Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Mechanisms of Imine Exchange Reactions in Organic Solvents

Maria Ciaccia[a] and Stefano Di Stefano*[a]

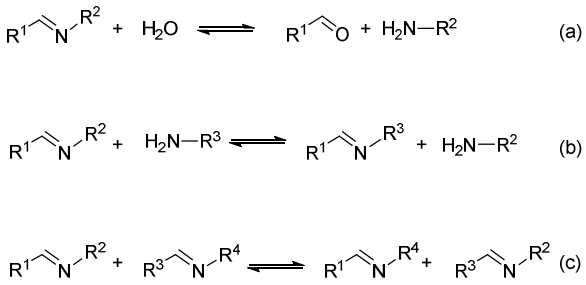
Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

The state of the art in the mechanisms operating in imine chemistry in organic solvents is critically discussed in the present review. In particular, the reaction pathways involved in imine formation, transimination and imine metathesis in organic media are taken into account, with aim at organizing the poor and sometimes scattered information available in the literature. It is shown that 4-membered cyclic transition states, either polar or apolar, can be considered a *leit-motiv* along all the chemistry of imines in organic solvents. However, it is pointed out that further investigations will be necessary to reach an adequate degree of knowledge of the mechanisms involved in such important reversible processes.

Introduction

Imines are compounds containing an azomethine linkage C=N connected to hydrogen or carbon atoms. These compounds are also referred to as Schiff bases, from the name of the chemist who first discovered the reaction between a carbonyl group and an amine.[1] More precisely, Schiff bases are formed from aromatic aldehydes and amines,[2] but the term is often extended to the whole variety of imines. Generally, the presence of at least one aromatic partner (the amine or the carbonyl compound) is necessary for ensuring stability to the correspondent imine.[3] They behave as Brønsted bases covering a wide range of pK_a.[4] Imines are usually prepared by condensation between an aldehyde or ketone and a primary amine, in the presence of dehydrating agents, such as molecular sieves, or *via* azeotropic distillation.[5] The removal of water is needed in order to drive the reaction to completeness, since the condensation between carbonyl and amino compounds is a reversible reaction.

Reversibility is an important feature of the C=N linkage. Imines are widely exploited by nature in many enzymatic processes[6] and by organic chemists in a variety of applications,[2,5b,7] mainly due to the reversibility of the reactions in which they are involved. Imines react reversibly with water (*hydrolysis*, which is the reverse process of imine formation), amines (*transimination*)[8] and preformed imines (*metathesis*), as depicted in Scheme 1.

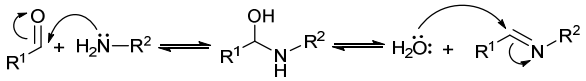


Scheme 1 Reversible reactions involving imines: (a) hydrolysis, (b) amine-imine exchange (transimination) and (c) imine-imine exchange (imine metathesis).

The mechanisms and catalysis of imine formation and exchange (Scheme 1, a and b) have been widely investigated in aqueous media, particularly in the 1960s and 1970s.[6a,9] Conversely, mechanistic studies on these reactions in organic solvents are surprisingly rare and still far from being exhaustive. Nevertheless, imine chemistry in organic media is receiving a constantly growing interest in the contemporary organic chemistry community. A collection of relevant papers concerning mechanistic studies on imine reactions in organic solvents is reviewed below as an attempt to highlight the lack of adequate information and full understanding in this area to date, rather than with the presumption to fill in such gap.

Mechanisms of imine formation in organic solvents

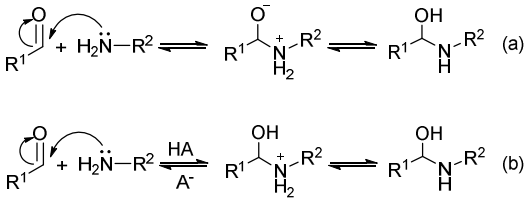
Imine formation is generally considered to occur in a stepwise fashion. In a first step, a tetrahedral intermediate (the carbinolamine) forms as the consequence of a nucleophilic attack of the amino group on the unsaturated carbon of the carbonyl compound. Subsequently, elimination of water from the tetrahedral intermediate occurs and the C=N linkage is generated (Scheme 2).



Scheme 2 Carbinolamine formation and decomposition steps in imine formation reaction.

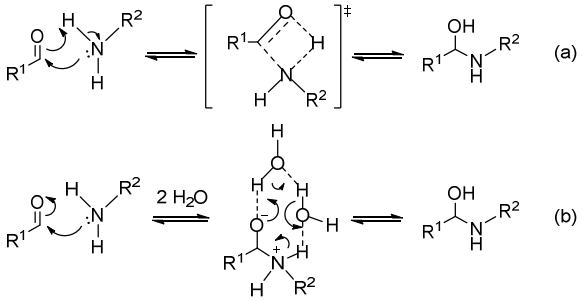
The carbinolamine is a labile species and is generally not isolated or detected.[10] The rate determining step of the reaction in water is pH-dependent,[11] being the decomposition of the tetrahedral intermediate at alkaline pH, and the nucleophilic attack at acid pH. The break-point is a function of the amine nature (pK_a). Only a little is known on the mechanism of this reaction in organic media but it can be easily imagined that a main difference in comparison with the mechanism in water lies in the feasible or unfeasible existence of charged species along the carbinolamine formation / decomposition pathway. In aqueous solution the

formation of the tetrahedral intermediate is a two step process involving charged labile species, either a zwitterion or a cation, depending on the pH (Scheme 3).[12]



Scheme 3 Carbinolamine formation *via* a zwitterion (a) and a cationic intermediate (b).

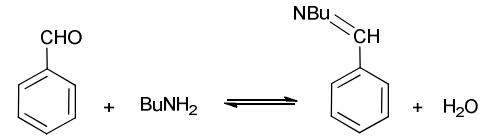
Although this mechanism reasonably occurs in water, to the best of our knowledge, there is no evidence for a similar sequence of reactive events in organic solvents. An alternative mechanism, not involving charged species, entails a cyclic polar four-membered transition state in which the proton is transferred directly from the nitrogen to the oxygen at the same time as the new C-N bond is forming in a concerted fashion (Scheme 4a). A similar process could occur in the decomposition of the carbinolamine (*vide infra*). Such a concerted mechanism has been supported by theoretical *ab initio* calculations. In agreement with previous literature regarding nucleophilic addition to carbonyl compounds,[13] Hall and Smith found out that zwitterionic minima are not predicted in the gas-phase energy surface of formation of the carbinolamine from a complex between methylamine and formaldehyde, or of its decomposition.[14] Zwitterions were instead predicted in the carbinolamine formation when two explicit water molecules were included in the reacting complex (Scheme 4b),[14,15] confirming the predictions by Jencks and co-workers based on secondary deuterium isotope effects.[12]



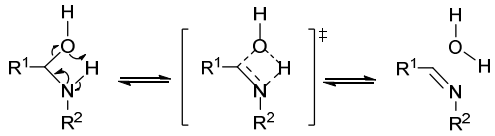
Scheme 4 Formation of the carbinolamine *via* concerted mechanism (a) and *via* zwitterion stabilized by two water molecules (b).

Recently, a kinetic study on the reversible condensation between benzaldehyde and butylamine (Scheme 5), used as a model of imine formation reaction, has been carried out in different organic solvents.[16] A significant influence of the nature of the solvent on the rate of the reaction was observed.

The achievement of the equilibrium in $CDCl_3$, the least polar of the examined solvents, was shown to be reached 37 times more slowly than in CD_3CN, the most polar one. This observation evidences a polar nature of the rate determining transition state. The reaction rate was found to be second order in all cases. Even more interestingly, in the protic solvent CD_3OD, the reaction was shown to be slower than in CD_3CN, confidently excluding an important role of the solvent as a proton shuttle. Thus, as stated before, the elimination step could occur through a cyclic polar four-membered transition state (Scheme 6), similarly to the addition step.



Scheme 5 Condensation reaction between benzaldheyde and butylamine.



Scheme 6 Decomposition of the carbinolamine *via* concerted mechanism.

A very exciting work by Rebek and co-workers[10d,e] concerns the stabilization of a carbinolamine intermediated in the cavity of a synthetic receptor in mesitylene. The encapsulation of the tetrahedral intermediate is a consequence of the condensation reaction between small aliphatic amines (*iso*- and *n*-butylamine, *iso*- and *n*-propylamine, cyclopropylamine and cyclobutylamine) and an anthracenecarboxaldehyde connected to the cavitand receptor (Fig. 1a). The cavitand confines the reactants in a limited space and the activation barrier is lowered as the carbinolamine formation becomes an intracomplex reaction from an "entropic standpoint".[10d] Once formed, the carbinolamine is strongly stabilized in its introverted position by hydrogen bonding with secondary amide groups present in the cavity. Elimination of water from the carbinolamine is retarded by the occurrence of a "transition barrier conferred by the need to reorganize the cavitand upon dehydratation". Interestingly, imine formation in toluene between the aldehyde cavitand and *n*-hexylamine, which is constrained to assume an extroverted orientation (Fig 1b), was found to be strictly first order in amine.[10e] This excludes any involvement of a second amine molecule previously suggested to act as a catalyst in the dehydratation step.[10d] The stabilization provided by the cavitand allowed direct observation and characterization of the carbinolamine by ^{1}H-NMR.

In summary, evidence of a two-step mechanism involving two subsequent cyclic polar four-membered transition states (Schemes 4a and 6) for imine formation in organic solvents has been collected. However, it is our opinion that the topic still requires a deeper and more extended investigation.

Transimination

Similar to imine formation, transimination proceeds reversibly through the formation of a tetrahedral intermediate (aminal) that subsequently decomposes to give a new imine and amine (Scheme 7). The position of the equilibrium depends on the relative basicity of the amines and is generally biased toward the formation of the imine incorporating the most basic amine.[17] The overall exchange process involves the transfer of two protons from the amine to the imine nitrogen atom.

In aqueous solution this process was shown to occur stepwise through the formation of charged transient species.[18] However, since the formation of a zwitterion is unlikely, as it would imply a

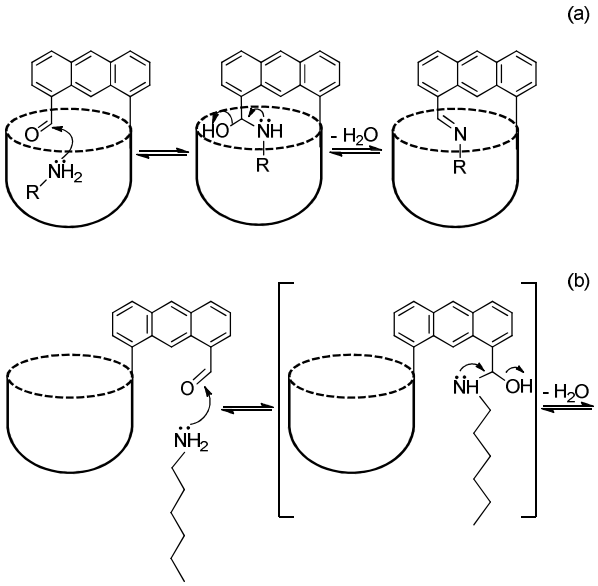
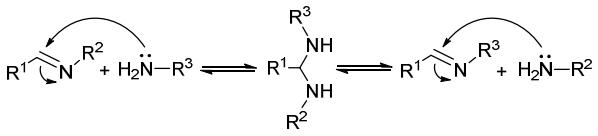


Fig. 1 Stabilization of the labile carbinolamine intermediate by inclusion in cavitand.

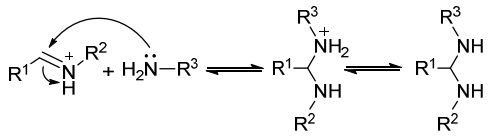


Scheme 7 General scheme of transimination *via* aminal formation.

negative charge on a nitrogen atom, catalysis by acid or solvent (*i.e.*, water) is required to allow the proton transfer.[4a,4c,18] On the other hand, a direct proton transfer between the nitrogen atoms in the formation and decomposition of the aminal has never been considered in protic solvents, and sometimes explicitly excluded.[19]

As a matter of fact, imines are known to usually react more rapidly than the corresponding carbonyl compounds toward nitrogen nucleophiles.[20] This difference in reactivity has been attributed to the higher basicity of the nitrogen atom compared to oxygen.[4a,4c,6a,7b] Acid catalysis activates the electrophile and provides the proton needed to avoid the accumulation of the negative charge on the nitrogen atom (Scheme 8). In these conditions the addition step is usually recognised as rate-determining when the amine nucleophile is less basic than the amine already condensed as the imine. Necessarily, the decomposition of the aminal is rate-determining when the reaction is considered to occur in the opposite direction.[4c,21] Catalysis of transimination by Lewis acids in water solution has been also shown.[20a]

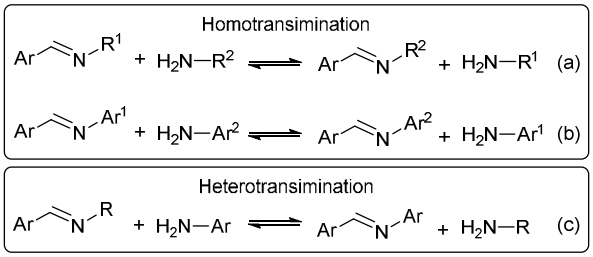
Very recently, transimination reactions in organic media have been the object of a systematic study. Exchange reactions between representative imines derived from several benzaldehydes and primary amines in different organic solvents at room temperature have been investigated.[16,22] In the course of these studies, the higher reactivity of Schiff bases compared to their parent aldehydes toward nitrogen nucleophiles in the absence of any added catalyst, was unexpectedly observed.



Scheme 8 Acid catalysed aminal formation.

For homotransiminations (Scheme 9, a and b), in which the involved amines are both aliphatic or aromatic, the collected kinetic data were shown to be fully consistent with a concerted proton transfer between the two nitrogen atoms in the formation and decomposition of the aminal, implying four-membered cyclic transition states (Scheme 10).

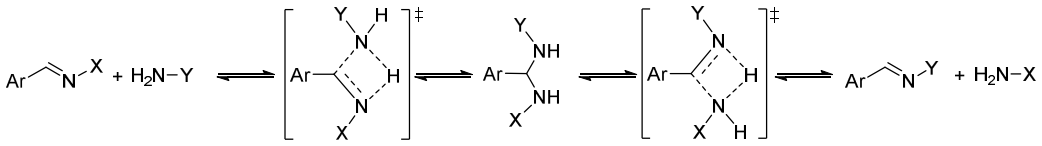
The transition states leading to reagents or products from the central aminal, were shown to be polar in the case of aliphatic amines and almost completely apolar when only aromatic amines are involved. The polar nature of the 4-membered transition states involved in the formation / decomposition of aliphatic aminals was also confirmed by *ab initio* calculations in the gas phase.[16] It was ascribed to non-synchronous formation and breaking of covalent bonds within the 4-membered activated complexes. On the other hand, in the case of homotransiminations with aromatic amines (Scheme 9b), change of solvent (CD_3CN, CD_3OD, CD_2Cl_2, $CDCl_3$) and substitution of the *para* position of the benzylidene ArCH= moiety with electron withdrawing (EWG) or electron realising (ERG) groups, did not afford any substantial effect on the reaction rate, supporting the non polar character of the involved transition states.[22]



Scheme 9 "homotransiminations" and "heterotransiminations". R indicates alkyl groups and Ar aromatic groups.

As for heterotransiminations (Scheme 9c), the effect of EWG and ERG on the *para* position of the benzylidene moiety on the reaction rate evidenced a polar nature of all transition states from and to the aminal (see Scheme 10). Both EWG and ERG resulted to be rate retarding with respect to hydrogen substituent, due to opposite stabilizing or destabilizing effects on the two consecutive asymmetric transition states of Scheme 10.[22]

The effect of the presence of Brønsted and Lewis acids on transimination reaction was investigated by Giuseppone and Lehn less than ten years ago.[23,24] They have shown that Sc^{III} triflate salts are able to catalyse the exchange reactions between sterically hindered imines, derived from 9-anthracenecarboxaldehyde, and several amines in chloroform. In the absence of the metal catalyst, such encumbered imines generally react very slowly with the amine partners. The authors compare the rate of the transimination reaction in the absence and presence of either Brønsted or Lewis acids, CF_3CO_2D and $Sc(OTf)_3$, respectively. $Sc(OTf)_3$ was shown to

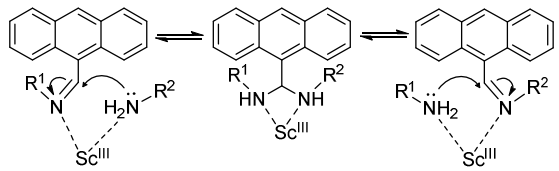


for homotransiminations, X = Y = alkyl or X = Y = aromatic

for heterotransiminations, X = alkyl and Y = aromatic

Scheme 10 Mechanism of transimination *via* cyclic four-membered transition states.

accelerate the reaction up to five orders of magnitude compared to the uncatalysed process and up to two orders of magnitude compared to the proton catalyst,[25] in the most favourable cases. In the proposed mechanism, the metal ion polarises the imine bond and assists the nucleophilic attack of the free amine. The reaction was suggested to proceed *via* fast equilibration between Sc^{III}, amine and imine to form a ternary intermediate that evolves to products (Scheme 11). The higher the basicity of the attacking amine, the lower the efficiency of the catalyst. The dependence of the catalyst efficiency on the basicity of the amine was attributed to a partial deactivation of the nucleophile due to a strong interaction with the metal center. Furthermore, the same interaction necessarily decreases the strength of Sc^{III} as an imine activator.

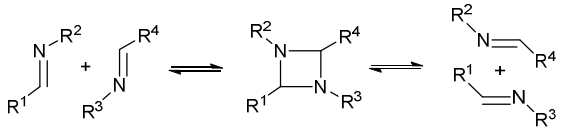


Scheme 11 Lewis acid catalysis of transimination reaction.

Again, as stated above for the imine formation, although transimination in organic solvents has been widely exploited in a variety of applications,[7c,e,26] an exhaustive comprehension of the mechanisms involved strongly calls for further investigations. It is important to stress here that the intrinsic reactivity of Schiff bases toward nitrogen nucleophiles is being only recently recognized,[16,22,26b] in contrast with the general belief that acid catalysis is needed.

Imine Metathesis

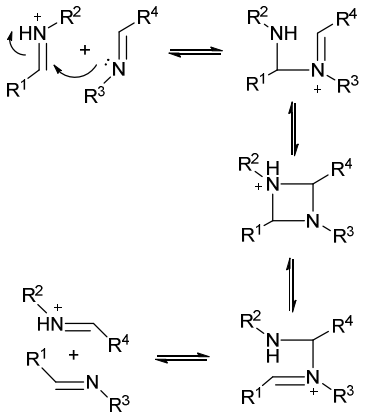
Imine metathesis is a scrambling reaction between two preformed imines which undergo exchange between their amine portions forming two new imines (see Scheme 1c). The mechanism of imine metathesis has been object of study since the early decades of the XX century. In 1922 Ingold and Piggott suggested a concerted mechanism involving the formation and decomposition of a 1,3-diazetidine intermediate (Scheme 12),[27] nowadays viewed as a symmetry forbidden [2π+2π] cycloaddition reaction.



Scheme 12 Concerted mechanism of imine metathesis.

In this section a series of papers, which report several catalysed imine metathesis rections in organic solvents, is discussed. At variance with imine formation and transimination, imine metathesis in organic solvents does not proceed in the absence of any catalyst, thus the description of a mechanism for the uncatalysed imine exchange is meaningless. In the following overview, the chronological order of appearance in the literature of the differently catalysed imine metathesis has been chosen as a presentation guideline.

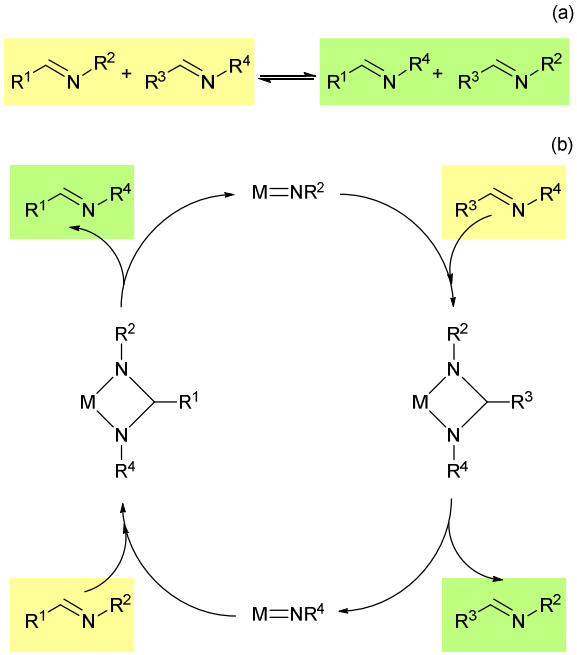
In 1974 a stepwise mechanism involving the formation of ionic intermediates was proposed by Messmer and co-workers.[28] The authors examined the kinetic behaviour of the reaction between *p*-nitrobenzylideneaniline and benzylidene-*p*-anisidine in different solvents at 36 °C and 110 °C, in the presence of collidine (trimethylpyridine) as a base and varying concentrations of trifluoroacetic acid. The reaction rate was shown to increase on increasing solvent polarity, in agreement with the formation of ionic species, as well as increasing concentrations of trifluoroacetic acid catalyst. On the other hand, the reaction did not proceed when carried out in neat trifluoroacetic acid, and very nearly so when the solvent used was pure collidine.[29] This behaviour was found to be in agreement with an acid catalysed nucleophilic attack of a neutral imine on a protonated imine, involving the formation of the three transient, charged intermediates shown in Scheme 13: in excess of acid, both imines are protonated and the nucleophilic attack is inhibited; in the absence of proton the exchange products are not found as acid catalysis is needed to efficiently activate the electrophile. Although the investigation was carried out within a narrow range of concentrations, the kinetics of the reaction was shown to be third order, first order in both imines and first order in triflouroacetic acid in compliance with the proposed mechanistic scheme.



Scheme 13 Polar mechanism of acid catalysed imine metathesis.

A renewed interest toward imine metathesis arose in the 1990s and 2000s in the wake of the success of olefin metathesis.[30] In

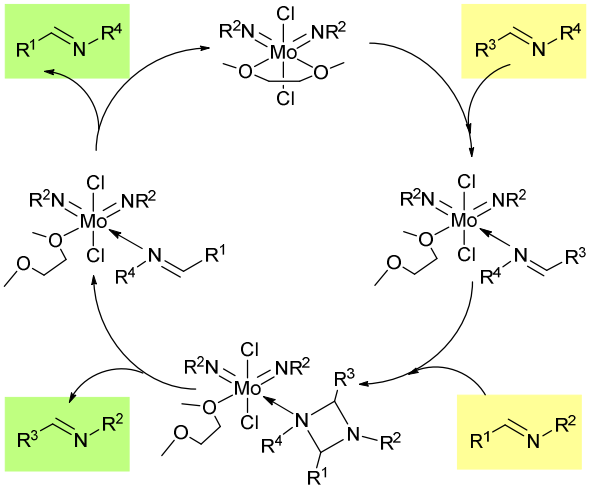
analogy with the latter reaction, a variety of transition metal complexes, containing a metal-imido group M=NR (M = Zr, Mo, Nb, Ti, Ta), were used to catalyse the metathesis.[31] The mechanism proposed for the metal catalysed version of the imine metathesis does not involve a direct reaction between the reacting imines. Conversely, the reaction seems to proceed *via* exchange reaction of each imine with the metal-imido group of the catalyst, resulting in the metathetic products. A general scheme of the catalytic cycle is depicted in Scheme 14. One of the imine reagents is coordinated by the metal center in the metal imide to form a diazametallacycle intermediate, which evolves into one of the imine products and a new metal-imide. The latter reacts with the second imine reactant forming a new cyclic intermediate which, in turn, decomposes into the other metathetic imine product and a metal imide, following a Chauvin-type mechanism.[32] The formation of diazametallacycles was confirmed by Bergman *et al.* in the course of studies on imine metathesis catalysed by zirconium complexes.[31a,b,f,h,33]



Scheme 14 Imine metathesis reaction (a) and Chauvin-type catalytic cycle (b).

The role of the metal catalyst was proved to be not straightforward in some cases. In their studies on imine metathesis catalysis by molybdenum bis(imide) complexes in benzene, Meyer and co-workers suggested that the catalytic activity could be the result of two concurrent mechanisms:[34] in addition to the Chauvin-type mechanism, the metal complex could simply act as a Lewis acid activator of the imine toward the nucleophilic attack of the other imine reactant (Scheme 15).

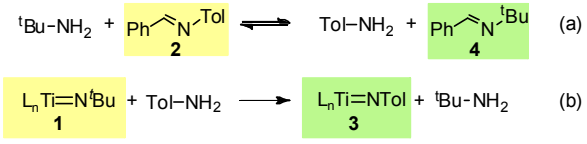
The role of the metal catalyst was also questioned by Mountford *et al*. In their work, the authors examined the metathesis between a titanium imido complex (**1**) and *N*-benzylidenetoluidine (**2**) in chloroform at 60 °C (Scheme 16).[35] The reaction was shown to give quantitative and stoichiometric conversion to the new metal-imido species (**3**). The rate of the reaction was found to be zero order in the metal complex. This observation is in contrast



Scheme 15 The molibdenum present in the imido complex complex acts as a simple Lewis acid activating one imine to the nucleophilic attack of the other imine.[34]

with the usually accepted catalytic cycle (Scheme 14) in which the formation of the metallacyclic intermediate is the rate-determining step. As an alternative, an amine mediated mechanism was suggested (Scheme 17): transimination between the imine reactant and traces of *tert*-butylamine present in the reaction mixture[36] releases toluidine (a) that is rapidly and quantitatively scavenged by the metal imido complex (b), restoring *tert*-butylamine. The reaction proceeds to complation *via* coupled transiminations until completeness. However, this pathway was found to be not fully consistent with the kinetic data collected in the investigation.

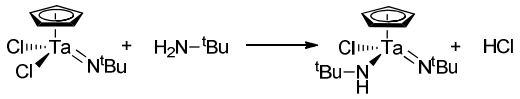
Scheme 16 Metal imide-imine metathesis between a titanium imido complex (**1**) and *N*-benzylidenetoluidine (**2**).



Scheme 17 Transimination between N-benzylidenetoluidine and *tert*-butylamine (a). The toluidine produced is irreversibly scavenged by **1** to form the toluidine-derivative of titanium imide **3** (b).

The role of traces of amines involved in the catalytic process was also investigated by Meyer and co-workers in a study on imine metathesis in the presence of a tantalum imido complex carried out in benzene at 70 °C.[37] The metathesis was found to be first order in the metal complex. Furthermore, a dependence on added amine concentration was observed. The occurrence of coupled transiminations, yielding the metathetic products and catalysed by the metal center, was taken into account but it was not considered as the main catalytic pathway. The proposed mechanism involves, instead, the liberation of HCl by direct reaction between the tantalo imido complex and the amine: the latter reacts with the complex in a rate determining step, replacing one of the ancillary chlorine ligands of the complex and releasing HCl (Scheme 18). The latter acts then as a Brønsted acid catalyst,

accelerating the imine metathesis by protonation of one of the imines.[28] This scheme would explain the first order dependence in complex concentration.



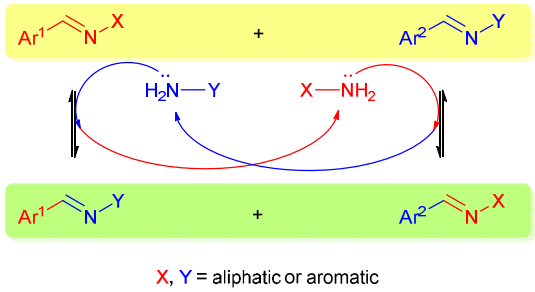
Scheme 18 Liberation of Brønsted acid from the reaction between amine and a tantalium imide complex.

To sum up, although deeply investigated, the mechanisms of metal imido catalysis of imine metathesis are still not generalisable nor completely understood.

An example of imine metathesis accelerated by nucleophilic catalysis in the absence of Brønsted or Lewis acids under mild conditions was reported by Lehn et al in 2012,[38] and represents an application of the well known iminium ion catalysis.[39] These authors studied the imine metathesis between two or three different imines in dimethyl sulfoxide at room temperature, and catalysis on this reaction by a secondary amine. The catalytic process involves separate reactions of L-proline with each of the reacting imines to form free amine and iminium cation, which in turn undergoes nucleophilic attack by the amine released in the reaction between the catalyst and the other imine reactant, yielding the metathetic products (Scheme 19).

In very recent investigations, transimination reactions were used to accelerate imine metathesis in different organic solvents under mild conditions, in the absence of acids.[16,22] Couples of imines derived from differently substituted benzaldehydes and aromatic or aliphatic amines were mixed together at room temperature in the presence of minute amounts of the amines used to synthesise the reagents (Scheme 20). The amines trigger a series of fast, uncatalysed transimination reactions having as products the metathetic products. Each amine is consumed in a transimination reaction that generates a new imine and amine, which, in turn, reacts with the other imine reagent producing the other product and regenerating the first amine.

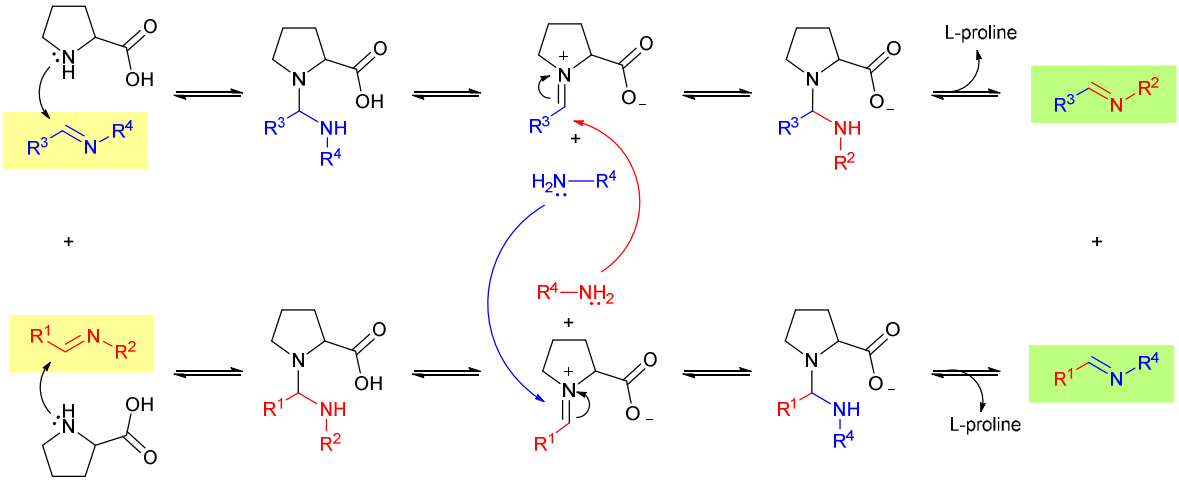
In Scheme 21 a typical imine metathesis **A** + **B** = **C** + **D** with the related transiminations is shown. The metathesis reaction between *N*-(*p*-methoxybenzylidene)*p*-toluidine (**A**) and *N*-benzylideneaniline (**B**) in CD_2Cl_2 at 25 °C to give *N*-(*p*-methoxybenzylidene)aniline (**C**) and *N*-benzylidenetoluidine (**D**) is obtained by a cascade of coupled transiminations involving catalytic amounts of aniline and/or toluidine.[22] Kinetic data were in full agreement with the proposed mechanism. On conditions that $K_{eq} = 1$ and $[A]_o = [B]_o$, a first order time dependence (k_{obs}), is theoretically expected for a general reversible reaction A + B = C + D, second order in both directions.[16,40] In the case of the reaction shown in Scheme 21, the equilibrium constant (K_{eq}) was found to be 1 within the experimental error. As expected, a first order time dependence was found when equimolar amounts of **A** and **B** were reacted, as shown in trace (a) of Fig. 2. Furthermore, in the particular case of X = *iso*-butylamine and Y = butylamine (see Scheme 20), the dependence of k_{obs} as a function of amine catalyst concentration was also investigated.[16] It was found that k_{obs} depends linearly on the amine catalyst concentration definitely corroborating the proposed mechanism.



X, Y = aliphatic or aromatic

Scheme 20 Imine metathesis catalysed by primary amines.

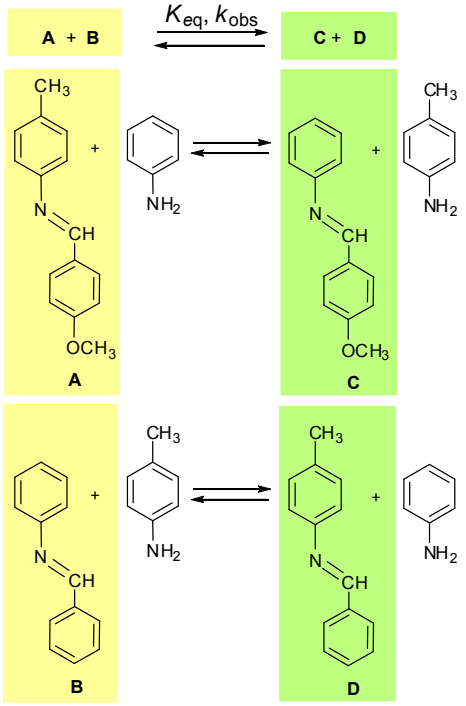
Fig. 2 shows that by the time that the catalysed reaction is practically complete, the background reaction is still at an early stage. Interestingly, the latter reaction shows the sigmoid shape typical of the logistic curve. This behaviour was also observed in other organic solvents such as CD_3CN, $CDCl_3$ and CD_3OD. It was demonstrated that, in the absence of any added catalyst, the occurrence of slow hydrolysis of the imines caused by reaction with trace amounts of adventitious water, generates the corresponding amines which, in turn, start to catalyse the control reaction (Scheme 21). The concentration of liberated amines increases on increasing reaction time, and the concentration-time profile of the control reaction resembles that of an autocatalytic process.



Scheme 19 Imine metathesis catalysed by proline.

Metathesis reactions between all possible imines (X and Y both aliphatic, X and Y both aromatic, X aliphatic and Y aromatic, Scheme 20) were found to be catalysed by both aliphatic or aromatic amines.[16,22]

In contrast with all the cases described above, the latter strategy allows catalysis of metathesis reaction by the same components contained in the reagents themselves. In other words, the intrinsically fast transimination reaction is exploited, with no need for added acid or metal catalysts, or for secondary amines.



Scheme 21 Metathesis reaction between *N*-(*p*-methoxybenzylidene) *p*-toluidine (**A**) and *N*-benzylideneaniline (**B**) leading to *N*-(*p*-methoxybenzylidene) aniline (**C**) and *N*-benzylidenetoluidine (**D**).

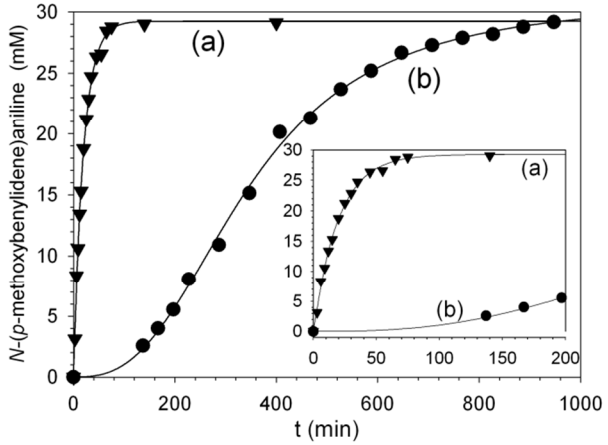


fig. 2 Reaction progress as a function of time for amine-catalyzed (a) and background (b) metathesis between 60 mM *N*-(*p*-methoxybenzylidene)*p*-toluidine and 60 mM *N*-benzylideneaniline in CD_2Cl_2 at 25 °C. Curve (a) is a plot of a first-order equation, curve (b) is a guide to the eye.

Conclusions

Mechanistic investigations concerning the three main reactions of imine chemistry (imine formation, transimination and imine metahesis) in organic solvents have been reviewed in this article. Mainly due to reversibility, these reactions are increasingly used in the applications of well established and emerging research areas, such as synthesis of interlocked molecules,[7c-e] dynamic combinatorial chemistry,[7c-e,26c,d] molecular motions[26a,41] and molecular recognition.[7g,h] Although the mechanistic information collected up to date leads to the idea of cyclic 4-membered transition states as a *leit-motiv* along all the chemistry of imines in organic solvents, additional studies will be necessary to reach an adequate degree of knowledge of the reaction pathways. Kinetic isotope effect experiments, as well as considering a wider variety of substrates, could provide further information on the nature of the transition states involved in such important processes.

Aknowledgements

Thanks are due to the Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR, PRIN 2010CX2TLM).

References and notes

[a] *Dipartimento di Chimica, Sapienza Università di Roma and Istituto CNR di Metodologie Chimiche (IMC-CNR), Sezione Meccanismi di Reazione, c/o Dipartimento di Chimica, Sapienza Università di Roma, P.le A. Moro 5, I-00185 Rome, Italy;Fax: +39 06 49913629; Tel: +39 06 49913057; E-mail: stefano.distefano@uniroma1.it*

1 H. Schiff, *Ann. Chem. Pharm.*, 1864, **131**, 118-119.
2 M. Sprung, *Chem. Rev.*, 1940, **26**, 297-338.
3 E. V. Anslyn and D. D. Dougherty, *Modern physical organic chemistry*, Sausalito, CA(USA), 2006, 597.
4 (a) E. H. Cordes and W. P. Jencks, *J. Am. Chem. Soc.*, 1962, **84**, 826-831; (b) E. H. Cordes and W. P. Jencks, *J. Am. Chem. Soc.*, 1963, **85**, 2843-2848; (c) K. Koehler, W. Sandstrom and E. H. Cordes, *J. Am. Chem. Soc.*, 1964, **86**, 2413-2419.
5 (a) R. B. Moffett and W. M. Hoehn, *J. Am. Chem. Soc.*, 1947, **69**, 1792; (b) R. Layer, *Chem. Rev.*, 1963, **63**, 489-510; (c) M. Freifelder, *J. Org. Chem.*, 1966, **31**, 3875.
6 (a) W. P. Jencks, *Catalysis in Chemistry and Enzymology*, McGraw-Hill, New York, 1969; (b) D. J. Hupe, Enzyme Reactions Involving Imine Formation, in *The Chemistry of Enzyme Action*, ed. M. I. Page, Elsevier Science Publisher, New York, 1984, pp. 271–299. (c) L. Stryer, *Biochemistry*,W. H. Freeman and Company, New York, 4th edn, 1995; (d) M. Hochgürtel, J.-M. Lehn, in *Fragment-based Approaches in Drug Discovery*, eds. R. Mannhold, H. Kubinyi and G. Folkers, Wiley-VCH: Weinheim, 2006; pp 361−364.
7 (a) *The Chemistry of the Carbon–Nitrogen Double Bond*, ed. S. Patai, Interscience, London, 1970; (b) F. A. Carey and R. J. Sundberg, *Advanced Organic Chemistry*, Springer, New York, 5th edn, 2007; (c) C. D. Meyer, C. S. Joiner and J. F. Stoddart, *Chem. Soc. Rev.*, 2007, **36**, 1705-1723; (d) N. Giuseppone, *Acc. Chem. Res.*, 2012, **45**, 2178-2188; (e) M. E. Belowich and J. F. Stoddart, *Chem. Soc. Rev.*, 2012, **41**, 2003–2024; (f) A. J. Bissette and S. P. Fletcher, *Angew. Chem. Int. Ed.*, 2013, **52**, 12800-12826; (g) S. H. Yoo, B. J. Lee, H. Kim and J. Suh, *J. Am. Chem. Soc.*, 2005, **127**, 9593-9602; (h) M. Ciaccia, I. Tosi, R. Cacciapaglia, A. Casnati, L. Baldini and S. Di Stefano, *Org. Biomol. Chem.*, 2013, **11**, 3642-3648; (i) S. Morales, F. G. Guijarro, J. L. García Ruano, M. B. Cid, *J. Am. Chem. Soc.*, 2014, **136**, 1082-1089.
8 In the following discussion only exchange reactions between amines will be taken into account. Neverthless, mechanistic information on transiminations in organic solvents involving oximes, hydrazones, semicarbazones etc. are nearly absent in the literature. See for

example of hydrazone exchange: (a) N. Giuseppone, J.-L. Schmitt and J.-M. Lehn, *Angew. Chem. Int. Ed.*, 2004, **43**, 4902-4906; (b) N. Giuseppone, J.-L. Schmitt and J.-M. Lehn, *J. Am. Chem. Soc.*, 2006, **128**, 16748-16763. For an example of oxime-imine exchange in aqueous solution see: A. Dirksen, T. M. Hackeng and P. E. Dawson, *Angew. Chem. Int. Ed.*, 2006, **45**, 7581-7584.

9 (a) G. M. Santerre, C. J. Hansrote, Jr. and T. I. Crowell, *J. Am. Chem. Soc.*, 1958, **80**, 12-15; (b) W. P. Jencks, *J. Am. Chem. Soc.*, 1959, **81**, 475-481; (c) R. B. Martin, *J. Phys. Org. Chem.*, 1964, **68**, 1369-1377; (d) W. P. Jencks, *Prog. Phys. Org. Chem.*, 1964, **2**, 63–128; (e) W. P. Jencks, *Acc. Chem. Res.*, 1976, **9**, 425-432; (f) M. J. Mäkelä and T. K. Korpela, *Chem. Soc. Rev.*, 1983, **12**, 309-329.

10 Isolation or detection of carbinolamine species has been rarely reported. See for example: (a) L. Floriani, E. Marianucci and P. E. Todesco, *J. Chem. Res.*, 1984, **1984**, 126; (b) J. A. Chudek, R. Foster and D. Young, *J. Chem. Soc., Perkin Trans. 2*, 1985, 1285-1289. (c) D. A. Evans, G. Borg and K. A. Scheidt, *Angew. Chem. Int. Ed.*, 2002, **41**, 3188-3191; (d) T. Iwasawa, R. J. Hooley, J. Rebek, Jr., *Science*, 2007, **317**, 493-496; (e) R. J. Hooley, T. Iwasawa and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2007, **129**, 15330-15339; (f) T. Kawamichi, T. Haneda, M. Kawano and M. Fujita, *Nature*, 2009, **461**, 633-635; (g) D.S. Yufit, and J.A.K. Howard, *J. Mol. Struct.* 2010, **984**, 182–185.

11 R. A. Y. Jones, *Physical and mechanistic organic chemistry*, Cambridge, Great Britain, 1984, 254-260.

12 S. Rosenberg, S. M. Silver, J. M. Sayer, and W. P. Jencks, *J. Am. Chem. Soc.*, 1974, **96**, 7986-7998.

13 (a) I. H. Williams, D. Spangler, D. A. Femec, G. M. Maggiora and R. L. Schowen, *J. Am. Chem. Soc.*, 1983, **105**, 31-40; (b) I. H. Williams, D. Spangler, G. M. Maggiora and R. L. Schowen, *J. Am. Chem. Soc.*, 1985, **107**, 7717-7723; (c) I. H. Williams, *J. Am. Chem. Soc.*, 1987, **109**, 6299-6307.

14 N. E. Hall and B. J. Smith, *J. Phys. Chem. A*, 1998, **102**, 4930-4938.

15 N. E. Hall and B. J. Smith, *J. Phys. Chem. A*, 1998, **102**, 3985-3990.

16 M. Ciaccia, R. Cacciapaglia, P. Mencarelli, L. Mandolini and S. Di Stefano, *Chem. Sci.*, 2013, **4**, 2253-2261.

17 D. Schultz and D. J. Nitschke, *J. Am. Chem. Soc.*, 2006, **128**, 9887-9892.

18 (a) J. L. Hogg, D. A. Jencks and W. P. Jencks, *J. Am. Chem. Soc.*, 1977, **99**, 4772-4778; (b) H. Fischer, F. X. DeCandis, S. D. Ogden and W. P. Jencks, *J. Am. Chem. Soc.*, 1980, **102**, 1340-1347.

19 J. Toullec and R. Razafindralambo, *J. Org. Chem.*, 1987, **52**, 826-831.

20 (a) B. E. Leach and D. L. Leussing, *J. Am. Chem. Soc.*, 1970, **93**, 3377-3384; (b) M. J. O'Donnell and M. L. Polt, *J. Org. Chem.*, 1982, **47**, 2663-2666.

21 L. do Amaral, W. A. Sandstrom and E. H. Cordes, *J. Am. Chem. Soc.*, 1966, **88**, 2225-2233.

22 M. Ciaccia, S. Pilati, R. Cacciapaglia, L. Mandolini and S. Di Stefano, *Org. Biomol. Chem.*, 2014, **12**, 3282-3287.

23 N. Giuseppone, J.-L. Schmitt, E. Schwartz and J.-M. Lehn, *J. Am. Chem. Soc.*, 2005, **127**, 5528-5539.

24 For catalysis of hydrazone exchange by lanthanide triflate salts see also ref. 8a and 8b.

25 A large rate enhancing effect on the transimination due to the presence of CF_3CO_2H was also observed in the case of reactions between benzylidenebutylamine and *iso*-butylamine in CD_3CN (see ref 16). It was ascribed to protonation of the imine which becomes a much more electrophilc partner in the reaction with the imine nucloephile. The elimination step is acid catalyzed as well.

26 (a) P. Kovaříček, J.-M. Lehn, *J. Am. Chem. Soc.*, 2012, **134**, 9446-9455; (b) K. Ziach, A. Kulesza and J. Jurczak, *Org. Biomol. Chem.*, 2014, **12**, 3827-3830; (c) A. Ciesielski, M. El Garah, S. Haar, P. Kovaříček, J.-M. Lehn and P. Samorì, *Nat. Chem.*, 2014, **6**, 1017-1023; (d) M. Ciaccia, I. Tosi, L. Baldini, R. Cacciapaglia, L. Mandolini, S. Di Stefano and C. A. Hunter, *Chem. Sci.*, 2014, DOI: 10.1039/c4sc02347a.

27 (a) C. K. Ingold and H. A. Piggott, *J. Chem. Soc.*, 1922, **121**, 2793-2804; (b) C. K. Ingold and H. A. Piggott, *J. Chem. Soc.*, 1923, **123**, 2745-2752.

28 G. Tóth, I. Pintér and A. Messmer, *Tetrahedron Lett.*, 1974, **15**, 735-738.

29 The very low, residual reactivity in collidine was abscribed to the possible protonation of one imine partner by traces of collidinium acid.

30 (a) R. H. Grubbs and W. Tumas, *Science*, 1989, **243**, 907-915; (b) R. R. Schrock, *Acc. Chem. Res.*, 1990, **23**, 158-165; (c) T. M. Trnka and R. H. Grubbs, *Acc. Chem. Res.*, 2001, **34**, 18-29; (d) S. Monfette and D. E. Fogg, *Chem. Rev.*, 2009, **109**, 3783-3816; (e) G. C. Vougioukalakis and R. H. Grubbs, *Chem. Rev.*, 2010, **110**, 1746-1787.

31 (a) K. E. Meyer, P. J. Walsh and R. G. Bergman, *J. Am. Chem. Soc.*, 1994, **116**, 2669-2670; (b) K. E. Meyer, P. J. Walsh and R. G. Bergman, *J. Am. Chem. Soc.*, 1995, **117**, 974-985; (c) G. K. Cantrell and T. Y. Meyer, *Organometallics*, 1997, **16**, 5381-5383; (d) G. K. Cantrell and T. Y. Meyer, *Chem. Commun.*, 1997, 1551-1552; (e) J. M. McInnes and A. J. Blake, P. Mountford, *J. Chem. Soc., Dalton Trans.*, 1998, 3623-3628; (f) S. W. Krska, R. L. Zuckerman and R. G. Bergman, *J. Am. Chem. Soc.*, 1998, **120**, 11828-11829; (g) W.-D. Wang and J. H. Espenson, *Organometallics*, 1999, **18**, 5170-5175; (h) R. L. Zuckerman, S. W. Krska and R. G. Bergman, *J. Am. Chem. Soc.*, 2000, **122**, 751-761; (i) J. W. Bruno and X. J. Li, *Organometallics*, 2000, **19**, 4672-4674.

32 J.-L. Hérisson and Y. Chauvin, *Macromol. Chem.*, 1970, **141**, 161-167.

33 A pre-catalyst such as Cp*CpZr=N^{t}Bu where Cp is cyclopentadienyl and Cp* is pentamethylcyclopentadienyl anion (see ref 31 f) was added in solution and generated the metal imide catalyst upon reaction with one of the imine reagents. In this specific case (ref 31 f) the sterically less hindered $Cp_2Zr=N^tBu$ could not be used because it was shown to give irreversible self-dimerization.

34 G. K. Cantrell and T. Y. Meyer, *J. Am. Chem. Soc.*, 1998, **120**, 8035-8042.

35 J. M. McInnes and P. Mountford, *Chem. Commun.*, 1998, 1669-1670.

36 Traces of amine are described as unavoidably present as a contaminant of the metal-imido catalyst.

37 M. C. Burland, T. W. Pontz and T. Y. Meyer, *Organometallics*, 2002, **21**, 1933-1941.

38 N. Wilhelms, S. Kulchat and J.-M. Lehn, *Helv. Chim. Acta*, 2012, **95**, 2635-2651.

39 (a) P. I. Dalko and L. Moisan, *Angew. Chem. Int. Ed.*, 2004, **43**, 5138-5175; (b) A. Erkkilä, I. Majander and P. M. Pihko, *Chem. Rev.*, 2007, **107**, 5416-5470.

40 P. L. Hammett, Physical Organic Chemistry, McGraw-Hill Book Company, New York, 2nd edn, 1970, p. 70.

41 M. V. Delius, E. M. Geertsema and D. A. Leigh, *Nat. Chem.*, 2010, **2**, 96-101.

Graphical abstract

Updated mechanisms operating in imine chemistry in organic solvents are reviwed and critically discussed.