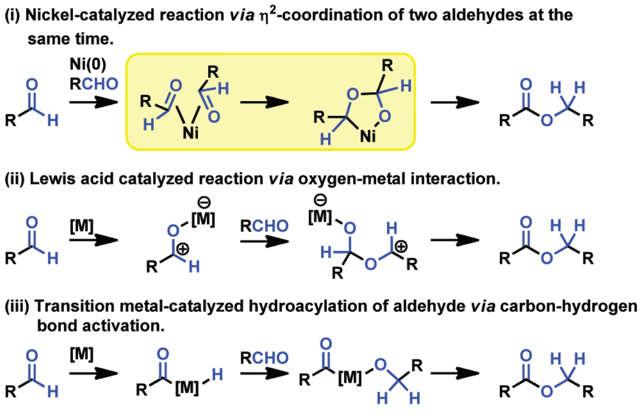


Figure 1. Proposed mechanisms for the Tishchenko reaction.

We have reported a nickel(0)/*N*-heterocyclic carbene[5] (NHC)-catalyzed Tishchenko reaction that can dimerize both aliphatic and aryl aldehydes via a reaction path that is totally different from that proposed for either Lewis acid or transition-metal catalysts (Figure 1).[6] A striking feature of the reaction mechanism for the nickel(0)-catalyzed reaction is that two aldehyde molecules are incorporated in all of the key reaction intermediates. Thus, the reactivity of these intermediates was expected to be more sensitive than other catalysts to the environment surrounding the formyl group of the aldehydes. This expectation was supported by the fact that the reaction rate of a homocoupling reaction of aliphatic aldehydes was much faster than that of aryl aldehydes in the nickel(0)/NHC-catalyzed reaction.[6] These observations convinced us that the nickel(0)/NHC catalyst meets the criteria for a possible new catalyst for the cross-coupling reaction of aldehydes, as mentioned above. This paper is the first report of a selective crossed Tishchenko reaction. The results of mechanistic experiments are included.

To confirm the potential of nickel(0) as a catalyst for the crossed Tishchenko reaction, the reaction conditions for the homocoupling reaction were applied.[6] The reaction of CyCHO (**A**^{1}) with an equimolar amount of PhCHO (**B**^{1}) in toluene at 60 °C in the presence of 2 mol % Ni(cod)$_2$ and IPrCl gave one cross-coupled ester, CyCOOCH$_2$Ph (**A**^{1}**B**^{1}), predominantly in 58% yield, with the concomitant formation of PhCOOCH$_2$Cy (**B**^{1}**A**^{1}), CyCOOCH$_2$Cy (**A**^{1}**A**^{1}), and PhCOOCH$_2$Ph (**B**^{1}**B**^{1}) in 4, 12, and 18% yield, respectively, and the selectivity was moderate (0.63). It should be emphasized that two aldehydes were employed in a 1:1 ratio. Encouraged by this result, we

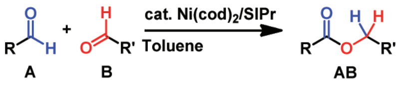
Received: November 14, 2010
Published: March 15, 2011

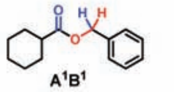
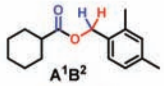
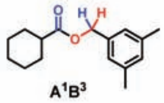
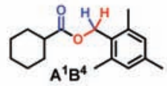
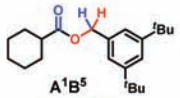
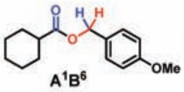
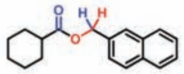
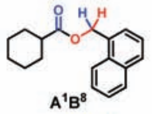
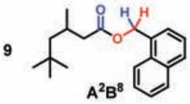
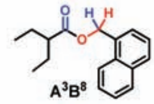
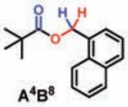
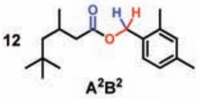
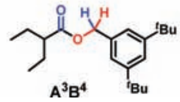
optimized the reaction conditions.[7] Heating an equimolar mixture of $\mathbf{A^1}$ with $\mathbf{B^1}$ in the presence of 2 mol % Ni(cod)$_2$ and SIPr gave $\mathbf{A^1B^1}$ with the highest selectivity (94% yield, 0.94 selectivity; Table 1, entry 1).

Once the optimized conditions for the desired reaction had been established, we turned to an investigation of the scope and limitations. A wide variety of combinations of substrates were examined, and the results are summarized in Table 1. Treatment of $\mathbf{A^1}$ with an equimolar amount of $\mathbf{B^1}$ or one of its disubstituted derivatives $\mathbf{B^2}$ and $\mathbf{B^3}$ resulted in the formation of the corresponding cross-coupled esters ($\mathbf{A^1B^1}$–$\mathbf{A^1B^3}$) in excellent yields with excellent selectivity (92–94% yield, 0.92–0.94 selectivity; entries 1–3). Although a decrease in selectivity was observed in the reaction of $\mathbf{A^1}$ with 2,4,6-trimethylbenzaldehyde ($\mathbf{B^4}$) (57% yield, 0.64 selectivity; entry 4), $\mathbf{B^5}$ having bulky substituents at the 3 and 5 positions gave excellent results (89% yield, 0.89 selectivity; entry 5). An electron-rich substrate ($\mathbf{B^6}$) and naphthaldehyde derivatives ($\mathbf{B^7}$ and $\mathbf{B^8}$) afforded the cross-coupled esters with excellent selectivity (0.87–0.98; entries 6–8).[8] Next, the cross-coupling reactions of various aliphatic aldehydes (1°, 2°, and 3°) with $\mathbf{B^8}$ were examined (entries 9–11), as $\mathbf{B^8}$ afforded the highest selectivity in the reaction with $\mathbf{A^1}$ (entry 8). As expected, the corresponding cross-coupled esters ($\mathbf{A^2B^8}$–$\mathbf{A^4B^8}$) were obtained as almost single products (0.93–0.99 selectivity). Recent attention to 1-naphthylmethyl esters has focused on their utility, for example, as an identification group to pursue the production of dendrimers[9] and antidiabetic drugs.[10] Although $\mathbf{A^2}$ and $\mathbf{A^3}$ can be employed in the reaction with other aryl aldehydes with no loss of selectivity (entries 12 and 13), a significant decrease in selectivity was observed in the case of $\mathbf{A^4}$.[7] It is noted that the aliphatic aldehyde (**A**) tends to become the carboxylic acid part and the aryl aldehyde (**B**) the alcohol part. This tendency was also observed in previous reports.[3f,g] One of the advantages of this catalyst system is its simplicity in the isolation of the products. In most cases, simple distillation can be used to isolate the products from the reaction mixture using a Kugelrohr distillation oven.

Plausible mechanisms are described in Figure 2. The formation of $\mathbf{C1_{BB}}$ would occur prior to the formation of $\mathbf{C1_{AB}}$. Some theoretical studies have demonstrated that a more electron-deficient π component can coordinate to nickel(0) in the η^2 mode more efficiently because of a strong back-bonding interaction.[11] Aryl aldehydes, which generally are more electron-deficient than aliphatic aldehydes, coordinate to nickel(0) to give $\mathbf{C1_{BB}}$. In fact, at −60 °C, the exclusive formation of $\mathbf{C1_{B^7B^7}}$ was observed by NMR spectroscopy in the reaction of $\mathbf{A^1}$ (5 equiv) and $\mathbf{B^7}$ (5 equiv) with Ni(cod)$_2$ and SIPr in toluene-d_8.[7] However, even at 25 °C, broadening of the resonances of the formyl hydrogen of $\mathbf{A^1}$ and $\mathbf{B^7}$ was observed. Thus, under the reaction conditions, the exchange of a coordinated **B** and a noncoordinated **A** generating $\mathbf{C1_{AB}}$ would take place much faster than the formation of homocoupled ester **BB** from $\mathbf{C1_{BB}}$. After the formation of $\mathbf{C1_{AB}}$, there might be two possible paths for the nickel(0)-catalyzed crossed Tishchenko reaction: via a dioxanickelacycle intermediate[12] (path 2A) or an acylnickel intermediate[13] (path 2B). In path 2A, oxidative cyclization of the aldehyde moieties in $\mathbf{C1_{AB}}$ would give dioxanickelacycle $\mathbf{C2_{AB}}$, after which β-hydrogen elimination and reductive elimination would yield the cross-coupled ester **AB**.[14,15] On the other hand, in path 2B, oxidative addition of the C–H bond of **A** in $\mathbf{C1_{AB}}$ to Ni(0) would generate Ni–H complex $\mathbf{C4_{AB}}$. Insertion of the C=O bond of **B** into Ni–H would then give rise to $\mathbf{C5_{AB}}$, after

Table 1. Nickel-Catalyzed Crossed Tishchenko Reaction of Aliphatic Aldehydes (A) with Aryl Aldehydes (B)[a]



Entry	AB	Condition[b]	Conv. of B[c] (%)	Yield[d] (%)	Selectivity[c]
1	 $\mathbf{A^1B^1}$	2/40/4	> 99	94(84)	0.94
2	 $\mathbf{A^1B^2}$	4/40/4	> 99	92(88)	0.92
3	 $\mathbf{A^1B^3}$	2/40/4	> 99	94(85)	0.94
4	 $\mathbf{A^1B^4}$	4/40/4	89	57	0.64
5	 $\mathbf{A^1B^5}$	2/40/4	> 99	89(81)	0.89
6	 $\mathbf{A^1B^6}$	2/40/4	> 99	87(82)	0.87
7	 $\mathbf{A^1B^7}$	4/50/2	98	92(83)	0.94
8	 $\mathbf{A^1B^8}$	2/50/2	66	64(47)	0.98
9	 $\mathbf{A^2B^8}$	4/50/2	61	61(66)	> 0.99
10[e]	 $\mathbf{A^3B^8}$	10/23/12	81	75(65)	0.93
11[f]	 $\mathbf{A^4B^8}$	10/23/12	83	73(65)	0.94
12	 $\mathbf{A^2B^2}$	4/40/4	90	82(66)	0.94
13	 $\mathbf{A^3B^4}$	4/40/4	> 99	88(83)	0.88

[a] Aldehydes (0.40, 1.00, or 2.00 mmol), Ni(cod)$_2$/SIPr (0.040 mmol), and toluene (2 mL) were reacted at the indicated temperature. [b] Catalyst loading (mol %)/temperature (°C)/time (h). [c] Conversions (%) of **B** and selectivities were determined by GC analysis. [d] Yields (%) of **AB** were determined by GC analysis; isolated yields are given in parentheses. [e] IPr was employed. [f] IMes was employed.

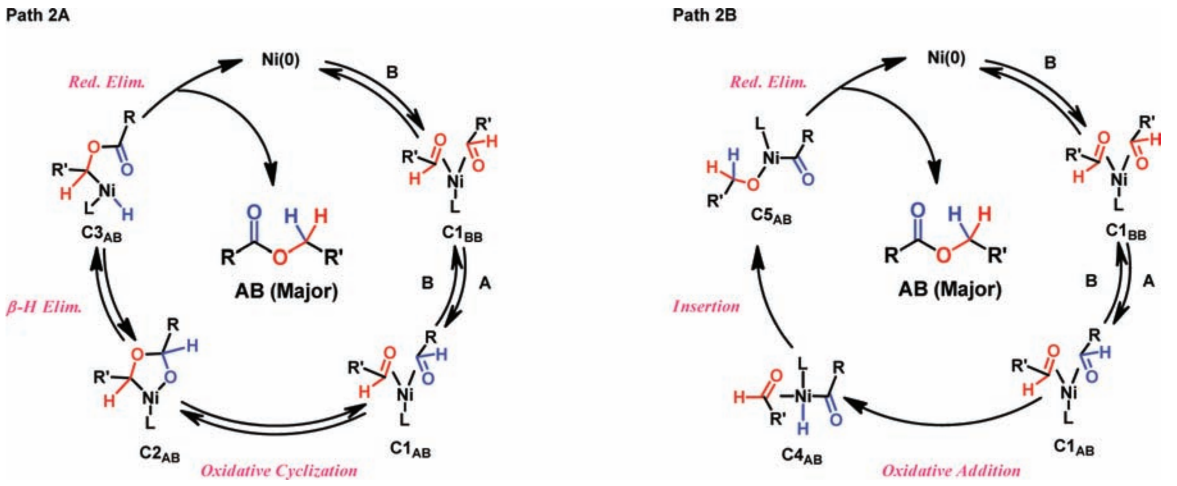
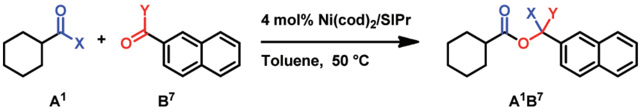


Figure 2. Plausible mechanisms for the nickel-catalyzed crossed Tishchenko reaction. (A) Reaction path via a dioxanickelacycle intermediate formed by oxidative cyclization. (B) Reaction path via an acylnickel intermediate formed by oxidative addition.

Table 2. Labeling Experiments for the Nickel-Catalyzed Crossed Tishchenko Reaction of $\mathbf{A}^1$ with $\mathbf{B}^7$



Experiment	X	Y	k_N[a]	KIE(N)[b]	Selectivity
I	H	H	12.9(1)	–	0.94
II	H	D	10.9(1)	1.2	0.93
III	D	H	6.4(3)	2.0	0.83[c]
IV	D	D	6.7(1)	1.9	0.85[d]

[a] Rate constant (10^{-5} mol m^{-3} s^{-1}) for the production of the ester in experiment N, where N is the roman numeral label for the experiment. [b] Kinetic isotope effect, estimated as KIE(N) = k_I/k_N. [c] The yields of ($\mathbf{A}^1$-$\boldsymbol{d}_1$)$\mathbf{B}^7$, $\mathbf{B}^7$($\mathbf{A}^1$-$\boldsymbol{d}_1$), ($\mathbf{A}^1$-$\boldsymbol{d}_1$)($\mathbf{A}^1$-$\boldsymbol{d}_1$), and $\mathbf{B}^7\mathbf{B}^7$ were 71, <1, 2, and 13%, respectively. [d] The yields of ($\mathbf{A}^1$-$\boldsymbol{d}_1$)($\mathbf{B}^7$-$\boldsymbol{d}_1$), ($\mathbf{B}^7$-$\boldsymbol{d}_1$)($\mathbf{A}^1$-$\boldsymbol{d}_1$), ($\mathbf{A}^1$-$\boldsymbol{d}_1$)($\mathbf{A}^1$-$\boldsymbol{d}_1$), and ($\mathbf{B}^7$-$\boldsymbol{d}_1$)($\mathbf{B}^7$-$\boldsymbol{d}_1$) were 77, <1, 3, and 10%, respectively.

which reductive elimination would result in the formation of **AB**.

To gain insight into the reaction mechanism, mechanistic studies were conducted utilizing the combination of $\mathbf{A}^1$ and $\mathbf{B}^7$. In order to explore the change in the concentration of each component, the crossed Tishchenko reaction of $\mathbf{A}^1$ with $\mathbf{B}^7$ (Table 1, entry 8) was monitored by GC analysis.[7] The rate constants for disappearance of $\mathbf{A}^1$ ($k_{\mathbf{A}\text{-cross}}$) and $\mathbf{B}^7$ ($k_{\mathbf{B}\text{-cross}}$) are zeroth-order with respect to the concentrations of $\mathbf{A}^1$ and $\mathbf{B}^7$, respectively. Moreover, the rate constant for production of $\mathbf{A}^1\mathbf{B}^7$ (k_I) was almost equal to $k_{\mathbf{A}\text{-cross}}$ and $k_{\mathbf{B}\text{-cross}}$, i.e., $k_{\mathbf{A}\text{-cross}} \approx k_{\mathbf{B}\text{-cross}} \approx k_\mathrm{I} \approx 13 \times 10^{-5}$ mol m^{-3} s^{-1}.

These results indicate that the coordination of the aldehydes to nickel(0) is not the rate-limiting step in the reaction. In addition, the reaction exhibits first-order dependence on the Ni(0)/SIPr catalyst. Moreover, we conducted labeling experiments to estimate the kinetic isotope effects (KIEs).[16] The measured KIEs are as follows; KIE(II) = 1.2, KIE(III) = 2.0, and KIE(IV) = 1.9 (see Table 2).[7] In these experiments, deuterium was exactly incorporated into the X and/or Y positions without loss of enrichment. In addition, scrambling of the deuterium in $\mathbf{A}^1$($\mathbf{B}^7$-$\boldsymbol{d}_1$) was not observed at all when $\mathbf{A}^1$($\mathbf{B}^7$-$\boldsymbol{d}_1$) was subjected to either the catalytic conditions (50 °C, 3 days) or more harsh conditions (100 °C, 2 h).[7] The observed KIE(III) is in the range of a primary KIE, clearly suggesting that the cleavage of the C–H bond in $\mathbf{A}^1$ or the Ni–H bond significantly contributes to the reaction rate. Thus, in path 2A, the rate-limiting step might be either the β-H elimination or the reductive elimination. However, the value of KIE(II), which is in the range of a normal secondary KIE, should not be observed in the β-H elimination step. Therefore, the rate-limiting step in the path 2A might be the reductive elimination.[17] In path 2B, the oxidative addition or the insertion could be the rate-limiting step. However, KIE(II) is consistent with neither of these possibilities. In the oxidative addition step, a KIE should not be observed for the aryl aldehyde. In the insertion step, an inverse secondary KIE should be observed because of the hybridization change of the formyl carbon of the aryl aldehyde from sp^2 to sp^3.[18] Thus, path 2A is more likely, and a very rapid pre-equilibrium process involving $\mathbf{C1}_\mathbf{BB}$ and $\mathbf{C3}_\mathbf{AB}$ prior to the reductive elimination might exist. In fact, no decarbonylation was observed in our system, although it was reported that decarbonylation occurred in the transition-metal-catalyzed Tishchenko reaction via an acylmetal intermediate such as $\mathbf{C4}_\mathbf{AB}$.[19]

The observed values of KIE(III) and KIE(IV) were almost the same, which suggests that the rate of the cross-coupling reaction relies mainly on the reactivity of the aliphatic aldehyde $\mathbf{A}^1$. This rationalization is also consistent with the decrease in selectivity observed when the deuterium was incorporated into $\mathbf{A}^1$ (Table 2, entries 3 and 4). Because cleavage of a Ni–D bond (from $\mathbf{C3}_\mathbf{AB}$ to **AB** in path 2A) generally requires a higher energy than for the corresponding Ni–H bond, the formation of **AB** is retarded and the ratio of **BB** increased.

In conclusion, we have demonstrated a selective crossed Tishchenko reaction for the first time by employing nickel(0) as a catalyst. This reaction can be applied to various combinations of aliphatic aldehydes with equimolar amounts of aryl aldehydes, and the corresponding cross-coupled esters are obtained in a highly selective manner.[20] Mechanistic studies revealed that all of the key intermediates might include two aldehyde molecules and that the reaction rate is controlled by the aliphatic aldehyde. We believe that the present study is the first step in a selective crossed

Tishchenko reaction of two aldehydes, and the study will contribute to the further development of the environmentally benign synthesis of esters.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Full experimental details and discussion of the optimization of reaction conditions, NMR experiments, reaction mechanism, and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

This work was supported by Grants-in-Aid for Scientific Research (21245028) and Encouragement for Young Scientists (B) (21750102) and a Grant-in-Aid for Scientific Research on Priority Areas "Advanced Molecular Transformations of Carbon Resources" from MEXT. S.O. and M.O. acknowledge the NAGASE Science and Technology Foundation and the Japan Petroleum Institution, respectively, for the Grants for Research. Y.H. expresses his special thanks for the Research Fellowship for Young Scientists (JSPS) and the Global COE Program "Global Education and Research Center for Bio-Environmental Chemistry" of Osaka University. We also gratefully acknowledge a reviewer for valuable comments and suggestions regarding the reaction mechanism.

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(5) The NHCs employed in this manuscript were the following: 1,3-bis(2,6-diisopropylphenyl)-4,5-dichloroimidazol-2-ylidene (IPrCl); 1,3-bis(2,6-diisopropylphenyl)imidazolin-2-ylidene (SIPr); 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr); and 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (IMes).

(6) Ogoshi, S.; Hoshimoto, Y.; Ohashi, M. *Chem. Commun.* **2010**, *46*, 3354–3356.

(7) For details, see the Supporting Information.

(8) In the course of evaluating the scope of electron-deficient aryl aldehydes, we carried out the crossed Tishcheko reaction of *p*-Cl- and *p*-NO_2-substituted benzaldehydes with CyCHO. However, the cross-coupled esters were not obtained at all; precipitations were observed instead, and we could not identify the products.

(9) For example, see: Vijayalakshmi, N.; Maitra, U. *J. Org. Chem.* **2006**, *71*, 768–774.

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