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Formal Asymmetric Cycloaddition of Activated α,β-Unsaturated Ketones with α-Diazomethylphosphonate Mediated by a Chiral Silver SPINOL Phosphate Catalyst

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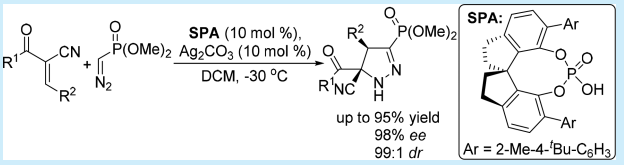
Supporting Information

ABSTRACT: An efficient method for preparing highly functionalized chiral nonspiro-phosphonylpyrazolines via an asymmetric formal 1,3-dipolar cycloaddition reaction of α-diazomethylphosphonate with activated, acyclic α,β-unsaturated ketones, bearing an additional nitrile electron-withdrawing group, has been developed, utilizing an in situ generated chiral silver phosphate catalyst, affording excellent stereoselectivities (up to 98% *ee*, 99:1 *dr*) and yields (up to 95%). A stepwise mechanism is proposed based upon density functional M11 calculations.



Pyrazoline is a privileged five-membered heterocycle found in many biologically active molecules[1−5] that have shown anticancer,[2] anticonvulsant,[3] antimicrobial,[4] and immunosuppressive activities.[5] Therefore, much research effort has been directed toward the development of synthetic methods for successfully constructing various pyrazoline derivatives.[6] Despite these achievements, developing protocols for the stereocontrolled formation of highly functionalized pyrazolines remains challenging and desirable. Furthermore, the biological activity of azaheterocyclic compounds can be enhanced significantly when a phosphonate functional group is introduced.[7] Therefore, the bioactivities of pyrazolines with incorporated phosphonates are anticipated. Several researchers have reported that reactions of diazophosphonates with olefinic dipolarophiles afford phosphonylpyrazoles via pyrazoline intermediates, with subsequent immediate aromatization in the presence of a strong base affording the more stable pyrazoles.[8] Only limited success was documented in the synthesis of racemic phosphonylpyrazolines.[6e,8d] From a structure−activity relationship (SAR) viewpoint, the configuration of stereogenic centers on the phosphonylpyrazoline core could significantly influence its biological activity. Therefore, the development of new approaches to the synthesis of chiral variants phosphonylpyrazoline is important for biological activity screening. In this respect, our group has achieved the synthesis of chiral spiro-phosphonylpyrazoline oxindoles,[6k,l] while chiral nonspiro-phosphonylpyrazolines derived from acyclic olefins have yet to be exploited. In this study, we aimed to prepare chiral nonspiro-phosphonylpyrazolines for the first time through the asymmetric catalytic 1,3-dipolar cycloaddition reaction of Seyferth−Gilbert reagent (**SGR**) to acyclic substituted α,β-unsaturated ketones.

Considering that the cycloaddition reaction of **SGR** with β-monosubstituted dipolarophiles results in two tautomers,[6e] we designed α,β-disubstituted unsaturated ketone **1a** containing a cyano group as the test dipolarophile for the asymmetric version of the reaction with **SGR** (**2**). The Smietana group has reported the reaction of *in situ* generated α,β-unsaturated nitriles with the **SGR** anion to achieve the aromatization of phosphonylpyrazoles via a pyrazoline intermediate, revealing that the cyano group on the pyrazoline ring was easily eliminated under strong basic conditions.[8a] This demonstrated that elimination of the cyano group must be avoided to realize the asymmetric synthesis of phosphonyl pyrazolines via the reaction of **1a** and **SGR** (**2**). We surmised that aromatization could be inhibited by performing the devised reaction in a weak base medium. After preliminary trials, we were delighted to find that the catalyst formed *in situ* from the chiral phosphoric acid (**CPA**)[9] (Figure 1) and silver carbonate smoothly promoted the reaction to afford the desired phosphonylpyrazoline. The results are shown in Table 1.

Chiral silver phosphates produced by 1,1′-spirobiindane-7,7′-diol (**SPINOL**)-based chiral phosphoric acids (**SPAs**, **I**) showed efficient catalytic performance. 6,6′-Diphenyl-substituted SPA **Ia** gave cycloaddition product **3aa** in 14% yield with 26% *ee* and 99:1 *dr* (Table 1, entry 1). Inspired by this result, we synthesized a series of SPAs and screened them in the model reaction. Introducing a methyl group at the *para*-position of the 6,6′-diphenyl substituents (**Ib**) led to a significant increase in the yield and stereoselectivity (65% yield, 55% *ee*, and 99:1 *dr*) (Table 1, entry 2). However, when

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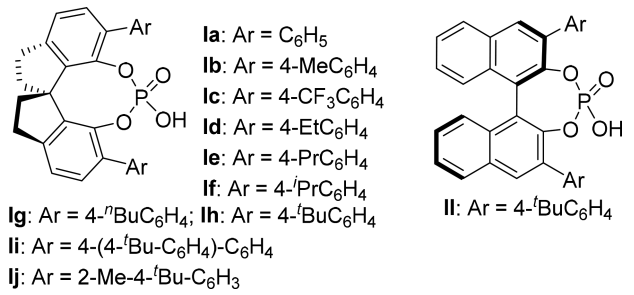
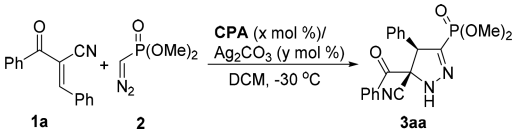


Figure 1. Chiral phosphoric acids screened in this study.

Table 1. Screening the Chiral Phosphoric Acids and Optimization the Reaction Conditions



1a 2 3aa

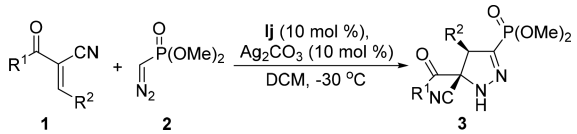
entry[a]	CPA	ratio (*x*/*y*)	yield (%)[b]	*dr*[c,d]	*ee* (%)[d]
1	**Ia**	1:1	14	99:1	26
2	**Ib**	1:1	65	99:1	55
3	**Ic**	1:1	10	99:1	33
4	**Id**	1:1	60	98:2	60
5	**Ie**	1:1	55	97:3	59
6	**If**	1:1	55	99:1	54
7	**Ig**	1:1	55	98:2	57
8	**Ih**	1:1	78	99:1	80
9	**Ii**	1:1	44	99:1	59
10	**Ij**	1:1	60	99:1	85
11	**II**	1:1	20	99:1	14
12	**Ij**	1:0.5	39	99:1	77
13	**Ij**	1:1.25	50	99:1	84
14	**Ij**	1:1.5	50	99:1	77
15[e]	**Ij**	1:1	66	98:2	90
16[f]	**Ij**	1:1	85	99:1	92
17[g]	**Ij**	1:1	86	99:1	92

[a]Conditions: Unless otherwise noted, all reactions were conducted with **1a** (0.15 mmol), **2** (0.1 mmol), **CPA** (10 mol %), and Ag_2CO_3 (10 mol %) in DCM (1.0 mL) at −30 °C for 3 days. [b]Isolated yield. [c]Ratio of major diastereomer to the total of the other three diastereomers. [d]Determined by chiral HPLC. [e]0.15 M of the reaction concentration. [f]0.2 M of the reaction concentration. [g]0.25 M of the reaction concentration.

electron-withdrawing substituents (−CF_3) were introduced in the same positions (**Ic**), inferior results were obtained compared with those of **Ib** (10% yield, 33% *ee*, and 99:1 *dr*; Table 1, entry 3). These results demonstrated that electron-withdrawing groups on the 6,6′-diphenyl substituents were detrimental to catalytic performance. Next, electron-donating *para*-substituents with increasing steric hindrance on the 6,6′-diphenyl rings were explored, affording SPAs **Id**−**Ih** that were applied in the model reaction. The silver phosphate produced by *para*-ethyl-substituted **Id** gave **3aa** in 60% yield with 60% *ee* and 98:2 *dr* (Table 1, entry 4), while *para*-propyl (**Ie**, 55% yield, 59% *ee*, 97:3 *dr*), *para*-isopropyl (**If**, 55% yield, 54% *ee*, 99:1 *dr*), and *para*-butyl (**Ig**, 55% yield, 57% *ee*, 98:2 *dr*) substituents afforded similar results (Table 1, entries 5−7). Introducing the more sterically hindered *tert*-butyl group into the SPA (**Ih**) resulted in substantially improved catalytic performance, affording a 78% yield with 80% *ee* and 99:1 *dr* (Table 1, entry 8). To further increase the steric hindrance of the 6,6′-disubstituents, SPAs **Ii** and **Ij** were synthesized and evaluated. Although **Ii** resulted in only a 44% yield with 59% *ee* and 99:1 *dr* (Table 1, entry 9), **Ij** afforded the highest enantioselectivity (85% *ee*; Table 1, entry 10). The silver phosphate from 1,10-binaphthol (BINOL)-based phosphoric acid (**II**) was also applied to this 1,3-dipolar cycloaddition reaction, but afforded **3aa** in only 20% yield with 14% *ee* and 99:1 *dr* (Table 1, entry 11). From these results, the silver phosphate from **Ij** was identified as the best catalyst. The effect of changing the ratio of SPA **Ij** to silver carbonate was investigated (Table 1, entries 10, 12−14). The results showed that a 1:1 ratio was the best choice, with decreased reactivity observed if either silver carbonate or SPA **Ij** were in excess (Table 1, entries 10 and 12−14). Other reaction parameters, including the concentration (Table 1, entries 10 and 15−17), the ratio of **1a** and **2**, catalyst loading, temperature, and solvent, were also optimized (see Supporting Information, SI). The best results were achieved when the reaction proceeded at −30 °C in dichloromethane (DCM) at a concentration of 0.2 M with 10 mol % **Ij** and 10 mol % silver carbonate.

With optimized conditions in hand, we further evaluated the substrate scope by employing a series of substituted chalcones in the cycloaddition reaction. The results are summarized in Table 2. The reaction tolerated a broad range of substrates, with both electron-donating and electron-withdrawing substituents on phenyl ring R^2 affording good results (Table 2, entries 1−10). The substituent pattern on ring R^2 had a small effect on the yield and enantioselectivity. Substituents at the 2-position afforded slightly lower yields and enantioselectivities

Table 2. Scope of Substituted Chalcones Applied to the Asymmetric Cycloaddition Reaction



1 2 3

entry[a]	R^1, R^2	*t* (d)	yield (%)[b]	*dr*[c,d]	*ee* (%)[d]
1	Ph, Ph	3	**3aa**, 85	99:1	92
2	Ph, 2-FC_6H_4	3	**3ab**, 83	97:3	82
3	Ph, 3-FC_6H_4	2	**3ac**, 94	99:1	90
4	Ph, 4-FC_6H_4	4	**3ad**, 96	98:2	91
5	Ph, 3-ClC_6H_4	3	**3ae**, 92	98:2	87
6	Ph, 4-ClC_6H_4	2	**3af**, 95	98:2	93
7	Ph, 3-BrC_6H_4	4	**3ag**, 94	99:1	89
8	Ph, 4-BrC_6H_4	2.5	**3ah**, 90	99:1	94
9	Ph, 4-$CF_3C_6H_4$	3	**3ai**, 76	99:1	89
10	Ph, 4-MeC_6H_4	4	**3aj**, 91	99:1	89
11	Ph, 2-naphthyl	5	**3ak**, 64	98:2	82
12	2-MeC_6H_4, Ph	3.5	**3ba**, 92	91:9	89
13	3-MeC_6H_4, Ph	4	**3ca**, 91	99:1	90
14	4-MeC_6H_4, Ph	4	**3da**, 86	99:1	91
15	4-ClC_6H_4, Ph	3	**3ea**, 73	97:3	83
16	2-MeC_6H_4, 4-FC_6H_4	2	**3bd**, 94	99:1	90
17	2-MeC_6H_4, 4-ClC_6H_4	2	**3bf**, 95	92:8	95
18	2-MeC_6H_4, 4-BrC_6H_4	2	**3bh**, 94	91:9	94

[a]Conditions: Unless otherwise noted, all reactions were conducted with **1** (0.3 mmol), **2** (0.2 mmol), **Ij** (10 mol %), and Ag_2CO_3 (10 mol %) in DCM (1.0 mL) at −30 °C. [b]Isolated yield. [c]Ratio of major diastereomer to the total of the other three diastereomers. [d]Determined by chiral HPLC.

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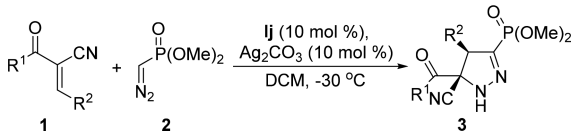
(Table 2, entries 2−4). Meanwhile, a β-naphthyl α,β-unsaturated ketone reacted smoothly to give the expected product only in 64% yield with 82% *ee* and 98:2 *dr* (Table 2, entry 11). α,β-Unsaturated ketones with various substituents on the other phenyl ring (R^1) attached to the carbonyl group were also tolerated in the reaction. In general, electron-donating substituents gave better results than electron-withdrawing groups (Table 2, entries 12−15). In contrast to R^2 phenyl ring substituents, substituents at the 2-position of the R^1 phenyl ring afforded almost the same good results (Table 2, entries 12−14).

To demonstrate the efficiency of this method, we next explored extending the substrate scope to other α,β-unsaturated ketones bearing an alkyl group (R^1) attached to the carbonyl group, with the results summarized in Table 3.

Table 3. Selected Other Substituted α,β-Unsaturated Ketones Applied to the Asymmetric Cycloaddition Reaction



1 2 3

entry[a]	R^1, R^2	*t* (d)	yield (%)[b]	*dr*[c,d]	*ee* (%)[d]
1	Me, Ph	6	**3fa**, 36	97:3	53
2	Et, Ph	6	**3ga**, 37	99:1	73
3	^{i}Pr, Ph	4	**3ha**, 61	98:2	77
4	^{t}Bu, Ph	4	**3ia**, 80	99:1	92
5	^{t}Bu, 3-MeC_6H_4	5	**3ib**, 74	90:10	84
6	^{t}Bu, 4-MeC_6H_4	5	**3ic**, 70	99:1	97
7	^{t}Bu, 4-MeOC_6H_4	7	**3id**, 53	99:1	93
8	^{t}Bu, 3-$NO_2C_6H_4$	2	**3ie**, 93	95:5	93
9	^{t}Bu, 4-$NO_2C_6H_4$	3	**3if**, 95	99:1	96
10	^{t}Bu, 3-BrC_6H_4	4	**3ig**, 93	98:2	93
11	^{t}Bu, 4-BrC_6H_4	4	**3ih**, 81	99:1	94
12	^{t}Bu, 3-ClC_6H_4	3	**3ii**, 93	99:1	93
13	^{t}Bu, 4-ClC_6H_4	3	**3ij**, 94	99:1	94
14	^{t}Bu, 2-FC_6H_4	6	**3ik**, 83	91:9	86
15	^{t}Bu, 3-FC_6H_4	4.5	**3il**, 94	99:1	92
16	^{t}Bu, 4-FC_6H_4	4	**3im**, 93	99:1	96
17	^{t}Bu, 4-$CF_3C_6H_4$	3	**3in**, 92	99:1	93
18	^{t}Bu, 3,4-$Cl_2C_6H_3$	2.5	**3io**, 95	98:2	96
19	^{t}Bu, 3,5-$F_2C_6H_3$	3	**3ip**, 89	94:6	92
20	^{t}Bu, 3,4-$F_2C_6H_3$	2.5	**3iq**, 94	98:2	96
21	^{t}Bu, 2-naphthyl	3	**3ir**, 94	99:1	91
22	^{t}Bu, ^{n}Bu	2	**3is**, 92	99:1	97
23	^{t}Bu, ^{i}Bu	1.5	**3it**, 92	99:1	98
24	^{t}Bu, *n*-C_5H_{11}	1.5	**3iu**, 88	99:1	97

[a]Conditions: Unless otherwise noted, all reactions were conducted with **1** (0.3 mmol), **2** (0.2 mmol), **Ij** (10 mol %), and Ag_2CO_3 (10 mol %) in DCM (1.0 mL) at −30 °C. [b]Isolated yield. [c]Ratio of major diastereomer to the total of the other three diastereomers. [d]Determined by chiral HPLC.

When R^1 was a methyl or ethyl group, low reactivity was observed, with only 36% and 37% yields with moderate enantioselectivities obtained after reacting for 6 days (Table 3, entries 1 and 2). Improved reactivity and enantioselectivity were observed as the size of the R^1 substituents was increased (Table 3, entries 3 and 4). When the R^1 group was ^{t}Bu, the product was obtained in a pleasing 80% yield, with 92% *ee* and 99:1 *dr* (Table 3, entry 4). Therefore, a series of α,β-unsaturated ketones bearing a ^{t}Bu group attached to the carbonyl were synthesized and subjected to this cycloaddition reaction. Good-to-excellent results were achieved by most of these substrates (Table 3, entries 5−21). Substrates bearing both electron-withdrawing and -donating substituents on the benzene ring (R^2) reacted smoothly to give the desired products with excellent enantioselectivities (84−97% *ee*) and good diastereoselectivities (90:10−99:1 *dr*; Table 3, entries 5−20). α,β-Unsaturated ketones bearing electron-withdrawing groups (Table 3, entries 8−20) gave slightly higher yields than those bearing electron-donating groups (Table 3, entries 5−7). A β-naphthyl-substituted feedstock also achieved excellent results (Table 3, entry 21). To our delight, substrates in which R^1 and R^2 were both aliphatic groups reacted well, affording the expected products with excellent yields and stereoselectivities (Table 3, entries 22−24).

To test the synthetic potential of the present approach, in the case of **1bd**, a mmol scale was successfully conducted and gave the desired product **3bd** (98% yield) with 92% *ee*, >99:1 *dr*.

The absolute configuration of the products was unambiguously determined to be (4*R*, 5*R*) by X-ray crystallographic analysis of **3ig** (Figure 2; CCDC 1474349), with other product configurations deduced from this result.

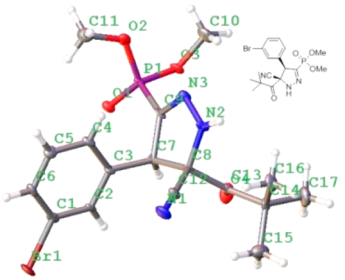


Figure 2. X-ray crystal structure of product **3ig**.

When varying the ratio of SPA (**Ij**) to silver carbonate in the model reaction from 1:0.5 to 1:1.5, it was found that the enantioselectivities varied slightly (77−85% *ee*), while dramatically different reactivities were observed (39−60% yields Table 1, entries 10 and 12−14). These results inspired us to explore the actual in situ formed catalyst and determine how it induced enantioselectivity. Density functional M11[10] with a standard 6-311+G(d,p) basis set (SDD[11] basis set for Ag) was employed to gain insight into the mechanism and the origin of enantioselectivity of this asymmetric 1,3-dipolar cycloaddition (Figure 3). Deprotonation of the diazophosphonate **2** by the silver phosphate catalyst would reversibly yield diazomethyl silver complex **6**. The theoretical study showed that the [3 + 2] cycloaddition could take place *via* a stepwise process (for detailed mechanistic studies, see SI). Intermolecular nucleophilic addition of the carbon atom of the diazomethane moiety in complex **6** to the *si* face of the β-carbon atom in α,β-unsaturated ketone **1**, activated by silver bicarbonate salt *via* transition state **7-ts-*RR***, leads to generation of a new C−C bond in intermediate **8-*RR***. The calculated activation free energy of this step was only 5.0 kcal/mol. Generation of intermediate **8-*RR*** was exergonic (12.3 kcal/mol), which indicated an irreversible process. Therefore, the enantioselectivity would be controlled by this step. Subsequent

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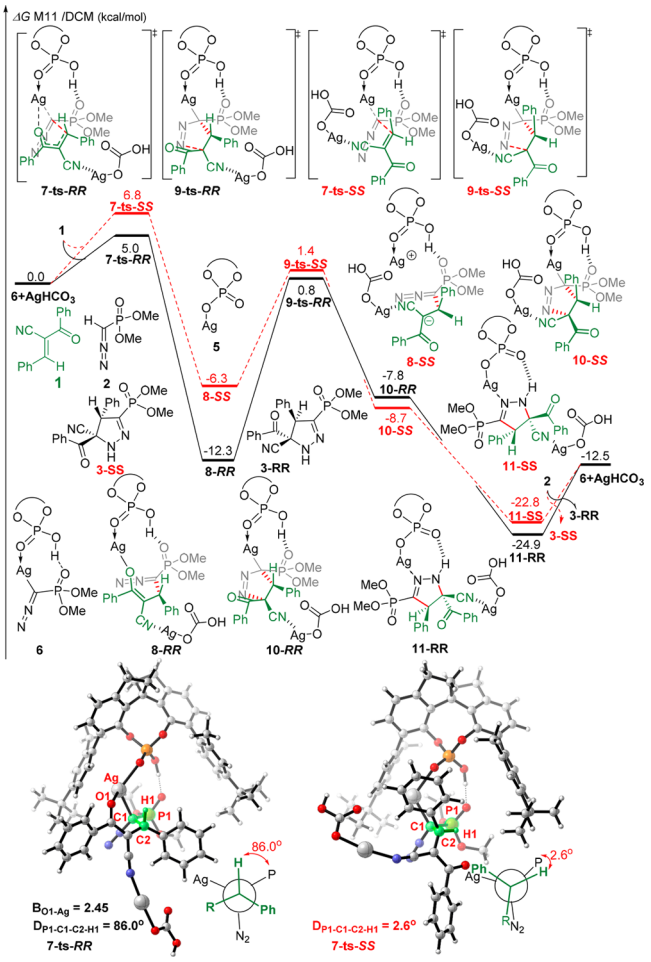

Figure 3. Free energy profiles for silver catalyzed asymmetric 1,3-dipolar cycloaddition. The values given by kcal/mol represent the relative free energies calculated by M11 method in dichloromethane solvent

cyclization with C−N bond formation generates five-membered ring-type intermediate **10-*RR*** via transition state **9-ts-*RR*** with a free energy barrier of 13.1 kcal/mol. The active catalyst, diazomethyl silver complex **6**, is rapidly regenerated following proton transfer, ligand exchange, and the release of product (***R*,*R***)-**3**.

In summary, we have developed a novel asymmetric 1,3-dipolar cycloaddition reaction between the Seyferth−Gilbert reagent and activated acyclic *α*,*β*-unsaturated ketones, bearing an additional nitrile electron-withdrawing group. The transformation is catalyzed by a chiral silver phosphate species formed *in situ* from an **SPA** and silver carbonate. Using this method, a series of nonspiro chiral phosphonylpyrazolines was accessed for the first time. We also explored the mechanism and rationalized how the catalyst induced enantioselectivity using density functional M11. This work provides a straightforward approach toward available nonspiro chiral phosphonylpyrazoline derivatives for biological activity assessment.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03436.

Experimental procedures and detailed characterization data of all new compounds (PDF)

Accession Codes

CCDC 1474349 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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