Asymmetric Phosphine Catalysis

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Engaging Allene-Derived Zwitterions in an Unprecedented Mode of Asymmetric [3 + 2]-Annulation Reaction

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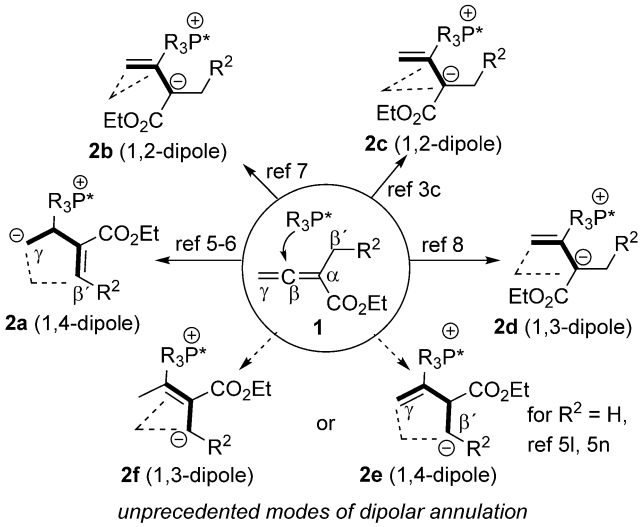
Dedicated to Professor Mohan Paul S. Ishar

Abstract: *Catalytic addition of chiral phosphine, that is, (R)- or (S)-SITCP, to an α-substituted allene ester generated a zwitterionic dipole. Under optimized reaction conditions, this dipole could engage isatine-derived N-Boc-ketimines in a novel mode of [3+2] annulation reaction. Pyrrolinyl spirooxindoles are thus afforded in high yields and with excellent enantioselectivities. The unprecedented annulation reaction successfully facilitated the construction of sp^3-rich and highly substituted 3,2′-pyrrolidinyl spirooxindoles supporting many chiral centers.*

Phosphine-catalyzed dipolar annulation reactions are one of the important classes of organocatalytic transformations, which are used to build a wide array of carbo- and heterocycles from simple building blocks.[1] Particularly, the annulation reactions of allene esters by nucleophilic phosphine catalysis have been employed with various electrophilic reagents.[2] Addition of a tertiary phosphine to allene ester **1** supporting substitution at β′-position generates a zwitterion that might trap different electrophilic substrates in one or more dipolar forms (**2a**–**e**; Scheme 1) and thereby deliver a range of diverse products. Manipulating novel variations of arresting the zwitterions **2** in dipolar annulation reactions in a highly selective and asymmetric fashion is an intriguing and a formidable synthetic challenge.[3] However, recent emergence of a range of structurally complex phosphines of diverse electronic as well as steric nature calls to exploit their immense potential in nucleophilic catalysis and building novel molecular architectures in asymmetric fashion. In this regard, novel modes of asymmetric annulation reaction engaging zwitterion **2** to deliver novel, structurally complex, and privileged architectures that could inspire diverse biological research programs are amongst the most interesting synthetic challenges.[4]



Scheme 1. Diverse modes of dipolar trapping of α-substituted allene esters derived zwitterions.

The zwitterionic dipole **2** may exist in different isomeric forms (**2a**–**f**) but has mostly been recognized by various electrophiles in [4+2] annulation reactions (1,4-dipole **2a**)[5] and by different nucleophilic substrates in [4+1] annulation reactions.[6] Zwitterions derived from α-substituted allene esters had also performed as 1,2-dipole (**2b**) in their reactions with azomethine imines, allylic alcohols, aromatic aldehydes, and α,β-unsaturated ketoesters.[7,2e] Phosphine-mediated annulation of allenoate **1** with dialkyl azodicarboxylate could selectively trap 1,2-dipole **2c**.[3c] α,β-Unsaturated iminoesters successfully trapped 1,3-dipole **2d** affording cyclopentene derivatives.[8] It is implied that the reactivity of zwitterion **2** is modulated by the nature of electrophilic partner as well as the structural features of the phosphines employed as catalysts in these dipolar annulation reactions. Hence, the mission of pursuing new electrophilic substrates exhibiting novel reactivity pattern for effective application in building unique and complex heterocycles is a major campaign in the field of asymmetric nucleophilic catalysis. This condition urged us to employ *N*-Boc isatinimines **3**, which are readily accessible yet underexplored in asymmetric synthetic chemistry. We were intrigued and motivated by the possible new modes of annulation reactions affording novel aza-ring

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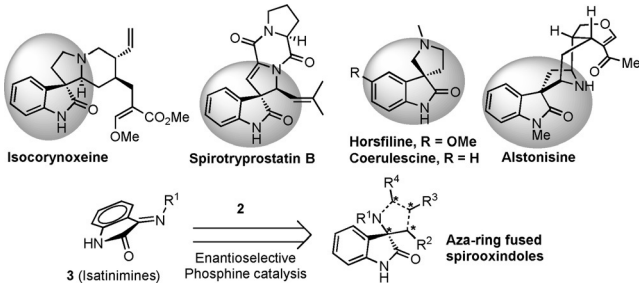
fused spirooxindoles (Scheme 1). Herein, we report the first diastereo- and enantioselective phosphine-catalyzed [3+2] annulation reaction of α-substituted allene esters (β–β′ 1,3-dipole) with isatine-derived ketimines that provides a facile access to 3,2′-pyrrolidinyl-spirooxindoles.

Only a few asymmetric synthesis methods are known to build spirooxindole scaffold, which represents a number of complex and diversely bioactive natural products and therapeutically relevant synthetic small molecules (Scheme 2).[9] In particular, synthetic access to aza-ring fused spirooxindole class of small molecules is dominated by [3+2] cycloaddition reactions of isatine-derived olefins with azomethine ylides.[10] Therefore novel asymmetric chemical transformations to build highly substituted aza-ring fused spirooxindoles need to be discovered.

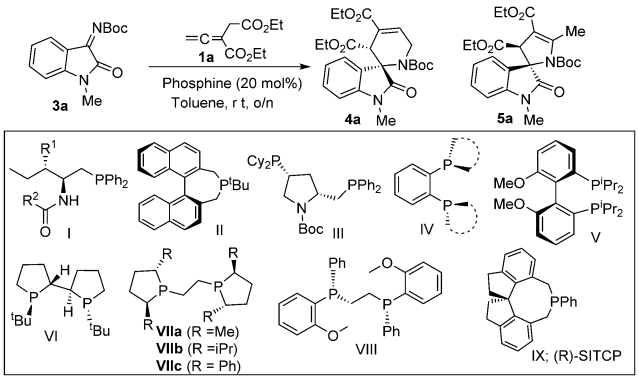


Scheme 2. Synthetic access to biologically relevant aza-spirooxindoles.

In view of the fact that steric and electronic nature of phosphine catalysts greatly influence the mode of an annulation reaction, our initial efforts commenced with a screening of various phosphine catalysts for an annulation reaction of allene ester **1a** with isatinimine **3a** (Scheme 1 and 2, Table 1; Supporting Information, Table S1). The reaction of the zwitterion **2** (generated by addition of 20 mol% of P*n*Bu$_3$ to **1a**) with isatinimine **3a** delivered a major product as a mixture of two diastereoisomers in good yield (entry 1, Table 1), which was identified as a [4+2] annulation adduct **4a**. Surprisingly, a minor but novel [3+2] adduct **5a** was also formed in very low yield. To the best of our knowledge, both **4a** and **5a** are products of novel annulation reactions of allenoate **1** with ketimine **3a**. Adduct **4a** depicts an inverted regioselectivity of annulation (**2e**, β′-addition to the imine; Scheme 1) as compared to previously reported [4+2] reactions of aldimines with **2** (**2a**, γ-addition to imine).[5b,c] Only in rare cases where α-methyl allene ester was used for a zwitterionic [4+2] annulation reaction with cyclic imine was this mode of annulation reported.[5l,n] On the other hand, the minor product **5a** although formed in trace amount is generated via an unprecedented mode of [3+2] annulation reaction of β′-substituted allene esters with isatinimines.

Unexpectedly, triphenylphosphine failed to catalyze the reaction (see the Supporting Information, Table S1 for details). On the other hand, trialkylphosphines efficiently catalyzed the annulation reaction to yield [4+2] adduct **4a** (entries 1–3, Table 1). However, the yield for **5a** remained disappointingly low in all these cases suggesting to employ more nucleophilic phosphines as catalysts. Recently, we had

Table 1: Optimization conditions for novel [3+2] annulation reaction.[a]



No.	Cat.	Conv.[b]	Yield [%][c] 4a	5a	d.r.[d] 4a/5a	*ee* [%][e] 4a[f]/5a
1	P*n*Bu$_3$	100	68	<5	1:2/–	–
2	PCy$_3$	100	64	<5	1:1/–	–
3	PBn$_3$	80	62	6	1:4/–	–
4	**Ia-k**[g]	<5	–	–	–	–
5	**II**	50	39	–	1:1.2/–	5/–
6	**III**	>70	51	–	1:1.7/–	40/–
7	**VI**	30	22	–	1:1/–	25/–
8	**VIIa**	100	62	<5	1:2/–	10/–
9	**VIIb**	90	74	<5	1:2/–	46/–
10	**VIIc**	90	68	<5	1:9/–	52/–
11	**VIIc**	90	45[h]	10	1:8/>99:1	41/21
12	**VIII**	0	–	–	–	–
13	**(*R*)-IX**	**>95**	**<5**	**76**	**1:5/>99:1**	**–/99.5**
14	**(*S*)-IX**	**>95**	**<5**	**68**	**1:5/>99:1**	**–/99.8**

[a] At the scale of 0.12 mmol of **3a** at 0.02 M concentration. [b] Based on **3a**. [c] Yield of isolated product. [d] Determined by ^{1}H NMR spectroscopy. [e] Determined by chiral-phase HPLC. [f] For major diastereoisomer. [g] See the Supporting Information, Table S1. [h] 0.04 M solution of **3a** was used; formation of additional unidentified products was observed.

successfully explored amino acid derived chiral alkyldiphenylphosphines **I** in a [3+2] annulation reaction of simple allene esters with cyclic olefins.[11] Unfortunately, these catalysts (**Ia–k**) could not provide much conversion in the annulation reaction of zwitterion **2** with imine **3a** (entry 4).[5j,12] The binepine monophosphine catalyst **II** that Fu et al. had successfully used for an enantioselective [4+2] annulation reaction of allene esters **1** with aldimines,[5c] in our hands, provided only low yield of **4a** (50% conversion) and with very low enantiomeric excess (entry 5). Proline-based catalyst **III** with bis(phospha) appendages displayed significant reactivity and afforded the [4+2] annulation adduct **4a** in acceptable yield and good diastereoselectivity; albeit with only moderate enantioselectivity (Table 1, entry 6). However, no trace of **5a** was observed. Bis(phosphine)s **IV** as well as the atropisomeric biphenyl phosphine **V** failed to provide any acceptable conversion (Supporting Table 1). More nucleophilic (*S*,*S*,*R*,*R*)-Tangphos (**VI**) catalyst also failed to provide encouraging result (entry 7).

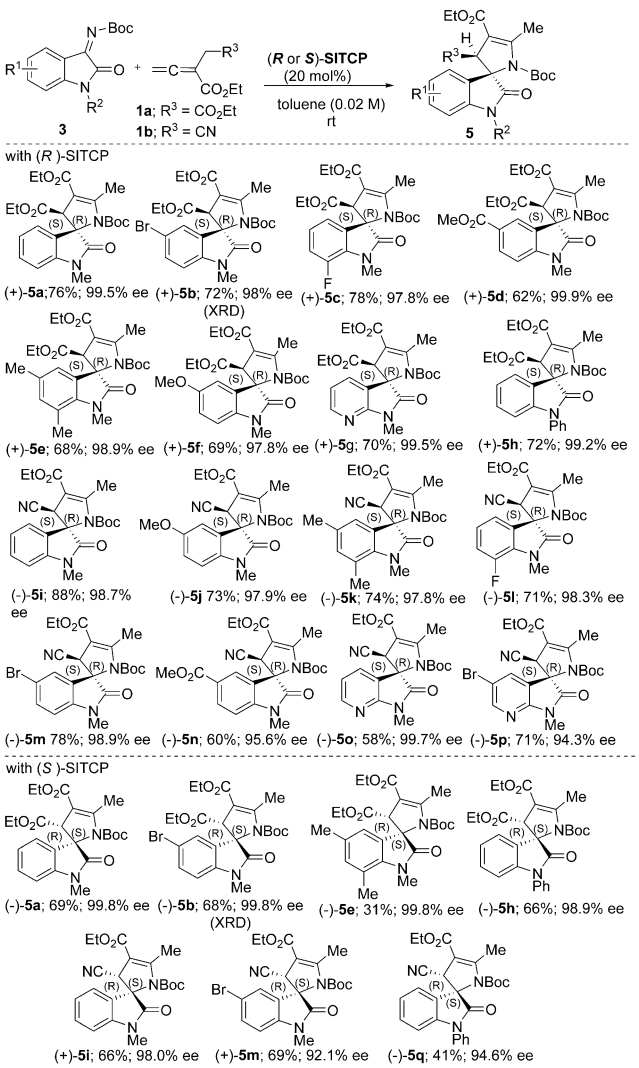
Interestingly, chiral bis(phospholane) catalysts **VIIa–c** that support an ethyl bridge between two phospholano rings afforded **4a** in good yields and moderate enantioselectivities (Table 1, entries 8–11) also produced [3+2] adduct **5a** in low

yield. However, phenyl-substituted **VIIc** formed [3+2] adduct **5a** in 10% yield as single diastereomer and with low enantioselectivity (entry 11). A diaryl bis(phosphine) with a similar ethyl bridge (**VIII**) failed to provide any product (entry 12). Gratifyingly, the hunt to find a catalyst that could steer the zwitterion into novel [3+2] mode of annulation reaction efficiently and stereoselectively ended with spiro-monophosphine **IX**, that is, (*R*)-SITCP, which catalyzed the reaction between ketamine **3a** and allene ester **1a** in toluene at room temperature to afford the desired novel [3+2] annulation adduct (+)-**5a** as major product in excellent yield and enantioselectivity (Table 1, entry 13). As expected, employing 20 mol% of the enantiomeric variant (*S*)-SITCP as catalyst under the optimized conditions successfully provided the opposite enantiomer, that is (−)-**5a**, in good yield and with excellent enantioselectivity (entry 14).

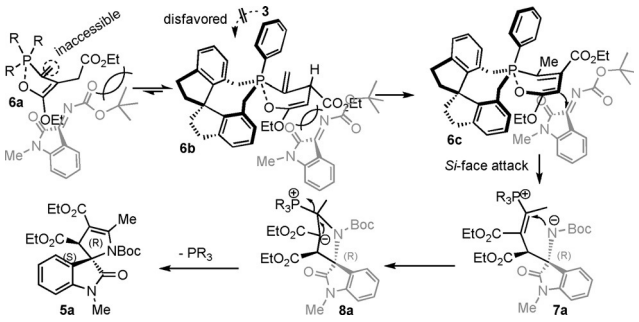
Under the optimized reaction conditions, and employing (*R*)-SITCP as catalyst, the annulation reaction of imines **3** bearing electron-poor aromatic rings with allene esters **1** successfully yielded the spirooxindoles **5a–d** in high yields and with excellent enantioselectivity (Scheme 3). The structure as well as absolute configuration of [3+2] adducts was unambiguously established by single-crystal X-ray analysis of (+)-**5b** (see the Supporting Information). Although the yields for [3+2] adducts derived from isatinimines supporting electron-rich phenyl rings dropped slightly, for spirooxindoles **5e**,**f** excellent enantioselectivities were realized (Scheme 2). Isatinimine bearing a pyridine ring, that is, 7-aza-isatinimine, also reacted well under the standard reaction condition to afford the aza-spirooxindole **5g** in high yield and with excellent enantioselectivity which shows the synthetic potential of this enantioselective phosphine catalysis. The reaction could also tolerate, along with *N*-methyl, *N*-phenyl derivatization of oxindole affording spirooxindole **5h** with similar efficiency and thus depicted a broader scope of this annulation reaction.

Furthermore, allene ester **1b** containing an α-cyanomethyl substitution was successfully utilized with different isatinimines to deliver the corresponding spirooxindoles (**5i–p**) in high yields and with excellent enantioselectivities (Scheme 2). (*S*)-SITCP was equally effective in the catalysis of novel [3+2] annulation reaction to afford a set of few more spirooxindoles (Scheme 3).

The ability of SITCP catalyst to engage the zwitterionic dipole **2** in a novel mode of annulation is mechanistically intriguing and needs further investigation. A proposal is nevertheless depicted in Scheme 4. β-phosphonium enolate formed by addition of trivalent phosphine to allene ester **1** tends to rearrange to a more stable pentavalent phosphorane **6a**.[13] γ-addition of **6a** to *E*-imine in isatine derived *N*-Boc-ketimines is plausibly blocked by the steric repulsion between *N*-Boc function and substitutions on phosphine as well as by ester moiety at α-position in allene **1** and thus driving the rearrangement of phosphorane **6a** to **6b**. The latter complex in case of SITCP catalyst not only keeps blocking the γ-position of allene for any nucleophilic addition but also avoids the imine due to steric repulsion by α-ester moiety. Isomerization of **6b** to relatively flat α,β-unsaturated β-methyl-β-phosphorane **6c** not only stabilizes the complex



Scheme 3. Scope of the [3+2] annulation reaction.

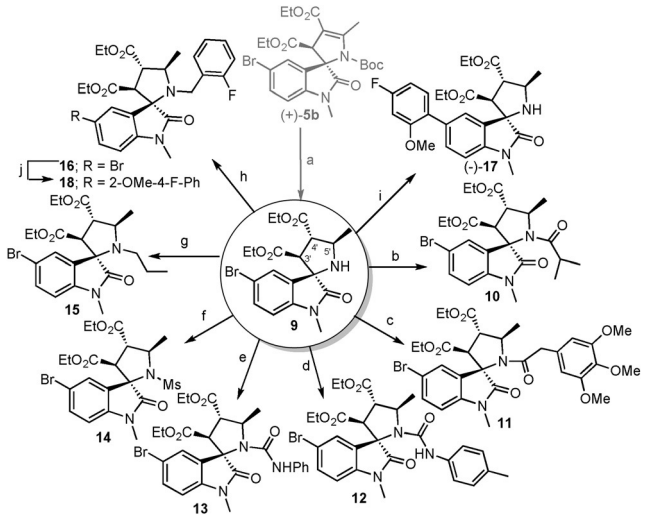


Scheme 4. Proposed mechanism of the [3+2] annulation reaction catalyzed by SITCP.

but also opens up room for approaching isatinimine (Scheme 4). Engaging *E*-imine **3** from *si*-face provides the least steric resistance to **6c**. A conjugated addition of the amide thus formed (**7a**) and finally elimination of the phosphine thus yield the adduct **5a** (Scheme 4).

To demonstrate the synthetic utility of enantiopure [3+2] cycloaddition products **5** in building natural product based

compound collection rich in structural features like sp^3 character and number of chiral centers, further transformation of (+)-**5b** was accomplished in the presence of $NaCNBH_3$ and trifluoroacetic acid under mild conditions to provide saturated pyrrolidinyl spirooxindole **9** embodying consecutive four chiral centers (d.r. ca. 10:1, Scheme 5). Stereoselective reduction of enamine (+)-**5b** was also observed with boron trifluoride diethyl etherate in combination with triethylsilane in a similar manner. Spirooxindole **9** was then further elaborated as illustrated in Scheme 5.



Scheme 5. Elaboration of [3+2] spirooxindole adduct. Reaction conditions: a) $NaCNBH_3$, TFA, DCM 0 °C to rt, or $BF_3{\cdot}Et_2O$, Et3SiH, DCE, 65–73 %, d.r. ca. 10:1; b) *i*PrCOCl, Et_3N, DCM, 79 %; c) 3,4,5-trimethoxyphenylacetic acid, DIPEA, HBTU, DMF, 60 °C, 43 %; d) TolNCO, Et_3N, DCM, rt, 56 %; e) PhNCO, Et_3N, DCM, rt, 54 %; f) MsCl, Et_3N, DCM, 0 °C to rt, 74 %; g) propionaldehyde, $NaBH(OAc)_3$, 1,2-DCE, rt, 91 %; h) 2-fluoro-benzaldehyde, $NaBH(OAc)_3$, 1,2-DCE, rt, 87 %; i) 4-fluoro-2-methoxyphenylboronic acid, $Pd(PPh_3)_4$, K_2CO_3, DMF/H_2O, 80 °C, 4 h, 82 %; j) 4-fluoro-2-methoxyphenyl-boronic acid, $Pd(PPh_3)_4$, K_2CO_3, DMF/H_2O, 80 °C, 4 h, 73 %.

The secondary amine in **9** was first decorated by amide formation reactions. Thus reaction of **9** with isobutyryl chloride in the presence of trimethylamine afforded amide **10** in 79 % yield. The absolute configuration of newly generated stereogenic centers at C4′ and C5′ positions was assigned on the basis of X-ray crystallographic analysis of the amide derivative **10** (see the Supporting Information for details). Similarly amide coupling reaction of **9** with 3,4,5-trimethoxyphenyl acetic acid in the presence of HBTU worked well to produce the corresponding amide **11**. The secondary amine in 3,2′-pyrrolidinyl-spirooxindole **9** could also be transformed into ureas **12** and **13** by reacting it with *p*-tolyl and phenyl isocyanate, respectively. Furthermore, sulfonylation reaction of **9** was tested with mesyl chloride to get the sulfonamide **14** in good yield. Reductive amination reactions of **9** with aliphatic and aromatic aldehydes, that is, propionaldehyde and 2-fluorobenzaldehyde, respectively, using sodium triacetoxy borohydride went smoothly to produce **15** and **16** in high yields. Suzuki coupling was also established with bromoaryl function of spirooxindole which provided aryl ring substituted spirooxindoles **17** and **18** in high yields. The elaboration of **9** thus generated a small library of sp^3-rich and highly substituted spirooxindoles **9**–**18** (Scheme 5).

In summary, we have unraveled a novel mode of asymmetric [3+2] annulation reaction between α-substituted allenes and isatine derived ketimines. The annulation reaction that is catalyzed by chiral phosphine (SITCP) is highly efficient and enantioselective. The pyrrolinyl spirooxindoles thus obtained via asymmetric annulation reaction could be transformed into a range of highly substituted 3,2′-pyrrolidinyl spirooxindoles embodying a number of consecutive chiral centers in single step transformations and thus building a sp^3-rich natural-product-based compound collection. The potential of this annulation with other electrophiles is currently being investigated in our laboratory.

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Keywords: allenes · asymmetric synthesis · phosphine catalysis · spirooxindoles · zwitterions

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