J|A|C|S COMMUNICATIONS

Published on Web 10/12/2010

Organocatalytic Asymmetric Synthesis of Substituted 3-Hydroxy-2-oxindoles via Morita−Baylis−Hillman Reaction

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Abstract: We report a highly enantioselective Morita−Baylis−Hillman (MBH) reaction of isatins and acrolein to provide enantiomerically enriched 3-substituted 3-hydroxyoxindoles, which could serve as valuable synthetic building blocks. This is also the first time that a ketone has been used as the electrophile and acrolein as the nucleophile in a highly enantioselective catalytic asymmetric MBH reaction. Hatakeyama's catalyst, β-isocupreidine (**1**), turned out to be a powerful catalyst for this transformation.

The catalytic asymmetric construction of tetrasubstituted carbon stereogenic centers is one of the major challenges in asymmetric catalysis. Among the available methods, the catalytic asymmetric addition of carbon nucleophiles to ketones is one of the most efficient synthetic routes. Despite achievements, the synthesis of tertiary alcohols via the catalytic asymmetric Morita−Baylis−Hillman (MBH) reaction has not been realized.[1]

Because of its versatility in the selective atom-economical synthesis of highly functionalized allylic alcohols, which are valuable building blocks in organic synthesis, the development of the catalytic asymmetric MBH reaction received much attention.[2] Since Hatakeyama and co-workers discovered a powerful catalyst, β-isocupreidine (β-ICD, **1**),[3] much progress has been made in this area, including the use of multifunctional organocatalysts and chiral Lewis acids for the addition of various activated alkenes to aldehydes[4] or aldimines.[5] However, to the best of our knowledge, the use of ketones as the electrophilic reaction partner has not been reported.[6] Remarkably, using a ketone electrophile in the catalytic asymmetric MBH reaction simultaneously forms a carbon skeleton and tetrasubstituted stereogenic center and thus extends the potential of this reaction. Furthermore, acrolein has not been used as the nucleophile in the catalytic asymmetric MBH reaction, although the aldehyde group of the resulting MBH adducts would be valuable for further transformation. Acrolein as the nucleophile has been tried in some aza-MBH reactions[5] and in only one case afforded the product with excellent ee.[5a] In this communication, we report the first example of a catalytic asymmetric MBH reaction using a ketone, isatin, as the electrophile and acrolein as the nucleophile; this reaction readily afforded 3-hydroxy-2-oxindoles with excellent enantioselectivity.

3-Substituted 3-hydroxyoxindoles are encountered in a large variety of natural and artificial bioactive compounds and can be used for the total synthesis of natural products such as CPC-1 and flustraminol (Figure 1).[7] Structure−activity relationship studies have revealed that the biological activities of these compounds are greatly affected by the configuration of the hydroxy group and the substituents at the C3 position of the oxindole.[8] Accordingly, the development of new synthetic methods for the synthesis of this structural motif is of paramount importance. While a variety of catalytic asymmetric methods have already been developed,[9]

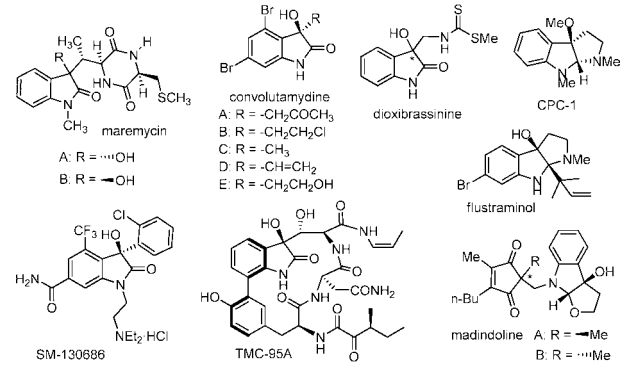
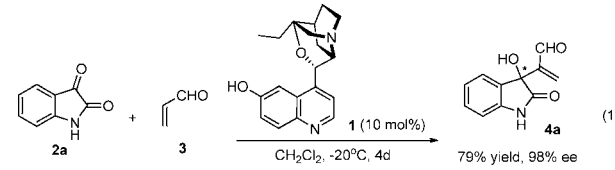


Figure 1

including nucleophilic addition to isatins,[9b−n] hydroxylation of 3-substituted oxindoles,[9o−q] and intramolecular arylation reactions,[9r,s] the synthesis of this subunit via a catalytic asymmetric MBH reaction has not been reported.[10]

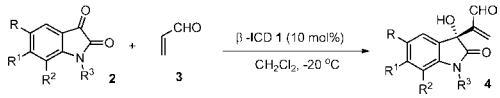
In our efforts to synthesize 3,3-disubstituted oxindoles for biological evaluation,[11] we realized that isatins are highly reactive, so we tried to develop an enantioselective MBH reaction employing this type of activated ketone to prepare substituted 3-hydroxyoxindoles. In view of the fact that the reaction of isatins and acrylate esters catalyzed by DBACO proceeds very slowly even at room temperature,[10a] we chose the more reactive nucleophile acrolein to react with isatin for optimization (for details, see the Supporting Information). Finally, β-ICD **1** turned out to be the most powerful catalyst, and the optimal reaction conditions were determined to be in air using CH_2Cl_2 in the presence of 10 mol % **1** at −20 °C (eq 1).



The substrate scope is shown in Table 1. The protecting group of isatin **2** (either methyl or benzyl) had little effect on the ee of the corresponding MBH adducts. Furthermore, the *N*-methyl- and *N*-benzyl-protected isatins **2b** and **2c** had good solubility in CH_2Cl_2, and the corresponding products **4b** and **4c** were obtained in excellent yield and ee (entries 2 and 3). This observation is very important, because the solubility of substituted unprotected isatins in CH_2Cl_2 is generally very poor, and the use of unprotected isatins except **2a** resulted in low conversion, although the ee of the corresponding products was excellent. The use of *N*-methyl- or *N*-benzyl-protected isatins **2d**−**w** afforded the corresponding products **4d**−**w** in good to excellent yield with excellent enantioslectivity (entries 4−23).

10.1021/ja107858z

Table 1. Substrate Scope



entry[a]	isatin **2**	**4**	yield (%)[b]	ee (%)[c]
1	**2a**: R, R^1, R^2, R^3 = H	**4a**	79	98
2	**2b**: R, R^1, R^2 = H, R^3 = Me	**4b**	96	98
3	**2c**: R, R^1, R^2 = H, R^3 = Bn	**4c**	97	96
4	**2d**: R = F, R^1, R^2 = H, R^3 = Me	**4d**	92	96
5	**2e**: R = F, R^1, R^2 = H, R^3 = Bn	**4e**	86	96
6	**2f**: R = Cl, R^1, R^2 = H, R^3 = Me	**4f**	83	96
7	**2g**: R = Cl, R^1, R^2 = H, R^3 = Bn	**4g**	88	96
8	**2h**: R = Br, R^1, R^2 = H, R^3 = Me	**4h**	79	97
9	**2i**: R = Br, R^1, R^2 = H, R^3 = Bn	**4i**	91	99
10	**2j**: R = Me, R^1, R^2 = H, R^3 = Me	**4j**	74	97
11	**2k**: R = Me, R^1, R^2 = H, R^3 = Bn	**4k**	85	95
12	**2l**: R = MeO, R^1, R^2 = H, R^3 = Me	**4l**	91	97
13	**2m**: R = MeO, R^1, R^2 = H, R^3 = Bn	**4m**	70	94
14	**2n**: R = NO_2, R^1, R^2 = H, R^3 = Me	**4n**	66	92
15	**2o**: R = NO_2, R^1, R^2 = H, R^3 = Bn	**4o**	80	90
16	**2p**: R = CF_3, R^1, R^2 = H, R^3 = Me	**4p**	65	90
17	**2q**: R = CF_3, R^1, R^2 = H, R^3 = Bn	**4q**	73	91
18	**2r**: R, R^2 = H, R^1 = Br, R^3 = Me	**4r**	90	96
19	**2s**: R, R^2 = H, R^1 = Br, R^3 = Bn	**4s**	95	95
20	**2t**: R, R^1 = H, R^2 = Cl, R^3 = Me	**4t**	86	96
21	**2u**: R, R^1 = H, R^2 = Cl, R^3 = Bn	**4u**	88	94
22	**2v**: R, R^2 = Br, R^1 = H, R^3 = Me	**4v**	96	93
23	**2w**: R, R^2 = Br, R^1 = H, R^3 = Bn	**4w**	93	91

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

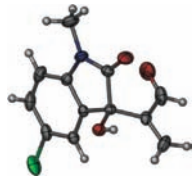
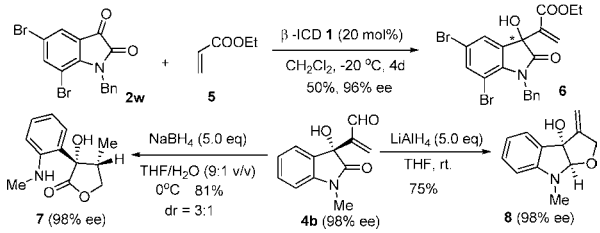


Figure 2. X-ray structure of **4f**.

The nature and position of the substitutents on the isatin had no obvious influence on the reaction outcome. The absolute configuration of product **4f** was determined to be *R* by X-ray analysis (Figure 2). The configurations of other compounds were tentatively assigned by comparing the signs of their optical rotations to that of **4f**.

Ethyl acrylate worked slowly, even using 20 mol % catalyst. For example, isatin **2w** reacted with **5** to afford the product **6** in only 50% isolated yield with 96% ee. Other nucleophiles afforded the corresponding products in moderate yield and ee.[12]

The thus-obtained products **4** potentially have wide application in organic synthesis.[13] For example, the reduction of product **4b** by $NaBH_4$ afforded lactone **7**[13e] in 81% yield with 3:1 dr, while reduction by $LiAlH_4$ provided 3a-hydroxyfuroindoline **8** in 75% yield as a single isomer. Compound **8** can be potentially used for the synthesis of the analogues of natural products (+)-madindoline.[14]



In conclusion, we have developed the first example of a catalytic asymmetric MBH reaction using a ketone as the electrophile and acrolein as the nucleophile. A variety of isatins worked well with acrolein to give the MBH adducts with excellent ee. Experiments in our lab now aim to expand the substrate scope of the catalytic asymmetric MBH reaction using ketones as the electrophile.

Acknowledgment. We are grateful for the financial support from the National Natural Science Foundation of China (20902025), the Shanghai Pujiang Program (10PJ1403100), Shanghai Talent Grooming Funding (2009015), and the 973 Program (2011CB808600).

Supporting Information Available: Experimental procedures, compound characterization, NMR spectra, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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JA107858Z