Rauhut–Currier Reaction

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Highly Enantioselective Intermolecular Cross Rauhut–Currier Reaction Catalyzed by a Multifunctional Lewis Base Catalyst**

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Abstract: *The highly enantioselective intermolecular cross Rauhut–Currier reaction of different active olefins catalyzed by a multifunctional chiral Lewis base was reported. The RC products were obtained in excellent yields (up to 98%), high chemo- and enantioselectivity (up to 96% ee). The reaction could be performed on a gram scale using 1 mol% of the multifunctional phosphine catalyst.*

The Rauhut–Currier (RC) reaction, first reported by Rauhut and Currier in 1963,[1] is an effective atom-economic method to construct densely functionalized molecules and has also been successfully applied in the synthesis of several natural products.[2] However, in comparison to the related Morita–Baylis–Hillman (MBH) reaction,[3] less progress has been made on this reaction during the past decades. In particular, cross RC reactions have suffered from the lack of efficient control of the selectivity.[4] In 2002, Krische and co-workers and Roush and co-workers resolved the issue of selectivity by employing bis-enones as substrates and tethering coupling partners of differing electrophilicity or introducing sufficient steric control.[5] In 2008, Scheidt got access to products of an intermolecular Rauhut–Currier process by modifying one of the olefins using a silyloxyallene substrate as an α-acylvinyl anion equivalent.[6] RC reactions mediated by a Lewis base made use of the binding affinity of the catalyst to one of the olefins. Examples of catalysts and substrates include DBU with 2-cyclohexen-1-one,[7a] an N-heterocyclic carbene with α,β-unsaturated aldehydes,[7b] an imidazole–LiCl catalyst system with nitroolefins,[7c,d] and phosphine with maleimide.[7e] Other concerns and studies focused on domino cyclizations initiated by cross RC reactions.[8] Studies of asymmetric RC reactions have mostly focused on the enantioselective intramolecular version first reported by Miller in 2007; catalysts include protected cysteine derivatives,[9a–c] α,α-diphenyl-L-prolinol,[9d] hydrogen-bonding catalysts,[9e] and chiral phosphines.[9h,i] The enantioselective intermolecular RC reaction of maleimides with allenoates and penta-3,4-dien-2-one disclosed by Shi et al. was initiated by quinidine-derived β-isocupreidine (β-ICD).[10] However, intermolecular Rauhut–Currier reactions still have some drawbacks such as the low reactivity and selectivity, higher catalyst loading, and limited substrate scope. The enantioselective intermolecular cross RC reaction is not known, which impedes its application in the organic synthesis. Hence, the development of a new organocatalyst with higher catalytic activity and more robustness for the intermolecular cross RC reaction, especially enantioselective transformations, is still considered a significant challenge.

The development of bifunctional catalysts that can activate both substrates during the bond-formation process has been an active and fruitful area of investigation in the past few years.[11] In these bifunctional organocatalysts, combinations of an aromatic hydroxy group and an amino group in the form of an acid amide, urea/thiourea, dipeptide, and squaramide have been the most popular hydrogen-bonding moieties as the Brønsted acid. Multifunctional organocatalysts combining known strategies in the bifunctional framework may offer new opportunities to improve the catalytic efficiency and broaden the scope of their utility.[12]

On the other hand, asymmetric reactions catalyzed by chiral phosphines as nucleophilic catalysts have advanced rapidly in the past decade in the areas of MBH reactions,[13] [3+2] and [4+2] cycloadditions,[14] γ-additions to allenoates,[15] and substitutions of MBH adducts[16] among others.[17] Although the very first RC reaction relied on an organophosphine catalyst, no enantioselective intermolecular RC reaction catalyzed by a chiral phosphine catalyst has been reported. Hence, we envisioned that multifunctional phosphine Lewis base catalysts may overcome the shortcomings of the intermolecular cross RC reaction. We combined a Lewis base (phosphine), an acid amide, and a phenol in the chiral amino acid scaffold to enhance the catalyst activity and selectivity (Scheme 1). Herein, we report the first enantioselective intermolecular RC reaction of distinguished active olefins catalyzed by the new multifunctional phosphine Lewis base catalysts.

Scheme 1. Multifunctional catalyst designed for the intermolecular RC reaction.

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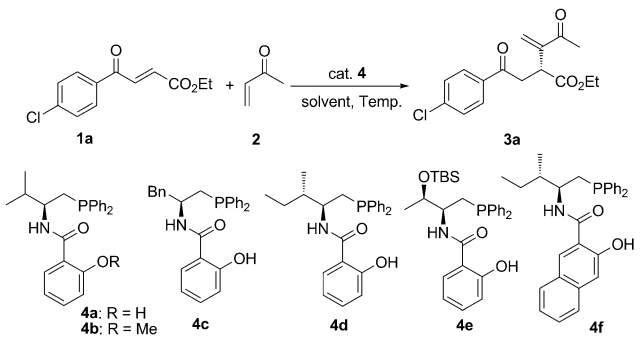
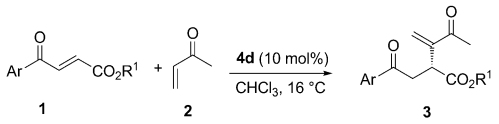
Table 1: Optimization of the catalyst and the reaction conditions.[a]



Entry	Cat.	Temp. [°C]	Solvent	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**4a**	16	$CHCl_3$	2	87	89
2	**4b**	16	$CHCl_3$	1.5	83	40
3	**4c**	16	$CHCl_3$	1.5	91	87
4	**4d**	16	$CHCl_3$	3	84	90
5	**4e**	16	$CHCl_3$	6	83	90
6	**4f**	16	$CHCl_3$	8	81	73
7[d]	**4d**	**16**	**$CHCl_3$**	**4**	**89**	**90**
8[e]	**4d**	16	$CHCl_3$	16	75	90

[a] Unless otherwise specified, all reactions were carried out with **1a** (0.1 mmol), MVK (0.3 mmol), and **4** (20 mol%) in solvent (0.5 mL). [b] Yields of isolated products. [c] Determined by HPLC analysis using a chiral stationary phase. [d] 10 mol% catalyst was used. [e] 5 mol% catalyst was used. TBS = *tert*-butyldimethylsilyl.

Table 2: Substrate scope for the RC reaction of various 3-aroyl acrylates and MVK.[a]



Entry	Ar	R^1	Product	*t* [h]	Yield [%][b]	*ee* [%][c]
1	4-ClC_6H_4	Et	**3a**	4	89	90
2	4-FC_6H_4	Et	**3b**	8	80	90
3	4-BrC_6H_4	Et	**3c**	4	91	89
4	C_6H_5	Et	**3d**	9	87	89
5	4-MeC_6H_4	Et	**3e**	16	98	90
6	4-$MeOC_6H_4$	Et	**3f**	4	97	87
7	3-BrC_6H_4	Et	**3g**	3	87	90
8	2-BrC_6H_4	Et	**3h**	4	85	82
9	2,4-$Cl_2C_6H_3$	Et	**3i**	2.5	94	84
10	2-thienyl	Et	**3j**	8	87	90
11	2-furyl	Et	**3k**	20	82	87
12	4-BrC_6H_4	Me	**3l**	3	95	91
13	4-BrC_6H_4	*i*Pr	**3m**	6	89	86
14	4-BrC_6H_4	Bn	**3n**	5	85	90
15[d]	4-BrC_6H_4	Et	**3o**	2	51	70

[a] Unless otherwise specified, all reactions were carried out with **1** (0.1 mmol), MVK (0.3 mmol) and **4d** (10 mol%) in $CHCl_3$ (0.5 mL) at 16°C. [b] Yields of isolated products. [c] Determined by HPLC analysis using a chiral stationary phase. [d] Acrolein (3.0 equiv) was used instead of MVK and *S*-**4c** (10 mol%) was used as catalyst.

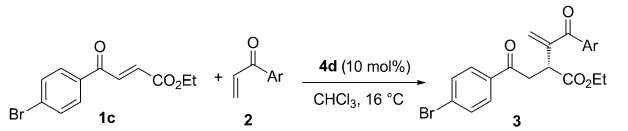
We initiated our investigations by seeking the best conditions for the intermolecular RC reaction between 3-aroyl acrylate **1a** and methyl vinyl ketone (**2**, MVK; Table 1). In the model reaction PPh_3 (20 mol%) catalyzed the reaction of **1a** with MVK in $CHCl_3$ at 16°C to produce the desired product in 45% yield (Table S1, entry 1). To our delight, when the multifunctional phosphine catalyst **4a** was used, the RC product **3a** was obtained in 87% yield and 89% *ee* (Table 1, entry 1). The methylated catalyst **4b** was used to elucidate the effect of the phenolic hydroxy group. As expected, although the reaction proceeded with good yields, the *ee* value decreased sharply to 40% (Table 1, entry 2). Catalysts with thiourea sulfamide or acid amide groups were clearly inferior to **4a** (Table S1, entries 2–6). To further improve the results, catalysts with different chiral backbone moieties were tested (Table 1, entries 3 and 4). Catalyst **4d** deriving from L-isoleucine offered the best results (84% yield, 90% *ee*). The bulkier catalyst **4e** showed no change in stereoselectivity over that of catalyst **4d** (Table 1, entry 5). The attempt to increase the steric bulk by introducing naphthyl also failed to improve the enantioselectivity (Table 1, entry 6). Lowering the catalyst loading had no effect on the stereoselectivity and the yield was highest when 10 mol% catalyst was used (Table 1, entries 7 and 8). No better results were obtained with other solvents and temperatures (Table S1, entries 7–12). Therefore, the best reaction conditions were identified: **4d** (10 mol%) as the catalyst, $CHCl_3$ as the solvent, 16°C as the reaction temperature.

With the optimal reaction conditions established, the scope of the intermolecular cross RC reaction was subsequently investigated (Table 2). The reaction was applicable to a wide range of 3-aroyl acrylates with different aryl substituents. High yields and excellent enantioselectivities were attained regardless of the electronic properties (Table 2, entries 1–7). Substrates bearing an *ortho*-substituted aromatic group reacted with slightly lower enantioselectivity probably due to steric hindrance (Table 2, entries 8 and 9). The reaction also tolerated 2-furyl- and 2-thiophenyl-containing substrates (Table 2, entries 10 and 11). Other substrates with various esters were also suitable, giving the corresponding products in 85–95% yield and 86–91% *ee* (Table 2, entries 12–14). When acrolein was employed, catalyst *S*-**4c** was found to be the best catalyst affording the RC adduct **3o** in 51% yield and 70% *ee* (Table 2, entry 15; Table S2). The absolute configuration of a representative RC product was determined unambiguously as *R* based on the X-ray crystal structure (Figure S1).[18]

Next, a number of aryl vinyl ketones were applied to the cross RC reaction. Regardless of the electronic properties, substrates with *meta*-, and *para*-substituted aryl units were well tolerated in the reaction giving high yields (up to 98%) and *ee* values (up to 96%; Table 3, entries 1–7). Substrates bearing an *ortho*-substituted aromatic group reacted with lower enantioselectivity probably due to steric hindrance (Table 3, entries 8 and 9). A high yield and *ee* value could also be achieved when furyl was introduced to the substrate (Table 3, entry 10). All of the results were far better than those obtained with the PPh_3 catalyst (Table S3).

In order to display the potential applicability of this methodology, we performed the reaction on a gram scale using 4 mmol of the 3-aroyl acrylate. First 5 mol% **4d** was used as the catalyst in 10 mL $CHCl_3$ (the same catalyst concentration as under the optimized reaction conditions)

Table 3: Substrate scope for the RC reaction of **1c** and aryl vinyl ketone **2**.[a]

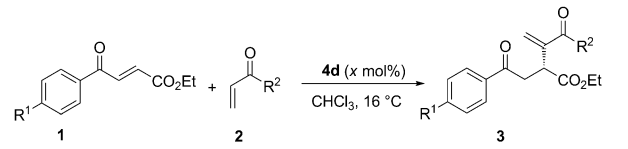


Entry	Ar	Product	Yield [%][b]	*ee* [%][c]
1	C_6H_5	**3p**	87	93
2	4-MeC_6H_4	**3q**	90	95.5
3	4-$MeOC_6H_4$	**3r**	89	96
4	4-FC_6H_4	**3s**	97	95
5	4-ClC_6H_4	**3t**	98	93
6	4-BrC_6H_4	**3u**	98	92
7	3-MeC_6H_4	**3v**	93	93
8	2-MeC_6H_4	**3w**	92	84
9	2,4-$Cl_2C_6H_3$	**3x**	78	69
10	2-furyl	**3y**	90	94

[a] Reaction was carried out with **1c** (0.1 mmol), **2** (0.2 mmol), and **4d** (10 mol%) in $CHCl_3$ (0.5 mL) at 16°C in 1.5 h. [b] Yields of isolated products. [c] Determined by chiral HPLC analysis using a chiral stationary phase.

providing **3e** in 90% yield and 89% *ee* (Table 4, entry 1). It was particularly gratifying that when we decreased the catalyst loading to 1 mol%, the reaction still smoothly proceeded in 1 mL $CHCl_3$ to provide **3c** in 95% yield and

Table 4: RC reactions on a multigram scale.

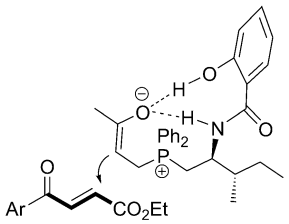


Entry	R^1	R^2	*x*	Product	Yield [%][c]	*ee* [%][d]
1[a]	Me	CH_3	5	**3e**, 1.18 g	90	89
2[b]	Br	CH_3	1	**3c,** 1.32 g	95	93
3[b]	F	CH_3	1	**3b,** 1.12 g	96	89
4[b]	Br	4-MeC_6H_4	1	**3p,** 1.61 g	94	93
5[b]	Br	4-BrC_6H_4	1	**3u**, 1.89 g	96	92

[a] Reaction was carried out with **1** (4 mmol), MVK (12 mmol), and **4d** (5 mol%) in $CHCl_3$ (10 mL) at 16°C for 70 h. [b] Reaction was carried out with **1** (4 mmol), **2** (8 mmol), and **4d** (1 mol%) in $CHCl_3$ (1 mL) at 16°C for 30 h. [c] Yields of isolated products. [d] Determined by HPLC analysis using a chiral stationary phase.

93% *ee* (Table 4, entry 2). The gram-scale reactions were also performed a catalyst loading of 1 mol% to obtain **3b**, **3p**, and **3u** in excellent yields and high *ee* values (Table 4, entries 3–5).

Based on the results of our experiments (Table 1, Figure S2) and previous reports,[9h,13a,14d,f,19] we propose the transition state shown in Scheme 2. The zwitterion formed by the phosphine and MVK is stabilized by hydrogen bonding between the phenolic hydroxy group and the acid amide group. The subsequent Michael addition favors the *Re* face to minimize steric repulsion. For more details on the proposed mechanism see Scheme S1 in the Supporting Information.



Scheme 2. Proposed transition state model.

In conclusion, we have developed a highly efficient enantioselective intermolecular cross Rauhut–Currier reaction of 3-aroyl acrylates and methyl vinyl ketone or aryl vinyl ketones. In the presence of the multifunctional phosphine catalyst **4d**, the reactions performed well with a series of substrates, delivering the desired products in excellent yields (up to 98%) and with excellent enantioselectivities (up to 96% *ee*). With the new catalyst, the asymmetric intermolecular cross Rauhut–Currier reaction with different active alkenes can be carried out on a gram scale with high yields and high enantioselectivity and with 1 mol% catalyst loading. To the best of our knowledge, **4d** is the most active organocatalyst so far developed for the cross RC reaction. Features of this method include the wide substrate scope, excellent yields, highly chemo- and enantioselectivity, and mild conditions. Further studies of the cross RC reaction and applications of the new multifunctional phosphine catalysts are currently underway in our group.

Experimental Section

General procedure: To a stirred solution of **1** (0.1 mmol) and catalyst **4d** (0.01 mmol) in $CHCl_3$ (0.5 mL) at 16°C, vinyl ketone **2** (0.3 mmol for MVK and 0.2 mmol for aryl vinyl ketone) was added by syringe in one portion. Then the reaction mixture was stirred at this temperature. After completion of the reaction (monitored by TLC), the reaction mixture was directly applied to a silica gel chromatography column (petroleum ether/ethyl acetate as eluent) to give product **3**.

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