Asymmetric Synthesis

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Organocatalytic Asymmetric Inverse-Electron-Demand Diels–Alder Reaction of Electron-Deficient Dienes and Crotonaldehyde**

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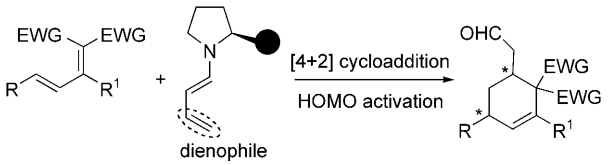
The catalytic asymmetric Diels–Alder reaction has been recognized as one of the most powerful and atom-economical protocols to construct chiral six-membered crabocycles. Over the past decades, numerous studies in this field have been presented involving LUMO-lowering activation of electron-deficient dienophiles by the catalysis of either metal-based[1] or organic molecules.[2] On the other hand, the frontier electron theory predicts that the suprafacial [4+2] cycloaddition could be controlled by the HOMO of the dienophile and the LUMO of the diene in the Diels–Alder reaction with inverse-electron-demand.[3] Although a diversity of asymmetric inverse-electron-demand hetero-Diels–Alder reaction has been well established,[4] examples of all-carbon-based catalytic asymmetric versions have been rarely reported,[5] and all fall into the LUMO-lowering strategy with the aid of Lewis acids.[6]

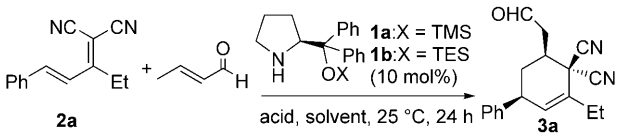
Recently our research group[7] has reported a highly α-regio- and stereoselective inverse-electron-demand aza-Diels–Alder reaction of α,β-unsaturated aldehydes by dienamine catalysis.[8] We observed a different reaction pattern for crotonaldehyde, from which the dienamine intermediate that is generated in situ exhibited β,γ-selectivity, but only moderate *ee* values were obtained. We envisaged that such catalytic activity might be applicable to a properly designed electron-deficient diene, as proposed in Scheme 1, thus an all-carbon-based asymmetric inverse-electron-demand Diels–Alder reaction could be developed via an unprecedented HOMO-controlling pathway for the dienophile.[9]

We initially investigated the possible reaction of readily available diene **2a** and crotonaldehyde catalyzed by the combination of secondary amine **1a** and benzoic acid in THF at 25 °C.[10] Pleasingly, the reaction proceeded smoothly, and diene **2a** was consumed after 24 hours. The desired Diels–Alder product **3a** was isolated in excellent enantioselectivity with a good d.r. ratio, while the yield was moderate owing to some side reactions (Table 1, entry 1; BA = benzoic acid). Solvent screening (Table 1, entries 2–5) indicated that higher yield could be obtained in toluene and 1,4-dioxane with the retention of stereoselectivity (Table 1, entries 4 and 5). Similar results were given when *o*-fluorobenzoic acid (OFBA) or acetic acid were used in 1,4-dioxane (Table 1, entries 6 and 7), but almost no reaction occurred in the absence of acid additive (Table 1, entry 8). In addition, slightly better results were afforded by using a higher concentration (compare Table 1, entry 9 and 10). A bulkier catalyst **1b** also provided similar stereocontrol, while a slower reaction rate was observed (Table 1, entry 11). Notably, a



Scheme 1. Proposed inverse-electron-demand Diels–Alder reaction by the HOMO-raising strategy. EWG = electron-withdrawing group

Table 1: Screening studies for the organocatalytic inverse-electron-demand Diels–Alder reaction.[a]



Entry	1	Solvent	Acid	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**1a**	THF	BA	57	88:12	96
2	**1a**	CH_2Cl_2	BA	45	87:13	94
3[e]	**1a**	MeCN	BA	37	81:19	88
4	**1a**	toluene	BA	70	90:10	98
5	**1a**	1,4-dioxane	BA	71	89:11	98
6	**1a**	1,4-dioxane	OFBA	75	90:10	97
7	**1a**	1,4-dioxane	AcOH	70	89:11	97
8	**1a**	1,4-dioxane	–	< 5	–	–
9[f]	**1a**	1,4-dioxane	BA	75	89:11	98 (85)[g]
10[h]	**1a**	1,4-dioxane	BA	64	89:11	98
11[f]	**1b**	1,4-dioxane	BA	63	91:9	97

[a] Unless noted otherwise, reactions were performed with 0.2 mmol of **2a**, 0.4 mmol of crotonaldehyde, 10 mol% of **1**, and acid in 2 mL of solvent at 25 °C for 24 hours. [b] Yield of isolated product. [c] Determined by ^{1}H NMR analysis. [d] Determined by HPLC on a chiral stationary phase after derivation (for the major isomer), see the Supporting Information. [e] Reaction time of 48 hours. [f] In 1 mL of solvent. [g] Data in parenthesis relate to the minor diastereomer. [h] In 4 mL of solvent. TES = triethylsilyl, THF = tetrahydrofuran, TMS = trimethylsilyl.

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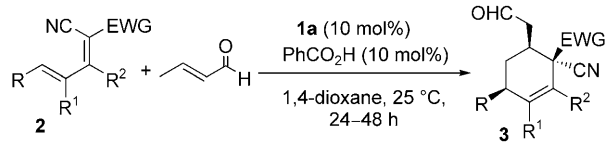
good *ee* value was also observed for the minor diastereomer (Table 1, entry 9).

Next, the new method for the synthesis of chiral cyclohexene derivatives was explored with a variety of dienes **2** and crotonaldehyde.[11] As summarized in Table 2, the reaction showed substantial generality resulting in broad substrate scope. Substitution at the δ position of the dienes had limited effect on the reaction outcomes. Excellent enantioselectivity with good d.r. ratios were obtained for a number of dienes bearing electron-withdrawing or -donating aryl and heteroaryl groups (Table 2, entries 1–10). Various substituents at the β position of the dienes could be well tolerated (Table 2, entries 11–15). Notably, a pentasubstituted diene also afforded good results (Table 2, entry 16). The dienes condensed from ethyl cyanoacetate and enals could be successfully utilized. The products possessing three chiral centers, including a quaternary carbon, were obtained in high enantio- and diastereoselectivity, while the yields were fair (Table 2, entries 17–19). Importantly, excellent stereocontrol was also gained for dienes bearing either δ-linear or -branched alkyl groups (Table 2, entries 20–22).

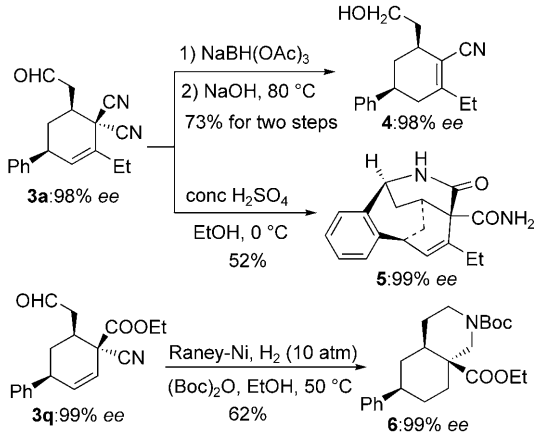
Table 2: Substrate scope of the organocatalytic Diels–Alder reaction.[a]



Entry	R	R^1, R^2	EWG	Product, yield [%][b]	d.r.[c]	*ee* [%][d]
1	Ph	H, Et	CN	**3a**, 75	89:11	98
2	*o*-ClC_6H_4	H, Et	CN	**3b**, 74	84:16	98
3	*m*-ClC_6H_4	H, Et	CN	**3c**, 67	89:11	98
4	*p*-ClC_6H_4	H, Et	CN	**3d**, 71	89:11	97
5	*p*-FC_6H_4	H, Et	CN	**3e**, 61	93:7	98
6	*p*-MeC_6H_4	H, Et	CN	**3f**, 72	90:10	97
7	*p*-$MeOC_6H_4$	H, Et	CN	**3g**, 68	90:10	97
8	1-napth	H, Et	CN	**3h**, 74	87:13	96
9	2-furyl	H, Et	CN	**3i**, 75	90:10	99
10	2-thienyl	H, Et	CN	**3j**, 72	87:13	97
11	Ph	H, Me	CN	**3k**, 76	81:19	94
12	Ph	H, *n*Pr	CN	**3l**, 68	89:11	99
13	Ph	H, *n*Pent	CN	**3m**, 72	90:10	96
14	Ph	H, *i*Bu	CN	**3n**, 70	87:13	99
15	Ph	H, H	CN	**3o**, 66	92:8	99
16	Ph	-$CH_2C_6H_4$-	CN	**3p**, 80	89:11	91
17	Ph	H, H	CO_2Et	**3q**, 44	94:6	99[e]
18	*m*-ClC_6H_4	H, H	CO_2Et	**3r**, 48	95:5	97
19	3,4-$Cl_2C_6H_3$	H, H	CO_2Et	**3s**, 52	93:7	96
20	Me	H, H	CO_2Et	**3t**, 45	92:8	99
21	*n*Pr	H, H	CO_2Et	**3u**, 43	90:10	99
22	*i*Pr	H, H	CN	**3v**, 57	86:14	98

[a] Reactions were performed with 0.2 mmol of **2**, 0.4 mmol of crotonaldehyde, 10 mol% of **1a**, and $PhCO_2H$ in 1 mL of 1,4-dioxane at 25 °C for 24–48 hours. [b] Yield of isolated product. [c] Determined by ^1H NMR analysis. [d] Determined by HPLC on a chiral stationary phase after derivation (for the major isomer), see the Supporting Information. [e] The absolute configuration of **3q** was determined by X-ray analysis after conversion into the 2,4-dinitrobenzenehydrozone derivative (see Figure 1).[12] The other products were assigned by analogy. napth = naphthyl.

We have performed some synthetic transformations with the multifunctional cycloadducts. As outlined in Scheme 2, the partial hydrolysis of one cyano group and subsequent decarboxylation could be easily realized by the treatment of the alcohol of **3a** with aqueous NaOH solution, thus affording a conjugate nitrile **4** without affecting the enantiopurity. Interestingly, under strong acidic conditions, a cascade cyano group hydrolysis/imine formation/Friedel–Crafts reaction of **3a** efficiently proceeded to deliver product **5** with a caged and bridged polycyclic framework, and whose structure was confirmed by X-ray analysis (see the Supporting Information).[12,13] In addition, a decahydroisoquinoline derivative **6** was smoothly constructed from **3q** (Figure 1) via a tandem cyano group hydrogenation/reductive amination reaction.[14]



Scheme 2. Synthetic transformations of cyclic adducts. Boc = *tert*-butoxycarbonyl.

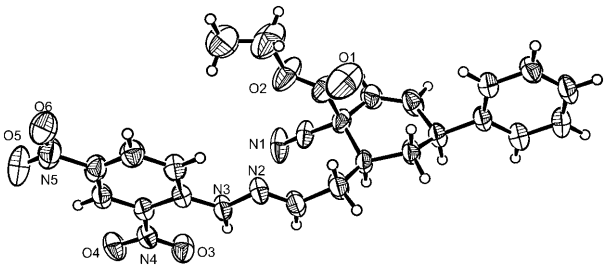


Figure 1. ORTEP plot of the 2,4-dinitrobenzenehydrozone derivative of enantiopure **3q** drawn with ellipsoids at 30% probability

In conclusion, we have developed the first organocatalytic asymmetric all-carbon-based inverse-electron-demand Diels–Alder reaction of electron-deficient dienes and crotonaldehyde through a HOMO-activation strategy.[15] Highly diastereo- and enantioenriched cyclohexene derivatives with substantial substitution diversity were smoothly delivered (up to 99% *ee*, d.r. up to 95:5). This method presented here may be helpful for expanding the utilities of unsaturated aldehydes

in aminocatalysis. More studies are currently underway and the results will be reported in due course.

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[11] Currently, other α,β-unsaturated aldehydes, such as 2-pentenal, were inert in this reaction and are yet to be explored further.

[12] CCDC 780401 (2,4-dinitrobenzenehydrozone derivative of **3q**) and CCDC 780402 (**5**) contain 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. The absolute configuration of the hydrozone derivative of **3q** was determined by anomalous dispersion effects in diffraction measurements on the crystal.

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[15] For the proposed catalytic mechanism of this cycloaddition reaction, see the Supporting Information.

