論文の内容の要旨

Development of Transition Metal-Catalyzed Aldehyde-Aldehyde Cross Aldol Reactions

（遷移金属触媒による異種アルデヒド間交差アルドール反応の開発）

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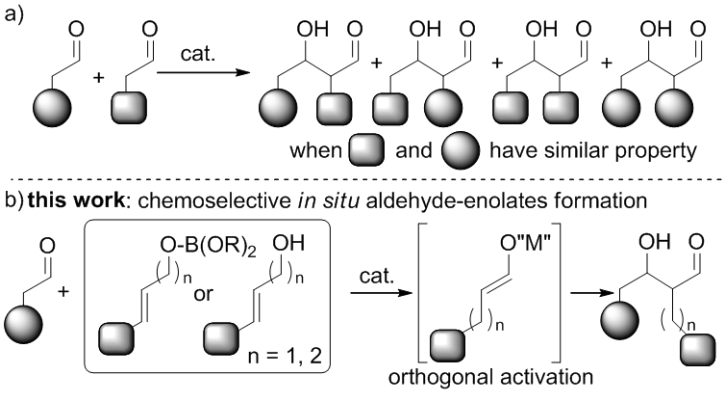
Introduction

Aldol reactions have been widely used in organic chemistry by their powerful capability in carbon-carbon bond-formation since the discovery by Wurtz in 1872. 1,3-Polyol units are very common structural motifs found in many natural products and pharmaceuticals. About 20% of top-selling drugs were occupied by polyketide-derived drugs and over 10 billion pounds per year revenue comes from polyketide-derived drugs[1]. For the synthesis of 1,3-polyol units



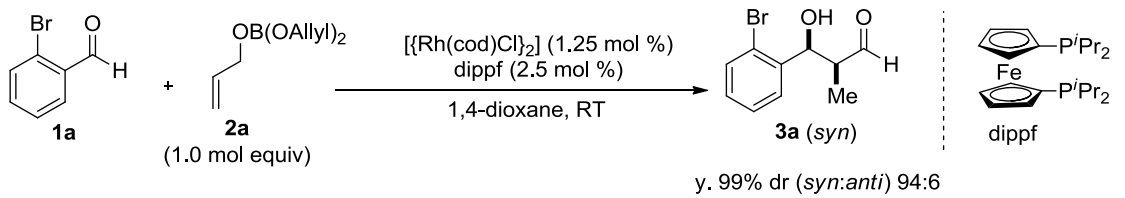
Scheme 1. cross-aldol reaction between two different aldehydes: a) conventional method starting from two aldehydes, and b) this work proceeding through the chemoselective generation of aldehyde enolates from primary allylic and homoallylic alcohols and allyloxy and homoallyloxyboranes.

via modern aldol process utilizing ketones, thioesters, esters, and other carboxylic acid derivatives as donor, several-step transformations, including protection and redox processes, aregenerally required to give a protected β-hydroxyaldehyde unit for the second aldol process. In the sense of step- and redox-economy, a cross-aldol reaction between two different aldehydes, in principle, provides much more efficient and straightforward access to polyketides.

Cross-aldol reactions between two different aldehydes are difficult, often affording mixtures of homo- and hetero-aldol products (***Scheme 1a***). As a state-of-the-art methodology, organocatalytic enantioselective direct aldehyde-aldehyde cross-aldol reactions have been developed, simply based on the steric and/or electronic bias between two different aldehydes. Cross-aldol reactions overriding the bias, for example, *propanal as an acceptor and another sterically more hindered aldehyde as a donors*, are however, extremely difficult. Thus, development of a new chemoselective, diastereoselective and enantioselective aldehyde-aldehyde cross-aldol process that override the bias is highly desirable.

Development of Rh-catalyzed aldehyde-aldehyde cross aldol reaction: *in situ* aldehyde-derived enolate formation via orthogonal activation[2,3]

Mukaiyama-type aldehyde-aldehyde cross-aldol reactions using silyl enol ethers have been investigated by several groups. In contrast, the use of aldehyde-derived enol boranes is rare due totheir unstable property compared to other enol boranes derived from ketones and carboxylic acid derivatives. Considering the synthetic utility and unstable property of aldehyde-derived B-enolates, I decided to investigate a cross-aldol reaction *via in situ* generation of an aldehyde-derived enolate from primary allylic and homoallylic alcohol borates as well as primary allylic and homoallylic alcohols as nucleophile precussors (***Scheme 1b***). To avoid handling unstable aldehyde-derived enol boranes, *in situ* generation of aldehyde-derived enol boranes through transition metal-catalyzed isomerization of triallyloxyboranes was investigated.After intensive optimization studies, a **Rh(cod)Cl dimer (1.25 mol%)** in combination with **dippf** (**1,1'-Bis(diisopropylphosphino)ferrocene**) **(2.5 mol%)** was found to be the best for realizing the desired isomerization/cross-aldol sequence at room temperature in good yield and diastereoselectivity (***Scheme 2***).

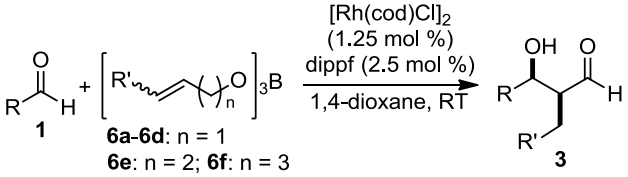


y. 99% dr (*syn*:*anti*) 94:6

Scheme 2 the optimal condition for isomerization/cross-aldol sequene

The substrate scope of the isomerization/cross-aldol sequence is summarized in **Table 1**. High *syn*-selectivity was observed in entries 1-11 using **6a** and various aromatic and heteroaromtic aldehydes (>95:5-90:10 dr). The results using substituted triallyloxyboranes **6b**-**6d** are summarized in entries 12-15. Triallyloxyborane **6b** as an *E*/*Z*-mixture (15:1), (*Z*)-**6c**, and (*Z*)-**6d** showed good reactivity, giving cross-aldol adducts in 84-93% yield with good *syn*-selectivity (entries 12, 14-15). On the other hand, (*E*)-**6c** had much lower reactivity, possibly due to slow isomerization, and the product was obtained in only 57% yield after 48 h (entry 13), whereas the diastereoselectivity was similar to that with (*Z*)-**6c**. The present Rh-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 with butanal-derived enolate generated from* **6b**, *and cross aldol adduct* **3s** *was obtained in 71% yield as unprotected β-hydroxy aldehyde*. In entry 19, the homoaldol adduct derived from propanal was not detected, indicating the synthetic utility of the present method based on the orthogonal activation of allyloxyboranes. In entries 20-24, homoallyloxyborane **6e** was applied for aromatic, heteroaromatic, and aliphatic aldehydes. Although the reactivity of **6e** was lower than allyloxyboranes, products were obtained in 60-97% yield and 91:9-83:17 dr. The reaction with trialkoxyborane **6f** with a remote carbon-carbon double bond, however, did not proceed at RT (entry 25).

Table 1: Substrate scope of aldehydes and triallyloxyboranes

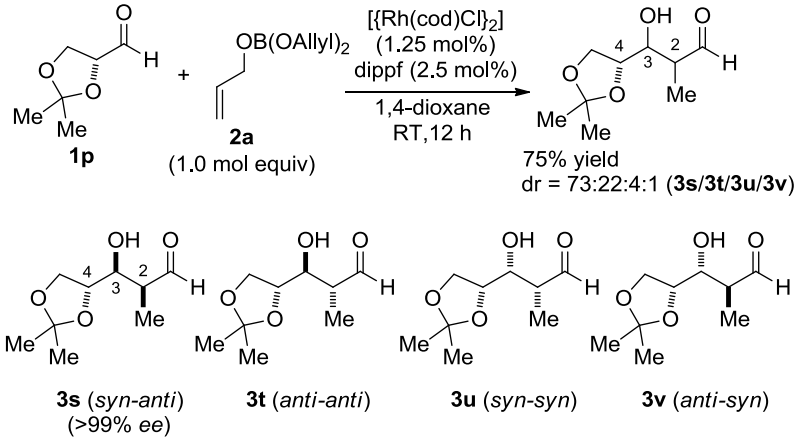


6a: R' = H; **6b**: R' = Me, mixture of (*E*) and (*Z*)-isomers; (*E*)-**6c**: R' = Et; (*Z*)-**6c**: R' = Et; (*Z*)-**6d**: R' = Pr
6e: R' = H (n = 2); **6f**: R' = H (n = 3)

entry	R	1	6	n	t [h]	3	dr syn:anti	% Yield
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[a]	$PhCH_2CH_2$-	**1a**	**6e**	2	96	**3w**	83:17	60
25	Ph-	**1c**	**6f**	3	36	**3d**	ND	0

[a] 2.5 mol% of $[Rh(cod)Cl]_2$ and 5 mol % of dippf were used

In addition, the present Rh/dippf catalyst was applied to chiral aldehydes (**1p**) without racemization, giving **3s** in 99%ee under mild conditions, that is, at room temperature in absence of strong base (***Scheme 3***). Second aldol reaction as well as mechanistic studies were also investigated. With the free secondary, primary allylic and homoallylic- alcohols, the expected isomerization/cross-aldol sequence also proceeded smoothly at room temperature. In summary, a method of Rh-catalyzed isomerization/cross aldol reaction of two different aldehydes have been established in this thesis.



Scheme 3. Rhodium-catalyzed isomerization/cross-aldol sequence using the chiral aldehyde **1p**.

Development of a catalytic asymmetric isomerization/aldehyde-aldehyde cross-aldol reaction[4]

Considering the importance of chiral compounds in current pharmaceutical industry, an asymmetric aldehyde-aldehyde cross-aldol reaction beyond steric and/or electronic bias between two different aldehydes is highly demanded. I have tried to achieve asymmetric isomerization/cross-aldol sequence with either using chiral phosphine/Rh complexes or chiral allylic boranes. Unfortunately, however, all tirals resulted in poor yield and/or poor stereoselectivity. After careful and intensive investigations of aldehyde-aldehyde cross aldol reaction again, finally, I have succeeded in developing a catalytic asymmetric isomerization/cross-aldol reaction, giving products in moderate to high yield (up to 95%), moderate to high diastereoselectivity (up to >20:1), and high enantioselectivity (up to 99% ee) for a range of substrates including aromatic, heteroaromatatic, aliphatic, and α,β-unsaturated aldehydes. The detail of this section was decribed in my thesis. In the future direction, I would like to develop a new catalyst that promotes the second aldol process under catalyst control.

References

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4) Lin, L.; Yamamoto, K.; Mitsunuma, H; Matsunaga, S.; Kanai, M. *Manuscript in preparation.*

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