Cycloaddition

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Phosphine-mediated Highly Enantioselective Spirocyclization with Ketimines as Substrates

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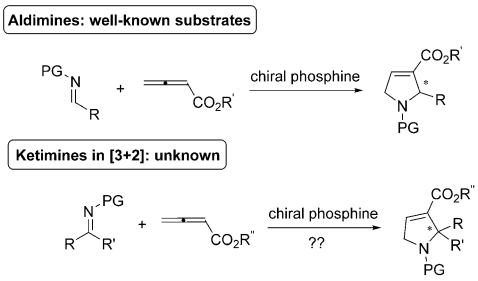
Abstract: *Phosphine-catalyzed enantioselective annulation reactions involving ketimines are a daunting synthetic challenge owing to the intrinsic low reactivity of ketimine substrates. A highly enantioselective [3+2] cycloaddition reaction that makes use of isatin-derived ketimines as reaction partners was developed. Notably, both simple and γ-substituted allenoates could be utilized, and various 3,2′-pyrrolidinyl spirooxindoles with a tetrasubstituted stereocenter were obtained in excellent yields and with nearly perfect enantioselectivity (>98% ee in all cases).*

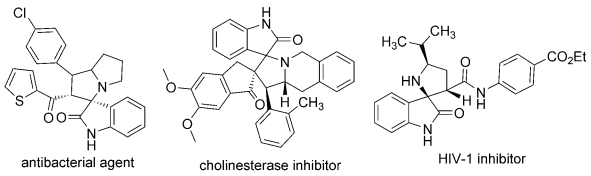
The ubiquity of spirocyclic frameworks in natural products has long been a factor in galvanizing organic chemists to explore their preparation through the construction of carbocyclic and heterocyclic precursors. Among established strategies, phosphine-triggered annulation reactions have proven to be an efficient and versatile approach ever since the pioneering discovery of phosphine-catalyzed [3+2] cyclization by Lu and co-workers.[1] Nitrogen-containing ring systems are prevalent molecular architectures that are widely found in natural products and are extremely valuable as synthetic intermediates. Phosphine-catalyzed allene–imine annulation[2] is one of the most powerful methods for constructing such motifs, and has been widely employed in numerous syntheses of natural products and bioactive molecules.[3] In the vast majority of reported examples, aldehyde-derived aldimines are the electrophilic reaction partners utilized in these reactions. Ketimines, on the other hand, are seldom used. The unpopularity of ketimines in phosphine catalysis is likely due to their intrinsic low reactivity, steric bulkiness, and the associated difficulty with stereochemical control. There are only two reports to date in which ketimines are employed for phosphine catalysis in a non-stereoselective manner,[4] and only one enantioselective example by Sasai and co-workers, which describes the use of cyclic ketimines in [4+2] annulation with allenoates.[5] Notably, the cyclic ketimines utilized by Sasai et al. were rather special and the reaction suffered from a relatively narrow substrate scope. As part of our continued interests in phosphine catalysis,[6] we became interested in developing an efficient strategy for the use of ketimine substrates in common phosphine-mediated annulation reactions for the construction of molecular structures of biological significance (Scheme 1).



Scheme 1. Utilization of imines in phosphine-catalyzed annualtion reactions.

Spirooxindoles are prominent structural motifs that are often found in natural products. Among different spirooxindole cores, the pyrrolidinyl spirooxindole frameworks represent a very important class owing to their excellent bioactivity profiles. Most of the current research efforts have been focused on the synthesis of 3,3′-pyrrolidinyl spirooxindoles,[7] however, 3,2′-pyrrolidinyl spirooxindoles are also undeniably important and display a broad spectrum of biological activities[8] (Scheme 2). There are only a handful of reports describing the synthesis of 3,2′-pyrrolidinyl scaffolds,[9] and these methods either employ very specific substrates or suffer from a narrow reaction scope. A novel approach for the efficient construction of such important structural motifs with broad substrate scope is thus highly desirable.

Our group has been intensively investigating enantioselective processes promoted by amino acid-derived phosphine catalysts over the past few years.[10] In particular, we have



Scheme 2. Examples of bioactive 3,2′-pyrrolidinyl spirooxindoles.

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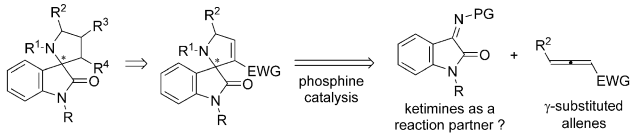
a keen interest in devising annulation strategies to access either synthetically useful or biologically significant cyclic structures, for example, [3+2] annulations,[11] [4+2] cycloadditions,[12] and [4+1] cyclizations.[13] For the efficient creation of 3,2′-pyrrolidinyl spirooxindoles, which contain a tetrasubstituted stereogenic center at the 3-position, we reasoned that a phosphine-catalyzed cycloaddition reaction employing isatin-derived ketimines would be an ideal strategy (Scheme 3). However, the reactivity of the ketimine starting



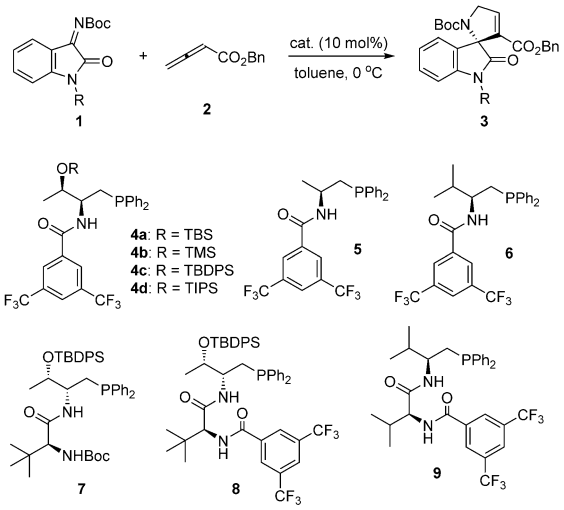
Scheme 3. Utilization of isatin-derived ketimines in phosphine-catalyzed reactions.

materials poses serious challenges. Despite the widespread use of isatin-derived ketimines in other reactions, for example, Mannich reactions,[14] Strecker reactions,[15] (aza) Friedel–Crafts additions,[16] aza-Morita–Baylis–Hillman reactions,[17] and aza-Henry reactions,[18] they have never been used in phosphine-catalyzed annulation reactions. We hypothesized that our amino acid based phosphine catalysts may provide sufficient activation for the challenging ketimine substrates, since such phosphines are very nucleophilic and are not hindered owing to the direct linkage of the phosphorus atom to a primary carbon. To make our method amenable for the synthesis of multisubstituted 3,2′-pyrrolidinyl spirooxindoles, we envisaged that γ-substituted allenes[19] could be used as reaction partners. Herein, we disclose the first phosphine-catalyzed [3+2] annulation with isatin-derived ketimines and simple/γ-substituted allenoates to form 3,2′-pyrrolidinyl spirooxindoles in a highly enantioselective manner.

We started our investigations by examining the cycloaddition of benzyl 2,3-butadienoate **2** with isatin-derived ketimines **1** in the presence of amino acid derived phosphine catalysts (Table 1). L-Threonine-derived phosphine amide catalysts (**4a**–**4d**) displayed remarkable catalytic activity, affording the desired spirocyclic 3-oxindolo-pyrrolines in good yields and with excellent *ee* values, and O-TBS-derived **4a** was found to be the best catalyst (Table 1, entries 1–4). All the other amino acid based phosphines were less effective (Table 1, entries 5–9). We further tested various N substituents on the ketimine scaffords and found that the N-Boc substrate **1a** was the most suitable (Table 1, entries 10–13). Under the optimized conditions, the reaction ran to completion in just a few minutes and afforded the desired annulation product **3a** in 83% yield and 98.9% *ee*.

With the optimized reaction conditions in hand, we subsequently established the scope of the reaction (Table 2). Ketimines derived from a wide range of isatin structures were all well tolerated, regardless of the electronic nature and substitution pattern of the aryl moieties of the ketimines. In all the cases examined, 3,2′-pyrrolidinyl spirooxindoles were produced in good yields and with 99% *ee* (Table 2, entries 1–14). Furthermore, the reaction could be repeated on a larger

Table 1: Enantioselective [3+2] cycloaddition of an allenoate **2** with ketimines **1**: reaction screening.[a]



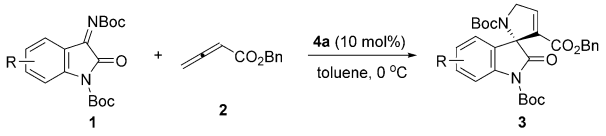
Entry	R/**1**	Cat.	*t* [min]	Yield [%][b]	*ee*[%][c]
1	Bn/**1a**	**4a**	30	82	95
2	Bn/**1a**	**4b**	30	78	90
3	Bn/**1a**	**4c**	30	83	86
4	Bn/**1a**	**4d**	30	85	91
5	Bn/**1a**	**5**	30	62	73
6	Bn/**1a**	**6**	30	72	67
7	Bn/**1a**	**7**	30	77	−53
8	Bn/**1a**	**8**	30	81	−76
9	Bn/**1a**	**9**	30	56	59
10	Me/**1b**	**4a**	10	65	93
11	Ph/**1c**	**4a**	5	92	93
12	Ac/**1d**	**4a**	5	79	98
13	Boc/**1e**	**4a**	5	81	99

[a] Reactions were performed with **1** (0.10 mmol), **2** (0.12 mmol) and **4a** (0.01 mmol) in toluene (1 mL) at 0°C. [b] Yield of isolated product. [c] The *ee* value was determined by HPLC analysis on a chiral stationary phase. TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl, TBDPS = *tert*-butyldiphenylsilyl, TIPS = triisopropylsilyl.

scale (Table 2, entry 15). The absolute configurations of the annulation products were assigned based on X-ray crystallographic analysis of **3h**.[20]

Since the utilization of γ-substituted allenes in the annulation reaction should result in the facile preparation of multisubstituted 3,2′-pyrrolidinyl spirooxindoles, we proceeded to test the feasibility of such reactions (Table 3). Allenes with both alkyl and aryl substituents at the γ-positions were found to be suitable for the reaction, and so were different isatin scaffolds. In all the examples examined, *ee* values of more than 98.0% were consistently obtained. In general, reactions of more sterically hindered γ-substituted allenoates proceeded with higher diastereoselectivity. Nota-

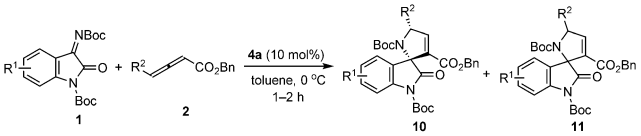
Table 2: The scope of **4a**-triggered [3+2] annulation of allene **2** with isatin-derived ketimines (**1**).[a]

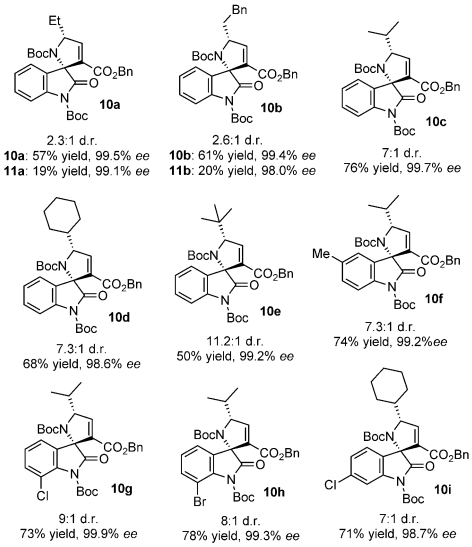


Entry	R	3	t [min]	Yield [%][b]	ee[%][c]
1	H	**3e**	5	83	98.9
2	4-Br	**3f**	5	80	99.9
3	4-Cl	**3g**	5	83	99.2
4	5-CH_3	**3h**	5	72	98.7
5	5-I	**3i**	30	82	99.0
6	5-OCH_3	**3j**	5	81	98.7
7	6-OCF_3	**3k**	5	75	98.9
8	6-Cl	**3l**	30	78	99.5
9	6-Br	**3m**	10	85	98.9
10	7-F	**3n**	30	71	99.6
11	7-Cl	**3o**	5	78	98.8
12	7-Br	**3p**	5	84	99.5
13	4,7-Cl	**3q**	5	72	99.7
14	5,7-CH_3	**3r**	5	83	99.4
15[d]	H	**3e**	5	81	99.0

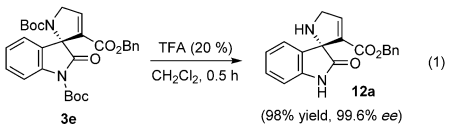
[a] Reactions were performed with **1** (0.10 mmol), **2** (0.12 mmol)and **4a** (0.01 mmol) in toluene (1 mL) at 0°C. [b] Yield of isolated product. [c] The *ee* value was determined by HPLC analysis on a chiral stationary phase. [d] The reaction was performed at 1 mmol scale.

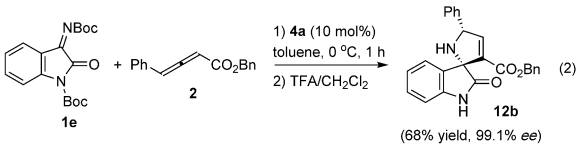
Table 3: Use of γ-substituted allenes in **4a**-triggered [3+2] annulation with ketimines (**1**).[a]





The reactions were performed with **1** (0.1 mmol), **2** (0.12 mmol), catalyst **4a** (0.01 mmol) in toluene (1 mL) at 0°C for 1 to 2 h. The d.r. ratios were determined by crude ^{1}H NMR analysis and the *ee* values were determined by HPLC analysis on a chiral stationary phase.





bly, all of the diastereomers were easily separable by silica-gel column chromatography. Accordingly, we obtained diastereomerically pure 3,2′-pyrrolidinyl spirooxindoles in nearly enantiomerically pure form (>98.0% *ee*). The absolute configurations of the products were assigned on the basis of X-ray crystallographic analysis of **10b**.[21]

In phosphine-catalyzed reactions involving imines, the nitrogen atom of the imine is commonly linked to a highly electron-withdrawing group, for example, a tosyl group, to render the substrate sufficiently reactive. However, such an activating group on nitrogen is often troublesome to remove at the end of the synthesis. Notably, the N-Boc ketimines employed in this study were sufficiently active, which made this method easily amenable to practical synthesis. Removal of the Boc protection in the annulation product **3e** was readily achieved by treating it with trifluoroacetic acid (TFA) to afford 3,2′-pyrrolidinyl spirooxindole **12a** in 98% yield and 99.6% *ee* [Eq. (1)]. The spirooxindole **12b** resulting from the cyclization involving γ-phenyl allenoate could also be obtained as a single diastereomer with excellent enantiomeric control upon cleavage of the Boc group by TFA treatment [Eq. (2)].

In conclusion, we have successfully applied ketimines for the first time in a highly enantioselective phosphine-catalyzed [3+2] annulation reaction. The use of isatin-derived ketimines and simple/γ-substituted allenoates as reaction partners led to the facile preparation of structurally novel and biologically significant 3,2′-pyrrolidinyl spirooxindoles in a highly enantioselective manner. We are currently investigating the use of other ketimines in phosphine-catalyzed enantioselective processes and evaluating the biological profiles of the spirooxindole structures synthesized.

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Keywords: [3+2] cycloaddition · acyclic ketimines · amino acids · phosphine catalysts · spirooxindoles

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[21] CCDC 1443731 contains the supplementary crystallographic data for this compound.

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