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Solvent-free direct aza-Friedel–Crafts reactions between 3,4-dihydroisoquinoline and 1- or 2-naphthols

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Abstract—A self-catalytic aza-Friedel–Crafts method was employed to generate 1-naphtholyl tetrahydroisoquinoline products under neat conditions. In addition, a derivative was prepared in its enantiomerically pure form and has shown moderate activity for asymmetric catalysis in the asymmetric diethylzinc addition to aldehydes.

The Friedel–Crafts reaction is an important reaction for C–C bond formation.[1] After over a century of development, it still attracts much research interest in both academia and industry. Brønsted acid- or Lewis acid-catalyzed imine or iminium Friedel–Crafts reactions (aza-Friedel–Crafts reactions) are important methods to construct a variety of nitrogen containing compounds.[2]

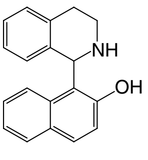
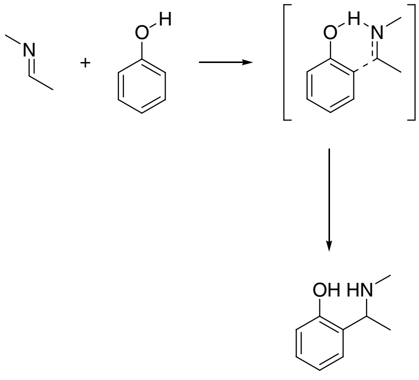
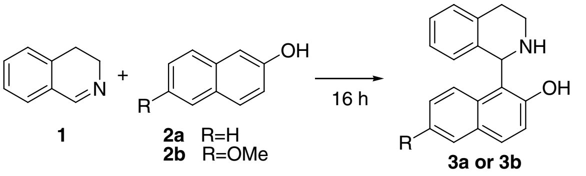


Figure 1. THIQNOL.



Scheme 1. Self-catalytic reaction between hydroxyl and imine.

Table 1. Optimization of reaction conditions[a]



Entry	2	Solvent[b]	Temperature (°C)	Yields[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	**2b**	Neat	25	NR
8	**2b**	Neat	60	62
9	**2b**	Neat	90	84
10	**2b**	Neat	120	Decomp'n
11	**2b**	Methanol	60	12
12	**2b**	Acetonitrile	60	16
13	**2b**	Dichloromethane	Reflux	NR
14	**2b**	Diethyl ether	Reflux	NR
15	**2b**	Nitromethane	60	9

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

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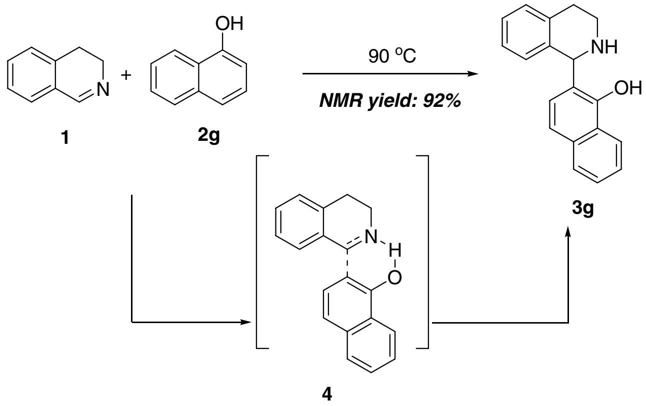
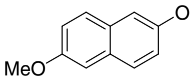
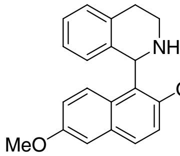
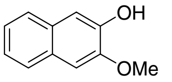
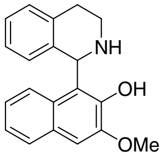
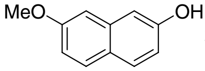
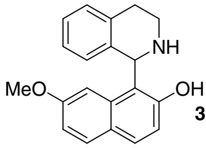
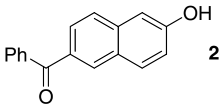
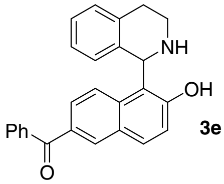
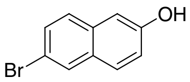
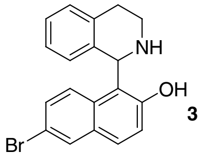
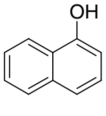
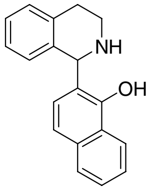


Scheme 2. The reaction of 3,4-dihydroisoquinoline and 1-napthol.

Recently, we have designed and synthesized a new class of chiral compounds, 1-naphtholyl tetrahydroisoquinolines, including the lead compound 1-(1,2,3,4-tetrahydroisoquinolin-1-yl)-naphthalen-2-ol (THIQNOL) (Fig. 1),[3,4] as potential chiral ligands for asymmetric synthesis and other applications.

In our initial report,[3] a cross-dehydrogenative-coupling (CDC)[5] was used to generate the corresponding chiral ligands. Alternatively, we also expected[4] that the compound could be formed through a Friedel–Crafts reaction.[6] We postulated that the hydroxyl group on 2-naphthol might act as a catalyst to bind the nitrogen in an imine and catalyze the reaction. In other words, the whole reaction is self-catalytic (Scheme 1). There-

Table 2. Self-catalytic reactions of 3,4-dihydroisoquinoline with 2-naphthols[a]

Entry	2	Product	Yield[b] (%)
1	 2b	 3b	62
2			84[c]
3			66[d]
4	 2c	 3c	81
5			60[e]
6	 2d	 3d	91
7			97[c]
8	 2e	 3e	54
9			12[c]
10	 2f	 3f	32
11			45[e]
12	 2g	 3g	73
13			92[c]

[a] Conditions: 3,4-dihydroisoquinoline (1.0 mmol), naphthol (1.0 mmol), at 60 °C; otherwise noted.

[b] Determined by NMR spectroscopy by using an internal standard.

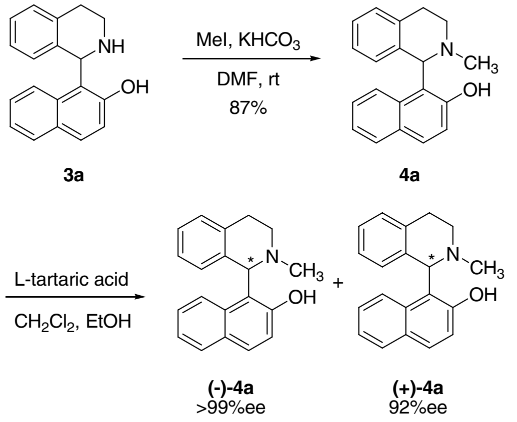
[c] At 90 °C.

[d] Water was used as solvent.

[e] At 90 °C; isolated yield after crystallization.

fore, the reaction might occur without any extra catalyst. Herein, we wish to report the synthesis of 1-naphtholyl tetrahydroisoquinolines directly by mixing the two starting materials in situ without any catalyst or solvent. The reaction proceeded with 100% 'atom economy'.[7]

To begin our study, 3,4-dihydroisoquinoline (**1**) was reacted with 2-naphthol (**2a**) under various conditions in the absence of any catalyst. After a series of experiments (Table 1), the reaction was found to proceed smoothly under neat conditions at 60 °C (Table 1, entry 1). The reaction could also be performed in air without a large reduction in yield. With 6-methoxy-2-naphthol (**2b**) being used as the substrate, the reaction gave a higher yield under neat conditions at 90 °C instead of 60 °C (Table 1, entry 9). The reaction of 2-naphthol and 6-methoxy-2-naphthol in various solvents all resulted in much lower yields (Table 1, entries 4–6 and 11–15).

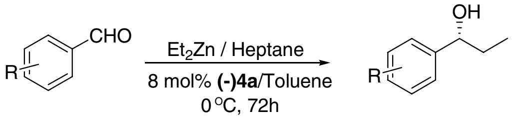


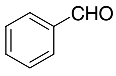
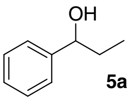
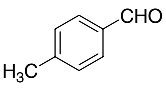
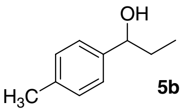
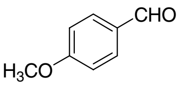
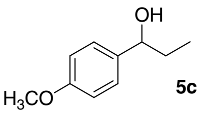
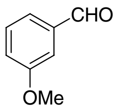
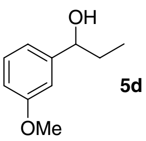
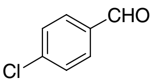
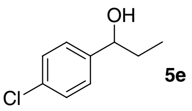
Scheme 3. Preparation of (−)-**4a**.

When 1-naphthol (**2g**) was reacted with 3,4-dihydroisoquinoline (**1**) under neat conditions, the desired product **3g** was obtained in 92% yield as a single regio-isomer. The regio-selectivity of the reaction was most likely the result of a 6-membered cyclic transition state **4**, which then gives the desired product **3g** after re-aromatization (Scheme 2). This experiment also provided an indirect validation of our initial hypothesis in Scheme 1.

With the optimized conditions in hand, various naphthols were subjected to the reaction to give a series of THIQNOL analogs. Representative results are listed in Table 2. A marked electronic effect was observed in the reaction: 2-naphthols with electron-donating substituents gave excellent yields (Table 2, entries 1–7, 12–13);

Table 3. Asymmetric addition of diethylzinc to aldehydes



Entry	2	Product	Yield[a] (%)	ee[b] (%)	Config[c]
1		 5a	72	69	*R*
2		 5b	85	53[d]	*R*
3		 5c	66	38	*R*
4		 5d	66	62	*R*
5		 5e	55	70	*R*

[a] Isolated yields.

[b] Determined by chiral HPLC.

[c] Configuration of the predominant enantiomer of the product.

[d] Run at room temperature for 24 h.

whereas 2-naphthols with electron-withdrawing substituents gave lower yields (Table 2, entries 8–11). These results are consistent with the proposed Friedel–Crafts-type mechanism of the reaction.

With the efficient method in hand, we attempted to synthesize THIQNOL derivatives asymmetrically. Initially, many catalytic systems were screened in an attempt to produce **3a** enantioselectively. Unfortunately, all these attempts failed to generate significant enantioselectivities. Consequently, various resolution methods were explored. A moderate enantiomeric excess (up to 58% ee) was obtained when using L-tartaric acid in dichloromethane as the resolution method. Unfortunately, it was found that enantiomerically enriched product **3a** racemized rapidly under weakly basic conditions.[8]

Subsequently, an attempt was made to obtain an optically active tertiary amine derivative of THIQNOL instead of the corresponding secondary amine present in the original THIQNOL. Compound **3a** was methylated with CH_3I in the presence of $KHCO_3$ to give **4a** in high yield. Fortunately, by using 0.5 equiv of L-tartaric acid in dichloromethane and ethanol, resolution of the two enantiomers of **4a** was achieved readily by filtering the diastereoisomeric tartaric acid salt. The less soluble salt was found to precipitate in an almost pure form. Then, hydrolysis of the less soluble salt gave (−)-**4a** in more than 99% enantiomeric excess (Scheme 3). On the other hand, workup of the solution generated (+)-**4a** in 92% ee.

With the optically-pure THIQNOL derivative in hand, its use as a chiral ligand for asymmetric reactions was examined briefly. THIQNOL (−)-**4a** was tested as a chiral catalyst in the addition of diethylzinc towards various aldehydes. The reaction gave the corresponding products in moderate yield and enantiomeric excess (Table 3). The *R* configuration was assigned by comparing the retention time of the major enantiomer with literature reports.[9]

In conclusion, we report here an efficient self-catalytic aza-Friedel–Crafts reaction between 3,4-dihydroisoquinoline and naphthols without any solvent or catalyst. The reaction generates various chiral THIQNOL derivatives. A method was developed to resolve the two enantiomers of a THIQNOL derivative. The enantiomerically pure derivative showed moderate catalytic activity and enantioselectivity in the asymmetric diethylzinc addition to aldehydes.

Acknowledgments

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