Synthetic Methods

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An Organocatalytic, δ-Regioselective, and Highly Enantioselective Nucleophilic Substitution of Cyclic Morita–Baylis–Hillman Alcohols with Indoles**

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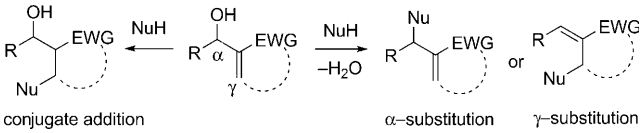
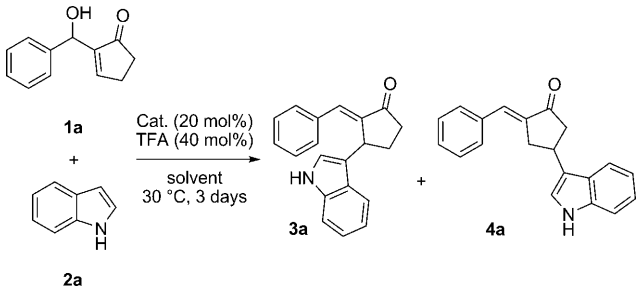
The direct substitution of alcohols with carbon and heteroatom nucleophiles without prederivatization is a significant chemical transformation owing to its green, economical, and environmentally benign properties where water is generated as the only side product.[1] Recently, researchers in the area of organocatalysis has made great progress in organic synthesis. While multiform organocatalysts can be successfully used in various addition reactions with carbonyl, imine, activated alkene, and others compounds,[2] the enantioselective nucleophilic substitution of alcohols catalyzed by organocatalysts is rare.[3] Because positively charged intermediates would be involved, it is a great challenge to exert enantioselective control in the nucleophilic substitution of alcohols.[4,5]

Recently, the Morita–Baylis–Hillman (MBH) adducts have attracted much attention in organic syntheses as valuable synthons and starting materials owing to their easy availability and versatile functionalities bearing allylic hydroxy and Michael acceptor units.[6] The reaction of MBH alcohols with a nucleophile could proceed through either conjugate addition,[7] or allylic substitution through dehydration to afford α- or γ-substituted products (Scheme 1)[8] Enantioselective reactions of MBH adducts with various O, N, and C nucleophiles have been achieved to provide the nucleophilic substitution products. These reactions have been carried out through transition-metal catalysis with palladium,[9] and organocatalysis with chiral phosphine[10a–b] and tertiary amine compounds.[10c–h] However, none of these asymmetric transformations directly uses MBH alcohols. Furthermore, the hydroxy group is not a good leaving group because free OH may participate in the asymmetric induction. Iminium activation is one of the most important methods in organocatalysis.[11] Inspired by the efficient enantioselective control of Michael acceptors by iminium activation, we proposed that iminium activation might be used in the nucleophilic substitution of MBH adducts derived from enones. A suitable catalyst should also contain an acid moiety to activate the hydroxy group of MBH alcohols. Herein, we report the enantioselective reaction of cyclopent-2-enone-derived MBH alcohols with indoles catalyzed by chiral 9-amino-9-deoxyepiquinine in combination with an acid. This approach yields an unexpected δ-regioselective product with good to excellent enantioselectivity.



Scheme 1. The reaction of MBH alcohols with a nucleophile. EWG = electron-withdrawing group, Nu = nucleophile.

Initially, the reaction of MBH alcohol **1a** with indole **2a** was carried out in dichloromethane (Scheme 2). It was reported that catalysts based on chiral primary amines could be successfully used in iminium activation for α,β-unsaturated ketones.[12] A chiral primary amine derived from cinchona alkaloid was used. In the presence of 9-amino-9-deoxyepiquinine (**C**, 20 mol%; Scheme 3) in combination with trifluoroacetic acid (TFA, 40 mol%) in CH_2Cl_2 at 30°C, the reaction provided γ-allylic substitution product **3a** in 18% yield with 55% *ee*. To our surprise, besides γ-product **3a** the δ-allylic substitution product **4a** was obtained in 50% yield with promising enantioselectivity (66% *ee*; Table 1, entry 1). In general, the nucleophilic substitution of allylic alcohol affords the product with α or γ regioselectivity (as shown in



Scheme 2. Nucleophilic substitution of MBH alcohol **1a** with indole **2a** through iminium catalysis.

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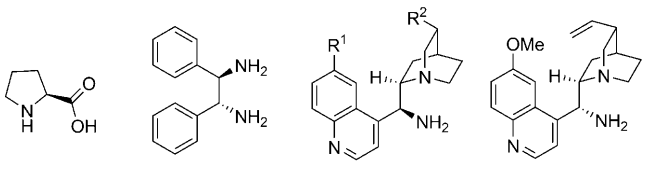


Scheme 3. Structures of the chiral amine catalysts.

Table 1: Selected screening studies of organocatalytic nucleophilic substitution of cyclic MBH alcohol **1a** with indole **2a**.[a]

Entry	Catalyst[b]	Solvent	Yield of **4a** [%][c]	*ee* of **4a** [%][d]
1	**C**	CH_2Cl_2	50	66
2	**C**	Et_2O	59	52
3	**C**	THF	28	85
4	**C**	EtOAc	70	49
5	**C**	*i*PrOAc	77	64
6	**C**	*i*PrOAc/THF (1:1)	45	89
7	**D**	*i*PrOAc/THF (1:1)	35	90
8	**E**	*i*PrOAc/THF (1:1)	35	80
9	**F**	*i*PrOAc/THF (1:1)	35	-47
10[e]	**C**	*i*PrOAc/THF (1:1)	70	75
11	**C**[f]	*i*PrOAc/THF (1:1)	18	63
12[g]	**C**	*i*PrOAc/THF (1:1)	92	89

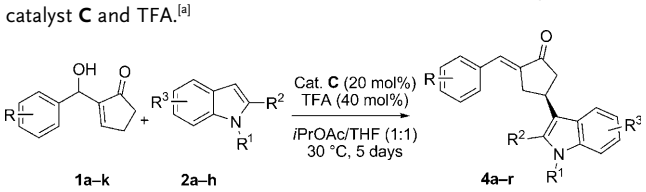
[a] Reaction conditions: unless otherwise noted reactions were performed with 0.2 mmol of **1a**, 0.2 mmol of **2a**, 0.04 mmol of catalyst **C**, and 0.08 mmol of TFA in 2 mL of solvent at 30 °C for 3 days. [b] With TFA as an acid additive. [c] Yield of isolated product. [d] Determined by HPLC on a chiral stationary phase. [e] At 50 °C. [f] TSA was used as an acid additive. [g] 0.4 mmol of **1a**; the reaction was carried out over 5 days and the yield is based on **2a**. THF = tetrahydrofuran, TSA = *p*-toluenesulfonic acid.

Scheme 1), while δ selectivity is unusual and unexpected. The reaction in Et_2O provided **4a** in 59% yield and 52% *ee*, but no γ product was detected (Table 1, entry 2). The examination of solvent effects revealed that in THF the reaction afforded the δ-product **4a** with good enantioselectivity (85% *ee*) but low yield and no γ product was observed (Table 1, entry 3); whereas ethyl acetate significantly facilitated the reaction and produced the δ-product **4a** in higher yield but with a relatively lower *ee* value (Table 1, entry 4). In isopropyl acetate, the reaction provided **4a** in 77% yield and 64% *ee* (Table 1, entry 5). Other solvents such as toluene, acetonitrile, methanol, and *N*,*N*-dimethylformamide were also tested; they were less effective for the reaction of **1a** with **2a** (see the Supporting Information). Based on these experimental results, a solvent mixture of *i*PrOAc/THF (1:1) was employed as the reaction medium. The enantioselectivity of the δ-product **4a** was increased up to 89% *ee*, but the yield still remained low (compare Table 1, entrie 6 versus 3 and 5). Although the yield could be increased to 70% by raising the reaction temperature to 50 °C, unfortunately the *ee* value decreased to 75% (Table 1, entry 10). To reach both high yield and enantioselectivity, we changed the ratio of **1a**/**2a** from 1:1 to 2:1, and prolonged the reaction time to 5 days, the yield of isolated δ-product **4a** could be raised up to 92% while still maintaining a high enantioselecitivity (89% *ee*; Table 1, entry 12).

An extensive screen of other chiral amine catalysts showed that cinchonine-derived catalyst **D** gave a slightly higher *ee* value of 90%, albeit with a lower yield of **4a** (Table 1, entry 7). Catalyst **E,** which has no double bond, afforded **4a** in low yield and with a low *ee* value (Table 1, entry 8 versus 6). The opposite enantiomer of the δ product was provided with a very low *ee* value by employing quinidine-derived primary amine catalyst **F** under the same reaction conditions (Table 1, entry 9). It was found that the TFA salt of (1*R*, 2*R*)-1,2-diphenylethane-1,2-diamine **B** was not able to promote the reaction. Proline (**A**) did not catalyze the reaction of **1a** with **2a** either. The acid additives had an obvious effect on the reactivity of the catalyst and enantioselectivity of the nucleophilic substitution. TFA exhibited specific reactivity for the reaction. If TSA was used as an acid additive, the reaction provided only 18% of **4a** with 63% *ee* (Table 1, entry 11). In the absence of any Brønsted acid as a co-catalyst, no product was observed and starting materials were recovered.

Optimal results for δ selectivity with high enantioselectivity were eventually obtained in the solvent mixture containing equal amounts of *i*PrOAc and THF in the presence of 20 mol% of 9-amino-9-deoxyepiquinine (**C**) in combination with TFA (40 mol%), which allowed the reaction to proceed smoothly within 5 days at 30 °C. Under the optimal reaction conditions we investigated the scope of δ products with different combinations of indoles and a variety of cyclic MBH alcohols. The results are summarized in Table 2. In each case, the corresponding δ products were obtained in good to excellent yields as single regioisomers. In general, for indole **2a**, variation in the MBH alcohols was well tolerated. For *para*-substituted MBH alcohols (**1b**–**1g**; Table 2, entries 2–7), regardless of having electron-donating or electron-withdrawing groups, gave good to excellent *ee* values (83–93%) for δ products. For *meta*-substituted MBH alcohols (**1h**–**1k**; Table 2, entries 8–11), high enantioselectivities (88–92% *ee*) and moderate to good yields (71–86%) were obtained. However, no reaction was observed with cyclohexenone-derived MBH alcohols and indole **2a**. The MBH alcohol with an alkyl substituent instead of an aryl one did not afford the product either, which indicated that the benzyl alcohol structure was necessary for the reaction of MBH alcohols with indoles. For indole derivatives, 5-bromoindole (**2e**), 5-methoxylindole (**2f**), 5-methylindole (**2g**), and 6-methylindole (**2h**) gave high yields with good enantioselectivities (Table 2, entries 15–18). Exceptionally, the reaction of 2-methylindole (**2b**) with **1a** provided a mixture of δ and γ product (δ/γ = 65:35) with a high enantioselectivity of δ product **4b** (93% *ee*; Table 2, entry 12). Whereas 2-phenylindole (**2d**) still exhibited exclusive δ regioselectivity with a lower enantioselectivity (Table 2, entry 14). The poor regioselectivity of 2-methylindole (**2b**) could be ascribed to its high nucleophilic character compared to simple indole.[13] *N*-Methylindole (**2c**) was less reactive under the reaction conditions. By increasing the reaction temperature to 40 °C, **2c** afforded the δ-product **4m** in 70% yield with only 47% *ee*.

Table 2: Reaction of MBH alcohols **1** with indoles **2** in the presence of catalyst **C** and TFA.[a]



2a: R^1=R^2=R^3=H **2b**: R^1=R^3=H, R^2=Me
2c: R^1=Me, R^2=R^3=H **2d**: R^1=R^3=H, R^2=Ph
2e: R^1=R^2=H, R^3=5-Br **2f**: R^1=R^2=H, R^3=5-OMe
2g: R^1=R^2=H, R^3=5-Me **2h**: R^1=R^2=H, R^3=6-Me

Entry	Alcohol **1**	R	Indole **2**	Prod. **4**	Yield [%][b]	*ee* [%][c]
1	**1a**	H	**2a**	**4a**	92	89
2	**1b**	*p*-F	**2a**	**4b**	87	91
3	**1c**	*p*-Cl	**2a**	**4c**	85	85
4	**1d**	*p*-Br	**2a**	**4d**	88	93
5	**1e**	*p*-Me	**2a**	**4e**	86	83
6	**1f**	*p*-OMe	**2a**	**4f**	81	90
7	**1g**	*p*-Ph	**2a**	**4g**	88	84
8	**1h**	*m*-OMe	**2a**	**4h**	76	90
9	**1i**	*m*-F	**2a**	**4i**	86	88
10	**1j**	*m*-Cl	**2a**	**4j**	80	92
11	**1k**	*m*-Br	**2a**	**4k**	71	90
12	**1a**	H	**2b**	**4l**	83[d]	93
13[e]	**1a**	H	**2c**	**4m**	70	47
14[e]	**1a**	H	**2d**	**4n**	85	57
15	**1a**	H	**2e**	**4o**	87	79
16	**1a**	H	**2f**	**4p**	90	86
17	**1a**	H	**2g**	**4q**	68	83
18	**1a**	H	**2h**	**4r**	72	80

[a] Reaction conditions: Unless otherwise noted reactions were performed with 0.4 mmol of **1**, 0.2 mmol of **2**, 0.04 mmol of catalyst **C**, and 0.08 mmol of TFA in 2 mL of solvent at 30 °C. [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase. [d] A mixture of δ and γ products was obtained (δ/γ = 65:35). [e] At 40 °C.

The remarkable decrease in *ee* value indicated that the NH group in the indole framework should play a significant role in enantiocontrol (compare Table 2, entry 1 versus 13).

The structure of the product **4d** was confirmed by X-ray crystal structure analysis, which demonstrated the δ regioselectivity of the reaction and deduced the absolute configuration of the newly creating chiral centre of **4d** to be *S* (Figure 1).[14] Although the allylic-substituted γ-product **3** could rearrange to the α-substitution product in the presence of an acid,[15] there was no α product observed in the product mixture. A control experiment showed that under the reaction conditions, it was impossible for γ-product **3a** to be directly converted into δ-product **4a**. Meanwhile, our results indicated that the Brønsted acid co-catalyst and the N–H group in the indole substrates were necessary for high enantioselectivity in the nucleophilic substitution of MBH alcohol catalyzed by the chiral primary amine. Based on the above experimental results, a plausible mechanism is proposed in Scheme 4. MBH alcohol **1a** was

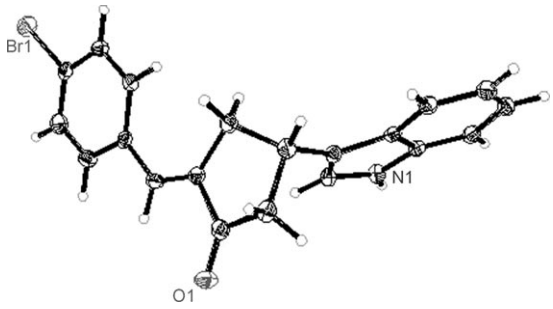
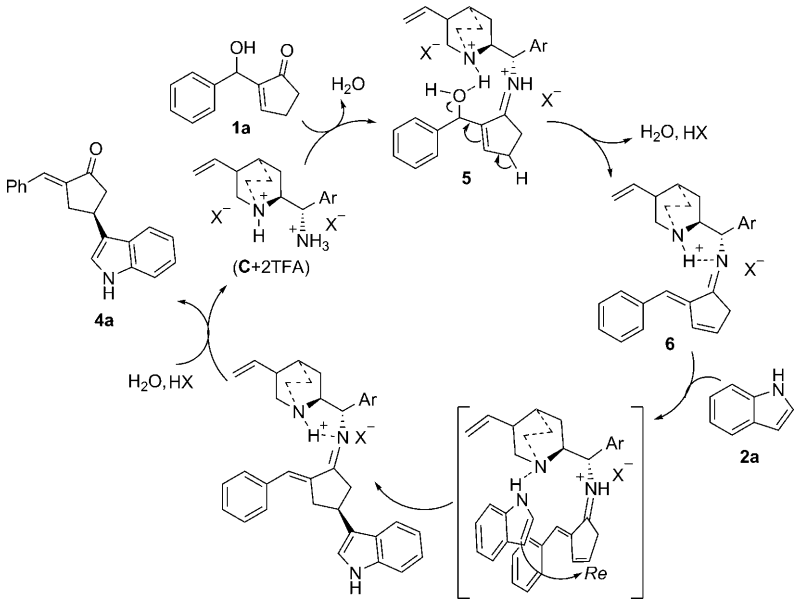


Figure 1. ORTEP plot of enantiomerically pure **4d** drawn with ellipsoids at 30% probability.

activated by forming the iminium ion **5** with the chiral primary amine catalyst **C**. A Brønsted acid such as TFA is induced the formation of the iminium ion. The activated OH group of the MBH alcohol undergoes a dehydration reaction to form the intermediate **6** through hydrogen bonding assisted by the protonated tertiary amine moiety in catalyst **C**. ESI-MS analyses showed the existence of intermediates **5** (*m*/*z* 494, without TFA) and **6** (*m*/*z* 476, without TFA) during the reaction of MBH **1a** with 20 mol% of catalyst **C** and co-catalyst TFA (40 mol%) at 30 °C for 1 day, but in the absence of indole **2a**.[16] Then indole **2a** attacks the butadiene unit of intermediate **6** from the *Re* face to form (*S*)-δ-product **4**. Although the reaction of cyclic MBH alcohols **1** with indoles **2** provided substitution products, the transformations could be described as a conjugate-type addition when considering the important unsaturated compound involved as reaction intermediate.[3b,c] To the best of our knowledge, there are only a few reports on the asymmetric reaction of cycloenones with indoles, the enantioselectivities obtained here are the best results so far.[17] Nevertheless, the mechanism of the reaction, especially for δ regioselectivity still needs more detail investigation.



Scheme 4. Plausible mechanism for the enantioselective formation of δ-product **4**.

In conclusion, we have presented the first direct enantioselective nucleophilic substitution of cyclic Morita–Baylis–Hillman alcohols with indoles under organocatalysis by using a chiral primary amine as the catalyst in combination with a Brønsted acid as the co-catalyst. Unexpected δ products were obtained with exclusive regioselectivity and high enantioselectivity (up to 93% *ee*). The reaction can be considered a new type of organocatalytic enantioselective nucleophilic substitution through iminium-ion-assisted dehydration of allylic alcohol and addition of a carbon nucleophile with an unsaturated unit. Investigations of the mechanism and scope of the present reaction with other nucleophiles are in progress.

Experimental Section

General Procedure: Catalyst **C** (13 mg, 0.04 mmol) was added to a solution of Morita–Baylis–Hillman alcohol **1** (0.4 mmol) and indole **2** (0.2 mmol) in 2 mL of *i*PrOAc/THF (1:1), followed by stirring for 5 min. Then TFA (6 μL, 0.08 mmol) was added and the resulting reaction mixture was heated at 30 °C till the reaction was complete (as evident by TLC; reaction times are given in the Supporting Information. The crude reaction mixture was then purified by column chromatography on silica gel (eluent: petroleum ether/EtOAc = 4:1) to afford the desired δ-product **4.**

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