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Rh-Catalyzed Aldehyde−Aldehyde Cross-Aldol Reaction under Base-Free Conditions: In Situ Aldehyde-Derived Enolate Formation through Orthogonal Activation

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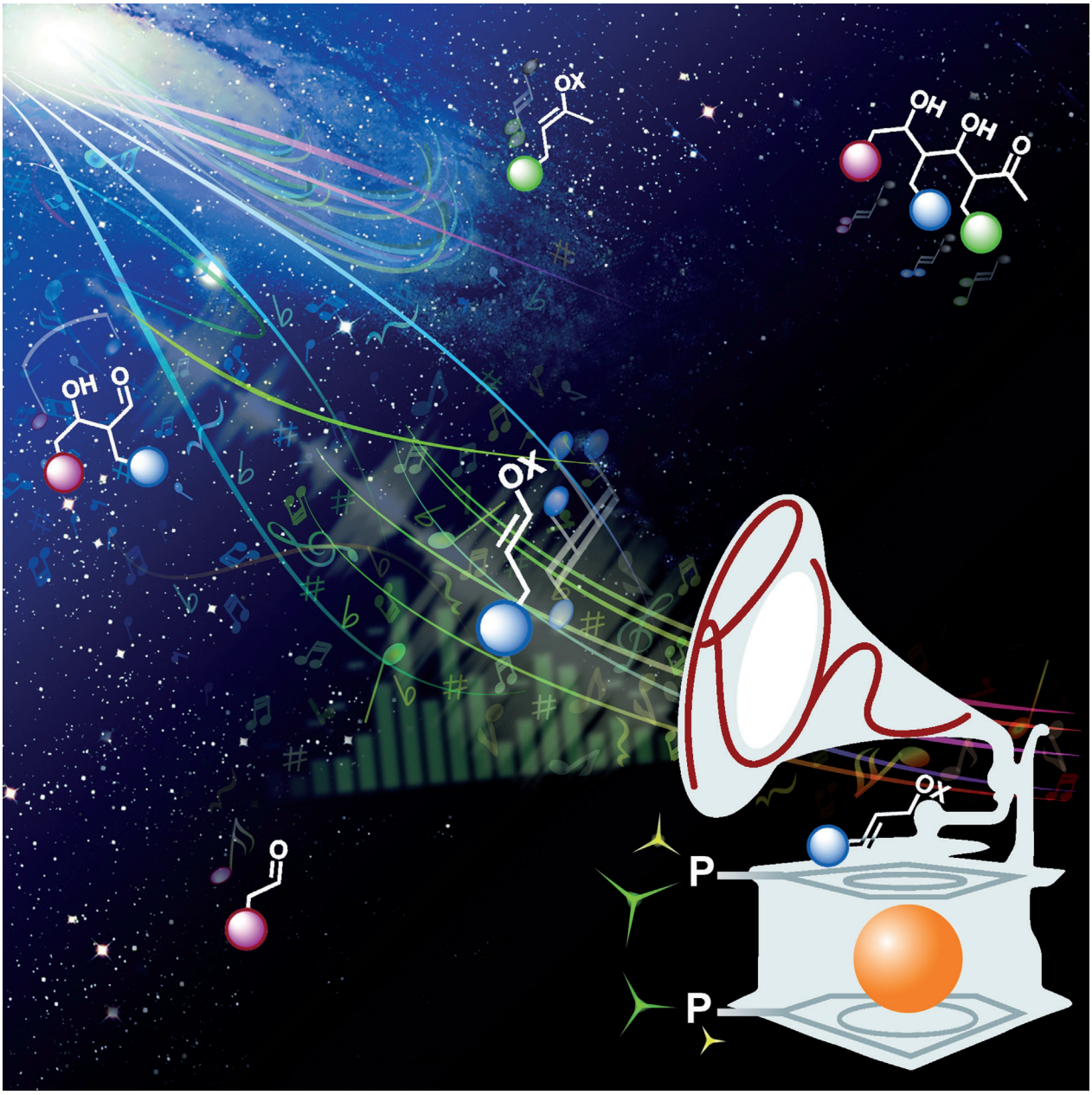
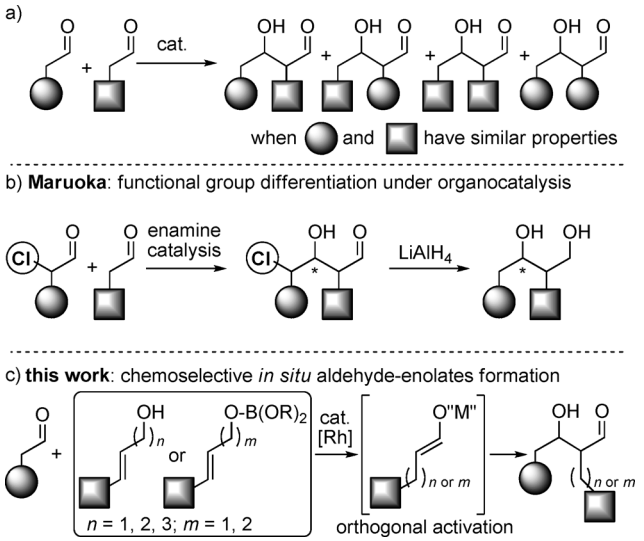


Abstract: The chemoselective generation of aldehyde-derived enolates to realize an aldehyde–aldehyde cross-aldol reaction is described. A combined Rh/dippf system efficiently promoted the isomerization/aldol sequence by using primary allylic, homoallylic, and bishomoallylic alcohols; secondary allylic and homoallylic alcohols; and trialkoxyboranes that were derived from primary allylic and homoallylic alcohols. The reaction proceeded at ambient temperature under base-free conditions, thus giving cross-aldol products with high chemoselectivity. Mechanistic studies, as well as its application to double-aldol processes under protecting-group-free conditions, are also described.

Keywords: aldol reaction · boron · homogeneous catalysis · rhodium · synthetic methods

Introduction

Aldol reactions are fundamental and important carbon–carbon bond-forming reactions.[1] A cross-aldol reaction between two different aldehydes provides straightforward redox-[2] and step-economical[3] access to 1,3-polyol frameworks.[4,5] The classical aldol-condensation reaction, which is usually performed under acid or base catalysis, is an early example of a highly atom-economical reaction.[6] However, the classical conditions are not useful for aldehyde–aldehyde cross-aldol reactions, owing to chemoselectivity problems. In the cross-aldol reaction between two different aldehydes, the chemoselective activation of one aldehyde as a donor and the other as an acceptor is difficult and often affords complex mixtures of homoaldols and heteroaldols (Scheme 1a). Therefore, most modern aldol methods utilize ketones, thioesters, esters, and other carboxylic-acid derivatives as donors to circumvent the inherent problem of chemoselectivity in aldehyde–aldehyde cross-aldol reactions. These processes and, in particular, their catalytic enantioselective variants that have been developed during the last two decades,[7] are synthetically useful and reliable. However, there remains much room for improvement in the application of these processes to the synthesis of 1,3-polyols in terms of the redox- and step-economy, because additional multistep transformations of aldol products, including protection and redox processes, are inevitably needed to generate β-hydroxy-protected aldehydes for the second aldol process.



Scheme 1. Cross-aldol reactions between two different aldehydes: a) conventional method, starting from two aldehydes; b) Maruoka's functional-group-differentiation strategy to realize chemoselective cross-aldol reactions; and c) this work, which proceeds through the chemoselective generation of aldehyde enolates from primary allylic alcohols and related compounds.

Since the early reports by MacMillan and co-workers, several "state-of-the-art" organocatalytic enantioselective direct aldehyde–aldehyde cross-aldol reactions have been developed.[8] Enamine catalysis is simply based on the inherent steric and/or electronic bias between the two different aldehydes. Cross-aldol reactions that override such a bias, such as those that use propanal as an acceptor and other sterically more-hindered aldehydes as donors, are extremely difficult to achieve. To realize high chemoselectivity in organocatalytic cross-aldol reactions between two different aliphatic aldehydes, Maruoka and co-workers recently reported an elegant solution based on the concept of functional-group differentiation.[9] As shown in Scheme 1b, α-chloroaldehydes that contained a sterically hindered electron-withdrawing group selectively acted as acceptors and the α-chloro group in the aldol product was removed by treatment with $LiAlH_4$.

Therefore, a method for the generation of an aldehyde-derived enolate from a non-carbonyl precursor through an orthogonal activation mode[10] should provide an alternative and complementary approach to chemoselective aldehyde–aldehyde cross-aldol products. Herein, we report a Rh-cata-

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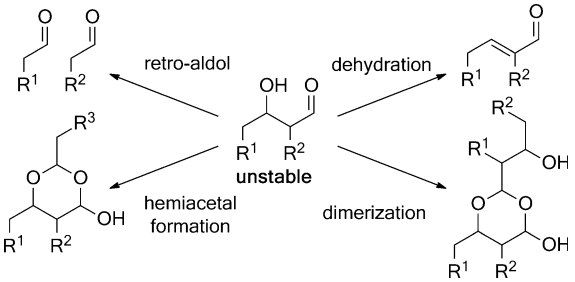
lyzed one-pot isomerization/cross-aldol sequence by using primary allylic, homoallylic, and bishomoallylic alcohols with their related allyloxy- and homoallyloxyboranes as donor precursors (Scheme 1c).[11] The isomerization and cross-aldol reaction proceeds at ambient temperature under neutral, base-free conditions.

Results and Discussion

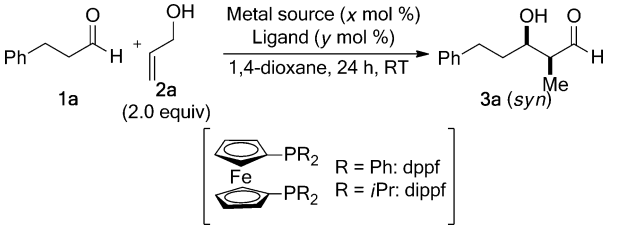
As a donor precursor, we planned to use primary allylic alcohols, which could, in principle, be readily isomerized under transition-metal catalysis to generate aldehyde-derived enolates or enols. Despite several reports on the use of secondary allylic alcohols as ketone-derived enolate precursors in aldol processes under transition-metal catalysis,[12,13] the use of primary allylic alcohols in the isomerization/aldol sequence has not been reported.[14–16] We expected difficulties with known transition-metal catalysts for isomerization/aldol processes with primary allylic alcohols, owing to the following factors: Most catalysts that are used for the isomerization of secondary allylic alcohols into either enols or enolates require high reaction temperatures and/or a strong base or Lewis acid additive to efficiently promote the isomerization/aldol sequence. Because unprotected β-hydroxy aldehydes are notoriously unstable, they may cause various side reactions in the presence of a base or Lewis acid additive, such as dimerization, hemiacetal formation, dehydration, and retroaldol reactions (Scheme 2).[17] Unprotected β-hydroxy aldehydes are often unstable at high temperatures, even under neutral conditions. Thus, it is essential to perform the isomerization and successive aldol processes under base-free neutral conditions, preferably at ambient (or lower) temperature.



Scheme 2. Properties of unstable, unprotected β-hydroxyaldehyde.

Based on these above-mentioned points, we investigated the model reaction between aliphatic aldehyde **1a** and allyl alcohol **2a** at ambient temperature without the addition of a bases or Lewis acid; optimization studies are summarized in Table 1. Although Rh complexes are well-known to isomerize primary allylic alcohols into enols and aldehydes,[18] initial screening revealed that the isomerization/aldol sequence at room temperature under neutral conditions without any base or acid was not a trivial task. The desired aldol product (**3a**) was not obtained with common ligands, such as dppe, dppp, and (*rac*)-BINAP (Table 1, entries 1–3). Because trace amounts of product **3a** were detected with dppf (Table 1, entry 4), we further modified this ferrocene-based ligand and dippf was found to be effective for this reaction. Indeed, a [{Rh(cod)Cl}$_2$]/dippf mixed system promoted the desired isomerization/aldol sequence to give compound **3a** in 75% yield (as determined by ^{1}H NMR spectroscopy; Table 1, entry 5). Other Rh sources, including cationic catalyst [Rh(cod)$_2$]BF$_4$, and various Ru sources were screened with the dippf ligand, but none of them gave superior yields (Table 1, entries 6–11). The loading of the optimized catalyst, [{Rh(cod)Cl}$_2$]/dippf (1:2), was successfully decreased to 2.5 mol% (based on Rh), whilst maintaining the yield

Table 1. Optimization studies of the isomerization/cross-aldol sequence with primary allyl alcohol **2a**.

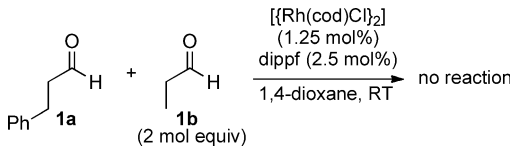


Entry	Metal source (mol%)	Ligand (mol%)	d.r.[a] (*syn*/*anti*)	Yield [%][a]
1	[{Rh(cod)Cl}$_2$] (5)	dppe (10)	ND	0
2	[{Rh(cod)Cl}$_2$] (5)	dppp (10)	ND	0
3	[{Rh(cod)Cl}$_2$] (5)	(*rac*)-BINAP (10)	ND	0
4	[{Rh(cod)Cl}$_2$] (5)	dppf (10)	ND	trace
5	[{Rh(cod)Cl}$_2$] (5)	dippf (10)	75:25	75
6	[{Rh(C$_2$H$_4$)$_2$Cl}$_2$] (5)	dippf (10)	75:25	65
7	[Rh(PPh$_3$)$_3$Cl] (10)	dippf (10)	75:25	15
8	[Rh(cod)$_2$]BF$_4$ (10)	dippf (10)	ND	0
9	[Rh(acac)(cod)] (10)	dippf (10)	ND	0
10	[{Ru(*p*-cymene)Cl$_2$}$_2$] (5)	dippf (10)	ND	0
11	[Ru(PPh$_3$)$_3$Cl$_2$] (10)	dippf (10)	ND	0
12	[{Rh(cod)Cl}$_2$] (1.25)	dippf (2.5)	75:25	72

[a] Determined by ^{1}H NMR spectroscopy of the crude mixture. [b] Yield of the isolated product after conversion into the corresponding dimethyl acetal with PPTS/MeOH and purification by column chromatography on silica gel. acac = acetylacetonate, ND = not determined.

Abstract in Japanese:

第一級アリルアルコール、トリアリルボレート、及びその類縁体からアルデヒド由来のエノラート（またはエノール）を高い化学選択性で発生させる手法を開発した。Rh/dippf 触媒を活用することで、塩基や酸などの添加物の非存在下、室温にて異性化と交差アルドール反応が進行し、異種アルデヒド間の交差アルドール生成物を得ることに成功した。

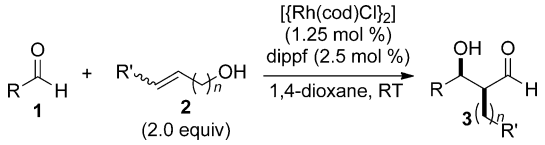


Scheme 3. Control experiment with propanal **1b** instead of allyl alcohol **2a**.

and diastereoselectivity (Table 1, entry 12). A control experiment by using propanal (**1b**) instead of allyl alcohol **2a** resulted in no reaction (Scheme 3); neither homoaldols nor heteroaldols were observed under the Rh/dippf catalysis. Thus, the Rh/dippf catalyst did not activate the aldehyde as a donor, but chemoselectively generated the aldehyde-derived enol (or enolate) from compound **2a** and promoted the desired cross-aldol process.

The scope of the Rh/dippf catalysis in terms of the donors was investigated and is summarized in Table 2 and Table 3. Because the unprotected β-hydroxy aldehydes were unstable and partially decomposed during purification by column chromatography on silica gel, the yields of the products in Table 2 were determined after their transformation into stable compounds, either the corresponding dimethyl acetal with PPTS/MeOH or the 1,3-diol with $NaBH_4$. Allyl alcohol **2a** (R′ = H), as well as other substituted primary allylic alcohols (**2b**–**2d**), gave their corresponding products in 68-90% yield and 86:14–82:18 d.r. (Table 2, entries 2–5). Notably, the scope of the primary alcohols was not limited to allylic alcohols. Homoallylic alcohol **2e** (n = 2) gave product **3d** in 74% yield and 83:17 d.r. after 24 h (Table 2, entry 6). Bishomoallyl alcohol **2f** (n = 3) was also tolerated, but the reactivity of compound **2f** was much lower than those of allylic and homoallylic alcohols **2a** and **2e**. Product **3e** was only obtained in 44% yield after 144 h (Table 2, entry 7). Alcohol **2g** (n = 4), with a C=C double bond at a more-remote position, was also investigated (Table 2, entry 8), but the isomerization of a C=C double bond was not observed at room temperature. The results in Table 2, entries 6–8 implied that a consecutive 1,3-hydride shift under the Rh/dippf catalysis was possible at room temperature, but appropriate directing of the Rh catalyst through coordination with the oxygen atom of the alcohol would be required. To compare the reactivity and diastereoselectivity of this Rh catalyst with previously reported systems, secondary alcohols were also briefly investigated as donor precursors. As summarized in Table 3, allylic secondary alcohols **4a**–**4d** gave their corresponding β-hydroxy ketones in 87–96% yield and 88:12–81:19 d.r. at room temperature (Table 3, entries 1–5). Homoallylic secondary alcohol **4e** was also tolerated, but its reactivity was only moderate. A long reaction time (72 h) was required to obtain products **5e** and **5f** in 97% and 70% yield, respectively (Table 3, entries 6–7).

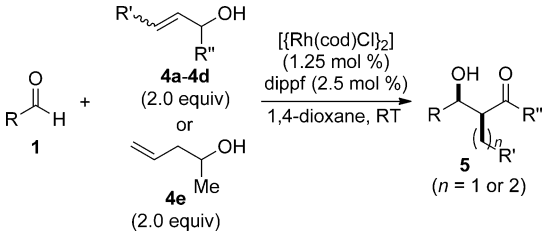
Table 2. Rh-catalyzed isomerization/cross-aldol sequence with primary allylic alcohols **2a**–**2d** and other primary alcohols **2e**–**2g**, which contained a remote C–C double bond.[a]



Entry	R	1	R′	n	2	t [h]	3	d.r.[b] (*syn*/*anti*)	Yield [%][c]
1	$PhCH_2CH_2$	**1a**	H	1	**2a**	24	**3a**	75:25	72
2	Ph	**1c**	H	1	**2a**	8	**3b**	86:14	73
3	Ph	**1c**	Me	1	**2b**	22	**3c**	83:17	90
4	Ph	**1c**	(*Z*)-Et	1	**2c**	25	**3d**	82:18	73
5	Ph	**1c**	(*Z*)-Pr	1	**2d**	22	**3e**	83:17	68
6	Ph	**1c**	H	2	**2e**	24	**3d**	83:17	74
7	Ph	**1c**	H	3	**2f**	144	**3e**	74:26	44
8	Ph	**1c**	H	4	**2g**	144	**3f**	ND	0

[a] Reaction conditions: compound **1** (0.4 mmol), compound **2** (2.0 mol equiv), in 1,4-dioxane (0.2 M) under an Ar atmosphere at ambient temperature. [b] Determined by ^{1}H NMR spectroscopy of the crude mixture. [c] Yield of the isolated product after conversion into either the corresponding dimethyl acetal with PPTS/MeOH or the 1,3-diol with $NaBH_4$ and purification by column chromatography on silica gel.

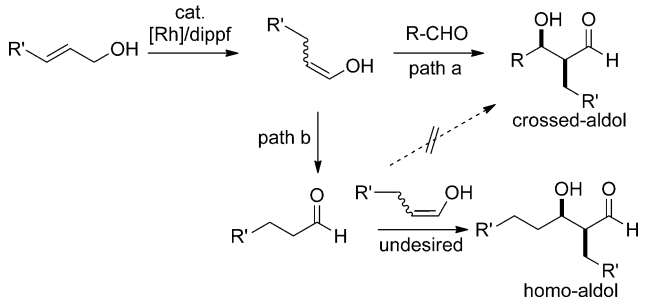
Table 3. Rh-catalyzed isomerization/cross-aldol sequence with secondary allylic and homoallylic alcohols **4a**–**4e**.[a]



Entry	R	1	R′	R″	4	t [h]	5	d.r.[b] (*syn*/*anti*)	Yield [%][c]
1	Ph	**1c**	H	Me	**4a**	10	**5a**	86:14	90
2	*n*-pentyl	**1d**	H	Me	**4a**	11	**5b**	83:17	96
3	Ph	**1c**	H	Et	**4b**	14	**5c**	86:14	91
4	Ph	**1c**	H	*n*-pentyl	**4c**	15	**5d**	88:12	95
5	Ph	**1c**	(*E*)-Me	Me	**4d**	13	**5e**	81:19	87
6	Ph	**1c**	H	Me	**4e**	72	**5e**	82:18	97
7	$PhCH_2CH_2$	**1a**	H	Me	**4e**	72	**5f**	78:22	70
8	Ph	**1c**	H	Me	**4a**	10	**5a**	86:14	90

[a] Reaction conditions: compound **1** (0.4 mmol), compound **4** (2.0 mol equiv), in 1,4-dioxane (0.2 M) under an Ar atmosphere at ambient temperature. [b] Determined by ^{1}H NMR spectroscopy of the crude mixture. [c] Yield of the isolated product in its β-hydroxy-ketone form after purification by column chromatography on silica gel.

Although the Rh/dippf catalyst successfully promoted the isomerization/aldol sequence under base-free conditions at room temperature as initially planned, there remained a problem to be solved if using primary allylic alcohols as donor precursors. In the isomerization/aldol sequence, the isomerization of primary allylic alcohols into enols (or Rh–enolates) proceeded without problem, but the aldol reaction (Scheme 4, path a) competed with the undesired protonation pathway to generate aldehydes (Scheme 4, path b). The generated aldehydes did not act as donors, as indicated by the

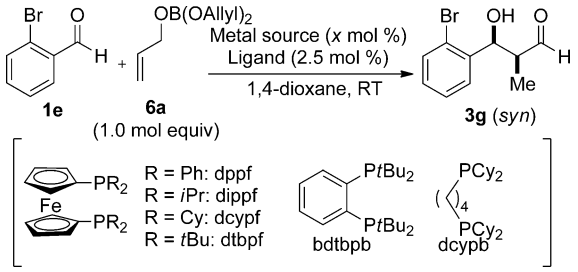


Scheme 4. Competitive undesired homoaldol formation through the undesirable tautomerization of enol intermediates into aldehydes.

control experiment in Scheme 3. Rather, the aldehydes that were generated through path b acted as acceptors, thereby generating undesired homoaldols that were derived from two molecules of allylic alcohols as minor byproducts. Separation of the homoaldols from the desired cross-aldol products in Table 2 was often problematic, in particular if an aliphatic aldehyde was used as an acceptor. To realize a more-efficient and truly chemoselective isomerization/aldol process, undesired isomerization of the enol (or enolate) intermediate into the corresponding aldehyde must be prevented whilst accelerating the desired cross-aldol pathway.

To suppress the above-mentioned undesired pathway, we planned to use an allyloxyborane as a donor precursor instead of an allyl alcohol. In contrast to the recent advances by using silyl enol ethers that were derived from aldehydes to demonstrate the aldehyde–aldehyde cross-aldol process,[19–21] the use of aldehyde-derived enol boranes is rare, possibly owing to their instability and propensity for polymerization.[22] We envisioned that the in situ generation of aldehyde-derived enol boranes through the isomerization of a C=C double bond under neutral conditions would provide a new convenient method for utilizing various aldehyde-derived enol boranes in organic synthesis.[23] Optimization of the reaction of triallyloxyborane **6a** is summarized in Table 4. Because the reaction rate of triallyloxyborane **6a** was slightly slower than those of allyl alcohols, screening was performed by using aldehyde **1e**, which contained an electron-withdrawing group. The trends in the metal and ligand effects in Table 4 were quite similar to those in Table 1. Ferrocene-based alkyl-phosphine ligands were critical for promoting the isomerization/aldol sequence and [{Rh(cod)Cl}$_2$], in combination with dippf, gave the highest reactivity, thereby affording product **3g** in 99% yield and 94:6 d.r. (Table 4, entry 2). The reaction also proceeded in 85% yield with dcypf, which contained two P(*c*-hex)$_2$ units (Table 4, entry 3); sterically more-hindered dtbpf, which contained P*t*Bu$_2$ units, had poor reactivity (Table 4, entry 4). We also re-screened other bidentate alkyl phosphines, bidentate aryl phosphines, and monodentate alkyl phosphines, but none of them gave good results (Table 4, entries 5–11). Other Rh sources showed less-satisfactory reactivities (Table 4, entries 12–15). Several Ru and Ir complexes were also screened (Table 4, entries 16–19),[24] but none of them

Table 4. Ligand and metal re-screening in the isomerization/cross-aldol sequence with triallyloxyborane **6a**.



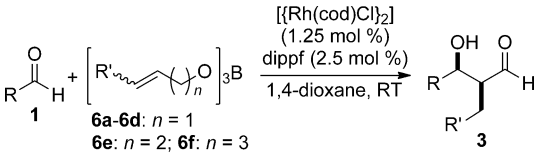
Entry	Ligand	Metal source (mol%)	*t* [h]	d.r.[a] (*syn*/*anti*)	Yield [%][a]
1	dppf	[{Rh(cod)Cl}$_2$] (1.25)	36	ND	<5
2	dippf	[{Rh(cod)Cl}$_2$] (1.25)	36	94:6	99
3	dcypf	[{Rh(cod)Cl}$_2$] (1.25)	36	91:9	85
4	dtbpf	[{Rh(cod)Cl}$_2$] (1.25)	36	ND	<5
5	bdtbpb	[{Rh(cod)Cl}$_2$] (1.25)	23	ND	0
6	dcypb	[{Rh(cod)Cl}$_2$] (1.25)	36	ND	0
7	dppe	[{Rh(cod)Cl}$_2$] (1.25)	36	ND	0
8	dppp	[{Rh(cod)Cl}$_2$] (1.25)	36	ND	0
9	(*rac*)-BINAP	[{Rh(cod)Cl}$_2$] (1.25)	36	ND	0
10	PCy$_3$[b]	[{Rh(cod)Cl}$_2$] (1.25)	36	ND	0
11	P*i*Pr$_3$[b]	[{Rh(cod)Cl}$_2$] (1.25)	36	ND	0
12	dippf	[Rh(PPh$_3$)$_3$Cl] (2.5)	23	91:9	77
13	dippf	[{Rh(C$_2$H$_4$)$_2$Cl}$_2$] (1.25)	23	92:8	89
14	dippf	[Rh(cod)$_2$]BF$_4$ (2.5)	36	ND	0
15	dippf	[Rh(acac)(cod)] (2.5)	36	ND	0
16	dippf	[{Ru(*p*-cymene)Cl$_2$}$_2$] (1.25)	36	ND	0
17	dippf	[Ru(PPh$_3$)$_3$Cl$_2$] (2.5)	36	ND	0
18	dippf	[RuHCl(CO)(PPh$_3$)$_3$] (2.5)	36	ND	0
19	dippf	[{Ir(cod)Cl}$_2$] (1.25)	36	ND	0

[a] Determined by ^{1}H NMR spectroscopy of the crude mixture. [b] 5 mol% of the ligand was used. dppf = 1,1′-bis(diphenylphosphanyl)-ferrocene, dcypf = 1,1′-bis(dicyclohexylphosphanyl)ferrocene, dtbpf = 1,1′-bis(di-*t*-butylphosphanyl)ferrocene, bdtbpb = 1,2-bis(di-*t*-butylphosphanyl)benzene, dppe = 1,2-bis(diphenylphosphino)ethane, dppp = 1,3-bis(diphenylphosphino)propane, BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl.

gave the desired products at room temperature. Thus, the Rh(cod)Cl dimer, in combination with the dippf ligand, was re-confirmed to be the optimal catalyst for the reaction by using triallyloxyborane **6a**.

The substrate scope of the isomerization/cross-aldol sequence is summarized in Table 5.[25] High *syn* selectivity was observed in Table 5, entries 1–11 by using compound **6a** and various aromatic and heteroaromtic aldehydes (>95:5–90:10 d.r.). Substituents at the *ortho*, *meta*, and *para* positions on the aromatic ring of the aldehydes were compatible and even sterically hindered 2,6-disubstituted aldehyde **1k** (Table 5, entry 7) and the less-electrophilic aldehyde **1l**, which contained two electron-donating MeO groups at the *ortho* and *para* positions (Table 5, entry 8), gave their corresponding aldol adducts without problem. The results with substituted triallyloxyboranes **6b–6d** are summarized in Table 5, entries 12–15. Triallyloxyboranes **6b** (as a 15:1 *E*/*Z* mixture), (*Z*)-**6c**, and (*Z*)-**6d** showed good reactivity, thus

Table 5. Rh/dippf-catalyzed isomerization/cross-aldol sequence with various trialkoxyboranes.[a]



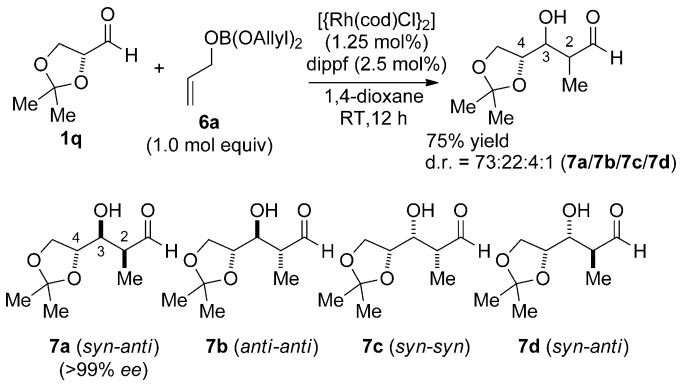
6a: R' = H; **6b**: R' = Me, mixture of (*E*) and (*Z*)-isomers; (*E*)-**6c**: R' = Et; (*Z*)-**6c**: R' = Et; (*Z*)-**6d**: R' = Pr
6e: R' = H (*n* = 2); **6f**: R' = H (*n* = 3)

Entry	R	1	6	*n*	*t* [h]	3	d.r.[b] (*syn*/*anti*)	Yield [%][c]
1	2-Br-C_6H_4	**1e**	**6a**	1	23	**3g**	94:6	99
2	3-Br-C_6H_4	**1f**	**6a**	1	36	**3h**	93:7	72
3	4-Br-C_6H_4	**1g**	**6a**	1	36	**3i**	93:7	83
4	3-Cl-C_6H_4	**1h**	**6a**	1	36	**3j**	91:9	95
5	4-F-C_6H_4	**1i**	**6a**	1	36	**3k**	93:7	87
6	4-NO_2-C_6H_4	**1j**	**6a**	1	36	**3l**	94:6	90
7	2,6-Cl_2-C_6H_3	**1k**	**6a**	1	36	**3m**	>95:5	85
8	2,4-$(MeO)_2$-C_6H_3	**1l**	**6a**	1	36	**3n**	90:10	78
9	Ph	**1c**	**6a**	1	36	**3b**	90:10	81
10	2-naphthyl	**1m**	**6a**	1	36	**3o**	90:10	75
11	2-furyl	**1n**	**6a**	1	36	**3p**	94:6	60
12	Ph	**1c**	**6b**	1	24	**3c**	90:10	93
13	Ph	**1c**	(*E*)-**6c**	1	48	**3d**	88:12	57
14	Ph	**1c**	(*Z*)-**6c**	1	12	**3d**	87:13	84
15	Ph	**1c**	(*Z*)-**6d**	1	12	**3e**	86:14	89
16	*n*-pentyl	**1d**	**6a**	1	27	**3q**	85:15	73
17	$PhCH_2CH_2$	**1a**	**6a**	1	36	**3a**	84:16	90
18	cyclohexyl	**1o**	**6a**	1	32	**3r**	74:26	62
19	Et	**1b**	**6b**	1	24	**3s**	75:25	71
20	Ph	**1c**	**6e**	2	24	**3c**	86:14	97
21	4-Br-C_6H_4	**1g**	**6e**	2	84	**3t**	91:9	87
22	4-MeO-C_6H_4	**1p**	**6e**	2	84	**3u**	84:16	84
23	2-furyl	**1n**	**6e**	2	60	**3v**	84:16	60
24	$PhCH_2CH_2$	**1a**	**6e**	2	96	**3w**	83:17	60
25	Ph	**1c**	**6f**	3	36	**3d**	ND	0

[a] Reaction conditions: compound **1** (0.4 mmol), compound **6** (1 mol equiv), in 1,4-dioxane (0.2 M) under an Ar atmosphere at ambient temperature. [b] Determined by ^{1}H NMR spectroscopy of the crude mixture. [c] Yield of the isolated product after conversion into either the corresponding dimethyl acetal with PPTS/MeOH or the 1,3-diol with $NaBH_4$ and purification by column chromatography on silica gel. [d] Yield of the isolated product in its β-hydroxy-aldehyde form after careful purification by column chromatography on silica gel. [e] 2.5 mol% of $[\{Rh(cod)Cl\}_2]$ and 5 mol% of dippf were used.

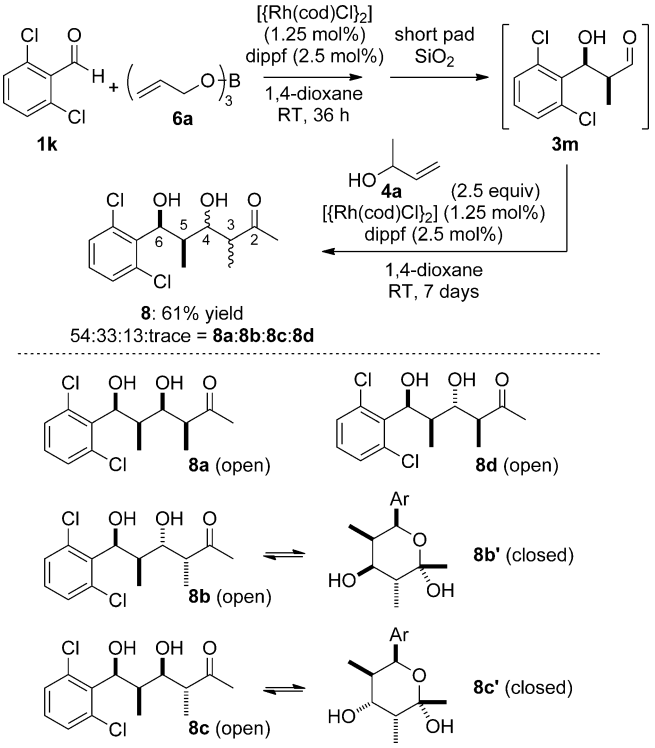
giving the cross-aldol adducts in 84–93% yield with good *syn* selectivity (Table 5, entries 12, 14, and 15). On the other hand, compound (*E*)-**6c** showed much-lower reactivity, possibly owing to slow isomerization, and the product was obtained in only 57% yield after 48 h (Table 5, entry 13), whereas the diastereoselectivity was similar to that with compound (*Z*)-**6c**. The diastereoselectivities in Table 5, entries 1–15 were higher than those in other related transition-metal-catalyzed isomerization/aldol sequences with secondary allylic alcohols. These results suggested that epimerization of the aldol products, which had caused erosion of the diastereoselectivity in some previous reports, was negligible under this Rh/dippf catalysis. This Rh catalyst was also applicable to enolizable aliphatic aldehydes (Table 5, entries 16–19). Although the *syn* selectivity was somewhat decreased, the desired cross-aldol adduct was obtained chemoselectively. In Table 5, entry 19, propanal chemoselectively reacted as an acceptor with the butanal-derived enolate that was generated from compound **6b** and cross-aldol adduct **3s** was obtained in 71% yield as an unprotected β-hydroxy aldehyde. In Table 5, entry 19, the homoaldol adduct that was derived from propanal was not detected, thus indicating the synthetic utility of this method based on the orthogonal activation of allyloxyboranes. In Table 5, entries 20–24, homoallyloxyborane **6e** was applied for aromatic, heteroaromatic, and aliphatic aldehydes. Although the reactivity of compound **6e** was lower than that of allyloxyboranes, the products were obtained in 60–97% yield and 91:9–83:17 d.r. However, the reaction with trialkoxyborane **6f**, which contained a remote C=C double bond did not proceed at room temperature (Table 5, entry 25).

Because this Rh/dippf-catalyzed reaction was performed under mild conditions, that is, at room temperature in the absence of a strong base, chiral aldehyde **1q** successfully gave compound **7a** as the major isomer without racemization in >99% *ee* (Scheme 5). The C2/C3 diastereoselectivity (**7a**+**7c**/**7b**+**7d**) was modest, but good C3/C4 diastereose-



Scheme 5. Isomerization/aldol sequence with chiral aldehyde **1q**.

lectivity (**7a**+**7b**/**7c**+**7d**) was observed. To further demonstrate the utility of this Rh/dippf catalysis, protecting-group-free consecutive aldol reactions with two different donors, that is, compounds **6a** and **4a**, were investigated (Scheme 6). The first aldol adduct (**3m**) was used in the second aldol reaction without protection of its β-hydoxy group. Although the second aldol reaction by using secondary allylic alcohol **4a** as a donor precursor required a long reaction time, possibly owing to steric hindrance, the double-aldol adducts (**8**) were obtained in 61% yield (from compound **3m**) in the ratio **8a**/**8b**/**8c**/**8d** = 54:33:13:trace. Double-aldol adduct **8a** was predominantly obtained in its open form, whilst adducts **8b** and **8c** were obtained as mixtures of their open- and closed forms in equilibrium. Aldehyde **1k** was chosen for



Scheme 6. Protecting-group-free consecutive aldol reactions by using two different donors, compounds **6a** and **4a**.

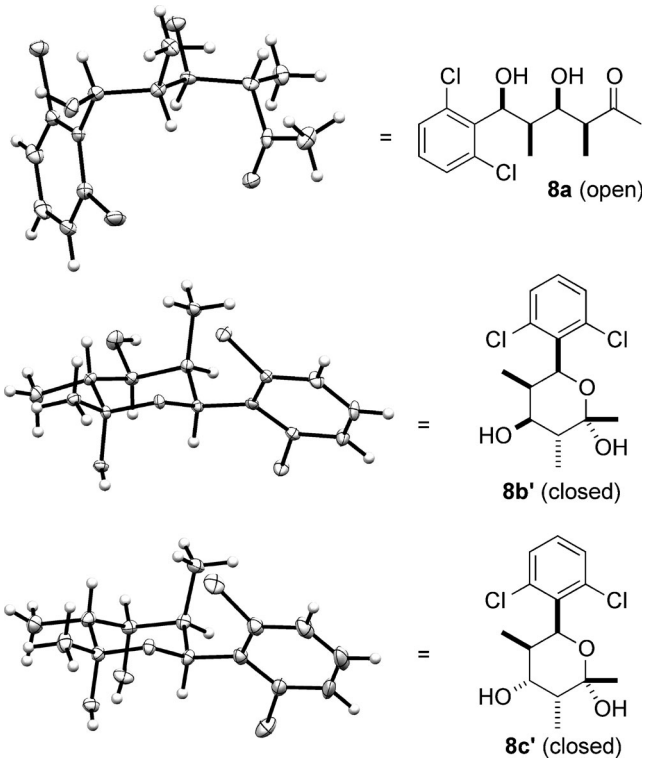
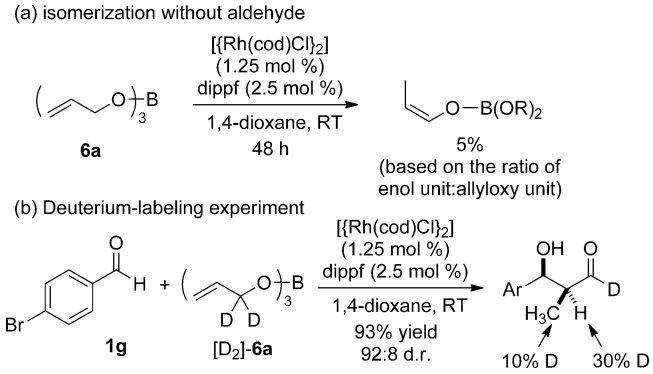


Figure 1. ORTEPs of compounds **8a**, **8b′** (closed form), and **8c′** (closed form); thermal ellipsoids are set at 50% probability.

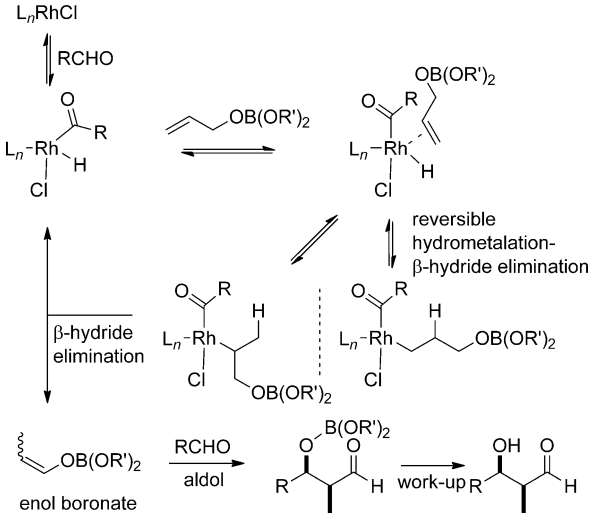
the consecutive aldol reaction in Scheme 6, because the double-aldol adducts that contained a 2,6-Cl_2-C_6H_3 unit was highly crystalline. The relative stereochemistry in compounds **8a**, **8b**, and **8c** was unequivocally determined by single-crystal X-ray analysis (Figure 1).[26]

This Rh/dippf catalyst promoted the isomerization/aldol sequence at ambient temperature. however, when triallyloxyborane **6a** was treated with the Rh/dippf catalyst (5 mol%) in the absence of an aldehyde acceptor, only 5% of the isomerized enol boronate (*Z*-major) was observed after 48 h at room temperature (Scheme 7a).[27] Because the Ru-catalyzed isomerization of triallyloxyborane **6a** into the corresponding enol boronate (*E*/*Z* mixture) has been reported,[24] the isomerized enol boronate should be thermodynamically more favorable than the starting triallyloxyborane (**6a**). Therefore, the result shown in Scheme 7a simply indicated that the isomerization in the absence of an aldehyde was much slower than that in the sequential isomerization/aldol process; indeed, the aldol reaction was complete within 36 h in many cases (Table 5, entries 1–19). To gain further insight into the reaction mechanism, deuterated triallyloxyborane [D_2]-**6a** was used in the isomerization/aldol sequence. As shown in Scheme 7b, deuterium labeling was not only observed at the methyl group, but also at the methine group in the product.[28] This result indicates that a reaction pathway that proceeds through the oxidative addition of Rh^I to the allylic C–H bond to form a π-allyl intermediate is less probable; in such a case, the deuterium label should be exclusively found on the methyl group.



Scheme 7. Mechanistic investigations: a) isomerization in the absence of an aldehyde; b) isomerization/aldol sequence with deuterated allyloxyborane [D_2]-**6a**.

A plausible catalytic cycle for the Rh-catalyzed isomerization/aldol sequence from allyloxy- and homoallyloxyboranes is shown in Scheme 8. On the basis of results in Scheme 7, we assume that a Rh–hydride species, which is initially generated by oxidative addition to the aldehyde, would be an active species for the isomerization process. Reversible hydrometalation/β-hydride-elimination processes should afford an enol-boronate intermediate.[29] In this Rh-catalyzed reaction, the scope of applicable phosphines was quite narrow (Table 4, entries 1–11) and only the dippf and dcypf ligands showed good performance. We think that the dippf and dcypf ligands, which are alkylphosphines with a ferrocene



Scheme 8. Plausible catalytic cycle of the Rh/dippf-catalyzed isomerization/aldol sequence of allyloxy boranes.

backbone, play a key role in accelerating the desired isomerization reaction at room temperature, whilst preventing undesirable pathways, such as decarbonylation and hydroacylation. The stereochemical outcome in the aldol reactions with enol boronates is known to be quite different from that with well-established enol borinates,[30,31] possibly owing to the differences in the Lewis acidities of the boron centers. Hoffmann et al. systematically studied aldol reactions with enol boronates that were derived from ketones and *syn*-aldol adducts were obtained as the major products, irrespective of the geometry of the enolate.[31] Thus, we assumed that the aldol reaction with the enol boronates that were derived from aldehydes would also give *syn*-aldol adducts as the major products, regardless of the geometry of the enol-boronate intermediate.[32,33]

Conclusions

In summary, we have reported the chemoselective generation of aldehyde-derived enolates to realize an aldehyde–aldehyde cross-aldol reaction. A combined Rh/dippf system efficiently promoted the isomerization/aldol sequence by using primary allylic, homoallylic, and bishomoallylic alcohols; secondary allylic and homoallylic alcohols; and trialkoxyboranes that were derived from primary allylic and homoallylic alcohols. The reaction proceeded at ambient temperature under base-free conditions, thus giving cross-aldol products with high chemoselectivity. The limitations of this system, in particular in consecutive protecting-group-free aldol reactions, were also clarified. Work to improve the reactivity and stereoselectivity of the aldol step, including the development of enantioselective variants, is actively underway in our group.[33]

Experimental Section

General Procedure for the Isolation of Dimethyl Acetals

A solution of 1,1′-bis(diisopropylphosphino)ferrocene (dippf, 4.3 mg, 2.5 mol%) and [{Rh(cod)Cl}$_2$] (2.5 mg, 1.25 mol%, cod = 1,5-cyclooctadiene) in 1,4-dioxane (2.0 mL) was added to a mixture of trialkoxyborane **6** (0.40 mmol) or primary alcohol **2** (0.80 mmol) and freshly distilled aldehyde **1** (0.40 mmol) in a flame-dried test tube. After completion of the reaction, the mixture was passed through a pad of silica gel and the filtrate was concentrated in vacuo to give the crude aldol adduct. Water (10 mL) was added to the residue and then products were extracted with Et_2O (3×10 mL). The combined organic phases were dried over anhydrous sodium sulfate, evaporated, and re-dissolved in MeOH (3.0 mL). Pyridinium *p*-toluenesulfonate (PPTS, 5 mol%) was added to the solution and the mixture was stirred for 12 h at RT. The mixture was poured into a saturated aqueous solution of $NaHCO_3$ (10 mL) and the products were extracted with Et_2O (5×10 mL). The combined organic phases were dried over anhydrous sodium sulfate and concentrated to give the crude acetal product. Purification by column chromatography on silica gel gave the dimethyl-acetal adducts.

General Procedure for the Isolation of 1,3-Diols

A solution of 1,1′-bis(diisopropylphosphino)ferrocene (dippf, 4.3 mg, 2.5 mol%) and [{Rh(cod)Cl}$_2$] (2.5 mg, 1.25 mol%) in 1,4-dioxane (2.0 mL) was added to a mixture of trialkoxyborane **6** (0.40 mmol) or primary alcohol **2** (0.80 mmol) and freshly distilled aldehyde **1** (0.40 mmol) in a flame-dried test tube. After completion of the reaction, MeOH (2.0 mL) was added and the mixture was cooled to 0 °C. Then, $NaBH_4$ (1.2 mmol) was added and the mixture was stirred overnight under an argon atmosphere. After evaporation, water (10 mL) and Et_2O (10 mL) were added to the residue and the organic phase was separated. The water phase was further extracted with Et_2O (3×10 mL). The combined organic phases were dried over anhydrous sodium sulfate, passed through a short pad of silica gel (eluted with Et_2O), and concentrated in vacuo. The diastereomeric ratio was determined by ^{1}H NMR spectroscopy of the crude 1,3-diol product and the crude material was purified by column chromatography on silica gel to give the 1,3-diol products.

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[25] Although triallyloxyboranes **6** contained three allyloxy units, 1.0 mol equiv of compound **6** was required to obtain good reactivity and diastereoselectivity. In the reaction of aldehyde **1c** with 0.33 mol equiv of compound **6a**, the Rh/dippf catalyst gave product **3b** in 51% yield with 83:17 d.r. after 36 h. In Table 5, the reaction between the aldehyde unit in the first aldol product and the enolate was only observed as a minor pathway in some cases, because sterically hindered branched aliphatic aldehydes showed much-lower reactivities than aryl aldehydes and linear alkyl aldehydes.

[26] CCDC 890240 (**8a**), CCDC 890241 (**8b′**, closed form), and CCDC 890242 (**8c′**, closed form) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[27] The yield in Scheme 7a was calculated based on the ratio of enol/allyloxy units in the boronate.

[28] The deuterium label of the aldol adduct in Scheme 7b was analyzed by NMR spectroscopy after conversion into its corresponding 1,3-diol, because the β-hydroxy aldehyde was unstable.

[29] Rh^{III}–hydride species that are generated from Rh^{I} catalysts and aldehydes are common intermediates in the Rh-catalyzed hydroacylation of alkenes. The Rh-catalyzed hydroacylation reaction also involves reversible hydrometalation/β-hydride-elimination processes of Rh^{III}–hydride species with alkenes. For a comprehensive review on transition-metal-catalyzed hydroacylation, including detailed mechanistic discussion, see: M. C. Willis, *Chem. Rev.* **2010**, *110*, 725.
[30] For a comprehensive review on aldol reactions with enol borinates, see: C. J. Cowden, I. Paterson, *Org. React.* **1997**, *51*, 1.
[31] R. W. Hoffmann, K. Ditrich, *Tetrahedron Lett.* **1984**, *25*, 1781.
[32] Although the isomerization of allyloxyborane in the absence of an aldehyde gave the (*Z*)-enol boronate as the major product (Scheme 7a), we could not determine the enolate geometry in the presence of an aldehyde.
[33] All attempts to induce enantioselectivity in this present Rh-catalyzed process with chiral Rh complexes and triallyloxyboranes failed. Thus, we believe that the Rh complex does not play a key role in the C–C bond-forming process. Thus, we are currently pursuing different approaches to achieve the catalytic asymmetric aldehyde–aldehyde cross-aldol reaction.

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