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Making Imines Without Making Water−Exploiting a Recognition-Mediated Aza-Wittig Reaction

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ABSTRACT

A recognition-mediated aza-Wittig reaction permits the efficient formation of an imine in dry $CDCl_3$ from an iminophosphorane and an aldehyde. The kinetic and thermodynamic parameters for this reaction are compared with those obtained from a condensation reaction between an aldehyde and an amine that forms the same product.

Dynamic covalent chemistry[1] (DCC) presents an opportunity to develop the chemistry of complex systems through the creation of collections of compounds, which interact and interconvert with each other through the breaking and reforming of covalent bonds and whose composition[2] is regulated by thermodynamics. Thus, the development of protocols based on DCC that establish and manage replication, organization, and evolution within synthetic molecular and supramolecular assemblies offer a programmed approach to predetermined dynamic behavior — so-called[3] systems chemistry. Among the various covalent bonds known to have a dynamic behavior, imines have attracted[4] special interest. Imines are formed typically by the reversible acid-catalyzed condensation of an amine with an aldehyde with extrusion of a molecule of water. Under some conditions, for example, in nonpolar solvents, the equilibrium lies far on the side of the starting materials and, to drive the C═N bond formation to completion, water must be removed through azeotropic distillation or by employing a chemical drying agent in the reaction mixture. These conditions limit the utility of this reaction, particularly in respect of exploiting molecular recognition associated with hydrogen bonds. Since recognition events are a prerequisite for directing events within dynamic libraries, there is a clear need to develop methods for the formation of imines under conditions that are compatible with recognition motifs used commonly in nonpolar solvents.

As part of our ongoing studies of self-replicating systems, we have been exploring[5] the consequences of recognition processes on the acceleration of cycloaddition reactions. Recently, our focus has shifted toward exploiting the implications of replication events in dynamic and reactive chemical systems and networks. As a first step, we reported[6] a dynamic replicating system based on imine formation using a classical condensation approach. However, given the limitations of imine formation in nonpolar solvents, we wished to develop an alternative method of imine formation.

(1) For general reviews on DCC see: (a) Lehn, J.-M. *Chem.−Eur. J.* **1999**, *5*, 2455. (b) Rowan, S. J.; Cantrill, S. J.; Cousins, G. R. L.; Sanders, J. K. M.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 898. (c) Corbett, P. T.; Leclaire, J.; Vial, L.; West, K. R.; Wietor, J.-L.; Sanders, J. K. M.; Otto, S. *Chem. Rev.* **2006**, *106*, 3652. (d) Otto, S.; Severin, K. *Top. Curr. Chem.* **2007**, *277*, 267.

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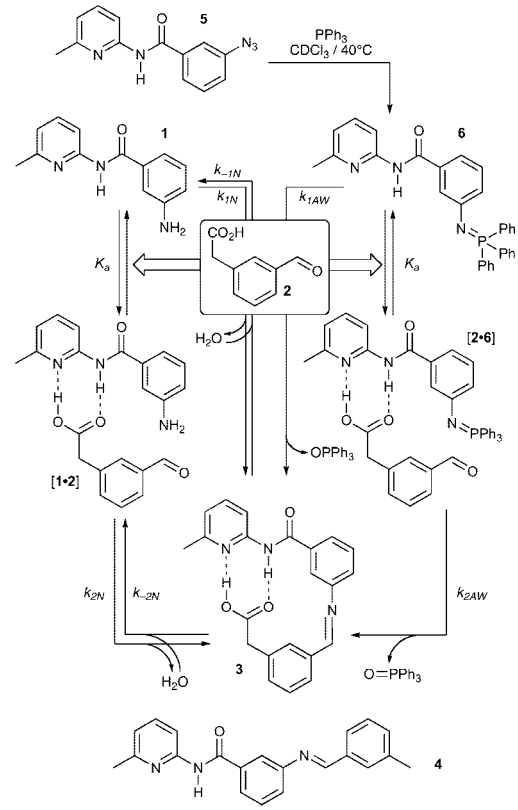
Although much less explored than its carbon-based cousin, the aza-Wittig reaction[7] offers an attractive method for imine formation. Reaction between an iminophosphorane[8] (generated from the Staudinger reaction[9] of the correponding azide with a triarylphosphine) and a carbonyl compond leads to the formation of a C═N bond in a similar manner to C═C bond formation by phosphonium ylids. In general, however, the reaction is rather inefficient when it is performed[10] in an intermolecular sense, although the intramolecular aza-Wittig reaction has attracted considerable attention as a result of its potential for the synthesis of nitrogen-containing heterocycles. In this communication, we compare and contrast the recognition-mediated formation of an imine in $CDCl_3$ through a traditional condensation-based approach and through an aza-Wittig reaction. We demonstrate that the recognition-mediated aza-Wittig methodology leads to efficient and high conversion to imine, thus establishing a new method for the formation of the dynamic imine bond in $CDCl_3$.

The traditional approach to the synthesis of imine **3** involves the reaction of amine **1** with aldehyde **2** in $CDCl_3$ at 25 °C (Scheme 1) with the removal of water. The formation of imine **3** occurs through bimolecular reaction of the amine and the aldehyde (k_{2N}/k_{-2N}, Scheme 1). However, the location of

Scheme 1



complementary recognition sites on amine **1** (amidopyridine) and aldehyde **2** (carboxylic acid), allows the association of these reactive partners in a binary complex [**1**•**2**] opening an alternative reaction channel leading to the formation of imine **3** (k_{1N}/k_{-1N}, Scheme 1). The formation of this complex arranges the reactive groups for a pseudointramolecular reaction within the [**1**•**2**] complex that should be accelerated strongly. In order to establish a baseline for comparison, we performed a control reaction between amine **1** and *m*-tolualdehyde in the presence of 4-bromophenylacetic acid ([**1**] = [*m*-tolualdehyde] = [4-bromophenylacetic acid] = 15 mM) in dry[11] $CDCl_3$ at 25 °C to form imine **4**. The extent of the reaction was assayed[12] at regular intervals by 500 MHz ^{1}H NMR spectroscopy and a concentration-time profile was constructed (Figure 1, open circles).

Kinetic simulation and fitting of this data to the appropriate bimolecular model (k_{2N} and k_{-2N}, Scheme 1) afforded the

(2) For some recent examples of DCC, see: (a) Cheeseman, J. D.; Corbett, A. D.; Shu, R.; Croteau, J.; Gleason, J. L.; Kazlauskas, R. J. *J. Am. Chem. Soc.* **2002**, *124*, 5692. (b) Otto, S.; Kubik, S. *J. Am. Chem. Soc.* **2003**, *125*, 7804. (c) Stulz, E.; Scott, S. M.; Bond, A. D.; Teat, S. J.; Sanders, J. K. M. *Chem.−Eur. J.* **2003**, *9*, 6039. (d) Gonzalez-Alvarez, A.; Alfonso, I.; Lopez-Ortiz, F.; Aguirre, A.; Garcia-Granda, S.; Gotor, V. *Eur. J. Org. Chem.* **2004**, 1117. (e) Ramström, O.; Lohmann, S.; Bunyapaiboonsri, T.; Lehn, J.-M. *Chem.−Eur. J.* **2004**, *10*, 1711. (f) Chichak, K. S.; Cantrill, S. J.; Pease, A. R.; Chiu, S.-H.; Cave, G. W. V.; Atwood, J. L.; Stoddart, J. F. *Science* **2004**, *304*, 1308. (g) Buryak, A.; Severin, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 7935. (h) Corbett, P. T.; Sanders, J. K. M.; Otto, S. *J. Am. Chem. Soc.* **2005**, *127*, 9390. (i) Milanesi, L.; Hunter, C. A.; Sedelinkova, S. E.; Waltho, J. P. *Chem.−Eur. J.* **2006**, *12*, 1081. (j) Shi, B.; Stevenson, R.; Campopiano, D. J.; Greaney, M. F. *J. Am. Chem. Soc.* **2006**, *128*, 8459. (k) Bulos, F.; Roberts, S. L.; Furlan, R. E. L.; Sanders, J. K. M. *Chem. Commun.* **2007**, 3092. (l) Ludlow, R. F.; Liu, J.; Li, H.; Roberts, S. L.; Sanders, J. K. M.; Otto, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 5762. (m) Haussmann, P. C.; Khan, S. I.; Stoddart, J. F. *J. Org. Chem.* **2007**, *72*, 6708. (n) Schultz, D.; Nitschke, J. R. *Chem.−Eur. J.* **2007**, *13*, 3660.

(3) (a) Kindermann, M.; Stahl, I.; Reimold, M.; Pankau, W. M.; von Kiedrowski, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 6750. (b) Stankiewicz, J.; Eckardt, L. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 342. (c) Corbett, P. T.; Sanders, J. K. M.; Otto, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 8858. (d) Sarma, R. J.; Nitschke, J. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 377. For a general review on Systems Chemistry see: (e) Ludlow, R. F.; Otto, S. *Chem. Soc. Rev.* **2008**, *37*, 101.

(4) Meyer, C. D.; Joiner, C. S.; Stoddart, J. F. *Chem. Soc. Rev.* **2007**, *36*, 1705.

(5) For some recent examples, see: (a) Pearson, R. J.; Kassianidis, E.; Slawin, A. M. Z.; Philp, D. *Chem.−Eur. J.* **2006**, *12*, 6829. (b) Kassianidis, E.; Philp, D. *Angew. Chem., Int. Ed.* **2006**, *45*, 6334. (c) Kassianidis, E.; Pearson, R. J.; Philp, D. *Chem.−Eur. J.* **2006**, *12*, 8789. (d) Bennes, R.; Philp, D. *Org. Lett.* **2006**, *8*, 3651. (e) Turega, S. M.; Philp, D. *Chem. Commun.* **2006**, 3684.

(6) del Amo, V.; Slawin, A. M. Z.; Philp, D. *Org. Lett.* **2008**, *10*, 4589.

(7) Reviews: (a) Palacios, F.; Alonso, C.; Aparicio, D.; Rubiales, G.; de los Santos, J. M. *Tetrahedron* **2007**, *63*, 523. (b) Eguchi, S. *ARKIVOC* **2005**, *2*, 98. (c) Fresneda, P. M.; Molina, P. *Synlett* **2004**, 1. (d) Eguchi, S.; Okano, T.; Okawa, T. *Rec. Res. Dep. Org. Chem.* **1997**, *1*, 337. (e) Molina, P.; Vilaplana, M. J. *Synthesis* **1994**, 197.

(8) (a) Staudinger, H.; Meyer, J. *Helv. Chim. Act.* **1919**, *2*, 635. (b) Patonay-Peli, E.; Litkei, G. *Synthesis* **1990**, 511. (c) Cambon, F. A. *Synth. Commun.* **1994**, *24*, 2653. (d) Shalev, D. E.; Chiacchiera, *J. Org. Chem.* **1996**, *61*, 1689.

(9) For a general review on the chemistry and properties of azides see: Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188, and references therein.

(10) Palacios, F.; Vicario, J.; Aparicio, D. *J. Org. Chem.* **2006**, *71*, 7690.

(11) $CDCl_3$ (99.8% atom D) was purchased from Aldrich as 100 g bottles. Bottles were opened under a positive pressure of Ar and the contents were stored over preactivated 4 Å molecular sieves. The water content was determined to be 14 ppm using Karl Fischer titration (Mettler Toledo DL32 Coulometer). Samples of aldehyde **2** and 4-bromophenylacetic acid contain one molecule of water of crystallization. Therefore, the solutions discussed here, which are prepared from these compounds, will have H_2O concentrations of 15 mM.

(12) The time course of each reaction was followed by 500 MHz ^{1}H NMR spectroscopy. The disappearance of the resonances arising from the aldehyde protons in **2** or *m*-tolualdehyde (δ = 9.9−10.1) and the simultaneous appearance of resonances arising from the imine protons in **3** or **4** (δ = 8.4−8.5) were monitored. Concentration vs time profiles were constructed by deconvolution of these resonances.

(13) von Kiedrowski, G. *SimFit, A program for the analysis of kinetic data, Version 1.0*; Ruhr-Universität Bochum: Germany, 1994.

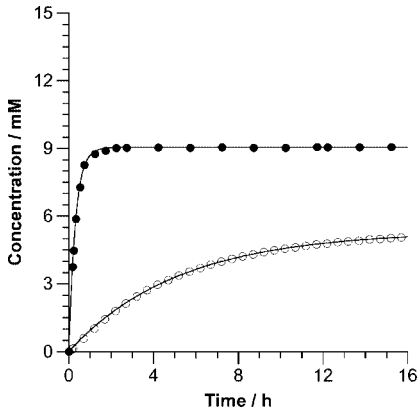


Figure 1. Rate profiles at 25 °C in dry $CDCl_3$ for the formation of imine **3** (●) or imine **4** (○) from amine **1** and aldehyde **2** or *m*-tolualdehyde, respectively. 4-Bromophenylacetic acid (15 mM) was added to the reaction involving *m*-tolualdehyde. The starting concentrations of amine and aldehyde were 15 mM. In both cases, the lines represent the best fit of the experimental data to the appropriate kinetic model (Scheme 1) using SimFit.[15] See Supporting Information for details.

best fit values for these rate constants: $k_{2N} = 1.27 \times 10^{-3}$ M^{-1} s^{-1} and $k_{-2N} = 1.09 \times 10^{-3}$ M^{-1} s^{-1}. Therefore, as expected, the equilibrium constant for imine formation in $CDCl_3$ is only 1.15. When the same reaction was performed using aldehyde **2** ([**1**] = [**2**] = 15 mM, dry $CDCl_3$, 25 °C), the concentration-time profile for the formation of imine **3** is dramatically different (filled circles, Figure 1). As expected, imine **3** is formed very rapidly as a result of fast, pseudointramolecular reaction through the [**1**•**2**] complex. However, imine formation stalls after only two hours at 60% conversion ([**3**] = 9 mM).

The introduction of recognition has had two effects on the reaction. First, the rate of reaction between the amine and the aldehyde is accelerated strongly through the [**1**•**2**] complex — initial rate of imine formation is accelerated by almost 30× (initial rate = 20.4 mM h^{-1} vs 0.73 mM h^{-1} for the control reaction between **1** and *m*-tolualdehyde). Second, the position of equilibrium has been shifted − the overall equilibrium constant for formation of **3** is now 6.00. However, this change in equilibrium constant only represents a stabilization of the system by ∼ 4 kJ mol^{-1} in the presence of recognition. We found this result surprising, as one might expect the noncovalent interactions used to assemble [**1**•**2**] to live on[13] in imine **3**, stabilizing it signficantly. Thus, the results of introducing recognition elements in order to guide imine formation in this system are somewhat unsatisfactory. Although we do accelerate the formation of imine **3**, the reaction stalls as a result of the issues associated with condensation reactions performed in nonpolar solvents such as $CDCl_3$ — in particular the formation of water as the reaction progresses.

To shed some light on the apparently poor stabilization of imine **3** by intramolecular hydrogen bonding, we performed a series of electronic structure calculations (B3LYP/6−31G(d,p)) on the possible conformations of imine product **3**. The results of these calculations are summarized in Figure 2a.

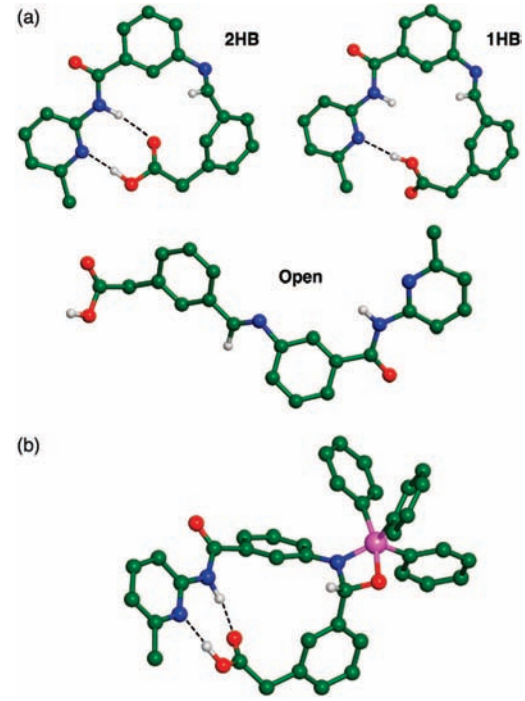


Figure 2. Ball and stick representations of the calculated (B3LYP/6−31G(d,p)) structures of (a) three conformations of imine **3** and (b) the 1,3,2-λ^5-oxazaphosphazetidine intermediate accessed by the [**2**•**6**] complex during the aza-Wittig reaction. Carbon atoms are colored green, oxygen atoms are colored red, nitrogen atoms are colored blue, hydrogen atoms are colored white and phosphorus atoms are colored mauve. Hydrogen bonds are represented by dashed lines. Most hydrogen atoms have been removed for clarity.

In conformation **2HB**, both hydrogen bonds used to assemble [**1**•**2**] are still present in imine **3**. However, this conformation is 20.0 kJ mol^{-1} less stable than conformation **1HB** which possesses one hydrogen bond only between the carboxylic acid proton and the amidopyridine ring nitrogen atom. Conformation **1HB** is, in turn, 13.4 kJ mol^{-1} less stable than the **Open** conformation. The hydrogen bonded conformations — although they contain stabilizing noncovalent interactions − incorporate significant distortion around the C═N unit. This distortion is energetically unfavorable and outweighs the stabilizing noncovalent interactions. These results help to explain why the recognition-mediated condensation reaction is relatively unsuccessful at shifting the equilibrium position for the formation of imine **3**. Although the complex [**1**•**2**] is relatively successful at accelerating the addition of the amine to the aldehyde, no stablizing hydrogen bonds can be sustained in the product.

A potential solution to our inability to alter the equilibrium position for the formation of imine **3** in $CDCl_3$ is to exploit a recognition-mediated irreversible process for imine formation. In this respect, the aza-Wittig reaction is ideal since it also affords an imine, however, the other product of the

reaction is triphenylphosphine oxide (TPPO), not water, and the reaction is irreversible. Thus, the location of complementary recognition sites in iminophosphorane **6** and aldehyde **2**, should allow the association of these reactive partners in a binary complex [**2**•**6**]. If, as a result of formation of this complex, the reactive groups are then oriented in a mutually suitable geometry for the aza-Wittig reaction to occur, the formation of imine **3** should be accelerated strongly. Thus, we performed a series of electronic structure calculations (B3LYP/6−31G(d,p)) on the transition states leading, from [**2**•**6**] to the corresponding imine **3**. As expected, the [**2**•**6**] complex can access a transition state leading to the four-membered ring 1,3,2-λ^5-oxazaphosphazetidine (Figure 2b) that is an accepted intermediate[14] in the aza-Wittig reaction. This species can then decompose, with loss of TPPO, to form imine **3**.

We next sought to verify these computational predictions by comparing the aza-Wittig reaction between aldehyde **2** and iminophosphorane **6** with the condensation reaction between amine **1** and aldehyde **2**. In all experiments, iminophosphorane **6** was prepared freshly by reacting azide **5** with an slight excess of PPh_3 in dry $CDCl_3$ at 40 °C under an Ar atmosphere. Formation of **6** proceeded quantitatively in about 3 h as assessed by ^1H and ^{31}P NMR spectroscopy.

To determine the magnitude of any rate acceleration arising from the formation of the binary complex [**2**•**6**], the rate of the recognition-mediated reaction was compared to the rate of the corresponding bimolecular aza-Wittig reaction between imino phosphorane **6** and *m*-tolualdehyde. The control aza-Wittig reaction was performed in dry $CDCl_3$ at 25 °C ([**2**] = [*m*-tolualdehyde] = [4-bromophenylacetic acid] = 15 mM) forming imine **4**. As before, the extent of the reaction was assayed at regular intervals by 500 MHz ^1H NMR spectroscopy and reaction progress was assessed as described previously. The concentration-time profile reveals (Figure 3, open circles) that the initial rate of formation of imine **4** through the bimolecular aza-Wittig pathway is similar (0.59 mM h^{-1}) to the condensation reaction between **2** and *m*-tolualdehyde (0.73 mM h^{-1}). However, in contrast to the condensation reaction, the irreversible nature of the aza-Wittig reaction ensures that the conversion to imine **4** is higher.

When the reaction was repeated with the recognition-capable aldehyde **2** in place of the control aldehyde ([**2**] = [**6**] = 15 mM; dry $CDCl_3$, 25 °C), the rate of formation of imine **3** increased dramatically (filled circles, Figure 3).

After 16 h, the conversion to imine **3** is now over 90%. The initial rate of imine formation is accelerated by over

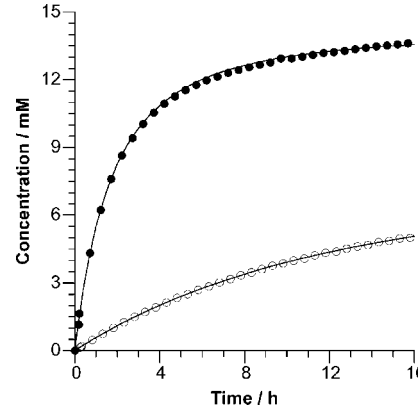


Figure 3. Rate profiles at 25 °C in dry $CDCl_3$ for the formation of imine **3** (●) or imine **4** (○) from iminophosphorane **6** and aldehyde **2** or *m*-tolualdehyde), respectively. 4-Bromophenyl acetic acid (15 mM) was added to the reaction involving *m*-tolualdehyde. The starting concentrations of iminophosphorane and aldehyde were 15 mM. In both cases, the solid lines represent the best fit of the experimental data to the appropriate kinetic model (Scheme 1) using SimFit.[13] See Supporting Information for details.

10× (initial rate = 6.26 mM h^{-1} vs 0.59 mM h^{-1} for the control reaction between **6** and *m*-tolualdehyde). The kinetic data allows us to estimate the kinetic effective molarity (kEM) generated in the [**2**•**6**] complex — the ratio k_{1AW}/k_{2AW} — is 1.2 M. The overall conversion to imine is 92% and the equilbrium constant for imine formation is now 132. Despite the fact that water is present in the $CDCl_3$ solution at the start of the reaction, no further water is produced in the formation of imine **3**.

In conclusion, we have demonstrated that with a careful design and location of recognition elements on the reaction partners, it is possible to exploit an aza-Wittig reaction to facilitate the synthesis of an imine under conditions that are normally unfavorable for direct condensation. The ability to form a reversible imine bond under kinetic control is especially significant for our long-term goal of constructing, with high efficiency and fidelity, chemical subsystems that can be deployed within chemical reaction networks. Experiments directed toward realization of this goal are currently under way in our laboratory.

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Supporting Information Available: Synthetic procedures and characterization for compounds **1** to **6**. Experimental details of kinetic experiments and kinetic simulation and fitting. Details of electronic structure calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) We have demonstrated previously that recognition processes can be exploited in stabilizing otherwise unfavorable products and, hence, make unfavorable reaction processes proceed in a productive sense. See, for example: (a) Bennes, R.; Philp, D.; Spencer, N.; Kariuki, B. M.; Harris, K. D. M. *Org. Lett.* **1999**, *1*, 1087. (b) Bennes, R.; Babiloni, M. S.; Hayes, W.; Philp, D. *Tetrahedron Lett.* **2001**, *42*, 2377.

(15) Cossio, F. P.; Alonso, C.; Lecea, B.; Ayerbe, M.; Rubiales, G.; Palacios, F. *J. Org. Chem.* **2006**, *71*, 2839.