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# Nickel-Catalyzed Cycloaddition of α,β,γ,δ-Unsaturated Ketones with Alkynes**

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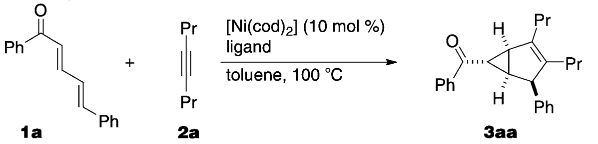
Transition-metal-catalyzed co-oligomerizations, involving a σ–π isomerization, of compounds containing unsaturated carbon–carbon bonds are very important synthetic methods for the atom-economical construction of structurally diverse molecular frameworks. The development of efficient catalysts for novel 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 α,β,γ,δ-unsaturated ketones, which contain a 1,3-diene fragment,[4,5] we explored the nickel-catalyzed cycloaddition of α,β,γ,δ-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 [Ni(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 P(4-MeC$_6$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 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).

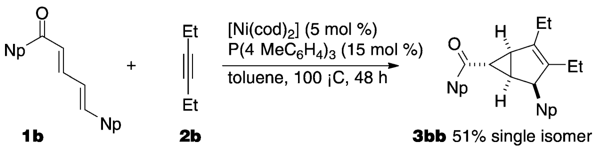
***Table 1:*** Optimization of reaction conditions.[a]



| Entry | Ligand | [mol %] | *t* [h] | Yield [%][b] |
|---|---|---|---|---|
| 1 | PPh$_3$ | 20 | 16 | 70 (57) |
| 2 | PCy$_3$ | 20 | 16 | 51 |
| 3 | PCyPh$_2$ | 20 | 16 | 67 |
| 4 | P(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 | P(4-MeC$_6$H$_4$)$_3$ | 30 | 48 | 82 (71) |
| 10 | P(3-MeC$_6$H$_4$)$_3$ | 30 | 48 | 50 |
| 11 | P(2-MeC$_6$H$_4$)$_3$ | 30 | 48 | $<1$ |
| 12 | P(4-MeOC$_6$H$_4$)$_3$ | 30 | 48 | 30 |
| 13 | P(4-FC$_6$H$_4$)$_3$ | 30 | 48 | 79 (67) |
| 14 | P(4-MeC$_6$H$_4$)$_3$ | 30 | 48 | 66[c] |
| 15 | P(4-MeC$_6$H$_4$)$_3$ | 30 | 48 | 78[d] |
| 16 | P(4-MeC$_6$H$_4$)$_3$ | 15 | 48 | 69[e] |

[a] Reaction conditions: [Ni(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] [Ni(cod)] (5 mol %). Yield of the isolated product. cod = 1,5-cyclooctadiene, Cy = cyclohexyl.

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.

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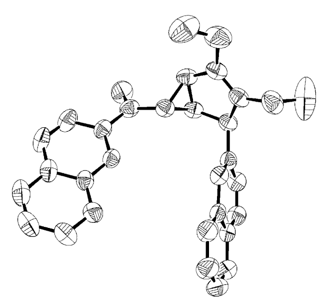
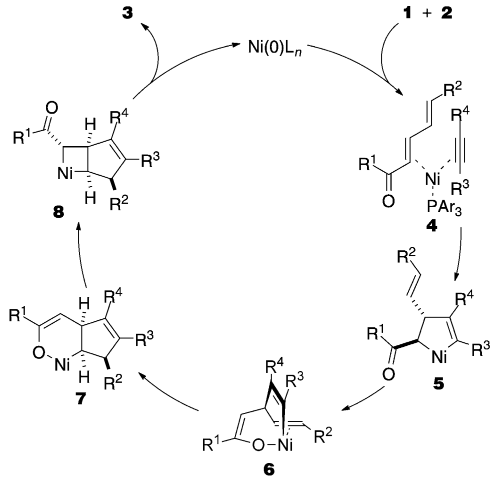


***Figure 1.*** ORTEP drawing of cycloadduct **3bb**. Hydrogen atoms are omitted for clarity and thermal ellipsoids are shown at 50% probability.[12]

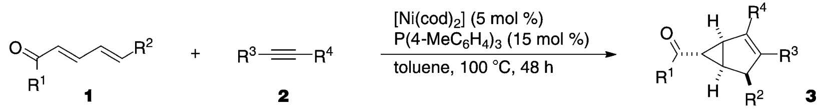
α,β,γ,δ-unsaturated carbonyl compounds **1** having different functional groups (Table 2). It was found that diarylsubstituted α,β,γ,δ-unsaturated ketones **1** reacted with **2a** in the presence of a nickel catalyst (5 mol%) to stereoselectively provide the corresponding substituted bicyclo[3.1.0]hexenes **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 α,β,γ,δ-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 catalyst (Table 2, entry 11). Although, diaryl-substituted α,β,γ,δ-unsaturated ketones participated in the cycloaddition with alkynes to furnish bicycloadducts in good to moderate yields, the reaction of the alkyl-substituted α,β,γ,δ-unsaturated ketone **1n** with **2a** resulted in the formation of **3na** in only 23% yield (Table 2, entry 12).[8]

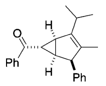
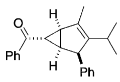
After demonstrating the scope of the reaction between α,β,γ,δ-unsaturated carbonyl compounds **1** and alkynes **2** with regards to substrates **1**, we briefly examined the reaction scope with regards to alkynes **2**. Both acyclic and cyclic alkynes participated in the reaction with **1a** to stereoselectively 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 $P(4\text{-}MeC_6H_4)_3$ (Table 2, entry 16). Terminal alkynes and aryl-substituted alkynes failed to participate in the reaction, a result that is pre-



***Scheme 2.*** Plausible reaction mechanism.

***Table 2:*** Stereoselective nickel-catalyzed reaction of α,β,γ,δ-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-$NCC_6H_4$ | Ph | **2a** | Pr | Pr | **3ca** | 60 |
| 2 | **1d** | 2-$MeC_6H_4$ | Ph | **2a** | Pr | Pr | **3da** | 49 |
| 3 | **1e** | 4-$MeOC_6H_4$ | 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-$CF_3C_6H_4$ | **2a** | Pr | Pr | **3ha** | 19 |
| 7 | **1i** | Ph | 4-$MeOC_6H_4$ | **2a** | Pr | Pr | **3ia** | 74 |
| 8 | **1j** | Ph | 3-$MeOC_6H_4$ | **2a** | Pr | Pr | **3ja** | 54 |
| 9 | **1k** | Ph | 2-$MeOC_6H_4$ | **2a** | Pr | Pr | **3ka** | 66 |
| 10 | **1l** | Ph | 4-$Me_2NC_6H_4$ | **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** | $C_5H_{11}$ | $C_5H_{11}$ | **3ac** | 64 |
| 15 | **1a** | Ph | Ph | **2d** | $-(CH_2)_{13}-$ | | **3ad** | 68 |
| 16 | **1a** | Ph | Ph | **2e** | Me | *i*Pr | **3ae**  | 53[c]<br>(**3ae**/**3ae′**, 7:2)[d] |
| | | | | | | | **3ae′**  | |

[a] Yield of the isolated product. [b] $[Ni(cod)_2]$ (10 mol%) and $P(4\text{-}MeC_6H_4)_3$ (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 $P(4\text{-}MeC_6H_4)_3$. [d] Ratio of the regioisomers.

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 α,β,γ,δ-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, $P(4\text{-}MeC_6H_4)_3$, 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 α,β,γ,δ-unsaturated carbonyl compounds with alkynes. Our study is the first to shed light on the unique reactivity of α,β,γ,δ-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. α,β,γ,δ-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, $CDCl_3$): $\delta = 7.60$ (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); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta =$ 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 ($[M]^+$, 83), 315 ($[M\text{-Et}]^+$, 47), 301 ($[M\text{-Pr}]^+$, 35), 239 ($[M\text{-PhCO}]^+$, 55), 105 ($[\text{PhCO}]^+$, 100); HRMS calcd for $C_{25}H_{28}O$: 344.2140 $[M]^+$; found: 344.2134.

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

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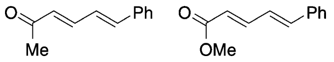

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[11] The inverse stereoisomer may result in repulsive steric interactions between the arylcarbonyl substituent and the cyclopentene ring; these interactions would cause difficulty in the 1,3-migration to form the corresponding stereoisomer of **8**.

[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.