

## The Ni-Mediated Cyclocarbonylation of Allyl Halides and Alkynes Made Catalytic. Evidence Supporting the Involvement of Pseudoradical Ni<sup>I</sup> Species in the Mechanism

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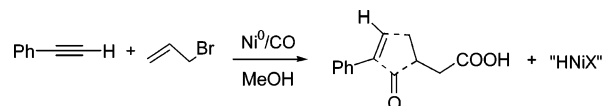
Among the different pentannulation methods, the metal-mediated [2 + 2 + 1] carbonylative cycloadditions represent the most straightforward way to synthesize the cyclopentane skeleton since three C–C bonds are formed in a single experimental operation. The Pauson–Khand reaction, originally mediated by cobalt and later found to undergo in the presence of other metal complexes,<sup>1</sup> fits within this strategy. In a similar approach, we have studied the scope and the selectivity arising from the cyclocarbonylation of allyl halides and acetylenes mediated by nickel<sup>2</sup> (a reaction which has precedents in the work of G. P. Chiusoli<sup>3</sup> and W. Oppolzer<sup>4</sup>) (Scheme 1).

The main advantages of this cycloaddition are its regio- and stereoselectivity as well as the mild reaction conditions required. However, the most promising feature compared with similar processes is its efficiency in the intermolecular version.<sup>5</sup> Thus, the vast majority of the pentannulations of this kind so far reported apply only to preformed enynes or strained olefins.

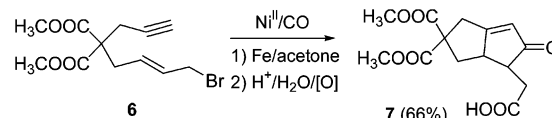
In our attempt to make the process catalytic in Ni, we introduced an excess of sodium ascorbate in the reaction mediated by Ni(COD)<sub>2</sub> under CO,<sup>6</sup> aimed at removing any hydrogen halide generated in the reaction<sup>7</sup> and also returning any Ni<sup>I</sup> species to the original Ni<sup>0</sup> oxidation state of the mediator. Studies on the pernicious allyl self-coupling reaction, leading the mediator to inactive Ni<sup>II</sup> halides, had pointed to the intervention of Ni<sup>I</sup> species generated from the  $\pi$ -allyl intermediate by valence dismutation.<sup>8</sup>

However, the cycloaddition reaction was completely inhibited under these conditions. We assumed, therefore, that Ni<sup>I</sup> free-radical-like species were also responsible for the cyclocarbonylation reaction. Alternatively, the catalytic species could thus be advantageously prepared by a single electron reduction of a Ni(II) salt. We chose the readily available phenylacetylene and allyl bromide as model substrate and tried different reductants compatible with acetone, the best solvent for this reaction.<sup>9</sup> We were pleased to record high turnovers in the presence of finely divided iron (up to 40). Unexpectedly, most of the excess of iron was consumed during the process. As a consequence, an oxidative workup to free the product from iron was necessary after the reaction was completed. Thus, we assigned a dual role to the iron: *to generate the reduced catalytic Ni<sup>I</sup> species and to be an efficient terminating agent*. An EPR spectrum of a sample taken after the initial reduction revealed the presence of Ni<sup>I</sup> evidenced by the three signals recorded at  $g = 2.246$ ,  $2.113$ , and  $2.005$ .<sup>10</sup> Another sample was taken shortly after the substrate had been added and CO uptake had started. In it, the three former signals had collapsed to a sharp single one at  $g = 2.001$  ( $\Delta H_{pp} \sim 13$  G). Although this value matches well with those for organic free radicals,<sup>11</sup> the high regio- and stereoselectivity of the resulting products rather supports the intervention of a free allyl ligand in a Ni(II) EPR-silent complex.<sup>12</sup> While any nickel halide or even Ni(acac)<sub>2</sub> in the presence of an excess of iodide ion<sup>13</sup> gave similar results, the absence of any nickel source or the replacement

**Scheme 1.** Ni-Mediated Carbonylative Cycloaddition of Allyl Halides and Alkynes



**Scheme 2.** Intramolecular Version (not optimized)

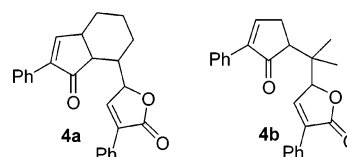


of iron metal by ferrous bromide or other metals (Zn, Mg)<sup>14</sup> led only to allyl self-coupling to form 1,5-hexadiene, complete inactivity, or formation of metallic nickel, respectively, suggesting a fine redox tuning for the cycloaddition reaction to be able to proceed. The presence of substoichiometric amounts of a Lewis acid (iodine or better AlBr<sub>3</sub>) was found to activate considerably the CO uptake.

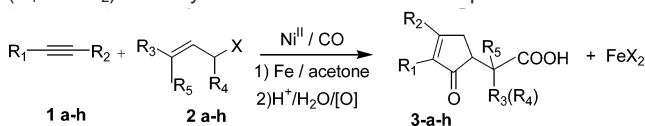
The present methodology was successfully extended to other alkynes and allyl halides of mechanistic significance as well as to one intramolecular version (Scheme 2). The corresponding results are collected in Table 1.

As can be seen from the table, in most cases, the corresponding 2-(5-cyclopent-2-enonyl)acetic acid adducts were obtained with yields ranging from good to excellent, improving those formerly obtained under stoichiometric conditions. In addition, the regioselectivities (controlled mainly by electronic effects) and stereoselectivities (arising from steric effects) were also improved.<sup>2a,c</sup> Again, the identity of the products obtained when starting from two positional allyl halide isomers and the similarity of the diastereomeric ratios (entries 10 and 11) point to the involvement of a  $\pi$ -allyl species.

Remarkable is the high yield of cyclopentenone adduct versus that from self-coupling when starting from an electrodefficient conjugated allyl component (entry 12). Moreover, one carbonyl only is inserted.<sup>2b</sup> For hindered allyl halides, such as prenyl bromide and 3-bromocyclohexene, the reaction is slower, allowing further insertion of an alkyne moiety into the transient acyl halide adduct in preference to the initiation of a new cycle (entries 9 and 13) giving **4a** and **4b**, respectively. The effect of steric hindrance was even emphasized with bis(trimethylsilyl)acetylene, in which case no CO uptake was recorded.



For practical purposes, turnovers of up to 20 with a high yield in cyclopentenone derivatives have been achieved in acetone as

**Table 1.** Catalytic Carbonylative Cycloaddition of Alkynes ( $R_1C\equiv CR_2$ ) and Allyl Halides under a CO Atmosphere<sup>a</sup>

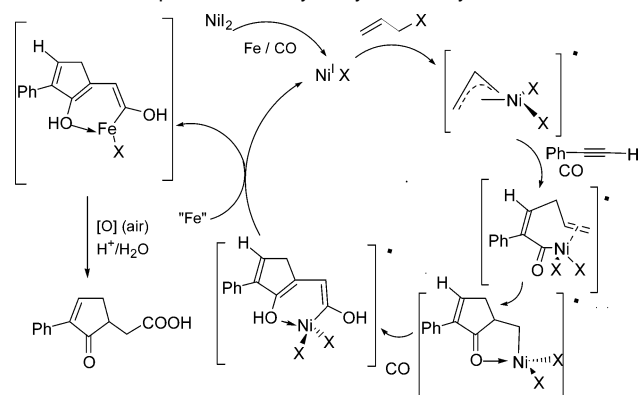
	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub> (R <sub>5</sub> )	R <sub>4</sub>	product (yield, %)	method
1	Ph	H	H(H)	H	<b>3a</b> (95)	a
2	Si(Me) <sub>3</sub>	H	H(H)	H	<b>3b</b> (68)	a
3	Me	CO <sub>2</sub> Et	H(H)	H	<b>3c</b> (78)	a
4	Me	CH <sub>2</sub> OMe	H(H)	H	<b>3d</b> (87)	a
5	CH <sub>2</sub> OMe	H	H(H)	H	<b>3e</b> (60)	a
6	Et	Et	H(H)	H	<b>3f</b> (80)	a
7	Bu	H	H(H)	H	<b>3g</b> (82)	b
8	Si(Me) <sub>3</sub>	Si(Me) <sub>3</sub>	H(H)	H	—	a
9	Ph	H	H-(CH <sub>2</sub> ) <sub>3</sub> -	H	<b>4a</b> (28)	a
10	Ph	H	Me(H)	H	<b>3h</b> (92) <sup>b</sup>	a
11	Ph	H	H(H)	Me	<b>3h</b> (90) <sup>c</sup>	b
12	Ph	H	CO <sub>2</sub> Me	H	<b>3a'</b> (73)	b
13	Ph	H	Me(Me)	H	<b>4b</b> (19)	a

<sup>a</sup> General conditions: (a) alkyne (5 mmol), allyl halide (5.8 mmol), I<sub>2</sub> (0.5 mmol) in 2 mL of CH<sub>2</sub>Cl<sub>2</sub> slowly added onto 10 μM iron powder (5 mmol), NiI<sub>2</sub> (0.25 mmol), NaI (0.50 mmol) in 2 mL of acetone, under a CO atmosphere, room temperature, and atmospheric pressure; (b) NiBr<sub>2</sub> and AlCl<sub>3</sub> replace NiI<sub>2</sub> and I<sub>2</sub>, respectively (see Supporting Information).

<sup>b</sup> Mixture of two diastereomers (95:5). Major isomer: (*R,R*) and (*S,S*) pair.<sup>2a</sup>

<sup>c</sup> Mixture of two diastereomers (90:10). Major isomer: (*R,R*) and (*S,S*) pair.<sup>2a</sup>

<sup>d</sup> As the corresponding methyl ester.

**Scheme 3.** Proposed Ni Catalytic Cyclocarbonylation

the solvent of choice following a probable catalytic cycle, in which the key step would be the transfer of the cycloadduct from the nickel to the iron (Scheme 3). With higher turnovers, the amount of products in which the alkyne has further inserted on the side chain (mixture of stereoisomers) becomes relevant. In connection with this finding is the oxidation of iron. With long reaction times, the iron is completely consumed. However, when the reaction was stopped just after the substrate had been added, iron was consumed up to around 0.5 equiv only.

We could not isolate any product derived from reduction of the adduct or the solvent. Thus, we conclude that iron is, in part, scavenging the acyl halide released from the reaction cycle, preventing it, in this way, from undergoing further alkyne insertion. This would be the reason this concurrent process acquires impor-

tance when the amount of iron decreases (at high turnovers). Spectroscopic data from the dry crude product and its reactivity toward aldehydes suggest an iron enolate as the most reasonable outgoing reaction product from iron.<sup>15</sup> The EPR spectrum also gave an account of the presence of some Fe<sup>III</sup>, but no signal ascribable to a free organic radical could be detected.

In conclusion, we report here a highly efficient catalytic method to synthesize *intermolecularly* the cyclopentane skeleton starting from products as simple as allyl halides, alkynes, and carbon monoxide under very mild reaction conditions by means of a stoichiometric amount of iron, acetone, and a catalytic amount of Ni halide.

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**Supporting Information Available:** Synthesis and characterization. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## References

- (1) For Pauson–Khand reactions, see: (a) Geis, O.; Schmalz, H. G. *Angew. Chem., Int. Ed.* **1998**, *37*, 911–915. (b) Gibson, S. E.; Stevenazzi, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1800–1810. (c) For Ni-catalyzed Pauson–Khand-type reactions, see: Zhang, M.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 4498–4499.
- (2) (a) Camps, F.; Coll, J.; Moretó, J. M.; Torras, J. *J. Org. Chem.* **1989**, *54*, 1969–1978. (b) Camps, F.; Moretó, J. M.; Pagès, L. *Tetrahedron* **1992**, *48*, 3147–3162. (c) Pagès, L.; Llebaria, A.; Camps, F.; Molins, E.; Miravittles, C.; Moretó, J. M. *J. Am. Chem. Soc.* **1992**, *114*, 10449–10461. (d) García-Gómez, G.; Moretó, J. M. *Chem.–Eur. J.* **2001**, *7*, 1503–1509.
- (3) Chiusoli, G. P.; Cassar, L. *Angew. Chem.* **1967**, *79*, 177–186.
- (4) (a) Oppolzer, W.; Keller, T. H.; Kuo, D. L.; Pachinger, W. *Tetrahedron Lett.* **1990**, *31*, 1265–1268. (b) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 38–52.
- (5) Ikeda, S. *Acc. Chem. Res.* **2000**, *33*, 511–519.
- (6) García-Gómez, G.; Camps, X.; Jaumà, A.; Moretó, J. M. *Inorg. Chim. Acta* **1999**, *296/1*, 94–102.
- (7) Protonolysis or “substitutive reduction” is one of the concurrent processes responsible for Ni oxidation: Chiusoli, G. P.; Bottaccio, G.; Camerini, A. *Chim. Ind. (Milan)* **1962**, *44*, 131–135.
- (8) (a) Kochi, J. K. *Pure Appl. Chem.* **1980**, *52*, 571–605. (b) Dayrit, F. M.; Schwartz, J. *J. Am. Chem. Soc.* **1981**, *103*, 4466–4473. (c) Hegedus, L. S.; Thompson, D. H. *J. Am. Chem. Soc.* **1985**, *107*, 5663–5669. (d) Tsou, T. T.; Kochi, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 7547–7560.
- (9) Cassar, L.; Chiusoli, G. P. *Tetrahedron Lett.* **1965**, *37*, 3295–3299.
- (10) (a) Farmer, P. J.; Reibenspies, J. H.; Lindahl, P. A.; Darendsbourg, M. Y. *J. Am. Chem. Soc.* **1993**, *115*, 4665–4674. (b) Lovecchio, F.; Gore, E. S.; Busch, D. H. *J. Am. Chem. Soc.* **1974**, *96*, 3109–3118.
- (11) (a) Griller, D.; Cooper, J. W.; Ingold, K. U. *J. Am. Chem. Soc.* **1975**, *97*, 4269–4275. (b) Cabiddu, S.; Fattuoni, C.; Lucarini, M.; Pedulli, G. F. *Tetrahedron* **1994**, *50*, 4001–4008.
- (12) In some Ni complexes with a formally odd oxidation state for the metal, the unpaired electron is fully localized on the ligand, and the complex is Ni-silent. See, for instance: Kreisman, P.; Marsh, R.; Preer, J. R.; Gray, H. B. *J. Am. Chem. Soc.* **1968**, *90*, 1067–1068.
- (13) Although, initially, an excess of iodide was added only to solubilize the Ni salt as tetraiodonickelate, the presence of iodide has proven to activate the reaction and is liable to operate as well as an efficient allyl activator and/or a stabilizing ligand. Without it, the reaction proceeds sluggishly.
- (14) Ikeda, S.; Sanuki, R.; Miyachi, H.; Miyashita, H.; Taniguchi, M.; Odashima, K. *J. Am. Chem. Soc.* **2004**, *126*, 10331–10338.
- (15) Besides a strong and broad peak at 3376 cm<sup>−1</sup>, the dry crude product shows strong peaks at 1684, 1595, and 1463 cm<sup>−1</sup> in the IR spectrum not present in the final adduct. The Mössbauer spectrum accounts for at least 85% of the dissolved iron as Fe(II). The reflux of the crude product in THF with an excess of paraformaldehyde gave 40% of 3-hydroxy-2-[5-(2-phenylcyclopent-2-enonyl)]propionic acid (one single isomer).

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