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Amine-promoted asymmetric [4+2] cycloadditions of α-acetoxymethyl allenoate and dual activated alkenes: stereoselective synthesis of poly-substituted cyclohexenes

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ABSTRACT

A chiral secondary amine-promoted asymmetric [4+2] cycloadditions of α-acetoxymethyl allenoate **1** and electron-deficient alkenes **2** have been developed. The reaction features the utilization of addition–elimination reaction between allenoate **1** and the secondary amine to generate the key 2-aminobutadiene intermediate, which subsequently undergoes [4+2] cycloaddition with alkenes in a stepwise fashion, delivering the substituted cyclohexenes with good stereoselectivity.

Since its discovery by Otto Diels and Kurt Alder in 1928,[1] the Diels–Alder reaction has been recognized as one of the most useful pericyclic reactions for the construction of cyclohexenes,[2] which has been widely used for the synthesis of numerous biologically active molecules[3] and natural products.[4] In this context, 2-aminobutadienes, derived from the condensation between α,β-unsaturated ketones and amines, are extremely valuable diene partners in the Diels–Alder reactions. For instance, the Enders group has elegantly developed the diastereoselective Diels–Alder reaction of dienamine with nitroalkenes based on a chiral auxiliary strategy.[5] In 2002, Barbas and co-workers reported the first amine-catalyzed direct [4+2] cycloaddition of α,β-unsaturated ketones with nitroalkenes.[6] Since then, the dienamine catalysis has added a powerful dimension to the Diels–Alder reactions.[7] From the mechanistic viewpoint, the key 2-aminobutadiene intermediates are generally formed via the 1,2-addition of the amine catalyst to the enone followed by H_2O elimination (Scheme 1, Eq. 1). Despite extensive studies and noteworthy advances in this field, the utilization of 2-methylene-3-oxobutanoate as α,β-unsaturated ketone substrate remains challenging. This may be attributed to the preferential 1,4-addition of amine,[8] thus rendering the desired formation of 2-aminobutadiene intermediate **A** less competitive (Scheme 1, Eq. 2). In 2013, our group successfully developed an efficient route to 2-aminobutadiene **A** using a process of 1,4-addition of amine to 2-acetoxymethyl allenoate **1** and subsequent 1,2-elimination of the acetate group (Scheme 1, Eq. 3).[9] The resulted dienamine **A** exhibits excellent diene reactivity toward the aza-Diels–Alder reaction with imine. As our ongoing interest in the transformations of allenoate,[10] we herein report the amine-promoted asymmetric [4+2] cycloadditions of 2-acetoxymethyl allenoate **1** with dual activated alkenes, which provide a facile access to the poly-substituted cyclohexenes with good stereoselectivity.

We commenced our investigation with the assessment of the reaction of **1** and 2-cyano-acrylate **2a** using our previously established experimental procedure, in which the amine-mediated cycloaddition and subsequent acidic hydrolysis were conducted in one pot. To our delight, with the assistance of the secondary amine (*S*)-**4a** (1.2 equiv) and K_3PO_4–$3H_2O$ (1.2 equiv), the desired cycloaddition product **3a** was isolated in as high as 98% yield albeit with low diastereoselectivity (Table 1, entry 1). Moreover, the major isomer ***trans*-3a** was afforded with 40% ee. The structural assignment of ***trans*-3a** was corroborated by X-ray crystallography of product **3g** (vide infra). To improve the stereoselectivity, the chiral secondary amine was further examined. Unfortunately, amines **4b**, **4c**, and **4d** did not exhibit any superior performance over **4a** (Table 1, entries 2–4). On the basis of these results, other reaction parameters were further investigated. A slight improvement of the stereoselectivity was observed when the reaction conducted at

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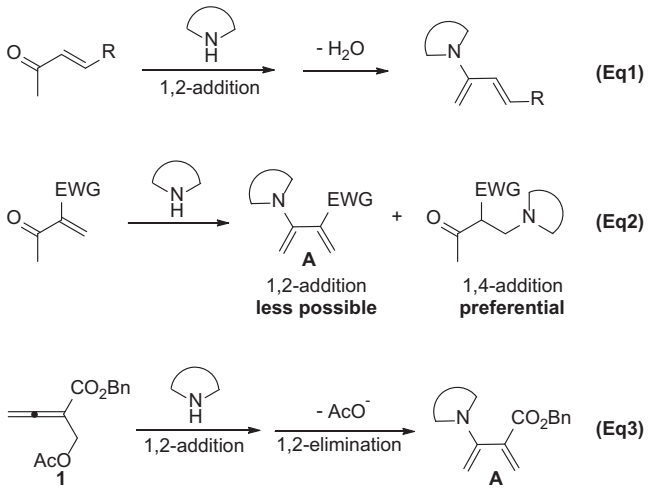


Scheme 1. Different routes to 2-aminobutadienes.

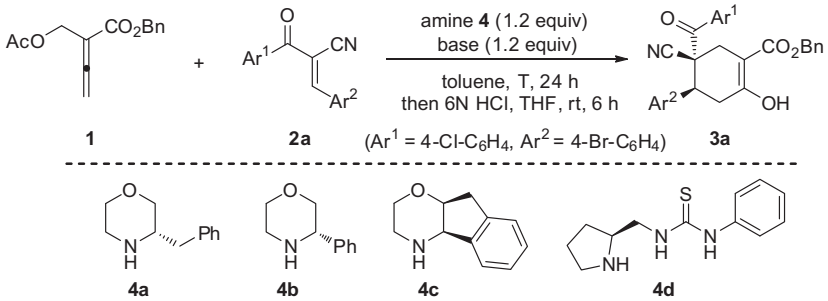
0 °C (Table 1, entry 5). The screening of base additive disclosed that Cs_2CO_3 was the optimal choice to give product **3a** with 49% enantioselectivity and 12.5:1 diastereoselectivity (Table 1, entry 11). Lower reaction temperature (−30 °C) improved the enantioselectivity to 66% while imposed a marginal effect on the diastereoselectivity (Table 1, entry 12). When the reaction was conducted at −45 °C, no improvement of stereoselectivity was observed and the isolated yield of **3a** dropped to 53% (Table 1, entry 13).

With the optimal reaction conditions in hand, we then turned our attention to the examination of substrate scope. As illustrated in Table 2, this one-pot method can be applied to an array of 2-cyano-acrylates **2**, affording the desired products in excellent yields and with moderate stereoselectivity. When the R^2 group of **2** was a 4-bromophenyl substituent, their R^1 groups with different electron properties (e.g., electron-neutral, -rich, or -deficient) were well tolerated and the corresponding products **3b**–**3f** were obtained in high yields with ca. 60% ee and 10:1 dr (Table 2, entries 1–6). Both 2-furyl and 2-thienyl groups were tolerated and products **3g**–**3h** were obtained with somewhat higher enantioselectivity and ca. 8:1 diastereoselectivity (Table 2, entries 7 and 8). The reaction of **2i** with an alkyl R^1 substituent also smoothly occurred, giving product **3i** with 62% ee and 10:1 dr (Table 2, entry 9). On the other hand, when R^1 of **2** was a 4-chlorophenyl group, the R^2 groups imposed little impact on the reaction yield while strongly affected the stereoselectivity (Table 2, entries 9–15). For instance, the reaction of substrate **2n** with a 2-bromophenyl group afforded product **3n** with 17:1 dr (Table 2, entry 13), implying a positive effect of steric hindrance on the diastereoselectivity.

The resulted products **3** could be further manipulated. Indeed, upon the treatment of **3g** with allyl carbonochloridate, allyl carbonate **5** was readily obtained, which was followed by the palladium-catalyzed decarboxylative alkylation under the Pd(0)/BINAP system,[11] affording compound **6** as a single isomer (Scheme 2).

The absolute configuration of **3g** was determined to be (4*S*,5*S*) by the X-ray crystal structure analysis.[12] The observed stereochemical outcome can be explained by the proposed mechanism depicted in Scheme 3. Firstly, the interaction between allonate **1** and amine **4a**, with the help of base additive, leads to the formation of dienamine **A**. We believe that the amine moiety in **A** might play dual steric effects on the asymmetric induction. One is to block the bottom face of **A** by its benzyl group. The other is to guide **2g** to approach from upper side in the fashion of *si*-face selectivity. As a result, intermediate **C** with (*S*)-configuration is enforced to be formed. Then, the newly formed stereocenter might control the intramolecular Michael addition, enabling the generation of thermodynamically favorable ***trans*-D**. Finally, intermediate **D** is hydrolyzed with aqueous hydrochloric acid to afford product ***trans*-3g** (Scheme 3).

Table 1
Condition optimization[a]



Entry	Amine	Base	*T* (°C)	Yield[b] (%)	ee[c] (%)	dr[d]
1	**4a**	K_3PO_4–$3H_2O$	rt	98	40	2.5:1
2	**4b**	K_3PO_4–$3H_2O$	rt	85	31	3:1
3	**4c**	K_3PO_4–$3H_2O$	rt	81	22	2:1
4	**4d**	K_3PO_4–$3H_2O$	rt	50	60	1:1
5	**4a**	K_3PO_4–$3H_2O$	0	97	45	4:1
6	**4a**	Et_3N	0	89	44	1.5:1
7	**4a**	DBU	0	90	45	2:1
8	**4a**	Na_2CO_3	0	90	51	1.7:1
9	**4a**	K_2CO_3	0	95	48	3:1
10	**4a**	Ag_2CO_3	0	85	40	2:1
11	**4a**	Cs_2CO_3	0	98	49	12.5:1
12	**4a**	Cs_2CO_3	−30	97	66	12.5:1
13	**4a**	Cs_2CO_3	−45	53	67	13:1

[a] Reaction conditions: **1** (0.2 mmol), **4** (1.2 equiv), **2a** (2 equiv), and base (1.2 equiv), toluene (2 mL), 24 h, then 6 N aqueous HCl (5 mL) and THF (5 mL), rt, 6 h.
[b] Combined isolated yield of ***trans***- and ***cis*-3a**.
[c] The ee of ***trans*-3a** was determined by HPLC.
[d] The diastereomer ratio was determined by ^{1}H NMR analysis of the crude reaction mixture.