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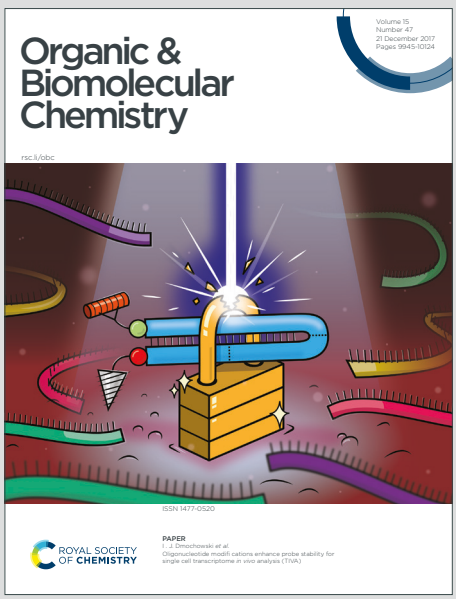

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ARTICLE

Enantioselective Vinylogous Aldol Reaction of Acyl Phosphonates with 3-Alkylidene oxindoles

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A simple strategy for yielding chiral tertiary α-hydroxyphosphonates that integrates two highly biologically relevant scaffolds such as 3-alkylidene-2-oxindoles and phosphonates has been described. The hydrogen bonding ability of the bifunctional thiourea catalyst allows simultaneous dual activation of vinylogous oxindole nucleophile and acylphosphonates electrophile affording hydroxyphosphonato-3-alkylidene-2-oxindoles as aldol adduct in high yield (up to 92%) and excellent stereocontrol (up to 99% *ee*).

Introduction

Hybrid molecules with two or more heterocycles or functional groups have unique characteristics that enable them to display dual mode of action against a variety of biological hosts.[1] Thus, designing such molecules from simple precursors have gained tremendous momentum in recent years.[2] Of particular, interest is the chiral organophosphonates with high biological activities and multifaceted applications in biology, medicine and agrochemicals.[3] A specific example would be the α-hydroxy phosphonates that are known antioxidants,[4a] renin inhibitors,[4b,c] herbicides, anti-human immunodeficiency virus (HIV) drug[4d,e] and have also shown promise for treating osteoporosis and other bone diseases.[4f-h] Apart from the bioactivity they also represent useful precursors for further transformations, resulting in many α-functionalized derivatives. While many synthetic methods exist for yielding racemic α-hydroxyphosphonates, the asymmetric synthesis is primarily focused on secondary α-hydroxy phosphonates *via* enzymatic[5] and metal-catalyzed reactions.[6] The more challenging tertiary α-hydroxy phosphonates still do not have any practical synthetic routes. Previously, the tertiary α-hydroxy phosphonates were synthesized *via* the addition of phosphites to ketones,[7] oxygenation of β–ketophosphonates[8] and the addition of carbon nucleophiles to α-ketophosphonates.[9] It is worth noting that the synthetically least explored tertiary α-hydroxy phosphonates may have higher structural rigidity and hence improved stability against protease enzymes, thus, enhancing its bioactivity. Classically, the chiral α-hydroxy phosphonates have been synthesized by proline catalyzed aldol addition of acetone to acyl phosphonates.[10] Additionally, asymmetric transformations have also been explored in the synthesis of tertiary α-hydroxyphosphonates.[11] It is important to note that while all these strategies yield secondary and the tertiary organophosphonates with high yield and selectivity, these reactions result into "terminal" derivatives that cannot be manipulated further due to lack of sufficient functional synthetic handles for further group transformations.

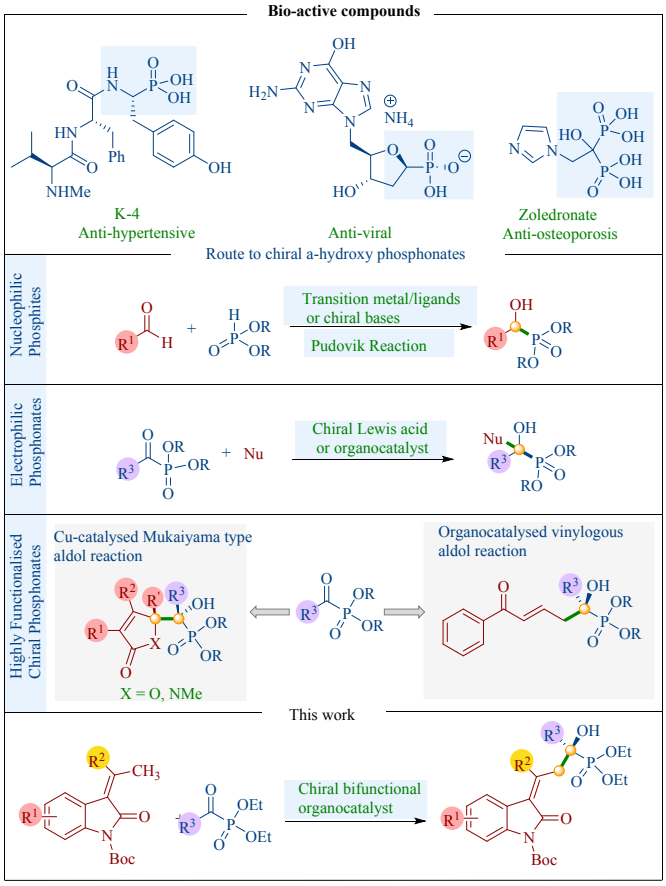

Figure 1. Representative bioactive compounds containing phosphonates and catalytic enantioselective methodologies for chiral phosphate synthesis.

Thus, a method that directly provides functionalized organophosphonates still remains a challenge. Towards this, an alternative strategy incorporating phosphonate moieties in various chiral functional molecules have been explored. An example of this is the relatively straightforward method by

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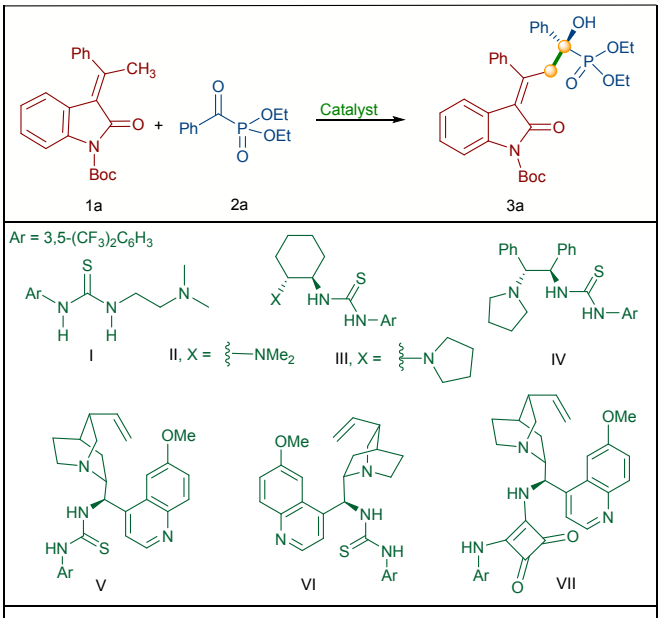
Pudovik-type reaction where a chiral base or a metal catalyst can directly form a carbon-phosphorous (C-P) bond stereoselectively.[12] Later, the use of functionalized phosphonates as electrophiles in the asymmetric catalytic reaction was demonstrated as an efficient route to obtain tertiary α-hydroxy phosphonates.[13] While these strategies resulted in tertiary α-hydroxy phosphonates derived from functionalized precursors, it did not allow achieving molecular diversity, again due to limited group transformations. This issue of obtaining functional tertiary α-hydroxy phosphonates that can be further manipulated can be addressed by simply integration with synthetically vulnerable nucleophiles such as the vinylogous nucleophiles. In fact, vinylogous nucleophiles like the 3-alkylidene oxindole would also provide multiple advantages as these themselves represent a privileged class of scaffolds that are ubiquitously found in many biologically active molecules and natural products.[14] Examples representing this strategy are limited in literature and some tertiary α-hydroxy phosphonates through asymmetric vinylogous aldol reactions have been elegantly demonstrated.[15] This limitation is due to the difficulties in obtaining selectivity with various heterocyclic vinylogous nucleophiles. Herein, we report the exploration of direct asymmetric vinylogous aldol reaction of 3-alkylidine-oxindole to acylphosphonates catalyzed by a bifunctional thiourea catalyst as illustrated in figure 1.

Results and discussion

Investigations were initiated to examine the feasibility of the vinylogous aldol reaction between 3 alkylidene-2-oxindole **1a** and acylphosphonates **2a**. Initially, the reaction was conducted in absence of catalyst at rt, but no reactivity was observed, which clearly shows the non-spontaneous nature of the reaction (Table 1, entry 1). To further testify our objective, a racemic version of the reaction was carried at rt using Et_3N as a base promotor, which unfortunately again resulted in no reaction (Table 1, entry 2). Interestingly, the same reaction, when performed with the racemic thiourea catalyst **I**, the desired aldol adduct **3a** was obtained in only 5% yield with very high diastereoselectivity (Table 1, entry 3). Further, the introduction of basic K_2HPO_4 additive in the reaction medium was found to influence the yield with no loss in diastereoselectivity (Table 1, entry 4). Next, to enhance the reactivity, the reaction was conducted at -20 °C and surprisingly, a significant increase in yield was observed (Table1, entry 5). This observation indicates the importance of temperature on the progress of the reaction. The chiral version of this reaction was then investigated by using series of bifunctional organocatalysts (**III**-**VII**). The reaction was first performed using Takemoto catalyst **II** and K_2HPO_4 as a basic additive in toluene at -20 °C, where desired product **3a** was formed in poor yield with moderate enantioselectivity (64%) and excellent *E/Z* selectivity (Table 1, entry 6).

Table 1. Catalyst screening and reaction optimization



Entry	Catalyst	Solvent	Yield (%)[b]	dr (E/Z)[c]	ee (%)[d]
1	-	Toluene	nr	nd	-
2	Et_3N	Toluene	0	nd	-
3	I	Toluene	5	>19:1	0
4e	I	Toluene	10	>19:1	0
5f	I	Toluene	72	>19:1	0
6	II	Toluene	20	>19:1	64
7	III	Toluene	15	>19:1	60
8	IV	Toluene	trace	nd	-
9	V	Toluene	50	>19:1	98
10	VI	Toluene	48	>19:1	-98
11	VII	Toluene	40	>19:1	80
12	V	DCM	30	>19:1	98
13	V	CH_3CN	10	>19:1	86
14	V	THF	15	>19:1	86
15g	V	Toluene	82	>19:1	98
16h	V	Toluene	80	>19:1	98

[a]Unless otherwise noted all the reactions were carried out with **1a** (0.12 mmol), **2a** (0.10 mmol) and catalyst (0.02 mmol) in toluene (1 mL) at rt for 96 h. [b]Isolated yield. [c]Determined by ^{1}HNMR. [d]Determined by chiral HPLC. [e]K_2HPO_4 (0.12 mmol), [f]K_2HPO_4 (0.12 mmol) at -20 °C. [g]**1a** (0.2 mmol) and K_2HPO_4 (0.2 mmol) at -20 °C. [h]**1a** (0.3 mmol) and K_2HPO_4 (0.3 mmol) at -20 °C.

For the improvement of reactivity and enantioselectivity, several other bifunctional tertiary-amine catalysts were screened such as *trans*- cyclohexane 1,2–diamine derived thiourea **III**, *trans*-1,2–diphenylethylene diamine derived thiourea **IV** and cinchona alkaloid derived thiourea (**V** and **VI**) and quinidine squaramide **VII**. Performing the reaction with catalyst **III**, yielded the adduct **3a** in only 15% yield, although, the reactivity was poor, moderate enantioselectivity (60%) and excellent *E/Z* selectivity (>19:1) were noticed (Table 1, entry 7). The *trans*-1,2–diphenylethylene diamine derived thiourea **IV** was then examined, and afforded **3a** in trace yield (Table 1,

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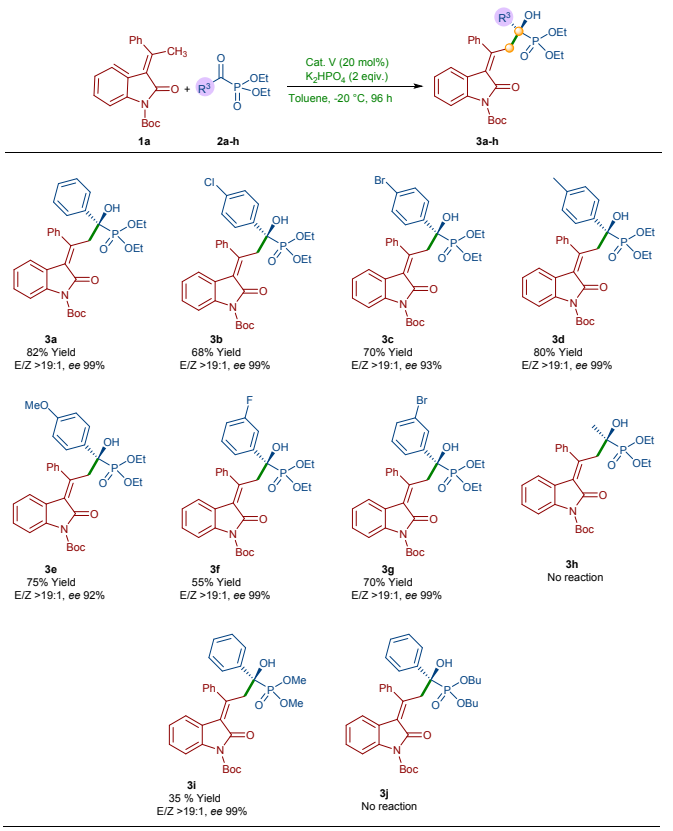
entry 8). To our delight, quinidine derived thiourea **V** turned out to be the most effective candidate with respect to reactivity and enantioselectivity, providing the adduct **3a** in good yield of up to 50% and very high enantioselectivity (99%) while maintaining excellent diastereoselectivity (Table 1, entry 9). Also, catalyst **VI**, a pseudoenantiomer of catalyst **V** when tested, delivered similar results as catalyst **V** with opposite enantiomer of the product **3a** (Table 1, entry 10).

Quinidine derived squaramide **VII** resulted the product **3a** in relatively low yield and enantioselectivity (Table 1, entry 11). Subsequently, when the reaction was performed at rt, corresponding **3a** was obtained in reduced yield with similar *E/Z* selectivity. Hence, catalyst **V** was considered for the optimized catalytic condition for the reaction procedure. Further varying solvents under optimal catalyst **V** although failed to improvise the reactivity as well as enantioselectivity in case of CH_3CN and THF, while DCM provided equivalent enantioselectivity up to 99% *ee* with diminished reaction yield (Table 1, entries 12-14). Finally, when the loading of the substrate 3-alkylidene-2-oxindole **1a** was increased from 1.2 equivalent to 2.0 equivalent, interestingly, there was a significant increase in the yield without affecting enantioselectivity and *E/Z* selectivity (Table 1, entry 15). Further increasing the loading of **1a** did not result any change in the yield and selectivity of the product (Table 1, entry 16).

With the optimal reaction conditions established (Table 1, entry 15), the generality of the asymmetric vinylogous aldol reaction was examined with respect to both the substrates, alkylidene-oxindole **1** and acylphosphonates **2** as shown in Table 2 and 3. A wide range of acylphosphonates **2** was reacted with alkylideneoxindole **1** (Table 2) in the optimized reaction conditions. The corresponding aldol products **3a**-**j** were obtained in moderate to good yields with single geometrical isomer and excellent enantioselectivities. The acylphosphonates bearing electron-withdrawing group -Cl and -Br at the *para*- position of the aryl group led to the marginal loss in reactivity and provided corresponding aldol adducts (**3b** and **3c)** in good to high yield (68%-70%) with outstanding enantioselectivities, respectively. In contrast, an electron-donating group such as Me at the *para*-position of the aryl group afforded corresponding aldol product **3d** in 80% yield with excellent selectivity of 99% *ee*. Similarly, OMe at the *para*-position of the aryl group delivered **3e** in high yield 75% with 92% *ee*. Interestingly, the acylphosphonates with halogen group at *meta*-position of the aryl group (**2f** and **2g**) yielded the corresponding aldol products (**3f** and **3g)** in 55% and 70% yield respectively with the same selectivity (>19:1 *dr* and 99% *ee*). Thus, it was concluded that while no significant influence of either electronic nature or steric effect of the substituents on the benzene ring of the acylphosphonates was observed on the selectivity, a slight decrease in yields was noticed between the halo and electron-donating groups. The scope of the reaction with less reactive aliphatic acylphosphonates was also studied but no progress in the reaction was observed. Moreover, when -OEt group of acylphosphonate was replaced with -OMe and -*n*Butyl groups, it was noted that -OMe containing acylphosphonates produced the corresponding adduct **3i** in poor yield (35%) and excellent selectivities. On the other hand, long chain containing *n*Butyl group failed to give any reactivity.

To further explore the substrate scope of the reaction, various alkylidene-oxindole donors **1b-k** were studied (Table 3). Based on these observations it was evident that irrespective of the electronic and steric aspect of the structure, such as electron releasing or withdrawing substituents present at different

Table 2. Substrate scope of α-hydroxyphosphonato)-alkylidene-oxindoles

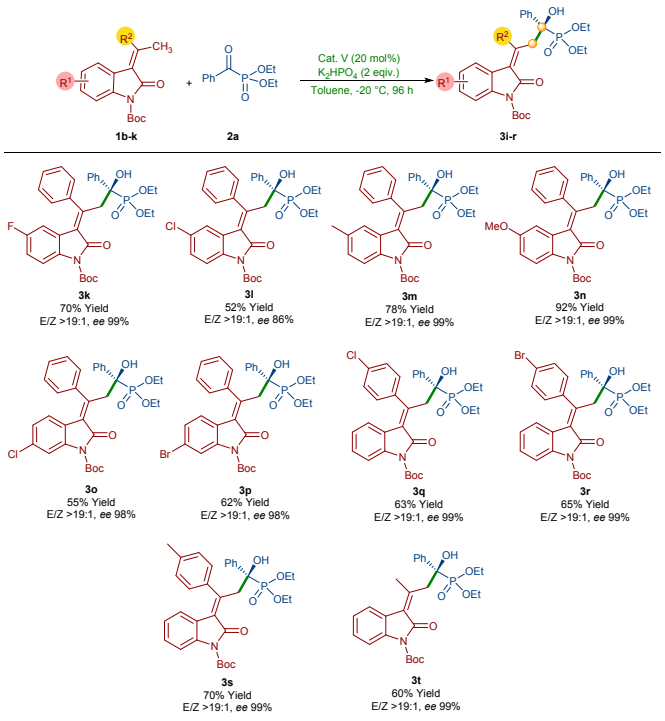


[a]Unless otherwise noted, reactions were carried out with **1a** (0.2 mmol), **2a** (0.1 mmol), K_2HPO_4 (0.2 mmol) and catalyst (0.02 mmol) in the toluene (1 mL) at -20 °C for 96 h. [b]Yield of the isolated product. [c]Determined by ^1H NMR. [d]Determined by chiral HPLC.

positions on a *benzo*- as well as on benzene ring of alkylidene-oxindole were well tolerated and corresponding adducts **3k-t** were obtained in good to excellent yields with equally high enantioselectivities (19:1 *dr* and 99% *ee*). Moreover, vinylogous donors bearing electron-withdrawing group on 5-position of *benzo*-core of alkylidene-oxindole (**1b** and **1c**) worked very well to provide corresponding aldol adduct (**3k** and **3l**) in 70% and 52% yield respectively with (slightly low in the case of **3j**) high stereocontrol (19:1 *dr* and 99% *ee*). In contrast, electron-donating group 5-Me on *benzo*-core of alkylidene-oxindole afforded the corresponding **3m** in 78% yield with excellent selectivity of 99% *ee*. The 5-OMe bearing *benzo*-core of alkylidene-oxindole delivered **3m** with both excellent yield (92%) and selectivity (99% *ee*) respectively. Moreover, 6-Cl and 6-Br alkylidene-oxindoles gave the aldol products (**3o** and **3p**) in 55% and 62% yield with equally high enantioselectivities. Interestingly, both electron-withdrawing group (*p*-Cl and *p*-Br)

and electron-donating group (*p*-Me) on the benzene ring connected with the double bond of donors, proceeded very smoothly and gave good to an excellent yield of the desired product. Other substituted alkylidene-oxindole such as **1g** and **1h** afforded **3q** and **3r** respectively, in similar yields (63% and 65%) and enantioselectivities (19:1 *dr*, 99% *ee*) while **1j** yielded **3s** in high yield with excellent stereocontrol. On the other hand, electron-donating substituents at the benzene ring connected with the double bond of donors did not show any large deviation in the yields of the product. Also, methyl substitution in place of phenyl carbon-carbon double bond of alkylidene-oxindole **1k** gave **3t** in good yield and very high enantioselectivity (19:1 *dr* and 99% *ee*).

Table 3. Substrate scope of α-hydroxyphosphonato)-alkylidene-oxindoles



[a]Unless otherwise noted, reactions were carried out with **1a** (0.2 mmol), **2a** (0.1 mmol), K_2HPO_4 (0.2 mmol) and catalyst (0.02 mmol) in the toluene (1 mL) at -20 °C for 96 h. [b]Yield of the isolated product. [c]Determined by ^{1}H NMR. [d]Determined by chiral HPLC.

We have confirmed the relative and absolute configuration of the vinylogous aldol adduct by X-ray crystal structure analysis of chiral α-hydroxy phosphonate derivative **3p** (Figure 2). The relative configuration of the major stereoisomer of aldol adduct was established to be *trans*. Since cinchona catalysts do not have their respective enantiomers thus limiting the accessibility of both product enantiomers, the reaction was performed between **1f** and **2a** under the established reaction conditions using cat. **VI**, a pseudoenantiomer of cat.**V**. Interestingly, the reaction resulted in **3p'** with similar yield and enantioselectivity, which was further confirmed by single-crystal X-ray analysis (Figure 1). This observation indicates the broad applicability of our protocol.

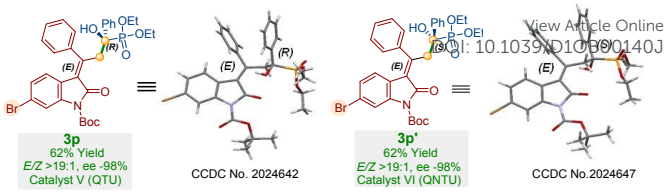
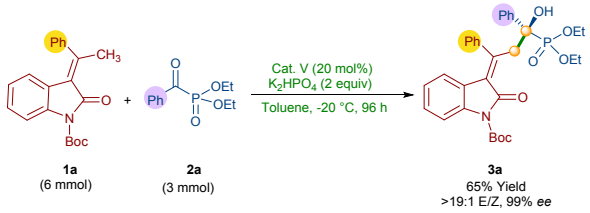


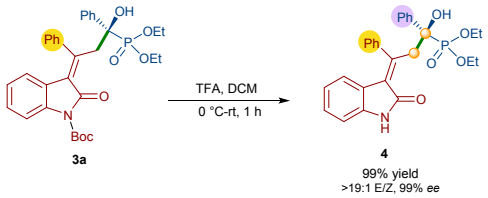
Figure 2. Single crystal X-ray of α-hydroxy phosphonate derivative **3o**.

To explore the practicality of the developed methodology, the optimized vinylogous aldol reaction was carried out at 0.5 mmol scale using only 20 mol% of the catalyst **V** (Scheme 1). The reaction proceeded smoothly in the optimized conditions and the expected product **3a** was isolated in 65% yield in the stipulated time with the same level of diastereo and enantioselectivity as observed for small scale experimentation.



Scheme 1. Scale up experiment of **3a**.

The optimized (α-hydroxyphosphonato)-alkylidene-oxindoles adduct **3a** was further processed for Boc deprotection by treating it with TFA which yielded **4** in excellent yield and selectivity (Scheme 2).



Scheme 2. Conversion of α-hydroxyphosphonato)-alkylidene-oxindoles product **3a**.

^{1}H NMR titration studies of the cat. **V** was conducted in toluene-d^8 and with an increasing amount of the keto-phosphonate. The low-field shifts of the C9-H (Figure 3) thiourea protons clearly indicated the H-bonding interaction with the α-ketophosphonate. Our NMR studies also showed the down field shift of *ortho* protons of the 3,5-bis (trifluoromethyl)phenyl catalyst moiety, strongly indicates the catalyst-substrate interaction (Figure 4). Furthurmore, a comparative evaluation shows the $(-CH_2)_2$, mutltiplet of **2a** at δ = 3.94 - 4.07 ppm clearly shifts in presence of catalyst (see SI. Figure S2).

To further investigate the mechanism, the formation of **3a** was monitored by ^{31}P NMR spectroscopy. The starting reaction mixture in toluene-d_8 showed signal in the ^{31}P NMR spectrum at δ = -1.22 ppm (ketophosphonate) and peak at δ = 6.68 ppm

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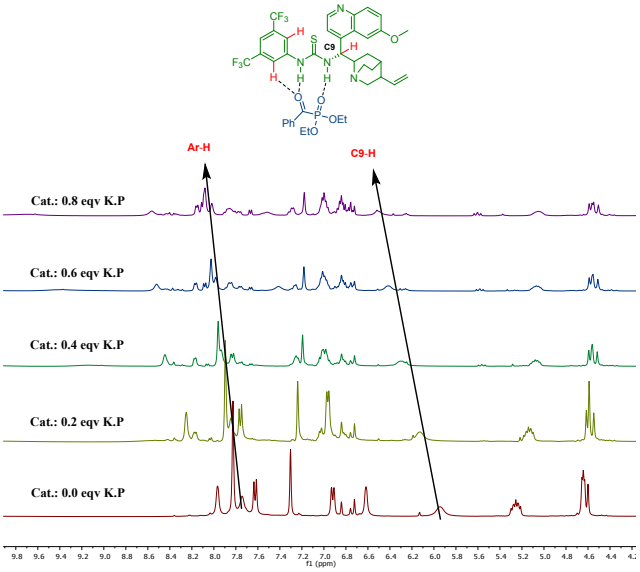
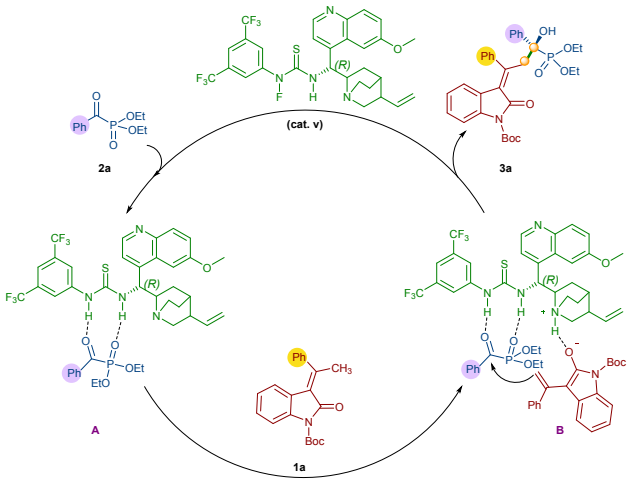


Figure 3. ^{1}H NMR spectra of the Cat. **V** (0.02 mmol in toluene-d_8) upon the addition of increasing amounts of α–keto-phosphonate.

(diethylphosphite). As time progressed, the ^{31}P NMR signals of the starting material disappeared gradually and the reaction was almost complete after 96 hours according to the ^{31}P NMR spectra (see SI. Figure S3).

On the basis of above observations of X-ray analysis and NMR studies, we proposed a plausible reaction mechanism (Scheme 4) for the vinylogous aldol reaction. Initially, the catalyst interacts with acyl phosphonate **2a** which is activated by hydrogen bonding giving an intermediate **A**, subsequently other reactant that is 3-alkylidene-2-oxindole is added to the reaction mixture gets deprotonated by tertiary amine leading to the formation *s-cis* dienolate through the *Si*-face to



Scheme 4. Plausible reaction mechanism.

acylphosphonate giving corresponding intermediate **B**. The desired product **3a** can be obtained from intermediate **B** by protonation regeneration of the catalyst for the next cycle. It is worth to note that the relative spatial arrangement of the two reacting partners, as synchronized by the bifunctional catalyst, establishes the selective attack to the *Si* face of the acylphosphonates.

Conclusions

In summary, we have demonstrated an efficient asymmetric vinylogous aldol reaction of 3-alkylidene-2-oxindoles to acylphosphonates catalyzed by bifunctional tertiary-amine thiourea organocatalyst. The stereocenter and the alkene geometries of the products were precisely controlled by the bifunctional amine-thiourea catalyst. A broad range of enantioenriched aldol adduct containing oxindole and acylphosphonates moiety could be synthesized in good to excellent yields with high *E/Z* (>19:1) and enantioselectivities (up to 99%).

Author Contributions

We strongly encourage authors to include author contributions and recommend using CRediT for standardised contribution descriptions. Please refer to our general author guidelines for more information about authorship.

Conflicts of interest

There are no conflicts to declare.

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