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Dynamic Covalent Metathesis in the C=C/C=N exchange between Knoevenagel Compounds and Imines

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ABSTRACT: Fast and reversible dynamic covalent C=C/C=N exchange takes place without catalyst in non-polar solvents between barbiturate-derived Knoevenagel (**Kn**) compounds and imines. A detailed study of the reaction indicates that it proceeds by an associative organo-metathesis mechanism involving the formation of a four-membered ring azetidine intermediate by addition of the imine C=N group to the C=C bond of the **Kn** compound. This intermediate could be generated cleanly and stabilized at low temperature by condensation of the *o,p*-dinitrophenyl **Kn** derivative with the cyclic imine 1-azacyclohexene. It was characterized by extensive NMR and Mass spectrometric studies. The process described represents a genuine dynamic covalent organo-metathesis through a four-membered ring adduct as intermediate. It paves the way for the exploration of a wide set of dynamic systems involving (strongly) polarized C=C bonds and various imines, extending also into covalent dynamic polymers and polymolecular assemblies.

1. INTRODUCTION

'Constitutional Dynamic Chemistry' (CDC)[(1)] involves the dynamic recombination of molecular components linked through either non-covalent interactions or reversible covalent bonds. Dynamic covalent chemistry (DCC)[(2)] is a highly effective method to create dynamic libraries of compounds of high structural diversity. Representative examples of reversible reactions compatible with the DCC concept include amine/carbonyl condensations[(3)], transesterifications[(4)], disulfide exchange[(5)], peptide exchange[(6)], boronic ester formation[(7)], olefin metathesis[(8)], and Diels-Alder condensation[(9)].

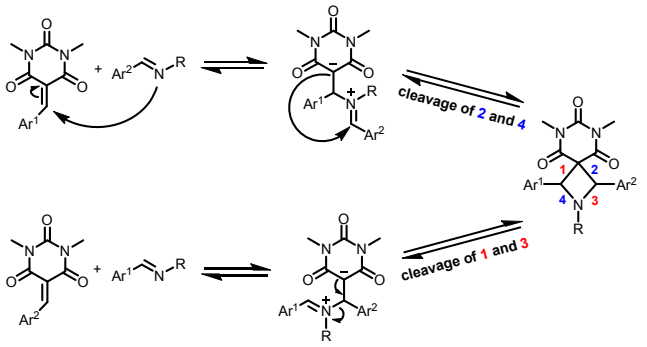
Among these reversible covalent reaction processes, the formation of imines by amine/carbonyl condensations and the exchange of their two components are of special interest in view of the widespread occurrence of imine compounds in organic chemistry as well as in biochemistry. Constitutional variation of imines results from exchange of their two components in general by a three step *dissociative mechanism* involving initial amine/carbonyl condensation, followed by back-hydrolysis to the initial components and recondensation with other partners to generate different imines, amounting to a C=N/C=N exchange process[(3)]. Conversely, it may also occur following an *associative mechanism* by addition of an amine to an already formed imine to give an aminal which then can lose either one of its two amine residues[(10)]. The related C=C/C=N and C=C/C=C exchange processes (involving in particular Knoevenagel-type compounds) also occur by a condensation-dissociation-recondensation sequence[(10)]. On the other hand, C=C/C=C recombination may be achieved following the well-established and widely used metal catalyzed metathesis reaction[(12)] involving C=C cleavage, formation of a metal carbene species and recombination through four membered ring intermediates containing the metal atom and three carbon centers.

It has been suggested that genuine C=N/C=N imine metathesis may take place by a mechanism involving the formation of a four-membered ring 1, 3-diazetidine intermediate[(13)]. Such a concerted mechanism is presently viewed as a symmetry forbidden [2π +2π] cycloaddition reaction according to the Woodward-Hoffmann rules[(14)]. However,

it was shown that imine metathesis is a stepwise process requiring acid catalysis, whereby protonation of one imine facilitates the nucleophilic attack of a second imine and subsequent formation of four-membered 1,3-diazetidine ring intermediate[10].

Organic metathesis reactions, including olefin metathesis as well as imine exchange/metathesis in organic solvents are considered to take place under catalysis[10],[12]. Interestingly, results obtained in our previous work [11] gave indication for the occurence of a C=C/C=N exchange reaction bearing the signs of a metathesis-like mechanism proceeding by nucleophilic reaction in absence of any added catalyst. It was carried out between Knoevenagel (Kn) compounds derivated from 1,3-dimethylbarbituric acid (DMBA) and imines in organic solvents of low polarity (chloroform, methylene chloride), realizing fast and reversible exchange between an imine C=N bond and a strongly polarized C=C bond (Scheme 1). These experimental results, in particular the very fast kinetics, as compared to the condensation-dissociation-recondensation exchange reactions performed in polar solvents, suggested a different, associative mechanism of metathesis-type, starting with the nucleophilic attack of the imine nitrogen on the highly polarized C=C double bond of the Kn compound, followed by formation of a four-membered azetidine intermediate and finally ring opening leading back to an imine and a Kn product (Scheme 1).

Scheme 1. Proposed associative mechanism for the metathesis reaction between a barbiturate Knoevenagel derivative and an imine through formation of an azetidine intermediate.



In view of both the novelty as well as the potential use of such a genuine C=C/C=N associative *organo-metathesis* (OM) process between a Kn compound and an imine, we performed studies aimed at confirming its mechanism and exploring its features. We herewith describe investigations on the influence of different parameters on the reaction rate, the exclusion of the alternative dissociative mechanism which would include hydrolysis of one or both components and the absence of participation of a catalyst. In addition, it was crucial to isolate and establish the formation of the intermediate.

2. RESULTS AND DISCUSSION

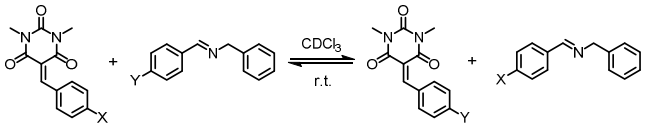
2.1 Structural effects on the Knoevenagel/Imine C=C/C=N exchange process

In our initial studies on C=C/C=N exchange between N-benzyl imines and Kn derivatives[11], an influence of the structure of the two partners on the shift of the equilibrium as well as on the reaction time was noted, with the formation of the well-conjugated Knoevenagel compound being strongly preferred. To extend these observations and further explore these effects on the Knoevenagel exchange reaction, a series of comparative experiments were conducted in order to more closely investigate the influence of substituents on the two partners of the exchange equilibrium (Scheme 2).

In a first set of experiments, the Knoevenagel compounds **Kn1-Kn6** were reacted with aldimines derived from benzylamine and para-substituted benzaldehydes **A2-A6** (Scheme 2) giving a mixture of just the four expected constituents as shown by the clean NMR spectra obtained (see Figure S1a for the case **Kn1** + **A5**). Some reactions have been performed in both directions giving very similar equilibrium mixtures (Table 1; Figure S1a). All experiments were run at a lower concentration (10 mM compared to others at 20 mM) in order to slow down the reaction. The results on rates and equilibria obtained taking **Kn1** as reference compound reacted with aldimines **A2-A6** are given in Table 1. They confirmed the previously observed preference for the preferred formation of the **Kn** compound bearing an EDG (electron donating group) not only from the point of view of the reaction equilibrium but also the reaction rate. The EDG enhances the conjugation to form a push-pull system and simultaneously increases the polarity of the double bond. Such well conjugated systems have minimal or no torsion between the aromatic

and barbituric moieties, as confirmed from crystal structures of several Knoevenagel compounds, bearing substituents such as methoxy and dimethylamino[15] and consequently have higher stability. Furthermore the equilibrium of the reaction of **Kn1** and **A2**-**A6** follows the order of higher electron-donating effect of the Y group of the aldimine, in line with the stronger conjugation of the **Kn2**-**Kn6** products.

Scheme 2. The C=C/C=N exchange reactions between Kn compounds Kn1-Kn6 and Aldimines A1-A6 in $CDCl_3$ at room temperature.



Kn1 X = CH_3 **A1** Y = CH_3
Kn2 X = NO_2 **A2** Y = NO_2
Kn3 X = Cl **A3** Y = Cl
Kn4 X = H **A4** Y = H
Kn5 X = OMe **A5** Y = OMe
Kn6 X = NMe_2 **A6** Y = NMe_2

Table 1. Effect of substituents on the time to reach thermodynamic equilibrium and on the equilibrium position.

Entry	Starting reactants	Reaction time[a] (min)	aldimine ratio (reactant: product)
1	Kn1 + A2	60	1 : 0.21
	Kn2 + A1	15	0.22 : 1
2	Kn1 + A3	15	1 : 0.55
	Kn3 + A1	7	0.55 : 1
3	Kn1 + A4	≤ 3[b]	1 : 0.90
	Kn4 + A1	11	0.91 : 1
4	Kn1 + A5	≤ 3	0.54 : 1
	Kn5 + A1	22	1 : 0.56
5	Kn1 + A6	≤ 3	0.09 : 1
	Kn6 + A1	30	1 : 0.09

[a] Reaction time indicates the time when no further change in composition could be observed

[b] A time of 2-3 min was necessary between dissolution of the reactants (< 10 sec) and recording of the first ^{1}H NMR spectrum for locking and shimming of the NMR spectrometer.

The steric hindrance plays also a significant role in the case of substituents in the ortho position. As expected, the introduction of a mesityl group in the Knoevenagel compound (see compound **Kn8** in SI) almost suppressed its reaction with aldimine **A6** (less than 5% reaction after 14h; see Figure S2 for ^{1}H NMR spectrum) as compared to the reaction of **Kn1** with **A6** (less than 3 min, Table 1). A related effect is observed for **Kn7** (bearing an o,p-dinitrophenyl), which also reacted very slowly. The crystal structure of the **Kn7** compound was obtained and indicated that the barbiturate and dinitrophenyl rings were in a perpendicular orientation (Scheme 3) with little conjugation between them.

Other types of imines were studied as well. Aldimines derived from aliphatic amines or the bulky adamantylamine also reacted quickly, but oximes and hydrazones did not react with the Knoevenagel compound **Kn1** even after several days. Therefore, the influence of nucleophilicity of imines was studied.

Generally, the reaction of Schiff bases was slower than that of aldimines derived from benzylamine, probably due to their lower nucleophilicity. A longer reaction time also makes it easier to compare the reactivity. For Schiff bases with EWG and EDG in para-position, reaching equilibrium took from 2.2 hours (-F) to 40 hours (-OMe) (Figure S3). Clearly, the electron density on the imine nitrogen plays crucial role as nucleophilic attack of the imine nitrogen on the double bond of the Knoevenagel compound is the first step of the mechanism.

Concerning the effect of the solvent, it was found out that it influences the reaction rate but there was no observable change in the equilibrium (Table S1) The reaction is fastest in weakly polar aprotic solvents such as chloroform and dichloromethane. Non-polar solvents like tetrachloroethylene negatively affect the reaction rate and aprotic polar solvents (acetonitrile) significantly slow down the reaction. The qualitative order of solvent effect on reaction rate was: chloroform ~ dichloromethane > tetrachloroethylene > acetonitrile in the order of decreasing rates.

Kinetic data were obtained for the metathesis reaction of **Kn1** and Schiff base **S2**. A Schiff base was used because the exchange reaction was much slower than with an aldimine (about 6 hours to reach equilibrium compared to less than ten minutes), making it possible to follow the reaction (Figure S4). During the initial period of the reaction (where the reverse reaction is still negligible), the plot of 1/ [**S2**] versus time was linear, corre-

sponding to a second order reaction, in agreement with the proposed bimolecular mechanism.

2.2 C=C/C=N Exchange reaction with other Knoevenagel-type compounds.

In order to gain some more information about the present C=C/C=N exchange process, the reaction of imines with Knoevenagel compounds derived from other acidic methylene groups was also explored. It was found that the Knoevenagel compounds formed from Meldrum's acid reacted with imines, in the same manner as those derived from DMBA, even though the reaction was slower. For instance, the reaction of imine **A5** with the Kn compound **Kn9**, derived from Meldrum's acid and benzaldehyde, gave also a mixture of just the four expected constituents **A5**, **Kn9**, **A4** and **Kn10** (Figure S1b). Compared to the reaction of **A5** and **Kn4** (less than 3 minutes), it took 40 minutes to reach the equilibrium. On the other hand, Knoevenagel compounds derived from malononitrile did not show any reaction with imines.

Taken together, these results correlate with the decreasing polarization of the C=C bond as reflected in the significant difference in acidity from DMBA and Meldrum's acid on one side and malononitrile on the other (pKa=4.68, pKa=4.83 and pKa=11.8, respectively)[16].

2.3 Operation of an associative organo-metathesis-type mechanism in the Knoevenagel/Imine C=C/C=N exchange reaction

Features of the C=C/C=N exchange reactions. In order to investigate whether or not the Knoevenagel/imine C=C/C=N exchange reaction proceeded through the alternative dissociative mechanism involving hydrolysis and subsequent formation of products, the direct product formation from the putative hydrolysis products (DMBA and aldehyde) under the defined present reaction conditions ($CDCl_3$, r.t.) was examined. It was found that no Knoevenagel compound was formed from DMBA and 4-methoxybenzaldehyde under present reaction conditions.

On the other hand, upon mixing DMBA with the Schiff base **S3** the equilibrium between starting compounds and products (**Kn5** and aniline) was established (about 30 min; Figure S5a), the Schiff base presumably acting initially as a weak base for the condensation and then being taken over by the more basic liberated aniline. No trace of aniline was detected in the initial solution of **S3**. Conversely, when **Kn5** was treated with aniline, immediate attack of the amine on the C=C bond took place, giving the same equilibrium mixture of the corresponding Schiff base **S3** and free DMBA in about 40 min (Figure S5b).

When benzyl amine, 4-methoxybenzaldehyde and DMBA were mixed, the formation of the imine was very fast (about 10% in 16 min) and preceded the emergence of the Kn compound ((see Figure S6a for ^{1}H NMR spectra; see Fig. S6b for the graph of the time dependence of the imine formation and the subsequent Kn formation). If the imine formation was not possible, as when a tertiary amine (N, N-dimethylbenzylamine) was used instead of benzyl amine, the reaction was much slower (less than 10% of 4-methoxybenzaldehyde was converted during the first 2 hours; see Figure S6c for ^{1}H NMR spectrum). In this case, the double condensation product of two DMBA molecules with the aldehyde component was observed in the mixture (see ref. 17 and Figure S6c) in strong contrast with the exchange reaction investigated here, where such double condensation was never observed.

Imine formation under the present reaction condition was much slower than the majority of our exchange reactions. Thus, when benzyl amine and benzaldehyde were mixed, 76% of benzaldehyde was converted to **A4** in 100 minutes, whereas for the exchange reaction **Kn4** + **A1** equilibrium was reached in about 11 minutes (see Table 1). Hydrolysis of all the present Knoevenagel compounds under the reaction conditions was extremely slow (less than 1% in 2 hours) as seen from the NMR spectra of the reaction mixture of **Kn4** and **A5** (Figure S7a). In fact, it took place only after the exchange reaction reached equilibrium, due presumably to some residual traces of water. It is thus very unlikely that the reaction would proceed through direct condensation of the imine with the very small amount of DMBA present in the reaction mixture.

Strong further indication in favour of the proposed associative mechanism and of exclusion of the dissociative "hydrolysis route" was obtained from an experiment where 4-dimethylaminobenzaldehyde (DMABA) was added to the equilibrating mixture of **Kn4** and **A5** (Figure 1). The exchange reaction between **Kn4** and **A5** (Figure 1)

was very quick (within 5 minutes), but the exchange side-products **Kn6** and **A6** were not observed in the reaction mixture even after 10 hours. Thus, no incorporation of DMABA neither into the aldimine nor in the Knoevenagel compound was observed in the course of the ongoing **Kn4-A5/Kn5-A4** exchange reaction and for several hours after the equilibrium was established. This is in strong contrast to the similar reaction when DMBA itself was used instead of the Knoevenagel compound where, after a few minutes, the added aldehyde took part in the reaction and was incorporated. It can be assumed that the lag time was necessary to allow for formation of the new imine. Furthermore, when the aldimine **A6** was added to the equilibrating mixture instead of DMABA, then the by-product **Kn6** was produced as expected (Figure S7b).

The same experiment was also repeated with other aldehydes (4-nitrobenzaldehyde, 4-chlorobenzaldehyde, thiophen-2-carbaldehyde) to exclude the possibility, that the reactivity of aldehyde influences the possibility of incorporation. In all cases, no incorporation was observed. When the Schiff base **S2** was used only traces of exchange side-products were detected after 10 hours, but in parallel with hydrolysis products (Figure S7c).

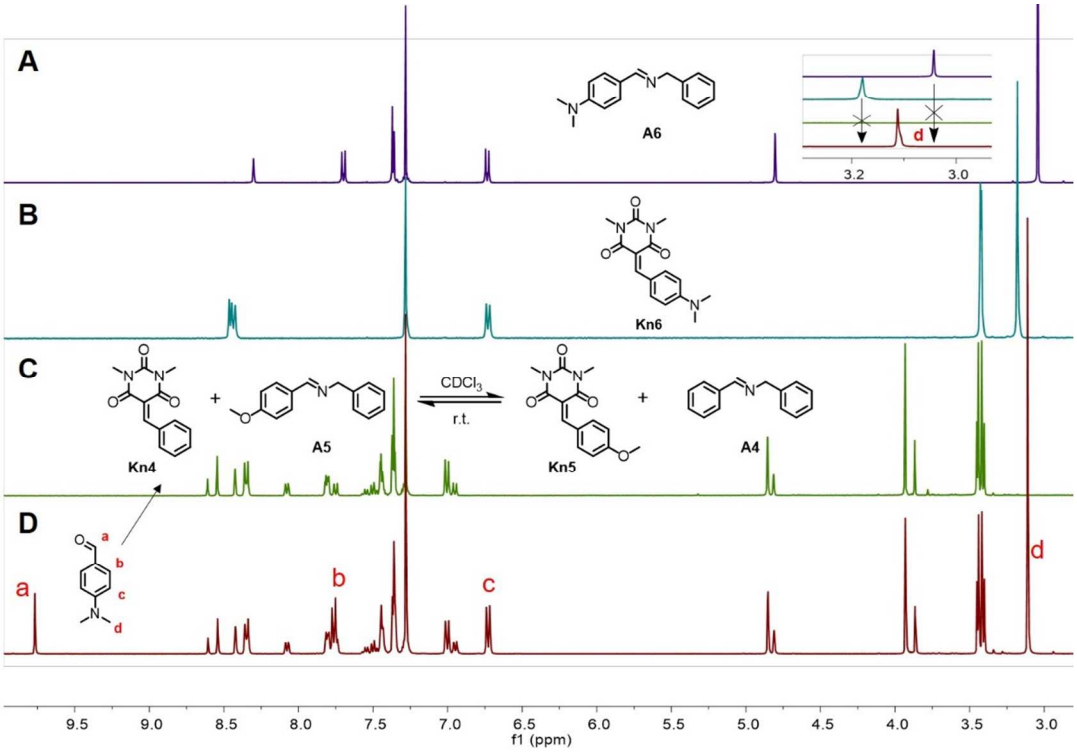


Figure 1. ^{1}H NMR spectra (400 MHz, $CDCl_3$, 298 K) of : (C) the equilibrating reaction mixture of **Kn4** and **A5** (20 mM each) after 10 minutes; the % of the compounds in the mixture were: 14% **Kn4**, 14% **A5**, 36% **Kn5**, 36% **A4**; (D) reaction mixture of **Kn4**, **A5** and 4-dimethylaminobenzaldehyde after 10 minutes, showing the same % as in (C) and no incorporation of the aldehyde; (A) and (B) for comparison, reference spectra of the possible by-products **A6** (A) and **Kn6** (B) that would be formed in case of incorporation of the 4-dimethylaminobenzaldehyde in mixture (D).

The 600 MHz 2D EXSY (exchange spectroscopy) experiments were measured in order to investigate the exchange rate of the Knoevenagel metathesis reaction (Figure 2). It took less than three minutes for the reaction of **Kn1** and **A5** to reach the equilibrium before 2D EXSY experiments were conducted. As expected for an associative mechanism (Scheme 1), all the exchange cross-peaks present in Figure 2 clearly show the reversible conversion of proton signals between the **Kn1 - A1** and **Kn5 - A5** pairs (see exchanges noted in Figure 2). From integration of the diagonal peaks and the cross-peaks for protons a and a', which provide the best data, one calculates that the conversion rates between Ha and Ha' in the equilibrium state are 0.490 Hz for a to a' and 0.285 Hz for the reverse reaction (the conversion rate was calculated three times from spectra using different mixing time and averaged, see SI for EXSY processing and calculation). One should note that during the exper-

iments, hydrolysis products were slowly generated (about 11.8% in 1 day).

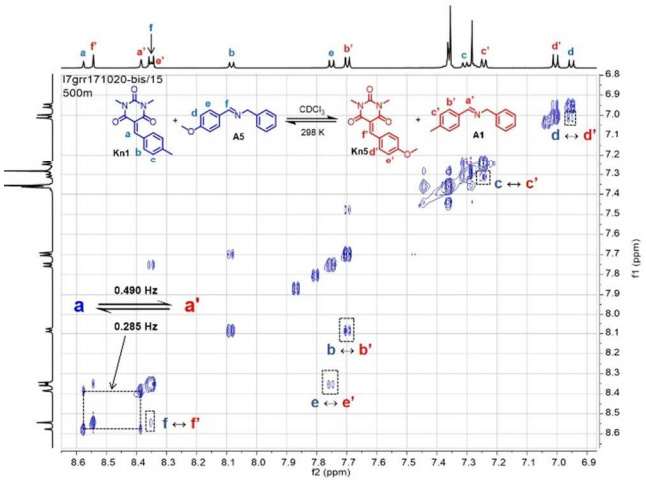


Figure 2. Two dimensional EXSY NMR spectrum (600 MHz, $CDCl_3$, 298 K, mixing time=500 ms) of reaction mixture started from **Kn1** and **A5** at 20 mM concentration of both starting compounds in 1:1 ratio. Exchange crosspeaks are highlighted. Other cross-peaks in the spectrum are due to the hydrolysis of the imines.

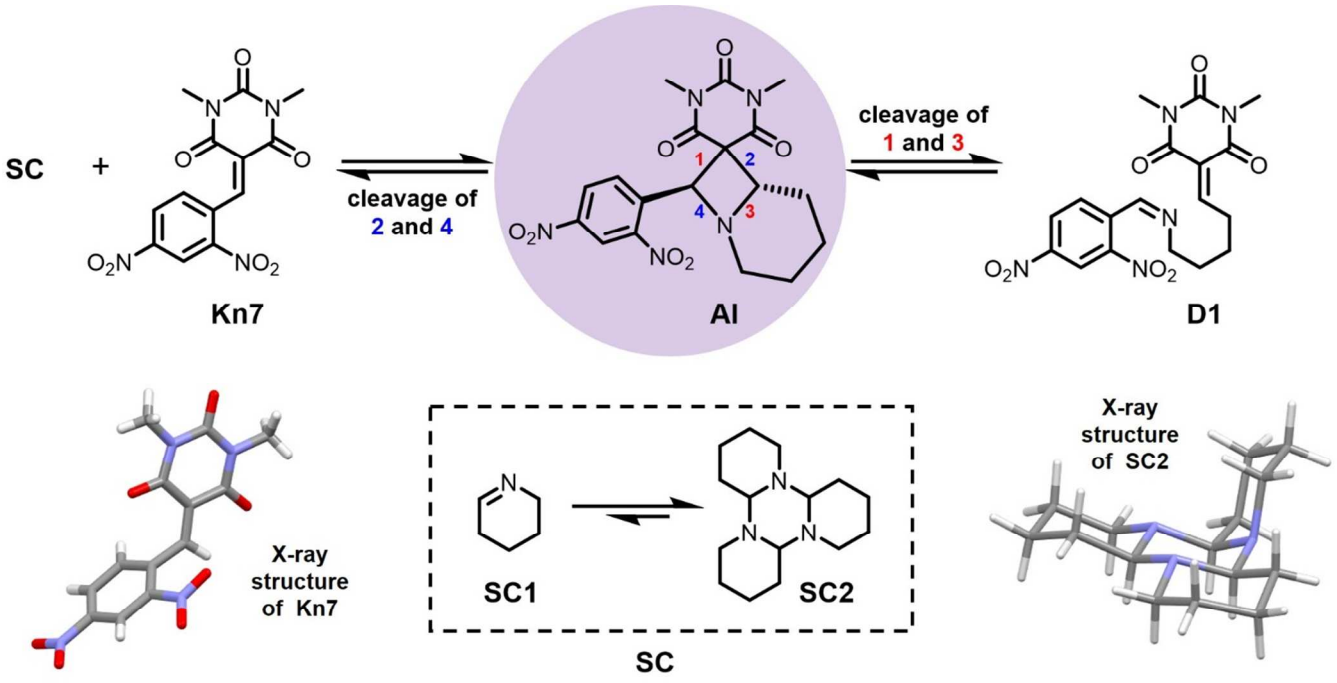
2.4 Associative Azetidine Organometathesis Mechanism.

We tried different methods to isolate or to catch the azetidine intermediate corresponding to the associative mechanism of this reaction. One was to introduce groups which would decrease the reactivity of the Kn compound and of the aldimine such as 4-dimethylamino in X position and thiophen in Y position of the two partners (see Scheme 2). Another approach was to slow down the reaction by cooling down the mixture of reactants. We also tried extensive measurements such as 2D NMR, high resolution ESMS, MALDI-TOF. Unfortunately, we never could detect the intermediate under these conditions.

In order to catch the azetidine intermediate, we explored strategies aimed at designing structures which might allow its detection and characterization or even its isolation.

Considering that a nitro group might be able to stabilize a four-membered ring in view of its strong electron withdrawing effect, the Knoevenagel compound **Kn2** was reacted with the imine **A4**. The exchange reaction was fast but no intermediate could be detected. For **Kn7** bearing an o, p-dinitrophenyl group the reaction was too slow (see above).

Scheme 3. Reaction of SC (cyclic imine SC1 and its trimeric derivatives SC2) with Kn7 to give the azetidine intermediate AI and exchange product D1.



Another approach was to try to stabilize the intermediate by condensing another ring onto the azetidine so that the incoming imine component would not fall off on cleavage of the two other bonds involved in a metathesis process (Scheme 3). To this end, cyclic imines were used as starting

materials instead of an acyclic N-benzyl imine. Among them, we investigated especially the six membered 1-azacyclohexene **SC1** (2, 3, 4, 5-tetrahydropyridine). The preparation and behavior of **SC1** was studied in aqueous solution[18] and was found to be in equilibrium with its trimeric condensation product **SC2** (Scheme 3), **SC3**, a rearrangement product of **SC2**, as well as a dimer **SC4** (see structures in Scheme S1). The **SC** mixture was prepared in ethanol solution and isolated from an ether solution (see ref. 18 and description in SI). We found that evaporation of this ether solution under vacuum afforded a crystalline product which was shown to be the trimer **SC2** by determination of its molecular structure by X ray crystallography (see in Scheme 3, bottom right, and in SI). The solution of these crystals in $CDCl_3$ contained a mixture **SC** of **SC1** and **SC2** in equilibrium as indicated by ^{1}H NMR spectroscopy. The solid state structure of **SC3** has been reported (18f) and has also been obtained in the present study.

For the present purposes, the thus obtained **SC** mixture of equilibrating **SC1** and **SC2** in $CDCl_3$ was used for all experiments and spectral data described below. When it was mixed with a solution of **Kn7** also in $CDCl_3$ in the ratio of 1: 1 **Kn7**: **SC**, the compounds reacted rapidly, generating already after 5 minutes a product **AI** as the dominant species (more than 80 %) in the mixture. The same result was obtained starting with a solution prepared from crystalline **SC2** (Scheme 3, bottom right). Thereafter, this species **AI** decomposed slowly in the solution (about 95% of **AI** decomposed in 10 hours, as observed by following the H5 proton signal in the NMR spectra at 25°C; see below for a more detailed description).

To better characterize the species **AI** as well as to minimize its decomposition, attempts to optimize the reaction conditions were pursued. It was eventually found that it could best be stabilized by simply conducting the reaction at lower temperature. We note at the outset that when the reaction of **Kn7** with **A4** was conducted at about -25°C, no reaction was observed by ^{1}H NMR spectroscopy; however, on letting the temperature of the mixture rise to room temperature, the exchange took place and the products formed, but no intermediate was detected. In contrast, when the reaction of **Kn7** with **SC** in the ratio 1:1.5 was performed at ≤ -25 ℃, the well-resolved and clean (> 99 % **AI** with respect to starting **Kn7**) ^{1}H NMR spectrum shown in Figure 3 was obtained in less than 3 min (time to record the spectrum). Note: the NMR spectrometer was also precooled to -25 ℃ before the insertion of the NMR tube and excess **SC** was used in order to consume all the **Kn7** in the mixture, providing the best NMR spectrum. All the peaks can be assigned as indicated and fit quite well with the chemical structure shown. To confirm this structure, 2D NMR experiments were conducted in the same conditions. The COSY spectrum provided correlations between the different protons (Figure 4). The correlation peak between the hydrogens 11, 11' is strong which means that they are close to each other, probably on a same carbon, with a large spin-spin coupling constant ($J_{11/11'}$ = 12 Hz) corresponding to a geminal coupling; the same holds for H8 and H8' ($J_{8/8'}$ = 13.2 Hz), which in addition have both correlation with H5. H1 and H2, H2 and H3 show weaker correlation signals (with $J_{1/2}$ = 2.4 Hz, $J_{2/3}$ = 8.4 Hz), indicating that they are 3 or 4 bonds away, as expected for the protons on the phenyl ring. The hydrogens 4 and 5 appear both as singlets in the 400 MHz ^{1}H NMR spectrum and are considered as being situated on the azetidine ring. However, in the 400 MHz COSY spectrum (Figure 4), whereas H4 shows no correlation, H5 is correlated with H8 and H8' of the neighboring methylene group. Indeed, in the 600 MHz ^{1}H NMR spectrum, the signal of H5 appears as an apparent dissymmetric triplet resulting from two overlapping doublets due to spin-spin coupling with H8 and H8' (coupling constants of 2.4 Hz and 3 Hz, see Fig. S9a). Besides, the H6 and H7 signals of the N-methyl groups, seen as a singlet, showed up as two close singlets located respectively at 3.416 ppm and 3.405 ppm (corresponding to a separation of 6.9 Hz) when the temperature was lowered to -35 ℃ (see fig. S9a).

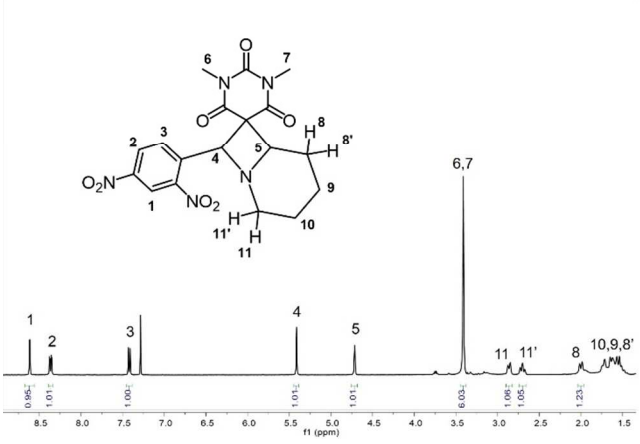


Figure 3. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, 248 K) of the intermediate **AI** formed from **SC** (1.5 eq.) and **Kn7**. Assignments rest also on the COSY and HSQC spectra shown in Figures 4 and 5.

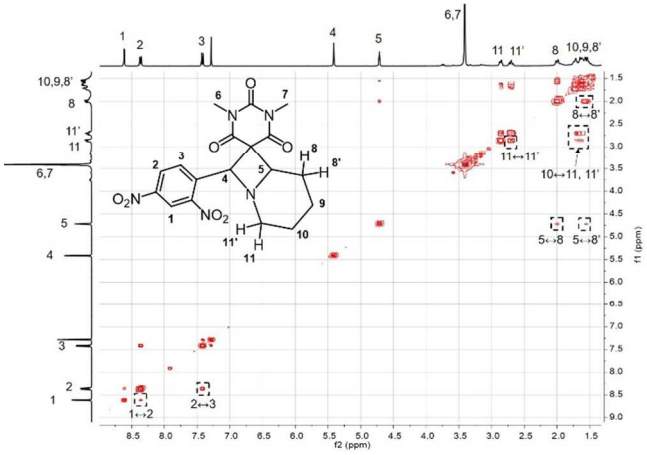


Figure 4. Two dimensional COSY spectrum (400 MHz, $CDCl_3$, 248 K) of the intermediate **AI** (see text for conditions).

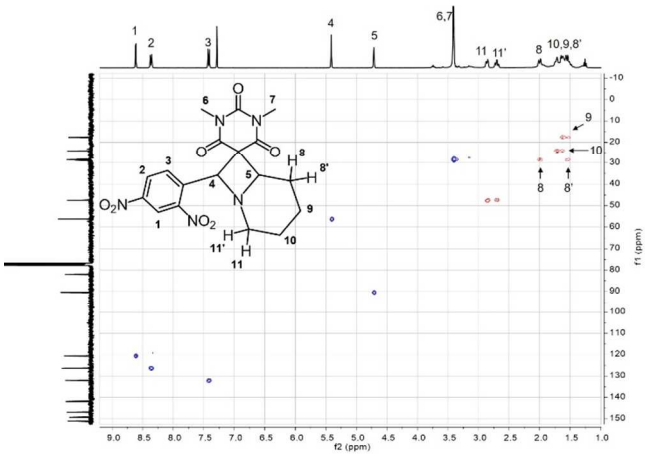


Figure 5. Two dimensional HSQC spectrum (400 MHz, $CDCl_3$, 248 K, -25°C) of the intermediate **AI**. Signals of different colors represent different chemical environments: the blue ones represent C-H correlations of -CH or -CH_3 while the red ones represent those of -CH_2 groups. The 13C NMR spectrum shown (vertical, left) was obtained at -35 ℃ as it is cleaner than that obtained at -25°C. (see Figure S9b for the full spectrum and peak assignments).

The HSQC (Heteronuclear Single-Quantum Correlation) spectrum was also measured (Figure 5) indicating that H11 and H11', as well as H8 and H8' belong to CH_2 groups. Besides, this experiment also shows the positions of the signals of H8', H9 and H10 in that order, which overlap partially in the ^{1}H NMR spectrum.

In addition, the HRMS (high resolution mass spectrum, precision ≤ 10 ppm) gave the correct strongly dominant mass peak at 416.1197 with strong intensity and fitting well with the simulation. (Figure S10)

All these characterization results gave strong evidence in favor of the structure of the intermediate **AI** containing a four-membered heterocyclic azetidine ring formed by addition of the imine group of **SC1** on the C=C bond of the Knoevenagel compound **Kn7**.

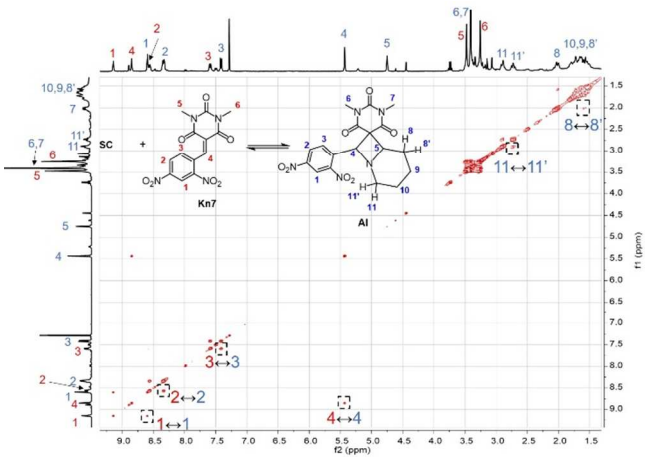


Figure 6. Two dimensional ROESY spectrum (400 MHz, $CDCl_3$, 298 K) of the intermediate **AI** along with excess **Kn7**. Chemical exchange crosspeaks were presented. The small signals are due to decomposition products formed at r.t. (see below).

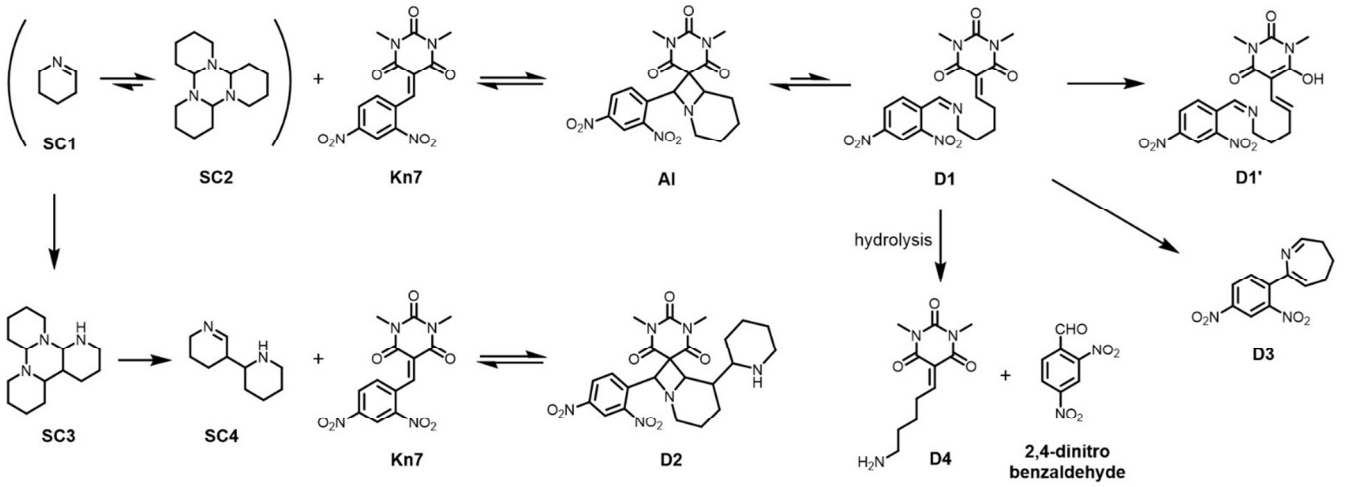
The 400 MHz ROESY (Rotating Frame Overhauser Effect Spectroscopy) spectrum was measured to observe chemical exchange signals (Figure 6). To this end, excess **Kn7** (1.5 eq.) was mixed with **SC** (1 eq.) in $CDCl_3$ at room temperature. An excess of **Kn7** was used in order to make sure that free **Kn7** will be present in the reaction mixture. The spectrum obtained shows that the H4 signal of **Kn7** has a crosspeak with H4 of **AI** indicating that they are exchanging. Similarly, all the aromatic hydrogens (H1- H3) of **Kn7** have crosspeaks with those of **AI**, respectively. On the other hand, H8 and H8', as well as H11 and H11', which have been shown to be located respectively on the same carbon, also have exchange crosspeaks. In order to exchange H8 with H8' and H11 with H11', **AI** has to dissociate reversibly into **SC1** and **Kn7** with **SC1** adding randomly from the front side and the backside of the plane of the C=C group of **Kn7**. One might also consider conformational exchange, i.e. inversion of the six-membered ring, but this process alone should in principle not exchange H8/8' and H11/11'. All these data confirmed that the start-

ing compounds **Kn7** and **SC** were reversibly converted to the intermediate **AI**.

When **Kn7** was reacted with 1-azacyclopentene[19], similar observations were made. An analogous intermediate **AI(5)** was formed at 248K but less cleanly than with 1-azacylohexene. Significantly, addition of azacyclohexene to a solution of **AI(5)** led to displacement of the azacyclopentene component even at 248K and faster at 298K, whereas the reverse process (i.e. for **AI** + azacyclopentene) did not take place (see SI Figure S11 for details). This result indicates that **AI** is more stable than **AI(5)**, in agreement with the expected lower stability of **AI(5)** due to increased strain resulting from the fusion of a five-membered ring to the azetidine moiety as compared to a six-membered ring. Furthermore, this displacement also points out that the intermediate **AI(5)** is dynamic, in line with the behavior of **AI** itself (see above).

A last point relates to the configuration of the substituents on the 4-membered azetidine ring of the intermediate. The condensation with the two cyclic imines may in particular be expected to yield the isomer with lowest strain, i.e. where the substituents are in trans relationship, as represented for **AI** in Scheme 3 and also supported by DFT computational results (see Figure S10c) Taken together the results accumulated give strong evidence for the proposed dynamic covalent metathesis mechanism involving a four-membered azetidine intermediate **AI**.

Scheme 4. Possible transformations of the intermediate AI involving the formation of the subsequent products D1, D1', D2, D3, D4 and 2, 4-dinitrobenzaldehyde.



2.5 Fate of the azetidine intermediate **AI**.

The intermediate **AI** can undergo different possible transformations as shown in Scheme 4.

In principle, the intermediate **AI** can undergo either cleavage of bonds 2 and 4 to give back **Kn7** and **SC1** (as shown above by the ROESY study, Figure 6) or go forward to **D1** by the cleavage of bonds 1 and 3 of the azetidine ring (Scheme3). However, **D1** could not be detected by ^{1}H NMR in the reaction mixture. One could consider that the bond 3 of **AI** has little tendency to cleave because it is located in a six-membered ring. Also, in the interconversion between **AI** and **D1**, very fast intramolecular recondensation may be expected to shift the equilibrium strongly towards **AI**.

In order to get insight into the fate of **AI**, a 30 mM 1:1 mixture of **Kn7** and **SC** (mixture of **SC1** and **SC2**), first prepared at ≤ -25 ℃, was followed by ^{1}H NMR as a function of time at room temperature (see Figure S12a for the ^{1}H NMR spectra of the decomposition process and Figure S12b for the kinetic curves of **AI**, **Kn7**, **D2** and **D3** evolution).

At the beginning (<10 min) **AI** (22.0 mM) and **Kn7** (4.6 mM) were the dominant species (> 90%). Then another species **D2** (detected by mass spectrometry) appeared, increased to 8.2 mM in the first 5 hours and later decreased to only 1.0 mM in 42 hours. This product **D2** is considered to be a by-product (Scheme 4) formed by reaction of **Kn7** and **SC4**, a dimer of **SC1** (see the corresponding MS peak for **SC4** and **D2** in Figure S15a). **SC4** is formed by cleavage of the rearranged trimer **SC3** (see ref. 18c, Schemes S1 and S2 and Figure 15c) itself formed from **SC2** in the equilibrating mixture.[18] Two other decomposition compounds appeared with time, which both may be consid-

ered to result from **D1**, the product of cleavage of **AI** along bonds 1,3 (Scheme 3): **D3** and **D1'**, the latter as a precipitate which started to show up after about 8 hours reaction time. Both have been identified by mass spectrometry. **D3** increased gradually from 0 to 3.9 mM in 42 hours and remained the same even after 5 days. It could be isolated from the reaction mixture by column chromatography. Its spectral features (clear ^{1}H NMR and mass spectra) agree with a structure **D3** (see Figures S13a-c for characterization of **D3**), a possible product derived from of **D1** (Scheme S3). The ^{1}H NMR and mass spectral data of the precipitate correspond to those expected for **D1'**, the tautomer of **D1** (see Figures S14a-c for the characterization of **D1'**).

Only trace amounts of 2, 4-dinitrobenzaldehyde (< 3%), the hydrolysis product of **D1**, could be observed after 5 days. The decomposition scheme of **AI**, the corresponding kinetic curves and the data for the decomposition products are described in the SI (Schemes S2 and S3, Figure S12-S15).

3. CONCLUSIONS

The present work establishes that the C=C/C=N exchange reaction between a barbiturate-derived Knoevenagel compound and an imine proceeds in organic solvents through an associative mechanism of organo-metathesis type (Scheme 1) without intervention of a metal or proton catalysis. Structural effects are in line with the influence of different parameters on the reaction equilibria, such as conjugation within the Knoevenagel compounds, nucleophilicity of the imine nitrogen and polarity of solvent. The results obtained also do not agree with an alternative dissociative mechanism which would proceed by hydrolysis of one or both components followed by recondensation. Moreover, the four-membered ring azetidine intermediate **AI** could be stabilized and characterized by NMR and HRMS spectroscopies. In a more general context, the present Knoevenagel metathesis process between (strongly) polarized C=C bonds and C=N bonds with a nucleophilic N site provides a novel, efficient tool for the creation of dynamic covalent libraries and for the generation of dynamic polymers by C=C/C=N recombination. It has also further potential in other fields such as complex molecule synthesis, organic materials and catalysis.

ASSOCIATED CONTENT

Supporting Information.
This material is available free of charge via the Internet at http://pubs.acs.org.
Experimental details, NMR spectra, and synthetic procedures, including Schemes S1-S3, Tables S1, S2 and Figures S1–S15 (PDF)

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Notes

The authors declare no competing financial interests.

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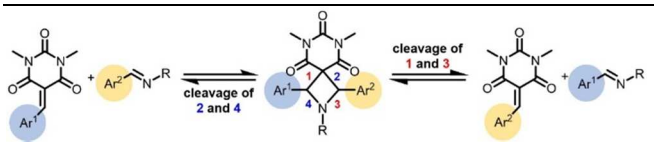
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