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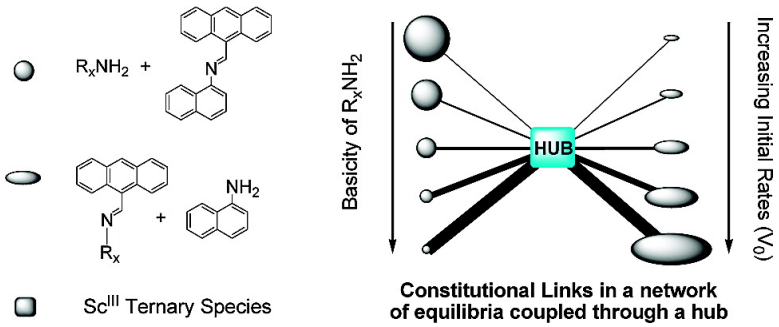


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# Scandium(III) Catalysis of Transimination Reactions. Independent and Constitutionally Coupled Reversible Processes

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***Abstract:*** $Sc(OTf)_3$ efficiently catalyzes the self-sufficient transimination reaction between various types of C═N bonds in organic solvents, with turnover frequencies up to 3600 $h^{-1}$ and rate accelerations up to $6 \times 10^5$. The mechanism of the crossover reaction in mixtures of amines and imines is studied, comparing parallel individual reactions with coupled equilibria. The intrinsic kinetic parameters for isolated reactions cannot simply be added up when several components are mixed, and the behavior of the system agrees with the presence of a unique mediator that constitutes the core of a network of competing reactions. In mixed systems, every single amine or imine competes for the same central hub, in accordance with their binding affinity for the catalyst metal ion center. More generally, the study extends the basic principles of constitutional dynamic chemistry to interconnected chemical transformations and provides a step toward dynamic systems of increasing complexity.

## Introduction

Over the last century, numerous studies have been devoted to C═N-type bonds,[1] firmly establishing their relevance in the fields of chemistry,[2] biology,[3] and material science.[4] Despite such a venerable age, the literature reveals that research activities related to these functional groups are more active than ever.[5] The versatility of this chemical linkage is mainly due to its fast and highly chemoselective formation from amino groups and carbonyl derivatives. A characteristic feature that has become of special interest is the reversibility of the C═N linkage and the resulting ability of imino-type compounds to undergo exchange of the two components against other functionally compatible partners. It is of particular value for the recently developed dynamic combinatorial (covalent) chemistry (DCC), belonging to the molecular domain of constitutional dynamic chemistry (CDC),[6,7] which covers reversible constitutional reorganization on both the molecular (covalent) and the supramolecular (noncovalent) levels.

DCC depends crucially on the availability of fast reversible reactions, allowing the generation of highly diverse libraries of interconnecting compounds, thus creating dynamic constitutional diversity for both biological and materials science purposes. Provided fast and efficient reversibility in water or organic solvents is achieved, the ubiquitous C═N unit, present, for example, in imines, hydrazones, and oximes, offers highly attractive potentialities for molecular CDC. Three different types of equilibrated reactions may allow the exchange of the amino fragment of the C═N units (Scheme 1). In the first case (a), the formation/hydrolysis mechanism,[1b] exchange of the components occurs via back-reaction with water to convert the imine bond into free amine and carbonyl, which can subsequently undergo reaction with another partner present in the reaction mixture. In the other two cases, transimination[8] (b) and imine metathesis[9] (c), the process is self-sufficient, not involving the mediation of a third constituent (i.e., water), and the exchange occurs without disruption of the C═N unit into free amine and carbonyl.[10] This feature is of special interest in CDC for at least three reasons: (a) numerous reactions have to be performed in anhydrous conditions; (b) a highly shifted equilibrium is often

(1) (a) Schiff, H. *Ann*. **1864**, *131*, 118. (b) Layer, R. W. *Chem. Rev*. **1963**, *63*, 489−510.
(2) Katritzky, A. R.; Meth-Cohn, O.; Rees, C. W. *Comprehensive Organic Functional Group Transformations*; Pergamon: Elmsford, NY, 1995; Vol. 3, pp 403−423.
(3) Stryer, L. *Biochemistry*; W. H. Freeman and Co.: San Francisco, CA, 1975; Chapter 18, pp 432−455.
(4) (a) Gray, G. W. *J. Chem. Soc*. **1958**, 552−555. (b) Simon, J.; Bassoul, P. *Design of Molecular Materials, Supramolecular Engineering*; Wiley: New York, 2000; Chapter 8, pp 405−427.
(5) A bibliographic research using SciFinder on more than 19 000 papers related to the term "imines" indicates that, since 1905, one-half of the publications appeared in the last 10 years.
(6) (a) Lehn, J.-M. *Chem.-Eur. J*. **1999**, *5*, 2455−2463. (b) Cousins, R. L.; Poulsen, S. A.; Sanders, J. K. M. *Curr. Opin. Chem. Biol*. **2000**, *4*, 270−279. (c) Rowan, S. J.; Cantrill, S. J.; Cousins, G. R. L.; Sanders, J. K. M.; Stoddart, J. F. *Angew. Chem*. **2002**, *114*, 938−993; *Angew. Chem., Int. Ed*. **2002**, *41*, 898−952.
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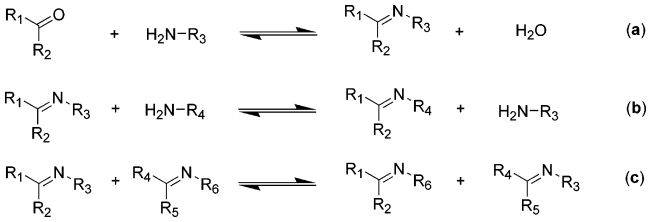
**10.1021/ja042469q CCC: $30.25** 

***Scheme 1.*** Types of Amine Exchange Processes Involving the Imine Bond: (a) Condensation and Hydrolysis; (b) Transimination; (c) Imine Metathesis



required for the design of dynamic materials, in particular, dynamers;[11−13] and (c) the decrease in number of constituents is advantageous for the determination of the composition of a dynamic library; indeed, the presence of significant amounts of starting materials (e.g., carbonyl and amino compounds) as well as of reaction intermediates (e.g. hemiaminal) may complicate the analyses of mixtures.

Although many systems have taken advantage of the reversibility of the imine-type bond in water, according to the condensation/hydrolysis process,[14] fast exchange of these key units in organic solvents remains difficult to achieve. This is particularly apparent for the more stable hydrazones and oximes, as judged from the small number of publications related to the catalysis of this reaction.[15] We have recently studied the rate of the transimination reaction in the presence of lanthanide ions as catalyst. The exchange rates increased linearly with a decrease in ionic radius, the most efficient catalyst being scandium(III).[16] In particular, exchange reactions involving molecular helical strands based on polyheterocyclic units linked by hydrazone-type connections could be efficiently catalyzed by scandium triflate in chloroform,[16,17] whereas protons did not afford more than traces of the exchanged products. We here report a more detailed study of this scandium-catalyzed exchange in Schiff bases (such as compounds **1** and **2**) and extend it to a broader range of C═N units (i.e., imines and oximes). We have investigated structural effects on the thermodynamic distribution of products (selectivity) as well as on the exchange rate. We also highlight the efficiency of the Lewis acid-catalyzed

***Scheme 2.*** Exchange Reaction between Imine **1** and Cyclopentylamine (Equimolar Ratio), Catalyzed by $Sc(OTf)_3$, and Leading to a Thermodynamic Equilibrium with Imine **2** and Naphthylamine

processes (turnover frequency, TOF up to $3.6 \times 10^3$ $h^{-1}$ at 25 °C), with respect to both the noncatalyzed (accelerations up to $6 \times 10^5$) and the Brönsted acid-catalyzed ones. Moreover, we broaden the applicability of this reaction by using microencapsulated scandium triflate, which has emerged as a promising supported catalyst, especially for further dynamic constitutional approaches. Finally, we show that the results obtained are consistent with a predominantly concerted transimination pathway, where both the imine and the free amine occupy the coordination sphere of the scandium in a ternary intermediate ("promnastic" effect).[15a] As a consequence, when several different components are brought together in constitutionally dynamic combinatorial systems, as compared to individual reactions, coupled equilibria are established through the formation of mediator species functioning as a hub where reagents and products compete for the same catalytic site.

## Results and Discussion

**I. Catalytic Aspects. A. Catalytic Efficiency of $Sc(OTf)_3$ in Exchange Processes.** To evaluate the catalytic efficiency of scandium triflate in exchange processes, we first studied the exchange between imine **1** and cyclopentylamine, leading to the equilibrium with the imine **2** and α-naphthylamine (Scheme 2), in deuterated chloroform in the presence of different amounts of $Sc(OTf)_3$ as catalyst. The evolution of the equilibrium was followed using $^1$H NMR at 25 and 60 °C for different percentages of metallic salt, and the data obtained are plotted in Figure 1.

The results indicate that the exchange process strongly depends on the percentage (with respect to amine) of scandium triflate in solution, as well as on the temperature. At 25 °C, the uncatalyzed reaction is characterized by an initial rate ($V_0$)[18] of $1.9 \times 10^{-2}$ mM $h^{-1}$ for an initial concentration $\mathbf{1}_i = 22.6$ mM, which is roughly 100 times slower than the rate when 20% of $Sc^{III}$ is added (1.96 mM $h^{-1}$). Raising the temperature to 60 °C increases the rate of the uncatalyzed exchange to 0.35 mM $h^{-1}$, whereas in the presence of 4 mol % of catalyst in the same conditions the rate increases to 10 mM $h^{-1}$ (i.e., an acceleration of a factor 30). In terms of selectivity, as long as low relative concentrations of catalyst are used (no more than 4 mol %), the ratios at equilibrium at both temperatures are equal to those obtained without scandium ions. For higher quantities (20 mol % of metal salt), the catalyst interferes with the thermodynamic equilibrium of the system and tends to favor compound **1** over **2**. Indeed, the ratio at equilibrium between imines **1** and **2** varies from 20/80 (4 mol % of $Sc^{III}$) to 60/40 (20 mol % of $Sc^{III}$) at 60 °C, and from 10/90 (4 mol % of $Sc^{III}$) to 40/60 (20 mol % of $Sc^{III}$) at 25 °C. This effect may be explained by the fact that $Sc^{III}$ is expected to coordinate more strongly the most basic

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(17) For an overview of the use of rare-earth metal triflates in organic synthesis, see: Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W.-L. *Chem. Rev.* **2002**, *102*, 2227−2302.

(18) The $V_0$ values were determined graphically from the corresponding plots of the evolution of the equilibria versus time.

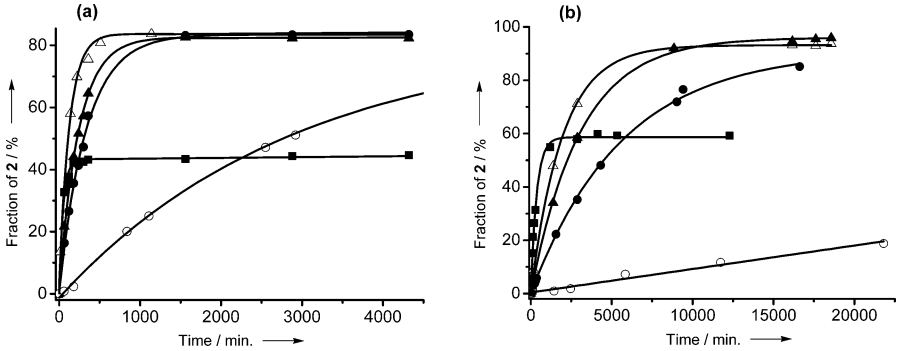



***Figure 1.*** Evolution with time of the equilibration between imines **1** and **2** described in Scheme 2 ($\mathbf{1}_i$ = 22.6 mM), using various amounts of $Sc(OTf)_3$ catalyst (added as a deuterated acetonitrile solution) and followed by the integration of the $^1H$ NMR signals of the imine proton at 60 °C (a) and 25 °C (b). The different amounts of catalyst used, relative to cyclopentylamine, are indicated as follows: ○ 0%; ● 0.5%; ▲ 2%; △ 4%; ■ 20%.

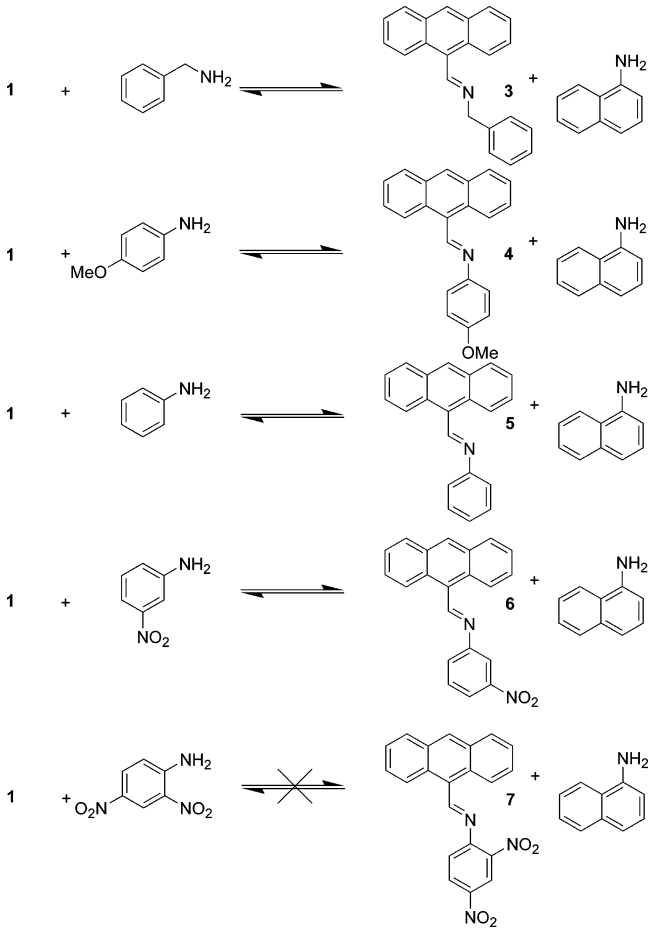
amine, here the cyclopentylamine,[19] thus shifting the equilibrium in favor of **2**, as was observed in the related case of a bis-imine.[12] As a consequence, the selectivity of the exchange depends on the relative affinity of scandium for the amines involved. Subsequently, the use of 4 mol % of $Sc^{III}$ appeared to be best suited for our purposes: it both maximizes the rate of the exchange process and does not interfere with the equilibrium, as obtained without catalyst, a crucial point for the formation of isoenergetic libraries of compounds.[6a]

**B. Exchange Equilibria and Kinetics**; **Structural Effects.** The influence of the nature of the amine on the kinetic and thermodynamic parameters of the exchange process was studied by comparing the uncatalyzed and $Sc(OTf)_3$-catalyzed reactions of the imine **1** with equimolar amounts of benzylamine, 4-methoxyaniline, aniline, 3-nitroaniline, or 2,4-dinitroaniline leading to imines **3**, **4**, **5**, **6**, and **7**, respectively (Scheme 3). The corresponding equilibria, given by the selectivities (*S*), the initial rates ($V_0$), and the turnover frequencies (TOF), are listed in Table 1.

In terms of selectivity (*y*/*x* ratio between the imines at equilibrium) and for both the catalyzed and the uncatalyzed pathways, the results correlate with the nucleophilicities of the amines which compete for imine formation, the most reactive/basic amine leading to the thermodynamically most stable imine (**2** > **3** > **4** > **5** > **1** > **6** > **7**), consistent with the literature data on the addition of amines to aldehydes.[20] The same general behavior was observed starting from the more basic imine **2** that undergoes exchange reactions with α-naphthylamine, benzylamine, allylamine, and isopentylamine to yield imines **1**, **3**, **8**, and **9**, respectively (Scheme 4 and Table 2).

The initial rates of the catalyzed ($V_0^C$) and uncatalyzed ($V_0^U$) amine exchange reactions of a number of imines are listed in Tables 1 and 2, together with the acceleration factors ($V_0^C/V_0^U$) and the turnover frequencies (TOF) of the catalyzed process. The initial exchange rate from **1** for the uncatalyzed pathway showed weak correlation with the structure of the free amine, the most basic exchanging the fastest (entry 1, Table 1).[21] In the case of the scandium triflate-catalyzed reaction, the trend was opposite. Indeed, the initial rates and TOF (up to 1.8 × $10^3$ $h^{-1}$) as well as the rate increase (up to 5 orders of magnitude) as compared to the control (uncatalyzed) experiments (entry 4, Table 1) displayed the sequence: aniline > 4-methoxyaniline ≫ 3-nitroaniline ≫ benzylamine ≫ cyclopentylamine. The results suggested that the exchange rates were highest for amines of comparable nucleophilicities, regardless of the direction of the reaction. Indeed, the initial rates were similar in both directions as was verified by starting from compound **2** in the presence of α-naphthylamine and different amounts of $Sc^{III}$ catalyst (Figure 2).

***Scheme 3.*** Exchange Reactions between Imine **1** and Benzylamine, 4-Methoxyaniline, Aniline, 3-Nitroaniline, or 2,4-Dinitroaniline (Equimolar Ratios) Leading to Thermodynamic Equilibria with Imines **3**, **4**, **5**, **6**, and **7**, Respectively; Undetectable Reaction in the Case of 2,4-Dinitroaniline




Similarly, the exchange reactions of compound **2** (containing the basic cyclopentylamine moiety) with benzylamine, allylamine, and isopentylamine leading to imines **3**, **8**, and **9**,

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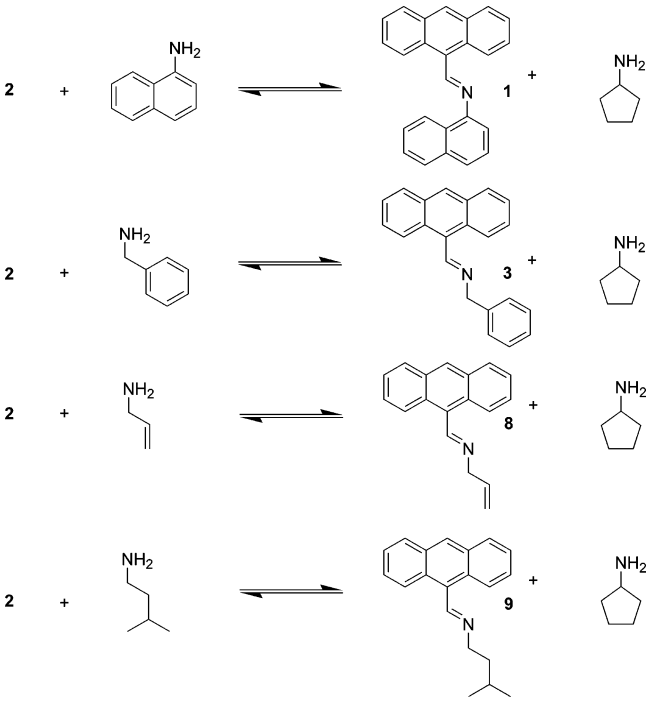
***Table 1.*** Values of the Selectivity Ratios (*S*), the Initial Catalyzed ($V_0^C$) and Uncatalyzed ($V_0^U$) Rates, and the Turnover Frequencies (TOF) for the Exchange Reactions Starting from Imine **1** and Leading to the Equilibria with the Imines **2**, **3**, **4**, **5**, **6**, and **7**, at 25 °C in $CDCl_3$ and in the Presence of 4 mol % of $Sc(OTf)_3$ Catalyst[a] (Schemes 2 and 4)

| entry | equilibrium $x \rightleftharpoons y$ | *S* (*y*/*x*) | $V_0^C$/mM h$^{-1}$ 4% $Sc(OTf)_3$ | $V_0^U$/mM h$^{-1}$ control | acceleration $V_0^C/V_0^U$ | TOF/h$^{-1}$ $Sc^{III}$ |
|---|---|---|---|---|---|---|
| 1 | **1** ⇌ **2** | 9/1 | 0.84 | $19 \times 10^{-3}$ | 45 | 0.93 |
| 2 | **1** ⇌ **3** | 7/3 | 18.6 | $6.0 \times 10^{-3}$ | $3.1 \times 10^4$ | 20.6 |
| 3 | **1** ⇌ **4** | 2/1 | $1.10 \times 10^3$ | $5.6 \times 10^{-3}$ | $1.9 \times 10^5$ | 1200 |
| 4 | **1** ⇌ **5** | 1/1 | $1.62 \times 10^3$ | $5.4 \times 10^{-3}$ | $3.0 \times 10^5$ | 1800 |
| 5 | **1** ⇌ **6** | 1/3 | 486 | | | 540 |
| 6 | **1** ⇌ **7** | →0[a] | nd | nd | nd | nd |

[a] Added as 45 mM acetonitrile solution; final solution contains 2 vol % acetonitrile in $CDCl_3$. [b] No detectable amount of **7** by $^1$H NMR.

***Scheme 4.*** Exchange Reactions between Imine **2** and α-Naphthylamine, Benzylamine, Allylamine, or Isopentylamine (Equimolar Ratios) in $CDCl_3$ and in the Presence of Catalytic Amounts of $Sc(OTf)_3$, Leading to Thermodynamic Equilibria with Imines **1**, **3**, **8**, and **9**, Respectively



respectively (Scheme 4, Table 2), showed a global behavior in which the more closely related the structures of the competing amines, the faster were the accelerations $V_o^C/V_o^U$ as compared to the controls without catalyst. Comparing the ratio of the reaction rates with and without catalyst minimizes the interferences of other factors, the intrinsic steric or electronic parameters. In terms of the absolute reaction rate, the best results were obtained for allylamine with a TOF of 2800 h$^{-1}$ (entry 3).

**C. Comparison of $Sc^{III}$ and $H^+$ as Exchange Catalysts; Solvent Effects.** To compare the relative catalytic efficiency of $Sc^{III}$ and protons, we examined the effect of hydrated $Sc(OTf)_3$ and of $CF_3CO_2D$ on different exchange reactions in deuterated chloroform starting from compounds **1** or **2** (Table 3).

In most of the cases studied, the use of identical percentages of $Sc^{III}$ or $H^+$ revealed the higher activity of the metal salt (in terms of initial rate) even though the exchange also proceeded efficiently using $H^+$. For example, the exchange between **1** and **3** at 25 °C was 15 times faster under scandium triflate catalysis than under $H^+$ catalysis (entry 4), while the initial rate of the exchange between **2** and **8** was 100 times greater with $Sc^{III}$ (entry 8) ($H^+$ and $Sc^{III}$ having similar selectivities). In the cases of the most basic amines, catalysis by $H^+$ is less efficient as protonation decreases the reactivity of the amines and, by scavenging the protons, prevents activation of the imines. For the less basic amines (entries 5 and 6, Table 3), these effects are less pronounced and proton catalysis becomes comparable to $Sc^{III}$ catalysis. Furthermore, in all cases where $V_0^C/V_0^H > 1$, attempts to increase $V_0^H$ by lowering the pH led to degradation of the imines.

Examining reactivities in different solvents showed that $Sc^{III}$ catalysis was most pronounced in solvents of low dielectric constant (Table 4). On the other hand, the use of coordinating solvents greatly decreased the effect of $Sc^{III}$, whereas it affected less the proton-catalyzed process.

**D. Effect of Ionic Radius on Metal Ion Catalysis.** Crossover experiments were conducted with salts of different trivalent metal ions. The initial rates and turnover frequencies in the exchanges involving **2** and allylamine catalyzed by different lanthanide triflates were found to be linearly correlated with the ionic radii of the trivalent ions (Figure 3). This behavior agrees with that already reported for exchange of hydrazine derivatives, which furthermore were much more reluctant to undergo proton catalysis.[16]

**E. Five-Component Competitive Experiment in a Dynamic Combinatorial Library Approach.** To extend the scope of such a catalytic system to DCC, we finally performed a direct competitive experiment involving the reaction of **1** with a mixture of cyclopentylamine, benzylamine, aniline, and dinitroaniline in equimolar ratios at 25 °C leading to a potential mixture of imines **1**, **2**, **3**, **5**, and **7**. The time dependence of the equilibration is shown in Figure 4.

After 4 days, the final composition of the mixture followed the order of nucleophilicities (55% of **2**; 41% of **3**; 2.3% of **5**; 1.7% of **1**; 0% of **7**), as expected from a superposition of the previous two-imine competitive experiments (see selectivities in Table 1). The initial reaction rate for the whole mixture was measured by observing via $^1$H NMR the disappearance of the CH═N signal of imine **1**. The results gave a $V_0^C$ of 2.72 mM h$^{-1}$ and a TOF of 0.75 h$^{-1}$, which are comparable to the $V_0^C$ and TOF values obtained for the reaction involving **1** and cyclopentylamine alone (Table 1, entry 1). These data are far from what one would predict if the reaction occurred independently (e.g., formation of the kinetic products at first, followed by their progressive equilibration to give the thermodynamic ones), based on the kinetic parameters determined (Table 1). Thus, for instance, one would have expected initial formation of imine **5** by exchange between **1** and aniline ($V_0^C$ = 1620 mM h$^{-1}$; TOF = 1800 h$^{-1}$; Table 1, entry 4).

***Table 2.*** Values of the Selectivity Ratios (*S*), the Initial Catalyzed ($V_0^C$) and Uncatalyzed ($V_0^U$) Rates, and the Turnover Frequencies (TOF) for the Exchange Reactions Starting from Imine **2** and Leading to Equilibria with the Imines **1**, **3**, **8**, and **9**, at 25 °C in the Presence of 4 mol % of $Sc(OTf)_3$ Catalyst[a] (Scheme 5)

| entry | equilibrium $x \rightleftharpoons y$ | $S$ ($y/x$) | $V_0^C$/mM h$^{-1}$ 4% $Sc(OTf)_3$ | $V_0^U$/mM h$^{-1}$ control | acceleration $V_0^C/V_0^U$ | TOF/h$^{-1}$ $Sc^{III}$ |
|---|---|---|---|---|---|---|
| 1 | **2** ⇌ **1** | 1/9 | 0.84 | $12.7 \times 10^{-3}$ | 66 | 0.93 |
| 2 | **2** ⇌ **3** | 2/3 | $1.1 \times 10^3$ | 8.54 | 128 | 1220 |
| 3 | **2** ⇌ **8** | 1/2 | $2.5 \times 10^3$ | 3.29 | 760 | 2830 |
| 4 | **2** ⇌ **9** | 5/4 | 813 | 0.89 | 913 | 900 |

[a] Added as 45 mM acetonitrile solution; final solution contains 2 vol % acetonitrile in $CDCl_3$.

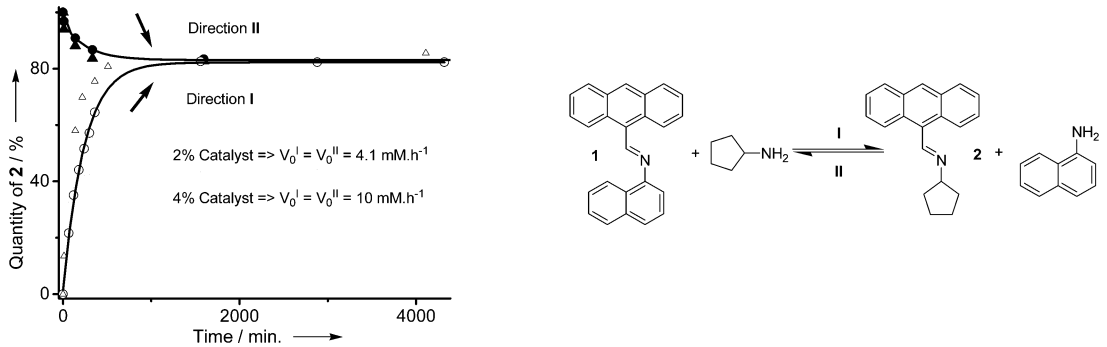



***Figure 2.*** Evolution with time of the formation and the disappearance of compound **2** in the equilibration between **1** and **2** ($\mathbf{1}_i = \mathbf{2}_i = 22.6$ mM) in $CDCl_3$ at 60 °C, starting from **1** and cyclopentylamine (1:1) (direction **I**) or **2** and α-naphthylamine (1:1) (direction **II**). The equilibria were followed by integration of the $^1$H NMR imine signals, in the presence of either 2 or 4 mol % $Sc(OTf)_3$, relative to free amines, labeled as follows: ○ 2% (**I**); △ 4% (**I**); ● 2% (**II**); ▲ 4% (**II**).

***Table 3.*** Comparative Values, Determined by $^1$H NMR, of the Selectivity Constants (*S*) and of the Initial $Sc^{III}$-Catalyzed ($V_0^C$) and Proton-Catalyzed ($V_0^H$) Rates for the Exchange Reactions between Imines **1**, **2**, **3**, **4**, **5**, **8**, and **9** (Schemes 4 and 5) in the Presence of Catalytic Amounts of $Sc(OTf)_3$ and $CF_3CO_2D$

| entry | equilibrium $x \rightleftharpoons y$ | temp /°C | $S$ ($y/x$) ($Sc^{III}$) | $S$ ($y/x$) ($H^+$) | $V_0^C$/mM h$^{-1}$ (% $Sc^{III}$) | $V_0^H$/mM h$^{-1}$ (% $H^+$) | $V_0^C/V_0^H$ |
|---|---|---|---|---|---|---|---|
| 1 | **1** ⇌ **2** | 60 | 4/1 | 7/3 | 10 (4%) | 1.2 (4%) | 8.3 |
| 2 | | 60 | 4/1 | 7/3 | 4.1 (2%) | 0.9 (2%) | 4.4 |
| 3 | | 60 | 2/3 | 2/3 | 10 (20%) | 5.5 (40%)[a] | 1.8 |
| 4 | **1** ⇌ **3** | 20 | 7/3 | 7/3 | 18.6 (4%) | 1.2 (4%) | 15.5 |
| 5 | **1** ⇌ **4** | 20 | 2/1 | 2/1 | $1.1 \times 10^3$ (4%) | $1.1 \times 10^3$ (4%) | 1 |
| 6 | **1** ⇌ **5** | 20 | 1/1 | 3/2 | $1.6 \times 10^3$ (4%) | $3.5 \times 10^3$ (4%) | 0.46 |
| 7 | **2** ⇌ **3** | 20 | 3/4 | 3/4 | $1.1 \times 10^3$ (4%) | 77 (4%) | 14.5 |
| 8 | **2** ⇌ **8** | 20 | 1/2 | 1/2 | $2.5 \times 10^3$ (4%) | 24.8 (4%) | 100 |
| 9 | **2** ⇌ **9** | 20 | 1/2 | 1/2 | 813 (4%) | 69 (4%) | 12 |

[a] Decomposition into free 9-anthracencarboxaldehyde (20 mol % relative to the sum of imines) was observed.

***Table 4.*** Comparative Values, Determined Using $^1$H NMR, of the Initial Rates ($V_0^C$ and $V_0^H$) in Various Deuterated Solvents at 60 °C for the Exchange Process between Imines **1** and **2** (Scheme 2) Using Catalytic Amounts of $Sc(OTf)_3$ and $CF_3CO_2D$

| entry | solvent | $V_0^C$/mM h$^{-1}$ (% $Sc^{III}$) | $V_0^H$/mM h$^{-1}$ (% $H^+$) | $V_0^U$/mM h$^{-1}$ control | $V_0^C/V_0^H$ ($V_0^C/V_0^U$) |
|---|---|---|---|---|---|
| 1 | $CDCl_3$ | 10 (4%) | 1.2 (4%) | 0.35 | 8.3 (28) |
| 2 | $C_2D_2Cl_4$ | 43 (4%) | | 1.25 | (34.4) |
| 3 | toluene-$d_8$ | 3.1 (4%) | 0.52 (4%) | $1.35 \times 10^{-2}$ | 11.7 (451) |
| 4 | $CDCl_3$/MeOD (95/5) | 1 (4%) | 1 (4%) | | 1 (−) |
| 5 | $CDCl_3$/MeOD (50/50) | 0.2 (4%) | 0.43 (4%) | | 0.46 (−) |
| 6 | DMSO-$d_6$ | $5.8 \times 10^{-2}$ (4%) | $9 \times 10^{-2}$ (4%) | $1.06 \times 10^{-2}$ | 0.64 (5.5) |

**F. Extension of $Sc^{III}$-Catalyzed Exchange to a Broader Range of C═N Units.** To gain further insight into the scope of the catalyzed reaction, we investigated different types of substrates such as those depicted in Scheme 5 with the corresponding thermodynamic and kinetic data appearing in Table 5. The reaction is compatible with the presence of electron rich and/or chelating groups such as phenol in the Schiff bases (entries 1, 2), even if a decrease in the accelerations values is observed. As it has been already described in the cases of heterocyclic helical molecular strands,[16] the efficiency of the exchange is also demonstrated for hydrazone derivatives, even those that do not contain pyrimidine or pyridine moieties (entry 3). Crossover experiments mixing different C═N-type bonds may also be performed, such as between hydrazones and oximes (entry 4). Nevertheless, attempts to exchange hydrazine, and even more hydroxylamine moieties, against amines failed due to a highly displaced equilibrium in favor of the most nucleophilic nitrogen group. The best result in terms of catalytic activity (accelerations up to $6 \times 10^5$ and TOF of more than 3600 h$^{-1}$) was obtained in exchange between the oxime **17** of cyclohexanone and benzylhydroxylamine (entry 5). This result is particularly interesting in view of the great reluctance of

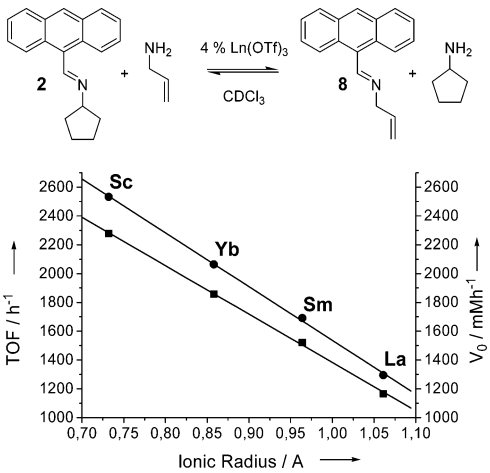



***Figure 3.*** Top: Equilibration between imines **2** and **8**. Bottom: Initial rates ($V_0^C$) (■) and turnover frequencies (TOF) (●) for amine exchange between imine **2** and allylamine under catalysis by different lanthanide triflates as a function of their ionic radius; equimolar ratio with allylamine; $\mathbf{1}_i$ = 22.6 mM, in the presence of 4% $Ln(OTf)_3$ (added as a deuterated acetonitrile solution).

oximes to undergo exchange.[15b] Last, but not least, the possibility of using highly stable five-membered ring imines as well as amidines with hydroxylamines might be of interest for future endeavors.

**G. $Sc^{III}$-Supported Catalyst.** As an extension of the $Sc^{III}$ catalysis in homogeneous solutions, we investigated different types of supported scandium triflate in organic solvents. Such a heterogeneous process is of special interest in view of its potential implementation in CDC. Indeed, the use of a supported catalyst to equilibrate a library offers the possibility to freeze the reaction by simply removing the supported metal ions from the solution. We chose two different techniques to support the scandium triflate: microencapsulation in polystyrene[22] and immobilization on ion-exchange resins.[23]

In the case of ion-exchange resins, no activity was preserved. With the polystyrene microencapsulated scandium (MC Sc-$(OTf)_3$) using acetonitrile as solvent (Scheme 6), the exchange proceeded in mild conditions for different C═N-type bonds investigated above, good catalytic activities being conserved as compared to the control experiments with free $Sc^{III}$ (Table 6).

**II. Mechanistic Aspects.** To obtain a first indication on the mechanistic pathway, the reaction of **1** with benzaldehyde (1:1 ratio) was performed at 25 °C in the presence of 4 mol % of $Sc(OTf)_3$.[24] After 3 days, no cross-product could be detected. Also, no direct imine metathesis between **1** and another Schiff base (formed from *p*-anisidine and benzaldehyde) was observed under the same conditions (25 °C and 4 mol % of catalyst). Indeed, even though traces of exchange products were detected via $^1H$ NMR, they appeared to mostly derive from the presence of residual water.[25]

These results indicate that the exchange described in Scheme 2 occurs via the transimination pathway (Scheme 1b).

**A. Effects of Catalyst Concentration.** At both 25 and 60 °C, the plots of the initial rates $V_0$ against the percentage of catalyst (Figure 5, left) display a plateau that is reached when more than 4 mol % of catalyst is used. These data fit those reported for the general acid-catalyzed imine formation,[26] where the catalyst accelerates the rate-determining addition step by polarizing the imine bond and facilitating the nucleophilic attack of the free amine, here through cation coordination to its nitrogen site (Scheme 7). At higher percentages of catalyst, the rate of the addition step forming the geminal diamino intermediate reaches a plateau due to deactivation of the amine by the Lewis acid center.

For low quantities of $Sc^{III}$ (0.05−4 mol %), the plot of log-($V_0$) against log($Sc^{III}$) shows a linear dependence of rate on catalyst concentration, demonstrating that the rate of the uncatalyzed reaction is comparatively negligible (Figure 5, right).[27] Moreover, the initial rate $V_0$ was found to be independent of both the imine and the amine concentrations,[28] so that the overall reaction is first order in this domain.

The behavior of the system revealed by the linear relationship between the ionic radius of the metal ion and the initial rates/turnover frequencies (Figure 3) is in favor of Lewis acid-type catalysis. This conclusion is also in agreement with the competition of coordinating solvents that can displace amines and imines from the metal ion and thus decrease the reaction rate (Table 4); the same holds when comparing proton catalysis with the more efficient $Sc^{III}$ catalysis (Table 3).

**B. Effects of Amine Basicities.** The results in Tables 1 and 2 show that the acceleration factors $V_0^C/V_0^U$ are largest for amines of basicity comparable to that of the amine engaged in the imine. Furthermore, for similar basicities, the accelerations are higher for less basic partners than for more basic ones. Indeed, the accelerations are greater (up to a factor of 300) when two aromatic amines are engaged in crossover experiments, as compared to what is obtained between aliphatic amines and aliphatic imines (Table 1, entry 4 and Table 2, entry 4), indicating that the activity of the scandium catalyst itself is affected by the global basicity of both amines and imines. Based on the data obtained for the effect of the nature of the components (Tables 1 and 2), one may propose that the rate of the exchange reaction is dependent upon three main factors: activation of the imine by $Sc^{III}$ coordination; deactivation of the amine by binding to $Sc^{III}$ ions; and deactivation of the $Sc^{III}$ by both the bound amine(s) and the imine(s). All three factors

(22) Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc*. **1998**, *120*, 2985−2986.
(23) (a) Kobayashi, S.; Nagayama, S. *J. Org. Chem*. **1996**, *61*, 2256−2257. (b) Yu, L.; Chen, D.; Li, J.; Wang, P. G. *J. Org. Chem*. **1997**, *62*, 3575−3581.
(24) For mechanistic studies of imine formation reactions (from amines and aldehydes) catalyzed by zinc(II) ions in organic solvents, see: Boate, A. R.; Eaton, D. R. *Can. J. Chem*. **1977**, *55*, 2432−2441.
(25) Hydrolysis of the imine bonds has been detected by the observation of the $^1H$ NMR aldehyde signal. This hydrolysis, catalyzed by $Sc^{III}$, is due to traces of water in the organic solvents (chloroform and acetonitrile) as well as to the water coordinated to the scandium ion (4.3 molecules of $H_2O$ were found by elemental analysis of $Sc(OTf)_3$). When the reaction was performed under the transimination protocol, hydrolysis did not occur as the aldehyde is not detected. Indeed, had this aldehyde formed, it should have been detectable, as in the presence of scandium, the transimination reaction was found to be faster than the condensation of aldehyde and amine. For example, the exchange of **1** and **5** exhibits a $V_0^C$ of $1.62 \times 10^3$ mM $h^{-1}$ with 4% $Sc^{III}$ (see, Table 1, entry 4), while the formation of compound **5**, from 9-anthracenecarboxaldehyde and aniline in the presence of 4% of catalyst, displays a rate of only 49.5 mM $h^{-1}$ (33 times slower). The control without catalyst has a value of 0.18 mM $h^{-1}$ ($9 \times 10^3$ times slower).
(26) For general acid catalysis, see: (a) Jencks, W. P. *J. Am. Chem. Soc.* **1959**, *81*, 475−481. (b) Sayer, J. M.; Jencks, W. P. *J. Am. Chem. Soc*. **1973**, *95*, 4277−4287.
(27) To avoid the in situ liberation of protons, as slowly occurs in $CDCl_3$, reactions intended to study the linear correlation between the initial rate and the catalyst concentration were performed in deuterated tetrachloroethane.
(28) Experiments were set up for 10 different values of imine concentration from 0.05 equiv to 0.9 equiv (1.13, 4.52, 6.78, 9.04, 11.3, 13.6, 15.8, 18.1, and 20.3 mM) relative to the amine (22.6 mM; 4 mol % catalyst); and for eight different values of amine concentration from 0.1 equiv to 1.8 equiv (2.26, 4.52, 9.04, 18.4, 27.1, 36.2, and 40.7 mM) relative to the imine (22.6 mM; 4 mol % catalyst).

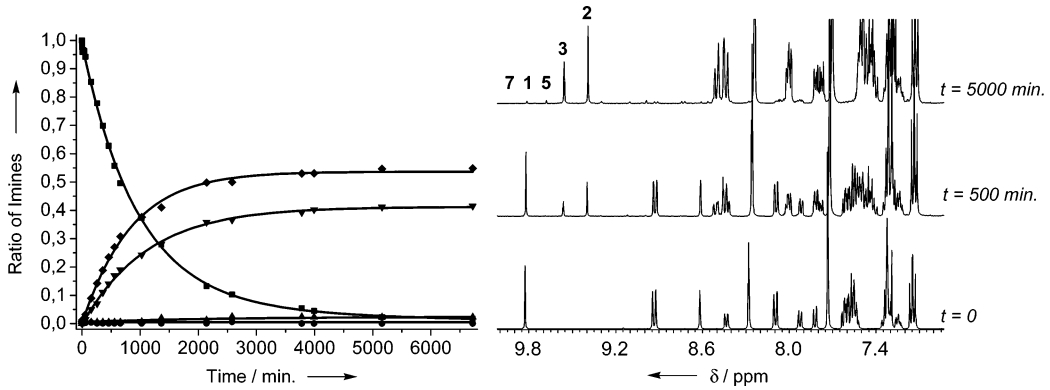
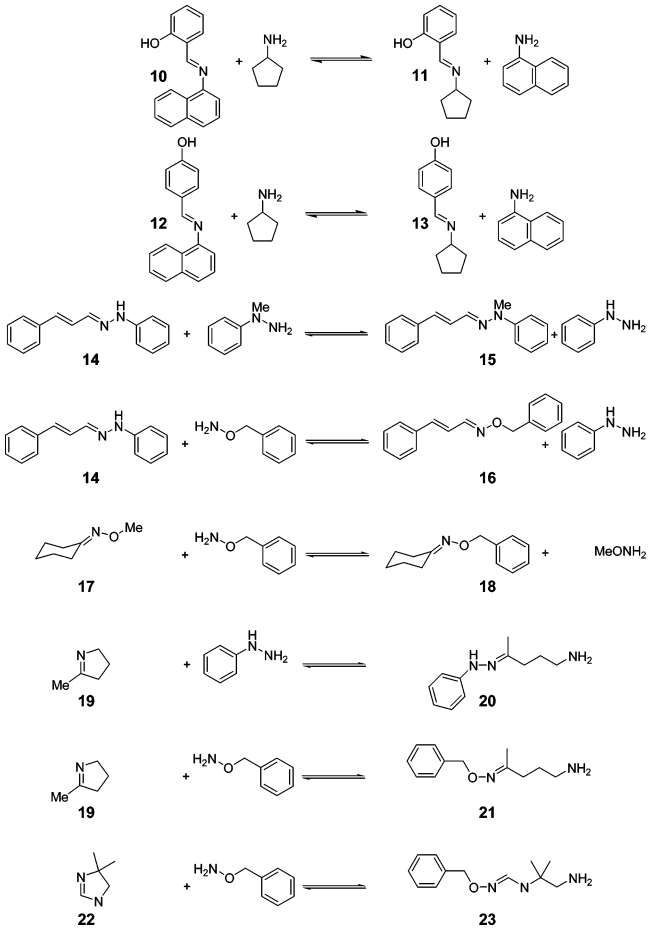



***Figure 4.*** Left: Evolution over time of the equilibration of the imines **1**, **2**, **3**, **5**, and **7** in $CDCl_3$ at 25 °C starting from imine **1** (**1**$_i$ 22.6 mM) mixed with equimolar amounts of the amines, cyclopentylamine, benzylamine, aniline, and 2,4-dinitroaniline, corresponding to the imines **2**, **3**, **5**, and **7** and using 16 mol % of $Sc(OTf)_3$ (relative to **1**) added as a $CD_3CN$ solution. The products are labeled as follows: ■ (**1**); ◆ (**2**); ▼ (**3**); ▲ (**5**); ● (**7**). Right: Selected 400 MHz $^1H$ NMR spectra at different times corresponding to the graph on the left.

***Scheme 5.*** Exchange Reactions between Various Imines, Hydrazones, Oximes, and an Imide in Deuterated Chloroform and in the Presence of Catalytic Amounts of $Sc(OTf)_3$, Added from a $CD_3CN$ Solution




increase with the basicity of the amine, whether free or engaged in the imine.

**C. Effects of Component Competition.** Bringing together the results discussed above, and comparing the separate equilibrating reactions (Tables 1 and 2) with the behavior observed for the five-membered competitive experiment (Figure 4), allows the formulation of a mechanism for the catalyzed transimination involving a ternary intermediate with simultaneous coordination of at least one amine and one imine (plus solvent molecules) to the mediator metal ion ("promnastic" effect).[15a] The behavior of the individual parallel reactions as compared to that of the mixture leads to a set of reactions coupled through a common catalyst that may be schematically represented according to the change in their constitutional connectivity, as depicted in Figure 6.

In this diagram, the reactions starting from imine **1** and various amines are represented using nodes and links having different sizes and thicknesses corresponding, respectively, to the relative thermodynamic ($S$) and kinetic ($V_0$) parameters that both depend on the relative basicity of the amines. In both cases, individual (left) and coupled (right) equilibria, the basicity of the amine determines the distribution $S$ at the equilibrium.[29] On the contrary, the initial rates $V_0$ follow an opposite sequence as a function of basicity on going from the individual to the competing system. Such a behavior agrees with the presence of a unique intermediate that constitutes the core of a network of competing reactions. In the mixed system, every single amine or imine competes for the same central hub, in accordance with its binding activity for the catalytic metal ion center. Thus, the most basic amine (cyclopentylamine) monopolizes the hub and determines the rate of the overall system because it acts as the most efficient competitor in the transimination process.[30]

The competitive mixed system (Figure 6, right) may be illustrated by the crossover reactions occurring between **1**, cyclopentylamine, and aniline, depicted in Scheme 8. We suggest that the rate-determining step, for each competitive catalytic cycle, is the addition reaction of the amine to the imine **1** through the ternary intermediates **A** and **A′**, on the following grounds: (1) the steps involving proton transfer display a rapid exchange on the NMR time-scale and present a negligible isotope effect;[31] (2) the elimination steps from the gem-diamino compounds (**B** and **B′**) are not rate determining as these intermediates are not observable in the NMR spectra (consequently, $k_{-1}$, $k_{-1}'$ ≫ $k_1$, $k_1'$, and $k_{-2}$, $k_{-2}'$ ≫ $k_2$, $k_2'$); and (3) the initial rate $V_0$ is independent of imine/amine concentrations in

(29) Spencer, J. N. *J. Chem. Educ.* **1992**, *69*, 281−284.
(30) A related behavior is found for carrier-mediated transport. See: Jacquez, J. A. *Biochim. Biophys. Acta* **1967**, *79*, 318−328. Also, in the transport of alkali ions by cryptates, the strongly bound potassium ions saturate the carrier and strongly decrease the transport rates, see: Kirch, M.; Lehn, J.-M. *Angew. Chem.* **1975**, *87*, 542−543; *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 555−556. Behr, J.-P.; Kirch, M.; Lehn, J.-M. *J. Am. Chem. Soc.* **1985**, *107*, 241−246.
(31) The reaction described in Scheme 2 was performed at 25 °C using deuterated cyclopentylamine and led to an identical initial rate as compared to the undeuterated amine.

***Table 5.*** Values of the Selectivity Constants ($S$), the Initial Catalyzed ($V_0^C$) and Uncatalyzed ($V_0^U$) Rates, and the Turnover Frequencies (TOF) for the Exchanges between Imines Hydrazones and Oximes Depicted in Scheme 5

| entry | equilibrium $x \rightleftharpoons y$ | $S$ ($y/x$) | $V_0^C$/mM h$^{-1}$ 4% Sc$^{III}$ | $V_0^U$/mM h$^{-1}$ control | acceleration $V_0^C/V_0^U$ | TOF/h$^{-1}$ Sc$^{III}$ |
|---|---|---|---|---|---|---|
| 1 | **10** ⇌ **11** | 50 | 27.4 | 0.96 | 28.5 | 30.4 |
| 2 | **12** ⇌ **13** | 7.7 | 97 | 6.8 | 14.5 | 108 |
| 3 | **14** ⇌ **15** | 1.5 | 21 | $5.1 \times 10^{-2}$ | 412 | 23.3 |
| 4 | **14** ⇌ **16** | 4.55 | 133 | 3.13 | 43 | 147 |
| 5 | **17** ⇌ **18** | 0.92 | 3250 | $5.4 \times 10^{-3}$ | $6 \times 10^5$ | 3616 |
| 6 | **19** ⇌ **20**[a] | | 0 | 0 | | |
| 7 | **19** ⇌ **21** | 1.5 | 813 | 1.27 | 640 | 903 |
| 8 | **22** ⇌ **23** | 1 | 0.84 | $4.84 \times 10^{-2}$ | 18 | 0.93 |

[a] The reaction was performed at both 25 and 60 °C.

***Scheme 6.*** Exchange Reactions Using Polystyrene Microencapsulated Scandium (MC Sc(OTf)$_3$) as Supported Catalyst (4 mol %) for Various Crossover-Type Reactions in $CD_3CN$

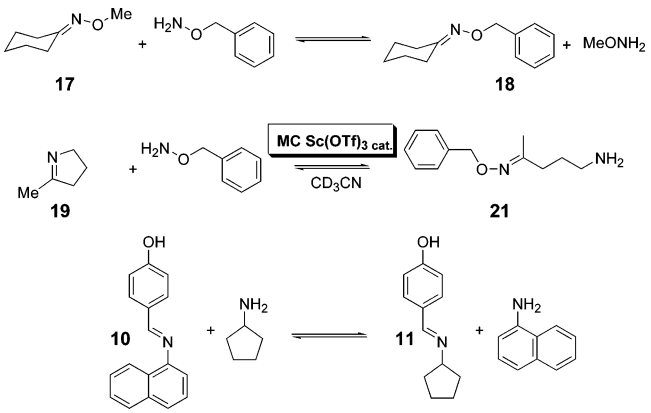



***Table 6.*** Values of the Turnover Frequencies (TOF) for the Exchanges between Imines Hydrazones and Oximes Depicted in Scheme 6 (**17**$_i$ = **19**$_i$ = **10**$_i$ = 22.6 mM), Using 4 mol % of Free Sc(OTf)$_3$ Catalyst[a] in $CDCl_3$, in $CD_3CN$, and Polystyrene Microencapsulated Sc$^{III}$ in $CD_3CN$[b] at 25 °C

| entry | equilibrium $x \rightleftharpoons y$ | TOF/h$^{-1}$ free Sc$^{III}$ ($CDCl_3$) | TOF/h$^{-1}$ free Sc$^{III}$ ($CD_3CN$) | TOF/h$^{-1}$ MC Sc$^{III}$ ($CD_3CN$) |
|---|---|---|---|---|
| 1 | **17** ⇌ **18** | 3616 | 230 | 160[c] |
| 2 | **19** ⇌ **21** | 903 | 451 | 185 |
| 3 | **10** ⇌ **11** | 108 | 33 | 23 |

[a] Added as a 45 mM acetonitrile solution; final solution contains 2 vol % acetonitrile solution. [b] Prepared according to ref 23. [c] Without Sc$^{III}$ in $CD_3CN$, no crossover product is detectable by NMR after 3 days.

the range studied (saturation effect),[28] corresponding to a $V_0^{max}$ and suggesting a rapid preequilibration (fast associations and exchanges between scandium and amine/imine ligands) with Michaelis−Menton-type kinetics. One may propose that the mediators **A** and **A′**, involved in the rate-determining step, assemble several amines or imines into their coordination spheres and that the maximum reaction rate is given by $V_0^{max} = k\mathbf{A}$. Finally, the results of Figure 2 ($V_0^I = V_0^{II}$) indicate that the proposed transimination reaction is symmetrical for the forward and the backward reactions ($k_1$ close to $k_1'$ and $k_2$ close to $k_2'$), as a result of the interplay between relative amine and imine basicities, that is, relative binding to the catalytic ion. In terms of microscopic steps for the conversion of **A** to **B** in Scheme 8, the addition is preceded by rapid preequilibria reestablishing the distribution of ligands in the first and second coordination spheres of the metal complex, followed by further rapid equilibria reestablishing this distribution with the products.

One may suppose that the nucleophile amine occupies the second coordination sphere of the catalyst, which could explain a zero-order dependence on reactants because a constant concentration of ions electrostatically localizes in the immediate vicinity. Such a rapid reversible amine coordination would result in intermediate states where no amine occupies the empty coordination site to deactivate the imine and may facilitate the addition of the outgoing (or incoming) amine to the activated imine.

When several amines are brought together in crossover experiments, the imine formation results from competition between the two pathways of Scheme 8. The results above (Table 1, entries 1 and 4) indicate that the formation of imine **5** (bottom pathway of Scheme 8) is about 2000 times faster than the formation of imine **2** (top pathway of Scheme 8). In the competitive experiment (both pathways operating simultaneously), the observed amount of **5** was never higher than 2.5% over the course of the exchange (Figure 4), and **2** is formed faster than **5**. This result is a clear illustration of the interplay of processes occurring in competitive experiments with mixtures. It may be rationalized by considering that the intermediate **A** is significantly more stable than **A′** because the lone pair of cyclopentylamine is more electron-rich than that of aniline, resulting in a stronger binding to Sc$^{III}$.[19] Consequently, the catalyst is preferentially surrounded in the coordination sphere by cyclopentylamine, which circumvents the incorporation of aniline and decreases the catalytic activity. One may generalize this interpretation by considering that the most strongly coordinated amine of any competitive mixture will dominate the denominator of the rate equation. This analysis holds for the more complex system described in Figures 4 and 6 (right) involving altogether five amines and five imines.[32] The present mechanistic study reveals that isoenergetic libraries,[6a] here sets of amines of similar basicities, are particularly well-adapted for the Sc$^{III}$-catalyzed transimination process, as they yield the fastest exchanges, as well as equi-distributions of products at equilibrium, a crucial aspect for further instruction/amplification of the dynamic system.

## Conclusions

We have shown that transimination reactions can be efficiently catalyzed by scandium(III) acting as a Lewis acid and produce turnovers up to 3600 h$^{-1}$ and rate accelerations up to $6 \times 10^5$. A wide variety of C=N-type bonds are exploitable

(32) Moreover, the reaction carried out under conditions that are typically used for constructing Hammett plots, that is, using the same constitutional mixture with a 4:1 ratio between **1** and each of the free amines, leads to a similar general behavior, with the product of the most strongly bound amine coming first, and the others following afterward.

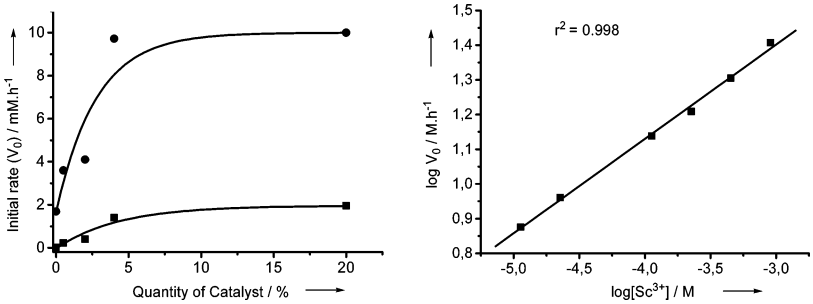
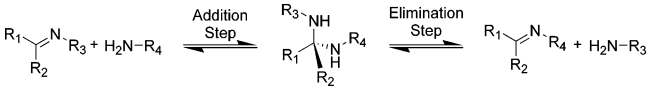



***Figure 5.*** Left: Dependence of the initial rate $V_0$ for the forward reaction of the equilibrium described in Scheme 2 (**1** = 22.6 mM) in $CDCl_3$, and determined using $^1$H NMR at 25 °C (■) and 60 °C (●), on the amount of catalyst used. Right: Plot of log($V_0$) against log($Sc^{III}$) for the equilibrium described in Scheme 2 at 60 °C in $C_2D_2Cl_4$, and for 0.05, 0.1, 0.5, 1, 2, and 4 mol % of catalyst.

***Scheme 7.*** General Representation of the Addition/Elimination Steps in the Transimination Process




using the optimal procedures that require only low amounts of catalyst and soft conditions. Microencapsulated catalyst represents a potentially useful tool, as it would be of major interest to realize the reshuffling of compound libraries on solid support, with or without an immobilized target, to both freeze and isolate the equilibrated amplified mixtures by simple filtration.

An analysis of the dependence of reaction rates and product distributions at equilibrium led to the formulation of a mechanism involving a ternary intermediate in which $Sc^{III}$ is simultaneously coordinated to amine and imine (as well as solvent) molecules. The application to mixtures of amines reveals the role played by coupled processes between competing components as compared to independent reactions. It was found that the closer are the basicities of the component amines, the faster are the rates of equilibration, thus stressing the advantage of isoenergetic (isobasic in the present case) libraries. Furthermore, the intrinsic kinetic parameters for isolated reactions cannot simply be added up when several components are mixed due to the formation of a hub in a networked system, where every single component competes for a unique catalyst. This competitive inter-relation results in a behavior of the mixture that is markedly different from what might be expected from consideration of the separate individual reactions. It bears ressemblance to processes such as enzymatic reactions or carrier-mediated transport through membranes in the presence of mixtures of competing substrates. The results obtained are of particular significance with respect to the implementation of dynamic combinatorial processes in chemical reactivity and catalysis. More generally, they extend the basic principles of constitutional dynamic chemistry to interconnected chemical transformations and provide a step toward dynamic systems of increasing complexity.

## Experimental Section

**Experimental Data for Compounds and Procedures. General Aspects.** All reagents and solvents were purchased at the highest commercial quality and were used without further purification unless otherwise noted. Deuterated chloroform used for the kinetic measurements was flashed through alumina immediately prior to use, to remove any trace of acid. Yields refer to purified spectroscopically ($^1$H NMR) homogeneous materials. $^1$H NMR spectra were recorded on a Bruker Avance 400 spectrometer. The spectra were internally referenced to the residual proton solvent signal. In the $^1$H NMR assignments, the chemical shifts are given in ppm. The coupling constants $J$ are listed in Hz. The following notation is used for the $^1$H NMR spectral splitting patterns: singlet (s), doublet (d), triplet (t), multiplet (m), large (l). The temperatures that are given for the kinetic and thermodynamic data were directly measured and regulated in the NMR probe using a thermocouple. Electrospray (ESI-TOF) studies were performed on a Bruker MicroTOF mass spectrometer (sample solutions were introduced into the mass spectrometer source with a syringe pump with a flow rate of 160 $\mu$L min$^{-1}$). Melting Points (Mp) were recorded on a Kofler Heizblock and on a Büchi Melting Point B-540 apparatus and are uncorrected. Microanalyses were performed by the Service de Microanalyze, Institut de Chimie, Université Louis Pasteur.

**General Procedures for the Synthesis of Isolated Imines.**

**Method a.** Equimolar amounts of amine (oxime or hydrazine) and aldehyde (or ketone) were solubilized or suspended in ethanol at a concentration of 0.1 M, and the reaction mixtures were refluxed overnight under vigorous stirring. The solutions were then either evaporated to dryness and the crude residues were purified by flash chromatography or, after cooling of the solutions to 0 °C, the precipitates formed from the reaction mixture were filtered and washed with cold ethanol and the compounds crystallized or precipitated from AcOEt/hexane mixtures.

**Method b.** One equivalent of aldehyde (or ketone) and 1.2 equiv of amine (or oxime) were heated neat, up at 80 °C, for 5 min. The excess of amine (or oxime) was then removed under vacuum, and the crude residues were crystallized or precipitated from AcOEt/hexane mixtures.

**General Procedure for Crossover Experiments and Determinations of Kinetic Data.** A typical protocol is realized by the preparation of a fresh $CDCl_3$ solution containing the compounds to exchange in a NMR tube (0.6 mL, 22.6 mM in imine) or a vial (2 mL, 22.6 mM in imine). The desired amounts of catalyst were immediately added to this mixture from a $CD_3CN$ solution (5−50 $\mu$L, 45 mM, 0.2−8.0 vol % of $CD_3CN$ in $CDCl_3$), prior to NMR measurements. The first spectrum was usually recorded 30 s after addition without spinning in the probe. The NMR tubes were topped with Teflon caps to keep a constant concentration.

**(*E*)-*N*-(Anthracen-10-ylmethylene)naphthalen-1-amine (1).** The product was synthesized using the general method a and was obtained as a bright yellow powder (yield 85%). Mp 151−152 °C. Anal. Calcd for $C_{20}H_{19}N$: C, 90.60; H, 5.17; N, 4.23. Found: C, 90.23; H, 5.23; N, 4.05. $^1$H NMR ($CDCl_3$): $\delta$ = 7.32 (d, $^3J$ = 7.3 Hz, 1H), 7.55−7.66 (m, 8H), 7.85 (d, $^3J$ = 7.8 Hz, 1H), 7.95 (d, $^3J$ = 8.8 Hz, 1H), 8.12 (d, $^3J$ = 8.3 Hz, 2H), 8.47 (d, $^3J$ = 7.3 Hz, 1H), 8.65 (s, 1H), 8.97 (d, $^3J$ = 8.8 Hz, 2H), 9.86 (s, 1H). $^{13}$C NMR ($CDCl_3$): 112.95, 124.25, 124.85, 125.45, 126.00, 126.15, 126.20, 126.50, 127.15, 127.40, 127.70, 128.80, 129.10, 130.90, 131.00, 131.35, 134.05, 150.30, 159.95. MS (electrospray): *m*/*z* 332.1 (100) M + H$^+$.

**(*E*)-*N*-(Anthracen-10-ylmethylene)cyclopentylamine (2).** The product was synthesized using the general method a and was obtained as a yellow, fluffy powder (yield 92%). Mp 95−96 °C. Anal. Calcd for

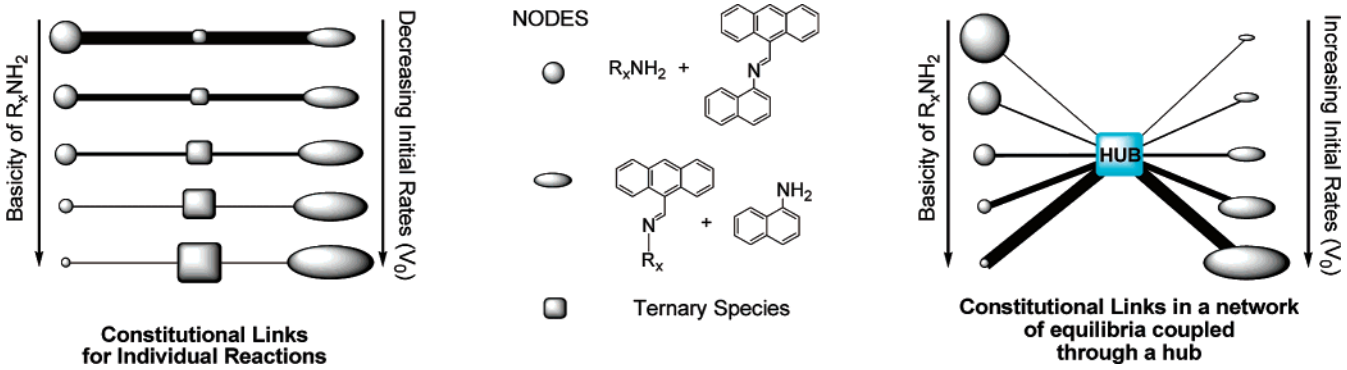
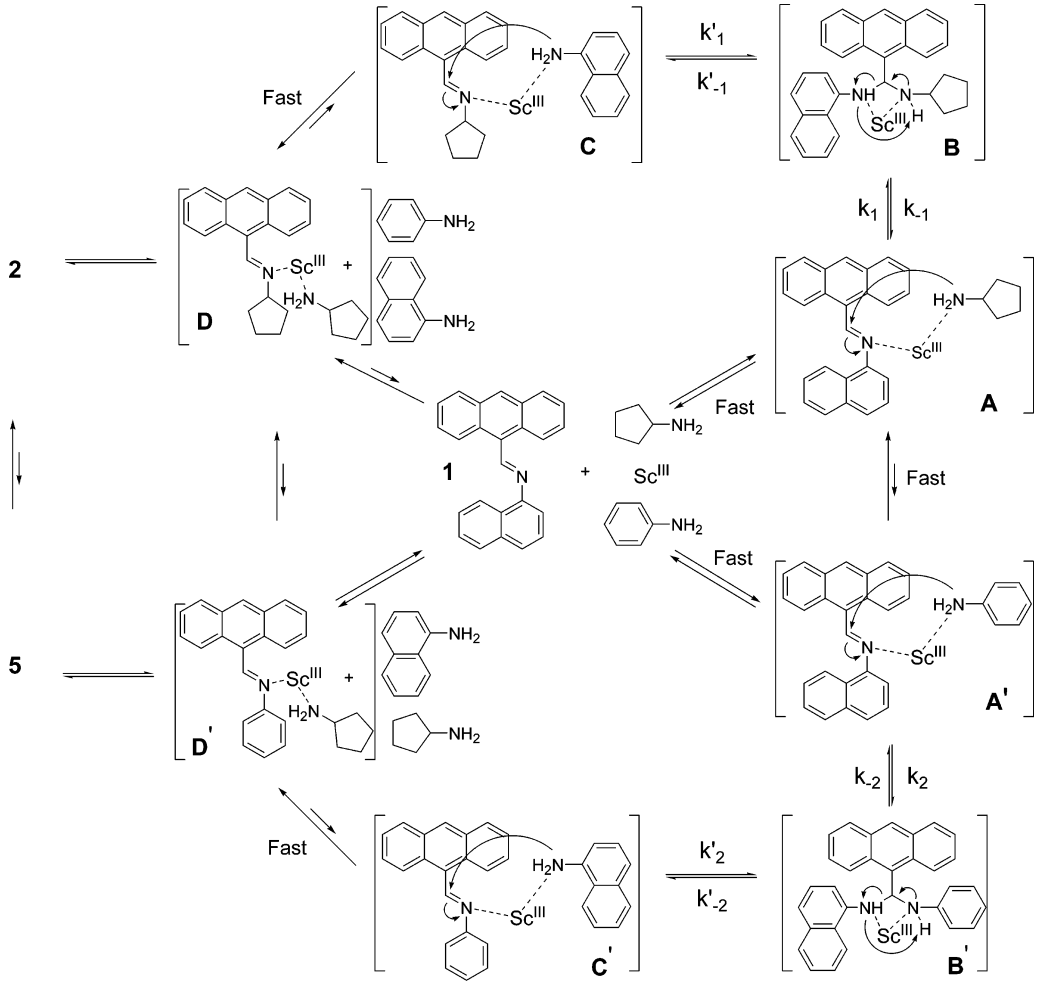



***Figure 6.*** Schematic representation of the constitutional connectivities and their related thermodynamic ($S$) and kinetic ($V_0$) parameters for: (left) the individual transimination reactions starting from imine **1** and various amines and proceeding via a ternary species involving catalyst, amine, and imine (see Scheme 3 and Table 1); (right) system interconnected through a common entity, the ternary species, hub (see, Figure 4). The relative size of the dots represents the relative abundance of products after reaching the equilibrium; the relative thickness of the bonds represents the relative initial rates of the reactions.

***Scheme 8.*** Simplified Schematic Representation of Two Competing Pathways for the Transimination Reaction That Involves a Simple Model Exchange between **1**, Cyclopentylamine, and Aniline[a]




[a] For clarity, the steps representing proton transfers are not depicted as they are not rate-determining, and $Sc^{III}$ represents coordinated $Sc^{III}(L)_x$ ions, with L being amine, imine, and solvent molecules.

$C_{20}H_{19}N$: C, 87.87; H, 7.01; N, 5.12. Found: C, 87.28; H, 7.07; N, 5.18. $^1H$ NMR ($CDCl_3$): $\delta = 1.80$ (l, 2H), 2.00 (l, 4H), 2.13 (l, 2H), 4.15 (qt, $^3J = 5.9$ Hz, 1H), 7.53 (m, 4H), 8.05 (d, $^3J = 8.3$ Hz, 2H), 8.49 (d, $^3J = 8.3$ Hz, 2H), 8.50 (s, 1H), 9.43 (s, 1H). $^{13}C$ NMR ($CDCl_3$): 24.95, 34.90, 73.35, 124.85, 125.20, 126.45, 128.70, 128.85, 129.90, 131.35, 157.55, 162.00. MS (electrospray): $m/z$ 274.15 (100) $M + H^+$.

**(*E*)-*N*-(Anthracen-10-ylmethylene)(phenyl)methylamine (3).** The product was synthesized using the general method a and was obtained as an orange solid (yield 72%). Mp 90−91°C. Anal. Calcd for $C_{22}H_{17}N$: C, 89.46; H, 5.80; N, 4.74. Found: C, 89.69; H, 5.88; N, 4.57. $^1H$ NMR ($CDCl_3$): $\delta = 5.19$ (s, 2H), 7.39 (m, 1H), 7.46 (m, 2H), 7.54 (m, 6H), 8.06 (d, $^3J = 7.6$ Hz, 2H), 8.54 (s, 1H), 8.56 (d, $^3J = 8.5$ Hz, 2H), 9.6 (s, 1H). $^{13}C$ NMR ($CDCl_3$): 67.2, 125.6, 126.0,

127.5, 128.0, 128.8, 129.0, 129.5, 129.7, 130.3, 130.9, 132.1, 139.2, 162.2. MS (electrospray): *m*/*z* 296.146 (100) M + H$^+$.

**(*E*)-*N*-(Anthracen-10-ylmethylene)-4-methoxybenzenamine (4).** The product was synthesized using the general method a and was obtained as a yellow powder (yield 84%). Mp 147−148 °C. Anal. Calcd for $C_{14}H_{13}NO$: C, 84.86; H, 5.50; N, 4.50. Found: C, 84.66; H, 5.56; N, 4.27. $^1$H NMR ($CDCl_3$): $\delta$ = 9.70 (s, 1H), 8.72 (d, $^3J$ = 8.8 Hz, 2H), 8.55 (s, 1H), 8.06 (d, $^3J$ = 8.3 Hz, 2H), 7.54 (m, 4H), 7.45 (d, $^3J$ = 8.8 Hz, 2H), 7.04 (d, $^3J$ = 8.8 Hz, 2H). $^{13}$C NMR ($CDCl_3$): 158.6, 157.7, 145.6, 131.4, 130.6, 130.3, 129.0, 127.7, 127.1, 125.4, 124.9, 122.3, 114.5, 55.6. MS (electrospray): *m*/*z* 312.134 (100) M + H$^+$.

**(*E*)-*N*-(Anthracen-10-ylmethylene)benzenamine (5).** The product was synthesized using the general method a and was obtained as yellow needle-shaped crystals (yield 84%). Mp 111−112 °C. Anal. Calcd for $C_{21}H_{15}N$: C, 89.65; H, 5.37; N, 4.98. Found: C, 89.71; H, 5.44; N, 4.84. $^1$H NMR ($CDCl_3$): $\delta$ = 5.19 (s, 2H), 7.39 (m, 1H), 7.46 (m, 2H), 7.54 (m, 6H), 8.06 (d, $^3J$ = 7.6 Hz, 2H), 8.54 (s, 1H), 8.56 (d, $^3J$ = 8.5 Hz, 2H), 9.6 (s, 1H). $^{13}$C NMR ($CDCl_3$): 121.80, 125.50, 126.20, 127.10, 128.05, 129.85, 130.15, 130.20, 131.45, 131.50, 132.15, 153.55, 160.85. MS (electrospray): *m*/*z* 282.12 (100) M + H$^+$.

**(*E*)-*N*-(Anthracen-10-ylmethylene)-3-nitrobenzenamine (6).** The product was synthesized using the general method a and was obtained as an orange powder (yield 65%). Mp 181−182 °C. Anal. Calcd for $C_{21}H_{15}N$: C, 77.29; H, 4.32; N, 8.58. Found: C, 76.78; H, 4.42; N, 8.21. $^1$H NMR ($CDCl_3$): $\delta$ = 9.77 (s, 1H), 8.81 (d, $^3J$ = 8.8 Hz, 2H), 8.63 (s, 1H), 8.25 (s, 1H), 8.18 (d, $^3J$ = 7.8 Hz, 1H), 8.08 (d, $^3J$ = 8.3 Hz, 2H), 7.73 (d, $^3J$ = 8.3 Hz, 2H), 7.61 (m, 3H), 7.63 (t, $^3J$ = 6.8 Hz, 2H). $^{13}$C NMR ($CDCl_3$): 162.0, 153.7, 135.2, 131.3, 131.1, 130.9, 130.1, 129.8, 129.3, 129.1, 127.9, 127.7, 128.8, 125.7, 125.5, 124.4, 123.5, 120.7, 120.5, 115.5. MS (electrospray): *m*/*z* 327.1 (100) M + H$^+$.

**(*E*)-*N*-(Anthracen-10-ylmethylene)-3,5-dinitrobenzenamine (7).** The product was synthesized using the general method a and was obtained as an orange powder (yield 63%). Mp 263−264 °C. Anal. Calcd for $C_{21}H_{15}N$: C, 67.92; H, 3.53; N, 11.32. Found: C, 67.92; H, 3.64; N, 11.32. $^1$H NMR ($CDCl_3$): $\delta$ = 7.61 (t, $^3J$ = 8.1 Hz, 2H), 7.71 (t, $^3J$ = 8.1 Hz, 2H), 8.14 (d, $^3J$ = 8.6 Hz, 2H), 8.55 (s, 2H), 8.72 (s, 1H), 8.93 (d, $^3J$ = 8.6 Hz, 2H), 9.00 (s, 1H), 9.88 (s, 1H). $^{13}$C NMR ($CDCl_3$): 115.35, 121.35, 124.05, 125.75, 128.55, 129.55, 131.25, 131.55, 133.60, 155.00, 163.75. MS (electrospray): *m*/*z* 372.1 (100) M + H$^+$.

**(*E*)-*N*-(Anthracen-10-ylmethylene)prop-2-en-1-amine (8).** The product was synthesized using the general method b and was obtained as a yellow solid (yield 75%). Mp 67−68 °C. Anal. Calcd for $C_{18}H_{15}N$: C, 88.13; H, 6.16; N, 5.71. Found: C, 88.09; H, 6.24; N, 5.63. $^1$H NMR ($CDCl_3$): $\delta$ = 4.63 (d, $^3J$ = 4.7 Hz, 2H), 5.32 (d, $^3J$ = 9.9 Hz, 1H), 5.44 (d, $^3J$ = 17.2 Hz, 1H), 6.32 (m, 1H), 7.55 (m, 4H), 8.06 (d, $^3J$ = 8.2 Hz, 2H), 8.51 (s, 1H), 8.52 (d, $^3J$ = 8.5 Hz, 2H), 9.50 (s, 1H). $^{13}$C NMR ($CDCl_3$): 65.60, 117.25, 125.55, 126.00, 127.45, 129.65, 129.70, 130.15, 130.80, 132.10, 136.80, 162.15. MS (electrospray): *m*/*z* 246.132 (100) M + H$^+$.

**(*E*)-*N*-(Anthracen-10-ylmethylene)-3-methylbutan-1-amine (9).** The product was synthesized using the general method b and was obtained as an orange waxy solid (yield 70%). Mp 56.5−57.5 °C. Anal. Calcd for $C_{20}H_{21}N$: C, 87.23; H, 7.69; N, 5.09. Found: C, 86.82; H, 7.66; N, 5.09. $^1$H NMR ($CDCl_3$): $\delta$ = 1.05 (d, $^3J$ = 6.3 Hz, 6H), 1.86 (m, 3H), 4.00 (t, $^3J$ = 7.0 Hz, 2H), 7.55 (m, 4H), 8.06 (d, $^3J$ = 8.2 Hz, 2H), 8.51 (s, 1H), 8.52 (d, $^3J$ = 8.5 Hz, 2H), 9.4 (s, 1H). $^{13}$C NMR ($CDCl_3$): 22.80, 26.30, 40.45, 61.80, 125.60, 126.00, 127.35, 129.35, 129.65, 129.85, 130.75, 132.10, 160.75. MS (electrospray): *m*/*z* 276.177 (100) M + H$^+$.

**(*E*)-2-((Naphthalen-1-ylimino)methyl)phenol (10).** The product was synthesized using the general method b and was obtained as an orange-brown powder (yield 77%). Mp 46−47 °C. Anal. Calcd for $C_{17}H_{13}NO$: C, 82.57; H, 5.30; N, 5.66. Found: C, 82.66; H, 5.36; N, 5.88. $^1$H NMR ($CD_3CN$): $\delta$ = 7.02 (t, $^3J$ = 7.4 Hz, 1H), 7.15 (d, $^3J$ = 8.2 Hz, 1H), 7.23 (d, $^3J$ = 7.0 Hz, 1H), 7.45−7.60 (m, 5H), 7.83 (d, $^3J$ = 7.0 Hz, 1H), 7.93 (dd, $^3J$ = 6.3 Hz and $^3J$ = 3.1 Hz, 1H), 7.93 (dd, $^3J$ = 5.8 Hz and $^3J$ = 3.1 Hz, 1H), 8.75 (s, 1H). $^{13}$C NMR ($CDCl_3$): 114.70, 118.05, 119.95, 120.25, 124.00, 126.70, 127.25, 127.45, 127.70, 128.70, 129.00, 133.20, 134.20, 134.80, 147.15, 162.20, 164.65. MS (electrospray): *m*/*z* 248.099 (100) M + H$^+$.

**(*E*)-2-((Cyclopentylimino)methyl)phenol (11).** The product was synthesized using the general method b and was obtained as an orange solid (yield 65%). Mp 34−35 °C. Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.35; H, 7.99; N, 7.52. $^1$H NMR ($CDCl_3$): $\delta$ = 1.73 (l, 4H), 1.88 (l, 2H), 1.96 (l, 2H), 3.80 (d, $^3J$ = 5.5 Hz, 1H), 6.89 (t, $^3J$ = 7.4 Hz, 1H), 6.98 (d, $^3J$ = 8.2 Hz, 1H), 7.26 (d, $^3J$ = 7.4 Hz, 1H), 6.89 (t, $^3J$ = 8.2 Hz, 1H), 8.37 (s, 1H). $^{13}$C NMR ($CDCl_3$): 24.50, 35.00, 70.45, 117.65, 119.15, 119.60, 131.80, 132.70, 162.20, 163.20. MS (electrospray): *m*/*z* 190.115 (100) M + H$^+$.

**(*E*)-4-((Naphthalen-1-ylimino)methyl)phenol (12).** The product was synthesized using the general method b and was obtained as a beige, sandlike solid (yield 78%). Mp 190−191 °C. Anal. Calcd for $C_{17}H_{13}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.35; H, 7.99; N, 7.52. $^1$H NMR ($CDCl_3$): $\delta$ = 7.00 (d, $^3J$ = 8.3 Hz, 2H), 7.15 (d, $^3J$ = 7.3 Hz, 1H), 7.55 (m, 3H), 7.77 (d, $^3J$ = 8.3 Hz, 1H), 7.92 (d, $^3J$ = 7.3 Hz, 1H), 7.95 (d, $^3J$ = 8.8 Hz, 2H), 8.36 (d, $^3J$ = 7.3 Hz, 1 H), 8.56 (s, 1H). $^{13}$C NMR ($CD_2Cl_2$): 112.60, 115.65, 123.85, 125.30, 125.50, 126.10, 126.80, 127.50, 129.75, 130.85, 133.95, 149.40, 157.20, 159.60, 159.65. MS (electrospray): *m*/*z* 262.118 (100) M + H$^+$.

**(*E*)-4-((Cyclopentylimino)methyl)phenol (13).** The product was synthesized using the general method b and was obtained as a reddish-orange powder (yield 41%). Mp 174−175 °C. Anal. Calcd for $C_{17}H_{13}$-NO: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.35; H, 7.99; N, 7.52. $^1$H NMR ($CDCl_3$): $\delta$ = 1.64−1.93 (m, 8H), 3.75 (qt, $^3J$ = 6.8 Hz, 1H), 6.70 (d, $^3J$ = 8.8 Hz, 2H), 7.52 (d, $^3J$ = 8.8 Hz, 2H), 8.22 (s, 1H). $^{13}$C NMR ($CDCl_3$): 24.60, 34.15, 71.65, 115.75, 121.70, 130.10, 159.45, 160.00. MS (electrospray): *m*/*z* 190.12 (100) M + H$^+$.

**(*E*)-1-Phenyl-2-((*E*)-3-phenylallylidene)hydrazine (14).** The product was synthesized using the general method b and was obtained as a yellow powder (yield 92%). Mp 175−176 °C. Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60. Found: C, 81.12; H, 6.39; N, 12.38. $^1$H NMR ($CDCl_3$): $\delta$ = 6.71 (d, $^3J$ = 16.1 Hz, 1H), 6.90 (t, $^3J$ = 7.4 Hz, 1H), 7.01−7.09 (m, 3H), 7.52 (d, $^3J$ = 8.8 Hz, 2H), 7.27−7.31 (m, 2H), 7.37 (d, $^3J$ = 7.3 Hz, 2H), 7.49 (d, $^3J$ = 7.3 Hz, 2H), 7.58 (d, $^3J$ = 9.2 Hz, 2H), 7.59 (s, 1H). $^{13}$C NMR ($CDCl_3$): 112.70, 120.20, 125.85, 126.55, 128.00, 128.75, 129.35, 134.10, 136.75, 139.80, 144.25. MS (electrospray): *m*/*z* 223.119 (100) M + H$^+$.

**(*E*)-1-Methyl-1-phenyl-2-((*E*)-3-phenylallylidene)hydrazine (15).** The product was synthesized using the general method a and was obtained as a yellow powder (yield 85%). Mp 112−113 °C. Anal. Calcd for $C_{16}H_{16}N_2$: C, 81.32; H, 6.82; N, 11.85. Found: C, 79.18; H, 6.71; N, 11.32. $^1$H NMR ($CDCl_3$): $\delta$ =7.40 (m, 3H), 7.32 (m, 6H), 7.12 (dd, $^3J$ = 8.8 and 15.6 Hz, 1H), 6.93 (m, 1H), 6.73 (d, $^3J$ = 15.6 Hz, 2H), 3.38 (s, 3H). $^{13}$C NMR ($CDCl_3$): 147.6, 137.2, 132.8, 129.0, 128.7, 127.7, 127.6, 126.3. MS (electrospray): *m*/*z* 236.3 (100) M + H$^+$.

**(1*E*,2*E*)-Cinnamaldehyde *O*-Benzyl Oxime (16).** The product was synthesized using the general method a and was obtained as a reddish-brown solid (yield 71%). Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 79.89; H, 6.37; N, 3.34. $^1$H NMR ($CDCl_3$) (mixture of the *s-trans* and *s-cis* isomers with a 1:2 ratio): $\delta$ = 5.20 and 5.24 (2s, 2H), 6.77 (dd, *AB* system, $^3J$ = 15.6 Hz and $^3J$ = 7.5 Hz, 1H), 6.88 (m, *AB* system, 1H), 7.20−7.60 (m, 9H), 7.99 (d, $^3J$ = 8.6 Hz, 1H), 8.60 (d, $^3J$ = 7.5 Hz, 1H). $^{13}$C NMR ($CDCl_3$): 193.70, 152.80, 151.05, 138.60, 131.30, 129.10, 128.80, 128.55, 128.50, 126.90, 125.20, 121.90. MS (electrospray): *m*/*z* 238.12 (100) M + H$^+$.

**Cyclohexanone *O*-Methyl Oxime (17).** The product was synthesized using the general method a and was obtained as a colorless liquid (yield 65%). Anal. Calcd for $C_7H_{13}NO$: C, 66.10; H, 10.30; N, 11.01. Found: C, 66.20; H, 10.25; N, 11.04. $^1$H NMR ($CDCl_3$): $\delta$ = 1.62 (l, 4H), 1.69 (l, 2H), 2.21 (t, $^3J$ = 5.8 Hz, 2H), 2.46 (t, $^3J$ = 5.8 Hz, 2H),

3.83 (s, 3H). $^{13}$C NMR ($CDCl_3$): 25.15, 25.70, 25.80, 27.00, 32.15, 60.90, 160.20. MS (electrospray): *m*/*z* 128.1 (100) M + $H^+$.

**Cyclohexanone *O*-Benzyl Oxime (18).** The product was synthesized using the general method a and was obtained as a slightly orange viscous liquid (yield 73%). Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.54; H, 8.54; N, 6.35. $^1$H NMR ($CDCl_3$): $\delta = 1.62-1.70$ (l, 6H), 2.24 (m, 2H), 2.54 (m, 2H), 5.09 (s, 2H), 7.29−7.32 (m, 5H). $^{13}$C NMR ($CDCl_3$): 55.85, 115.05, 122.95, 129.35, 129.50, 131.85, 137.30, 144.5, 159.40. MS (electrospray): *m*/*z* 204.13 (100) M + $H^+$.

**(*E*+*Z*)-5-Aminopentan-2-one *O*-Hydroxy(phenyl)methyl Oxime (21).** The product was synthesized using the general method a and was obtained as an orange viscous oil (yield 75%). Anal. Calcd for $C_{13}H_{20}N_2O$: C, 69.87; H, 8.80; N, 13.58. Found: C, 70.10; H, 8.91; N, 13.70. $^1$H NMR ($CDCl_3$) (mixture of the *E* and *Z* isomers with a 1:2 ratio, respectively): $\delta = 1.38$ (l, 2H), 1.66 (tt, $^3J = 7.3$ Hz and $^3J = 7.0$ Hz, 2H), 1.88 and 1.90 (2s, 3H), 2.24 and 2.43 (2t, $^3J = 7.3$ Hz, 2H), 2.69 (t, $^3J = 7.0$ Hz, 2H), 5.08 and 5.09 (2s, 2H), 7.30−7.40 (m, 5H). $^{13}$C NMR ($CDCl_3$): 14.32, 20.00, 26.80, 29.85, 30.30, 33.30, 41.75, 41.95, 75.70, 75.75, 128.35, 128.40, 128.65, 128.70, 129.05, 129.10, 139.20, 139.25, 158.80, 159.60. MS (electrospray): *m*/*z* 221.15 (100) M + $H^+$.

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