Thiourea-catalyzed Intramolecular Allylic Amination: Synthesis of Dihydroquinoline Derivatives

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The dihydroquinoline structure exists in a large number of natural products and biologically active molecules.[1] Particularly, many of these naturally occurring 1,2-dihydroquinolines and their synthetic analogs are important precursors for the synthesis of natural products and pharmaceuticals.[2] Therefore, the development of new and efficient synthetic routes for the preparation of dihydroquinoline analogs is of importance to both organic synthetic and medicinal chemistry.[3–12] Recently, efficient synthetic methodologies for the preparation for dihydroquinolines have focused on catalytic systems. Some notable examples include the cascade reaction of anilines with alkynes catalyzed by transition metals such as palladium,[3] ruthenium,[4,5] silver,[6] and gold[7]; the condensation reaction of anilines with ketones catalyzed by scandium triflate,[8] silicotungstic acid,[9] and zeolite[10]; the allylation of quinolines mediated by indium[11]; and metal-catalyzed allylic amination.[12] The organocatalyst-mediated carbon–carbon and carbon–heteroatom bond formations have gained considerable attention because organocatalysis is one of the most powerful and environmentally benign processes.

As a part of the research program related to the development of synthetic methods for the formation of carbon–carbon[13] and carbon–heteroatom bonds,[14] we recently reported the organocatalytic α-alkylation of cyclic ketones by S_N1-type reaction of alcohols.[15] We then turned our attention to an intramolecular version of S_N1-type reaction of alcohols.[16] To the best of our knowledge, there are no examples for organocatalytic synthesis of dihydroquinolines from 2-aminophenyl-1-en-3-ol derivatives using intramolecular allylic amination reaction. Here, we report an efficient synthetic method to 1,2-dihydroquinoline derivatives involving intramolecular S_N1-type amination of N-protected 2-aminoaryl-1-en-3-ols catalyzed by an organocatalyst at room temperature.

To determine suitable reaction conditions for the intramolecular allylic amination reaction of N-protected 2-aminophenyl-substituted allyl alcohol, we chose (*E*)-4-phenyl-2-(2-(tosylamino)phenyl)but-3-en-2-ol (**1a**) to optimize the reaction conditions by varying the catalyst, additives, and solvent. The results are summarized in Table 1.

Both palladium complex **I** and phosphoric acid **II** gave the dihydroquinoline product in moderate yields (Figure 1). The catalyst system comprising thiourea **III** with trimethylsilyl chloride (TMSCl) as additive afforded the dihydroquinoline **2a** with high yield (Table 1, entries 1–3). We then examined the reactivity with catalyst **III** in the presence of various additives, such as benzoic acid, trifluoroacetic acid (TFA), trifluoromethanesulfonic acid (TfOH), 2,4-dinitrobenzensulfonic acid (DNBS), HCl, and HBr (Table 1, entries 3–9). Among the additives probed, the best result (85% yield) was achieved when the reaction was conducted in HBr (Table 1, entry 9). A survey of the reaction media indicated that several common solvents, such as dichloromethane, chloroform, methyl *tert*-butyl ether (MTBE), tetrahydrofuran (THF), and toluene were well tolerated in this allylic amination (Table 1, entries 9–14). Among the solvents probed, the best result was achieved when the reaction was conducted in toluene (Table 1, entry 9). The combination of catalyst **III** and HBr showed the highest activity for this ally lamination. With the use of catalyst III or HBr alone, the reaction gave **2** in low yields (Table 1, entries 15 and 16).

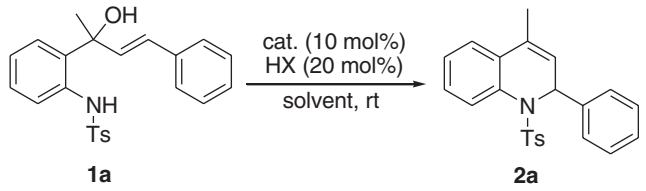
With the optimal reaction conditions in hand, the scope of the reaction was explored, as seen in Table 2. Organocatalyst **III**-catalyzed intramolecular allylic amination reaction of N-protected 2-aminophenyl-substituted allyl alcohol proved to be a general approach for the synthesis of versatile 1,2-dihydroquinolines **2**. The thiourea-catalyzed synthesis of substituted dihydroquinolines could tolerate a methoxy-, chloro-, or naphthyl group at the terminal position of the allylic alcohol moiety, giving **2b–2e** with 85–98% yields (entries 1–4). Moderate yield was obtained when styryl-substituted allylic alcohol **1f** was used as the substrate (entry 5).

We next attempted to extend our strategy to develop the asymmetric version of this organocatalyzed intramolecular allylic amination reaction. In the presence of the chiral catalyst **IV**, the intramocular allylic amination reaction of (*E*)-4-phenyl-2-(2-(tosylamino)phenyl)but-3-en-2-ol (**1a**) proceeded to afford the chiral product **2a**∗ with moderate enantioselectivity (40% ee, Scheme 1).

Although the reason for the observed reactivity of this catalyst system is still unclear, we suppose that it is nucleophilic addition of the sulfonamide unit to the allylic cation moiety, as shown in Scheme 2. The halophilic thiourea catalyst might effectively induce ionization of allylic alcohol **1** in the presence of HBr to generate the allylic carbocation intermediates **3**, in which the thiourea is associated with the bromide anion.

In conclusion, we have developed an efficient thiourea-catalyzed intramolecular allylic amination reaction of N-protected 2-aminophenyl-substituted allyl alcohol, which proved to be a general approach for the synthesis of versatile

Table 1. Optimization of the reaction conditions[a]



1a **2a**

Entry	Cat.	HX	Solvent	Time (h)	Yield (%)
1	**I**	—	PhMe	1	61
2	**II**	—	PhMe	2	57
3	**III**	Me_3SiCl	PhMe	0.5	70
4	**III**	$PhCO_2H$	PhMe	1	10
5	**III**	TFA	PhMe	1	43
6	**III**	TfOH	PhMe	1	50
7	**III**	DNBS	PhMe	1	51
8	**III**	HCl	PhMe	0.5	73
9	**III**	HBr	PhMe	1	89
10	**III**	HBr	CH_2Cl_2	0.5	35
11	**III**	HBr	$CHCl_3$	1	40
12	**III**	HBr	Et_2O	1	57
13	**III**	HBr	MTBE	1	45
14	**III**	HBr	THF	0.5	70
15	—	HBr	PhMe	1	35
16	**III**	—	PhMe	5	trace

[a] Reactions were carried out with **1a** (0.3 mmol), catalyst (0.03 mmol), and HX (0.06 mmol) in solvent (1.0 mL).

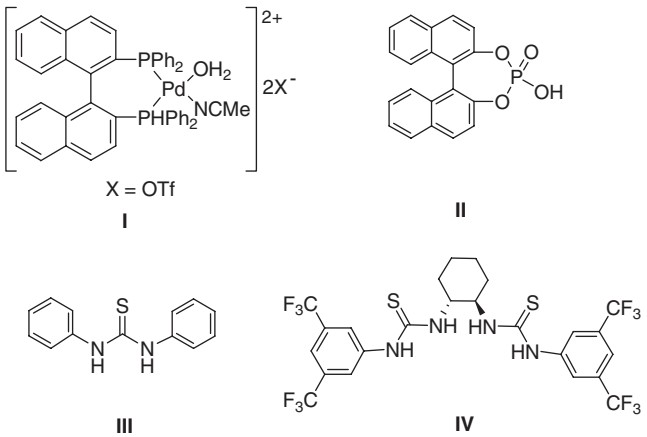


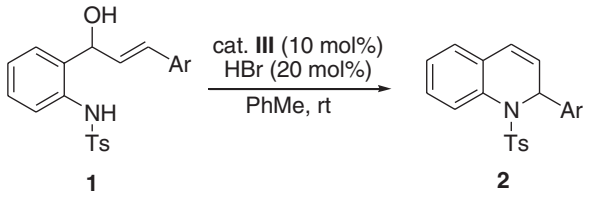
Figure 1. Structure of the catalysts.

1,2-dihydroquinolines **2**. The desired 1,2-dihydroquinolines **2** were obtained in moderate to high yields (65–98%) in 1 h at room temperature. Further details and application of this asymmetric version of intramolecular S_N1-type amination will be presented in due course.

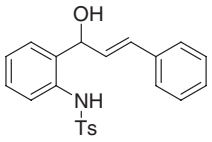
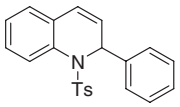
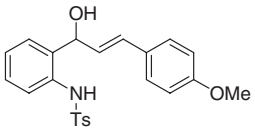
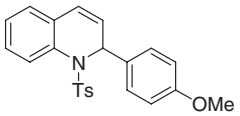
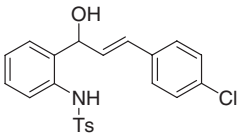
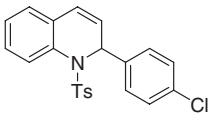
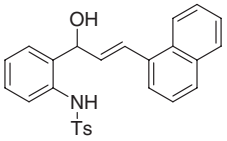
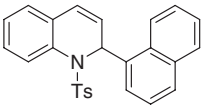
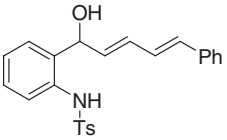
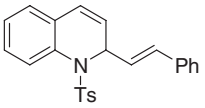
Experimental

General. All reagents and solvents were commercial grade and used without purification. Thin-layer chromatography (TLC) analyses were carried out on precoated silica gel plates with the F_{254} indicator. Visualization was accomplished by UV light (254 nm), with I_2, *p*-anisaldehyde, ninhydrin, and phosphomolybdic acid solution as indicators. Purification of reaction products was carried out by flash chromatography

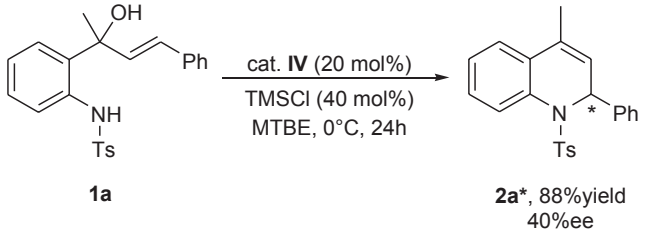
Table 2. Thiourea-catalyzed intramolecular allylic amination[a]



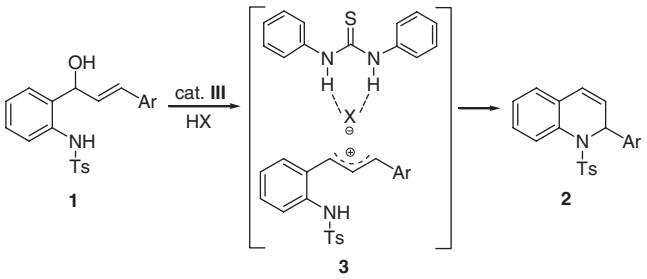
1 **2**

Entry	Alcohol, **1**	Product **2**	Yield (%)
1	 **1b**	 **2b**	98
2	 **1c**	 **2c**	96
3	 **1d**	 **2d**	94
4	 **1e**	 **2e**	85
5	 **1f**	 **2f**	65

[a] Reactions were carried out with 1 (0.3 mmol), catalyst **III** (0.03 mmol), and HBr (0.06 mmol) in toluene (1.0 mL) for 1 h.



Scheme 1. Asymmetric version of thiourea-catalyzed intramolecular allylic amination.



Scheme 2. Proposed reaction mechanism.

using Merck (Germany) silica gel 60 (230–400 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a Jeol ECS 400 (400 MHz for ^{1}H; 100 MHz for ^{13}C) instrument (Tokyo, Japan). Chemical shift values (δ) are reported in ppm relative to Me_4Si (0.0 ppm). The enantiomeric excesses were determined by HPLC, which was performed on Younglin M930 and M9100 Series instrument (Young Lin, Seoul, Korea), and measured at 254 nm using Chiralpak IC column (Daicel, Tokyo, Japan). (*E*)-4-Phenyl-2-(2-(tosylamino)phenyl)but-3-en-2-ol (**1a**) and (*E*)-3-aryl-1-(2-(tosylamino)phenyl)prop-2-en-1-ol derivatives **1b–1e** were prepared in accordance with literature methods.[12]

General Procedure for the Thiourea-catalyzed Intramolecular Allylic Amination. To a stirred solution of 2-aminophenyl-1-en-3-ols **1** (0.3 mmol) in toluene (0.8 mL) was added the catalyst **III** (0.03 mmol) and hydrobromic acid (0.06 mmol) at room temperature. The reaction mixture was stirred for 1 h at room temperature. After completion of the reaction, the resultant solution was concentrated *in-vacuo* and the obtained residue was purified by flash chromatography (EtOAc/hexane, 1:5) to afford product **2**.

4-Methyl-2-phenyl-1-tosyl-1,2-dihydroquinoline (2a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 7.8 Hz, 1H), 7.41–7.32 (m, 4H), 7.24–7.18 (m, 4H), 7.14–7.08 (m, 3H), 6.97 (d, J = 7.8 Hz, 1H), 5.91 (d, J = 4.2 Hz, 1H), 5.63 (d, J = 4.2 Hz, 1H), 2.35 (s, 3H), 1.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 138.5, 136.1, 132.9, 129.1, 128.6, 128.4, 128.2, 127.9, 127.6, 127.4, 127.2, 126.5, 126.3, 125.5, 57.0, 21.7, 21.5.

2-Phenyl-1-tosyl-1,2-dihydroquinoline (2b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J =7.9 Hz, 1H), 7.38–7.30 (m, 4H), 7.26–7.18 (m, 4H), 7.14–7.06 (m, 3H), 6.95 (d, J = 7.9 Hz, 1H), 6.27 (d, J = 9.6 Hz, 1H), 6.02 (d, J = 6.0 Hz, 1H), 5.87 (dd, J = 9.6, 6.0 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 138.4, 136.1, 132.9, 129.1, 128.6, 128.4, 128.2, 127.9, 127.6, 127.4, 127.2, 126.5, 126.3, 125.5, 57.0, 21.5.

2-(4-Methoxyphenyl)-1-tosyl-1,2-dihydroquinoline (2c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 7.6 Hz, 1H), 7.33 (d, J = 8.0 Hz, 2H), 7.23–7.18 (m, 3H), 7.14–7.08 (m, 3H), 7.04 (d, J = 8.0 Hz, 2H), 6.95 (d, J = 7.6 Hz, 1H), 6.26 (d, J = 9.6 Hz, 1H), 5.98 (d, J = 6.0 Hz, 1H), 5.87 (dd, J = 9.6, 6.0 Hz, 1H), 3.81 (s, 3H); 2.35(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 137.7, 136.2, 135.3, 132.9, 129.2, 129.1, 128.7, 128.2, 127.7, 127.4, 127.3, 126.7, 126.4, 126.2, 126.2, 125.4, 56.8, 21.6, 21.1.

2-(4-Chlorophenyl)-1-tosyl-1,2-dihydroquinoline (2d). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 7.24–7.10 (m, 6H), 6.96 (d, J = 8.0 Hz, 1H), 6.28 (d, J = 9.6 Hz, 1H), 5.98 (d, J = 6.0, 1H), 5.85 (dd, J = 9.6, 6.0 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6; 136.9, 136.0, 133.8, 132.7, 129.2, 128.9, 128.6, 128.5, 127.6, 127.2, 126.6, 126.4, 126.0, 125.9, 56.2, 21.6.

1-(Naphthalen-1-yl)-1-tosyl-1,2-dihydroquinoline (2e). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.76–7.58 (6H, m), 7.40–7.33 (4H, m), 7.07–7.19 (4H, m), 6.96 (1H, d, J = 1.62, 7.33 Hz), 6.33 (1H, d, J = 9.60 Hz), 6.16 (1H, d, J = 5.86 Hz), 5.93 (1H, dd, J = 5.88, 9.58 Hz), 2.34 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.4, 136.1, 135.6, 133.0, 132.8, 128.7, 128.4, 128.3, 128.0, 127.7, 127.5, 126.5, 126.3, 126.1, 126.0, 125.9, 125.7, 57.0, 21.5.

(*E*)-2-Styryl-1-tosyl-1,2-dihydroquinoline (2f). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77–7.71 (m, 1H), 7.35–7.31 (m, 2H), 7.28–7.26 (m, 1H), 7.26–7.10 (m, 6H), 7.09–7.06 (m, 2H), 6.98–6.93 (m, 1H), 6.55–6.50 (m, 1H), 6.19–6.15 (m, 1H), 6.05–6.03 (m, 1H), 5.75–5.69 (m, 1H), 5.59–5.56 (m, 1H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.5, 136.4, 136.0, 133.0, 132.1, 129.1, 128.4, 128.2, 127.8, 127.5, 127.2, 126.6, 126.5, 126.0, 125.4, 125.3, 56.2, 21.7.

Asymmetric Version for the Thiourea-catalyzed Intramolecular Allylic Amination of 1a. To a stirred solution of (*E*)-4-phenyl-2-(2-(tosylamino)phenyl)but-3-en-2-ol (**1a**, 0.2 mmol) in MTBE (0.8 mL) was added catalyst **IV** (0.04 mmol) and Me_3SiCl (0.08 mmol) at 0°C. The reaction mixture was stirred for 1 day at 0°C. After completion of the reaction, the resultant solution was concentrated *in-vacuo* and the obtained residue was purified by flash chromatography (EtOAc/hexane, 1:5) to afford product **2a**∗.

4-Methyl-2-phenyl-1-tosyl-1,2-dihydroquinoline (2a∗). $[\alpha]_D^{23}$ = +27.9 (c = 1.00, $CHCl_3$); HPLC (85:15, *n*-hexane:*i*-PrOH, 254 nm, 1.0 mL/min) Chiralpak IC column, t_R = 25.4 min (major), t_R = 30.2 min (minor), 40% ee.

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