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Enantioselective γ-addition reaction of rhodanines to allenoates catalyzed by chiral phosphine-carbamate

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ABSTRACT

Phosphine-catalyzed enantioselective γ-additions of rhodanines to allenoates have been developed for the first time. With the employment of chiral cyclohexane-based phosphines, a wide range of substituted rhodanine derivatives containing tertiary chiral centers were constructed in good yields and high enantioselectivities.

1. Introduction

Rhodanines are valuable skeletons found in many natural products and pharmaceuticals.[1] The asymmetric addition reactions involving rhodanines were served as feasible tools for the construction of chiral rhodanine scaffolds.[2,3] In these approaches, 5-substituted rhodanines and α,β-unsaturated rhodanines were used as the nucleophile and electrophiles, respectively. For example, the enantioselective Michael addition,[2a] Michael/Michael tandem reaction[2b] and α-amination[2c] of 5-substituted rhodanines were developed by Ye's group and Veselý's group. On the other hand, the Michael/Michael tandem reaction,[3a] Diels-Alder reaction[3b] and Michael/aldol tandem reaction[3c] between α,β-unsaturated rhodanines and different reagents were reported by Ye's group and Peng's group. In all works mentioned above, chiral amines were applied as catalysts to promote the enantioselective reactions by enamine, iminium or deprotonation activation mode. It's well known there are various activation modes in asymmetric organocatalysis. The application of different activation mode would develop new partners for the enantioselective reaction involving rhodanine compounds, and provide chiral structure-diversiform rhodanines.

In the past two decades, chiral tertiary phosphines have been widely used as nucleophilic catalysts in asymmetric catalysis.[4] Various enantioselective reactions involving electron-deficient olefins could be efficiently promoted by the chiral phosphines. In the presence of tertiary phosphine, a suitable nucleophile could attack the γ-position of allenoates/alkynoates to perform γ-addition reaction.[5–7] Among the asymmetric version, nitrogen-containing cyclic compounds were the most used nucleophiles.[6h,7a,7b,7d–7f] To the best of our knowledge, the γ-addition reaction of rhodanine to allenoate or alkynoate has never been reported. As mentioned above, the study of phosphine-catalyzed asymmetric reaction of rhodanine is vacant. As a continuing interest in the enantioselective phosphine catalysis to construct chiral heterocyclic compounds,[8] we have applied chiral tertiary phosphines to promote the enantioselective γ-addition reaction of rhodanines to allenoates. Herein, we report the preliminary results of our study on this reaction.

2. Results and discussion

We began our investigation with the γ-addition reaction of 5-substituted rhodanine **1a** with allenoate **2a** in the presence of 10 mol% phosphine-thiourea **4a**[9b] in toluene at 25 °C. As we expected, rhodanine **1a** converted completely in 10 min and the desired product was obtained in 79% yield with 35% ee (Table 1,

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entry 1). Then we screened the chiral cyclohexane-based phosphines with different Brønsted acid group (Fig. 1, Table 1). The results indicated the H-bond donor played an important role for the γ-addition reaction. With thiourea as H-bonding donator, phosphines **4b** and **4c**[9a] exhibited lower chemical yield and poor enantioselectivity (entries 2 and 3 vs entry 1). With a squaramide as H-bond donor, compounds **5a-5c**[8b] were inefficient for the model reaction, no product could be detected even after 24 h (entry 4). To our delight, the application of phosphine-amides **6a** and **6b**[8e] could provide better enantioselectivity (entries 5 and 6). In the presence of organocatalyst **6b**, the γ-addition reaction was achieved in 83% yield with 84% ee (entry 6). Then, we focused on the amide-containing phosphines. However, phosphines **7a** and **7b**[8e] bearing additional chiral scaffold and H-bonding group could not provide higher yield or enantioselectivity than phosphine-amide **6b** (entries 7 and 8 vs entry 6). To our surprise, phosphine-carbamate **8a** offered similar results as phosphine-amide **6a** (entry 9 vs entry 6). We prepared several phosphine-carbamates by the condensation between (1*R*,2*R*)-2-(diphenylphosphanyl)cyclohexan-1-amine and Boc_2O or chloroformate (Scheme 1). The variation of carbamate structure could not improve the results (entries 9–13). Moreover, we examined phosphine-sulfonamide **9**, which exhibited the same level of yield and enantioselectivity as the phosphine-thiourea **4b** and **4c** (entry 14 vs entries 2 and 3). The moderate-to-good yield of the model reaction resulted from the side reaction. Therefore, phosphine-carbamate **8a** was selected as the chiral organocatalyst to further optimize the reaction conditions.

Subsequently, the optimization of other reaction parameters (solvent, ratio of substrates, additive, substrate concentration, temperature and catalyst loading) was carried out with phosphine **8a**. As shown in Table 2, in toluene analogues, the model reaction could complete in 10 min and provided the desired product in 84–87% ee. For the sake of side reaction, in xylenes and mesitylene the chemical yields were lower than in toluene (entries 2–5 vs entry 1). With CH_2Cl_2 as solvent, the γ-addition reaction exhibited lower yield and lower enantioselectivity than the reaction using toluene or its analogue as solvent (entry 6 vs entries 1–5). When etheric solvents such as ether, MTBE and THF were used as solvent, different results were obtained. Comparing with toluene, the chemical yields were decreased, while same level of enantioselectivity was attained in ether and THF (entries 7–9 vs entry 1). In addition, the polar solvents including EtOAc, CH_3CN and EtOH provided worse results (entries 10–12). The results of solvent survey indicated toluene was the most suitable one for the γ-addition reaction. The ratio of rhodanine **1a** to allenoate **2a** had an effect to the selectivity rather than the reaction rate. Increasing the ratio of **2a**/**1a** from 1.5 to 2 led to a slightly lower enantioselectivity, while reducing the ratio of **2a**/**1a** from 1.5 to 1 resulted in a slightly lower yield (entries 13 and 14 vs entry 1). The addition of 4 Å molecular sieves could improve the enantioselectivity to 93% ee. However, it had a negative effect on the chemoselectivity, providing a decreased chemical yield (entry 15 vs entry 1). To improve the yield in the presence of molecular sieves, different substrate concentration was investigated (entries 15–18). The substrate concentration affected the reaction rate, yield and enantioselectivity. The higher substrate concentration (0.4 M of rhodanine) led to faster reaction rate, lower chemical yield and lower enantioselectivity (entry 16). The results showed 0.1 M concentration was more suitable than other concentration examined (entry 17). When the γ-addition reaction was performed at 0 °C, the reaction rate became slower, and similar results were obtained in a longer reaction time (entry 19 vs entry 17). The further lower temperature −20 °C gave a significant decrease in yield due to a low conversion (entry 20 vs 17). Due to the fast reaction rate at 25 °C, a decreased catalyst loading (5 mol%) was examined, which led to a significant decrease in yield for the sake of a lower conversion (entry 21 vs 17). Therefore, the

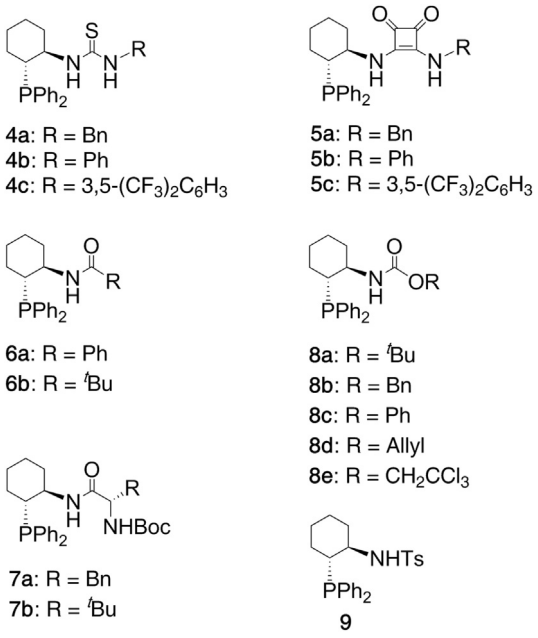
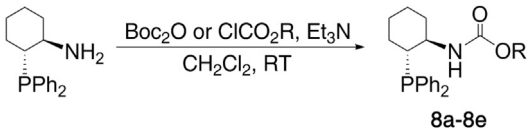
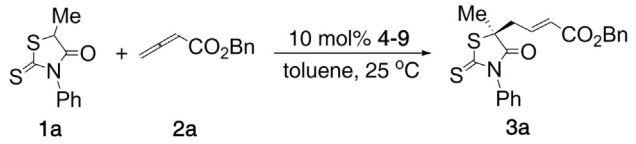


Fig. 1. Structures of the chiral phosphines screened.



Scheme 1. Synthetic route of phosphine-carbamates **8a-8e**.

Table 1
Screening of the chiral phosphine organocatalysts[a].



Entry	Catalyst	Time	Yield (%)[b]	Ee (%)[c]
1	**4a**	10 min	79	−35
2	**4b**	10 min	30	−5
3	**4c**	10 min	33	−4
4	**5**	24 h	NR[d]	nd[e]
5	**6a**	10 min	49	53
6	**6b**	10 min	83	84
7	**7a**	10 min	63	57
8	**7b**	10 min	73	79
9	**8a**	10 min	81	85
10	**8b**	10 min	56	75
11	**8c**	10 min	58	70
12	**8d**	10 min	63	76
13	**8e**	10 min	67	84
14	**9**	10 min	34	−1

[a] The reactions were performed with rhodanine **1a** (0.1 mmol), allenoate **2a** (0.15 mmol) and 10 mol% catalyst in 0.5 mL toluene at 25 °C.
[b] Isolated yields.
[c] Determined by HPLC analysis.
[d] No reaction.
[e] Not determined.