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Chiral Phosphoric Acid Catalyzed Enantioselective Decarboxylative Alkylation of β-Keto Acids with 3-Hydroxy-3-indolyloxindoles

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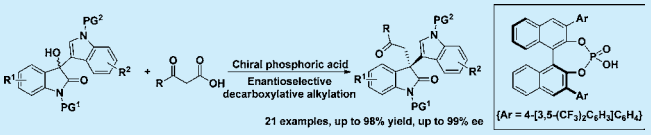
Supporting Information

ABSTRACT: A chiral phosphoric acid catalyzed enantioselective decarboxylative alkylation of β-keto acids with 3-hydroxy-3-indolyloxindoles is described in this context. This method tolerates a series of aromatic and aliphatic β-keto acids as well as substituted 3-hydroxy-3-indolyloxindoles, affording the corresponding chiral 3-functionalized 3-indolyloxindoles in high yields (up to 98%) and enantioselectivities (up to 99% ee).



The 3,3′-bisindoline unit bearing an all-carbon quaternary stereocenter (Figure 1, highlighted in red) is a privileged

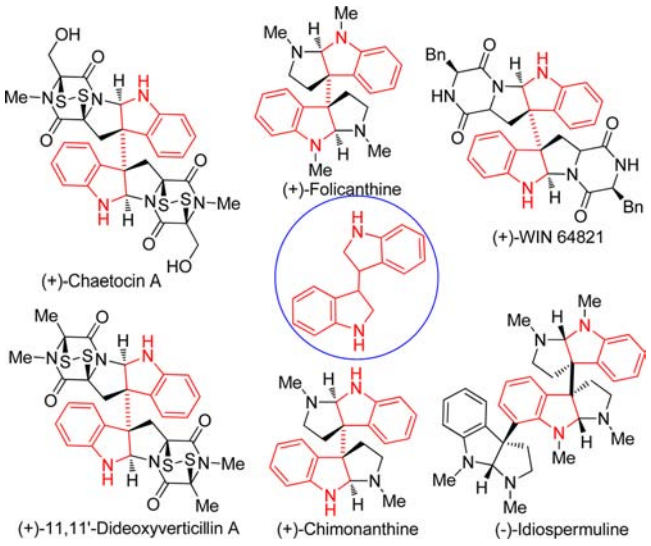
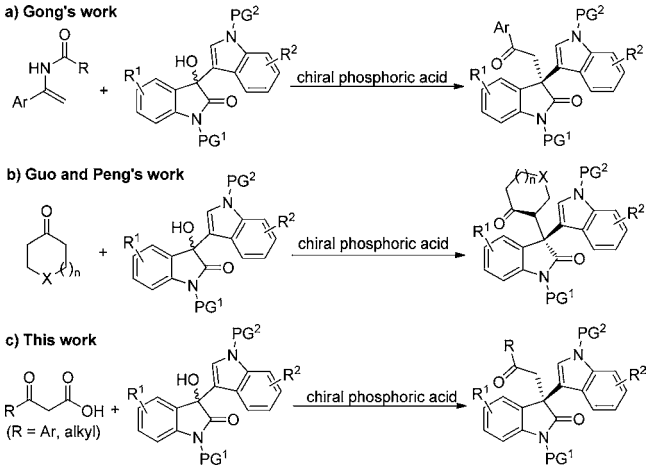


Figure 1. 3,3′-Bisindoline-based alkaloids bearing an all-carbon quaternary stereocenter.

substructure which is present in a large family of alkaloids with important biological and pharmaceutical activities.[1,2] Catalytic asymmetric transformation of 3-hydroxy-3-indolyloxindoles represents one of the feasible methods for the construction of 3,3′-bisindoline frameworks. In this context, Gong and co-workers developed an enantioselective nucleophilic substitution of 3-hydroxy-3-indolyloxindoles with enamides of aromatic methylketones for the synthesis of 3-functionalized 3- indolylox-indoles and the cyclotryptamine alkaloid (+)-folicanthine (Scheme 1a),[3a] whereas the group of Guo and Peng disclosed an organocatalytic asymmetric alkylation of 3-hydroxy-3-indolyloxindoles with unmodified ketones (Scheme 1b).[3b] While these publications are excellent, the enantioseletive

Scheme 1. Catalytic Asymmetric Alkylation of 3-Hydroxy-3-indolyloxindoles



alkylation of acyclic alkyl ketones with 3-hydroxy-3-indolylox-indoles still suffers from unsatisfactory results.

The utility of β-keto acids as ketone enolate equivalents in the catalytic asymmetric decarboxylative transformations[4] has been well established by our group[5] and others.[6] Many electrophilic partners, including nitroalkenes, carbonyl compounds, alkyl halides, and imines, have been successfully employed in the enantioselective decarboxylative reactions of β-keto acids. However, the use of alcohols as electrophiles for the asymmetric decarboxylative alkylation of β-keto acids remains elusive. Recently, we found that chiral phosphoric acids could facilitate the asymmetric alkylation of β-keto acids with 3-hydroxy-3-indolyloxindoles under mild reaction conditions, delivering the corresponding oxindoles bearing an all-carbon quaternary stereocenter in high yields (up to 98%) and enantioselectivities

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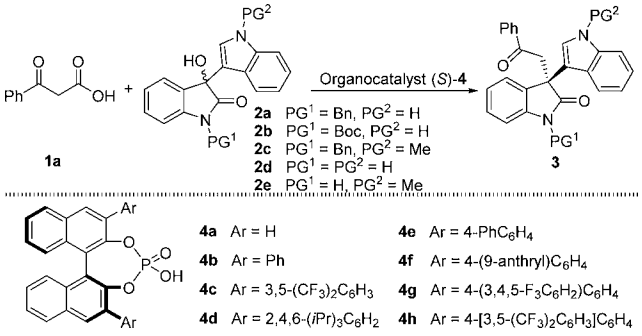
(up to 99% ee). Herein, we report our preliminary results on this subject.

Our studies were initiated with the reaction between 3-oxo-3-phenylpropanoic acid **1a** and racemic 3-hydroxy-3-indolyloxindole **2a**[7] by using phosphoric acid catalysts.[8,9] The results are shown in Table 1. Under the room temperature conditions, the simplest catalyst **4a** was able to catalyze this reaction slowly to give the desired product **3a** in a moderate yield (entry 1). Employment of anhydrous Na_2SO_4 as a dehydration agent significantly improved reaction rate, giving a quantitative yield, but without any enantioselectivity (entry 2). Subsequent screening of chiral phosphoric acids **4b**–**h** revealed that the aryl group at the 3,3′-position of the BINOL backbone had a significant effect on catalytic activity as well as enantioselectivity (entries 3–9). Among them, (*S*)-**4h** was identified as the optimal catalyst in terms of chiral induction ability (entry 9). Further improvement in enantioselectivity was achieved by decreasing reaction temperature with a prolonged reaction time (entries 10–12). Subsequent attempts to conduct the reaction at −50 °C failed (entry 13). Following these evaluations of chiral catalyst and reaction temperatures, a solvent screen was undertaken (entries 14–17). Among the solvents tested, dichloromethane was found to be the best with respect to reaction activity and enantioselectivity. Reducing the catalyst loading from 10 to 5 mol % was also acceptable, giving a comparable result under standard reaction conditions (entry 18). Finally, it was found that an excess of *β*-keto acid **1a** was necessary to get the maximum yield, since an undesired decarboxylation process cannot be excluded (entries 19 and 20). It is worth noting that the presence of the N-protecting group at the oxindolyl moiety proved to be essential for the reaction activity and asymmetric induction (entries 21–24). *N*-Boc- and *N*-benzylisatin-derived 3-hydroxyoxindoles **2b** and **2c** were also found to be suitable substrates, providing the chiral 3-functionalized 3-indolyloxindoles **3b** and **3c** with high yields (86% and 88%, respectively) and enantioselectivities (89% ee and >99% ee, respectively) (entries 21 and 22). However, no reaction was observed for substrates **2d** and **2e** (entries 23 and 24) wherein the N-protecting group at the oxindolyl moiety was absent.

After determination of the optimal conditions, the scope of this decarboxylative alkylation was investigated, and the results are summarized in Scheme 2. We first tested the reaction of four 3-hydroxy-3-indolyloxindoles with 3-oxo-3-phenylpropanoic acid **1a** under the established conditions. The corresponding alkylation products **3f**–**i** were obtained in high yields (83–94%) with excellent enantioselectivities (90–94% ee). Next, the substrate scope of *β*-keto acids was explored by the reaction with 3-hydroxy-3-indolyloxindole **2a** under the optimal conditions. We were pleased to find that a broad range of phenyl-substituted *β*-keto acids with substituents in the *ortho*-, *meta*-, or *para*-position of phenyl ring proceeded well to furnish the desired products **3j**–**q** in good to excellent levels of yield (71–98%) and enantioselectivity (86–99% ee). Other aryl-substituted *β*-keto acids such as 3-(naphthalen-2-yl)-3-oxopropanoic acid and 3-(furan-2-yl)-3-oxopropanoic acid could also be successfully employed in this decarboxylative alkylation reaction, delivering the desired products (**3r** and **3s**) in good to high yields and enantioselectivities. In addition, alkyl-substituted *β*-keto acids participated in this reaction to afford the corresponding products **3t**–**v** in 65–71% yield with 88–93% ee.

The tolerance of *N*-methyl on the indole moiety encouraged us to carry out the enantioselective decarboxylative alkylation of 3-(4-methoxyphenyl)-3-oxopropanoic acid with 3-hydroxy-3-indolyloxindole **2f** under the established conditions. This substrate **2f** was readily synthesized from commercially available *N*-methylisatin and *N*-methylindole[7b] and then was proved to be suitable for our protocol to produce 3-functionalized 3-

Table 1. Catalyst Screening and Condition Optimization[a]



entry	4/3	solvent	temp (°C)	time (h)	yield[b] (%)	ee[c] (%)
1[d]	(*S*)-**4a**/**3a**	CH_2Cl_2	25	12	30	0
2	(*S*)-**4a**/**3a**	CH_2Cl_2	25	12	99	0
3	(*S*)-**4b**/**3a**	CH_2Cl_2	25	12	60	0
4	(*S*)-**4c**/**3a**	CH_2Cl_2	25	12	66	17
5	(*S*)-**4d**/**3a**	CH_2Cl_2	25	12	61	8
6	(*S*)-**4e**/**3a**	CH_2Cl_2	25	12	73	21
7	(*S*)-**4f**/**3a**	CH_2Cl_2	25	12	70	6
8	(*S*)-**4g**/**3a**	CH_2Cl_2	25	12	54	60
9	(*S*)-**4h**/**3a**	CH_2Cl_2	25	12	52	63
10	(*S*)-**4h**/**3a**	CH_2Cl_2	0	24	93	82
11	(*S*)-**4h**/**3a**	CH_2Cl_2	−20	24	92	84
12	(*S*)-**4h**/**3a**	CH_2Cl_2	−35	36	90	93
13	(*S*)-**4h**/**3a**	CH_2Cl_2	−50	36	0	--
14	(*S*)-**4h**/**3a**	$ClCH_2CH_2Cl$	−35	36	50	41
15	(*S*)-**4h**/**3a**	$CHCl_3$	−35	36	82	60
16	(*S*)-**4h**/**3a**	toluene	−35	36	40	35
17	(*S*)-**4h**/**3a**	THF	−35	36	0	
18[e]	(*S*)-**4h**/**3a**	CH_2Cl_2	−35	36	87	90
19[f]	(*S*)-**4h**/**3a**	CH_2Cl_2	−35	36	78	93
20[g]	(*S*)-**4h**/**3a**	CH_2Cl_2	−35	36	90	93
21	(*S*)-**4h**/**3b**	CH_2Cl_2	−35	36	86	89
22	(*S*)-**4h**/**3c**	CH_2Cl_2	−35	36	88	>99
23	(*S*)-**4h**/**3d**	CH_2Cl_2	25 or 0	36	0	
24	(*S*)-**4h**/**3e**	CH_2Cl_2	25 or 0	36	0	

[a]General reaction conditions: **1a** (0.15 mmol), **2** (0.1 mmol), Na_2SO_4 (100 mg), and catalyst **4** (10 mol %) in solvent (2 mL) at the given temperature for the stated time. [b]Isolated yield. [c]Determined by HPLC analysis on a chiral stationary phase. The absolute stereochemistry was assigned by comparison of the optical rotation with literature reported data (ref 3a). [d]The reaction was performed in the absence of Na_2SO_4. [e]5 mol % of catalyst was used. [f]0.1 mmol of **1a** was used. [g]0.2 mmol of **1a** was used.

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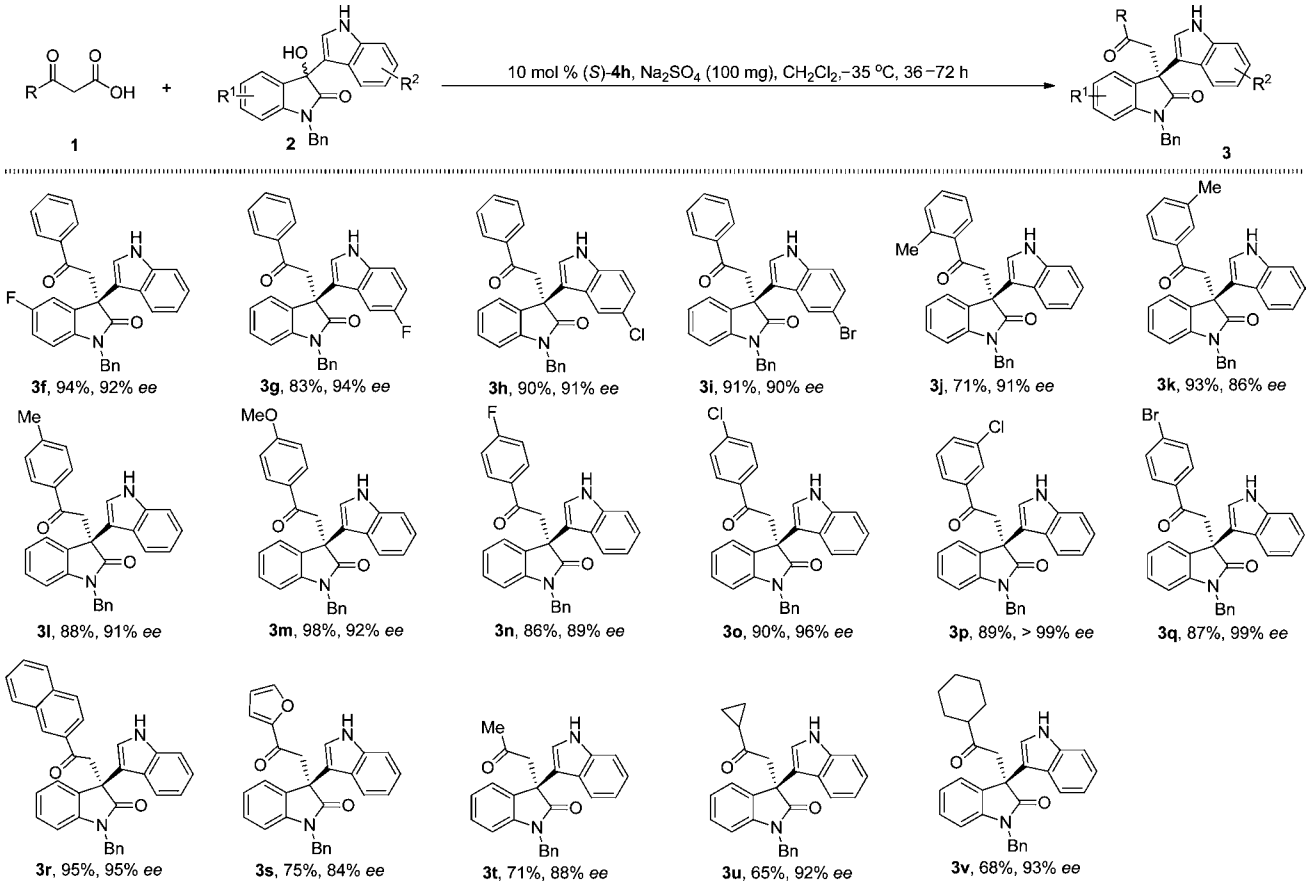
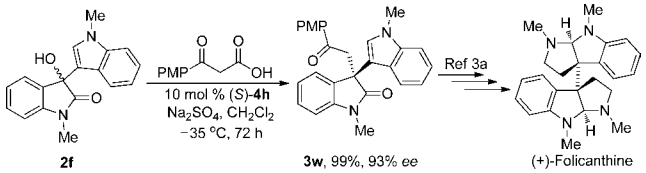
Scheme 2. Scope of the Decarboxylative Alkylation of β-Keto Acids 1 with 3-Hydroxyoxindoles 2[a–c]



[a]Reaction conditions: **1** (0.15 mmol), **2** (0.1 mmol), Na_2SO_4 (100 mg), and chiral phosphoric acid (*S*)-**4h** (10 mol %) in CH_2Cl_2 (2 mL) at −35 °C for 36−72 h. [b]Isolated yield. [c]ee value was determined by HPLC analysis on a chiral stationary phase.

indolyloxindole **3w** in almost quantitative yield with 93% ee (Scheme 3). The compound **3w** is a known intermediate in the

Scheme 3. Preparation of the Key Intermediate 3w for Access to Alkaloid (+)-Folicanthine (PMP = 4-Methoxyphenyl)



synthesis of cyclotryptamine alkaloid (+)-folicanthine (created by Gong and co-workers),[3a] and our methodology complements Gong's elegant approach to this ketone.

To cast some light on the mechanism, the electrospray ionization mass spectrometry (ESI-MS) method was used to study this decarboxylative alkylation reaction. An ESI-MS measurement of a mixture of 3-(4-fluorophenyl)-3-oxopropanoic acid, 3-hydroxy-3-indolyloxindole **2a**, and the catalyst (*S*)-**4h** in dichloromethane displayed a base peak at *m*/*z* 541.1540, pertaining to the existence of the alkylation intermediate **5** [HRMS (ESI) calcd for $C_{32}H_{23}FN_2NaO_4^+$ (**5** + Na^+) 541.1534] (Figure 2). Nevertheless, isolation of this intermediate was not successful by chromatography on silica gel due to rapid decomposition. In the control experiment, we found that the corresponding acetophenone could not react with 3-hydroxy-3-

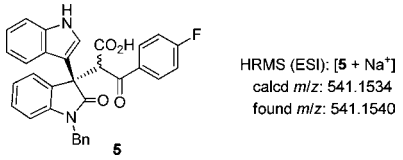


Figure 2. Structure of intermediate **5**.

indolyloxindole under our standard conditions. These results clearly indicate that the alkylation occurs prior to the decarboxylation step in this asymmetric decarboxylative reaction.

On the basis of our experimental results and previous studies,[3a,b] the reaction is proposed to begin with the formation of a chiral iminium phosphate ion pair upon treatment of 3-hydroxyoxindole **2** with the phosphoric acid catalyst, followed by a conjugate addition with the β-keto acid and subsequent decarboxylation (Figure 3). The stereochemistry could be ascribed to the hydrogen-bond interaction between the catalyst and the carboxylic acid group of the β-keto acid, allowing the enol of β-keto acid to only attack the iminium species from the *Re* face and thus giving the *R*-configured alkylation product.

In summary, we have developed a chiral phosphoric acid catalyzed enantioselective decarboxylative alkylation of β-keto acids with 3-hydroxy-3-indolyloxindoles. This method tolerates a series of aryl- and alkyl-substituted β-keto acids, affording the corresponding 3-functionalized 3-indolyloxindoles bearing an all-carbon quaternary stereocenter in high yields (up to 98%) and enantioselectivities (up to 99% ee). With our protocol, a key

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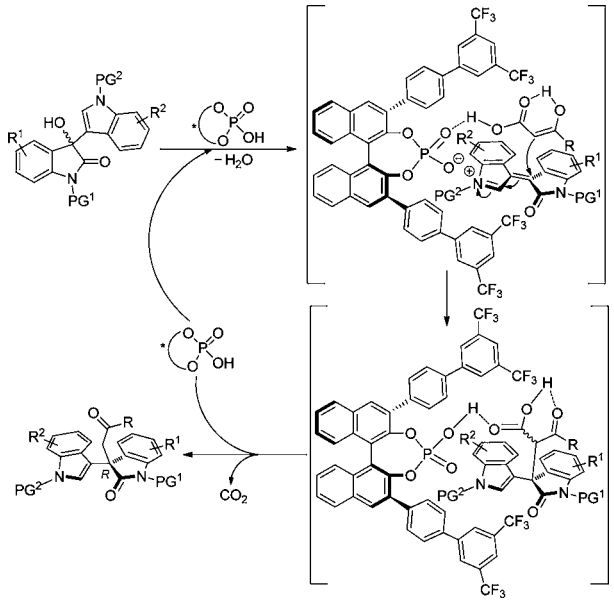

Figure 3. Proposed reaction pathway.

intermediate for 3,3′-bisindoline alkaloid (+)-folicanthine can be readily obtained. A mass spectroscopy analysis indicated that the alkylation of β-keto acids with 3-hydroxy-3-indolyloxindoles could occur prior to the decarboxylation step. Further investigations focused on other variants of enantioselective decarboxylative reactions catalyzed by chiral phosphoric acids are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectral data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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