

Nickel-Catalyzed Cycloaddition of $\alpha,\beta,\gamma,\delta$ -Unsaturated Ketones with Alkynes**

Hiroaki Horie, Takuya Kurahashi,* and Seiji Matsubara*

Transition-metal-catalyzed co-oligomerizations, involving a σ - π isomerization, of compounds containing unsaturated carbon-carbon bonds are very important synthetic methods for the atom-economical construction of structurally diverse molecular frameworks. The development of efficient catalysts for novel reactions of various compounds containing unsaturated carbon-carbon bonds is a challenging task.^[1]

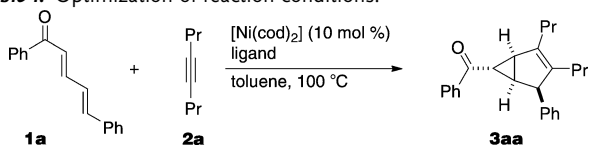
Recently, we have reported the development of nickel-catalyzed intermolecular co-oligomerizations of alkynes and alkenes tailored to selectively yield 1,3-dienes or 1,3,5-trienes.^[2,3] In the course of our studies, we became intrigued by the use of different compounds containing unsaturated carbon-carbon bonds, as reaction partners in place of an alkene, to prepare diverse polyconjugated compounds. In view of the potentially unique reactivity of $\alpha,\beta,\gamma,\delta$ -unsaturated ketones, which contain a 1,3-diene fragment,^[4,5] we explored the nickel-catalyzed cycloaddition of $\alpha,\beta,\gamma,\delta$ -unsaturated ketones and alkynes. As a result of our investigations, we found that the reaction proceeded in an unexpected manner to afford bicyclo[3.1.0]hexenes.^[6,7]

First, we evaluated the reaction of **1a** with **2a** in the presence of $[\text{Ni}(\text{cod})_2]$ (10 mol %) and PPh_3 (20 mol %) in toluene at 100 °C for 16 hours. This reaction afforded the bicyclo[3.1.0]hexene **3aa** in 70 % yield (Table 1, entry 1). Among the ligands examined, PPh_3 gave the best yield of the cycloadduct (Table 1, entries 2–5). In studies to determine the best molar ratio of Ni^0 and PPh_3 for the reaction, it was found that the reaction of **1a** with **2a** provided **3aa** in 63 % yield, along with some unreacted **1a**, when the ratio of Ni^0/PPh_3 was 1:3 (Table 1, entry 7). By prolonging the reaction time to 48 hours, the yield of **3aa** was increased to 76 % (Table 1, entry 8). Detailed examination of various triarylphosphines revealed that when $\text{P}(4\text{-MeC}_6\text{H}_4)_3$ was used as a ligand for the reaction, the yield of **3aa** improved to 82 % (Table 1, entries 9–13). In addition, the highest yield was obtained when the molar ratio of **1a** to **2a** was 1:2 (Table 1, compare entry 9 with entries 14 and 15). The reaction of **1a** with **2a** in

the presence of 5 mol % nickel catalyst also afforded **3aa** in 69 % yield upon isolation (Table 1, entry 16).

Having determined the optimal reaction conditions, we next confirmed the stereochemistry of the cycloadduct by

Table 1: Optimization of reaction conditions.^[a]



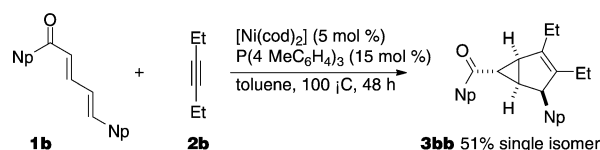
Entry	Ligand	[mol %]	<i>t</i> [h]	Yield [%] ^[b]
1	PPh_3	20	16	70 (57)
2	PCy_3	20	16	51
3	PCyPh_2	20	16	67
4	$\text{P}(\text{NMe}_2)_3$	20	16	48
5	PMePh_2	20	16	< 1
6	PPh_3	12	16	65
7	PPh_3	30	16	63
8	PPh_3	30	48	76 (64)
9	$\text{P}(4\text{-MeC}_6\text{H}_4)_3$	30	48	82 (71)
10	$\text{P}(3\text{-MeC}_6\text{H}_4)_3$	30	48	50
11	$\text{P}(2\text{-MeC}_6\text{H}_4)_3$	30	48	< 1
12	$\text{P}(4\text{-MeOC}_6\text{H}_4)_3$	30	48	30
13	$\text{P}(4\text{-FC}_6\text{H}_4)_3$	30	48	79 (67)
14	$\text{P}(4\text{-MeC}_6\text{H}_4)_3$	30	48	66 ^[c]
15	$\text{P}(4\text{-MeC}_6\text{H}_4)_3$	30	48	78 ^[d]
16	$\text{P}(4\text{-MeC}_6\text{H}_4)_3$	15	48	69 ^[e]

[a] Reaction conditions: $[\text{Ni}(\text{cod})_2]$ (10 mol %), ligand, **1a** (0.5 mmol), and 4-octyne (**2a**; 1.0 mmol, 2 equiv) in 2 mL of toluene at 100 °C.

[b] Yield as determined by NMR spectroscopy. Yield of the isolated products is given in parentheses. [c] **2a** (0.75 mmol, 1.5 equiv). [d] **2a** (1.25 mmol, 2.5 equiv). [e] $[\text{Ni}(\text{cod})_2]$ (5 mol %). Yield of the isolated product. cod = 1,5-cyclooctadiene, Cy = cyclohexyl.

performing the reaction of **1b** with **2b** (Scheme 1). The reaction provided **3bb** in 51 % yield as a single isomer. The molecular structure of **3bb** was confirmed using X-ray crystal structure analysis that showed that **3bb** has *cis-exo* stereochemistry at the ring fusion (Figure 1).

To demonstrate the synthetic utility of this transformation, we examined the reaction of 4-octyne **2a** with various



Scheme 1. Nickel-catalyzed reaction of **1b** with **2b**. Np = 2-naphthyl.

[*] H. Horie, Dr. T. Kurahashi, Prof. Dr. S. Matsubara
Department of Material Chemistry, Graduate School of Engineering
Kyoto University, Kyoto 615-8510 (Japan)
E-mail: tkuraha@orgxn.mbox.media.kyoto-u.ac.jp
matsubar@orgxn.mbox.media.kyoto-u.ac.jp

[**] This study was supported by Grants-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) (Japan). T.K. also acknowledges the support of the Asahi Glass Foundation, Kansai Research Foundation, and Toyota Physical and Chemical Research Institute.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201104286>.

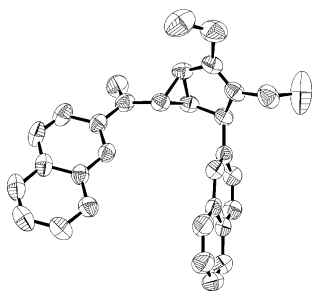
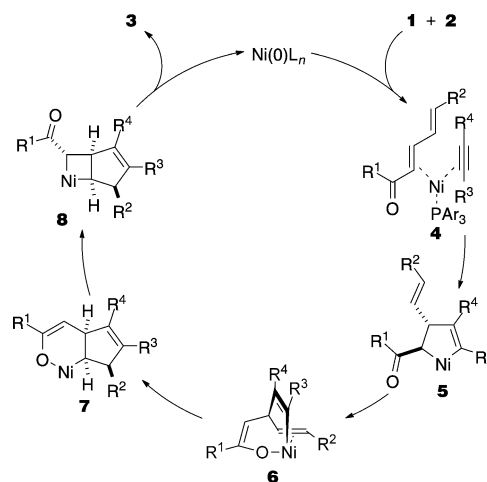


Figure 1. ORTEP drawing of cycloadduct **3bb**. Hydrogen atoms are omitted for clarity and thermal ellipsoids are shown at 50% probability.^[12]

$\alpha,\beta,\gamma,\delta$ -unsaturated carbonyl compounds **1** having different functional groups (Table 2). It was found that diarylsubstituted $\alpha,\beta,\gamma,\delta$ -unsaturated ketones **1** reacted with **2a** in the presence of a nickel catalyst (5 mol %) to stereoselectively provide the corresponding substituted bicyclo[3.1.0]hexenes **3**. Among the examined aryl substituents at R^1 , an aryl group with an electron-withdrawing group afforded a higher yield of cycloadduct **3** (Table 2, entry 1 versus entry 3). In the case of the reaction of **1e** with alkyne **2a**, preferential oligomerization of **2a** was observed (Table 2, entry 3). Meanwhile, among the examined aryl substituents at R^2 , an aryl group with an electron-donating group afforded a higher yield of **3** (Table 2, entries 7–10 versus entry 6). Competitive coordination of the

electron-deficient γ,δ -unsaturated carbon–carbon moiety of **1h** to Ni^0 may slow the initial formation of the five-membered nickelacycle **5** (Scheme 2). In addition, we found that heteroaryl substituents at both R^1 and R^2 were tolerated to yield bicyclo[3.1.0]hexenes **3** (Table 2, entries 4, 5, and 11). The reaction of 2-thienyl-substituted $\alpha,\beta,\gamma,\delta$ -unsaturated ketone **1m** with **2a** afforded **3ma** in 47% yield. The yield of **3ma** was improved to 66% by using 10 mol % of the nickel



Scheme 2. Plausible reaction mechanism.

Table 2: Stereoselective nickel-catalyzed reaction of $\alpha,\beta,\gamma,\delta$ -unsaturated ketones **1** with alkynes **2** to form bicyclo[3.1.0]hexenes **3**.

Entry	1	R^1	R^2	2	R^3	R^4	3	Yield [%] ^[a]
1	1c	4-NCC ₆ H ₄	Ph	2a	Pr	Pr	3ca	60
2	1d	2-MeC ₆ H ₄	Ph	2a	Pr	Pr	3da	49
3	1e	4-MeOC ₆ H ₄	Ph	2a	Pr	Pr	3ea	28
4	1f	2-furyl	Ph	2a	Pr	Pr	3fa	53
5	1g	3-pyridyl	Ph	2a	Pr	Pr	3ga	41
6	1h	Ph	4-CF ₃ C ₆ H ₄	2a	Pr	Pr	3ha	19
7	1i	Ph	4-MeOC ₆ H ₄	2a	Pr	Pr	3ia	74
8	1j	Ph	3-MeOC ₆ H ₄	2a	Pr	Pr	3ja	54
9	1k	Ph	2-MeOC ₆ H ₄	2a	Pr	Pr	3ka	66
10	1l	Ph	4-Me ₂ NC ₆ H ₄	2a	Pr	Pr	3la	67
11	1m	Ph	2-thienyl	2a	Pr	Pr	3ma	66 ^[b]
12	1n	Ph	Me	2a	Pr	Pr	3na	23
13	1a	Ph	Ph	2b	Et	Et	3ab	64
14	1a	Ph	Ph	2c	C ₅ H ₁₁	C ₅ H ₁₁	3ac	64
15	1a	Ph	Ph	2d	–(CH ₂) ₁₃ –		3ad	68
16	1a	Ph	Ph	2e	Me	iPr	3ae	53 ^[c]
							3ae/3ae', 7:2 ^[d]	

[a] Yield of the isolated product. [b] $[Ni(cod)_2]$ (10 mol %) and $P(4-MeC_6H_4)_3$ (30 mol %). [c] The combined yield of the two regioisomers is given. The reaction was carried out using $PCyPh_2$ (15 mol %), in place of $P(4-MeC_6H_4)_3$. [d] Ratio of the regioisomers.

catalyst (Table 2, entry 11). Although, diaryl-substituted $\alpha,\beta,\gamma,\delta$ -unsaturated ketones participated in the cycloaddition with alkynes to furnish bicycloadducts in good to moderate yields, the reaction of the alkyl-substituted $\alpha,\beta,\gamma,\delta$ -unsaturated ketone **1n** with **2a** resulted in the formation of **3na** in only 23% yield (Table 2, entry 12).^[8]

After demonstrating the scope of the reaction between $\alpha,\beta,\gamma,\delta$ -unsaturated carbonyl compounds **1** and alkynes **2** with regards to substrates **1**, we briefly examined the reaction scope with regards to alkynes **2**. Both acyclic and cyclic alkynes participated in the reaction with **1a** to stereoselectively afford bicyclo[3.1.0]hexenes **3** (Table 2, entries 13–15). Moderate regioselectivity of the reaction with an unsymmetrical alkyne **2e** was achieved by using sterically more-hindered ligands $PCyPh_2$, in place of $P(4-MeC_6H_4)_3$ (Table 2, entry 16). Terminal alkynes and aryl-substituted alkynes failed to participate in the reaction, a result that is pre-

sumably due to rapid oligomerization of the alkynes.

While the mechanism of this reaction has not been completely elucidated, based on our observed results we propose the following reaction mechanism to account for the formation of bicyclo[3.1.0]hexenes **3**, and the stereochemical outcome of the reaction (Scheme 2). The reaction is initiated by the coordination of $\alpha,\beta,\gamma,\delta$ -unsaturated ketone **1**, and alkyne **2** to Ni^0 . Oxidative cyclization leading to the formation of nickelacycle **5** is followed by ring expansion to form a seven-membered oxanickelacycle **6** by 1,3-migration.^[9] The subsequent intramolecular insertion of the olefin affords bicyclo intermediate **7**,^[10] which undergoes 1,3-migration and reductive elimination to give cycloadduct **3** and regenerate the starting Ni^0 catalyst. The *cis* stereochemistry of the ring fusion in bicyclo[3.1.0]hexene **3** may be ascribed to an intramolecular *syn* carbonickelation of the olefin in intermediate **6**. The configuration of substituent R^2 is also established by this process. The stereochemistry of the arylcarbonyl substituent on the cyclopropane ring may have resulted from the steric repulsion between this substituent and the cyclopentene ring.^[11] The regioselectivity of the reaction can be rationalized by looking at intermediate **4**, in which the direction of alkyne coordination minimizes the steric repulsion between the bulkier R^4 substituent and the ligand on the nickel. Thus, the addition of **1a** to **2e** using sterically more-hindered ligands, PCyPh_2 , affords **3ae** with a regioselectivity ratio of 7:2 (Table 2, entry 16), while the reaction of **1a** with **2e** using sterically less-hindered ligands, $\text{P}(4\text{-MeC}_6\text{H}_4)_3$, affords **3ae** with lower regioselectivity (57 %, **3ae/3ae** = 2:1).

In conclusion, we have developed an unprecedented reaction, which forms bicyclo[3.1.0]hexene by a nickel catalyzed intermolecular stereoselective reaction of $\alpha,\beta,\gamma,\delta$ -unsaturated carbonyl compounds with alkynes. Our study is the first to shed light on the unique reactivity of $\alpha,\beta,\gamma,\delta$ -unsaturated carbonyl compounds in the transition-metal-catalyzed cycloaddition of compounds containing unsaturated carbon-carbon bonds. Further efforts to expand the scope of the chemistry and applications for the synthesis of complex molecules are now in progress.

Experimental Section

Representative procedure: The reaction was performed in a 5 mL sealed vessel equipped with a Teflon-coated magnetic stirrer bar. $\alpha,\beta,\gamma,\delta$ -Unsaturated ketone **1a** (0.50 mmol) and alkyne **2a** (1.0 mmol) were added to a solution of bis(1,5-dicyclooctadiene)-nickel (7 mg, 0.025 mmol) and tri(4-methylphenyl)phosphine (23 mg, 0.075 mmol) in toluene (2 mL) in a dry box. The vessel was taken outside the dry box and heated at 100 °C for 48 h. The resulting reaction mixture was cooled to ambient temperature, filtered through a pad of silica gel and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (*n*-hexane/ethyl acetate = 40:1) to give the corresponding bicyclohexene **3aa**. Yellow powder, mp: 37–39 °C (AcOEt). ¹H NMR (500 MHz, CDCl_3): δ = 7.60 (d, *J* = 7.5 Hz, 2H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.26 (t, *J* = 7.5 Hz, 1H), 7.16 (d, *J* = 7.5 Hz, 2H), 4.43 (d, *J* = 7.0 Hz, 1H), 2.72 (dd, *J* = 7.0, 3.0 Hz, 1H), 2.53 (td, *J* = 7.0, 3.0 Hz, 1H), 2.36 (t, *J* = 3.0 Hz, 1H), 2.29–2.11 (m, 3H), 1.75 (m, 1H), 1.56 (m, 2H), 1.35 (m, 1H), 1.23 (m, 1H), 0.97 (t, *J* = 7.0 Hz, 3H), 0.82 ppm (t, *J* = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl_3): δ =

199.19, 142.50, 141.44, 137.97, 136.90, 132.34, 128.50, 128.37, 128.29, 127.80, 126.36, 54.81, 39.39, 36.45, 32.52, 30.52, 28.32, 21.61, 21.15, 14.14, 13.96 ppm; IR (KBr): $\tilde{\nu}$ = 2957, 1645, 1449, 1382, 1221, 704 cm^{-1} ; MS (EI): *m/z* (%): 344 ($[\text{M}]^+$, 83), 315 ($[\text{M-Et}]^+$, 47), 301 ($[\text{M-Pr}]^+$, 35), 239 ($[\text{M-PhCO}]^+$, 55), 105 ($[\text{PhCO}]^+$, 100); HRMS calcd for $\text{C}_{25}\text{H}_{28}\text{O}$: 344.2140 $[\text{M}]^+$; found: 344.2134.

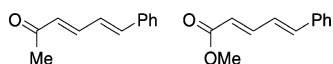
Received: June 21, 2011

Published online: August 19, 2011

Keywords: cycloaddition · homogeneous catalysis · isomerization · nickel · transition metals

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- [12] CCDC 837536 (**3bb**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.