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[18] Complexes screened for activity included $Na[Co(CO)_4]$, $[Ph_4P][Co(CO)_4]$, $[nBu_4N][Co(CO)_4]$, and $[Cp_2Co][Co(CO)_4]$.
[19] During the screening phase, $Na[Co(CO)_4]$ (2 mol%, 16 h, 80 °C, 6900 kPa (1000 psi) CO, triglyme) reacted with propylene oxide to give a mixture of products, yielding mostly acetone (6%) and poly(β-hydroxybutyrate) (40%).
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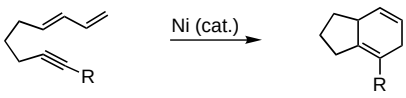
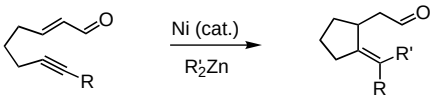
Remarkably High 1,5-Diastereoselectivity in a Nickel-Catalyzed Conjugate Addition of Me_2Zn and Carbonyl Compounds to 1,ω-Dienynes with Through-Space Coupling**

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

Carbon – carbon-bond formation is the most important and fundamental process in organic synthesis. In particular, the coupling reaction of unsaturated C–C bonds mediated by low-valent transition metals is a rapidly growing field and is now an indispensable strategy in synthetic chemistry.[1] Since the pioneering work of Wilke and co-workers,[2] nickel complexes have been widely utilized as efficient catalysts for C–C-bond formations.[3] Intramolecular variants such as the [4+2] cycloaddition reaction of 1,ω-dienynes [Eq. (1)],[4] cyclization of 1,ω-bis(enones),[5] ω-dienyl aldehydes,[6] and ω-alkynyl enones [Eq. (2)][7] are all useful methods for the synthesis of rather complex cyclic molecules of physiological interest.[8]



(1)



(2)

We report herein the four-component reaction of dimethylzinc, carbonyl compounds (aldehydes, ketones), and dienes and alkynes of 1,ω-dienylalkynes **1** in the presence of a catalytic amount of $[Ni(acac)_2]$ (acac = acetylacetonato) at room temperature to provide alkylidene cyclopentanes **2a**,**b** ($X = C(CO_2Et)_2$) and their heterocyclic analogues **2c**–**e** (X = O, NTs) in good yields and with excellent stereoselectivity (Table 1). This four-component reaction may be regarded as an extended version of the reactions portrayed in Equation (1) (a two-component coupling of a diene and an alkyne) and in Equation (2) (a three-component coupling of organozinc, alkyne, and enone).

The scope of the present reaction was examined with various 1,ω-dienynes **1a**–**e** (1.0 mmol) in the presence of a catalytic amount of $[Ni(acac)_2]$ (0.1 mmol), an aldehyde or ketone (2.0 mmol), and dimethylzinc (2.4 mmol) in dry THF at room temperature under nitrogen. All the 1,ω-dienynes **1a**–**e** were so reactive that almost all the reactions were complete within 1 h at room temperature, irrespective of R^1 and X of **1** and of the carbonyl compounds (Table 1). The conjugate addition of $[Me_2Zn]$ and of the carbonyl compound to 1,ω-dienynes **1** occurs at the terminal positions of the alkyne and the diene moieties, respectively; the through-space interactions of the alkyne and diene groups ensure C–C coupling at the internal positions. Terminal alkyne **1a** provided **2a** in moderate yield (Table 1, entry 1), whereas internal alkynes **1b**–**e** general gave more satisfactory results (Table 1, entries 2 – 11). Especially rewarding here is that the 1,ω-dienynes tethered by a nitrogen (**1c**) or an oxygen (**1d**,**e**) reacted with similar ease and furnished pyrrolidine and tetrahydrofuran derivatives, respectively, in reasonable yields. Bulky substituents around the carbonyl group either retard the reaction (Table 1, entry 10) or cause a decrease in yield (Table 1, entry 11). The reaction displayed a remarkably high level of stereoselectivity (> 97%, in most cases) between the cycloalkane methine and the OH-bearing carbon centers as well as excellent stereoselectivity (100%) with respect to the exocyclic tri- and tetrasubstituted double bonds.[9]

The structures of **2** were tentatively assigned by analogy with the structure of piperidine derivative **4**, which was

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Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

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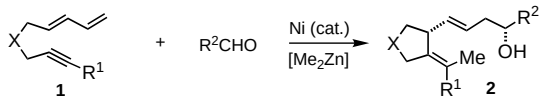
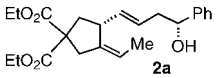
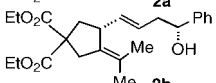
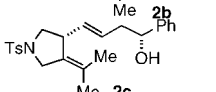
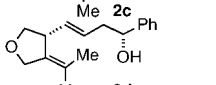
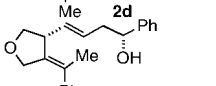
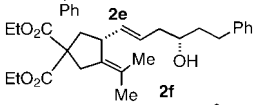
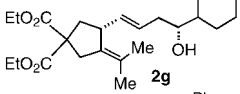
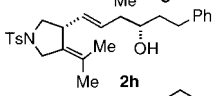
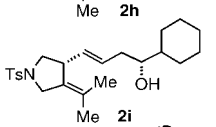
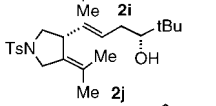
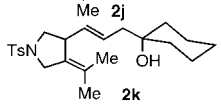
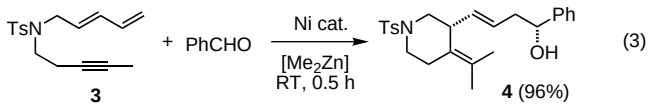
Table 1. Ni-catalyzed coupling reaction of 1,ω-dienynes, carbonyl compounds, and dimethylzinc.[a]



Entry	1	Carbonyl compound	t [h]	2	Yield [%][b]	Ratio[c]
1	**a**	PhCHO	1	 **2a**	45	11:1
2	**b**	PhCHO	1	 **2b**	63	7:1
3	**c**	PhCHO	1	 **2c**	67	>30:1
4	**d**	PhCHO	0.5	 **2d**	71	>30:1
5	**e**	PhCHO	1	 **2e**	61	7:1
6	**b**	$PhCH_2CH_2CHO$	1	 **2f**	89	>30:1
7	**b**		1	 **2g**	64	>30:1
8	**c**	$PhCH_2CH_2CHO$	1	 **2h**	64	>30:1
9	**c**		1	 **2i**	71	>30:1
10	**c**	*t*BuCHO	2	 **2j**	67	12:1
11	**c**		1	 **2k**	33	

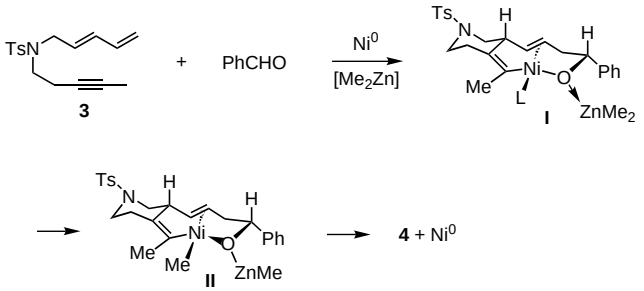
[a] See Experimental Section for procedure. [b] Yield of isolated product. [c] The ratio of diastereomers was determined on the basis of the ^{1}H NMR spectra (400 MHz).

obtained as a single diastereomer in almost quantitative yield by reacting **3** and benzaldehyde under the standard conditions [Eq. (3)]; to our delight, a crystalline solid was formed which was suitable for X-ray crystallographic analysis.[10]



(3)

A plausible reaction mechanism for the nickel(0)-catalyzed coupling reaction is shown in Scheme 1.[11] Either a concerted or a stepwise mechanism could be involved in the oxidative cyclization of nickel(0) metal with aldehyde, alkyne, and diene to give rise to intermediate **I**, which would then undergo migration of a methyl group from zinc(II) to nickel(II) to afford a methylvinylnickel(II) intermediate **II**. The intermediate **II** undergoes reductive elimination to provide **4** and an active



Scheme 1. Plausible reaction mechanism for the Ni-catalyzed four-component coupling reaction.

nickel(0) species. It is premature to discuss the origin of 1,5-diastereoselectivity. This issue will be addressed in the near future with the help of quantum mechanics and additional experimental data. A scenario outlined in Scheme 1 also agrees well with the stereoselective formation of (*Z*)-**2a** and (*Z*)-**2e**, the structures of which were determined on the basis of NOE experiments.

The conditions applied to the present reaction is essentially the same as those developed in our laboratories[12] for a three-component coupling reaction ([Me_2Zn], 1,3-dienes, and carbonyl compounds) in which [Me_2Zn] and the carbonyl compounds undergo conjugate addition to the 1,3-dienes in a 1,4-fashion and provide 3-hexenols; however, no such products were detected at all for all the reactions of **1** and **3** examined so far. This indicates that an alkyne is an excellent reaction partner.

In conclusion, we have developed a nickel-catalyzed conjugate addition reaction of [Me_2Zn] and carbonyl compounds to 1,ω-dienynes **1** and **3**, which afford cycloalkanes and their heterocyclic analogues **2** and **4**, respectively, in good yields. The products **2** and **4** are characterized by the stereodefined exocyclic tri- and tetrasubstituted double bonds (100% purity) and also by the remarkably high 1,5-diastereomeric purity (>97%, in most cases) with respect to C2 of cycloalkane rings and C4 of *trans*-4-hydroxy-1-butenyl side chains. Synthetic applications and further methodological studies, including a fully intermolecular version of the present four-component coupling reaction, that is, a coupling of four independent reaction partners, are in progress.

Experimental Section

2f (Table 1, entry 6): Dihydrocinnamaldehyde (268 mg, 2.0 mmol) and dimethylzinc (2.4 mL, 1M in hexane) were added successively to a homogeneous solution of [Ni(acac)$_2$] (25.6 mg, 0.1 mmol) and **1b** (278 mg, 1.0 mmol) in dry THF (5 mL). The reaction mixture was stirred at room temperature for 1 h under N_2 and then quenched by the addition of HCl (2M, 20 mL). The mixture was extracted twice with ethyl acetate. The combined organic extract was washed with a saturated $NaHCO_3$ solution and a saturated NaCl solution and then dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography over silica gel (hexane/ethyl acetate 12:1) to give **2f** (380 mg, 89%). R_f = 0.56 (hexane/ethyl acetate 2:1); IR (neat): $\tilde{\nu}$ = 3480 (s), 2930 (s), 1732 (s), 1497 (m), 1252 (s), 1191 (s), 1062 (m), 972 (m), 700 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 1.23 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H), 1.58 (s, 3H), 1.66 (s, 3H), 1.76 (dt, J = 6.2, 8.4 Hz, 2H), 2.06 (dt, J = 13.7, 7.8 Hz, 1H), 2.11 (dd, J = 5.1, 13.2 Hz, 1H), 2.22 (dtm, J = 13.7, 5.5 Hz, 1H), 2.58 (dd, J = 8.4, 13.2 Hz, 1H), 2.68 (dt, J = 13.9, 8.4 Hz, 1H), 2.78 (br ddd, J = 6.2, 8.4, 13.9 Hz, 1H), 2.83 (br d, J = 15.3 Hz, 1H), 2.98 (br d, J = 15.3 Hz, 1H), 3.35

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(br d, $J = 5.1$ Hz, 1H), 3.60 (dddm, $J = 5.5$, 7.8, 8.4 Hz, 1H), 4.16 (q, $J = 7.1$ Hz, 2H), 4.17 (q, $J = 7.1$ z, 2H), 5.30 (br ddd, $J = 5.5$, 7.8, 15.2 Hz, 1H), 5.39 (br dd, $J = 5.9$, 15.2 Hz, 1H), 7.16–7.32 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): $\delta = 14.1$, 20.9, 30.7, 35.3, 38.4, 40.5, 40.8, 44.1, 59.4, 70.2, 125.7, 125.8, 128.5, 133.1, 136.3, 140.3, 172.3 ppm; elemental analysis calcd for $C_{26}H_{36}O_5$: C 72.87, H 8.47; found: C 72.94, H 8.29.

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[9] The two isomers of **2** are apparently as a result of the relative configuration of the 1,5-stereogenic centers and not that of exocyclic double bonds. For example, PCC oxidation of a 7:1 mixture of **2e** provided the corresponding ketone as a single isomer, which furnished a 1:1 mixture of **2e** upon reduction with $NaBH_4$.

[10] CCDC-178844 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

[11] A similar reaction mechanism has been reported for a Ni-catalyzed alkylative carbocyclization of alkynyl enones [e.g., Eq. (2)] and for a Ni-catalyzed three-component coupling reaction of alkynes, aldehydes, and organozinc compounds: a) A. V. Savchenko, J. Montgomery, *J. Am. Chem. Soc.* **1996**, *118*, 2099–2100; b) X. Q. Tang, J. Montgomery, *J. Org. Chem.* **1999**, *64*, 9310–9313; c) K. K. D. Amarasinghe, S. K. Chowdhury, M. J. Heeg, J. Montgomery, *Organometallics* **2001**, *20*, 370–372.

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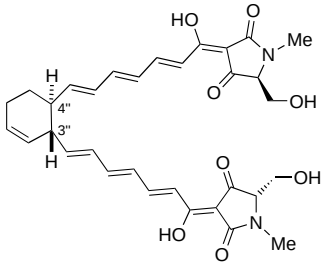
Total Synthesis of Polycephalin C and Determination of the Absolute Configurations at the 3″,4″ Ring Junction**

Deborah A. Longbottom, Angus J. Morrison, Darren J. Dixon, and Steven V. Ley*

Tetramic acids (2,4-pyrrolidinediones) are an important family of nitrogen-containing heterocycles, well known for their potent antibiotic, antiviral, antifungal, and cytotoxic activity.[1] Many tetramic acid natural products are highly complex frameworks containing several stereogenic centers. It is this complexity, together with the fact that these targets have potential or known biological activity, which makes their synthesis a worthwhile and challenging goal for the organic chemist, particularly so when the natural product is in short supply from the natural source.

In 1998, Nowak and Steffan isolated polycephalin C (**1**) as a new member of this group of natural products from *Physarum polycephalum*.[2] Polycephalin C (**1**) is a bis(trienoyltetramic acid), linked by an unusual asymmetric cyclohexene ring. The



polycephalin C (**1**)
showing unknown 3",4" absolute stereochemistry

tetramic acid unit of each terminus is derived from (*S*)-*N*-methyl serine and is linked by a fully conjugated *all-E*-triene chain to the cyclohexene ring. This unusual tetramic acid is thought to be one of several metabolites responsible for the yellow color of the wild-type plasmodia of *Physarum polycephalum*.[2]

Although the structure elucidation had established that the relative stereochemistry at the 3″,4″ ring junction of the natural product was *trans*, the absolute configuration at these positions had not been determined.[2] Therefore, intrigued by both the novel structure of this unusual polyenoyltetramic acid and the need to define the absolute stereochemistry at

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