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Chiral Calcium Phosphate Catalyzed Asymmetric Alkenylation Reaction of Arylglyoxals with 3-Vinylindoles

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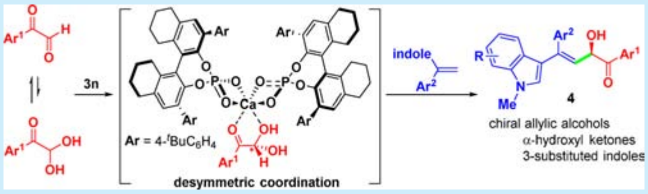
Ⓢ *Supporting Information*



ABSTRACT: A highly efficient alkenylation reaction of arylglyoxals with 3-vinylindoles catalyzed by chiral calcium phosphate is described. Structurally diverse allylic alcohols bearing indole and carbonyl units are prepared in excellent yields, good diastereoselectivities, and high to excellent enantioselectivities. These products are good building blocks for the synthesis of polysubstituted chiral tetrahydrocarbozol-2-ones. The mechanism study indicates that the most likely role of the catalyst is to activate the hydrate of arylglyoxal and control the stereoselectivity via desymmetric coordination.

The direct catalytic alkenylation of unsaturated double bonds is a highly challenging and valuable $C_{sp3}-C_{sp2}$ bond-forming strategy in organic synthesis.[1] This enormously important method has been extensively used in the synthesis of allylic amines,[2] alcohols,[3] and other allylic compounds.[4] Among the reported examples, alkenylboronates[5] and alkenylmetal compounds[6] are two types of commonly used alkenylation reagents. Other compounds, such as functionalized allenoates[7] and vinylogous azaenamine,[8] are also suitable donors for the construction of special molecules containing allylic skeletons. By comparison, alkene is the most ideal alkenylation reagent because this type of reagent can give a straightforward path to allylic compounds via catalytic nucleophilic addition to unsaturated double bonds in an economic and environmentally benign manner. However, the reported methodologies in this respect are very rare.[9] A possible obstacle is the weak nucleophilic ability of alkene. Recently, we reported a chiral Brønsted acid catalyzed alkenylation of imines with 3-vinylindoles for the construction of indole-substituted allylic amines.[10] We envisioned that various structurally diverse allylic compounds bearing indole units could be prepared through the introduction of different prochiral electrophiles to react with 3-vinylindoles.[11] As part of our continuous efforts in this field, we report here a chiral calcium phosphate[12] catalyzed asymmetric alkenylation reaction of 3-vinylindoles and arylglyoxals, leading to allylic alcohols bearing indole and carbonyl units in excellent yields and enantioselectivities. The reaction mechanism and application of alkenylation reaction in the synthesis of structurally complex indole compounds were also investigated.

Initially, we chose 3-vinylindole **1a** and phenylglyoxal **2a** as reactants and chiral phosphoric acid[13] **3a** as catalyst. In the promotion of catalyst **3a**, the reaction of 3-vinylindole **1a** and phenylgloxal **2a** proceeded smoothly and generated the desired product **4a** in excellent yield with a good *E*/*Z* ratio and moderate ee (Table 1, entry 1). Encouraged by the preliminary experimental results, chiral phosphoric acids **3b−g** were screened in this reaction; however, better results were not obtained (Table 1, entries 2−7). We found that this reaction could take place in the absence of phosphoric acid, which increased the difficulty to control the stereoselectivity.[14] Consequently, we turned our attention toward finding other highly efficient catalysts. According to Hosomi's work, $CaCl_2$ was a suitable catalyst for the aldol reaction of silyl enolates and arylgloxals.[15] We envisioned that the chiral alkali or alkaline earth phosphates would be good catalysts for our reaction. Therefore, the phosphates **3h−m** derived from the optimal chiral phosphoric acid **3a** were prepared and investigated under a nitrogen atmosphere. Notably, these chiral phosphates greatly increased the reaction speed, leading to the product **4a** in excellent yield with a good *E*/*Z* ratio within 1 h (Table 1, entries 8−13). Among them, the chiral calcium phosphate **3l** gave the best experimental results (Table 1, entry 12). The enantioselectivity of **4a** increased to 88% when this reaction was conducted at 0 °C (Table 1, entry 14). Then chiral calcium phosphate **3n** derived from H8-BINOL was prepared and introduced in this reaction. In the promotion of 10 mol % of **3n**, compound **4a** was obtained in quantitative yield with exceptional stereoselective outcomes (Table 1, entry 15).

After obtaining the optimal reaction conditions, we examined the substrate scope of this reaction. First, various substituents were introduced onto the phenyl ring of arylglyoxals. Phenylglyoxals bearing *para*-substituted phenyls were good reaction partners in this reaction, no matter whether an electron-withdrawing or electron-donating group was involved; the corresponding products were obtained in excellent yield with high *E*/*Z* ratios and enantioselectivities (Table 2, entries 2−5). Similar results were observed with respect to the 2-CF_3-phenylglyoxal (Table 2, entry 6). Furthermore, 6-methoxy-2-

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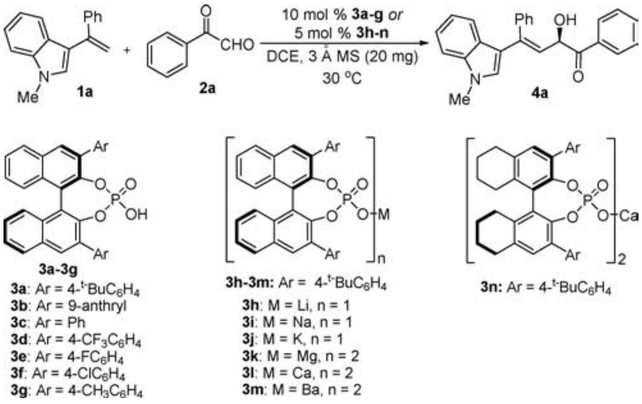
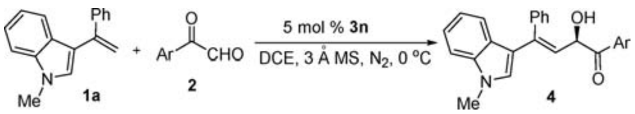
Table 1. Optimization of Reaction Conditions for the Alkenylation of Arylgloxals[a]



entry	3	time (h)	yield[b] (%)	*E*/*Z*[c]	ee[d] (%)
1	**3a**	6	99	86:14	65
2	**3b**	6	93	87:13	14
3	**3c**	6	97	86:14	62
4	**3d**	6	89	80:20	50
5	**3e**	6	94	79:21	62
6	**3f**	6	84	85:15	49
7	**3g**	6	92	78:22	49
8	**3h**	1	94	84:16	28
9	**3i**	1	>99	85:15	82
10	**3j**	1	>99	84:16	85
11	**3k**	1	>99	86:14	49
12	**3l**	1	99	83:17	86
13	**3m**	1	95	80:20	63
14[e]	**3l**	1	93	87:13	88
15[e,f]	**3n**	6	>99	86:14	93

[a] **1a**:**2a** = 1:1; C_{1a} = 0.1 M; entries 8–15: 30 mg of 3 Å MS, N_2. [b] Isolated yield. [c] Determined by HPLC analysis of the crude mixture. [d] Determined by chiral HPLC. [e] At 0 °C. [f] **1a**/**2a** = 1:1.2.

Table 2. Substrate Scope of Arylglyoxals[a]



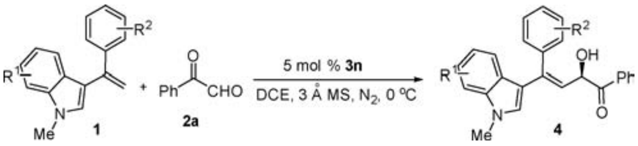
entry	4	Ar	time (h)	yield[b] (%)	*E*/*Z*[c]	ee[d] (%)
1	**4a**	C_6H_5	6	>99	86:14	93
2	**4b**	4-FC_6H_4	6	>99	87:13	90
3[e]	**4c**	4-BrC_6H_4	6	99	85:15	89
4[e]	**4d**	4-$CF_3C_6H_4$	6	85	86:14	84
5	**4e**	4-$MeOC_6H_4$	28	92	86:14	90
6	**4f**	2-$CF_3C_6H_4$	6	99	88:12	80
7[e]	**4g**	6-MeO-2-naphthyl	6	>99	86:14	96
8	**4h**	2,4-$F_2C_6H_3$	6	99	81:19	84
9	**4i**	3,4-$F_2C_6H_3$	6	>99	86:14	90
10	**4j**	3,4-$(MeO)_2C_6H_3$	8	>99	87:13	82
11	**4k**	3,4-$(OCH_2O)C_6H_3$	8	>99	86:14	83

[a] **1a**/**2** = 1:1.4. [b] Isolated yield. [c] Determined by ^1H NMR analysis of the crude mixture. [d] Determined by chiral HPLC. [e] **1a**/**2** = 1:1.2.

naphthylglyoxal gave the highest enantioselectivity (96% ee) in this section (Table 2, entry 7). Other phenylglyoxals bearing two substituents were also investigated. All of them generated the corresponding products with good results (Table 2, entries 8–11).

Various substituted 3-vinylindoles were also examined. The results were summarized in Table 3. 3-Vinylindoles bearing substituted indole groups were good reaction partners in this reaction, and the *E*/*Z* ratios were affected by the positions of the substituents. For example, the 5- or 6-substituted reactants produced the corresponding products in excellent outcomes (Table 3, entries 1–4); however, the 4-chloroindole-substituted 3-vinylindole gave the compound **4p** in a moderate *E*/*Z* ratio. Fortunately, both of the two diastereoisomers of **4p** had excellent enantioselectivities (Table 3, entry 5). The *E*/*Z* ratio decrease was possibly caused by the steric influence of the 4-Cl group. 3-Vinylindoles bearing substituted phenyl groups were also investigated. The steric effect of *ortho*-substituents of phenyl could affect the stereoselective outcomes. For example, the 2-Cl substituent greatly damaged the *E*/*Z* ratio (Table 3, entry 7). With respect to the 3- or 4-monosubstituted phenyl-involved 3-vinylindoles, both the electron-deficient and electron-rich phenyl-substituted molecules were good reaction partners and gave the corresponding products in excellent yields, good to high *E*/*Z* ratios, and excellent enantioselectivities (Table 3, entries 8–12). 3-Vinylindoles bearing two substitutions were also investigated; both of them gave excellent results under mild reaction conditions (Table 3, entries 13 and 14). The absolute configuration of **4m** (*E*,*R*) was established by X-ray single-crystal analysis.[16] The stereochemistries of compounds **4a–y** were assigned by analogy with those of **4m**.

Table 3. Substrate Scope of 3-Vinylindoles[a]



entry	4	R^1	R^2	time (h)	yield[b] (%)	*E*/*Z*[c]	ee[d] (%)
1	**4l**	5-Cl	H	6	93	90:10	93
2	**4m**	5-Br	H	6	92	89:11	92
3	**4n**	5-Me	H	7	91	88:12	89
4	**4o**	6-F	H	6	>99	83:17	93
5	**4p**	4-Cl	H	23	91	60:40	94/96
6	**4q**	H	2-F	6	>99	88:12	95
7	**4r**	H	2-Cl	6	99	75:25	95/97
8	**4s**	H	3-F	6	>99	88:12	93
9	**4t**	H	3-Cl	6	88	85:15	93
10	**4u**	H	3-MeO	6	63	84:16	89
11	**4v**	H	4-F	6	>99	86:14	91
12	**4w**	H	4-Me	6	99	81:19	93
13	**4x**	H	3,5-Me_2	6	>99	84:16	91
14	**4y**	5-Br	4-F	7	77	90:10	96

[a] **1**/**2a** = 1:1.2. [b] Isolated yield. [c] Determined by ^1H NMR analysis of the crude mixture. [d] Determined by chiral HPLC.

The possible reaction mechanism was then investigated. First, we studied the interactions between substrates and calcium phosphate **3n** by ^1H NMR. The ^1H NMR of 3,4-dimethoxyphenylglyoxal indicated that two forms, the aldehyde and corresponding hydrate, existed simultaneously (Figure 1, a). When the catalyst **3n** and 3,4-dimethoxyphenylglyoxal were mixed, we found the ratio of hydrate increased and the chemical shift of its H_a changed obviously. However, the chemical shift of H_b of the aldehyde form still remained at 9.66 ppm (Figure 1b).

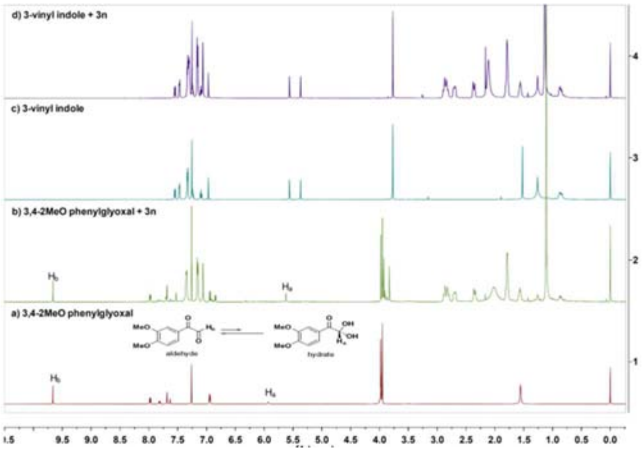
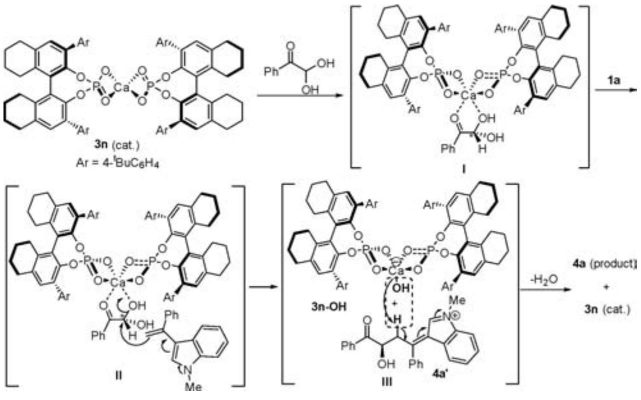


Figure 1. ^{1}H NMR study of the interaction between substrates and catalyst **3n**: (a) ^{1}H NMR for 3,4-(MeO)$_2$phenylglyoxal; (b) ^{1}H NMR for the mixture of 3,4-(MeO)$_2$phenylglyoxal and **3n**; (c) ^{1}H NMR for 3-vinylindole **1a**; (d) ^{1}H NMR for the mixture of 3-vinylindole **1a** and **3n**.

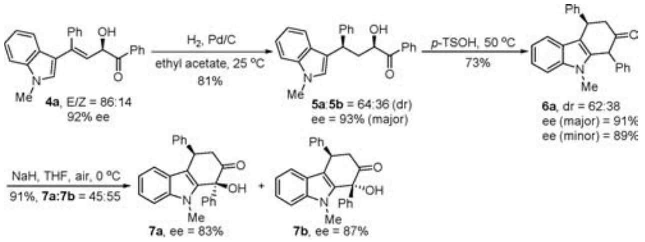
This phenomenon probably indicated that the true activation took place after the calcium phosphate **3n** coordinated with hydrate of phenylglyoxal and then increased the speed of the reaction, and the aldehyde form of phenylglyoxal could not be activated by **3n**. The interaction of 3-vinylindole and catalyst **3n** was then studied. We found the chemical shift of *N*-methyl-3-vinylindole did not change after we mixed it with catalyst **3n** (Figure 1c,d), leading to the conclusion that the catalyst **3n** could not activate the 3-vinylindole. Based on these results, we thought this reaction proceeded via monoactivation; i.e., the catalyst acted as a Lewis acid and activated the hydrate of phenylglyoxal. Thus, the possible reaction mechanism is depicted as Scheme 1. The hydrate of phenylglyoxal coordinated with **3n** via the formation of a five-membered cycle (Scheme 1, I), and its terminal carbon became chiral after this desymmetric coordination. The 3-vinylindole attacked the hydrate of phenylglyoxal from the bottom and replaced the hydroxyl which coordinated with **3n** (Scheme 1, II), producing a basic intermediate **3n**-OH and the vinylogous iminium **4a′** (Scheme 1, III). The final product **4a** was generated through the deprotonation of **4a′** by **3n**-OH, and the catalyst **3n** was released (Scheme 1).

Scheme 1. Proposed Reaction Mechanism



The products we obtained in this reaction could be readily converted into other indole compounds. For example, the compound **4a** generated the indole-substituted α-hydroxyl ketone **5a** and **5b** by reduction. After we treated **5a** with *p*-methylbenzenesulfonic acid, an indole-fused cyclohexanone formed via intramolecular nucleophilic addition, dehydration, and the subsequential enol to ketone tautomerism process. Under the basic conditions, the α-C−H bond was oxidized by oxygen, producing **7a** in good yield, but the diastereoselectivity was poor and the enantioselectivity decreased slightly (Scheme 2). The absolute configuration of **7a** was determined by single X-ray analysis.[16]

Scheme 2. Synthetic Application



In conclusion, the chiral calcium phosphate **3n** was proven to be a good catalyst for the direct catalytic alkenylation of arylglyoxals with 3-vinylindoles. Structurally diverse indole-substituted allylic alcohols were produced in high yields, good diastereoselectivities, and high to excellent enantioselectivities. The ^{1}H NMR study indicated that the most likely role of chiral calcium phosphate catalyst is to activate the hydrate of phenylglyoxal and control the stereoselectivities via a desymmetric coordination manner. The method presented in this work was used to prepare structurally complex indole molecules.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00143.

Experimental procedures; analytical data; NMR and HPLC spectra (PDF)
X-ray data for **4m** (CIF)
X-ray data for **7a** (CIF)

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Notes

The authors declare no competing financial interest.

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(16) CCDC 1472556 (**4m**) and CCDC 1522615 (**7a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.