Suzuki Coupling Reactions in Ether-Functionalized Ionic Liquids: The Importance of Weakly Interacting Cations

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Imidazolium- and pyridinium-based ionic liquids with ether/polyether substituents have been evaluated as solvents for palladium-catalyzed Suzuki C−C coupling reactions. In general, reactions proceed more efficiently in these solvents compared to other ionic liquids, which is believed to be due to better stabilization of the palladium catalyst, involving weak interactions with the ether groups. The position and the number of oxygen atoms in the ether side chain strongly influence the outcome of the coupling reactions in the imidazolium-based ionic liquids, whereas for the pyridinium-based liquids no influence is observed. Carbene derivatives, generated from the imidazolium-based ionic liquids, are believed to play a role by terminating the catalytic cycle, and representative species have been isolated and characterized from stoichiometric reactions.

Introduction

Ionic liquids (ILs) have been extensively evaluated as alternative solvents for performing and enhancing a variety of catalyzed reactions.[1] In general, ILs are good media for catalyst immobilization, which allows for efficient recycling, but despite the large range of reactions that operate in ILs, it is not always clear what other advantages they offer over other more classical organic solvents or water. It should be noted, however, that most catalyzed reactions have been evaluated in a very limited selection of ILs, despite the potentially huge numbers (millions) of different functionalized ILs that could be made. Moreover, continuous rational design and synthesis of new ILs should eventually lead to superior IL-based processes. The range of organic solvents available for chemical reactions is limited to, at most, a few hundred practical solvents. Consequently, the development of ILs with functional groups,[2] providing identical or similar electron-donating properties to that of the major classes of organic solvents, e.g., IL alcohol, nitrile, ether, etc., will increase considerably the utility of ILs, thereby offering new opportunities in catalysis.

In order to design enhanced solvent systems for specific catalytic reactions, it is essential to determine and understand the reaction mechanism and points at which solvation effects are highly influential. Indeed, elucidation of reaction mechanisms in ionic liquids are now emerging,[3] and a growing body of papers are focused directly on the role of solvation.[4,5] While these studies are largely confined to ILs that do not contain functional groups, it has recently been shown that C−C coupling reactions employing palladium(II) salts as precatalysts are more effective in ionic liquids containing nitrile-functionalized cations.[6] This increase in activity is believed to be due to enhanced stabilization of catalytically active palladium species via the nitrile group, thus suppressing the formation of inert palladium aggregates.[7]

In this paper, we report on the application of ether- and polyether-functionalized ILs as solvents for Suzuki coupling reactions. Ether-functionalized ILs have been known for some time,[8] but as far as we are aware, use of this class of ILs as a medium for catalyzed reactions has not been previously reported. Our rationale for their implementation in Suzuki reactions is based on the notion that the ether moiety helps to stabilize the

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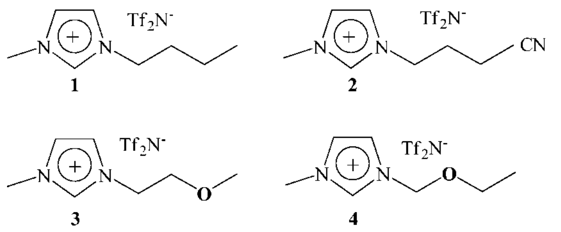


Figure 1. Structure of imidazolium-based ILs evaluated in this report.

Table 1. Obtained Yields from Suzuki Coupling Reactions of Iodobenzene and Phenylboronic Acid in Different Tf_2N-Based ILs[a]

entry	IL	biphenyl (%)
1	**1**	64
2	**2**	55
3	**3**	86
4	**4**	9
5	**3**[b]	8
6	**11**	85
7	**12**	85
8	**14**	57

[a] Conditions: a mixture of iodobenzene (0.5 mmol), phenylboronic acid (0.55 mmol), and Na_2CO_3 (1.05 mmol in 0.5 mL of H_2O), and $PdCl_2(CH_3CN)_2$ (1.12 mol %) based on iodobenzene in IL (1.0 mL) were heated at 100 °C for 4 h. Yield corresponds to biphenyl analyzed by GC. [b] Using **7** as the precatalyst.

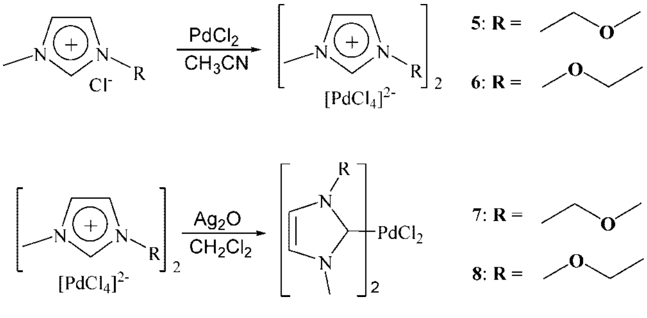
active catalytic species via weak interactions, thereby facilitating and increasing output. The outcome of our experiments is described herein.

Results and Discussion

In order to evaluate the influence of the cationic component of the ionic liquid, the standard Suzuki reaction between iodobenzene and phenylboronic acid was conducted in four different ILs with bis(trifluoromethylsulfonyl)amide as the anion, depicted in Figure 1. The results are listed in Table 1 with the actual reaction conditions specified in the footnote. Yields obtained in 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)amide, [C4mim][Tf_2N] (**1**), and 1-butyronitrile-3-methylimidazolium bis(trifluoromethylsulfonyl)amide [C3CNmim][Tf_2N] (**2**), are in good agreement with those reported previously.[6a,9] Significantly higher yields were obtained when an ionic liquid containing a 1-methoxyethyl substituent, namely, 1-(1-methoxyethyl)-3-methylimidazolium bis(trifluoromethylsulfonyl)amide, [C2OC1mim][Tf_2N] (**3**), was used. In contrast, 1-(1-ethoxymethyl)-3-methylimidazolium bis(trifluoromethylsulfonyl)amide, [C1OC2mim][Tf_2N] (**4**), an isomer of **3**, afforded very low yields of the coupling product.

The higher yield of biphenyl obtained when using **3** as compared to the other imidazolium-based ILs is presumably due to the presence of the $CH_2CH_2OCH_3$ functionality, which has the ability to establish weak interactions that help stabilize the active palladium catalyst (see below) and/or facilitate the solvation of the NaI byproduct produced during the reaction. It has previously been shown that nonfunctionalized ILs weakly solvate chloride ions and consequently inhibit catalytic reactions that require elimination of halide.[10,11] The solvation enthalpy of I^- in **1** and **3** was estimated using a literature procedure[10] and was found to be identical within experimental error (ΔH_{solv} 45 kJ/mol, based on the assumption that three cationic centers surround and interact with each I^- ion, consistent with obtained X-ray structures),[12] thereby ruling out differences in salt solvation being responsible for differences in catalytic activity.[13] It should be noted that coupling reactions proceed in IL in the presence of water, and it is likely that the water greatly facilitates solvation of the salt byproduct, which would otherwise suppress catalytic activity. This hypothesis is entirely reasonable given that halides are more nucleophilic in ILs, as compared to water, where halides are well solvated.[10] In this context it is also worth mentioning that a triphasic system composed of an ionic liquid phase containing the catalyst, an organic phase to absorb the organic product, and an aqueous phase to capture the salt byproduct has been shown to facilitate coupling reactions.[14]

Scheme 1. Palladium Complexes Prepared and Studied As Precatalysts



Since solvation properties of inorganic salts are similar and do not appear to be the source of differences in reactivity, it is more likely that intermolecular interactions between the IL and the palladium catalyst are more important. In order to rationalize the observed differences in coupling activity employing the isomeric ILs, **3** and **4**, the possibility of imidazolium carbene formation was studied. Accordingly, complexes **5** and **6** were prepared by heating **3** or **4** with $PdCl_2$ in acetonitrile (Scheme 1). Subsequent reaction of **5** or **6** in the presence of Ag_2O affords the corresponding carbene complexes **7** and **8**, in good yield.

The formation of carbene complexes **7** and **8** is easily established via ^{13}C NMR by the highly deshielded diagnostic resonances at 171.7 and 170.4 ppm, respectively, representing the coordinated C-2 position. Complex **7** is stable in CH_2Cl_2, whereas **8** rapidly decomposes at room temperature in wet organic solvents, where the C−O bond in the N-substituent is

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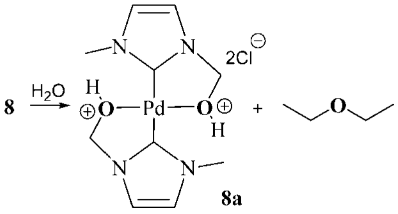
(12) The estimation of ΔH_{solv} using the method described in ref 10 monitors the chemical shift of the proton in the 2-position of the ring as a function of the concentration of the imidazolium salt in acetonitrile. At low concentration the ions are assumed to be completely solvated, and at high concentration it is assumed that they interact. The interactions, while being predominantly Coulombic, also involve H-bonding between the 2-proton of the imidazolium cation and the iodide anion, thus influencing the chemical shift of the 2-proton. For the ether-containing anion in **3** we also explored the interaction between the protons on the C atoms next to the O atoms of the ether groups, but no correlation was observed, so any contribution toward solvation from the ether group was ignored.

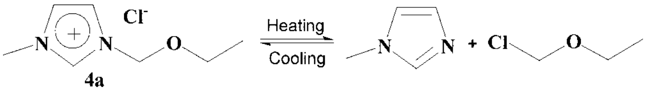
(13) Electrospray ionization mass spectrometry was also used to determine if **3** interacted more strongly with inorganic salts compared to **1**. It is well known that ionic liquids are often observed as aggregates in ESI-MS. Halide impurities are also observed forming aggregates with the ionic liquid cations. However, in a direct comparison of **1** and **3** containing NaI no differences were observed between the aggregates observed, indicating that the magnitudes of the interaction between the two IL cations and iodide are essentially the same. See for example:(a) Dyson, P. J.; McIndoe, J. S.; Zhao, D. *Chem. Commun.* **2003**, 508. (b) Dyson, P. J.; Khalaila, I.; Luettgen, S.; McIndoe, J. S.; Zhao, D. *Chem. Commun.* **2004**, 2204. (c) Bini, R.; Bortolini, O.; Chiappe, C.; Pieraccini, D.; Siciliano, T. *J. Phys. Chem. B* **2007**, *111*, 598.

(14) Carmichael, A. J.; Earle, M. J.; Holbrey, J. D.; McCormac, P. B.; Seddon, K. R. *Org. Lett.* **1999**, *1*, 997.

Scheme 2. Decomposition of 8 to 8a



Scheme 3. Thermoreversible Formation of Methylimidazole and Chloro Methyl Ether from 4a



cleaved to afford **8a** and diethyl ether (Scheme 2). The decomposition of **8** in CH_2Cl_2 exposed to air was monitored by ^1H NMR spectroscopy. Two sets of multiplets centered at 3.81 and 1.28 ppm, attributable to the OCH_2CH_3 group, gradually disappear and are replaced by two new peaks at 3.50 and 1.25 ppm, which match the chemical shifts reported for diethyl ether. The tentative assignment of **8a** is based on an additional peak at 10.8 ppm, which matches well with a related compound reported by Brookhart.[15]

Using complex **7** as the precatalyst for the coupling reaction in IL **3** affords the biphenyl product in very low yield (8%, Table 1, entry 5). Due to the significantly reduced stability of **8**, it was not evaluated for catalytic activity. While the low yield obtained with **7** does not rule out the importance of carbene species in the catalytic cycle, it seems unlikely that **7** is the active species responsible for coupling when solvated in **3**. It is worth noting that carbene species formed in situ from Pd(0) precursors are more active than those prepared with the method described above, although bis-carbene palladium(II) chloride complexes are known to give low yields in coupling reactions.[16,17] Moreover, the facile decomposition of **8** is an important indication that similar deactivation processes are possible during catalysis and could explain the poor yield when the reaction is performed in **4**. This hypothesis is further supported by the fact that the chloride analogue, **4a**, is unstable at high temperatures (see Scheme 3).[18] A related process to that depicted in Scheme 3 could also be responsible for the low activity in the coupling reaction, since the formation of methylimidazole could poison the catalytic species. In a control experiment using pure 1-methylimidazole as the solvent and $PdCl_2(CH_3CN)_2$ as the precatalyst in the presence of a base (Na_2CO_3), the yield of biphenyl from the reaction of phenyl boronic acid and iodobenzene is <3% after heating at 100 °C for 4 h.

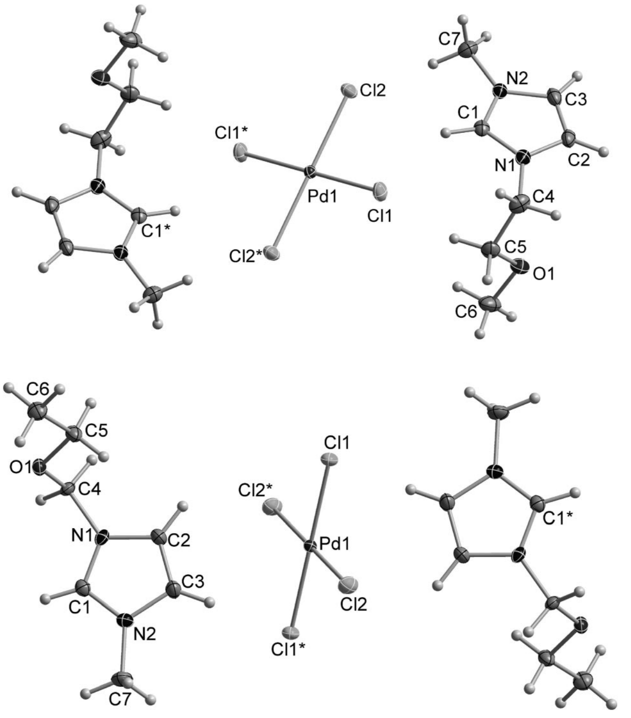


Figure 2. (Top) Representation of **5**. Thermal ellipsoids are drawn at the 50% probability level; starred atoms are obtained by the symmetry operation $-x, -y, -z$. Key bond lengths (Å) and angles (deg): Pd(1)−Cl(1) 2.3236(4), Pd(1)−Cl(2) 2.3242(4), C(5)−O(1) 1.428(2), C(6)−O(1) 1.440(2), C(4)−N(1) 1.477(2), N(2)−C(1)−N(1) 108.3(2), C(1)−N(1)−C(4) 125.4(2). (Bottom) Representation of **6**. Thermal ellipsoids are drawn at the 50% probability level; starred atoms are obtained by an inversion translation symmetry operation. Key bond lengths (Å) and angles (deg): Pd(1)−Cl(1) 2.315(1), Pd(1)−Cl(2) 2.323(1), C(4)−O(1), 1.396(7), C(5)−O(1) 1.447(7), C(4)−N(1) 1.488(7), N(2)−C(1)−N(1) 108.5(5), C(1)−N(1)−C(4) 125.5(5).

The solid-state structures of complexes **5**−**8** are shown in Figures 2 and 3, with key bond parameters given in the captions. In **5**−**8** the bond distances and angles within the imidazolium ring differ only slightly, and these parameters are comparable with other imidazolium salts.[19,20]

The C−O bond distances in **5**−**8** vary according to the position of the oxygen in the side chain. In **5** and **7**, where the oxygen atom is separated by two carbons from N, the C(5)−O(1) distance is 1.428(2) and 1.413(3) Å, respectively, whereas in **6** and **8**, where the oxygen atom is separated only by a CH_2 group, the electron-withdrawing effect of the imidazolium ring results in a shortening of the C−O bond (C(4)−O(1) distances of 1.396(7) and 1.391(8) Å, respectively). Coordination of the imidazolium C-2 position to the Pd center, as in **7** and **8**, leads to a minor contraction of the N1−C1−N2 bond angle by ca. 3° compared to that observed in **5** and **6**. Furthermore, bond distances in the imidazolium ring and the side chain are slightly shortened upon coordination, consistent with other Pd-imidazolium complexes.

As expected of square-planar palladium(II) complexes, there are no significant intra- or intermolecular interactions involving

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(15) Brookhart, M.; Grant, B.; Volpe, A. F., Jr *Organometallics* **1992**, *11*, 3920.

(16) Mathews, C. J.; Smith, P. J.; Welton, T. *Chem. Commun.* **2000**, 1249.

(17) Palladium carbene complexes with phosphorus ligands such as Ph_3P often give high yields of C−C coupling products. However, there are several reports that show that palladium carbene complexes are poor catalysts. For example, see refs 3 and 7 and: (a) Saito, S.; Yamaguchi, H.; Muto, H.; Makino, T. *Tetrahedron Lett.* **2007**, *48*, 7498.

(18) Heating **4a** under vacuum above 150 °C in a Schlenk tube results in decomposition with the initial formation of 1-methylimidazole and chloromethyl ethyl ether as gases at the temperature used. The two components re-form **4a** on cooling at the top of the Schlenk tube. A trace amount of 1-methylimidazole can be detected in the ^1H NMR spectrum following this process.

(19) For X-ray structures of imidazolium chlorides: (a) Saha, S.; Hayashi, S.; Kobayashi, A.; Hamaguchi, H. *Chem. Lett.* **2003**, *32*, 740. (b) Kaerkkaeinen, J.; Asikkala, J.; Laitinen, R. S.; Lajunen, M. K. *Z. Naturforsch. B* **2004**, *59*, 763. (c) Holbrey, J. D.; Reichert, W. M.; Nieuwenhuyzen, M.; Johnston, S.; Seddon, K. R.; Rogers, R. D. *Chem. Commun.* **2003**, 1636.

(20) For X-ray structures of imidazolium bromides and iodides: (a) Ozawa, R.; Hayashi, S.; Saha, S.; Kobayashi, A.; Hamaguchi, H. *Chem. Lett.* **2003**, *32*, 948. (b) Vygodskii, Y. S.; Lozinskaya, E. I.; Shaplov, A. S.; Lyssenko, K. A.; Antipin, M. Y.; Urman, Y. G. *Polymer* **2004**, *45*, 5031. (c) Nakakoshi, M.; Shiro, M.; Fujimoto, T.; Machinami, T.; Seki, H.; Tashiro, M.; Nishikawa, K. *Chem. Lett.* **2006**, *35*, 1400.

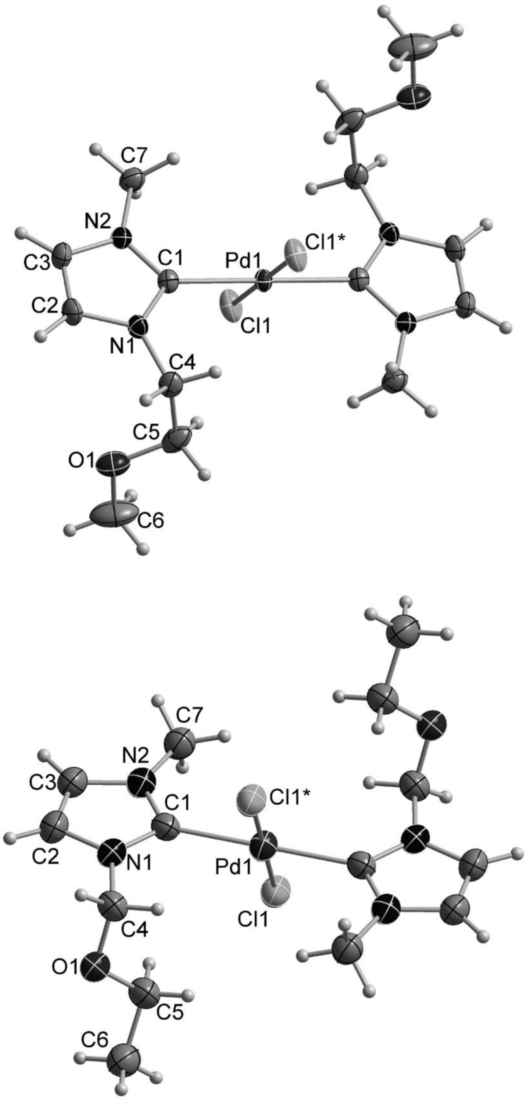

Figure 3. (Top) Graphical representation of **7**. Thermal ellipsoids are drawn at the 50% probability level; starred atoms are obtained by an inversion translation symmetry operation. Key bond lengths (Å) and angles (deg): C(1)−Pd(1) 2.025(2), Pd(1)−Cl(1) 2.3080(5), C(5)−O(1) 1.413(3), C(6)−O(1) 1.420(3), C(4)−N(1) 1.465(2), C(4)−C(5) 1.511(3), C(1)−Pd(1)−Cl(1) 89.23(5), N(2)−C(1)−N(1) 105.2(2), C(1)−N(1)−C(4) 123.9(2). (Bottom) Graphical representation of **8**. Thermal ellipsoids are drawn at the 50% probability level; starred atoms are obtained by an inversion translation symmetry operation. Key bond lengths (Å) and angles (deg): C(1)−Pd(1) 2.048(6), Pd(1)−Cl(1) 2.322(2), C(4)−O(1) 1.391(8), C(5)−O(1) 1.439(8), C(4)−N(1) 1.468(8), C(5)−C(6) 1.49(1), C(1)−Pd(1)−Cl(1) 89.4(2), N(1)−C(1)−N(2) 104.7(5), C(1)−N(1)−C(4) 125.2(5).

the palladium center; the closest oxygen−palladium distance is ca. 4.8 and 4.2 Å in **7** and **8**. However, a number of long-distance hydrogen bonding interactions to the chloride exist, in the range of 2.8 Å originating from H3A, H4A, and H7B (in **7**) and H3A and H6B (in **8**). The torsion angle between the plane of the imidazolium ring and the plane defined by atoms Pd and two Cl atoms is 71.2(2)° in **7** and 66.6(4)° in **8**.

It is probable that strong interactions between the ionic liquid and palladium catalyst (i.e., species with carbenoid centers derived from the IL) inhibit catalysis. Thus, on the basis of the data presented in Table 1, it is not unreasonable to assume that weak covalent interactions between the ether O atoms and the palladium could be important. Indeed, in reactions involving IL **2**, it has been shown that both palladium nanoparticles and palladium(II)-centered complexes are implicated within the catalytic system, and both are probably stabilized via interactions with the nitrile group.[6] Thus, in order to examine the role of the ether group on the catalytic activity and to reduce any potential problem arising from carbene formation,[21] the new, previously unreported pyridinium salts 1-(1-methoxyethyl)-3-methylpyridinium chloride, [C2OC1mpy][Cl] (**9**), and 1-(1-ethoxymethyl)-3-methylpyridinium chloride, [C1OC2mpy][Cl] (**10**), were prepared. Reaction of **9** and **10** with lithium bis(trifluoromethylsulfonyl)amide affords the room-temperature ILs 1-(1-methoxyethyl)-3-methylpyridinium bis(trifluoromethylsulfonyl)amide, [C2OC1mpy][Tf_2N] (**11**), and 1-(1-ethoxymethyl)-3-methylpyridinium bis(trifluoromethylsulfonyl)amide, [C1OC2mpy][Tf_2N] (**12**), respectively (Figure 4).

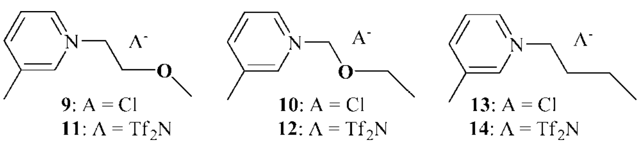

Figure 4. Ether-functionalized and nonfunctionalized 3-methylpyridinium salts **9**−**14**.

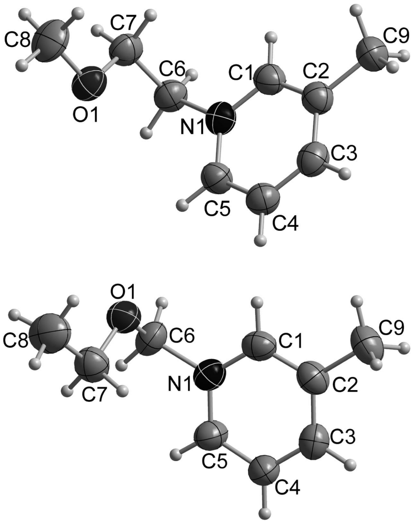

Figure 5. (Top) Graphic representation of **9**. Thermal ellipsoids are drawn at the 50% probability level. Key bond lengths (Å) and angles (deg): C(6)−N(1) 1.489(5), C(6)−C(7) 1.496(5), C(7)−O(1) 1.422(5), C(8)−O(1) 1.432(5), C(7)−O(1)−C(8) 111.1(3). (Bottom) Graphic representation of **10**. Thermal ellipsoids are drawn at the 50% probability level. Key bond lengths (Å) and angles (deg): C(6)−N(1) 1.514(6), C(6)−O(1) 1.391(6), C(7)−O(1) 1.448(7), C(7)−C(8) 1.503(9), C(6)−O(1)−C(7) 113.6(4).

The structures of **9** and **10** were elucidated in the solid state by single-crystal, X-ray diffraction, and representations of the cations are shown in Figure 5, with key bond parameters given in the caption. As observed in **5**−**8** the length of the C−O bond in **9** and **10** is related to number of methylene spacers between the oxygen and pyridinium moieties. Analogous with the imidazolium salts, a closer proximity of the pyridinium ring to the oxygen is reflected in a shorter C−O distance, with C(6)−O(1) equal to 1.391(6) Å in **10**, compared to the C(7)−O(1) bond distance of 1.422(5) Å in **9**.

Using ILs **11** and **12** as the reaction solvents for the coupling reaction described above, the biphenyl product was obtained in

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(21) Formation of carbenes from pyridinium salts cannot be excluded; see: Albrecht, M.; Stoeckli-Evans, H. *Chem. Commun.* **2005**, 4705.

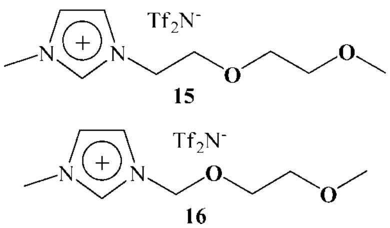


Figure 6. Imidazolium-based room-temperature ILs with polyether groups.

85% yield in both cases and almost an identical yield was obtained when the reaction is performed in **3** (entries 3, 6, and 7, Table 1). In contrast to the imidazolium ILs **3** and **4**, both types of pyridinium-based ionic liquids provide the same activity for the Suzuki coupling reaction, indicating that, in the absence of carbene interactions, higher activities are obtained. Furthermore, a comparison of **11** and **12** with the nonfunctionalized equivalent IL, **14**, confirms that incorporation of an ether group enhances catalysis (in **14** biphenyl is obtained in 57%, entry 8, Table 1) presumably due to effects similarly proposed for the nitrile IL **2**, i.e., involving weak interactions, but providing enough stabilization of key active palladium intermediates in the catalytic cycle and in the resting state. The electronic properties of the ether group are similarly matched with those of the nitrile group on the basis of the superior activity they provide in the reaction, and this advantage is further demonstrated in recycling experiments (see below).

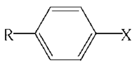
The role of polyether groups incorporated into an IL was also evaluated in the coupling reaction under the conditions identical to those described above. ILs **15** and **16** (Figure 6) afforded the biphenyl product in 62% and 11% yield, respectively. These yields are lower than those observed in the related monoether ILs **3** and **4**, possibly due to the formation of more stable (and therefore less catalytically active) species, by virtue of the polyether chain that can form multiple interactions with the catalyst.

The highest yields of biphenyl-coupled product were obtained when the ether-functionalized ILs **3**, **11**, and **12** were employed, being superior to the other ionic liquids tested. Since **11** is less expensive than **3** and having greater stability than other ILs of the series, it was selected as the solvent for testing a range of different Suzuki reactions. As shown in Table 2, Suzuki reactions using various types of para-substituted aryl halide precursors performed in **11** using $PdCl_2(CH_3CN)_2$ as the precatalytic species resulted in excellent yields of the expected aryl–aryl-coupled product; reaction conditions are provided in the footnotes of Table 2.

The yields of the coupling products are near quantitative when activated aryl iodides are employed as substrates, while aryl bromides afford moderate to good yields of the bis-aryls. Very low yields were observed with aryl chlorides, typically less than 5%. Nevertheless, it is apparent that ionic liquid **11** is an excellent medium in which to conduct Suzuki reactions, being tolerant to all the substrate functional groups evaluated.

On the basis of the versatility of **11** as a solvent for Suzuki coupling reactions, recycling experiments were investigated for the reaction of 1-iodo-4-nitrobenzene and iodobenzene with phenylboronic acid using $PdCl_2(CH_3CN)_2$ as the precatalyst. Since the 1-iodo-4-nitrobenzene substrate is highly activated, a quantitative yield of the product was obtained in each cycle during the testing of the five batches. For iodobenzene, the catalyst solution of **11** was recycled five times with no decrease in activity (Figure 7) and with complete recovery of the active catalyst. The palladium content in the organic phase was analyzed by ICP-OES and found to be below the detection limit of the instrument (<1 ppm).

Table 2. Suzuki Coupling of Various Aryl Halides with Phenylboronic Acid in 11[a]

Entry		Yield (%)
1	R = NO_2, X = I	>99
2	R = NO_2, X = Br	92
3	R = CN, X = I	>99
4	R = CN, X = Br	87
5	R = OMe, X = I	>99
7	R = H, X = Br	63
8[b]	R = COOH, X = I	>99

[a] Conditions: a mixture of the aryl halide (0.5 mmol), phenylboronic acid (0.55 mmol), and Na_2CO_3 (1.05 mmol in 0.5 mL of H_2O), and $PdCl_2(CH_3CN)_2$ (1.12 mol%) based on the aryl halide in **11** (1.0 mL) were heated at 100 °C for 4 h, and the products were analyzed by GC using biphenyl as external standard. [b] Same conditions as (a) except using Na_2CO_3 (1.3 mmol in 1.5 mL of H_2O) and analyzed with ^1H NMR using a literature method.[22]

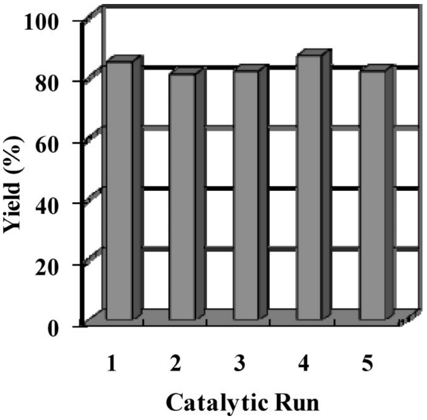


Figure 7. Recycling of the IL–catalyst solution for the reaction of iodobenzene and phenylboronic acid. Conditions: a mixture of iodobenzene (0.5 mmol), phenylboronic acid (0.55 mmol), and Na_2CO_3 (1.05 mmol in 0.5 mL of H_2O), and $PdCl_2(CH_3CN)_2$ (1.12 mol%) based on iodobenzene in IL **11** (1.0 mL) were heated at 100 °C for 4 h. Yields correspond to biphenyl product determined by GC.

In conclusion, it has been shown that ether-functionalized ILs are excellent solvents in which to conduct Suzuki coupling reactions. Not only are yields of the coupling product higher than when other ionic liquids are tested, but ether-based Ils are tolerant to, and unreactive with, substrates featuring a range of different functional groups. Furthermore, product extraction is facile under biphasic conditions, where palladium is not detected in the organic phase, and accordingly multiple recycling of the catalyst solution can be achieved without loss of activity. The superior yields obtained in the ether-functionalized ILs are proposed to be due to weak interaction between the IL cation and the palladium active species, such interactions being present

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(22) Joaquin, C. G.; Raphael, L.; Richard, M. C. *J. Am. Chem. Soc.* **2005**, *127*, 5097.

in the catalytic intermediates, which might otherwise decompose. Overall, these interactions appear to prevent catalyst decomposition and aggregation. The pyridinium-based ether-functionalized ILs are preferred over the imidazolium counterparts due to their increased stability and inability to form carbene-containing species.

Classical neutral oxygen-based donor solvents such as diethyl ether, tetrahydrofuran, or 1,4-dioxane are highly volatile and flammable; moreover tetrahydrofuran and 1,4-dioxane are also toxic. Thus, ILs with incorporated ether groups can be considered as promising nonvolatile and reusable solvent alternatives. Additionally, a number of advantages over nonfunctionalized and nitrile-functionalized ILs in Suzuki coupling reactions are observed, and ether-functionalized ILs may prove to be highly useful in other reactions in which the ether group can facilitate catalyst stabilization.

Experimental Section

Compounds **1** (converted from 1-butyl-3-methylimidazolium chloride[23]), **2**,[24] **3**, **4**,[25] and **13**[23] were prepared according to literature methods. 3-Picoline, 2-chloroethyl methyl ether, 2-chloromethyl ethyl ether, 1-bromo-2-(2-methoxyethoxy)ethane, 1-bromo-1-(2-methoxyethoxy)methane, lithium bis(trifluoromethylsulfonyl)amide, and palladium dichloride were purchased from Aldrich and used as received. Solvents were dried using the appropriate reagents and distilled prior to use. Syntheses of imidazolium salts and palladium complexes were performed under an inert atmosphere of dry nitrogen using standard Schlenk techniques. NMR spectra were obtained at 20 °C on a Bruker DMX 400 instrument using $SiMe_4$ as an external standard for the ^1H and ^{13}C spectra. IR spectra were recorded as solids on a Perkin-Elmer FT-IR 2000 system. Electrospray mass spectra were measured on a Thermo Finnigan LCQ Deca XP plus spectrometer according to a literature protocol.[26] Elemental analyses were carried out at the EPFL. Melting points were determined on a Stuart Scientific SMPS instrument. Inductively coupled plasma spectroscopy was performed using a Perkin-Elmer Optima 2000DV instrument. The concentration of palladium was determined by comparison of the spectral line intensity (340.45 nm) in the sample against that of a commercial standard.

Synthesis of 5 and 6. A mixture of $PdCl_2$ (0.18 g, 1.0 mmol) and **3** (for **5**) or **4** (for **6**) (2 mmol) in acetonitrile (10 mL) was heated at 60 °C for 5 h. After removal of the solvent, the resulting orange solid was washed with diethyl ether (2 × 2 mL) and dried under vacuum.

5: Yield: 99%. Mp: 107 °C. ^1H NMR (CD_3CN): δ 9.34 (s, 1H), 7.53 (s, 1H), 7.47 (s, 1H), 4.49 (t, J(H, H) = 4.8 Hz, 2H), 3.99 (s, 3H), 3.79 (t, J(H, H) = 4.8 Hz, 2H), 3.35 (s, 3H). ^{13}C NMR (CD_3CN): δ 137.1, 123.2, 122.8, 67.0, 58.1, 49.4, 35.4. IR (cm^{-1}) 3144, 3099, 2984, 1081. Anal. Calcd for $C_{14}H_{26}Cl_4N_4O_2Pd$ (%): C 31.69, H 4.94, N 10.56. Found: C 31.77, H 4.95, N 10.49.

6: Yield: 96%. Mp: 103 °C. ^1H NMR (CD_3CN): δ 9.50 (s, 1H), 7.56 (s, 1H), 7.50 (s, 1H), 5.68 (s, 2H), 4.00 (s, 3H), 3.68 (q, J(H, H) = 7.0 Hz, 2H), 1.20 (t, J(H, H) = 7.0 Hz, 3H). ^{13}C NMR (CD_3CN): δ 137.3, 124.0, 121.4, 78.6, 65.6, 36.3, 14.1. IR (cm^{-1}): 3116, 3084, 3054, 2987, 2909, 1103. Anal. Calcd for $C_{14}H_{26}Cl_4N_4O_2Pd$ (%): C 31.69, H 4.94, N 10.56. Found: C 31.72, H 4.95, N 10.54.

Synthesis of 7 and 8. A mixture of **5** (for **7**) or **6** (for **8**) (0.53 g, 1.0 mmol) and Ag_2O (0.23 g, 1.0 mmol) was stirred in dichloromethane (10 mL) for 24 h at room temperature with the exclusion of light. The resulting mixture was filtered, and the yellow filtrate was concentrated to ca. 5 mL. Dropwise addition of diethyl ether (5 mL) to the solution resulted in the precipitation of a pale yellow solid, which was filtered, and the solid was washed with diethyl ether (2 × 2 mL) and dried under vacuum.

7: Yield: 78%. Mp: 172 °C. ^1H NMR (CD_2Cl_2): δ 7.05 (s, 1H), 6.91 (s, 1H), 4.70 (m, 2H), 4.04−4.20 (overlapped broad signal, 5H), 3.40 (s, 3H). ^{13}C NMR (CD_2Cl_2): δ 171.7, 124.1, 123.5, 74.1, 60.7, 55.7, 40.3. IR (cm^{-1}): 3156, 3126, 3101, 2983, 2940, 2878, 2833, 1113. Anal. Calcd for $C_{14}H_{24}Cl_2N_4O_2Pd$ (%): C 36.74, H 5.29, N 12.24. Found: C 36.82, H 5.33, N 12.24.

8: Yield: 58%. ^1H NMR (CD_2Cl_2): δ 7.14 (s, 1H), 7.00 (s, 1H), 5.93−5.91 (overlapping signal, 2H), 4.18−4.16 (overlapping signal, 3H), 3.83−3.72 (overlapping broad signal, 2H), 1.28−1.27 (overlapping signal, 3H). ^{13}C NMR (CD_2Cl_2): δ 170.4, 122.9, 119.9, 79.5, 64.9, 37.7, 14.8. Anal. Calcd for $C_{14}H_{24}Cl_2N_4O_2Pd$ (%): C 36.74, H 5.29, N 12.24. Found: C 36.81, H 5.30, N 12.25.

Synthesis of 9 and 10. 9: A mixture of 3-picoline (9.3 g, 0.10 mol) and 2-chloroethyl methyl ether (10.4 g, 0.11 mol) was stirred at 80 °C for 48 h. The reaction mixture was cooled to room temperature; acetonitrile (100 mL) and activated carbon (3.0 g) were added to the reaction mixture, then it was heated to 80 °C for 24 h and subsequently filtered. After removal of the solvent, the resulting product solidified upon cooling to 0 °C. The obtained solid was washed with diethyl ether (3 × 30 mL) and dried under vacuum for 24 h. Yield: 92%. ESI-MS (CH_3OH): (m/z) $[C2OC1mpy]^+$ 152. ^1H NMR (D_2O): δ 8.57 (s, 1H), 8.54 (d, J(H, H) = 8.0 Hz, 1H), 8.29 (d, J(H, H) = 8.0 Hz, 1H), 7.83 (t, J(H, H) = 8.0 Hz, 1H), 4.64 (t, J(H, H) = 4.8 Hz, 2H), 3.85 (t, J(H, H) = 4.8 Hz, 2H), 3.35 (s, 3H), 2.44 (s, 3H). ^{13}C NMR (D_2O): δ 146.5, 144.1, 141.8, 139.9, 127.4, 70.2, 60.7, 58.4, 17.7. IR (cm^{-1}): 3010, 2939, 2877, 2812, 1104. Anal. Calcd for $C_9H_{14}ClNO$ (%): C 57.60, H 7.52, N 7.46. Found: C 57.66, H 7.53, N 7.44.

10: A mixture of 3-picoline (9.3 g, 0.10 mol) and 2-chloromethyl ethyl ether (10.4 g, 0.11 mol) was stirred in diethyl ether (100 mL) for 3 h at room temperature. The resulting mixture was filtered, washed with diethyl ether (3 × 30 mL), and dried under vacuum for 24 h. Yield: 95%. ESI-MS (CH_3OH): (m/z) $[C1OC2mpy]^+$ 152. ^1H NMR (D_2O): δ 8.70 (s, 1H), 8.66 (d, J(H, H) = 8.0 Hz, 1H), 8.36 (d, J(H, H) = 8.0 Hz, 1H), 7.91 (t, J(H, H) = 8.0 Hz, 1H), 5.76 (s, 2H), 3.60 (q, J(H, H) = 7.0 Hz, 2H), 2.46 (s, 3H), 1.12 (t, J(H, H) = 7.0 Hz, 3H); ^{13}C NMR (D_2O): δ 147.9, 142.0, 140.1, 139.8, 127.5, 88.6, 67.1, 17.7, 13.9. IR (cm^{-1}): 3012, 2935, 2845, 1097. Anal. Calcd for $C_9H_{14}ClNO$ (%): C 57.60, H 7.52, N 7.46. Found: C 57.67, H 7.58, N 7.45.

Synthesis of 11, 12, and 14. $Li(N[SO_2CF_3]_2)$ (14.4 g, 0.05 mol) was added at room temperature to a solution of **9** (for **11**) or **10** (for **12**) (9.4 g, 0.05 mol) or **13** (for **14**) (11.5 g, 0.05 mol) in water (20 mL). The formed ionic liquid phase was separated and washed with water (3 × 5 mL) and then dried under vacuum.

11: Yield: 72%. ESI-MS (CH_3OH): (m/z) $[C2OC1mpy]^+$ 152; $[N(SO_2CF_3)_2]^-$ 280. ^1H NMR (CD_3CN): δ 8.26 (s, 1H), 8.24 (d, J(H, H) = 8.0 Hz, 1H), 8.06 (d, J(H, H) = 8.0 Hz, 1H), 7.62 (t, J(H, H) = 8.0 Hz, 1H), 4.35 (t, J(H, H) = 4.8 Hz, 2H), 3.53 (t, J(H, H) = 4.8 Hz, 2H), 3.01 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (CD_3CN): δ 146.4, 144.4, 142.2, 139.6, 127.2, 120.0 (q, J(C−F) = 318.6 Hz), 69.9, 61.2, 58.2, 17.5. IR (cm^{-1}): 3095, 2971, 2901, 1176, 1131, 1050. Anal. Calcd for $C_{11}H_{14}F_6N_2O_5S_2$ (%): C 30.56, H 3.26, N 6.48. Found: C 30.58, H 3.33, N 6.44.

12: Yield: 80%. ESI-MS (CH_3OH): (m/z) $[C1OC2mpy]^+$ 152; $[N(SO_2CF_3)_2]^-$ 280. ^1H NMR (CD_3COCD_3): δ 9.05 (s, 1H), 9.03 (d, J(H, H) = 8.0 Hz, 1H), 8.64 (d, J(H, H) = 8.0 Hz, 1H), 8.20 (t, J(H, H) = 8.0 Hz, 1H), 6.13 (s, 2H), 3.80 (q, J(H, H) = 7.2 H, 2H), 2.72 (s, 3H), 1.26 (t, J(H, H) = 7.2 Hz, 3H). ^{13}C NMR (CD_3CN): δ 147.8, 142.0, 140.1, 139.6, 127.6, 120.0 (q, J(C−F) = 318.6 Hz), 89.0, 67.0, 17.6, 13.9; IR (cm^{-1}): 3074, 2988, 2901,

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Table 3. Crystallographic Data for 5−10

	5	**6**	**7**	**8**	**9**	**10**
formula	$C_{14}H_{26}C_{14}N_4O_2Pd$	$C_{14}H_{26}C_{14}N_4O_2Pd$	$C_{14}H_{24}Cl_2N_4O_2Pd$	$C_{14}H_{24}Cl_2N_4O_2Pd$	$C_9H_{14}ClNO$	$C_9H_{14}ClNO$
M	530.59	530.59	457.67	457.67	187.66	187.66
T [K]	100(2)	100(2)	140(2)	140(2)	140(2)	140(2)
cryst syst	monoclinic	monoclinic	monoclinic	triclinic	orthorhombic	orthorhombic
space group	$P2(1)/c$	$P2(1)/n$	$P2(1)/c$	$P\bar{1}$	$P2(1)2(1)2(1)$	$Pbca$
a [Å]	9.1492(5)	9.4722(8)	8.0002(3)	7.358(4)	8.8805(7)	7.259(3)
b [Å]	16.4016(13)	11.2768(11)	8.5597(3)	7.773(5)	9.562(3)	14.394(3)
c [Å]	7.0218(3)	10.2127(4)	14.3238(4)	9.257(3)	12.161(4)	18.926(7)
α [deg]	90.0	90.0	90.0	100.98(5)	90.0	90.0
β [deg]	96.581(4)	94.212(6)	96.815(3)	91.83(4)	90.0	90.0
γ [deg]	90.0	90.0	90.0	117.05(5)	90.0	90.0
V [Å^3]	1046.76(11)	1087.93(15)	973.95(6)	458.7(4)	1032.7(5)	1977.5(11)
Z	2	2	2	1	4	8
density [Mg/m^3]	1.683	1.620	1.56	1.657	1.207	1.261
μ [mm^{-1}]	1.412	1.359	1.239	1.316	0.326	0.341
2θ range [°]	$3.69 \leq 2\theta \leq 27.52$	$3.36 \leq 2\theta \leq 27.51$	$2.7616 \leq 2\theta \leq 27.4194$	$3.02 \leq 2\theta \leq 27.58$	$3.13 \leq 2\theta \leq 27.57$	$3.03 \leq 2\theta \leq 24.51$
no. of reflns collected	20 906	24 274	7450	3846	8563	11 022
no. of indep reflns	2398 [$R_{int} = 0.0301$]	2492 [$R_{int} = 0.0297$]	2083 [$R_{int} = 0.0121$]	1971 [$R_{int} = 0.0648$]	2244 [$R_{int} = 0.0436$]	1647 [$R_{int} = 0.0673$]
GooF on F^2	1.188	1.482	1.117	1.116	1.136	1.122
final R_1, wR_2 [$I > 2\sigma(I)$]	0.0189, 0.0410	0.0446, 0.1293	0.0192, 0.0459	0.0680, 0.1880	0.0834, 0.2447	0.0546, 0.1589

1175, 1132, 1108, 1049. Anal. Calcd for $C_{11}H_{14}F_6N_2O_5S_2$ (%): C 30.56, H 3.26, N 6.48. Found: C 30.59, H 3.31, N 6.46.

14: Yield: 90%. ESI-MS (CH_3OH): (*m/z*) $[C4mpy]^+$ 150; $[N(SO_2CF_3)_2]^-$ 280. ^1H NMR (CD_3CN): δ 8.70 (s, 1H), 8.59 (d, J(H, H) = 8.0 Hz, 1H), 8.29 (d, J(H, H) = 8.0 Hz, 1H), 7.86 (t, J(H, H) = 8.0 Hz, 1H), 4.50 (t, J(H, H) = 7.8 Hz, 2H), 2.48 (s, 3H), 1.92 (m, 2H), 1.28 (m, 2H), 0.88 (t, J(H, H) = 7.8 Hz, 3H). ^{13}C NMR (CD_3CN): δ 145.9, 143.8, 141.3, 139.9, 127.4, 120.0 (q, J(C−F) = 318.6 Hz), 60.5, 32.6, 18.7, 17.7, 12.7. IR (cm^{-1}): 3075, 2967, 2939, 2880, 1506, 1347, 1328, 1175, 1132, 1051. Anal. Calcd for $C_{12}H_{16}F_6N_2O_4S_2$ (%): C 33.49, H 3.75, N 6.51. Found: C 33.52, H 3.78, N 6.48.

General Catalytic Suzuki C−C Coupling Procedure. Reactions were performed in a 10 mL two-necked flask fitted with a septum and reflux condenser equipped with a gas-inlet adaptor. Iodobenzene (0.5 mmol, 1 equiv) and the ionic liquid (1.0 mL) were added, followed by phenylboronic acid (0.55 mmol, 1.1 equiv), Na_2CO_3 (1.05 mmol, 2.1 equiv) in water (0.5 mL), and finally the palladium complex (0.0056 mmol, 1.12 mol % based on iodobenzene). The mixture was heated to 100 °C and stirred vigorously for 4 h. Subsequently the mixture was cooled to room temperature and extracted with diethyl ether (3 × 5 mL). The combined extracts were washed with brine and water and then dried with $MgSO_4$. The biphenyl product was obtained following filtration and removal of the solvent under vacuum. The product was characterized by GC and ^1H NMR spectroscopy. For the recycling experiments, the IL phase, which contained the catalyst, was washed with diethyl ether (3 × 5 mL) and placed under vacuum for 18 h prior to reuse. The samples for ICP analysis were prepared according to a literature method.[27] In brief, the combined diethyl ether extracts (15 mL) were evaporated to dryness, and HNO_3 (65%, 10 mL) and HCl (37%, 30 mL) were added. The mixture was heated for 5 h and then evaporated to dryness. The residue was dissolved in perchloric acid (10 mL, 71%), heated for 3 h, and evaporated to dryness. The residue was dissolved in 10 mL of HNO_3 (2%) aqueous solution and then analyzed.

Structural Characterization of 5−10. Single crystals of **5**−**10** suitable for X-ray diffraction studies were obtained by slow evaporation of diethyl ether into acetonitrile solution at −21 °C. Crystals were measured on a KUMA KM4/Sapphire CCD diffractometer (**7**), a Bruker Apex II CCD (**5** and **6**), and a mar345 IPDS (**8**−**10**). Crystallographic data for **5**−**10** are shown in Table 3. Data reduction was performed using CrysAlis RED.[28] Absorption corrections were applied to all structures; SADABS (**5** and **6**),[29] SCALE3 ABSPACK (**7**),[28] and DELABS (**8**−**10**) were employed.[30] Structure solution and refinement was performed using the SHELX97 software package,[31] and graphical representations of the structures were made with Diamond.[32] Structures were solved by direct methods and successive interpretation of the difference Fourier maps, followed by full matrix least-squares refinement (against F^2). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed in their geometrically generated positions and refined using a riding model.

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