Synthetic Methods

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Amine-Promoted Asymmetric (4+2) Annulations for the Enantioselective Synthesis of Tetrahydropyridines: A Traceless and Recoverable Auxiliary Strategy**

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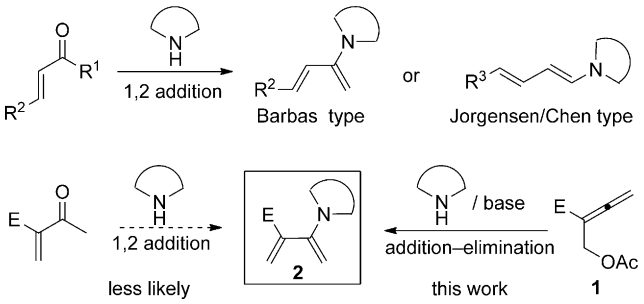
Substituted tetrahydropyridines and piperidines are common six-membered heterocycles found in biologically active natural products and synthetic pharmaceuticals.[1] One of the most versatile and reliable methods to prepare this class of six-membered heterocycles is the aza-Diels–Alder reaction.[2] Particularly, the recent development of dienamine catalysis[3] has added a powerful dimension to the aza-Diels–Alder reaction, which strongly relies on the formation of the dienamines developed by the groups of Barbas,[4] Jørgensen,[5] and Chen[5] by 1,2-addition of the amine catalyst to enone or enal (Scheme 1). Despite extensive studies and noteworthy

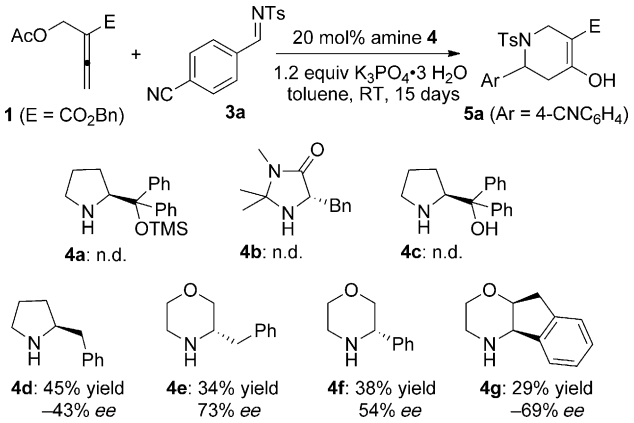


Scheme 1. Methods of dienamine formation. E = CO_2R.

advances in this field, the utilization of 2-methylene-3-oxobutanoate, a molecule potentially prone to polymerization,[6] as an enone-type substrate remains challenging. This may be due to their competitive Michael addition,[7] which renders the required dienamine intermediate **2** less likely to be formed (Scheme 1).

We address this issue using an unprecedented and alternative approach, namely a 2-methylene-3-oxobutanoate equivalent formed through an addition–elimination reaction between a secondary amine and 2-(acetoxymethyl)buta-2,3-dienoate (**1**; Scheme 1). Indeed, we have recently demonstrated that **1** readily reacts with a Lewis base catalyst, undergoing a continuous process, including Michael-addition of the catalyst and 1,2-elimination of the acetate group, to form a 1,*n*-bis electrophilic intermediate ($n = 3, 4$).[8] Thus, we envisioned that dienamine **2** would also result from the reaction of **1** and secondary amines with the assistance of a base by a similar addition–elimination process (Scheme 1). Herein we report an amine-promoted asymmetric (4+2) annulation of **1** with *N*-tosylimine for the enantioselective synthesis of tetrahydropyridine. Furthermore, an analogue of intermediate **2** was detected by ^{1}H NMR spectroscopy, which represents a novel type of push–pull dienamine,[9] and provides a route to a 2-methylene-3-oxobutanoate equivalent in dienamine chemistry.

We initiated our research by examining various chiral secondary amines **4** as catalysts for the reaction of **1** (1 equiv) and imine **3a** (2 equiv) in toluene solution in the presence of $K_3PO_4 \cdot 3H_2O$ (1.2 equiv; Scheme 2). Commonly used amines



Scheme 2. Screening of chiral secondary amines. Bn = benzyl, n.d. = not determined, Ts = *p*-toluenesulfonyl.

4a–**4c** were found to be inactive. This may be attributed to the large steric hindrance around the secondary amine center, which should strongly inhibit the Michael addition of amine to substrate **1**. Indeed, amine **4d**, with the less steric benzyl group, led to the desired (4+2) annulation product **5a** very slowly, but gave an encouraging 45% yield and 43% *ee*. We then turned our attention to chiral morpholine derivatives **4e**–**4g**, which are readily synthesized by a known procedure from commercially available amino alcohols.[10] We were delighted to find that **4e** was the optimal one, resulting in the

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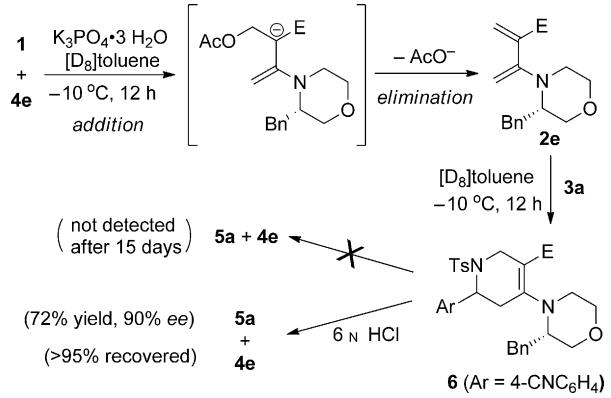
isolation of **5a** in 34% yield and 73% *ee*, although a very long reaction time (15 days) was also required at room temperature (Scheme 2).

Disappointingly, we failed to improve the catalytic reaction through screening a variety of bases, solvents, reaction temperature, and additives.[11] Thus, we made recourse to an alternative strategy. We found that the reaction of **1** (0.2 mmol) and **4e** (0.24 mmol) in [D_8]toluene solution in the presence of $K_3PO_4 \cdot 3H_2O$ (0.24 mmol) could go to completion within 12 h, even at −10 °C (Scheme 3), and

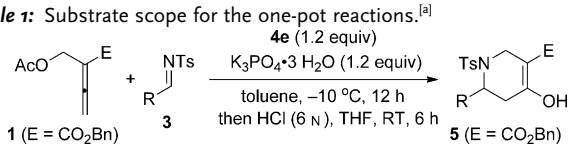


Scheme 3. Stoichiometric Reactions. E = CO_2Bn.

^{1}H NMR analysis clearly demonstrated the formation of dienamine **2e** (Supporting Information, Figure S1). This result strongly implied that the corresponding addition–elimination process would be a fast step (Scheme 3). A relatively rapid and complete conversion of **2e** into the (4+2) annulation intermediate **6**, which was detected by ESI-HRMS analysis (Figure S2), was also observed when imine **3a** (0.4 mmol) was subsequently added (Scheme 3). To our surprise, neither product **5a** nor catalyst **4e** were detected, even when the reaction mixture was stirred at room temperature for 15 days. This observation may be attributed to the fact that enamine intermediate **6** is so stable that its hydrolysis is sluggish under these conditions,[12] which may be an intrinsic obstruction to the development of an optimal catalytic version. However, simple treatment of the reaction mixture with aqueous hydrochloric acid (6 N) allowed the isolation of **5a** in 72% yield with 90% *ee*. Furthermore, amine **4e** was also easily recovered in quantitative yield without column chromatography (Scheme 3).[13] In this way, amine **4e** acts as a traceless and recoverable auxiliary.[14]

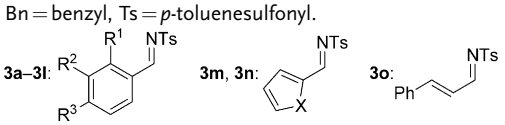
These results notwithstanding, we continued our pursuit of a synthetically useful 2-methylene-3-oxobutanoate equivalent for the enantioselective synthesis of tetrahydropyridines using dienamine **2e**. In view of the inefficiency of the catalytic reaction, we chose to focus on the development of a strategy utilizing a traceless and recoverable auxiliary. Ultimately, we identified a one-pot method: slow addition of **1** into a toluene solution of **4e** (1.2 equiv), **3d** (2 equiv), and $K_3PO_4 \cdot 3H_2O$ (1.2 equiv) at −10 °C, and subsequent acidic workup by the addition of aqueous hydrochloric acid (6 N) and THF after

Table 1: Substrate scope for the one-pot reactions.[a]



Entry	3	5	Yield [%][b]	*ee* [%][c]
1	**3a** (R^1 = H, R^2 = H, R^3 = CN)	**5a**	90	91
2	**3b** (R^1 = H, R^2 = H, R^3 = F)	**5b**	94	92
3	**3c** (R^1 = H, R^2 = H, R^3 = Cl)	**5c**	94	92
4	**3d** (R^1 = H, R^2 = H, R^3 = Br)	**5d**	91	94
5	**3e** (R^1 = H, R^2 = H, R^3 = CF_3)	**5e**	81	88
6	**3f** (R^1 = H, R^2 = H, R^3 = Me)	**5f**	85	90
7	**3g** (R^1 = H, R^2–R^3 = –OCH_2O–)	**5g**	53	90
8	**3h** (R^1 = H, R^2 = H, R^3 = H)	**5h**	86	87
9	**3i** (R^1 = H, R^2 = NO_2, R^3 = H)	**5i**	88	80
10	**3j** (R^1 = Br, R^2 = H, R^3 = H)	**5j**	91	95
11	**3k** (R^1 = NO_2, R^2 = H, R^3 = H)	**5k**	53	95
12	**3l** (R^1 = CO_2Me, R^2 = H, R^3 = H)	**5l**	94	95
13	**3m** (X = S)	**5m**	64	92
14	**3n** (X = O)	**5n**	80	70
15	**3o**	**5o**	51	85

[a] Reaction conditions: **1** (0.2 mmol), **4e** (1.2 equiv), **3** (2 equiv), and $K_3PO_4 \cdot 3H_2O$ (1.2 equiv), toluene (2 mL), −10 °C, 24 h, then aqueous HCl (6 N, 5 mL) and THF (5 mL), RT, 6 h. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. Bn = benzyl, Ts = *p*-toluenesulfonyl.

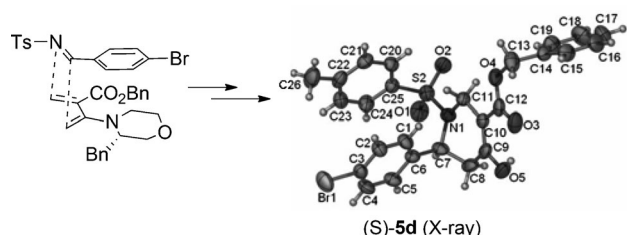


completion of the [4 + 2] annulation, could afford product **5a** in 90% yield and 91% *ee* (Table 1).[11]

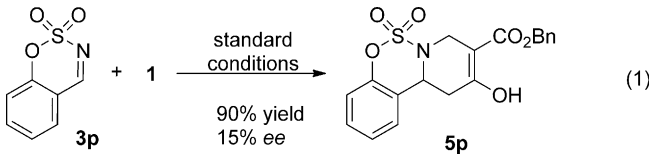
As illustrated in Table 1, this one-pot method can be applied to an array of aryl *N*-tosylimines, affording the desired products in excellent yields and enantioselectivities. Generally, the aromatic ring can be *ortho*-, *meta*-, or *para*-substituted. It can also bear an electron-withdrawing or an electron-donating group, although the latter case gives slightly worse results with respect to the reaction yield and enantioselectivity. Some other heteroaromatic *N*-tosylimines, such as **3m** and **3n**, were also tested, both of which worked well to give the corresponding products in good yields and enantioselectivities. The substrate *trans*-styrenyl *N*-tosylimine smoothly undergoes (4+2) annulation to deliver **5o** in 51% yield and 85% *ee*. In all cases, quantitative amounts of amine **4e** were recovered with > 95% purity.

The absolute configuration of **5d** was determined to be *S* by X-ray crystal structure analysis.[18] The stereochemistry of all other products is assigned by analogy. The observed enantioselectivity can be explained by the proposed transition-state model shown in Scheme 4. Because the bottom face of dienamine **2e** is blocked by its benzyl group, tosylimine **3d** approaches from the upper side to furnish the Diels–Alder reaction in an *endo* fashion, delivering the observed (*S*)-**5d** (Scheme 4).

Furthermore, cyclic imine **3p** reacted well with **1** under the standard conditions, affording product **5p** in 90% yield, albeit with very low *ee* [Eq. (1)]. This low enantioselectivity is



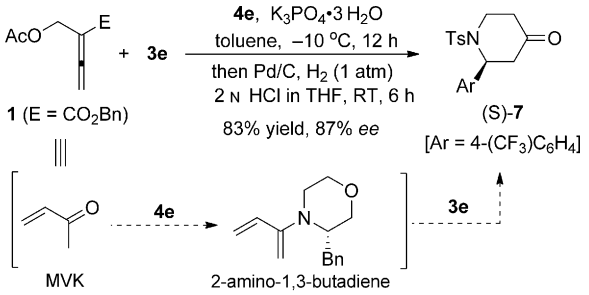
Scheme 4. Proposed transition state model. Thermal ellipsoids set at 20% probability.



(1)

believed to arise from the *cis* configuration of imine **3p**. Thus, we speculate that the tetrahedral geometry of the sulfonate on imine **3p** might disturb the secondary orbit effect on the corresponding transition state, thus making the *endo* cyclization less favorable. Nevertheless, obtaining a full understanding of the turnover in stereoselectivity will require further investigation, and the sequence of Mannich and Michael additions can not be completely excluded at this stage.[4i–k,15]

As the product has a benzyl 3-oxobutanoate substructure (enolate form), it is amenable to decarboxylation under normal Pd/C-catalyzed hydrogenation conditions. Indeed, piperidin-4-one derivative (*S*)-**7**[16] was readily isolated in 83% overall yield with 87% *ee* when the reaction mixture was instead treated with Pd/C and acidic THF solvent under hydrogen atmosphere at room temperature for 6 h (Scheme 5). This shows that compound **1** is capable of serving



Scheme 5. A methyl vinyl ketone (MVK) equivalent for (4+2) annulation with *N*-tosylimine.

as a methyl vinyl ketone (MVK) equivalent for (4+2) annulation with tosylimine (Scheme 5). MVK is also a challenging substrate in dienamine chemistry. Although a few 2-amino-1,3-butadienes have been sporadically reported, their synthesis always requires multiple steps and rigorous reaction conditions.[17]

In summary, we have developed a route to a 2-methylene-3-oxobutanoate equivalent for dienamine chemistry through the reaction of substrate **1** with a chiral secondary amine. The resulting dienamine intermediate **2e** is shown to readily undergo aza-Diels–Alder reaction with tosylimine. Although the **4e**-catalyzed reaction provides unsatisfying results, the stoichiometric version affords substituted tetrahydropyridines in good to excellent yields and enantioselectivities. Amine **4e** can be recovered quantitatively through a simple workup, thus serving as a traceless and recoverable auxiliary. Further studies regarding the development of other (4+2) annulations and applications of this method are ongoing and will be reported in due course.

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[18] CCDC 920167 (**5d**) 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.

