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Organocatalytic Enantioselective 1,3-Dipolar Cycloadditions between Seyferth–Gilbert Reagent and Isatylidene Malononitriles: Synthesis of Chiral Spiro-phosphonylpyrazoline-oxindoles

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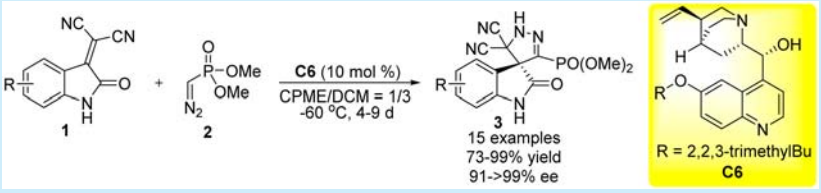
Supporting Information



ABSTRACT: A new method has been developed for the catalytic enantioselective 1,3-dipolar cycloaddition of the Seyferth–Gilbert reagent (SGR) to isatylidene malononitriles using a cinchona alkaloid derivative as a catalyst. This method allowed for the synthesis of a series of chiral spiro-phosphonylpyrazoline-oxindoles in good yields with excellent enantioselectivities. The synthetic utility of this method was further demonstrated by its use in a three-component domino reaction involving isatin, malononitrile, and SGR based on sequential Knoevenagel condensation and 1,3-dipolar cycloaddition reactions.

Chiral organophosphonates have attracted significant interest from researchers working in various fields because of their diverse range of biological activities and applications,[1] which led to a major impetus toward their synthesis.[2] Pyrazolines are heterocyclic compounds that have been reported to exhibit a variety of intriguing biological properties.[3] Furthermore, the bioactivities of pyrazolines can be enhanced by incorporation with phosphonates.[4] For this reason, the development of new methods for the synthesis of chiral phosphonylpyrazolines are highly desired. However, there have been very few reports pertaining to the synthesis of racemic phosphonylpyrazolines,[5] let alone investigations directed toward the development of catalytic enantioselective reactions for the synthesis of chiral variants of these products.

The chiral Lewis acid mediated asymmetric 1,3-dipolar cycloaddition reactions of olefinic dipolarophiles and diazo compounds (e.g., diazoacetates) have been well documented in the literature and represent a straightforward and efficient approach to the synthesis of chiral pyrazolines.[6] In contrast, catalytic asymmetric 1,3-dipolar cycloaddition reactions involving the Seyferth–Gilbert reagent (SGR), which could be used as an isosteric analogue of diazoacetate for the synthesis of chiral phosphonylpyrazolines, have not yet been reported. The lack of reports in this area could be attributed to the unique steric and electronic properties of the SGR. The development of a catalytic system capable of efficiently catalyzing the enantioselective 1,3-dipolar cycloaddition reactions of the SGR to provide access to various chiral phosphonylpyrazolines therefore remains a challenging and interesting area of synthetic chemistry.

In fact, racemic phosphonylpyrazolines have been documented as intermediates during the 1,3-dipolar cycloaddition reactions of olefinic dipolarophiles with the Bestmann–Ohira reagent (BOR), which was smoothly converted to an anion of the SGR in situ under basic reaction conditions. The aromatization of the resulting phosphonylpyrazolines via deprotonation resulted in the corresponding phosphonyl pyrazoles (Scheme 1).[7] Two studies were recently reported in the literature concerning the synthesis of racemic phosphonylpyrazolines via 1,3-dipolar cycloaddition reactions involving BOR or an SGR analogue by choosing an appropriate dipolarophile or exercising effective control over the reaction conditions.[5e,7e]

The catalytic asymmetric [3 + 2] reactions of isatylidene malononitriles allow for the facile construction of spirocyclic oxindoles with two contiguous quaternary centers.[8] Spirocyclic oxindoles are privileged synthetic motifs that constitute a large family of natural products and exhibit a broad range of biological activities.[9] For this reason, the combination of chiral spirocyclic oxindoles with pyrazolines bearing a phosphonate moiety represents an exciting prospect.

Herein, we report for the first time the catalytic asymmetric 1,3-dipolar cycloaddition reaction of the SGR with a series of isatylidene malononitriles using cinchona alkaloid derivative as a catalyst. This reaction provided rapid access to the corresponding series of chiral spiro-phosphonylpyrazoline-oxindoles bearing two adjacent quaternary carbons in high yields and excellent enantioselectivities.

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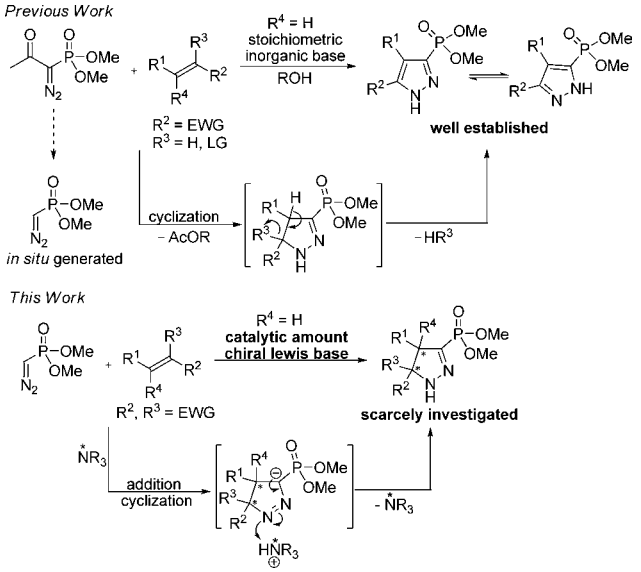
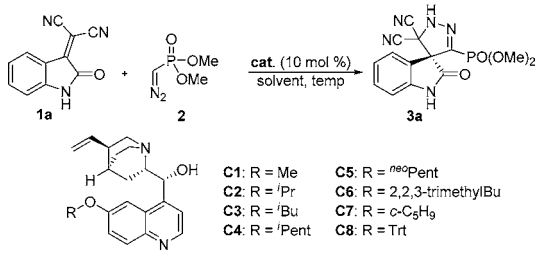
Scheme 1. 1,3-Dipolar Cycloaddition Reactions of SGR and Olefinic Dipolarophiles



A preliminary survey revealed that quinine could promote the asymmetric cycloaddition reaction of the SGR with isatylidene malononitrile **1a** to give the desired spiro-phosphonylpyrazoline-oxindole **3a** in poor yield (11%) with good enantioselectivity (75% ee) (Table 1, entry 1).[10] Lowering the reaction temperature from +25 to −40 °C led to a significant increase in both the yield and enantioselectivity of the reaction up to 49% and 96% ee, respectively, following an extended reaction time of 36 h (Table 1, entries 1 and 2). However, further increasing the reaction time to 96 h led to a decrease in the yield to 6%, albeit with the same enantioselectivity (Table 1, entry 3). This reduction in the yield was attributed to the decomposition of the product in the DCM solvent during the reaction to other unidentified materials, which were subsequently detected by TLC. Several other solvents, including Et_2O, THF, 2-Me-THF, ^{t}BuOMe, and CPME, were screened in an attempt to increase the stability and the yield of the product (Table 1, entries 4−8). An excellent yield was achieved when the reaction was conducted in THF, although the enantioselectivity was very low at only 20% ee (Table 1, entry 5). The reaction proceeded with both moderate yield (55%) and enantioselectivity (55% ee) when it was conducted in CPME (Table 1, entry 8), and this yield could be further improved to 95% when the reaction time was extended to 96 h (Table 1, entry 9). This result indicated that the product was stable in CPME.

Significant variations have been seen in the stereochemical performances of cinchona alkaloid catalysts toward 1,3-dipolar cycloaddition reactions in different solvents. These differences in the performance of the catalysts could be attributed to the impact of the different solvents on the preferred conformation of the cinchona alkaloids through the rotation of their $C_4'-C_9$ and C_8-C_9 bonds.[11] Thus, the preferred conformation in solution could play a critical role in determining the nature of the chiral control exerted by the catalyst during the reaction. When DCM was used as the solvent, quinine would have adopted its preferred conformation, which would have led to the observed excellent enantioselectivity for the 1,3-dipolar cycloaddition reaction. It was envisaged that a similar conformation could be achieved in CPME by modifying the

Table 1. Selected Screening Results for the 1,3-Dipolar Cycloaddition Reaction between the SGR and Isatylidene Malononitrile



entry[a]	cat.	solvent	temp (°C)	time (h)	yield[b] (%)	ee[c] (%)
1	**C1**	DCM	25	22	11	75
2	**C1**	DCM	−40	36	49	96
3	**C1**	DCM	−40	96	6	96
4	**C1**	Et_2O	−40	36	55	48
5	**C1**	THF	−40	36	98	20
6	**C1**	2-Me-THF	−40	36	72	32
7	**C1**	^{t}BuOMe	−40	36	38	48
8	**C1**	CPME	−40	36	55	55
9	**C1**	CPME	−40	96	95	55
10	**C2**	CPME	−40	96	72	56
11	**C3**	CPME	−40	96	72	66
12	**C4**	CPME	−40	96	84	52
13	**C5**	CPME	−40	96	90	79
14	**C6**	CPME	−40	96	92	80
15	**C7**	CPME	−40	96	89	58
16	**C8**	CPME	−40	96	61	58
17	**C6**	CPME/DCM = 1/3	−40	72	92	93
18	**C6**	CPME/DCM = 1/3	−60	9 d	84	98

[a]All reactions were performed on a 0.1 mmol scale using **1a** (0.1 mmol), **2** (0.12 mmol) and catalyst (0.01 mmol) in anhydrous solvent (0.05 M). [b]Isolated yield. [c]Determined by HPLC analysis. CPME = cyclopentyl methyl ether.

structure of the cinchona alkaloid.[11b,12] In view of the accessibility of cinchona alkaloid derivatives, we decided to modify quinine by changing the substituent at C_6. Indeed, a survey of several modified catalysts revealed that the enantioselectivity of the reaction could be improved by increasing the steric bulk of the substituents. When catalysts **C5** and **C6** bearing bulky neopentoxy and 2,2,3-trimethylbutoxy substituents were used in the reaction, the enantioselectivity improved to 79% ee and 80% ee, respectively. To achieve both good yield and enantioselectivity, we investigated the effect of using a mixed solvent system. Pleasingly, the use of a 3:1 (v/v) mixture of DCM and CPME led to a significant increase in the enantioselectivity of the reaction to 93% ee, which was further improved to 98% ee when the temperature of the reaction was reduced to −60 °C (Table 1, entry 18).

With the optimized reaction conditions in hand, we proceeded to investigate the substrate scope of the reaction, and the corresponding chiral spiro-phosphonylpyrazoline-oxindoles were obtained in high yields and excellent enantioselectivities. As shown in Scheme 2, the electronic properties of the substituents on the aryl ring of isatylidene malononitriles had no discernible impact on the enantioselectivity of the reaction, although substrates bearing an electron-donating group generally afforded lower yields of the

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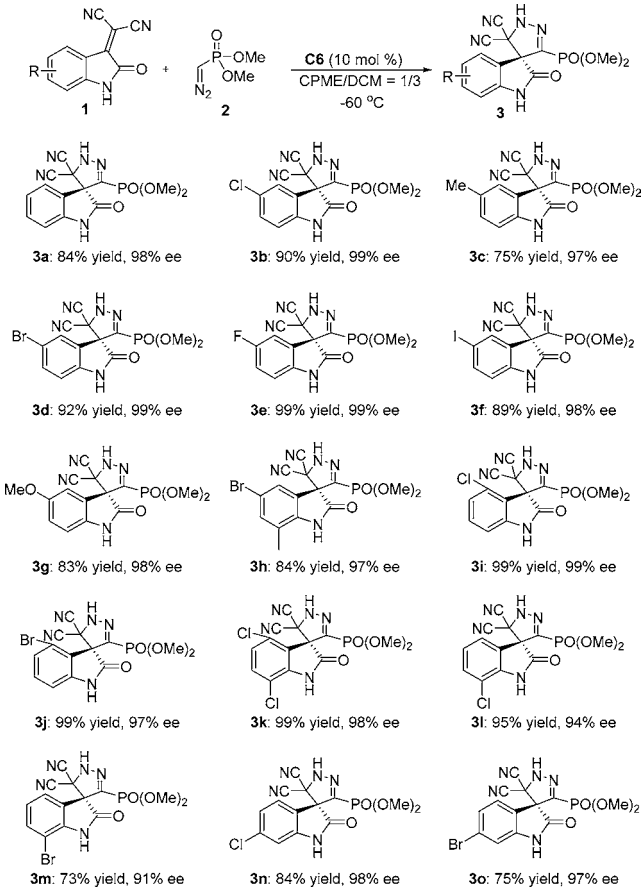
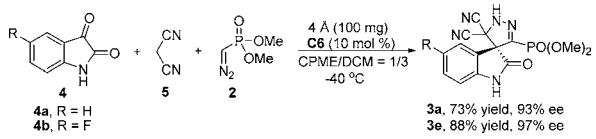
Scheme 2. Substrate Scope for the 1,3-Dipolar Cycloaddition Reactions between SGR and Isatylidene Malononitriles[a]

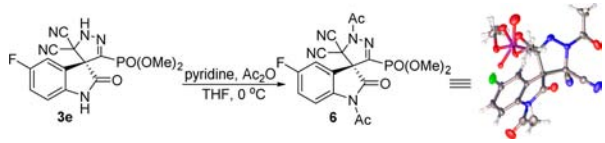


[a]All reactions were performed on a 0.1 mmol scale using **1** (0.1 mmol), **2** (0.12 mmol), and **C6** (0.01 mmol) in anhydrous solvent (0.05 M) for 96 h or 9 d at −60 °C. Isolated yield by flash chromatography. Enantioselectivities were determined by HPLC analysis.

Scheme 3. One-Pot Construction of Chiral Spiro-pyrazoline-oxindoles



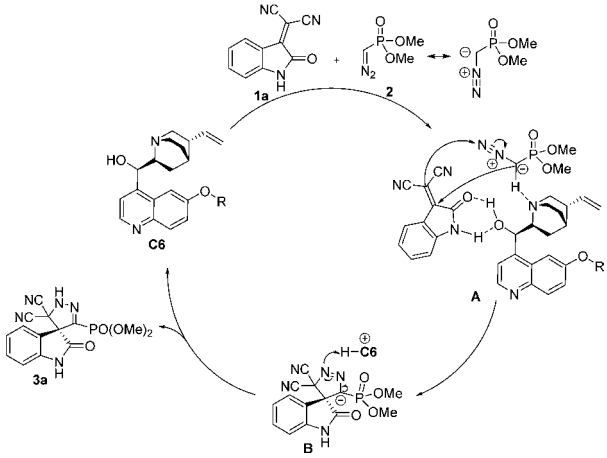
Scheme 4. Single-Crystal X-ray Structure of 6[a]



[a]See the Supporting Information for experimental details.

Based on previous results, we have proposed a plausible mechanism for the current reaction (Scheme 5). The cinchona alkaloid derivative could act as a bifunctional catalyst in that the hydroxyl group could act as a Brønsted acid to activate the isatylidene malononitrile via hydrogen bonding and the amine moiety could act as a base to activate the SGR to attack the C_3 position of the isatylidene malononitrile from its *Si* face. Different from the Lewis acid mediated direct 1,3-dipolar cycloaddition reactions, this [3 + 2] cycloaddition reaction was assumed to proceed via a Michael-type 1,4-addition and cyclization sequence. The resulting intermediate would then undergo an intramolecular hydrogen transfer to form the final chiral spiro-pyrazoline-oxindole.

Scheme 5. Proposed Mechanism



corresponding products (Scheme 2, **3c** and **3g**). The position of the substituent was found to have a slight impact on the enantioselectivity of the reaction. For example, isatylidene malononitriles with C_7 substituents gave slightly lower enantioselectivities (Scheme 2, **3h**, **3k**, **3l**, and **3m**).

Encouraged by the straightforward nature of these 1,3-dipolar cycloaddition reactions for the efficient synthesis of chiral spiro-phosphonylpyrazoline-oxindoles, we further evaluated the synthetic potential of this reaction by investigating the construction of several valuable compounds according to a convergent three-component reaction strategy. Based on a domino Knoevenagel condensation/1,3-dipolar cycloaddition sequence, we conducted a three-component reaction between readily available isatin, malononitrile, and the SGR which was efficiently catalyzed by the cinchona alkaloid derivative **C6** (see the Supporting Information for the experimental details). Compared with the straightforward two-component reactions (**3a**, 92% yield, 93% ee; **3e**, 95% yield, 98% ee), the enantioselectivities of this reaction are maintained, albeit with a slight decrease in the yields of the reaction (Scheme 3).

The absolute configurations of the cycloaddition products of this reaction were determined on the basis of the analysis of the X-ray crystal structure of **6**, which was prepared by diacetylating of **3e** (Scheme 4).[13]

In conclusion, we have reported for the first time the catalytic asymmetric 1,3-dipolar cycloaddition of the SGR with a series of isatylidene malononitriles using a cinchona alkaloid derivative as a catalyst. These reactions proceeded smoothly to give the corresponding chiral spiro-phosphonylpyrazoline-oxindoles in good yields with excellent enantioselectivies. The first catalytic asymmetric three-component reaction between isatin, malononitrile and the SGR has also been developed. Investigations toward evaluating the bioactivity of the chiral spiro-phosphonylpyrazoline-oxindoles generated in this study, as well as research toward identifying further applications for the SGR in asymmetric reactions, are currently underway in our laboratory.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and detailed characterization data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(10) See the Supporting Information for details of investigation of the reaction conditions.

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(13) CCDC 1036430 (**6**) 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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