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# Mechanism and diastereoselectivity of the reactions between naphthols and imines

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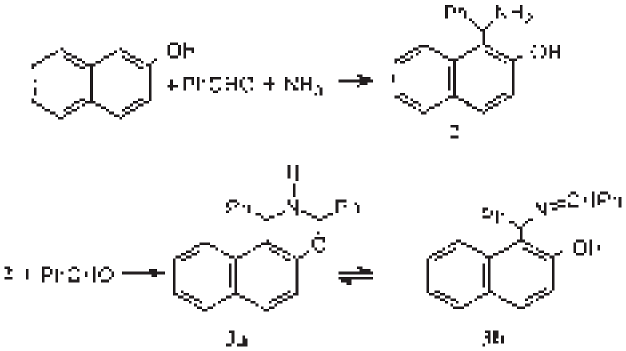
The mechanism of the title reactions involves a proton donor-acceptor interaction which is responsible also for the observed equilibration of diastereomers.

**Keywords:** diasteroselectivity, napthols, imines

Recently, the Betti reaction[2] has received renewed interest[3] and literature reports new investigations[4] for synthetic chiral purposes.[5] The original Betti reaction[2] was performed using β-naphthol (**1**), benzaldehyde and ammonia, (in the ratio 1:2:1) to obtain *N*-benzylidene-1-(α-aminobenzyl)-2-naphthol **3**, probably *via* **2**, which equilibrates in a ring-chain tautomerism[6] according to Scheme 1.



**Scheme 1**

Following treatment with HCl, **3** produces the base **2**.

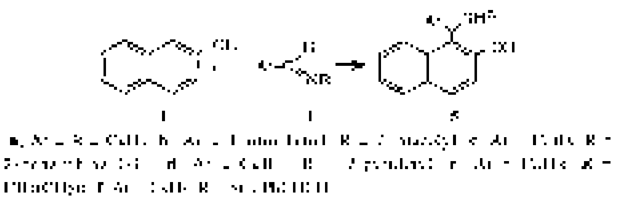
The Betti reaction is of interest for two reasons.

i) A C–C bond is formed under mild experimental conditions.
ii) There is the possibility of asymmetric induction which is of interest in synthetic chemistry.

We now report some mechanistic implications of the reactions between β-naphthol (**1**) and homocyclic, heterocyclic, aliphatic imines and with a chiral aldimine, (S)-*N*-benzylidene-1-phenylethanamine. This latter reaction produces optically pure amino-phenols, which are possible ligands in asymmetric synthesis.

## Results

When equimolar amounts of β-naphthol (**1**) and imines **4** are mixed in light petroleum or in $CH_2Cl_2$, compounds **5** are obtained, as shown in Scheme 2.[2] Table 1 reports the yields of **5**, and relevant experimental conditions.



**Scheme 2**

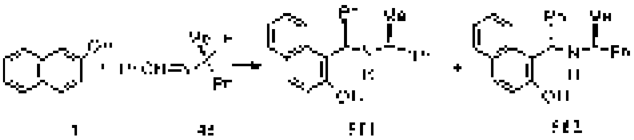
The reactions in Scheme 2 occur also in the presence of less than 0.5 equivalent (with respect to the reactants) of $CH_3SO_3H$. In the presence of more than 1 equivalent of $CH_3SO_3H$, no reaction was observed. The reaction of Scheme 1 has been attributed to base catalysis,[8] but we cannot confirm this statement.

Compound **5a** was also obtained[5] by mixing **1** and benzaldehyde with aniline (in the molar ratio 1:1:1). In this case, the yields of **5a** were slightly lower than that of the reaction carried out directly with **4a**.

The $^1$H NMR spectrum of the mixtures of **1**, aldehydes and amines (*i.e.* the precursors of the imines **4**) recorded at different reaction times, initially show an increase in signals related to imines **4**. These signals disappear at the end of the reaction.

Under the present experimental conditions, 2-methoxynaphthalene, sodium β-naphtholate (obtained from β-naphthol and NaH), α-bromo-β-naphthol, phenol, 4-methoxyphenol, 4-methylphenol, 3,5-dimethylphenol, were unreactive towards **4f**.

The reaction between **1** and **4f** produced high yields of the naphthyl derivatives **5f1** and **5f2** (Scheme 3).



**Scheme 3**

The reaction was carried out under different experimental conditions, and the main results are shown in Table 2.

For the reaction carried out in $CH_2Cl_2$ at room temperature, the diastereomeric ratio (at 95% of conversion) was 15:85. When the reaction was carried out at –20°C (entries 6, 6bis), the diastereomeric ratio was inverted: 60:40 both after 7 and 40 days (50% and 75% of conversion, respectively). It is noteworthy that the same reaction mixture (entry 6ter), stored for 7 days at room temperature showed the inverse diastereomeric ratio (40/60 at 84% of conversion).

Clearly, there is a kinetic control at low temperature and a re-equilibration (by thermodynamic control) at high temperature. We should emphasize that the equilibration of two diastereoisomers is not frequently observed.[10,11]

Attempts to purify **5f1** (impure of **5f2**) by crystallization from methanol (or other solvents) produced crystals enriched with **5f2** and the same diastereomeric ratio was found by analyzing the composition of the mother liquors. X-Ray diffraction of a single crystal of pure **5f2** (Fig.1) established the absolute configuration of this diastereomer, and, consequently, of **5f1**.

Complete salification of the imine does not permit the reaction. Yields are unaffected by the presence of $Et_3N$ or $CH_3SO_3H$.

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**Table 1** Reactions between equimolar amount of β-naphthol and imines

| Entry | Imine | Solvent | Reaction temp./°C | Catalyst[a] | Reaction time/days | Conversion/% |
|---|---|---|---|---|---|---|
| 1 | **4a** | $CH_2Cl_2$ | 35 | $Et_3N$ | 4 | 70[b] |
| 2 | **4a** | $CH_2Cl_2$ | 35 | – | 4 | 72 |
| 3 | **4a**[c] | $CH_2Cl_2$ | 35 | – | 4 | 60 |
| 4 | **4a** | $CH_2Cl_2$ | 35 | $CH_3SO_3H$[d] | 4 | 65 |
| 5 | **4b** | l.p.[e] | 90 | $Et_3N$ | 4 | 60[b] |
| 6 | **4b** | l.p.[e] | 90 | – | 4 | 65 |
| 7 | **4c** | $CH_2Cl_2$ | 20 | $Et_3N$ | 4 | 70 |
| 8 | **4c** | $CH_2Cl_2$ | 20 | – | 2 | 66 |
| 9 | **4d**[c] | $CH_2Cl_2$ | 20 | – | 4 | 81 |
| 10 | **4e**[c] | $CH_2Cl_2$ | 20 | – | 5 | 85 |

[a][catalyst]/[imine] = 5 × $10^{-1}$; [b]The reaction mixture was tested by polarimetric measurements: no optical activity was detected; [c]the reaction was performed by mixing equimolar amount of **1**, aldehyde and amine; [d]no reactions was observed when [catalyst]/[imine]≥ 1; [e]light petroleum.

**Table 2** Reactions between equimolar amount of β-naphthol (**1**) and imine **4f** in $CH_2Cl_2$ (unless otherwise indicated)

| Entry | Catalyst[a] | Temperature/°C | Conversion[b] | Time/days | Diastereomeric ratio (**5fl**:**5f2**) |
|---|---|---|---|---|---|
| 1 | – | 20 | 75 | 1 | 50:50 |
| 1 bis | – | 20 | 95 | 10 | 15:85 |
| 2 | $Et_3N$ | 20 | 50 | 10 | 50:50 |
| 3 | $CH_3SO_3H$ | 20 | 87 | 10 | 20:80 |
| 4 | $CH_3SO_3H$[c] | 20 | 88 | 10 | 17:83 |
| 5 | $CH_3SO_3H$ | 0 | 38 | 0.1 | 58:42 |
| 6 | – | –20 | 50 | 7 | 60:40 |
| 6 bis | – | –20 | 75 | 40 | 60:40 |
| 6ter | – | 20 | 84 | 7 | 40:60 |
| 7 | _d | 20 | 40 | 0.1 | 60:40 |
| 7 bis | _d | 20 | 84 | 3 | 60:40 |
| 8 | _e | 20 | 27 | 1 | 50:50 |
| 9 | _f | 20 | 60 | 1 | 48:52 |
| 9 bis | _f | 20 | 86 | 10 | 20:80 |
| 10 | _g | 20 | 98 | 15 | 28:72 |

[a][catalyst]/[imine] ≈ 1 × $10^{-1}$; [b]calculated from $^1$H NMR spectrum of the crude reaction mixture; [c][catalyst]/[imine] ≈ 5 × $10^{-1}$; [d]in THF; [e]in $CHCl_3$; [f]reaction carried out by mixing equimolar amounts of β-naphthol, benzaldehyde and (S)-1-phenylethanamine; [g]reaction carried out by using **1**:**4f** in a 1:2 molar ratio.

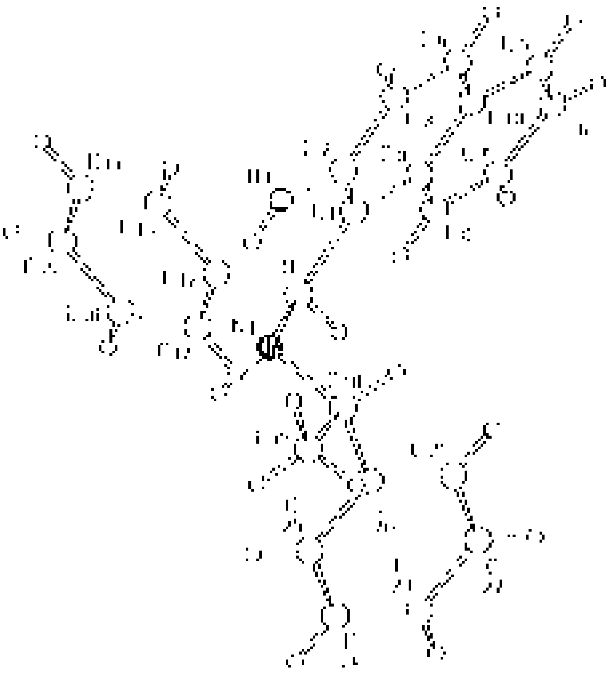

**Fig. 1** Perspective view of **5f2** from x-ray diffraction data.

The addition reaction of imines to naphthols appears in this case to be far from the usual pattern of behaviour of imines in addition reaction. The reaction in our case is probably caused by a preliminary proton donor/acceptor equilibrium which forces the reaction centres towards a position close to that of the transition state and toward the Wheland intermediate. This is shown in Scheme 6.

When the OH group of naphthol protonates the C=N nitrogen this action starts a double activation. The double activation consists of a positivisation of the electrophilic carbon and the enhancement of the electron density of the α position of the naphthalene.

The reaction pathway of Scheme 6 not only explains the lack of reaction in strong acid and basic catalysis, but also the unreactivity of the β-methoxynaphthalene.

Scheme 7 confirms Scheme 6 in explaining the isomerization S,S to R,S of **5f**, by considering the hydrogen bonding interaction between OH and NH group to be essential in the isomerization pathway.

We emphasize that the diastereomeric ratios of Table 2 cannot be ascribed to simple enthalpic/entropic control[16] on the rate of formation of **5f1** and **5f2**. The predominance of one diastereomer over the other depends on the relative activation free energy of the reaction of **5f1** and **5f2** to the common intermediate **8**. In present case, there is a thermodynamic control of the diastereomeric ratio arising from the reversibility of the carbon attack on the α position of β-naphthol.

## Experimental

Crystal data of **5f2**: $C_{25}H_{23}NO$, M=353.44, orthorhombic, $a$=9.807(6), $b$=9.826(5), $c$=42.446(4) Å, V=4090.7(7) $Å^3$ $T$=293°K, space group $P2_12_12_1$ (no. 19), Z=8; $\mu$=0.069 $mm^{-1}$.

Final R factors: $R_1$=0.0670, $wR_2$=0.1761.

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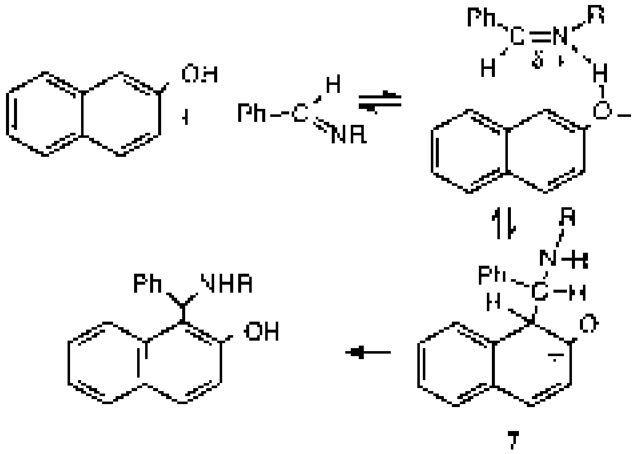

Scheme 6

for selected research topics 1997–1999). Many thanks are due to Prof. Magda Monari for X-ray diffraction discussion.

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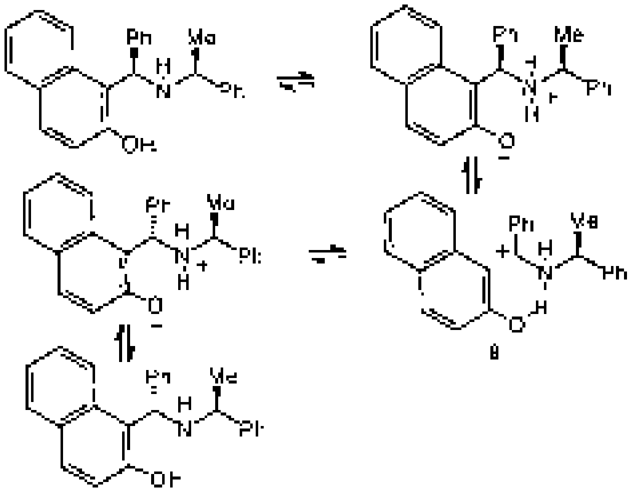

Scheme 7

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