Synthetic Methods

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Rhodium-Catalyzed Cross-Aldol Reaction: In Situ Aldehyde-Enolate Formation from Allyloxyboranes and Primary Allylic Alcohols**

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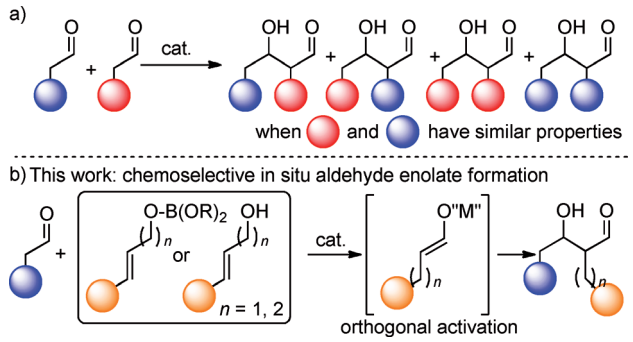
The aldol reaction is one of the most fundamental carbon–carbon bond-forming reactions. A cross-aldol reaction between two different aldehydes, in principle, provides the most straightforward step- and redox-economical[1] access to polyketides.[2,3] Numerous modern aldol methods,[4] however, utilize ketones, thioesters, esters, and other carboxylic acid derivatives as donors to circumvent the problems inherent to aldehyde–aldehyde cross-aldol reactions. Thus, additional multistep transformations of aldol products, including protection and redox processes, are required to generate β-hydroxy-protected aldehydes. In the cross-aldol reaction between two different aldehydes, chemoselective activation of one aldehyde as a donor and the other aldehyde as an acceptor is difficult, and often affords mixtures of homo- and heteroaldol products (Scheme 1a). As a state-of-the-art methodology, several organocatalytic enantioselective direct aldehyde–aldehyde cross-aldol reactions have been developed,[5] but enamine catalysis is realized simply based on the inherent steric and/or electronic bias between the two different aldehydes. Cross-aldol reactions that override the bias, for example, propanal as an acceptor and other sterically more hindered aldehydes as donors, are extremely difficult.[6] A method to generate an aldehyde-derived enolate from a non-carbonyl precursor through an orthogonal activation mode[7–9] would provide an alternative and complementary approach to obtaining aldehyde–aldehyde cross-aldol products (Scheme 1b). Herein, we report a rhodium-catalyzed one-pot isomerization/cross-aldol sequence using primary allylic and homoallylic alcohol borates as well as primary allylic and homoallylic alcohols as nucleophile precursors. The isomerization and cross-aldol reaction proceeds at ambient temperature, even when using readily enolizable aldehydes, such as propanal, as acceptors.



Scheme 1. Cross-aldol reaction between two different aldehydes: a) conventional method starting from two aldehydes, and b) this work proceeding through the chemoselective generation of aldehyde enolates from primary allylic and homoallylic alcohols and allyloxy and homoallyloxyboranes.

Preformed silyl enol ethers derived from aldehydes have been utilized to avoid the chemoselectivity problem in the aldehyde–aldehyde cross-aldol process, as demonstrated by Yamamoto and co-workers,[10] Denmark and co-workers,[11] and others.[12] In contrast, the use of aldehyde-derived enol boranes is rare because they are unstable and prone to polymerization.[13] Considering the synthetic utility of other enol boranes derived from ketones and carboxylic acid derivatives,[14] the development of a new method to utilize various aldehyde-derived enol boranes is highly desirable.

To avoid handling unstable aldehyde-derived enol boranes, we first investigated the in situ generation of aldehyde-derived enol boranes through transition-metal-catalyzed isomerization of triallyloxyboranes[15] in the presence of acceptor aldehydes. Optimization studies of the one-pot isomerization/cross-aldol sequence using 2-bromobenzaldehyde (**1a**) and triallyloxyborane (**2a**) are summarized in Table 1. With [{Rh(cod)Cl}$_2$] (1.25 mol%, 2.5 mol% of [Rh]; cod = 1,5-cyclooctadiene), various phosphine ligands were screened (entries 1–12). Monodentate phosphines did not afford the aldol adduct (entries 1–3). Among the bidentate diarylphosphines (entries 4–7), only dppf gave the desired product, albeit in poor yield (entry 7). Electronic and steric modifications of the ferrocene-based ligand effectively improved the reactivity of the rhodium catalysts (entries 8–10), and dippf, bearing P*i*Pr$_2$ units, gave the best results, thus giving the product **3a** in 99% yield and 94:6 d.r. at room temperature after 23 hours (entry 8). In contrast, the sterically more hindered dtbpf bearing P*t*Bu$_2$ units had poor reactivity (entry 10). We also examined other bidentate alkyl phosphines, but the desired reaction did not proceed (entries 11 and 12). Other rhodium sources, including the

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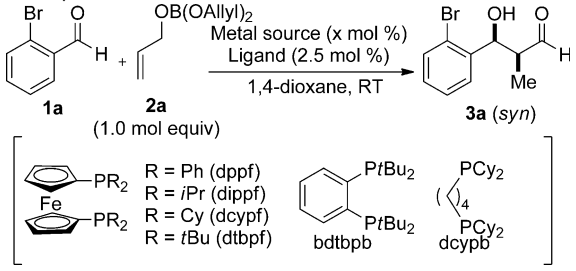
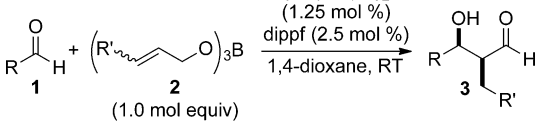
Table 1: Optimization studies.



Entry	Ligand	Metal source [*x* mol%]	*t* [h]	*syn*/*anti*[a]	Yield [%][a]
1	PPh_3[b]	[{Rh(cod)Cl}$_2$] (1.25)	36	n.d.	0
2	PCy_3[b]	[{Rh(cod)Cl}$_2$] (1.25)	36	n.d.	0
3	$PiPr_3$[b]	[{Rh(cod)Cl}$_2$] (1.25)	36	n.d.	0
4	dppe	[Rh(cod)Cl]$_2$ (1.25)	36	n.d.	0
5	dppp	[{Rh(cod)Cl}$_2$] (1.25)	36	n.d.	0
6	*rac*-binap	[{Rh(cod)Cl}$_2$] (1.25)	36	n.d.	0
7	dppf	[{Rh(cod)Cl}$_2$] (1.25)	36	n.d.	< 5
8	dippf	[{Rh(cod)Cl}$_2$] (1.25)	23	94:6	99
9	dcypf	[{Rh(cod)Cl}$_2$] (1.25)	36	91:9	85
10	dtbpf	[{Rh(cod)Cl}$_2$] (1.25)	36	n.d.	< 5
11	bdtbpb	[{Rh(cod)Cl}$_2$] (1.25)	36	n.d.	0
12	dcypb	[{Rh(cod)Cl}$_2$] (1.25)	36	n.d.	0
13	dippf	[Rh(PPh_3)$_3$Cl] (2.5)	23	91:9	77
14	dippf	[{Rh(C_2H_4)Cl}$_2$] (1.25)	23	92:8	89
15	dippf	[Rh(cod)$_2$]BF_4 (2.5)	36	n.d.	0
16	dippf	[Rh(acac)(cod)] (2.5)	36	n.d.	0
17	dippf	[{Ru(*p*-cymene)Cl_2}$_2$] (1.25)	36	n.d.	0
18	dippf	[Ru(PPh_3)$_3Cl_2$] (2.5)	36	n.d.	0
19	dippf	[RuHCl(CO)(PPh_3)$_3$] (2.5)	36	n.d.	0
20	dippf	[{Ir(cod)Cl}$_2$] (1.25)	36	n.d.	0

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture. [b] 5 mol% of ligands were utilized. acac = acetylacetonate, binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, cod = 1,5-cyclooctadiene.

Table 2: Rhodium-catalyzed isomerization/cross-aldol reaction sequence with triallyloxyboranes.[a]



2a: R' = H; **2b**: R' = Me (mixture of *E* and *Z* isomers); (*E*)-**2c**: R' = Et; (*Z*)-**2c**: R' = Et; (*Z*)-**2d**: R' = Pr

Entry	R	1	2	*t* [h]	3	*syn*/*anti*[b]	Yield [%][c]
1	2-BrC_6H_4	**1a**	**2a**	23	**3a**	94:6	99
2	3-BrC_6H_4	**1b**	**2a**	36	**3b**	93:7	72
3	4-BrC_6H_4	**1c**	**2a**	36	**3c**	93:7	83
4	3-ClC_6H_4	**1d**	**2a**	36	**3d**	91:9	95
5	4-FC_6H_4	**1e**	**2a**	36	**3e**	93:7	87
6	4-$NO_2C_6H_4$	**1f**	**2a**	36	**3f**	94:6	90
7	2,6-$Cl_2C_6H_3$	**1g**	**2a**	36	**3g**	> 95:5	85
8	2,4-$(MeO)_2C_6H_3$	**1h**	**2a**	36	**3h**	90:10	78
9	Ph	**1i**	**2a**	36	**3i**	90:10	81
10	2-naphthyl	**1j**	**2a**	36	**3j**	90:10	75
11	2-furyl	**1k**	**2a**	36	**3k**	94:6	60
12	Ph	**1i**	**2b**	24	**3l**	90:10	93
13	Ph	**1i**	(*E*)-**2c**	48	**3m**	88:12	57
14	Ph	**1i**	(*Z*)-**2c**	12	**3m**	87:13	84
15	Ph	**1i**	(*Z*)-**2d**	12	**3n**	86:14	89
16	*n*-pentyl	**1l**	**2a**	27	**3o**	85:15	73
17	$PhCH_2CH_2$	**1m**	**2a**	36	**3p**	84:16	90
18	cyclohexyl	**1n**	**2a**	32	**3q**	74:26	62
19	Et	**1o**	**2b**	24	**3r**	75:25	71[d]

[a] Reaction was run using 0.4 mmol of **1** and **2** in 1,4-dioxane (0.2 M) under Ar at ambient temperature. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Yield of isolated product was determined after conversion into either the dimethylacetal with cat. PPTS/MeOH or the 1,3-diol with $NaBH_4$, and purification by silica gel column chromatography. [d] Yield of the isolated β-hydroxy aldehyde form after careful purification by silica gel column chromatography. PPTS = pyridinium *para*-toluenesulfonate.

cationic [Rh(cod)$_2BF_4$], had less satisfactory reactivity (entries 13–16). In entries 17–20, several ruthenium and iridium complexes were also screened,[16] but none of them gave the desired product at room temperature. Thus, the [{Rh(cod)Cl}$_2$] in combination with the dippf ligand was selected as the optimal catalyst.

The substrate scope of the isomerization/cross-aldol sequence is summarized in Table 2.[17] Because nonprotected β-hydroxy aldehydes are generally unstable and partially decompose during the purification using silica gel column chromatography, the yield of the isolated products was determined after transformation into stable compounds, such as the dimethylacetal using PPTS/MeOH or the 1,3-diol using $NaBH_4$. High *syn* selectivity was observed for the reaction shown in entries 1–11 using **2a** and various aryl and heteroaryl aldehydes (**1a**–**1k**; > 95:5–90:10 d.r.). Substituents at the *ortho*, *meta*, and *para* positions on the aromatic ring of aldehydes were compatible, and even the sterically hindered 2,6-disubstituted aldehyde **1g** (entry 7) and the less electrophilic aldehyde **1h** bearing two electron-donating MeO-groups at the *ortho* and *para* positions (entry 8) gave the expected aldol adducts without problem. The results using the substituted allyloxy boranes **2b**–**2d** are summarized in entries 12–15. The allyloxyborane **2b** as an *E*/*Z*-mixture, (*Z*)-**2c**, and (*Z*)-**2d** showed good reactivity, thus giving cross-aldol adducts in 84–93% yield with good *syn* selectivity (entries 12, 14, and 15). In contrast, (*E*)-**2c** had much lower reactivity, possibly because of slow isomerization, and the product was obtained in only 57% yield after 48 hours (entry 13) with a diastereoselectivity similar to that obtained with (*Z*)-**2c**. The present rhodium-catalyst was also applicable to enolizable aliphatic aldehydes (entries 16–19). Although the *syn* selectivity was somewhat decreased, the desired cross-aldol adduct was obtained chemoselectively. In entry 19, propanal chemoselectively reacted as an acceptor and the cross-aldol adduct **3r** was obtained in 71% yield. In entry 19, the homoaldol adduct derived from propanal was not detected, thus indicating the synthetic utility of the present method based on the orthogonal activation of allyloxyboranes. Because the present reaction was performed under mild reaction conditions, that is, at room temperature in the absence of a strong base, the chiral aldehyde **1p** was successfully utilized without racemization to give **3s** as the major isomer in greater than 99% *ee* (Scheme 2). Although C2/C3 diastereoselctivity (**3s** + **3u**)/(**3t**+**3v**) was modest, good C3/C4 diastereoselctivity (**3s** + **3t**)/(**3u**+**3v**) was

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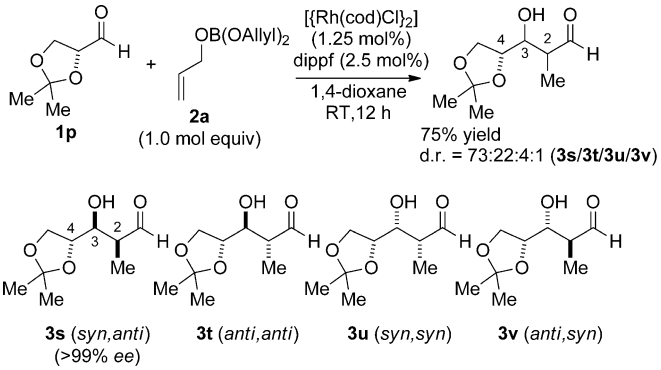
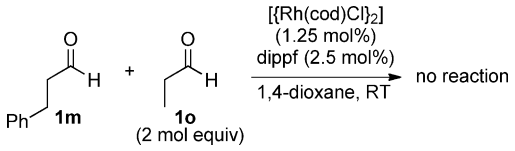


Scheme 2. Rhodium-catalyzed isomerization/cross-aldol sequence using the chiral aldehyde **1p**.

observed. The control experiment shown in Scheme 3 using 3-phenylpropanal and propanal resulted in no reaction. Neither the homo- nor heteroaldol adduct was observed. Thus, it is clear that the present Rh/dippf catalyst does not activate the

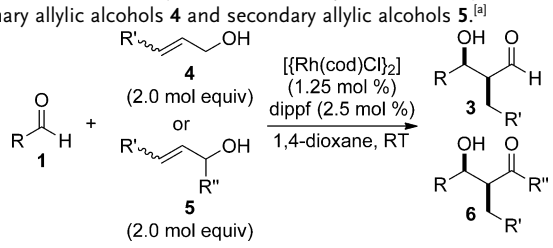


Scheme 3. Negative control experiment using two different aldehydes.

aldehyde as a donor, but chemoselectively generates aldehyde-derived enolates from allyloxyboranes. The Rh/dippf catalyst could promote the isomerization of allyloxyboranes into enol boranes through a 1,3-hydride shift via a π-allyl rhodium complex,[15] and the aldol reaction of enol boranes proceeded via a cyclic transition state to afford the *syn*-aldol adducts.

The present Rh/dippf catalyst was also directly applicable to free primary allylic alcohols.[18] As shown in Table 3, the isomerization/cross-aldol sequence proceeded smoothly at room temperature, and products were obtained in 68–90% yield albeit in somewhat lower *syn* selectivity (86:14–75:25 d.r.) than that using allyloxyboranes. The previously reported methods for the isomerization/cross-aldol sequence[9] were only applied to secondary allylic alcohols, and the current protocol is the first example of an one-pot isomerization/cross-aldol sequence with primary allylic alcohols. To compare the reactivity and diastereoselectivity of the present rhodium catalyst with other systems, we briefly investigated the reaction with secondary allylic alcohols (**5**). As summarized in entries 6–10, the cross-aldol products, β-hydroxy ketones **6**, were obtained in 88:12–81:19 d.r. and 96–87% yield at room temperature after 10–15 hours. In the case of using allylic alcohols as precursors, isomerization of allylic alcohols would afford either the enol[19] or rhodium enolate[20] intermediate. Based on the control experiment shown in Scheme 2, the enol or rhodium enolate intermediate should directly react with acceptor aldehydes before undesirable tautomerization or protonation to give the aldehydes,[21] which are unreactive as donors under the reaction conditions.

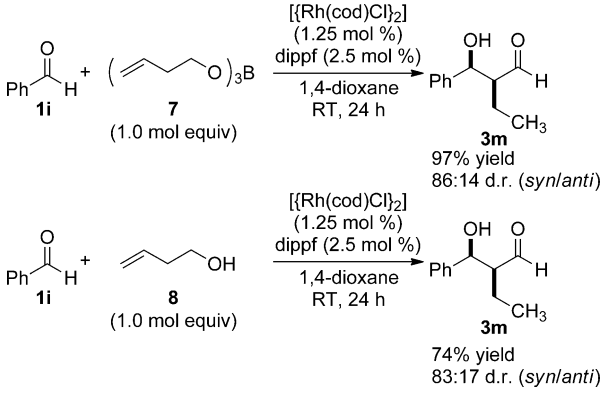
Table 3: Rhodium-catalyzed isomerization/cross-aldol sequence with primary allylic alcohols **4** and secondary allylic alcohols **5**.[a]



Entry	R	**1**	R′	R″	**4** or **5**	*t* [h]	**3** or **6**	*syn*/*anti*[b]	Yield [%]
1	Ph	**1i**	H	H	**4a**	8	**3i**	86:14	73[c]
2	$PhCH_2CH_2$	**1m**	H	H	**4a**	24	**3p**	75:25	72[c]
3	Ph	**1i**	Me	H	**4b**	22	**3l**	83:17	90[c]
4	Ph	**1i**	(*Z*)-Et	H	**4c**	25	**3m**	82:18	73[c]
5	Ph	**1i**	(*Z*)-Pr	H	**4d**	22	**3n**	83:17	68[c]
6	Ph	**1i**	H	Me	**5a**	10	**6a**	86:14	90[d]
7	*n*-pentyl	**1l**	H	Me	**5a**	11	**6b**	83:17	96[d]
8	Ph	**1i**	H	Et	**5b**	14	**6c**	86:14	91[d]
9	Ph	**1i**	H	*n*-pentyl	**5c**	15	**6d**	88:12	95[d]
10	Ph	**1i**	(*E*)-Me	Me	**5d**	13	**6e**	81:19	87[d]

[a] Reaction was run using 0.4 mmol of **1** and 2.0 mol equiv of **4** or **5**, in 1,4-dioxane (0.2 M) under Ar at ambient temperature. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Yield of isolated product was determined after conversion into either dimethylacetal with cat. PPTS/MeOH or 1,3-diol with $NaBH_4$, and purification by silica gel column chromatography. [d] Yield of isolated β-hydroxy ketone form after purification by silica gel column chromatography.

To further expand the synthetic utility of the Rh/dippf catalyst, we investigated the homoallyloxyborane **7** and primary homoallylic alcohol **8** as donors. The isomerization of the carbon–carbon double bond from the remote position, possibly by consecutive 1,3-hydride shift via the π-allyl rhodium complex, proceeded without problem, and the cross-aldol adduct **3m** was obtained in good yield and *syn* selectivity after 24 hours (Scheme 4). It is noteworthy that the present protocol was not restricted to allyloxyboranes and allylic alcohols. Additional investigations into using other alkoxyboranes and alcohols bearing a remote carbon–carbon double bond are ongoing.



Scheme 4. The isomerization/cross-aldol sequence using the homoallyloxyborane **7** and homoallylic alcohol **8**.

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In summary, we developed an alternative approach to cross-aldol adducts derived from two different aldehydes. A Rh/dippf catalyst promoted the isomerization of primary allyloxy and homoallyloxyboranes as well as primary allylic and homoallylic alcohols at ambient temperature, chemoselectively, thus affording aldehyde-derived enolates in situ. The isomerization/cross-aldol sequence proceeded in one pot, thereby giving cross-aldol adducts in greater than 95:5–74:26 *syn* selectivity and 99–57% yield using allyloxy- and homoallyloxyboranes. Studies towards enantioselective variants using either a chiral rhodium catalyst[22] or chiral alkoxyboranes as well as applications to consecutive cross-aldol reactions for 1,3-polyol synthesis are actively ongoing.

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mol equiv of **2a**, the Rh/dippf catalyst gave product **3i** in 51% yield with 83:17 d.r. after 36 h.
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