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(*R/S*)-BINOL-α-Phosphoryloxy Enecarbamate-Mediated and (*R/S*)-Titanium(IV) BINOLates-Catalyzed Enantioselective Intramolecular Heck/Aza-Diels–Alder Cycloaddition (IHADA): An Expedient Methodology

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Abstract: An (*R/S*)-titanium(IV) BINOLate-catalyzed highly enantioselective intramolecular Heck/aza-Diels–Alder cycloaddition (IHADA) cascade was developed to prepare tetrahydropyridoindoles (tHPs) and octahydropyrazinopyridoindoles (oHPPs) from *in situ* generated (*R/S*)-BINOL α-phosphoryloxy carbamate (**αPPC2**) in one pot. Chiral cooperativity between (*R/S*)-αPPC2 and (*R/S*)-titanium(IV) BINOLate was observed and successfully utilized for the construction of various tHPs (7 examples) and oHPPs (17 examples).

Keywords: aza-Diels–Alder reaction; cyclopalladation; octahydropyrazinopyridoindoles; phosphonoene carbamate; synergistic catalysis

Introduction

Hetero Diels–Alder reactions are the mainstay in heterocycle and natural product synthesis.[1] The aza-Diels–Alder reaction is an important tool in regio-, diastereo- and enantioselective syntheses of the functionalized heterocycles[2] due to recent advancements in the activation of imine systems towards cycloaddition.[3] Therefore efforts have been made towards the intramolecular Heck/aza-Diels–Alder (IHADA) cycloaddition cascade by reacting Ti(IV)-BINOLate-stabilized imines and *in situ* generated acyclic α-phosphoryloxy enecarbamate. This cycloaddition reaction may proceed either in a concerted and/or in a stepwise manner using tandem Mannich–Michael reaction and/or $[4\pi+2\pi]$cycloaddition respectively.[4]

The 2,3-bis(methylene)-2,3-dihydroindole system, particularly indole-2,3-quinodimethane (**1**),[5,6] is a distinguished diene in the Diels–Alder reaction which efficiently provides tetrahydro- or dihydrocarbazoles and their related compounds.[7] Recently, several reports have appeared[8] on the synthesis of heterocycles by intramolecular Heck reaction.[9] Such cascade processes are ideal organic transformations with respect to atom economy and overall efficiency.[10]

Our recent research endeavours on developing effective methodologies for useful organic transformations[11] to construct molecules of interest led us to develop a highly enantioselective method of intramolecular Heck/aza-Diels–Alder coupling using indole-2,3-quinodimethanes as the diene and various imines as the dienophile.

Results and Discussion

Indole-2,3-quinodimethane (**1**) could be generated from acyclic α-phosphoryloxy enecarbamate by an intramolecular Heck reaction[7a] which, in turn, may be trapped *in situ* by an appropriate dienophile (imine) to provide tetrahydropyridoindole (**tHP**, Figure 1).The Heck coupling mediated approach for the generation of **αPPC1** as diene precursor is more effective than the reported methods of preparation for indole-2,3-quinodimethanes,[5,12] *via* either 1,4-elimination of 2,3-disubstituted indoles[13] or thermal degradation of thieno[3,4-*b*]-indole dioxides.[14] Furthermore, we en-

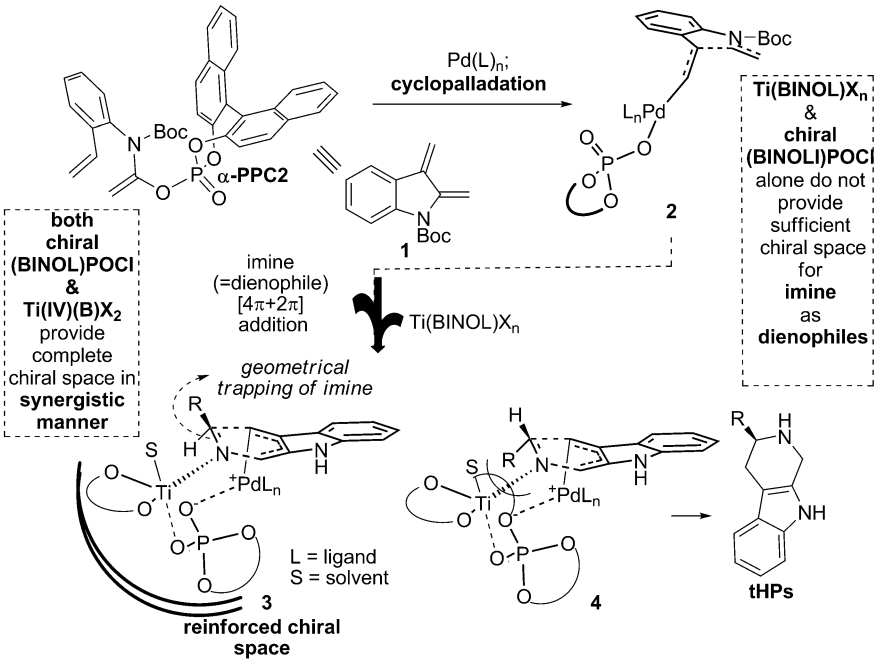


Figure 1. Schematic representation of plausible chiral cooperativity during the aza-Diels–Alder coupling in an IHADA cascade showing the chiral space generated by chiral (*R*/*S*)-Ti(IV) BINOLate and phosphoryl reagents.

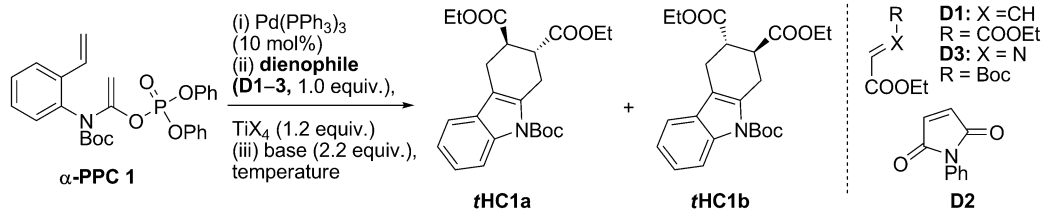
visaged that this strategy could be extended to a general enantioselective synthesis of octahydropyrazinopyridoindoles (*o***HPP**), which is a key intermediate for the neuroleptic drug Centbutindole (Biriperone) as well as for several biologically active molecules.[15]

The α-phosphoryloxy enecarbamate (**αPPC1**) was generated *in situ* and was used as a model precursor for the formation of indole-2, 3-quinodimethane (**1**). After protection of the *o*-vinylamides with Boc_2O/DMAP, the treatment of the resultant imide with KHMDS (1.2 equiv.) and $(PhO)_2P(O)Cl$ afforded **αPPC1**, which was used as such with 10 mol% of $Pd(PPh_3)_4$ in the presence of KHMDS (1.02 equiv.), Ti(IV) reagents (10 mol%) and diethyl fumrate in DMF at −40 °C to give the enantioselective formation of tetrahydrocarbazoles (**tHC**, entries 1–5, Table 1). The preparation of various *o*-vinylamides was accomplished by our earlier reported methodology of oxidative–decarboxylative coupling using desired acrylic acid and phenylacetamide derivatives in the presence of $Pd(OAc)_2$ (10 mol%) as catalyst and Fe(III)·EDTA-H_2O_2 complex (1.0 equiv.) as oxidant in aqueous media (pH ~ 7.8).[11b] Utilization of *trans*-diethyl fumarate (**D1**, entries 1–17, Table 1) for the standardization of the reaction at lower temperature was carried out in polar solvents, where *N,N*-dimethylformamide (DMF) and *N,N′*-dimethylpropyleneurea (DMPU) gave better results than *N,N*-dimethylacetamide (DMA), and CH_3CN, while MeTHF, toluene and hexaflourobenzene (HFB) were less effective. The enantioselectivity of the reaction was increased by employing chiral Ti(IV) complexes with BINOL[16] and (−)-menthol.[17]

The optimized reaction conditions were successfully utilized in the cycloaddition reaction of diethyl fumrate (**D1**) and *N*-phenylsuccinimide (**D2**, entries 18–20, Table 1) to give the respective products ***t*HC1a** and ***t*HC2a** in good yield with excellent enantioselectivity in presence of the (*R* or *S*)-Ti(IV) BINOLates and achiral **αPPC1**. The same reagent system gave low enantioselectivity in the case of an imine as dienophile (**D3**, entries 21–23, Table 1). This may be due to the geometrical orientation of the imine lone pair.[18] In order to explore the possibility of generating stereoselectivity in the cycloaddition reaction, the *R*- or *S*-binapthol-derived phosphoryl chloride was synthesized and used with Ti(IV) chiral complex (BINOLate) as Lewis acid catalyst under the same optimized conditions. It was found that BINOL-derived phosphoryloxy enecarbamate (**αPPC2**) intermediate and Ti(IV) BINOLate alone could not generate the chiral scaffolds (entry 22, Table 1 and entry 8, Table 2), but resulted in excellent enantioselectivity when used in combination (Figure 1), the capability of the BINOL-phosphoric acid as imine activator was also analyzed by the set of experiment replacing the Ti complex, where we have obtained poor results both in terms of yield and enantioselectivity under the standardized reaction conditions (Table 2, entry 9).

The mechanism involves a Heck/aza-Diels–Alder cascade in the formation of the five-membered inter-

Table 1. Optimization of the conditions for the intramolecular aza-Diels–Alder reaction.



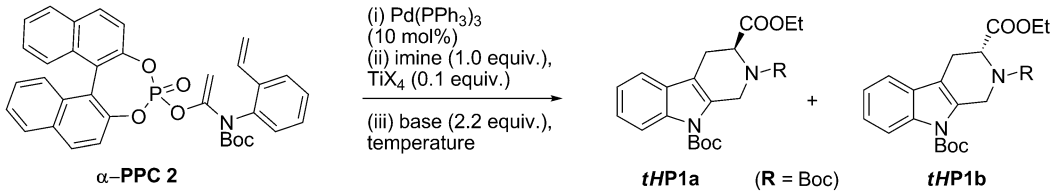
Entry[a]	Solvent, Temperature	Base	TiX_4[b]	Yield [%]	**tHC1a/tHC1b [%]**[c]
1	DMF, −20 °C	K_2CO_3	$Ti(IV)Cl_4$	10	1:1
2		K_2CO_3	$Ti(IV)(O\text{-}i\text{-}Pr)_2Cl_2$	25	1:1
3		K_2CO_3	$Ti(IV)(O\text{-}i\text{-}Pr)_4$	16	1:1
4		K_2CO_3	(+)-$Ti(IV)(menthyl)_2Cl$	24	1:1.25
5		K_2CO_3	(+)-$Ti(IV)(BINOL)_2Cl_2$	21	1:1.53
6		LiHMDS	(+)-$Ti(IV)(menthyl)_2(O\text{-}i\text{-}Pr)_2$	48	1:1.66
7		LiHMDS	$Ti(IV)(BINOL)_2(O\text{-}i\text{-}Pr)_2$	44	1:1.85
8		KHMDS	(+)-$Ti(IV)(menthyl)_2Cl$	69	1:2.08
9		KHMDS	(+)-$Ti(IV)(BINOL)_2Cl_2$	64	1:2.5
10	MeTHF, −20 °C	KHMDS	(+)-$Ti(IV)(BINOL)_2Cl_2$	12	nd
11	DMA, −20 °C	KHMDS	(+)-$Ti(IV)(BINOL)_2Cl_2$	62	1:2.5
12	DMPU, −20 °C	KHMDS	(+)-$Ti(IV)(BINOL)_2Cl_2$	79	1:3.33
13	CH_3CN, −20 °C	KHMDS	(+)-$Ti(IV)(BINOL)_2Cl_2$	58	1:2
14	HFB, −20 °C	KHMDS	(+)-$Ti(IV)(BINOL)_2Cl_2$	41	nd
15	DMPU, −30 °C	KHMDS	(+)-$Ti(IV)(BINOL)_2Cl_2$	72	1:4
16	DMPU, −40 °C	KHMDS	(+)-$Ti(IV)(BINOL)_2Cl_2$	65	1:12.5
17	DMPU, −50 °C	KHMDS	(+)-$Ti(IV)(BINOL)_2Cl_2$	55	1:100
18	DMF, −40 °C	KHMDS	(+)-$Ti(IV)(BINOL)_2Cl_2$	41	1:2.5
19	DMPU, −40 °C	KHMDS	(+)-$Ti(IV)(BINOL)_2Cl_2$	62	1:50
20	DMA, −40 °C	KHMDS	(+)-$Ti(IV)(BINOL)_2Cl_2$	60	1:2.85
21	DMF, −40 °C	KHMDS	(+)-$Ti(IV)(BINOL)_2Cl_2$	32	1:1.66
22	DMPU, −40 °C	KHMDS	(+)-$Ti(IV)(BINOL)_2Cl_2$	71	1:2.5
23	DMA, −40 °C	KHMDS	(+)-$Ti(IV)(BINOL)_2Cl_2$	45	1:1.85

[a] Entries 1–17 are with **D1**, entries 18–20 are with **D2** as dienophile [for intramolecular Heck/aza-Diels–Alder (IHDA)] and entries 21–23 are with **D3** as imine as dienophile [for intramolecular aza-Diels–Alder (IHADA)].
[b] 10 mol% Lewis acid was used.
[c] Determined through ^1H NMR and HPLC.

mediate *via* cyclopalladation (**2**, Figure 1). The chiral phosphoryl substrate may get chelated with the Pd to form a chiral intermediate which on subsequent stabilization with the Ti(IV) BINOLates-imine complex [formed *in situ* using $TiCl_4$ (1.0 equiv.), *R*- or *S*-BINOL (0.9 equiv.) and desired imine] provides greater chiral space or in other terms enhances positive synergistic chiral catalysis[19] to increase the stereoselectivity due to the effective trapping of the geometrical arrangement of the imine (**3** and **4**, Figure 1). Ti(IV) BINOLate plays a primary role in imine activation by suppressing the plausible role of *in situ* generated chiral phosphate as imine activator and forms the ion-pair association with the cationic palladium complex (**3**) resulting in the chiral synergism through asymmetric counter anion-directed catalysis.[20]

The *R,R*-spatial arrangement of **αPPC2a** and Ti(IV) complex was found to provide positive chiral synergistic catalysis whereas *R,S* and *S,R* combinations showed lesser enantioselectivity than the corresponding *R,R*-combination. The lowered stereoselection in the latter cases supports the mutual chiral space reinforcement resulting enhanced stereoselectivity in the former case. Similar results were obtained in the absence of imine (dienophile) where the [4π + 2π]cycloadduct was formed between the two molecules of chiral **αPPC2a** enantioselectively and afforded the stereoisomers ***t*HP2a** and ***t*HP2b** in a 97.5:2.5 ratio. The stereochemistry of the obtained ***t*HP1a–2a** was determined through converting them to their deprotected analogues (*S*)-2,3,4,9-tetrahydro-1*H*-pyrido-[3,4-*b*]indole-3-carboxylic acid[21] known in the literature by treating them with HCl-dioxane followed by basic hydrolysis. Utilization of different imines **D3–D18** (Table 3**)** as dienophile imine, provided moderate to good yields with excellent enantioselectivities for the compounds ***t*HP3a–10a** and ***o*HPP1a–17a**[22] under the optimized reaction conditions. The use of DMPU not only increased the rate of the reaction but was also easily removed by a simple aqueous treatment.

Table 2. The standardization of the reaction conditions using (*R* or *S*)-BINOL-derived phosphoryl chloride under the intramolecular Heck/aza-Diels–Alder cascade conditions for 4.5 h at −40 °C using **D8** as dienophile.



Entry	Solvent, Temperature	Base	TiX_4 (0.1 equiv)	Yield [%]	*ee* [%]
1	DMPU, −20 °C	K_2CO_3	Ti(IV)(BINOL)Cl_2	38	85.1
2	DMPU, −20 °C	LHMDS	Ti(IV)(menthyl)$_2$Cl	48	66
3	DMPU, −20 °C	LHMDS	Ti(IV)(BINOL)Cl_2	44	90.4
4	DMPU, −20 °C	KHMDS	Ti(IV)(BINOL)Cl_2	69	78.5
5	DMPU −40 °C	KHMDS	Ti(IV)(BINOL)Cl_2	64	92
6	MeTHF, −40 °C	KHMDS	Ti(IV)(BINOL)Cl_2	48	73.8
7	DMF, −40 °C	KHMDS	Ti(IV)(BINOL)Cl_2	32	78.5
8	DMPU, −40 °C	KHMDS	no LA[a]	23[b]	24.8
9	DMPU, −40 °C	KHMDS	no LA[c]	12	16

[a] LA = Lewis acid, BINOL = (*R*)-BINOL and M = (−)-menthol.
[b] The reaction was operated for 9.5 h under similar conditions.
[c] The reaction carried out in the presence of (*R*)-BINOL-phosphoric acid.

The BINOL residue was purified and reused after regeneration. In an alternative work-up procedure the reaction mixture was triturated with *n*-hexane to isolate the desired solid products in high NMR purity. In order to make the process more practical, a one-pot reaction cascade was developed using DMPU in the presence of KHMDS (2.2 equiv.) as base to provide the desired products (**tHP1a–9a** and **oHPP1a–17a**) in moderate to good yields with excellent enantioselectivity using various α-phosphoryloxy enecarbamates (**α-PPC2a–g)** and dienophiles (**D3–D18**, Table 3).

Conclusions

In conclusion we have successfully synthesized various **tHPs-** and **oHPPs**-based molecules using an intramolecular Heck/aza-Diels–Alder coupling cascade as a fast, one-pot access. This may be useful to construct heterocyclic scaffolds under easily workable and mild reaction conditions with an easy work-up procedure. Hence, it may be considered as a powerful tool in developing ideal reaction processes and has high utility as transition metal-mediated homogenous synergistic dual catalysis in the synthesis of natural products incorporating tetrahydropyridoindole substructures.

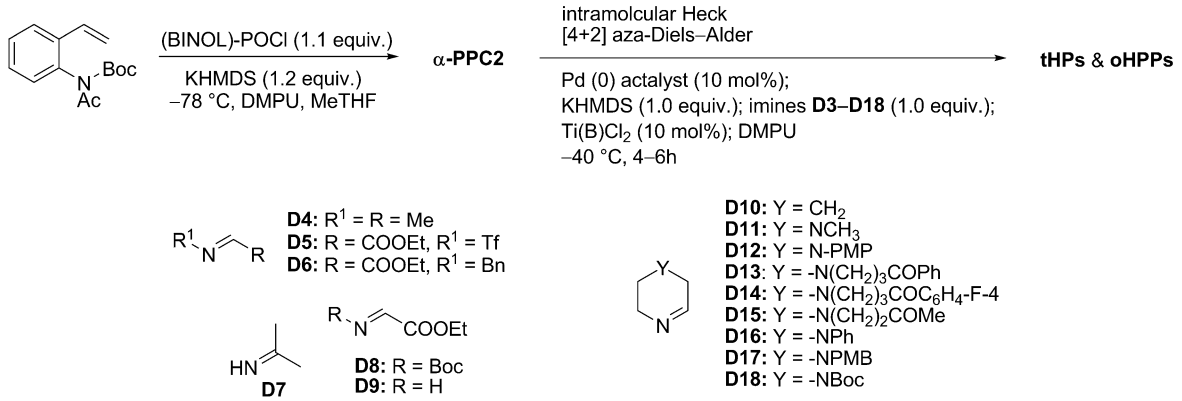
Experimental Section

Representative Two-Pot Procedure

Step 1: To a solution of desired imide (1.2 mmol) in MeTHF (24 mL) were added HMPA (0.23 mL, 1.32 mmol) and $(PhO)_2P(O)Cl$ (0.28 mL, 1.35 mmol). The resultant mixture was cooled to −78 °C and treated with KHMDS (0.5 M solution in toluene, 5.80 mL, 2.7 mmol). After being stirred at −78 °C for 0.5 h, the reaction was quenched with 3% NH_4OH and diluted with diethyl ether. The resultant mixture was allowed to warm to room temperature over 20 min and extracted with EtOAc. The organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude α-phosphoryloxy enecarbamate (**αPPC1**) thus obtained was used immediately without further purification.

Step 2: To a solution of the above crude material in DMPU (4 mL) were added KHMDS (1.1 mmol), $Pd(PPh_3)_4$ (0.52 mg, 0.045 mmol), **D1–2** (4.0 mL, 1 mmol), $TiCl_4$ (0.05 mL. 0.1 mmol) and BINOL (28.3 mg, 0.1 mmol). The resultant mixture was stirred at −40 °C for 4.5 h. Work-up procedure A: after the completion of the reaction the mixture was warmed to room temperature and the stagnant reaction mixture was diluted with hexane from the side of the RB flask which allowed the slow dissolution with the solvent mixture, which results in separation of the desired octahydropyrazinopyridoindole as a solid that was filtered through a G_3 sinter and washed with Et_2O:MeOH (10:0.5 mL) to afford the pure compound. Work-up B: after warming to room temperature, the resultant mixture was quenched with 1 mL saturated NH_4Cl solution, diluted with EtOAc, washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica gel, 5% EtOAc/hexanes) gave *ca.* 2:1 mixture of ***t*HC1a** (pale yellow oil or solid).

Table 3. Scope of the reaction with various imines (**D4–17**) and chiral-αPPC (**αPPC2a–g**) derivatives under Heck/aza-Diels–Alder cascade, the yield and *ee* are reported following the one-pot access procedure in DMPU as solvent at −40 °C.



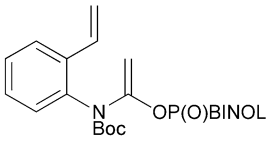
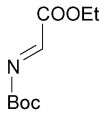
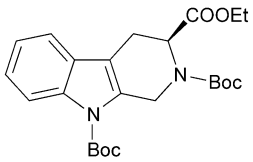
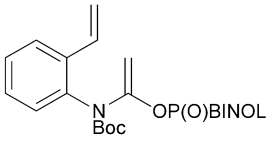
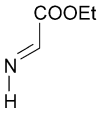
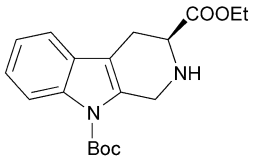
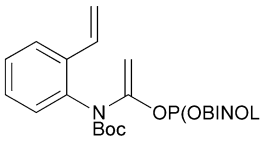
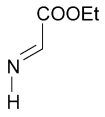
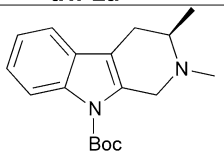
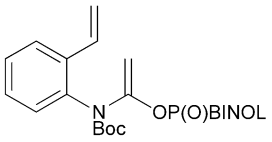
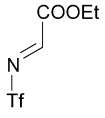
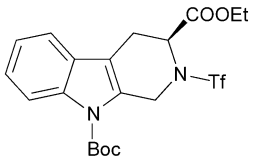
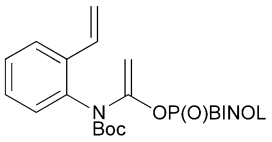
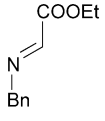
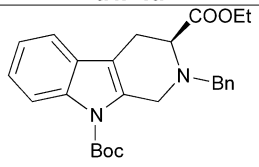
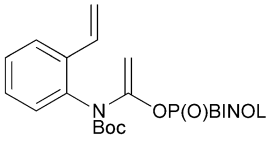
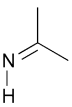
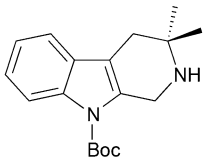
Entry	α–Phosphoryloxy enecarbamate (αPPC2)[a]	Dienophile (D4–D18)[b]	Product	Yield [%][c]	*ee* [%][d]
1	 αPPC2a	 D8	 *tH*P1a	64	92
2	 αPPC2a	 D9	 t*H*P2a	63	96
3	 αPPC2a	 D9	 t*H*P3a	68	88
4	 αPPC2a	 D5	 tHP4a	72	97
5	 αPPC2a	 D6	 *t*HP5a	67	95
6	 αPPC2a	 D7	 tHP6a	81	-

Table 3. (Continued)

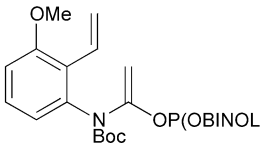
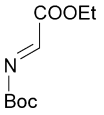
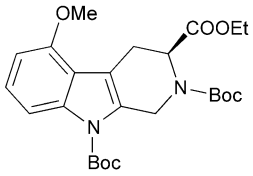
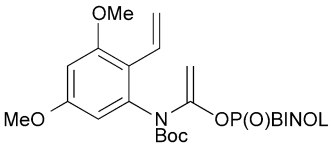
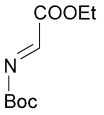
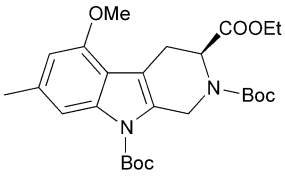
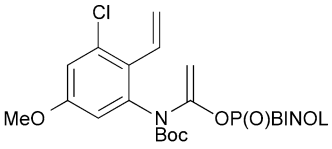
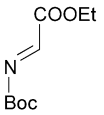
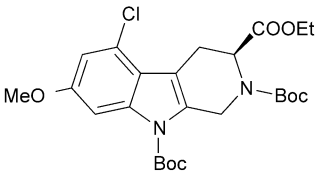
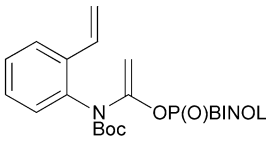
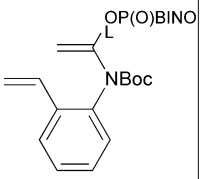
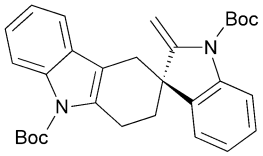
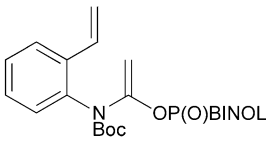
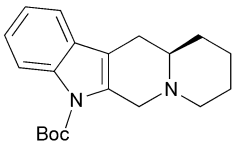
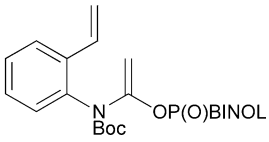
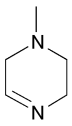
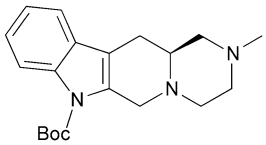
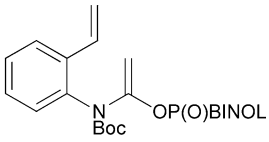
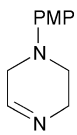
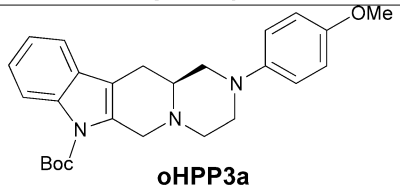
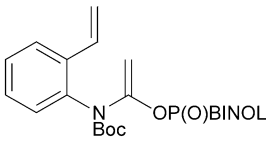
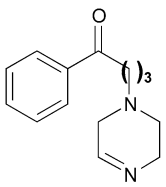
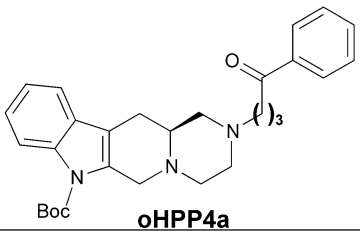
Entry	α–Phosphoryloxy enecarbamate (αPPC2)[a]	Dienophile (D4–D18)[b]	Product	Yield [%][c]	*ee* [%][d]
7	 αPPC2b	 D8	 tHP7a	72	96
8	 αPPC2c	 D8	 tHP8a	76	95
9	 αPPC2d	 D8	 tHP9a	74	94
10	 αPPC2b	 αPPC2b	 tHC2a	82	95
11	 αPPC2a	 D10	 oHPP1a	62	96
12	 αPPC2a	 D11	 oHPP2a	61	94
13	 αPPC2a	 D12	 oHPP3a	68	92
14	 αPPC2a	 D13	 oHPP4a	65	95

Table 3. (Continued)

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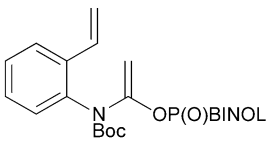
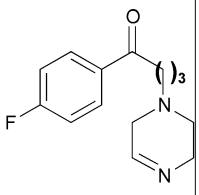
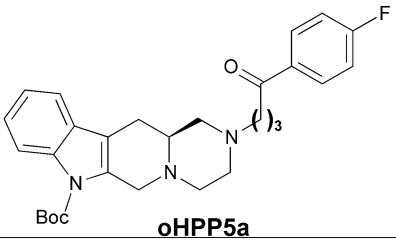
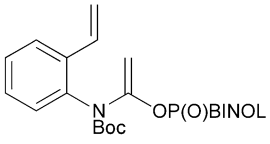
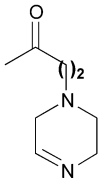
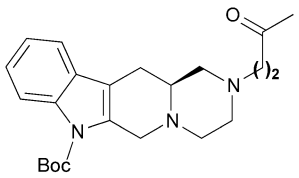
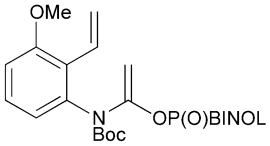
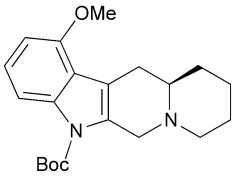
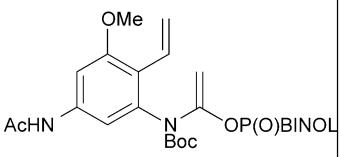
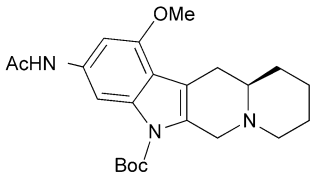
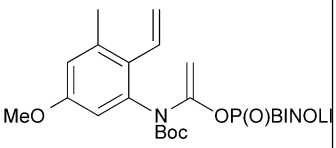
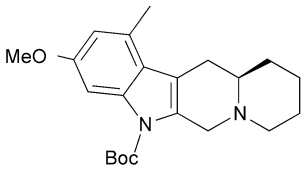
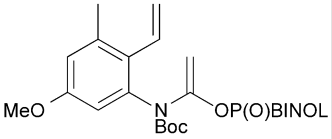
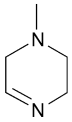
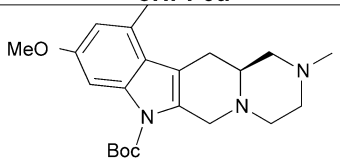
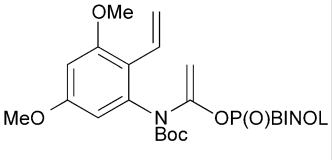
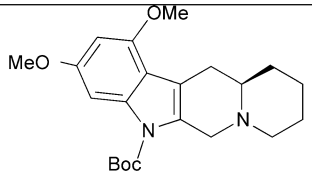
15	 αPPC2a	 D14	 oHPP5a	55	96
16	 αPPC2a	 D15	 oHPP6a	62	94
17	 αPPC2b	 D10	 oHPP7a	68	96
18	 αPPC2e	 D10	 oHPP8a	64	94
19	 αPPC2f	 D10	 oHPP9a	61	98
20	 αPPC2f	 D11	 oHPP10a	62	92
21	 αPPC2c	 D10	 oHPP11a	68	95

Table 3. (Continued)

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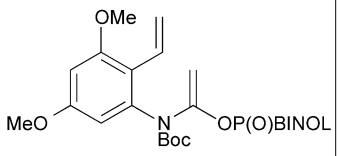
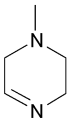
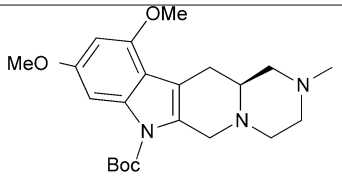
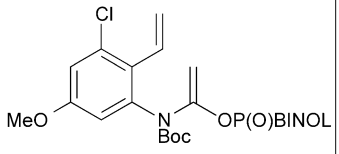
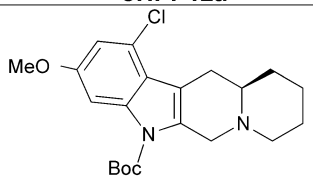
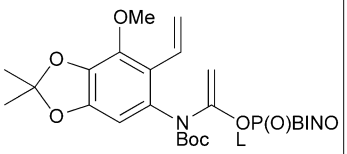
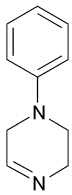
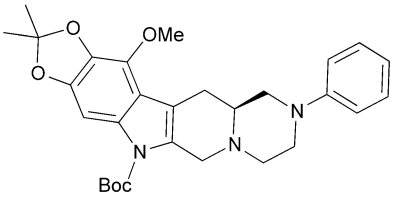
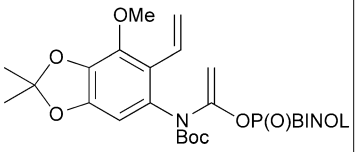
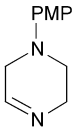
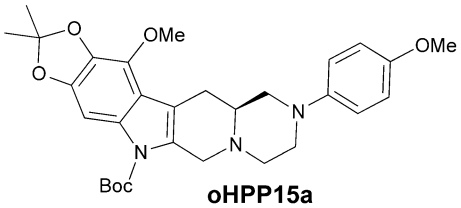
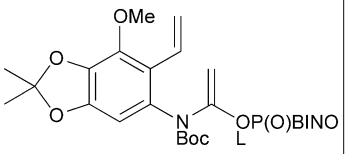
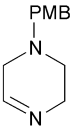
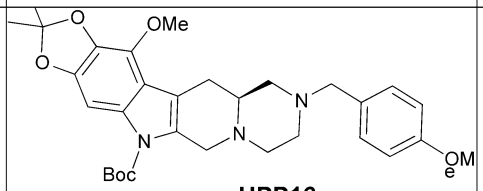
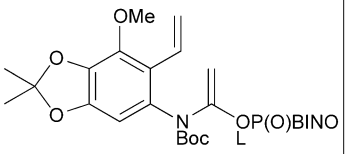
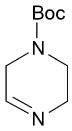
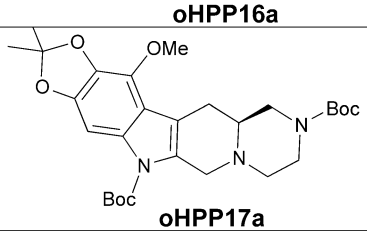
22	 αPPC2c	 D11	 oHPP12a	65	94
23	 αPPC2c	 D10	 oHPP13a	54	96
24	 αPPC2g	 D16	 oHPP14a	67	95
25	 αPPC2g	 D12	 oHPP15a	64	93
26	 αPPC2g	 D17	 oHPP16a	61	95
27	 αPPC2g	 D18	 oHPP17a	71	96

[a] α-Phosphoryloxy enecarbamates (**α-PPC2a–g**) were synthesized *in situ* and used without purification.
[b] Formation of imine was carried out using a Dean-Stark apparatus in the presence of $TiCl_4$ (5 mol%) in benzene.
[c] Isolated yield.
[d] Determined through ^1H NMR and chiral HPLC.

One Pot Procedure

The general procedure of the two-pot methodology (step 1) was performed in DMPU (0.5 mL) in place of HMPA using (*R*)-BINOL-phosphoryl chloride (1.02 mmol) with the desired dienophile (**D3–D18**) and after 3.5 h at −78 °C, and step 2 was followed within the same pot without carrying out work-up.

Acknowledgements

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