Phosphine Catalysis

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Asymmetric Synthesis of Spiropyrazolones through Phosphine-Catalyzed [4+1] Annulation**

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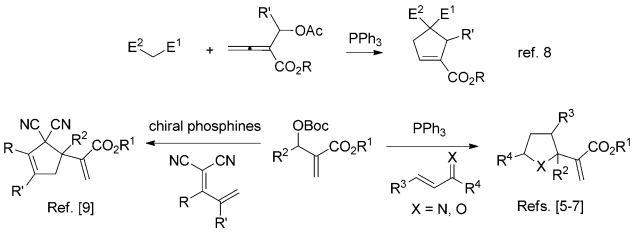
Abstract: *An enantioselective synthesis of spiropyrazolones from allenoate-derived MBH acetates and pyrazolones through a phosphine-mediated [4+1] annulation process has been developed. Spiropyrazolones were readily prepared in good chemical yields and good to high enantioselectivities. This is the first asymmetric example in which α-substituted allenoates were utilized as a C_4 synthon for phosphine-catalyzed [4+1] annulation.*

Over the past decade, nucleophilic phosphine catalysis has emerged as a powerful approach to structurally diverse and synthetically valuable carbocyclic and heterocyclic building blocks in organic chemistry.[1] Pioneered by Lu and co-workers,[2] different types of phosphine-catalyzed cycloaddition reactions have been developed over the years. In particular, [3+2] annulations of allenoates/alkynes or Morita–Baylis–Hillman (MBH) acetate/carbonates with alkenes or imines have been widely explored and established as an effective method for contructing a wide range of highly functionalized five-membered ring systems.[3] However, other types of [*m*+*n*] annulations were studied to a much lesser extent,[4] and the discovery of different cyclization modes with novel reaction partners is highly desirable.

Phosphine-catalyzed [4+1] annulations represent an alternative approach for the formation of five-membered ring systems, and the successful development of this type of annulation is dependent on careful selection and utilization of C_4 and C_1 synthons for the projected cyclization. Recently, MBH carbonates were used as a new C_1 synthon in phosphine-catalyzed [4+1] annulations for the construction of five-membered heterocyclic ring structures by Zhang,[5] Chen,[6] and He.[7] Mechanistically, all the above reactions are initiated by the addition of a phosphine to an MBH carbonate to in situ generate a 1,1-dipolar synthon, which reacts with various conjugated electrophilic reaction partners. Another type of [4+1] annulation was disclosed by Tong in 2010,[8] in which 2,3-butadienoate, an α-substituted allenoate, was utilized as a C_4 synthon under phosphine catalysis, affording cyclopentene products (Scheme 1). Asymmetric versions of



Scheme 1. Reported [4+1] annulations.

[4+1] annulations are very scarce; to the best of our knowledge, there is only one report in the literature. Shi utilized dicyano-2-methylenebut-3-enoates as a C_4 synthon in the annulation reaction with MBH carbonates, for the asymmetric synthesis of highly functionalized cyclopentenes.[9] However, the utilization of α-substituted allenoates in asymmetric [4+1] annulations is unknown. It thus became our goal to develop an asymmetric variant of this promising transformation.

Pyrazolone and their derivatives are important structural motifs that widely occur in biologically active molecules and pharmaceutical agents,[10] and they are also synthetically valuable for the construction of heterocyclic and spirocyclic structures.[11] Recently, 4-spiro-5-pyrazolones were found to be inhibitors of type-4 phosphodiesterase,[12] resulting in the need for efficient synthetic approaches to this challenging structural motif. We envisioned that 4-spiro-5-pyrazolone structural motifs may be conveniently assembled through a phosphine-mediated [4+1] annulation reaction. The high acidity of two protons at position 4 of 5-pyrazolone suggests that it may be a suitable C_1 synthon in the proposed annulation. By employing 2,3-butadienoate as a reaction partner, 4-spiro-5-pyrazolones could be readily constructed (Scheme 2). In recent years, our group has investigated enantioselective processes promoted by amino acid based chiral phosphines, and the reactions we have disclosed include: (aza)-MBH reactions, allylic alkylation, Michael addition, γ addition, and a number of [3+2] and [4+2] cycloaddition reactions.[13] Herein, we describe the first

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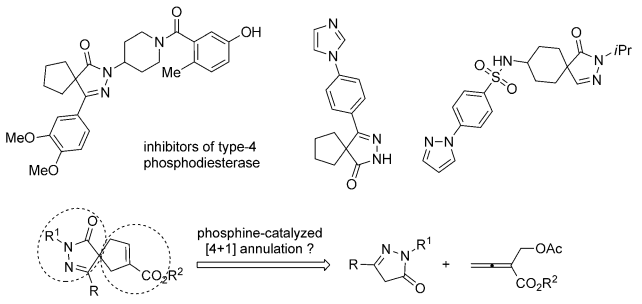


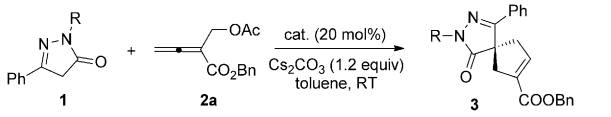
Scheme 2. Selected bioactive spiropyrazolones and proposed synthesis through phosphine-catalyzed [4+1] annulation reaction.

application of α-substituted allenoates in phosphine-catalyzed enantioselective [4+1] annulation for the formation of optically enriched 4-spiro-5-pyrazolones.

We first tested the feasibility of our proposed [4+1] annulation process. Toward this end, 1,3-diphenyl-1*H*-pyrazol-5(4*H*)-one (**1a**) and 2-(acetoxymethyl)buta-2,3-dienoate (**2a**) were treated with amino acid derived phosphines in the presence of Cs_2CO_3 (Table 1). To our delight, the annulation took place smoothly, and the reaction was completed within a few hours. In the presence of valine-derived bifunctional phosphines containing a carbamate or a sulfonamide, the annulation product was obtained in high yield, but with low enantioselectivity (Table 1, entries 1 and 2). When phosphine-thiourea **4c** was used, both yield and *ee* were poor (Table 1, entry 3). Phosphine amide **4d** turned out to be a promising catalyst, furnishing the desired [4+1] annulation product in 78% yield and with 71% *ee* (Table 1, entry 4). A more sterically hindered adamantyl amide did not offer further improvement (Table 1, entry 5). We next examined phosphine amide catalysts derived from different amino acids. Alanine-based catalyst **5** afforded the spiropyrazolone **3a** with 77% *ee* (Table 1, entry 6). Examination of L-threonine-derived *O*-silylated phosphines showed that **6a** was a good catalyst, furnishing the desired product with a slightly improved *ee* value (Table 1, entry 7). However, dipeptide phosphines turned out to be ineffective (Table 1, entries 10–11). Having identified **6a** as the best catalyst, we next examined the influence of N substitution of the pyrazolone on the reaction. Variation of the N substituent on pyrazolone showed that *tert*-butyl was the best group (Table 1, entry 12). Decreasing the concentration of the reaction slightly enhanced the results, and the desired annulation product was obtained in 82% yield and with 91% *ee* (Table 1, entry 13). The use of different α-substituted allenonate esters for the annulation, the employment of different base additives, or the lowering of the reaction temperature did not result in further improvement (see the Supporting Information for details).

With the optimized reaction conditions in hand, we next established the scope of this annulation process (Table 2). Both electron-rich and electron-deficient aryl substituents on the pyrazolones were well-tolerated, and the reaction was also applicable to aryl rings with different substitution patterns (Table 2, entries 1–11). Moreover, when pyrazolones with heteroaromatic rings were utilized, equally good results

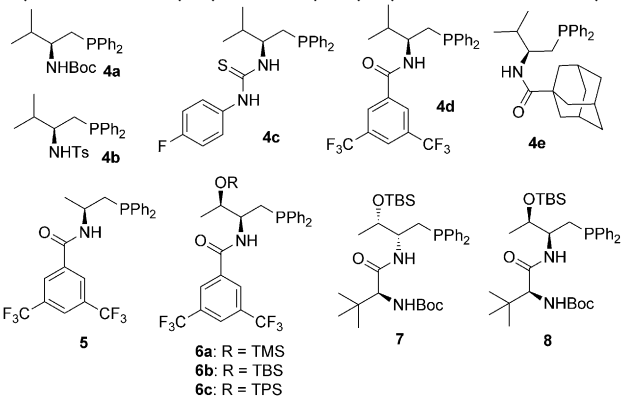
Table 1: Enantioselective [4+1] annulation of pyrazolones **1** to 2-(acetoxymethyl)buta-2,3-dienoate (**2a**) catalyzed by amino acid derived phosphines.[a]



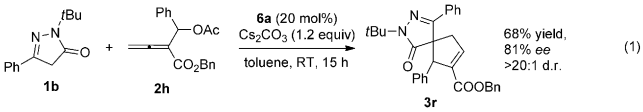
1 **2a** **3**

Entry	R/**1**	Cat.	*t* [h]	Yield [%][b]	*ee* [%][c]
1	Ph/**1a**	**4a**	2	78	36
2	Ph/**1a**	**4b**	1	82	30
3	Ph/**1a**	**4c**	8	36	24
4	Ph/**1a**	**4d**	3	78	71
5	Ph/**1a**	**4e**	3	69	55
6	Ph/**1a**	**5**	3	72	77
7	Ph/**1a**	**6a**	3	83	78
8	Ph/**1a**	**6b**	3	79	68
9	Ph/**1a**	**6c**	3	71	68
10	Ph/**1a**	**7**	2	74	49
11	Ph/**1a**	**8**	2	85	54
12	*t*Bu/**1b**	**6a**	6	80	90
13[d]	*t*Bu/**1b**	**6a**	6	82	91

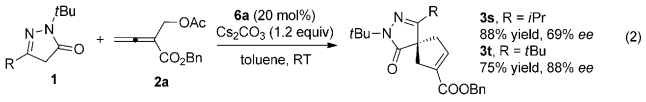
[a] Reactions were performed with **1a** (0.12 mmol), **2a** (0.1 mmol), Cs_2CO_3 (0.12 mmol), and the catalyst (0.02 mmol) in toluene (1 mL) at room temperature. [b] Yields of isolated products. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The reaction was run in 1.5 mL of toluene. Boc = *tert*-butyloxycarbonyl, TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl, TPS = triphenylsilyl, Ts = 4-toluenesulfonyl.



were obtained (Table 2, entries 13–16). The absolute configurations of the annulation products were assigned based on a single-crystal X-ray analysis of a derivative of **3k**.[14] Furthermore, we examined the feasibility of utilizing β′-substituted allenoate in this [4+1] annulation. The annulation between allenoate **2h** and pyrazolone **1b** proceeded smoothly, and the desired product was obtained virtually as a single diastereomer, and with 81% *ee* [Eq. (1)]. When *tert*-butyl-substituted pyrazolone was used, high enantioselectivity was attainable [Eq. (2)]. However, only moderate enantioselectivity was obtained when *iso*-propyl-substituted pyrazo-

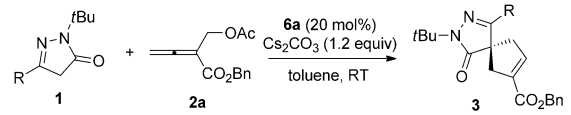


1b **2h** **3r** (1)



(2)

Table 2: Asymmetric synthesis of spiropyrazolones **3**.[a]

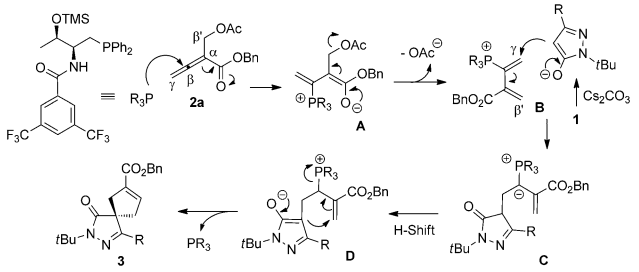


Entry	R	**3**	*t* [h]	Yield [%][b]	*ee* [%][c]
1	C_6H_5	**3b**	6	82	91
2	2-Me-C_6H_4	**3c**	12	77	86
3	3-Br-C_6H_4	**3d**	8	76	91
4	3-Cl-C_6H_4	**3e**	8	80	91
5	3-NO_2-C_6H_4	**3f**	6	80	91
6	4-F-C_6H_4	**3g**	8	79	90
7	4-Me-C_6H_4	**3h**	12	81	87
8	4-OMe-C_6H_4	**3i**	12	75	90
9	4-CF_3-C_6H_4	**3j**	8	77	90
10	4-NO_2-C_6H_4	**3k**	6	88	92
11	4-Br-C_6H_4	**3l**	8	83	90
12	2-naphthyl	**3m**	10	71	86
13	2-furyl	**3n**	12	84	87
14	2-thienyl	**3o**	12	81	90
15	3-thienyl	**3p**	12	76	88
16	3-pyridyl	**3q**	18	57	85

[a] Reactions were performed with **1** (0.24 mmol), **2a** (0.20 mmol), Cs_2CO_3 (0.24 mmol), and **6a** (0.04 mmol) in toluene (3 mL) at room temperature. [b] Yields of isolated products. [c] Determined by HPLC analysis on a chiral stationary phase.

lone was employed, and high enantioselectivity was also not attainable for other pyrazolones containing less-hindered/linear alkyl groups.[16]

A possible mechanism depicting the formation of [4+1] annulation products is shown in Scheme 3.[8,3n] The reaction is initiated by the nucleophilic attack of the phosphorus atom on

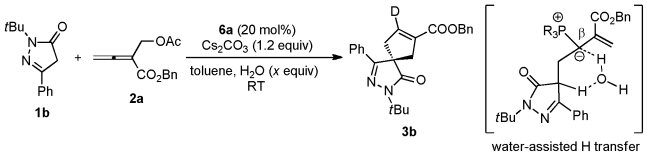


Scheme 3. Proposed reaction mechanism.

the 2,3-butadienoate **2a** to form intermediate **A**. Subsequent elimination of an acetate group gives **B**, which is most likely attacked at the γ-carbon position by the enolate derived from pyrazolone **1** to give rise to phosphonium ylide **C**. Proton transfer takes place to give intermediate **D**. This is followed by an intramolecular Michael addition and elimination of the phosphine catalyst to furnish the final [4+1] annulation adduct **3**.

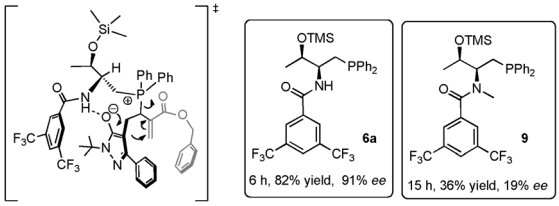
We have done some preliminary investigations on the proposed mechanistic pathway of the reaction. In light of excellent reports on the influence of water on cycloaddition reactions,[15] our reaction was performed in the presence of various amounts of D_2O. As shown in Table 3, deuterium incorporation at the β position of the adduct was observed.

Table 3: The effect of H_2O on the [4+1] annulation.[a]



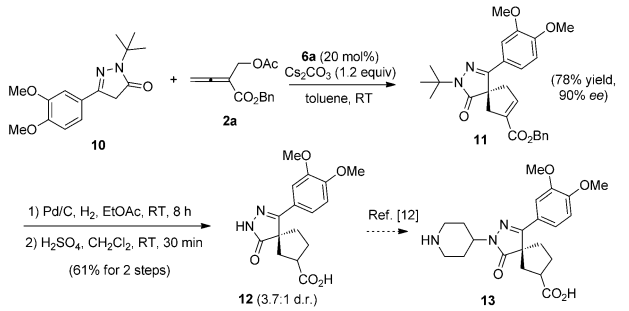
Entry	D_2O (*x* equiv)	*t* [h]	D [%]	Yield [%][b]	*ee* [%][c]
1	–	6	0	82	91
2	1	5	25	75	82
3	2	5	29	81	83
4	3	5	32	80	82
5	5	5	34	76	83
6	10	5	45	73	78
7[d]	D_2O/toluene	5	89	61	65

[a] Reactions were performed with **1b** (0.12 mmol), **2a** (0.1 mmol), Cs_2CO_3 (0.12 mmol), D_2O (*x* equiv), and **6a** (0.02 mmol) in toluene (1.5 mL) at room temperature. [b] Yields of isolated products. [c] Determined by HPLC analysis on a chiral stationary phase. [d] *V*/*V* = 4:1.



The reactions were slightly faster, and enantioselectivities were reduced. When annulation product **3b** (with H) was treated with D_2O, no deuterium incorporation occurred. We believed that the hydrogen-bonding interaction contributed significantly to the asymmetric induction in our catalytic systems, thus also carried out studies to demonstrate its importance. Employment of N-methylated catalyst **9** led to the formation of the cyclization product **3a** in 36% yield and with only 19% *ee*. Under otherwise identical conditions, the use of catalyst **6** with its free NH group resulted in 82% yield and 91% *ee*. Based on the above experimental results, we propose that a water molecule participates in the 1,3-proton transfer.[17] The key hydrogen-bonding interactions between the NH group of the amide and the pyrazolone enolate is crucial for the stereochemical outcome of the reaction (see the transition state depicted in Table 3). When water was added to the reaction system, the hydrogen-bond network was disrupted, and erosion of enantioselectivity was observed. We also applied the [4+1] annulation described here to synthesize a structural analogue of spiropyrazolone, which provided an entry to chiral inhibitors of type-4 phosphodiesterase (Scheme 4).

In conclusion, we have disclosed an efficient phosphine-catalyzed [4+1] annulation for the synthesis of highly



Scheme 4. Synthesis of potential inhibitors of type-4 phosphodiesterase.

optically enriched 4-spiro-5-pyrazolones, which are a class of compounds with potentially great biological significance. It is noteworthy that this is the first time that substituted pyrazolones were used in cycloaddition, and that this report also represents the first asymmetric application of α-substituted allenoates in [4+1] annulation. Various chiral spirocyclic structures may be accessible by using the documented approach, which we are currently investigating.

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