

Cobalt-Catalyzed Hydroarylations and Hydroaminations of Alkenes in Tunable Aryl Alkyl Ionic Liquids

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S Supporting Information

ABSTRACT: Tunable aryl alkyl ionic liquids (TAAILs) are a promising class of imidazolium- or triazolium-based ionic liquids. Contrary to "standard" all-alkyl ionic liquids, these carry an aryl ring together with a linear or branched alkyl chain. Their application in the cobalt-catalyzed hydroarylation/hydroamination of alkenes and anilines is presented. The catalytic system is tolerant toward air and is scalable and reusable. It has been successfully used for the synthesis of pharmacologically relevant primary to tertiary aryl amines.



n the quest for more sustainability in chemistry, ionic Uliquids (ILs) are regarded as one of the most potent solvents of the future,¹⁻⁴ e.g., for application in catalysis.⁴⁻⁶ Their negligible vapor pressure minimizes emission into the environment, because of which they are often labeled as "green solvents".^{7,8} At the same time, they are highly thermally, chemically, and electrochemically stable. Most importantly, due to their modular design, their properties can be fine-tuned and thus can be tailored to a specific task.9-12 For this endeavor, we use a new generation of ionic liquids, the tunable aryl alkyl ionic liquids (TAAILs),¹³⁻¹⁹ with the additional opportunity of fine-tuning the electronic structure of the cation through the aryl ring substitution pattern.^{20,21} For example, the increased solubility of metal salts in TAAILs has been applied to the extraction of noble metals and rare earth elements.²² The ability of ionic liquids to dissolve both metal salts and organic substrates allows access to intriguing reusable catalytic systems.^{4-6,23} The utility of TAAILs has previously been demonstrated in the industrially relevant platinum-catalyzed hydrosilylation of olefins.²⁴

Similarly, hydroaminations and hydroarylations are among the most sought-after reactions because of their high atom economy.^{25–30} In particular, we were interested in the intermolecular addition of anilines to olefins (Scheme 1). Common approaches for this reaction include the use of ligand-modulated late transition metals,^{31–40} strong Brønsted acids,^{41–47} and earth-abundant metals.^{48–51} There are some reports on the use of ionic liquids in this type of reaction,^{52–57} especially for the reaction of the more reactive acetylenes⁵⁸ and activated olefins⁵⁹ or for reactions (co)catalyzed by Brønsted acids.^{60–62}

Our approach combines the use of earth-abundant metal catalysts, namely, cobalt chloride, with the fine-tuning ability of the TAAILs. We present an easy-to-use catalytic system that is tolerant toward air, reusable, and allows product isolation by distillation. The scope has been explored, showing that the system enables access to pharmacologically relevant substituted aromatic amines. Scheme 1. Representative Catalyst Systems for the Markovnikov Hydroarylation/Hydroamination of Activated Olefins and Anilines



At first, the required TAAILs had to be synthesized in reasonable quantities following the general synthetic procedure (Scheme 2). An improved protocol for the synthesis of the aryl

Scheme 2. Modular Approach for the Synthesis of TAAILs



imidazoles allowed facile scale-up and purification by distillation. All TAAILs were accessible in three steps from commercial starting materials in quantities of up to 500 g. The different counterions, aryl substituents, and alkyl chains of the TAAILs can be widely varied in a modular fashion. An overview of the synthesized TAAILs is given in Table S1 (see the Supporting Information (SI)).

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We initially screened several commercially available metal salts in the reaction of styrene and aniline in the ionic liquid **1a** (1-butyl-3-(2-methylphenyl)imidazolium bis(trifluoromethanesulfonyl)imide) (Table 1). The reaction mainly yielded

Table 1. Screening of Different Catalysts

	Ph + PhNH (3 equi	[cat.] (2 mol %) 2 1a (0.5 mL) 140 °C, 6 h	► Ph	NH ₂ + HN 2a Ph	√ ^{Ph} 3a		
no.	cat.	2a/3a yield/%	no.	cat.	2a/3a yield/%		
1	FeCl ₃ ·6H ₂ O	18:16 (37) ^a	9	LiNTf ₂ ^b	4:4		
2	CoCl ₂ ·6H ₂ O	16 :14 (39) ^{<i>a</i>}	10	none ^b	3:3		
3	NiCl ₂ ·6H ₂ O	13:12	11	$Fe(acac)_2$	2:0		
4	MoO_2Cl_2	7:6	12	FeSO ₄ ·7H ₂ O	7:6		
5	RuCl ₃ ·3H ₂ O	17:15 (31) ^a	13	$Fe(C_2O_4)$	7:7		
6	AuCl	10:8	14	$Co(OAc)_2 \cdot 4H_2O$	13:11		
7	$LaCl_3 \cdot H_2O$	10:10	15	$Co(NO_3)_2 \cdot 6H_2O$	16:13		
8	HOTf ^c	8:8	16	Ni(OAc) ₂ ·4H ₂ O	12:10		
 ^a2a, yield after 24 h. ^bAfter 24 h. ^c5 mol %. Legend: 1a = 1-butyl-3-(2-methylphenyl)imidazolium bis(trifluoromethanesulfonyl)imide. 							

the hydroarylation product **2a** and the hydroamination product **3a**. Among several earth-abundant metal salts and noble metal salts, iron(III) chloride, cobalt(II) chloride hexahydrate, and ruthenium(III) chloride trihydrate performed best (Table 1, entries 1, 2, and 5). Other transition metal chlorides, as well as triflic acid, were less efficient (Table 1, entries 3, 4, and 6–8). Without added catalyst, the yield after 24 h is as low as 3% (Table 1, entry 10). Metal salts other than chlorides were also less active (Table 1, entries 11–16). We chose to further optimize the reaction using CoCl₂·6H₂O since it is an inexpensive and abundant metal salt, which also showed a slightly better performance after 24 h reaction time, where complete conversion of styrene was observed, compared to FeCl₃·6H₂O. Dissolving CoCl₂·6H₂O in the catalytic mixture

Table 2. Screening of the Ionic Liquid^a

leads to an almost instant color change from red to green, indicating the formation of a cobalt chloride aniline complex. The product ratio 2a:3a was approximately 3:2, regardless of the metal salt being used. This selectivity is similar to other reports.^{60–62} For a high selectivity toward the monoalkeny-lated products, a 3-fold excess of aniline was required. The excess aniline can be reisolated after the catalytic run.

Next, we screened several ionic liquids as solvent for the reaction (Table 2). The choice of the counterion (X) (Scheme 2) is very important for the catalytic performance of the system (Table 2, entries 1-7). Only the TAAILs containing the weakly coordinating counterions NTf_2 (Table 2, entry 1) and B_{ArF} (Table 2, entry 6) were able to mediate the reaction. This dependence on the counterion has been reported for related catalytic systems.⁴³ Upon variation of the chain length (R^2) (Scheme 2), we found a pronounced influence on the catalytic activity (Table 2, entries 8-12). In the undecyl-substituted IL 1k, the chain length is at an optimum (Table 2, entry 11). Similarly, the choice of the aryl substitution pattern (R^1) (Scheme 2) is important for an efficient catalytic conversion (Table 2, entries 13-19). For optimum performance, one ortho substituent has to be present. Among the tested ionic liquids, 1q was the most efficient solvent for the reaction (Table 2, entry 17). Again, the product ratio of 2a:3a was approximately 3:2 in all TAAILs, which shows that the selectivity is not governed by the catalytic system but by the intrinsic properties of the substrates. We also compared the performance of other "standard" ionic liquids (Table 2, entries 20-22). In general, these performed worse compared to the TAAILs. The reaction does not proceed in the absence of an ionic liquid (Table 2, entries 23 and 24), although the catalyst is completely dissolved in the latter mixtures. This shows that the highly polar environment, which is formed by the ionic liquids,⁶³ is necessary for an efficient catalytic reaction.^{26,64,65}

Screening of the catalyst load and reaction temperature showed that although there are some changes in selectivity the highest yields are still obtained by employing 2 mol % catalyst at 140 °C reaction temperature (Table S2, see SI). At higher

	Ph 🔶 +	CoCl ₂ • 6 H ₂ O (2 mol %) (3 equiv) IL (0.5 mL) 140 °C, 24 h	NH ₂ + Ph 2a	HN ^{Ph} Ph 3a	
no.		2a/3a yield/%	no.		2a/3a yield/%
	IL, $R^1 = 2$ -Me, $R^2 = C_4 H_{9}$, (X)			IL, $R^2 = C_{11}H_{23}$, $X = NTf_{2}$, (R^1)	
1	$1a (X = NTf_2)$	39:22	13	$\mathbf{1m} \ (\mathbf{R}^1 = 2 \cdot \mathbf{MeO})$	47:16
2	$\mathbf{1b} (\mathbf{X} = \mathbf{OMs})$	0:0	14	$\ln (R^1 = 2\text{-}EtO)$	54:27
3	1c (X = OTs)	0:0	15	1o $(R^1 = 4-Br)$	34:23
4	1d (X = TFA)	0:0	16	$\mathbf{1p} \ (\mathbf{R}^1 = 4\text{-}\mathbf{OMe})$	37:23
5	1e (X = Br)	0:0	17	$1q (R^1 = 2, 4-Me_2)$	59 :29
6	$\mathbf{1f} (\mathbf{X} = \mathbf{B}_{\mathrm{ArF}})$	26:26	18	$\mathbf{lr} \ (\mathbf{R}^1 = \mathbf{H})$	4:3
7	1g (X = DCA)	0:0	19	$1s (R^1 = 2, 4, 6-Me_3)$	30:18
	IL , $R^1 = 2$ -Me, R^2 , $X = NTf_2$			other solvents	
8	$\mathbf{1h} \left(\mathbf{R}^2 = \mathbf{C}_3 \mathbf{H}_7 \right)$	15:11	20	[UndecMim][NTf ₂]	19:15
9	1i $(R^2 = C_6 H_{13})$	13:9	21	[EMim][NTf ₂]	4:2
10	$1j (R^2 = C_9 H_{19})$	47:24	22	[P ₆₆₆₁₄][NTf ₂]	13:6
11	$1\mathbf{k} (\mathbf{R}^2 = \mathbf{C}_{11}\mathbf{H}_{23})$	55 :25	23	PhNO ₂	0:0
12	$11 (R^2 = C_{14}H_{22})$	14:10	24	none	0:0

 a OMs – methane sulfonate, OTs – *p*-toluene sulfonate, TFA – trifluoroacetate, B_{ArF} – tetrakis(3,5-bis(trifluoromethylphenyl))borate, DCA – dicyanamide, UndecMim – 1-methyl-3-undecylimidazolium, EMim – 1-ethyl-3-methylimidazolium, P₆₆₆₁₄ – trihexyltetradecylphosphonium.

temperatures, **2a** is obtained as the sole product, which is caused by decomposition of **3a**, as indicated by prolonging the reaction time at 140 °C (Table S3, see SI). Adding excess amounts of water or performing the reaction in air only leads to a slight decrease in yield (Table S4, see SI). In the latter case, a color change from green to pink indicates oxidation to Co(III). Water-free cobalt(II) chloride is an equally efficient catalyst (Table S4, entry 4). To our delight, the reaction is scalable. A 5-fold increase of catalyst and reactants only led to a slight decrease in yield (Table S4, entry 5). It has to be emphasized that the amount of the TAAIL **1q** was not increased, rendering the reaction even more efficient.

The fact that all reactants and products are volatile, while the ionic liquid and the metal salt are not, enables the catalytic system to be reused (Table 3). Distillation of the reaction

Table 3. Reusability^a



^{*a*}Purification by vacuum distillation. ^{*b*}Conversion of styrene, determined by GC.

mixture under high vacuum at 120 °C is possible due to the high thermal stability of the TAAILs, as indicated by TG measurements on closely related TAAILs.⁶⁶ The system can be reused up to 4 times without loss of activity. Then, the achieved conversion drops by 10%.

Under the optimized reaction conditions, several aniline derivatives were reacted with styrene derivatives (Table 4). The highest yield of 76% was achieved for 4-nitroaniline (Table 4, entry 3). In this case, nearly no hydroamination product was observed. In general, the selectivity and reactivity are determined by the electronic and steric properties of the aniline. This reaction protocol also allows for the efficient and scalable synthesis of new and promising agents for the treatment of cancer. For example, **2i** was obtained in 60% yield in a single step. It has been shown to inhibit the proliferation of several related cell lines.⁶⁷ The reaction of *N*-methyl aniline with styrene also preferably yields the hydroarylation product **2j** (Table 4, entry 10). Other styrene derivatives, such as 4-*tert*-butylstyrene (Table 4, entry 11) and indene (Scheme 3), were also tolerated.

The reaction was also performed using norbornene as a substrate (Table 5). In general, the selectivity toward the hydroamination product was higher. For example, the selectivity with 4-nitroaniline as substrate in this reaction is completely inverted, yielding nearly quantitative amounts of the hydroamination product 3o (Table 5, entry 3). Other terminal or unstrained cyclic aliphatic alkenes were unreactive under these reaction conditions.

In conclusion, we have developed a versatile catalytic system for the hydroarylation and hydroamination of aryl amines with alkenes in TAAILs. An efficient scale-up procedure allows access to sufficient quantities of the solvent. Among several transition metal salts, the inexpensive cobalt(II) chloride performed best. The choice of the ionic liquid was shown to





"Isolated yields. ^bOn a 5 mmol scale, ^cIn parentheses: not isolated. Yield determined by GC-MS.

Scheme 3. Reaction of Indene and Aniline^a



^{*a*}Isolated yields.

Table 5. Substrate Scope with Norbornene and Anilines^a

	NHR ² CoC 2 + (2) 1 q (2) 1 q (1) 140 (3 equiv)	$\begin{array}{c} H_2 \cdot 6 H_2 O \\ \hline mol \%) \\ \hline 0.5 mL) \\ ^{\circ}C, 24 h \end{array}$	NHR ² +	NR ² 3m-q
no.	\mathbb{R}^1	\mathbb{R}^2	2 yield/% ^b	3 yield/%
1 ^b	Н	Н	2m , 34	3m , 54
2	4-OMe	Н	2n , 33	3n , 18
3	4-NO ₂	Н	20 , (0)	30 , 97
4	2-Me	Н	2p , 25	3p , 74
5	Н	Me	2q , (8)	3q , 60
^{<i>a</i>} Isolated gGC-MS.	yields. ^b In pare	entheses: no	t isolated. Yield	determined by

have a strong impact on the catalyst efficiency. The aryl orthosubstituted TAAILs outperformed the "standard" aryl alkyl ionic liquids by far. The selectivity toward the hydroamination and hydroarylation product is determined by the electronic and steric properties of the different substrates, providing access to pharmacologically relevant structures.

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ASSOCIATED CONTENT

S Supporting Information

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Supplemental figures and tables, experimental details, characterization data, and NMR spectra for all synthesized compounds (PDF)

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The authors declare no competing financial interest.

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