# Decarboxylative Aldol Reactions of Allyl β-Keto Esters via Heterobimetallic Catalysis

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The direct aldol reaction is a versatile approach toward the construction of building blocks for use in synthesis.[1] Selective formation of the enolate in the presence of the aldehyde poses a significant challenge in the development of a direct aldol reaction. Recent advances toward this goal include metal-catalyzed deprotonation of the nucleophile,[2] transition metal-mediated reductive aldol condensations of unsaturated carbonyl compounds,[3] decarboxylative aldol reactions of malonic acid half thioesters,[4] and proline-catalyzed aldol condensations of aldehydes and ketones.[5] Although considerable progress has been made, transition metal-mediated direct aldol reactions are an underdeveloped approach.[6] The propensity of transition metals to form a carbon-bound enolate that is less reactive toward nucleophilic addition has limited the ability to develop a catalytic reaction (eq 1).[7] However, under the appropriate conditions, an in situ generated transition metal complex may serve as an intermediate in an aldol reaction process.[8] This report describes a heterobimetallic catalyst system that promotes the direct aldol reaction of allyl β-keto esters and aldehydes.[9]

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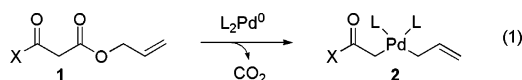
Our initial investigations focused on the use of Pd(0) to catalyze the intermolecular aldol reaction of allyl 4,4-dimethyl-3-oxopentanoate **3** with aldehydes. A report by Tsuji described intramolecular aldol reactions of allyl β-keto esters promoted by Pd(0).[6a] In contrast, the reaction of β-keto ester **3** and 3-phenylpropanal **4a** in the presence of Pd$_2$(dba)$_3$ yielded only 14% of the desired product **5a** (entry 1, Table 1). Although complete consumption of **3** occurred, the relatively low production of **5a** was attributed to a competing reaction pathway that results in the conversion of **3** to the Carroll rearrangement product, 2,2-dimethylhept-6-en-3-one.[10] A survey of bidentate phosphine ligands (entries 2−5) resulted in only a modest increase in yield, with DIOP being the optimal ligand under the reaction conditions (entry 5). At this stage in our investigation, we postulated that the inclusion of a metal salt might favor either the formation of an oxygen bound metal enolate or the increase in the electrophilicity of the aldehyde, ultimately leading to a more selective reaction.[11] Indeed, the addition of a catalytic amount (5 mol %) of various metal chloride salts resulted in a higher yield of **5a** (entries 6−10). The metal chloride salt YbCl$_3$ was the best catalyst, affording the aldol product **5a** in 93% isolated yield (entry 10).[12] The YbCl$_3$-catalyzed reaction required the addition of an equimolar amount of DIOP to the total amount of metal employed in the reaction, suggesting that the phosphine ligand was acting as a ligand for both metals.[13] The optimized reaction conditions utilized 5 mol % Pd(0), 5 mol % YbCl$_3$, and 10 mol % DIOP.

The heterobimetallic Pd(0)−Yb(III) catalytic reaction conditions proved to be effective for a variety of aldehydes in the aldol reaction

Table 1. Decarboxylative Aldol Reactions of β-Keto Ester **3**[a]

entry	ligand[b]	metal salt[c]	% yield[d]
1	−	−	14
2	dppe	−	15
3	dppf	−	20
4	BINAP	−	10
5	DIOP	−	27
6	DIOP	FeCl$_3$	40
7	DIOP	ZnCl$_2$	68
8	DIOP	CuCl$_2$	40
9	DIOP	LaCl$_3$	60
10	DIOP	YbCl$_3$	93

[a] Reactions were carried out using 2.5 mmol allyl 4,4-dimethyl-3-oxopentanoate, 1 mmol 3-phenylpropanal, and 2.5 mol % Pd$_2$dba$_3$ in CH$_2$Cl$_2$ (0.5 M) at room temperature for 24 h under Ar, followed by flash chromatography on silica gel. [b] In the absence of metal salt, 5 mol % ligand was added to the reaction; with the addition of metal salt, 10 mol % ligand was added; dppe: 1,2-bis(diphenylphosphino)ethane, dppf: 1,1′-bis(diphenyl-phosphino)ferrocene, BINAP: (±)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, DIOP: (±)-*O*-isopropylidene-*trans*-2,3-dihydroxy-1,4-bis-(diphenylphosphino)butane. [c] 5 mol % metal salt was added to the reaction. [d] Isolated yield.

of β-keto ester **3** and allyl acetoacetate **6** (Table 2).[14] Aliphatic aldehydes (entries a and b) and olefin-containing aldehydes (entries c and d) were effective substrates for the reaction. Benzaldehyde (entry e) was less reactive toward nucleophilic addition, even after additional YbCl$_3$ (5 mol %) was included in the reaction. However, the decarboxylative aldol reaction of *p*-nitrobenzaldehyde proceeded well under the optimized conditions (entry f). The catalytic reaction also proved to be general for benzyl and silyl ethers (entries g−i). Our investigations also included diastereoselective additions to α-substituted aldehydes (entries j−l). The decarboxylative aldol reaction involving 2-phenylpropanal resulted in 86% isolated yield of **5j** (2:1 dr) and 95% of **7j** (1.5:1 dr). The reaction also required 10 mol % YbCl$_3$ to achieve significant levels of conversion. Pyrancarboxaldehyde was a better substrate for the reaction, affording the diastereomeric products in a ratio of **5k** in 1.6:1 dr and 84% yield and **7k** in 1.5:1 dr and 84% yield. The highest diastereoselectivities were obtained in the reaction of *N*-Boc-valinal where **5l** was produced in a 5:1 ratio favoring the syn isomer (73% isolated yield of the major diastereomer) and **7l** was formed in a 6:1 diastereomeric ratio (77% isolated yield of the major diastereomer). Confirmation of the syn diastereomer was achieved through Baeyer−Villiger oxidation of **5l** using *m*-CPBA and TFA deprotection to yield norstatine.[15]

We propose a catalytic cycle that requires both Yb(III) and Pd-(0) for the formation of the product (Scheme 1). In the presence of Pd(0), YbCl$_3$ facilitates the formation of the aldol adduct **8**.[16] An

Table 2. Decarboxylative Aldol Reactions of β-Keto Esters Catalyzed by Pd(0)− and YbCl$_3$−DIOP Complexes[a]

entry	aldehyde	yield 5 (%)[b]	yield 7 (%)[b]
a	PhCH$_2$CH$_2$CHO	**5a** (93)	**7a** (81)
b	PhCH$_2$CHO	**5b** (86)	**7b** (84)
c	E-C$_5$H$_{11}$CH=CH(CH$_2$)$_2$CHO	**5c** (90)	**7c** (83)
d	Z-C$_2$H$_5$CH=CH(CH$_2$)$_2$CHO	**5d** (75)	**7d** (76)
e[c]	PhCHO	**5e** (70)	**7e** (73)
f	p-NO$_2$-C$_6$H$_4$CHO	**5f** (81)	**7f** (76)
g	BnOCH$_2$CHO	**5g** (93)	**7g** (82)
h	TBSOCH$_2$CHO	**5h** (75)	**7h** (72)
i	TBSOCH$_2$CH$_2$CHO	**5i** (83)	**7i** (80)
j[c]		**5j** (86, 2:1 dr[e])	**7j** (95, 1.5:1 dr[e])
k		**5k** (84, 1.6:1 dr[f])	**7k** (84, 1.5:1 dr[f])
l[d]		**5l** (73, 5:1 syn:anti[f])	**7l** (77, 6:1 syn:anti[f])

[a] Reactions were carried out using 2.5 mmol allyl β-keto ester, 1 mmol aldehyde, 2.5 mol % Pd$_2$dba$_3$, 5 mol % YbCl$_3$, and 10 mol % DIOP in CH$_2$Cl$_2$ (0.5 M) at room temperature for 24 h under Ar, followed by flash chromatography on silica gel. [b] Isolated yield. [c] 2.5 mol % Pd$_2$dba$_3$, 10 mol % YbCl$_3$, and 15 mol % DIOP were used in the reaction. [d] 5 mol % Pd$_2$dba$_3$, 10 mol % YbCl$_3$, and 20 mol % DIOP were used in the reaction. [e] The ratio was determined by ^{1}H NMR of the crude reaction mixture. [f] The ratio was determined by isolation of each diastereomer.

Scheme 1. Proposed Catalytic Cycle for the Heterobimetallic Decarboxylative Aldol Condensation
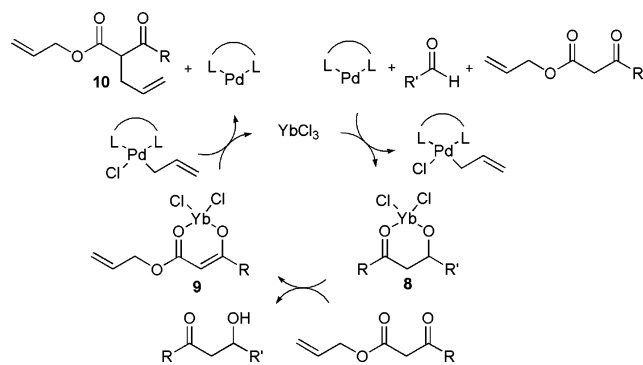
exchange reaction then results in the formation of the aldol product and **9**, which undergoes an alkylation reaction with the Pd(II) allyl species to regenerate a Pd(0) species and yield the α-allyl-β-keto ester **10**. The reaction requires >2 equiv of allyl β-keto ester to be present for this purpose, and a stoichiometric amount of **10** is produced. Conducting the reaction with an equivalent amount of methyl acetoacetate and allyl-β-keto ester **6** was also successful. Mechanistic investigations of the role of each metal in the reaction are ongoing.

In summary, we have developed a mild and selective heterobi-metallic-catalyzed decarboxylative aldol reaction. The reaction is promoted by Pd(0)− and Yb(III)−DIOP complexes and involves the in situ formation of a ketone enolate from allyl β-keto esters followed by addition of the enolate to aldehydes. The reaction is a new example of heterobimetallic catalysis[17] in which the optimized reaction conditions require the addition of both metals. Future investigations will focus on expansion of the reaction scope to include other electrophiles.

Supporting Information Available: Experimental procedures and characterization of all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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