Asymmetric Catalysis

DOI: 10.1002/anie.201201542

Enantioselective Synthesis of α-Alkylidene-γ-Butyrolactones: Intramolecular Rauhut–Currier Reaction Promoted by Acid/Base Organocatalysts**

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In a little over a decade, enantioselective organocatalysis has been developed as a complementary methodology to metal- and biocatalysis in synthetic organic chemistry.[1] Among the achievements, carbon–carbon bond-forming reactions using chiral organocatalysts play an outstanding role in enabling the highly selective creation of useful skeletons for natural product synthesis.[2] The Rauhut–Currier (RC) reaction is known to provide ready access to α-substituted enones through the coupling of two different α,β-unsaturated carbonyl compounds, one of which serves as a latent enolate.[3,4] To date, attractive systems based on achiral catalysis have been developed for the RC process,[5] although few examples of synthetically useful enantioselective RC transformations have been reported. The first breakthrough in the enantioselective RC reaction was reported by Aroyan and Miller[6a] in 2007 with further contributions by the groups of Gladysz,[6b] Christmann,[6c] and Wu.[6d] These groups succeeded in the development of the enantioselective cycloisomerization of bis(enones) or enal-enones.[6] Meanwhile, Gu, Xiao, and co-workers extended this reaction to nitroolefins.[7] Scheidt and co-workers[8a] and Shi and co-workers[8b] presented the intermolecular RC reaction of silyloxyallenes and allenoates catalyzed by $Sc(OTf)_3$/(*R*,*R*)-Ph-Pybox or β-ICD. Highly selective construction of complex frameworks through the enantioselective RC reaction has been a challenge in asymmetric synthetic chemistry.

We envisioned that the desymmetrization of the prochiral dienones **2**, which are easily accessible from readily available materials, by the RC reaction as a straightforward and atom-economical way to prepare α-alkylidene-γ-butyrolactones **1** (Figure 1).[9] The α-alkylidene-γ-butyrolactone skeleton is

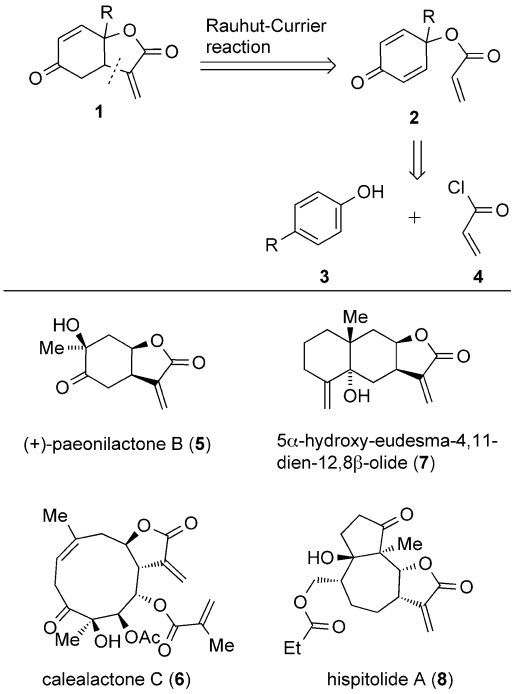

Figure 1. Retrosynthetic analysis of compound **1** and examples of α-alkylidene-γ-butyrolactones isolated from natural sources.

common to a vast number of natural products, such as paeonilactone B (**5**), calealactone C (**6**), and the tricyclic compounds **7** and **8**, which exhibit various biological activities (e.g. anticancer, antimalarial, antiviral, antibacterial, antifungal, anti-inflammatory, etc.; Figure 1).[10]

As the first step in the development of the designated RC reaction, achiral Lewis base (LB) catalysts were evaluated using **2a** as a prototypical substrate (Table 1). The Morita–Baylis–Hillman (MBH) reaction is known to be accelerated in the presence of a Brønsted acid.[11] Given the similarity of the MBH and RC reactions, phenol (50 mol%) was added to the reaction of **2a** to increase the reaction rate.[12] To our delight, PPh_3 was found to efficiently promote the reaction and the desired product **1a** was obtained in 81% yield (Table 1, entry 1). In contrast, PPh_3 without phenol (entry 2) or an

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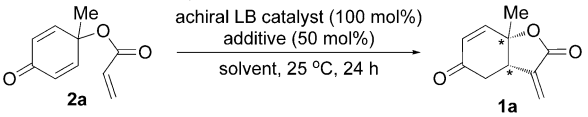
[**] This work was supported by the CREST project of the Japan Science and Technology Corporation (JST) and a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology (Japan). We thank the Deutsche Forschungsgemeinschaft (scholarship for A.G., International 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).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201201542.

Table 1: Achiral LB catalyzed RC reaction.



Entry	Achiral LB catalyst	Solvent	Additive	Yield [%][a]
1	PPh_3	CH_2Cl_2	phenol	81
2	PPh_3	CH_2Cl_2	none	16
3	DMAP, DBU or DABCO	CH_2Cl_2	phenol	< 10
4	PPh_3[b]	CH_2Cl_2	phenol	63
5	PPh_3	CH_3Cl	phenol	53
6	PPh_3	toluene	phenol	72
7	PPh_3	MeCN	phenol	65
8	PPh_3	THF or MeOH	phenol	trace
9	PPh_3	CH_2Cl_2	(*S*)-binol	37[c]

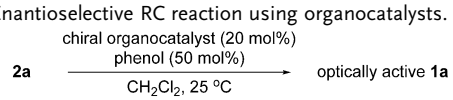
[a] Determined by ^{1}H NMR spectroscopy. [b] 20 mol%. [c] *rac*-**1a** was obtained. Binol = 1,1′-bi-2-naphthol, DABCO = diazabicyclo-[2.2.2]octane, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMAP = 4-(dimethylamino)pyridine.

amine catalyst such as DMAP, DBU, or DABCO (entry 3) barely catalyzed the cycloisomerization reaction, thus affording a low yield of **1a**.[5a,b] Reduction of the catalyst loading to 20 mol% still maintained a moderate yield (entry 4). Among the solvents tested, halogenated solvents (entries 1 and 5), toluene (entry 6), and MeCN (entry 7) 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 9).

Next, various chiral catalysts were tested as shown in Table 2. β-ICD and catalysts **9**–**15**, some of which are known to mediate the enantioselective MBH-type processes,[11,13] showed no activity (Table 2, entry 1). (*S*)-binap and (*S*)-mop gave 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 as a result of its connection at the phosphorus atom to a primary carbon atom, caught our attention.[11h] 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 using the phosphinothiourea catalyst **16b**[6d,14] (entry 8). Finally the acid/base organocatalyst (*S*)-**16c**[15] was found to yield an acceptable outcome with over 80% *ee* (entries 9–12). A lower reaction temperature also led to a drastic improvement in the enantioselectivity (entry 10). In the absence of phenol, a higher reaction rate was observed and the high enantioselectivity was maintained (entry 11). The best result (99% yield, 98% *ee*) was obtained when the reaction was performed in $CHCl_3$ at 0 °C in the absence of phenol (entry 12).

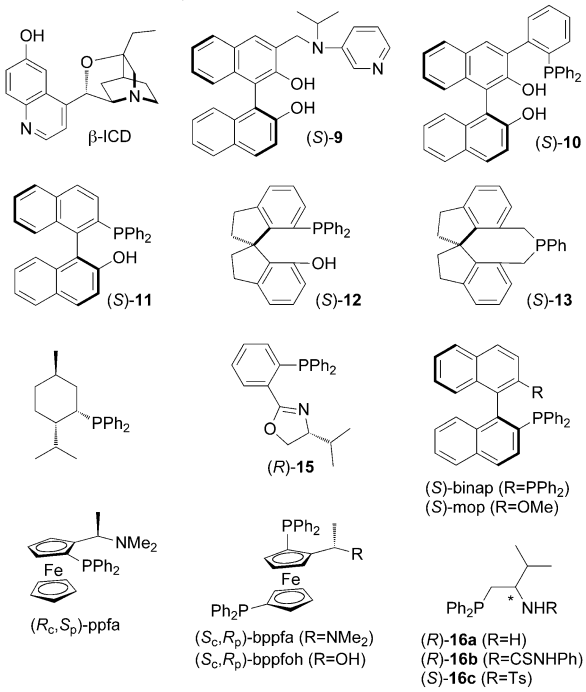
With the optimized reaction conditions in hand, attention was given to the substrate scope (Scheme 1). Aliphatic- and aromatic-substituted starting materials (**2**) were successfully cyclized to give the α-alkylidene-γ-butyrolactones **1** in good yields and high enantioselectivities. The lactones were

Table 2: Enantioselective RC reaction using organocatalysts.



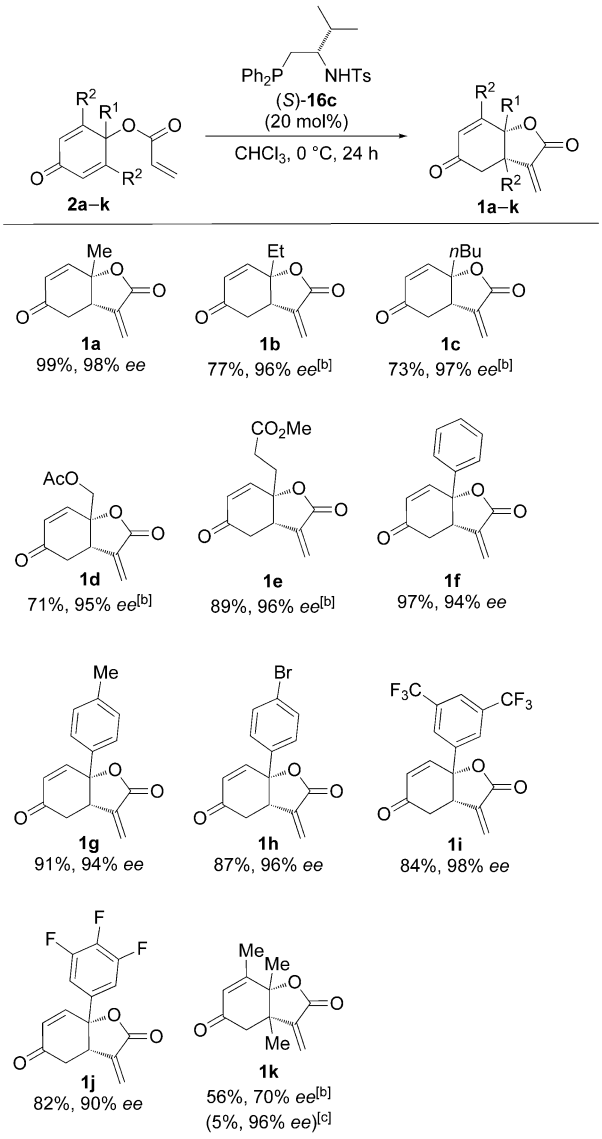
Entry	Chiral organocatalyst	*t* [h]	Yield [%][a]	*ee* [%][b]
1	β-ICD or **9**–**15**	48	no reaction	–
2	(*S*)-binap	18	6	20
3	(*S*)-mop	22	16	0
4	(R_c,S_p)-ppfa	18	72	20
5	(S_c,R_p)-bppfa	19	13	9
6	(S_c,R_p)-bppfoh	19	3	9
7	(*R*)-**16a**	18	52	60
8	(*R*)-**16b**	20	trace	–
9	(*S*)-**16c**	19	77	80
10[c]	(*S*)-**16c**	48	80	93
11[c,d]	(*S*)-**16c**	24	87	93
12[c,d,e]	(*S*)-**16c**	24	99	98

[a] Determined by ^{1}H NMR spectroscopy. [b] Determined by HPLC (Daicel Chiralpak IC). [c] At 0 °C. [d] Without phenol. [e] In $CHCl_3$. Ts = 4-toluenesulfonyl.



determined to be *cis* configured by using NOESY experiments conducted on **1a**. In all cases, a single diastereomer was obtained.[16] The aliphatic substrates **2b–e** were cyclized with high enantioselectivity (95–98% *ee*), although a higher catalyst loading and longer reaction times were needed (30 mol%, 72 h). Interestingly, aromatic-substituted substrates were more reactive than aliphatic substrates.[17] The reaction of the aromatic-substituted substrates **2f–j** afforded the corresponding products **1f–j** in good yields (82–97%) with high enantioselectivities (90–98% *ee*).

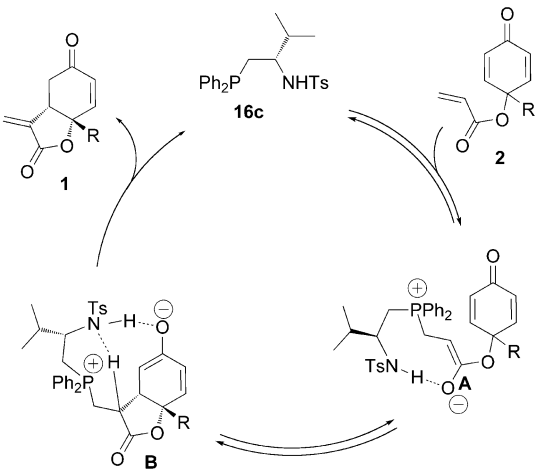
The construction of a structural motif bearing two contiguous, quaternary, stereogenic centers is considered challenging in organic synthesis.[18] When substrate **2k** was subjected to this enantioselective reaction, the corresponding lactone **1k** was obtained in 56% yield and 70% *ee*. To improve the yield and enantioselectivity, phenol (50 mol%)



Scheme 1. Scope of the enantioselective RC reaction. Yields of isolated **1**. The *ee* values of **1** were determined by HPLC (Daicel Chiralpak IA, IB, IC, AD or AD3). [b] Reaction conditions: (*S*)-**16c** (30 mol%), $CHCl_3$, 0°C, 72 h. [c] Phenol (50 mol%) was used with the optimized reaction conditions.

was added as an extraneous proton shuttle. An increase in the *ee* value to 96% was established, albeit along with significant reduction in the chemical yield.

The proposed mechanism of the RC reaction using the chiral catalyst **16c** bearing both Brønsted acid (BA; -NHTs) and Lewis base (-PPh_2) moieties is shown in Scheme 2. First the Michael addition of the LB moiety to the acrylate unit of **2** generates the phosphonium enolate **A**,[19] which is stabilized by the BA. Second, the enolate **A** reacts with one of the olefins on the dienone. This second Michael addition results in the formation of the intermediate **B**. To avoid steric interactions between the *i*Pr substituent of the chiral catalyst **16c** and the R substituent in the substrate, the reaction using (*S*)-**16c** favors the (*S*,*S*)-configured intermediate **B**. Finally,



Scheme 2. Proposed mechanism of the RC reaction.

proton transfer from the α position of a carbonyl group of the lactone to the enolate anion in **B** through the BA moiety results in the formation of the chiral α-alkylidene-γ-butyrolactone **1**, along with regeneration of the organocatalyst through a retro-Michael reaction. Since the BA moiety plays an important role in smoothly promoting the reaction,[20] we agree with the report, presented by Miller and co-workers on the bis(enone) cyclization, which states that the proton-transfer step is rate determining.[6a,e]

In conclusion, we have developed a highly atom-economical, chemo-, diastereo-, and enantioselective approach to the medicinally important α-alkylidene-γ-butyrolactone core using an organocatalytic Rauhut–Currier reaction. Further investigation of the reaction mechanism and the application of this method to natural product synthesis are underway and will be reported in due course.

Experimental Section

General procedure: A screw-cap tube was charged with the catalyst (*S*)-**16c** (0.05--0.08 mmol, 20--30 mol%) and a solution of dienone **2** (0.25 mmol) in chloroform (0.5 mL) at 0°C. The reaction mixture was stirred until the reaction reached completion as determined by TLC analysis. After purification by column chromatography on silica gel (hexanes/ethylacetate 1:1) the desired product **1** was obtained as a colorless oil or a white solid.

Received: February 25, 2012
Published online: ■■ ■■, ■■■■

Keywords: asymmetric catalysis · lactones · Michael addition · organocatalysis · synthetic methods

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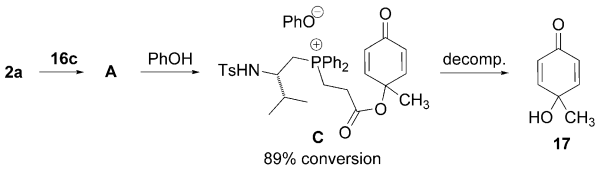

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Communications

Asymmetric Catalysis

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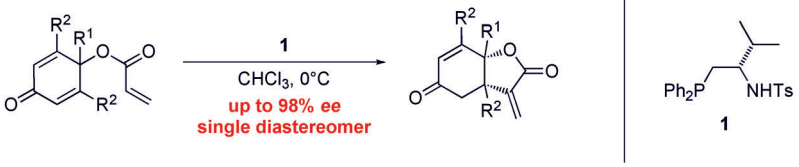
Enantioselective Synthesis of α-Alkylidene-γ-Butyrolactones: Intramolecular Rauhut–Currier Reaction Promoted by Acid/Base Organocatalysts



Teaming up: The title reaction has been developed to deliver the product α-alkylidene-γ-butyrolactones as single diastereomers with up to 98% *ee* (see scheme; Ts = 4-toluenesulfonyl). The enantioselective process is catalyzed by **1**, which contains both Lewis base and Brønsted acid moieties.