Nickel-catalyzed coupling of allyl chlorides and enynes†

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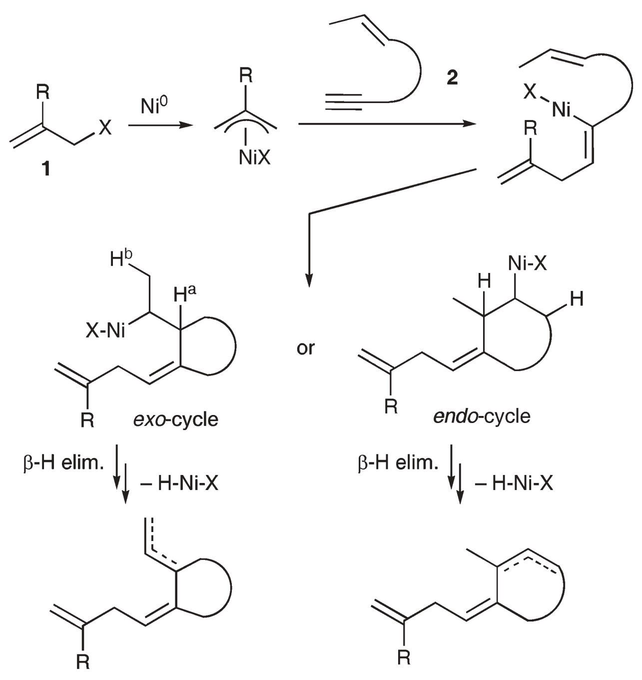
The Ni-catalyzed coupling of allyl chlorides and enynes has been developed; the cyclization of enynes was triggered by the addition of π-allylnickel species to the alkyne part, followed by the incorporation of the alkene part.

There is considerable interest in transition metal-catalyzed reactions due to their wide applications in organic synthesis. The development of catalytic, sequential, multi-component reactions is a particularly important subject.[1] In our research and development of new organonickel chemistry, we have discovered Ni-catalyzed sequential C–C bond-forming reactions.[2] We describe here a new Ni-catalyzed coupling of allyl halides **1** with enynes **2**. The cyclization of **2** is triggered by the addition of π-allylnickel species to the alkyne part, followed by the incorporation of the alkene part.[3–5] The generated *exo*- or *endo*-cyclic intermediate should undergo β-hydrogen elimination to give the corresponding cyclic product (Scheme 1).



Scheme 1 The concept of Ni-promoted sequential C–C bond formation.

Initially, an enyne **2a** was treated with allyl chloride (**1a**: X = Cl, 2 equiv. *vs.* **2a**) in the presence of Ni(cod)$_2$ (10 mol%), PPh$_3$ (20 mol%) and Zn powder (200 mol%) in MeCN at room temperature. After 4 h, **2a** was completely consumed and the coupling product **3aa** was obtained along with **4a**,[6] which was derived from the cycloisomerization of **2a** without the incorporation of an allyl unit (run 1 in Table 1). After some investigation, we found that the use of an excess amount of **1a** (*ca.* 10 equiv.) improved the product ratio of **3aa** to **4a** (run 3 in Table 1).‡ Product **3aa** was determined to have a *Z*-geometry by a NOESY experiment. This indicates that the reaction proceeded *via* the *syn*-addition of the π-allylnickel species to the alkyne part of **2a**, followed by 5-*exo*-cyclization. Neither PPh$_3$ nor Zn could be omitted from the reaction (runs 4 and 5 in Table 1). The addition of Et$_3$N promoted the formation of the allylic alkynylation product **5aa** rather than the desired cyclic product **3aa** (run 6 in Table 1). In the reaction, β-hydrogen elimination of the *exo*-cyclic intermediate provided **3aa**, along with the release of H–Ni–Cl. Zinc powder reduces this species, due to the regeneration of the Ni^0 species.[7] The choice of X in **1** is essential for the reaction. Allyl bromide (**1**: X = Br) was not suitable for the cyclization reaction (run 7 in Table 1) since an allylzinc reagent was derived from the reaction with Zn.[8,9] The use of acetate (X = OAc) and carbonate (X = OCO$_2$Me) caused the formation of **5aa** (runs 8 and 9 in Table 1).[10]

Using the optimized reaction conditions, we examined the Ni-catalyzed sequential coupling of some enynes **2** (Table 2). The reaction with β-methallyl chloride (**1b**) provided **3ba** in moderate yield (entry 1 in Table 2). A malononitrile derivative **2b** also reacted with **1a** to give the corresponding **3ab** in 45% yield (entry 2 in Table 2). In the reaction with **2c**, the obtained **3ac** was a mixture of ethylidene- and vinyl-substituted cyclopentanes (entry 3 in Table 2). These isomers were derived by the elimination of H^a and H^b atoms, respectively, from the corresponding 5-*exo*-cyclic intermediate. The reaction with **2d** afforded a vinyl-substituted cyclopentane **3ad** (entry 4 in Table 2). A cyclohexene-substituted enyne **2e** also reacted with **1a** to give an alkylidene-substituted bicyclic product **3ae** (entry 5 in Table 2).

When **2f** was treated with **1a** in the presence of the catalytic system, a six-membered cyclic product **6af** was obtained, along with a five-membered cyclic **3af** (eqn. (1)). In the reaction, the stereochemistry of **6af** could not be determined. On the other hand, the reaction with **2g**, which has a methyl group at the vinyl position, gave the corresponding **6ag** in 73% yield as the sole product (Scheme 2). The product was determined to have an *E*-geometry by a NOESY experiment. If the reaction proceeded *via* 6-*endo*-cyclization (see the "*endo*-cycle" depicted in Scheme 1), (*Z*)-**6ag** would be obtained. Inversion of the configuration can be explained by a process that involves the formation of 5-*exo*-cyclized **7**, followed by cyclopropanation leading to **8**, which then undergoes β-carbon elimination to produce **9**.[11] Although **8** has

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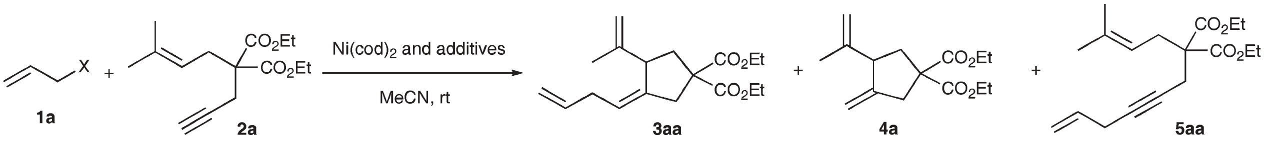
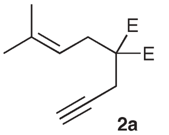
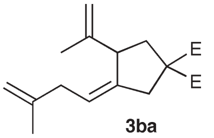
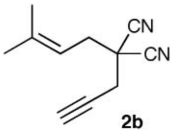
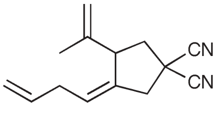
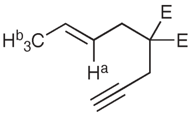
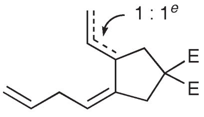
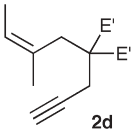
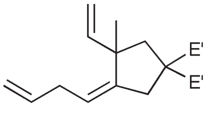
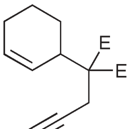
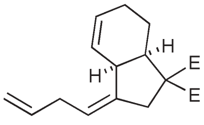
Table 1 The reaction of **1a** with **2a**[a]



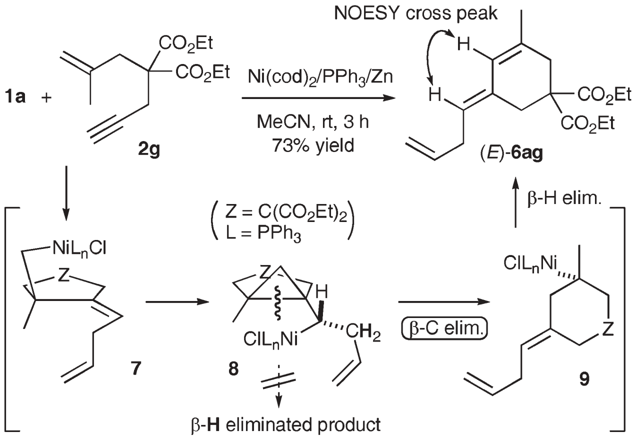
	1a		Additives				Yield (%)[d]		
Run	X	Equiv.	PPh$_3$[b]	Zn[c]	Et$_3$N[c]	Time/h	**3aa**	**4a**	**5aa**
1	Cl	2	Yes	Yes	No	4	(41)	(34)	0
2	Cl	6	Yes	Yes	No	4	(62)	(10)	0
3	Cl	10	Yes	Yes	No	4	75	Trace	0
4	Cl	10	No	Yes	No	24	0	0	0
5	Cl	10	Yes	No	No	24	0	0	0
6	Cl	10	Yes	Yes	Yes	2	Trace	0	68
7	Br	10	Yes	Yes	No	2	(26)	(15)	0
8	OAc	10	Yes	Yes	No	24	(15)	0	(35)
9	OCO$_2$Me	10	Yes	Yes	No	2	0	0	88

[a] Conditions: Ni(cod)$_2$ (10 mol%) in MeCN at room temperature. [b] Yes: 20 mol% addition; No: no addition. [c] Yes: 200 mol% addition; No: no addition. [d] Isolated yield. NMR yields are in parentheses.

Table 2 The reaction of **1** with **2**[a]

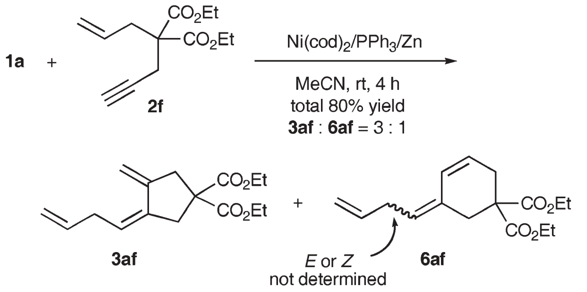
Entry	2[b]	Product (S)	Yield (%)[c]
1[d]	 **2a**	 **3ba**	41
2	 **2b**	 **3ab**	45
3	 **2c**	 **3ac**	64
4	 **2d**	 **3ad**	65
5	 **2e**	 **3ae**	70

[a] Conditions: **1a** (R = H, 5 mmol), **2** (0.5 mmol), Ni(cod)$_2$ (10 mol%), PPh$_3$ (20 mol%), Zn (200 mol%) in MeCN (3 mL) at rt for 4 h. [b] E = CO$_2$Et, E′ = CO$_2$Me. [c] Isolated yield. [d] The reaction was carried out with **1b** (R = Me) instead of **1a**. [e] Determined by ^{1}H NMR.



Scheme 2 Domino coupling of **1a** (X = Cl) with **2g** *via* the formation of three C–C bonds and the cleavage of one C–C bond.

β-hydrogen atoms (depicted in bold in Scheme 2), the product that would result from β-hydrogen elimination was not observed. The conversion to **9**, with a relief of ring strain in the cyclopropane part of **8**, would be a more favorable process than β-hydrogen elimination.[12] Finally, β-hydrogen elimination at the allylic position of **9** led to (*E*)-**6ag**. The reaction proceeds *via* a domino process with the formation of three C–C bonds and the cleavage of one C–C bond.



(1)

In summary, we have demonstrated a Ni-catalyzed coupling of allyl chlorides and enynes. The reaction proceeds *via* the addition of the π-allylnickel species to the alkyne part, followed by the incorporation of the alkene part to generate the *exo*-cyclic intermediate. Sequential β-hydrogen elimination led to the formation of **3**. On the other hand, an intermediate such as **7**, which does not have any β-hydrogen atoms, underwent cyclopropanation, followed by β-carbon elimination to lead to the formation of **6**. Further studies are in progress in our laboratory.

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Notes and references

‡ Typical experimental procedure (run 3 in Table 1): In a 20 mL three-necked flask were placed Ni(cod)$_2$ (0.05 mmol), PPh$_3$ (0.1 mmol), Zn dust (1.0 mmol) and MeCN (3 mL), and the mixture stirred at room temperature for 10 min. To this suspension was added **2a** (0.5 mmol) and **1a** (X = Cl, 5 mmol) at room temperature, and the mixture stirred at the same temperature for 4 h. After the addition of aqueous HCl (5%, 30 mL), the aqueous layer was extracted with Et$_2$O (10 mL × 3). The combined organic layer was washed with brine, dried over MgSO$_4$ for 30 min, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane–AcOEt, 4 : 1) to yield **3aa** (75%) as a colorless oil.

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7. Although the details are not yet clear, an excess of **1a** (X = Cl) may also require the regeneration of the Ni^0 species. We propose that the π-allylnickel(II) chloride depicted in Scheme 1 undergoes reduction by half an equivalent of Zn to give a π-allylnickel(I) species. The reaction of **2a** with the π-allylnickel(I) species gives **3aa**, along with the release of a nickel(I) hydride (H–Ni^I). The H–Ni^I species would be treated with **1a** and Zn to generate π-allylnickel(II) hydride, which undergoes a reductive elimination to produce propene, along with the regeneration of the Ni^0 species. For the reductive elimination of π-allylnickel(II) hydride, see: H. Bönnemann, *Angew. Chem., Int. Ed. Engl.*, 1970, **9**, 736.
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9. Whereas allyl bromide (**1a**, X = Br) instantly reacted with Zn powder in MeCN at room temperature to give the allylzinc reagent, the reaction using the chloride (**1a**, X = Cl) did not occur.
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