

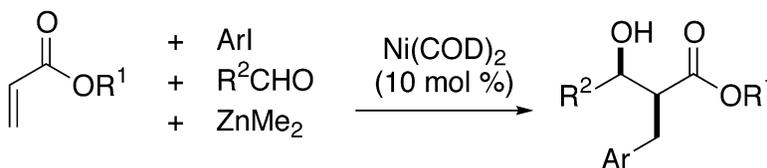
Communication

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A New Catalytic Conjugate Addition/Aldol Strategy That Avoids Preformed Metalated Nucleophiles

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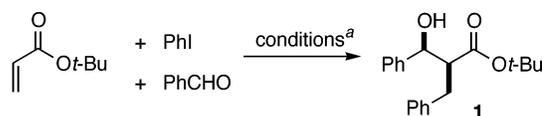
The functionalization of α,β -unsaturated carbonyls by a conjugate addition/aldol sequence is a central transformation in organic synthesis. Strategies initiated by organocuprate additions are the most widely used,¹ and related sequences involving organozirconiums,² organozincs,³ organoboranes,⁴ and other metals have also been developed. These procedures, while extraordinarily powerful in many contexts, often involve experimentally demanding operational procedures given the air, moisture, or thermal instabilities of many of the requisite metalated nucleophiles. For these reasons, a complementary protocol that involves the direct introduction of a haloaromatic without requiring the discreet production of a metalated reagent would provide considerable advantages.^{5–7}

It is widely appreciated that transition metals cleanly promote the conjugate addition of aryl iodides to α,β -unsaturated carbonyls. In the case of Pd(0)-catalyzed Heck reactions, oxidative addition of Pd(0) to the aryl iodide is followed by migratory insertion of the alkene to allow regioselective introduction of the aryl unit to the β -position of the unsaturated carbonyl.⁸ However, this strategy is typically not amenable to a conjugate addition/aldol sequence because β -hydride elimination terminates the pathway to produce a β -functionalized α,β -unsaturated carbonyl product. Several examples of the direct Ni-catalyzed conjugate addition of aryl and alkenyl iodides to unsaturated carbonyls without accompanying β -hydride elimination have been reported, but these strategies typically require > 100 mol % of the nickel catalyst, and processes of this type have not been coupled with aldol functionalization because all examples involved either protonation or reduction of the transient kinetic transition metal enolate.⁹ Herein, we report a novel catalytic four-component strategy that allows the direct coupling of aryl iodides, aldehydes, acrylates, and dimethylzinc to produce conjugate addition/aldol products without requiring the formation of a metalated aryl organometallic.

Our initial studies began with an investigation of the addition of phenyl iodide, *tert*-butyl acrylate, and benzaldehyde under various conditions. After extensive variation of the nickel precatalyst, ligands, Lewis acidic cocatalysts, solvent, and stoichiometry, an efficient protocol was not found, and Procedure A noted below (Scheme 1) is representative of the reaction efficiencies observed. Although the desired three-component couplings were observed, the process was plagued by poor catalyst turnover, the need for extended reaction times at elevated temperature, and poor diastereoselectivities.

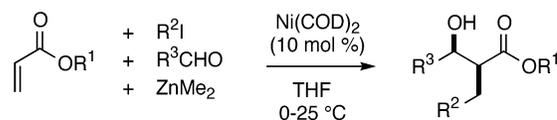
However, the catalytic process in the presence of dimethylzinc was examined, and a remarkable change was noted. In contrast to the example cited above (Procedure A, Scheme 1), the coupling of phenyl iodide, *tert*-butyl acrylate, benzaldehyde, and dimethylzinc was completed in 1 h at 0 °C with only 10 mol % Ni(COD)₂ (Procedure B, Scheme 1).¹⁰ Despite the potential for many undesired competing reactions such as the direct or catalytic addition of dimethylzinc to the acrylate, aldehyde, or aryl iodide, the reaction chemoselectivity was very clean, affording the desired conjugate

Scheme 1^a



^a Procedure A: NiCl₂ (100 mol %), pyridine, Zn⁰, THF, reflux, 24 h, 79% (2:1 dr). Procedure B: Ni(COD)₂ (10 mol %), ZnMe₂, THF, 0 °C, 1 h, 88% (86:14 dr).

Table 1.^a



entry	R ¹	R ²	R ³	% yield ^b (dr)
1	<i>t</i> -Bu	Ph	Ph	88 (86:14)
2	CH ₃	Ph	Ph	76 (89:11)
3	<i>t</i> -Bu	Ph	<i>p</i> -C ₆ H ₄ -OCH ₃	73 (82:18)
4	<i>t</i> -Bu	Ph	2-furyl	76 (84:16)
5	<i>t</i> -Bu	Ph	CH ₂ CH ₃	75 (85:15)
6	<i>t</i> -Bu	Ph	CH(CH ₃) ₂	78 (88:12)
7	<i>t</i> -Bu	Ph	C(CH ₃) ₃	71 (66:34)
8	<i>t</i> -Bu	Ph	acetone	54% (- -)
9	<i>t</i> -Bu	1-naphthyl	Ph	71 (87:13)
10	<i>t</i> -Bu	<i>p</i> -C ₆ H ₄ -CH ₃	Ph	79 (88:12)
11	<i>t</i> -Bu	<i>m</i> -C ₆ H ₄ -CO ₂ Et	Ph	54 (87:13)
12	<i>t</i> -Bu	<i>m</i> -C ₆ H ₄ -CH ₂ OTBS	Ph	73 (88:12)

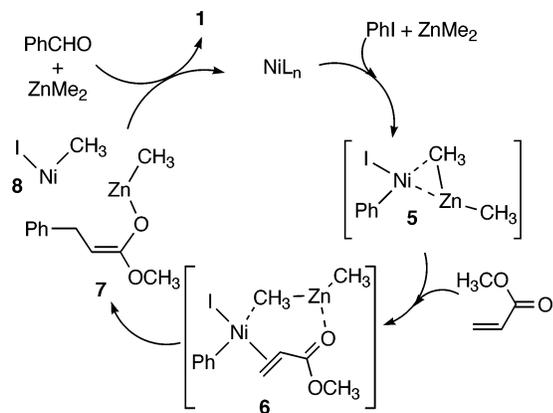
^a Typical stoichiometry: aldehyde (2.0 equiv), aryl iodide (2.0 equiv), dimethylzinc (1.5 equiv), acrylate (1.0 equiv). ^b The % yield is the combined yield of both diastereomers.

addition/aldol product 1 in 88% yield with 86:14 dr in favor of the syn diastereomer.

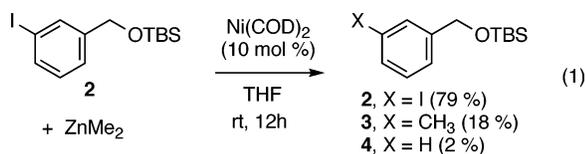
The scope of this process with respect to the aldehyde and aryl iodide appears to be broad (Table 1). The aldehyde may be aromatic, heteroaromatic, or aliphatic with primary, secondary, and tertiary substitution at the aldehyde-bearing carbon, and a simple ketone was also tolerated (entry 8). Across this range of aldehydes (entries 1–7), the yields and diastereoselectivities were uniformly good with the exception of suppressed diastereoselectivity in the case of a tertiary aldehyde (entry 7). The aryl iodide may also be functionalized, with alkyl, ester, and protected hydroxyalkyl units as well as a bicyclic aromatic being cleanly introduced (entries 9–12). Although the yield of addition with an ester-functionalized aryl group was somewhat suppressed, there are obvious advantages of avoiding the requirement for preparing a metalated organometallic in the presence of lithium reagent-sensitive functional groups.¹¹ Variation of the acrylate component beyond simple changes in the ester group, however, is problematic, as chemoselectivity issues complicate the additions involving more elaborate α,β -unsaturated carbonyls.

A key mechanistic question centers on the potential involvement of arylzincs as reactive intermediates. Notably, Knochel has reported

Scheme 2



that *alkylzincs* may be produced from diethylzinc and alkyl iodides with nickel catalysis; however, the corresponding process has not been reported for aryl iodides.¹² To probe this issue, we examined the reaction of aryl iodide **2** with dimethylzinc in the presence of Ni(COD)₂ (eq 1). After 12 h at room temperature, GCMS and NMR analysis revealed a 79% recovery of aryl iodide **2**, 18% of compound **3** derived from cross-coupling of ZnMe₂ with **2**, 2% of dehalogenated product **4**, and <1% of the biaryl that would be derived from arylzinc cross-coupling with **2**. Cross-coupling product **3** could be produced either by a standard cross-coupling mechanism or by metathesis of **2** with ZnMe₂ to generate an arylzinc and methyl iodide followed by organozinc alkylation. To distinguish these mechanisms, the experiment noted in eq 1 was repeated in the presence of CD₃I (3 equiv), and no *d*₃-**3** was produced.¹³ On the basis of these experiments, we conclude that arylzincs are not produced in an appreciable quantity under the catalytic conditions. The likely dual role of the organozinc is to reduce the Ni(II) catalyst back to a catalytically active form and to activate one or more of the reaction components via a Lewis basic or Lewis acidic interaction.^{14–16}



On the basis of these observations, we propose that the rate-accelerating role of the organozinc likely involves catalyst modification at an early stage of the reaction (Scheme 2). Interaction of the organozinc with the oxidative addition adduct as depicted in tentative structure **5**, or possibly with the Ni(0) species that undergoes oxidative addition, could potentially explain the significant rate acceleration in comparison with reactions that lack the organozinc component.^{17–19} The conversion of **6** to **7** and **8** could proceed by several possible mechanisms including migratory insertion or oxidative addition, either with or without the involvement of electron transfer/capture pathways.²⁰ Zinc enolate **7** is the likely species that undergoes aldol addition.

In summary, a novel approach for effecting catalytic conjugate addition/aldol sequences from commercially available reagents has been developed. Significantly, this method avoids the typical requirement of preparing sensitive, metalated, organometallic

nucleophiles. Although methyl addition is not observed, dimethylzinc plays an important role in reaction acceleration. Expansion of the scope of this new reaction as well as better understanding the complex role of the organozinc in this and other metal-catalyzed processes are under active investigation in our laboratories.

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

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