Tetrahedron 66 (2010) 1045–1050

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Self-catalytic, solvent-free or in/on water protocol: aza-Friedel–Crafts reactions between 3,4-dihydroisoquinoline and 1- or 2-naphthols

Patricia D. MacLeod, Zhiping Li, Chao-Jun Li *

Department of Chemistry, McGill University, 801 Sherbrooke St. West, Montréal, QC, Canada H3A 2K6

ARTICLE INFO

Article history:
Received 26 May 2009
Accepted 29 September 2009
Available online 6 November 2009

ABSTRACT

A self-catalytic protocol was developed using an aza-Friedel–Crafts method to generate 1-naphthoyl tetrahydroisoquinoline products under solvent-free conditions or in/on water. Yields were increased with the use of water. The reaction proceeded with 100% atom economy in the absence of any additional catalyst.

1. Introduction

With the advent of green chemistry, chemists are searching for innovative new approaches for the generation, purification, and use of chemical products, which adhere to the 12 principles laid out by Anastas and Warner.[1] For synthetic purposes, innovations to be sought involve the minimization of derivatizations, the minimization of auxiliary substances, the minimization of the number of steps, and the maximization of incorporation of starting materials and reagents. Minimizing solvent involves either making solvent completely unnecessary or if one must be used, then an innocuous solvent is preferable. It is even more desirable, reactions, which take place either neat,[2] or in an alternative media such as water[3] or others[4] can impart improved selectivity, enhance reactivity or ameliorate the ease of separation or purification. The concepts of atom economy[5] and step economy[6] provide the guiding principles to design more efficient synthesis.

With our continued interest in the synthesis of tetrahydroisoquinoline-based structures, we recently designed and synthesized a new class of chiral compounds, including the lead compound 1-(1,2,3,4-tetrahydroisoquinolin-1-yl)-naphthalen-2-ol (THIQNOL) (Fig. 1).[7] The molecules based on this structure have the potential to be chiral ligands for asymmetric synthesis and agents for biological applications. In our earliest report,[7a] a cross-dehydrogenative-coupling (CDC) reaction[8] was utilized in the synthesis of the corresponding chiral ligands. We envisaged that similar structures could be generated in a simple fashion by designing a reaction that could be self-catalytic. This idea goes beyond simply avoiding unnecessary stoichiometric reagents; it also eliminates the added catalyst, which in turn, eliminates the need for additional separation steps. If we successfully design a reaction, which uses the starting reagents' intrinsic functionalities to provide the means to initiate the reaction, we should be able to achieve the following:

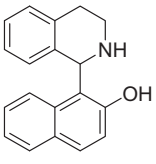


Figure 1. THIQNOL.

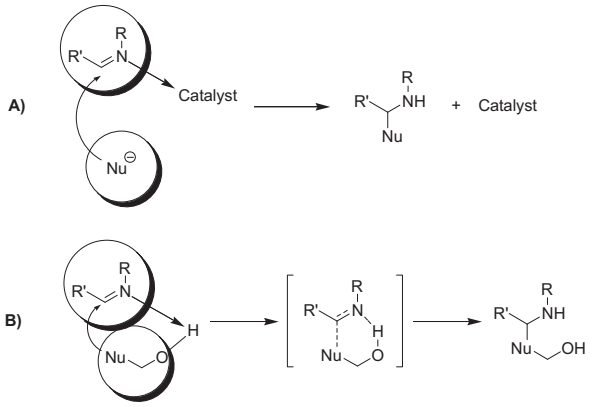
- A self-catalytic reaction: the process would be pseudo-intramolecular, which would be entropically favored and allow for the reaction to occur without added catalyst.
- A solvent-free reaction: a self-catalytic reaction would require the starting materials to come within close proximity to each other. Solvent-free conditions should enhance the yield.
- Added reactivity in water: the hydrophobic effect of the water on the starting reagents should lead to further enhanced yields by decreasing the volume change of activation.

In this case, the reaction could become self-catalytic by allowing a hydroxyl group on a naphthol to act as a catalyst and bind the nitrogen in an imine, which would then generate the product through an aza-Friedel–Crafts reaction in the absence of added Brønsted or Lewis acid catalyst (Scheme 1).[7b,9]

The aza-Friedel–Crafts reaction is a popular method used to synthesize numerous nitrogen-containing molecules. A variation of the Friedel–Crafts reaction,[10] it is generally known as an atom-economical way to form a carbon–carbon bond through the addition of an electron-rich arene to an imine and often involves the use of a stoichiometric or catalytic amount of Brønsted acid,[11] Lewis acid[12] or organocatalyst,[13] as well as organic solvents. Recent examples of aza-Friedel–Crafts reactions in literature often involve

* Corresponding author.
E-mail address: cj.li@mcgill.ca (C.-J. Li).

0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.11.008



Scheme 1. Typical Lewis or Brønsted acid catalyzed system (Path A) versus the proposed self-catalytic system (Path B).

the addition of indoles to imino esters of glyoxylates,[14] or other imines,[15] as well as other, more specific reactions.[16] These reactions however, generally take place in organic solvents. Some work on Friedel–Crafts reactions has been done in water,[3e] namely the addition of indoles to glyoxylates[17] and alkenes[18]; however there are few examples of aza-Friedel–Crafts reactions in water.[19] Examples in literature have also shown that the C=N double bond of 3,4-dihydroisoquinolines is susceptible to nucleophilic attack by strong electrophiles,[20] and there are also examples of the addition of naphthol to imines formed in situ.[21] Herein, we provide further details on the synthesis of 1-naphthoyl tetrahydroisoquinolines under solvent-free conditions, in the absence of added catalyst. In addition we describe the synthesis and expanded scope of the same reaction in water. The reaction occurred with 100% atom economy in the absence of added catalyst.

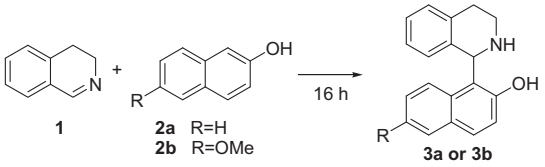
2. Results and discussion

2.1. Reactions under solvent-free conditions

Our study began with the reaction between 3,4-dihydroisoquinoline (**1**) and 2-naphthol (**2a**), in the absence of catalyst under various conditions. Performing the reaction under neat conditions at 60 °C led to the optimal yield (Table 1, entry 1). In addition, carrying out the reaction in air did not lead to a substantial reduction in yield. However, when 6-methoxy-2-naphthol (**2b**) was used as a substrate, executing the reaction under neat conditions at 90 °C, as opposed to 60 °C, led to a higher yield (Table 1, entry 9). Furthermore, reacting 2-naphthol and 6-methoxy-2-naphthol in a variety of organic solvents consistently resulted in much lower yields (Table 1, entries 4–6 and 12–16). It should also be noted that both substrates provided their corresponding products when the reaction took place in degassed water, albeit in lower yields than under neat conditions (Table 1, entries 7 and 17). To fully appreciate the scope of the neat conditions however, we continued our investigation into the synthesis of these molecules by performing the reactions under neat conditions.

Reacting 1-naphthol (**2g**) with 3,4-dihydroisoquinoline (**1**) under neat conditions resulted in attaining product **3g** as a single regioisomer in 92% yield. We believe that this regioselectivity can be explained as the result of a six-membered cyclic transition state, which can re-aromatize to yield product **3g**. This result also indirectly validates our original hypothesis in Scheme 2. The optimized conditions were applied to various naphthols to yield a series of THIQNOL® analogs to evaluate the scope and limitations of this reaction. These results are illustrated in Table 2. Not

Table 1
Optimization of reaction conditions[a]

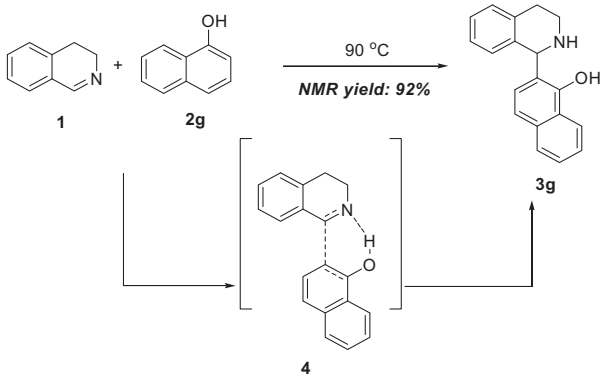


1 **2a** R=H **2b** R=OMe **3a or 3b**

Entry	2	Solvent[b]	Temperature (°C)	Yield[c] (%)
1	**2a**	Neat	60	92 (87)
2	**2a**	Neat	90	83
3	**2a**	Neat	90[d]	66
4	**2a**	Toluene	60	41
5	**2a**	THF	60	6
6	**2a**	Dichloroethane	60	20
7	**2a**	Water	60	70
8	**2a**	Neat	25	HP
9	**2b**	Neat	60	62
10	**2b**	Neat	90	84
11	**2b**	Neat	120	dec
12	**2b**	Methanol	60	12
13	**2b**	Acetonitrile	60	16
14	**2b**	Dichloromethane	Reflux	NR
15	**2b**	Diethyl ether	Reflux	NR
16	**2b**	Nitromethane	60	9
17	**2b**	Water	60	65

[a] Condition: 3,4-dihydroisoquinoline (1.0 mmol) and naphthol (1.0 mmol).
[b] When solvent was used, 3 mL solvent was used.
[c] NMR yields were determined by NMR by using an internal standard; isolated yields is given in parentheses.
[d] Under microwave conditions.

surprisingly, the presence of electron-withdrawing substituents on the naphthol ring resulted in lower yields (Table 2, entries 7–10) as compared to the excellent yields naphthols with electron-donating substituents provided (Table 2, entries 1–6). However, it must be noted that owing to the heavier molecular weight of the electron-withdrawing naphthols, there was proportionally more solid present in the corresponding reactions. This made the reaction more inefficient because the reactants were not able to be properly mixed before the solid product, which inhibited the stirring, was generated.

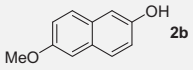
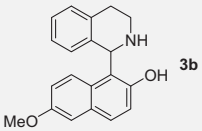
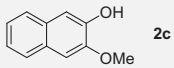
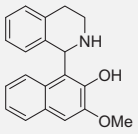
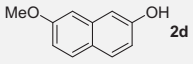
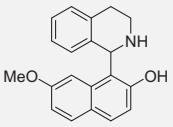
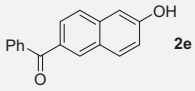
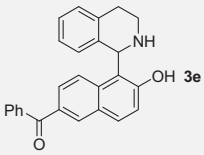
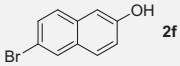
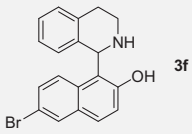
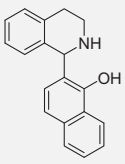


Scheme 2. Hydrogen-bonding assisted C–C bond formation.

2.2. Reactions on water

While attempting to expand the scope of this reaction, we found that 3-hydroxy-2-naphthoic acid (**2h**) would not react with 3,4-dihydroisoquinoline (**1**) under the solvent-free conditions. Initially, this result was unsurprising due to the strongly electron-withdrawing nature of the substrate. We then reduced[22] the substrate to obtain the corresponding dialcohol, 3-hydroxymethyl-2-naphthol (**2i**) and once again attempted the reaction. Under neat conditions,

Table 2
Self-catalytic reactions between 3,4-dihydroisoquinoline and naphthols[a]

Entry	2	Product	Yield[b] (%)
1	 2b	 3b	62
2			84[c]
3	 2c	 3c	81
4			60[d]
5	 2d	 3d	91
6			97[c]
7	 2e	 3e	54
8			12[c]
9	 2f	 3f	32
10			45[d]
11	 2g	 3g	73
12			92[c]

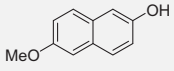
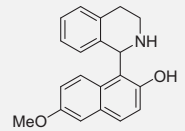
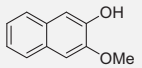
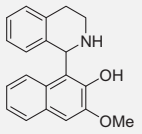
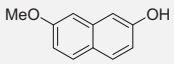
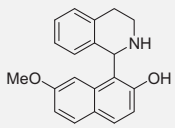
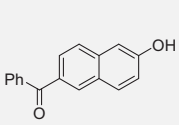
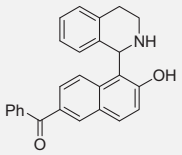
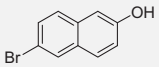
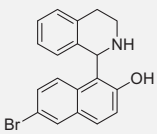
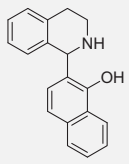
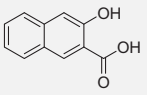
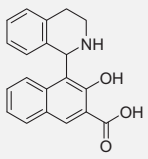
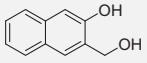
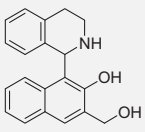
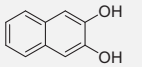
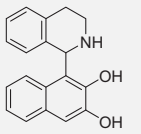
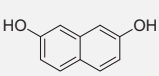
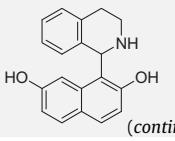
[a] Conditions: 3,4-dihydroisoquinoline (1.0 mmol), naphthol (1.0 mmol), at 60 °C; otherwise noted.
[b] Determine by NMR spectroscopy by using an internal standard.
[c] At 90 °C.
[d] At 90 °C; isolated yield after crystallization.

at both 60 °C and 90 °C, the reaction failed to react and produce the desired product.

Operating under our previous assumptions about this type of reaction, we decided to attempt the above reactions in degassed water, hoping that a hydrophobic effect of the water on the starting materials would lead to better reactivity. Gratifyingly, we found that both substrates produced their corresponding products in excellent yields when the reaction was performed at 80 °C. With our hypothesis confirmed, we then decided to determine if performing this reaction with water as solvent with the previously used naphthols would lead to different results, more specifically, if we could use water to increase the yield of the electron-withdrawing substituted naphthols.

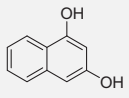
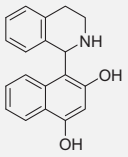
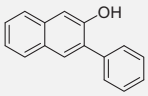
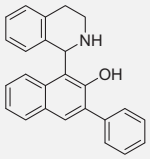
We were pleased to discover that water did indeed provide an increase in the yield of all substrates, resulting in excellent yields as seen in Table 3. When electron-withdrawing substituents are present (Table 3, entries 4 and 5), the yields are still somewhat lower, however they are much higher than when performed neat. Dihydroxy-substituted naphthalene rings were also used as substrates, yielding good amounts of products (Table 3, entries 9–12). These substrates previously gave a mixture of products, which we were unable to separate when they had been used under the neat conditions. Interestingly, when 2,3-dihydroxynaphthalene (**2j**) was reacted with 2 equiv of 3,4-dihydroisoquinoline, the product only

Table 3
Self-catalytic reactions between 3,4-dihydroisoquinoline and naphthols[a]

Entry	2	Product	Yield[b] (%)
1	 2b	 3b	89
2	 2c	 3c	100
3	 2d	 3d	95
4	 2e	 3e	75
5	 2f	 3f	85
6	 2g	 3g	96
7	 2h	 3h	83
8	 2i	 3i	90
9	 2j	 3j	76
10			89[c]
11	 2k	 3k	72

(*continued on next page*)

Table 3 (*continued*)

Entry	2	Product	Yield[b] (%)
12	 **2l**	 **3l**	86
13	 **2m**	 **3m**	71

[a] Conditions: 3,4-dihydroisoquinoline (1.2 mmol), naphthol (1.0 mmol), at 80 °C; otherwise noted.
[b] Isolated yield.
[c] 2 equiv 3,4-dihydroisoquinoline used.

incorporated 1 equiv. There was no evidence of product **3j** undergoing further reaction with the second equivalent of 3,4-dihydroisoquinoline. In addition, we investigated the effect of a catalytic amount of external Brønsted acid on the reaction. In the presence of 10 mol % of HCl, H_3PO_4 or HOAc, the yields as shown by ^{1}H NMR of the crude reaction mixture were similar to the results that we obtained in the absence of such protonic acids (Table 3, entry 1).

As neither the starting materials nor products are significantly soluble in water, a hydrophobic effect is the most likely explanation for these increased yields[23]; the nearly insoluble hydrophobic starting materials are brought closer together by the water, which increases the efficiency of the reaction by decreasing the volume change of activation.

3. Conclusions

By using an aza-Friedel–Crafts reaction the direct addition of a variety of naphthols to 3,4-dihydroisoquinoline was achieved to yield THIQNOL derivatives with 100% atom economy in the absence of added catalyst. These reactions were first accomplished under neat conditions with good yields. This reaction was then improved upon by performing the reaction in water, resulting in excellent yields and an expanded scope, most likely due to a hydrophobic effect. Isolation of the products is simple due to the absence of added catalyst. In essence, we have shown that by using the functionalities of starting materials, we can design a reaction to be self-catalytic, which in turn is enhanced by the solvent-free conditions or the use of water as solvent. Such a design provides a prototype for other potential reactions.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded on Varian 300 and 400 MHz spectrometers and the chemical shifts were reported in parts per million (δ) relative to internal standard TMS (0 ppm) for $CDCl_3$ or internal solvent signal (2.49 ppm) for DMSO. The peak patterns are indicated as follows: s, singlet; br s, broad singlet; d, doublet; t, triplet; dt, doublet of triplet; dq, doublet of quartet; ddd, doublet of doublet of doublet; dtd, doublet of triplet of doublet; m, multiplet; q, quartet; dq, doublet of quartet. The coupling constants, *J*, are reported in hertz (Hz). ^{13}C NMR spectra were obtained at 75 and 100 MHz spectrometers and referenced to the internal solvent signals (central peak is 77.0 ppm in $CDCl_3$ or 39.5 ppm in DMSO). HRMS were obtained by Kratos MS25RFA Mass Spectrometer. IR spectra were recorded by an ABB Bomem MB100 instrument. Melting points were recorded by Melting Point Apparatus, Gallenkamp. All reagents were weighed and handled in air at room temperature. All reagents were purchased from Aldrich and were used without further purification.

4.1.1. General procedure for reactions under neat conditions. Unless otherwise noted, the corresponding naphthol derivative (1.0 mmol) was placed in a flask under nitrogen and to it was added 3,4-dihydroisoquinoline[20c] (1.0 mmol). The resulting mixture was stirred for 16 h at 60 °C, whereupon no liquid remained. The resulting mixture was recrystallized from chloroform and hexane and collected to give the desired product **3**.

*4.1.2. 1-(1,2,3,4-Tetrahydroisoquinolin-1-yl)-naphthalen-2-ol (**3a**).* Mp 148–150 °C; IR (KBr pellet): ν_{max} 3289, 3056, 3018, 2954, 2921, 2886, 2834, 1622, 1597, 1462, 1230, 807, 738 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.01 (d, *J*=8.8 Hz, 1H), 7.79 (d, *J*=7.6 Hz, 1H), 7.49 (t, *J*=8.4 Hz, 1H), 7.33 (t, *J*=7.6 Hz, 1H), 7.11–7.05 (m, 3H), 6.87–6.83 (m, 1H), 6.61 (d, *J*=7.6 Hz, 1H), 6.03 (s, 1H), 3.45–4.40 (m, 1H), 3.30–3.12 (m, 2H), 2.89 (d, *J*=14 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) 155.8, 149.7, 136.2, 133.8, 129.6, 128.8, 128.6, 126.9, 126.9, 126.6, 126.2, 122.5, 121.3, 120.2, 55.7, 44.0, 29.4; MS (EI) *m*/*z* (%) 275 (M^+, 100), 258, 229, 215; HRMS Calcd for $C_{19}H_{17}NO$: 275.1310; found: 275.1307.

*4.1.3. 6-Methoxy-1-(1,2,3,4-tetrahydroisoquinolin-1-yl)-naphthalen-2-ol (**3b**).* Mp 148–151 °C; IR (KBr pellet) ν_{max} 3315, 2963, 2932, 2835, 1601, 1517, 1384, 1366, 1246, 1160, 1034, 866 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.92 (d, *J*=9.6 Hz, 1H), 7.61 (d, *J*=9.2 Hz, 1H), 7.17–7.02 (m, 5H), 6.87–6.83 (m, 1H), 6.59 (d, *J*=8.0 Hz, 1H), 5.97 (s, 1H), 3.92 (s, 3H), 3.48–3.44 (m, 1H), 3.32–3.15 (m, 2H), 2.89 (d, *J*=14.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 155.0, 153.9, 136.1, 133.8, 129.0, 128.5, 128.2, 126.8, 126.5, 126.1, 122.9, 120.5, 119.2, 118.5, 107.0, 55.8, 55.3, 43.9, 29.4; MS (EI) *m*/*z* (%) 305 (M^+, 100), 288, 261, 125, 174, 151, 131; HRMS Calcd for $C_{20}H_{19}NO_2$: 305.1416; found: 305.1418.

*4.1.4. 3-Methoxy-1-(1,2,3,4-tetrahydroisoquinolin-1-yl)-naphthalen-2-ol (**3c**).* Mp 154–156 °C; IR (KBr pellet) ν_{max} 3284, 3060, 2970, 2933, 2833, 1456, 1423, 1322, 1256, 1119, 745 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.95 (d, *J*=8.4 Hz), 7.72 (d, *J*=8.4 Hz), 7.40–7.30 (m, 2H), 7.11–7.05 (m, 3H), 6.87–6.84 (m, 1H), 6.63 (d, *J*=7.6 Hz, 1H), 6.05 (s, 1H), 3.94 (s, 3H), 3.54–3.50 (m, 1H), 3.35–3.20 (m, 2H), 2.90 (d, *J*=14.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ 149.6, 148.1, 142.8, 136.0, 133.9, 128.6, 128.4, 127.5, 127.0, 126.7, 126.2, 124.6, 123.2, 121.2, 119.0, 106.6, 55.7, 55.6, 43.8, 29.3; MS (EI) *m*/*z* (%) 305 (M^+), 288, 174, 159, 131 (100); HRMS Calcd for $C_{20}H_{19}NO_2$: 305.1416; found: 305.1412.

*4.1.5. 7-Methoxy-1-(1,2,3,4-tetrahydroisoquinolin-1-yl)-naphthalen-2-ol (**3d**).* Mp 126–130 °C; IR (KBr pellet) ν_{max} 3527, 3286, 2990, 2961, 2889, 2837,1622, 1517, 1482, 1387, 1221, 1135, 1032, 829 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.68 (d, *J*=8.4 Hz, 1H), 7.62 (d, *J*=8.4 Hz, 1H), 7.27 (d, *J*=2 Hz, 1H), 7.10–7.09 (m, 2H), 7.01–6.98 (m, 1H), 6.92–6.87 (m, 2H), 6.67 (d, *J*=8.0 Hz, 1H), 5.91 (s, 1H), 3.86 (s, 3H), 3.52–3.49 (m, 1H), 3.31–3.23 (m, 2H), 2.87 (d, *J*=14.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 158.6, 156.4, 136.2, 134.5, 133.8, 130.3, 129.4, 128.6, 126.8, 126.6, 126.2, 123.6, 117.5, 114.5, 100.7, 55.9, 44.0, 29.4; MS (EI) *m*/*z* (%) 305 (M^+), 288, 174, 131 (100); HRMS Calcd for $C_{20}H_{19}NO_2$: 305.1416; found: 305.1413.

*4.1.6. [6-Hydroxy-5-(1,2,3,4-tetrahydroisoquinolin-1-yl)-naphthalen-2-yl]-phenyl-methanone (**3e**).* Addition of 6-benzoyl-2-naphthol (0.2 mmol) to 3,4-dihydroisoquinoline (0.2 mmol). Mp 138–142 °C; IR (KBr pellet) ν_{max} 3034, 1685, 1654, 1609, 1559, 1473,

1355, 1283, 1243, 1210, 1141, 721 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.25 (s, 1H) 8.13 (d, J=8.8 Hz, 1H), 8.04 (d, J=10.8 Hz, 1H), 7.89 (d, J=8.0 Hz, 2H), 7.80 (d, J=9.2 Hz, 1H), 7.65–7.61 (m, 1H), 7.60–7.52 (m, 2H), 7.17–7.12 (m, 3H), 6.95–6.91 (m, 1H), 6.62 (d, J=8.00 Hz, 1H), 6.10 (s, 1H), 3.59–3.55 (m, 1H), 3.39–3.27 (m, 2H), 2.93 (d, J=12.8 Hz, 1H), 2.76 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 196.2, 158.4, 138.0, 136.0, 133.8, 133.3, 132.0, 131.5, 131.4, 129.8, 128.7, 128.2, 126.9, 126.8, 126.3, 121.7, 121.1, 119.0, 118.4, 109.5, 55.7, 43.9, 29.3; MS (EI) m/z (%) 379 (M^+), 248, 171 (100), 131; HRMS Calcd for $C_{26}H_{21}NO_2$: 379.1572; found: 379.1563.

*4.1.7. 6-Bromo-1-(1,2,3,4-tetrahydroisoquinolin-1-yl)-naphthalen-2-ol (**3f**).* Washed with $CHCl_3$ for purification. Mp 168–170 °C; IR (KBr pellet) ν_{max} 3047, 3018, 2401, 1612, 1586, 1495, 1451, 1362, 1259, 1237, 1212, 1151, 1023, 957, 863 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.94 (d, J=2.0 Hz, 1H), 7.88 (d, J=8.8 Hz, 1H), 7.61 (d, J=8.4 Hz, 1H), 7.55 (dd, 1H, J=2.0, 9.0 Hz), 7.14–7.07 (m, 3H), 6.90–6.86 (m, 1H), 6.54 (d, J=7.6 Hz, 1H), 5.98 (s, 1H), 3.56–3.52 (m, 1H), 3.36–3.22 (m, 2H), 2.90 (d, J=14.4 Hz, 1H), 2.69 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ 156.2, 135.8, 133.9, 131.9, 130.6, 130.0, 129.4, 128.8, 128.7, 126.8, 126.7, 126.3, 123.2, 121.4, 118.3, 116.0, 55.8 44.0, 29.3; MS (EI) m/z (%) 353 (M^+, 100) 324, 309, 257, 228, 132; HRMS Calcd for $C_{19}H_{16}NO^{79}Br$: 353.0415; found: 353.0407; HRMS Calcd for $C_{19}H_{16}NO^{81}Br$: 355.0395; found: 355.0403.

*4.1.8. 2-(1,2,3,4-Tetrahydroisoquinolin-1-yl)-naphthalen-1-ol (**3g**).* Mp 117–120 °C; IR (KBr pellet): ν_{max} 3305, 3050, 3015, 2950, 2915, 1577, 1491, 1456, 1390, 1121, 1085, 805 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.18 (d, J=8.4 Hz, 1H), 7.75 (d, J=7.6 Hz, 1H), 7.40–7.33 (m, 2H), 7.29 (d, J=8.4 Hz, 1H), 7.14–7.11 (m, 1H), 7.08–7.03 (m, 2H), 6.97–6.93 (m, 1H), 6.81 (d, J=8.0 Hz, 1H), 5.11 (s, 1H), 3.19–3.14 (m, 1H), 3.09–3.01 (m, 1H), 2.96–2.90 (m, 1H), 2.74–2.69 (m, 1H); ^{13}C NMR ($CDCl_3$, MHz, ppm) δ 152.8, 136.0, 133.8, 133.7, 128.8, 127.4, 127.4, 127.1, 126.6, 126.0, 125.8, 125.5, 124.7, 122.1, 119.4, 117.7, 60.8, 42.2, 29.0; MS (EI) m/z (%) 275 (M^+, 100), 258, 229, 215, 144, 132; HRMS Calcd for $C_{19}H_{17}NO$: 275.1310; found: 275.1307.

4.2. General procedure for reactions in water

Unless otherwise noted, 3,4-dihydroisoquinoline (0.2 mmol) and the corresponding naphthol (0.2 mmol) were placed under nitrogen atmosphere and degassed water (0.4 mL) was added to the capped vessel. The reaction mixture was heated to 80 °C and stirred overnight. The resulting solids were filtered by vacuum, washed with diethyl ether, and dried in a 60 °C oven.

*4.2.1. 3-Hydroxy-4-(1,2,3,4-tetrahydroisoquinolin-1-yl)-2-naphthoic acid (**3h**).* Addition of 3-hydroxy-2-naphthoic acid (0.5 mmol) to 3,4-dihydroisoquinoline (0.5 mmol) in 1.0 mL water. Mp 180–181 °C; IR (solid): ν_{max} 3019, 1660, 1622, 1592, 1454, 1362, 1336, 1256, 993, 736 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 9.54 (br s, 1H), 9.09 (br s, 1H), 8.41 (s, 1H), 7.93 (d, J=8.0 Hz, 1H), 7.52 (m, 1H), 7.27–7.16 (m, 3H), 7.02–6.98 (m, 1H), 6.48 (d, J=7.6 Hz, 1H), 6.40 (br s, 1H), 3.63–3.53 (m, 2H), 3.38–3.29 (m, 2H), 3.05 (d, J=16.4 Hz, 1H); ^{13}C NMR (DMSO, 75 MHz, ppm) 169.7, 161.2, 135.3, 134.1, 132.2, 131.9, 130.1, 128.4, 128.3, 126.9, 126.7, 125.4, 125.1, 121.6, 121.5, 120.8, 113.1, 53.3, 41.6, 25.6; HRMS Calcd for $C_{20}H_{18}NO_3$: 320.1281; found: 320.1282.

*4.2.2. 3-(Hydroxymethyl)-1-(1,2,3,4-tetrahydroisoquinolin-1-yl)-naphthalen-2-ol (**3i**).* Addition of 3-(hydroxymethyl)naphthalen-2-ol (1.7 mmol) to 3,4-dihydroisoquinoline (1.7 mmol) in 2.5 mL water. Mp 154–157 °C; IR (solid): ν_{max} 2951, 1622, 1495, 1451, 1410, 1366, 1262, 1251, 1178, 1008, 746 cm^{-1}; ^1H NMR (DMSO, 400 MHz, ppm) δ 8.10 (d, J=8.8 Hz, 1H), 7.84–7.80 (m, 2H), 7.49–7.45 (m, 1H), 7.28 (t, J=7.2 Hz, 1H), 7.14 (d, J=7.2 Hz, 1H), 7.07 (t, J=7.2 Hz, 1H), 6.88–6.84 (m, 1H), 6.47 (d, J=7.6 Hz, 1H), 6.00 (s, 1H), 5.09 (s, br, 1H), 4.57–4.47 (m, 2H), 3.37–3.33 (m, 2H), 3.16–3.04 (m, 2H), 2.83 (d, J=13.6 Hz, 1H); ^{13}C NMR (DMSO, 75 MHz, ppm) δ 153.8, 137.1, 134.4, 132.5, 132.3, 128.6, 128.3, 127.3, 126.4, 126.2, 126.1, 125.8, 124.9, 122.2, 121.6, 118.1, 58.5, 54.5, 42.5, 28.8; HRMS Calcd for $C_{20}H_{20}NO_2$: 306.1489; found: 306.1491.

*4.2.3. 1-(1,2,3,4-Tetrahydroisoquinolin-1-yl)naphthalene-2,3-diol (**3j**).* Mp 162–166 °C; IR (solid): ν_{max} 3261, 1510, 1455, 1424, 1254, 1243, 1176, 945, 748 cm^{-1}; ^1H NMR (DMSO, 400 MHz, ppm) δ 7.97 (d, J=8.4 Hz, 1H), 7.61 (dd, J=8.4, 1.2 Hz, 1H), 7.30–7.26 (m, 1H), 7.20 (td, J=8.0, 1.2 Hz, 1H), 7.15 (d, J=6.8 Hz, 1H), 7.09–7.06 (m, 2H), 6.90–6.86 (m, 1H), 6.38 (d, J=8.0 Hz, 1H), 5.98 (s, 1H), 3.40–3.35 (m, 1H), 3.14–3.09 (m, 2H), 2.90–2.84 (m, 1H); ^{13}C NMR (DMSO, 75 MHz, ppm) δ 148.3, 147.3, 137.0, 134.2, 128.5, 128.0, 127.9, 126.5, 126.4, 126.2, 125.8, 123.4, 122.3, 121.5, 118.8, 109.0, 54.5, 42.3, 28.6; HRMS Calcd for $C_{19}H_{18}NO_2$: 292.1332; found: 292.1330.

*4.2.4. 1-(1,2,3,4-Tetrahydroisoquinolin-1-yl)naphthalene-2,7-diol (**3k**).* Mp 150–153 °C; IR (solid): ν_{max} 3293, 3285, 1618, 1471, 1350, 1220, 1198, 1135, 838 cm^{-1}; ^1H NMR (DMSO, 400 MHz, ppm) δ 9.62 (br s, 1H), 7.65 (d, J=8.8 Hz, 1H), 7.59 (d, J=8.4 Hz, 1H), 7.30 (s, 1H), 7.14 (d, J=7.2 Hz, 1H), 7.08 (t, J=7.2 Hz, 1H), 6.91–6.86 (m, 2H), 6.71 (d, J=8.4 Hz, 1H), 6.54 (d, J=8.0 Hz, 1H), 5.74 (s, 1H), 4.28 (br s, 1H), 3.37–3.33 (m, 1H), 3.15–3.00 (m, 2H), 2.82 (d, J=14.4 Hz, 1H); ^{13}C NMR (DMSO, 75 MHz, ppm) δ 156.3, 156.1, 137.2, 135.0, 134.4, 130.1, 128.9, 128.6, 126.3, 126.1, 125.8, 122.5, 117.5, 116.2, 114.6, 103.8, 54.8, 42.9, 28.9; HRMS Calcd for $C_{19}H_{18}NO_2$: 292.1332; found: 292.1331.

*4.2.5. 4-(1,2,3,4-Tetrahydroisoquinolin-1-yl)naphthalene-1,3-diol (**3l**).* Mp 173–175 °C; IR (solid): ν_{max} 2908, 1570, 1502, 343, 1163, 1082, 725 cm^{-1}; ^1H NMR (DMSO, 400 MHz, ppm) δ 10.1 (br s, 1H), 7.83 (d, J=8.4 Hz, 1H), 7.53 (d, J=8.0 Hz, 1H), 7.31–7.27 (m, 1H), 7.13–7.05 (m, 3H), 6.97 (t, J=7.2 Hz, 1H), 6.90 (d, J=8.0 Hz, 1H), 6.72 (s, 1H), 5.68 (s, 1H), 3.37–3.33 (m, 2H), 3.14–3.06 (m, 1H), 2.98–2.91 (m, 1H), 2.79 (d, J=15.2 Hz, 1H); ^{13}C NMR (DMSO, 75 MHz, ppm) δ 154.4, 154.1, 137.2, 134.2, 134.1, 128.4, 127.0, 126.2, 126.0, 125.8, 125.4, 121.8, 121.2, 120.3, 113.6, 99.5, 53.1, 42.5, 28.8. HRMS Calcd for $C_{19}H_{18}NO_2$: 292.1332; found: 292.1333.

*4.2.6. 3-Phenyl-1-(1,2,3,4-tetrahydroisoquinolin-1-yl)naphthalen-2-ol (**3m**).* Mp 135–138 °C; IR (solid): ν_{max} 3288, 1623, 1455, 1425, 1259, 1116, 767 cm^{-1}; ^1H NMR (DMSO, 400 MHz, ppm) δ 12.40 (br s, 1H), 8.04 (d, J=8.4 Hz, 1H), 7.84 (d, J=8.4 Hz, 1H), 7.79 (s, 1H), 7.59 (d, J=7.6 Hz, 1H), 7.53–7.50 (m, 1H), 7.41–7.29 (m, 4H), 7.12–7.11 (m, 2H), 6.94–6.90 (m, 1H), 6.71 (d, J=8.0 Hz, 1H), 6.11 (s, 1H), 3.55–3.49 (m, 1H), 3.34–3.23 (m, 2H), 2.88 (d, J=13.6 Hz, 1H); ^{13}C NMR (DMSO, 75 MHz, ppm) δ 154.0, 142.8, 128.4, 136.2, 134.0, 133.0, 132.6, 129.9, 129.6, 129.0, 128.7, 128.1, 127.9, 127.1, 127.1, 126.9, 126.7, 126.2, 122.9, 121.2, 118.6, 55.8, 43.8, 29.3 HRMS Calcd for $C_{25}H_{22}NO$: 352.1696; found: 352.1697.

Acknowledgements

This work was supported by the Canada Research Chair (Tier I) Foundation (C.-J.L.), the Canada Foundation for Innovation, Natural Sciences and Engineering Research Council (Canada), the ACS-GCI Pharmaceutical Roundtable, and McGill University.

References and notes

1. Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University: New York, NY, 1998.
2. (a) Tanaka, T. *Solvent-free Organic Synthesis*; Wiley-VCH: Weinheim, 2003; (b) Cave, G. W. V.; Raston, C. L.; Scott, J. L. *Chem. Commun.* **2001**, 2159–2169.
3. For reviews on chemistry in water: (a) *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blacky Academic and Professional: London, 1998; (b) Li, C.-J.; Chan, T.-H.

Organic Reactions in Aqueous Media; John Wiley: New York, NY, 1997; (c) Lindstrom, U. M. *Chem. Rev.* **2002**, *102*, 2751–2772; (d) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023–2035; (e) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095–3166; (f) Herrerías, C. I.; Yao, X.; Li, Z.; Li, C.-J. *Chem. Rev.* **2007**, *107*, 2546–2562.

4. (a) Seddon, K. R. *J. Chem. Technol. Biotechnol.* **1997**, *68*, 351–356; (b) Holbrey, J. D.; Seddon, K. R. *Clean Technol. Environ. Policy* **1999**, *1*, 223–236; (c) Welton, T. *Chem. Rev.* **1999**, *99*, 2071–2084; (d) Dzyuba, S. V.; Bartsch, R. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 148–150; (e) Leitner, W. *Acc. Chem. Res.* **2002**, *35*, 746–756; (f) Jessop, P. G.; Ikariya, T.; Noyori, R. *Science* **1995**, *269*, 1065–1069.
5. (a) Trost, B. M. *Science* **1991**, *254*, 1471–1477; (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259–281.
6. Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40–49.
7. (a) Li, Z.; Bohle, D. S.; Li, C.-J. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 8928–8933; (b) Li, C. -J.; McLeod, P.; Li, Z.; Feng, J. U.S. Patent WO 2007098608, 2007.
8. For other references from our group on CDC reaction, see: (a) Li, Z.; Li, C.-J. *Eur. J. Org. Chem.* **2005**, 3173–3176; (b) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 6968–6969; (c) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 3672–3673; (d) Li, Z.; Li, C.-J. *Org. Lett.* **2004**, *6*, 4997–4999; (e) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2006**, *128*, 56–57; (f) Li, Z.; MacLeod, P. D.; Li, C.-J. *Tetrahedron: Asymmetry* **2006**, *17*, 590–597.
9. MacLeod, P. D.; Li, Z.; Feng, J.; Li, C.-J. *Tetrahedron Lett.* **2006**, *47*, 6791–6794.
10. For reviews on Friedel–Crafts reaction: (a) Olah, G. A. *Friedel–Crafts and Related Reactions*; Wiley: New York, NY, 1963; (b) Olah, G. A. *Friedel–Crafts Chemistry*; Wiley: New York, NY, 1973; (c) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550–556 and references therein; (d) Jørgensen, K. A. *Synthesis* **2003**, 1117–1125.
11. Selected examples: (a) Zeng, M.; Kang, Q.; He, Q.-L.; You, S.-L. *Adv. Synth. Catal.* **2008**, *350*, 2169–2173; (b) Wang, B.-Y.; Jiang, R.-S.; Li, J.; Shi, M. *Eur. J. Org. Chem.* **2005**, 4002–4008; (c) Zhou, W.; Xu, L.-W.; Yang, L.; Zhao, P.-Q.; Xia, C.-G. *J. Mol. Catal. A: Chem.* **2006**, *249*, 129–134; (d) Terada, M.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 292–293.
12. Selected examples: (a) Luo, Y.; Li, C.-J. *Chem. Commun.* **2004**, 1930–1931; (b) Chen, Y. J.; Ge, C.-S.; Wang, D. *Synlett* **2000**, 1429–1432; (c) Yamazaki, S.; Morikawa, S.; Iwata, Y.; Yamamoto, M.; Kuramoto, K. *Org. Biomol. Chem.* **2004**, *2*, 3134–3138; (d) Huang, J.-W.; Shi, M. *Tetrahedron Lett.* **2003**, *44*, 9343–9347.
13. (a) Dessole, G.; Herrera, R. P.; Ricci, A. *Synlett* **2004**, 2374–2378; (b) Török, B.; Abid, M.; London, G.; Esquibel, J.; Török, M.; Mhadgut, S. C.; Yan, P.; Prakash, S. G. K. *Angew. Chem., Int. Ed.* **2005**, *44*, 3086–3089.
14. (a) Huang, T.; Li, C.-J. *Tetrahedron Lett.* **2000**, *41*, 6715–6719; (b) Zhao, J.-L.; Liu, L.; Zhang, H.-B.; Wu, Y.-C.; Wang, D.; Chen, Y.-J. *Synlett* **2006**, 96–100; (c) Jiang, B.; Huang, Z.-G. *Synthesis* **2005**, 2198–2204; (d) Lei, F.; Chen, Y.-J.; Sui, Y.; Liu, L.; Wang, D. *Synlett* **2003**, 1160–1164.
15. (a) Enders, D.; Narine, A. A.; Toulgoat, F.; Bisschops, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5661–5665; (b) Esquivias, J.; Arrayás, R. G.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 629–633; (c) Johannsen, M. *Chem. Commun.* **1999**, 2233–2234; (d) Jia, Y.-X.; Xie, J.-H.; Duan, H.-F.; Wang, L.-X.; Zhou, Q.-L. *Org. Lett.* **2006**, *8*, 1621–1624; (e) Wang, Y.-Q.; Song, J.; Hong, R.; Li, H.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 8156–8157.
16. (a) Chen, Y.-J.; Ge, C.-S.; Wang, D. *Synlett* **2000**, 1429–1432; (b) Shirakawa, S.; Berger, R.; Leighton, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 2858–2859; (c) Malassene, R.; Toupet, L.; Hurvois, J.-P.; Moinet, C. *Synlett* **2002**, 895–898; (d) Sasamoto, N.; Dubs, C.; Hamashima, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2006**, *128*, 14010–14011.
17. Zhuang, W.; Jørgensen, K. A. *Chem. Commun.* **2002**, 1336–1337.
18. Manabe, K.; Aoyama, N.; Kobayashi, S. *Adv. Synth. Catal.* **2001**, *343*, 174–176.
19. Shirakawa, S.; Kobayashi, S. *Org. Lett.* **2006**, *8*, 4939–4942.
20. (a) Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341–3370; (b) Chrzanowska, M. *Tetrahedron: Asymmetry* **2002**, *13*, 2497–2500; (c) Pelletier, J. C.; Cava, M. P. *Synthesis* **1987**, 474–477.
21. (a) Betti, M. *Org. Synth.* **1941**, *1*, 381–410; (b) Betti, M. *Gazz. Chim. Ital.* **1907**, *36*, 392–395; (c) Szatmári, I.; Martinek, T. A.; Lázár, L.; Fülöp, F. *Tetrahedron* **2003**, *59*, 2877–2884; (d) Szatmari, I.; Martinek, T. A.; Lazar, L.; Koch, A.; Kleinpeter, E.; Neuvonen, K.; Fulop, F. *J. Org. Chem.* **2004**, *69*, 3645–3653; (e) Cardellicchio, C.; Ciccarella, G.; Naso, F.; Perna, F.; Tortorella, P. *Tetrahedron* **1999**, *55*, 14685–14692; (f) Dong, Y.; Li, R.; Lu, J.; Xu, X.; Wang, X.; Hu, Y. *J. Org. Chem.* **2005**, *70*, 8617–8620; (g) Wang, X.; Dong, Y.; Sun, J.; Xu, X.; Li, R.; Hu, Y. *J. Org. Chem.* **2005**, *70*, 1897–1900.
22. For reduction: Miller, L. E.; Hanneman, W. W.; John, W. L. S.; Smeby, R. R. *J. Am. Chem. Soc.* **1954**, *76*, 296–297.
23. (a) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159–164; (b) Fokin, V. V.; Sharpless, K. B. *Angew. Chem.* **2001**, *113*, 3563–3565; (c) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275–3279.