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Competition Between Insertion and Conjugate Addition in Nickel-Catalyzed Couplings of Enones With Unsaturated Functional Groups

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Abstract: The intra- and intermolecular couplings of enones with alkynes or enones in the presence of organozincs under Ni(COD)$_2$ catalysis resulted in three general reaction pathways: direct conjugate addition, cyclization with alkylation, and cyclization with reduction. The effects of substrate structural variations on selectivities among these three pathways were investigated.
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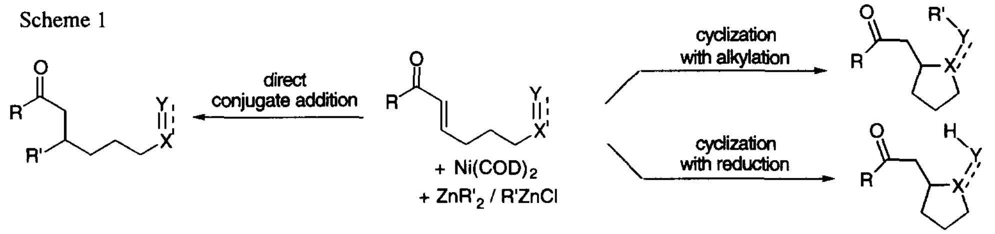
Recent results from our laboratories demonstrated that efficient cyclizations could be carried out upon treatment of enones possessing unsaturated side chains with Ni(COD)$_2$ and an organozinc.[1] Three distinct reaction pathways were observed: cyclization with alkylation by the organozinc, cyclization with reduction, and direct conjugate addition (Scheme 1). Selectivities were highly dependent upon substrate structure, organozinc structure, and ligand structure. Given that our previous studies were carried out with substrates that would afford five-membered rings in the pathways involving cyclization with reduction or alkylation, we have studied the efficiency of intramolecular processes that afford rings larger than five-membered[2] as well as related intermolecular processes.

Scheme 1



The intramolecular couplings of enones and alkynes were first investigated (Scheme 2, Table 1).[1a] Exocyclic ring closures of alkynyl enones **1a** and **1b** to produce cycloadducts **2a** and **2b** or **3a** and **3b** were efficient in the production of five- and six-membered rings, in yields ranging from 54-92 %. However, cyclizations of **1c** (n = 3) at 0.02 M concentration led to both monomeric and dimeric products. Cyclizations with ZnMe$_2$ / MeZnCl conducted in the absence of triphenylphosphine afforded sixteen-membered macrocycle **4c**, seven-membered ring adduct **2c**, and direct conjugate addition product **5c**, all in low yield. Cyclizations conducted in the presence of triphenylphosphine with Et$_2$Zn afforded cycloheptanes **2c** and **3c** by an exocyclic pathway along with direct conjugate adduct **5c** in low yield, with no trace of dimeric products being observed. Cyclizations of **1d** (n = 4) with ZnMe$_2$ / MeZnCl in the absence of triphenylphosphine produced eighteen-membered macrocycle **4d** in 30 % yield and direct conjugate adduct **5d** in 19 % yield. No cyclic products were observed with phosphine-promoted cyclizations of **1d** (n = 4). All reactions were conducted in THF at 0 °C, with the exception of the phosphine-promoted reductive cyclization of **1c** (n = 3) which required elevated temperatures (35 °C) to achieve satisfactory rates.

Scheme 2

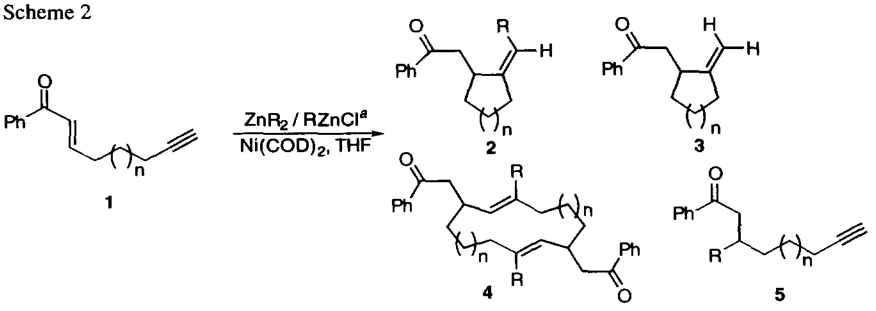


Table 1. Alkynyl Enone Cyclizations

n	R	added ligand	products (yield)[a]
1	Me	none	**2a** (82 %)
1	Et	PPh_3	**3a** (92 %)
2	Me	none	**2b** (54 %)
2	Et	PPh_3	**3b** (66 %), **2b** (10 %)
3	Me	none	**2c** (14 %), **4c** (10 %[b]), **5c** (3 %)
3	Et	PPh_3	**2c** & **3c** (1:1, 10 %), **5c** (5 %)
4	Me	none	**4d** (30 %[b]), **5d** (19 %)

[a]Unless otherwise noted, all products were obtained in >95% isomeric purity as ascertained ^1H NMR. Alkylative cyclizations were most efficient with organozincs generated from a 3:2 stoichiometry of MeLi with $ZnCl_2$. Reductive cyclizations were most efficient with commercial Et_2Zn and with a catalyst prepared from 4:1 PPh_3 : $Ni(COD)_2$. [b]Obtained as an inseparable mixture of diastereomers.

Intermolecular three-component couplings were also investigated,[3] and reagent concentration was found to be important (Scheme 3, Table 2). Reactions were carried out at 0 °C with 0.1 M concentrations of substrate, 1.2 equiv. of alkyne, and the organozinc mixture obtained from treatment of 3 equiv. of zinc chloride with 2.5 equiv. of alkyllithium or organomagnesium halide. A related procedure that employed commercial dimethylzinc was reported by Sato and Ikeda while our work was in progress.[4a] Our results, described in Table 2, employed the optimal concentration described above of the organozinc unless otherwise noted. Higher concentrations of the alkyne afforded byproduct **8** derived from multiple incorporation of the alkyne fragment, and higher concentrations of the organozinc produced the direct conjugate addition product **7** in small amounts along with modest yields of the desired three-component coupling product **6**. In an extreme case employing 15 equiv. of alkyne, product **8** was obtained in 68 % yield along with 20 % of three-component coupling product **6**. Interestingly, the addition of triphenylphosphine in experiments employing sp^3-hybridized organozincs bearing β-hydrogens did not promote β-hydride elimination as in the intramolecular cases.[1a] A direct comparison of reactions with and without triphenylphosphine is provided for couplings involving 1-octyne. Couplings involving phenylacetylene were not efficient in the presence of triphenylphosphine. We have not actively pursued reductive couplings with hydrogen atom introduction in the intermolecular variant of this process since excellent procedures from Lipschutz,[5] Schwartz,[6] and the Searle group[7] exist for preparation of the hydrogen-substituted product (**6**, R^2 = H) by hydrozirconation / conjugate addition of terminal alkynes.[8]

Scheme 3

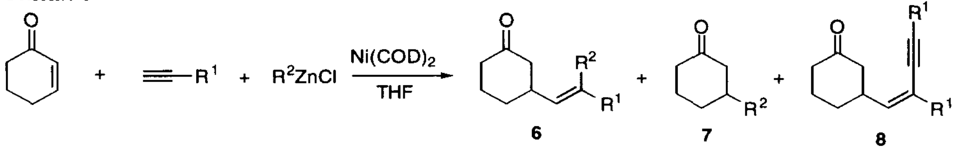


Table 2. Three-Component Couplings

method	R^1	R^2	product (yield)[a]
A	Ph	Me	**6** (62 %)
A	Ph	*n*-Bu	**6** (65 %), **7** (10 %)[b]
A	Ph	*n*-Bu	**8** (68 %), **6** (20 %)[c]
A	Ph	$CH=CH_2$	**6** (48 %)
A	*n*-hexyl	Me	**6** (62 %)
B	*n*-hexyl	Me	**6** (64 %)[d]

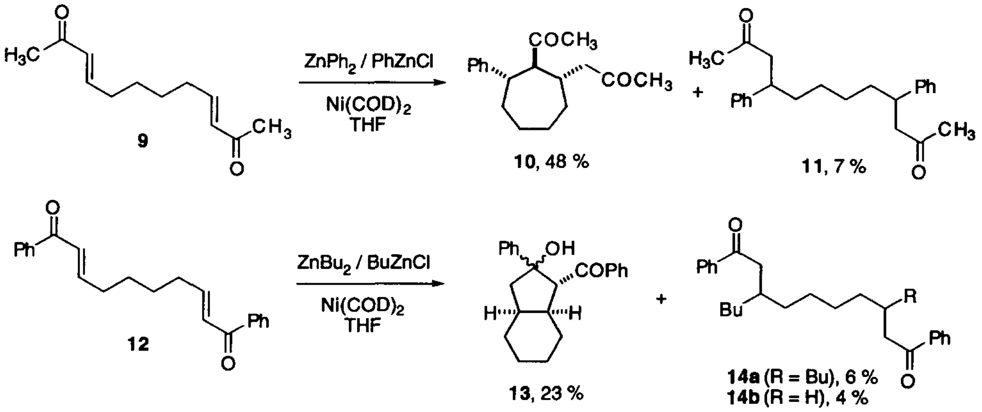
method	R^1	R^2	product (yield)[a]
A	*n*-hexyl	*n*-Bu	**6** (57 %)[e]
B	*n*-hexyl	*n*-Bu	**6** (62 %)[f]
A	*n*-hexyl	Ph	**6** (23 %),[f] **7** (47 %)
B[g]	*n*-hexyl	Ph	**6** (24 %),[f] **7** (60 %)
B	*n*-hexyl	Ph	**6** (21 %),[f] **7** (40 %)

Method A: No additional additives were present. Method B: The catalyst was prepared from 2:1 PPh_3:$Ni(COD)_2$, and 1.2 equiv. of TMSCl (relative to cyclohexenone) was added. [a]Unless otherwise noted, all products were obtained in >95% isomeric purity as ascertained by ^1H NMR. [b]**6** and **7** (R^1 = Ph, R^2 = *n*-Bu) were only partially separable. [c]Fifteen equiv. of alkyne were used. [d]Obtained as an 8:1 mixture of regioisomers as ascertained by ^1H NMR. [e]Obtained as a 3:1 mixture of regioisomers as ascertained by ^1H NMR. [f]Obtained as a 10:1 mixture of regioisomers as ascertained by ^1H NMR. [g]The catalyst was prepared from a 1:1 ratio of PPh_3 and $Ni(COD)_2$.

Cyclizations of bis-enones were next investigated (Scheme 4).[1b,9] With substrates possessing a four-carbon tether between the two enone β-carbons, organozinc structure was crucial in determining the reaction pathway. As in our previous studies involving five-membered ring formation,[1b] reactions employing diphenylzinc exclusively produced compounds derived from direct conjugate addition. In a 0.02 M reaction in which a solution of diphenylzinc / phenylzinc chloride was added by syringe drive to a THF solution of bis-enone **9** and 5 mol % $Ni(COD)_2$, phenyl group conjugate addition followed by intramolecular Michael addition of the kinetic zinc enolate to afford seven-membered ring adduct **10** was observed along with a low yield of acyclic double addition product **11**.[10] Higher concentrations and faster addition of the organozinc led to increased amounts of **11**. However, whereas reactions with dibutylzinc produced reductive cyclization products almost exclusively in our studies involving five-membered ring formation,[1b] different selectivities were obtained as the ring size increased. With bis-enones possessing four or more carbons in the tether chain, low yields of acyclic mono- and di-addition products along with cyclic compounds analogous to **10** were typically observed. In one instance, bicyclononane **13**, derived from reductive cyclization of bis-enone **12**, was obtained in 23 % yield as a mixture of two diastereomers along with several byproducts derived from butyl group conjugate addition.

In summary, with inter- and intramolecular couplings of enones with alkynes, alkyne insertion generally occurred at a faster rate than conjugate addition. 5-Exo and 6-exo cyclizations of alkynyl enones were efficient, but dimerization pathways predominated in attempts to produce seven- and eight-membered rings. Intermolecular three-component couplings involving enones, alkynes, and organozincs were efficient under appropriate conditions, although direct organozinc conjugate addition and multiple incorporation of the alkyne were competitive in some instances. With bis-enones, reductive cyclizations employing dibutylzinc to afford five-membered rings occurred at a faster rate than conjugate addition, whereas six-membered ring reductive cyclizations were much less efficient and occurred at a rate roughly comparable to conjugate addition. A mechanistic rational for these observations will be reported in due time.

Scheme 4



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