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Article

Synthesis and Evaluation of *N*-Diaminophosphoryl Aminothioureas as Bifunctional Catalysts for Vinylogous Aldol Reactions of Isatins and 2(3*H*)-Furanones

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Cite This: *ACS Omega* 2023, 8, 3190−3197

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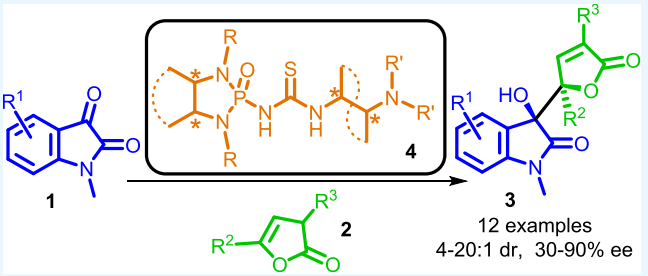
ABSTRACT: The organocatalytic asymmetric direct vinylogous aldol reaction of *N*-methylisatins **1** and γ-butenolides **2** to provide 3-hydroxy-2-oxindole derivatives **3** was investigated. A series of *N*-diaminophosphoryl aminothiourea catalysts **4** was synthesized, and their utility for the stereoselective formation of **3** was examined.



INTRODUCTION

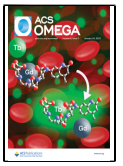
Naturally occurring as well as synthetic 3-alkyl-3-hydroxy-2-oxindole derivatives and related 2-oxindoles with γ-butenolide units at C3 have attracted considerable interest in recent years (Figure 1). These oxindoles display a wide range of biological activities, and the 3-alkyl-3-hydroxy-2-oxindole unit has been identified as a privileged motif[1] for biological activity. For example, convolutamydine A (**1**) and B (**2**) change the characteristics of, and induce differentiation of, HL-60 cells, respectively.[2] Convolutamydine E (**3**)[3] is active against several cancer cell lines (KB, KB/VJ-300, and U937) and inhibits cell division in fertilized sea-urchin eggs. Dioxibrassinine (**4**) is a phytoalexin with antifungal activity[4] and maremycin B (**5**) is active against several cancer cell lines.[5] Several synthetic 3-hydroxy-3-substituted-2-oxindole derivatives are also of interest. For example, **6** and its analogues are inhibitors of yeast α-glycosidase,[6] γ-butenolide containing oxindoles such as **7** have anticancer activity,[7] and 3-aryl derivatives such as **8** have neuroprotective and BK channel opening activity[8] (Figure 1). Structurally related oxindole derivatives such as 3-indolyl-3-hydroxy-2-oxindoles[9] and spirooxindoles,[9b−d] in which the two substituents at C-3 are incorporated into a ring, have also been actively investigated.

Given the importance of 3-substituted-3-hydroxy-2-oxindoles, their synthesis has been intensely investigated in recent years.[10] The stereoselective addition of carbon nucleophiles to isatin derivatives[11] is the prevalent approach to this class of compounds and metal-catalyzed as well as organocatalyzed versions of such reactions are reported.[11] Asymmetric organocatalysis has emerged as a dominant theme in organic synthesis, and significant advances have been made in the development and application of new organocatalysts for the enantioselective synthesis of bioactive compounds.[12] However, the direct vinylogous aldol reactions of 2(3*H*)-furanones (a class of γ-butenolides) with isatins are uncommon and only one report of a metal-catalyzed process[11e] and a sole study of an achiral, tertiary amine-mediated version[11f] are available. Our interest in such reactions stems from our earlier studies on organocatalyzed direct vinylogous aldol reactions of γ-crotonolactone with aldehydes employing bifunctional organocatalysts.[13] Herein, we report initial results on the organocatalytic direct vinylogous aldol reaction of selected *N*-methylisatins **1** and 2(3*H*)-furanones **2** to provide **3**.

At the outset, we chose to examine *N*-diaminophosphoryl aminothioureas **4** as potential catalysts for the desired vinylogous aldol reaction (Figure 2).

We anticipated activation of the isatin by hydrogen-bonding with the thiourea[14] and simultaneous activation of the γ-butenolide by deprotonation with the tertiary amine. It should be noted that, compared to the more conventional *N*-aryl aminothioureas, the corresponding *N*-diaminophosphoryl thioureas are far less explored as organocatalysts and only two studies with such thioureas are reported.[15] Moreover, these studies have only examined enamine-forming versions of the catalysts and there are opportunities for noncovalent catalysis and reaction development with *N*-diaminophosphoryl aminothioureas containing a basic functionality (e.g., a tertiary amine). We anticipated that enantiomerically enriched,

Received: October 14, 2022
Accepted: December 23, 2022
Published: January 9, 2023



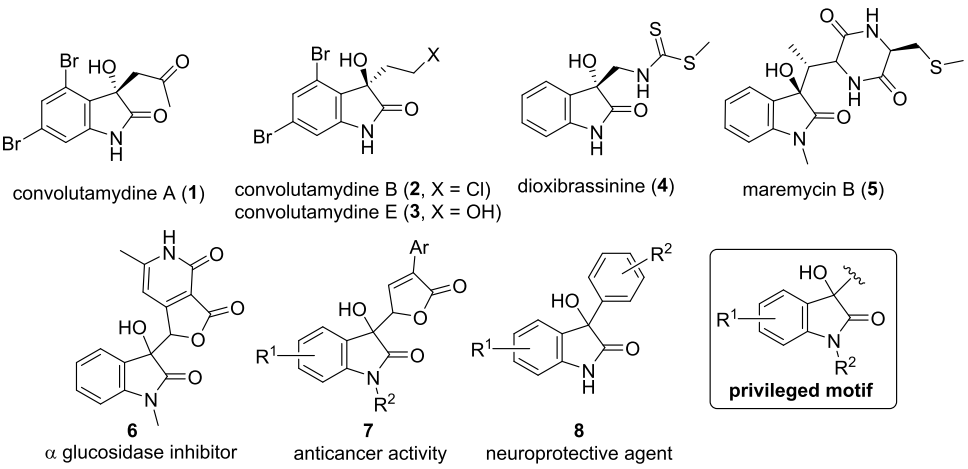


Figure 1. Selected 3-alkyl/aryl-3-hydroxy-2-oxindole derivatives.

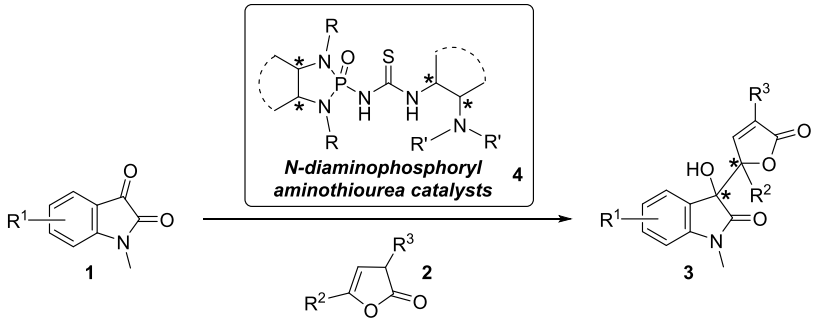


Figure 2. Asymmetric vinylogous aldol reaction of 2(3*H*)-furanones and isatins.

diamine-derived, bifunctional catalysts of this type would offer stereocontrol of the vinylogous aldol reaction.

RESULTS AND DISCUSSION

Our studies began with the synthesis of *N*-diaminophosphoryl aminothioureas **4**, the potential catalysts for the vinylogous aldol reaction. The general strategy for their preparation involved the synthesis of a series of chiral diamine-derived diaminophosphoryl chlorides **6** (Figure 2) and their conversion to the isothiocyanate derivatives **7** by adaptation of reported methods for related compounds.[16] Subsequent reaction of **7** with selected diamines **8** provided **4** (65−88% yield over three steps for **4a**−**4n**, and 91% yield over two steps, from the commercially available diaminophosphoryl chloride, for **4o**). This strategy and the catalysts **4** prepared for this study are shown in Figure 3.

Analysis of the ^{1}H NMR spectra of the phosphoramide-based catalysts revealed an interesting feature of their conformation in solution. We had anticipated that the N−H^a proton (Figure 4), which is flanked by the thiocarbonyl and the phosphoryl groups, would resonate more downfield than the N−H^b proton. However, N−H^b resonates more downfield than N−H^a. A plausible reason for this is a preference for the thiourea conformation in which N−H^b is internally hydrogen-bonded to the P═O oxygen (Figure 4), which results in a downfield shift of H^b.[17] This trend is observed for all of the catalysts **4** prepared in this study; H^b appears in the δ 9.50−δ 10.7 range, whereas the *N*−H^a appears in the δ 6.35−δ 6.93 range. The ^{1}H NMR data for previously reported[17b] phosphoryl thioureas similar to **4** is also indicative of intramolecular H-bonding (Figure 4). It may be noted that H^a and H^b are easily assigned by ^{1}H−^{1}H COSY spectroscopy (H^b correlates with NCH^c in the pendant diamine, and this correlation is absent for H^a). The N−H^b chemical shifts for **4a**, **4k**, and **4n** are representative (Figure 4). These observations suggested that the diaminophosphoryl thioureas **4** may function as conformationally constrained single H-bond donors in solution.

Initial studies were aimed at identifying the most suitable catalyst from the series of *N*-diaminophosphoryl thioureas **4** (Figure 3). We chose to examine the vinylogus aldol reaction of *N*-methylisatin (**1a**, 1.0 equiv) and α-angelica lactone (**2a**, 1.5 equiv) in the presence of 10 mol % of **4** for these studies. All reactions were conducted in diethyl ether at ambient temperature, and the observations are summarized in Table 1.

All of the *N*-diaminophosphoryl aminothioureas **4** were able to catalyze the vinylogous aldol reaction with moderate to excellent diastereoselectivity (dr = 2.5:1 to 20:1) in favor of the diastereomer **3a**. The yields (17−46%) and enantiomeric excess (6−77%) for **3a** were highly dependent on the structure of catalyst **4**, and hence, an analysis of the results as a function of structural changes in **4** is instructive.

The average yield (26%) and enantiomeric excess (53%) for catalysts containing a cyclohexanediamine-derived phosphoramide (Table 1, entries 1−9, catalysts **4a**−**4i**) is better than the average yield (20%) and enantiomeric excess (32%) for catalysts containing a 1,2-diphenylethanediamine-derived phosphoramide (Table 1, entries 10−15, catalysts **4j**−**4m**). Within the **4a**−**4i** series, the following observations are notable.

A comparison of the catalysts **4a**, **4b**, and **4c** indicates that an increase in the size of the tertiary amine pendant

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ACS Omega 2023, 8, 3190−3197

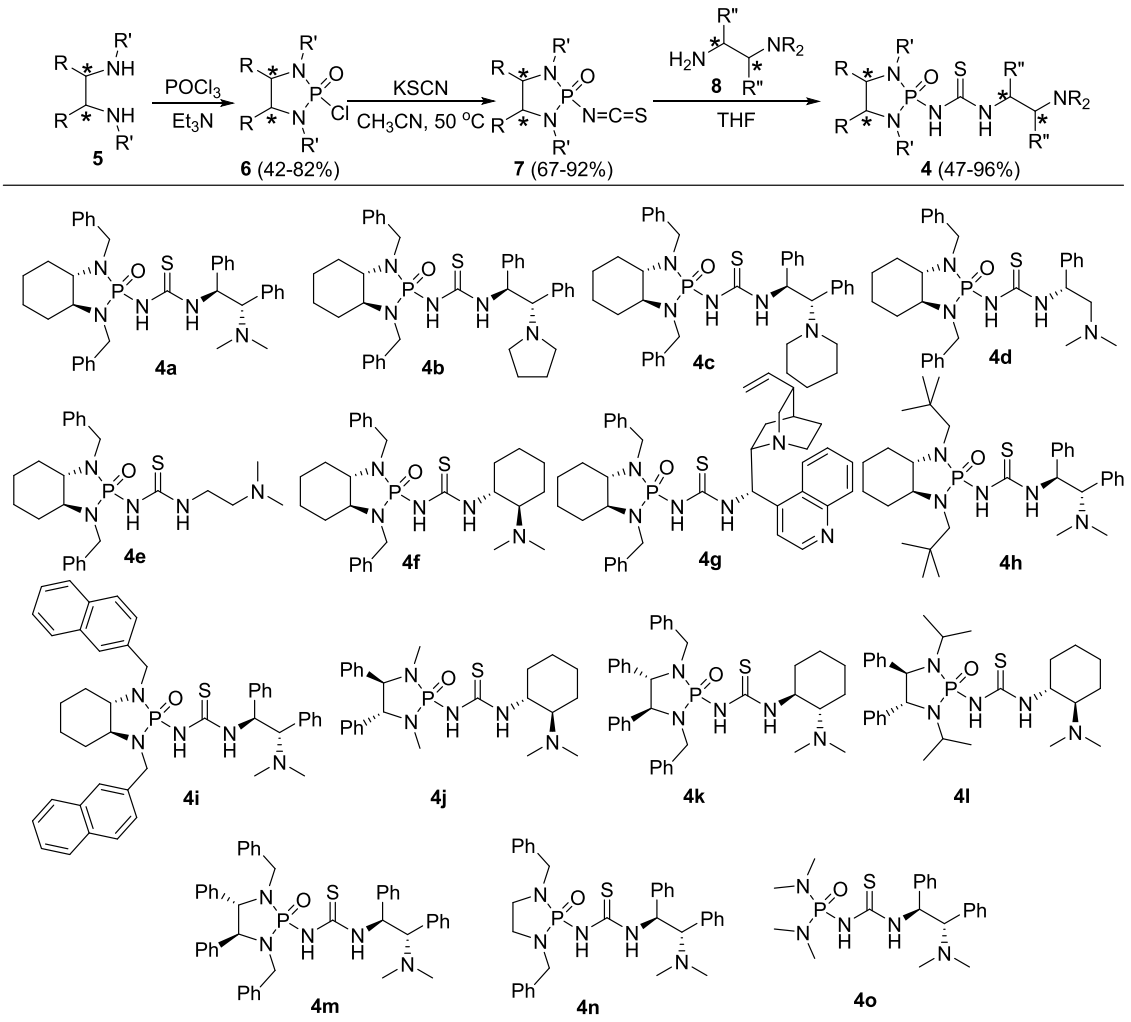

Figure 3. Synthesis of *N*-diaminophosphoryl aminothiourea catalysts **4** examined in this study.

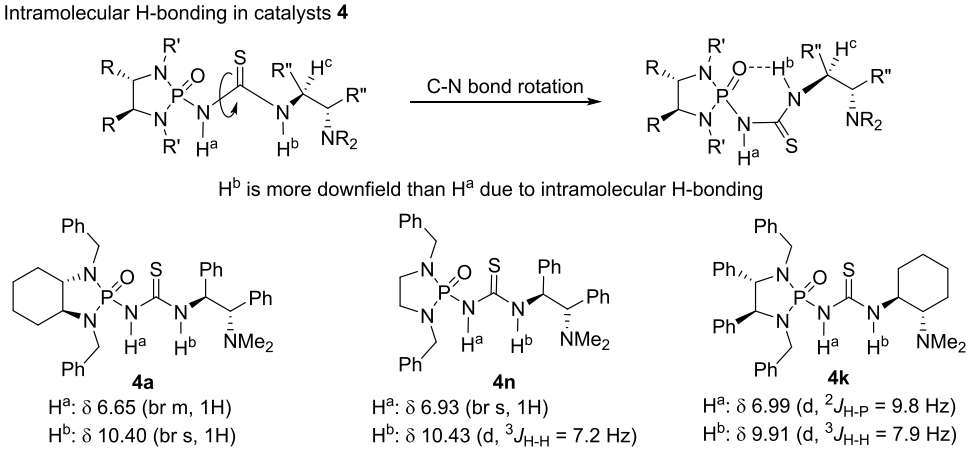

Figure 4. Intramolecular hydrogen bonding in *N*-diaminophosphoryl thioureas **4**.

(dimethylamino, pyrrolidinyl, and piperidinyl group) decreases the enantiomeric excess (compared to that obtained with **4a**) of the product (Table 1, entries 1−3). Successive removal of stereocenters in the diamine pendant in **4a**, to give catalysts **4d** and **4e**, also causes incremental loss of enantiomeric excess (Table 1, entries 4 and 5, 52% ee with **4d** and 19% ee with **4e**). Replacing the 1,2-diphenylethanediamine pendant in **4a** with a cyclohexanediamine- (**4f**) or a quinine-derived diamine (**4g**) also reduces the enantioselectivity for **3a** (Table 1, entries 6 and 7). The effect of a change to the *N*-alkyl group in the phosphoramide portion of **4a** was also examined. Replacing the *N*-benzyl group in **4a** with a neopentyl group (catalyst **4h**) resulted in a significant loss of enantioselectivity (Table 1, entries 1 and 8), whereas replacement with a 2-naphthyl group (catalyst **4i**) had a less pronounced effect (Table 1, entries 1 and 9). This observation suggests that an aryl functionality in

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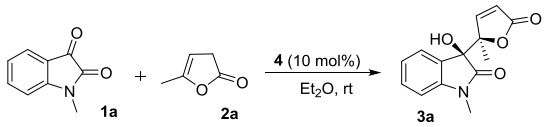
ACS Omega 2023, 8, 3190−3197

Table 1. Vinylogous Aldol Reaction of 1a and 2a Catalyzed by 4



entry	cat.	time (h)	yield 3a (%)[a]	dr	ee (%)[b]
1	**4a**	48	46	20:1	77
2	**4b**	48	19	20:1	73
3	**4c**	48	20	8.3:1	65
4	**4d**	20	30	6.2:1	52
5	**4e**	26	19	20:1	19
6	**4f**	24	31	20:1	48
7	**4g**	16	24	2.5:1	30
8	**4h**	48	25	20:1	43
9	**4i**	48	20	20:1	72
10	**4j**	16	17	3.2:1	6
11	**4k**	12	17	3.7:1	14
12	**4l**	16	20	5:1	44
13	**4m**	26	25	20:1	62
14	**4n**	18	35	6.6:1	61
15	**4o**	22	26	2.2:1	48

[a]Isolated yield. [b]Chiral HPLC analysis.

the *N*-group in the phosphoramide has a beneficial effect on enantioselectivity. Curiously, this *N*-group change has no effect on the diastereoselectivity of the reaction, which remains uniformly high (20:1) for **4a**, **4h**, and **4i**.

Notable structure-selectivity trends were also observed in the **4j**−**4l** series of catalysts. Incremental changes in the size[18] of the *N*-group in the phosphoramide portion (*N*-methyl in **4j**, *N*-benzyl in **4k**, and *N*-isopropyl in **4l**) are beneficial for the diastereoselectivity (**4j**, 3.2:1; **4k**, 3.7:1; **4l** 5.1:1) as well as the enantiomeric excess of **3a** (6% ee (with **4j**), 14% ee (with **4k**), 44% ee (with **4l**)) obtained with these catalysts (Table 1, entries 10−12).

Results with the catalysts **4m**, **4n**, and **4o** reveal the effect of changes to the phosphoramide portion while retaining the *N*,*N*-dimethylamino-1,2-diphenylethanediamine portion in the best catalyst (**4a**) in the series. Replacing the cyclohexanediamine-derived phosphoramide in **4a** with a 1,2-diphenylethanediamine phosphoramide (catalyst **4m**) has a notable detrimental effect on the enantioselectivity (77% ee with **4a** and 62% ee with **4m**) but not the diastereoselectivity. The use of an achiral cyclic phosphoramide (catalyst **4n**) lowers the enantiomeric excess (61%) and the diastereoselectivity (6.6:1, Table 1, entries 1 and 14). Curiously, the enantioselectivity with **4m** and **4n** is similar. An acyclic and achiral phosphoramide unit (catalyst **4o**) is detrimental to the diastereoselectivity as well the enantioselectivity of the reaction (Table 1, entries 1 and 15).

These observations lead to the following conclusions regarding structural features in **4**: (1) A cyclic phosphoramide functionality is important. (2) Chirality in the pendant diamine is important, but the pendant should be acyclic with a relatively small tertiary amine group. (3) Phosphoramide *N*-groups with aryl rings perform better than simple alkyl groups in cyclohexanediamine-derived phosphoramides, but *N*-alkyl groups are beneficial in stilbenediamine-derived phosphoramides. (4) In catalysts based on a 1,2-diphenylethanediamine-derived phosphoramide, a diphenylethanediamine pendant is better than a cyclohexanediamine pendant. (5) The best catalysts in the two groups (catalyst **4a** in **4a**−**4i** and catalyst **4m** in **4j**−**4n**) both have *N*-benzyl groups in the phosphoramide and a dimethylamino group in the pendant.

The (3*S*,2′*R*) diastereomer **3a** is obtained as the major diastereomer in all of the above reactions, and the absolute configuration of **3a** was established as 3*S*,2′*R* by X-ray crystallographic analysis (Figure 5).[19] Notably, this selectivity is opposite to the diastereoselectivity (3*S*,2′*S*) reported for the metal-catalyzed version[11e] of the reaction.

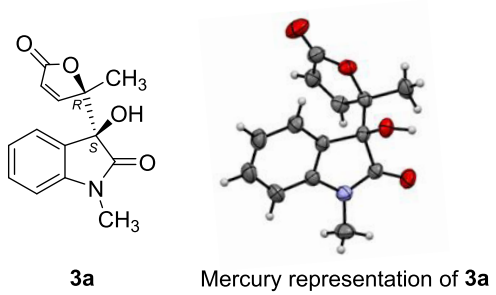


Figure 5. X-ray crystal structure of the vinylogous aldol product **3a**.

A comparison of the well-known and widely used, aminothiourea-containing, bifunctional organocatalyst **7**[20] and catalyst **4a** is particularly interesting. Under the optimized reaction conditions, **7** provided the diastereomer **3b** (26%) but with negligible enantiomeric excess (3%) and also with opposite diastereoselectivity ((3*S*,2′*S*)) compared to **3a** (Scheme 1). Although it could be reasoned that a comparison of **4a** and **7** is subjective, since unlike **7**, the 1,2-diaminocyclohexane unit is absent in **4a**, and it should be noted that the results with the 1,2-diaminocyclohexane-derived catalysts **4f** (dr 20:1; 42% ee), **4k** (dr 3.7:1; 14% ee), and **4l** (dr 5:1; 44% ee), although not better than **4a**, are still superior to those obtained with **7**. These observations indicate a distinct advantage of the diaminophosphoryl functionality in the context of the vinylogous aldol reaction being studied.

Having identified **4a** as the catalyst of choice, its performance in a selection of solvents was also examined.[21] However, these studies only confirmed that diethyl ether was the best solvent for the reaction of **1a** and **2a**. The optimized conditions were therefore used to examine the substrate scope of the vinylogous aldol reaction with a selection of substituted isatins as well as 2(3*H*)-furanones, and the results are summarized in Figure 6.

The substrate study identifies some limitations of the vinylogous aldol reaction of **1** and **2**. Although the diastereoselectivity of the reaction is high in several cases (four examples with dr 20:1, and two examples with dr >10:1), considerable variation is observed in the yield and the enantiomeric excess of **3** (23−90% ee). Although a distinct trend in the variation of stereoselectivity as a function of substitution in the isatin is not apparent, the yield of the reaction clearly depends on substitution in the 2(3*H*)-furanone. It is plausible that the yields for reactions with **2a** are affected by the decomposition of **2a** during the reaction since periodic addition of **2a** (0.38 equiv added in four portions at 3 h intervals) does increase the yield of **3a** (50%, 20:1 dr), but not significantly. However, this modification has a detrimental effect on the enantiomeric excess of **3a** (50% ee). Compared to reactions with **2a**, the reaction of *N*-methylisatin

https://doi.org/10.1021/acsomega.2c06637
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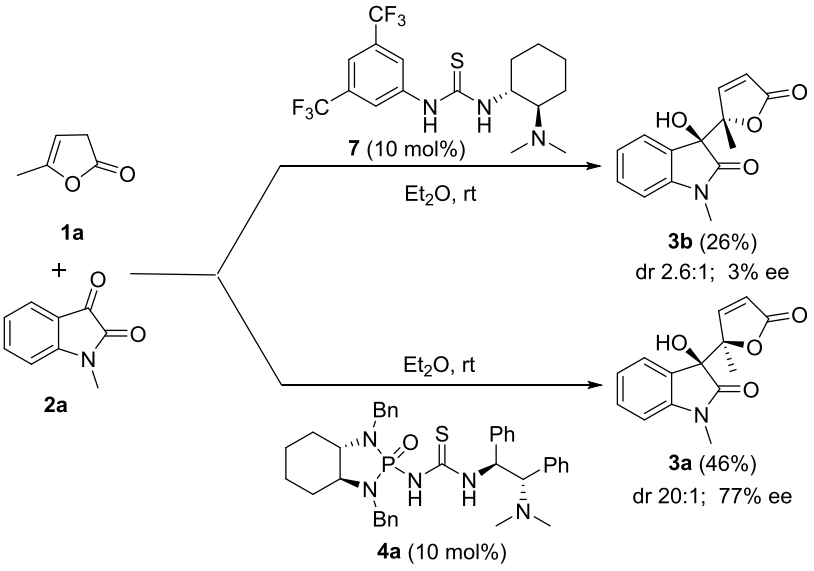
Scheme 1. Stereodivergent Vinylogous Aldol Reactions of 1a and 2a with Catalysts 4a and 7



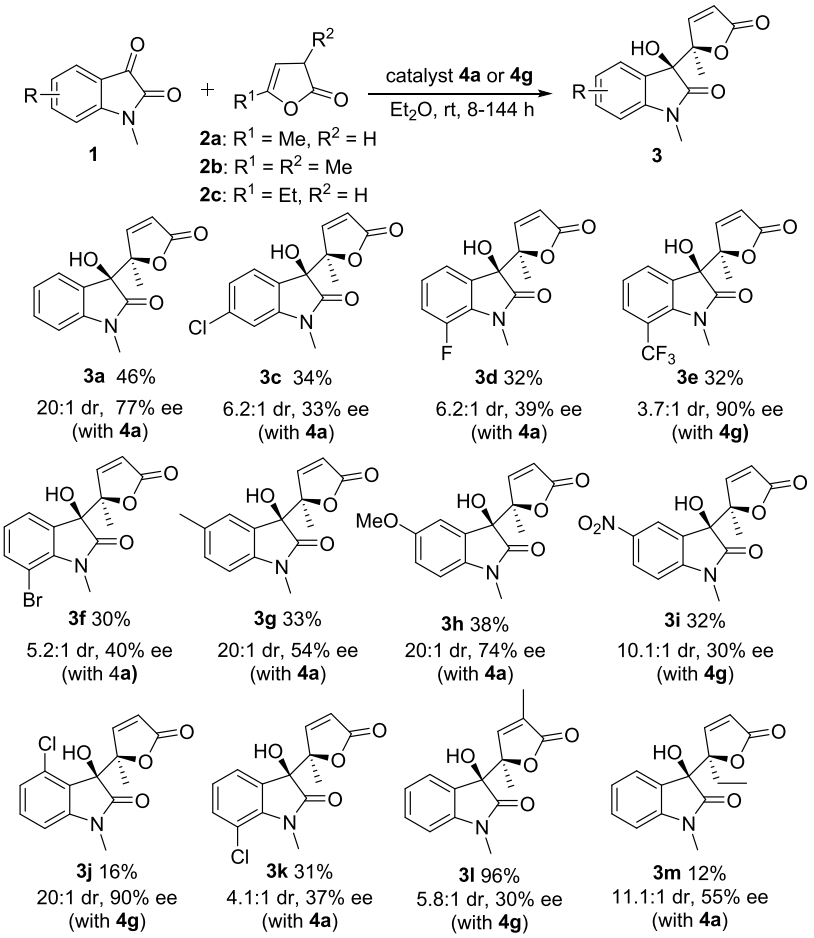


Figure 6. Substrate scope of the vinylogous aldol reaction of isatins and 2(3*H*) furanones.

1a and the furanone **2b** proceeds in notably high yield (90% of **3l**). This suggests that the low yield of the reactions with **2a** could be due to nucleophilic addition at the furanone carbonyl in **2a** or in **3a**, prior to protonation of the aldolate species, and this undesired side reaction may be hindered by substitution α to the lactone carbonyl. This could lead to the higher yield of **3l** obtained from **2b**. The low yield of **3m** is probably a consequence of steric hindrance of the aldol reaction (ethyl substituent at the reaction site in **2c**, compared to a methyl group in **2a**). Side reactions of the *N*-methylisatin could also be an issue since it is completely consumed in all of the reactions, but this is not reflected in the yield of **3**. We anticipate that all

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ACS Omega 2023, 8, 3190−3197

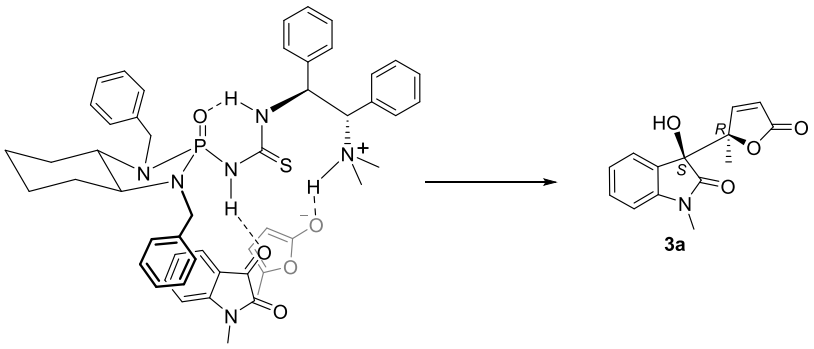

Figure 7. Proposed transition state assembly leading to the formation of **3a**.

of the aldol products are stable under the reaction conditions and some evidence for this was obtained by treating **3a** with catalyst **4a** in ether at ambient temperature for 48 h. Only unreacted **3a** was recovered (90%) from this reaction, and the enantiomeric excess of recovered **3a** was unaffected. A similar reaction conducted with the minor diastereomer **3b** and catalyst **4a** indicated that **3b** is also stable under the reaction conditions.

A plausible transition state assembly that explains the origin of the stereoselectivity of the vinylogous aldol reaction of **1a** and **2a** in the presence of catalyst **4a** to provide **3a** is shown in Figure 7. Taking into account that **4a** is internally hydrogen-bonded, and hence functions as a single hydrogen-bond donor, only the free thiourea N−*H* in **4a** is hydrogen-bonded to the isatin carbonyl group. The furanone-derived enolate is hydrogen-bonded with the ammonium functionality (obtained by deprotonation of the furanone by the tertiary amine) in the pendant diamine in **4a**. The chirality of the 1,2-diphenylethanediamine pendant controls the relative orientation of the isatin and the furanone (isatin placed above the furanone as shown), and this exposes the Si face of the enolate γ-carbon to the Si face of the isatin carbonyl group. It is plausible that stabilizing interactions involving the phosphoramide *N*-benzyl group and the isatin may also favor this assembly. The change in the enantiomeric excess of **3a** due to variation of the *N*-substituent in the cyclohexanediamine portion of **4** provides some support for this hypothesis (77% ee for **3a** with **4a** (*N*-benzyl) as the catalyst and 72% ee with **4i** (*N*-2-naphthyl), but only 43% ee with **4h** (*N*-neopentyl)). The comparable results obtained with **4m** and **4n** also suggest that *N*-substitution in the cyclic phosphoramide portion of **4** plays an important role. These organizing elements result in the preferential formation of the (3*S*,2′*R*) diastereomer **3a**.

In conclusion, we have prepared a series of *N*-diaminophosphoryl aminothioureas with basic as well as hydrogen-bonding functionalities. These phosphoramides function as bifunctional organocatalysts in the vinylogous aldol reaction of 2(3*H*) furanones and isatins. This is the first report of an organocatalyzed, asymmetric version of the described reaction. In addition, the diastereoselectivity of this organocatalytic reaction is opposite to that offered by a metal-based catalyst[11e] and by a conventional aminothiourea organocatalyst. Despite some limitations, the results presented here provide a basis for future versions of the organocatalytic vinylogous aldol reactions of 2(3*H*) furanones and isatins. Current efforts focus on these studies as well as the conversion of aldol products **3** to other oxindole-derived motifs.

EXPERIMENTAL SECTION

General Procedure for the Vinylogous Aldol Reaction of *N*-Methylisatins 1 and 2(3*H*)-Furanones 2. *N*-Methylisatin **1** (1.0 equiv) and furanone **2** (1.5 equiv) were added to a solution of the catalyst **4** (5−10 mol %) in diethyl ether (1 mL) at ambient temperature, and the mixture was stirred for the specified time. After completion of the reaction (TLC), the mixture was concentrated, the residue was dissolved in a minimum amount of THF, and the solution was applied to a column packed with a slurry of flash silica gel in hexanes/EtOAc. Elution of the column provided the aldol product **3** as an inseparable mixture of diastereomers. The preparation **3a** is representative.

(*S*)-3-Hydroxy-1-methyl-3-((*R*)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)indolin-2-one (3a). The reaction of *N*-methylisatin **1a** (40 mg, 0.25 mmol) and α-angelica lactone **2a** (37 μL, 0.38 mmol) in the presence of phosphoramide catalyst **4a** (16 mg, 0.02 mmol) in Et_2O (1 mL) for 19 h according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 4:2), 30 mg (46%) of **3a** as an off-white solid.

MP: 133.5−137.0 °C; IR (neat): 3407, 3364, 3077, 2923, 2853, 1754, 1706, 1609, 1495, 1467, 1364, 1295, 1254, 1204, 1164, 1116, 1088, 1047, 951, 906, 866, 824, 751 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.45 (d, 1H, J = 7.6 Hz,), 7.39−7.31 (m, 2H), 7.09 (td, 1H, J = 7.6, 0.9 Hz), 6.83 (d, 1H, J = 7.8 Hz), 5.94 (d, 1H, J = 5.7 Hz), 3.19 (s, 3H), 1.71 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6, 171.9, 156.3, 143.6, 130.8, 126.5, 125.7, 123.6, 122.9, 108.9, 90.4, 79.0, 26.6, 18.3. HRMS (APPI, pos.): m/z 259.0847 (259.0844 calc. for $C_{14}H_{13}NO_4$ $(M)^+$) and 260.0920 (260.0923 calc. for $C_{14}H_{14}NO_4$ $(M + H)^+$). HPLC: Chiralpak IA (hexane/*i*-PrOH, 90/10, flow rate 1 mL min^{-1}, λ = 247 nm): t_{major} = 20.75 min, t_{minor} = 24.16 min, 77% ee; $[\alpha]_D^{22}$ + 96.8 (c 0.5, CH_2Cl_2). Crystals of **3a** that were suitable for X-ray diffraction analysis were obtained by slow evaporation of a solution of **3a** in $CDCl_3$.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c06637.

Experimental procedures, spectral data; ^1H and ^{13}C spectra for compounds **3**, **4**, **6**, and **7**; and HPLC traces for **3** (PDF)

https://doi.org/10.1021/acsomega.2c06637
ACS Omega 2023, 8, 3190−3197

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

These investigations were supported by the Natural Sciences and Engineering Research Council of Canada and the Canada Foundation for Innovation. The authors thank Dr. Jian-Bin Lin, Centre for Chemical Analysis, Research and Training, Memorial University, for X-ray crystallography of **3a**.

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https://doi.org/10.1021/acsomega.2c06637
ACS Omega 2023, 8, 3190−3197