Asymmetric Synthesis

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A Concise Assembly of Electron-Deficient 2,4-Dienes and 2,4-Dienals: Regio- and Stereoselective *exo*-Diels–Alder and Redox Reactions through Sequential Amine and Carbene Catalysis**

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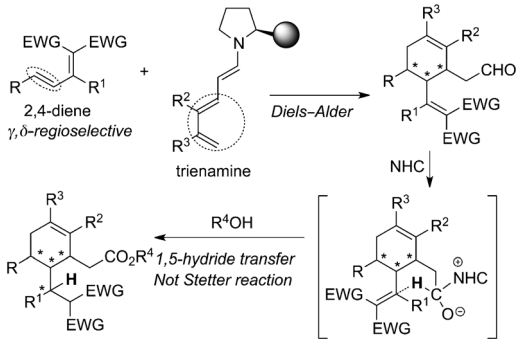
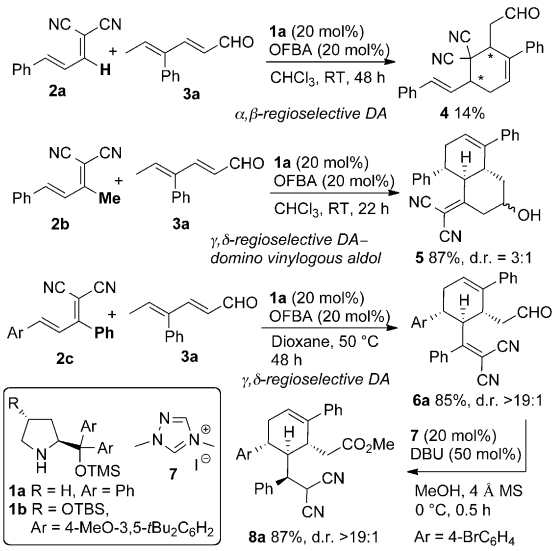
The use of a hydride donor for transfer hydrogenation of electrophilic carbonyl, imine, or activated alkene groups has been established as one of the most powerful tools in organic synthesis. A number of hydride donors, such as alcohols, formic acid, or Hantzsch esters, have been successfully applied under either metal- or organocatalysis.[1] Interestingly, the inherent electrophilic aldehyde group that contains a C–H bond, has been also elegantly used in rhodium-catalyzed hydroacylation reactions through C–H activation.[2] More importantly, in 2006, Scheidt and co-workers firstly reported that organic N-heterocyclic carbenes (NHCs) could mediate the hydroacylation of activated ketones with aldehydes through hydride transfer,[3] rather than the traditional acyl anion transfer pathway (benzoin reaction).[4] This protocol was compatible to a variety of aldehydes and activated ketones;[5] nevertheless, to our knowledge, there is still no report on the conjugate reduction of activated alkenes through hydride transfer from aldehyde compounds under the catalysis of NHCs, probably because the acyl anion transfer version (Stetter reaction) is more competitive.[4]

Recently, we and other groups disclosed a new trienamine reactive mode of 2,4-dienal substrates, which demonstrated to be successful in asymmetric Diels–Alder reactions with diverse electron-deficient dienophiles through HOMO activation.[6] Such a catalytic tool is tolerant to a broad spectrum of functional groups, thus giving versatile synthetic opportunities to construct chiral compounds with high molecular complexity. We envisaged that a γ,δ-regioselective Diels–Alder cycloaddition of electron-deficient 2,4-dienes with 2,4-dienals might be developed by using trienamine activation, as proposed in Scheme 1. Thus, the obtained multifunctional cycloadducts could serve as ideal substrates for the study of a carbene-catalyzed conjugate reduction through 1,5-hydride transfer from an aldehyde group.[7] Nevertheless, such an unprecedented sequence might be highly challenging, because the perfect control on regio-, chemo-, and stereoselectivity must be achieved in both amine- and carbene-catalyzed steps.[8]



Scheme 1. Proposed Diels–Alder and redox reactions through sequential amine and carbene catalysis. EWG = electron-withdrawing group.

The initial reaction of electron-deficient 2,4-diene **2a** from cinnamaldehyde and malononitrile and 2,4-dienal **3a** in the presence of chiral amine **1a**[9] (Scheme 2) was complicated owing to poor regioselectivity and other reaction patterns,[10]



Scheme 2. Rational design of electron-deficient 2,4-diene substrates to realize γ,δ-regioselective Diels–Alder (DA) and redox reactions. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; OFBA = *o*-fluorobenzoic acid; TMS = trimethylsilyl; TBS = *tert*-butyldimethylsilyl.

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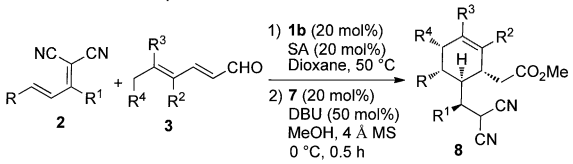
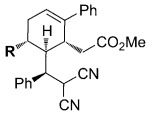
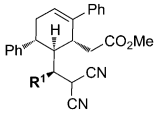
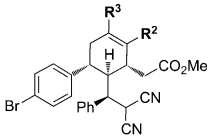
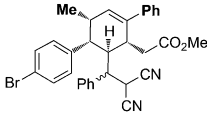
and product **4** was mainly isolated but still in a very low yield. We reasoned that γ,δ-regioselectivity might be facilitated by introducing a substituent at the β-position to increase steric hindrance. In fact, the expected cycloaddition took place smoothly with 2,4-diene **2b**, but a domino intramolecular vinylogous[11] aldol reaction occurred to give the bicyclic product **5** as a diastereomeric mixture.[12] Consequently, the β-phenyl-substituted 2,4-diene **2c** without an active γ-C–H group was employed, and the γ,δ-regioselective cycloadduct **6a** was pleasingly produced in a high yield in 1,4-dioxane, with exclusive anomalous *exo* control even at higher temperature. As a result, the bulky benzylidenemalononitrile motif would not only act as a highly electron-withdrawing group, but also significantly contribute to abnormal *exo* selectivity, probably because of steric reason.[13] More importantly, it was found that Scheidt's triazolium salt **7** was a good carbene precursor for the designed 1,5-hydride transfer reaction.[12] The diastereoselective conjugate reduction of activated alkene **6a** took place efficiently in methanol, and ester product **8a** was obtained as a single diastereomer. It should be noted that the Stetter reaction product was not detected under the current catalytic conditions. Therefore, the presence of another β-substituent on the skeleton of the 2,4-diene is crucial for the success of both γ,δ-regioselective Diels–Alder and redox reactions, probably because the generation of an all-carbon quaternary center is unfavorable in the other reaction pattern.

After having established the Diels–Alder and intramolecular 1,5-hydride transfer pathways of 2,4-diene **2c** and 2,4-dienal **3a**, we turned our attention to develop a one-pot asymmetric version. We found that the reaction failed when simultaneously combining amine and carbene catalysis together; however, the later redox reaction could proceed smoothly by directly adding triazolium salt **7** (20 mol%), DBU (50 mol%), and methanol to the finished Diels–Alder solution without further workup.[12] Salicylic acid was found to be a superior additive in the Diels–Alder reaction step, and a remarkable *ee* value (98%) was obtained for product **8a** by employing the bulky amine **1b** (Scheme 2) developed in our group (Table 1).[14]

Consequently, we explored the reactions of a variety of 2,4-dienes **2** and 2,4-dienals **3** in the presence of amine **1b** in combination with salicylic acid. Then the intramolecular redox reaction was directly carried out to give the ester products **8**. The results are summarized in Table 1. The one-pot Diels–Alder/redox sequence exhibited excellent diastereoselectivity, and a single diastereomer was generally produced. 2,4-Dienes **2** bearing diverse δ-aryl groups with either electron-donating or -withdrawing substitutions or heteroaryl groups were well-tolerated in reactions with 2,4-dienal **3a**, and the corresponding products **8a**–**8k** were produced with outstanding *ee* values and moderate to good yields (Table 1, entries 1–11). Notably, 2,4-dienes bearing branched alkyl groups at δ-position were also compatible, giving the expected products **8l** and **8m** with good data (Table 1, entries 12 and 13).[15] Furthermore, diverse aryl or heteroaryl groups were tolerated at the β-position of 2,4-dienes **2**, and products **8n**–**8q** were obtained in similar good results (Table 1, entries 14–17). Notably, the domino vinylogous aldol reaction as that of **2b** (Scheme 2) did not happen

Table 1: Substrate scope and limitations.[a]



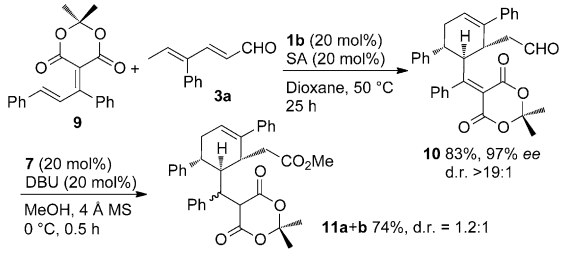
Entry	Product **8**		*t* [h][b]	Yield [%][c]	*ee* [%][d]
1		**8a** R = 4-BrC_6H_4	12	72	98
2		**8b** R = 2-ClC_6H_4	15	73	98[e]
3		**8c** R = 3-ClC_6H_4	24	75	99
4		**8d** R = 4-$CF_3C_6H_4$	12	72	96
5		**8e** R = 4-Br-2-FC_6H_3	12	66	98
6		**8f** R = Ph	20	78	99
7		**8g** R = 4-$MeOC_6H_4$	40	61	97
8		**8h** R = 1-naphthyl	40	59	97
9		**8i** R = 2-furyl	60	76	96
10		**8j** R = 2-thienyl	60	69	96
11		**8k** R = 2-pyridyl	60	69	96
12		**8l** R = *i*Pr	17	59	96
13		**8m** R = *c*Hex	48	52	92
14		**8n** R^1 = 4-ClC_6H_4	40	59	97
15		**8o** R^1 = 3,4-$Cl_2C_6H_3$	22	55	93
16		**8p** R^1 = 4-MeC_6H_4	40	72	98
17		**8q** R^1 = 2-furyl	40	56	99
18		**8r** R^1 = *i*Pr	40	61	99
19		**8s** R^1 = *c*Hex	48	58	99
20		**8t** R^2 = R^3 = H	24	65	94
21		**8u** R^2 = H, R^3 = Me	20	62	88
22		**8v** R^2 = Et, R^3 = H	60	61	98
23		**8w** (d.r. = 2:1)	24	67	98/99

[a] Reactions were performed with diene **2** (0.12 mmol), 2,4-dienal **3** (0.1 mmol), amine **1b** (20 mol%), and salicylic acid (SA; 20 mol%) in dioxane (0.5 mL) at 50°C. After completion, salt **7** (20 mol%), DBU (50 mol%), 4 Å MS (30 mg), and MeOH (0.5 mL) were added at 0°C and stirred for 30 min. [b] For DA reaction step. [c] Yield of isolated product for two steps. [d] Determined by HPLC analysis using a chiral stationary phase. [e] The absolute configuration of **8b** was determined by X-ray analysis, see the Supporting Information.[16] The other products were assigned by analogy.

for 2,4-dienes with a branched alkyl group at the β-position. Thus, the following carbene-mediated redox reaction could be conducted to provide products **8r** and **8s**, also in exclusive diastereocontrol (Table 1, entries 18 and 19). Moreover, a few 2,4-dienals were further tested in reactions with 2,4-diene **2c**. Good data were afforded for products **8t**–**8v** (Table 1, entries 20–22), but a low d.r. value was observed for product **8w** from 4-phenyl-2,4-heptadienal in the redox step, probably because of the steric effect of the additional methyl substituent; nevertheless, the *ee* values were excellent for both separable diastereomers (Table 1, entry 23).

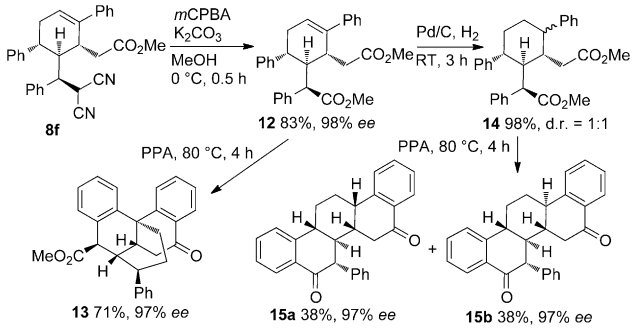
The γ,δ-regioselective Diels–Alder reaction of a 2,4-diene **9** from chalcone and Meldrum's acid with 2,4-dienal **3a** also proceeded smoothly catalyzed by amine **1b** and salicylic acid,

thereby leading to cycloadduct **10** in excellent diastereo- and enantioselectivity and with good yield. The carbene-mediated intramolecular redox reaction also took place efficiently, giving two separable diastereomers **11a** and **11b** in almost the same ratio. In comparison with the former substrates, such a low diastereoselectivity may be ascribed to the different structure of the Meldrum's acid motif. As a result, more stereodivergency could be introduced with this type of 2,4-dienes (Scheme 3).[17]



Scheme 3. Sequential Diels–Alder/redox reactions with substrate from Meldrum's acid.

The multifunctional properties of the products allow the further synthetic transformations to access complex, natural-product-like frameworks in high efficacy. As illustrated in Scheme 4, the malononitrile moiety of **8f** could be smoothly converted to a carboxylate group, giving compound **12** in



Scheme 4. Constructions of complex polycyclic structures. *m*CPBA = *m*-chloroperbenzoic acid.

a good yield.[18] Interestingly, a bridged product **13** bearing a highly congested all-carbon quaternary chiral center was produced in exclusive diastereocontrol by treating **12** with polyphosphoric acid (PPA), through double intramolecular Friedel–Crafts reactions.[12] Furthermore, the C=C bond of intermediate **12** could be hydrogenated to give a diastereomeric mixture **14**, which was also submitted to the treatment with PPA to produce separable steroid-like polycyclic architectures **15a** and **15b**.[19]

In conclusion, we have developed a highly stereo-, chemo-, and γ,δ-regioselective anomalous *exo*-Diels–Alder cycloaddition with electron-deficient β-substituted 2,4-dienes and 2,4-dienals by using a trienamine activation strategy. The resulting multifunctional cycloadducts contain perfectly positioned functional groups, which could undergo an unprecedented 1,5-hydride transfer from the C–H group of an aldehyde to an activated alkene under sequential catalysis of a carbene. A spectrum of diversely structured chiral products have been efficiently produced, thus allowing the concise constructions of polycyclic frameworks with high chemical and stereogenic complexity. Currently the development of an asymmetric version of hydride transfer with aldehydes is under investigation.

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[12] For more details, see the Supporting Information.

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[15] 2,4-Dienes with a linear alkyl group at the δ-position have not been produced yet.

[16] CCDC 909394 (**8b**) 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.

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