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Chiral Metal Phosphate Catalysis: Highly Asymmetric Hetero-Diels-Alder Reactions

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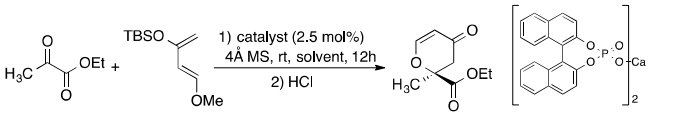
We report a highly enantioselective hetero-Diels-Alder reaction of α-keto esters and isatins catalyzed by chiral calcium BINOL-derived phosphates. The structure of the catalyst is detailed by X-ray crystal structure analysis.

The catalytic enantioselective hetero-Diels-Alder (HDA) reaction[1] is arguably the most powerful way of constructing six-membered heterocycles bearing a chiral tertiary or quaternary carbon center in a single step from commercially available substrates. Indeed, the most typical products involving carbonyl compounds in the HDA reaction are tetrahydropyran derivatives, which occur frequently in the structural motifs of biologically active natural products.[2] Although asymmetric HDA reactions of aldehydes have been extensively studied,[1b] ketone substrates, in contrast, are much less reactive in HDA reactions due to electronic and steric properties, and are still challenging substrates for chemists.[3] After Jørgensen first showed the asymmetric HDA reaction of α-keto esters in the presence of Cu(II) complexes,[3a,b] progress has been made using Lewis acids such as Yb(III),[3c] Ti(IV)[3d], Cu(I),[3f] as well as organocatalysts.[3g] Despite these creative efforts, notable drawbacks persist. For example, low enantioselectivities on substrates bearing bulky alkyl and aryl groups were observed even after rigorous exclusion of air and moisture. Therefore, we report a more efficient asymmetric HDA reaction of ketones with broader substrate scope and milder reaction conditions that we believe could allow chemists an improved methodology for such synthesis.

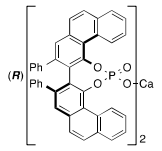
In recent years, chiral phosphoric acids have been proven to be powerful catalysts for a variety of transformations.[4] Meanwhile, alkali and alkaline-earth metal salts of chiral phosphates also draw some attention.[5] Inspired by our previous success,[6] we theorized an activation model in which alkaline earth metal phosphate can coordinate with 1,2-dicarbonyl compounds to activate one of the carbonyls and promote HDA reaction with dienes.

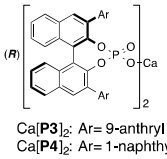
We initiated our investigation with the reaction of ethyl pyruvate **1a** and *trans*-3-(*tert*-Butyldimethylsilyloxy)-1-methoxy-1,3-butadiene (Danishefsky's diene) **2** in the presence of racemic calcium BINOL phosphate. To our delight, the reaction proceeded smoothly to the product with 94% yield at room temperature (Table 1, entry 1) and there was nearly no background reaction (entry 2). Then we evaluated different BINOL-based phosphate calcium salts. The enantiomeric excess can reach to 82% with calcium VAPOL phosphate Ca[**P2**]$_2$ in DCM (entry 3). With calcium 9-anthryl-BINOL phosphate, a lower yield was obtained, but with slightly higher ee (entry 4). Finally, improvement to 99% ee was achieved with 2.5 mol % calcium 1-naphthyl-BINOL phosphate Ca[**P4**]$_2$ at room temperature (entry 5). Although the reaction was found to tolerate several solvents, the most suitable solvent was methylene chloride (entries 5-7). It should be noted that, under the same conditions, phosphoric acid PA4 alone did not promote the reaction, with respect to both yield and enantioselectivity (entry 8).

Table 1. Asymmetric HDA reaction of ethyl pyruvate



entry	catalyst	solvent	yield (%)[a]	ee (%)[b]
1	Ca[**P1**]$_2$	DCM	94	0
2	-	DCM	0	-
3	Ca[**P2**]$_2$	DCM	90	82
4	Ca[**P3**]$_2$	DCM	84	86
5	Ca[**P4**]$_2$	DCM	95	99
6	Ca[**P4**]$_2$	toluene	85	87
7	Ca[**P4**]$_2$	diethyl ether	89	91
8	**PA4**	DCM	0	-

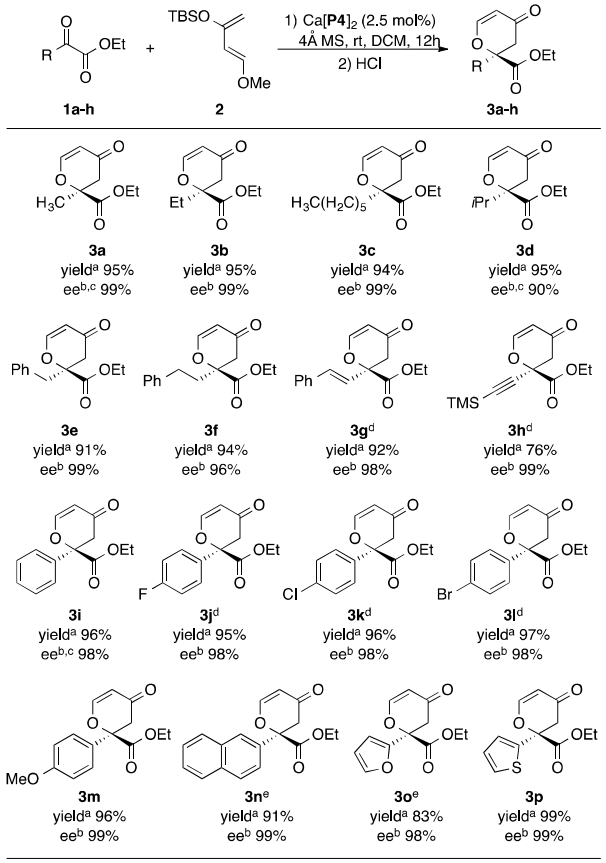




[a] Reaction conditions: **1a** (1.0 equiv.), **2** (1.3 equiv.), 2.5 mol % catalyst, with solvent indicated 0.05 M and 4Å MS 20 mg/mL. Isolated yield showed. [b] Ee determined by HPLC analysis on chiral stationary phases.

With the optimized conditions in hand, we next examined the scope of the transformation. A very wide range of α-keto esters with vastly different substitution provided high yields as well as high enantioselectivities in the reaction (Table 2). The α-keto esters with longer alkyl chain substitution, such as ethyl (**1b**), hexyl (**1c**) and phenethyl (**1f**), all gave high enantioselectivities, leading to the products bearing a variety of substituted quaternary carbon stereocenters. The sterically hindered isopropyl group also provided a substrate that resulted in excellent yield and slightly lower ee (90%, **3d**) for the reaction. Ethyl 3-phenylpyruvate (**1e**), which was used as a mixture of oxo/enol tautomers (about 5:1 ratio) due to the acidity of the α-proton, formed the product in 91% yield with 99% ee (**3e**). When an unsaturated system was present in the substrate (**1g**), the diene can react with the carbonyl group selectively and leave the double bond untouched under the reaction conditions, with 98% ee (**3g**). Encouraged by this, we employed a α-keto ester with triple bond (**1h**). Again, the diene reacted with the carbonyl group even faster to form product with good yield and excellent ee (**3h**).

Table 2. Substrate scope for asymmetric HDA reaction of α-keto esters

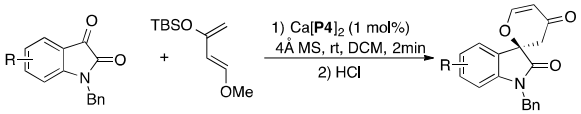


[a] Reaction conditions: **1** (1.0 equiv.), **2** (1.3 equiv.), 2.5 mol % Ca[**P4**]$_2$, in DCM (0.05 M) with 4Å MS 20 mg/mL. Isolated yield showed. [b] Ee determined by HPLC analysis on chiral stationary phases. [c] The absolute configurations were determined by comparison of the optical rotations with literature values. [d] Reaction time: 4 hours. [e] Reaction time: 1 hour.

Remarkably, excellent selectivity was also observed when ethyl benzoylformate was used as the substrate with direct phenyl substitution (**3i**). Different electron-withdrawing and -donating substituents on para-position of the aromatic ring all furnished HDA products in high yields, regardless of their electronic properties, with excellent enantioselectivities (**3j-m**). The more sterically hindered 2-naphthyl-substituted α-keto ester (**1n**) provided the desired product with high enantioselectivity, although a longer reaction time was required. In addition, heteroaromatic rings like furan and thiophene were feasible partners in this transformation, giving the HDA products in good to high yields and excellent enantioselectivities (**3o**, **3p**).

Oxindoles bearing a chiral quaternary carbon center at the 3-position are important structural motifs present in alkaloid natural products as well as biologically active compounds.[2d-f, 7] However, there is no example of obtaining this variant by a highly enantioselective HDA reaction of isatins.[3k] Considering the similarity of α-keto esters with isatin, we turned our attention to isatin, which could form oxindole with a spiro-carbon stereocenter after asymmetric HDA reaction. We chose to study benzyl-protected isatin due to its availability and ease in deprotection.

Table 3. Asymmetric HDA reaction of Isatin



entry	R	5	yield (%)[a]	ee (%)[b]
1[c]	H	**5a**	95	98
2[c,d]	H	**5a**	95	99
3[d]	H	**5a**	95	99
4[d]	4-Cl	**5b**	96	99[e]
5[d]	5-OMe	**5c**	98	96
6	5-F	**5d**	95	93
7	5-Cl	**5e**	96	93
8	5-Br	**5f**	95	93
9	6-Br	**5g**	96	97
10	7-Cl	**5h**	97	98

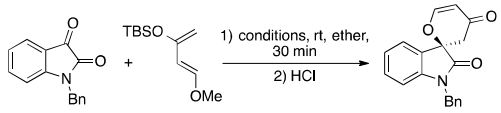
[a] Reaction conditions: **4** (1.0 equiv.), **2** (1.3 equiv.), 1.0 mol % catalyst, in DCM (0.05 M) with 4Å MS 20 mg/mL. Isolated yield showed. [b] Ee determined by HPLC analysis on chiral stationary phases. [c] 2.5 Mol% catalyst, reaction finished in 30 s. [d] Reaction performed in diethyl ether. [e] The absolute configurations of **5b** were determined by X-ray structure of the crystal (CCDC 1009077).

We applied the optimized conditions discovered previously, and isatin was consumed in less than 30 seconds and the HDA product was isolated with 98% ee at room temperature (Table 3, entry 1). Diethyl ether was proved to be equally efficient in this transformation (entry 2). Enantioselectivity was still maintained at a lower catalyst loading of 1 mol% with slightly longer reaction time (entry 3). The introduction of different substituents on the isatin core all provided products with excellent yields and enantioselectivities, irrespective of their steric and electronic nature (entries 3-10).

In order to understand the role of the molecular sieves in the reaction, we performed a series of relevant experiments (Table 4). In the HDA reaction of benzyl-protected isatin **4a**, different sizes of molecular sieves were used, and the beneficial effect did not change (Table 4, entries 1-3). The reaction could proceed without any catalyst, and product was isolated with 21% yield in 30 minutes (entry 4). 4Å MS could not promote the reaction significantly, for a very similar amount of the product was obtained with the same reaction time when only MS was applied without Ca[**P4**]$_2$ (entry 5). Catalyst Ca[**P4**]$_2$ alone can afford the product with 93% yield and 92% ee (entry 6). These showed molecular sieves could just activate the catalyst in situ. To further confirm that high enantioselectivity can be observed without the presence of molecular sieves in the reaction, we let the catalyst and 4Å MS stir in diethyl ether for 5 minutes first, then removed the MS fast and carefully by filtration,

followed by adding two substrates. High yield and enantioselectivity were back as well as the reaction rate (entry 7). Next, we did another experiment similar to entry 7, but added water back to the dried catalytic ether solution after removing the MS (2μL of water to 3.1mg of catalyst), then added the two substrates. As expected, the yield and ee dramatically diminished (entry 8). This proved our hypothesis that water can interfere the coordination between the catalyst and substrate, and the role of MS is removing the trace amounts of water in the catalyst. Also, the phosphoric acid could not promote the reaction significantly with or without MS, since the product was obtained with similar yield and no ee (entries 9 and 10). So the phosphate and the ingredient of MS did not form ion pair, which may catalyze the reaction.

Table 4. Molecular sieves studies



4a **2** **5a**

entry	catalyst (1 mol%)	Molecular sieves	yield (%)[a]	ee (%)[b]
1[c]	Ca[**P4**]$_2$	3Å MS	95	99
2[c]	Ca[**P4**]$_2$	4Å MS	95	99
3[c]	Ca[**P4**]$_2$	5Å MS	95	99
4	no	no	21	0
5	no	4Å MS	20	0
6	Ca[**P4**]$_2$	no	93	92
7[c,d]	Ca[**P4**]$_2$	4Å MS	94	98
8[d,e]	Ca[**P4**]$_2$	4Å MS/ water	43	68
9	**PA4**	no	21	0
10	**PA4**	4Å MS	22	0

[a] Reactions were performed with **4a** (1.0 equiv.), **2** (1.3 equiv.) in diethyl ether (0.05 M) and other conditions indicated from each entry. If not specified, all entries were stopped at 30 minutes. Isolated yield showed. [b] Ee determined by HPLC analysis on chiral stationary phases. [c] Reaction finished in 2 minutes. [d] 4Å MS was filtered off before substrate was added. [e] 2μL of water was added after removing MS.

Although some mechanistic proposals have been made by others,[5a,c] the actual alkaline earth metal phosphates structural evidence and its elucidation is still absent, and this prevents exploration of the transition state and new activation development. To address this issue, a crystal of the catalyst Ca[**P4**]$_2$ was obtained from the same conditions which it was prepared (DCM and MeOH as solvents), and its structure was examined by X-ray crystal structure analysis (Figure 1, CCDC 1009078).

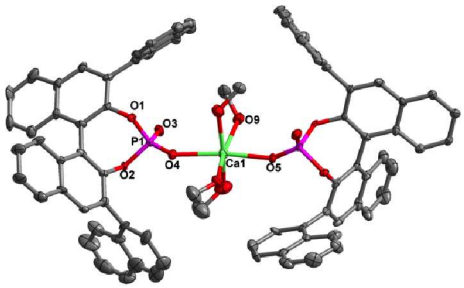


Figure 1. ORTEP representation of Ca[**P4**]$_2$ (hydrogen atoms are omitted for clarity; ellipsoids drawn at 50% probability level).

Interestingly, both of the chiral phosphates are monodentate rather than bidentate to the calcium ion. The calcium ion possesses distorted octahedral geometry with two phosphates and four methanol molecules. The bond length of Ca1-O5 is 2.277(7)Å, which is shorter than Ca1-O9 bond (2.349(8)Å) from Methanol. This shows the negative charge of the phosphate oxygen helps form stronger interaction with calcium ion. The P1-O3 bond length is 1.476(8)Å and it is approximately equal to P1-O4 bond (1.480(7)Å). The bond angle of O3-P1-O4 is 119.5(4) and the distance between P1 and Ca1 is 3.546(3)Å, which, along with Ca1-O4 bond length, explains the monodentate character of the phosphate from the geometrical point of view.

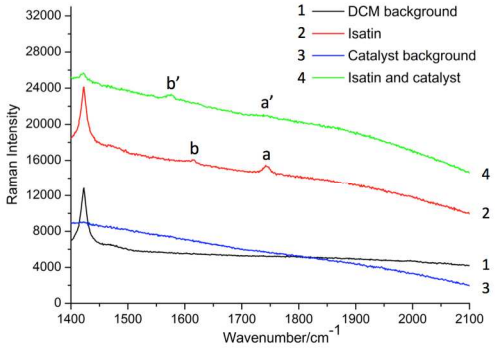


Figure 2. Raman spectra: (1) methylene chloride background, (2) benzyl-protected isatin **4a** in methylene chloride, (3) Ca[**p4**]$_2$ in methylene chloride and (4) benzyl-protected isatin **4a** and Ca[**p4**]$_2$ (1:1) in methylene chloride.

Next, Raman spectroscopy analysis was used to probe the interaction between 1,2-dicarbonyl substrate and catalyst (Figure 2). In methylene chloride (0.1 M), both carbonyl vibrations of benzyl-protected Isatin **4a** show up on Raman spectrum. The ketone carbonyl vibration shows up at 1739 cm^{-1} (a in Figure 2, lit.[8] IR value: 1737 cm^{-1}) and the wavenumber for amide carbonyl is 1609 cm^{-1} (b in Figure 2, lit.[17] IR value: 1605 cm^{-1}). The catalyst Ca[**P4**]$_2$ shows no peaks in the range of 1400 cm^{-1} to 2100 cm^{-1}. When a solution of both 4a and catalyst Ca[P4]$_2$ (1:1 molar equivalent) in DCM was tested, the vibrational frequency shifts were observed for both of the carbonyls, from 1739 cm^{-1} to 1731 cm^{-1} for ketone carbonyl (a' in Figure 4) and 1609 cm^{-1} to 1572 cm^{-1} for amide carbonyl (b' in Figure 4) respectively. The interference of the C=O bond vibrations indicates both of the carbonyls coordinate with the Calcium catalyst when they are mixing together. In addition, the decrease of the ketone carbonyl bond vibration energy suggests the C=O bond gets activated by coordination.

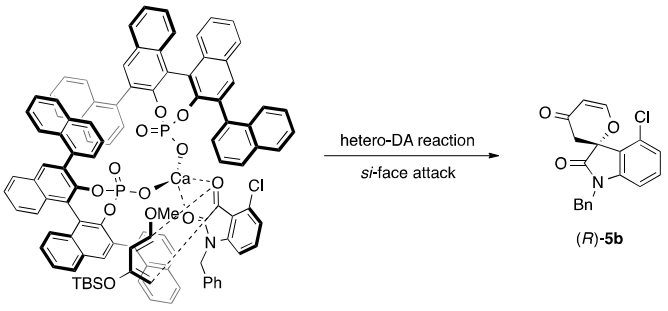


Figure 3. Proposed transition state for the Ca phosphate catalyzed asymmetric hetero-DA reaction.

On the basis of the catalyst structural information and Raman spectroscopy analysis, we have devised a transition state model to rationalize the observed enantioselectivity (Figure 3). In the presence of Ca phosphate, the 1,2-dicarbonyls chelate to Calcium (II) cation to form the intermediate in which the *re* face of the carbonyl is shielded by the 1-naphthyl group, hence Danishefsky's diene attacks from the *si* face to afford the corresponding product **5b**, which matches the experimentally observed stereochemistry.

Conclusions

In summary, we have developed highly enantioselective hetero-Diels-Alder reaction of α-keto esters with Danishefsky's diene by applying calcium phosphates as catalysts. The scope of this transformation is very broad, and the conditions are mild with high efficiency. This system is also proven to be effective on isatin substrates and this afforded highly asymmetric HDA reaction of isatins. Importantly, the structure of the catalyst was characterized, for the first time, by X-ray crystal structure analysis, and the chelation between substrates and catalyst was studied by Raman spectroscopy analysis. The transition state described thereafter could not only provide considerable insight into the origin of enantioselectivity for HDA reaction but also aid in the development of new transformations. On going studies include further expansion of the reaction scope and synthetic utility.

Notes and references

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