Organocatalysis

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Asymmetric [3+2] Cycloadditions of Allenoates and Dual Activated Olefins Catalyzed by Simple Bifunctional *N*-Acyl Aminophosphines**

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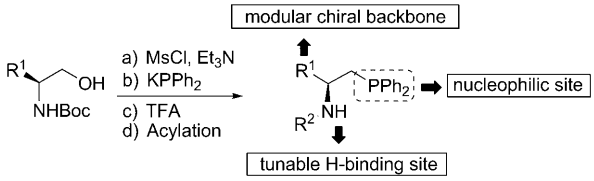
Recently, phosphine-catalyzed [3+2] cycloadditions of allenoates with electron-deficient olefins and imines—a process which provides efficient access to a variety of synthetically useful carbo- and heterocycles from readily available starting materials—have received considerable research interest[1,2] since the pioneering works of Lu and co-workers.[1j] As a result of continuing efforts from many research groups in this field, an array of new annulation reactions were disclosed, in which α- or γ-substituted allenoates,[3] allylic compounds,[4] and electron-deficient olefins[5] were recognized as novel "three-carbon-atom units" and "two-carbon-atom units". However, the development of enantioselective variants of these transformations has met with very limited success. Up to now, only a handful of chiral organocatalysts[6,7] have been found to be effective for this kind of reaction, most of which are monodentate phosphines.[6] Recently, two excellent research reports highlighted the great potential of phosphine-containing molecules bearing additional active sites as efficient catalysts in this kind of reaction. Miller and co-workers pioneered the use of multifunctional α-amino acid derived phosphines as efficient catalysts for allenoate–enone cycloadditions.[7a] In addition to the high *ee* values achieved, this system also provided regioselectivity opposite to those obtained with monodentate phosphine catalysts in similar reactions. Later, Jacobsen and co-workers demonstrated bifunctional phosphine-containing thioureas catalyzed allenoate–imine cycloadditions with excellent enantioselectivities.[7b]

The problem of regioselectivity is common in [3+2] cycloadditions of allenoates with electron-deficient olefins. Such a problem could be circumvented by using dual activated olefins, which was recently disclosed by Lu and co-workers.[8] Despite this advantage, to the best of our knowledge, no asymmetric example of this kind of reaction has been reported. Recently, our group has focused on the development of chiral organocatalysts from natural α-amino acids, a cheap and readily accessible chiral source, and their applications in various organic transformations.[9] α-Amino acid derived aminophosphines and their N-protected counterparts have been used as efficient chiral ligands for numerous metal-based reactions.[10] We envisaged that their modular, bifunctional structures would also make them excellent candidates for organocatalysts (Scheme 1). Herein, we describe highly regio- and enantioselective [3+2] cycloadditions between allenoates and arylidenemalononitriles and analogues catalyzed by bifunctional *N*-acyl aminophosphines derived from α-amino acids.



Scheme 1. Catalyst design for [3+2] cycloadditions. Ms = methanesulfonyl; TFA = trifluoroacetic acid.

The *N*-acyl aminophosphines employed in this research were easily accessed in four steps from commercially available Boc-protected amino alcohols (Boc = *tert*-butyloxycarbonyl) through modified literature procedures.[11] The structures of these catalysts are shown in Figure 1.

Initial experiments were performed with the reaction between phenylidenemalononitrile **1a** and ethyl 2,3-butadienoate **2** for catalysts evaluation (Table 1). Firstly, the influence of the structures of the N-protecting groups on the reaction was examined with catalysts **4a–g** derived from L-phenylalanine. Catalyst **4c** with the most acidic NH function led to a racemic product after a long reaction time (Table 1, entry 3). The catalysts with the less acidic benzoyl group (**4f**) and trifluoroacetyl group (**4g**) gave the highest *ee* values, although a low yield was observed with **4f** (Table 1, entries 6 and 7). The above observations, together with those of Miller's, all support the important role that the hydrogen-bonding effect may play in the transition state of this kind of

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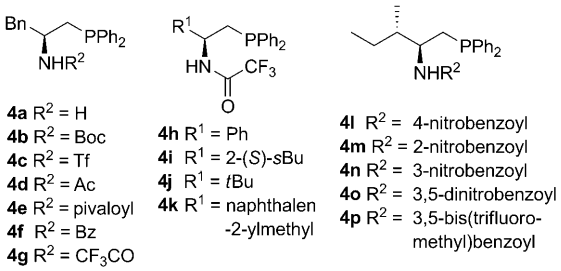
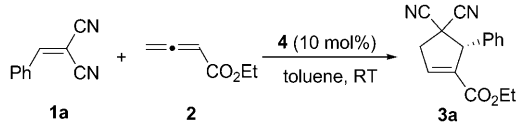


Figure 1. Organocatalysts tested in this study. Bn = benzyl; Tf = trifluoromethanesulfonyl; Bz = benzoyl.

Table 1: Screening of catalysts for the asymmetric [3+2] cycloaddition of phenylidenemalononitrile **1a** and ethyl 2,3-butadienoate **2**.[a]



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

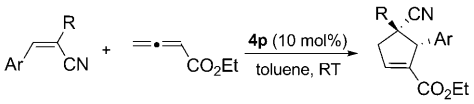
Entry	Catalyst	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**4a**	48	72	39
2	**4b**	24	76	25
3	**4c**	72	54	5
4	**4d**	48	72	51
5	**4e**	48	40	61
6	**4f**	48	29	73
7	**4g**	72	54	72
8	**4h**	24	99	32
9	**4i**	12	80	70
10	**4j**	72	87	78
11	**4k**	72	80	82
12	**4l**	24	47	77
13	**4m**	24	18	54
14	**4n**	6	72	76
15	**4o**	2	94	83
16	**4p**	1	87	85
17[d]	**4p**	12	65	86

[a] All reactions were carried out with **1a** (0.1 mmol) and ethyl 2,3-butadienoate **2** (0.2 mmol) in the presence of **4** (0.01 mmol) in toluene (1.0 mL) at room temperature. [b] Yields of isolated products. [c] Determined by chiral HPLC analysis. [d] 20 mol% of **4p** was used and the reaction was conducted at 0°C.

reaction.[12] Subsequent examination of catalysts **4h–k** with various chiral backbones gave more encouraging results (Table 1, entries 8–11). The enantioselectivity seemed to be dependent on the steric hindrance of R^1 group, and the bulkiest catalyst **4k** (R^1 = naphthalen-2-ylmethyl) gave the highest *ee* value, and also required a long reaction time (Table 1, entry 11). In view of the cost, accessibility, and exceptionally high catalytic activity of catalyst **4i** derived from L-isoleucine (Table 1, entry 9), further optimization efforts were performed by modifying the structure of this catalyst (Table 1, entries 12–17). We then turned back to the tuning of the NH function. Considering the good enantioselectivity obtained with the *N*-benzoyl **4f** and the ready modifiability of both the electronic and steric environment of the benzoyl group, we used several substituted benzoyl groups to replace the trifluoroacetyl group in catalyst **4i** (Table 1, entries 12–17). In general, the presence of electron-withdrawing substituents on the benzene ring is beneficial for the reaction, although catalyst **4m** with a 2-nitro group provided poor yield and *ee* value (Table 1, entry 13), probably because of the likely presence of an intramolecular hydrogen-bonding between the NH function and the nitro group in this catalyst. The best catalyst **4p** with a 3,5-ditrifluoromethylbenzoyl group gave the desired product with 87% yield and 85% *ee* in only 1 h (Table 1, entry 16). Lowering the reaction temperature to 0°C did not bring an apparent enhancement in the enantioselectivity, but a longer reaction time was required and a reduced yield was observed (Table 1, entry 17).[13] Notably, in all the cases examined above, exclusive regioselectivity was observed with **3a** as the single cycloadduct.

Having established the optimal conditions, we then explored the generality of this reaction with a variety of dual activated olefins (Table 2). The reaction is tolerant of a broad range of olefins derived from aromatic aldehydes, providing a series of chiral cyclopentenes in high yields and with good to excellent enantioselectivities. However, olefins derived from aliphatic aldehydes are not suitable substrates for this reaction system.[14] A significant *ortho* site effect of the Ar group was observed: apparently higher enantioselectivities were obtained for *ortho*-substituted substrates, irrespec-

Table 2: Enantioselective [3+2] cycloadditions of ethyl 2,3-butadienoate **2** with **1** catalyzed by **4p**.[a]

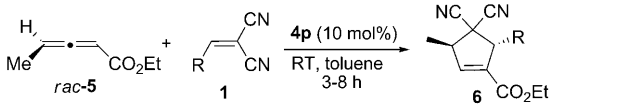


R = CN, **1a-o**
R = CO_2Et, **1p-u**
2
R = CN, **3a-o**
R = CO_2Et, **3p-u**

Entry	**1**, Ar	Products	Yield [%][b]	*ee* [%][c]
1	**1a**, Ph	**3a**	87	85
2	**1b**, 2-FC_6H_4	**3b**	99	93
3	**1c**, 2-ClC_6H_4	**3c**	92	96
4	**1d**, 2-BrC_6H_4	**3d**	99	97
5	**1e**, 2-$MeOC_6H_4$	**3e**	99	91
6	**1f**, 2,5-$MeOC_6H_3$	**3f**	99	91
7	**1g**, 2,4-$Cl_2C_6H_3$	**3g**	99	95
8	**1h**, 1-naphthyl	**3h**	99	93
9	**1i**, 4-FC_6H_4	**3i**	79	85
10	**1j**, 4-ClC_6H_4	**3j**	99	87
11	**1k**, 4-BrC_6H_4	**3k**	88	86
12	**1l**, 4-$MeOC_6H_4$	**3l**	99	80
13	**1m**, 3-FC_6H_4	**3m**	93	86
14	**1n**, 3-ClC_6H_4	**3n**	96	85
15	**1o**, 2-naphthyl	**3o**	81	86
16[d,f]	**1p**, Ph	**3p**	93	90
17[d,f]	**1q**, 2-BrC_6H_4	**3q**	87	99
18[d,f]	**1r**, 3-BrC_6H_4	**3r**	82	92
19[d,f]	**1s**, 4-BrC_6H_4	**3s**	90	92
20[d,f]	**1t**, 2-FC_6H_4	**3t**	88	97
21[e,f]	**1u**, 2-thienyl	**3u**	80	80

[a] Unless otherwise noted, all reactions were carried out with **1** (0.1 mmol) and **2** (0.2 mmol) in the presence of **4p** (0.01 mmol) in toluene (1.0 mL) for 1 h at room temperature. [b] Yields of isolated products. [c] Determined by chiral HPLC analysis. [d] The product was obtained with 95:5 d.r. as determined by ^{1}H NMR spectroscopy. [e] The product was obtained with 85:15 d.r. as determined by ^{1}H NMR spectroscopy. [f] Reaction time: 6 h.

tive of the electronic nature of the substituents (Table 2, entries 2–8). In addition, substrates bearing electron-withdrawing substituents in general gave higher *ee* values than those with electron-donating substituents. More importantly, substrates **1p–u** (2-cyano-3-arylacrylates) with two different electron-withdrawing functions, which would allow selective transformation to other useful structures, are also well tolerated in the reaction. The corresponding chiral cyclopentenes containing adjacent quaternary and tertiary stereocenters were obtained in high yields with exclusive regioselectivity and good to excellent diastereoselectivities and enantioselectivities (Table 2, entries 16–21).[15] Notably, when PPh_3 was employed as the catalyst for accesses to racemic cyclopentenes **3p–u**, poor regioselectivities and moderate diastereoselectivities were observed. To our delight, γ-substituted racemic allenoate **5** also underwent the reaction smoothly to give the desired products **6** in high yields and moderate diastereoselectivities,[16] albeit with somewhat decreased *ee* values (Scheme 2).

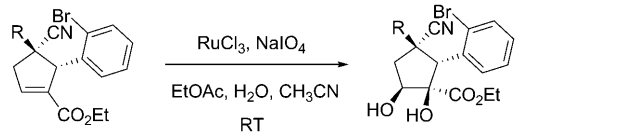


1a R = Ph
1k R = 4-BrC_6H_4
1m R = 3-FC_6H_4
1o R = 2-naphthyl

6a: 99% yield, 77% *ee*, d.r. = 5:1
6k: 99% yield, 81% *ee*, d.r. = 6:1
6m: 92% yield, 82% *ee*, d.r. = 5.5:1
6o: 93% yield, 70% *ee*, d.r. = 4:1

Scheme 2. The reaction between *rac*-**5** and **1** catalyzed by **4p**.

To illustrate the utility of the present [3+2] cycloaddition reaction, the enantiomerically enriched adducts **3d** and **3q** were subjected to the dihydroxylation conditions reported by Fu and co-workers[3d] to afford diastereomerically pure polyfunctional cyclopentanes **7a** and **7b** in good to excellent yields (Scheme 3).[16]



R = CN, **3d**
R = CO_2Et, **3q**

R = CN, **7a**: 97% yield, d.r. > 19:1
R = CO_2Et, **7b**: 74% yield, d.r. > 19:1

Scheme 3. The dihydroxylation reactions of **3d** and **3q**.

On the basis of previous studies and the results of our experiments, we proposed a possible transition state similar to that of Miller's to explain the stereochemical results of the present reaction (Figure 2). The catalyst assembles the allenoate by a synergistic action of its two functional groups to form a zwitterrion. Then the dipolarophile may approach the zwitterion preferentially from the *Si* face to minimize the steric repulsion from the R^1 and phenyl groups of the catalyst. The diastereoselectivities observed in substrates **1p–u** suggest that the cycloaddition step might have proceeded in a stepwise manner.

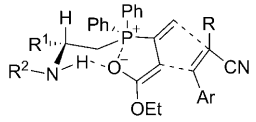


Figure 2. Possible transition state.

In conclusion, we have realized the first asymmetric organocatalytic [3+2] cycloaddition between allenoates and dual activated olefins using novel bifunctional *N*-acyl aminophosphine catalysts. The ready availability of the catalysts, high yields, good to excellent enantioselectivities, and mild reaction conditions make our system a valuable complement to currently existing methods for accessing synthetically useful multifunctional chiral cyclopentenes. Efforts toward the application of the *N*-acyl aminophosphine catalysts in other related reactions are currently underway in our laboratories.

Experimental Section

Representative procedure (see Table 2, entry 1): To a stirred solution of 2-benzylidenemalononitrile **1a** (0.1 mmol) and catalyst **4p** (0.01 mmol) in toluene (1.0 mL), fresh ethyl 2,3-butadienoate (0.2 mmol) was added by a syringe in one portion. Then the reaction mixture was vigorously stirred for 1 h at room temperature. The crude reaction mixture was directly purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate) to furnish the corresponding product.

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[11] See the Supporting Information for details.

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[15] See the Supporting Information for details of the determination of compound **3s** configurations.

[16] The configurations of product **6a** and **7** were determined by NOSY spectra. See the Supporting Information for details.

