# Chemo- and regioselective cyclotrimerization of monoynes catalyzed by a nickel(0) and zinc(II) phenoxide system†

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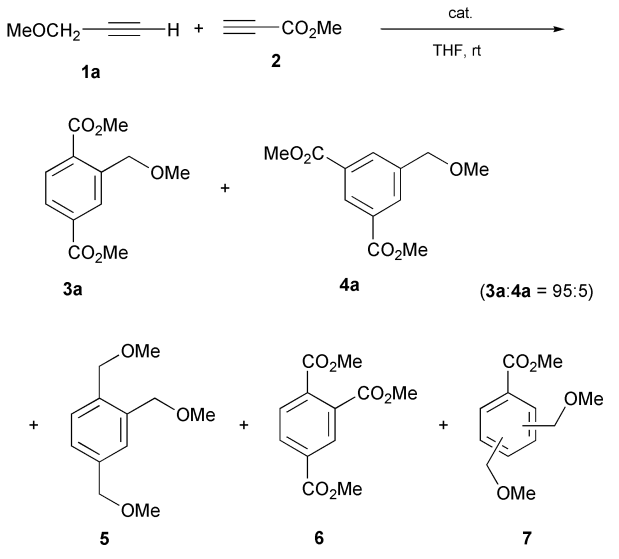
**A binary metal system of nickel(0) and zinc(II) phenoxide catalyzed the chemo- and regioselective cyclotrimerization of monoynes.**

There is considerable interest in organotransition-metal chemistry based on their wide application in organic syntheses. Over the past few years, we have studied the development of new organonickel chemistry.[1,2] In the course of this research, we found that cyclotrimerization (or [2 + 2 + 2] cycloaddition) of enones and alkynes occurred in the presence of both nickel(0) and some other metal species such as aluminum phenoxide or zinc halide.[3,4] Inspired by the synergistic effects of binary metal catalysts, we applied this concept to the cyclotrimerization of two or three different monoynes,[5] in which the control of chemo- and regioselectivity is a crucial problem. We report here the remarkable effects of a zinc(II) phenoxide co-catalyst in the nickel(0)-catalyzed cyclotrimerization of monoynes.[6]

We first investigated the reaction of methyl propargyl‡ ether (**1a**) with methyl propiolate (**2**) (Scheme 1). When a THF solution of **2** (2 eq.) was added dropwise with stirring over 5 min at rt to a THF solution of **1a** (1 eq.), Ni(acac)$_2$ (5 mol%), PPh$_3$ (10 mol%), Et$_2$Zn (50 mol%), and PhOH (80 mol%), a mixture of two regioisomeric cycloadducts **3a** and **4a**, which were formed by the chemoselective coupling of one molecule of **1a** and two molecules of **2**, was obtained in 78% yield (Table 1, run 1). The major isomer (95% selectivity) was determined to be **3a** by the spectral analyses. Other benzene derivatives such as **5**, **6**, and **7** were not obtained in this reaction. In contrast, when the reaction was carried out without both Et$_2$Zn and PhOH, chemoselectivity did not occur (runs 1 and 2 *vs.* run 3). While other metal species such as Et$_2$Zn itself, ZnCl$_2$, and aluminum phenoxides also assisted the nickel catalyst in the cycloaddition, a noticeable amount of **6** was detected by GC analysis (runs 5–8). The results indicate that the remarkable chemoselectivity is due to the effects of a zinc phenoxide prepared from Et$_2$Zn and PhOH *in situ*.[7,8]

We explored the scope of the chemo- and regioselective cyclotrimerization of various **1** with **2** in the presence of Ni(0)–PPh$_3$–Et$_2$Zn–PhOH (Scheme 2). In each reaction, competing self-trimerizations were suppressed. When **2** was added slowly over 60 min to the reaction medium involving hex-3-yne (**1c**),

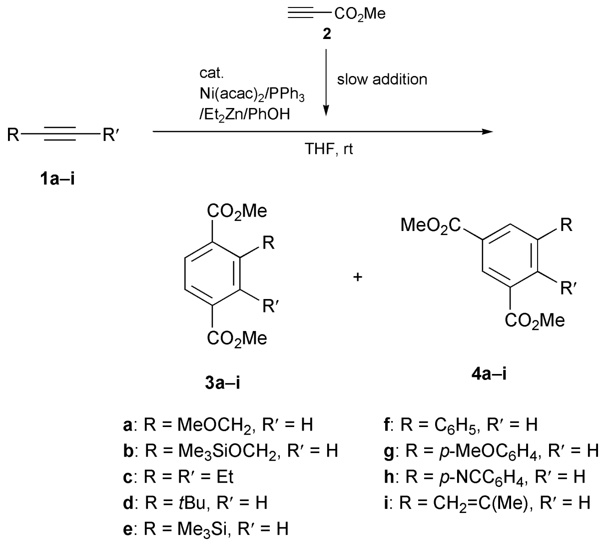


**Scheme 1**

**Table 1** Catalytic cycloaddition of **1a** and **2**[a]

| Run | Catalytic system | Yield[b] (%)<br>(**3a** + **4a**) | **5** | **6** | **7** |
|---|---|---|---|---|---|
| 1 | Ni(acac)$_2$–PPh$_3$–Et$_2$Zn–PhOH[c] | 81 (78) | 0 | 0 | 0 |
| 2 | Ni(cod)$_2$–PPh$_3$–Et$_2$Zn–PhOH[d] | (67) | 0 | 0 | 0 |
| 3 | Ni(cod)$_2$–PPh$_3$[e] | 10 | 19 | 19 | 11 |
| 4 | Ni(acac)$_2$–Et$_2$Zn–PhOH[f] | 0 | 0 | 0 | 0 |
| 5 | Ni(acac)$_2$–PPh$_3$–Et$_2$Zn[g] | 30 | 0 | 8 | 4 |
| 6 | Ni(cod)$_2$–PPh$_3$–Et$_2$Zn[h] | 29 | 0 | 13 | 5 |
| 7 | Ni(cod)$_2$–PPh$_3$–ZnCl$_2$[i] | 38 | 0 | 26 | 4 |
| 8 | Ni(acac)$_2$–PPh$_3$–Me$_3$Al–PhOH[j] | 21 | 0 | 56 | 4 |

[a] All reactions were carried out as follows: a THF solution of **2** (2 eq.) was added dropwise over 5 min at rt to a THF solution of **1a** (1 eq.) and catalysts. [b] GC yield. Isolated yield is in parentheses. The yield of **7** is estimated on the basis of those of **3**–**6**. [c] Ni(acac)$_2$–PPh$_3$–Et$_2$Zn–PhOH = 0.05:0.1:0.5:0.8. [d] Ni(cod)$_2$–PPh$_3$–Et$_2$Zn–PHOH = 0.05:0.1:0.4:0.8. [e] Ni(cod)$_2$–PPh$_3$ = 0.05:0.1. [f] Ni(acac)$_2$–Et$_2$Zn–PhOH = 0.05:0.5:0.8. [g] Ni(acac)$_2$–PPh$_3$–Et$_2$Zn = 0.05:0.1:0.5. [h] Ni(cod)$_2$–PPh$_3$–Et$_2$Zn = 0.05:0.1:0.4. [i] Ni(cod)$_2$–PPh$_3$–ZnCl$_2$ = 0.05:0.1:0.4. [j] Ni(acac)$_2$–PPh$_3$–Me$_3$Al–PhOH = 0.05:0.1:0.5:0.8.



**Scheme 2**

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† Electronic supplementary information (ESI) available: experimental and characterization data. See http://www.rsc.org/suppdata/cc/b0/b008882j/

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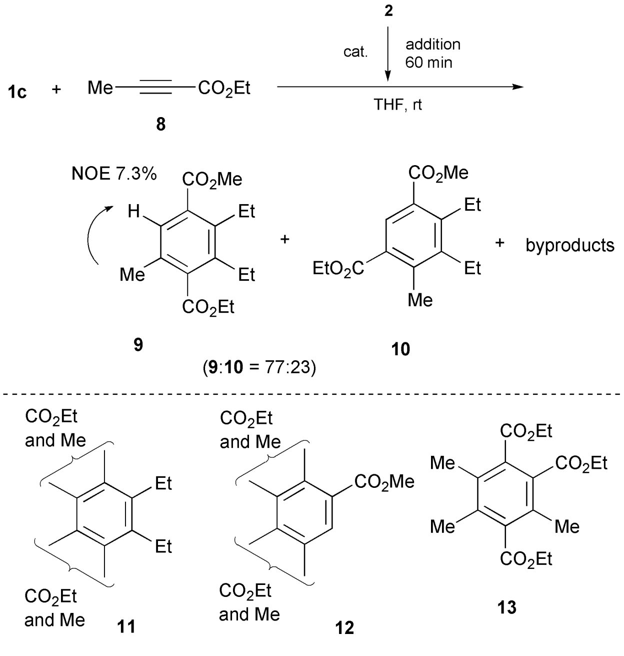
**Table 2** Cylocotrimerization of **1** and **2** in the presence of Ni(acac)$_2$–PPh$_3$–/Et$_2$Zn–PhOH[a]

| Entry | **1** | Add. time/min | Product(s) | Yield[b] (%) | Ratio[c] (**3**:**4**) |
|---|---|---|---|---|---|
| 1 | **1a** | 5 | **3a**, **4a** | 78 | 95:5 |
| 2 | **1b** | 5 | **3b**, **4b** | 60 | 95:5 |
| 3 | **1c** | 60 | **3c** | 41 | 100:0 |
| 4 | **1d** | 60 | **3d**, **4d** | 50 | 92:8 |
| 5 | **1e** | 20 | **3e**, **4e** | 64 | 90:10 |
| 6 | **1f** | 10 | **3f**, **4f** | 53 | 94:6 |
| 7 | **1g** | 20 | **3g**, **4g** | 55 | 93:7 |
| 8 | **1h** | 60 | **3h** | 49 | 100:0 |
| 9 | **1i** | 20 | **3i**, **4i** | 68 | 93:7 |

[a] All reactions were carried out as follows: a solution of **2** (2 mmol) in THF (2 mL) was added dropwise with stirring to a mixture of **1** (1 mmol), Ni(acac)$_2$ (0.05 mmol), PPh$_3$ (0.1 mmol), Et$_2$Zn (1.0 M in hexane, 0.5 mL), and PhOH (0.8 mmol) in THF (5 mL) at rt. [b] Isolated yield. [c] Determined by integration of the aryl protons of $^1$H NMR.

the cross-cyclotrimerization adduct **3c** was obtained as the sole product (Table 2, entry 3). *tert*-Butylacetylene (**1d**) and (trimethylsilyl)acetylene (**1e**) were also applied to the cyclotrimerization (entries 4 and 5). Biaryl compounds **3f–h** were synthesized from the reaction with the corresponding arylacetylenes **1f–h**, respectively (entries 6–8). The presence of an electron-withdrawing group on arylacetylene tended to increase the regioselectivity. A conjugated enyne **1i** reacted with **2** to give an α-methylstyrene derivative **3i** with an excellent regioselectivity (entry 9).

Interestingly, the cyclotrimerization of three different monoynes was also effectively promoted by the nickel(0) and zinc phenoxide system mentioned above. Thus, when **2** (1 eq.) was added dropwise over 60 min to a mixture of **1c** (1 eq.) and ethylbut-2-ynoate (**8**, 1 eq.) in the presence of the binary metal catalyst (Scheme 3), a mixture of three-component cycloadduct **9** and its regioisomer **10** was preferentially obtained along with small amounts of other benzene derivatives **3c**, **11**, and **12** (Table 3, run 1). On the other hand, in the reactions without zinc phenoxide, the desired **9** and **10** were obtained in lower yields (runs 2–4).



**Scheme 3**

The transition-metal-catalyzed cyclotrimerization of alkynes has been extensively studied by several research groups.[9] However, in contrast to intramolecular reactions,[10] a fully intermolecular reaction has not yet been established as a useful synthetic method. We have demonstrated that the binary metal system of nickel(0) and zinc(II) phenoxide effectively catalyzes the chemo- and regioselective cyclotrimerization of two or three different monoynes. While the detail is being investigated further in our laboratory, the present finding should help address a longstanding problem in the cyclotrimerization.

**Table 3** Cyclotrimerization of **1c**, **2**, and **8**[a]

| | | Yield[b] (%) | |
|---|---|---|---|
| Run | Catalytic system | (**9** + **10**) | Byproducts[c] |
| 1 | Ni(cod)$_2$–PPh$_3$–Et$_2$Zn–PhOH[d] | 45 (48) | **3c** (4) + **11** (1) + **12** (8) |
| 2 | Ni(cod)$_2$–PPh$_3$[e] | (< 3) | **8** (> 90% recovery) |
| 3 | Ni(cod)$_2$–PPh$_3$–Et$_2$Zn[f] | (13) | **11** + **12** (total 5) + other products |
| 4 | Ni(cod)$_2$–PPh$_3$–Me$_3$Al–PhOH[g] | 24 (27) | **3c** (5) + **6** (3) + **11** (2) + **12** (7) + **13** (13) |

[a] All reactions were carried out as follows: a THF solution of **2** (1 eq.) was added dropwise with stirring over 60 min at rt to a THF solution of **1c** (1 eq.), **8** (1 eq.), and catalysts. [b] Isolated yield. GC yield is in parentheses. [c] The yield of **12** (*m/z* = 308) is estimated on the basis of that of **11**. [d] Ni(cod)$_2$–PPh$_3$–Et$_2$Zn–PhOH = 0.05:0.1:0.5:0.8. [e] Ni(cod)$_2$–PPh$_3$ = 0.05:0.1. [f] Ni(acac)$_2$–PPh$_3$–Et$_2$Zn = 0.05:0.1:0.5. [g] Ni(cod)$_2$–PPh$_3$–Me$_3$Al–PhOH = 0.05:0.1:0.4:0.8.

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‡ The IUPAC name for propargyl is prop-2-ynyl.

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