EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201402530

Ionic-Liquid-Assisted Metal-Free Oxidative Coupling of Amines To Give Imines

Antonio Monopoli,*[a] Pietro Cotugno,[a] Francesco Iannone,[a] Francesco Ciminale,*[a] Maria Michela Dell'Anna,[b] Piero Mastrorilli,[b] and Angelo Nacci[a,c]

Dedicated to C.I.N.M.P.I.S on the occasion of its 20th anniversary

Keywords: Ionic liquids / Imines / Amines / Oxidation / Oxygen / Green chemistry

An oxidative coupling of amines to give imines in ionic liquids (ILs) under metal-free aerobic conditions has been developed. The high efficiency achievable in ILs is mechanistically explained in terms of activation of the starting materials (benzylamine and molecular oxygen) by an initial electron transfer, promoted by the ionic nature of the solvent. Reactivity data of variously *p*-substituted benzylamines show a general deactivating effect, which would imply a change in the rate-determining step in the reaction mechanism.

Introduction

Imines are important and versatile intermediates in organic chemistry as they represent useful building blocks for the synthesis of biologically active molecules, agrochemicals, dyes, fine chemicals, and pharmaceuticals.[1] Classically, imines are synthesized by condensation of a carbonyl compound with a primary amine.[2] However, due to problems related to the high reactivity of aldehydes or ketones, which often result in the formation of unwanted products, in the last decade, a number of alternative protocols have been developed, including oxidation of secondary amines,[3] catalytic condensation of primary amines with alcohols,[4] and homocondensation of amines under oxidative conditions.[5]

However, these methods can suffer from drawbacks connected with the use of expensive catalysts,[5a,6] harsh reaction conditions,[7] stoichiometric amounts of unstable oxidant species,[3a,8] radical initiators,[5b,9] toxic reactants, or harmful and non-environmentally-friendly solvents.[10] As a consequence, the search for milder and greener conditions for the synthesis of imines is still an open challenge for chemists.

In this field, the oxidative homocoupling of primary amines to give imines is of particular interest [Equation (1)]. Very promising metal-free protocols based on biomimetic systems[11] have been proposed to achieve this transformation, as have photocatalysts[12] and also efficient methods using inexpensive and recyclable transition metal catalysts and new materials.[10b,13]

$$2\ RCH_2NH_2 \xrightarrow{[ox]} RCH_2N{=}CHR + NH_3 + H_2 \quad (1)$$

However, despite the number of protocols devoted to the oxidative homocondensation of amines, carrying out these reactions in environmentally friendly solvents remains unexplored, and, to the best of our knowledge, no examples of successful methods performed in ionic liquids (ILs)[14] have been reported until now. Continuing our interest in the use of ILs in organic synthesis,[15] we recently found that the *N*-alkylation of arylamines with alkyl chlorides can be performed in high yields and with high selectivities in molten tetraalkylammonium salts at 100 °C.[15d] However, this reaction is not applicable to benzylamines, since appreciable amounts of the corresponding homocondensed imines were detected in addition to the alkylation product.

As confirmed by repeating the reaction in the absence of the alkyl chloride, the formation of the homocondensed imine of benzylamine might have been the result of simple aerobic heating of the amine dissolved in the molten salt, apparently without the need for any catalyst or additive.

A general survey of the literature devoted to this subject showed that the oxidative homocondensation of benzylamines generally requires the presence of special oxidising agents,[3a,11] or metal catalysts,[6,16,17] and a sole recent example reports on a thermally promoted aerobic oxidation

[a] Department of Chemistry, University of Bari "Aldo Moro", Via Orabona 4, 70126 Bari, Italy
E-mail: antomono@libero.it
antonio.monopoli@uniba.it
francesco.ciminale@uniba.it
www.chimica.uniba.it
[b] DICATECh, Politecnico di Bari, Via Orabona, 4, 70126 Bari, Italy
[c] CNR – ICCOM, Department of Chemistry, University of Bari "Aldo Moro", Via Orabona, 4, 70126 Bari, Italy

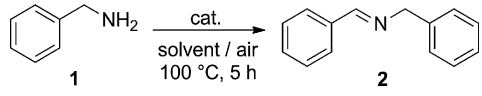
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201402530.

in water.[18] Due to the synthetic importance of this reaction, we decided to investigate the role of the molten salt in promoting this process.

Results and Discussion

We first carried out a screening of oxidation conditions using the model substrate phenylmethanamine (**1**) in tetrabutylammonium bromide (TBABr) (Table 1). To evaluate the real ionic liquid effect, we compared the oxidation in TBABr with that carried out in molecular solvents (DMA, toluene, and H_2O) in the absence of catalysts or any other additive (Table 1, runs 2–5).

Table 1. Aerobic oxidative homocoupling of benzylamine in TBABr.[a]



1 2

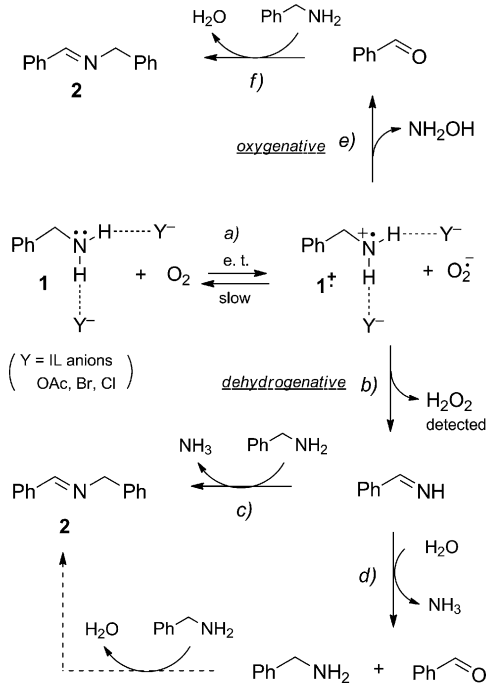
Run	Solvent	Catalyst/oxidant	Conv. [%][b]	Selectivity [%][b]
1	–	air	10	99
2	DMA	air	12	98
3	toluene	air	7	98
4	H_2O	air	6	92
5	TBABr	air	57	98
6	TBABr	$CuBr_2$ (0.2 mol-%)	39	97
7	TBABr	$CuBr_2$ (1 mol-%)	45	98
8	TBABr	$Cu(OAc)_2$ (1 mol-%)	38	96
9	TBABr	$FeCl_3$ (1 mol-%)	53	97
10	TBABr	$FeCl_3$ (3 mol-%)	51	95
11	TBABr	$Pd(OAc)_2$ (0.1 mol-%)	58	81
12	TBABr	Pt/Al_2O_3	53	95
13[c]	TBABr	O_2	98	96
14[c]	TBABr	N_2	28[d]	98

[a] Reaction conditions: **1** (0.25 mmol), molten TBABr (0.4 g) or solvent (3 mL), stirred under air at 100 °C for 5 h. [b] Conversions and selectivities were evaluated by GLC and ^1H NMR spectroscopy. [c] Reactions under O_2 (or N_2) at atmospheric pressure. [d] Obtained under N_2 in non-deaerated IL.

These initial experiments confirmed that the molten salt assisted the oxidative coupling. In TBABr, benzylamine (**1**) was selectively converted into the homocondensed product *N*-benzylidene-(phenyl)-methanamine (**2**) in 57% yield, whereas oxidation in the molecular solvents was unproductive and virtually comparable to the solventless process (Table 1, run 1).

Next, we paid attention to the possible presence of metal contaminants that could be responsible for the activation in TBABr. Conscious that chemicals can contain small amounts of metals (especially molten salts), and that cross-contamination is always a pernicious possibility that must be taken into account,[19] after completion of the coupling experiments, we carried out ICP analyses of the reaction mixture, searching for detectable amounts of metals such as Fe,[10b] Pd,[6b,16,17] Pt,[6c] and Cu,[13b] which are known to promote these reactions. Only Fe (53 ppb) and Cu (81 ppb) were found at detectable levels. Notwithstanding this, in order to exclude the contribution by any metal to the reaction mechanism, catalytic tests were carried out by adding each of the four metals cited above to the reaction mixture. This revealed that none of them promotes the oxidative coupling in TBABr (Table 1, runs 6–12). In particular, in the case of iron and copper, the addition of 3 mol-% of $FeCl_3$ (Table 1, run 10) or copper salts (Table 1, runs 6 and 7) seemed to have rather a detrimental effect compared to when the reaction was run without any metal (Table 1, run 5).

By carrying out reactions under an oxygen or inert atmosphere in addition to those carried out under air, we found that the reaction conversions increased with the partial pressure of O_2. Reactions run under O_2 gave higher conversions than those run under air or under an inert atmosphere (Table 1, runs 5, 13, and 14). These findings suggest that oxygen is likely to be involved in the rate-determining step of the oxidative coupling (see Scheme 1).

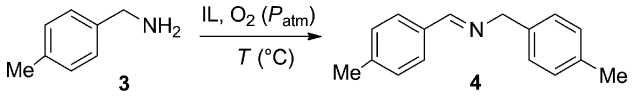


Scheme 1. Plausible pathways for the oxidative coupling of benzylamine in ILs.

Investigations were extended to other ionic liquids such as several tetraalkylammonium-, butylpyridinium (Bupy)-, and butylmethylimidazolium (Bmim)-based ILs. Table 2 summarizes the most representative results obtained using *p*-methylbenzylamine (**3**) as the model substrate.

The reaction temperature was chosen depending on the melting point of the solvent salts. In most of the ILs tested, the reactions were carried out at 100 °C. At this temperature, conversions were almost complete within 1 h (Table 2, runs 1–6). The occurrence of side-reactions involving the solvent, such as Hofmann elimination, discouraged us from using higher temperatures with tetraalkylammonium salts (Table 2, run 14). In low-melting ILs bearing AcO^- and Cl^- anions, the reactions could be carried out at 50 °C to give excellent yields of the coupling product in double the reaction time (Table 2, runs 15–17).

Table 2. Oxidative coupling of *p*-tolylamine in ILs (TEA = tetraethylammonium).[a]



Run	IL	*T* [°C]	Time [h]	Yield [%][b]
1	TBAOAc	100	0.5	98
2[c]	TBACl	100	1	93
3	TBABr	100	1	95
4	TEAOAc	100	0.5	96
5	[Bmim]OAc	100	0.5	98
6	[Bmim]Cl	100	1	98
7	[Bmim]Br	100	1	74
8	[Bmim]BF_4	100	1	43
9	[BuPy]Br	100	0.5	95
10	[BuPy]PF_6	100	1	5
11[d]	TBABr (wet)	100	1	51
12[e]	TBACl (wet)	100	1	65
13	TBAOH·*x*H_2O	100	1	10
14	TBAOAc	120	0.5	93
15	TEAOAc	50	1	95
16	[Bmim]OAc	50	2	95
17	[Bmim]Cl	50	2	88

[a] Reaction conditions: IL (0.4 g), *p*-methylbenzylamine (0.25 mmol) heated at the appropriate temperature under an oxygen atmosphere. [b] GLC yields. [c] The salt was previously dried under vacuum for 8 h at 50 °C. [d] Water (25 μL) was added to the TBABr before starting the reaction. [e] The salt was exposed to the air.

Results pertaining to the screening of ionic solvents show that the nature of the IL cation has only a negligible effect on the reactivity (Table 2, runs 1, 4, and 5). The reactivity appears to be principally influenced by the anion. The AcO^-, Cl^-, and Br^- anions (Table 2, runs 1–7, 9, and 14–17) were found to promote the coupling much better than BF_4^- and PF_6^- (Table 2, runs 8 and 10).

Recently, we interpreted a similar solvent effect, observed for the *N*-alkylation of arylamines in ionic liquids,[15d] as reflecting the capability of the solvent to accept a hydrogen bond. Such a hydrogen-bond basicity of ILs is largely a function of the anion, and is quantitatively expressed by its Kamlet–Taft β parameter: 1.16 (AcO^-), 1.00 (Cl^-), 0.67 (Br^-), 0.37 (BF_4^-), 0.21 (PF_6^-).[20] However, a closer inspection of the reactivity data pertaining to reactions in TBA-based ILs (Table 2, runs 1–3) reveals that the qualitative correlation with β fails in the case of TBACl, which, judging from β values, should have been better performing than TBABr. Control experiments (Table 2, runs 11 and 12), which were planned after considering the higher hygroscopicity of TBACl[21] and the difficulty in handling this solvent under anhydrous conditions, confirmed that the water content in the ILs was important, and that it had a detrimental effect on the coupling reaction.

This can be easily understood in terms of competition between hydrogen bonding of water to the anion – which contributes significantly to the hydrophilicity of the IL[14a] – and the essential benzylamine/anion hydrogen bonding. Consistent with these findings, the massive presence of water in tetrabutylammonium hydroxide (TBAOH·H_2O) can explain the disappointing results observed in this ionic medium (Table 2, run 13). However, it cannot be excluded that poor results obtained in BF_4^- and PF_6^- based ILs might also be wholly or partly due to protonation of the benzylamine by the HF that it is known to be generated in these ionic liquids at high temperatures.[24]

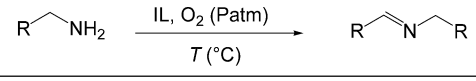
With the aim of extending the scope of the method, we examined a series of substituted benzylamines (*p*-Me, *p*-MeO, *p*-F, *p*-Cl, *o*-Me), α-naphthylmethanamine, and a few non-benzylic alkylamines, evaluating both the effect of any substituents on the aromatic ring and the influence of the amine skeleton on the efficiency of the homocoupling reaction. For each substrate, the reaction conditions (IL, temperature, and reaction time) were varied to try to obtain the maximum yield under the mildest conditions.

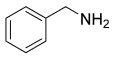
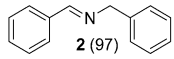
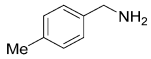
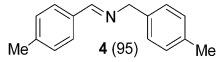
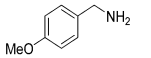
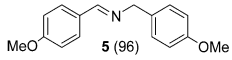
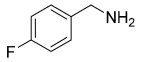
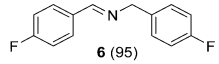
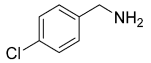
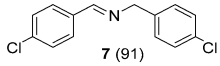
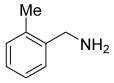
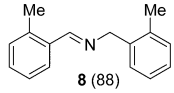
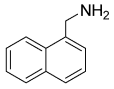
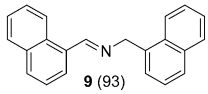
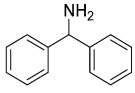
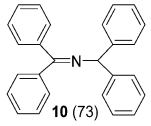
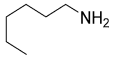
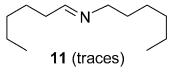
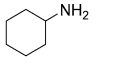
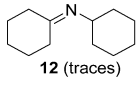
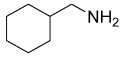
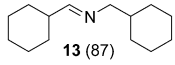
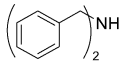
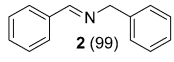
The results listed in Table 3 show that non-benzylic alkylamines, such as hexylamine and cyclohexylamine, were practically inert towards oxidative coupling, producing only traces of the imines after longer reaction times (Table 3, runs 10 and 11). In contrast to this, and very surprisingly, cyclohexylmethanamine reacted at 50 °C in 3 h to give the oxidative coupling product (i.e., **13**) in good yield (Table 3, run 12).

The results of the reactions of the benzylamines, including α-naphthylmethanamine, show that the oxidative coupling is sensitive to both electronic and steric effects. The latter can clearly be seen in the fact that some sterically hindered amines, such as *o*-tolylmethanamine, α-naphthylmethanamine, and particularly diphenylmethanamine provided the corresponding coupling products (i.e., **8**, **9**, and **10**) less efficiently than unsubstituted benzylamine (Table 3, runs 1 and 7–9). As expected,[12c] inert alkylamines and anilines – the latter are incompatible with homocoupling as a result of their lack of an α hydrogen – could be successfully used in cross-coupling reactions with benzylamines (Table 4). In reactions with anilines (Table 4, entries 1–5), however, the longer reaction times and lower yields indicated a slower formation of cross-coupling products. This is consistent with the considerably weaker nucleophilicity of aromatic amines than aliphatic amines; coupling with the latter resulted in fact in almost complete conversions and very good yields (Table 4, entries 6–8). Exploiting the electronic effect of the substituents on the nucleophilicity, we could obtain higher yields of cross-coupling products with anilines bearing electron-donating groups. For instance, a 60% yield was obtained for *p*-OMe-substituted substrate, vs. 25% for a *p*-F-substituted aniline (Table 4, entries 4 and 2).

We also observed that the cross-coupling product, *N*-benzylideneaniline (**14**), was forming after the homocoupling product, *N*-benzylidenebenzylamine (**2**), apparently by exchange of aniline for benzylamine. This process would reasonably start with nucleophilic addition of aniline to the homocoupled product (i.e., **2**). Moreover, in the case of anilines, steric effects also seem to be important, as evidenced by the fact that cross-coupling with *o*-bromoaniline was unsuccessful (Table 4, entry 5).

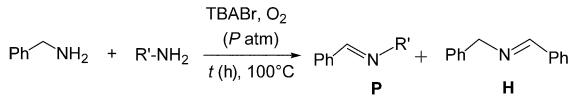
Table 3. Oxidative homocoupling of various amines in ILs.[a]

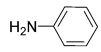
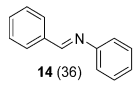
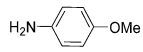
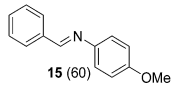
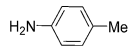
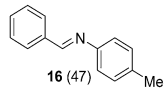
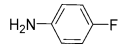
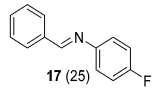
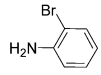
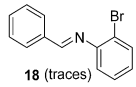
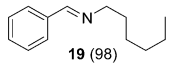
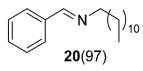


Run	Amine	IL	T [°C]	t [h]	Product [%][b]
1		TEAOAc	50	1	 2 (97)
2		TEAOAc	50	1	 4 (95)
3		TEAOAc	100	1	 5 (96)
5		TEAOAc	50	2	 6 (95)
6		TEAOAc	100	2	 7 (91)
7		TEAOAc	50	2	 8 (88)
8		TBABr[c]	100	1.5	 9 (93)
9		TBABr	100	3	 10 (73)
10		TEAOAc	100	3	 11 (traces)
11		TBABr	100	3	 12 (traces)
12		TEAOAc	50	3	 13 (87)
13		TBABr	100	5	 2 (99)

[a] General reaction conditions: IL (0.4 g), amine (0.25 mmol) heated at the appropriate temperature under an oxygen atmosphere. [b] GLC yields. [c] In TEAOAc, 1-naphthylamide was the major product (81%).[22]

Table 4. Oxidative cross-coupling of benzylamine in TBABr.[a]



Run	R'-NH2	t [h]	Conv. [%]	Product (% yield)[b]	Select. P:H[b]
1		6	98	 14 (36)	37:63
2		6	93	 15 (60)	65:35
3		6	98	 16 (47)	48:52
4		6	91	 17 (25)	35:65
5		6	99	 18 (traces)	0:100
6		4	99	 19 (98)	98:2
7		4	99	 20(97)	97:3
8		4	99	21 (94)	95:5

[a] General reaction conditions: IL (0.4 g), benzylamine (0.25 mmol), amine (0.5 mmol) heated at 100 °C under an oxygen atmosphere. [b] GLC yields.

Returning to the homo-coupling reaction, (see Table 3), the results with *para*-substituted benzylamines relative to benzylamine show that oxidative coupling in ILs is disfavoured by both electron-donating (*p*-MeO) and electron-withdrawing (*p*-Cl) substituents (Table 3, runs 1, 3, and 6).

Reactivity data more reliable for mechanistic interpretation are reported in Table 5 as conversions in TBABr at 100 °C after a shorter reaction time (15 min). These clearly show that all *p*-substituents (MeO, Me, F, and Cl), regardless of their electronic character, exert a general deactivating effect. This would typically imply a change in rate-determining step in a two-step reaction sequence.[23]

Table 5. Reactivity data for *p*-substituted benzylamines.

Substituent X (σ_p)	Conversion [%] after 15 min
p-Cl (+0.23)	67
p-F (+0.06)	93
H (0)	95
p-Me (–0.17)	88
p-MeO (–0.27)	61

Consistent with this unusual electronic substituent effect, and with the other results described above, we propose the mechanism shown in Scheme 1. In the first step, a one-electron transfer from amine **1** to dioxygen generates the radical ion pair $\mathbf{1}^{+\cdot}$ $O_2^{-\cdot}$, which would be particularly stabilized by solvation in IL as a result of ion–ion interactions with the ionic components of the solvent, and specific hydrogen bonds between the aminium radical $\mathbf{1}^{+\cdot}$ and the IL anions.

Such a stabilization, which could be the reason behind the observed activating effect of ILs, has precedent in two recently reported reactions of amines to give ionic products, namely *N*-alkylations of anilines,[15d] and protonation equilibria of aliphatic amines.[25]

Moreover, various catalytic oxidative couplings of benzylamine are reported to involve the same radical ions $\mathbf{1}^{+\cdot}$ and $O_2^{-\cdot}$.[12a,13c,13d] However, in those cases, the formation of the radical ions does not occur by direct electron transfer as in the case of the ILs, but is instead mediated by the catalyst. Apart from this difference, our mechanistic proposal parallels that of the literature.

Furthermore, concerning our thought that ILs could be capable of promoting the direct one-electron oxidation of an amine by O_2, it is interesting to note that in TBABr, we have been able to use *p*-toluidine as a redox mediator in a radical thiol–ene addition without the ruthenium polypyridyl photocatalyst[26] that, in the original reaction carried out in MeCN,[27] was reported to be necessary to catalyse the oxidation of the amine by O_2. After generation of the active species by single-electron transfer, the oxidative coupling would proceed by dehydrogenation of aminium radical $\mathbf{1}^{+\cdot}$ by superoxide, giving rise to an imine intermediate and H_2O_2 (path *b*). Then, the final imine product would simply be the result of a condensation of the imine intermediate with the starting benzylamine, in the case of homocoupling (path *c*), or of an aliphatic amine or aniline, in the case of heterocoupling reactions. Qualitative detection of H_2O_2 by means of a colorimetric assay[28] provided good direct evidence for the dehydrogenation pathway described above, but an oxygenation pathway could not be completely excluded as a viable alternative.

According to this alternative pathway, the coupled imine might originate from an oxygenative C–N bond cleavage of the aminium radical to give hydroxylamine and benzaldehyde, followed by condensation of the latter with benzylamine (steps *e* and *f*). A similar question was already posed regarding aerobic photocatalytic oxidation on TiO_2, and the oxygenative pathway was determined to be preferred, based on the fact that a significant amount of benzaldehyde was detected in the reaction of dibenzylamine.[12c]

However, the fact that we did not detect benzaldehyde in the reaction of dibenzylamine in TBABr (Table 3, run 13) testifies for a preferred dehydrogenative pathway. On the other hand, this result also indicates that our experimental conditions are unfavourable for imine hydrolysis, thus ruling out that the possibility that the coupled imine can derive from hydrolysis of the intermediate imine (Scheme 1, step *d*), followed by condensation of the resulting benzaldehyde with the starting benzylamine.

Finally, concerning the observed substituent effect, it is worth considering that a change in the rate-determining step may occur between steps *a* and *b*, which have different electronic demands. Step *a* would be made rate-determining by the presence of electron-withdrawing substituents (e.g., *p*-F and *p*-Cl, $\sigma > 0$). These are predicted to slow down a one-electron oxidation, as demonstrated in the electrochemical oxidation of *N*,*N*-dimethylbenzylamines whose peak potentials were found to give a good Hammett correlation, with a negative ρ value of –0.94.[29] On the other hand, step *b* would become rate-determining in the presence of electron-donating groups. In fact, substituents such as *p*-OMe and *p*-Me ($\sigma < 0$) may reasonably be expected to have a retarding effect on the radical cation dehydrogenation that would amount to a deprotonation along with a hydrogen-atom abstraction.

Conclusions

In conclusion, we have developed a protocol for the aerobic oxidation of amines to give imines using ionic liquids as reaction media. The high efficiency achievable in ILs is mechanistically explained in terms of activation of the starting materials (benzylamine and molecular oxygen) by an initial electron transfer, which may be promoted by the ionic nature of the solvent.

Therefore, the presented process, which does not require the use of any metal catalyst or organic oxidizing agent, competes favourably with most of the reported protocols, which require higher temperatures, catalysts, additives, and longer reaction times. To the best of our knowledge, this represents the first example of metal-free oxidative coupling of amines to give imines in ionic liquids.

Experimental Section

General Information: All the starting amines, TBAOH·H_2O (40% in H_2O), and metal derivatives (listed in Table 1) were sourced commercially and used as received. Molecular solvents (toluene, DMA, and water) were distilled before use. Ionic liquids TBABr, TBAOAc, [Bmim]Cl, [Bmim]BF_4, [BuPy]Br (from Fluka), [Bmim]-Br, TEAOAc, TBACl (from Aldrich), [Bmim]OAc, and [BuPy]PF_6 (from ABCR) were dried before use, yields of the imine products were determined by GLC using decane as an internal standard. To identify the reaction products, first they were isolated by column chromatography on neutral aluminum oxide (Al_2O_3, 50–200 μm, from Baker). Next, the products were identified by comparison of their GC–MS and NMR spectroscopic data with those reported in the literature (see below and Supporting Information). NMR spectra are recorded in $CDCl_3$ with a 400 MHz spectrometer.

Typical Homocoupling Procedure: In a vial (5 mL) equipped with a screw cap and a magnetic stirrer bar, and connected by a side-arm to an oxygen line, IL (0.4 g), benzylamine (0.25 mmol), and decane (internal standard, for GLC yields) were stirred and heated for the appropriate reaction time (see Tables 1, 2, and 3). The mixture was washed with aqueous $NaHCO_3$ and then extracted with Et_2O (5 × 1 mL). Then the combined organic layers were dried with anhydrous $MgSO_4$, the solvent was removed in vacuo, and the crude mixture was purified by chromatography on a short pad of Al_2O_3 (eluent hexane/diethyl ether). The isolated products were identified by comparison of their spectroscopic data with those reported in the literature.

(*E*)-*N*-Benzylidene-1-phenylmethanamine (2): ^{1}H NMR: δ = 4.82 (s, 2 H), 7.15–7.45 (m, 8 H), 7.8 (d, J = 4.5 Hz, 2 H), 8.35 (s, 1 H) ppm. ^{13}C NMR: δ = 65.09, 127.04, 128.04, 128.33, 128.54, 128.63, 130.79, 136.27, 139.39, 161.89 ppm; see ref.[30]

(*E*)-*N*-(4-Methylbenzylidene)-1-*p*-tolylmethanamine (4): ^{1}H NMR: δ = 2.35 (s, 3 H), 2.39 (s, 3 H), 4.80 (s, 2 H), 7.25 (m, 6 H), 7.7 (d, J = 8.2 Hz, 2 H), 8.38 (s, 1 H) ppm. ^{13}C NMR: δ = 21.22, 21.61, 64.92, 128.09, 128.37, 129.27, 129.42, 133.82, 136.55, 136.61, 141.06, 161.76 ppm; see ref.[30]

(*E*)-*N*-(4-Methoxybenzylidene)-1-(4-methoxyphenyl)methanamine (5): ^{1}H NMR: δ = 3.75 (s, 3 H), 3.79 (s, 3 H), 3.80 (s, 3 H), 4.75 (s, 2 H), 6.78–6.90 (m, 4 H), 7.21 (d, J = 8.2 Hz, 2 H), 7.70 (d, J = 8.3 Hz, 2 H), 8.30 (s, 1 H) ppm. ^{13}C NMR: δ = 55.31, 55.39, 64.43, 113.97, 114.04, 129.23, 129.29, 129.86, 131.76, 158.72, 160.97, 161.74 ppm; see ref.[30]

(*E*)-*N*-(4-Fluorobenzylidene)-1-(4-fluorophenyl)methanamine (6): ^{1}H NMR: δ = 4.75 (s, 2 H), 7.00–7.15 (m, 4 H), 7.25 (m, 2 H), 7.75 (m, 2 H), 8.32 (s, 1 H) ppm. ^{13}C NMR 64.31, 115.50 (d, $J_{C,F}$ = 21.1 Hz): δ = , 115.95 (d, $J_{C,F}$ = 22.0 Hz), 129.50 (d, $J_{C,F}$ = 8.1 Hz), 130.40 (d, $J_{C,F}$ = 8.5 Hz), 132.52 (d, $J_{C,F}$ = 3.1 Hz), 135.11 (d, $J_{C,F}$ = 3.3 Hz), 160.55, 162.83 (d, $J_{C,F}$ = 243.8 Hz), 164.33 (d, $J_{C,F}$ = 250.5 Hz) ppm; see ref.[31]

(*E*)-*N*-(4-Chlorobenzylidene)-1-(4-chlorophenyl)methanamine (7): ^{1}H NMR: δ = 4.75 (s, 2 H), 7.15–7.40 (m, 6 H), 7.65 (m, 2 H), 8.30 (s, 1 H) ppm. ^{13}C NMR: δ = 64.25, 128.76, 129.05, 129.38, 129.60, 132.95, 134.59, 137.00, 137.78, 160.00 ppm; see ref.[30]

(*E*)-*N*-(2-Methylbenzylidene)-1-*o*-tolylmethanamine (8): ^{1}H NMR: δ = 2.30 (s, 3 H), 2.51 (s, 3 H), 4.83 (s, 2 H), 7.10–7.31 (m, 7 H), 7.90 (m, 1 H), 8.71 (s, 1 H) ppm. ^{13}C NMR: δ = 19.85, 19.48, 63.52, 126.22, 126.33, 127.28, 127.92, 128.47, 130.25, 130.39, 130.99, 134.41, 136.27, 137.76, 137.88, 160.05 ppm; see ref.[31]

(*E*)-1-(Naphthalen-1-yl)-*N*-(naphthalen-1-yl-methylene)methanamine (9): ^{1}H NMR: δ = 5.39 (s, 2 H), 7.42–7.60 (m, 7 H), 7.80–7.95 (m, 5 H), 8.25 (d, J = 8.4 Hz, 1 H), 8.95 (d, 1 H), 9.09 (s, 1 H) ppm. ^{13}C NMR: δ = 63.65, 124.52, 124.65, 125.42, 125.80, 125.89, 126.10, 126.21, 126.31, 127.40, 128.01, 128.82, 128.93, 129.39, 131.34, 131.58, 131.86, 131.93, 134.05, 134.13, 135.75, 162.51 ppm; see ref.[32]

***N*-(Diphenylmethylene)-1,1-diphenylmethanamine (10):** ^{1}H NMR: δ = 5.55 (s, 1 H), 7.05 (m, 2 H), 7.10–7.45 (m, 16 H), 7.8 (m, 2 H) ppm. ^{13}C NMR: δ = 70.00, 126.85, 127.79, 127.97, 128.20, 128.53, 128.60, 128.66, 128.94, 130.25, 136.94, 140.05, 145.20, 167.17 ppm; see ref.[33]

(*E*)-1-Cyclohexyl-*N*-(cyclohexylmethylene)methanamine (13): This product could not be purified satisfactorily by chromatography because of its ease of hydrolysis. It was identified by GC–MS (EI): m/z (%) = 207 (1) $[M]^+$, 152 (18), 139 (8), 124 (100), 95 (17), 55 (27); see ref.[34]

(*E*)-*N*-Benzylideneaniline (14): ^{1}H NMR: δ = 7.20 (m, 3 H), 7.35–7.45 (m, 5 H), 7.88–7.91 (m, 2 H), 8.48 (s, 1 H) ppm. ^{13}C NMR: δ = 121.05, 126.00, 128.92, 128.99, 129.32, 131.54, 136.42, 152.29, 160.38 ppm; see ref.[30]

(*E*)-*N*-Benzylidene-4-methoxybenzenamine (15): ^{1}H NMR: δ = 8.48 (s, 1 H), 7.90–7.87 (m, 2 H), 7.47–7.45 (m,3 H), 7.52–7.21 (m, 2 H), 6.95–6.92 (m, 2 H), 3.83 (s,3 H) ppm. ^{13}C NMR: δ = 158.4, 158.3, 144.9, 136.4, 131.0, 128.7, 128.6, 122.2, 114.4, 55.5 ppm.

(*E*)-*N*-Benzylidene-4-methylbenzenamine (16): ^{1}H NMR: δ = 8.46 (s, 1 H), 7.91–7.88 (m, 2 H), 7.46 (m, 3 H), 7.21–7.12 (m, 4 H), 2.37 (s, 3 H) ppm. ^{13}C NMR: δ = 159.6, 149.5, 136.4, 135.8, 131.2, 129.8, 128.74, 128.72, 120.8, 21.0 ppm.

(*E*)-*N*-Benzylidene-4-fluorobenzenamine (17): ^{1}H NMR: δ = 8.41 (s, 1 H), 7.90 (dd, J = 8.5, 5.5 Hz, 2 H), 7.40–7.37 (m, 2 H), 7.24–7.13 (m, 5 H) ppm. ^{13}C NMR: δ = 164.8 (d, $J_{C,F}$ = 250.8 Hz), 158.8, 151.9, 132.6 (d, $J_{C,F}$ = 2.9 Hz), 130.8 (d, $J_{C,F}$ = 8.9 Hz), 129.2, 126.1, 120.9, 116.0 (d, $J_{C,F}$ = 21.9 Hz) ppm.

(*E*)-*N*-Benzylidenehexan-1-amine (19): ^{1}H NMR: δ = 0.89 (t, J = 6.9 Hz, 3 H), 1.35 (m, 6 H), 1.75 (m, 2 H), 3.60 (m, 2 H), 7.40 (m, 3 H), 7.50 (m, 2 H), 8.30 (s, 1 H) ppm. ^{13}C NMR: δ = 14.81, 22.99, 27.84, 31.30, 31.92, 62.52, 128.61, 128.82, 130.64, 136.71, 160.89 ppm; see ref.[35]

(*E*)-*N*-Benzylidenedodecan-1-amine (20): ^{1}H NMR: δ = 8.27 (s, 1 H), 7.72 (d, J = 3.0 Hz, 2 H), 7.40 (t, J = 3.0 Hz, 3 H), 3.60 (t, J = 6.0 Hz, 2 H), 1.69 (t, J = 6.0 Hz, 2 H), 1.29 (d, J = 20.6 Hz, 18 H), 0.88 (t, J = 6.0 Hz, 3 H) ppm. ^{13}C NMR: δ = 160.6, 136.5, 130.5, 128.6, 128.1, 61.9, 31.9, 31.1, 29.70, 29.65, 29.60, 29.50, 29.36, 27.5, 22.7, 14.2 ppm.

(*E*)-*N*-Benzylidene-2-phenylethanamine (21): ^{1}H NMR: δ = 8.14 (s, 1 H), 7.70–7.68 (m, 2 H), 7.39–7.38 (m, 3 H), 7.29–7.17 (m, 5 H), 3.85 (t, J = 7.0 Hz, 2 H), 3.01 (t, J = 7.5 Hz, 2 H) ppm. ^{13}C NMR: δ = 161.4, 139.9, 136.2, 130.5, 129.0, 128.5, 128.3, 128.0, 126.0, 63.1, 37.5 ppm.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR and mass spectra of the reaction products.

Acknowledgments

Partial financial support for this work from the Ministry of University and Scientific Research of Italy (MIUR) and from the University of Bari is gratefully acknowledged.

[1] a) M. A. Fox, J. N. Younathan, *Tetrahedron* **1986**, *42*, 6285–6291; b) S. I. Murahashi, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2443–2465; *Angew. Chem.* **1995**, *107*, 2670–2693; c) H. Wang, R. E. Partch, Y. Li, *J. Org. Chem.* **1997**, *62*, 5222–5225; d) J. P. Adams, *J. Chem. Soc. Perkin Trans. 1* **2000**, *2*, 125–139; e) P. G. Cozzi, *Chem. Soc. Rev.* **2004**, *33*, 410–421; f) J. S. M. Samec, A. H. Ell, J. E. Bäckvall, *Chem. Eur. J.* **2005**, *11*, 2327–2334; g) H. Sun, F. Z. Su, J. Ni, Y. Cao, H. Y. He, K. N. Fan, *Angew. Chem. Int. Ed.* **2009**, *48*, 4390–4393; *Angew. Chem.* **2009**, *121*, 4454–4457; h) O. Rios-Bern, S. O. Flores, I. Cordova, M. A. Valenzuela, *Tetrahedron Lett.* **2010**, *51*, 2730–2733; i) B. Gnanaprakasam, J. Zhang, D. Milstein, *Angew. Chem. Int. Ed.* **2010**, *49*, 1468–1471; *Angew. Chem.* **2010**, *122*, 1510–1513; j) Y. Shiraishi, Y. Sugano, S. Tanaka, T. Hirai, *Angew. Chem. Int. Ed.* **2010**, *49*, 1656–1660; *Angew. Chem.* **2010**, *122*, 1700–1704; k) Y. Shiraishi, M. Ikeda, D. Tsukamoto, S. Tanaka, T. Hirai, *Chem. Commun.* **2011**, *47*, 4811–4813; l) S. Furukawa, Y. Ohno, T. Shishido, K. Teramura, T. Tanaka, *ACS Catal.* **2011**, *1*, 1150–1153.

[2] a) S. Nieto, J. M. Dragna, E. V. Anslyn, *Chem. Eur. J.* **2010**, *16*, 227–232; b) L. R. Reddy, M. Prashad, *Chem. Commun.* **2010**, *46*, 222–224; c) B. Miriyala, S. Bhattacharyya, J. S. Williamson, *Tetrahedron* **2004**, *60*, 1463–1471; d) R. S. Varma, R. Dahiya, S. Kumar, *Tetrahedron Lett.* **1997**, *38*, 2039–2042.

[3] a) K. C. Nicolaou, C. J. N. Mathison, T. Montagnon, *Angew. Chem. Int. Ed.* **2003**, *42*, 4077–4082; *Angew. Chem.* **2003**, *115*, 4211–4216; b) K. Yamaguchi, N. Mizuno, *Angew. Chem. Int. Ed.* **2003**, *42*, 1480–1483; *Angew. Chem.* **2003**, *115*, 1518–1521; c) H. Choi, M. P. Doyle, *Chem. Commun.* **2007**, 745–747; d) A. Dhakshinamoorthy, M. Alvaro, H. Garcia, *ChemCatChem* **2010**, *2*, 1438–1443; e) L. Aschwanden, T. Mallat, M. Maciejewski, F. Krumeich, A. Baiker, *ChemCatChem* **2010**, *2*, 666–673.

[4] a) M. S. Kwon, S. Kim, S. Park, W. Bosco, R. K. Chidrala, J. Park, *J. Org. Chem.* **2009**, *74*, 2877–2879; b) J. W. Rigoli, S. A. Moyer, S. D. Pearce, J. M. Schomaker, *Org. Biomol. Chem.* **2012**, *10*, 1746–1749.

[5] a) K. Shimizu, K. Ohshima, Y. Tai, M. Tamura, A. Satsuma, *Catal. Sci. Technol.* **2012**, *2*, 730–738; b) T. Mukaiyama, A. Kawana, Y. Fukuda, J. Matsuo, *Chem. Lett.* **2001**, *30*, 390–391; c) S. I. Murahashi, Y. Okano, H. Sato, T. Nakae, N. Komiya, *Synlett* **2007**, 1675–1678; d) M.-H. So, Y. Liu, C.-M. Ho, C.-M. Che, *Chem. Asian J.* **2009**, *4*, 1551–1561; e) S. Kodama, J. Yoshida, A. Nomoto, Y. Ueta, S. Yano, M. Ueshima, A. Ogawa, *Tetrahedron Lett.* **2010**, *51*, 2450–2452.

[6] a) E. R. Klobukowski, R. J. Angelici, L. K. Woo, *Catal. Lett.* **2012**, *142*, 161–167; b) K. Shimizu, K. Ohshima, K. Shimura, M. Tamura, A. Satsuma, *Green Chem.* **2011**, *13*, 3096–3100; c) W. He, L. Wang, C. Sun, K. Wu, S. He, J. Chen, P. Wu, Z. Yu, *Chem. Eur. J.* **2011**, *17*, 13308–13317; d) L. Aschwanden, B. Panella, P. Rossbach, B. Keller, A. Baiker, *ChemCatChem* **2009**, *1*, 111–115; e) A. Grirrane, A. Corma, H. Garcia, *J. Catal.* **2009**, *264*, 138–144.

[7] S. M. Landge, V. Atanassova, M. Thimmaiah, B. Toeroek, *Tetrahedron Lett.* **2007**, *48*, 5161–5164.

[8] G. Chu, C. Li, *Org. Biomol. Chem.* **2010**, *8*, 4716–4719.

[9] L. Liu, Z. Wang, X. Fu, C.-H. Yan, *Org. Lett.* **2012**, *14*, 5692–5695.

[10] a) L. Aschwanden, T. Mallat, F. Krumeich, A. Baiker, *J. Mol. Catal. A* **2009**, *309*, 57–62; b) R. I. Khusnutdinov, A. R. Baygusina, R. I. Aminov, *Russ. J. Org. Chem.* **2012**, *48*, 1059–1061.

[11] a) H. Yuan, W. J. Yoo, H. Miyamura, S. Kobayashi, *J. Am. Chem. Soc.* **2012**, *134*, 13970–13973; b) A. E. Wendlandt, S. S. Stahl, *Org. Lett.* **2012**, *14*, 2850–2853; c) M. Largeron, M. B. Fleury, *Angew. Chem. Int. Ed.* **2012**, *51*, 5409–5412; *Angew. Chem.* **2012**, *124*, 5505–5508.

[12] a) J. H. Park, K. C. Ko, E. Kim, N. Park, J. H. Ko, D. H. Ryu, T. K. Ahn, J. Y. Lee, S. U. Son, *Org. Lett.* **2012**, *14*, 5502–5505; b) X. Lang, W. Ma, Y. Zhao, C. Chen, H. Ji, J. Zhao, *Chem. Eur. J.* **2012**, *18*, 2624–2631; c) X. Lang, H. Ji, C. Chen, W. Ma, J. Zhao, *Angew. Chem. Int. Ed.* **2011**, *50*, 3934–3937; *Angew. Chem.* **2011**, *123*, 4020–4023; d) N. Li, X. Lang, W. Ma, H. Ji, C. Chen, J. Zhao, *Chem. Commun.* **2013**, *49*, 5034–5036.

[13] a) H. Huang, J. Huang, Y.-M. Liu, H.-Y. He, Y. Cao, K.-N. Fan, *Green Chem.* **2012**, *14*, 930–934; b) R. D. Patil, S. Adimurthy, *Adv. Synth. Catal.* **2011**, *353*, 1695–1700; c) C. Su, M. Acik, K. Takai, J. Lu, S.-J. Hao, Y. Zheng, P. Wu, Q. Bao, T. Enoki, Y. J. Chabal, K. P. Loh, *Nature Commun.* **2012**, *3*, 1–9; d) F. Su, S. C. Mathew, L. Mohlmann, M. Antonietti, X. Wang, S. Blechert, *Angew. Chem. Int. Ed.* **2011**, *50*, 657–660; *Angew. Chem.* **2011**, *123*, 683–686; e) Z. Zhang, F. Wang, M. Wang, S. Xu, H. Chen, C. Zhang, J. Xu, *Green Chem.* **2014**, DOI: 10.1039/c3gc42312c.

[14] a) J. P. Hallett, T. Welton, *Chem. Rev.* **2011**, *111*, 3508–3576; b) C. D. Hubbard, P. Illner, R. van Eldik, *Chem. Soc. Rev.* **2011**, *40*, 272–290.

[15] a) V. Calo, A. Nacci, A. Monopoli, *J. Organomet. Chem.* **2005**, *690*, 5458–5466; b) A. Monopoli, A. Nacci, V. Calò, F. Ciminale, P. Cotugno, A. Mangone, L. C. Giannossa, P. Azzone, N. Cioffi, *Molecules* **2010**, *15*, 4511–4525; c) P. Cotugno, A. Monopoli, F. Ciminale, N. Cioffi, A. Nacci, *Org. Biomol. Chem.* **2012**, *10*, 808–813; d) A. Monopoli, P. Cotugno, M. Cortese, C. D. Calvano, F. Ciminale, A. Nacci, *Eur. J. Org. Chem.* **2012**, 3105–3111; e) A. Monopoli, P. Cotugno, G. Palazzo, N. Ditaranto, B. Mariano, N. Cioffi, F. Ciminale, A. Nacci, *Adv. Synth. Catal.* **2012**, *354*, 2777–2788; f) V. Calò, V. Fiandanese, A. Nacci, A. Scilimati, *Tetrahedron* **1994**, *50*, 7283–7292; g) P. Cotugno, M. Casiello, A. Nacci, P. Mastrorilli, M. M. Dell'Anna, A. Monopoli, *J. Organomet. Chem.* **2014**, *752*, 1–5.

[16] S.-I. Murahashi, T. Hirano, T. Yano, *J. Am. Chem. Soc.* **1978**, *100*, 348–350.

[17] M. C. Lubinu, L. D. Luca, G. Giacomelli, A. Porcheddu, *Chem. Eur. J.* **2011**, *17*, 82–85.

[18] L. Liu, S. Zhang, X. Fu, C.-H. Yan, *Chem. Commun.* **2011**, *47*, 10148–10150.

[19] a) N. Leadbeater, M. Marco, *J. Org. Chem.* **2003**, *68*, 5660–5667; b) R. Arvela, N. Leadbeater, M. Sangi, V. Williams, P. Granados, R. A. Singer, *J. Org. Chem.* **2005**, *70*, 161–168; c) N. Leadbeater, *Nature Chem.* **2010**, *2*, 1007–1009.

[20] For Kamlet–Taft parameters of IL ions, see: L. Crowhurst, P. R. Mawdsley, J. M. Perez-Arlandis, P. A. Salter, T. Welton, *Phys. Chem. Chem. Phys.* **2003**, *5*, 2790–2794.

[21] J. G. Huddleston, A. E. Visser, W. M. Reichert, H. D. Willauer, G. A. Broker, R. D. Rogers, *Green Chem.* **2001**, *3*, 156–164.

[22] 1-Naphthylamide was the major product in TEAOAc, as a result of an overoxidation of secondary imine **9**, which was formed by the coupling of naphthylmethanamine. As a further confirmation, a certain amount of pure **9** was placed in TEAOAc under the reaction conditions, and this gave 1-naphthylamide in 2 h.

[23] a) R. A. Jones, *Physical and Mechanistic Organic Chemistry*, 2nd ed., Cambridge University Press **1984**, p. 43–45; b) N. S. Isaacs, *Physical Organic Chemistry*, Longman Scientific & Technical, **1987**, p. 146–148.

[24] a) P. Wasserscheid, T. Welton (Eds.), *Ionic Liquids in Synthesis*, 2nd ed., Wiley-VCH, Weinheim, Germany, **2008**; b) E. S. Putilova, G. V. Kryshtal, G. M. Zhdankina, N. A. Troitskii, S. G. Zlotin, *Russ. J. Org. Chem.* **2005**, *41*, 512–516.

[25] F. D'Anna, S. Marullo, P. Vitale, R. Noto, *J. Org. Chem.* **2009**, *74*, 6224–6230.

[26] In a typical experiment, cyclohexene (0.5 mmol) and benzylthiol (2.5 equiv.) were stirred at 100 °C in the presence of TBABr (0.4 g) and *p*-toluidine (0.25 mmol), under an oxygen atmosphere. After 2 h, GC–MS analysis revealed a 75% conversion to the expected thiol–ene addition product [i.e., benzyl(cyclohexyl)sulfane, 70% yield] and small percentages of the dibenzyl disulfide (20%) and the dibenzyl sulfide (10%). The same reaction performed in the absence of *p*-toluidine gave a similar degree of conversion, the disulfide was the sole product.

[27] E. L. Tyson, Z. L. Niemeyer, T. P. Yoon, *J. Org. Chem.* **2014**, *79*, 1427–1436.

[28] G. Su, Y. Wei, M. Guo, *AJAC* **2011**, *2*, 879–884.

[29] J. R. Lindsay Smith, D. Masheder, *J. Chem. Soc. Perkin Trans. 2* **1976**, 47–51.

[30] H. Yuan, W.-J. Yoo, H. Miyamura, S. Kobayashi, *J. Am. Chem. Soc.* **2012**, *134*, 13970–13973.

[31] E. Zhang, H. Tian, S. Xu, X. Yu, Q. Xu, *Org. Lett.* **2013**, *15*, 2704–2707.

[32] K. Onto, T. Hatakeyama, M. Takeo, S. Uchiito, M. Tokuda, H. Suginome, *Tetrahedron* **1998**, *54*, 8403–8410.

[33] P. Eisenberger, A. M. Bailey, C. M. Crudden, *J. Am. Chem. Soc.* **2012**, *134*, 17384–17387.

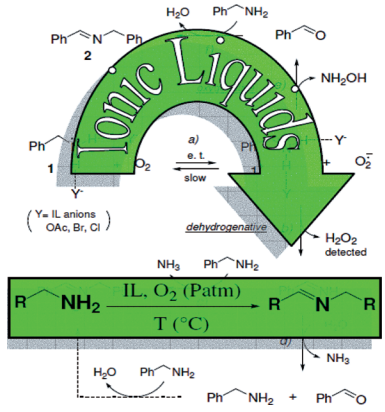
[34] E. Gebauer-Henke, W. Leitner, A. Prokofieva, H. Vogta, T. E. Müller, *Catal. Sci. Technol.* **2012**, *2*, 2539–2548.

[35] Z. Zhu, J. H. Espenson, *J. Am. Chem. Soc.* **1996**, *118*, 9901–9907.

Received: May 13, 2014
Published Online: ■

Oxidative Coupling

An oxidative coupling of amines to give imines in ionic liquids (ILs) under metal-free aerobic conditions has been developed. The efficiency achievable in ILs is explained in terms of activation of the reactants (benzylamine and O_2) by an initial electron transfer, promoted by the ionic medium.



A. Monopoli,* P. Cotugno, F. Iannone, F. Ciminale,* M. M. Dell'Anna, P. Mastrorilli, A. Nacci **1–8**

Ionic-Liquid-Assisted Metal-Free Oxidative Coupling of Amines To Give Imines

Keywords: Ionic liquids / Imines / Amines / Oxidation / Oxygen / Green chemistry

