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Phosphoric acid-catalyzed 1,2-rearrangements of 3-hydroxy-indolenines to indoxyls and 2-oxindoles: reagent-controlled regioselectivity enabled by dual activation

Eva Schendera,[a] Stephanie Lerch,[a] Thorsten von Drathen,[a] Lisa-Natascha Unkel[a] and Malte Brasholz[a]*

Abstract: *A common synthetic route to indoxyl- and 2-oxindole alkaloids utilizes the oxidation of indoles to 3-hydroxyindolenines, followed by acid-mediated 1,2-rearrangement. However, controlling the regioselectivity is often challenging and there is an ongoing need for new reaction conditions allowing to steer product selectivity. We report here that phosphoric acids are ideal organocatalysts for the highly regioselective 1,2-rearrangement of 3-hydroxyindolenines to 2-oxindoles, with a predictable product selectivity arising from an efficient dual activation mode.*

Spirocyclic indoxyls and 2-oxindoles constitute fascinating classes of oxygenated indole alkaloids, and many of these natural products possess highly attractive medicinal properties such as analgesic, antihypertensive, antitumor or antiviral activity (Figure 1).[1]

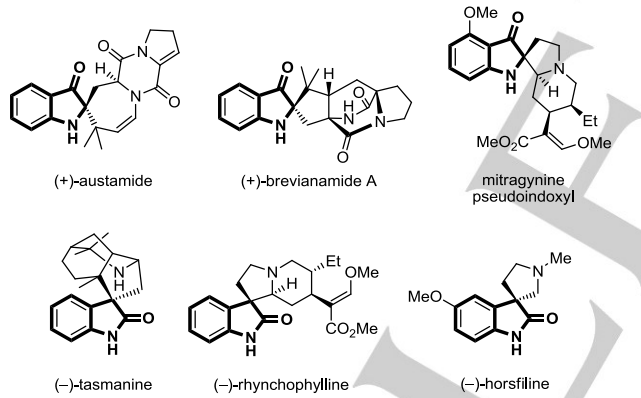
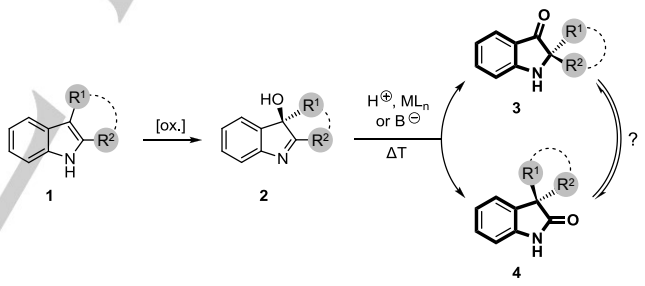


Figure 1. Natural spiroindoxyl and spirooxindol alkaloids.

Numerous structurally complex spiroindoxyls and -oxindoles have been targets of total synthesis,[2] and a well-known synthetic route to these compounds utilizes the oxidation of 1*H*-indoles **1** to 3-hydroxyindolenines **2**, followed by acid- or base-mediated 1,2-rearrangement (Scheme 1).[3] The oxidation of indoles **1** to intermediates **2** can be performed employing stoichiometric oxidants like peracids,[4] oxaziridines,[5] hypervalent iodine(III) reagents,[6] DMDO[7] and H_2O_2 in combination with aspartyl peptides,[8] or alternatively, by catalytic photooxygenation.[6a,9] The subsequent semipinacol rearrangement to indoxyls **3** proceeds at elevated temperatures and typically, sodium methoxide in methanol[4b,7a,10] is used, or Brønsted acids like HCl, formic and acetic acid,[5a,11] as well as stoichiometric amounts of Lewis acids like $BF_3{\cdot}OEt_2$[12] or lanthanide triflates.[5a,7b,8,12a,13] However, the semipinacol rearrangement is in competition with an alternate 1,2-rearrangement pathway leading to 2-oxindoles **4**, and as a result, controlling the regioselectivity of the protocol is often challenging, particularly when the substrate **2** shows little or no bias for one of the competing reaction pathways. Moreover, a possible equilibration between indoxyls **3** and 2-oxindoles **4** under the reaction conditions may complicate matters, which has been demonstrated to occur in at least one example of a boron trifluoride-mediated rearrangement.[12b]



Scheme 1. Oxidation of 1*H*-indoles **1** to 3-hydroxyindolenines **2** and 1,2-rearrangements to 2,2-disubstituted indoxyls **3** and 3,3-disubstituted 2-oxindoles **4**.

A recent example from natural product synthesis illustrated the difficulty of steering the regioselectivity of the competing 1,2-rearrangement pathways. A 2,3-diaryl-substituted hydroxyindolenine **2** served as a key intermediate in the formal total synthesis of the marine natural product diazonamide A, however, it underwent a moderately selective scandium triflate-mediated rearrangement to generate a 2:1 mixture of regioisomers, in favor of the undesired indoxyl product.[14]

Clearly, there is a need for reaction conditions that lead to predictable results in the 1,2-rearrangements of compounds **2**, and herein we report that phosphoric acid derivatives as simple as diphenyl phosphate (DPP) selectively and reliably promote the formation of 2-oxindoles **4** in many cases and under catalytic conditions. Secondly, we report that 3-alkyl-2-aryl-substituted substrates **2** are in fact switchable systems, for which product selectivity can be controlled by choosing between either phosphoric acid organocatalysis, or acetic acid as a stoichiometric promoter.

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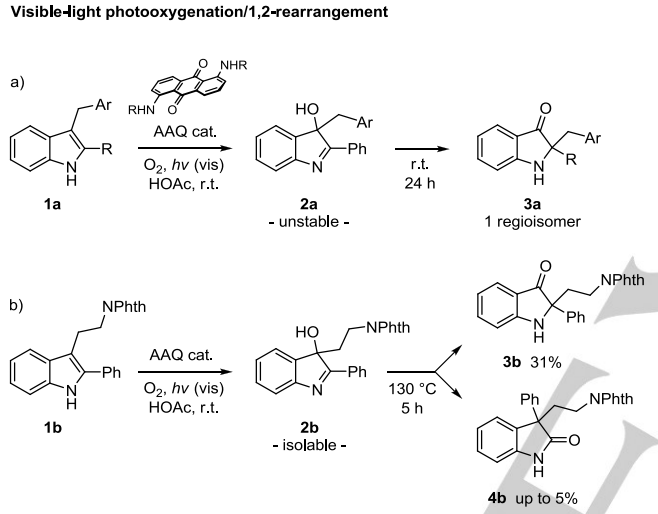
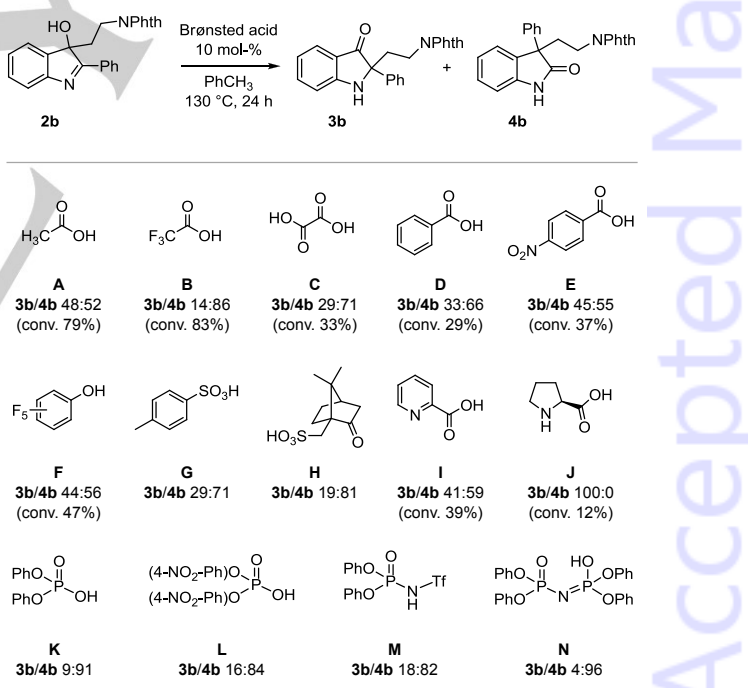
Our interest in the 1,2-rearrangements of hydroxyindolenines was stimulated by our recently reported photooxygenation of 2,3-disubstituted indoles **1a**, efficiently catalyzed by visible light-absorbing aminoanthraquinones (Scheme 2a).[9a] Intermediates **2a**, bearing a migration-prone C3-arylmethyl substituent, could not be isolated, but in acetic acid solution they underwent an instantaneous semipinacol rearrangement at room temperature, to furnish 2,2-disubstituted indoxyls **3a** as single products. As we extended our photooxygenation method to 2-phenyltryptamine derivative **1b**,[7b] we could however readily isolate the stable hydroxyindolenine **2b**, as its acid-mediated rearrangement requires elevated temperatures. When **2b** was generated and the reaction mixture in acetic acid was subsequently heated to 130°C for 5 h, the indoxyl **3b** was obtained in 31% yield, but notably, the 2-oxindole regioisomer **4b** was also formed, in amounts up to 5% (Scheme 2b).



Scheme 2. Aminoanthraquinone-catalyzed photooxygenation/1,2-rearrangements of a) indoles **1a** to 2,2-disubstituted indoxyls **3a** and b) of tryptamine derivative **1b** to the regioisomeric products **3b** and **4b**. AAQ = 1,5-diaminoanthraquinone derivative.

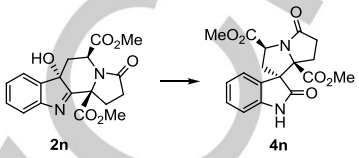
While the 1,2-rearrangement of hydroxyindolenine **2b** has previously been studied in the presence of various stoichiometric transition metal Lewis acids,[7b] we were intrigued by investigating the same reaction but using Brønsted acids, and under catalytic conditions. Consequently, we compared a range of Brønsted acid organocatalysts **A**-**N** in the rearrangement of **2b**, and as shown in Scheme 3, carboxylic, sulfonic, phenolic and phosphoric acids were employed. All reactions were performed in toluene solution, using 10 mol-% of catalyst, and heated to 130 °C for 24 h (sealed reaction vials). The catalyst screening showed that the relatively weak carboxylic acids like acetic acid (**A**), benzoic acid derivatives (**D**,**E**,**I**) as well as perfluorophenol (**F**) led to incomplete conversions between 29-79% after 24 h, and hardly any regioselectivity between products **3b** and **4b** was observed. Employing stronger sulfonic acids (**G**,**H**) allowed for full conversion of substrate **2b** and the oxindole product **4b** was formed with good selectivities of up to 81% in the case of camphor sulfonic acid (CSA, **H**). Trifluoroacetic acid (**B**) showed a similarly attractive selectivity for oxindole **4b**, with a slightly reduced conversion of 83% after 24 h. L-Proline (**J**) on the other hand exclusively promoted the formation of the indoxyl product **3b**, however, no catalytic turn-over was observed, resulting in only 12% conversion after 24 h. Finally, we compared the phosphoric acid catalysts **K**-**N**, which all gave full conversion of **2b** and which all offered high regioselectivity in favour of the oxindole **4b**. Imidodiphosphoric acid **N** produced product **4b** with 96% selectivity, however, using more readily available diphenyl phosphate (DPP, **K**) also gave an attractive product ratio of 91:9 in favour of **4b**. For comparison with the organic acid catalysts **A**-**N**, we also performed the rearrangement of **2b** using 10 mol-% of methanolic HCl in toluene (130 °C, 24 h) and this reaction gave 63% conversion and a ratio of **3b**/**4b** of 56:44. Further, we carried out the reaction in neat acetic acid (**A**, 130 °C, 24 h) and we made the very useful observation that under these conditions not only conversion of **2b** was complete after 24 h, but also, the regioselectivity improved, to reproducibly generate indoxyl **3b** with a good selectivity of 75% (*see below for a possible explanation*). Hence, with this last result and the phosphoric acid-catalyzed procedure, we effectively established a set of metal-free reaction conditions which allowed us to switch the regioselectivity in the acid-induced rearrangement of 3-hydroxyindolenine **2b**, and consequently we set out to investigate the applicability to differently substituted substrates.



Scheme 3. Catalyst screening for the 1,2-rearrangement of substrate **2b**. All reactions were performed at c = 50 µM of **2b** in $PhCH_3$, and in sealed vials. Regioisomer ratios were determined by analysis of crude ^{1}H-NMR spectra.

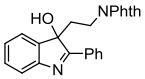
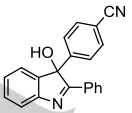
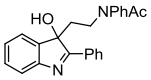
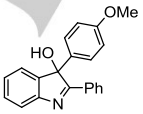
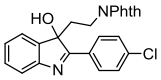
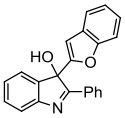
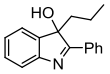
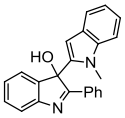
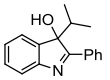
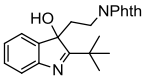
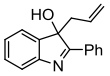
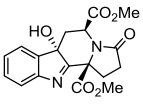
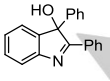
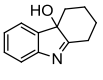
Table 1 shows a set of fourteen 3-hydroxyindolenines **2b**-**2o** which were reacted either in neat acetic acid (**A**) or using 10 mol-% of DPP (**K**), with temperatures ranging from 80-130 °C and within 24 h reaction time. We found that the 3-alkyl-2-aryl-

substituted substrates **2b**-**2e** are indeed switchable, leading either to indoxyl products **3** when using HOAc, or to 2-oxindoles **4** when using catalytic DPP (10 mol-%) in toluene, with good to excellent regioselectivities and isolated yields. The examples **2f** and **2g** however show that substrates bearing C3-substituents with a very high migrational aptitude like isopropyl and allyl, almost exclusively undergo the 'simple' semipinacol rearrangement leading to the indoxyl products **4f** and **4g** (compound **2a** of Scheme 2a also belongs into this category). We next examined 2,3-diarylated substrates **2h**-**2l**. Generally, these compounds all underwent very clean and perfectly selective rearrangement with catalytic DPP, exclusively generating the oxindole products **4h**-**4l**. In contrast with a previous report, the selectivity in the HOAc-mediated reaction is poor for substrate **2h**[11c] and **2j** (which form 1:1 mixtures of products) and only in case of the 3-(4-cyanophenyl)-2-phenyl-substituted indolenine **2i**, a slight preference in favor of indoxyl **3i** could be observed. Yet again, substrates **2k** and **2l** with electron-rich C3-heteroaryl groups undergo exclusive rearrangement to oxindoles **4k** and **4l** with catalytic DPP, and surprisingly also in HOAc. Finally, the examples **2m**-**2o** illustrate the behavior of 2,3-dialkyl-substituted hydroxyl-indolenines and compounds **2m** and **2n** undergo highly selective rearrangement to their oxindole congeners **4m** and **4n**, irrespective of the conditions used. In case of the tryptophane-derived substrate **2n**, the spirocyclic oxindole product **4n** was obtained with formally inverted configuration at the spirocyclic center (stereochemical assignments based on NOESY experiments), which is consistent with previous observations.[7b,8]



Compound **2o** in turn was found highly unstable to our conditions and generated a complex mixture of undefined products.

Table 1. Scope and regioselectivity of the Brønsted acid-mediated 1,2-rearrangement of substrates **2** to products **3** and **4**.

substrate		conditions	T [°C]	*r.r.* **3**/**4** [%][a]	**3** [%][b]	**4** [%][b]	substrate		conditions	T [°C]	*r.r.* **3**/**4** [%][a]	**3** [%][b]	**4** [%][b]
2b		(A) HOAc (B) DPP	130 130	75:25 9:91	**3b** 52 **3b** 6	**4b** 14 **4b** 67	**2i**		(A) HOAc (B) DPP	130 130	64:36 0:100	**3i** 37 -/-	**4i** 36 **4i** 40
2c		(A) HOAc (B) DPP	130 130	83:17 29:71	**3c** 82 **3c** 16	**4c** 3 **4c** 55	**2j**		(A) HOAc (B) DPP	130 130	50:50 0:100	**3j** 47 -/-	**4j** 47 **4j** 76
2d		(A) HOAc (B) DPP	130 130	81:19 8:92	**3d** 76 **3d** 6	**4d** 10 **4d** 58	**2k**		(A) HOAc (B) DPP	130 130	0:100 0:100	-/- -/-	**4k** 97 **4k** 95
2e		(A) HOAc (B) DPP	130 130	85:15 17:83	**3e** 65 **3e** 16	**4e** 10 **4e** 53	**2l**		(A) HOAc (B) DPP	130 130	0:100 0:100	-/- -/-	**4l** 98 **4l** 97
2f		(A) HOAc (B) DPP	130 80	95:5 92:8	**3f** 85 **3f** 86	**4f** 0 **4f** 7	**2m**		(A) HOAc (B) DPP	80 130	8:92 0:100	**3m** 6 -/-	**4m** 71 **4m** 89
2g		(A) HOAc (B) DPP	130 130	100:0 100:0	**3g** 78 **3g** 70	-/- -/-	**2n**		(A) HOAc (B) DPP	130 80	0:100 0:100	-/- -/-	**4n** 68 **4n** 89
2h		(A) HOAc (B) DPP	130 130	50:50 3:97	**3h** 46 **3h** 0	**4h** 43 **4h** 95	**2o**		(B) DPP (B) DPP	80 25	-/- -/-	-/- **3o** <5	-/- -/-

Reaction time 24 h in all cases, in neat HOAc **A** (conditions A) or in $PhCH_3$ and using 10 mol-% DPP **K** (conditions B). All reactions were performed in selead vials. [a] Determined by ^{1}H-NMR of crude products. [b] Isolated yields after chromatography.

In order to gain mechanistic insight, we first investigated the effect of the reaction temperature. Temperature-conversion profiles were recorded for the reaction of substrate **2b**, at temperatures ranging from 25-150 °C, and using neat HOAc as well as phosphoric acid catalysts **K** and **M** (see Figures S3a-S3c, supporting information). These data clearly showed that the

required temperature for the induction of the rearrangement of **2b** is at least 100 °C irrespective of the acid used, and thus it is mostly dependent on substrate structure, and only marginally influenced by the acid pK_a. Further, no interconversion between products **3b** and **4b** occured under the Brønsted-acidic conditions. For the 2,3-diarylated substrates **2h**-**2j**, the minimum reaction temperature was similarly determined to be 100 °C.

In terms of the catalytic activity and regioselectivity, a close inspection of the data in Scheme 3 shows that there is no clear correlation between acid pK_a, conversion of substrate **2b** or product ratio (Figure S1). Consequently, we studied the catalyst-substrate binding by ^{1}H-NMR spectroscopy in solution. Job-plots[15] were acquired for the 2,3-diphenyl-substituted hydroxyindolenine **2h**, in [D_6]-benzene or [D_8]-toluene solution and using acid catalysts **A**, **B** and **K**-**N** (Figure 2a), and the chemical shifts of the *ortho*-protons of the peripheral phenyl rings of **2h** (δ = 7.46 and 8.38 ppm in [D_6]-benzene in the uncomplexed form) were used for binding quantification (see Figures S2a-S2g). HOAc (**A**) shows only very weak and unspecific binding to substrate **2h**, and a saturation could not even be achieved using 10 molar equivalents of the acid. This might explain why the regioselectivity of the 1,2-rearrangement using catalytic HOAc differs markedly from the reaction in HOAc as solvent. By contrast, TFA (**B**) shows strong binding and the curve has a maximum at χ_i (molar fraction) of 0.33, indicating a 2:1 binding stoichiometry between the acid and substrate **2h**. The same is observed with diphenyl phosphate (DPP, **K**). Triflimide catalyst **M** and (4-Nitrophenyl)phosphate catalyst **L**, both with much decreased pK_a compared to DPP, even more strongly bind substrate **2h**, and each in a well-defined 1:1 complex (saturation is observed at χ_i = 0.50) for which we propose the structure shown in Scheme 2b. Imidodiphosphoric acid **N** in turn is a weak 1:1 binder.

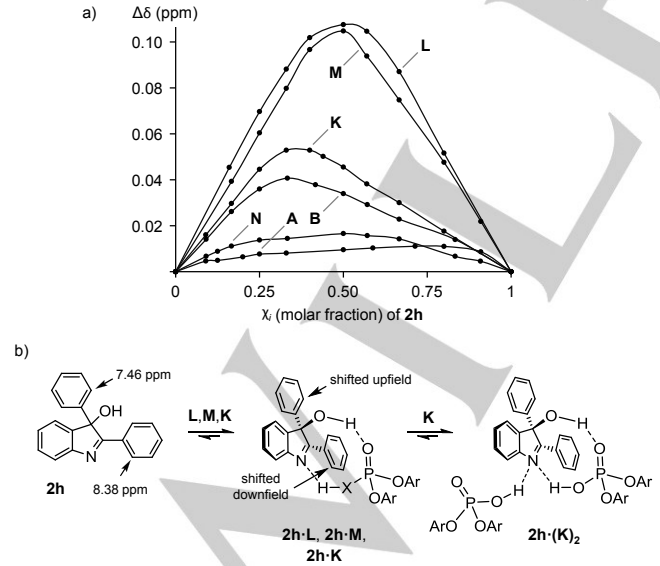
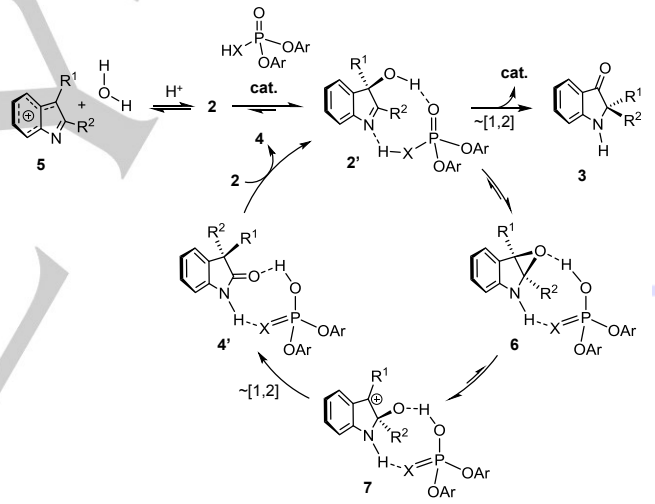


Figure 2. a) Job-plot analysis of the binding between substrate **2h** and catalysts **A**, **B** and **K**-**N** in [D_6]-benzene or [D_8]-toluene solution. Lines serve as guide to the eye. b) Complexation leading to the proposed 1:1 complexes **2h**·**L**, **2h**·**M** and **2h**·**K**, and the 2:1 complex **2h**·**(K)$_2$**.

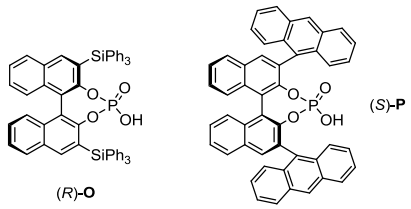
We can presently only speculate about the structure of the DPP-complex **2h·(K)$_2$**, but we think it is probably identical to the complexes **2h·L** and **2h·M**, with one additional weak hydrogen bond-contact between the indoline nitrogen and a second phosphate molecule (Figure 2b).

A proposed mechanism for the phosphoric acid-catalyzed rearrangement is shown in Scheme 4. Substrate **2** equilibrates with indolyl cation **5**, but complexation with the catalyst shifts the equilibrium to the 1:1-complex **2'**, from which a suprafacial [1,2]-shift leads to product **3** (the indoxyl is a free, unbound species in solution according to ^{1}H-NMR analysis, see Figure S2h). However, the dual activation[16] in complex **2'** strongly promotes the formation of epoxide **6**, and this pathway generally outcompetes the 'simple' semipinacol rearrangement **2'**→**3**. Ring-opening of **6** to the benzylic cation **7** is again facilitated by dual activation, and even more when substituent R^1 is electron-donating, which is particularly well-illustrated by the examples **2k** and **2l** with electron-rich C3-heteroaryl groups. Finally, an irreversible [1,2]-shift of the substituent R^2 in **7** generates the complex-bound oxindole **4'** (Figure S2h), with a formally inverted configuration at C3.[7b,8] Reaction of complex **4'** with substrate **2** releases the oxindole product **4** and closes the catalytic cycle.



Scheme 4. Proposed mechanism.

The equilibrium between hydroxyinolenine **2** and the planar indolyl cation **5** shown in Scheme 4 suggests that a dynamic kinetic resolution may be feasible using chiral phosphoric acid catalysis. In preliminary experiments, we have screened a number of BINOL-phosphate derived catalysts in the rearrangement of reference substrate **2b** (again using 10 mol-% of catalyst at 130 °C in $PhCH_3$, Table S1),[17] however, with only limited success so far. The *bis*-silylated catalyst (*R*)-**O** for instance offers excellent regiocontrol in favour of oxindole **4b** (**3b**/**4b** = 3:97) but both rearrangement products are fully racemic. Conversely, catalyst (*S*)-**P** induces no regioselectivity (**3b**/**4b** 46:54), but generates at least the indoxyl product (+)-**3b** with promising enantioselectivity (*e.r.* 13:87; the oxindole **4b** has *e.r.* 35:65).



In summary, we developed a phosphoric acid-catalyzed, highly regioselective rearrangement of 3-hydroxyindolenines to 2-oxindoles and this method is reliable and broadly applicable to a large variety of substrates. NMR studies suggest that the high level of regioselectivity observed in the phosphoric-acid catalyzed reaction originates from bidentate 1:1 binding between substrate and catalyst, leading to an efficient dual substrate activation. We are currently exploring applications of this method in natural product synthesis, and improvements to the enantioselective variant of the reaction are under development.

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Keywords: • organocatalysis • phosphoric acids • rearrangements • oxindoles • alkaloids

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[17] The room-temperature semipinacol rearrangement of a compound of type **2a** (R, Ar = Ph) to its corresponding indoxyl **3a** has been reported in one example, using a BINOL-derived phosphoric acid catalysts and with moderate *e.r.*, see reference 9b.

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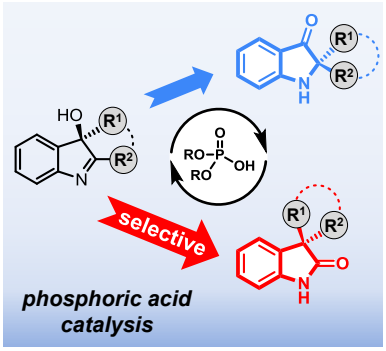
Rearrangements

Acid-induced 1,2-rear-rangements of hydroxyindolenines lead to indoxyls and 2-oxindoles, but controlling product selectivity is often challenging. Phosphoric acids were found to be ideal organocatalysts for inducing the highly regioselective rearrangement to 2-oxindoles in many examples.



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Phosphoric acid-catalyzed 1,2-rear-rangements of 3-hydroxyindolenines to indoxyls and 2-oxindoles: reagent-controlled regioselectivity enabled by dual activation