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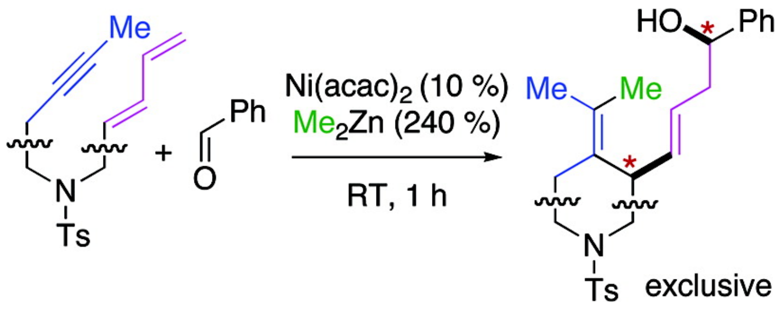

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ARTICLES

Nickel-Catalyzed Addition of Dimethylzinc to Aldehydes across Alkynes and 1,3-Butadiene: An Efficient Four-Component Connection Reaction

Masanari Kimura, Akihiro Ezoe, Masahiko Mori, and Yoshinao Tamaru*

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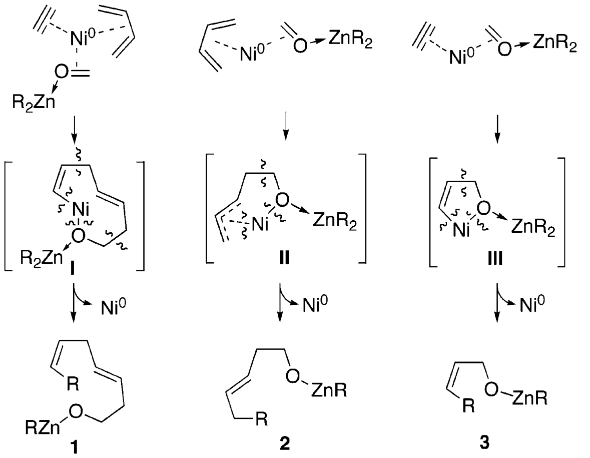
Abstract: In the presence of 10 mol % of Ni(acac)$_2$, four components comprising Me$_2$Zn, alkynes, 1,3-butadiene, and carbonyl compounds combine in this order in 1:1:1:1 ratio to furnish (3*E*,6*Z*)-octadien-1-ols **1** in good yields. Similarly, the coupling reaction of Me$_2$Zn, 1,ω-dienynes **5**, and carbonyls furnishes 1-alkylidene-2-(4′-hydroxy-(1′*E*)-alkenyl)cyclopentanes and −cyclohexanes **6** and their oxygen and nitrogen heterocycle derivatives in good yield and an excellent level of 1,5-diastereoselectivity with respect to the cycloalkane methine carbon and the OH-bearing carbon of the C2 side chain. The reaction is completed in most cases within 1 h at room temperature under nitrogen, tolerates an ester, a hydroxy, an allyl and propargyl ethers, an allylamino, and a pyridyl functionalities, and accommodates a variety of aromatic and aliphatic alkynes and carbonyls (aldehydes and ketones).

Introduction

Compared with many precedents for the nickel-catalyzed linear and cyclic oligomerization (and cycloisomerization) of alkynes and dienes,[1,2] only a few have been reported for the reactions involving nucleophilic and/or reductive addition of alkynes and dienes toward carbonyl compounds. This is in contrast to the early transition-metal catalyzed[3] or promoted reactions,[4] which have been proved to be very efficient for the reactions involving carbonyl components through the involvement of oxametallacycles.[1,3,4] This is mainly due to the high oxophilicity of early transition metals (e.g., D_o (Ti−O) = 159.5 kcal·mol^{-1}).[5] In this context, Montgomery's report[6] that appeared in 1997 is remarkable, which has demonstrated that an Ni^0 complex nicely catalyzes addition of organozincs to carbonyls incorporating alkynes as a mediator and furnishes stereochemically defined allyl alcohols **3** in good yields (eq c, Scheme 1, D_o (Ni−O)[5] = 89.2 kcal·mol^{-1}).[7] Two years later, we also reported that a similar type reaction takes place for 1,3-dienes and provides (*E*)-homoallyl alcohols **2** in excellent yields (eq b, Scheme 1).[8]

Scheme 1. Ni-Catalyzed Multicomponent Connection Reactions



(a) Present Work (b) Our previous work (c) Montgomery's work

The two reactions b and c shown in Scheme 1 proceed with similar ease under similar reaction conditions. Accordingly, we

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(1) (a) Tsuji, J. In *Transition Metal Reagents and Catalysts*; Wiley: Chichester, U.K., 2000. (b) Hegedus, L. S. Transition Metal Organometallics in Organic Synthesis. In *Comprehensive Organometallic Chemistry*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Tokyo, 1995; Vol. 12. (c) Shirakawa, E.; Hiyama, T. *J. Organomet. Chem*. **2002**, *653*, 114. (d) Dunach, E.; Franco, D.; Olivero, S. *Eur. J. Org. Chem*. **2003**, *9*, 1605.

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(3) (a) Crowe, W. E.; Rachita, M. J. *J. Am. Chem. Soc*. **1995**, *117*, 6787. (b) Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc*. **1996**, *118*, 3182 and references therein.

(4) (a) Szymoniak, J.; Moise, C. Synthesis and Reactivity of Allyltitanium Derivatives. In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley: Weinheim, Germany, 2002, pp 451−474. (b) Sato, F. *Yuki Gosei Kagaku Kyokaishi* **2002**, *60*, 891. (c) Fryatt, R.; Christie, S. D. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 447. (d) Taber, D. F.; Campbell, C. L.; Louey, J. P.; Wang, Y.; Zhang, W. *Curr. Org. Chem*. **2000**, *4*, 809.

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(7) Nickel-promoted or -catalyzed reductive coupling of dienes and carbonyls: (a) Sato, Y.; Takimoto, M.; Hayashi, K.; Katsumata, T.; Takagi, K.; Mori, M. *J. Am. Chem. Soc*. **1994**, *116*, 9771. (b) Kimura, M.; Ezoe, A.; Shibata, K.; Tamaru, Y. *J. Am. Chem. Soc*. **1998**, *120*, 4033. (c) Kimura, M.; Fujimatsu, H.; Ezoe, A.; Shibata, K.; Shimizu, M.; Matsumoto, S.; Tamaru, Y. *Angew. Chem*. **1999**, *111*, 410; *Angew. Chem., Int. Ed*. **1999**, *38*, 397. (d) Sato, Y.; Takimoto, M.; Mori, M. *J. Am. Chem. Soc*. **2000**, *122*, 1624. (e) Shibata, K.; Kimura, M.; Shimizu, M.; Tamaru, Y. *Org. Lett*. **2001**, *3*, 2181. (f) Loh, T. P.; Song, H. Y.; Zhou, Y. *Org. Lett*. **2002**, *4*, 2715. (g) Sawaki, R.; Saito, N.; Mori, M. *J. Org. Chem*. **2002**, *67*, 656 and references therein. For a review, see: (h) Ikeda, S. *Angew. Chem., Int. Ed*. **2003**, *42*, 5120.

(8) (a) Kimura, M.; Matsuo, S.; Shibata, K.; Tamaru, Y. *Angew. Chem., Int. Ed*. **1999**, *38*, 3386. (b) Kimura, M.; Shibata, K.; Koudahashi, Y.; Tamaru, Y. *Tetrahedron Lett*. **2000**, *41*, 6789. (c) Shibata, K.; Kimura, M.; Kojima, K.; Tanaka, S.; Tamaru, Y. *J. Organomet. Chem*. **2001**, *624*, 348.

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wondered what might take place if all the reactive components, Me$_2$Zn, an alkyne, 1,3-butadiene, and an aldehyde, were subjected to a nickel-catalyzed reaction (eq a, Scheme 1).

Apparently, in terms of entropy, the reaction forming **1**, incorporating the four different reactants, one molecule each, is at a disadvantage compared with the reactions giving **2** and **3**. The objective **1** might form among a large number of hetero- and/or homocoupling products[9] including **2** and **3**. In terms of enthalpy, however, the reaction leading to **1**, likely involving **I**, is expected to be favored over the reactions leading to **2** and **3**, which proceed through **II** and **III**, respectively, since for **I** unsaturation number of reactants changes by 3 (from 4 to 1), while for **II** and **III** they change by 2 (from 3 to 1 and from 2 to 0, respectively).

Results and Discussion

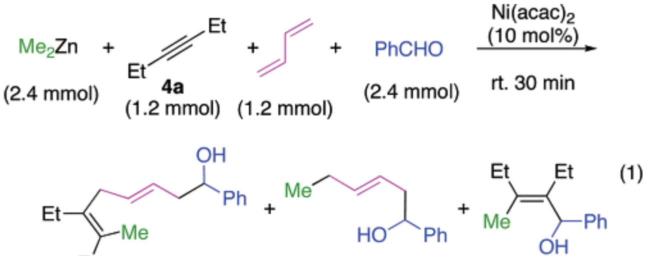
1. Ni^0-Catalyzed Intermolecular Four-Component Connection Reaction of Me$_2$Zn, Alkynes, 1,3-Butadiene, and Carbonyl Compounds. To our delight, without any modulation of our reaction conditions applied to the formation of **2**,[8] a mixture of Me$_2$Zn, 3-hexyne (**4a**), 1,3-butadiene, and benzaldehyde combined to one another in this order and selectively provided **1a** in 68% isolated yield (eq 1 and run 1, Table 1). The anticipated **2a** and **3a** were also isolated, but only in lower yields. The reaction proceeded smoothly at room temperature and was completed within 1 h.

Under similar conditions, other two alkynes of significant electronic difference, a conjugated alkyne **4b** (runs 3 and 4, Table 1) and an electron-deficient alkyne **4c** (runs 5 and 6), were examined and found to provide the corresponding four-component connection products **1b** and **1c**, respectively, with remarkably high selectivity. Fortunately, the reaction of these alkynes turned out to be more selective than that of **4a**; **2a** was obtained as a minor product in the lower yields, and no type **3** products were produced. These data clearly indicate that the reaction leading to **1** proceeds faster than that leading to **2** and the reaction rate leading to **3** is slowest.

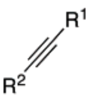
The reactions were examined under two conditions that only differ about the relative amounts of an alkyne and 1,3-butadiene to the amounts of other reactants: **conditions *a***: *an alkyne (1.2 mmol), 1,3-butadiene (1.2 mmol)*, an aldehyde (1 mmol), Me$_2$Zn (2.4 mmol), and Ni(acac)$_2$ (10 mol %); **conditions *b***: *an alkyne (4.0 mmol) 1,3-butadiene (4.0 mmol)*, an aldehyde (1 mmol), Me$_2$Zn (2.4 mmol), and Ni(acac)$_2$ (10 mol %). The results are shown pairwise all through Tables 1 and 2. At a glance of these tables, it becomes apparent that the conditions *b* using 4 equiv each of an alkyne and a diene give better yields than the conditions *a* with respect to the isolated yields of **1**, with only one exception of the reaction of **4c** (runs 5 and 6, Table 1).

The reaction shows a wide spectrum of compatibility with other aromatic (runs 7 and 8, Table 1) and aliphatic aldehydes

Scheme 2. Structure of Alkynes **4** Examined

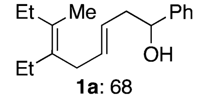
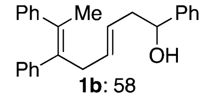
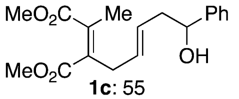
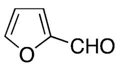
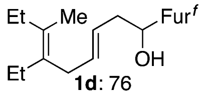
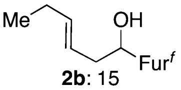
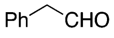
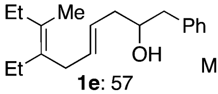
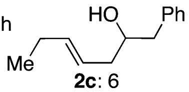
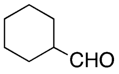
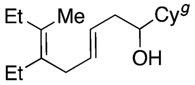
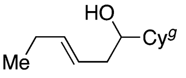
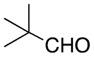
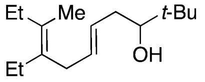
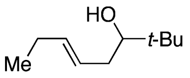
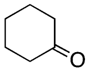
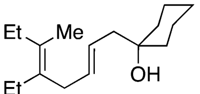
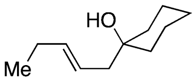


1a: 68% **2a**: 12% **3a**: 13%

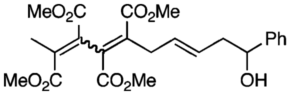


4a: R^1 = R^2 = Et
4b: R^1 = R^2 = Ph
4c: R^1 = R^2 = CO$_2$Me
4d: R^1 = Et, R^2 = Ph
4e: R^1 = Me, R^2 = SiMe$_3$
4f: R^1 = Me, R^2 = CH$_2$CH$_2$OH
4g: R^1 = Me, R^2 = CH$_2$CH$_2$O-2-Py

Table 1. Ni-Catalyzed Four-Component Connection Reaction of Me$_2$Zn, Symmetric Alkynes, Butadiene, and Carbonyl Compounds

run	alkyne	carbonyl	% isolated yield	
1[a]	**4a**	PhCHO	 **1a**: 68	**2a**: 12[d]
2[b]	**4a**	PhCHO	**1a**: 73	**2a**: 1[d]
3[a]	**4b**	PhCHO	 **1b**: 58	**2a**: 5
4[b]	**4b**	PhCHO	**1b**: 84	**2a**: 16
5[c,h]	**4c**	PhCHO	 **1c**: 55	**2a**: 5
6[b,h]	**4c**	PhCHO	**1c**: 43	**2a**: 0[e]
7[a]	**4a**		 **1d**: 76	 **2b**: 15
8[b]			**1d**: 83	**2b**: 10
9[a]	**4a**		 **1e**: 57	 **2c**: 6
10[b]			**1e**: 76	**2c**: 1
11[a]	**4a**		 **1f**: 64	 **2d**: 12
12[b]			**1f**: 82	**2d**: 9
13[a]	**4a**		 **1g**: 58	 **2e**: 20
14[b]			**1g**: 67	**2e**: 8
15[a,i]	**4a**		 **1h**: 20	 **2f**: 72
16[b,i]			**1h**: 51	**2f**: 0

[a] Reaction conditions: an alkyne (1.2 mmol), 1,3-butadiene (1.2 mmol), an aldehyde (1.0 mmol), Me$_2$Zn (2.4 mmol, 1 M hexane), and Ni(acac)$_2$ (0.1 mmol) in THF (5 mL) at room temperature. The reaction time was 30 min, unless otherwise noted. [b] Reaction conditions: an alkyne (4.0 mmol), 1,3-butadiene (4.0 mmol), an aldehyde (1.0 mmol), Me$_2$Zn (2.4 mmol, 1 M hexane), and Ni(acac)$_2$ (0.1 mmol) in THF (5 mL) at room temperature. The reaction time was 30 min, unless otherwise noted. [c] Except with alkyne (2.0 mmol) under the same conditions as in footnote a. [d] **3a** (13%) for run 1 and **3a** (6%) for run 2. [e] 6,7,8,9-Tetramethoxycarbonyl-1-phenyldeca-3,6,8-trien-1-ol (**3′**, 14%). [f] Fur = 2-fury. [g] Cy = cyclohexyl. [h] 24 h. [i] 17h.

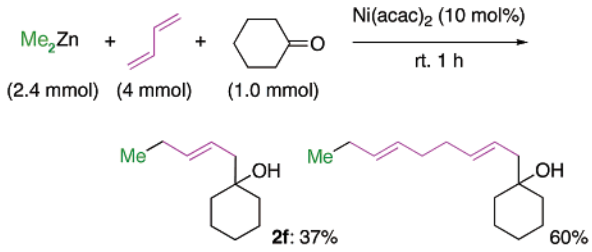


3′

(runs 9−14). Here again, no type **3** products were formed at all. It should be noted that among aldehydes, phenylacetaldehyde (runs 9 and 10) is notorious for its high tendency to undergo aldol and many other side reactions, yet it behaves as usual as other aliphatic aldehydes. It is also worth mentioning that, as having been reported by us,[8a] the nickel-catalyzed three-component connection reaction of Me_2Zn, 1,3-butadiene, and aldehydes (eq b, Scheme 1), especially with sterically demanding aldehydes, suffers from a competitive formation of 1:2:1 adducts. For the reaction with more sterically demanding ketones, the relative ratios of a 1:1:1 adduct to a 1:2:1 adduct are inversed. For example, the reaction with cyclohexanone gives rise to **2f** in 37% yield (a 1:1:1 product) together with a 1:2:1 adduct, 1-cyclohexyl-deca-3,7-diene-1-ol in 60% yield (eq 2).[10] In contrast to this, in the present reaction, no such a 1:2:1 adduct is formed at all (runs 15 and 16, Table 1). In this context, the selective formation of the 1:1:1 adducts **2d**−**f**, particularly **2f** (run 15), suggests that an alkyne has a strong tendency to prohibit 1:2:1 adduct formation, where an alkyne might occupy one of the coordination sites of a nickel metal of an intermediate, making coordination of a second molecule of 1,3-butadiene to a nickel atom improbable (vide infra, Mechanistic Consideration).[8a] The reaction giving rise to **2f**, rather than an object **1h**, as a major product (run 15, Table 1) may be regarded as a nice modification of the three-component connection reaction (eq 2), especially when a ketone is a reaction partner, where an alkyne **4** serves mostly as a dummy component to prevent the 1:2:1 adduct formation. The situation changes dramatically in the presence of large excesses of **4a** and butadiene (conditions *b*, run 16, Table 1), where no trace of **2f** is formed; instead, the objective **1h** is obtained in greatly improved yield. Similar trends are seen for the reactions of sterically demanding cyclohexanecarboxaldehyde (runs 11 and 12) and pivalaldehyde (runs 13 and 14). This may be a natural consequence for reactions where one of the reactants is unreactive, in this case an alkyne, where the use of the particular reagent in excess facilitates the reaction and improves the yield.

All the results shown in Table 1 combine to indicate that the reaction giving rise to **1** proceeds much faster than that leading to **2**, and the process leading to **3** is the slowest, although the relative rates slightly depend on the kinds of alkynes and carbonyls. It should be noted that the electron-deficient alkyne **4c** reacts exceptionally slowly and takes 24 h for completion of the reaction even under conditions *b*, where an unique byproduct, composed of Me_2Zn, **4c**, butadiene, and benzaldehyde in a ratio of 1:2:1:1, 6,7,8,9-tetramethoxycarbonyl-1-phenyldeca-3,6,8-trien-1-ol (**3′**, 14%), is detected.

Table 2 summarizes the results for the four-component connection reaction examined with unsymmetrical alkynes **4d**−**g** (Scheme 2). To our embarrassment, almost no regioselectivity was observed, despite a large steric and electronic bias between the alkyne substituents (runs 1−4).

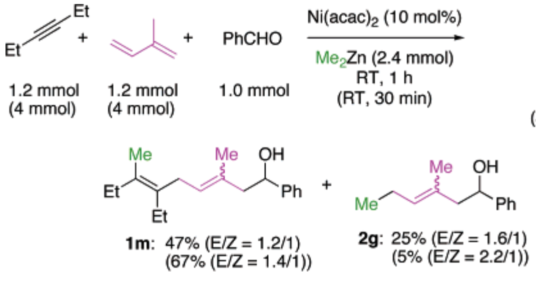


(2)

To influence the regioselectivity, alkynes **4f** and **4g** bearing substituents of coordination ability,[11] such as 2-hydroxyethyl and 2-(pyridin-2-yloxy)ethyl groups, were examined; however, no apparent changes in regioselectivity were observed (runs 5−8). The regioselectivity does not depend on reaction conditions *a* or *b*. The reactions under conditions *b* recorded ca. 10% increase in the yields.

These results are in contrast to high regioselectivity reported by Jamison[12] for the reductive coupling of alkynes and aldehydes promoted by a catalytic system, Ni−Et_3B, which shows a strong tendency to deliver an $SiMe_3$ group at the β-position and a phenyl group at the γ-position of the allyl alcohol products. Interestingly, however, the byproducts **3b** and **3c** (runs 3, 4, and 6, Table 2) were obtained as a single isomer; the regioselectivity being in accord with Jamison's observation.[12] These results suggest that the reactions leading to **2** and **3** proceed via transition states polar in nature, while the reaction leading to **1** proceeds through a less polar transition state where an alkyne participates (vide infra, Mechanistic Consideration).

Equation 3 shows the results of isoprene as a diene component (under conditions *a* and *b*, the latter being shown in parentheses). The expected four-component connection product **1m** was obtained as a major product together with the three-component connection product **2g** as a minor product. Although the regioselectivity and the chemical yield of **1m** are acceptable, the stereoselectivity is not, giving rise to almost a random mixture of (*E*)- and (*Z*)-isomers with respect to the double bond originating from isoprene. Reactions with other symmetric alkynes **4b** and **4c** showed almost the same results regarding the yields and the regio- and stereoselectivities of **1** and **2**. Accordingly, we did not pursue further the reaction with isoprene.



(3)

2. Ni^0-Catalyzed Intramolecular Four-Component Connection Reaction of Me_2Zn, 1,ω-Dienynes 5, and Carbonyl Compounds. The entropic disadvantage and the poor regioselectivity associated with the reaction of eqs 1 and 3 are expected to be settled by tethering the alkyne and the diene moieties by a chain of an appropriate length. In fact, 1,ω-dienyne **5** reacted with Me_2Zn and aldehydes (and ketones) in

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(9) Montgomery, J. *Science of Synthesis*; Trost, B. M., Lautens, M., Eds.; Thieme: Stuttgart, 2001; Vol. 1, pp 11−62.

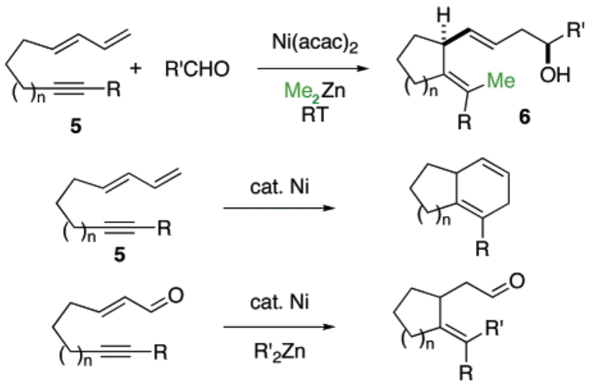
(10) Unpublished results.

(11) (a) Sole, D.; Cancho, Y.; Llebaria, A.; Moreto, J. M.; Delgado, A. *J. Am. Chem. Soc.* **1994**, *116*, 12133. (b) Stüdemann, T.; Ibrahim-Ouali, M.; Knochel, P. *Tetrahedron* **1998**, *54*, 1299. (c) Na, Y.; Chang, S. *Org. Lett.* **2000**, *2*, 1887.

(12) (a) Huang, W.-S.; Chan, J.; Jamison, T. F. *Org. Lett.* **2000**, *2*, 4221. (b) Colby, E. A.; Jamison, T. F. *J. Org. Chem.* **2003**, *68*, 156. (c) Miller, K. M.; Huang, W.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 3442.

an expected fashion and provided 1-alkylidene-2-(4′-hydroxy-(1′*E*)-alkenyl)cycloalkanes **6** in excellent yields (eq 4, Scheme 3).[13]

Scheme 3. Ni-Catalyzed Cyclization of 1,ω-Dienynes **5** and 1,ω-Alkyn-enals



(4)

(5)

(6)

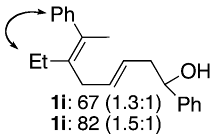
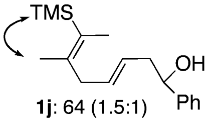
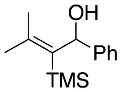
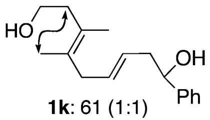
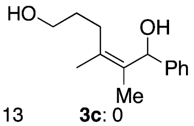
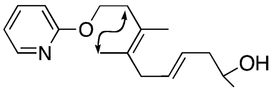
It may be worth noting that the present *four*-component connection reaction may be regarded as an extended version of the nickel-catalyzed reactions portrayed in eq 5, *two*-component connection reactions of alkynes and dienes,[14] and in eq 6, *three*-component connection reactions of alkylzincs, alkynes, and enones.[15] The structural similarity of the starting materials and the dramatic difference in the product types in eqs 4−6 may demonstrate the versatile reactivity of nickel catalysis.

Results for the reactions forming cyclopentane and cyclohexane rings are summarized in Tables 3 and 4, respectively, where an aldehyde is fixed as benzaldehyde and the tether groups of **5** are varied widely.

As is apparent from Tables 3 and 4, all 1,ω-dienynes, except **5k** and **5*l***, are so reactive that all reactions are completed within 1 h at room temperature, irrespective of the tether length and the kind of its constituents (sp^3-carbon, benzo-type sp^2-carbon, a nitrogen, and an oxygen atom). The exceptionally low reactivity that **5k** displays may be attributed to a large allylic strain[16] that the product **6k** experiences between the trimethylsilyl group and the phenyl group, being placed in closeproximity (run 5, Table 4). A similar retardation, but to a lesser extent, was observed for the reaction of **5*l*** (run 6, Table 4).

Terminal alkyne **5a** provided a cyclization product **6a** in modest yield (run 1, Table 3), whereas all the internal alkynes **5b**−***l*** gave products **6b**−***l*** in good to excellent yields. Especially rewarding here is that the 1,ω-dienynes tethered by an oxygen atom reacted as usual and furnished tetrahydrofuran (**6d**,**e**, runs 4 and 5, Table 3), tetrahydropyran (**6j**, run 4, Table 4), and chroman derivatives (**6k**,***l***, runs 5 and 6, Table 4) in reasonable yields. We were afraid the reaction of substrates **5d**,**e**,**j**−***l***, commonly sharing an allylic C−O bond, might become very complex because of the bond cleavage by an Ni^0 complex.[17] From a similar point of view, the selective formation of pyrrolidines (run 3, Table 3) and piperidines (runs 2 and 3, Table 4) is also remarkable. The piperidines **6h** and **6i** are regioisomeric to each other with respect to the position of the nitrogen atom. The reaction is also tolerant of a free hydroxy group (run 6, Table 3), though requiring an extra 1 equiv of Me_2Zn to quench the proton (footnote d, Table 3).

Table 2. Ni-Catalyzed Four-Component Connection Reaction of Me_2Zn, Unsymmetrical Alkynes **4d**−**g**, 1,3-Butadiene, and Benzaldehyde[a]

run	alkyne	% isolated yield[e]		
1[a]	**4d**	 **1i**: 67 (1.3:1)	**2a**: 8	
2[b]		**1i**: 82 (1.5:1)	**2a**: 10	
3[a]	**4e**	 **1j**: 64 (1.5:1)	**2a**: 12	 **3b**: 6
4[b]		**1j**: 77 (1.5:1)	**2a**: 13	**3b**: 7
5[c]	**4f**	 **1k**: 61 (1:1)	**2a**: 13	 **3c**: 0
6[d]		**1k**: 70 (1:1)	**2a**: 0	**3c**: 4
7[a]	**4g**	 **1l**: 91 (1.4:1)	**2a**: 8	
8[b]		**1l**: 94 (1.4:1)	**2a**: 0	

[a] See footnote a in Table 1. [b] See footnote b in Table 1. [c] Me_2Zn (3.6 mmol, 1 M hexane) under conditions in footnote a. [d] Me_2Zn (7.2 mmol, 1 M hexane) under conditions in footnote b. [e] Products **1** are mixtures of regioisomers with respect to the substituents pointed with double-headed arrows. The ratios are estimated by ^{13}C NMR and shown in parentheses.

Table 5 summarizes the conjugative addition reactions of Me_2Zn to a variety of carbonyl compounds across **5c** and **5f**, forming cyclopentane derivatives. In Table 6 are also summarized the reactions of **5m** and some typical aliphatic aldehydes and ketones forming methylenecyclohexane derivatives. No apparent differences between aliphatic aldehydes (Tables 5 and 6) and aromatic aldehydes (Tables 3 and 4) were observed in the reactivity and yields, demonstrating a wide applicability of the present nickel-catalyzed reaction. As usual, however, ketones provided the expected products, albeit in somewhat lower but still acceptable yields (runs 4−6, Table 5 and run 4, Table 6).

The most interesting aspect of the present intramolecular four-component connection reaction is the high remote 1,5-diastereoselectivity, giving rise to *syn*-**6** in favor of *anti*-**6**, in ratios higher than ca. 10:1.

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(13) Ezoe, A.; Kimura, M.; Inoue, T.; Mori, M.; Tamaru, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 2784.

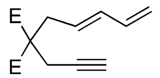
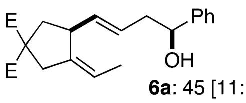
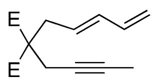
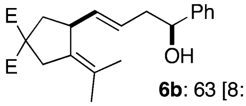
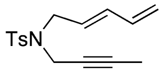
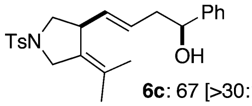
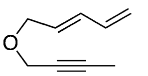
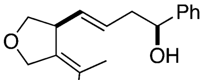
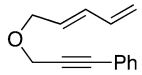
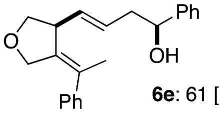
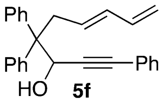
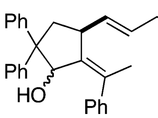
(14) (a) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813. (b) Tamao, K.; Kobayashi, K.; Ito, Y. *SYNLETT* **1992**, 539.

(15) (a) Montgomery, J. *Acc. Chem. Res.* **2000**, *33*, 467. (b) Ni, Y.; Amarasinghe, K. K. D.; Ksebati, B.; Montgomery, J. *Org. Lett.* **2003**, *5*, 3771. (c) Mahandru, G. M.; Skauge, A. R. L.; Chowdhury, S. K.; Amarasinghe, K. K. D.; Heeg, M. J.; Montgomery, J. *J. Am. Chem. Soc.* **2003**, *125*, 13481. (d) Mahandru, G. M.; Liu, G.; Montgomery, J. *J. Am. Chem. Soc.* **2004**, *126*, 3698.

(16) (a) Gascon-Lopez, M.; Motevalli, M.; Paloumbis, G.; Bladon, P.; Wyatt, P. B. *Tetrahedron* **2003**, *59*, 9349. (b) Sukopp, M.; Marinelli, L.; Heller, M.; Brandl, T.; Goodman, S. L.; Hoffmann, R. W.; Kessler, H. *Helv. Chim. Acta* **2002**, *85*, 4442. (c) Fernandez-Zertuche, M.; Robledo-Perez, R.; Meza-Avina, M. E.; Ordonez-Palacios, M. *Tetrahedron Lett.* **2002**, *43*, 3777. (d) Hitchcock, S. R.; Nora, G. P.; Casper, D. M.; Squire, M. D.; Maroules, C. D.; Ferrence, G. M.; Szczepura, L. F.; Standard, J. M. *Tetrahedron* **2001**, *57*, 9789.

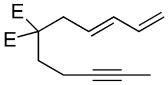
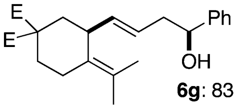
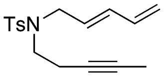
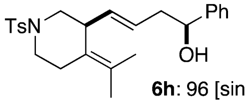
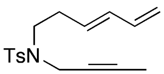
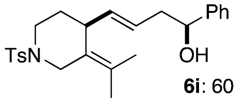
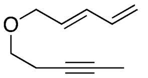
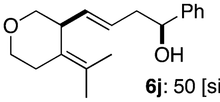
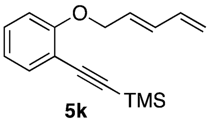
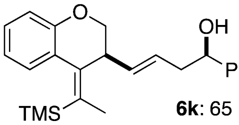
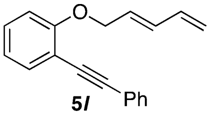
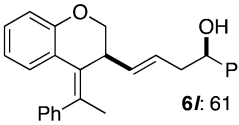
(17) (a) Consiglio, G.; Piccolo, O.; Roncetti, L. *Tetrahedron Lett.* **1986**, *42*, 2043. (b) Didiuk, M. T.; Morken, J. P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 7273. (c) Morken, J. P.; Didiuk, M. T.; Hoveyda, A. H. *Tetrahedron Lett.* **1996**, *37*, 3613. (d) Nomura, N.; RajanBabu, T. V. *Tetrahedron Lett.* **1997**, *38*, 1713. (e) Didiuk, M. T.; Morken, J. P.; Hoveyda, A. H. *Tetrahedron* **1998**, *54*, 1117. (f) Taniguchi, T.; Ogasawara, K. *Angew. Chem., Int. Ed.* **1998**, *37*, 1136.

Table 3. Ni-Catalyzed Conjugative Addition of Me_2Zn toward Benzaldehyde across 1,ω-Dienynes: Formation of Five-Membered Ring[a]

Run	1,ω-Dienyne **5**	Time (h)	Product **6**[b] (% Isolated) [ratio][c]
1	 **5a**	1	 **6a**: 45 [11:1]
2	 **5b**	1	 **6b**: 63 [8:1]
3	 **5c**	1	 **6c**: 67 [>30:1]
4	 **5d**	0.5	 **6d**: 70 [>30:1]
5	 **5e**	1	 **6e**: 61 [8:1]
6	 **5f**	3.5[d]	 **6f**: 77 [4:1][e]

[a] Reaction conditions: **5** (1 mmol), benzaldehyde (2 mmol), $Ni(acac)_2$ (10 mol %), Me_2Zn (2.4 mmol, 1 M hexane) in THF (5 mL) at room temperature under N_2. E stands for CO_2Et. [b] Yield refers to the isolated, spectroscopically homogeneous material. [c] Diastereomeric ratio determined by ^1H NMR (400 MHz). Only the major isomers are shown. [d] Me_2Zn (3.6 mmol) was applied. [e] Diastereomers arising from the configurational isomerism of the carbon bearing the OH group.

Table 4. Ni-Catalyzed Conjugative Addition of Me_2Zn toward Benzaldehyde across 1,ω-Dienynes **5**: Formation of Six-Membered Ring[a]

Run	1,ω-Dienyne **5**	Time (h)	Product **6**[b] (% Isolated) [ratio][c]
1	 **5g**	1	 **6g**: 83 [8:1]
2	 **5h**	1	 **6h**: 96 [single]
3	 **5i**	1	 **6i**: 60 [7:1]
4	 **5j**	1	 **6j**: 50 [single]
5	 **5k**	19	 **6k**: 65 [10:1]
6	 **5*l***	2	 **6*l***: 61 [10:1]

[a] For reaction conditions, see footnote a in Table 3. E, Ts, and TMS stand for CO_2Et, *p*-toluenesulfonyl, and trimethylsilyl groups, respectively. [b] Yield refers to the isolated, spectroscopically homogeneous material. [c] Diastereomeric ratio determined by ^1H NMR (400 MHz). Only the major isomers are shown.

As is illustrated above, the reaction is applicable to cyclization forming five- and six-membered rings; however, it has turned out that it is not applicable to the cyclization forming larger ring sizes. As is shown in Scheme 4, all the substrates structurally designed to facilitate the cyclization either by the Ingold−Thorpe effect[18] with geminal phenyl groups, the substrate **5n** aimed to form seven-membered ring, or by making an alkyne and a diene units close together with vicinal substitution on cyclohexane and cyclopentane rings, the substrates **5o** and **5p** aimed to form eight-membered rings, failed to provide the expected products. Under usual conditions, **5n**−**p** reacted smoothly and disappeared within 1−2 h; however, even under dilution conditions (5 times with THF), no discrete spots ascribable to expected products were observed on the TLC of the reaction mixtures, displaying continuous tailing bands. Only the product isolated at random by means of flash column chromatograph over silica gel, followed by the further purification by means of GPC of the fraction was **7**, a product of the type **3** (eq 2). Curiously, no products of the type **2** were detected, though in the intermolecular reaction the type **2** products were the major side products (Tables 1 and 2 and eq 2). There results indicate that the alkynyl and dienyl moieties of **5n**−**p** participate to each other in manners completely different from those of the tethered **5a**−**m** (Tables 3−6) and also from those where they are present free in space (Tables 1 and 2).

Finally, we examined Et_2Zn and Ph_2Zn in place of Me_2Zn. The reaction of **5b** and benzaldehyde with Et_2Zn is shown in eq 8, which turned out to provide rich information from a mechanistic point of view. The cyclization product **6m** was obtained as a minor product. Interestingly, no **6m′** was produced at all. This is in good accord with Montgomery's work,[9,15] where he states that even alkyl groups that bear β-hydrogens with respect to the nickel metal of an alkyl(vinyl)nickel(II) intermediate selectively undergo reductive elimination without accompanying β-H elimination (cf., Mechanistic Consideration). An alkynyl bishomoallyl alcohol **8** was obtained as a major product, which is a product expected from our previous work: the Ni-catalyzed, Et_2Zn-promoted reductive coupling of 1,3-dienes and carbonyls.[7b,c,e]

These results indicate that the reaction course hangs in a subtle balance depending on the kind of organozincs; Me_2Zn favors course a over b in Scheme 1 (**1** vs **2**), while Et_2Zn favors course b over a. In course b, Et_2Zn selectively delivers a hydrogen at the proximal allylic position of a η^3-allylnickel intermediate **II** (R = Et) and furnishes a bishomoallyl alcohol **8**, not a homoallyl alcohol **2** (R = H) (vide infra, a scheme shown in the green rectangle in Scheme 5).

The reaction with Ph_2Zn is shown in eq 9. Although the yield of **6n** was not optimized yet (a single experiment), Ph_2Zn turned

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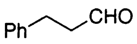
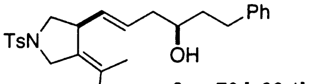
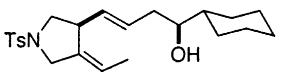
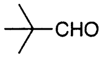
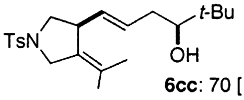
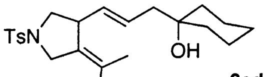
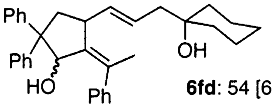
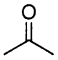
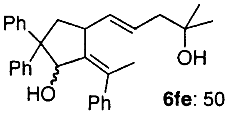
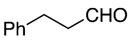
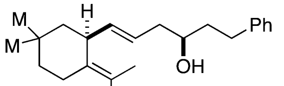
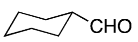
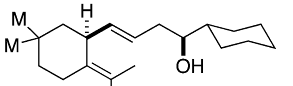
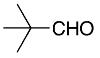
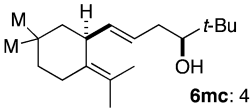
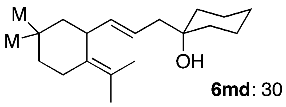
(18) (a) Tei, T.; Sato, Y.; Hagiya, K.; Tai, A.; Okuyama, T.; Sugimura, T. *J. Org. Chem.* **2002**, *67*, 6593. (b) Saettel, N. J.; Wiest, O. *J. Org. Chem.* **2003**, *68*, 4549. A review: (c) Cooper, N. J.; Knight, D. W. *Tetrahedron* **2004**, *60*, 243−269.

Table 5. Ni-Catalyzed Conjugative Addition of Me_2Zn toward Aliphatic Aldehydes and Ketones across **5c** and **5f** Forming Five-Membered Ring Compounds[a]

Run	Carbonyl	Time (h)	Product **6**[b] (% Isolated) [ratio][c]
1		1	 **6ca**: 70 [>30:1]
2		1	 **6cb**: 75 [>30:1]
3		2	 **6cc**: 70 [12:1]
4		1	 **6cd**: 40
5		22	 **6fd**: 54 [6:1][d]
6		22	 **6fe**: 50 [3:1][d]

[a] Reaction conditions: **5c** or **5f** (1 mmol), an aliphatic aldehyde or an aliphatic ketone (2 mmol), $Ni(acac)_2$ (10 mol %), Me_2Zn (2.4 mmol for **5c** and 3.6 mmol for **5f**, 1 M hexane) in THF (5 mL) at room temperature under N_2. [b] Yield refers to the isolated, spectroscopically homogeneous material. [c] Diastereomeric ratio determined by ^1H NMR (400 MHz). Only the major isomers are shown. [d] Diastereomer due to OH stereochemistry.

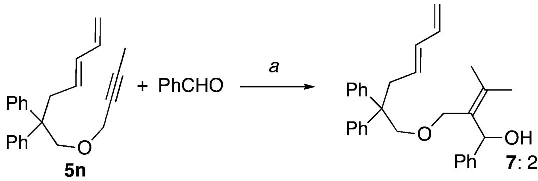
Table 6. Ni-Catalyzed Conjugative Addition of Me_2Zn toward Aliphatic Aldehydes and Ketones across 2-[(2*E*,4)-Pentadienyl]-2-(3-pentynyl)Malonic Acid Dimethyl Ester (**5m**) Forming Six-Membered Ring Compounds[a]

Run	Carbonyl	Time (h)	Product **6**[b] (% Isolated) [ratio][c]
1		1	 **6ma**: 61[8:1][d]
2		1	 **6mb**: 60 [single]
3		4	 **6mc**: 43 [single]
4		5	 **6md**: 30

[a] Reaction conditions: **5m** (1 mmol), an aliphatic aldehyde or an aliphatic ketone (2 mmol), $Ni(acac)_2$ (10 mol %), Me_2Zn (2.4 mmol, 1 M hexane) in THF (5 mL) at room temperature under N_2. [b] Yield refers to the isolated, spectroscopically homogeneous material. [c] Diastereomeric ratio determined by ^1H NMR (400 MHz). Only the major isomers are shown. [d] M stands for CO_2Me.

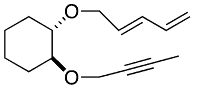
out to react in a way similar to Me_2Zn (run 4, Table 3). The two products, **6n** and **6e**, obtained in eq 9 and in run 5 of Table 3, respectively, are stereoisomeric to each other with respect to the tetrasubstituted exocyclic double bonds, which may further demonstrate the synthetic utility of the present nickel-catalyzed reaction.

Scheme 4. Attempts for Seven- and Eight-Membered Ring Formation

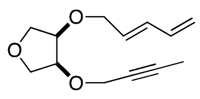


5n **7**: 28% (7)

[a]$Ni(acac)_2$ (10 mol%), Me_2Zn (2.4 mmol), RT, 2 h

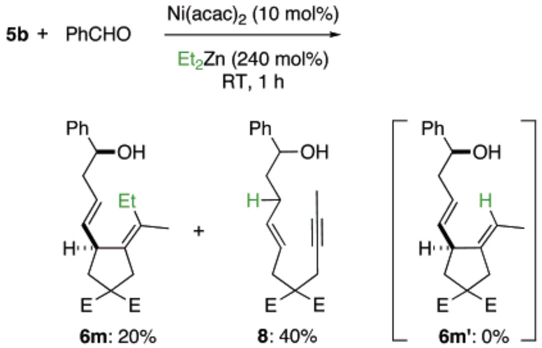


5o

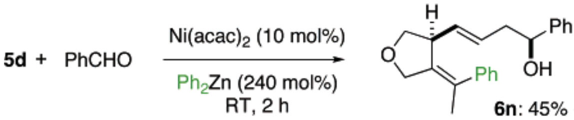


5p

Trialkylboranes work similarly,[7b,8b] but are somewhat inferior to dialkylzincs. For example, Me_3B (240 mol % in THF) reacted with **5d** and benzaldehyde to give **6d** (>30:1) in 30% isolated yield (cf., run 4, Table 3). Treatment of Et_3B (240 mol %) with **5b** and benzaldehyde yielded **6m** and **8** in 8 and 50% isolated yields, respectively (cf., eq 8).



6m: 20% **8**: 40% **6m'**: 0% (8)



(9) **6n**: 45% (8:1)

3. Structure Determination of Products. The structures of **6c**, **6h**, and **6i** were determined unequivocally by means of X-ray crystallographic analyses.[19] The structures of **1b**, **6a**, **6e**, and **6n** were determined on the basis of NOE experiments. It is clarified that the diastereomeric isomers **6** are due to 1,5-diasteremers and not due to the stereochemistry about the exocyclic nor the side chain double bonds. Detail is described in Supporting Information.

4. Mechanistic Consideration. In Scheme 5 are illustrated four pathways, paths *a*−*d*, that the present nickel-catalyzed four-component connection reaction might follow. In pathway *a*, a nickel^0 species undergoes oxidative cyclization across an aldehyde and a diene and forms a square-planar (*E*)-2-oxa-1-nickellacyclohept-5-ene **IV**, where the C5−C6−C7 unit forms

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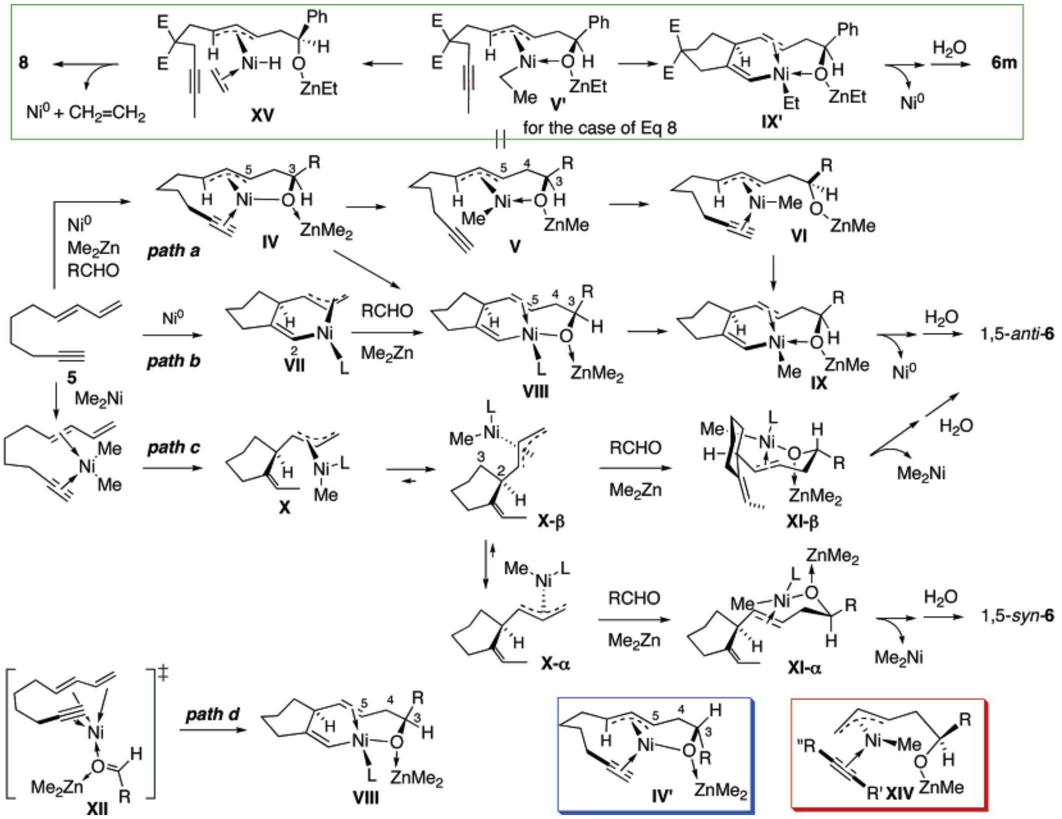
(19) Crystallographic data (excluding structure factors) for the structures reported in this article have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-178844 (**6h**), CCDC-201806 (a 3,5-dinitrobenzoic acid ester of **6c**), and CCDC-201807 (a 3,5-dinitrobenzoic acid ester of **6i**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, U.K. (fax: (+44)1223−336−033; e-mail: deposit@ccdc.cam.ac.uk).

Scheme 5. Plausible Pathways for the Ni-Catalyzed Addition of Me_2Zn toward an Aldehyde across 7,9-Dienyldecan-1-yne (a Model Compound)[a]



[a] The symbol E in the green rectangle stands for CO_2Et.

an η^3-allylnickel bond and an alkyne coordinates to the Ni^{II} center. During this event, the polarization of the aldehyde C═O by Me_2Zn coordination to the oxygen atom might help the $nickel^0$ species undergo oxidative addition upon the diene unit. At this stage, 1,5-*anti*-diastereoselection is established. An alternative intermediate **IV′** leading to 1,5-*syn*-**6**, shown in the blue rectangle in Scheme 5, is apparently unfavorable as compared with **IV**, since **IV′** suffers from eclipsing repulsion between the substituent R on the C3 and the ring C5 carbon. Migration of a methyl group from Zn^{II} to Ni^{II} forms an intermediate **V**, which would undergo rearrangement, accompanying alkyne coordination, to give rise to a square-planar intermediate **VI**, characterized by a methyl σ-bond, an η^3-allyl, and an η^2-alkyne. Cis-addition of the allylnickel moiety of **VI** upon the coordinating alkyne forms **IX**,[19] which is destined to undergo reductive elimination and liberate 1,5-*anti*-**6** and an active Ni^0 species.

In pathway *b*, at first, oxidative cyclization of an Ni^0 species upon an alkyne and diene takes place to give an allylvinylnickel(II) intermediate **VII**, an intermediate having been invoked frequently to rationalize the nickel-catalyzed [4 + 2]cycloaddition reactions (cf., eq 5).[13] However, in the presence of an aldehyde, the intermediate **VII** might have an opportunity to undergo nucleophilic addition to the aldehyde to furnish an oxanickellacycle **VIII**, during which 1,5-*anti*-selection results, placing the substituent of the aldehyde anti with respect to the C4−C5 bond. Migration of a methyl group from Zn^{II} to Ni^{II} furnishes an intermediate **IX**, being the same as that derived along pathway *a*. Pathway *a* might also merge pathway *b* through isomerization of **IV** to **VIII** via a mechanism similar to the isomerization of **VI** to **IX**.[20]

A third pathway, path *c*, starts with coordination of Me_2Ni upon an alkyne (η^2) and an internal double bond (η^2) of a diene. A Me_2Ni species may be formed by transmetalation between $Ni(acac)_2$ and Me_2Zn. Addition of a methyl group upon the alkyne and bond formation between the internal termini of the alkyne and the diene might generate a square-planar complex **X**, which is apparently highly sterically congested and would readily isomerize to **X-*β*** via rotation around the single bond connecting the cyclohexane ring and further to **X-α** via an $\eta^3-\eta^1-\eta^3$ isomerization sequence. As is apparently seen from the molecular models, steric repulsion becomes more substantial as going from **X-*β*** to **XI-*β*** as well as from **X-α** to **XI-α**. Hence, this route seems unlikely.

The fourth route, path *d*, proceeds through a transition state **XII**, where all the reactants form a tetrahedron around an Ni^0, and they function in such a way as the $nickel^0$ metal as a two-electron donor, the alkyne as a 2π component, the diene as a 4π component, and the aldehyde as a two-electron acceptor, totally comprising a cyclic 10-electron quasi-aromatic system.

The formation of **8** as a major product by the reaction with Et_2Zn (eq 8) seems to exclude an intermediacy of the common intermediate **VIII,** involved in pathways *b* and *d* as well as in a fork of pathway *a*. Instead, as is shown in the green rectangle of Scheme 5, the results of eq 8 suggest that an intermediate **V′** (Et−Ni in place of Me−Ni of **V**) is responsible for generation of **6m** and **8.** The ethylnickel(II) intermediate **V′**, in addition to being capable of giving rise to **6m**, would undergo *β*-H

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(20) (a) Llebaria, A.; Camps, F.; Moreto, J. M. *Tetrahedron* **1993**, *49*, 1283. (b) Cui, D.-M.; Tsuzuki, T.; Miyake, K.; Ikeda, S.; Sato, Y. *Tetrahedron* **1998**, *54*, 1063. (c) Garcia-Gomez, G.; Moreto, J. M. *J. Am. Chem. Soc.* **1999**, *121*, 878.

elimination and reductive elimination delivering a hydrogen to the allylic terminus proximal to the OH-bearing carbon and finally liberates a mixture of **8**, an Ni^0 species, and ethylene.

The lack of regioselectivity encountered in the intermolecular reactions of unsymmetrical alkynes (Table 2) might be rationalized on the basis of the structure of an intermediate **XIV**, shown in the red rectangle of Scheme 5 (an equivalent to **VI** for an intramolecular reaction). The central nickel^{II} of **XIV** is coordinatively saturated and located in the middle between an allylic terminal CH$_2$ group and a methyl group of a similar steric size; hence, an access of unsymmetric alkynes to the Ni^{II} atom is expected to be free from any restrictions imposed by steric, electronic, and coordination effects. On the other hand, large steric and coordination effects are expected, if an intermediate such as **VII** were involved (path *b*), where the alkyne carbon bearing bulky substituents as well as the substituents of coordination ability would monopolize the C2 position, since the position is free from strain and located nicely for the coordinating groups to interact with the Ni^{II} metal as L.

An intervention of **XIV** might also be supported by the results in runs 11−16, Table 1. The alkyne in **XIV** might effectively prevent another butadiene molecule from approaching the Ni^{II} and, hence, prohibit a 1:2:1 adduct formation of Me$_2$Zn, butadiene, and a bulky carbonyl (cf., eq 2).[8a]

To detect intermediates, we examined the reaction of **5b** in the absence of an aldehyde under catalytic (conditions *a*) and stoichiometric conditions using 1 equiv of Ni(cod)$_2$. However, the reactions proceeded slowly, taking almost 2−3 h for complete disappearance of **5b**. In all cases, the reaction mixtures became very dirty, showing many tailing spots on TLC. No fractions separated at random by means of flash column chromatography showed characteristic absorptions in the ^{1}H NMR spectra ascribable to compounds expected from the intermediates in Scheme 5 (including a [4 + 2]cycloaddition product). These results indicate that a carbonyl compound is essential to selectively promote the facile connection reaction of R$_2$Zn, an alkyne, and a diene.

After all, pathway *a* seems to be the most plausible, which accounts for all the observations, regardless of inter- and intramolecular four-component connection reactions: the high yield formation of **1**, with no regioselectively for unsymmetric alkynes, the 1,5-diastereoselective formation of **6**, the selective formation of **2** (1:1:1 adducts and not 1:2:1 adducts of Me$_2$Zn, butadiene, and carbonyls). The mechanism is especially backed by the fact that the reaction in eq 8 gives rise to a mixture of **6m** and **8**.

Typical Experimental Procedure

Ni-Catalyzed Four-Component Connection Reaction of Me$_2$Zn, 3-Hexyne, 1,3-Butadiene, and 2-Furaldehyde (run 7, Table 1). Into a flask containing Ni(acac)$_2$ (25.7 mg, 0.1 mmol) purged with N$_2$ were successively added THF (5 mL), 3-hexyne (98.6 mg, 1.2 mmol), 1,3-butadiene (0.11 mL, 1.2 mmol), 2-furaldehyde (96.1 mg, 1.0 mmol), and dimethylzinc (2.4 mL, 1 M in hexane) via syringe at room temperature. The homogeneous solution was stirred at room temperature for 30 min under N$_2$ and then quenched by adding 2 M HCl (25 mL). The mixture was extracted twice with ethyl acetate, and the combined extracts were washed with saturated NaHCO$_3$ and with brine, dried (MgSO$_4$), and concentrated in vacuo. The residue was purified by flash column chromatography over silica gel (hexane/ethyl acetate = 16:1, v/v) to give **1d** in 76% yield (189 mg) and **2b** in 15% yield (25 mg). R_f (**1d**) = 0.46, R_f (**2b**) = 0.39 (hexane/ethyl acetate = 4:1, v/v). The structure of **2b** was confirmed by comparison of the spectral data (IR, ^{1}H NMR) with those of authentic sample.[8a]

(3*E*,6*E*)-6-Ethyl-1-(2-furyl)-7-methyl-3,6-nonadien-1-ol (1d). IR (neat) 3361 (s), 2963 (s), 1439 (m), 1373 (m), 1149 (m), 1010 (s), 968 (m), 734 (s) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.92 (t, J = 7.7 Hz, 3 H), 0.95 (t, J = 7.7 Hz, 3 H), 1.60 (s, 3 H), 1.98 (q, J = 7.7 Hz, 2 H), 2.02 (q, J = 7.7 Hz, 2 H), 2.56 (m, 2 H), 2.72 (d, J = 6.2 Hz, 2 H), 4.68 (t, J = 6.2 Hz, 1 H), 5.36 (dt, J = 15.4, 7.1 Hz, 1 H), 5.52 (dt, J = 15.4, 6.2 Hz, 1 H), 6.22 (br d, J = 3.3 Hz, 1 H), 6.31 (dd, J = 1.8, 3.3 Hz, 1 H), 7.36 (br d, J = 1.8 Hz, 1 H); HRMS calcd for C$_{16}$H$_{24}$O$_2$: 248.1776, found *m/z* (relative intensity) 249 (M$^+$ + 1, 7), 248.1777 (M$^+$, 41), 230 (18), 152 (100), 136 (22).

Ni-Catalyzed Reaction of Me$_2$Zn, 1,ω-Dienyne 5h and Benzaldehyde (run 2, Table 4). To a homogeneous solution of Ni(acac)$_2$ (25.6 mg, 0.1 mmol) and **5h** (303 mg, 1 mmol) in dry THF (5 mL) were successively added benzaldehyde (212 mg, 2.0 mmol) and dimethylzinc (2.4 mL, 1 M in hexane). The mixture was stirred at room temperature for 1 h under N$_2$ and then poured into ice-cold water. After addition of 2M HCl (5 mL), the mixture was extracted twice with ethyl acetate. The combined organic extracts were washed with saturated NaHCO$_3$ and with brine, dried (MgSO$_4$), and concentrated in vacuo. The residue was purified by flash column chromatography over silica gel (hexane/ethyl acetate = 12:1, v/v) to give **6h** in 96% yield (408 mg). *Rf* (**6h**) = 0.20 (hexane/ethyl acetate = 4:1, v/v).

(3*S,4′*S**)-4-Isopropylidene-3-[4-hydroxy-4-phenyl-(1*E*)-butenyl]-*N*-(*p*-toluenesulfonyl)piperidine (6h).** mp 92.0−93.0 °C (hexane−dichloromethane); IR (KBr disk) 3460 (m), 1340 (s), 1169 (s), 1103 (m), 932 (m) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.61 (s, 6 H), 2.08−2.24 (m, 2 H), 2.32 (dd, J = 3.7, 11.4 Hz, 1 H), 2.40 (s, 3 H), 2.43−2.51 (m, 3 H), 3.37 (m, 1 H), 3.76 (m, 1 H), 3.78 (dm, J = 11.4 Hz, 1 H), 4.73 (br dd, J = 5.5, 7.0 Hz, 1 H), 5.50 (ddt, J = 1.5, 15.6, 7.1 Hz, 1 H), 5.67 (br dd, J = 5.7, 15.6 Hz, 1 H), 7.24−7.36 (m, 5 H), 7.30 (d, J = 8.2 Hz, 2 H), 7.62 (d, J = 8.2 Hz, 2 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 19.9, 20.1, 21.5, 25.4, 39.8, 42.7, 47.1, 51.1, 73.7, 125.9, 126.8, 127.2, 127.4, 127.7, 128.4, 129.6, 133.4, 134.0, 143.3, 144.1; HRMS calcd for C$_{25}$H$_{31}$O$_3$NS: 425.2025. Found *m/z* (relative intensity): 425.2042 (M$^+$, 1), 407 (2), 319 (100), 278 (17).

Conclusion

We have demonstrated that Ni(acac)$_2$ can be nicely utilized as a catalyst for the four-component connection reaction of Me$_2$Zn, alkynes, 1,3-butadiene, and carbonyl compounds in this order in 1:1:1:1 ratio to furnish (3*E*,6*Z*)-octadien-1-ols **1** with high stereoselectivity and in excellent yields. The same conditions are applicable to the coupling reaction of Me$_2$Zn, 1,ω-dienynes **5**, and carbonyls, furnishing 1-alkylidene-2-(4′-hydroxy-(1′*E*)-alkenyl)cyclopentanes and −cyclohexanes **6** and their oxygen and nitrogen heterocycles with an excellent level of 1,5-diastereoselectivity. The reaction proceeds smoothly at room temperature, tolerates an ester, a hydroxy, an allyl ether, a propargyl ether, an allylamino, and pyridyl functionalities, andaccommodates a variety of aromatic and aliphatic alkynes and carbonyls (aromatic and aliphatic aldehydes and ketones).[21] The reaction constitutes one of the few Ni-catalyzed nucleophilic addition reactions of alkynes and dienes toward carbonyl compounds.

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(21) The present catalytic system seems not to be applicable to thioether compounds, e.g., phenyl 1-propynyl sulfide and 2-(2-butynyl)-2-(2,4-pentadienyl)-1,3-dithiane. Under usual conditions, the reactions of these sulfides proceeded slowly (at room temperature for 3−12 h) and provided intractable mixtures of products. The reaction of bis(trimethylsilylmethyl)-zinc with **5j** and benzaldehyde was completed within 30 min; however, a complex mixture of products resulted (7 to 8 spots on TLC).

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Supporting Information Available: Experimental procedures and characterization data and ^{1}H NMR spectra for all new compounds **1**, **3**−**8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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