Catalytic Conjugate Addition of Cyanide to Enones: Cooperative Catalysis of Ni(0) and Gd(OTf)$_3$

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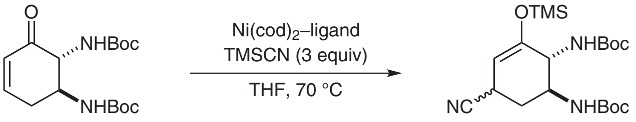
Abstract: An efficient, synthetically useful catalytic cunjugate addition of cyanide to enones was developed using cooperative catalysis of Ni(0) and Gd(OTf)$_3$. The co-catalyst, Gd(OTf)$_3$, dramatically accelerated the reaction. The substrate scope is broad, including cyclic, linear, branched, and aromatic enones. Synthetic efficiency of the key conversion in our Tamiflu synthesis, conjugate cyanation of an enone, was significantly improved by using this new method. Gadolinium triflate is supposed to facilitate the oxidative addition of Ni(0) to enones, which constitutes a key step in the catalytic cycle.

Key words: cooperative catalysis, conjugate addition, cyanide, nickel, gadolinium

The conjugate addition of cyanide to enones is a useful reaction in organic synthesis. The control of regioselectivity (1,4-addition vs. 1,2-addition) in this reaction is a major concern. After Nagata's pioneering work using Et$_2$AlCN as a nucleophile,[1] several hard-metal-mediated reactions were reported.[2–4] In our synthesis of Tamiflu (**4**),[5] an important anti-influenza drug, however, we utilized an entirely distinct method for introducing cyanide to enones (such as **1r** and **1s**): Ni(0)–cyclooctadiene (cod) complex catalyzed conjugate cyanation using TMSCN as a nucleophile. Whereas the hard-metal-mediated conditions were not effective (no reaction) for conjugate cyanation of enones, such as **1r** and **1s** containing multiple Lewis basic sites, the Ni-catalyzed reaction proceeded in high yield under mild conditions. This method was rather primitive, however, with regard to the following points: (1) high catalyst loading (10–50 mol%), and (2) prolonged reaction time (3–65 h).[5] Moreover, substrate generality of this method has yet to be determined. In this communication, we report that the catalyst activity improved dramatically in the presence of a Gd(OTf)$_3$ co-catalyst, leading to a highly general and synthetically useful catalytic conjugate addition of cyanide to enones.

To optimize the reaction conditions, we first studied the effects of ligands on Ni using enone **1s** as a model substrate (Table 1). In the absence of any additive ligand, product **3s** was obtained in ca. 80% yield using 20 mol% of Ni(cod)$_2$ at 70 °C in THF for 11 hours (entry 1). Using 10 mol% of the catalyst, however, results were not stable; the reaction did not complete in most cases even after prolonged reaction time with producing insoluble and inactive Ni powder. Thus, additive ligand effects were next studied to stabilize the catalyst. In the presence of additional cod (10 mol%), the reaction completed in 24 hours even using 10 mol% of Ni(cod)$_2$ (entry 2). Further studies revealed that norbornadiene (nbd) was the optimal ligand, and the reaction was complete in 8 hours (entry 3). When phosphine ligands were used instead of diene ligands, however, the reaction was very sluggish.

Table 1 Optimization of the Reaction Conditions: Effects of Ligands



1s **3s**

Entry	Ni (mol%)	Ligand (mol%)	Time (h)	Yield (%)
1	20	–	11	80
2	10	cyclooctadiene (10)	24	>95
3	10	norbornadiene (30)	8	>95

We then applied the preliminarily optimized conditions to a more challenging substrate, 3-methyl-2-cyclohexen-1-one (**1e**). The reaction, however, did not proceed at all at room temperature (Table 2, entry 1). To facilitate the reaction, the effects of additives were studied. The presence of a catalytic amount (10 mol%) of Lewis acids, especially rare-earth-metal triflates, dramatically accelerated the reaction (Table 2, entries 2–6).[6] Specifically, Gd(OTf)$_3$ gave the best result (94% yield, entry 5). TBSCN can be also used as the nucleophile (entry 7), giving the product in comparable yield to TMSCN.[7] Catalyst loading could be reduced to 5 mol% without a significant loss of reaction efficiency (entry 8). Gadolinium triflate itself did not catalyze the reaction in the absence of the Ni catalyst (entry 9: no reaction). Therefore, the dramatic acceleration observed in the presence of Gd(OTf)$_3$ was due to the cooperative catalysis of Ni(0) and Gd(OTf)$_3$.[8]

Substrate scope was examined under the optimized conditions (Table 3). In all cases studied, the acceleration effect of Gd(OTf)$_3$ was remarkable (entries 1–6, 8–11).[9] The reaction time was significantly decreased, and the products were afforded in high yields. Specifically, in the case of a substrate for quaternary carbon synthesis (**1e**) and phenyl

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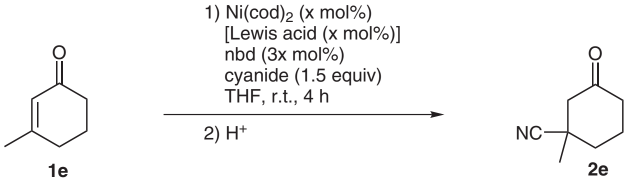
Table 2 Optimization of the Reaction Conditions: Effects of Lewis Acid Co-Catalyst



Entry	Catalyst loading (x)	Lewis acid	Cyanide	Yield (%)[a]
1[b]	5	–	TMSCN	0
2	10	$Sc(OTf)_3$	TMSCN	65
3	10	$Y(OTf)_3$	TMSCN	86
4	10	$La(OTf)_3$	TMSCN	92
5	10	$Gd(OTf)_3$	TMSCN	94
6	10	$Yb(OTf)_3$	TMSCN	70
7	10	$Gd(OTf)_3$	TBSCN	91[c]
8	5	$Gd(OTf)_3$	TBSCN	81[c]
9[d]	5	$Gd(OTf)_3$	TBSCN	0

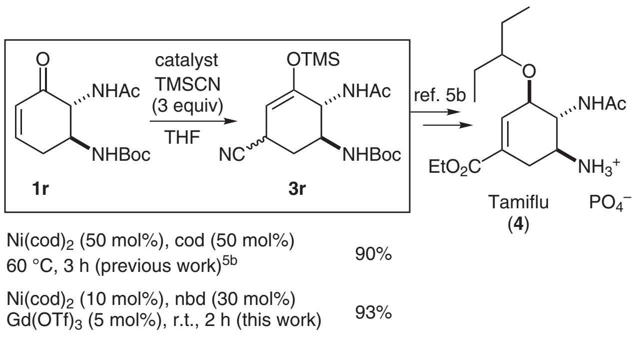
[a] Isolated yield.

[b] Reaction time was 44 h.

[c] Yield as enol silyl ether by quenching the reaction with SiO_2.

[d] In the absence of Ni catalyst.

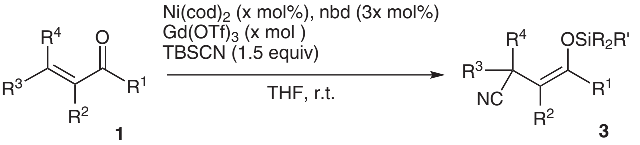
ketone **1f**, no reaction proceeded in the absence of $Gd(OTf)_3$ (entries 8 and 10). By contrast, yields were greater than 80% in the presence of $Gd(OTf)_3$ (entries 9 and 11). Substrate generality under the present reaction conditions was broad, covering cyclic, aryl, and linear enones. Catalyst loading could be reduced to 2 mol%.[10] In all entries, the reactions were completely 1,4-selective, and 1,2-adducts were not detected.

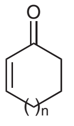
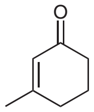
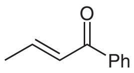
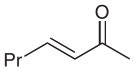
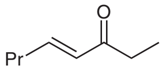
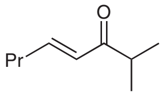
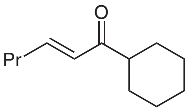
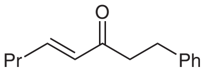
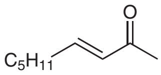
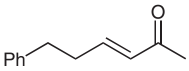
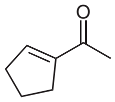
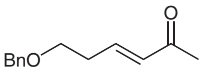
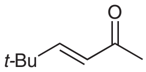
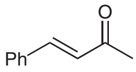


Scheme 1 Application to a key conversion in Tamiflu synthesis

The synthetic utility of this reaction was demonstrated by applying to the conjugate cyanation of **1r**, a key conversion in our Tamiflu (**4**) synthesis.[5b,11] In the previous conditions in the absence of $Gd(OTf)_3$, the conjugate cyanation of **1r** was promoted in the presence of 50 mol% of $Ni(cod)_2$–cod (1:1) in THF at 60 °C for three hours. Product **3r** was obtained in ca. 90% yield. By contrast, **3r**

Table 3 Catalytic Conjugate Addition of Cyanide to Enones Using Ni and $Gd(OTf)_3$

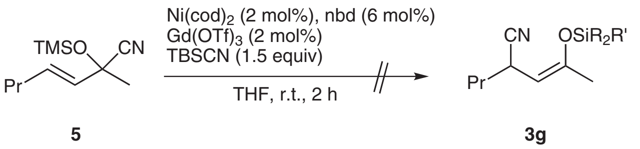


Entry	Substrate		x (mol%)	Time (h)	Yield (%)[a]
1[b]		**1a**: n = 0	5	19	24[c]
2		**1a**: n = 0	2	3	88
3[b]		**1b**: n = 1	2	4	77[c]
4		**1b**: n = 1	2	1	89
5[b]		**1c**: n = 2	5	19	8[c]
6		**1c**: n = 2	5	0.25	84
7		**1d**: n = 3	5	1	84
8[b]		**1e**	5	44	0
9		**1e**	5	4	81
10[b]		**1f**	2	44	0
11		**1f**	2	0.25	95
12		**1g**	2	2	87
13		**1h**	2	3	90
14		**1i**	2	4	94
15		**1j**	2	6	96
16		**1k**	2	4	94
17		**1l**	2	2	88
18		**1m**	2	1	85
19		**1n**	10	4	75
20		**1o**	2	2	79
21		**1p**	2	3	49
22		**1q**	10	0.25	83

[a] Isolated yield.

[b] Using TMSCN in the absence of $Gd(OTf)_3$.

[c] Yields of β-cyano ketone after quenching the reaction with 1 M HCl.



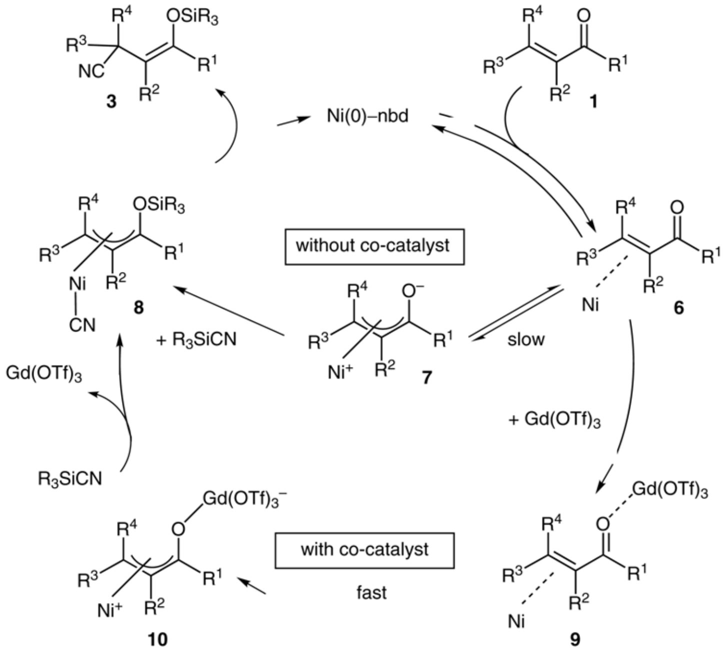
Scheme 2 Experimental supports suggesting that 1,4-adducts are kinetically controlled products

was obtained in 93% yield in the presence of 10 mol% Ni(cod)$_2$–nbd (1:3) and 5 mol% Gd(OTf)$_3$ at room temperature for two hours (Scheme 1). Compound **3r** was converted into **4** in six steps.[5b]

Although detailed studies are required to clarify the reaction mechanism, the present Ni(0)- and Gd(OTf)$_3$-catalyzed reaction likely proceeds via a completely different mechanism compared to the previous hard-metal-mediated conjugate cyanation reactions, in which the regioselectivity was controlled based on the thermodynamic stability of the 1,4-adducts compared to the 1,2-adducts.[1,2] Specifically, in the present reaction, the regioselectivity is kinetically controlled; cyanide rearrangement did not proceed at all when subjecting TMS-protected cyanohydrin **5** derived from **1g** to the reaction conditions (Scheme 2). These results sharply contrast with the previous finding that 1,4-adducts are produced from the corresponding 1,2-adducts via rearrangement in the presence of hard-metal-derived reagents or catalyst.[1–3]

Based on the above information regarding the origin of the regioselectivity, as well as on the previously reported reaction mechanism of Ni-catalyzed conjugate addition reactions to enones,[12] we postulate the catalytic cycle shown in Scheme 3. First, an enone coordinates to Ni(0), affording olefin complex **6**. This initial step requires an open coordination site on Ni. Therefore, olefin ligands (nbd or cod), which datively coordinate to Ni, are suitable compared to strongly coordinating phosphine ligands. The subsequent oxidative addition of an enone to Ni(0) produces a π-oxa–nickel complex **7**. This step is reversible, and the forward reaction might be sluggish or does not proceed in the absence of the Lewis acid co-catalyst. On the other hand, in the presence of Gd(OTf)$_3$, this π-oxa–nickel formation step should be greatly accelerated through coordination of the carbonyl oxygen atom to the hard Lewis acid (**9** and **10**). Then, the generated enolate **10** is trapped with the silyl group of the cyanide source (TMSCN or TBSCN), which proceeds concomitantly with cyanide transfer from silicon to nickel, affording **8**. Gadolinium triflate is regenerated in this step. Reductive elimination occurs selectively at the β-position, affording product **3**, with regeneration of the active Ni(0) catalyst.

In summary, we developed a synthetically useful catalytic conjugate addition of cyanide to enones using cooperative catalysis of Ni(0) and Gd(OTf)$_3$. This new method exhibited a broad substrate scope. Specifically, the reaction from enone **1r** containing multiple Lewis basic sites proceeded smoothly under mild conditions, which significantly enhanced the synthetic efficiency of Tamiflu. Enone **1r** is a totally unreactive substrate under the conventional conjugate cyanation conditions using hard-metal cyanide as a nucleophile. The hard Lewis acid co-catalyst, Gd(OTf)$_3$, is thought to facilitate the catalytic cycle by accelerating the oxidative addition of Ni(0) to enones. Detailed studies to clarify the reaction mechanism as well as extension of this platform reaction to a catalytic asymmetric variant are currently ongoing.



Scheme 3 Proposed catalytic cycle

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(6) Yields of **2e** using other Lewis acid co-catalysts: 13% ($\mathrm{TiCl_4}$), 71% ($\mathrm{ZnI_2}$), 51% [$\mathrm{Cu(OTf)_2}$], 89% ($\mathrm{BF_3{\cdot}OEt_2}$).

(7) When using TMSCN as a nucleophile, the 1,4-addition products, enol TMS ethers, overreacted with the starting enones under the reaction conditions in the presence of $\mathrm{Gd(OTf)_3}$ in some cases, leading to diminished yields of the 1,4-products. For example, when 2-cyclohepten-1-one (**1c**) was used as a substrate, the reaction using TMSCN produced a complex mixture, yielding only 40% of the 1,4-addition product. On the other hand, the reaction using TBSCN was clean, yielding 92% of **3c**.

(8) For previous examples of Ni(0) and Lewis acid catalyzed reactions, see: (a) Nakao, Y.; Yada, A.; Ebata, S.; Hiyama, T. *J. Am. Chem. Soc.* **2007**, *129*, 2428. (b) Nakao, Y.; Hirata, Y.; Tanaka, M.; Hiyama, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 385. (c) Nakao, Y.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 2448. (d) Mori, N.; Ikeda, S.; Sato, Y. *J. Am. Chem. Soc.* **1999**, *121*, 2722. (e) Baxter, R. D.; Montgomery, J. *J. Am. Chem. Soc.* **2008**, *130*, 9662.

(9) In the absence of $\mathrm{Gd(OTf)_3}$, TBSCN was not an effective nucleophile; the yield of **3b** decreased to as low as 6% using TBSCN in the absence of $\mathrm{Gd(OTf)_3}$, whereas the yield was 77% using TMSCN in the absence of $\mathrm{Gd(OTf)_3}$ (Table 3, entry 3).

(10) **General Procedure for Ni/$\mathrm{Gd(OTf)_3}$-Catalyzed Conjugate Addition of Cyanide to Enones (Table 2, entry 4)**

The reaction was performed using degassed solvents under Ar atmosphere. To a solution of $\mathrm{Ni(cod)_2}$ (1.7 mg, 0.006 mmol) in THF (0.2 mL), norbornadiene (1.83 μL, 0.018 mmol) was added. Gadolinium triflate (3.6 mg, 0.006 mmol) was added to the mixture, followed by the addition of 2-cyclohexene-1-one (**1b**: 29.0 μL, 0.30 mmol). Then, TBSCN (63.6 mg, 0.45 mmol) in THF (0.1 mL) was added to start the reaction. After stirring for 1 h, the reaction mixture was directly loaded on $\mathrm{SiO_2}$ column (Caution! Highly toxic HCN is generated in this step. This operation should be conducted in a well-ventilated hood), and purified by flash column chromatography ($\mathrm{SiO_2}$, $\mathrm{Et_2O}$–hexane, 1:20) to afford **3b** (62.6 mg, 0.264 mol) in 89% yield.

(11) For the latest review of Tamiflu synthesis, see: Shibasaki, M.; Kanai, M. *Eur. J. Org. Chem.* **2008**, 1839.

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