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Convenient Synthesis of Tetrahydro-γ-carbolines and Tetrahydroquinolines through a Chemo- and Regioselectivity Switch by a Brønsted Acid Catalyzed, One-Pot, Multicomponent Reaction

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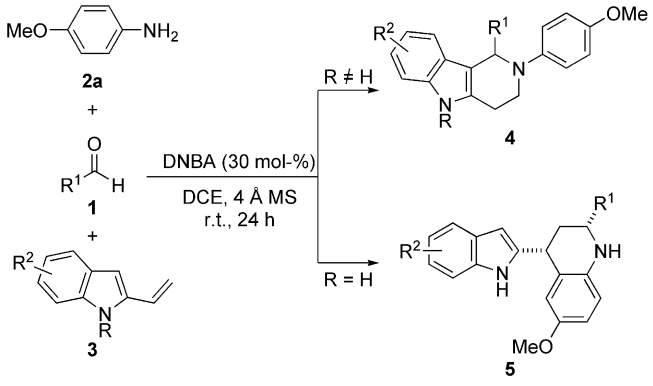
Keywords: Chemoselectivity / Multicomponent reactions / Nitrogen heterocycles / Fused-ring systems

An efficient, one-pot, multicomponent reaction of aldehydes **1**, *p*-methoxyaniline (**2a**), and 2-vinylindoles **3** was developed. This approach provides a practical approach to synthetically and biologically significant tetrahydro-γ-carboline and tetrahydroquinoline derivatives in good yields through a chemo- and regioselectivity switch, which can be tuned by simply changing the substituent on the indole component under identical reaction conditions.

Introduction

Heterocyclic chemistry is one of the most important disciplines in organic chemistry.[1] Among the various heterocyclic systems discovered and developed, nitrogen-containing ones play a fundamental role in the context of both chemistry and biology.[2] Tetrahydro-γ-carboline and tetrahydroquinoline are two especially outstanding fused heterocyclic ring systems prevalent in natural and unnatural heterocyclic compounds possessing significant biological activities and pharmacophores of neuroleptic,[3a] antipsychotic,[3c] antagonistic,[3f–3g] antimalarial,[3i–3j] and antitumoral[3d–3e] agents, among others.[3b,3h] Consequently, great efforts have been devoted to the construction of tetrahydro-γ-carboline[4] and tetrahydroquinoline[5] frameworks in the area of organic/drug synthesis. Very recently, we developed two distinct efficient approaches to tetrahydro-β-carbolines/tetrahydroquinolines[6] and tetrahydrocarbazoles[7] based on iminium catalysis and hydrogen-bonding catalysis, respectively. As a continuation of this program, we document here an unprecedented practical approach for the synthesis of tetrahydro-γ-carboline and tetrahydroquinoline through a chemo- and regioselectivity switch under identical reaction conditions, specifically the Brønsted acid catalyzed, one-pot, multicomponent reactions of aldehydes **1**, aniline **2a**, and 2-vinylindoles **3** (Scheme 1).



Scheme 1. Chemo- and regioselectivity switch in the Brønsted acid catalyzed, one-pot, multicomponent reactions of aldehydes **1**, aniline **2a**, and 2-vinylindoles **3**.

Multicomponent reactions (MCRs),[8] which involve the production of desired compounds by the reaction of three or more simple and/or readily accessible starting reagents in a one-pot fashion, provide significant advantages over traditional stepwise strategies in terms of cost, waste, time, and atom economy, and these reactions constitute an extremely popular research field in both academic and industrial domains.[9] However, chemo- and stereoselectivities of MCRs have been widely accepted as a significant challenging task for synthetic organic chemists.[10]

Results and Discussion

Initially, we investigated the three-component reaction of benzaldehyde (**1a**) 2-aminophenol (**2b**), and 1-benzyl-2-vinyl-1*H*-indole (**3a**) in the presence of common Brønsted acid catalysts in the hope of gaining the designed cascade

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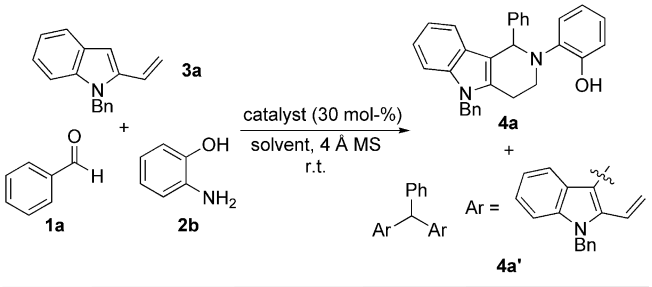
tetrahydro-γ-carboline product **4a** (Table 1). To our delight, with 30 mol-% of these Brønsted acids in dichloromethane, all reactions proceeded smoothly and cleanly to give **4a** in moderate to good yields (45–69% yield; Table 1, Entries 1–6) together with some double Friedel–Crafts alkylation side product **4a′**;[11] 3,5-dinitrobenzoic acid (DNBA) was found to be the best acid (69% yield; Table 1, Entry 6). Further efforts were then directed toward improving the yield of cascade product **4a**[7] while suppressing the double Friedel–Crafts alkylation side reaction. Our studies on the solvents with DNBA as the catalyst showed that this one-pot, three-component reaction was general with a wide range of solvents (Table 1, Entries 6–12).[12] However, the reaction proceeded better in halogenated solvents (Table 1, Entries 6–8) than in other solvents, such as diethyl ether, toluene, acetonitrile, and ethanol (Table 1, Entries 9–12), and 1,2-dichloroethane proved to be the best solvent choice. Moreover, a brief survey of aniline substrates **2** disclosed that *p*-methoxyaniline (**2a**) was the most suitable amine component.[12] With 30 mol-% DNBA in 1,2-dichloroethane, the reaction of benzaldehyde (**1a**), *p*-methoxyaniline (**2a**), and 1-benzyl-2-vinyl-1*H*-indole (**3a**) efficiently provided desired product **4b** in high yield and with only a trace amount of side product (Table 1, Entry 13).

Table 1. Optimization conditions for the one-pot, multicomponent synthesis of tetrahydro-γ-carboline **4a**.[a]



Entry	Catalyst	Solvent	*t* [h]	% Yield of **4a**[b]
1	HOAc	CH_2Cl_2	96	54
2	$PhCO_2H$	CH_2Cl_2	112	62
3	$pTSA·H_2O$	CH_2Cl_2	96	55
4	(±)-CSA	CH_2Cl_2	96	40
5	$MeSO_3H$	CH_2Cl_2	96	45
6	DNBA	CH_2Cl_2	96	69
7	DNBA	$CHCl_3$	64	74
8	DNBA	DCE	48	76
9	DNBA	Et_2O	84	45
10	DNBA	toluene	70	60
11	DNBA	CH_3CN	69	56
12	DNBA	EtOH	66	57
13	DNBA	DCE	24	83[c,d]

[a] Unless otherwise noted, reactions were carried out with **1a** (0.30 mmol), **2b** (0.30 mmol), **3a** (0.45 mmol), 4 Å MS (100 mg), and catalyst (0.090 mmol) in solvent (1.5 mL) at room temperature. [b] Isolated yield of **4a**. [c] *p*-Methoxyaniline (**2a**) was used instead of **2b**, and product **4b** was obtained. [d] The structure of corresponding product **4b** was confirmed by X-ray analysis. $pTSA·H_2O$ = *p*-toluenesulfonic acid monohydrate, (±)-CSA = (±)-camphorsulfonic acid, DNBA = 3,5-dinitrobenzoic acid, DCE = 1,2-dichloroethane.

We obtained the crystal of novel tetrahydro-γ-carboline product **4b** from a mixture of hexane and ethyl acetate, and its structure was further confirmed by X-ray crystallographic analysis (Figure 1).[13]

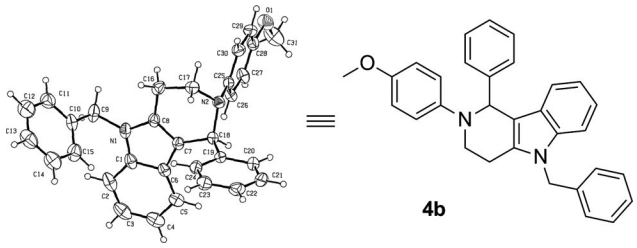
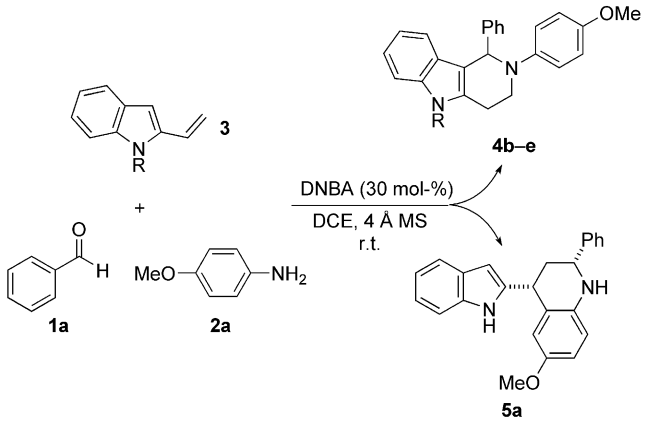


Figure 1. X-ray crystal structure of tetrahydro-γ-carboline **4b**.

Next, investigation of the substitution effects on the nitrogen group of 2-vinylindole **3** led us to the discovery of an unprecedented chemo- and regioselectivity switch in this Brønsted acid catalyzed, one-pot, multicomponent reaction. Only unexpected tetrahydroquinoline product **5a** was obtained in high yield (87%; Table 2, Entry 2) with excellent diastereoselectivity (>95:5) when *N*-free 2-vinylindole **3b** was employed in the reaction.[14,15] Meanwhile, all of the other *N*-substituted (R = Me, allyl, or Ts) 2-vinylindoles **3c**–**e** were compatible in the reaction to provide tetrahydro-γ-carboline products **4c**–**e** without formation of tetrahydroquinoline products. Although complete understanding of the chemo- and regioselectivity switch in this Brønsted acid catalyzed reaction has not yet been reached, we believe that tetrahydroquinoline product **5a** was the re-

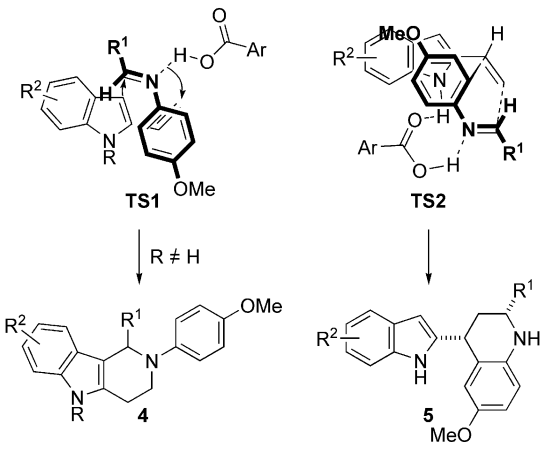
Table 2. Significant chemo- and regioselectivity switch in the Brønsted acid catalyzed, one-pot, multicomponent reaction.[a]



Entry	**3a**–**e**	*t* [h]	Product, % Yield[b]
1	**3a**: R = Bn	24	**4b**, 83
2	**3b**: R = H	24	**5a**, 87[c]
3	**3c**: R = Me	24	**4c**, 85
4	**3d**: R = allyl	48	**4d**, 82
5	**3e**: R = Ts	48	**4e**, 79

[a] Reactions were carried out with **1a** (0.30 mmol), **2a** (0.30 mmol), **3a**–**e** (0.45 mmol), 4 Å MS (100 mg), and DNBA (0.090 mmol) in DCE (1.5 mL) at room temperature. [b] Isolated yield. [c] *dr* > 95:5, determined by NMR spectroscopic analysis of the crude reaction mixture.

sult of a formal inverse-electron-demand aza-Diels–Alder process due to the hydrogen bonding between the Brønsted acid DNBA and the *N*-free 2-vinylindole **3b** (Scheme 2).

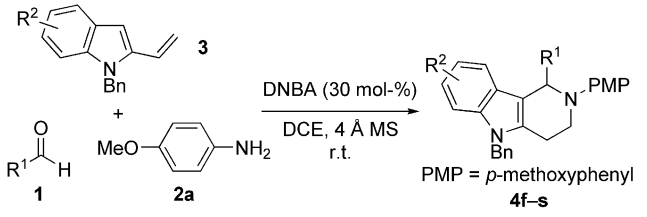


Scheme 2. Proposed transition states in this Brønsted acid catalyzed, one-pot, multicomponent reaction.

With optimal conditions in hand, we subsequently explored the scope of this chemo- and regioselectivity switch protocol in the synthesis of tetrahydro-γ-carbolines and tetrahydroquinolines. As seen from Table 3, a variety of tetrahydro-γ-carbolines were obtained in high yields when *N*-benzyl 2-vinylindoles **3** were employed with aldehydes **1** and aniline **2a** in the presence of 30 mol-% DNBA. A wide range of aromatic aldehydes were well tolerated and furnished the corresponding products in good yields (67–88%; Table 3, Entries 1–9). The electronic properties and the steric hindrance of the substituent at the aromatic ring had little influence on the reaction outcome. Aromatic aldehydes possessing electron-donating groups gave good yields (Table 3, Entries 1 and 2), whereas aldehydes with electron-withdrawing substituents at the *para* and *meta* positions underwent the sequential process more efficiently and gave higher yields (Table 3, Entries 3–7). Moreover, multisubstituted aromatic aldehydes were also successfully engaged in the reaction (87% yield; Table 3, Entry 9). Furthermore, this protocol was satisfactorily tolerated by the 2-vinylindole component (Table 3, Entries 10–14). Vinylindoles with either electron-donating or electron-withdrawing substituents at the C-5 position smoothly participated in the reaction, providing the desired products in high yields (70–85%).

Finally, we explored the synthesis of tetrahydroquinolines by using the reaction of *N*-free 2-vinylindoles **3** with aldehydes **1** and aniline **2** in the presence of 30 mol-% DNBA (55–88%, Table 4). As shown, this switch approach to tetrahydroquinoline synthesis was well tolerant by the aldehyde and 2-vinylindole components, as significant changes in both were achieved with no detrimental effects on the yields; these results are comparable to the corresponding tetrahydro-γ-carboline synthesis (Table 4, Entries 1–7). Meanwhile, anilines **2c** and **2d** can also participate in this process, providing the desired products in good yields (Table 4, Entries 8 and 9). We obtained the crystal of tetrahydroquinoline product **5b** and its relative configuration was further confirmed by X-ray crystallographic analysis (Figure 2).[13]

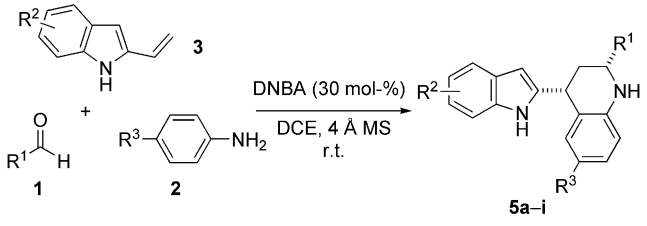
Table 3. Scope of the one-pot, multicomponent synthesis of tetrahydro-γ-carbolines.[a]



Entry	R^1	R^2	*t* [h]	Product, % Yield[b]
1	4-MeOPh (**1b**)	H (**3a**)	72	**4f**, 68
2	4-MePh (**1c**)	H (**3a**)	72	**4g**, 70
3	4-FPh (**1d**)	H (**3a**)	48	**4h**, 78
4	4-ClPh (**1e**)	H (**3a**)	42	**4i**, 88
5	4-BrPh (**1f**)	H (**3a**)	42	**4j**, 75
6	4-NO_2Ph (**1g**)	H (**3a**)	18	**4k**, 85
7	3-NO_2Ph (**1h**)	H (**3a**)	22	**4l**, 84
8	2-BrPh (**1i**)	H (**3a**)	70	**4m**, 67
9	3,4-F_2-Ph (**1j**)	H (**3a**)	48	**4n**, 87
10	4-ClPh (**1e**)	5-MeO (**3f**)	42	**4o**, 85
11	4-ClPh (**1e**)	5-Me (**3g**)	48	**4p**, 81
12	4-ClPh (**1e**)	5-F (**3h**)	18	**4q**, 78
13	4-ClPh (**1e**)	5-Cl (**3i**)	22	**4r**, 70
14	4-ClPh (**1e**)	5-Br (**3j**)	48	**4s**, 75

[a] Reactions were carried out with **1** (0.30 mmol), **2a** (0.30 mmol), **3** (0.45 mmol), 4 Å MS (100 mg), and DNBA (0.090 mmol) in DCE (1.5 mL) at room temperature. [b] Isolated yield.

Table 4. Scope of the one-pot, multicomponent synthesis of tetrahydroquinolines.[a]



Entry	R^1	R^2	R^3	*t* [h]	Product, % Yield[b,c]
1	Ph (**1a**)	H (**3b**)	OMe (**2a**)	24	**5a**, 87
2	4-NO_2Ph (**1g**)	H (**3b**)	OMe (**2a**)	24	**5b**, 65
3	4-MePh (**1c**)	H (**3b**)	OMe (**2a**)	36	**5c**, 72
4	Ph (**1a**)	5-MeO (**3k**)	OMe (**2a**)	24	**5d**, 71
5	Ph (**1a**)	5-Me (**3l**)	OMe (**2a**)	24	**5e**, 82
6	Ph (**1a**)	5-F (**3m**)	OMe (**2a**)	48	**5f**, 84
7	Ph (**1a**)	5-Cl (**3n**)	OMe (**2a**)	48	**5g**, 88
8	Ph (**1a**)	H (**3b**)	H (**2c**)	48	**5h**, 64
9	Ph (**1a**)	H (**3b**)	Cl (**2d**)	48	**5i**, 55

[a] Reactions were carried out with **1** (0.30 mmol), **2** (0.30 mmol), **3** (0.45 mmol), 4 Å MS (100 mg), and DNBA (0.090 mmol) in DCE (1.5 mL) at room temperature. [b] Isolated yield. [c] *dr* > 95:5, determined by NMR spectroscopic analysis of the crude reaction mixture.

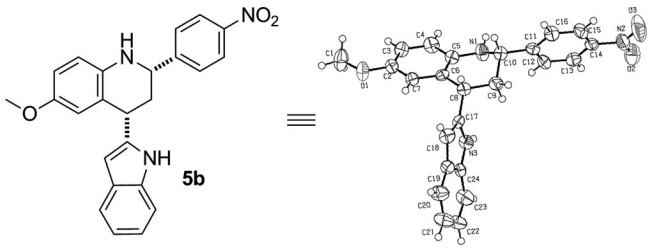


Figure 2. X-ray crystal structure of tetrahydroquinoline **5b**.

Conclusions

In summary, we have developed an efficient one-pot, three-component reaction of aldehydes **1**, *p*-methoxyaniline (**2a**), and 2-vinylindoles **3**. The chemo- and regioselectivity of the reaction can easily be tuned by changing the protecting group of the indole component; two kinds of structurally different products can be obtained in good yields, providing a practical approach to obtain synthetically and biologically important tetrahydro-γ-carboline and tetrahydroquinoline derivatives. Further studies on the mechanism and the asymmetric version of this reaction are actively underway in this laboratory.

Experimental Section

Typical Procedure: A reaction vial equipped with a magnetic stirring bar was sequentially charged with **1a** (32 mg, 0.30 mmol), **2a** (37 mg, 0.30 mmol), 4 Å MS (100 mg), DCE (1.5 mL), and DNBA (19 mg, 0.090 mmol). The mixture was stirred at room temperature for 15 min and **3a** (105 mg, 0.45 mmol) was then added. The resulting solution was stirred at the same temperature until the reaction was complete (TLC). The crude reaction mixture was directly subjected to column chromatography (petroleum ether/ethyl acetate, 15:1) to afford **4b** as a white solid in 83% yield. R_f = 0.40 (petroleum ether/ethyl acetate, 8:1).

Supporting Information (see footnote on the first page of this article): General experimental methods and characterization data.

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[12] For details, see the Supporting Information.

[13] CCDC-769054 (for **4b**) and -769055 (for **5b**) 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.

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