

Surprising Role of Aryl Halides in Nickel-Catalyzed Reductive Aldol Reactions

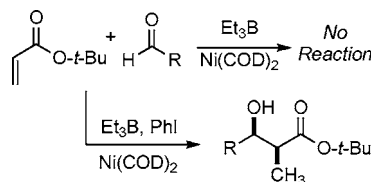
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ABSTRACT



A new nickel-catalyzed method for the reductive aldol addition of acrylates and aldehydes has been developed. An unexpected requirement for an aryl iodide additive was found in the process, and the effect was shown to be linked to an initiation step.

Conjugate addition/aldol and reductive aldol sequences of α,β -unsaturated carbonyls provide powerful strategies for the synthesis of complex ketones and carboxylic acid derivatives. Processes involving conjugate addition typically employ organocuprates,¹ organozincs,² organoboranes,³ or organozirconium reagents.⁴ In contrast, reductive aldol sequences typically use reducing agents such as silane derivatives⁵ or hydrogen gas⁶ as the terminal reductant.^{7,8} Alternatively, our group recently disclosed a procedure for conjugate addition/aldol addition involving aryl iodides directly while using commercially available dimethylzinc as a promoter, thus avoiding the requirement for prior synthesis of a metalated nucleophile (Scheme 1; Table 1, entry 1).⁹ Since the component that adds as a nucleophile (the aryl iodide) is

structurally distinct from the reducing agent (dimethylzinc), the opportunity exists for addition of the aryl iodide and organozinc to be competitive. Given the tremendous number of products that are potentially accessible from the multi-component character of the reaction, the development of selective processes poses a significant challenge in chemoselectivity (Scheme 2). Additionally, the impact of each reagent on the reactivity characteristics of the other reagents can further complicate issues in chemoselectivity. Herein, we describe the interdependence of the reactivity patterns of the various components. Not only can tuning the structure of the reducing agent completely change the course of the reactions, but additives that are not incorporated into the

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Scheme 1. Conjugate Addition/Aldol and Reductive Aldol Products

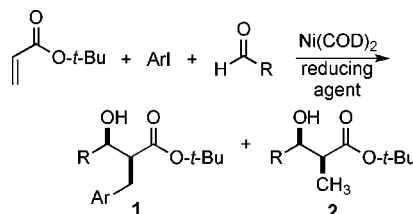
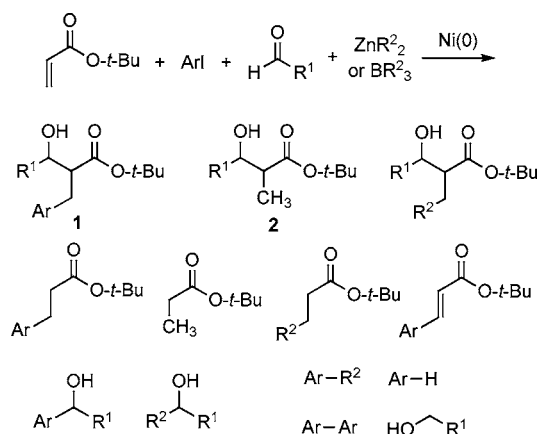


Table 1. Impact of Reducing Agent Structure^a

entry	reducing agent	% yield (1:2)	(syn:anti) of 1	(syn:anti) of 2
1	ZnMe ₂	88 (>98:2)	86:14	
2	ZnEt ₂	87 (67:33)	90:10	60:40
3	BEt ₃	92 (5:95)		88:12

^a Reaction conditions: *tert*-butyl acrylate (1.0 equiv), benzaldehyde (1.5 equiv), phenyl iodide (2.0 equiv), reducing agent (2.0 equiv), Ni(COD)₂ (10 mol %), THF, 65 °C.

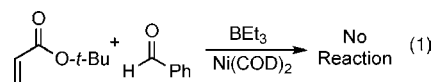
product structures can also have a profound impact on the manner in which the other reagents combine.¹⁰ This study provides the first examples of nickel-catalyzed reductive aldol processes and illustrates a novel role of aryl iodides in reaction initiation.

Scheme 2. Possible Reaction Products

In initially exploring the impact of reducing agent structure on the nickel-catalyzed conjugate addition/aldol addition sequence involving aryl iodides, we compared Ni(COD)₂-catalyzed addition of *tert*-butyl acrylate, phenyl iodide, and benzaldehyde employing dimethylzinc, diethylzinc, and

triethylborane as the reducing agent (Table 1). Whereas dimethylzinc promoted addition of the aryl iodide component to afford product **1** (Table 1, entry 1), diethylzinc and triethylborane favored the reductive aldol pathway to give product **2** (Table 1, entries 2 and 3). Preparatively useful selectivity for product **2** was best obtained with triethylborane, whereas diethylzinc afforded a 2:1 mixture of products.

Given that the triethylborane-mediated variant provided a high-yielding, syn-selective procedure for effecting the reductive aldol reaction, we repeated the reaction in the absence of phenyl iodide under otherwise identical conditions. To our surprise, the coupling of *tert*-butyl acrylate, benzaldehyde, and triethylborane with Ni(COD)₂ afforded none of the expected reductive aldol product **2**, and starting materials were cleanly recovered under conditions that afforded high yields of **2** in the presence of phenyl iodide (eq 1). As noted above (Table 1, entry 3), a small amount



(ca 5%) of the conjugate addition/aldol product **1** accompanied formation of the major product **2** in triethylborane-mediated reductive aldol processes. When the aryl iodide is used in excess, only trace amounts are consumed in the course of the reaction. Quantities of aryl iodide as low as 5–10 mol % are sufficient to promote the efficient formation of **2**.

To elucidate whether **1** and **2** are produced simultaneously or sequentially in the triethylborane-mediated reaction, we measured their production as the reaction progressed in an experiment that employed a 1:1.2:1 stoichiometry of *tert*-butyl acrylate, benzaldehyde, and phenyl iodide with 10 mol % Ni(COD)₂. After 1 min at rt, 4% conversion was noted, with a 10:1 ratio of **1:2**. As the reaction progressed, the concentration of **1** remained relatively constant while **2** slowly accumulated, until the reaction was quenched after 7 h at 94% conversion with a 5:95 ratio of **1:2**. Even though a full equivalent of phenyl iodide was used, the burst of **1** noted during the first minute of the reaction corresponded to the full amount of **1** generated during the reaction. Compound **1** clearly results from an initiation event that likely generates the active catalyst species responsible for the formation of **2**.

To gain further insight into the requirements for the initiating species, we examined several aromatic components

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(8) For reducing agents other than silanes, boranes, and H₂, see: (a) Willis, M. C.; Woodward, R. L. *J. Am. Chem. Soc.* **2005**, 127, 18012. (b) Inoue, K.; Ishida, T.; Shibata, I.; Baba, A. *Adv. Synth. Catal.* **2002**, 344, 283. (c) For a recent example of intramolecular diethylzinc-mediated reductive aldols: Lam, H. W.; Joensuu, P. M.; Murray, G. J.; Fordyce, E. A. F.; Prieto, O.; Luebbers, T. *Org. Lett.* **2006**, 8, 3729.

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(10) For an example of the interdependence of catalyst, ligand, and reducing agent structure in a reductive aldol, see ref 5c.

that could potentially participate in oxidative addition or electron-transfer events (Table 2). An electron-rich aromatic

Table 2. Impact of Initiator Structure^a

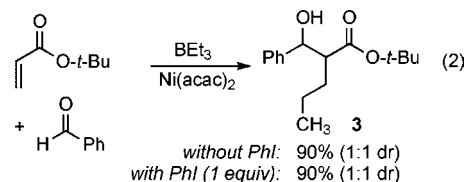
entry	additive	% yield of 2 (dr)
1	PhI	87 (88:12)
2	<i>p</i> -(MeO)C ₆ H ₄ I	85 (88:12)
3	2-iodo- <i>m</i> -xylene	0
4	PhBr	0
5	PhOTf	0
6	C ₆ H ₅ CN	10
7	Ph ₂ C=O	0
8	CH ₃ I	80 (86:14)
9	CH ₃ CH ₂ I	0
10	HI	19

^a Reaction conditions: *tert*-butyl acrylate (1.0 equiv), benzaldehyde (1.5 equiv), initiator (1.0 equiv), triethylborane (2.0 equiv), Ni(COD)₂ (10 mol %), THF, 65 °C.

iodide serves as an effective initiator for the reductive aldol sequence (Table 2, entry 2), but a hindered aryl iodide does not (Table 2, entry 3). Bromobenzene, phenyl triflate, cyanobenzene, and benzophenone are completely ineffective as reaction initiators (Table 2, entries 4–7). The only nonaromatic initiator that exhibited effectiveness was methyl iodide, which also allowed the reductive aldol reaction to proceed efficiently in good yield (Table 2, entry 8). In contrast, ethyl iodide was ineffective as an initiator, and HI-promoted reactions proceeded in low yield (Table 2, entries 9 and 10).

Given the special role of organic iodides that lack steric hindrance, we surmised that oxidative addition of nickel(0) to the C–I bond was a critical step in reaction initiation. This suggested that a Ni(II) precatalyst may potentially serve as an effective catalyst source without aryl iodide initiators. To probe this question, Ni(acac)₂ was examined as a precatalyst, and a third entirely distinct reaction pathway was observed. Treatment of *tert*-butyl acrylate, benzaldehyde, and triethylborane with 10 mol % Ni(acac)₂ in THF, either in the presence or the absence of phenyl iodide with no appreciable change in rate, resulted in the production of

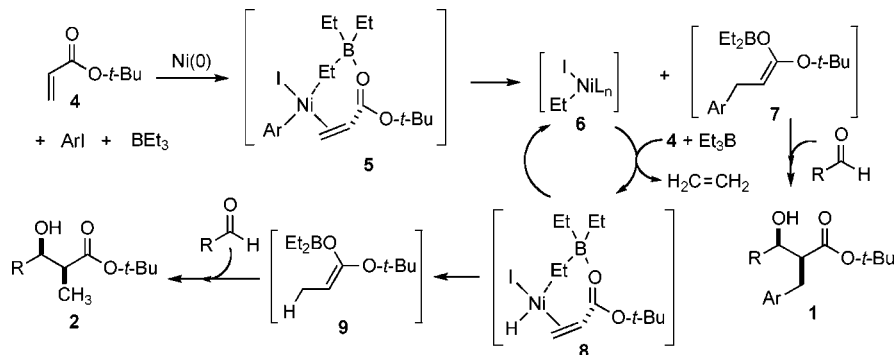
product **3** derived from ethyl conjugate addition followed by aldol trapping (eq 2). Therefore, the reactivity of the



catalyst derived from Ni(COD)₂ and phenyl iodide is clearly different from other readily available sources of Ni(II). This Ni(acac)₂-catalyzed process may be useful, especially in applications involving more complex alkylboranes derived from hydroboration.¹¹

On the basis of the above analysis, we propose that the aryl iodide plays a key role in the initiation step of the triethylborane-mediated reductive aldol reaction. A possible mechanistic sequence proceeds as follows (Scheme 3). Oxidative addition of Ni(0) to the aryl iodide and coordination of acrylate **4** and triethylborane will afford intermediate **5**. Reorganization of **5** to an ethyl(iodo)nickel species **6** and boron enolate **7** may proceed by a migratory insertion, transmetalation sequence. The role of triethylborane as a Lewis acid to activate the enone and as a Lewis base (via a bridging ethyl group) to activate the nickel center derives from our prior computational study of enone/alkyne reductive couplings, which described the nature of such interactions with Ni(0) and dimethylzinc.¹² Boron enolate **7** then undergoes syn aldol addition with the aldehyde to provide product **1**, which is thus solely derived from this required initiation step. The resulting ethyl(iodo)nickel species **6** then complexes with the acrylate and triethylborane concomitant with loss of ethylene to generate nickel hydride **8**.¹³ Reorganization of **8** to boron enolate **9** is accompanied by the regeneration of ethyl(iodo)nickel species **6**.¹⁴ Syn aldol addition of **9** with the aldehyde then provides compound **2**, which is the major product of the reaction. Species **6** is thus a likely active catalyst for formation of the reductive aldol product **2**, and aldol product **1** is a byproduct of the initiation step that generates active catalyst **6**. While the proposed role of the aryl iodide as an initiator that modifies the structure of the active catalyst is novel, precedent involving a related

Scheme 3. Proposed Mechanism for Initiation and Addition Steps



effect was noted in an elegant study from Cheng that described an initiation effect of organic iodides in palladium-catalyzed silaboration of allenes.¹⁵ In the Cheng work, a proposal was made that the initiation step generates a boron-containing byproduct, which then participates in the productive catalytic cycle, whereas our work proposes that catalyst modification is responsible for the effect observed.

The scope of this reductive aldol process was then examined (Table 3). Simple, monosubstituted acrylates were the only Michael acceptors studied that underwent efficient couplings. The scope of aldehydes, however, included a number of structural variations. A variety of aromatic aldehydes were examined, and electron-rich (Table 3, entry 2), heteroaromatic (Table 3, entry 3), electron-deficient (Table 3, entry 4), and halogen-containing aromatic iodides (Table 3, entry 5) were all tolerated. Consistent with our observation that an aryl iodide initiator was required, only entry 5 did not require the addition of phenyl iodide. The reaction also tolerated unbranched aliphatic enolizable aldehydes (Table 3, entry 6), α -branched enolizable aldehydes (Table 3, entry 7), and an α -benzyloxy aliphatic aldehyde (Table 3, entry 8). Whereas good to excellent syn selectivity was observed in all cases, diastereoselection with an α -alkoxy aldehyde (Table 3, entry 8) was poor. In summary, three

(11) 9-BBN derivatives derived from terminal olefins effectively proceed in Ni(acac)₂-catalyzed processes, but yields are modest and mixtures of conjugate addition/aldol trapping and conjugate addition/protonation products are obtained. For examples of nickel-catalyzed conjugate additions of alkenyl and aryl boranes, see: (a) Yoshida, K.; Ogasawara, M.; Hayashi, T. *J. Am. Chem. Soc.* **2002**, *124*, 10984. (b) Yanagi, T.; Sasaki, H.; Suzuki, A.; Miyaura, N. *Synth. Commun.* **1996**, *26*, 2503.

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(13) For examples of other classes of nickel-catalyzed reductive couplings employing triethylborane, see: (a) Kimura, M.; Ezoe, A.; Shibata, K.; Tamaru, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4033. (b) Huang, W.-S.; Chan, J.; Jamison, T. F. *Org. Lett.* **2000**, *26*, 4221.

(14) Nickel enolate aldol reactions are also possible, although several nickel complexes of chiral phosphines or *N*-heterocyclic carbenes participate with no observable enantioselection.

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Table 3. Scope of Nickel-Catalyzed Reductive Aldol Reactions^a

entry	R	% yield of 2 (dr)
1	Ph	87 (88:12)
2	<i>p</i> -(MeO)C ₆ H ₄	88 (87:13)
3	2-furyl	91 (88:12)
4	<i>p</i> -(NC)C ₆ H ₄	86 (90:10)
5	<i>m</i> -(I)C ₆ H ₄	73 (89:11)
6	(CH ₂) ₅ CH ₃	80 (86:14)
7	(CH ₃ CH ₂) ₂ CH	68 (96:4)
8	BnO(CH ₃)CH	60 (45:45:5:5) ^b

^a Reaction conditions: *tert*-butyl acrylate (1.0 equiv), aldehyde (1.5 equiv), phenyl iodide (1.0 equiv), triethylborane (2.0 equiv), Ni(COD)₂ (10 mol %), THF, 65 °C. ^b The two major isomers are derived from a syn aldol process.

distinct pathways (conjugate arylation/aldol, conjugate alkylation/aldol, or conjugate reduction/aldol) have been identified for the nickel-catalyzed multicomponent addition of acrylates, aldehydes, aryl iodides, and a reducing agent (organozinc or organoborane). Each pathway may be selectively accessed by careful choice of catalyst and reagent structure. Whereas the impact of varying catalyst structure and reducing agent structure is not surprising, the observation that aryl iodides dramatically change the course of reactions even when they are not incorporated into the product structure is of considerable conceptual interest. Evidence is presented that the role of the aryl iodide is linked to an initiation step that alters the catalyst structure, and we anticipate that this finding may be useful in many contexts.

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Supporting Information Available: Experimental procedures and a copy of spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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