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Nickel-catalyzed carbonylative cycloaddition of allyl halides and alkenes

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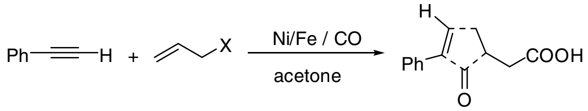
ABSTRACT

The carbonylative addition between allyl halides and alkenes is described. The [2+2+1] reaction is catalyzed by Ni(I), and takes place with different strained alkenes under very mild conditions. Changes in solvent and use of different amounts of water in the reaction produce changes on the final products obtained.

The intermolecular [2+2+1] carbonylative cycloadditions mediated by transition metals showed to be a very important reaction tools in organic synthesis,[1] and significant progress including catalytic variants have been reported. In particular, the scope and the selectivity of the cyclocarbonylation of allyl halides and acetylenes[2] have been studied in our laboratory. This reaction has a precedent in the work of Chiusoli[3] and Oppolzer[4] (Scheme 1).

As shown in Scheme 1, three bonds are formed in one single synthetic operation in an intermolecular way. In a previous Letter,[5] we successfully turned the reaction into one catalytic in nickel, and we proposed a possible mechanism involving a pseudoradical Ni(I) species. The reaction works very well with different types of acetylenes, with yields ranging from good to excellent and high regio and stereoselectivities.

We concluded that this method would find a wide application in organic synthesis, and we decided to extend further the reaction scope by studying the carbonylative cyclization, under similar conditions, with alkenes. Since under the conventional conditions plain olefins showed no reactivity, the literature precedents for similar reactions[6] prompted us to try the reaction with allenes, ketenes, vinyl ketones, and strained olefins. The reaction proceeded in most of the cases giving only complex mixtures.[7] However, with strained olefins like norbornene, only two types of adducts were obtained.



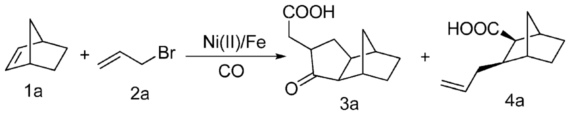
Scheme 1. Ni catalyzed cyclocarbonylation of allyl halides and alkynes.

In our first attempts, a mixture of two major compounds, as depicted in Scheme 2, was obtained.

This result has a precedent in the early work of Larock,[8] in a carbonylative cyclization mediated by organopalladium compounds. However, in our case the reaction is catalytic in Ni, with turnovers ranging up to 40, and we are able to tune the yield in both products by changing the reaction conditions.

Thus, the reaction takes place either in acetone or in THF and the results obtained, using the norbornene/allyl bromide system as the reaction model and water in variable amounts as additive, are shown in Table 1.

Changes in solvent and the introduction of different amounts of water produced changes in the yield and ratio of the two products **3** and **4**. In general, the presence of small amounts of water, when acetone is used as the solvent, did not produce big changes on the



Scheme 2. Reaction of norbornene and allyl bromide.

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Table 1
Reaction between norbornene and allyl bromide by adding different amounts of water

	Solvent	Additive	Yield **3a** (%)	Yield **4a** (%)
1	Acetone	—	68	20
2	Acetone	H_2O (1 equiv)	51	43
3	Acetone	H_2O (2 equiv)	45	39
4	Acetone	H_2O (20 equiv)	7	38
5	THF	—	50	25
6	THF	H_2O (1 equiv)	—	12
7	THF	H_2O (2 equiv)	—	4

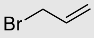
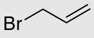
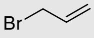
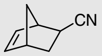
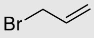
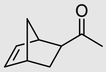
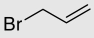
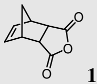
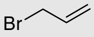
recoveries, but led to partial inhibition of the second carbonylation and, therefore, an increase in the yield of the product **4a**. Taking into account the results obtained with acetone, the reaction was tried using THF, a solvent not liable to generate water, in order to enhance the yield of product **3a**. However, while the reaction gave similar yields of both products, it proved extremely sensitive to the presence of water, leading to a dramatic lowering of the reaction yield. In these cases (Table 1, entries 6 and 7), only the open product **4a** was obtained, albeit in very low yield. Surprisingly, the reaction took place either in acetone or in THF in the absence of additives (Lewis acids, water or alcohols), which were necessary in the carbonylative cycloaddition with acetylenes previously described.[9]

Taking into account the mechanism already proposed[5] (Scheme 3) for this type of carbonylative cycloaddition, we can suggest that after the first addition of the allyl nickel complex to the double bond and carbonyl insertion, the key intermediate II would arise and from it the reaction can follow two possible paths: toward the cyclopentanone **3** through a carbometallation, or toward the open product **4** by an external nucleophilic attack. By lowering the amount of water, the interception of the acyl species II by water would be hampered and the internal insertion of II to III favored, deriving, after the second carbonyl insertion and the corresponding transmetalation, to the acyl iron which after hydrolysis would yield the cyclopentanone **3**. On the contrary, the presence of water would affect the coordination of the metal to the double bond in intermediate II, favoring the formation of compound **4.** However, an excess of water produces a deleterious effect, probably by interaction with the catalytic system.

The reaction was further extended to different strained olefins and substituted allyl halides in order to study the influence of steric and electronic effects on the reaction course. The results obtained[10] with different norbornenes are shown in Table 2.

As has been observed in the case of acetylenes, changes in the substitution of the olefin 1 did not produce big changes in the resulting reaction products, with total yields (both products combined) around 75–95%, and only the two mentioned products **3** and **4** were found. The use of norbornadiene as a reagent (entry 3) yielded 79% of product **4b**, after only 3 h of reaction and adding

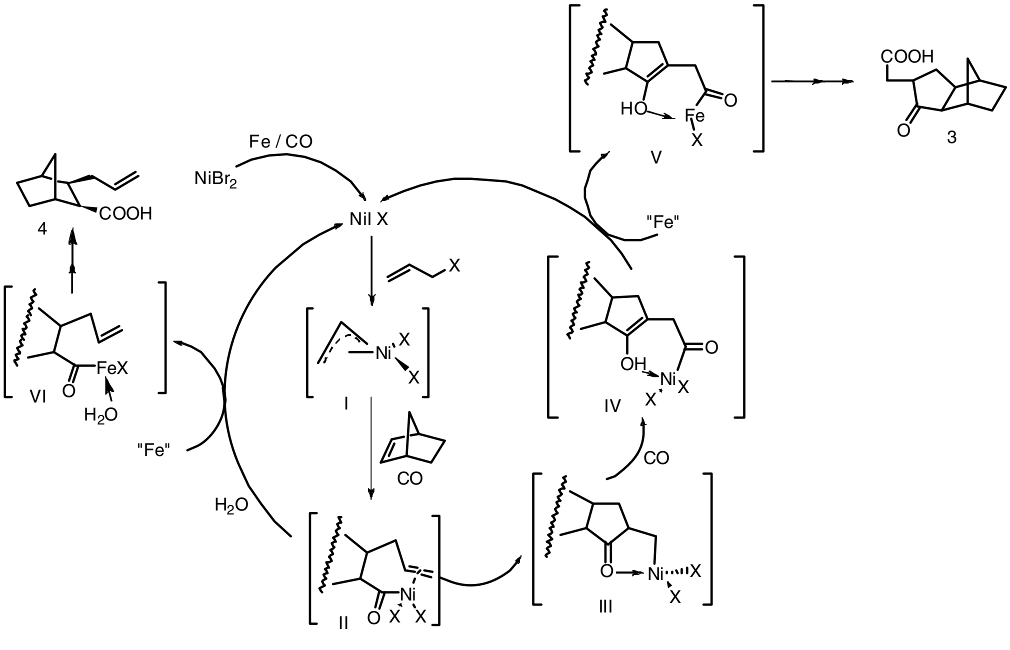
Table 2
Results using different norbornenes

	Alkene	Allyl	Solvent	Yield 3[a]	Yield 4[a]
1	 **1a**	 **2a**	Acetone	68% **3a**	20% **4a**
2	 **1a**	 **2a**	THF	50% **3a**	25% **4a**
3	 **1b**	 **2a**	Acetone	—	79% **4b**
4	 **1c**	 **2a**	Acetone	72% **3c**[b]	16% **4c**[b]
5	 **1d**	 **2a**	Acetone	49% **3d**[b]	46% **4d**[b]
6	 **1e**	 **2a**	Acetone	75% **3e**[c]	—

[a] Reaction conditions: alkene (5 mmol) and allyl halide (5.8 mmol) slowly added onto 10 μm iron powder (5 mmol), $NiBr_2$ (0.25 mmol), NaI (1.5 mmol) in 2 mL of acetone, under CO atmosphere, room temperature and atmospheric pressure.

[b] Mixture of regioisomers, 1:1 ratio.

[c] Yield after anhydride opening and final esterification.



Scheme 3. Proposed mechanism.

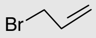
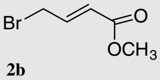
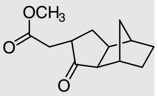
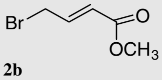
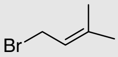
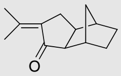
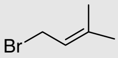
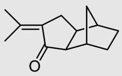
only 1 equiv of allyl (to prevent a second reaction, involving the other double bond of the norbornadiene, with the unreacted allyl component). Although the reaction proceeds in the expected way, in this case, the easy reaction of the remaining double bond with the allyl halide gives rise to a complex mixture of mono, di-open and cyclocarbonylated products with their corresponding diastereomers. Reagents **1c** and **1d** also yielded the typical products **3** and **4**, but due to the fact that the starting products were a mixture of *endo*/*exo*, four isomers were obtained for each of the two products, showing little regioselectivity (as expected with 6-substituted norbornenes[11]), with a ratio of about 1:1 between the two regioisomers, as seen by ^{13}C NMR.

The steric hindrance or electronic effects in the allyl derivatives **2** have an effect, in accordance with the results of the carbonylative cycloaddition with acetylenes, as shown in Table 3.

When the allyl halide **2b** was used, both the cyclopentanone and the open product **4f** were obtained in similar yields in the absence of water. However, the cyclopentanone obtained (**5f**) had only inserted one molecule of carbon monoxide. We know from the previous study with acetylenes that with such allyl systems with an electron-withdrawing substituent, the second carbonylation is inhibited.[5] Accordingly, the cycloadduct **5f** was obtained. Furthermore, when 1 equiv of water was added to the reaction mixture, the only product obtained was **4f,** due to the inhibition of the cyclization after the first carbonylation.

A different behavior was also observed in the case of trisubstituted allyl bromides (prenyl bromide, entry **2c**). The main product obtained corresponded to a cyclopentanone derivative **5g**, with only a single carbonylation taking place. However, in this case, the inhibition of the second carbonylation could be accounted for by the steric hindrance brought up by the presence of the two methyl substituents. That produces, on one hand, the decrease of the reaction rate and, on the other, it would hamper the nickel (or iron in the transmetallated species) coordination to the oxygen of the carbonyl (intermediate III, Scheme 3). Now coplanarity of the metal and the α-carbonyl hydrogen is possible, and so β-elimination ensues before the second carbonylation preventing further reaction and yielding the cyclopentanone **5g** as the major product. The two typical products generated in this reaction, **3g** and **4g**, were also obtained in low yield. In this case, the presence of water did not improve the selectivity of the reaction toward the open product and simply diminishes considerably its global yield.

Table 3
Reaction of norbornene with different allyl halides

	Alkene	Allyl	Solvent	Yield **3**[a]	Yield **4**[a]	Yield (others)[a]
1	 **1a**	 **2a**	Acetone	68% **3a**	20% **4a**	—
2	 **1a**	 **2b**	Acetone	—	48% **4f**	 45% **5f**
3	 **1a**	 **2b**	Acetone (1 equiv H_2O)	—	73% **4f**	—
4	 **1a**	 **2c**	Acetone	15% **3g**	12% **4g**	 64% **5g**
5	 **1a**	 **2c**	Acetone (1 equiv H_2O)	14% **3g**	10% **4g**	 23% **5g**

[a] Reaction conditions: alkene (5 mmol) and allyl halide (5.8 mmol) slowly added onto 10 μm iron powder (5 mmol), $NiBr_2$ (0.25 mmol), and NaI (1.5 mmol) in 2 mL of acetone, under CO atmosphere, room temperature and atmospheric pressure.

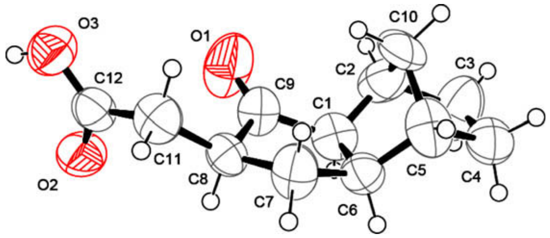


Figure 1. X-ray structure of **3a**.

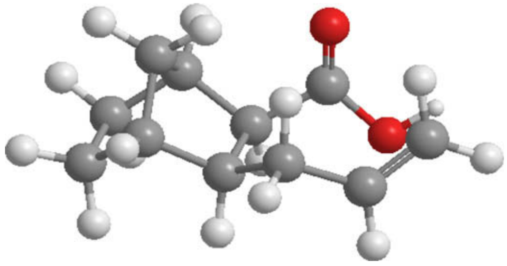


Figure 2. Model structure of **4a.**

This reaction has proven to be fully stereoselective. The structure of **3a** (Fig. 1), obtained by X-ray analysis, shows that both the allyl and the carbon monoxide have approached the norbornene structure from the *exo* face, as expected from a carbometallation. This configuration is the only one found in all products **3** as well as in the open product **4** (Fig. 2).

The *exo* configuration of the adducts may also be expected from the relevant steric demand of the nickel ligands component approaching the norbornene substrate despite the known better overlapping from the *endo* face.

In conclusion, we present here a reaction between norbornenes and allyl halides, using catalytic amounts of a cheap metal (Ni), under mild conditions (atmospheric pressure and room temperature), and starting with very simple and economic reagents (plus carbon monoxide and iron), obtaining two major products whose ratio can be tuned by carefully adding water.

Acknowledgments

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9. Manuscript in preparation.
10. *General procedure (reagents **1a** and **2a**)*: In a 50 mL three necked flask, provided with an efficient magnetic bar, 55 mg of $NiBr_2$ (0.25 mmol), 225 mg of NaI (1.5 mmol), and 300 mg of iron powder are introduced. The internal atmosphere is filled with CO, setting the internal pressure equal to the atmospheric one. Acetone (2.0 mL) is introduced in the reaction flask by means of a syringe. After 30 min, the CO uptake reaches up to 10–12 mL, and a solution of 5.8 mmol of allyl bromide and 5.0 mmol of norbornene is added dropwise by means of a syringe pump. After 4–5 h, the reaction is over (CO uptake, approx. 220 mL). The solvent is removed, and the contents of the flask are transferred to a separation funnel washing the flask (with the remaining iron) with dichloromethane. The reaction mixture darkens deeply in contact with the air. The solution is treated with portions of 5 N HCl solution until no further discoloration is observed. After washing the organic phase with water to neutralization, the organic layer is treated with a solution of $Na_2S_2O_3$ (to remove any I_2 produced by oxidation), washed again with water, and dried on $MgSO_4$. After removal of the solvent and flash chromatography (CH_2Cl_2/CH_3OH) the corresponding products **3a** and **4a** are obtained.
    Compound **3a**. IR (CH_2Cl_2) ν(cm^{-1}): 3600–3000 (O–H), 1734 (C=O), 1710 (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ 0.90–1.10 (m, 3H, $C\mathit{H}_2$); 1.16 (d, 2H, *J*(H,H) = 8 Hz, $C\mathit{H}_2$); 1.20 (d, 1H, *J*(H,H) = 20 Hz, $C\mathit{H}_2$); 1.53 (bd, 2H, *J*(H,H) = 8 Hz, $C\mathit{H}_2$); 2.16 (d, 2H, *J*(H,H) = 11 Hz, C*H*); 2.24 (t, 1H, *J*(H,H) = 9 Hz, C*H*); 2.58 (br s, 1H, $C\mathit{H}_2$); 2.40–2.80 (m, 3H, C*H*, $C\mathit{H}_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.7 (t); 27.8 (t); 31.6 (t); 32.8 (t); 33.9 (t); 38.7 (d); 40.6 (d); 42.0 (d); 44.9 (d); 54.0 (d); 178.1 (s); 218.5 (s). HRMS (E.I.) (*M*+): 208.1092 (theoretical: 208.1095). Elemental Anal.: C, 69.33; H, 7.91 (calcd: C, 69.21; H, 7.74).
    Compound **4a**. IR (CH_2Cl_2) ν(cm^{-1}): 3600–3000 (O–H), 3077 (C=CH), 1702 (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ 1.10–1.20 (m, 3H, $C\mathit{H}_2$); 1.45–1.60 (m, 2H, $C\mathit{H}_2$); 1.83 (d, 1H, *J*(H,H) = 10 Hz, $C\mathit{H}_2$); 1.85–2.00 (m, 2H, C*H*, $C\mathit{H}_2$); 2.13 (br s, 1H, C*H*); 2.10–2.20 (m, 1H, $C\mathit{H}_2$); 2.43 (br s, 1H, C*H*); 2.51 (d, 1H, *J*(H,H) = 9 Hz, C*H*); 4.97 (d, 1H, *J*(H,H) = 10 Hz, $C\mathit{H}_2$); 4.99 (d, 1H, *J*(H,H) = 17 Hz, $C\mathit{H}_2$); 5.75 (ddt, 1H, *J*(H,H) = 7, 10, 17 Hz, C*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.6 (t); 28.9 (t); 34.2 (t); 34.8 (t); 38.9 (d); 40.1 (d); 45.5 (d); 50.7 (d); 115.6 (t); 137.3 (d); 180.5 (s). HRMS (E.I.) (*M*+): 180.1146 (theoretical: 180.1146). Elemental Anal.: C, 73.87; H, 9.20 (calcd: C, 73.30; H, 8.95).
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