Coordination Chemistry and Mechanisms of Metal-Catalyzed C–C Coupling Reactions, Part 12[+]

Nonaqueous Ionic Liquids: Superior Reaction Media for the Catalytic Heck-Vinylation of Chloroarenes

Volker P. W. Böhm and Wolfgang A. Herrmann*[a]

Dedicated to Prof. Dr. Armin de Meijere on the occasion of his 60th birthday

Abstract: Nonaqueous ionic liquids, that is molten salts, constitute an activating and stabilizing noninnocent solvent for the palladium-catalyzed Heck-vinylation of all types of aryl halides. Especially with chloroarenes an improved activity and stability of almost any known catalyst system is observed as compared to conventional, molecular solvents (e.g. dimethylformamide (DMF), dimethylacetamide (DMAc), *N*-methyl-2-pyrrolidinone (NMP), or dioxane). Thus, even catalytic amounts of ligand-free $PdCl_2$ yield stilbene from technically interesting chlorobenzene and styrene in high yield (turnover number (TON) = 18) without the need for further promoting salt additives such as tetraphenylphosphonium chloride. The scope of the new reaction medium is outlined for the first time for the vinylation of various aryl halides using different mono- and disubstituted olefins as well as a variety of known palladium(0) and palladium(II) catalyst systems. Furthermore, a novel means of catalyst recycling is presented and its scope is evaluated.

Keywords: alkenes · arenes · Heck reaction · nonaqueous ionic liquids · palladium

Introduction

The palladium-catalyzed arylation of olefins with aryl halides is generally referred to as the Heck reaction.[1] This reaction has received considerable attention, primarily due to the enormous synthetic potential to generate sp^2-sp^2 carbon–carbon bonds.[2] However, the reaction suffers from limitations that have so far precluded many industrial applications.[3] Typically, a relatively large amount of catalyst (>1 mol%) is needed for reasonable conversions and often catalyst recycling is hampered.[2]

Various approaches towards catalyst improvement have been described.[4] Most effort was reported to be achieved with activated, electron-poor chloroarenes by the use of highly basic, sterically hindered phosphanes,[5] the use of N-heterocyclic carbenes (NHC),[6] the use of palladacycles,[7, 8] the use of a large excess of coordinating ligands, for example triphenylphosphane[9] or tris(2,4-di-*tert*-butylphenyl)phosphite (tbp),[10] the use of heterogeneous Pd/C[11] or Pd/MgO,[12] or the use of nanostructured palladium clusters.[13] Only few approaches have reported success in the activation of chlorobenzene or even deactivated, electron-rich chloroarenes in general. These approaches include the use of palladium(II) dichloride with an excess of phosphonium salts[14] or the use of palladium(0) complexes of dibenzylideneacetone (dba) with sterically demanding tris(*tert*-butyl)phosphane[15] or bis(*tert*-butyl)ferrocenylphosphane.[16]

Approaches other than the improvement of the catalyst or ligand are rare. Chloroarenes can be activated by reaction with hexacarbonylchromium, which reduces the electron density on the aromatic system,[17] or by addition of a nickel(II) cocatalyst in the presence of sodium iodide, which was reported to transform the chloroarene into more reactive iodoarenes in situ.[18]

We present here a completely different approach to activate chloroarenes. It has long been known that the Heck reaction is performed best in polar solvents such as dimethylformamide (DMF), dimethylacetamide (DMAc), *N*-methyl-2-pyrrolidinone (NMP), and 1,4-dioxane.[2] In addition, the beneficial effect of tetraalkylammonium salts on the activity and stability of palladium(II) catalysts has been described.[19]

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[a] Prof. Dr. W. A. Herrmann, V. P. W. Böhm
Anorganisch-chemisches Institut
Technische Universität München
Lichtenbergstrasse 4, 85747 Garching (Germany)
Fax: (+49) 89-28913473
E-mail: herrmann@zaphod.anorg.chemie.tu-muenchen.de

[+] Part 11: See reference [22a].

Bearing these facts in mind, we chose nonaqueous ionic liquids (NAIL) as the solvent. The possibility to use NAIL as solvents in catalysis is known.[20] It has been applied in the Heck reaction[21] but the beneficial effect on less reactive substrates was discovered only recently.[22] In the following we report outstanding activities for various literature catalysts in the reaction of chloroarenes with different olefins using molten salts as reaction media. Additionally, a novel approach for the the catalyst-recycling and its scope is presented.

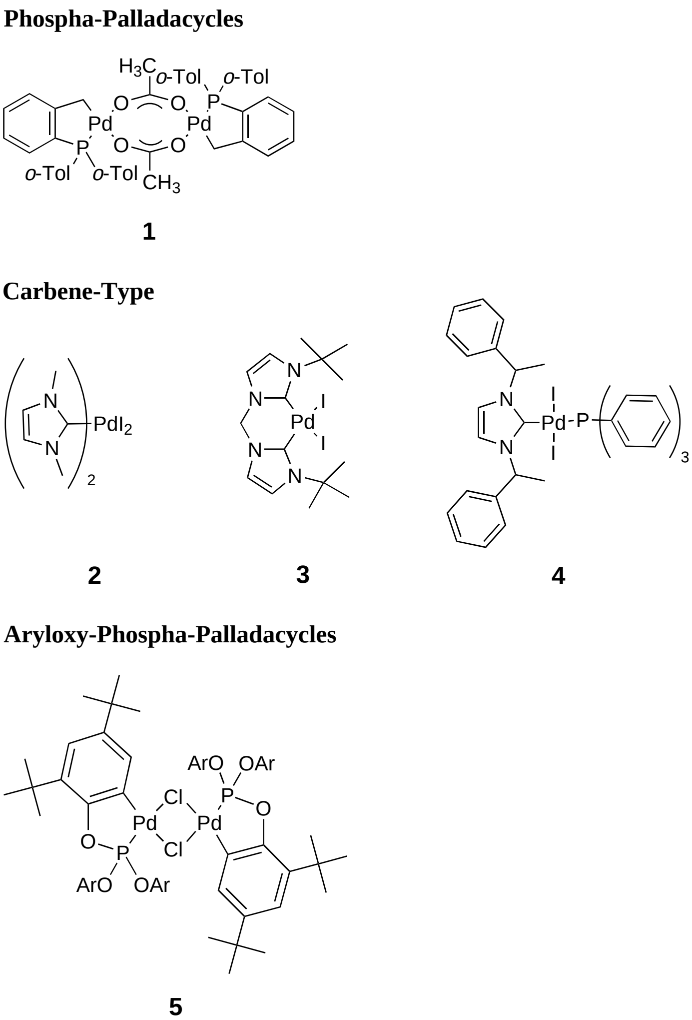
Results and Discussion

Vinylation of chlorobenzene

The oxidative addition of chloroarenes to palladium(0) complexes needs elevated temperatures.[23] Thus, it was clear to us that the activation of chlorobenzene in the Heck reaction also needed similar temperatures. The palladacycle *trans*-di(μ-acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium(II) (**1**) (Scheme 1) constitutes an established, stable catalyst for the Heck reaction at elevated temperatures and was therefore chosen for preliminary studies.[7, 22] For the activation of electron-poor chloroarenes with catalyst **1**, the addition of tetra-*n*-butylammonium bromide [NBu$_4$]Br was necessary. Initially we chose conditions which are known to work well in DMAc.[7]

Experiments revealed that temperatures of 130 °C are necessary for stilbene to be formed from chlorobenzene and styrene in [NBu$_4$]Br with catalyst **1** using sodium acetate Na(OAc) as the base. Raising the temperature to 150 °C results in much higher turnover numbers (TON) of 36 [mol product per mol palladium]. Like in traditional, molecular solvents the addition of further activating additives such as [PPh$_4$]Cl or [AsPh$_4$]Cl yields stilbene quantitatively from 1 mol % catalyst **1** (TON = 48, entry 25, Table 4).[7c]

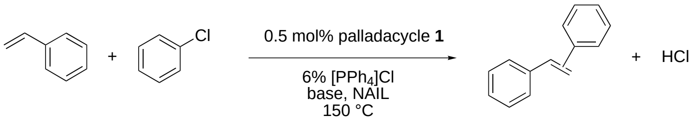
Abstract in German: *Ionische Flüssigkeiten bzw. Salzschmelzen sind aktivierende und stabilisierende Lösungsmittel für die Heck-Vinylierung von Halogenaromaten mit Palladium-Katalysatoren. Besonders mit Chloraromaten wird im Vergleich zu konventionellen, molekularen Lösungsmitteln (z. B. DMF, DMAc, NMP oder Dioxan) eine erhöhte Aktivität und Stabilität bei beinahe allen literaturbekannten Katalysatorsystemen beobachtet. Auf diese Weise können z. B. katalytische Mengen des ligandenfreien PdCl$_2$ das technisch interessante Chlorbenzol mit Styrol in hoher Ausbeute zu Stilben umsetzen (TON = 18), ohne daß weitere aktivierende Salzzusätze wie Tetraphenylphosphonium-chlorid nötig sind. In Bezug auf dieses Reaktionsmedium beschreiben wir erstmals ausführlich die Vinylierung von Halogenaromaten und deren Umsetzung mit unterschiedlichen mono- und disubstituierten Olefinen mit einer Vielzahl literaturbekannter Palladium(0)- und Palladium(II)-Katalysatorsysteme. Zusätzlich wird ein neues Verfahren zur Rückgewinnung des Katalysatorsystems vorgestellt und dessen Leistungsfähigkeit diskutiert.*



Scheme 1. Structurally defined palladium(II) catalysts for the Heck reaction. OAr = 2,4-di-*tert*-butylphenoxy.

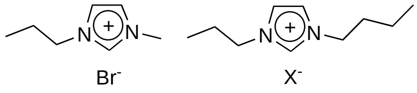
Comparison of different NAIL shows that [NBu$_4$]Br and [NBu$_4$]OAc constitute the most efficient solvents for the activation of chlorobenzene by palladacycle **1** (entries 1 and 2, Table 1). At first, the results with [NBu$_4$]OAc as the solvent or the base were disappointing until we realized that extremely careful drying and degassification were necessary here. Storing the solid [NBu$_4$]OAc over potassium hydroxide prior to degassing the melt for various hours furnishes a suitable base for further experiments. Similar properties of [NBu$_4$]OAc and [NBu$_4$]Br were observed in the reaction of deactivated *p*-bromoanisole and *n*-butyl acrylate. Tetra-*n*-butylammonium salts with the noncoordinating anions hexafluorophosphate or tetrafluoroborate were not tested due to their high melting points; for the same reason [NBu$_4$]I was not used either. Most commonly used imidazolium salts proved to be a bad choice whether they bear halide anions, like 1-methyl-3-propylimidazolium bromide ([MPIm]Br; **6**) and 1-butyl-3-propylimidazolium bromide ([BPIm]Br; **7**), or noncoordinating hexafluorophosphate anions, like 1-butyl-3-propylimidazolium hexafluorophosphate ([BPIm]PF$_6$; **8**) (see Scheme 2 and entries 5, 10, 11, Table 1). The observation that coordinating halide anions are necessary for a beneficial solvent effect prevented us from testing the room-temperature liquid tetrachloroaluminate imidazolium salts (Im-[AlCl$_4$]) as the solvent. The Lewis acidic medium would

Table 1. Heck olefination of chlorobenzene with styrene and palladacycle **1**.[a]



Entry	Solvent (NAIL)	Base	*t* [h]	Yield [%][b]
1	$[NBu_4]OAc$	–	14	54
2	$[NBu_4]Br$	Na(OAc)	18	51
3	$[Oct_3NMe]Br$	Na(OAc)	15	45
4	Aliquat 336[c]	Na(OAc)	15	32
5	[MPIm]Br (**6**)	Na(OAc)	19	22
6	Ph_3CCl	Na(OAc)	16	21
7	TBHDP[d]	Na(OAc)	16	19
8	[e]	Na(OAc)	15	17
9	$[NBu_4]Cl$	Na(OAc)	15	15
10	[BPIm]Br (**7**)	Na(OAc)	16	11
11	$[MBIm]PF_6$ (**8**)	Na(OAc)	15	5
12	$[NBu_4]Br$	$[NBu_4]OAc$	15	52
13	$[NBu_4]Br$	HCOONa	16	49[f]
14	$[NBu_4]Br$	Bu_3N	15	46
15	$[NBu_4]Br$	Et_3N	16	46
16	$[NBu_4]Br$	Cs_2CO_3	15	45
17	$[NBu_4]Br$	$NaHCO_3$	15	44
18	$[NBu_4]Br$	K_2CO_3	16	41
19	$[NBu_4]Br$	K_3PO_4	16	38

[a] Conditions: 1.0 equiv chlorobenzene, 1.5 equiv styrene, 1.2 equiv base. [b] GC yield using diethyleneglycol-di-*n*-butyl ether as internal standard. [c] Aliquat 336 = tri-*n*-octylmethylammonium chloride. [d] TBHDP = tri-*n*-butyl-*n*-hexadecylphosphonium bromide. [e] Aliquat 336/$[NBu_4]Br$ 1:1. [f] Ethylbenzene and biphenyl as major by-products.



6 **7** (X = Br)
8 (X = PF_6)

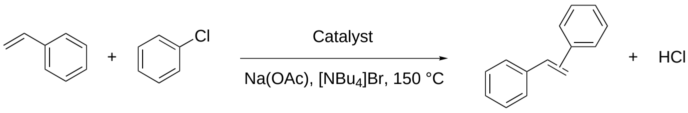
Scheme 2. Imidazolium salts liquid at ambient temperature.

additionally be contradictory to the basic medium necessary for the Heck reaction. Also tri-*n*-butyl-*n*-hexadecylphosphonium bromide (TBHDP) did not work satisfactory in contrast to literature reports (entry 7, Table 1).[21] This was astonishing since $[PPh_4]Cl$ constitutes an activating additive with catalyst **1** (vide supra). Even carbenium salts such as trityl chloride (Ph_3CCl) can be used as the solvent (entry 6, Table 1). Obviously, the nature of the salt and especially the nature of the anion has a strong influence on the catalyst activity. Despite the elevated temperatures, we never observed problems due to decompostion of the solvent, only $[NBu_4]OAc$ becomes brownish at these temperatures.

Screening for the optimum base showed most inorganic bases including Et_3N and Bu_3N to be equally capable of furnishing stilbene. Differences in TON were generally small in contrast to observations in molecular solvents.[15] Especially between $[NBu_4]OAc$ and the much cheaper Na(OAc) only an insignificant difference was observed. Nevertheless, variances regarding the stability of the catalyst **1** could be detected. Palladium black precipitation with K_3PO_4 occurred readily, whereas Na(OAc), $[NBu_4]OAc$, Et_3N, Bu_3N, Cs_2CO_3, or K_2CO_3 used to give no decomposition at all. Stronger bases like KOH or KO*t*Bu rendered useless as they lead to decomposition of the catalyst and additionally of $[NBu_4]Br$ in a Hofmann-type elimination.[24] We ascribe the indifference in TON towards the nature of the base to the good solubility of all bases in $[NBu_4]Br$ at 150 °C. Thus, any base which is capable of reductively eliminating HX from the hydrido palladium species $HPd(L)_2X$ can be used. The problem of solubility does not require attention. As a result, Cs_2CO_3 can be replaced by much more economic bases like Na(OAc).

Encouraged by the initial success with palladacycle **1**, we also tested other catalysts for the coupling of chlorobenzene and styrene. Diiodo-bis(1,3-dimethylimidazolin-2-ylidene)-palladium(II) (**2**),[6a] diiodo-(1,1′-methylene-3,3′-*tert*-butylimidazolin-2,2′-ylidene)palladium(II) (**3**),[25] *trans*-diiodo-(1,3-di(1′-(*R*)-phenylethyl)imidazolin-2-ylidene)triphenylphosphinopalladium(II) (**4**),[6c, 26] and *trans*-di(μ-chloro)-bis-*P*,*C*-{2-[di-(2,4-di-*tert*-butylphenylato)phosphinoxyl]-3,5-di-*tert*-butyl-phenyl}dipalladium(II) (**5**)[27] are thermostable under the reaction conditions described earlier. Testing reveals high activity of the catalysts which is better than results reported in the literature with molecular solvents (entries 5, 8, 9, 10, Table 2; entries 4, 5, Table 3).[6a, 6c, 27, 28] With catalyst **5** the addition of an excess of the phosphite tbp resulted in a dramatic drop of activity which is in contrast to the behavior with bromoarenes in molecular solvents (entries 15, 20, Table 2).[27] The same dropping of activity is observed when the ligand tbp is used in excess with palladium(II) diacetate $Pd(OAc)_2$ (entry 17, Table 2).

Table 2. Heck olefination of chlorobenzene with styrene in $[NBu_4]Br$ using different catalysts.[a]



Entry	Catalyst	Pd [mol%]	Additive [mol%]	*t* [h]	Yield [%][b]
1	$Pd_2(dba)_3$	1	$P(tBu)_3$ (2)	17	74
2	$Pd(PCy_3)_2$	1	–	17	67
3	$(CH_3CN)_2PdCl_2$	1	$[PPh_4]Cl$ (6)	17	65
4	$Pd(PPh_3)_4$	1	–	17	55
5	**4**	1	–	17	53
6	$Pd[P(o\text{-Tol})_3]_2$	1	–	17	51
7	$Pd(OAc)_2$	1	PPh_3 (4)	16	50
8	**2**	1	–	17	48
9	**3**	1	–	17	45
10	**5**	1	–	17	45
11	$PdCl_2$	1	–	17	43
12	$Pd(OAc)_2$	1	PCy_3 (4)	18	41
13	$Pd(OAc)_2$	1	$P(o\text{-Tol})_3$ (3)	18	41
14	$(CH_3CN)_2PdCl_2$	1	$[AsPh_4]Cl$ (6)	18	34
15	**5**	1	tbp[c] (1)	17	32
16	$Pd(OAc)_2$	1	–	16	20
17	$Pd(OAc)_2$	1	tbp[c] (10)	15	9
18	colloid[d]	10	$[AsPh_4]Cl$ (1)	18	6
19	$Pd_2(dba)_3$	1	–	17	5
20	**5**	1	tbp[c] (5)	16	2

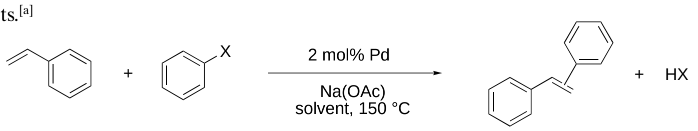
[a] 1.0 equiv chlorobenzene, 1.5 equiv styrene, 1.2 equiv base. [b] GC yield using diethyleneglycol-di-*n*-butyl ether as internal standard. [c] tbp = tris(2,4-di-*tert*-butylphenyl)phosphite. [d] $Pd_{75}Pt_{25}[N(Octyl)_4]$ colloid.

Ligand-free palladium(II) salts constitute attractive substitutes for complicated, organometallic catalysts but used to suffer from low activity and early palladium black precipitation.[2] $PdCl_2$ and $Pd(OAc)_2$ were tested under the conditions described above. Despite low reactivity of $Pd(OAc)_2$, $PdCl_2$ was found to catalyze the transformation surprisingly well albeit high palladium concentrations are necessary (entries 11, 16, Table 2; entry 27, Table 4). These results made us wonder whether phosphane ligands were necessary at all for the catalytic activity. The comparison of a mixture of $Pd(OAc)_2$ and four equivalents of PPh_3, three equivalents of tri(*o*-tolyl)phosphane ($P(o\text{-}Tol)_3$) or four equivalents of tri(cyclohexyl)phosphane (PCy_3) with ligand-free $Pd(OAc)_2$ proved the beneficial effect of phosphane addition (entries 7, 12, 13, Table 2). The bulky phosphite tbp cannot replace the phosphanes in contrast to observations in molecular solvents (entry 17, Table 2).[10] In fact, an excess of tbp constitutes the only example of a less reactive catalyst system in $[NBu_4]Br$ than in DMF with either palladacycle **5** or $Pd(OAc)_2$ (entry 6, Table 3). $[PPh_4]Cl$ is known to furnish active catalysts from dichloro-bis(acetonitrilo)palladium(II).[14] With this catalyst system an enhancing effect was observed despite the competitive existence of two salts (entry 3, Table 2). In contrast to observations with palladacycle **1**, $[AsPh_4]Cl$ does not have a similar effect (entry 14, Table 2).[22a]

The use of phosphane-free palladium(0) sources like $Pd_2(dba)_3$ does not give satisfactory results (entry 19, Table 2) neither does the use of preformed colloids (entry 18, Table 2) in respect to the results obtained with $PdCl_2$. With Pd° the addition of phosphane ligands markedly enhances the activity. Using $Pd(PPh_3)_4$ yields stilbene at a TON of 55 (entry 4, Table 2). Higher TONs can also be achieved with $Pd(PCy_3)_2$ and $Pd[P(o\text{-}Tol)_3]_2$ (entries 2 and 6, Table 2). Also the very active catalyst system $Pd_2(dba)_3$ and $P(t\text{Bu})_3$ furnishes stilbene with a TON up to 74 even if Cs_2CO_3 is replaced by Na(OAc) (entry 1, Table 2). With this catalyst tri-*n*-octylmethylammonium chloride (Aliquat 336) furnishes a similar TON although the anion has changed to chloride (entry 26, Table 4). Furthermore, upon the addition of phoshane ligands, the Pd^0 complexes become more active than the corresponding Pd^{II} complexes although without phosphane ligands it is the other way around.

Attempts to make the system more efficient by the in situ formation of bromoarenes from the corresponding chloroarenes with a cocatalyst failed. Nickel(II) dichloride has been reported to catalyze halide exchanges on carbon atoms suggesting the use of a bimetallic catalyst system with palladacycle **1**.[18] Despite the promising literature report neither higher yields were observed nor was bromobenzene detected in the reaction with **1**/$NiCl_2$.

Table 3. Comparison of the solvent effect on the Heck olefination of bromo- and chlorobenzene with styrene and different catalysts.[a]



Entry	Catalyst	Yield [%][b]					
		$t = 2$ h X = Cl DMF	$t = 2$ h X = Cl $[NBu_4]Br$	$t = 18$ h X = Cl DMF	$t = 18$ h X = Cl $[NBu_4]Br$	$t = 2$ h X = Br DMF	$t = 2$ h X = Br $[NBu_4]Br$
1	$Pd_2(dba)_3/2\,P(t\text{Bu})_3$	56	86	72	92	> 99	100
2	$(CH_3CN)_2PdCl_2/6\,[PPh_4]Cl$	23	37	69	85	59	> 99
3	**1**/5 $[AsPh_4]Cl$	19	37	41	84	57	100
4	**2**	0	4	3	51	20	> 99
5	**5**	1	11	5	49	4	39
6	**5**/5 tbp	15	0	35	4	25	9
7	$PdCl_2$	0	7	0	50	16	94
8	$Pd(OAc)_2/3\ P(o\text{-}Tol)_3$	3	11	29	46	50	86
9	$Pd_2(dba)_3$	0	1	2	8	1	14
10	$Pd(PPh_3)_4$	4	24	17	65	38	92

[a] 1.0 equiv PhX, 1.5 equiv styrene, 1.2 equiv Na(OAc). [b] GC yield using diethyleneglycol-di-*n*-butyl ether as internal standard.

Scope and limitations

In order to judge the solvent effect, we compared $[NBu_4]Br$ directly with the commonly used molecular solvent DMF (Table 3). All tested catalysts show *increased yields* in the coupling of chlorobenzene with styrene using Na(OAc) as the base. Catalyst **5**, with an excess of five equivalents of the phosphite ligand tbp, was the only negative exception (Entry 6, Table 3). Although the active catalyst systems $Pd_2(dba)_3/P(t\text{Bu})_3$ or $PdCl_2/[PPh_4]Cl$ are taking less advantage from the NAIL on the longer time scale, the reaction rates are significantly increased by the NAIL for these catalysts, too. This conclusion can be drawn considering the yields of stilbene from chlorobenzene after 2 h (Table 3). Even more pronounced effects are observed for less active catalysts like the NHC-complex **2**, $Pd(PPh_3)_4$, or $PdCl_2$. The unusual long-term thermal stability of the catalysts in $[NBu_4]Br$ most probably accounts to the significant differences in the yields of stilbene after 15 h at 150 °C. The same conclusion can be drawn on a more qualitative scale if the points of palladium black formation are compared. The catalysts decompose later in $[NBu_4]Br$—if they do at all—than they do in DMF under conditions *ceteris paribus*. But also the activation of the catalyst is an important feature as the yields after 2 h also differ much in both solvents. For example, with the system $Pd_2(dba)_3/P(t\text{Bu})_3$ after 2 h already 86 % stilbene has formed at a TON of 43 from chlororbenzene and styrene (entry 1, Table 3). This is much more than reported in the literature.[15, 16] Similar effects can be observed for bromobenzene (Table 3). Palladacycle **1** has its reaction rate doubled; and the catalyst **2** and $PdCl_2$ run even about five times faster than in DMF.

To evaluate the actual amount of $[NBu_4]Br$ necessary for a maximum effect, we tested different molar ratios of $[NBu_4]Br$ and DMF with catalyst **1** in the coupling of chlorobenzene and styrene (Figure 1). Indeed, pure $[NBu_4]Br$ is necessary for

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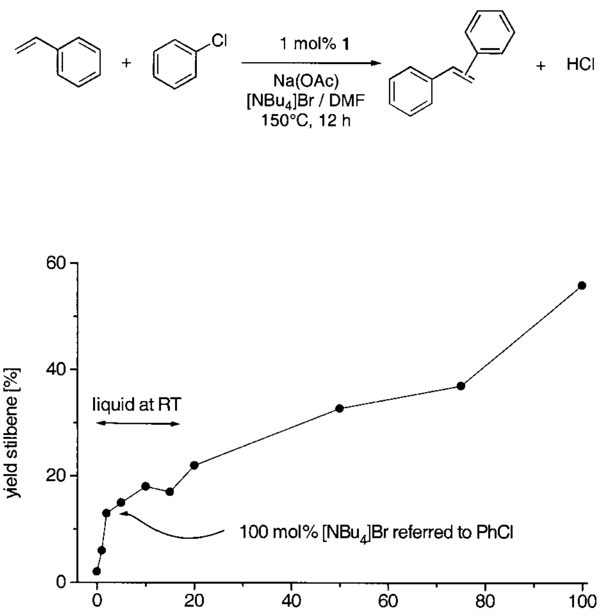


Figure 1. The effect of the molar ratio of [NBu4]Br and DMF {n([NBu$_4$]Br)/[n([NBu$_4$]Br) + n(DMF)]} on the coupling yield of chlorobenzene with styrene using 1 mol% palladacycle **1** as the catalyst. Conditions: 0.06 mmol **1**, 0.32 mmol chlorobenzene, 0.48 mmol styrene, 0.38 mmol Na(OAc), 13 mmol {[NBu$_4$]Br + DMF}; $T = 150$ °C. PhCl = chlorobenzene; RT = room temperature.

achieving a saturation point of effecting TON. Although the greater effects on the TON are achieved at lower [NBu$_4$]Br ratios, one might even consider the molecular solvent to have a poisoning effect on the reaction as the maximum TON is reached only with pure [NBu$_4$]Br. Furthermore, the actual molar amount of solvent being necessary to run the reaction in [NBu$_4$]Br constitutes only about 10% of the amount of pure DMF needed. This corresponds to five equivalents or 500 mol% of [NBu$_4$]Br in the reaction.

As [NBu$_4$]Br with a melting point of 103 °C needs high temperatures of over 120 °C to have the viscosity of the melt reduced to an extent which makes magnetical stirring effectively possible, one has to use other NAIL for lower reaction temperatures. Thus, we tested the imidazolium salts **6**–**8** as well as Aliquat 336 and tri-n-octylmethylammonium bromide ([Oct$_3$NMe]Br) which are liquid at—or close to—room temperature (Table 2). In all these NAIL with palladacycle **1** and the system Pd$_2$(dba)$_3$/P(tBu)$_3$ TOF and TON are lower than in [NBu$_4$]Br (vide supra). At milder reaction temperatures of 80 °C reasonable TON were not obtained as the solubility of the base is reduced.

Generally, all types of chloroarenes, bromoarenes, iodoarenes, and benzoic acid anhydride[29] can be coupled under the conditions described. Various examples of these substrates for different catalysts are given in Table 4. The results obtained are not easily comparable to literature results or to each other as the conditions have not been optimized in all cases.

PdCl$_2$ couples p-iodotoluene with a TON of 10000 (entry 1, Table 4) and palladacycle **1** furnishes stilbene from benzoic acid anhydride at a TON of 1000 (entry 21, Table 4). Despite the high activity of PdCl$_2$ for bromoarenes and activated chloroarenes including almost quantitative conversion of chlorobenzene it is not capable of coupling p-chloroanisole efficiently (entry 30, Table 4). The same observation was made for palladacycle **1** and Pd(PPh$_3$)$_4$ (entries 29, 31, Table 4). Only Pd$_2$(dba)$_3$/P(tBu)$_3$ achieves a reasonable TON with deactivated chloroarenes (entry 28, Table 4).

Changing of the olefin is interesting with respect to possible applications as well as to mechanistic questions regarding the influence of the NAIL on elemental steps in the catalytic cycle. To study the effect of the olefin in Heck reactions, n-butyl acrylate, different substituted styrenes, butyl vinyl ether, and the disubstituted α-methyl-n-butyl acrylate in the presence of palladacycle **1** and PdCl$_2$ were examined. The results are summarized in Table 4. n-Butyl acrylate and N,N-dimethylacrylamide give similar TONs to that of styrene (entries 6, 7, Table 4). However, the catalyst activity was lower for the electron-rich butyl vinyl ether and 4-methoxystyrene (entries 3, 4, 8, 9, 13, 16, 17, Table 4). Nevertheless, TONs up to 45000 have been achieved for the first time.

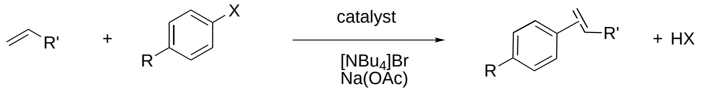
It is obvious from Table 4 that both the electronic nature of the olefin and steric hindrance are decisive factors for the catalysts' efficiency. The influence of electronic factors is seen from reactions of 4-substituted styrenes (entries 8–12, Table 4). Here, electron-withdrawing groups increase the yield of the corresponding stilbene, and vice versa. p-Trifluoromethylstyrene gives a TON of 910 in the coupling with bromobenzene whereas p-methoxystyrene only achieves a TON up to 500 when PdCl$_2$ is used as the catalyst. Using n-butyl methacrylate as an example for a 1,1-disubstituted olefin, it became evident that the palladacycle catalyst **1** and PdCl$_2$ are less sensitive towards steric hindrance in [NBu$_4$]Br than in molecular solvents (entries 14, 15, Table 4).[2, 7b]

In agreement with reported data for Heck reactions concerning enol ethers,[30] both catalysts show the usual regioselectivity. Electron-rich aryl substrates, for example 4-bromoanisole, favor α-arylation, whereas electron-poor aryl derivatives, for example 4-bromoacetophenone, strongly favor β-arylation (entries 3, 4, 16, 17, Table 4). This result suggests that the rate-determining step in the Heck reaction of aryl bromides is *not* the oxidative addition to the reactive palladium catalyst, but rather the insertion of the olefin into the arylpalladium intermediate. This assumption is further supported by the competitive reaction of styrene and n-butyl acrylate with 4-bromoacetophenone, which led to a mixture of 31% 4-acetylstilbene and 69% n-butyl 4-acetylcinnamate with palladacycle **1** and 22% 4-acetylstilbene and 78% n-butyl 4-acetylcinnamate with PdCl$_2$.

Catalyst recycling

The described NAIL protocol is of further advantage because the catalyst and the rather expensive solvent can be recycled. Recycling was tested in the reaction of bromobenzene and styrene using 1 mol% of palladium. The solvent and the catalyst **1** were used again after distillation of the reactants and products in vacuo (130 °C, 10^{-2} mbar). Figure 2 shows a graphical comparison of the yields of stilbene isolated with palladacycle **1** and PdCl$_2$ for consecutive runs.

Table 4. Survey on the possible Heck olefinations in $[NBu_4]Br$.[a]



Entry	R′	R	X	Catalyst	Pd [mol %]	Additive [mol %]	*T* [°C]	*t* [h]	Yield [%][b]	TON
1	C_6H_5	CH_3	I	$PdCl_2$	0.01	–	130	14	100	10000
2	C_6H_5	$COCH_3$	Br	**1**	0.0001	–	120	60	100	1000000
3	OC_4H_9	$COCH_3$	Br	**1**	0.1	–	130	13	70	700[c]
4	OC_4H_9	$COCH_3$	Br	$PdCl_2$	0.2	–	130	14	98	490[d]
5	C_6H_5	H	Br	colloid[e]	5	–	130	18	40	8
6	$CON(CH_3)_2$	H	Br	**1**	0.1	–	130	14	99	990
7	$COOC_4H_9$	H	Br	**1**	0.01	–	130	14	80	8000
8	*p*-$H_3COC_6H_4$	H	Br	**1**	0.01	–	130	13	45	45000
9	*p*-$H_3COC_6H_4$	H	Br	$PdCl_2$	0.1	–	130	14	50	500
10	*p*-$H_3CC_6H_4$	H	Br	**1**	0.01	–	130	13	72	72000
11	*p*-$H_3CC_6H_4$	H	Br	$PdCl_2$	0.1	–	130	14	68	680
12	*p*-$F_3CC_6H_4$	H	Br	$PdCl_2$	1	–	130	14	91	910
13	OC_4H_9	H	Br	$PdCl_2$	0.2	–	130	14	69	345[f]
14	[g]	H	Br	**1**	0.1	–	130	14	72	720[h]
15	[g]	H	Br	$PdCl_2$	1	–	130	14	100	100[i]
16	OC_4H_9	OCH_3	Br	**1**	0.1	–	130	13	40	400[j]
17	OC_4H_9	OCH_3	Br	$PdCl_2$	0.2	–	130	13	52	260[k]
18	C_6H_5	OCH_3	Br	**1**	0.1	–	120	17	79	790
19	$COOC_4H_9$	OCH_3	Br	**1**	1	–	120	17	>99	100[l]
20	C_6H_5	OCH_3	Br	$PdCl_2$	0.1	–	130	14	69	690
21	C_6H_5	H	C(O)OC(O)Ph	**1**	0.1	–	160	19	100	1000
22	C_6H_5	NO_2	Cl	$PdCl_2$	0.1	–	130	14	99	990
23	C_6H_5	$COCH_3$	Cl	**1**	0.1	$[AsPh_4]Cl$ (0.1)	150	15	99	990
24	C_6H_5	$COCH_3$	Cl	$PdCl_2$	0.1	–	130	14	97	970
25	C_6H_5	H	Cl	**1**	2	$[AsPh_4]Cl$ (20)	150	16	96	48
26	C_6H_5	H	Cl	$Pd_2(dba)_3$	1	P(*t*Bu)$_3$ (2)	150	15	67	67[m]
27	C_6H_5	H	Cl	$PdCl_2$	5	–	150	45	89	18
28	C_6H_5	OCH_3	Cl	$Pd_2(dba)_3$	3	P(*t*Bu)$_3$ (6)	150	40	74	25
29	C_6H_5	OCH_3	Cl	$Pd(PPh_3)_4$	2	–	150	15	<1	0[n]
30	C_6H_5	OCH_3	Cl	$PdCl_2$	3	–	150	40	5	2
31	C_6H_5	OCH_3	Cl	**1**	4	$[PPh_4]Cl$ (2)	150	14	18	5[n]

[a] 1.0 equiv ArX, 1.5 equiv olefin, 1.2 equiv Na(OAc). [b] GC yield using diethyleneglycol-di-*n*-butyl ether as internal standard. [c] 33 % (*E*), 23 % (*Z*), 15 % (1/1). [d] 42 % (*E*), 37 % (*Z*), 20 % (1/1). [e] $Pd_{75}Pt_{25}[N(Octyl)_4]$ colloid. [f] 17 % (*E*), 24 % (*Z*), 29 % (1/1). [g] Using *n*-butyl methacrylate as the olefin. [h] 44 % *n*-butyl 2-benzylacrylate, 24 % *n*-butyl (*E*)-2-methylcinnamate, 4 % *n*-butyl (*Z*)-2-methylcinnamate. [i] 62 % *n*-butyl 2-benzylacrylate, 33 % *n*-butyl (*E*)-2-methylcinnamate, 5 % *n*-butyl (*Z*)-2-methylcinnamate. [j] 13 % (*E*), 7 % (*Z*), 20 % (1,1). [k] 10 % (*E*), 14 % (*Z*), 27 % (1,1). [l] $[NBu_4]OAc$ as the solvent and base. [m] Aliquat 336 as the solvent. [n] Stilbene as major product by aryl scrambling.

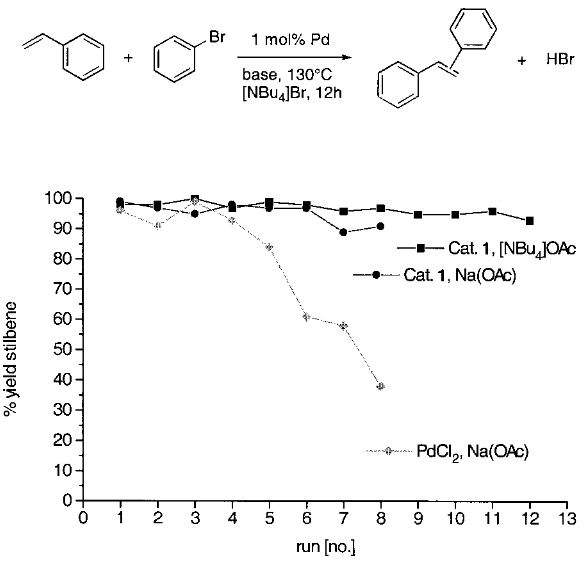


Figure 2. Recycling of the catalyst and the NAIL. Palladacycle **1** {Na(OAc) and $[NBu_4]OAc$} and $PdCl_2$ {Na(OAc)} in [NBu4]Br (1 mol % Pd). Conditions: 1.0 equiv bromobenzene, 1.5 equiv styrene, 1.2 equiv base, 1 mol % Pd; $[NBu_4]Br$; $T = 130$ °C. Isolation of analytically pure stilbene by vacuum distillation.

If Na(OAc) was used as the base, sodium bromide was the only product which could not be removed from the catalyst system by distillation. This limited the recycling to eight consecutive runs. To overcome this problem $[NBu_4]OAc$ can be used as the base furnishing the solvent as the by-product. Recycling is possible although with palladacycle **1** after the fourth run visible palladium black formation occurred and after the sixth run the melt became very viscous. Workup of the reaction mixture after the eighth run showed that there was still 23 % of the palladacycle **1** left structurally unchanged along with free P(*o*-Tol)$_3$ and the corresponding phosphine oxide. For $PdCl_2$ it was astonishing to be able to recycle the system successfully several times, as heavy palladium black formation was observed already during the first run. Albeit that decreasing yields of stilbene were obtained during the recycling procedure, it was possible to filter off the NaBr and the palladium black precipitates after eight recycling runs by dissolving the mixture in acetone. After evaporation of the acetone the filtrate can be used again and stilbene was obtained in 60 % yield. Using both procedures in conjunction, the insoluble by-products like NaBr and palladium black can be separated and removed by filtration after several recycling

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runs, whereas the soluble catalyst and the $[NBu_4]Br$ can be reused for further recyclings again. As with the distilling of the products no loss of the catalyst can occur, this protocol constitutes the *first recycling procedure for the Heck reaction* which does not suffer from metal leaching.[21, 22]

Mechanism

The observed effects of NAIL as solvents can have various reasons. In the literature the co-catalytic effect of tetraalkylammonium salts has been ascribed to 1) phase-transfer catalysis[19, 31] and increased polarity of the solvent,[19] 2) facilitating oxidative addition and reductive elimination during a Pd^0/Pd^{II} catalytic cycle,[32] and 3) enabling a hypothetical Pd^{II}/Pd^{IV} catalytic cycle.[33] Furthermore, the effect is sometimes attributed to the stabilization of palladium(0) colloids which may be formed in situ.[34]

In favor of point (1) is the fact that NAIL indeed constitute extremely polar media which would stabilize ionic and polar transition states in the catalytic cycle and could thus lead to an increased overall reaction rate. However, this fact cannot account for all observations; for eaxmple, it does not explain the prolonged thermal stability of the catalysts (Table 3 and Figure 2). Phase-transfer catalysis can be ruled out here because the addition of small amounts of water resulted in lower TON, lower catalyst lifetime, and increased by-product formation.

Point (2) has been discussed in full detail for the system $Pd(OAc)_2/PPh_3$ by means of cyclic voltammetry and NMR spectroscopy.[32] The results suggest an anionic $[AcO\text{-}Pd\text{-}(PPh_3)_2]^-$ complex to be the most active catalyst species. Similar observations have been made for $[P(o\text{-}Tol)_3]$ proposing a $[AcO\text{-}Pd\text{-}P(o\text{-}Tol)_3]^-$ ion to be the effective catalyst.[7c, 35] In addition, the observations with $P(o\text{-}Tol)_3$ also show an enhanced stability of the anionic palladium(0) complex compared to the parent bis(tri-*o*-tolylphosphane)palladium(0) compound. These observations suggest the salt effect to be a general principle for palladium(0)–phosphane systems. This can explain the observations made here for both palladium(0) and, after in situ reduction, palladium(II)–phosphane systems.[36] On the other hand, this does not explain the efficiency of ligand-free catalysts or complexes bearing only nondissociative ligands like the NHC complexes **2** or **3**.

Finally, point (3) has led to much speculation in the literature.[7a] Discussions about a Pd^{II}/ Pd^{IV} catalytic cycle being active in competition to the established Pd^0/Pd^{II} mechanisms have led to the proposal of a nucleophile-assisted addition of the olefin on the palladium(II) center and subsequent oxidative addition of the aryl halide to form a palladium(IV) species. In the following steps, the palladium(II) catalyst is re-formed after product formation by β-hydride elimination and reductive elimination of HX.[33] The important point of this proposal is the nucleophilic attack on the π-coordinated olefin. Thus, the addition of nucleophilic anions like $[AcO]^-$, Br^-, or Cl^- should lead to greater overall rates. The higher efficiency of Br^- over Cl^- is in full accordance to this mechanism because of the nucleophilicity order $I^- > Br^- > Cl^- > F^-$. Although the aforementioned arguments can explain the efficiency of palladium(II) complexes, they do not give credence for palladium(0) catalysts because these cannot be oxidized to palladium(II) under the reaction conditions.

The occurrence of palladium(0) colloids during the reaction cannot be ruled out. Tetraalkylammonium salts are in fact frequently used to stabilize colloids.[34] In favor of this hypothesis is the observation that colloids can be active catalysts in the Heck reaction of bromoarenes and activated chloroarenes.[13, 37] Also the observation of long activity of the catalysts during the recycling procedures despite blackening of the reaction mixture supports this view (vide supra). All attempts to isolate colloids from reaction mixtures or to form and isolate colloids under reaction conditions have failed until now. Further contrary hints have been obtained by the direct application of defined colloids,[13b] which resulted in much lower TONs than the use of most molecular catalysts (entry 18, Table 2; entry 5, Table 4). Also the use of a reducing agent like sodium formate to force the formation of palladium(0) colloids does not result in higher yields in the Heck reaction with chlorobenzene (entry 13, Table 1). The observation of different TONs for various catalysts would not be expected if defined colloids of similar structure were produced (Table 2).

An in situ transformation of chloroarenes to the corresponding bromoarenes can be ruled out. We never detected bromoarenes in the reaction mixtures and bimetallic approaches to force this reaction have failed also (vide supra).

In summary, no general conclusion about the active catalytic species or the definite effect of the NAIL and its anion can be drawn for all the catalysts that have been used. It is likely that different reasons account for each type of catalyst. For palladium(0) complexes and palladium(II)–phosphane mixtures, we suggest the *anion effect* forming active, anionic $[Br\text{-}Pd^0\text{-}ligand]^-$ species to be predominant. For thermally stable palladium(II) complexes like palladacycles **1** and **5** or NHC complex we favor the above-mentioned reason for the observed effect after in situ reduction to palladium(0). But we cannot definitely rule out any effects on a Pd^{II}/Pd^{IV} catalytic cycle. A critical observation in this respect is the isolation of 23 % palladacycle **1** from the recycling runs. Ligand-free palladium(II) salts however are most likely reduced thermally to extremely active colloids. Early blackening of the reaction mixture indicates the in situ reduction to palladium(0) but recycling of the catalyst is still possible for many more runs (Figure 2). The latter rules out the sole formation of inactive palladium black aggregates.

Conclusion

Molten salts—especially $[NBu_4]Br$—as media for the Heck reaction have various advantages as novel solvents for the Heck-vinylation of aryl halides. Improved catalyst efficiencies compared to all previously described molecular solvents have been observed for reactions of bromoarenes and chloroarenes. Advantages with regard to conventional solvents are based on high activity as well as improved thermal stability and life-time during the reaction. In this respect, even less active catalysts like palladium(II) dichloride and tetrakis(triphenylphosphane)palladium(0) can be efficiently used for the coupling of chloroarenes.

NAIL protocols are *homogeneous one-phase reactions* despite catalyst recycling being possible like in two-phase catalysis or in heterogeneous catalysis. No leaching of the catalyst into the product and thus no loss of metal was achieved for the first time in the Heck reaction. NAIL protocols require significantly less solvent due to the good solubility of all reactants making the price for the solvent per reaction comparable to NMP or DMAc. Furthermore, these conditions enable the use of most inorganic bases to replace the expensive Cs_2CO_3.

The NAIL protocols presented in this paper are likely to serve as a future general concept for Heck catalysis. Especially the possibility to recycle catalyst and solvent efficiently by distilling the reactants and products under reduced pressure constitutes an alternative means of reducing the effective palladium concentration.

Concerning the mechanism of the Heck reaction in these novel solvents, more research is necessary to establish and confirm the reasons for the observed phenomena. Highly active colloids could be responsible as could an effect of the salt on a Pd^0/Pd^{II} or Pd^{II}/Pd^{IV} mechanism. In this respect it seems likely that each type of catalyst calls for a different explanation.

Experimental Section

Materials and methods: Reactions were carried out with the use of vacuum line, Schlenk, and syringe techniques under an atmosphere of nitrogen if not stated otherwise. Palladium(II) diacetate and palladium(II) dichloride were gifts from Degussa-Hüls company. Phosphanes were either prepared by literature methods[38] or obtained from Aldrich or Strem. Other chemicals were purchased from Fluka and Aldrich. Palladium complexes were prepared according to literature procedures: $Pd_2(dba)_3$,[39] *trans*-di(μ-acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium(II) (**1**),[7b, 40] *trans*-di(μ-chloro)-bis-*P*,*C*-{2-[di-(2,4-di-*tert*-butylphenylato)phosphinoxyl]-3,5-di-*tert*-butylphenyl}dipalladium(II) (**5**),[27] $(CH_3CN)_2PdCl_2$,[41] diiodo-bis(1,3-dimethylimidazolin-2-ylidene)palladium(II) (**2**),[6a] diiodo-(1,1′-methylene-3,3′-*tert*-butylimidazolin-2,2′-ylidene)palladium(II) (**3**),[25, 42] *trans*-diiodo-(1,3-di(1′-(*R*)-phenylethyl)imidazolin-2-ylidene)triphenylphosphinopalladium(II) (**4**),[26] tetrakis(triphenylphosphane)palladium(0),[43] bis(tri-*o*-tolylphosphane)palladium(0).[44]

Except for work-up of reaction mixtures, all operations were carried out under nitrogen. *N*,*N*-dimethylformamide was degassed prior to use. Other solvents were dried and degassed according to a literature procedure.[45] The NAIL were dried and degassed by exposing their melt to vacuum for at least 2 h prior to use. The degree of drying and degassing was found to drastically influence the catalysis results. $[NBu_4]OAc$ was stored over KOH prior to being dried and degassed under vacuum (vide supra).

Physical and analytical methods: NMR spectra (^1H, ^{13}C, ^{31}P) were recorded on a Jeol JMX-GX 400 instrument and are referenced to residual protons in the solvent (^1H), the solvent carbon-13 signal (^{13}C), or 85 % H_3PO_4 as an external standard (^{31}P). NMR multiplicities are abbreviated as s = singlet, t = triplet, dt = double triplet, sept = septet, m = multiplet. Coupling constants *J* are given in Hz. GC-MS spectra were measured on a Hewlett Packard gas chromatograph GC 5890 A equipped with a mass-selective detector MS 5970 B. Elemental analyses were carried out by the Microanalytical Laboratory at the TU München. Catalysis yields were generally determined by gas chromatography and the products were identified by comparison to authentic samples.

General procedure for Heck olefinations: In a 100 mL Schlenk flask the NAIL (giving a melt of approximately 3 mL) was degassed prior to adding the other reagents (vide supra). After cooling the NAIL to room temperature, the catalyst, the base (1.2 mmol), and diethyleneglycol-di-*n*-butyl ether (50 mg, GC standard) were added. The reaction mixture was degassed under vacuum and nitrogen was passed through the mixture to ensure an inert reaction atmosphere. The olefin (1.5 mmol) and the aryl halide (1.0 mmol) were then added last because of the possible loss by evaporation. The reaction was heated to the appropriate temperature and stirred. Work-up was achieved by deluting with water (3 mL) at room temperature, extracting with dichloromethane (3 × 1 mL), and drying with magnesium sulfate. The products were examined by GC/MS, or purified by recrystallization or flash chromatography.

Recycling procedure: Catalysis was performed as described above but a short-necked Schlenk flask was used. After completion of the reaction, the mixture was heated to 130 °C and vacuum was applied over a glass bridge (10^{-2} mbar). Products and starting materials were then distilled from the NAIL and subsequently frozen out of the gas phase into a flask by liquid nitrogen. Products had to be prevented from early solidification by using a heat gun. Further purification of the isolated product was achieved by recrystallization or flash chromatography.

Preparation of NAIL

1-Methyl-3-propylimidazolium bromide (6): Methylimidazole (14.8 g, 14.3 mL, 180 mmol) was dissolved in anhydrous THF, and 1-bromopropane (27.1 g, 20.0 mL, 220 mmol) was added. The mixture was heated at 70 °C for 10 h. Excess starting materials and the solvent were removed at 80 °C in vacuo. Compound **6** was obtained as an analytically pure pale yellow liquid (32.9 g; 89 % yield). ^1H NMR (400 MHz, D_2O, 25 °C): $\delta = 0.79$ (m, $^3J(H,H) = 7.3$ Hz, 3 H; CH_3), 1.78 (dt, $^3J(H,H) = 7.3$ Hz, $^3J(H,H) = 7.0$ Hz, 2 H; CH_2), 3.82 (s, 3 H; NCH_3), 4.08 (t, $^3J(H,H) = 7.0$ Hz, 2 H; NCH_2), 7.38 (s, 1 H; NCH), 7.43 (s, 1 H; NCH), 8.68 (s, 1 H; NC(H)N); $^{13}C\{^1H\}$ NMR (100.5 MHz, D_2O/CD_3OD, 25 °C): $\delta = 10.5$ (CH_2), 23.3 (CH_3), 36.3 (NCH_2), 51.4 (NCH_3), 122.6 (NCH), 123.9 (NCH), 136.2 (NC(H)N); $C_7H_{13}N_2Br$ (205.10): calcd C 40.99, H 6.39, N 13.66; found C 40.76, H 6.51, N 13.38.

1-Butyl-3-propylimidazolium bromide (7): Compound **7** was prepared according to the description for **6** from 1-butylimidazole and 1-bromopropane. Yield = 85 %; ^1H NMR (400 MHz, D_2O, 25 °C): $\delta = 0.75-0.81$ (m, 6 H; CH_3), 1.12 – 1.26 (m, 2 H; CH_2), 1.68 – 1.81 (m, 4 H; CH_2), 4.05 – 4.09 (m, 4 H; NCH_2), 7.40 (s, 2 H; NCH); 8.70 (s, 1 H; NC(H)N); $^{13}C\{^1H\}$ NMR (100.5 MHz, D_2O/CD_3OD, 25 °C): $\delta = 10.2$, 13.0, 19.1, 23.1, 31.5, 49.6 (NCH_2), 51.4 (NCH_2), 122.6 (2 C; NCH), 135.4 (NC(H)N); $C_{10}H_{19}N_2Br$ (247.18): calcd C 48.59, H 7.75, N 11.33; found C 48.33, H 7.86, N 11.22.

1-Butyl-3-propylimidazolium hexafluorophosphate (8): 1-Butyl-3-propylimidazolium bromide (2.5 g, 10 mmol) was dissolved in water (20 mL) and potassium hexafluorophosphate (3.7 g, 20 mmol) was added. The mixture was stirred at room temperature for 24 h during which a pale yellow second phase with a density higher than water separated. The aqueous phase was removed and the salt was dried in vacuo. Compound **9** was obtained as an analytically pure pale yellow liquid (2.2 g; 69 % yield). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 0.76-0.79$ (m, 6 H; CH_3), 1.18 – 1.21 (m, 2 H; CH_2), 1.73 – 1.76 (m, 4 H; CH_2), 4.00 – 4.07 (m, 4 H; NCH_2), 7.30 (s, 2 H; NCH), 8.38 (s, 1 H; NCHN); $^{13}C\{^1H\}$ NMR (100.5 MHz, $CDCl_3$, 25 °C): $\delta = 9.6$, 12.4, 18.6, 22.6, 31.0, 49.0 (NCH_2), 50.7 (NCH_2), 121.8 (NCH), 121.9 (NCH), 134.4 (NCHN); $^{31}P\{^1H\}$ NMR (161.9 MHz, $CDCl_3$, 25 °C): $\delta = -143.7$ (sept., $^1J(F,P) = 711.2$ Hz); $C_{10}H_{19}F_6N_2P$ (312.24): calcd C 38.47, H 6.13, N 8.97; found C 38.58, H 6.22, N 8.77.

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