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BIFUNCTIONAL-BENZOTHIADIAZINE-CATALYZED REGIO- AND STEREOSELECTIVE ALDOL REACTIONS USING A 1,3-ACETONEDICARBOXYLIC ACID MONOESTER

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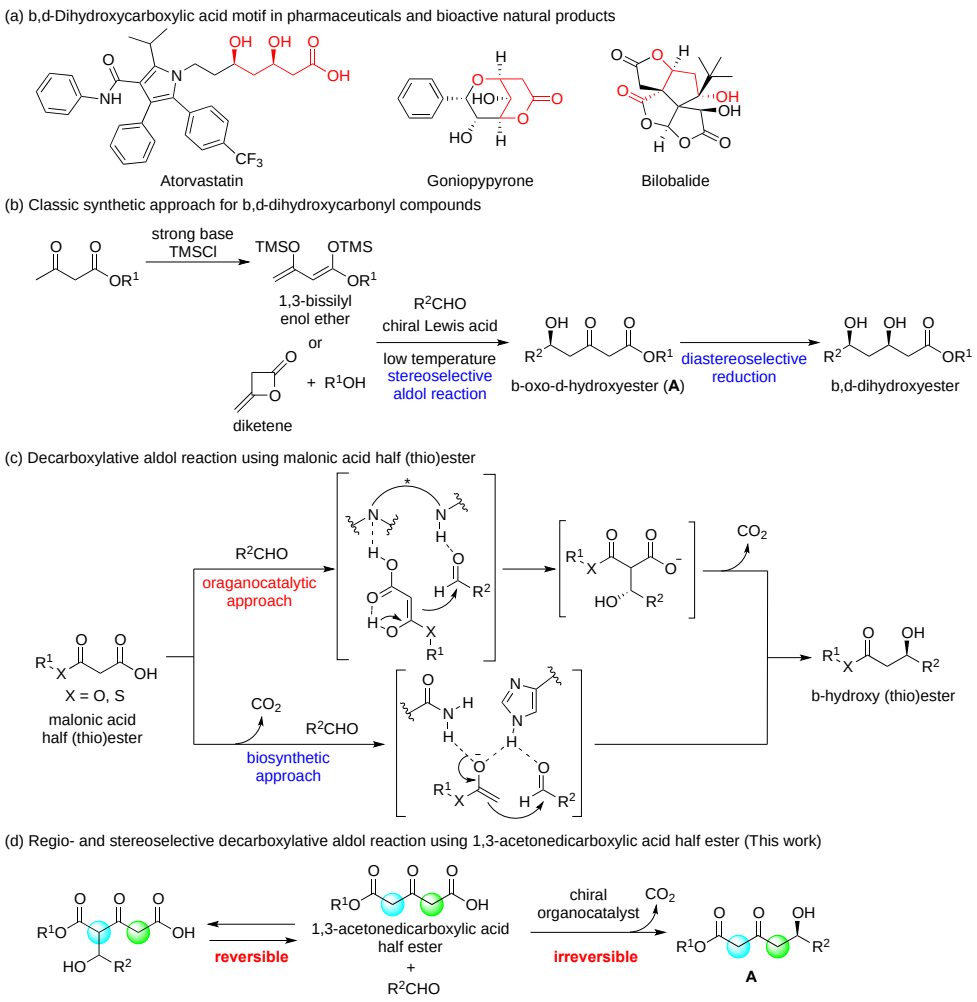
Abstract – Regio- and stereoselective decarboxylative aldol reactions of a 1,3-acetonedicarboxylic acid monoester were achieved using an aminobenzothiadiazine organocatalyst. The products were obtained with perfect regioselectivity and moderate to good enantioselectivity using various aromatic aldehydes. Subsequently, the thus obtained adducts were efficiently converted into various chiral building blocks.

Chiral β,δ-dihydroxycarboxylic acid moieties represent an important structural motif in various pharmaceuticals and bioactive natural products (Scheme 1a).[1-4] For example, atorvastatin, which inhibits the activity of HMG-CoA reductase in the mevalonate pathway, is a representative medicine for the treatment of hyperlipidemia and one of the best-selling pharmaceuticals.[1] Thus, many research groups have investigated the asymmetric synthesis of atorvastatin.[2] As the key structure can be readily derived from the corresponding optically pure β-oxo-δ-hydroxyester (**A**) by established methods using appropriate reducing agents,[5] most synthetic routes incorporate this transformation.[2c,e,f] Therefore, we became interested in developing a concise and efficient synthetic route to key intermediate **A**. Although several asymmetric aldol reactions using silyl enol ethers and diketene in the presence of chiral Lewis acids have been developed,[6-8] these methods require low reaction temperatures and the tedious preparation of reagents to attain high enantioselectivity (Scheme 1b). A mild and atom-economical synthetic route to **A** is thus still highly desirable.

Decarboxylative reactions of β-ketocarboxylic acids are a powerful tool for the synthesis of α-functionalized ketone substructures.[9] In particular, the organocatalytic decarboxylative aldol reaction of malonic acid half (thio)esters[10] can efficiently provide the optically active β-hydroxy(thio)esters under

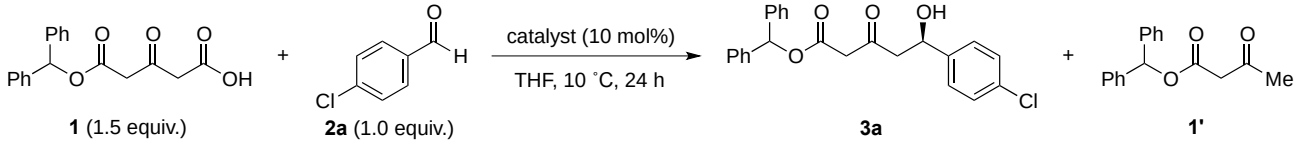
mild conditions. This reaction mimics the biosynthesis of polyketides,[11] in which the side chains of histidine and asparagine stabilize the reaction intermediate by forming a multiple-hydrogen-bond network (Scheme 1c). Although several groups have reported the use of 1,3-acetonedicarboxylic acids in decarboxylative aldol reactions, dicarboxylic acids generally react with two equivalents of aldehyde to provide the β,β′-dihydroxyketones.[12] To efficiently synthesize chiral β-oxo-δ-hydroxyester **A**, we envisioned that 1,3-acetonedicarboxylic acid half esters, which contain two active methylene moieties with distinct activities, could undergo the decarboxylative aldol reaction to provide **A** as the sole regioisomer. Specifically, based on the different reactivities of two reaction sites, the active β-ketoacid methylene moiety could react irreversibly with the aldehyde due to the subsequent decarboxylation, whereas the β-ketoester methylene could react reversibly with the electrophile (Scheme 1d). Herein, we describe the first regio- and stereoselective decarboxylative aldol reactions of a 1,3-acetonedicarboxylic acid half ester using a chiral bifunctional benzothiadiazine catalyst, as well as the derivatization of the thus obtained aldol adducts into a variety of versatile chiral building blocks.



Scheme 1. Strategy for the Asymmetric Synthesis of β-Oxo-δ-hydroxyester **A**

We initially screened potential catalysts for the asymmetric decarboxylative aldol reaction using β-ketoacid **1** as a nucleophile (Table 1). Treatment of **1** with aldehyde **2a** in the presence of urea catalyst **4a** afforded the desired product (**3a**) as a single regioisomer, albeit in low yield and stereoselectivity (entry 1). To improve the yield and enantioselectivity, the bifunctional hydrogen-bond-donor catalysts **4b-e** were examined. The use of thiourea **4b**[13] and squaramide **4c**,[14] which are stronger hydrogen-bond donors than urea **4a**, increased the yield, but the stereoselectivity remained almost identical (entries 2 and 3). Although cinchona-alkaloid-derived sulfonamide **4d**[15] gave the best yield of **3a**, it exhibited lower enantioselectivity (entry 4). In contrast, the recently developed benzothiadiazine catalyst **4e**,[16] which is a powerful hydrogen-bond donor with a rigid backbone, provided **3a** in moderate yield and enantioselectivity (entry 5). The use of acid catalysts such as BINOL-derived phosphoric acid **4f**[17] and copper/bis(oxazoline) complex **4g**[9e,10b] resulted in the recovery of starting materials **1** and **2** without the formation of decarboxylated byproduct **1′** (entries 6 and 7). Interestingly, catalysts **4a-e**, which bear tertiary amines, showed different reactivity than **4f** and **4g**, i.e., **1** was completely consumed using **4a-e**. These results suggest that deprotonation of **1** by the amines is crucial for the decarboxylation.

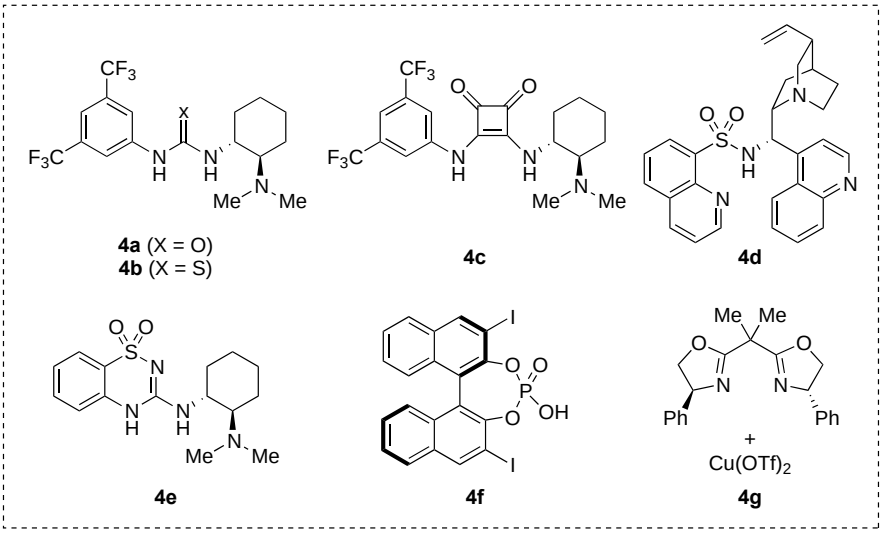
Table 1. Catalyst Screening



1 (1.5 equiv.) **2a** (1.0 equiv.) **3a** **1'**

entry	catalyst	yield[a] (%)	ee[b] (%)
1	**4a**	23	15
2	**4b**	33	11
3	**4c**	39	12
4	**4d**	45	9
5	**4e**	42	52
6	**4f**	N. D.	-
7	**4g**	N. D.	-

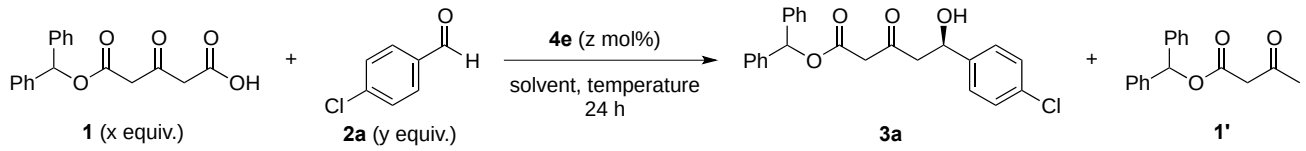
[a]Isolated yield. [b]Determined by chiral HPLC analysis.



Using the optimal catalyst **4e**, we further investigated the reaction conditions to improve the yield and selectivity (Table 2). Although the use of an excess of either carboxylic acid **1** or aldehyde **2a** slightly lowered the selectivity (entries 2 and 3), increasing the catalyst loading to 30 mol% improved the enantioselectivity to 63% ee with a slight decrease in the chemical yield (entry 4). Lowering the reaction

temperature to suppress the formation of **1′** afforded the **3a** in 56% yield and 66% ee (entry 5). Changing the solvent from THF to a nonpolar solvent such as CH_2Cl_2 or toluene significantly diminished both the yield and enantioselectivity (entries 6 and 7). Finally, in contrast to the results shown in entry 2, the portion-wise addition of 3.0 equivalents of β-ketoacid **1** successfully improved the yield of **3a** to 81% while maintaining the stereoselectivity (entry 8).

Table 2. Optimization of Reaction Conditions

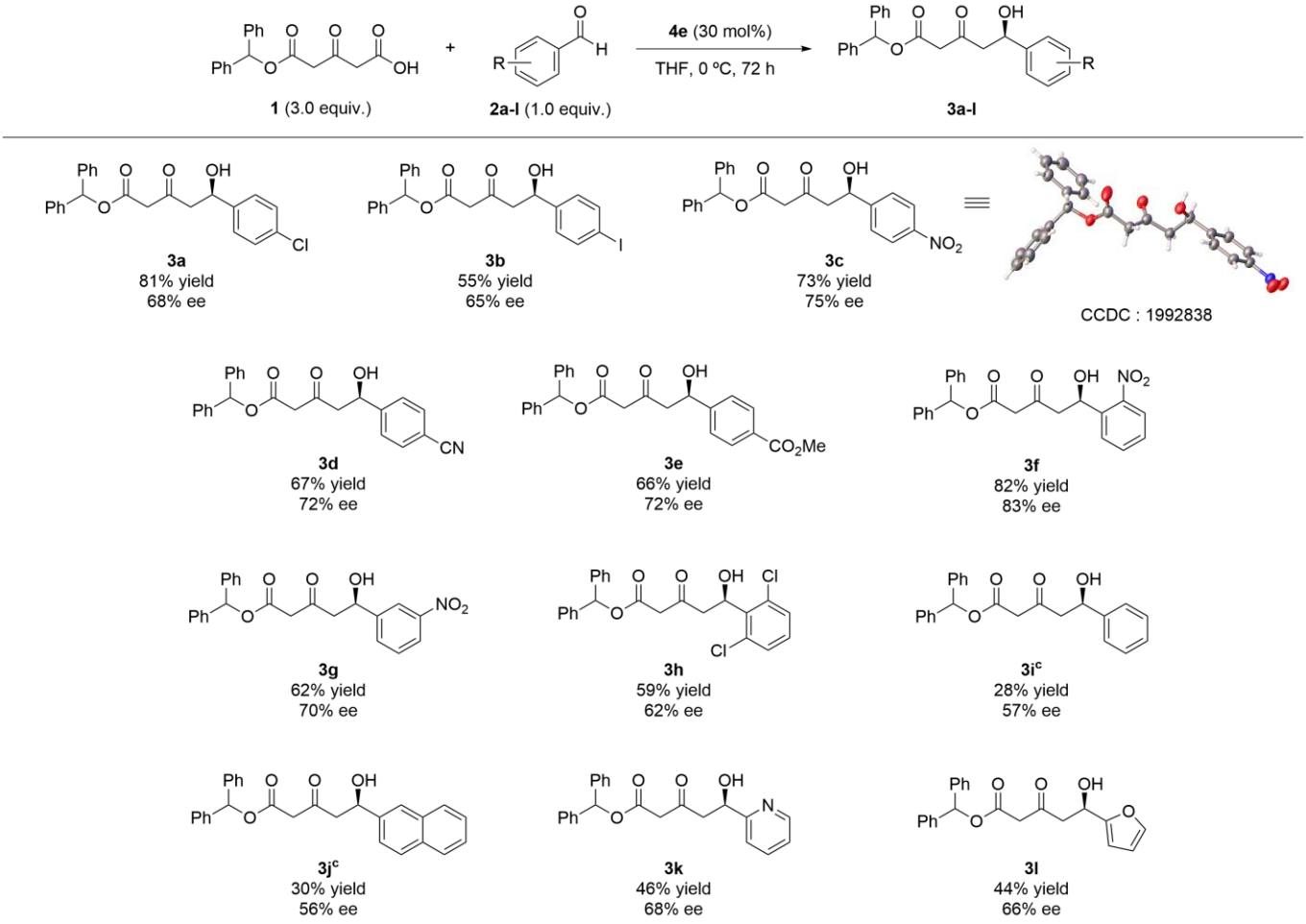


entry	**1** (x equiv.)	**2a** (y equiv.)	**4e** (z mol %)	solvent	temperature (˚C)	yield[a] (%)	ee[b] (%)
1	1.5	1.0	10	THF	10	42	52
2[c]	3.0	1.0	10	THF	10	29	44
3	1.0	5.0	10	THF	10	65	40
4	1.5	1.0	30	THF	10	37	63
5	1.5	1.0	30	THF	0	56	66
6	1.5	1.0	30	CH_2Cl_2	0	17	17
7	1.5	1.0	30	toluene	0	27	17
8[c,d]	1.0 x3	1.0	30	THF	0	81	68

[a]Isolated yield. [b]Determined by chiral HPLC analysis. [c]Reaction was performed for 72 h. [d]**1** (1.0 equiv.) was added 3 times at 0, 24, and 48 h.

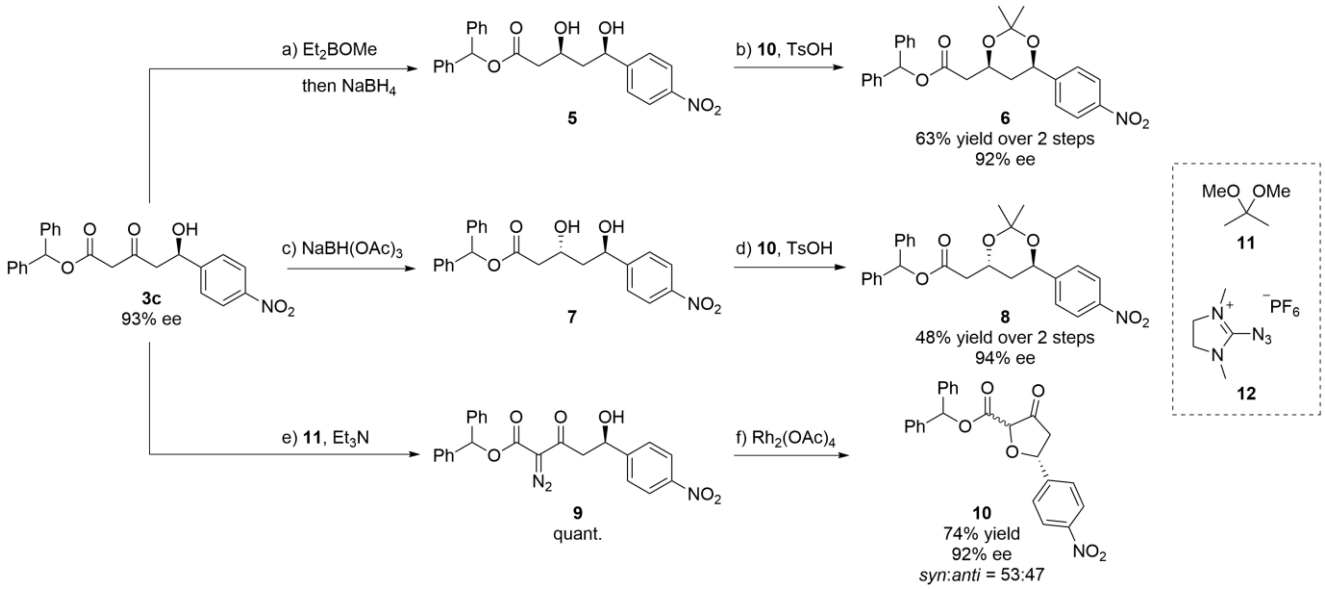
With the optimized reaction conditions in hand, we then investigated the substrate scope with respect to aldehydes[18] (Table 3). Aromatic aldehydes that bear halogen atoms at the *para* position afforded the corresponding δ-hydroxy-β-ketoesters **3a** and **3b** in good to high yield with moderate enantioselectivity. The presence of electron-withdrawing groups such as nitro, cyano, or ester groups at the *para* position of the aromatic ring increased the yield and stereoselectivity of **3c-3e**. The *para*-nitro adduct **3c** was obtained as a white crystalline solid, and a single-crystal X-ray diffraction analysis revealed its absolute configuration (*R*).[19] Aromatic aldehydes that bear a nitro group at the *ortho* or *meta* position provided adducts **3f** and **3g** in 82% and 62% yield, respectively, with good enantioselectivity, despite the steric hindrance. The sterically more hindered 2,6-disubstituted benzaldehyde **2h** retarded the reaction slightly, but successfully provided the adduct **3h**, albeit in decreased yield and enantioselectivity (59% yield, 62% ee). Benzaldehyde and 2-naphthaldehyde did not afford the corresponding adducts **3i** and **3j** at 0 °C, but both could be obtained in low yield upon increasing the reaction temperature to 10 °C. Notably, heteroaromatic aldehydes were applicable in this decarboxylative aldol reaction, affording the pyridine- and furan-containing adducts **3k** and **3l**, respectively, in acceptable yield with moderate selectivities.

Table 3. Substrate Scope[a,b]



[a]Isolated yield. [b]Ee values were determined by chiral HPLC analysis. [c]Reaction was performed at 10 °C.

Finally, we wanted to demonstrate the synthetic utility of this method by generating several valuable derivatives of aldol adduct **3c** (Scheme 2). It is worth mentioning that the obtained aldol adducts can be readily recrystallized to improve their optical purity. For example, recrystallized β-hydroxyketone **3c** (93% ee) was subjected to reduction with diethylmethoxyborane and sodium borohydride to furnish *syn*-1,3-diol **5**. Subsequently, diol **5** was protected with 2,2-dimethoxypropane **11** in the presence of a catalytic amount of *p*-toluenesulfonic acid to provide the corresponding acetonide **6** (92% ee) as an isolable single diastereomer in 63% yield over two steps. In contrast, the *anti*-selective reduction of β-hydroxyketone **3c** was achieved with sodium triacetoxyborohydride to give *anti*-1,3-diol **7**, which was similarly treated with 2,2-dimethoxypropane **11** to afford the corresponding acetonide **7** (94% ee) in 48% yield over two steps as the sole diastereomer. Subsequently, we investigated the construction of a heterocyclic ring system. After treating β-ketoester **3c** with azide **12**, Rh-catalyzed intramolecular O-H bond insertion of the resulting diazo adduct **9** furnished dihydro-3-furanone **10** (92% ee) as a mixture of two diastereomers (*syn*:*anti* = 53:47) in 74% yield.



Scheme 2. Derivatization of aldol adduct **3c**. Reagents and conditions: (a) Et_2BOMe (1.1 equiv.), THF/MeOH (4:1, v/v), −78 °C, 1 h; then $NaBH_4$ (1.1 equiv.), −78 °C, 17 h; (b) **11** (15 equiv.), $TsOH·H_2O$ (10 mol%), CH_2Cl_2, rt, 14 h, 63% yield over 2 steps; (c) $NaBH(OAc)_3$ (5.0 equiv.), MeCN/AcOH (3:1, v/v), −40 °C to 0 °C, 21 h; (d) **11** (15 equiv.), $TsOH·H_2O$ (10 mol%), CH_2Cl_2, rt, 24 h, 48% yield over 2 steps; (e) **12** (1.2 equiv.), Et_3N (2.0 equiv.), THF/MeCN (4:1, v/v), 0 °C, 3 h, quant.; (f) $Rh_2(OAc)_4$ (2.5 mol%), CH_2Cl_2, 30 °C, 16 h, 74% yield, *syn*:*anti* = 53:47.

In conclusion, we have developed a regio- and stereoselective organocatalytic decarboxylative aldol reaction of 1,3-acetonedicarboxylic acid half esters. In this reaction, the bifunctional benzothiadiazine catalyst with a rigid skeleton and a strong hydrogen-bond-donor ability is critical for the formation of enantioenriched β-oxo-δ-hydroxyesters with various substituents. Moreover, using product **3c**, the diastereoselective reduction of the ketone and the construction of dihydro-3-furanone were accomplished in good yield to provide versatile chiral building blocks for the efficient synthesis of various bioactive compounds. Further investigations into the mechanistic origins of the stereoselectivity are currently in progress in our laboratory.

EXPERIMENTAL

Optimized General Procedure for the Decarboxylative Aldol Reaction.

A 10 mL test tube equipped with a Teflon-coated screw cap was charged with a magnetic stirring bar, aldehyde **2** (0.100 mmol, 1.0 equiv.), catalyst **4e** (9.7 mg, 0.030 mmol, 30 mol%), and THF (1.0 mL), before the mixture was cooled to 0 °C. Carboxylic acid **1** (93.6 mg, 0.300 mmol, 3.0 equiv.) was added in portions (1.0 equiv.) at 0, 24, and 48 h to the stirred mixture. After stirring for 72 h at 0 °C, the solution

was concentrated under reduced pressure, and the residue was purified using column chromatography on silica gel to afford the adducts **3**. The ee values were determined by chiral HPLC analysis.

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SUPPORTING INFORMATION

Supplementary data (experimental procedures, characterization for new compounds, including ^{1}H and ^{13}C NMR spectra) associated with this article can be found, in the online version, at URL: https://www.heterocycles.jp/newlibrary/downloads/PDFsi/26637/103/1

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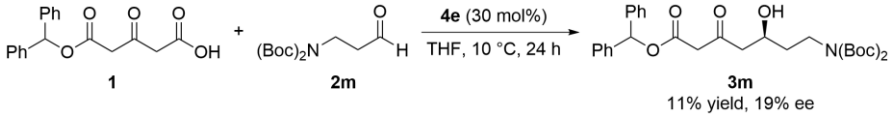
18. So far, the decarboxylative aldol reaction using an aliphatic aldehyde **2m** resulted in low yield and enantioselectivity.



19. X-Ray diffraction analysis was conducted using optically pure sample of **3c** after single recrystallization. CCDC 1992838 contains the supplementary crystallographic data for this paper. This information can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.