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PPh_3-catalyzed synthesis of dicyano-2-methylenebut-3-enoates as efficient dienes in catalytic asymmetric inverse-electron-demand Diels–Alder reaction†

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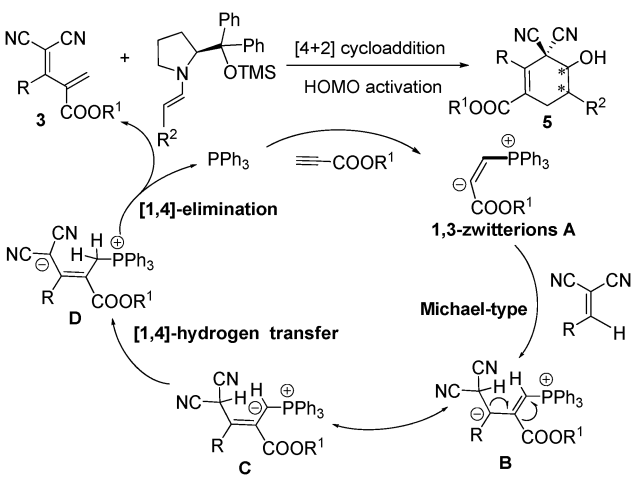
We present here the synthesis of dicyano-2-methylenebut-3-enoates as novel Diels–Alder dienes through an efficient PPh_3-catalyzed strategy, and an unprecedented PPh_3-catalyzed addition/all-carbon-based asymmetric inverse-electron-demand Diels–Alder sequence reaction is disclosed for the first time.

The catalytic asymmetric Diels–Alder reaction (DAR) has been recognized as one of the most powerful and convergent strategies for the stereoselective construction of six-membered functionalized cyclic frameworks, often containing multiple stereocenters. As a result of its importance and versatility in the synthesis of diverse natural products, organic chemists are paying increasing attention to the development of novel asymmetric methodologies in this field. Catalytic asymmetric variants of these [4 + 2] reactions have been achieved for different diene–dienophile combinations,[1] showing in several instances outstanding synthetic utility. On the other hand, compared with other classic reactions, it presents more difficulties due to the governing strict principle of generation of DAR including the suitable matching of diene with dienophile in accordance with the electronic orbital theory.[2] Indeed, a long-standing limitation for the progress of asymmetric DAR is the lack of appropriate and effective dienes. For these reasons, we wish to address our contribution to the novel diene development of Diels–Alder reaction through the synthesis of dicyano-2-methylenebut-3-enoates as novel Diels–Alder dienes *via* the PPh_3-catalyzed addition reaction of propiolates with α,α-dicyanoolefins.

Owing to the properties of strong nucleophilicity and ease of ylide formation, as well as leaving group ability, tertiary phosphanes as nucleophiles catalyzing the addition reactions[3] have attracted wide attention, and elegant examples have been reported.[4] However, to the best of our knowledge, there is no precedent for the PR_3-catalyzed reactions of alkyl propiolates and α,α-dicyanoolefins. We postulated that the reaction of alkyl propiolates with α,α-dicyanoolefins could be initiated, in the presence of PPh_3, by activating propiolates to generate the 1,3-zwitterions **A**,[5] which undergo Michael-type reaction with dicyanoolefins to give intermediates **B**. Due to the ability of PPh_3 to stabilise an adjacent carbanion, intermediates **B** may coexist with intermediates **C**. Subsequent [1,4]-hydrogen transfer of intermediates **B** or **C** formed the intermediates **D**. Finally, the catalytic cycle was completed by [1,4]-elimination of PPh_3, and dicyano-2-methylenebut-3-enoates **3** were afforded (Scheme 1). Our next studies were motivated by dicyano-2-methylenebut-3-enoates as dienes in frontier-molecular-orbital-controlled DAR with the HOMO of dienophiles *via* an enamine-activated system. Recently, Jøgensen and co-workers[6] reported the first catalytic asymmetric inverse-electron-demand Diels–Alder reaction (IEDDAR)[7] of aliphatic aldehydes with α,β-unsaturated α-ketoesters through enamine activation.[8] The reaction generally exhibited high stereoselectivity with the characteristics of a concerted HOMO of dienophiles mechanism by *in situ* generation of the electron-rich chiral enamine. Afterwards, although several organocatalytic asymmetric IEDDAR have been well described, to date, examples of all-carbon-based catalytic asymmetric versions[8a,9] are surprisingly scarce. Undoubtedly, the novel diene-led development of



Scheme 1 PPh_3-catalyzed synthesis of dicyano-2-methylenebut-3-enoates as dienes in catalytic asymmetric IEDDAR.

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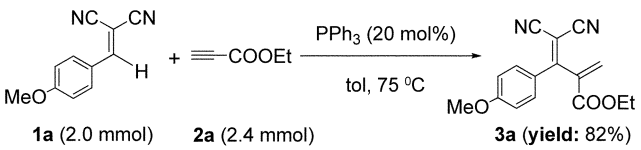
all-carbon-based asymmetric IEDDAR is particularly appealing. Herein, we present an all-carbon-based asymmetric IEDDAR of novel dicyano-2-methylenebut-3-enoates with aliphatic aldehydes by employing a similar strategy (Scheme 1), and disclose an unprecedented PPh_3-catalyzed addition/all-carbon-based asymmetric inverse-electron-demand Diels–Alder sequence reaction.

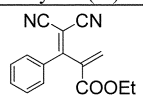
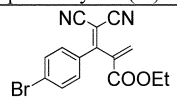
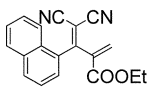
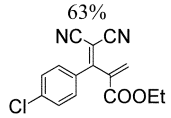
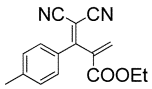
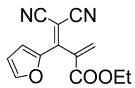
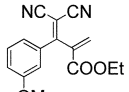
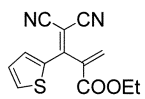
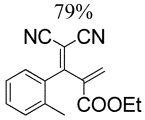
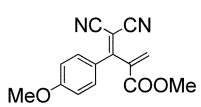
To explore the possibility of the asymmetric IEDDAR, dicyano-2-methylenebut-3-enoates were synthesized to evaluate the efficacy of [4 + 2] cycloaddition (Table 1). During the elaboration of standard conditions (see ESI†), reaction of arylidenemalononitrile (**1a**) as a model substrate with **2a** was performed with a catalytic amount of PPh_3 (20 mol%) in toluene at 75 °C, and the corresponding product **3a** was obtained in 82% yield under the optimized conditions. Next, we sought to expand the scope of the synthesis of dicyano-2-methylenebut-3-enoates and a variety of arylidenemalononitriles subjected to the reaction conditions. Gratifyingly, arylidenemalononitrile substrates bearing various substituents, including those with electron-rich and electron-poor aromatics, as well as heterocycles, participated well in the reaction and provided the dicyano-2-methylenebut-3-enoate products in moderate to high yields (63–91% yield).

Subsequently, we tested the efficacy of asymmetric IEDDAR with **3a** as a diene by employing an enamine-activated strategy in Table 2, and a model reaction of **3a** with

Table 1 Synthesis of dienes under the optimized conditions[a]

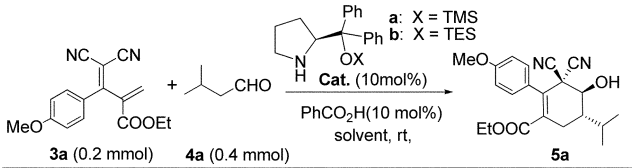


1a (2.0 mmol) **2a** (2.4 mmol) **3a** (**yield:** 82%)

entry	product/yield (%) [b]	entry	product/yield (%) [b]
1	 69%	6	 63%
2	 68%	7	 65%
3	 83%	8	 91%
4	 79%	9	 89%
5	 79%	10	 75%

[a] Unless otherwise noted, the reaction was conducted with arylidenemalononitriles **1** (2.0 mmol) and alkyl propiolates **2** (2.4 mmol) in the presence of PPh_3 (20 mol%) in toluene at 75 °C. [b] Isolated yield.

Table 2 Results of survey of the organocatalytic IEDDAR of diene **3a**[a]



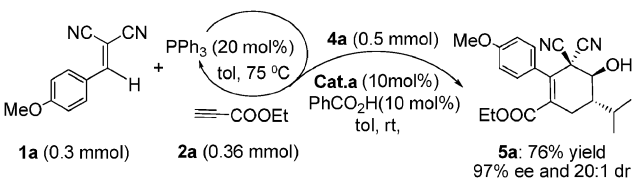
3a (0.2 mmol) **4a** (0.4 mmol) **5a**

entry	Cat.	solvent	yield (%) [b]	dr [c]	ee (%) [d]
1	**a**	MeCN	81	10:1	30
2	**a**	CH_2Cl_2	83	20:1	56
3	**a**	$CHCl_3$	72	4:1	70
4	**a**	THF	<10	n.d	n.d
5	**a**	Et_2O	<10	n.d	n.d
6	**a**	toluene	94	20:1	97
7	**a**	*m*-xylene	90	2:1	92
8	**b**	toluene	81	20:1	97

[a] The reactions was performed with **3a** (0.2 mmol) and **4a** (0.4 mmol) for 6 h at room temperature. [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopy and chiral HPLC. [d] The ee values were determined by HPLC, and the configuration was assigned by comparison of HPLC data and X-ray crystal data of **5i**.

isobutyraldehyde **4a** was performed at room temperature in the presence of the readily available (*S*)-diphenylprolinol trimethylsilyl ether **a** (10 mol%) and benzoic acid (10 mol%)[10] in CH_3CN. The result indicated that the reaction went smoothly, and afforded the desired product in 81% yield, while a low enantioselectivity (30% ee) was observed (entry 1). We found that the solvent used had a significant effect on the yield and stereochemical outcome (entries 1–7). Gratifyingly, subsequent screening of solvent uncovered that toluene was the most suitable, highly enantioselective [4 + 2] cycloaddition reaction was carried out with 97% ee and 94% yield (entry 6), and an excellent diastereoselectivity (20 : 1 dr) in the adduct **5a** was demonstrated. Notably, a bulkier catalyst **b** showed similar stereocontrol but with a relatively low yield of 81% (entry 8). In order to establish a more practical method, we further optimized the reaction process on the basis of the aforementioned success. As indicated in Scheme 2, to our delight, the product **5a** was also obtained in 76% yield with excellent stereoselectivity (97% ee and 20 : 1 dr) through the PPh_3-catalyzed addition/asymmetric IEDDAR sequence reaction (for further details see ESI†).

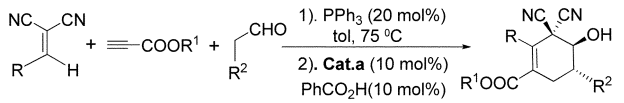
Having established optimal reaction conditions, we explored the scope of this PPh_3-catalyzed addition/asymmetric IEDDAR sequence in Table 3. The reaction of alkyl propiolates with a variety of substituted arylidenemalononitriles, including those bearing electron-withdrawing and -donating substituents on the aryl ring, and of heterocyclic arylidenemalononitriles with aliphatic aldehydes was examined. The results showed that all reactions afforded the desired products with excellent enantioselectivities (93–99% ee, entries 1–20), and in general,



1a (0.3 mmol) **2a** (0.36 mmol) **5a**: 76% yield
97% ee and 20:1 dr

Scheme 2 The PPh_3-catalyzed addition/asymmetric IEDDAR sequence.

Table 3 Structural variations for the PPh_3-catalyzed addition/asymmetric IEDDAR sequence[a]



1	2	3			5	
entry	R	R^1	R^2	yield(%)[b]	dr[c]	ee(%)[d]
1	4-$MeOC_6H_4$	Et	*i*Pr	(**5a**) 76	20:1	97
2	Ph	Et	*i*Pr	(**5b**) 66	20:1	97
3	1-napthyl	Et	*i*Pr	(**5c**) 65	4:1	99 (97)[e]
4	4-MeC_6H_4	Et	*i*Pr	(**5d**) 79	20:1	99
5	3-$MeOC_6H_4$	Et	*i*Pr	(**5e**) 72	19:1	99
6	3-MeC_6H_4	Et	*i*Pr	(**5f**) 72	8:1	96
7	2-MeC_6H_4	Et	*i*Pr	(**5g**) 71	2:1	97 (94)
8[f]	4-BrC_6H_4	Et	*i*Pr	(**5h**) 59	19:1	95
9[f]	4-ClC_6H_4	Et	*i*Pr	(**5i**) 60	20:1	97
10[f]	4-FC_6H_4	Et	*i*Pr	(**5j**) 52	10:1	93
11[f]	4-$CF_3C_6H_4$	Et	*i*Pr	(**5k**) 43	20:1	99
12[f]	3-BrC_6H_4	Et	*i*Pr	(**5l**) 45	10:1	96
13[f]	3-ClC_6H_4	Et	*i*Pr	(**5m**) 60	9:1	99
14[f]	2-FC_6H_4	Et	*i*Pr	(**5n**) 50	3:1	97 (99)
15	2-furyl	Et	*i*Pr	(**5o**) 86	9:1	99
16	2-thienyl	Et	*i*Pr	(**5p**) 85	20:1	97
17	4-$MeOC_6H_4$	Et	Et	(**5q**) 71	2:1	92 (90)
18	4-$MeOC_6H_4$	Et	Ph	(**5r**) 62	17:1	99
19	4-$MeOC_6H_4$	Me	*i*Pr	(**5s**) 70	15:1	93
20	4-BrC_6H_4	Me	*i*Pr	(**5t**) 58	18:1	96

[a] Unless otherwise noted, the reaction sequence was conducted with arylidenemalononitriles **1** (0.3 mmol), alkyl propiolates **2** (0.36 mmol) and aliphatic aldehydes **3** (0.5 mmol). For experimental details, see ESI†. [b] Isolated yield. [c] Determined by ^1H NMR spectroscopy and chiral HPLC. [d] The ee values were determined by HPLC, and the configuration was assigned by comparison of HPLC data and X-ray crystal data of **5i**. [e] Values in parentheses are ee of minor diastereomer. [f] 0.4 mmol isobutyraldehyde was used.

high to excellent diastereoselectivities could be obtained, albeit with poor diastereoselectivities for the substrates bearing 1-napthyl (entry 3) and with substituents at the *ortho* position of the aryl ring (entries 7 and 14). Notably, moderate to high yields were obtained for a number of arylidenemalononitriles bearing phenyl, 1-napthyl, electron-donating aryl and heterocyclic groups (65–86% yield, entries 1–7, 15–16 and 19). By contrast, electron-withdrawing aryl substituted arylidenemalononitriles gave products with moderate yields (43–60% yield, entries 8–14 and 20). In addition to isobutyraldehyde, other aliphatic aldehydes, such as butyraldehyde and phenylacetaldehyde were also tested. As expected, the catalytic system also proved to be efficient for these dienophiles, again leading to satisfactory results (up to 99% ee, 17 : 1 dr and 71% yield), albeit with a poor diastereoselectivity when employing butyraldehyde (entries 17 and 18). The relative and absolute configurations of the products were determined by X-ray crystal analysis of **5i**.

In summary, we have disclosed the synthesis of dicyano-2-methylenebut-3-enoates as novel Diels–Alder dienes *via* a new PPh_3-catalyzed addition reaction, and an unprecedented PPh_3-catalyzed addition/all-carbon-based asymmetric IEDDAR sequence reaction was presented for the first time, affording the products in high levels of enantio- and diastereoselectivity.

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