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Aminocatalyzed asymmetric Diels–Alder reaction of 2,4-dienals and rhodanine/hydantoin derivatives†

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Aminocatalyzed asymmetric Diels–Alder reaction between 2,4-dienals and rhodanine/hydantoin derivatives *via* trienamine mechanism has been developed to synthesize various spirocyclic compounds with good yields (up to 98%) and excellent stereoselectivities (up to 99% ee and >19 : 1 dr).

Rhodanine (2-thioxo-1,3-thiazolidin-4-one) as a compound of great importance in medicinal chemistry has been intensively explored by pharmacological scientists for a long time.[1] As a privileged scaffold in new drug discovery, structural modifications of rhodanine have led to the development of many potent and selective drugs.[2] For instance, rhodadyns that are formed through the condensation of rhodanine with active carbonyl compounds have recently attracted tremendous attention.[2] Typically, compound **1a**, known as BH3I-1, is a widely used inhibitor of the Bcl-2 protein that plays an important role in cancer treatment;[3] **1b–1d** have been identified as potent antibacterial drugs.[4] However, it should also be noted that the reactivities of this group of compounds as Michael addition acceptors may, in some occasions, complicate their use in cell-based assays or *in vivo*. Antibacterial drug **1b**, for example, can react with glutathione and other free thiols within a cell.[5] Thus it seems that further structural modifications of rhodadyns are desirable.

As structural analogues of rhodanine, hydantoins and their derivatives are a class of bioactive molecules that are widely used in medicinal chemistry[6] and agrochemistry[7] (**2a–c**, Fig. 1). Most recently, Deprez and co-workers[8] demonstrated that *N*-aryl-hydantoin derivatives (**2b**, **2c**) can be used as nonsteroidal, selective androgen receptor modulators (SARM). Compared to the traditional steroidal androgen receptor modulator, they exhibited higher oral bioavailability and the anabolic activity

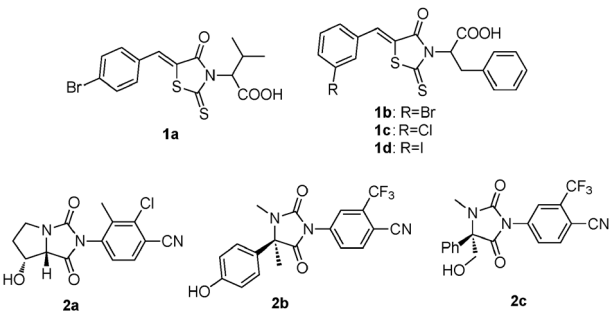

Fig. 1 Selected bioactive substances containing the rhodanine/hydantoin structure.

far outweighs the androgenic effect. What's more, the difference in biological activities between enantiomers has also been identified. For instance, the enantiomer of **2c** was proved to be inactive. This makes the asymmetric synthesis of structures which contain the *N*-aryl-hydantoin motif meaningful. This prompted us to develop new strategies for the convenient constructions of new scaffolds that incorporate the structural elements of rhodanine[9] and hydantoin derivatives.

Diels–Alder cycloaddition is one of the most powerful methods in the construction of six-membered carbo- or heterocycles.[10] In most traditional asymmetric Diels–Alder reactions, chiral catalysts catalyzed the cycloaddition process by employing a LUMO-lowering strategy as means of activating electron-deficient dienophiles[11] rather than taking advantage of the alternative strategy of HOMO-raising activation of electron-rich dienes.[12] Very recently, Chen and Jørgensen[13] jointly demonstrated that an aminocatalyst was able to promote the Diels–Alder reaction between dienal and dienophile through a trienamine intermediate that formed between the catalyst and the dienal, in which process the catalyst activated the dienal by rising the HOMO of the dienal. This newly developed method has been proved to be a very powerful protocol in the stereoselective construction of densely functionalized cyclic scaffolds and spirocyclic compounds.[14,15] In this paper, rhodanine/hydantoin derivatives **5** were successfully employed as dienophiles

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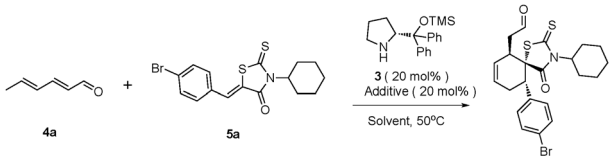
Table 1 Screening of reaction conditions[a]



Entry	Solvent	Additive	Yield[b] (%)	ee[c] (%)	dr[d]
1	Toluene	*o*-F-$C_6H_4CO_2H$	63	89	>19 : 1
2	Dioxane	*o*-F-$C_6H_4CO_2H$	60	88	>19 : 1
3	CH_3CN	*o*-F-$C_6H_4CO_2H$	40	73	>19 : 1
4	CPME	*o*-F-$C_6H_4CO_2H$	40	89	>19 : 1
5	$CDCl_3$	*o*-F-$C_6H_4CO_2H$	90	94	>19 : 1
6	$CDCl_3$	*o*-NO_2-$C_6H_4CO_2H$	52	93	>19 : 1
7	$CDCl_3$	*p*-MeO-$C_6H_4CO_2H$	78	94	>19 : 1
8	$CDCl_3$	$C_6H_5CO_2H$	87	93	>19 : 1
9	$CDCl_3$	*N*-Boc-*L*-Phe	57	93	>19 : 1
10	$CDCl_3$	*N*-Boc-*L*-Trp	73	93	>19 : 1

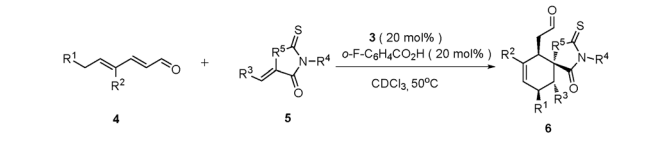
[a] Reaction conditions: **5a** (0.10 mmol, 1.0 eq.), **4a** (0.20 mmol, 2.0 eq.), catalyst **3** (20 mol%) and acid (20 mol%) in solvent (1.0 mL) at 50 °C for 72 h. [b] Yield of the isolated product. [c] Enantiomeric excess was determined by chiral HPLC after **6a** was converted into the corresponding α,β-unsaturated ester ($Ph_3P{=}CH_2CO_2Me$, THF, r.t.). [d] Determined by ^{1}H NMR analysis of the crude reaction mixture. CPME = cyclopentyl methyl ether.

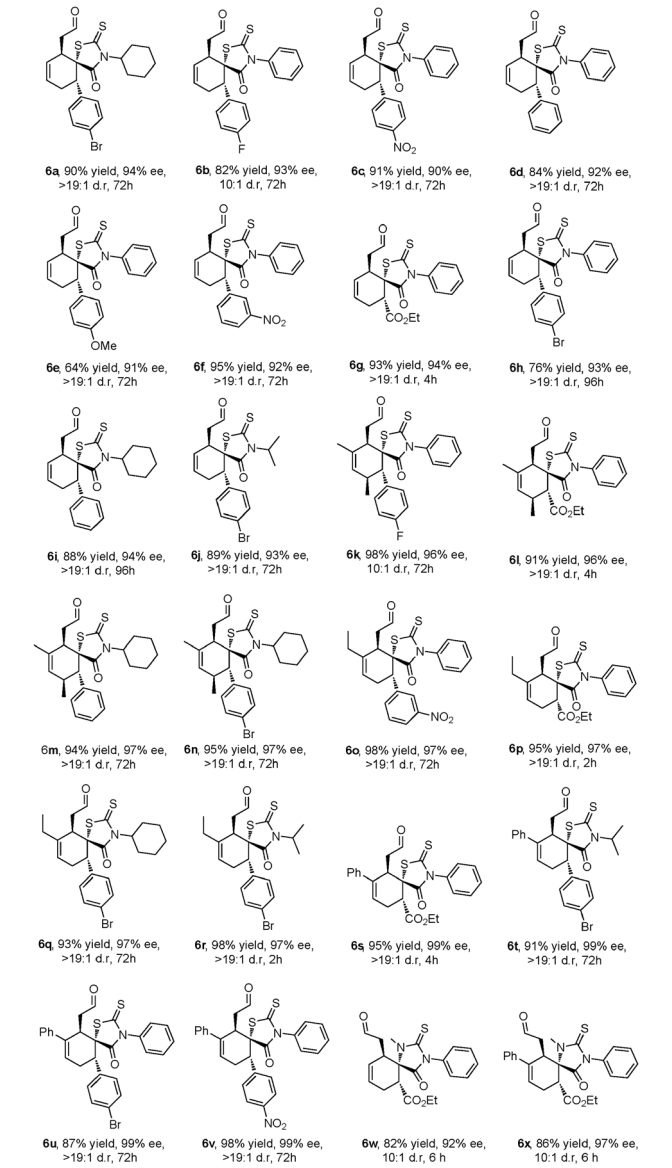
to participate in the asymmetric Diels–Alder reaction with various 2,4-dienals **4**, leading to the construction of structurally complex compounds containing the rhodanine/hydantoin motif.

We initially performed the asymmetric Diels–Alder reaction between rhodadyn **5a** and dienal **4a** in different solvents, in the presence of 20 mol% of diphenylprolinol silyl ether **3** and 20 mol% of *o*-F-$C_6H_4CO_2H$ as a combination of catalyst.[16] It was gratifying to see that in all cases excellent diastereoselectivities (dr >19 : 1) were observed, and the ee values were satisfying (Table 1, entries 1, 2, 4 and 5) with the exception of CH_3CN (entry 3). However, the isolated yields of the asymmetric process varied greatly, depending on the solvents used. For example, only 40% of yield was observed when the reactions were carried out in CH_3CN and CPME (entries 3 and 4), and moderate yields were obtained in the cases of toluene and dioxane (entries 1 and 2). In contrast, when the reaction was carried out using $CDCl_3$ as solvent,[17] the yield of the isolated product was dramatically improved to 90% (entry 5). In our opinion, such enormous variation could mainly be attributed to the difference of the solubility of **5a** in these solvents. Having the optimized solvent ascertained, we subsequently turned our attention to the effect of acid additives on this asymmetric procedure. The results demonstrated that additives did not play an important role in the controlling of stereoselectivities, and all other acid additives probed failed to give a better result compared to that of *o*-F-$C_6H_4CO_2H$ in terms of the yield (entries 6–10).

With the optimal reaction condition in hand, the substrate scope of the reaction was then investigated by employing various combinations of 2,4-dienals **4** and rhodanine derivatives **5**, and the results are summarized in Table 2. It should be noted that the R^3 substituent of substrate **5** affected the

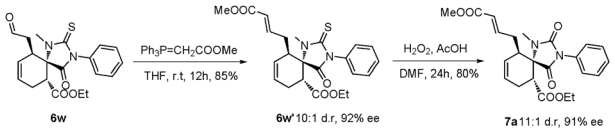
Table 2 Generality of organocatalytic Diels–Alder reaction





Reaction conditions: **5** (1.0 mmol, 1.0 eq.), **4** (2.0 mmol, 2.0 eq.), cat **3** (20 mol%) and *o*-F-$C_6H_4CO_2H$ (20 mol%) in $CDCl_3$ (C = 0.1 M) at 50 °C for specified time, in reaction leading to **6j**, 3.0 mmol (3.0 eq.) of **4a** was used. The yields are those of isolated products. The dr values were determined by ^{1}H NMR analysis of the crude reaction mixture. The ee values were determined by chiral HPLC after the product was converted into the corresponding ester ($Ph_3P{=}CH_2CO_2Me$, THF, r.t.).

reaction substantially with respect to the reaction rate. When $R^3{=}CO_2Et$, the reactions completed smoothly just after 2–4 hours, leading to products **6g**, **6l**, **6p** and **6s** in good yields and excellent diastereo-(dr >19 : 1) and enantioselectivities (up to 99% ee). However, the reactions turned out to be much slower when the R^3 substituent was exchanged by various aromatic rings (72–96 h). It appeared that the properties of the



Scheme 1 Elaboration of the Diels–Alder cycloaddition product.

substituent on the aromatic rings had very limited influence on the reaction in terms of stereoselectivities, while the electron-donating substituent afforded relatively low yield (**6e**, 64% yield). Interestingly, rhodanine derivatives with R^3 substituent of the *p*-F-C_6H_4 group afforded the desired products with slightly decreased dr values (**6b**, **6k**, 10 : 1 dr). The substituents on the nitrogen atom of **5** barely affected the asymmetric process.

We then paid our attention to the substrate scope of the 2,4-dienals. Gratifyingly, when 4-ethyl-2,4-dienal was employed, products **6o** to **6r** were obtained with much higher yields and enantioselectivities compared to that of **4a**. It was noteworthy that structurally more complicated 4-phenyl-2,6-dienal gave the desired products **6s–6v** with almost perfect stereoselectivities. Products **6k–6n** that bore four consecutive chiral centers could also be easily prepared using 4,6-disubstitued-2,4-hexadienal as diene, with up to 98% yield and excellent diastereo- and enantioselectivities. It should be noted that the established method was also applicable to the reaction with the *N*-aryl-thiohydantoin derivative. As shown in Table 2, products (**6w**, **6x**) could be easily prepared in good yields with excellent enantio- (>90% ee) and slightly decreased diastereoselectivities (10 : 1 dr).

The relative and absolute configurations of the sequential reaction products were assigned on the basis of X-ray crystal structural analysis of the product **6j** (see the ESI†).

As an effort to transform the *N*-aryl-thiohydantoin motif into the corresponding *N*-aryl-hydantoin motif, the Diels–Alder cycloaddition product **6w** was then converted into the corresponding α,β-unsaturated ester, followed by treatment with H_2O_2 to afford the desired structure that incorporated the hydantoin motif. The product **7a** could be obtained in high yield with simple manipulation (Scheme 1).

To conclude, the asymmetric Diels–Alder cycloaddition of 2,4-dienals **4** and rhodanine derivatives has been established with high yield and excellent diastereo- and enantioselectivities. The optimized reaction condition was also applicable to the reaction of 2,4-dienals and thiohydantoin derivatives, the adducts of which may serve as valuable scaffolds in new drug discovery and natural product synthesis. Exploration of the application of the Diels–Alder cycloaddition product in medicinal chemistry is currently under way in our laboratories.

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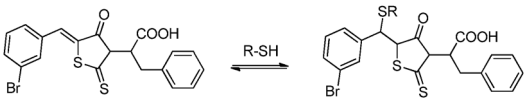

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