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Enantioselective intramolecular Rauhut–Currier reaction catalyzed by chiral phosphinothiourea†

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Chiral organophosphine-catalyzed enantioselective Rauhut–Currier reaction has been disclosed for the first time. With L-valine-derived phosphinothiourea, the intramolecular Rauhut–Currier reaction of bis(enones) was achieved in good yields (up to 99%) with excellent enantioselectivities (up to 99.4% ee).

The Rauhut–Currier (RC) reaction, also known as vinylogous Morita–Baylis–Hillman reaction, involves the coupling of one active alkene/latent enolate to a second Michael acceptor, creating a new C–C bond between the α-position of one activated alkene and the β-position of a second alkene under the influence of a nucleophilic catalyst.[1,2] In 1999, Moore and Erguden revealed an intramolecular transannular Rauhut–Currier reaction in the synthesis of natural product waihoensene.[3] The pioneering methodological studies of the intramolecular Rauhut–Currier reaction were demonstrated by Roush *et al.*[4] and Krische *et al.*,[5] respectively, in 2002. The first enantioselective version of the intramolecular Rauhut–Currier reaction was presented by Miller's group using *N*-acetyl cysteine as a catalyst.[6] Later on, a chiral rhenium complex involving phosphine was used as the catalyst by Gladysz and Seidel for the process.[7] Recently Christmann and co-workers developed a crossed intramolecular Rauhut–Currier reaction catalyzed by diphenylprolinol silyl ether *via* dienamine activation.[8] Meanwhile, Wang *et al.*[9] and Scheidt *et al.*[10] made a progress in the enantioselective intermolecular RC-type reactions.

It's well known that tertiary phosphine catalysts are efficient nucleophiles for the RC reaction.[1] However, to the best of our knowledge, there have been no reports of the enantioselective RC reaction promoted by the phosphine-based organocatalyst.[11,12] We have found that the amino acid-derived phosphinothioureas were highly efficient in the asymmetric Morita–Baylis–Hillman reaction.[13,14] As a follow-up of our work, we would like to disclose the application of phosphinothioureas as organocatalyst for the asymmetric RC reaction. Herein we report the first organophosphine-catalyzed enantioselective RC reaction.

Initially, the enantioselective RC reaction of bis(enone) **4a**[15] was selected as the model reaction to evaluate the natural amino acid-derived bifunctional organocatalysts (Fig. 1). The reactions were performed with 20 mol% catalyst in CH_2Cl_2 at 25 °C, and the results were summarized in Table 1. The results indicated that phenyl thioureas **1a–1d** had low catalytic activity and the desired products were obtained in poor yields (entries 1–4). However, the enantioselectivity was sensitive to the chiral backbone, and phosphinothiourea **1d** derived from L-valine gave better result than the corresponding thioureas **1a–1c** (entry 4, 97% ee with 34% yield). To improve the catalytic activity, L-valine-based organocatalysts with different thiourea scaffolds were explored and it was found that the aromatic thioureas provided better enantioselectivity than the aliphatic thioureas (entries 4–8 *vs.* 9–11). Among all the screened phosphinothioureas, none but catalyst **1k** showed good catalytic activity, the RC reaction was accomplished in 3.5 days and a chemical yield of 85% was obtained (entry 11). In comparison, the L-valine-derived amide **2** and sulfonamide **3** were examined. As shown in Table 1, the thiourea organocatalysts **1d–1k** could achieve better enantioselectivity than the corresponding amide **2** (entries 4–11 *vs.* 12). Although sulfonamide **3** could provide excellent

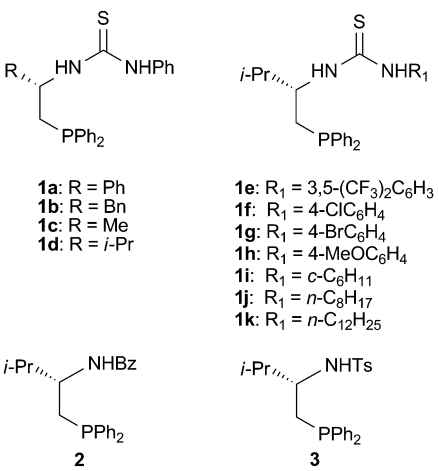

Fig. 1 Structures of the screened phosphine-based organocatalysts.

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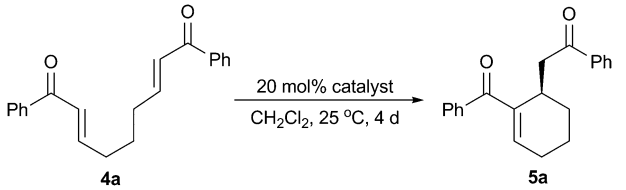
Table 1 Screening of the catalysts for the intramolecular Rauhut–Currier reaction of **4a**[a]



4a **5a**

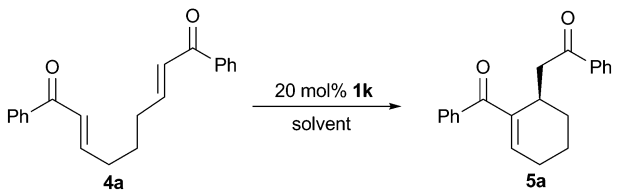
Entry	Catalyst	Yield[b] (%)	ee[c] (%)
1	**1a**	18	75
2	**1b**	28	93
3	**1c**	23	83
4	**1d**	34	97
5	**1e**	23	96
6	**1f**	34	97
7	**1g**	42	95
8	**1h**	20	96
9	**1i**	25	88
10	**1j**	30	94
11[d]	**1k**	85	89[e]
12	**2**	18	75
13	**3**	21	96

[a] Unless stated otherwise, the reactions were performed with 20 mol% of organocatalyst and 0.2 mmol of **4a** in 1 mL CH_2Cl_2 (0.2 M) at 25 °C for 4 d. [b] Isolated yield. [c] Determined by HPLC using a Chiralpak AD-H column. [d] The reaction time is 3.5 days. [e] $[\alpha]_D^{14}$ +26.3 (*c* 0.4, $CHCl_3$).

enantioselectivity, the chemical yield was unsatisfactory (entry 13). According to the optical rotation values reported,[6] the absolute configuration of the desired product was assigned as *R*-configuration.

The survey of solvent was then studied. As shown in Table 2, the RC reaction was sensitive to the solvent. In toluene, $CHCl_3$, ether and CH_3CN, the products were obtained in good-to-excellent enantioselectivities (74%–90% ee) with

Table 2 Optimization of the reaction conditions[a]



4a **5a**

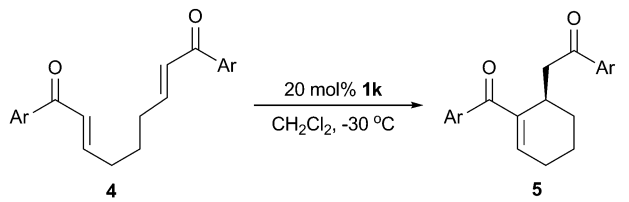
Entry	Solvent	Temp/°C	Conc./M	Time/d	Yield[b] (%)	ee[c] (%)
1	CH_2Cl_2	25	0.2	3.5	85	89
2	Toluene	25	0.2	4.0	62	75
3	$CHCl_3$	25	0.2	4.0	70	82
4	Ether	25	0.2	3.5	72	74
5	CH_3CN	25	0.2	3.5	77	90
6	EtOH	25	0.2	0.4	51	36
7	*t*-BuOH	25	0.2	2.5	74	50
8	DMSO	25	0.2	4.5	5	48
9	THF	25	0.2	4.5	4	91
10	CH_2Cl_2	25	0.1	4.0	52	89
11	CH_2Cl_2	25	0.3	3.5	86	89
12	CH_2Cl_2	40	0.3	3.5	87	88
13	CH_2Cl_2	0	0.3	3.5	84	96
14	CH_2Cl_2	−20	0.3	3.5	88	99
15	CH_2Cl_2	−30	0.3	4.0	80	99.4

[a] The reactions were performed with 20 mol% of **1k** and 0.2 mmol of **4a**. [b] Isolated yield. [c] Determined by HPLC using a Chiralpak AD-H column.

moderate-to-good yields (62%–77%, entries 2–5). In the protonic polar solvents, such as EtOH and *t*-BuOH, the reaction could complete in a shorter time than in other solvents screened, but the enantioselectivities were unsatisfactory (entries 6 and 7). While in non-protonic polar solvent, such as DMSO, the catalyst **1k** was inefficient (entry 8). Although the highest enantioselectivity was observed in THF, the reaction was too sluggish to provide high yield (entry 9, 91% ee and 4% yield). The solvent survey revealed that CH_2Cl_2 was the most suitable solvent for the asymmetric RC reaction (entry 1, 89% ee and 85% yield). Thus the reaction was performed in CH_2Cl_2 in order to further optimize the reaction conditions. The results indicated that the enantioselectivity was constant in different substrate concentrations, but lower concentration (0.1 M) resulted in an obvious decrement of the chemical yield (entries 1, 10 and 11). In addition, lower reaction temperature provided better enantioselectivity. In the context of −30 °C, the desired product was achieved in 99.4% ee with a comparable yield (entry 15 *vs.* entries 11–14).

When the optimal reaction conditions were established, a variety of substrates were investigated and the results were summarized in Table 3. The results indicated that the reaction had a wide substrate scope with respect to bis(enones). The desired products were obtained in excellent enantioselectivity (90–99.4% ee) in all the cases examined except *p*-NO_2-substituted substrate **4b**. Both the reactivity and the enantioselectivity were affected by the electronic environment at the enones. The bis(enones) with an electron-withdrawing substituent at the phenyl group were more reactive than those with an electron-donating substituent, whereas the latter could

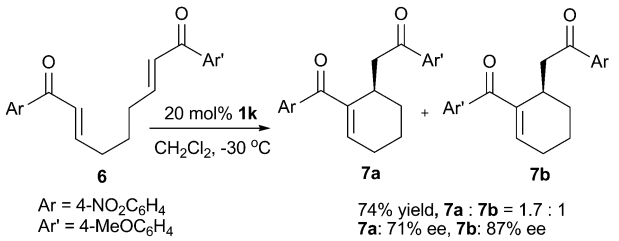
Table 3 The substrates scope of the intramolecular Rauhut–Currier reaction[a]



4 **5**

Entry	Ar	Time/d	Yield[b] (%)	ee[c] (%)
1	C_6H_5 (**a**)	4.0	80	99.4
2	4-$NO_2C_6H_4$ (**b**)	0.25	92	81
3	2-FC_6H_4 (**c**)	0.4	99	98
4	4-FC_6H_4 (**d**)	2.0	93	96
5	2-ClC_6H_4 (**e**)	2.5	99	93
6	3-ClC_6H_4 (**f**)	1.0	93	95
7	4-ClC_6H_4 (**g**)	1.5	98	93
8	2-BrC_6H_4 (**h**)	3.5	95	90
9	3-BrC_6H_4 (**i**)	1.0	90	93
10	4-BrC_6H_4 (**j**)	1.0	91	90
11	3-MeC_6H_4 (**k**)	5.0	72	99
12	4-MeC_6H_4 (**l**)	5.0	70	99
13[d]	4-MeC_6H_4 (**l**)	2.5	85	99
14[d]	4-$MeOC_6H_4$ (**m**)	5.0	64	99
15	Naphtha-2-yl (**n**)	3.0	91	96
16	Furan-2-yl (**o**)	4.0	74	96

[a] Unless stated otherwise, the reactions were conducted with 20 mol% of **1k** and 0.2 mmol of **4** in 0.67 mL CH_2Cl_2 (0.3 M) at −30 °C. [b] Isolated yield. [c] Determined by HPLC using a Chiralpak AD-H or AS-H column. [d] 40 mol% of catalyst **1k** was used.



Scheme 1 The RC reaction of unsymmetrical bis(enone).

afford a higher enantioselectivity (entries 2–10 *vs.* 11–14). The less reactive substrates could produce a high chemical yield while increasing the catalyst loading from 20 mol% to 40 mol % (entries 13 and 14). Comparing with the *para*- and *ortho*-substituted analogues, substrates **4f** and **4i** bearing the *meta*-substituted aromatic group provided a slightly higher enantioselectivity probably due to the electronic effect (entry 6 *vs.* entries 5 and 7, entry 9 *vs.* entries 8 and 10). The RC reaction of furan analogue **4o** proceeded smoothly providing 74% yield and 96% ee of the corresponding adduct (entry 16).

In addition, the unsymmetrical substrate **6** bearing both a strong electron-withdrawing group and a strong electron-donating group was investigated (Scheme 1). Due to the electronic effect, the bis(enone) **6** provided a regioisomeric mixture in favor of **7a**.[16] Compared to the corresponding symmetrical bis(enones) **4b** and **4m**, the enantioselectivity was remarkably decreased (Table 3, entries 2 and 14 *vs.* Scheme 1). The results indicated that both the alkene activation by a nucleophilic catalyst and the coupling of an activated alkene to a second Michael acceptor had influence on the RC reaction.

In summary, we have developed a highly enantioselective intramolecular Rauhut–Currier reaction of bis(enones) catalyzed by bifunctional phosphinothiourea derived from natural amino acid. As the first example of the organophosphine-catalyzed enantioselective intramolecular Rauhut–Currier reaction, the catalytic system is highly efficient and it also achieved up to 99% yield with an excellent enantioselectivity (up to 99.4% ee). Further investigations of the reaction mechanism and to extend the scope of this reaction are now in progress.

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