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Construction of adjacent spiro-quaternary and tertiary stereocenters through phosphine-catalyzed asymmetric [3 + 2] annulation of allenoates with alkylidene azlactones†

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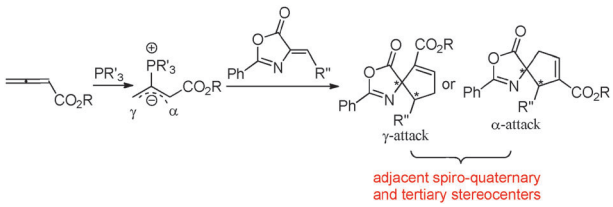
A novel axially chiral spiro-phosphine-catalyzed highly regio-, diastereo- and enantioselective [3 + 2] cycloaddition of alkylidene azlactones with various allenic esters has been developed, affording the corresponding functionalized spirocyclic products in moderate to excellent yields under mild conditions. These spirocyclic products as masked amino acids can be easily transformed into aspartic amino acid analogues.

The catalytic asymmetric construction of quaternary stereocenters has been intensively studied in the past few decades and has reached a high level of productivity for various reaction types.[1] In contrast, as for the simultaneous formation of adjacent quaternary and tertiary stereocenters, only a limited number of highly diastereo- and enantioselective protocols are available.[1,2] Among those, phosphine catalyzed allenoate addition of trisubstituted olefins to form cyclopentene molecular complexity[3,4] is a brilliant strategy to construct two adjacent stereocenters. Besides, these cycloaddition adducts are useful in both organic and medicinal chemistry.[5] Regarding the asymmetric version of this reaction,[6] since the pioneering work of catalytic asymmetric Lu's [3 + 2] cycloaddition of allenes with olefins was reported by Zhang in 1997,[6a] Fu and co-workers have recently developed a series of axially chiral binaphthyl framework containing phosphines catalyzed asymmetric cycloaddition of allenoates with electron-deficient olefins to afford the corresponding cycloadducts in good yields with excellent diastereo- and enantioselectivities.[7] Moreover, Marinetti and co-workers have also discovered that chiral phosphines based on a planar chiral 2-phospha[3]ferrocenophane scaffold were efficient catalysts for this asymmetric reaction as well.[8] Furthermore, various multifunctional chiral phosphines derived from natural amino acids have been also realized as powerful catalysts to promote [3 + 2] cycloaddition of allenoates with electron-deficient olefins, affording a variety of cyclopentene derivatives in good yields with high diastereo- and enantioselectivities under mild conditions.[9]



Scheme 1 Reaction model.

As part of our ongoing investigation on the phosphine catalyzed [3 + 2] cycloaddition,[10] herein we wish to report an interesting chiral phosphine catalyzed asymmetric [3 + 2] cycloaddition of allenoates with alkylidene azlactones, furnishing the spiro cycloadducts in good yields with excellent diastereo- and enantioselectivities. This new asymmetric [3 + 2] cycloaddition catalyzed by chiral phosphines features the simultaneous formation of adjacent spiro-quaternary and tertiary stereocenters in a single step and the obtained spiro cycloadducts could generate an interesting family of conformation constrained α-amino acids.[11] The corresponding reaction model has been depicted in Scheme 1. Since two regioisomers derived from γ-attack and α-attack could be produced at the same time in the presence of tertiary phosphine, we first attempted to carefully examine the reaction outcome with various chiral phosphines.

Initial examinations using alkylidene azlactone **1a** and benzyl 2,3-butadienoate **2a** as the substrates in the presence of various chiral phosphines **CP1–CP10** (10 mol%) (see Fig. S1 in the ESI†) in toluene were aimed at determining their catalytic activities in this [3 + 2] cycloaddition reaction system. The results of these experiments are summarized in Table S1 (ESI†). We found that only product **3a** derived from γ-attack was obtained with these chiral phosphines. The corresponding spiro-cycloadduct **3a** was obtained in low yields and low ee values in the presence of axially chiral binaphthyl skeleton containing phosphines **CP1–CP3** at room temperature. Using **CP1** as the catalyst gave **3a** in 8% yield with 20% ee and the other two chiral phosphines afforded barely no product (Table S1, entries 1–3 (ESI†)). Subsequently we examined several multifunctional chiral phosphines derived from natural amino acids (**CP4–CP6**) and some commercially available chiral phosphines (**CP7–CP10**). Using **CP4** or **CP7** as the chiral phosphine

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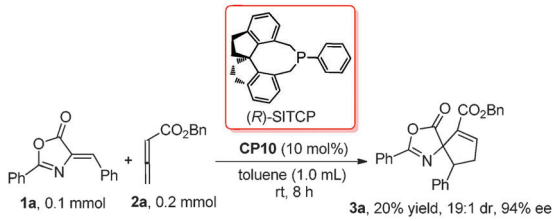
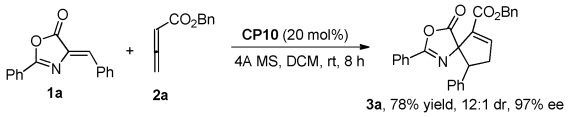
† Electronic supplementary information (ESI) available: Experimental procedures and characterization data of new compounds. CCDC 853417 (**3b**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc17709a



Scheme 2 Screening of chiral phosphines.



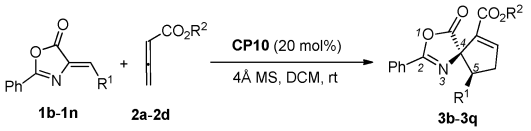
Scheme 3 Optimization of the reaction conditions.

produced **3a** in 23% yield with >10 : 1 dr and 14% ee value or in 38% yield with 9 : 1 dr and 32% ee value (Table S1, entries 4 and 7 (ESI†)). The use of **CP5**, **CP6**, and **CP8** as the catalysts gave the desired product in low yields but with no ee value (Table S1, entries 5, 6 and 8 (ESI†)). Chiral phosphine **CP9** was also inefficient in this reaction (Table S1, entry 9 (ESI†)). Gratefully, we found that using chiral phosphine **CP10** (*R*)-SITCP[12] as the catalyst, **3a** was produced in 20% yield with 19 : 1 dr and 94% ee (Scheme 2).

With the identification of the best catalyst in this reaction, we next attempted to further optimize reaction conditions by screening of the solvent and reaction temperature (see Table S2 in the ESI† for details). We found that using 20 mol% **CP10** as the catalyst, 4 Å MS as the additive and carrying out the reaction in dichloromethane (DCM) at room temperature for 8 h gave **3a** in 78% yield with 12 : 1 dr and 97% ee value, which served as the best reaction conditions for this reaction (Scheme 3).

With the identification of the optimal reaction conditions, the generality of this **CP10** catalyzed asymmetric [3 + 2] annulation was examined using a variety of aryl or alkyl-substituted azlactones **1** and allenic esters **2**. The results are summarized in Table 1. All of the reactions proceeded smoothly to give the corresponding products **3** in moderate to good yields with high diastereo- and excellent enantioselectivities under the optimal reaction conditions (Table 1). Whether R^1 is an electron-rich or -deficient aromatic ring, the reactions proceeded smoothly to give the corresponding spiro-cycloadducts **3b–3j** in good yields with 85–99% ee values, respectively (Table 1, entries 1–9). Only in the case of *ortho*-BrC_6H_4 azlactone **1d**, the corresponding adduct **3d** was obtained in good yields along with relatively lower ee value (85% ee), perhaps due to the steric influence (Table 1, entry 3). When R^1 is a heteroaromatic group (R^1 = 2-furan, 2-thiophene) or a sterically more bulky 2-naphthalene moiety, the reactions also proceeded efficiently to afford the corresponding products **3k–3m** in 65–68% yields with 94–96% ee values (Table 1, entries 10–12). Changing the aromatic group to aliphatic group provided the corresponding product **3n** in 68% yield with 79% ee (Table 1, entry 13). The other allenic esters such as ethyl-, isopropyl- and *tert*-butyl 2,3-butadienoates are also suitable substrates to this asymmetric [3 + 2] cycloaddition, giving the corresponding products in 77–91% yields with 91–95% ee values and excellent diastereoselectivities. The absolute configuration of **3b** has been assigned by X-ray

Table 1 Scope of the asymmetric [3 + 2] annulation to afford products **3b–3q**



Entry[a]	**1** (R^1)	**2** (R^2)	Yield[b] (%)	dr[c]	ee[d] (%)
1	**1b** (4-BrC_6H_4)	**2a** (Bn)	**3b**: 80	> 19 : 1	96[e]
2	**1c** (3-BrC_6H_4)	**2a** (Bn)	**3c**: 96	> 19 : 1	95
3	**1d** (2-BrC_6H_4)	**2a** (Bn)	**3d**: 90	> 19 : 1	85
4	**1e** (4-ClC_6H_4)	**2a** (Bn)	**3e**: 85	> 19 : 1	95
5	**1f** (3,4-$Cl_2C_6H_3$)	**2a** (Bn)	**3f**: 75	> 19 : 1	93
6	**1g** (4-$CH_3C_6H_4$)	**2a** (Bn)	**3g**: 76	15 : 1	99
7	**1h** (4-$CH_3OC_6H_4$)	**2a** (Bn)	**3h**: 66	13 : 1	96
8	**1i** (4-$NO_2C_6H_4$)	**2a** (Bn)	**3i**: 69	> 19 : 1	93
9	**1j** (4-CNC_6H_4)	**2a** (Bn)	**3j**: 83	> 19 : 1	93
10	**1k** (2-furyl)	**2a** (Bn)	**3k**: 65	> 19 : 1	95
11	**1l** (2-thienyl)	**2a** (Bn)	**3l**: 66	> 19 : 1	94
12	**1m** (2-naphthyl)	**2a** (Bn)	**3m**: 68	> 19 : 1	96
13	**1n** (^{i}pr)	**2a** (Bn)	**3n**: 68	> 19 : 1	79
14	**1a** (Ph)	**2b** (Et)	**3o**: 77	> 19 : 1	95
15	**1a** (Ph)	**2c** (^{i}Pr)	**3p**: 91	> 19 : 1	94
16	**1a** (Ph)	**2d** (^{t}Bu)	**3q**: 89	> 19 : 1	91

[a] The reactions were carried out with **1a** (0.1 mmol), **2a** (0.2 mmol), **CP10** (0.02 mmol) and 4 Å MS (30 mg) in DCM (3.0 mL) at rt for 8 h. [b] Isolated yield by column chromatography. [c] Diastereomeric ratios determined by ^{1}H NMR spectroscopy. [d] Determined by chiral HPLC analysis. [e] The absolute configuration of **3b** has been determined by X-ray diffraction as (4*R*, 5*S*).

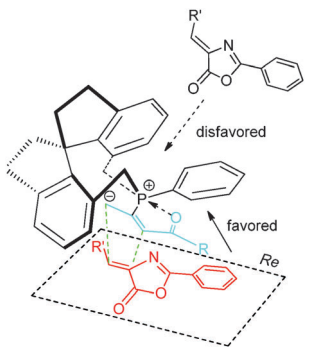
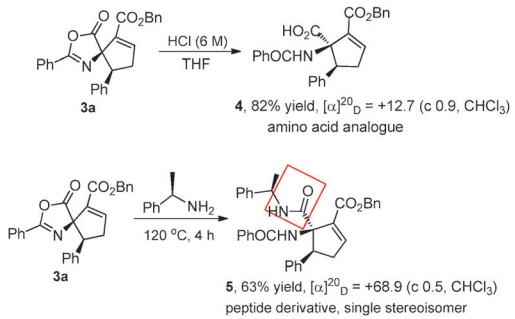


Fig. 1 A plausible transition state.

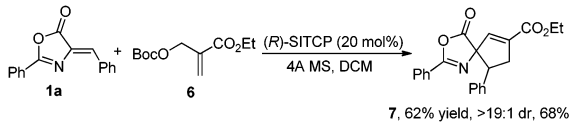
diffraction as 4*R*, 5*S*. The ORTEP drawing of **3b** and the CIF data are summarized in the ESI.†

The possible transition state of this asymmetric [3 + 2] annulation is illustrated in Fig. 1 which may account for the stereoselectivity. The azlactone **1** could approach the zwitterionic intermediate[3e,13] generated from a chiral phosphine and an allenoate through *Re* face or *Si* face. In our case, the azlactone **1** may attack the zwitterionic intermediate from the *Re* face to form the products due to the steric interaction, which is also in accordance with the experimental results.

The synthetic utility of the reaction products was demonstrated by nucleophilic ring opening of the cycloaddition product **3a** (Scheme 4). Treatment with 6 M HCl for 4 h at 80 °C provided *N*-Bz protected α-amino acid **4** in good yield and >10 : 1 dr.[14] Moreover, a simple ring opening reaction of **3a** with (*R*)-phenylethylamine gave a peptide bond containing product **5** in 63% yield as a single stereoisomer.[2b,15]



Scheme 4 Ring opening products.



Scheme 5 Chiral phosphine catalyzed [3 + 2] annulation of MBH carbonate **6** with **1a**.

Furthermore, *O*-Boc protected aliphatic Morita–Baylis–Hillman (MBH) adduct **6** was taken instead of allenoate in this asymmetric reaction under the same reaction conditions. The desired spiro-cycloadduct **7** was obtained in 62% yield along with 68% ee value and excellent diastereoselectivity (Scheme 5).

In summary, we have developed a novel axially chiral spiro-phosphine-catalyzed highly regioselective, diastereoselective and enantioselective [3 + 2] annulation of allenoates with azlactones, affording the corresponding functionalized cycloadducts in good to excellent yields with adjacent spiro-quaternary and tertiary stereocenters under mild conditions. These products as masked amino acids could be easily transformed into a variety of useful amino acid analogues such as different aspartic acid analogues.[16]

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