Tetrahedron 69 (2013) 1202–1209

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Facile synthesis of α-methylidene-γ-butyrolactones: intramolecular Rauhut–Currier reaction promoted by chiral acid–base organocatalysts

Shinobu Takizawa [a], Tue Minh-Nhat Nguyen [a], André Grossmann [a,b], Michitaka Suzuki [a], Dieter Enders [b], Hiroaki Sasai [a,*]

[a] The Institute of Scientific and Industrial Research (ISIR), Osaka University, Mihogaoka, Ibaraki-shi, Osaka 567-0047, Japan
[b] Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, 52074 Aachen, Germany

ARTICLE INFO

Article history:
Received 1 October 2012
Received in revised form 11 November 2012
Accepted 12 November 2012
Available online 28 November 2012

Keywords:
Rauhut–Currier
Enantioselective
Organocatalysts
α-Methylidene-γ-butyrolactones
Intramolecular

ABSTRACT

The acid–base organocatalyzed intramolecular Rauhut–Currier (RC) reaction of the dienone enolates has been developed. The enantioselective RC process produces the highly functionalized α-methylidene-γ-butyrolactones as a single diastereomer with up to 98% ee.

1. Introduction

Enantioselective organocatalysis has been recognized as an environmentally benign and practical methodology for asymmetric organic synthesis.[1] Among the achievements, C–C bond-forming reactions using chiral organocatalysts play an outstanding role in enabling highly selective syntheses of biologically important compounds.[2] The Rauhut–Currier (RC) reaction, in which two α,β-unsaturated carbonyl compounds are used as the substrates, provides a readily access to α-substituted enones, where one of the α,β-unsaturated carbonyl compounds acts as a latent enolate (Fig. 1, Eq. 1).[3,4] In contrast to the related Morita–Baylis–Hillman (MBH) and aza-MBH reactions,[5] where the latent enolate reacts with another carbonyl compound or imine (Eqs. 2 and 3), the RC reaction lacks reactivity and selectivity. The use of two different α,β-unsaturated carbonyl compounds on the RC reaction led to a mixture of the homo- and hetero-couplings. Therefore, until now, limited numbers of attractive systems have been developed for the RC reaction.[6,7] The first breakthrough in the enantioselective RC reaction was reported by Miller in 2007 with further contributions by Gladysz, Christman and Wu. These groups succeeded in the enantioselective RC reaction of bis(enones) or enal-enones utilizing cysteine-derived thiolates,[7a] rhenium-phosphine complexes,[7b] prolinol derivatives with AcOH,[7c] or valine-derived phosphinothioureas[7d] as catalysts, respectively. Gu and Xiao extended this reaction to nitroolefins.[8] Scheidt and Shi presented the intermolecular reaction of silyloxyallenes and allenoates catalyzed by $Sc(OTf)_3$·(*R*,*R*)-Ph-Pybox or β-ICD.[9] More recently, asymmetric [4+2] annulations via aza-RC reaction have been realized with chiral amino phosphine catalyst.[10] Highly selective construction of complex frameworks via the enantioselective RC reaction has been a challenge in asymmetric synthetic chemistry.

We envisioned that desymmetrization of the prochiral dienones **2**, which are easily accessible from readily available phenols,[11] via the RC reaction is a straightforward and atom economical way to prepare α-methylidene-γ-butyrolactones **1** (Fig. 2).[12] The α-methylidene-γ-butyrolactone skeleton exhibiting various biological activities is a common to a vast number of natural products, such as paeonilactone B (**3**), calealactone C (**4**) and tricyclic compounds **5** and **6** (Fig. 3).[13]

We have also developed several highly efficient MBH-type reactions promoted by acid–base organocatalysts (Fig. 4).[14] An appropriate positions of both the Brønsted acid (BA) and the Lewis base (LB) units on one chiral back bone could facilitate a synergistic cooperation to generate the designated chiral enolate **I**, the enantioselective RC reaction of **2** (Fig. 2) would take place with high chemo-, diastereo- and enantioselectivities. In this manuscript, we

* Corresponding author. E-mail address: sasai@sanken.osaka-u.ac.jp (H. Sasai).

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http://dx.doi.org/10.1016/j.tet.2012.11.046

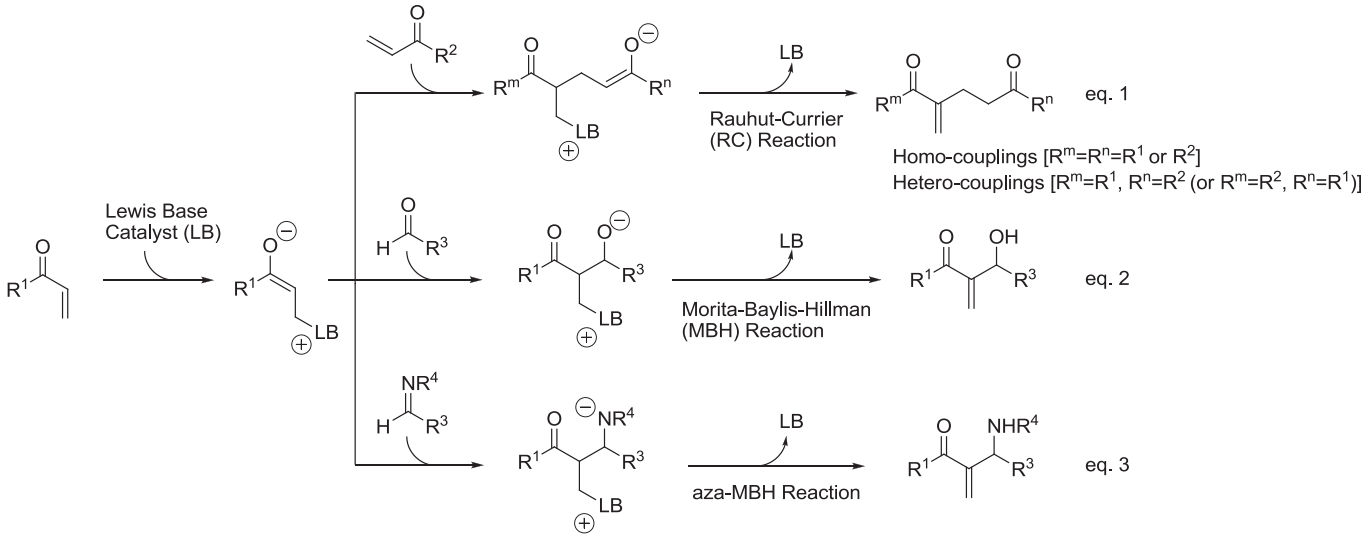


Fig. 1. Comparison of Rauhut–Currier reaction with MBH type reactions.

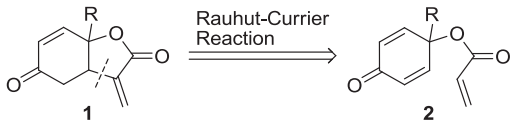


Fig. 2. Retrosynthesis of α-methylidene-γ-butyrolactones **1** via the RC process.

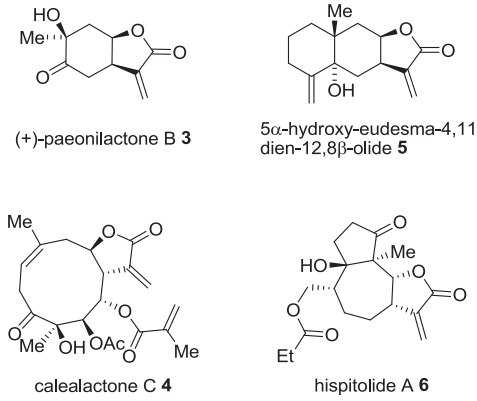


Fig. 3. α-Methylidene-γ-butyrolactones isolated from natural sources.

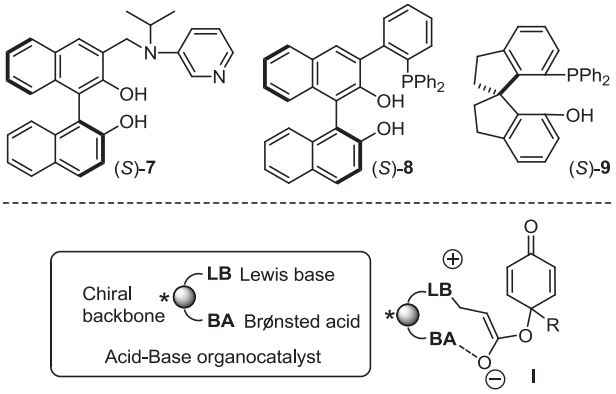


Fig. 4. Acid–base organocatalysts for the aza-MBH reactions and the estimated key intermediate **I** for the RC reaction.

report the details of the acid–base organocatalyzed intramolecular RC reaction of **2**.[15] The present enantioselective RC process produces the highly functionalized α-methylidene-γ-butyrolactones **1** as a single diastereomer with up to 98% ee.

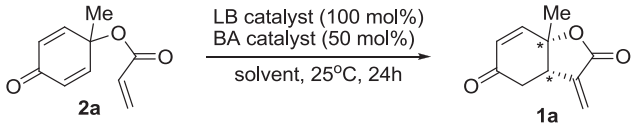
2. Results and discussion

As the first step in the development of the designated RC reaction, achiral LB catalysts were evaluated using **2a** as a prototypical substrate (Table 1). The MBH reaction is known to be accelerated in the presence of a BA.[5] Given the similarity of the MBH and RC reactions, various BAs were added to the reaction of **2a** in order to increase the reaction rate. Among the LBs (DMAP, DBU or DABCO) and BAs (TFA, $PhCO_2H$, thiourea **10** or phosphoric acid **11**) examined (Table 1, entries 1–6), the combination of PPh_3 (100 mol %) and phenol (C_6H_5OH)[16] (50 mol %) or C_2H_5NHTs (50 mol %) was found to efficiently promote the reaction to give the desired product **1a** in 81% yield, 90% yield, respectively (entries 1 and 2). In the absence of phenol, PPh_3 rarely catalyze the cycloisomerization affording a low yield of **1a** (entry 7). Reducing a LB catalyst loading to 20 mol % still maintained moderate yield (entry 8), however reduction of a BA catalyst (20 mol %) led to a decreasing the reaction rate (entry 9). Among the solvents tested, halogenated solvents (entries 1, 10 and 11), toluene (entry 12) and MeCN (entry 13) provided **1a** in moderate to good yields. When (*S*)-BINOL was used as a chiral Brønsted acid, no asymmetric induction onto **1a** was observed (entry 15).[17]

Next, we tested chiral organocatalysts for the RC reaction of **2a** as shown in Table 2. β-ICD, catalysts **7**–**9**, and **12**–**15**, some of which are known to mediate the enantioselective MBH-type processes,[5,14,18] showed no activity (Table 2, entry 1). (*S*)-BINAP and (*S*)-MOP could give the product but in low yields with low or no selectivity (entries 2 and 3). The ferrocenyl phosphine (R_c,S_p)-PPFA promoted the reaction in 72% yield and 20% ee (entry 4), whereas (S_c,R_p)-BPPFA and (S_c,R_p)-BPPFOH exhibited low catalytic activities (entries 5 and 6). During this screening process, the chiral organocatalysts **16** possessing a highly nucleophilic phosphine due to their connection at the phosphorus atom to a primary carbon caught our attention.[5h] As expected, (*R*)-**16a** was able to promote the RC reaction to afford **1a** in 52% yield and 60% ee (entry 7).

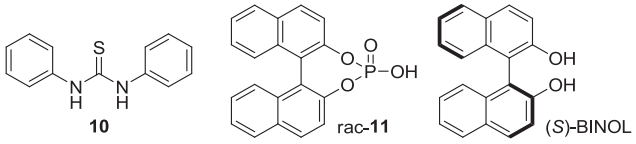
In contrast, no catalytic activity was observed when using the phosphinothiourea catalyst **16b**[7d,19] (entry 8). These results can be attributed to the over-stabilization of the enolate intermediate **Ia** by relatively high acidic N–H in the thiourea catalyst or the

Table 1
Achiral LB–BA catalyzed RC reaction



Entry	LB catalyst	BA catalyst	Solvent	Yield[a] (%)
1	PPh_3	C_6H_5OH	CH_2Cl_2	81
2	PPh_3	C_2H_5NHTs	CH_2Cl_2	90
3	DMAP, DBU or DABCO	C_6H_5OH	CH_2Cl_2	<10
4	PPh_3	TFA or $PhCO_2H$	CH_2Cl_2	<10
5	PPh_3	**10**	CH_2Cl_2	32
6	PPh_3	**11**	CH_2Cl_2	29
7	PPh_3	None	CH_2Cl_2	16
8	PPh_3[b]	C_6H_5OH	CH_2Cl_2	63
9	PPh_3	C_6H_5OH[b]	CH_2Cl_2	43
10	PPh_3	C_6H_5OH	CH_3Cl	53
11	PPh_3	C_6H_5OH	$(CH_2Cl_2)_2$	60
12	PPh_3	C_6H_5OH	Toluene	72
13	PPh_3	C_6H_5OH	MeCN	65
14	PPh_3	C_6H_5OH	THF, MeOH or H_2O	Trace
15	PPh_3	(*S*)-BINOL	CH_2Cl_2	37[c]

[a] Determined by ^1H NMR.
[b] 20 mol %.
[c] *rac*-**1a** was obtained.



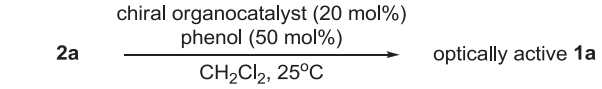
formation of protonated species **IIa** from the enolate **Ia** (Scheme 1). In fact, the ^{31}P NMR spectroscopic data of **2a** with PPh_3 (1 equiv) or **16d** (1 equiv) and an excess amount of phenol (10 equiv) made visible a signal of phosphonium enone **II** (**IIb**: 24.4 ppm, **IIc**: 28.9 ppm) via the corresponding intermediate **I**. The structure of **IIb,c** was also supported by the ^1H and ^{13}C NMR spectroscopic data and ESI-HRMS. A few hours later compound **17** obtained as a decomposition product from **II** was observed.

Finally the acid–base organocatalyst (*S*)-**16d**[20] was found to yield acceptable outcome with over 80% ees (entries 10–13). A lower reaction temperature led to a drastic improvement in the enantioselectivity (entry 11). In the absence of phenol, a higher reaction rate was observed and the high enantioselectivity was maintained (entry 12). The best result (99% isolated yield, 98% ee) was obtained when the reaction was performed in $CHCl_3$ at 0 °C in the absence of phenol (entry 13).

With the optimized conditions in hand, we focused on the substrate scope (Scheme 2). Aliphatic and aromatic substituted starting materials **2** were successfully cyclized to give α-methylidene-γ-butyrolactones **1** in good yields and high enantioselectivities. The lactones were determined to be *cis*-configured via NOESY experiments conducted on **1a**. In all cases a single diastereomer was obtained.[21] Aliphatic substrates **2b–f** were cyclized in high enantioselectivity (92–98% ee), although higher catalyst loading and longer reaction times (30 mol %, 72 h) had to be used. Interestingly, aromatic substituted substrates were more reactive than aliphatic substrates.[22] The reaction of aromatic substituted substrates **2g–l** yielded the corresponding products **1g–l** in good yields (82–97%) with high enantioselectivities (88–98% ee). However, no reaction took place to give **1m** and **1n** when the substrates **2m** and **2n** with methyl substitutes on the terminal olefin on the acrylate or α-positions of dienone were employed.

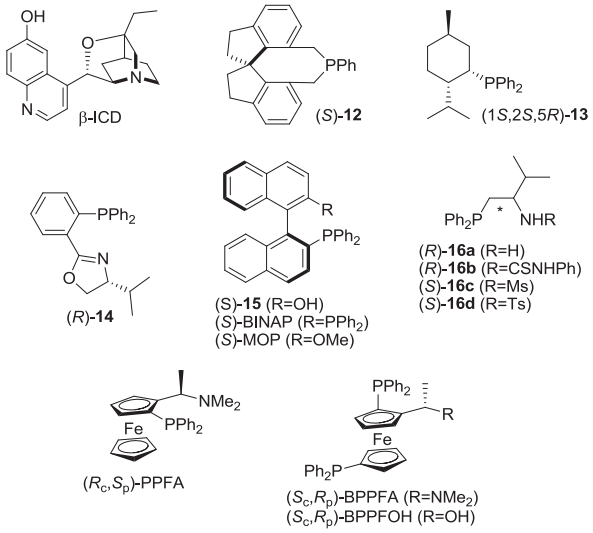
The construction of structural motifs bearing two contiguous, quaternary, stereogenic centers is considered as especially

Table 2
Enantioselective RC reaction using an organocatalyst



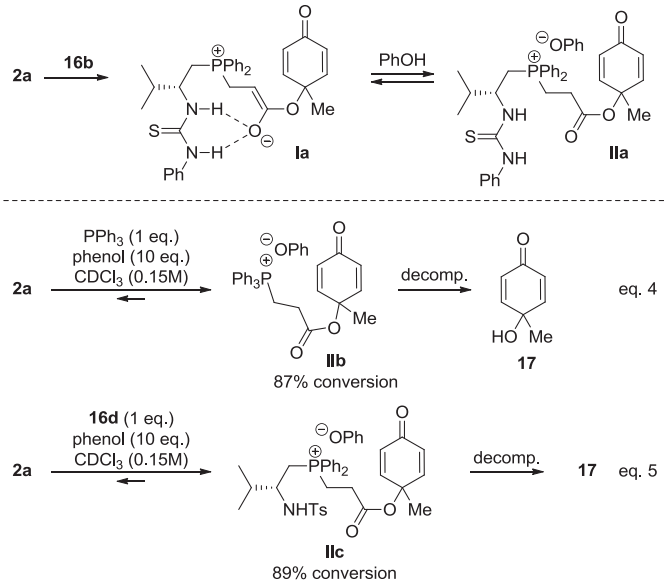
Entry	Chiral organocatalyst	Time [h]	Yield[a] [%]	ee [%][b]
1	β-ICD, **7–9** or **12–15**	48	No reaction	—
2	(*S*)-BINAP	18	6	20
3	(*S*)-MOP	22	16	*rac*
4	(R_c,S_p)-PPFA	18	72	20
5	(S_c,R_p)-BPPFA	19	13	9
6	(S_c,R_p)-BPPFOH	19	3	9
7	(*R*)-**16a**	18	52	60
8	(*R*)-**16b**	19	Trace	—
9	(*S*)-**16c**	24	55	45
10	(*S*)-**16d**	19	77	80
11[c]	(*S*)-**16d**	48	80	93
12[c,d]	(*S*)-**16d**	24	87	93
13[c,d,e]	(*S*)-**16d**	24	99[f]	98

[a] Determined by ^1H NMR.
[b] Determined by HPLC (Daicel Chiralpak IC).
[c] At 0 °C.
[d] Without phenol.
[e] In $CHCl_3$.
[f] Isolated yield.



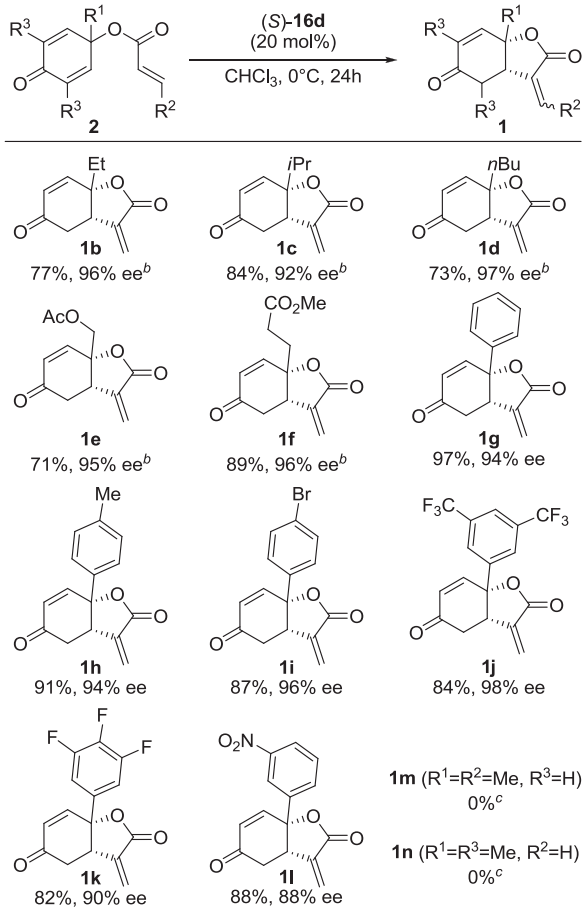
challenging in organic synthesis.[23] When **2o** was applied for this enantioselective reaction, the corresponding lactone **1o** was obtained in 56% yield and 70% ee (Table 3, entry 1). In order to improve the yield and enantioselectivity, various amounts of BAs were added as extraneous proton-shuttle reagents. The increasing amount of phenol led to a significantly increasing of the ee value of **1o** to 96%, albeit dropping to lower chemical yields (entries 1–4). Among the BAs tested, sterically less-hindered and electron rich phenol derivatives, such as 2-naphthol and 4-methoxyphenol led to **1o** in synthetically useful yields with over 90% ee (entries 6 and 12). The recent MBH investigations carried out by Masson and Zhu showed that the addition of 2-naphthol in aza-MBH reaction mediated by β-ICD derivatives led to an improvement of enantioselectivities via a dual activation mechanism.[24] Similarly, in the presence of achiral BAs in this RC reaction of **2o**, a second Michael reaction may become highly stereoselective via a dual activation mechanism by (*S*)-**16d** and achiral BAs (Scheme 4, intermediate **I′**).

The use of disubstituted phenols in the preparation of the starting materials would lead to racemic dienones **2p** and **2q** (Tables 4 and 5). We were intrigued by the opportunity to



Scheme 1. Stabilization of phosphonium salts.

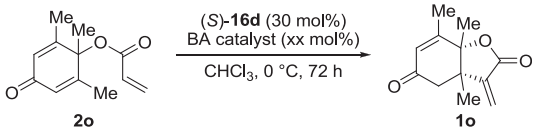
investigate the relative propensity to induce cyclization onto the Michael acceptors in an intramolecular competition (**1p** versus **1p**′ and **1q** versus **1q**′). As such, racemic substrates **2p** and **2q** were



[a]Isolated yields of **1**. Ee of **1** was determined by HPLC (Daicel Chiralpak IA, IB, IC, AD or AD3). [b]Reaction conditions: (*S*)-**16d** (30 mol%), $CHCl_3$, 0°C, 72h. [c]Quantitative recovery of starting material.

Scheme 2. Scope of the enantioselective RC reaction of **1**.[a]

Table 3
Effects of the BA catalysts on RC reaction of **2o**



Entry	BA catalyst (xx mol %)	Isolated yield [%]	ee [%][a]
1	None	56	70
2	C_6H_5OH (10)	62	74
3	C_6H_5OH (30)	42	81
4	C_6H_5OH (50)	5	96
5	4-MeO–C_6H_4OH (10)	44	89
6	4-MeO–C_6H_4OH (30)	36	90
7	2-MeO–C_6H_4OH (30)	45	72
8	2,4,6-Me_3–C_6H_2OH (30)	47	74
9	4-NO_2–C_6H_4OH (30)	Trace	—
10	(*R*)- or (*S*)-BINOL	Trace	—
11	2-Naphthol (10)	46	89
12	2-Naphthol (30)	38	93

[a] Determined by HPLC (Daicel Chiralpak IC).

assembled and subjected to optimized reaction conditions using (*S*)-**16d**. Regarding regioselectivity, intramolecular cyclization occurs exclusively at the less hindered side of the dienone on both substrates. Although the products and the recovering starting materials were obtained in good enantioselectivities, decomposition of **2** led to moderate total yields of (*S*,*S*)-**1** and (*R*)-**2**. The addition of phenol (Table 4, entries 2 to 4 and Table 5, entry 1) and 2-naphthol (Table 4, entry 5 and Table 5, entry 2) could improve the enantioselectivity.

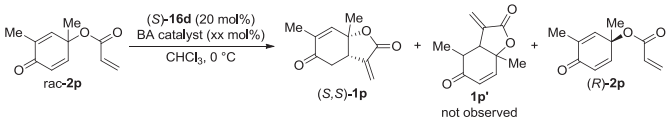
To demonstrate the synthetic utility of the highly functionalized RC product **1a**, a variety of transformations were performed (Scheme 3). The allyl alcohol **17** could be formed by Luche reduction of **1a** in the presence of $Yb(OTf)_3$[25] (step a). Bromination of **1a** followed by elimination formed vinyl bromide **18** (step b).[26] Furthermore, the Michael addition of dibenzyl malonate to **1a** with K_2CO_3 with PPh_3 produced the single diastereomer **18** in 67% yield.[10,27]

The proposed mechanism of the RC reaction using the chiral catalyst **16d** bearing both Brønsted acid (**BA**: –NHTs) and Lewis base (**LB**: $-PPh_2$) moieties is shown in Scheme 4. First the Michael addition of the **LB** moiety to the acrylate unit of **2** generates the phosphonium enolate **I** stabilized by the **BA**, which can react with one of the olefines on the dienone part. This second Michael process forms intermediate **III**. In order to avoid steric interactions between the ^{i}Pr-substituent of the chiral catalyst **16d** and the R-substituent in the substrate, the reaction using (*S*)-**16d** may afford the (*S*,*S*)-configuration intermediate **IIIa**. The proton-transfer from the α-position of a carbonyl group of the lactone to the enolate anion part in **IIIa** through the **BA** moiety results in the formation of the chiral α-methylidene-γ-butyrolactones **1**, along with regeneration of the organocatalyst via retro-Michael reaction. Since the **BA** moiety plays an important role to promote the reaction,[28] we agree with the report of Miller on the bis(enone) cyclization that the proton-transfer step is rate determining.[7a,e]

3. Conclusions

In summary we developed a highly atom economical, chemo-, diastereoselective approach to the medicinally important cores α-methylidene-γ-butyrolactones via an organocatalytic Rauhut–Currier (RC) reaction. The Brønsted acidic sulfonamide and nucleophilic phosphine in **16d** cooperatively function to promote the intramolecular RC process with high enantioselectivities. Further details on the reaction mechanism and the application of this

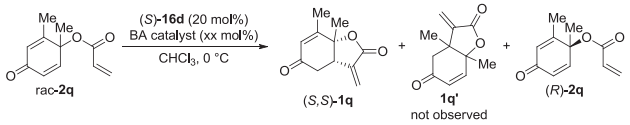
Table 4
RC reaction of racemic **2p** with catalyst (*S*)-**16d**



Entry	BA catalyst (xx mol %)	Ratio **1p**:**2p**	% Total yields of **1p**, **2p**[a]	% ee of (*S*,*S*)-**1p**, (*R*)-**2p**[b]
1	None	73:27	64	54, 70
2	C_6H_5OH (10)	71:29	62	56, 88
3	C_6H_5OH (20)	52:48	68	86, 60
4	C_6H_5OH (30)	50:50	73	86, 62
5	2-Naphthol (30)	40:60	76	94, 50

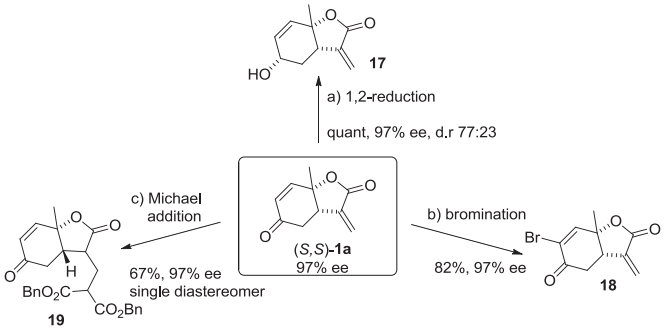
[a] Determined by ^1H NMR.
[b] Determined by HPLC (Daicel Chiralpak IC).

Table 5
RC reaction of racemic **2q** with catalyst (*S*)-**16d**



Entry	BA catalyst (xx mol %)	Ratio **1q**:**2q**	% Total yields of **1q**, **2q**[a]	% ee of (*S*,*S*)-**1q**, (*R*)-**2q**[b]
1	C_6H_5OH (30)	40:60	66	87, 76
2	2-Naphthol (30)	64:36	64	88, 72

[a] Determined by ^1H NMR.
[b] Determined by HPLC (Daicel Chiralpak IC).



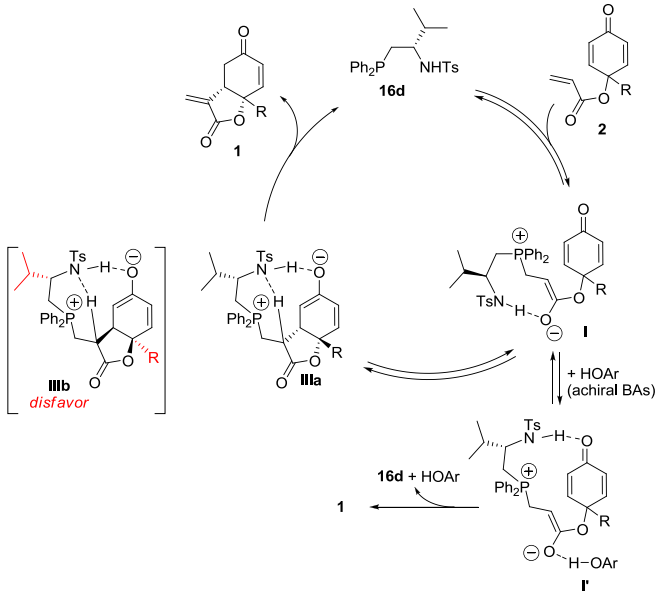
Scheme 3. Synthetic transformations of (*S*,*S*)-**1a**. (a) $Yb(OTf)_3$ (1.1 equiv), $NaBH_4$ (1.1 equiv), MeOH, 0 °C, 15 min, quant. (dr 77:23, determined by ^1H NMR); (b) Br_2 (1.05 equiv), CH_2Cl_2, 0 °C, 30 min, 82%; (c) dibenzyl malonate (1.1 equiv), PPh_3 (2.0 equiv), K_2CO_3 (2.0 equiv), CH_2Cl_2, rt, 6 h, 67%.

method in natural product synthesis are part of the current research and will be reported in due course.

4. Experimental section

4.1. General information

^1H, ^{13}C, ^{19}F, and ^{31}P NMR spectra were recorded with JEOL JMN LA-400 FT NMR or JNM ECA600 FT NMR (^1H NMR 400 MHz, ^{13}C NMR 100 MHz, ^{19}F NMR 376 MHz, ^{31}P NMR 255 MHz). ^1H NMR spectra are reported as follows: chemical shift in parts per million (δ) relative to the chemical shift of $CHCl_3$ at 7.26 ppm, integration, multiplicities (s=singlet, d=doublet, q=quartet, t=triplet, m=multiplet), and coupling constants (Hertz). ^{13}C NMR spectra reported in ppm (δ) relative to the central line of triplet for $CDCl_3$ at 77 ppm CF_3CO_2H or H_3PO_4 used as external standards for ^{19}F or ^{31}P NMR, respectively. FT-MS spectra were obtained with LTQ Orbitrap XL (Thermo Fisher Scientific). ESI-MS spectra were obtained with JMS-T100LC (JEOL). FAB-MS spectra were obtained with JMS-700 (JEOL). Optical rotations were measured with JASCO P-1030 polarimeter. HPLC analyses were performed on a JASCO HPLC system (JASCO PU 980 pump and UV-975 UV/Vis detector) using a mixture of hexane and 2-propanol or EtOH as eluents. FT-IR spectra were recorded on a JASCO FT-IR system (FT/IR4100). Mp was measured with SHIMADZU DSC-60. Column chromatography on SiO_2 was performed with Kishida Silica Gel (63–200 μm). Commercially available organic and inorganic compounds were used without further purification except for the solvent, which was distilled from sodium/benzophenone or CaH_2.



Scheme 4. Proposed mechanism of the RC reaction.

4.2. General procedure for the preparation of dienone (2)

A round bottom flask was charged with a solution of 4-hydroxy-2,5-cyclohexadien-1-one (2 mmol) in CH_2Cl_2 (10 mL) followed by the addition of NEt_3 (4 mmol). Acrolyl chloride (4 mmol) was added dropwise. The reaction mixture was allowed to stir for 10 min at room temperature. The reaction was then quenched with water, extracted with CH_2Cl_2, and dried over Na_2SO_4. The solvent was removed in vacuo and the crude product was purified by silica gel column chromatography using *n*-hexane/AcOEt as an eluent to give the desired product **2** as a yellow oil or white solid.

Compound **2c** (R^1=^{i}Pr, R^2=R^3=H): 53% yield; white solid; mp 83–85 °C; IR (KBr) ν (cm^{-1}) 2950, 1729, 1667, 1630, 1402, 1266, 1190, 1096, 966, 902, 852; ^{1}H NMR ($CDCl_3$): δ 6.74 (d, *J*=10.5 Hz, 2H), 6.34 (d, *J*=17.4 Hz, 1H), 6.29 (d, *J*=10.5 Hz, 2H), 6.05 (dd, *J*=17.4, 10.5 Hz, 1H), 5.81 (d, *J*=10.3 Hz, 1H), 2.17–2.08 (m, 1H), 0.93 (s, 3H), 0.92 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 193.4, 167.1, 143.0, 136.2, 130.9, 123.7, 81.4, 47.1, 35.3; HRMS (APCI) calcd for $C_{12}H_{15}O_3$, *m*/*z*=207.1021 [$(M+H)^+$]; found, *m*/*z*=207.1012.

Compound **2l** (R^1=3-NO_2–C_6H_4, R^2=R^3=H): 68% yield; yellow solid; mp 80–83 °C; IR (KBr) ν (cm^{-1}) 3062, 1730, 1658, 1610, 1450, 1383, 1123, 1091, 987, 880; ^{1}H NMR ($CDCl_3$): δ 8.39 (t, *J*=2.1 Hz, 1H), 8.26–8.21 (m, 1H), 7.75–7.69 (m, 1H), 7.59 (t, *J*=8.0 Hz, 1H), 6.99 (d, *J*=11.0 Hz, 2H), 6.53 (dd, *J*=17.2, 1.1 Hz, 1H), 6.44 (d, *J*=11.0 Hz, 2H), 6.27 (dd, *J*=17.4, 10.5 Hz, 1H), 6.01 (dd, *J*=10.3, 1.1 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 184.8, 163.9, 148.7, 145.9, 139.1, 133.1, 131.3, 130.2, 129.1, 127.5, 123.8, 120.6, 76.6; HRMS (ESI) calcd for HRMS (ACPI) calcd for $C_{15}H_{12}NO_5$, *m*/*z*=286.0715 [$(M+H)^+$]; found, *m*/*z*=286.0709.

Compound **2m** (R^1=R^2=Me, R^3=H): 59% yield; yellow solid; mp 75–78 °C; IR (KBr) ν (cm^{-1}) 2945, 1783, 1649, 1453, 1335, 1267, 1098, 948, 889, 812; ^{1}H NMR ($CDCl_3$): δ 6.89 (d, *J*=10.1 Hz, 2H), 6.25 (d, *J*=10.1 Hz, 2H), 5.95–5.81 (m, 1H), 5.17 (d, *J*=7.3 Hz, 1H), 3.10 (d, *J*=6.9 Hz, 3H), 1.57 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 185.1, 170.1, 149.0, 129.5, 128.1, 119.1, 74.4, 39.1, 26.1; HRMS (ESI) calcd for $C_{11}H_{12}NaO_3$, *m*/*z*=215.0684 [$(M+Na)^+$]; found, *m*/*z*=215.0674.

Compound **2n** (R^1=R^3=Me, R^2=H): 36% yield; white solid; mp 116–118 °C; IR (KBr) ν (cm^{-1}) 2991, 1732, 1628, 1410, 1299, 1191, 1138, 1060, 977, 888; ^{1}H NMR ($CDCl_3$): δ 6.67 (s, 2H), 6.36 (dd, *J*=17.4, 1.4 Hz, 1H), 6.06 (dd, *J*=17.4, 10.5 Hz, 1H), 5.82 (dd, *J*=10.1, 1.4 Hz, 1H), 1.89 (s, 6H), 1.55 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 186.4, 164.7, 143.8, 134.5, 131.2, 128.4, 74.9, 26.4, 15.9; HRMS (APCI) calcd for $C_{12}H_{15}O_3$, *m*/*z*=207.1021 [$(M+H)^+$]; found, *m*/*z*=207.1011.

4.3. General procedure for enantioselective RC reaction of 2

A screw cap tube was charged with the catalyst (*S*)-**16d** (0.05–0.08 mmol, 20–30 mol %) and the solution of dienone **2** (0.25 mmol) in $CHCl_3$ (0.5 mL) at 0 °C. The reaction mixture was stirred until the reaction had reached completion by monitoring with TLC analysis. After the purification via column chromatography, the desired product **1** was obtained as colorless oil or white solid.

Compound **1c** (R^1=^{i}Pr, R^2=R^3=H): 84% yield, 92% ee; white solid; mp 81–84 °C; $[\alpha]_D^{22}$ −124.1 (*c* 0.25, $CHCl_3$); IR (KBr) ν (cm^{-1}) 2971, 1763, 1679, 1398, 1356, 1248, 1160, 1138, 1110, 1049; ^{1}H NMR ($CDCl_3$): δ 6.63 (dd, *J*=10.5, 1.8 Hz, 1H), 6.33 (d, *J*=3.2 Hz, 1H), 6.11 (d, *J*=10.5 Hz, 1H), 5.60 (d, *J*=3.2 Hz, 1H), 3.49–3.44 (m, 1H), 2.84 (d, *J*=5.0 Hz, 2H), 2.32–2.22 (m, 1H), 1.13 (t, *J*=5.0 Hz, 6H); ^{13}C NMR ($CDCl_3$): δ 194.7, 145.2, 138.2, 130.6, 122.7, 84.7, 40.3, 37.6, 35.7, 17.4, 16.6; HRMS (APCI) calcd for $C_{12}H_{15}O_3$, *m*/*z*=207.1021 [$(M+H)^+$]; found, *m*/*z*=207.1012; Chiralpak IC, *n*-hexane/2-propanol=4/1, flow rate 0.5 mL/min, 25 °C, 215 nm, first peak: t_R=30.1 min, second peak: t_R=32.5 min.

Compound **1l** (R^1=3-NO_2–C_6H_4, R^2=R^3=H): 82% yield, 88% ee; yellow solid; mp 105–108 °C; $[\alpha]_D^{22}$ −18.6 (*c* 0.3, $CHCl_3$); IR (KBr) ν (cm^{-1}) 3021, 1750, 1684, 1589, 1325, 1268, 1154, 1164, 1098, 970, 859; ^{1}H NMR ($CDCl_3$): δ 8.28 (s, 1H), 8.14 (d, *J*=8.2 Hz, 1H), 7.7 (d, *J*=8.2 Hz, 1H), 7.50 (t, *J*=8.2 Hz, 1H), 6.65 (dd, *J*=10.5, 1.8 Hz, 1H), 6.38 (d, *J*=3.6 Hz, 1H), 6.26 (d, *J*=10.1 Hz, 1H), 5.62 (d, *J*=2.7 Hz, 1H), 3.47 (m, 1H), 2.84 (d, *J*=2.5 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 193.8, 169.9, 147.9, 142.9, 142.8, 141.4, 132.5, 129.6, 128.2, 124.5, 121.5, 116.9, 93.4, 41.3, 35.7; HRMS (APCI) calcd for $C_{15}H_{12}NO_5$, *m*/*z*=286.0715 [$(M+H)^+$]; found, *m*/*z*=286.0709; Chiralpak IA, *n*-hexane/2-propanol=4/1; flow rate 0.5 mL/min, 25 °C, 215 nm, first peak: t_R=34.3 min, second peak: t_R=46.1 min.

4.4. RC reaction of racemic 2 with catalyst (*S*)-16d

rac-**2p**: yellow oil; IR (KBr) ν (cm^{-1}) 2986, 1730, 1642, 1402, 1273, 1190, 1048, 980, 889, 812; ^{1}H NMR ($CDCl_3$): δ 6.88 (dd, *J*=10.1, 3.2 Hz, 1H), 6.66 (m, 1H), 6.36 (dd, *J*=17.6, 1.1 Hz, 1H), 6.21 (d, *J*=9.6 Hz, 1H), 6.06 (dd, *J*=17.2, 10.3 Hz, 1H), 5.83 (dd, *J*=10.1, 1.4 Hz, 1H), 1.88 (s, 3H), 1.56 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 185.7, 164.6, 148.7, 144.0, 134.9, 131.5, 128.1, 127.8, 74.8, 26.3, 15.6; HRMS (ESI) calcd for $C_{11}H_{12}NaO_3$, *m*/*z*=215.0684 [$(M+Na)^+$]; found, *m*/*z*=215.0674.

(*S*,*S*)-**1p**: 80% ee; $[\alpha]_D^{22}$ −6.0 (*c* 0.1, $CHCl_3$); yellow oil; IR (KBr) ν (cm^{-1}) 2973, 1768, 1627, 1617, 1485, 1291, 1153, 1083, 980, 879; ^{1}H NMR ($CDCl_3$): δ 6.36 (s, 1H), 6.27 (d, *J*=3.2 Hz, 1H), 5.56 (*J*=2.7 Hz, 1H), 3.33–3.28 (m, 1H), 2.89–2.77 (m, 2H), 1.76 (s, 3H), 1.70 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 195.0, 168.6, 142.2, 137.8, 135.8, 122.3, 80.9, 45.2, 36.2, 24.2, 15.6; HRMS (ESI) calcd for $C_{11}H_{12}NaO_3$, *m*/*z*=215.0684 [$(M+Na)^+$]; found, *m*/*z*=215.0674; Chiralpak IC, *n*-hexane/2-propanol=4/1; flow rate 0.5 mL/min; 25 °C; 215 nm, first peak: t_R=18.1 min, second peak: t_R=22.6 min.

(*R*)-**2p**: 80% ee; $[\alpha]_D^{22}$ −41.6 (*c* 0.1, $CHCl_3$); Chiralpak IC, *n*-hexane/2-propanol=4/1, flow rate 0.5 mL/min, 25 °C, 215 nm, first peak: t_R=13.9 min, second peak: t_R=25.7 min.

rac-**2q**: yellow oil; IR (KBr) ν (cm^{-1}) 2989, 1730, 1668, 1627, 1401, 1285, 1191, 1053, 983, 880; ^{1}H NMR ($CDCl_3$): δ 6.85 (d, *J*=10.1 Hz, 1H), 6.41 (dd, *J*=17.1, 1.4 Hz, 1H), 6.22 (dd, *J*=10.1, 1.8 Hz, 1H), 6.15–6.08 (m, 2H), 5.88 (dd, *J*=10.3, 1.1 Hz, 1H), 1.91 (s, 3H), 1.53 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 185.5, 164.2, 159.1, 149.9, 132.2, 127.7, 127.5, 126.7, 76.3, 26.2, 17.7; HRMS (ESI) calcd for $C_{11}H_{12}NaO_3$, *m*/*z*=215.0684 [$(M+Na)^+$]; found, *m*/*z*=215.0674.

(*S*,*S*)-**1q**: 68% ee; $[\alpha]_D^{22}$ 4.0 (*c* 0.1, $CHCl_3$); yellow oil; IR (KBr) ν (cm^{-1}) 2917, 1716, 1614, 1629, 1456, 1280, 1271, 1053, 1025, 989; ^{1}H NMR ($CDCl_3$): δ 6.27 (d, *J*=3.2 Hz, 1H), 5.85 (s, 1H), 5.55 (d, *J*=2.7 Hz, 1H), 3.37–3.31 (m, 1H), 2.87–2.75 (m, 2H), 2.02 (s, 3H), 1.75 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 194.1, 168.3, 157.3, 137.2, 127.5, 121.9, 82.2, 46.1, 35.5, 22.7, 18.4; HRMS (ESI) calcd for $C_{11}H_{12}NaO_3$, *m*/*z*=215.0684 [$(M+Na)^+$]; found, *m*/*z*=215.0674; Chiralpak IB, *n*-hexane/ethanol=19/1, flow rate 0.5 mL/min, 25 °C, 215 nm, first peak: t_R=38.9 min, second peak: t_R=41.2 min.

(*R*)-**2q**: 56% ee, $[\alpha]_D^{22}$ −140.8 (*c* 0.25, $CHCl_3$); Chiralpak IC, *n*-hexane/2-propanol=4/1, flow rate 0.5 mL/min, 25 °C, 215 nm, first peak: t_R=48.7 min, second peak: t_R=54.2 min.

4.5. Synthetic transformations of (*S*,*S*)-1a

Compound **17**: a solution of (*S*,*S*)-**1a** (26.7 mg, 0.150 mmol, 97% ee) and $Yb(OTf)_3$ (105.4 mg, 0.165 mmol) in MeOH (0.5 mL) was stirred at room temperature for 15 min. And then $NaBH_4$ (6.4 mg, 0.165 mmol) was added slowly at 0 °C. The reaction was stirred for 15 min at 0 °C, quenched with saturated aqueous solution of NH_4Cl, and then extracted with CH_2Cl_2, and dried over Na_2SO_4. The filtrate was evaporated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt=2/1) to give the product **17** (27.0 mg, 0.150 mmol, quant., 97% ee, dr 77:23). Minor diastereomer: ^{1}H NMR ($CDCl_3$): δ 6.30 (d, *J*=3.2 Hz, 1H), 5.88 (d, *J*=10.5 Hz, 1H), 5.73 (d, *J*=10.5 Hz, 1H), 5.64 (d, *J*=3.2 Hz, 1H), 4.33–4.27 (m, 1H), 3.19–3.13 (m, 1H), 2.42–2.34 (m, 1H), 1.93–1.85 (m, 1H), 1.59 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 166.2, 138.3, 133.3, 130.6,

121.6, 81.1, 62.4, 43.6, 32.3, 26.2. Major diastereomer: colorless oil; $[\alpha]_D^{22}$ 105.3 (*c* 0.1, $CHCl_3$); IR (KBr) ν (cm^{-1}) 3416, 2931, 1752, 1404, 1284, 1183, 1130, 1063, 929, 748; ^1H NMR ($CDCl_3$): δ 6.21 (s, 1H), 5.80 (d, *J*=10.3 Hz, 1H), 5.65 (d, *J*=10.3 Hz, 1H), 5.55 (s, 1H), 3.99–3.93 (m, 1H), 2.86–2.80 (m, 1H), 2.11–2.03 (m, 1H), 1.67–1.59 (m, 1H), 1.35 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 169.3, 138.2, 133.1, 130.6, 121.4, 80.9, 62.3, 43.4, 32.2, 26.0; Chiralpak IC, *n*-hexane/2-propanol=4/1, flow rate 0.5 mL/min, 25 °C, 215 nm, first peak: t_R=21.6 min, second peak: t_R=26.6 min; HRMS (ESI) calcd for $C_{10}H_{12}NaO_3$, *m*/*z*=203.0684 [$(M+Na)^+$]; found, *m*/*z*=203.0677; Chiralpak IC, *n*-hexane/2-propanol=4/1, flow rate 0.5 mL/min, 25 °C, 215 nm, first peak: t_R=11.9 min, second peak: t_R=13.1 min.

Compound **18**: to a solution of (*S*,*S*)-**1a** (26.7 mg, 0.150 mmol) in 0.3 mL CH_2Cl_2 at 0 °C was added Br_2 (8.2 μL, 0.158 mmol). The reaction was allowed to stir for 30 min at 0 °C and then 0.1 mL of NEt_3 was added and the reaction was warmed to room temperature. The reaction mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt=2/1) to give the product **18** (31.7 mg, 0.123 mmol, 82% yield, 97% ee). White solid; mp 144–146 °C; $[\alpha]_D^{22}$ 13.3 (*c* 0.41, $CHCl_3$); IR (KBr) ν (cm^{-1}) 2925, 1767, 1688, 1435, 1389, 1253, 1182, 1067, 935, 821; ^1H NMR ($CDCl_3$): δ 7.06 (s, 1H), 6.35 (d, *J*=3.4 Hz, 1H), 5.62 (d, *J*=3.4 Hz, 1H), 3.40–3.36 (m, 1H), 3.10 (dd, *J*=12.6, 2.8 Hz, 1H), 2.95 (dd, *J*=12.6, 5.5 Hz, 1H), 1.77 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 186.8, 167.8, 147.2, 136.7, 125.1, 123.4, 81.8, 45.2, 35.9, 23.9; Chiralpak IB, *n*-hexane/ethanol=19/1, flow rate 0.5 mL/min, 25 °C, 250 nm, first peak: t_R=47.9 min, second peak: t_R=51.7 min; HRMS (ESI) calcd for $C_{10}H_9BrNaO_3$, *m*/*z*=280.9612 [$(M+Na)^+$]; found, *m*/*z*=280.9607.

Compound **19**: A solution of dibenzyl malonate (48.6 μL, 0.198 mmol) and K_2CO_3 (49.8 mg, 0.360 mmol) in CH_2Cl_2 (0.18 mL) at room temperature was stirred for 10 min, and then solution of (*S*,*S*)-**1a** (32.1 mg, 0.180 mmol) and PPh_3 (94.4 mg, 0.360 mmol) in CH_2Cl_2 (0.18 mL) was added. The reaction was stirred for 6 h at room temperature, quenched with saturated aqueous solution of NH_4Cl, extracted with AcOEt, and then dried over Na_2SO_4. The filtrate was evaporated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt=2/1) to give the product **19** (55.5 mg, 0.120 mmol, 67% yield, 97% ee, single diastereomer). Colorless oil; $[\alpha]_D^{22}$ −40.9 (*c* 1.5, $CHCl_3$); IR (KBr) ν (cm^{-1}) 2952, 1767, 1740, 1687, 1453, 1380, 1214, 1155, 1096, 1036; ^1H NMR ($CDCl_3$): δ 7.33–7.25 (m, 10H), 6.59 (d, *J*=10.5 Hz, 1H), 6.01 (d, *J*=10.5 Hz, 1H), 5.13 (s, 2H), 5.12 (s, 2H), 4.04 (dd, *J*=6.0, 2.8 Hz, 1H), 2.63 (m, 2H), 2.49 (m, 2H), 2.21 (m, 2H), 1.61 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 194.2, 175.4, 168.6, 168.4, 135.2, 129.2, 128.7, 128.5, 128.4, 80.0, 67.6, 48.8, 47.0, 42.0, 35.4, 27.5, 24.3; Chiralpak IB, *n*-hexane/ethanol=8/1, flow rate 0.5 mL/min, 25 °C, 215 nm, first peak: t_R=48.0 min, second peak: t_R=59.5 min; HRMS (ESI) calcd for $C_{27}H_{26}NaO_7$, *m*/*z*=485.1576 [$(M+Na)^+$]; found, *m*/*z*=485.1576.

Acknowledgements

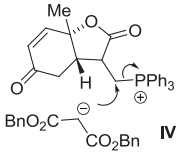
This work was supported by the CREST project of the Japan Science and Technology Corporation (JST), Grant-in-Aid for Scientific Research on Innovative Areas 'Advanced Molecular Transformations by Organocatalysts' from The Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan. We thank Deutsche Forschungsgemeinschaft (scholarship for A.G., International Research Training Group 'Selectivity in Chemo- and Biocatalysis'—SeleCa, Germany). We acknowledge the technical staff of the Comprehensive Analysis Center of ISIR, Osaka University (Japan).

References and notes

1. For selected reviews on organocatalysis, see: (a) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, 2005; (b) Dalko, P. I. *Enantioselective Organocatalysis: Reactions and Experimental Procedures*; Wiley-VCH: Weinheim, 2007; (c) Pellissier, H. *Tetrahedron* **2007**, *63*, 9267; (d) Special issue on organocatalysis (Ed.: List, B.)*Chem. Rev.* **2007**, *107*, 5413; (e) Marcia De Figueiredo, R.; Christmann, M. *Eur. J. Org. Chem.* **2007**, 2575; (f) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638; (g) MacMillan, D. W. C. *Nature* **2008**, *455*, 304; (h) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178; (i) Nielsen, M.; Worgull, D.; Zweifel, T.; Gschwend, B.; Bertelsen, S.; Jørgensen, K. A. *Chem. Commun.* **2011**, 632.
2. (a) Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today* **2007**, *12*, 8; (b) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570; (c) Walji, A. M.; MacMillan, D. W. C. *Synlett* **2007**, 1477; (d) Xu, L.-W.; Luo, J.; Lu, Y. *Chem. Commun.* **2009**, 1807; (e) Núñez, M. G.; García, P.; Moro, R. F.; Díez, D. *Tetrahedron* **2010**, *66*, 2089; (f) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167; (g) Ishikawa, H.; Honma, M.; Hayashi, Y. *Angew. Chem., Int. Ed.* **2011**, *50*, 2824.
3. Rauhut, M. M.; Currier, H. U.S. Patent 3,074,999; American Cyanamid, 1963.
4. For a short review on RC reaction, see Aroyan, C. E.; Dermenci, A.; Miller, S. J. *Tetrahedron* **2009**, *65*, 4069.
5. For recent reviews and reports on MBH-type reaction, see: (a) Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 4614; (b) Ma, G.-N.; Jiang, J.-J.; Shi, M.; Wei, Y. *Chem. Commun.* **2009**, 5496; (c) Declerck, V.; Martinez, J.; Lamaty, F. *Chem. Rev.* **2009**, *109*, 1; (d) Carrasco-Sanchez, V.; Simirgiotis, M. J.; Santos, L. S. *Molecules* **2009**, *14*, 3989; (e) Basavaiah, D.; Reddy, B. S.; Badsara, S. S. *Chem. Rev.* **2010**, *110*, 5447; (f) Mansilla, J.; Saá, J. M. *Molecules* **2010**, *15*, 709; (g) Wei, Y.; Shi, M. *Acc. Chem. Res.* **2010**, *43*, 1005; (h) Wang, S.-X.; Han, X.; Zhong, F.; Wang, Y.; Lu, Y. *Synlett* **2011**, 2766; (i) Zhong, F.; Han, X.; Wang, Y.; Lu, Y. *Angew. Chem., Int. Ed.* **2011**, *50*, 7837; (j) Han, X.; Wan Zhong, F.; Lu, Y. *J. Am. Chem. Soc.* **2011**, *133*, 1726; (k) Zhong, F.; Luo, J.; Chen, G.-Y.; Dou, X.; Lu, Y. *J. Am. Chem. Soc.* **2012**, *134*, 10222; (l) Zhong, F.; Han, X.; Wang, Y.; Lu, Y. *Chem. Sci.* **2012**, *3*, 1231; (m) Han, X.; Zhong, F.; Wang, Y.; Lu, Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 767.
6. (a) Wang, L.-C.; Luis, A. L.; Agapiou, K.; Jang, H.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 2402; (b) Frank, S. A.; Mergott, D. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 2404; (c) Mergott, D. J.; Frank, S. A.; Roush, W. R. *Org. Lett.* **2002**, *4*, 3157; (d) Methot, J. L.; Roush, W. R. *Org. Lett.* **2003**, *5*, 4223; (e) Winbush, S. M.; Mergott, D. J.; Roush, W. R. *J. Org. Chem.* **2008**, *73*, 1818; (f) Seidel, F. O.; Gladysz, J. A. *Adv. Synth. Catal.* **2008**, *350*, 2443; (g) Yao, W.; Wu, Y.; Wang, G.; Zhang, Y.; Ma, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 9713; (h) Qiao, Y.; Kumar, S.; Malachowski, W. P. *Tetrahedron Lett.* **2010**, *51*, 2636; (i) Liu, W.; Zhou, J.; Zheng, C.; Chen, X.; Xiao, H.; Yang, Y.; Guo, Y.; Zhao, G. *Tetrahedron* **2011**, *67*, 1768; (j) Ma, J.; Xie, P.; Hu, C.; Huang, Y.; Chen, R. *Chem.—Eur. J.* **2011**, *17*, 7418.
7. (a) Aroyan, C. E.; Miller, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 256; (b) Seidel, F.; Gladysz, J. A. *Synlett* **2007**, 986; (c) Marqués-López, E.; Herrera, R. P.; Marks, T.; Jacobs, W. C.; Könning, D.; de Figueiredo, R. M.; Christmann, M. *Org. Lett.* **2009**, *11*, 4116; (d) Gong, J.-J.; Li, T.-Z.; Pan, K.; Wu, X.-Y. *Chem. Commun.* **2011**, 1491; (e) Aroyan, C. E.; Dermenci, A.; Miller, S. J. *J. Org. Chem.* **2010**, *75*, 5784; (f) Selig, P. S.; Miller, S. J. *Tetrahedron Lett.* **2011**, *52*, 2148; (g) Dermenci, A.; Selig, P. S.; Domaoal, R. A.; Spasov, K. A.; Anderson, K. S.; Miller, S. J. *Chem. Sci.* **2011**, *2*, 1568; (h) Cowen, B. J.; Miller, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 10988.
8. Wang, X.-F.; Peng, L.; An, J.; Li, C.; Yang, Q.-Q.; Lu, L.-Q.; Gu, F.-L.; Xiao, W.-J. *Chem.—Eur. J.* **2011**, *17*, 6484.
9. (a) Reynolds, T. E.; Binkley, M. S.; Scheidt, K. A. *Org. Lett.* **2008**, *10*, 2449; (b) Zhao, Q.-Y.; Pei, C.-K.; Guan, X.-Y.; Shi, M. *Adv. Synth. Catal.* **2011**, *353*, 1973.
10. (a) Shi, Z.; Yu, P.; Loh, T.-P.; Zhong, G. *Angew. Chem., Int. Ed.* **2012**, *51*, 7825; (b) Jin, Z.; Yang, R.; Du, Y.; Tiwari, B.; Ganguly, R.; Chi, Y. R. *Org. Lett.* **2012**, *14*, 3226.
11. (a) Schweizer, J.; Lattrell, R.; Hecker, E. *Experientia* **1975**, *31*, 1267; (b) Stern, A. J.; Swenton, J. S. *J. Org. Chem.* **1988**, *53*, 2465; (c) McKinley, J.; Aponick, A.; Raber, J. C.; Fritz, C.; Montgomery, D.; Wigal, C. T. *J. Org. Chem.* **1997**, *62*, 4874; (d) Sunasee, R.; Clive, D. L. J. *Chem. Commun.* **2010**, 701; (e) Yakura, T.; Omoto, M.; Yamauchi, Y.; Tian, Y.; Ozono, A. *Tetrahedron* **2010**, *66*, 5833.
12. For recent reviews on the synthesis of α-methylidene-γ-butyrolactones, see: (a) Kitson, R. R. A.; Millemaggi, A.; Taylor, R. J. K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9426; (b) Ramachandran, P. V.; Yip-Schneider, M. T.; Schmidt, C. M. *Future Med. Chem.* **2009**, *1*, 179.
13. (a) Rodriguez, E.; Towers, G. H. N.; Mitchell, J. C. *Phytochemistry* **1976**, *15*, 1573; (b) Picman, A. K. *Biochem. Syst. Ecol.* **1986**, *14*, 255; (c) Ghantous, A.; Gali-Muhtasib, H.; Vuorela, H.; Saliba, N. A.; Darwiche, N. *Drug Discovery Today* **2010**, *15*, 668.
14. (a) Matsui, K.; Takizawa, S.; Sasai, H. *J. Am. Chem. Soc.* **2005**, *127*, 3680; (b) Matsui, K.; Takizawa, S.; Sasai, H. *Synlett* **2006**, 761; (c) Matsui, K.; Tanaka, K.; Horii, A.; Takizawa, S.; Sasai, H. *Tetrahedron: Asymmetry* **2006**, *17*, 578; (d) Takizawa, S.; Matsui, K.; Sasai, H. *J. Synth. Org. Chem. Jpn.* **2007**, *65*, 1089; (e) Takizawa, S.; Inoue, N.; Hirata, S.; Sasai, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 9725; (f) Takizawa, S.; Horii, A.; Sasai, H. *Tetrahedron: Asymmetry* **2010**, *21*, 891; (g) Takizawa, S.; Inoue, N.; Sasai, H. *Tetrahedron Lett.* **2011**, *52*, 377; (h) Takizawa, S.; Kiriyama, K.; Ieki, K.; Sasai, H. *Chem. Commun.* **2011**, 9227.
15. Takizawa, S.; Nguyen, T. M.-N.; Grossmann, A.; Enders, D.; Sasai, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 5423.
16. Yamada, Y. M. A.; Ikegami, S. *Tetrahedron Lett.* **2000**, *41*, 2165.
17. (a) McDougal, N. T.; Schaus, S. E. *J. Am. Chem. Soc.* **2003**, *125*, 12094; (b) McDougal, N. T.; Trevellini, W. L.; Rodgen, S. A.; Kliman, L. T.; Schaus, S. E. *Adv. Synth. Catal.* **2004**, *346*, 1231.
18. (a) Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219; (b) Shi, M.; Xu, Y.-M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4507; (c)

Kawahara, S.; Nakano, A.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Org. Lett.* **2003**, *5*, 3103; (d) Shi, M.; Chen, L.-H. *Chem. Commun.* **2003**, 1310; (e) Shi, M.; Chen, L.-H.; Li, C.-Q. *J. Am. Chem. Soc.* **2005**, *127*, 3790; (f) Deng, H.-P.; Shi, M. *Eur. J. Org. Chem.* **2012**, 183.

19. In the absence of phenol, the reaction of **2a** using **16b** (20 mol %) gave the product **1a** in low yield (12%) with 60% ee.
20. Krauss, I. J.; Leighton, J. L. *Org. Lett.* **2003**, *5*, 3201.
21. The absolute configuration of **1** was assigned by comparison with an optical rotation of the synthetic analog reported in the literature. See Ref. 11d.
22. This discrepancy in reactivity would be attributable to the Thorpe–Ingold effect Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, *107*, 1080.
23. For a discussion on synthesis of natural products bearing contiguous, quaternary stereogenic centers, see Peterson, E. A.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11943.
24. Abermil, N.; Masson, G.; Zhu, J. *Org. Lett.* **2009**, *11*, 4648.
25. Ruano, J. L. G.; Fernández-Ibáñez, M. A.; Fernández-Salas, J. A.; Maestro, M. C.; Márquez-López, P.; Rodríguez-Fernández, M. M. *J. Org. Chem.* **2009**, *74*, 1200.
26. Rubush, D. M.; Morges, M. A.; Rose, B. J.; Thamm, D. H.; Rovis, T. *J. Am. Chem. Soc.* **2012**, *134*, 13554.
27. Without using PPh_3, **18** was formed with 57% yield in 78:22 dr. The high diastereoselectivity (a single diastereomer was obtained) likely resulted from a favorable S_N2 reaction of intermediate **IV**.



IV

28. (a) Santos, L. S.; Pavam, C. H.; Almeida, W. P.; Coelho, F.; Eberlin, M. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 4330; (b) Aggarwal, V. K.; Fulford, S. Y.; Lloyd-Jones, G. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1706; (c) Price, K. E.; Broadwater, S. J.; Jung, H. M.; McQuade, D. T. *Org. Lett.* **2005**, *7*, 147; (d) Raheem, I. T.; Jacobsen, E. N. *Adv. Synth. Catal.* **2005**, *347*, 1701; (e) Price, K. E.; Broadwater, S. J.; Walker, B. J.; McQuade, D. T. *J. Org. Chem.* **2005**, *70*, 3980; (f) Buskens, P.; Klankermayer, J.; Leitner, W. *J. Am. Chem. Soc.* **2005**, *127*, 16762; (g) Robiette, R.; Aggarwal, V. K.; Harvey, J. N. *J. Am. Chem. Soc.* **2007**, *129*, 15513; (h) Santos, L. S. *Eur. J. Org. Chem.* **2008**, 235; (i) Amarante, G. W.; Milagre, H. M. S.; Vaz, B. G.; Ferreira, B. R. V.; Eberlin, M. N.; Coelho, F. *J. Org. Chem.* **2009**, *74*, 3031; (j) Amarante, G. W.; Benassi, M.; Milagre, H. M. S.; Braga, A. A. C.; Maseras, F.; Eberlin, M. N.; Coelho, F. *Chem.—Eur. J.* **2009**, *15*, 12460; (k) Roy, D.; Patel, C.; Sunoj, R. B. *J. Org. Chem.* **2009**, *74*, 6936; (l) Dong, L.; Qin, S.; Su, Z.; Yang, H.; Hu, C. *Org. Biomol. Chem.* **2010**, *8*, 3985.