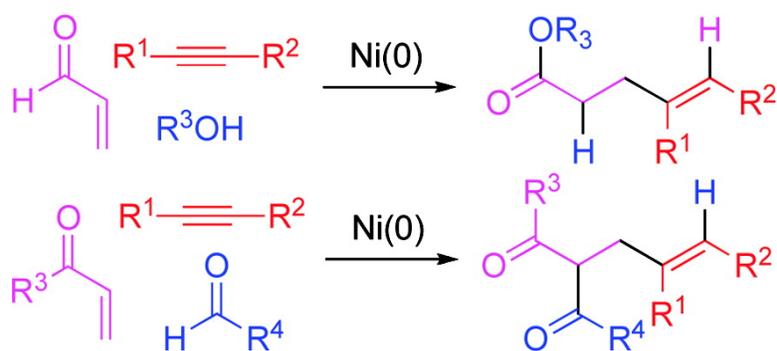


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## Fully Intermolecular Nickel-Catalyzed Three-Component Couplings via Internal Redox

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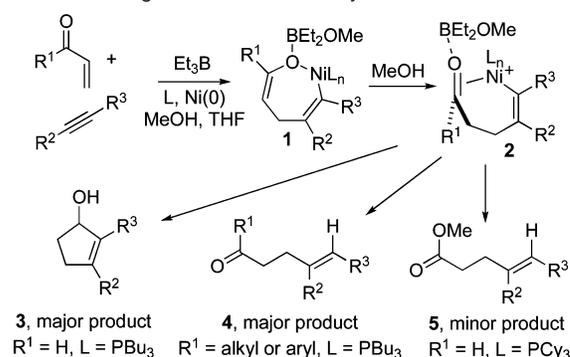
Transition-metal-catalyzed reductive couplings have seen extensive developments in recent years and have been demonstrated with a broad array of catalysts and substrate combinations. In reactions of this type, two  $\pi$ -systems such as aldehydes, enones, alkynes, dienes, or allenes are typically combined with a reducing agent such as elemental hydrogen, silanes, boranes, or organozincs. During the coupling event, the two  $\pi$ -systems are joined via C–C bond formation and undergo a net two-electron reduction, while the reducing agent undergoes a net two-electron oxidation.<sup>1</sup> Whereas many transition-metal-catalyzed processes such as enyne cycloisomerizations do not require a reducing agent, the nature of the catalysts and substrate combinations are often very different from the catalysts and substrate combinations that undergo reductive couplings. The vast majority of cycloisomerization processes involve olefin formation via  $\beta$ -hydride elimination of a metal alkyl.<sup>2</sup>

The nickel-catalyzed [3+2] reductive cycloaddition of enals and alkynes with various reducing agents to afford cyclopentenol **3** was recently described by our laboratories (Scheme 1).<sup>3</sup> When enones rather than enals were employed, simple reductive coupling to afford  $\gamma,\delta$ -unsaturated ketone **4** was instead observed.<sup>4</sup> Formation of metallacycle **1** followed by protonation to afford alkenyl nickel species **2** was a key step in both pathways, whereas the fate of intermediate **2** diverged to either product **3** or **4** depending upon whether enals or enones were used as starting materials. During the course of these investigations, we found that a third minor pathway was possible for enals, wherein methyl ester **5** was produced in low yield when PCy<sub>3</sub> was used as ligand.

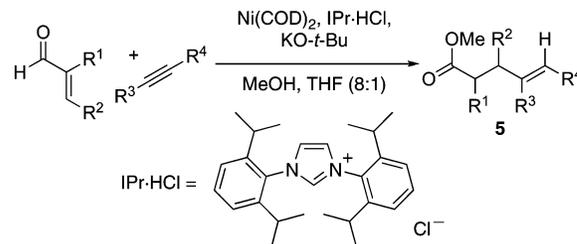
Whereas the formation of **3** or **4** is formally a reductive cycloaddition or coupling, the generation of **5** instead involves an internal redox process, wherein the aldehyde is oxidized and the alkyne is reduced.<sup>5</sup> We therefore anticipated that a reducing agent may not be required for the formation of compound **5**. Attempting its formation in the absence of Et<sub>3</sub>B illustrated that the reducing agent is indeed not required. Reaction optimization suggested that optimal conditions for formation of compound **5** involve treatment of an enal and alkyne with Ni(COD)<sub>2</sub> and IPr in a methanol/THF solvent system (Table 1). Using this optimized procedure, a number of examples of the procedure were carried out. As illustrated, the process tolerates substitution at either the  $\alpha$ - or  $\beta$ -position of the enal as well as aryl or alkyl functionality on the alkyne.

In light of the previously proposed mechanism for generation of compounds **3** and **4**, we suggest that metallacycle **6** is a key intermediate in the generation of product **5** (Scheme 2).<sup>6</sup> Protonation of the enolate moiety of **6** by methanol would generate species **7**, followed by the addition of MeO<sup>−</sup> to the complexed aldehyde to produce hemiacetal **8**. Aldehyde insertion into a nickel methoxide species could also be involved in the formation of **8**.  $\beta$ -Hydride elimination of this species would then afford nickel hydride **9**, which would produce the observed product **5** upon reductive elimination.<sup>7</sup> Alternatively, addition of uncomplexed *N*-heterocyclic carbene to the aldehyde of **7** could be responsible for hydride transfer to nickel,

**Scheme 1.** Divergent Reaction Pathways



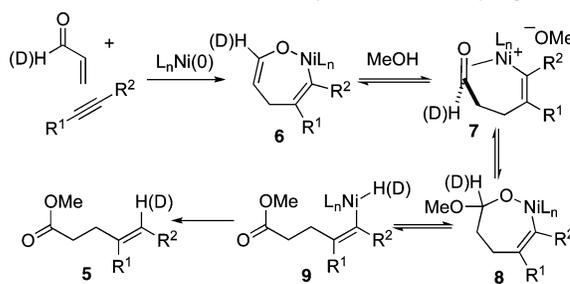
**Table 1.** Three-Component Enal, Alkyne, Alcohol Additions<sup>a</sup>



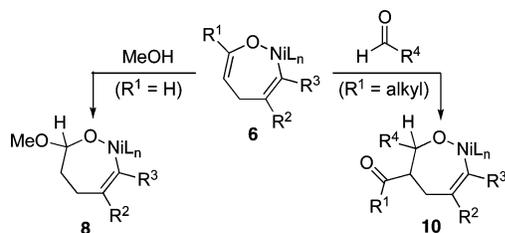
entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	% yield (regioselectivity)
1	H	n-Pr	Ph	Me	75 (53:47)
2	H	n-Pr	Et	Et	52
3	H	n-Pr	n-Pent	Me	76 (73:27)
4	Me	H	Ph	Me	85 (75:25)
5	H	(CH <sub>2</sub> ) <sub>2</sub> Ph	Et	Et	45

<sup>a</sup> Reaction conditions: enal (1.0 equiv), alkyne (1.5 equiv), Ni(COD)<sub>2</sub> (0.1 equiv), IPr-HCl (0.1 equiv), KO-*t*-Bu (0.1 equiv), MeOH/THF (8:1), 50 °C, 2 h.

**Scheme 2.** Mechanism of Enal, Alkyne, Alcohol Couplings



followed by acyl transfer to methanol.<sup>5</sup> As noted in Scheme 2, incorporation of deuterium at the aldehyde carbon leads to deuteration of the alkene C–H in product **5** by the mechanism depicted, and this result was confirmed with >95% deuterium incorporation at the expected alkene position in the Table 1, entry

**Scheme 3.** Strategies for Oxametalacycloheptadiene Synthesis

5 example. This deuterium-labeling analysis unambiguously rules out the possibility that methanol serves as a hydride source concomitant with formaldehyde generation.

Upon considering the proposed mechanism for the formation of compound **5** (Scheme 2), we anticipated that other structurally related nickel alkoxide species could potentially participate in mechanistically related processes. A requirement for the proposed mechanistic pathway is the generation of a metallacyclic alkoxide that possesses an accessible  $\beta$ -hydrogen. We reasoned that an aldol addition reaction of metallacyclic enolate **6** would generate species **10**,<sup>8</sup> which bears structural similarity to the key hemiacetal **8** proposed in the generation of **5** (Scheme 3).

Our exploratory experiments thus focused on the catalytic addition of enals, alkynes, and aldehydes with Ni(0) catalysts in the absence of protic solvents in order to avoid undesired enolate protonation. At the outset, avoiding undesired pathways (such as homocoupling) in a fully intermolecular catalytic coupling of three  $\pi$ -components appeared to be a daunting task.<sup>9</sup> This is particularly true since nickel-catalyzed couplings of enones with alkynes, aldehydes with alkynes, and alkyne trimerizations are all well precedented processes.<sup>1</sup> Thus we were very pleased to observe that treatment of a mixture of an enone, an aldehyde, and an alkyne to Ni(COD)<sub>2</sub> with either PCy<sub>3</sub> or IPr as ligand in toluene directly afforded 1,3-diketone products **11** in good yield with a high degree of chemoselectivity. Using these optimized procedures, a number of illustrations of this three-component coupling of enones, alkynes, and aldehydes were carried out (Table 2). The enone may be functionalized with a variety of groups at the carbonyl carbon and at the  $\alpha$ -position, although  $\beta$ -substitution on the enone is not tolerated. The alkyne may be aromatic, nonaromatic, or terminal. As illustrated by entries 1–12, the alkyne regioselectivities are reversed depending on the choice of ligand (PCy<sub>3</sub> vs IPr). Whereas regiochemical reversals had been noted in reductive couplings involving similarly substituted alkynes,<sup>10</sup> the reversal of regioselectivity with aromatic and terminal alkynes is unprecedented in non-directed nickel-catalyzed reductive couplings.<sup>11</sup> Finally, both aromatic and aliphatic aldehydes are tolerated depending on ligand structure. The participation of aliphatic aldehydes requires PCy<sub>3</sub>, whereas aromatic aldehydes participate with either PCy<sub>3</sub> or IPr-derived catalysts.

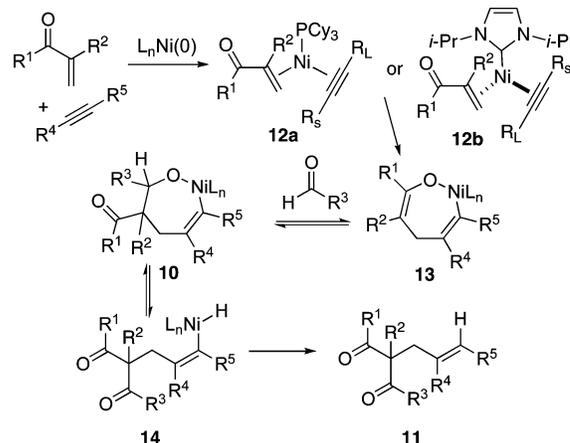
With respect to synthetic utility of this transformation, we note that allylations of 1,3-dicarbonyls provide straightforward entries to the substructures prepared in Table 2. However, the unsymmetrical 1,3-diketones and the stereodefined allylic electrophiles required for synthesis of the products in Table 2 typically require prior preparation (often multistep), and the direct catalytic union of enones, alkynes, and aldehydes represents a greatly improved method for preparation of the compounds depicted. Additionally, the *O*-acylation that sometimes plagues attempts at enolate *C*-acylation in conjugate addition/acylation strategies is avoided by the procedure described herein.<sup>12</sup>

We suggest that the mechanism of the enone, alkyne, aldehyde three-component couplings proceed by a similar pathway to that proposed above for enal, alkyne, alcohol three-component couplings.

**Table 2.** Three-Component Enone, Alkyne, Aldehyde Additions<sup>a</sup>

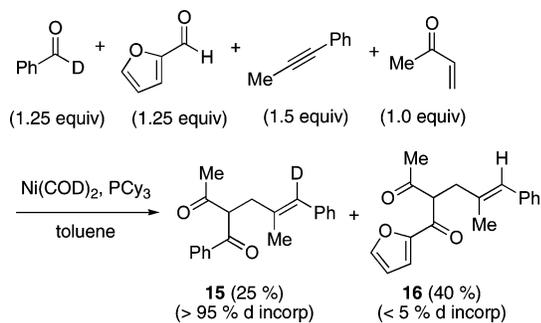
entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	ligand	% yield (regioselect)
1	Me	H	Ph	Et	Et	IPr	66
2	Me	H	Ph	Et	Et	PCy <sub>3</sub>	70
3	<i>n</i> -Pent	H	Ph	Ph	Me	IPr	61 (72:28)
4	<i>n</i> -Pent	H	Ph	Me	Ph	PCy <sub>3</sub>	76 (>95:5)
5	<i>n</i> -Pent	H	Ph	Ph	H	IPr	60 (>95:5)
6	<i>n</i> -Pent	H	Ph	H	Ph	PCy <sub>3</sub>	56 (90:10)
7	Me	H	2-furyl	Ph	Me	IPr	86 (80:20)
8	Me	H	2-furyl	Me	Ph	PCy <sub>3</sub>	77 (>95:5)
9	Me	Me	Ph	Ph	Me	IPr	47 (61:39)
10	Me	Me	Ph	Me	Ph	PCy <sub>3</sub>	65 (87:13)
11	Me	H	Ph	Ph	Me	IPr	72 (80:20)
12	Me	H	Ph	Me	Ph	PCy <sub>3</sub>	79 (>95:5)
13	<i>n</i> -Pent	H	<i>i</i> -Pr	Me	Ph	PCy <sub>3</sub>	50 (>95:5)
14	Et	H	<i>i</i> -Pr	Me	Ph	PCy <sub>3</sub>	42 (>95:5)
15	Et	H	Cy	Me	Ph	PCy <sub>3</sub>	46 (>95:5)

<sup>a</sup> Reaction conditions, IPr variant: enone (1.0 equiv), alkyne (1.5 equiv), aldehyde (2.0 equiv), Ni(COD)<sub>2</sub> (0.1 equiv), IPr-HCl (0.1 equiv), KO-*t*-Bu (0.1 equiv), toluene, 90 °C, 1 h. PCy<sub>3</sub> variant: enone (1.0 equiv), alkyne (1.5 equiv), aldehyde (2.0 equiv), Ni(COD)<sub>2</sub> (0.1 equiv), tricyclohexyl phosphine (0.2 equiv), toluene, 90 °C, 1 h.

**Scheme 4.** Mechanism of Enone, Alkyne, Aldehyde Couplings

$\pi$ -Complexes **12a** and **12b** are accessible via complexation of the enone and alkyne to Ni(0) (Scheme 4). The sterically demanding environment of the IPr ligand may favor orientation of the small alkyne substituent proximal to the ligand as in **12b**, whereas the smaller size of PCy<sub>3</sub> may favor the opposite orientation **12a** to minimize interactions of the large alkyne substituent with the enone  $\beta$ -carbon.<sup>10</sup> Oxidative cyclization to metallacycle **13** is followed by aldol addition of the nickel enolate to the aldehyde.<sup>6</sup> The resulting nickel aldolate **10** undergoes  $\beta$ -hydride elimination to nickel-hydride **14**,<sup>13</sup> which then affords product **11** upon reductive elimination. Notably, a prior report from our laboratory described a stoichiometric process involving aldol reactions of bicyclic metallacycles derived from alkynyl enals;<sup>8a,b</sup> however, by changing to an intermolecular process with enone starting materials and a different ligand environment, the catalytic generation of structurally different products by a distinct mechanistic pathway now becomes possible.

Deuterium-labeling experiments are again useful in evaluating the proposed mechanism (Scheme 5). Upon carrying out the Ni(COD)<sub>2</sub>/PCy<sub>3</sub>-catalyzed coupling of *d*<sub>1</sub>-benzaldehyde, methyl vinyl ketone, and 1-phenyl propyne, deuterated product **15** was obtained

Scheme 5. Deuterium-Labeling Studies<sup>a</sup>

<sup>a</sup> Yields are based upon methyl vinyl ketone.

in 73% yield with >95% deuterium incorporation at the expected alkenyl position. The same result was obtained with the  $\text{Ni(COD)}_2/\text{IPr}$  catalyst system with the reversed regioselectivity as expected. To probe the molecularity of the formal 1,5-hydrogen migration, a crossover experiment was performed. Beginning with 1.25 equiv each of *d*<sub>1</sub>-benzaldehyde and 2-furaldehyde, methyl vinyl ketone (1.0 equiv) and 1-phenyl propyne (1.5 equiv), a catalytic coupling involving the  $\text{Ni(COD)}_2/\text{PCy}_3$ -based conditions was performed. Product **15** was obtained in 25% yield with >95% deuterium incorporation, whereas product **16**, obtained in 40% yield, possessed <5% deuterium incorporation. A related crossover experiment with 3-hexyne and the  $\text{Ni(COD)}_2/\text{IPr}$  catalyst system also afforded >95% deuterium incorporation in the phenyl-containing product. These experiments unambiguously establish an intramolecular hydrogen migration and rule out alternate mechanisms that could involve a preformed nickel-hydride active catalyst.<sup>14</sup>

Analogies to a number of classical organic–organic reactions can be drawn to the processes reported herein. For example, the Cannizzaro<sup>15</sup> and Evans-Tishchenko<sup>16</sup> reactions involve a hydride transfer event from hemiacetal intermediates to an electrophilic unit. The formation of product **5** (Scheme 2) and product **11** (Scheme 4) involves a conceptually related hydride transfer event, but the hydride transfer to an alkyne is now allowed by these new procedures. Therefore, the developments in this paper may be viewed as unusual extensions of these classical reactions, albeit with very different mechanisms involved.

In summary, two distinct three-component catalytic processes have been discovered: the coupling of alcohols, alkynes, and enals, and the coupling of aldehydes, alkynes, and enones. Both of the processes involve internal redox and proceed in the absence of reducing agents that have previously been required in many nickel-catalyzed couplings of these classes of reagents. The high extent of chemoselectivity is unusual, particularly for aldehyde, enone, alkyne couplings that involve three different  $\pi$ -components. We believe that engineering internal redox into reactions of this type will constitute a strategy of broad utility.<sup>17</sup>

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**Supporting Information Available:** Full experimental details and copies of NMR spectral data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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