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FULL PAPER

Cross-conjugated Trienamine Catalysis with α′-Alkylidene 2-Cyclohexenones: Application in β,γ-Regioselective Aza-Diels–Alder Reaction

Zhi Zhou,[a] Zhou-Xiang Wang,[a] Qin Ouyang,[b] Wei Xiao,[a] Wei Du,[a] and Ying-Chun Chen*[a,b]

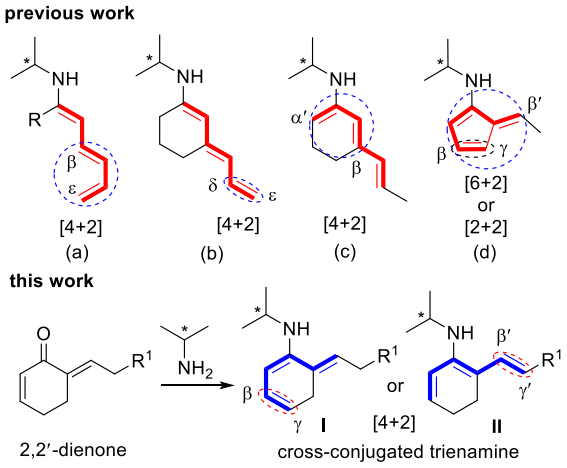
Dedication ((optional))

Abstract: *Endo*-type cross-conjugated trienamines between highly congested α′-alkylidene 2-cyclohexenones and a chiral primary amine catalyst serve as HOMO-raised dienophiles in inverse-electron-demand aza-Diels–Alder cycloadditions with a number of 1-azadiene substrates. The reactions exhibit exclusive β,γ-regioselectivity, and multifunctional products with high molecular complexity are efficiently constructed in excellent diastereo- and enantioselectivity (>19:1 *dr*, up to 99% *ee*).

Introduction

Over the past years, asymmetric trienamine catalysis of chiral amines has been established as a powerful protocol for the remote functionalization of polyconjugated carbonyl compounds in a highly stereoselective manner.[1] While β,ε-regioselective cycloaddition reactions were commonly observed for 2,4-dienal molecules,[2,3] the structural complexity of the analogous dienone substrates enables more versatile strategies for the development of a variety of regioselective reactions. The similar β,ε-regioselective normal-electron-demand Diels–Alder cycloadditions as those of 2,4-dienals have been furnished with linear 2,4- or 3,5-dienones through the formation of extended trienamine species (Scheme 1, a).[4] In addition, the application of interrupted β-allylic cyclic enones could accomplish either δ,ε-regioselective inverse-electron-demand cycloadditions or ε-regioselective bisvinylogous additions (Scheme 1, b).[5] In contrast, cross-conjugated trienamine intermediates would be preferably generated with cyclic 2,4-dienone materials in the presence of a primary amine catalyst, and α′,β-regioselective formal [4+2] cycloadditions would occur with electron-deficient dienophiles (Scheme 1, c).[6] As a result, the application of structurally diverse polyunsaturated ketone substrates may have high potentials to uncover new reaction modes via amine-based catalysis.

To the best of our knowledge, the direct β,γ-regioselective functionalization of cyclic enone substrates via aminocatalysis has been less explored.[7] Recently, we successfully established the diversified intermolecular asymmetric cycloaddition reactions of α′-alkylidene 2-cyclopentenones catalyzed by cinchona-derived primary amines. The γ,β′-regioselective [6+2] and β,γ-regioselective [2+2] cycloadditions were developed through the in situ generation of formal 4-aminofulvene intermediates (Scheme 1, d).[8] Inspired by this success, we envisaged that the cross-trienamine intermediates generated from the analogous α′-alkylidene 2-cyclohexenones and a primary amine would participate in different kinds of regioselective cycloaddition reactions, either in an *endo*-**I** or an *exo*-**II** pattern. As a result, the HOMO-raised β,γ- or β′,γ′-C=C bond might perform as an ideal dienophile partner in an inverse-electron-demand Diels–Alder-type cycloaddition reaction with an electron-deficient diene,[9,10] successfully furnishing a previously undisclosed reactive version with cyclic enone substances (Scheme 1).



Scheme 1. Diverse trienamine modes of various dienone substrates.

Results and Discussion

Consequently, the initial screening studies were conducted with readily available α′-propylidene cyclohexen-2-one[11] **1a** and a variety of electron-deficient dienes. It was pleasing that 3-styryl-1,2-benzoisothiazole-1,1-dioxide[12] **2a**

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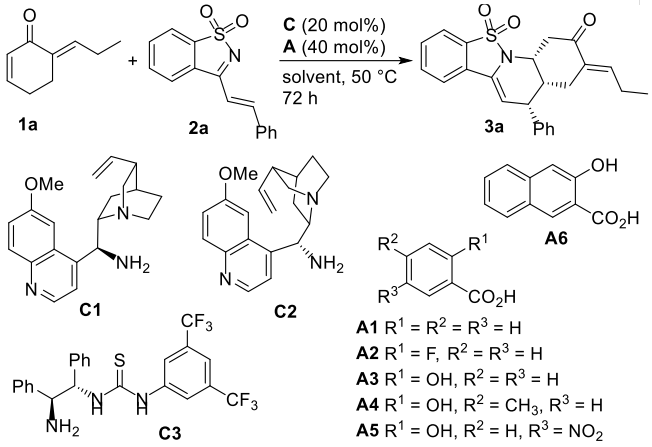
Table 1. Screening studies of [4+2] cycloaddition of α′-propylidene cyclohexen-2-one **1a** and 1-azadiene **2a**[a]



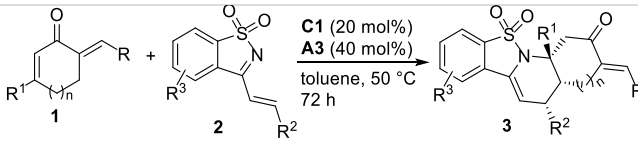
Entry	1	Solvent	Acid	Yield (%)[b]	*ee* (%)[c]
1	**C1**	Toluene	**A1**	62	86
2	**C2**	Toluene	**A1**	65	–73
3	**C3**	Toluene	**A1**	Trace	/
4	**C1**	Toluene	**A2**	63	85
5	**C1**	Toluene	**A3**	76	93
6	**C1**	Toluene	**A4**	74	92
7	**C1**	Toluene	**A5**	73	90
8	**C1**	Toluene	**A6**	59	78
9	**C1**	$CHCl_3$	**A3**	71	86
10	**C1**	$PhCF_3$	**A3**	78	89
11	**C1**	*m*-Xylene	**A3**	68	91
12	**C1**	THF	**A3**	Trace	/
13	**C2**	Toluene	**A3**	72	–83
14[d]	**C1**	Toluene	**A3**	70	92

[a] Unless noted otherwise, reactions were performed with 2,2′-dienone**1a** (0.2 mmol), 1-azadiene **2a** (0.1 mmol), amine **C** (20 mol%) and acid **A** (40 mol%) in solvent (1.0 mL) at 50 °C for 72 h. [b] Isolated yield. [c] By HPLC analysis on a chiral stationary phase; *dr* >19:1 by ^{1}H NMR analysis. [d] At 0.5 mmol scale (for **2a**).

was a suitable partner, and the desired aza-Diels–Alder cycloaddition[13] occurred smoothly in toluene at 50 °C, using 9-amino-9-deoxyepiquinine **C1** and benzoic acid **A1** as the catalysts.[14] In addition, the reaction exhibited exclusive β,γ-regioselectivity and *endo*-selectivity, and cycloadduct **3a** was isolated in 62% yield after 72 h, along with a good *ee* value (Table 1, entry 1). 9-Amino-9-deoxyepiquinidine **C2** gave the product with an opposite configuration in moderate enantiocontrol (Table 1, entry 2). Nevertheless, bifunctional catalyst **C3** could not catalyze the reaction (Table 1, entry 3).[15] Subsequently, an array of acid additives were tested in combination with amine **C1** (Table 1, entries 4–8), and salicylic acid **A3** gave the best results (Table 1, entry 5). Later, a few solvents were explored with amine **C1** and acid **A3** (Table 1, entries 9–12), but inferior results were generally obtained, and even no reaction happened in THF (Table 1, entry 12). We further investigated the reaction with amine **C2** and salicylic acid **A3**, and a better *ee* value was also obtained (Table 1, entry 13). Finally, it was found that the reaction proceeded smoothly at a larger scale catalyzed by **C1** and **A3**, and the similar good data were attained (Table 1, entry 14).

With the optimized catalytic conditions in hand, we then investigated a variety of α′-alkylidene cyclic ketones and 3-vinyl-1,2-benzoisothiazole-1,1-dioxides under the catalysis of amine **C1** and acid **A3**. The results are summarized in Table 2. At first, a number of cyclohexen-2-ones bearing variously structured α′-alkylidene substitutions were explored in reactions with 1-azadiene **2a**. It was pleasing that 2,2′-dienones with either linear or branched β′-alkyl groups could be well tolerated, and excellent enantioselectivity was generally obtained (Table 2, entries 1–10). In addition, 2,2′-dienones with β′-aryl or -heteroaryl substitutions also exhibited comparable reactivity, and high to outstanding enantiocontrol was observed (Table 2, entries 11–14). It was noteworthy that a 2,2′-dienone bearing a β-methyl group still showed good reactivity, and product **3o** with a quaternary chiral center was smoothly produced (Table 2, entry 15). Nevertheless, the analagous cyclopenten-2-ones generally showed much lower reactivity probably due to the more congested structures, and only a low yield with a moderate *ee* value was obtained for an α′-isopropylidene substrate (Table 2, entry 16). On the other hand, an array of 1-azadienes with diverse aryl or heteroaryl groups were further explored, and the corresponding cycloadducts were produced in high to excellent enantioselectivity (Table 2, entries 17–27). Unfortunately, 1-azadienes with alkyl substitutions failed to participate in the cycloaddition reactions. Moreover, a few substrates were studied by the catalysis of amine **C2** and acid **A3**, and the cycloadducts with an opposite configuration were generally furnished with good enantioselectivity (data in parentheses).

Table 2. Substrate scope and limitations of [4+2] cycloadditions[a]



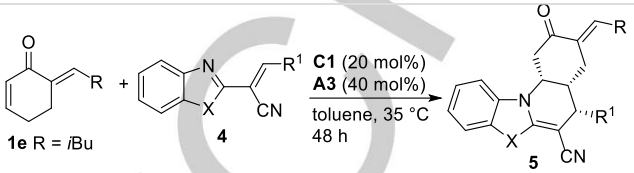
Entry	R, R^1	R^2, R^3	Yield (%)[b]	*ee* (%)[c]
1	Et, H	Ph, H	**3a**, 76 (72)	93 (–83)
2	Me, H	Ph, H	**3b**, 75	81

3	*n*Pr, H	Ph, H	**3c**, 78 (73)	96 (–85)
4	*n*Pent, H	Ph, H	**3d**, 76	93
5	*i*Bu, H	Ph, H	**3e**, 80	95
6	$PhCH_2CH_2$, H	Ph, H	**3f**, 83 (72)	91 (–81)
7	*i*Pr, H	Ph, H	**3g**, 82	97
8	3-Pent, H	Ph, H	**3h**, 81 (74)	98 (–94)
9	*c*Pent, H	Ph, H	**3i**, 78	93
10	*c*Hex, H	Ph, H	**3j**, 82 (78)	99 (–91)
11	Ph, H	Ph, H	**3k**, 82	95[d,e]
12	4-$MeOC_6H_4$, H	Ph, H	**3l**, 78	86[e]
13	4-$NO_2C_6H_4$, H	Ph, H	**3m**, 76	90[e]
14	2-Thienyl, H	Ph, H	**3n**, 72	86[e]
15	Ph, Me	Ph, H	**3o**, 72	89
16[f]	*i*Pr, H	Ph, H	**3p**, 36	77
17	*i*Bu, H	3-ClC_6H_4, H	**3q**, 81	90
18	*i*Bu, H	2-F-4-BrC_6H_3, H	**3r**, 76	92
19	*i*Bu, H	4-BrC_6H_4, H	**3s**, 85	90
20	*i*Bu, H	3-MeC_6H_4, H	**3t**, 80	91
21	*i*Bu, H	2-$MeOC_6H_4$, H	**3u**, 76	95
22	*i*Bu, H	4-$MeOC_6H_4$, H	**3v**, 78	91
23	*i*Bu, H	2-Thienyl, H	**3w**, 82	92
24	$PhCH_2CH_2$, H	4-BrC_6H_4, H	**3x**, 81	91
25	$PhCH_2CH_2$, H	4-$MeOC_6H_4$, H	**3y**, 72	89
26	*i*Bu, H	Ph, 5,7-Me_2	**3z**, 82	90
27	*i*Bu, H	Ph, 6-Cl	**3aa**, 78	93

[a] Unless noted otherwise, reactions were performed with cyclohexen-2-one derivative **1** (0.2 mmol) and 1-azadiene **2** (0.1 mmol), amine **C1** (20 mol%), acid **A3** (40 mol%) in toluene (1.0 mL) at 50 °C for 72 h. Data in parentheses were obtained with amine **C2**. [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase; *dr* >19:1 by ^{1}H NMR analysis. [d] The absolute configuration of **3k** was determined by X-ray analysis.[16] The other products were assigned by analogy. [e] The *ee* value was determined after derivation, see the SI. [f] Cyclopenten-2-one derivative was used.

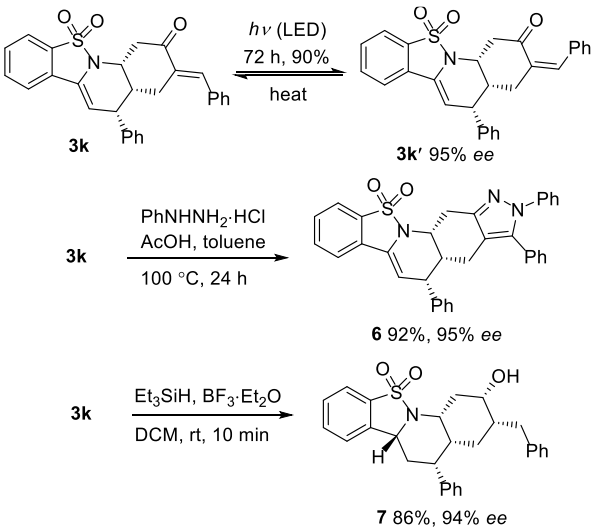
Apart from the 1-azadienes derived from saccharins, we found that the much less explored 2-vinyl-benzo[*d*]oxazoles[17] **4** also demonstrated to be good partners in cycloaddition reactions with α′-alkylidene cyclic enones under the same catalytic conditions. As summarized in Table 3, a spectrum of benzo[*d*]oxazole derivatives with aryl, heteroaryl or even alkyl substitutions could be smoothly utilized, and the complex heterocyclic systems **5a**–**g** were produced in moderate yields with high enantioselectivity (Table 3, entries 1–7). In addition, the benzo[*d*]thiazole analogue showed comparable reactivity, and an excellent *ee* value was obtained for product **5h** (Table 3, entry 8).

Table 3. Asymmetric aza-Diels–Alder reaction of benzo[*d*]oxazole- or benzo[*d*]thiazole-based 1-azadienes **4**[a]



Entry	X	R^1	Yield (%)[b]	*ee* (%)[c]
1	O	Ph	**5a**, 76	92
2	O	4-FC_6H_4	**5b**, 76	92
3	O	3-BrC_6H_4	**5c**, 75	91
4	O	4-MeC_6H_4	**5d**, 72	91
5	O	2-$MeOC_6H_4$	**5e**, 70	89
6	O	2-Thienyl	**5f**, 78	90
7	O	*i*Pr	**5g**, 74	93
8	S	Ph	**5h**, 65	98

[a] Reactions were performed with 2,2′-dienone **1** (0.2 mmol), 1-azadiene **4** (0.1 mmol), amine **C1** (20 mol%) and acid **A3** (40 mol%) in toluene (1.0 mL) at 35 °C for 48 h. [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase; *dr* >19:1 by ^{1}H NMR analysis.



Scheme 2. Synthetic transformations of cycloadduct **3k**.

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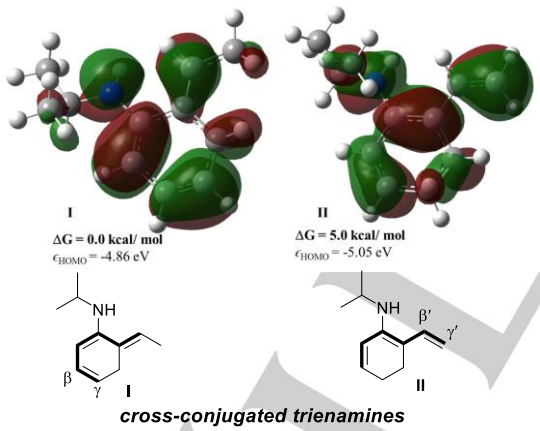
Interestingly, cycloadduct **3k** could be isomerized to the *Z*-configured product **3k′** in a high yield, simply by the irradiation of a LED lamp, while the inverse conversion could be realized by heating (Scheme 2). Additionally, the enone functional group of **3k** efficiently reacted with phenylhydrazine to furnish a pyrazole derivative **6**. Importantly, the full reduction of both enone and enamide functionalities could be smoothly achieved with Et_3SiH and $BF_3{\cdot}Et_2O$, and the product **7** was obtained in exclusive diastereocontrol.

In order to get some insight into the regioselectivity, density functional theory (DFT) calculations were performed to analyze the possibility and reactivity of the simplified cross-conjugated trienamine intermediates, either in an *endo*-**I** or an *exo*-version **II**. The geometries of **I** and **II** were optimized at b3lyp/6-31G(d) level. The energies were calculated at b3lyp/6-31G++(d,p) level (toluene as solvent). As shown in Scheme 3, the Gibbs free energy of intermediate **I** was 5.0 kcal/mol lower than that of intermediate **II**, which suggested that the *endo*-version **I** might be more stable than the *exo*-version **II** in the balance of diverse trienamine modes. Since the raise of the energy of the highest occupied molecular orbital (ϵ_{HOMO}) of dienophile partner in the inverse-electron-demand Diels–Alder-type reaction would reduce HOMO-LUMO energy gap, and further promote the reaction, the ϵ_{HOMO} of both intermediates were also studied, showing that ϵ_{HOMO} of **I** was 0.19 eV higher than that of **II**. These results implied that the intermediate **I** had not only higher stability but also higher reactivity to promote the inverse-electron-demand Diels–Alder-type reaction, which were consistent with our experimental results.



Scheme 3. DFT calculation study on the trienamine intermediates.

Conclusions

We have investigated the reactions of α′-alkylidene 2-cyclohexenone substrates under the catalysis of cinchona alkaloid based primary amines. *Endo*-type cross-conjugated trienamine intermediates were preferably generated, which subsequently served as ideal dienophiles in inverse-electron-demand aza-Diels–Alder cycloadditions with diversely structured electron-deficient 1-azadienes. These reactions also exhibited exclusive β,γ-regioselectivity and *endo*-diastereoselectivity, and a number of fused heterocyclic systems were efficiently constructed with moderate to excellent enantioselectivity (up to 99% *ee*), which might be useful in medicinal chemistry. We believe that the new trienamine mode with congested 2,2′-dienones would have high potentials to design more asymmetric reactions, and even accomplish some novel reaction pathways. More results will be reported in due course.

Experimental Section

General

For the synthesis of starting materials, full characterization data, NMR spectra, and HPLC traces, see the Supporting Information.

General procedure for amine-catalyzed aza-Diels–Alder reaction

The reaction was carried out with α′-alkylidene cyclic enone **1** (0.2 mmol), 1-azadiene **2** (0.1 mmol), amine **C1** (0.02 mmol) and salicylic acid **A3** (0.04 mmol) in dry toluene (1.0 mL) at 50 ºC until consumption of **2**, which was monitored by TLC analysis. Purification by flash chromatography on silica gel (EtOAc/petroleum ether) gave the *endo*-cycloadduct **3**.

(4a*R*,5*S*,12a*R*,*E*)-5-Phenyl-3-propylidene-3,4,4a,5-tetrahydro-1*H*-benzo[4,5]isothiazolo[2,3-a]quinolin-2(12a*H*)-one 11,11-dioxide (3a): Obtained as a white solid in 76% yield after flash chromatography and the enantiomeric excess was determined to be 93% by HPLC analysis on Chiralpak AD-H column (30% 2-propanol/*n*-hexane, 1 mL/min), UV 254 nm, t_{major} = 13.79 min, t_{minor} = 18.40 min; $[\alpha]_D^{20}$ = +28.6 (*c* = 1.60 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): *δ* (ppm) 7.82 (d, *J* = 8.4 Hz, 1H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.65 (t, *J* = 7.2 Hz, 1H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.43-7.40 (m, 2H), 7.35-7.33 (m, 1H), 7.29-7.26 (m, 2H), 6.72 (t, *J* = 6.6 Hz, 1H), 5.82 (m, 1H), 4.45 (m, 1H), 4.26 (m, 1H), 3.66 (dd, *J* = 18.6 Hz, 1.8 Hz, 1H), 2.74 (dd, *J* = 18.6 Hz, 3.6 Hz, 1H), 2.60 (m, 1H), 2.30 (m, 1H), 2.02 (dd, *J* = 16.8 Hz, 4.8 Hz, 1H), 1.80 (m, 2H), 0.90 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): *δ* (ppm) 195.3, 144.0, 140.4, 133.2, 133.1, 132.8, 131.6 130.1, 129.5, 128.7, 127.9, 127.3, 121.2, 120.8, 112.5, 102.9, 53.8, 43.5, 41.6, 38.0, 23.2, 21.1, 12.5; ESI-HRMS: calcd. for $C_{24}H_{23}NO_3S$+Na^+ 428.1296, found 428.1299.

(4a*R*,5*R*,12a*R*,*E*)-3-(3-Methylbutylidene)-2-oxo-5-phenyl-2,3,4,4a,5,12a-hexahydro-1*H*-benzo[4,5]oxazolo[3,2-a]quinoline-6-carbonitrile (5a): Obtained as a white solid in 76% yield after flash chromatography and the enantiomeric excess was determined to be 92% by HPLC analysis on Chiralpak AD-H column (40% 2-propanol/*n*-hexane, 1 mL/min), UV 254 nm, t_{major} = 6.83 min, t_{minor} = 11.26 min; $[\alpha]_D^{20}$ = –31.1 (*c* = 1.10 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* (ppm) 7.41-7.31 (m, 3H), 7.26-7.23 (m, 3H), 7.17 (t, *J* = 7.6 Hz, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.92-6.86 (m, 2H), 4.58 (m, 1H), 3.70 (d, *J* = 10.4 Hz, 1H), 2.99 (dd, *J* = 18.0 Hz, 5.6 Hz, 1H), 2.71 (dd, *J* = 18.0 Hz, 10.8 Hz, 1H), 2.63 (dd, *J* = 16.8 Hz, 2.4 Hz, 1H), 2.50 (m, 1H), 2.39 (m, 1H), 1.99-1.75 (m, 3H), 0.94 (d, *J* = 6.4 Hz, 3H), 0.90 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): *δ* (ppm) 195.6, 159.4, 146.8, 142.7, 140.2, 131.5, 130.6, 128.9, 128.4, 127.9, 124.4, 122.4, 119.7, 118.5, 112.5, 110.3, 106.8, 55.9, 50.7, 40.5, 40.3, 38.7, 37.0, 28.2, 26.6, 22.7, 22.3; ESI-HRMS: calcd. for $C_{27}H_{26}N_2O_2$+Na^+ 433.1886, found 433.1890.

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Keywords: organocatalysis • trienamine • regioselectivity • cyclic enones • aza-Diels–Alder cycloaddition

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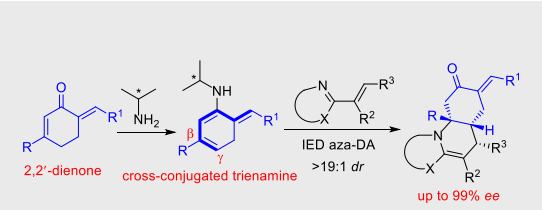

Endo-type cross-conjugated trienamines between α′-alkylidene 2-cyclohexenones and a chiral primary amine catalyst serve as HOMO-raised dienophiles in inverse-electron-demand aza-Diels–Alder cycloadditions with a number of 1-azadiene substrates. A diversity of chiral heterocyclic systems were efficiently constructed in excellent stereoselectivity.

*Zhi Zhou, Zhou-Xiang Wang, Qin Ouyang, Wei Xiao, Wei Du, and Ying-Chun Chen**

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