Organocatalysis

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Biphenyl-Derived Phosphepines as Chiral Nucleophilic Catalysts: Enantioselective [4+1] Annulations To Form Functionalized Cyclopentenes**

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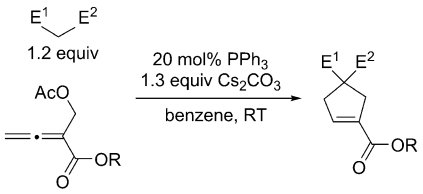
Abstract: *Because of the frequent occurrence of cyclopentane subunits in bioactive compounds, the development of efficient catalytic asymmetric methods for their synthesis is an important objective. Introduced herein is a new family of chiral nucleophilic catalysts, biphenyl-derived phosphepines, and we apply them to an enantioselective variant of a useful [4+1] annulation. A range of one-carbon coupling partners can be employed, thereby generating cyclopentenes which bear a fully substituted stereocenter [either all-carbon or heteroatom-substituted (sulfur and phosphorus)]. Stereocenters at the other four positions of the cyclopentane ring can also be introduced with good stereoselectivity. An initial mechanistic study indicates that phosphine addition to the electrophilic four-carbon coupling partner is not the turnover-limiting step of the catalytic cycle.*

During the past decade, chiral tertiary phosphines have increasingly been employed not only as ligands in transition-metal-catalyzed reactions,[1] but also as enantioselective nucleophilic catalysts for a broad spectrum of useful transformations.[2,3] Studies by our group and by others have established that 1,1′-binaphthyl-derived phosphepines (e.g., **1**) are effective for a diverse array of interesting processes.[4–6] In contrast, to the best of our knowledge, there have been no applications of axially chiral biphenyl-derived phosphepines (**2**) as asymmetric nucleophilic catalysts.[7]

The use of chiral phosphines as nucleophilic catalysts for the synthesis of five-membered rings has been a focus of particular interest,[8] due in part to the occurrence of cyclopentane subunits in a wide range of bioactive molecules,[9] and the powerful methods of Lu and co-workers for convergent [3+2] annulation have been especially well-explored.[10,11] With regard to the enantioselective construction of quaternary stereocenters,[12] nearly all reports have described the generation of spirocyclic structures.[8,13,14]

One complication in some of these [3+2] reactions is the formation of regioisomeric products.[10] In 2010, Tong and co-workers described a complementary [4+1] annulation, which combines structural features of the three-carbon partners from the [3+2] reactions of Lu and co-workers (allenoates and Morita–Baylis–Hillman derivatives) in a four-carbon partner [Eq. (1)].[15] Such a [4+1] approach obviates the formation of regioisomeric products.[16,17]



(1)

E^1, E^2 = electron-withdrawing group

As part of an ongoing program to demonstrate the utility and the versatility of asymmetric nucleophilic catalysis,[18] we embarked on the development of an enantioselective variant of this [4+1] annulation. At the point that we completed our study,[19] we were not aware of any progress by others toward this objective. However, this year the group of Lu has described asymmetric reactions which furnish spirocyclic products with good *ee* values [Eq. (2)],[20] and this has prompted us to disclose our independent investigation. Herein, we report the first use of biphenyl-derived phosphepines **3** and **4** as enantioselective nucleophilic catalysts, specifically, their application in [4+1] annulations to generate cyclopentenes bearing non-spirocyclic, fully substituted stereocenters [either all-carbon or heteroatom-substituted; Eq. (3)].[21,22]

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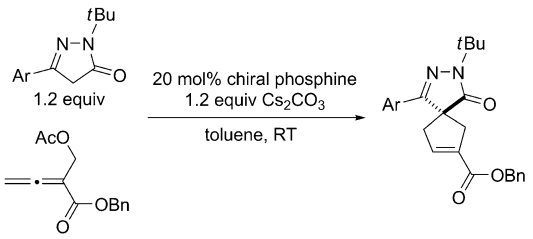


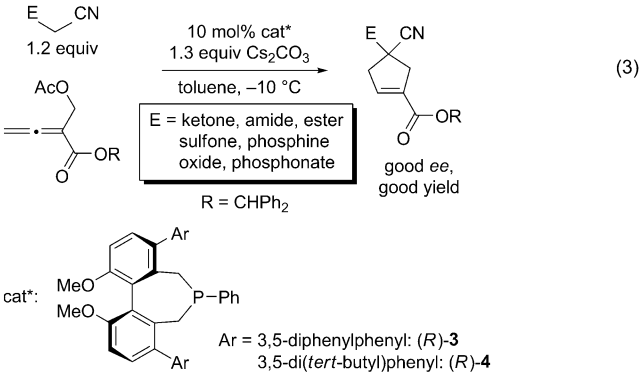
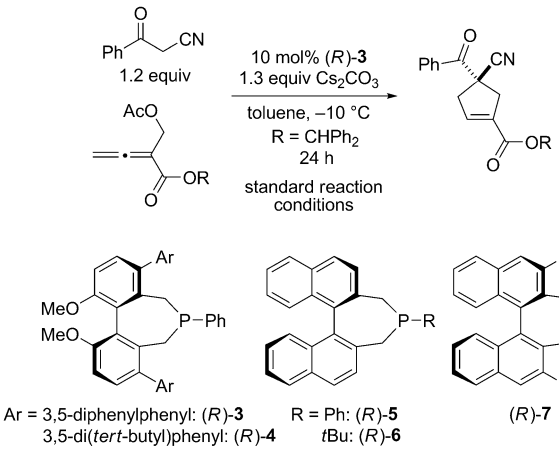


Table 1: Phosphepine-catalyzed enantioselective [4+1] annulation: Effect of reaction parameters.[a]



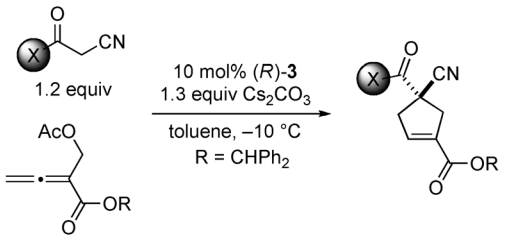
Entry	Change from the standard reaction conditions	*ee* [%][b]	Yield [%][c]
1	(*R*)-**5**, instead of (*R*)-**3**	−38	70
2	(*R*)-**6**, instead of (*R*)-**3**	6	26
3	(*R*)-**7**, instead of (*R*)-**3**	76	>95
4	none	94	>95
5	(*R*)-**4**, instead of (*R*)-**3**	91	92
6	5 mol% (*R*)-**3**	93	64
7	no Cs_2CO_3	92	32
8	2,6-lutidine, instead of Cs_2CO_3	92	56
9	RT	89	>95
10	R = Bn, instead of $CHPh_2$	89	88
11	2.0 equiv of added water	82	40
12	under air, instead of nitrogen	93	90

[a] All data are the average of two experiments. [b] A negative *ee* value signifies that the major product of the reaction is the *R* enantiomer. [c] The yield was determined through the use of ^1H NMR spectroscopy, with CH_2Br_2 as an internal standard.

Upon determining that an array of chiral 1,1′-binaphthyl-derived phosphepines ((*R*)-**5**–**7**), which we have reported to be useful in other nucleophile-catalyzed processes,[5] was not sufficiently effective for a model [4+1] annulation (the coupling of benzoylacetonitrile with an allenoate; Table 1, entries 1–3), we chose to synthesize and examine the utility of biphenyl-derived phosphepines. We were pleased to determine that the new chiral phosphines (*R*)-**3** and (*R*)-**4** afford the desired cyclopentene bearing a quaternary stereocenter with high *ee* values and yields (entries 4 and 5).[23] If the catalyst loading is decreased to 5%, the reaction does not proceed to completion after 24 hours (entry 6). The annulation is also slower in the absence of Cs_2CO_3 and when Cs_2CO_3 is replaced with 2,6-lutidine (entries 7 and 8). Slightly lower enantioselectivity and/or yield are observed at room temperature or when a different ester is attached to the allene (benzyl rather than benzhydryl; entries 9 and 10). The presence of two equivalents of water is deleterious for the coupling (entry 11), whereas adventitious moisture and oxygen have a relatively small impact (entry 12).[24]

Next, we investigated the scope of this new method, catalyzed by (*R*)-**3**, for the enantioselective synthesis of functionalized cyclopentenes which bear an all-carbon quaternary stereocenter (Table 2).[25] A variety of α-cyano ketones are suitable nucleophilic coupling partners, thus furnishing the annulation product with good *ee* values and yields. In the case of aromatic ketones, the aryl ring can be electron-rich or electron-poor (entries 2 and 3). A thienyl ketone can be employed as a reactant (entry 4), as can alkyl ketones with alkyl groups which range from primary to tertiary (entries 5–7). The scope of the process is not limited

Table 2: α-Cyano ketones, amides, and esters as nucleophiles in phosphepine-catalyzed enantioselective [4+1] annulations.[a]



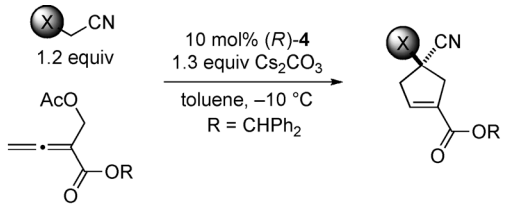
Entry	X	*ee* [%]	Yield [%][b]
1	Ph	94	85
2	4-$MeOC_6H_4$	94	97
3	4-$MeO_2CC_6H_4$	94	83
4[c]	2-thienyl	90	88
5	*n*Hex	93	90
6	Cy	93	96
7	*t*Bu	94	75
8	NMe_2	83	73
9	NPh_2	91	93
10	N(Me)OMe	86	73
11	*N*-morpholinyl	88	86
12[d]	OMe	82	61

[a] All data are the average for two experiments. [b] Yield of purified product. [c] Reaction was run at 0°C. [d] Reaction was run with 20% (*R*)-**3**. Cy = cyclohexyl.

to α-cyano ketones, as both α-cyano amides (including a diphenyl amide and a Weinreb amide) and an α-cyano ester serve as useful substrates (entries 8–11).[26]

However, when we applied this method with either an α-cyano sulfone or an α-cyano phosphonate as the nucleophilic partner, the target cyclopentene was produced with moderate enantioselectivity (<80% *ee*). In contrast, by employing a related biphenyl-derived phosphepine [(*R*)-**4**] as the chiral catalyst, we were able to achieve asymmetric [4+1] annulations with improved *ee* values, thereby enabling the efficient synthesis of enantioenriched α-cyano sulfones,[27] phosphine oxides, and phosphonates (Table 3).

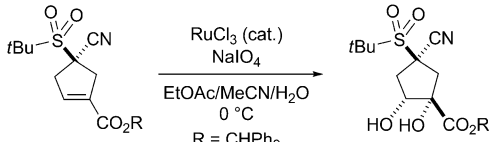
Table 3: α-Cyano sulfones, phosphine oxides, and phosphonates as nucleophiles in phosphepine-catalyzed enantioselective [4+1] annulations.[a]



Entry	X	*ee* [%]	Yield [%][b]
1	SO_2Ph	89	96
2	SO_2Cy	86	89
3	SO_2tBu	94	97
4	$POPh_2$	84	86
5	$PO(OPh)_2$	87	88

[a] All data are the average for two experiments. [b] Yield of purified product.

The cyclopentene products of these catalytic asymmetric [4+1] annulations are well-poised for the introduction of additional stereocenters on the five-membered ring. For example, dihydroxylation and epoxidation of the illustrated α-cyano sulfone affords two new stereocenters with high diastereoselectivity [Eqs. (4) and (5); MCPBA = *meta*-chloroperbenzoic acid].



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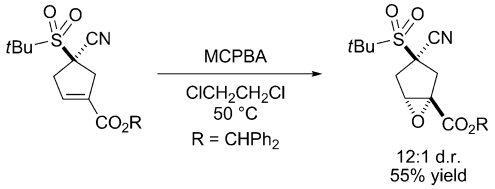
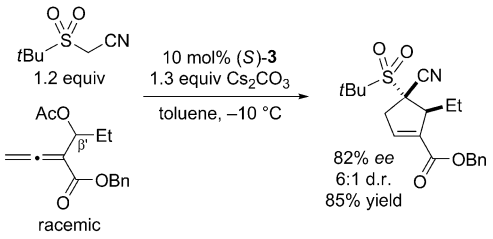


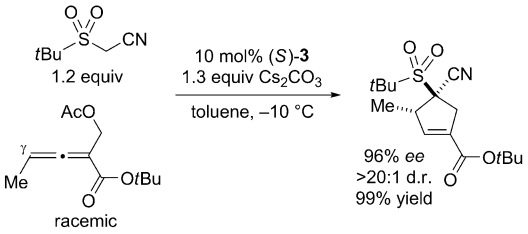
(5)

The ability to achieve enantioselective [4+1] annulations of allenoates which include a substituent in the β′ position would add an important dimension to the scope of this method, as the product would bear contiguous quaternary and tertiary stereocenters. In their original report, Tong and co-workers provided one example of a PPh_3-catalyzed reaction of a β′-substituted allenoate (with benzoylacetonitrile; 2:1 d.r.).[15] In a preliminary study, we have obtained a promising lead with an α-cyano sulfone as the nucleophile [Eq. (6)].[28]



(6)

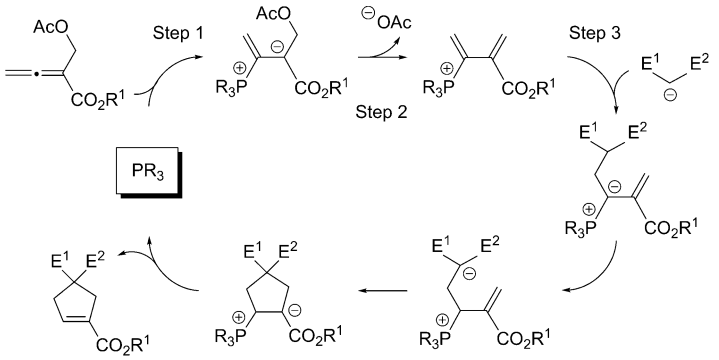
To the best of our knowledge, the [4+1] annulations reported by Tong and co-workers have not previously been described for allenes which bear a γ substituent. We were therefore pleased to observe that (*S*)-**3** not only catalyzes the reaction of such a partner, it also furnishes the desired cyclopentene with a good *ee* value, diastereoselectivity, and yield [Eq. (7)].



(7)

Tong and co-workers have suggested that phosphine-catalyzed [4+1] annulations may proceed through the pathway outlined in Scheme 1.[15] To gain insight into the mechanism of the reaction catalyzed by (*R*)-**3**, we determined the rate law for the coupling illustrated in Table 1. This study was conducted at room temperature without Cs_2CO_3 (under these conditions, the annulation proceeds in 89% *ee* and >95% yield), because of the poor solubility of Cs_2CO_3 in toluene. The rate law for this process is first-order in catalyst and zeroth-order in the nucleophile and the allenoate. Furthermore, according to ^{31}P NMR spectroscopy, the primary resting state of the phosphine during a catalytic asymmetric annulation is not the free phosphine, but instead a phosphonium salt. Taken together, these data are consistent with the suggestion that elementary steps such as Steps 1 and 3 (Scheme 1) are unlikely to be turnover-limiting.

In summary, we have established for the first time that biphenyl-derived axially chiral phosphepines can serve as useful enantioselective nucleophilic catalysts. Specifically, we have applied these phosphines to asymmetric [4+1] annula-



Scheme 1. Outline of a possible pathway for phosphine-catalyzed [4+1] annulations (Tong and co-workers).

tions which provide functionalized cyclopentenes with good *ee* values and yields. An array of either all-carbon quaternary stereocenters or fully substituted heteroatom-bearing stereocenters can be generated in this process from readily available nucleophilic partners. The synthesis of even more highly functionalized/stereochemically rich products is possible through the use of substituted allenoates or through diastereoselective reactions of the product cyclopentenes. Determination of the rate law for a [4+1] annulation catalyzed by phosphepine **3** suggests that the turnover-limiting step occurs after the addition of the chiral phosphine to the allenoate, and likely after the addition of the second coupling partner as well. Additional studies directed at expanding the scope of enantioselective nucleophilic catalysis by chiral phosphines are underway.

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[23] Although we have not yet pursued systematic studies of 3,3′-substituted biphenyl-derived phosphepines, our investigations of binaphthyl-based phosphepines suggest that the substituted aromatic groups in the 3- and 3′-positions may play a significant role in enhancing enantioselectivity.

[24] Exposure of (*R*)-**3** and (*R*)-**4** (as solids) to air for 21 days led to essentially no phosphine oxide (< 5 %) according to ^{31}P NMR spectroscopy. Exposure of toluene solutions to air for 8 days led to about 10 % oxidation of (*R*)-**3** and about 55 % oxidation of (*R*)-**4**.

[25] Notes: a) On a gram-scale, the reaction illustrated in Table 2, entry 1 proceeded in 93 % *ee* and 76 % yield (1.12 g), with 88 % recovery of the catalyst as the phosphine oxide (after oxidation with *t*BuOOH); b) The absolute configurations of eight of the [4+1] annulation products described herein were determined by X-ray crystallography (see the Supporting Information).

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[28] Notes: a) The minor diastereomer is formed in 28 % *ee*; b) We have not yet examined the impact of the choice of ester on the *ee*, d.r., and yield.

