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The First Catalytic Asymmetric Morita-Baylis-Hillman Reaction of Acrolein with Aromatic Aldehydes

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We report the first example of catalytic asymmetric Morita-Baylis-Hillman reaction of acrolein with aromatic aldehydes. The use of 10 mol% of Hatakeyama's catalyst *β*-isocupreidine **C4**, in combination with 20 mol% of 2,6-dimethoxybenzoic acid, could catalyze the reaction to give the desired products in up to 81% *ee*.

Keywords Morita-Baylis-Hillman reaction, acrolein, *β*-isocupreidine, 2,6-dimethoxybenzoic acid, organocatalysis

Introduction

The catalytic asymmetric Morita-Baylis-Hillman (MBH) reaction is a powerful tool for the selective atom-economical synthesis of highly functionalized allylic alcohols which are valuable building blocks in synthetic organic and natural product chemistry.[1] Accordingly, much effort has gone to this field,[2] and tremendous progress has been made in the past decade since Hatakeyama and co-workers discovered a powerful catalyst, *β*-isocupreidine **1** (*β*-ICD), for this valuable reaction.[3] Notable achievements include the use of multifunctional organocatalysts and chiral Lewis acids for the addition of different activated alkenes to aldehydes.[2] Surprisingly, the use of acrolein as the nucleophilic reaction partner to react with aldehydes has not been reported in the catalytic enantioselective MBH reaction,[4] as far as we know, although the use of acrylic esters, acrylonitrile, methyl vinyl ketone or cyclic enones as the nucleophiles has been extensively studied. Considering the resulting MBH adducts contain a versatile aldehyde group, the use of acrolein as the nucleophile to develop catalytic asymmetric MBH reactions would be highly desirable.

Recently, during our efforts in the catalytic asymmetric synthesis of 3,3-disubstituted oxindoles,[5] we developed the highly enantioselective catalytic MBH reaction of isatins with acrolein.[5a] Later, it was found that the racemic version of this reaction could be run in ethylene glycol without the use of any catalyst.[6] The high reactivity that acrolein showed in the reaction with isatins encouraged us to develop a catalytic asymmetric MBH reaction of acrolein and aldehydes. However, initial studies revealed that the reaction of benzaldehyde with acrolein underwent very slowly, so the more reactive *p*-nitrobenzaldehyde **1a** was undertaken for condition optimization, and typical results were shown in Table 1.

Results and Discussion

A variety of cinchona alkaloid-based catalysts were examined, but only Hatakeyama's catalyst *β*-ICD **C4** could promote the reaction and afford product **3a** in 78% yield, with 64% *ee* (Entry 2, Table 1). Other bifunctional catalysts such as **C1**—**C2** did not work at −30 ℃, and **C3** catalyzed this reaction very slowly (Entry 1, Table 1). The study of solvent effects revealed that acetone was the most suitable solvent, when using **C4** as the catalyst (Entries 2—5, Table 1). A variety of Brønsted acids were used as additives to further improve the *ee* (Entries 6—11, Table 1). While the addition of hydrogen-bond donor **A1**—**A3** decreased the *ee* of **3a** (Entries 6—8, Table 1), the addition of (*R*)-**A4** obviously improved the *ee* to 72%, but the yield of **3a** was only 45% even the reaction was run for 48 h (Entry 9, Table 1). The addition of (*S*)-**A4** greatly decreased the *ee* of **3a** from 64% to 38% (Entry 10, Table 1), which further confirmed the addition of Brønsted acid additives could influence the stereochemical control of this reaction. Surprisingly, the addition of benzoic acid **A5** could improve the *ee* to 74%, but the reaction was slowed down (Entry 11, Table 1).

The finding that the addition of carboxylic acid could improve the enantioselectivity was interesting. Generally, the accepted mechanism of tertiary amines catalyzed MBH reaction is that the tertiary amines function as Lewis bases to activate nucleophilic elec-

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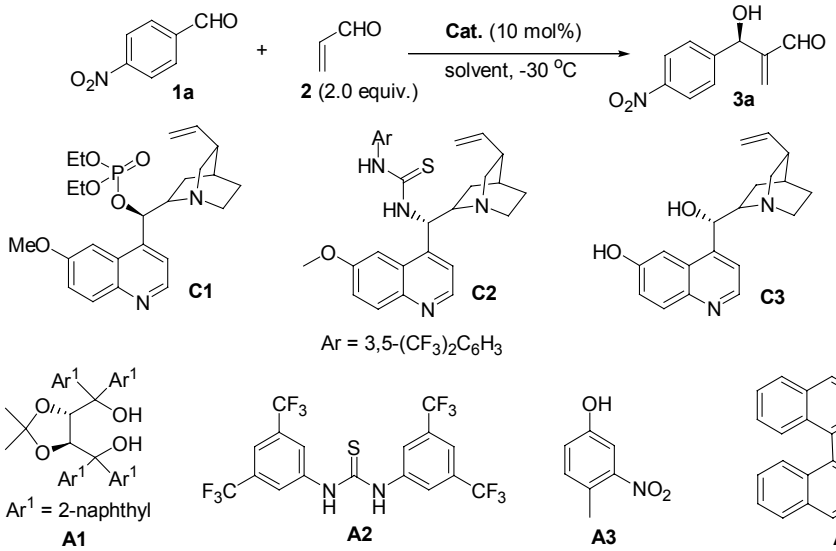
Table 1 Condition optimization



Entry[a]	Cat.	Additive (20 mol%)	Solvent	Time/h	Yield[b]/%	*ee*[c]/%
1	**C3**	—	Acetone	240	trace	25
2	**C4**	—	Acetone	12	78	64
3	**C4**	—	CH_3CN	12	33	21
4	**C4**	—	EtOAc	12	58	46
5	**C4**	—	THF	12	67	13
6	**C4**	**A1**	Acetone	72	72	53
7	**C4**	**A2**	Acetone	72	74	53
8	**C4**	**A3**	Acetone	48	97	55
9	**C4**	(*R*)-**A4**	Acetone	48	45	72
10	**C4**	(*S*)-**A4**	Acetone	48	89	38
11	**C4**	**A5**	Acetone	72	78	74

[a] Run on a 0.25 mmol scale. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

tron-deficient olefins.[1,7] Accordingly, the addition of hydrogen-bond donors such as phenols to activate the electrophilic reaction partner is a common method to improve the reactivity and enantiofacial control.[1] However, to the best of our knowledge, the addition of a carboxylic acid, in combination with a tertiary amine, to improve the reaction outcome has not been reported.[8] This is reasonable because the addition of carboxylic acid would protonate the tertiary amine moiety of the catalyst, which resulted in the catalyst poison. In light of this, the observation that the addition of benzoic acid would improve the *ee* was very impressive and would have potential use in the development of catalytic asymmetric MBH reaction.

On the basis of this finding, a series of different substituted benzoic acids were synthesized and tried in the reaction of **1a** and **2**, using acetone as the solvent at −30 ℃, with 10 mol% of **C4** and 20 mol% of additive, as shown in Table 2. The phenyl substituent of benzoic acid indeed affected the reaction. Benzoic acids with electron-withdrawing groups greatly decreased the reactivity (Entries 1—2, Table 2), and **A6** as the additive terminated the reaction, possibly due to its high acidity which completely protonated the amine catalyst. Benzoic acids **A9**—**A18**, with different electron-releasing groups at different position were examined (Entries 4—13, Table 2), and the highest *ee* was obtained by using 3,6-dialkoxyl substituted acids **A15** and **A16** (Entries 10—11, Table 2), and up to 77% *ee* was obtained for adduct **3a**. It should be mentioned that when benzoic acid derivatives were used, the reaction was greatly slowed down, as compared with that in the absence of additive (Entry 2, Table 1). As **A15** could be easily synthesized, it was used as the additive for further screenings.

The ratio of *β*-ICD **C4** and **A15** was also found to influence the reaction outcome (Entries 1—4, Table 3). The use of 20 mol% of **A15** and 10 mol% of *β*-ICD **C4** afforded the product **3a** in acceptable yield with improved *ee* (Entry 2, Table 3). We further examined the influence of the amount of acrolein, and found that the use of 4.0 equiv. of acrolein could improve the yield of **3a** to 87%, without the loss of ee (Entry 6, Table 3).

Based on the above screenings, the optimum condition was determined to run the reaction at −30 ℃ using

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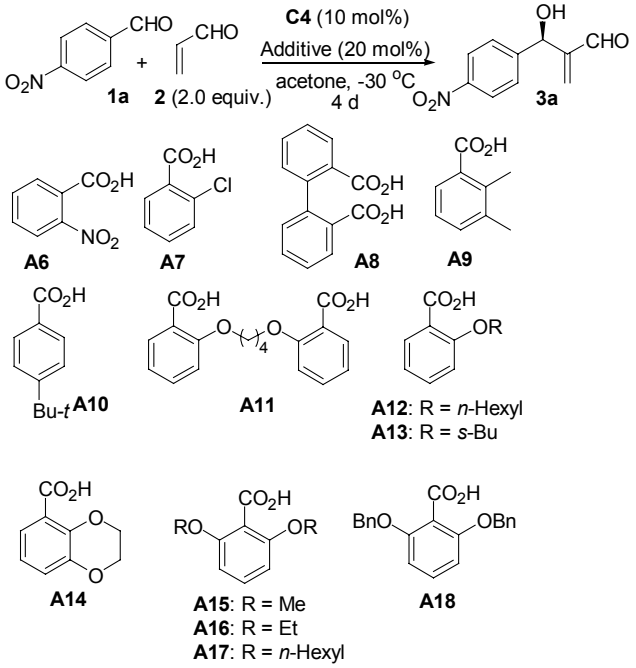
Table 2 Effects of different acid additives

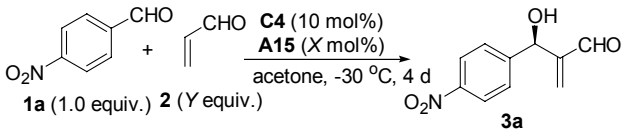


Entry[a]	Additive	Yield[b]/%	*ee*[c]/%
1	**A6**	NR	—
2	**A7**	25	71
3	**A8**	39	75
4	**A9**	91	74
5	**A10**	95	75
6	**A11**	48	73
7	**A12**	89	75
8	**A13**	74	76
9	**A14**	44	75
10	**A15**	71	77
11	**A16**	79	77
12	**A17**	45	76
13	**A18**	68	70

[a] Run on a 0.25 mmol scale. [b] Isolated yield. [c] Determined by chiral HPLC analysis

acetone as the solvent, with 10 mol% of *β*-ICD **C4** and 20 mol% of **A15**. Under this condition, differently substituted aromatic aldehydes were examined, and it was observed that electron-withdrawing groups would facilitate this reaction. With nitro substituent at any position of the phenyl ring, aldehydes **1a**—**1c** could work (Entries 1—4, Table 4), even the nitro group at the *ortho* position. Up to 81% *ee* could be obtained for product **1a** when running the reaction at −40 ℃, but the yield is lower (Entry 2, Table 4). With one *cyano*, trifluoromethyl or two chloro groups on the phenyl ring, substituted benzaldehydes **1d**—**1i** could work to give corresponding products **3d**—**3i** in moderate to good yield (Entries 5—10, Table 4).

Table 3 Effects of different amount of **A15** and acrolein

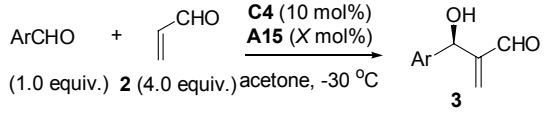


Entry[a]	*X*	*Y*	Yield[b]/%	*ee*[c]/%
1	10	2.0	88	74
2	20	2.0	71	77
3	40	2.0	68	77
4	100	2.0	45	77
5	20	3.0	82	77
6	20	4.0	87	77
7	20	5.0	76	77

[a] Run on a 0.25 mmol scale. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

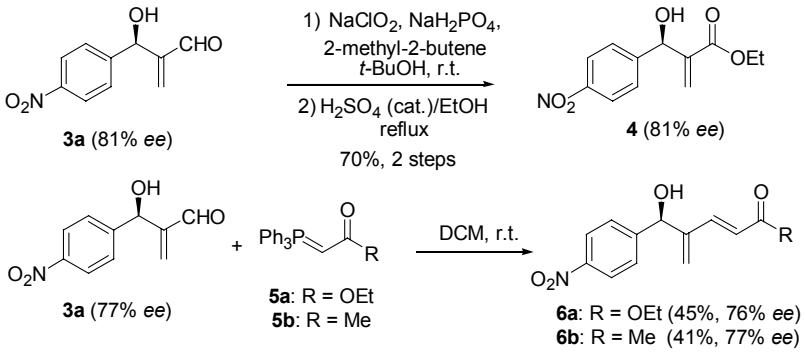
This protocol had a limitation that less reactive aryl aldehydes, without strong electron-withdrawing effect, were inefficient for the reaction with acrolein. The reaction of aryl aldehydes **1j**—**1k** and acrolein could not take place with the addition of **A15**, and both reactions were accordingly carried out in the absence of **A15**. Products **3j**—**3k** were obtained in only moderate yield and *ee* (Entries 11—12, Table 4). It was also found that aryl aldehydes, with electron-releasing substituents, failed to react with acrolein to give the corresponding products under this condition.

Table 4 Substrate scope



Entry[a]	Ar	*X*	Time/d	**3**	Yield[b]/%	*ee*[c]/%
1	4-$NO_2C_6H_4$ (**1a**)	20	4	**3a**	87	77
2[d]	4-$NO_2C_6H_4$ (**1a**)	20	6	**3a**	45	81
3	3-$NO_2C_6H_4$ (**1b**)	20	4	**3b**	34	78
4	2-$NO_2C_6H_4$ (**1c**)	20	5	**3c**	25	60
5	4-CNC_6H_4 (**1d**)	20	4	**3d**	60	73
6	3-CNC_6H_4 (**1e**)	20	4	**3e**	36	73
7	4-$CF_3C_6H_4$ (**1f**)	20	5	**3f**	28	69
8	2,4-$Cl_2C_6H_3$ (**1g**)	20	5	**3g**	57	69
9	3,4-$Cl_2C_6H_3$ (**1h**)	20	5	**3h**	33	75
10	3,5-$Cl_2C_6H_3$ (**1i**)	20	5	**3i**	52	68
11[e]	3-ClC_6H_4 (**1j**)	0	5	**3j**	29	56
12[f]	2-naphthyl (**1k**)	0	4	**3k**	10	30

[a] Run on a 0.30 mmol scale. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] At −40 ℃. [e] Run on a 1.0 mmol scale, −20 ℃. [f] Run on a 1.0 mmol scale, 25 ℃.



The thus obtained MBH adducts **3** could be readily transformed to other building blocks. For example, the aldehyde group of product **3a** could be oxidized to give the correspongding product **4**. By comparing the optical rotation of product **4** with literature report,[9] the absolute configuration of product **3a** was determined to be *R*, and those of other adducts were tentatively assigned by analogy. The Wittig reaction of product **3a** and ylide **5** could give multifunctional products **6** in moderate yield, without loss of enantioselectivity.

Conclusions

In conclusion, we have developed the first example of catalytic asymmetric Morita-Baylis-Hillman reaction of acrolein with aromatic aldehydes, which affords highly functional products with an aldehyde group for versatile elaboration. The combination of Hatakeyama's catalyst *β*-isocupreidine with 2,6-dimethoxybenzoic acid has been identified as a useful catalyst system for the reaction, which gives the desired products in up to 81% *ee*. The development of more efficient system to improve the reactivity, enantioselectivity and substrate scope is now in progress in our laboratory.

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