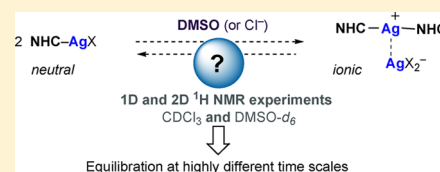# Structure of Silver−N-Heterocyclic Carbenes in Solution: Evidence of Equilibration in DMSO at Very Different Time Scales by ^{1}H NMR Experiments

Elsa Caytan and Sylvain Roland*

Sorbonne Universités, UPMC Univ Paris 6, Institut Parisien de Chimie Moléculaire UMR CNRS 8232, 4 place Jussieu, F-75005 Paris, France

S *Supporting Information*

ABSTRACT: Ag−N-heterocyclic carbene (NHC) complexes can occur as neutral $[(NHC)AgX]$ and/or ionic $[(NHC)_2Ag][AgX_2]$ species in solution. Herein, the behavior of four complexes bearing common bulky N,N'-diaryl NHCs was examined in DMSO. ^{1}H NMR experiments performed systematically in CDCl$_3$ and in DMSO-d_6 were used to detect DMSO or chloride ion induced equilibration between the neutral and ionic forms at very different time scales. We observed that solubilization of IMesAgCl and SIMesAgCl in DMSO at 300 K led in less than a few minutes to a complete equilibration. Here, magnetization exchange rate constants were determined from EXSY experiments. In contrast, IPrAgCl and SIPrAgCl, which possess more bulky NHCs, were found to exhibit much lower exchange rates (or no exchange) at 300 K. IPrAgCl was shown to slowly generate an increasing amount of homoleptic cationic complex in DMSO for several hours before reaching equilibrium. In this case, the initial rate of formation of the cationic complex was determined.

ilver−N-heterocyclic carbenes (AgNHCs) have been widely used in organometallic chemistry and catalysis, mainly as carbene transfer agents to generate other metal NHCs.[1−3] On the other hand, AgNHCs have attracted more and more interest as biologically active organometallic complexes.[4] AgNHCs provide a convenient platform for drug design owing to the high diversity of NHC structures potentially accessible by various synthetic pathways and the relative stability of the Ag−carbon bond.[1,5] Currently, more information is needed to gain a better understanding of the factors governing their biological activity. Among these, lipophilicity, which is recognized as a prime physicochemical descriptor of active molecules, presumably plays an essential role. The lipophilicity of AgNHCs is related to the nature of the NHC ligand and, to a lesser extent, to that of the metal counterion. In addition, it must be highly dependent on the exact structure of the complexes in solution.

AgNHCs have been characterized as neutral $[(NHC)AgX]$ (**I**) or cationic $[(NHC)_2Ag][AgX_2]$ (**II**) complexes in solution.[1] Either of the forms **I** and **II** can preferentially be obtained by the classical Ag$_2$O method depending on the nature of (i) the substituents of the heterocycle, (ii) the counterion (coordinating or noncoordinating anion), and (iii) the solvent of the reaction (apolar or polar). Most AgNHCs have been characterized by NMR spectroscopy in CDCl$_3$ or CD$_2$Cl$_2$ (i.e., an apolar solvent), and only a few examples in DMSO-d_6 have been reported.[6] Therefore, a determination of the "true" structure of these complexes in DMSO remains underexplored. The isolated complexes **I** or **II** have both been employed to prepare stock solutions in DMSO for biological assays. However, there is no evidence for a unique structure (**I** or **II**) to be preserved under these conditions, which are usually different from those of the structural analyses (e.g., NMR experiments). Since the seminal

work of Lin and co-workers,[7] many authors have suggested that **I** and **II** could be in equilibrium, as shown in Figure 1. This was
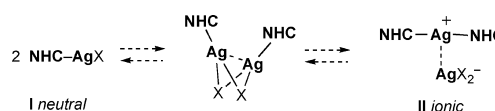
Figure 1. Possible equilibrium and intermediate between neutral AgNHC **I** and homoleptic cationic complex **II**.

supported by the different ^{13}C NMR patterns observed for the carbenic carbon, suggesting that exchanges occur,[8−10] presumably with a wide range of exchange rates. Recently, ^{13}C-enriched 1-mesityl-3-methylimidazol-2-ylidene silver complexes with various halogen ions were used to investigate NHC ligand exchange by variable-temperature ^{13}C NMR spectroscopy.[11] This study based on the ^{13}C NMR pattern of the carbenic carbon revealed that, with this NHC ligand, forms **I** and **II** were in equilibrium in CD$_2$Cl$_2$ in the NMR time scale presumably via an associative process, as suggested by the concentration-dependent coalescence temperature observed. To the best of our knowledge, equilibration at time scales different from that of NMR was not explored.

In previous work, we found that AgNHCs **1−4** (Figure 2), which possess structurally close bulky N,N'-diaryl NHCs, had relatively different activities as antibacterial and anticancer agents.[12] This prompted us to investigate their structures in solution in DMSO. Herein, we show that simple ^{1}H NMR experiments associated with systematic analyses of AgNHCs in
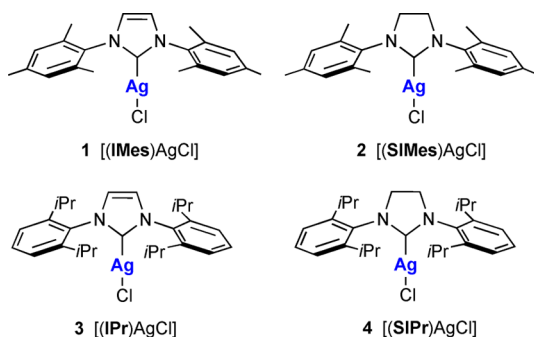
Figure 2. AgNHCs investigated in this study.

both CDCl$_3$ and DMSO-d_6 can be used as a convenient strategy to detect NHC exchange processes between forms **I** and **II** at very different time scales. Comparison of **1**−**4** enables fine evaluation of the influence of steric and electronic effects. We demonstrate that the occurrence of the equilibrium and its rate are highly sensitive to modifications in the NHC structure.

A first series of experiments was performed with the complex [(IMes)AgCl] (**1**). Complex **1** was initially synthesized through the Ag$_2$O route in an apolar solvent (CH$_2$Cl$_2$) and was exclusively isolated as its neutral form (**I**) after crystallization in THF (73% yield).[13] Later on, it was shown that the synthetic method employed had an important influence on the **I**:**II** ratio. An increased amount of homoleptic [(IMes)$_2$Ag][AgCl$_2$] complex **II** was obtained by use of a more polar solvent such as DMSO in the synthesis (34% detected in the crude reaction mixture by ^{1}H NMR in CDCl$_3$).[14] As previously observed,[11] we found that the NMR solvent used for the analyses also played an essential role in the ratio observed. In CDCl$_3$, the ^{1}H NMR spectrum of **1** (crude reaction mixture) shows a single set of signals corresponding to the neutral form **I** (Figure 3a and Figure
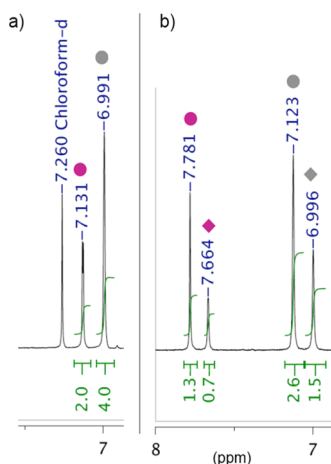

Figure 3. ^{1}H NMR spectrum of [(IMes)AgCl] (**1**) recorded in (a) CDCl$_3$ and (b) DMSO-d_6 (t = 10 min): (●) neutral complex **I**; (◆) ionic complex **II**. The concentration was 0.04 M for both experiments. Enlargements of the area of the aromatic protons are shown.

S1 in the Supporting Information). When the same sample is analyzed in DMSO-d_6, two sets of signals corresponding to both forms **I** and **II** with a ratio of 78:22 are observed (Figure 3b and Figure S2 (Supporting Information)),[15] therefore indicating that an equilibration takes place in DMSO, independently of the solvent used for the reaction.

To confirm the occurrence of a dynamic process, exchange spectroscopy (EXSY) experiments were performed with complex **1** in DMSO-d_6 at different mixing times (τ_m = 20, 40, 60, 90, 300, and 800 ms). The corresponding 2D spectra, showing strong positive cross peaks, clearly demonstrate that **I** and **II** are in equilibrium at room temperature (300 K), as presented in Figure 4 for the aromatic protons. The exchange is
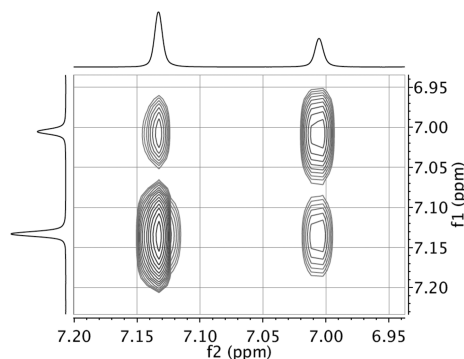

Figure 4. ^{1}H NMR 2D (EXSY) spectrum of [(IMes)AgCl] (**1**) recorded in DMSO-d_6 at T = 300 K. The mixing time (τ_m) was 300 ms. An enlargement of the area of the aromatic protons (H of the mesityl groups) is shown.

highly visible at 300 ms for all protons of the complex with no NOE detectable (Figure S3 (Supporting Information)). This indicates that **I** and **II** are in the slow exchange regime on the NMR time scale, although the exchange is already detectable at 20 ms. In the ^{13}C NMR spectrum, a signal with a pattern corresponding to the carbenic carbon (two doublets) is detectable at 181.4 ppm (Figure S4 (Supporting Information)). The coupling constants of 177.5 and 205 Hz ($^1J_{C-Ag}$) are consistent with those of a cationic form (**II**).[9] This was confirmed by HMBC experiments, which showed a correlation between the aromatic protons of the minor isomer **II** and the signal of the carbenic carbon (Figure S5 (Supporting Information)). It was suggested that fluxional behavior of AgNHCs results in a lack of C−Ag coupling.[7,14] However, this might be associated with high exchange rates on the NMR time scale. Here, although an exchange occurs on the NMR time scale, the carbenic carbon of the cationic form (**II**) of **1** can be detected and is associated with a well-defined pattern. The carbenic carbon of the neutral species **I** is not detectable, likely due to its lower intensity. The integrated diagonal and cross-peak intensities in the 2D-EXSY experiments (Table S2 (Supporting Information)) were used to determine the exchange rate constants k'_1 and k'_{-1} of the magnetization,[16] which is a first-order exchange reaction. The values at τ_m = 60 ms were selected for close normalized cross-peak magnetization values in the three exchange systems, and no detectable NOE. For complex **1**, the calculation gives exchange rate constants of 1.68 ± 0.2 and 1.06 ± 0.05 s^{-1} for k'_1 and k'_{-1}, respectively (see the Supporting Information).

Similar experiments were performed with complex **2**, bearing the corresponding saturated ligand SIMes. Complex **2**, which was prepared in refluxing CH$_2$Cl$_2$ by treatment of the imidazolinium salt with Ag$_2$O, is known to give lower yields than **1** due to the formation of significant amounts of the cationic species **II**, considered as a side product.[14] The cationic form **II** can be separated by precipitation. We isolated two batches of complex **2** after either one or two precipitation steps. These batches, analyzed by ^{1}H NMR in CDCl$_3$, show different proportions of **I**

and **II**, in ratios of 97:3 (Figure S6 (Supporting Information)) and 91:9. These ratios do not change over time (after several hours) and are not concentration dependent, therefore indicating that no equilibration occurs in CDCl$_3$. When complex **2** (initial ratio 97:3) was analyzed in DMSO-d_6 at the same concentration, a 75:25 mixture of **I** and **II** was observed due to a rapid equilibration (in less than 2 min) (Figure S7 (Supporting Information)). However, in contrast to **1**, no positive exchange cross peaks between **I** and **II** are detected in EXSY experiments performed at 300 K and at a τ_m of 60 ms, whereas NOE effects (negative cross peaks) are clearly visible. This demonstrates that the exchange is slower for complex **2** than for **1**. For SIMesAgCl (**2**), exchange cross peaks only become apparent at a mixing time of 90 ms along with more intense NOE effects. At 380 K, the exchange cross peaks in the EXSY experiments are clearly visible with no associated NOE effects (Figure S8 (Supporting Information)). At this temperature, the values of exchange rate constants were found to be 1.61 ± 0.32 s^{-1} for k'_1 and 2.03 ± 0.15 s^{-1} for k'_{-1} from the integration of cross-peak and diagonal magnetizations (see the Supporting Information). These values are in the same range as those obtained for complex **1** at a lower temperature (300 K) and, therefore, are consistent with a slower exchange process for **2**.

It was initially suggested from ^{13}C NMR studies with Ag complexes derived from triazoliums that the exchange process between **I** and **II** could be altered in the presence of chlorides.[8] A ^{13}C NMR study performed with 1-mesityl-3-methylimidazol-2-ylidene silver chloride also showed that forms **I** and **II** are in equilibrium in CD$_2$Cl$_2$ and that the exchange rate increased in the presence of chloride ions.[13] We studied the effect of chloride ions in DMSO-d_6. We observed that the addition of Me$_3$BnCl (0.9 equiv) to complex **2** increased the amount of **II** in solution from 25 to 29% (Figure S9 (Supporting Information)) and thus had a slight effect on the equilibrium. It should be noted that, in contrast to **1**, complex **2** is not fully soluble in DMSO at a concentration of 0.04 M. However, after addition of Cl$^-$, all of the residual precipitate is rapidly solubilized. The so-formed solution was found to be stable for 3 months at 20 °C (Table S1 (Supporting Information)). More interestingly, when similar experiments were repeated in CDCl$_3$, the addition of Cl$^-$ was found to promote a rapid equilibration of forms **I** and **II** with a ratio after 10 min of 72:28 that remains unchanged over time (Figure 5 and Figure S10 (Supporting Information)). This demonstrates that the exchange process with complex **2** is not limited to polar solvents but can be induced in an apolar solvent in the presence of chloride ions.

Next, we investigated the effect of the solvent on the possible equilibration of complexes **3** and **4**, which are structurally close to **1** and **2**, with more bulky NHC ligands (IPr and SIPr). Complex **3** was characterized as a 97:3 mixture of **I** and **II** in CDCl$_3$ (Figure S11 (Supporting Information)). The same batch analyzed in DMSO-d_6 exhibits a similar ratio of 98:2 (after 10 min), first suggesting that no equilibration occurs (Figure 6a and Figure S12 (Supporting Information)). However, when the same sample was controlled after 16 h at 20 °C, a different ratio of 89:11 was measured (Figure 6b and Figure S13 (Supporting Information)). At a mixing time of 800 ms, no positive exchange cross peaks are visible between the neutral and cationic forms and only NOE effects are observed (weak negative cross-peaks) (Figure S14 (Supporting Information)). This suggests that a slow equilibration takes place in DMSO-d_6 on a time scale which is not comparable to that of complexes **1** and **2** (NMR time scale). This equilibration could be reproduced by using the same batch of
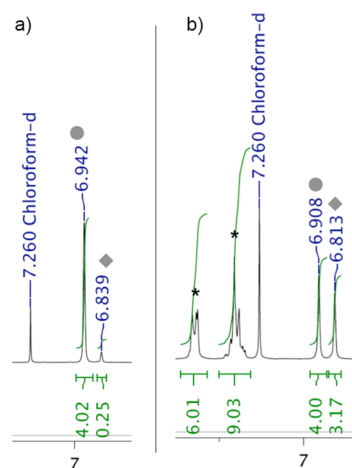
Figure 5. ^{1}H NMR spectrum of [(SIMes)AgCl] (**2**) recorded in (a) CDCl$_3$ and (b) CDCl$_3$ in the presence of Me$_3$BnCl (*) (2.1 equiv): (●) neutral complex **I**; (◆) ionic complex **II**. The concentration was 0.04 M for both experiments. Enlargements of the area of the aromatic protons are shown.
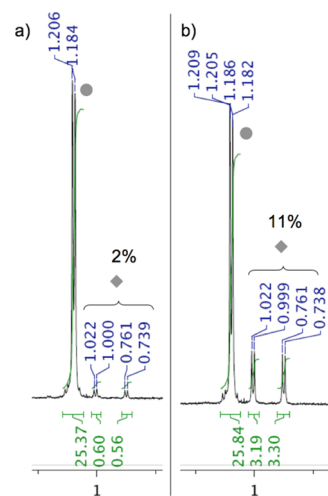
Figure 6. ^{1}H NMR spectrum of [(IPr)AgCl] (**3**) recorded in DMSO-d_6 at (a) t = 10 min and (b) t = 16 h: (●) neutral complex **I**; (◆) ionic complex **II**. The concentration was 0.04 M for both experiments. Enlargements of the area of the CH_3 groups (isopropyl) are shown.

IPrAgCl (commercial supplier). However, when the experiment was repeated with a different batch previously prepared by the classical Ag$_2$O route, no equilibration was observed at the same temperature.[17] In this case, a temperature of 320 K was required for a slow equilibration to take place to give a **I**:**II** ratio of 93:7 after 72 h. Addition of the precursor imidazolium chloride (IPr·HCl, 0.5 equiv) to a solution of **3** in DMSO-d_6 was found to induce the equilibration at 300 K to give 7% of **II** after 24 h. This suggests that low amounts of chloride-containing compounds could favor the process. In the experiments at 320 K, the concentration variation of forms **I** and **II** as a function of time was determined by integration of the CH_3 signals of the isopropyl groups in the ^{1}H NMR spectra (Table S4 and Figure S15 (Supporting Information)). The plots of 1/[**I**] as a function of time clearly show that the reaction of formation of the cationic complex **II** is not a second-order reaction as expected for a simple one-step dimerization-like process (Figure 1) or a pseudo-second-order reaction (Figure S16 (Supporting Information)). This suggests that other species or a multistep equilibrated

reaction associated with a more complex rate law is involved. Plotting the concentration of **II** as a function of time gave the initial rate of formation of **II**. A value of 0.1×10^{-6} mol L^{-1} s^{-1} was obtained from the slope at $[\mathbf{II}] = 0$ (Figure S17 (Supporting Information)). Finally, complex **4**, possessing the saturated NHC analogue SIPr, was observed as its neutral form **I** (>98%) in both CDCl$_3$ and DMSO-d_6. In the latter case, no change is observed over time (after 16 h), suggesting that no equilibration occurs (Figures S14 and S15 (Supporting Information)). It is likely, by analogy with SIMesAgCl, that the isomerization rate of SIPrAgCl is lower than that of IPrAgCl. However, due to the low solubility of SIPrAgCl in DMSO (Table S1 (Supporting Information)), the kinetics were not investigated further.

In conclusion, we have shown that standard ^{1}H NMR experiments can be used as a convenient tool to detect fluxional behaviors of AgNHCs over a wide range of exchange rates. Different protocols are required to detect the exchanges on the different time scales. Four silver(I) complexes bearing common NHC ligands, which can be considered as structurally similar, have been investigated. The results, along with those in the literature, show that the occurrence of an equilibrium between neutral and cationic complexes and the equilibration rate are highly dependent on the NHC structure. This suggests that careful attention should be paid to the "true" structure of AgNHCs in solution. In most cases, DMSO was found to promote the equilibration of forms **I** and **II**. Exchange reactions with bulky NHC ligands are relevant for catalytic applications where NHC transfer reactions from AgNHCs are involved. Here, transfer of NHCs in polar solvents and its mechanism need to be further explored. The very different fluxional behaviors observed for IMes/SIMes and IPr/SIPr could account for the results reported in the preparation of other metal NHCs by using AgNHCs **1**−**4** as precursors.[18] In the case of rapid exchange rate, the equilibrium might also be displaced in response to changes in environmental conditions (e.g., lipophilicity). In this case, AgNHCs may act as "adaptable" complexes in biological media.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information
Text, tables, and figures giving full NMR spectra for all experiments and details of the solubility/stability of **1**−**4** in DMSO. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
*E-mail for S.R.: sylvain.roland@upmc.fr.

Notes
The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

■ REFERENCES
(1) For general reviews on AgNHCs, see: (a) Garrison, J. C.; Youngs, W. J. *Chem. Rev.* **2005**, *105*, 3978. (b) Lin, I. J. B.; Vasam, C. S. *Coord. Chem. Rev.* **2007**, *251*, 642. (c) Lin, J. C. Y.; Huang, R. T. W.; Lee, C. S.; Bhattacharyya, A.; Hwang, W. S.; Lin, I. J. B. *Chem. Rev.* **2009**, *109*, 3561.
(2) For general reviews on metal NHCs and applications in catalysis, see: (a) Bourissou, D.; Guerret, O.; Gabbai, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39. (b) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*,

1290. (c) Hahn, F. E.; Jahnke, M. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 3122. (d) Diez-Gonzalez, S.; Marion, N.; Nolan, S. P. *Chem. Rev.* **2009**, *109*, 3612.
(3) For examples of AgNHCs as catalysts, see: (a) Sentman, A. C.; Szilárd, C.; Waymouth, R. M.; Hedrick, J. L. *J. Org. Chem.* **2005**, *70*, 2391. (b) Wang, D.; Zhang, B.; He, C.; Wu, P.; Duan, C. *Chem. Commun.* **2010**, *46*, 4728. (c) Chen, M.-T.; Landers, B.; Navarro, O. *Org. Biomol. Chem.* **2012**, *10*, 2206. (d) Taşci, Z.; Kunduracıoğlu, A.; Kani, İ.; Çetinkaya, B. *ChemCatChem* **2012**, *4*, 831.
(4) (a) Hindi, K. M.; Panzner, M. J.; Tessier, C. A.; Cannon, C. L.; Youngs, W. J. *Chem. Rev.* **2009**, *109*, 3859. (b) Teyssot, M. L.; Jarrousse, A. S.; Manin, M.; Chevry, A.; Roche, S.; Norre, F.; Beaudoin, C.; Morel, L.; Boyer, D.; Mahiou, R.; Gautier, A. *Dalton Trans.* **2009**, 6894. (c) Mercs, L.; Albrecht, M. *Chem. Soc. Rev.* **2010**, *39*, 1903. (d) Gautier, A.; Cisnetti, F. *Metallomics* **2012**, *4*, 23. (e) Oehninger, L.; Rubbiani, R.; Ott, I. *Dalton Trans.* **2013**, *42*, 3269. (f) Liu, W.; Gust, R. *Chem. Soc. Rev.* **2013**, *42*, 755.
(5) Benhamou, L.; Chardon, E.; Lavigne, G.; Bellemin-Laponnaz, S.; César, V. *Chem. Rev.* **2011**, *111*, 2705.
(6) Mainly homoleptic cationic AgNHCs have been characterized in DMSO-d_6. For examples see: (a) Siciliano, T. J.; Deblock, M. C.; Hindi, K. M.; Durmus, S.; Panzner, M. J.; Tessier, C. A.; Youngs, W. J. *J. Organomet. Chem.* **2011**, *696*, 1066. (b) Pellei, M.; Gandin, V.; Marinelli, M.; Marzano, C.; Yousufuddin, M.; Dias, H. V. R.; Santini, C. *Inorg. Chem.* **2012**, *51*, 9873. (c) Kriechbaum, M.; Hölbling, J.; Stammler, H.-G.; List, M.; Berger, R. J. F.; Monkowius, U. *Organometallics* **2013**, *32*, 2876. (d) Hahn, F. E.; Radloff, C.; Pape, T.; Hepp, A. *Chem. Eur. J.* **2008**, *14*, 10900. (e) Rit, A.; Pape, T.; Hahn, F. E. *J. Am. Chem. Soc.* **2010**, *132*, 4572. (f) Rit, A.; Pape, T.; Hepp, A.; Hahn, F. E. *Organometallics* **2011**, *30*, 334.
(7) Wang, H. M. J.; Lin, I. J. B. *Organometallics* **1998**, *17*, 972.
(8) Guerret, O.; Solé, S.; Gornitzka, H.; Teichert, M.; Trinquier, G.; Bertrand, G. *J. Am. Chem. Soc.* **1997**, *119*, 6668.
(9) Iglesias, M.; Beetstra, D. J.; Knight, J. C.; Ooi, L.-L.; Stasch, A.; Coles, S.; Male, L.; Hursthouse, M. B.; Cavell, K. J.; Dervisi, A.; Fallis, I. A. *Organometallics* **2008**, *27*, 3279.
(10) Tapu, D.; Dixon, D. A.; Roe, C. *Chem. Rev.* **2009**, *109*, 3385.
(11) Su, H.-L.; Pérez, L. M.; Lee, S.-J.; Reibenspies, J. H.; Bazzi, H. S.; Bergbreiter, D. E. *Organometallics* **2012**, *31*, 4063.
(12) (a) Roland, S.; Jolivalt, C.; Cresteil, T.; Eloy, L.; Bouhours, P.; Hequet, A.; Mansuy, V.; Vanucci, C.; Paris, J.-M. *Chem. Eur. J.* **2011**, *17*, 1442. (b) Eloy, L.; Jarrousse, A.-S.; Teyssot, M.-L.; Gautier, A.; Morel, L.; Jolivalt, C.; Cresteil, T.; Roland, S. *ChemMedChem* **2012**, *7*, 805.
(13) Ramnial, T.; Abernethy, C. D.; Spicer, M. D.; McKenzie, I. D.; Gay, I. D.; Clyburne, J. A. C. *Inorg. Chem.* **2003**, *42*, 1391.
(14) de Frémont, P.; Scott, N. M.; Stevens, E. D.; Ramnial, T.; Lightbody, O. C.; Macdonald, C. L. B.; Clyburne, J. A. C.; Abernethy, C. D.; Nolan, S. P. *Organometallics* **2005**, *24*, 6301.
(15) Complex **1** is fully soluble in both CDCl$_3$ and DMSO-d_6. A different **I**:**II** ratio (1:1) was previously reported for complex **1** in DMSO-d_6.[11] This might be ascribed to the different concentrations used.
(16) Ernst, R. R.; Bodenhausen, G.; Wokau, A. *Principle of Nuclear Magnetic Resonance in One and Two Dimensions*; Oxford University Press: Oxford, U.K., 1983.
(17) We assume that trace amounts of residual species (e.g., imidazolium precursor) likely induce equilibration in the commercial batch.
(18) For instance, Ag−carbene transfer reactions can be used to generate SIMesAuCl and IMesAuCl, whereas the preparation of SIPrAuCl and IPrAuCl requires the free carbene route. See ref 1c and: de Frémont, P.; Scott, N. M.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2005**, *24*, 2411.