VIP Asymmetric Catalysis

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# Trienamine Catalysis with 2,4-Dienones: Development and Application in Asymmetric Diels–Alder Reactions**

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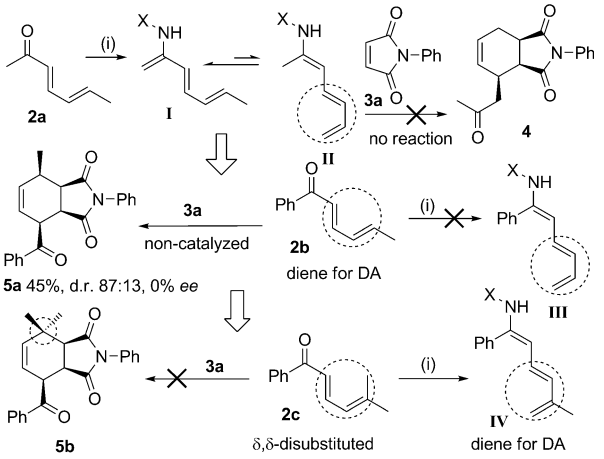
Since the seminal papers at the beginning of this century,[1] asymmetric organocatalysis based on chiral amines has been extensively and actively explored. A variety of catalytic modes, which includes enamine, iminium, dienamine, and SOMO pathways, have been elegantly applied to a large number of asymmetric reactions, especially for aliphatic and α,β-unsaturated aldehyde substrates.[2] Very recently, our group as well as Jørgensen and co-workers have reported a new reactive model, trienamine catalysis, for 2,4-dienals. This method relies on the generation of an electron-rich triene system in situ, which can perform as a diene counterpart in the Diels–Alder (DA) reaction with an electron-deficient dienophile, and gives exclusive β,ε-regioselectivity along with excellent stereoselectivity.[3]

It would be reasonable that such a trienamine catalytic protocol should also be applicable to 2,4-dienone analogues as the common enamine or iminium catalysis for α-enolizable ketones or α,β-unsaturated ketones, respectively.[2a,b] Unfortunately, as outlined in Scheme 1, the expected trienamine catalysis was unsuccessful and almost no reaction occurred between hepta-3,5-dien-2-one (**2a**) and the dienophile *N*-phenylmaleimide (**3a**) when catalyzed by a primary amine, such as 9-amino-9-deoxyepiquinine (**1a**, Table 1).[4] As the two different trienamine intermediates **I** and **II** could be formed, we reasoned that trienamine **I** might be preferred, which would not promote the desired cycloaddition. As a result, dienone **2b**, which does not contain an α-enolizable alkyl group, was used under the same conditions. However, the α,δ-regioselective DA cycloadduct **5a** was isolated as the sole product, albeit in low yield. It was later confirmed that this reaction proceeded in a noncatalyzed manner, and substrate **2b**, rather than the trienamine **III**, directly acted as the diene.[5] We envisaged that the introduction of another methyl group at the δ position of the dienone, as in the structure of the 2,4-dienone **2c**, would significantly inhibit the reaction that proceeds through the undesired DA pathway, as




***Scheme 1.*** Logical development of trienamine catalysis for 2,4-dienone substrates. Conditions: i) **1a** (20 mol%), TFA (40 mol%), 60°C, toluene. X = 9-quinyl.

a quaternary center shown in the proposed product **5b** has to be formed. Moreover, the electron-donating effect of the δ-methyl group would also increase the HOMO energy of the resulting trienamine intermediate **IV**,[6] which would further facilitate the amine-catalyzed DA process.

To our gratification, it was found that the expected DA reaction of **2c** and **3a** catalyzed by amine **1a** and trifluoroacetic acid (TFA) in toluene at 60°C was efficient.[7] Cycloadduct **6a** was isolated as a single *endo* diastereomer and, more pleasingly, with excellent enantioselectivity (Table 1, entry 1). It should be noted that only a trace amount of the noncatalyzed DA product **5b** was detected, as proposed before. Subsequently, a number of reaction parameters were explored. A much lower yield was obtained when the weaker *o*-fluorobenzoic acid (OFBA) was used (Table 1, entry 2), but good results were achieved in the presence of salicylic acid (SA, Table 1, entry 3).[8] Both the yield of the reaction and the *ee* value were decreased by applying sulfonic acids as the additives (Table 1, entries 4 and 5). A lower yield and *ee* value were obtained in chloroform (Table 1, entry 6), and almost no reaction occurred in THF (Table 1, entry 7). The yield also decreased upon lowering the loading of TFA, but without effect on the enantioselectivity (Table 1, entry 8). Other chiral primary amines derived from cinchona alkaloids were also tested. 9-Amino-9-deoxy-epicinchonidine (**1b**) provided the same enantioselectivity as **1a** but with a lower yield (Table 1, entry 9), whereas the demethylated derivative **1c**[4f] could not catalyze this reaction (Table 1, entry 10). Furthermore, 9-amino-9-deoxyepiquinidine (**1d**) and 9-amino-9-deoxyepicinchonine (**1e**) delivered unsatisfying results and the product

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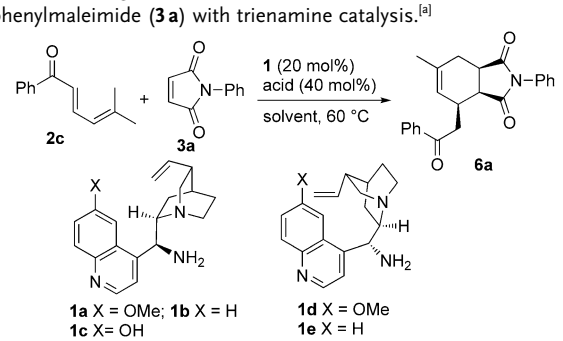
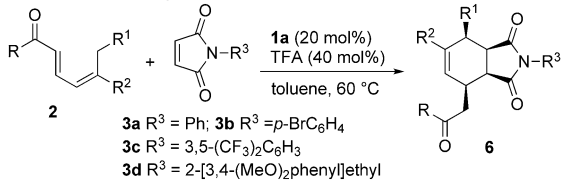
***Table 1:*** Screening studies of the Diels–Alder reaction of dienone **2c** and *N*-phenylmaleimide (**3a**) with trienamine catalysis.[a]




| Entry | 1 | Solvent | Acid | *t* [h] | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|---|
| 1 | **1a** | toluene | TFA | 24 | 75 | 92 |
| 2 | **1a** | toluene | OFBA | 36 | 30 | 87 |
| 3 | **1a** | toluene | SA | 36 | 70 | 94 |
| 4 | **1a** | toluene | TfOH | 24 | 61 | 71 |
| 5 | **1a** | toluene | TsOH | 24 | 70 | 81 |
| 6 | **1a** | $CHCl_3$ | TFA | 24 | 69 | 88 |
| 7 | **1a** | THF | TFA | 24 | – | – |
| 8[d] | **1a** | toluene | TFA | 39 | 50 | 93 |
| 9 | **1b** | toluene | TFA | 24 | 50 | 93 |
| 10 | **1c** | toluene | TFA | 24 | <10 | – |
| 11 | **1d** | toluene | TFA | 24 | 51 | 74[e] |
| 12 | **1e** | toluene | TFA | 24 | 40 | 66[e] |
| 13 | **1d** | toluene | SA | 36 | 80 | 88[e] |
| 14[f] | **1a** | toluene | TFA | 24 | 78 | 87 |
| 15[g] | **1a** | toluene | TFA | 18 | 85 | 93 |

[a] Unless noted otherwise, reactions were performed with **2c** (0.12 mmol), **3a** (0.1 mmol), **1** (20 mol%), and acid (40 mol%) in solvent (1 mL) at 60°C. [b] Yield of isolated product. [c] By HPLC analysis on a chiral stationary phase; d.r. > 95:5 by $^1$H NMR analysis. [d] With 20 mol% of TFA. [e] For the opposite enantiomer. [f] At 70°C. [g] With 30 mol% of **1a** and 60 mol% of TFA. TfOH: trifluoromethanesulfonic acid; TsOH: *p*-methylbenzenesulfonic acid.

***Table 2:*** Substrate scope of the Diels–Alder reaction.[a]




| Entry | R | $R^1$ | $R^2$ | 3 | *t* [h] | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|---|---|
| 1 | Ph | H | Me | **3a** | 24 | **6a**, 75 | 92 |
| 2 | Ph | H | Me | **3b** | 24 | **6b**, 80 | 92 |
| 3 | Ph | H | Me | **3c** | 24 | **6c**, 84 | 93 |
| 4 | Ph | H | Me | **3d** | 42 | **6d**, 80 | 89 |
| 5 | *p*-$ClC_6H_4$ | H | Me | **3c** | 16 | **6e**, 84 | 94 |
| 6[d] | *m*-$BrC_6H_4$ | H | Me | **3b** | 46 | **6f**, 70 | 92 |
| 7 | *p*-$MeC_6H_4$ | H | Me | **3c** | 24 | **6g**, 84 | 90 |
| 8 | 1-naphthyl | H | Me | **3b** | 24 | **6h**, 80 | 89[e] |
| 9 | 1-naphthyl | H | Me | **3c** | 18 | **6i**, 84 | 94 |
| 10 | 2-furyl | H | Me | **3b** | 36 | **6j**, 80 | 90 |
| 11 | 2-styryl | H | Me | **3b** | 48 | **6k**, 80 | 96 |
| 12 | Ph-C≡C- | H | Me | **3b** | 48 | - | - |
| 13 | Ph | H | X[f] | **3b** | 48 | **6l**, 67 | 96 |
| 14[d] | Ph | $-(CH_2)_3-$ | | **3b** | 36 | **6m**, 70 | 82 |
| 15 | Ph | $-(CH_2)_2-$ | | **3b** | 60 | **6n**, 70 | 62 |
| 16 | Ph | H | Ph | **3b** | 48 | **6o**, 46 | 85 |
| 17 | 2-styryl | H | Ph | **3b** | 48 | **6p**, 70 | 89 |
| 18[d] | *p*-$ClC_6H_4$ | H | Me | **3c** | 34 | **6e**, 70 | 80[g] |
| 19[d] | *p*-$MeC_6H_4$ | H | Me | **3c** | 34 | **6g**, 75 | 82[g] |

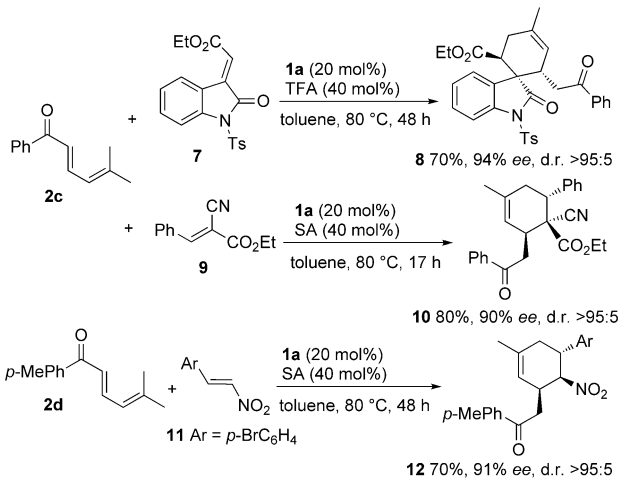
[a] Reactions were performed with **2** (0.12 mmol), **3** (0.1 mmol), **1a** (20 mol%), and TFA (40 mol%) in toluene (1 mL)at 60°C. [b] Yield of isolated product. [c] By HPLC analysis on a chiral stationary phase; d.r. > 95:5 by $^1$H NMR analysis. [d] SA was used. [e] The absolute configuration of **6h** was determined by X-ray analysis.[10] The other products were assigned by analogy. [f] X = 4-methyl-3-pentenyl. [g] For the opposite enantiomer catalyzed by **1d**.

was the opposite configuration (Table 1, entries 11 and 12). Nevertheless, a much improved yield and *ee* value could be obtained in combination with SA (Table 1, entry 13). A slightly lower enantioselectivity was achieved at 70°C with **1a** as the catalyst (Table 1, entry 14). A better yield with similar enantioselectivity could be obtained by using a higher catalyst loading (Table 1, entry 15).

With the optimized reaction conditions in hand, we then investigated a variety of 2,4-dienones and maleimides in the reaction catalyzed by **1a** (20 mol%) and TFA (40 mol%) in toluene at 60°C. The results are summarized in Table 2. At first, it was found that a slightly higher yield could be obtained by using maleimides **3b** or **3c** with an *N*-aryl group that contains electron-withdrawing substituents, probably owing to the enhancement of dienophilicity (Table 2, entries 2 and 3). Pleasingly, good results were also obtained for *N*-alkylmaleimide **3d**, although a longer reaction time was required (Table 2, entry 4). A series of 2,4-dienones with diverse substituents were also explored. 1-Aryl substrates with electron-withdrawing or electron-donating groups were tolerated, which gave the cycloadducts in good yields and excellent enantioselectivity (Table 2, entries 5–9). Similar results were achieved with a 2-furyl-substituted dienone (Table 2, entry 10). Importantly, a functionalized dienone with a 2-styryl group could be used, and a remarkable *ee* value was obtained (Table 2, entry 11). Unfortunately, the analogous dienone substrate with a 2-phenylethynyl group exhibited no reactivity under the same conditions (Table 2, entry 12). Moreover, a δ,δ-unsymmetrically disubstituted dienone showed excellent regioselectivity, and the less hindered product **6l** was exclusively generated (Table 2, entry 13). Nevertheless, diminished enantioselectivity was obtained for a cyclohexylidene dienone (Table 1, entry 14), and only a moderate *ee* value was obtained for a dienone with a cyclopentylidene motif (Table 2, entry 15). The catalytic reaction was also applicable to δ-phenyl-substituted dienones (Table 2, entries 16 and 17). In comparison, 9-amino-9-deoxyepiquinidine **1d** was further tested for other dienone substrates and the cycloadducts with the opposite configuration were delivered with good *ee* values (Table 2, entries 18 and 19).[9]

To further demonstrate the generality of the chiral primary amine based trienamine catalysis, more dienophiles were explored in the reaction with δ,δ-disubstituted dienones **2**. As outlined in Scheme 2, 3-olefinic oxindole **7** with an *N*-tosyl (Ts) group could react with **2c**, but a higher temperature (80°C) was required. Spirocyclic oxindole **8** was obtained from this reaction with outstanding diastereo- and enantioselectivity. Furthermore, benzylidenecyanoacetate **9** and

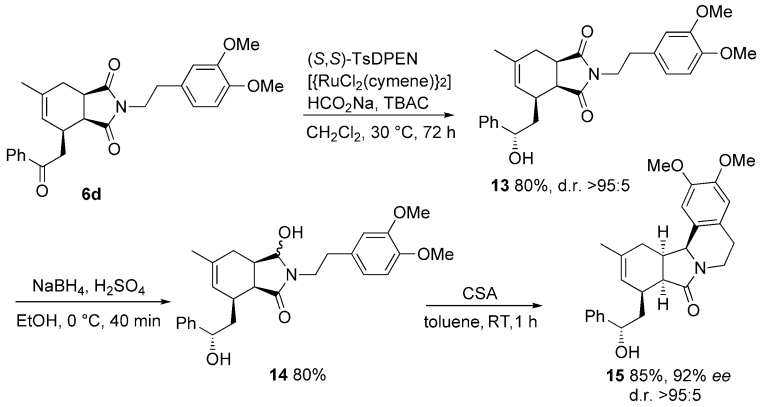



***Scheme 2.*** Diels–Alder reaction of other types of dienophiles.

nitroalkene **11** were also tested and SA was found to be a better acid additive in these reactions. Gratifyingly, high stereoselectivity was still obtained for the corresponding products **10** and **12**, respectively, even under such relatively harsh conditions. It should be noted that, in contrast to trienamine catalysis with 2,4-dienals, *endo* selectivity, rather than the abnormal *exo* selectivity,[3b,d] was obtained for the cycloaddition of nitroalkene **11** to 2,4-dienone **2d**.[11]

The multifunctional characteristics of the 2,4-dienone DA products can be used in chemoselective transformations to access frameworks with high molecular complexity. For example, the ketone group of adduct **6d** can be diastereoselectively converted to the chiral alcohol **13** by employing Noyori's (*S*,*S*)-TsDPEN-Ru transfer-hydrogenation system.[12] Moreover, by using the reaction procedures reported by Stang and White, the fused tetracyclic product **15** could be efficiently constructed with remarkable diastereoselectivity, based on a sequential reduction/Friedel–Crafts reaction sequence (Scheme 3).[13]

In conclusion, we have developed an asymmetric Diels–Alder cycloaddition of 2,4-dienones by the trienamine catalysis of readily available chiral primary amines of cinchona alkaloids. The success of this catalytic mode was based on the logical design and analysis of the results of the reactions. Currently, the application of 2,4-dienones with a δ,δ-disubstituted pattern was necessary for the amine-catalyzed Diels–Alder reaction, otherwise the 2,4-dienones would directly act as dienes in a noncatalyzed cycloaddition.[9] In addition, the presence of an aryl or 2-styryl group at the α position to the carbonyl group was also required to suppress the detrimental formation of the unreactive trienamine intermediate.[7] A diverse range of electron-deficient dienophiles have been successfully applied, which gave an array of multifunctional cyclohexene derivatives in moderate to excellent enantioselectivity (up to 96% *ee*) and exclusive *endo* selectivity (>95:5). We believe that this work will arouse more research interest in asymmetric aminocatalysis of unsaturated carbonyl compounds. Such studies are actively under way in this laboratory, and more results will be reported in due course.




***Scheme 3.*** Construction of a chiral polycyclic framework. TBAC = tetrabutylammonium chloride, CSA = camphorsulfonic acid.

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[9] More 2,4-dienones without δ,δ-disubstituted patterns have been tested, but only the noncatalyzed DA cycloadducts were obtained, see the Supporting Information.

[10] CCDC 864374 (**6h**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[11] The absolute configuration for compounds **8**, **10**, and **12** has been assigned on the basis of a presumed common catalytic mechanism similar to that of cycloadducts **6**. In addition, the relative configuration for products **10** and **12** has been further studied by 2D NMR and NOE analysis, see the Supporting Information.

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