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Phosphine-Catalyzed Enantioselective [4 + 3] Annulation of Allenoates with C,N-Cyclic Azomethine Imines: Synthesis of Quinazoline-Based Tricyclic Heterocycles

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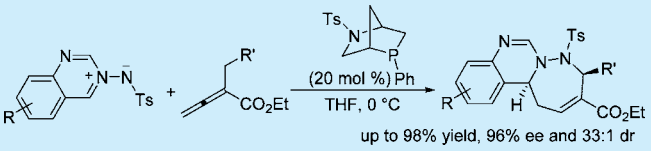
Supporting Information

ABSTRACT: With the use of a commercially available chiral phosphine as the catalyst, the first catalytic enantioselective [4 + 3] annulation of allenoates with C,N-cyclic azomethine imines is developed. The reaction works efficiently under mild reaction conditions to afford seven-membered ring-fused quinazoline-based tricyclic heterocycles in high yields with good to excellent diastereo- and enantioselectivities.



Quinazoline occurs as a key heterocyclic motif in a wide range of synthetic drugs, pharmaceuticals, agrochemicals, bioactive natural products, and materials.[1] Quinazoline derivatives have showed extremely diverse biological activities such as anticancer, anti-inflammatory, antimalarial, antihypertensive, anticonvulsant, and antituberculosis activities.[1] Numerous quinazoline-based commercial drugs such as Gefitinib, Erlotinib, Canertinib, Afatinib, and Vandetanib have demonstrated the importance of quinazoline pharmacophore. Many multicyclic quinazoline derivatives also displayed exceptional bioactivities such as insecticidal, antiasthmatic, antitumor, and antihypertensive activity.[1] Beyond these bioactive functions, quinazoline and its derivatives had been used as building blocks for synthesis of natural alkaloids.[2] Since quinazoline derivatives are commonly evaluated in drug discovery efforts, continuous efforts have been devoted to the development of synthetic methods for novel quinazoline derivatives.[1]

Azomethine imines, which are easily accessible and stable compounds, have extensively been employed as efficient 1,3-dipoles in cycloaddition reactions for the synthesis of various dinitrogen-fused heterocyclic frameworks.[3] Their asymmetric [3 + 2] cycloaddition reactions had been intensely studied. Numerous metal or organocatalyst-catalyzed asymmetric [3 + 2] cycloaddition reactions of azomethine imines with alkenes,[4] alkynes,[5] aldehydes,[6] cyclobutenone,[7] arylacetic acid derivatives,[8] allenoates,[9] or azlactones[10] have been developed to provide five-membered nitrogen-containing heterocycles. A few metal or organocatalyst-catalyzed asymmetric [3 + 3] cycloaddition reactions of azomethine imines have also been reported for synthesis of six-membered dinitrogen-fused heterocycles.[6c,11−14] In contrast, asymmetric higher-order cycloaddition of azomethine imines such as [4 + 3] cycloaddition has received much less attention and successful examples are extremely rare. *N*-Heterocyclic carbene-catalyzed enantioselective cycloaddition of azomethine imines and enals represented the only asymmetric [4 + 3] example, providing a simple excess to chiral hexahydropyrazolodiazepinone derivatives.[15] Since seven-membered heterocyclic moieties play a key role in many biologically active compounds, and at the same time, the construction of seven-membered ring is a challenging task,[16] developing new annulation reaction for the synthesis of seven-membered ring-fused heterocycles is highly desirable.

Chiral phosphine-catalyzed asymmetric annulation reactions have seen rapidly growing use in the assembly of synthetically useful or biologically significant complex carbocyclic and heterocyclic scaffolds[17] and natural products.[18] A variety of asymmetric annulation reactions have been achieved for the construction of four-, five-, and six-membered cyclic skeletons.[17] Among these annulation reactions, phosphine-catalyzed [4 + 3] annulations have less been explored, only limited successful nonasymmetric examples were reported.[19] Especially, to the best of our knowledge, no asymmetric [4 + 3] annulation catalyzed by chiral phosphine has yet been developed to access seven-membered ring in a enantioselective form.

Azomethine imines have successfully been applied in phosphine-catalyzed asymmetric [3 + 2] and [3 + 3] annulations for synthesis of chiral dinitrogen-fused heterocycles (Scheme 1a−c),[9,14,19b] but their asymmetric [4 + 3] annulation under phosphine catalysis remains unsolved. From a mechanistic perspective, phosphine-catalyzed annulations are typically postulated to involve the in situ formation of phosphonium (di)enolate zwitterions, which subsequently undergo coupling with electrophiles. However, phosphonium (di)enolate zwitter-

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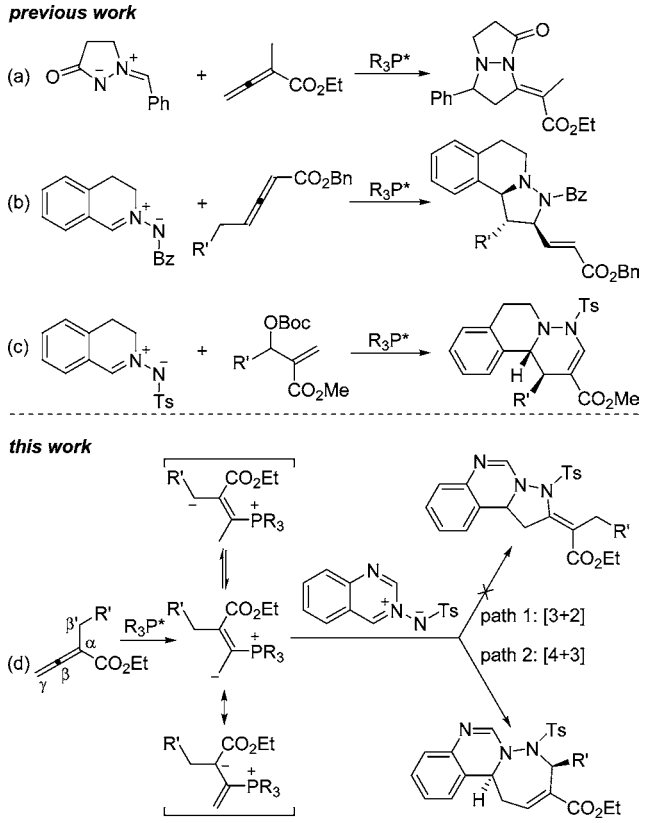
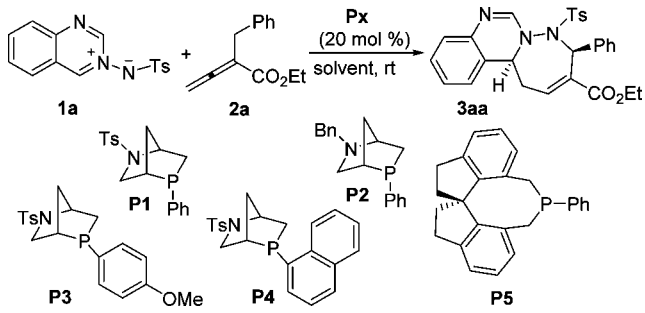
Scheme 1. Phosphine-Catalyzed Asymmetric Annulations of Azomethine Imines



ions from α-substituted allenoates may act as two- or four-carbon synthon; the competing [3 + 2] and [4 + 3] paths may concurrently exist (Scheme 1d), leading to low chemoselectivity and poor yields for [4 + 3] cycloadducts. Hence, development of phosphine-catalyzed asymmetric [4 + 3] annulation is certainly difficult. Herein, we present the first example of chiral phosphine-catalyzed enantioselective [4 + 3] annulation reaction, affording chiral seven-membered ring-fused quinazoline-based tricycles with high chemo-, diastereo-, and enantioselectivity (Scheme 1d).

Since quinazoline derivatives have widely been applied in discovery of novel bioactive compounds,[1] it promoted us to choose quinazoline-based azomethine-imines as 1,3-dipole for the phosphine-catalyzed annulations. We initially explored the reaction of azomethine imine **1a** with allenoate **2a** with the use of commercially available chiral phosphines as the catalyst (Table 1). In the presence of Kwon phosphine **P1**, allenoate **2a** reacted smoothly with azomethine imine **1a** in dichloromethane at room temperature to give the desired product **3aa** in 90% yield with good dr (9:1) and 80% ee (entry 1). In particular, the reaction displayed excellent chemoselectivity, and no [3 + 2] annulation product was observed. We next screened other phosphines to improve diastereo- and enantioselectivity. Benzyl-substituted Kwon phosphine **P2** could catalyze the reaction to afford the product **3aa** in excellent yield, albeit with moderate diastereo- and enantioselectivity (entry 2). Phosphines **P3** and **P4** displayed similar catalytic capability to that of **P1** (entries 3−4). Although spirocyclic phosphine **P5** could also deliver 80% ee, it only gave **3aa** in 46% yield with poor dr (entry 5). With the use of Kwon phosphine **P1** as the catalyst, the solvent screening revealed that THF is the optimal solvent, providing the product **3aa** in 95%

Table 1. Screening of Reaction Conditions[a]



entry	Px	solvent	t (h)	yield (%)[b]	dr[c]	ee (%)[c]
1	**P1**	CH_2Cl_2	4	90	9:1	80
2	**P2**	CH_2Cl_2	5	91	5:1	50
3	**P3**	CH_2Cl_2	5	92	7:1	72
4	**P4**	CH_2Cl_2	5	76	6:1	80
5	**P5**	CH_2Cl_2	7	46	1.3:1	80
6	**P1**	DCE[d]	6	95	9:1	80
7	**P1**	$CHCl_3$	9	70	7:1	60
8	**P1**	toluene	12	85	8:1	83
9	**P1**	THF	7	95	11:1	87
10[e]	**P1**	THF	30	97	20:1	94

[a]Unless otherwise specified, all reactions were performed with **1a** (0.125 mmol), **2a** (0.19 mmol), and catalyst (0.025 mmol) in 2 mL of solvent at room temperature. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]DCE: 1,2-dichloroethane. [e]The reaction was performed at 0 °C.

yield with 11:1 dr and 87% ee (entries 6−9). To our delight, a decrease in temperature to 0 °C could remarkably enhance stereoselectivities, leading to **3aa** in 97% yield with 20:1 dr and 94% ee (entry 10). Notably, even the amount of azomethine imine **1a** was scaled up to 0.6 g, the reaction still proceeded very well under the optimal conditions to afford the cycloadduct **3aa** in 95% yield with 20:1 dr and 93% ee. Obviously, there was no significant loss of diastereoselectivity, enantioselectivity, and yield, compared with the reaction at 0.125 mmol of scale (Table 1).

With the optimal reaction conditions in hand, further studies were focused on the evaluation of the substrate scope of α-substituted allenoates in this asymmetric [4 + 3] annulation (Table 2). Various allenoates bearing both electron-donating and withdrawing groups on benzene ring reacted with azomethine imine **1a**, providing the seven-membered ring-fused tricyclic heterocyclic products **3** in excellent yields (93−98%) with good to excellent diastereoselectivities and excellent enantioselectivities (90−96%) (entries 1−17). The electronic properties of substituents on benzene ring have little effect on the yields, diastereo-, and enantioselectivities (entries 1−17). The steric properties have also not remarkable effect on the yields and enantioselectivities but seem to have significant influence on diastereoselectivities. For example, an *ortho*-chloro substituent on benzene ring could lead to relative low diastereoselectivity (entry 10), which might be caused by the large steric hindrance between *ortho*-chloro-substituted aryl group and 3,4-dihydroquinazoline ring. 2-Naphthyl-substituted allenoate (**2r**) displayed good compatibility with the standard reaction conditions, providing the desired product **3ar** in good yield with excellent diastereo- and enantioselectivity (entry 18). A special carboxylate-substituted allenoate **2s** also worked well to produce the cycloadduct **3as** in high yield with 20:1 dr and 95% ee (entry 19). Particularly, alkyl substituted allenoates **2t** and **2u** were

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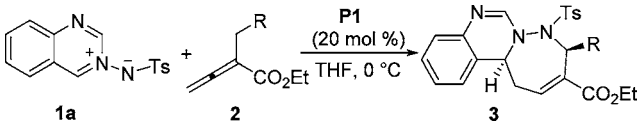
Table 2. Substrate Scope with Respect to Allenoates[a]



entry	R	t (h)	3	yield (%)[b]	dr[c]	ee (%)[c]
1	Ph (**2a**)	30	**3aa**	97	20:1	94
2	3-MeC_6H_4 (**2b**)	72	**3ab**	97	20:1	92
3	4-MeC_6H_4 (**2c**)	72	**3ac**	95	25:1	92
4	3-$MeOC_6H_4$ (**2d**)	44	**3ad**	96	25:1	93
5	3,5-$MeO_2C_6H_3$ (**2e**)	20	**3ae**	95	20:1	95
6	4-*t*-BuC_6H_4 (**2f**)	36	**3af**	96	25:1	94
7	2-FC_6H_4 (**2g**)	40	**3ag**	96	14:1	96
8	3-FC_6H_4 (**2h**)	27	**3ah**	95	19:1	94
9	4-FC_6H_4 (**2i**)	30	**3ai**	98	33:1	94
10	2-ClC_6H_4 (**2j**)	60	**3aj**	94	5:1	90
11	3-ClC_6H_4 (**2k**)	12	**3ak**	98	20:1	94
12	4-ClC_6H_4 (**2l**)	43	**3al**	96	25:1	93
13	3-BrC_6H_4 (**2m**)	12	**3am**	93	20:1	94
14	4-BrC_6H_4 (**2n**)	30	**3an**	96	25:1	96
15	3-$CF_3C_6H_4$ (**2o**)	12	**3ao**	95	17:1	94
16[d]	4-$CF_3C_6H_4$ (**2p**)	12	**3ap**	98	30:1	94
17	4-$CO_2MeC_6H_4$ (**2q**)	72	**3aq**	98	15:1	96
18	2-naphthyl (**2r**)	72	**3ar**	82	16:1	94
19	CO_2Et (**2s**)	10	**3as**	60	20:1	95
20	H (**2t**)	72	**3at**	70		90
21	Me (**2u**)	96	**3au**	95	20:1	70

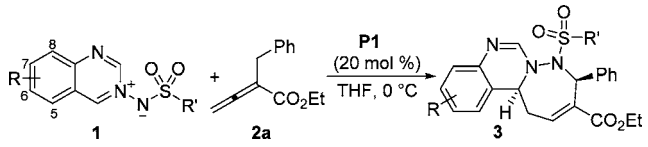
[a]Unless otherwise specified, all reactions were performed with **1a** (0.125 mmol), **2** (0.19 mmol), and **P1** (0.025 mmol) in THF (2 mL) at 0 °C. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]At 5 °C.

compatible with the current phosphine catalysis conditions (entries 20−21). *α*-Methyl allenoate **2t** underwent the reaction to give the product **3at** in 70% yield and 90% ee (entry 20), in contrast, *α*-ethyl allenoate **2u** showed excellent reactivity and diastereoselectivity but lower enantioselectivity (entry 21). The absolute configurations of the [4 + 3] annulation products were determined by the single-crystal X-ray diffraction analysis of the product **3am**.[20]

The scope of azomethine imines was also evaluated, and the results are shown in Table 3. 6-Fluoro-substitued azomethine imine **1b** performed efficiently to afford the corresponding product **3ba** in excellent yield with 30:1 dr and 94% ee. Strangely, 7-bromo-substitued azomethine imine **1c** provided inferior results, in comparison with the substrate **1b**. Although 7-bromo substituent is far from the reactive center, it displayed significant negative effect on the reactivity and selectivity, leading to the product **3ca** with lower yield, diastereo-, and enantioselectivity. The reaction of electron-rich azomethine imine **1d** with allenoate **2a** proceeded smoothly to give the cycloadduct **3da** in 97% yield with 30:1 dr and 90% ee. Variation of arylsulfonyl protecting groups in azomethine imines were well tolerated, giving the desired cycloadducts (**3ea**−**3ia**) in excellent yields with excellent diastereo- and enantioselectivities.

Since diazepines are important bioactive molecules[21] and also functioned as key scaffolds in asymmetric synthesis,[22] we explored their synthesis with the products **3** as the starting material. As shown in Table 4, treatment of the products **3** with mCPBA in DCE at 40 °C for 12 h led to oxidation-ring-opening of tricyclic heterocycles, affording chiral 2,3,4,7-tetrahydro-1*H*-

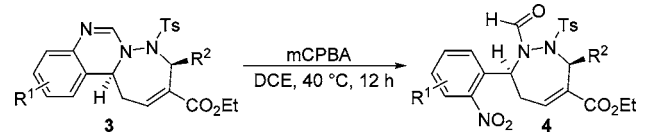
Table 3. Substrate Scope with Respect to Azomethine Imines[a]



entry	1 (R/R′)	t (h)	3	yield (%)[b]	dr[c]	ee (%)[c]
1	6-F/4-MeC_6H_4 (**1b**)	16	**3ba**	96	30:1	94
2[d]	7-Br/4-MeC_6H_4 (**1c**)	96	**3ca**	85	8:1	83
3	6-Me/4-MeC_6H_4 (**1d**)	72	**3da**	97	30:1	90
4	H/Ph (**1e**)	72	**3ea**	96	20:1	93
5	H/2-MeC_6H_4 (**1f**)	40	**3fa**	95	11:1	92
6	H/4-$MeOC_6H_4$ (**1g**)	16	**3ga**	91	20:1	93
7	H/4-*t*-BuC_6H_4 (**1h**)	40	**3ha**	98	20:1	93
8	H/4-ClC_6H_4 (**1i**)	42	**3ia**	96	13:1	92

[a]Unless otherwise specified, all reactions were performed with **1a** (0.125 mmol), **2** (0.19 mmol), and **P1** (0.025 mmol) in THF (2 mL) at 0 °C. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]In DCM (2 mL) at 5 °C.

Table 4. Oxidation-Ring-Opening of Tricyclic Products 3[a]

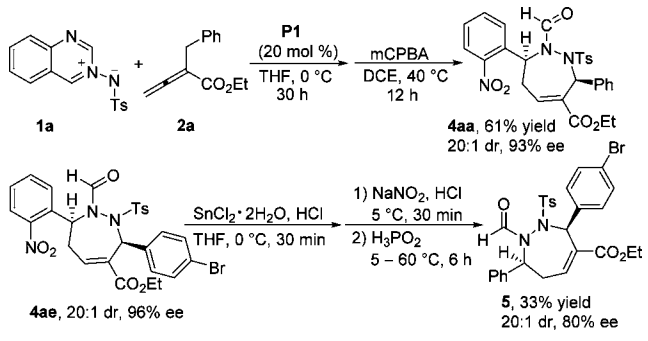


entry	R^1 in **4**	R^2 in **4**	**4**	yield (%)[b]	dr[c]	ee (%)[c]
1	H	Ph	**4aa**	73	20:1	92
2	H	4-MeC_6H_4	**4ab**	85	20:1	92
3	H	2-FC_6H_4	**4ac**	84	20:1	92
4	H	4-ClC_6H_4	**4ad**	70	25:1	93
5	H	4-BrC_6H_4	**4ae**	78	20:1	96
6	H	2-naphthyl	**4af**	72	16:1	93
7	H	CO_2Et	**4ag**	71	20:1	95
8	5-F	Ph	**4ba**	86	30:1	94

[a]Unless otherwise specified, all reactions were performed with **3** (0.1 mmol) and **mCPBA** (0.8 mmol) in DCE (2 mL) at 40 °C for 12 h. [b]Isolated yield. [c]Determined by chiral HPLC analysis.

1,2-diazepine derivatives **4** in 70−86% yield and 92−96% ee. Various tricyclic products (**3**) succumbed to the oxidation conditions, giving the diverse chiral monocyclic products with retention of diastereo- and enantiochemistry. It is worth noting that the synthesis of **4aa** could be achieved through one-pot sequential annulation/oxidation-ring-opening reaction in 61% yield with 20:1 dr and 93% ee (Scheme 2). Furthermore,

Scheme 2. Oxidation-Ring-Opening of Tricyclic Products 3



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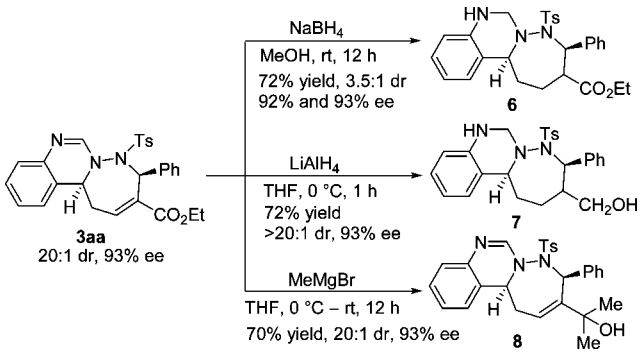
reduction of nitro group in **4ae** followed by diazotization and treatment with H_3PO_2 can remove NO_2 to give the compound **5**. Other synthetic utility of the products had also been investigated. As illustrated in Scheme 3, with the use of $NaBH_4$ as the reducing

Scheme 3. Synthetic Applications of the Products 3



agent, both alkene and imine moieties of the product **3aa** were reduced to give the compound **6**. In the presence of $LiALH_4$, imine and ester moieties were all reduced to afford the alcohol **7** in 72% yield without loss of dr and ee. The addition of the Grignard reagent to the ester moiety led to the alcohol product **8**.

In summary, we have developed the first catalytic enantioselective [4 + 3] annulation of allenoates with azomethine imines using a commercially available chiral phosphine. A wide range of substrates with regard to both the allenoates and azomethine imines were tolerated. The reaction worked very well at hundreds of milligram scale. The products were further transformed into other biologically significant compounds, specifically, with the use of an oxidation-ring-opening procedure, chiral monocyclic diazepine derivatives were synthesized.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02885.

Experimental procedure, characterization data, HPLC analysis data, NMR spectra, and X-ray crystallographic data (PDF)

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Notes

The authors declare no competing financial interest.

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