ACES

DOI: 10.1002/asia.201500604

CHEMISTRY
AN ASIAN JOURNAL
Full Paper

Combinatorial Chemistry

Dynamic Covalent Chemistry of Nucleophilic Substitution Component Exchange of Quaternary Ammonium Salts

Sirinan Kulchat and Jean-Marie Lehn*[a]

Abstract: Dynamic covalent libraries (DCLs) of quaternary ammonium cations were set up by reversible nucleophilic substitution (S_N2' and S_N2) exchange reactions of ammonium salts and tertiary amines. The reactions were conducted at 60 °C to generate thermodynamically and kinetically controlled mixtures of quaternary ammonium compounds and tertiary amines, and were accelerated by using iodide as a nucleophilic catalyst. Microwave irradiation was used to assist the exchange reaction between the pyridinium salts and pyridine derivatives. Finally, experiments towards the generation of dynamic ionic liquids were performed. The results of this study pave the way for the extension of dynamic combinatorial chemistry to nucleophilic substitution reactions.

Introduction

Constitutional dynamic chemistry (CDC), and in particular on the molecular level dynamic covalent chemistry (DCC), play an increasingly important role in diverse research fields.[1] DCC is based on the implementation of reversible reactions to generate dynamic covalent libraries (DCLs) of molecular constituents interconverting through component exchange and are at thermodynamic equilibrium.[2] These libraries may contain the full set of constituents resulting from all possible combinations of the available components, although they can remain virtual,[2a] depending on the reaction and the conditions. Representative examples of reversible reactions implemented in DCC by different research groups over the last decade comprise amine/carbonyl condensation,[3] disulfide exchange,[4] olefin metathesis,[5] imine exchange,[6] Knoevenagel/imine exchange,[6a,7] Knoevenagel/Knoevenagel exchange,[7] boronic ester formation,[8] peptide exchange,[9] and Diels–Alder condensation.[10] CDC, both molecular and supramolecular, also provides new perspectives in areas such as materials science[11] and drug design.[12] To further extend the realm of DCC, there is a constant requirement for new reversible reactions to generate DCLs of increasing structural and chemical diversity and complexity.

More than a century ago, the first preparation and study of the chiral ammonium salt $Me(Et)N^+(All)PhI^-\cdot CHCl_3$ in 1903[13a] revealed the occurrence of spontaneous racemization by reversible dissociation into amine and allyl halide. The rate of racemization depended on the type of anion, decreasing in the sequence $I > Br > Cl$.[13b] Half a century later, in 1954 a procedure for the spontaneous resolution of this salt was described and its optical activity was confirmed.[14] Another half a century later in 2001, the solid-state molecular structure of this salt was determined[15a] and its conglomerate formation features were investigated.[16] In the case of the similar salt $Me(All)N^+(CH_2Ph)PhX^-$ (X = Br, I), the spontaneous resolution was attempted but it was found that the crystals underwent lamellar racemic twinning.[15b] Racemization was proposed to occur by means of attack of the halide at the γ position of the allyl group of the quaternary cation following a S_N2' mechanism.[15a] Recently, chiral ammonium salts were frequently used as catalysts in asymmetric synthesis,[17] as ionic liquids,[18] and in crystal engineering.[19] Furthermore, the reaction of other ammonium salts such as *N*-benzyl-*N*,*N*-dimethylanilinium salt with nucleophilic carbanions[20] and the reversibility of the nucleophilic reaction between benzylbromide and *N*,*N*-dimethylaniline were investigated.[21] The nucleophilic substitution between pyridine and derivatives of benzyl bromide to afford pyridinium bromide (Menschutkin reaction) was examined in both molecular solvents and ionic liquids.[22] Additionally, pyridinium salts are easily accessed and are versatile precursors to nitrogen-containing heterocycles. They are exploited for the total synthesis of natural products as well as in asymmetric or regioselective addition reactions.[23]

We report here our work on the generation of dynamic covalent libraries based on nucleophilic substitution reactions. More specifically, we present a study of new DCC processes involving the exchange of the tertiary amine component of quaternary ammonium salts based on S_N2' and S_N2 types of nucleophilic substitution reactions. We also describe the ability of iodide to act as a nucleophile to catalyze the exchange between components. Iodide catalysis was reported in the self-assembly of donor–acceptor [3]catenanes.[24] Furthermore, microwave irradiation was used to assist the exchange between

[a] *Dr. S. Kulchat, Prof. Dr. J.-M. Lehn*
Laboratoire de Chimie Supramoléculaire, ISIS
Université de Strasbourg
8 allée Gaspard Monge, 67000 Strasbourg (France)
E-mail: lehn@unistra.fr

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/asia.201500604.

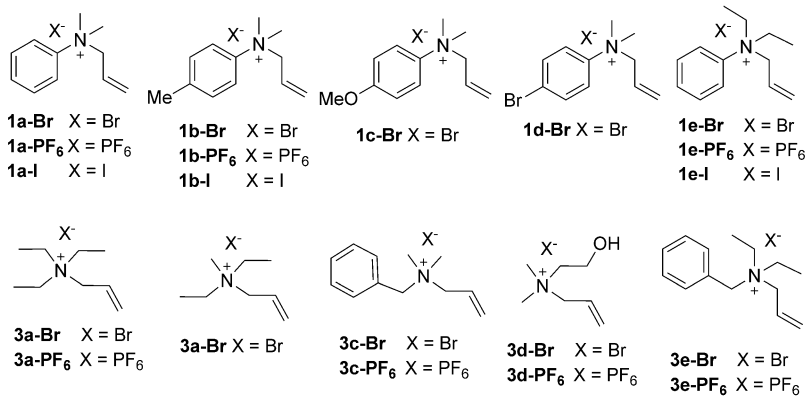


Figure 1. Structures of the quaternary allyl ammonium salts of aromatic *N*,*N*-dialkylanilinium-derived (**1a**–**e**) and aliphatic (**3a**–**e**) types used in the present study.

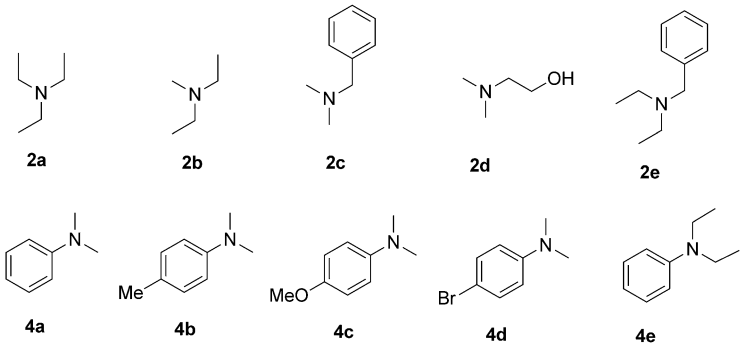


Figure 2. Structure of aliphatic (**2a**–**e**) and *N*,*N*-dimethylaniline-type aromatic (**4a**–**e**) tertiary amines used in the present study.

pyridinium salts and pyridine derivatives. Finally, as some ammonium salts in our study are ionic liquids,[25] we explored the generation of dynamic ionic-liquid libraries in molecular solvents. All the processes investigated were followed by ^{1}H NMR spectroscopy and the fractions of the different compounds in the DCLs were determined by signal integration.

Abstract in Thai:

งานวิจัยนี้ศึกษาเกี่ยวกับการสร้างฐานข้อมูลของสารประกอบแบบไดนามิกของสารประกอบเกลือควอเตอร์นารีแอมโมเนียมแคทไอออนโดยผ่านปฏิกิริยาผันกลับได้ของการแทนที่แบบนิวคลีโอฟิลิก (S_N2' และ S_N2) ของเกลือควอเตอร์นารีแอมโมเนียม และเทอเชียรีเอมีน ในการทำปฏิกิริยาที่อุณหภูมิ 60 องศาเซลเซียสจะทำให้เกิดสารผสมที่ถูกควบคุมทางเทอร์โมไดนามิกและคิเนติกของสารประกอบควอเตอร์นารีแอมโมเนียมและเทอเชียรีเอมีนโดยใช้ไอโอไดด์เป็นเป็นนิวคลีโอฟิลิกคะตะลิสต์และได้ใช้คลื่นไมโครเวฟเป็นตัวช่วยในการเร่งปฏิกิริยาการแลกเปลี่ยนระหว่างเกลือพิริดิเนียมและอนุพันธ์ของพิริดีนนอกจากนี้ได้มีการทดลองเกี่ยวกับการทำให้เกิดของเหลวไดนามิกไอออนโดยผลการศึกษาในครั้งนี้ทำให้ขยายวงกว้างของศาสตร์ทางเคมีคอมไบเนทอเรียลแบบไดนามิก โดยผ่านปฏิกิริยาการแทนที่แบบนิวคลีโอฟิลิก

Results and Discussion

Exchange Processes between Quaternary Allyl Ammonium Salts and Tertiary Amines through S_N2'-Type Nucleophilic Substitution

Quaternary allyl ammonium salts are obtained by reaction of an allyl halide with a tertiary amine. Based on the work, mentioned above, on the racemization of optically active quaternary allyl ammonium salts, the reversibility of the process requires the dissociation into a tertiary amine and allyl halide by means of attack of the anion on the allyl double bond within the salt following an S_N2' mechanism.[15a] On the basis of this reversible reaction we have generated dynamic covalent libraries based on quaternary allyl ammonium salts and tertiary amines. The capacity of various ammoniums salts **1a**–**1e** or **3a**–**3e** (Figure 1) to undergo exchange with several aliphatic (**2a**–**e**) and *N*,*N*-dimethylaniline-type aromatic (**4a**–**e**) tertiary amines (Figure 2) was evaluated at a 1:1 ratio and at a 20 mM concentration in the absence or in the presence of iodide as nucleophilic catalyst in the form of tetraethyl- or tetrabutylammonium iodide (TEAI or TBAI, respectively).

The exchange reaction between **1a**-Br and **2a** was selected first as a model for S_N2' exchange to identify the most suitable solvent among $CDCl_3$, [D_6]DMSO, MeOD, CD_3CN, and CD_3CN/D_2O 90:10 at a 20 mM concentration. Exchange was found to occur in all of these solvents as shown in the Supporting Information. However, the best conditions for exchange were in CD_3CN at 60 °C, for which the fastest rate of exchange to give **3a**-Br and **4a** was observed (see the Supporting Information). In the reaction mixtures, a trace amount (≈3%) of the amino-Claisen product 2-allyl-*N*,*N*-dimethylaniline (**VIII**)[26] was detected in the ^{1}H NMR spectrum, which showed a characteristic peak at $\delta = 3.93$ ppm ($-CH_2CH{=}CH_2$), and was confirmed by its electrospray high-resolution mass spectrum (peak at *m*/*z* 162.128 $[M+H]^+$). To investigate the reversibility of this exchange, the reaction of **3a**-Br and **4a** under varying conditions (see the Supporting Information) did not occur even after 14 days. These results indicated that the equilibrium of the exchange reaction was irreversible, being strongly shifted towards **3a**-Br and **4a**. Another exchange was performed by mixing **1a**-Br and **2c** in CD_3CN at 60 °C, thereby yielding **3c**-Br (43%) and **4a** (40%) (see the Supporting Information). Similarly, reaction between **1a**-Br and **2d** gave the exchange products **3d**-Br and **4a** after a few hours but this reaction was irreversible.

The rate constants (see the Experimental Section) and compound distributions for the exchange reaction of **1a**-Br with the aliphatic amines (**2a**–**2e**) were determined by using

^{1}H NMR spectroscopy (Table 1). The equilibrium constants for the exchange processes were calculated from the product distributions in the cases where equilibrium had been reached (see the Experimental Section).

In all six cases, **1a**-Br underwent exchange with the aliphatic tertiary amine **2a**–**e** giving products **3a**–**e**-Br, but the reverse reactions did not take place, which indicates that the reaction was complete, with the equilibrium being strongly shifted towards the formation of the aliphatic allyl ammonium product. The addition of iodide (1 equiv TEAI) resulted in an acceleration of up to approximately twofold (see the Supporting Information). To expand the study, the exchange reaction between **3c**-Br and **2a** was evaluated in CD_3CN at 60 °C as shown in the Supporting Information. It did not produce the corresponding exchange products. Similarly, for the reverse reaction, starting from a mixture of **3a**-Br and **2c** the exchange products were not formed even after three days. These results suggested that quaternary aliphatic ammonium salt could not undergo exchange with tertiary amines.

As seen above, *N*-allyl-*N*,*N*-dimethylanilinium bromide (**1a**-Br) did exchange with aliphatic tertiary amines but these reactions were irreversible. Consequently, it appeared that to achieve reversibility, it would be necessary to perform the exchange reactions between aromatic partners. To this end, the reactions of *N*-allyl-*N*,*N*-anilinium salt (**1a**–**e**-Br) with *N*,*N*-dimethylaniline-type aromatic tertiary amines (**4a**–**e**) were investigated in CD_3CN at 60 °C at a 1:1 ratio and 60 mM final concentration with TBAI (1 equiv) as catalyst. It was found that the exchange between **1a**-Br and the aromatic tertiary amines was now indeed reversible (Figure 3). The results, compound distributions, and rate constants of the exchange reactions are listed in Table 2. The distributions were the same for both the forward and reverse reactions, which indicates that thermodynamic equilibrium had been reached. Furthermore, the reactions were accelerated by a factor of about 1.5 to 2 upon addition of iodide (TBAI) as nucleophilic catalyst.

During the exchange processes (**1e**-Br+**4a**) and (**1e**-Br+**4b**), marked line broadening was observed for the aromatic ^{1}H NMR spectroscopy signals of liberated diethylaniline both in the presence and absence of iodide ions (see the Supporting Information). This could be due to the formation of the radical cation of free diethylaniline by oxidation under the conditions of the experiments. When the corresponding iodide **1e**-I was used in the exchange reaction with **4b** (Table 2, entry 5) no such line broadening of liberated diethylaniline was observed (see the Supporting Information for more details). When *N*-allyl-4-bromo-*N*,*N*-dimethylanilinium bromide (**1d**-Br) was combined with *N*,*N*-dimethylaniline (**4a**) neither the forward nor the reverse reaction was observed. This indicated that 4-bromo-*N*,*N*-dimethylaniline was too stable and that the bromide ion was not nucleophilic enough to react at the γ-allyl carbon atom of **1d**-Br to liberate dimethyl aniline, hence, the exchange reaction did not occur but decomposition was observed.

The influence of the counter anion on the exchange reaction between quaternary allyl ammonium salts and tertiary amines

Table 1. Kinetic and thermodynamic parameters for the exchange reaction between the *N*-allyl-*N*,*N*-dimethylanilinium salts **1a**-Br and **1e**-Br and the aliphatic tertiary amines **2a**–**2e** (1:1) at 20 mM concentration in CD_3CN at 60 °C. In this table only the organic cation is indicated; all anions are bromide.

Entry	Starting compounds	[a]	Compound distribution [%][b]							k[c]	$t_{1/2}$ [h][d]
			1a	**2a**	**3a**	**4a**	**a**	**b**	**c**		
1	**1a+2a**	f_b	<1	<1	44	44	3	n.a.[e]	8	0.622	16
		f_c	<1	<1	47	48	1	<1	3	1.070	12
			1a	**2b**	**3b**	**4a**	**a**	**b**	**c**		
2	**1a+2b**	f_b	2	<1	44	44	4	n.a.[e]	4	0.530	18
		f_c	7	<1	44	44	2	<1	3	0.892	13
			1a	**2c**	**3c**	**4a**	**a**	**b**	**c**		
3	**1a+2c**	f_b	5	<1	48	44	–[f]	n.a.[e]	3	0.779	14
		f_c	6	<1	47	44	–[f]	–[f]	2	1.353	8
			1a	**2d**	**3d**	**4a**	**a**	**b**	**c**		
4	**1a+2d**	f_b	7	<1	47	46	–[f]	n.a.[e]	<1	0.672	16
		f_c	4	<1	49	47	–[f]	–[f]	<1	1.180	13
			1a	**2e**	**3e**	**4a**	**a**	**b**	**c**		
5	**1a+2e**	f_b	11	12	32	34	8	n.a.[e]	4	0.729	20
		f_c	9	5	37	39	5	<1	5	1.203	12
			1e	**2e**	**3e**	**4e**	**a**	**b**	**c**		
6	**1e+2e**	f_b	5	16	28	43	8	n.a.[e]	<1	0.056	24
		f_c	4	14	31	43	7	2	<1	0.084	18

[a] f_b, forward reaction in the absence of catalyst; f_c, forward reaction in the presence of TEAI (1 equiv) as catalyst. [b] Proportion [%] of the different compounds: **a** = allyl bromide, **b** = allyl iodide, **c** = Amino-Claisen rearrangement product. Error on ^{1}H NMR spectroscopy signal integration is ≈4%. [c] Rate constant [10^{-3} M^{-1} s^{-1}]. [d] Half-life. [e] n.a., not applicable. [f] Compound not observed.

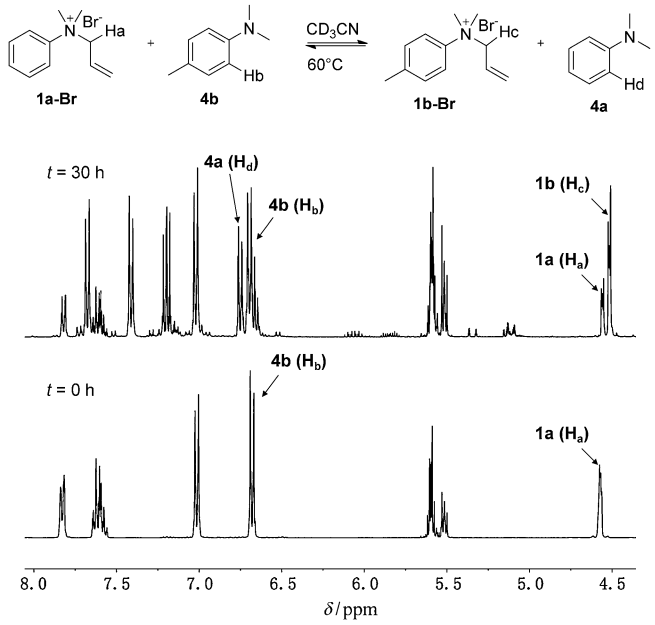


Figure 3. ^{1}H NMR spectroscopy study of the nucleophilic substitution exchange of *N*-allyl-*N*,*N*-dimethylanilinium bromide (**1a**-Br) and *N*,*N*,*4*-trimethylaniline (**4b**) by observation of the signals of the aromatic H_a and H_d proton (**4a** and **4b**) and the α-CH_2– proton signal of the allyl group (**1a**-Br and **1b**-Br), before (bottom, $t = 0$ h) and after (top, $t = 30$ h) exchange at equilibrium.

may provide information on both the role of the nucleophilicity of the anion as well as on the mechanism of the reaction, that is, whether it might also proceed by means of direct nucleophilic reaction of the amine itself at the γ-carbon atom. To this end, the ammonium salt **1a**-PF_6 with the non-nucleophilic hexafluorophosphate anion (PF_6^-) was prepared and tested for its reaction with the aromatic amine **4b** (Scheme 1). The reaction was very slow giving only 5% **1b**-PF_6 after 162 hours, about 40 times slower than that for the bromide salt. This result confirmed that as expected the nucleophilicity of the counterion (e.g., bromide or iodide) strongly influences the reaction at the γ-carbon of the allyl group to liberate dimethylaniline and allylhalide. However, the formation of a small amount of **1b**-PF_6 might also indicate that **4b** was able to react directly at the γ-carbon of the allyl chain to give the exchange product **1b**-PF_6.

In the reactions of **1a**-Br with the aliphatic amines **2a** or **2b**, small amounts of allyl bromide were detected. In contrast, for the exchange between **1a**-Br and **2c** or **2d** no allyl bromide was observed. This would suggest that **2c** or **2d** might also react to some extent directly at the γ-carbon of the allyl group of **1a**-Br (Scheme 2b). We have tested this hypothesis by treating **2c** and **2d** with the salt **1a**-PF_6 that has hexafluorophosphate as counteranion, which would not be expected to perform a nucleophilic reaction like the halides (see the Supporting Information). The results show that **3c**-PF_6 and **3d**-PF_6 do in fact form under these conditions at similar rates as for the bromide salts in the absence of iodide as catalyst ($0.172 \times 10^{-3}\,M^{-1}s^{-1}$ for **1a**-PF_6 and **2c**; $0.325 \times 10^{-3}\,M^{-1}s^{-1}$ for **1a**-PF_6 and **2d**). This indicates that direct reaction of the amine on the allyl group does indeed take place, at least partially. Furthermore, the reaction of **1a**-PF_6 with **2a** was about 20 times slower than that of **1a**-Br with **2a**. This difference in reactivity might be due to the steric bulk, which would hinder the direct reaction of the more bulky amine **2a** at the γ-carbon of the allyl group of **1a**-Br relative to amines **2c** and **2d** (see also the Supporting Information)

Mechanism of the Amine-Exchange Processes between Quaternary Allyl Ammonium Salts and Tertiary Amines

The exchange of the amine moiety between quaternary *N*-allyl-*N*,*N*-dimethylanilinium salts and a tertiary amine may occur by means of an S_N2 or S_N2' mechanism. The former occurs by direct attack of the amine on the α-carbon of the allyl group. The S_N2' process involves reaction at the γ-carbon and may itself follow either a direct (attack of the amine) or an indirect (through allyl halide formation) pathway. The latter is the mechanism described in the racemization studies.[15a] However, for the quaternary benzyl ammonium salts studied below, exchange is expected to proceed by means of S_N2 attack on the benzylic carbon center. An S_N1 process starting with dissociation of the quaternary cation may be considered unlikely in the absence of substituents stabilizing the cation formed.

The two S_N2' pathways are outlined in Scheme 2 and involve:

i) an indirect pathway (Scheme 2a) involving a) the nucleophilic attack of a bromide anion at the γ-carbon of the allyl group of the *N*-allyl-*N*,*N*-dimethylanilinium salt (**I**) to liberate *N*,*N*-dimethylaniline (**II**) and allylbromide (**III**), b) subsequent reaction of **III** with the introduced tertiary amine **IV** or **VI** to furnish the exchange product **V** or **VII** in an irreversible or a reversible process, respectively, with an aliphatic **IV** or an aromatic **VI** tertiary amine.

ii) a direct pathway (Scheme 2b) whereby the tertiary amine introduced reacts directly at the γ-carbon of the allyl group to provide the exchange product **V** or **VII**.

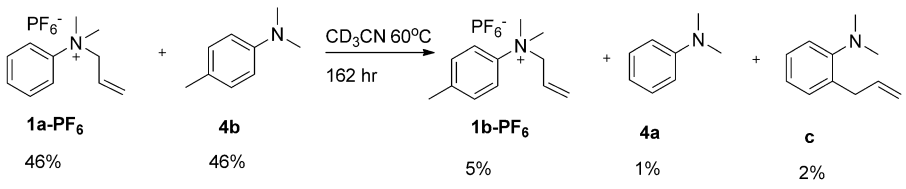
In addition, trace amounts of the amino-Claisen rearrangement product of the *N*-allyl-*N*,*N*-dimethylanilinium cation were also observed as a side reaction during the exchange process.

Taken together, the results obtained indicate that the exchange reactions studied here may occur by the indirect pathway, via intermediate allyl bromide/halide as well as by the direct pathway, by attack on the free amine at the γ-carbon of the allyl group. The presence of catalytic iodide anions may be expected to favor the indirect pathway via the formation of allyl iodide. Some comments can be made on the basis of the results obtained: 1) much faster exchange rates for bromide than for PF_6^- salts are observed for the aromatic aniline compounds together with the formation of allyl bromide, which favors an indirect S_N2' mechanism (entries 1 and 3 in Table 2); 2) with the more nucleophilic aliphatic benzylamines there is a comparatively small rate difference between bromide and PF_6^- salts and no allylbromide is observed, which indicates that the direct mechanism is favored (entries 3 and 4 in Table 1); 3) steric bulk also affects the exchange process, slowing down the rate and shifting it towards the indirect mechanism, as is particularly notable in the case of N(diethyl) on

Table 2. Kinetic and thermodynamic parameters for the exchange reaction between the *N*-allyl-*N*,*N*-anilinium salts **1a**–**1e** and the *N*,*N*-dimethylaniline-type aromatic tertiary amines **4a**–**4e** (1:1) at 60 mM concentration in CD_3CN at 60 °C. In this table only the organic cation is indicated; all anions are bromide except entries 5 and 6 where the anions are iodides.

Entry	Starting compounds	[a]	Compound distribution [%][b]								k[c]	$t_{1/2}$ [h]	K_b[d]	K_c[e]
			1a	**4b**	**1b**	**4a**	**a**	**b**	**c**	**d**				
1	**1a**+**4b**	f_b	13	19	28	29	4	n.a.[f]	4	3	0.252	11	4.5	4.9
		f_c	13	18	29	33	3	1	2	1	0.516	6		
	1b+**4a**	r_b	10	16	25	40	4	n.a.[f]	2	3	0.177	9		
		r_c	11	15	25	40	3	1	1	3	0.283	4		
			1a	**4c**	**1c**	**4a**	**a**	**b**	**c**	**d**				
2	**1a**+**4c**	f_b	9	13	36	35	3	n.a.[f]	4	–[g]	0.353	10	14.2	12.9
		f_c	10	14	36	35	2	<1	2	–[g]	0.598	6		
	1c+**4a**	r_b	8	10	39	39	3	n.a.[f]	2	–[g]	0.089	13		
		r_c	8	9	39	39	2	<1	2	–[g]	0.097	8		
			1e	**4a**	**1a**	**4e**	**a**	**b**	**c**	**d**				
3	**1e**+**4a**	f_b	6	27	19	34	10	n.a.[f]	2	2	0.266	13	10.7	10.8
		f_c	5	22	22	37	9	2	1	2	0.522	10		
	1a+**4e**	r_b	2	19	20	42	13	n.a.[f]	–[g]	4	0.372	6		
		r_c	3	18	22	42	10	<1	2	3	0.501	3		
			1e	**4b**	**1b**	**4e**	**a**	**b**	**c**	**d**				
4	**1e**+**4b**	f_b	6	15	28	40	7	n.a.[f]	3	1	0.217	14	22.3	26.1
		f_c	6	14	31	40	4	1	3	1	0.358	9		
	1b+**4e**	r_b	2	12	28	46	8	n.a.[f]	2	2	0.244	5		
		r_c	2	11	29	47	6	1	3	1	0.236	2		
	anion I^-		**1e**	**4b**	**1b**	**4e**	**a**	**b**	**c**	**d**				
5	**1e**+**4b**	f_b	4	9	34	45	n.a.[f]	3	2	3	0.385	11	46.2	
	1b+**4e**	r_b	4	7	31	46	n.a.[f]	3	5	4	0.155	10		
	anion I^-		**1a**	**4b**	**1b**	**4a**	**a**	**b**	**C**	**d**				
6	**1a**+**4b**	f_b	13	21	33	29	n.a.[f]	3	1	–[g]	0.483	6	4.2	
	1b+**4a**	r_b	14	15	30	36	n.a.[f]	2	3	–[g]	0.234	6		
7	**1d**+**4a**	f_b	no reaction											
		f_c	no reaction											

[a] f_b, forward reaction in the absence of catalyst; f_c, forward reaction in the presence of TBAI (1 equiv) as catalyst; r_b, reverse reaction in the absence of catalyst; r_c, reverse reaction in the presence of TBAI (1 equiv) as catalyst. [b] Proportion [%] of the different compounds: **a** = allyl bromide, **b** = allyl iodide, **c** and **d** = amino-Claisen rearrangement products. Error on ^{1}H NMR spectroscopy signal integration, ≈4%. [c] k, rate constant [10^{-3} M^{-1}s^{-1}]. [d] K_b, equilibrium constant of the blank reaction. [e] K_c, equilibrium constant of the catalyzed reaction. [f] n.a., not applicable. [g] Compound not observed.



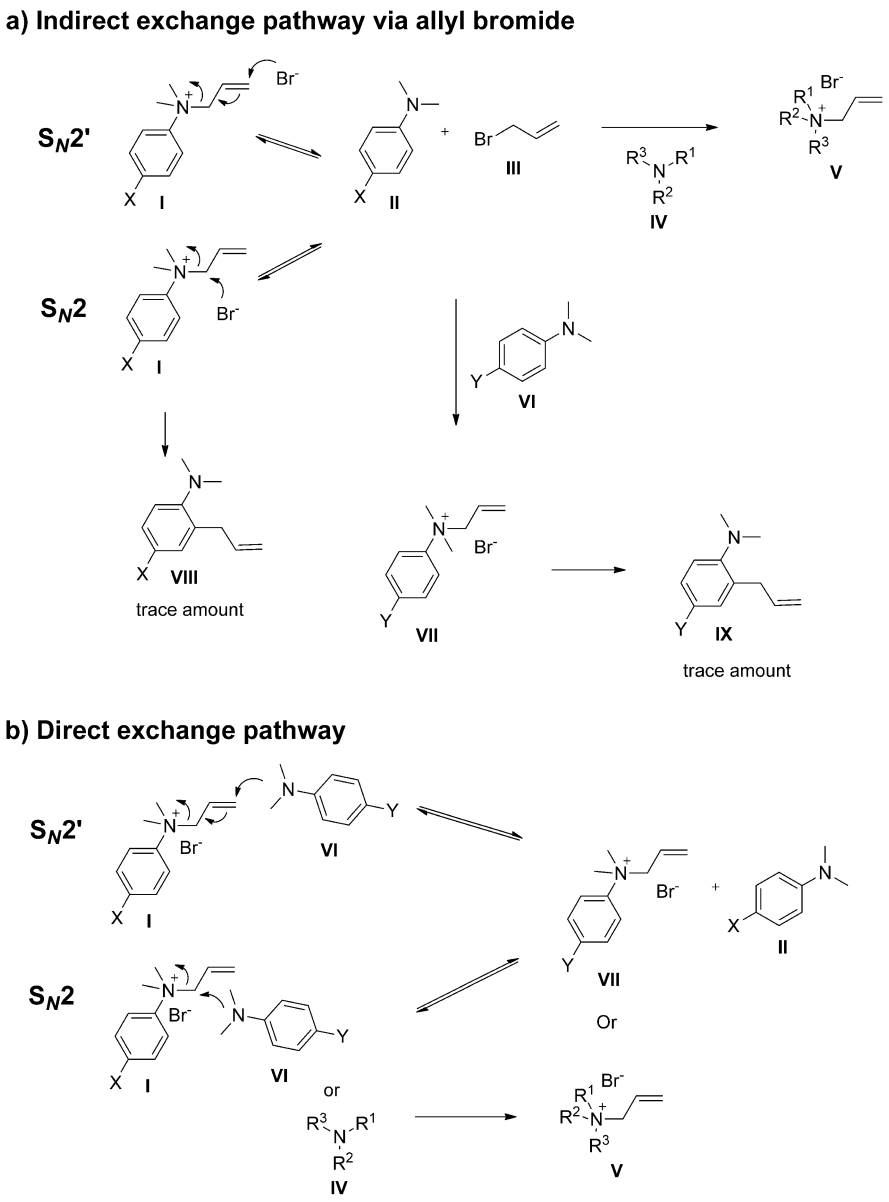
Scheme 1. Exchange reaction of **1a**-PF_6 and **4b**. Percentage (±4%) of compounds after 162 h reaction time. **c** = Amino-Claisen rearrangement product.

both partners (entry 6, Table 1). Of course, the different mechanisms probably coexist and may be favored depending on various factors (nucleophilicity of the amine, steric bulk, nature of the counteranion, etc.).

Exchange processes between quaternary benzyl ammonium salts and tertiary amines by means of S_N2-type nucleophilic substitution

DCC involving exchange of the tertiary amine may also take place with quaternary benzyl ammonium salts. Along these lines, we extended the generation of DCLs of quaternary ammonium cations by the exploring amine-exchange reactions between the *N*-benzyl-*N*,*N*-dimethylanilinium salts (**5a**–**c**-Br) and the tertiary amines (**4a**–**c**).

An evaluation of the effect of the iodide anion as catalyst by addition of tetrabutylammonium iodide (TBAI) on the exchange reaction of **5a**-Br and **4b** (see the Supporting Information) indicated similar reaction rates using one or two equiva-



Scheme 2. Possible pathways for exchange of the amine moiety between *N*-allyl-*N*,*N*-dimethylanilinium bromide and an aliphatic or aromatic tertiary amine by means of an S_N2' mechanism.

lents. Therefore, addition of one equivalent of iodide was chosen for the exchange study. The exchange reactions between the salts **5a**–**c**-Br and the tertiary dimethylaniline amines **4a**–**c** were studied in CD_3CN at 60 °C as depicted in Table 3. The reactions in the forward and reverse directions gave similar product distributions, which indicated that they were reversible and at thermodynamic equilibrium. They also were approximately twofold faster in both directions on addition of iodide (1 equiv). To investigate the role of the bromide ion in assisting the exchange reaction, the salt **5a**-OTf was prepared by exchange of the bromide ion of **5a**-Br against trifluoromethanesulfonate (OTf^-) as counterion. The exchange of **5a**-OTf and **4b** (see the Supporting Information) was slower than **5a**-Br and **4b** by a factor of about 76, which confirmed that the presence of the nucleophile bromide strongly increased the rate of reaction. Similarly, the reaction of **5a**-PF_6 (PF_6^- as a counter anion) with **4b** (see the Supporting Information), gave the exchange products **5b**-PF_6 (13%) and **4a** (13%) at 137 hours, which is slower than **5a**-Br and **4b** by a factor of 215. In comparison, the exchange reaction of quaternary benzyl ammonium salts with aromatic tertiary amine (**5a**-Br+**4b**, Table 3, entry 1; rate constant $6.66\times10^{-3}\,M^{-1}s^{-1}$) was faster than the exchange of quaternary allyl ammonium salt (**1a**-Br+**4b**; rate constant $0.663\times10^{-3}\,M^{-1}s^{-1}$, with a final solution 20 mM) by about tenfold.

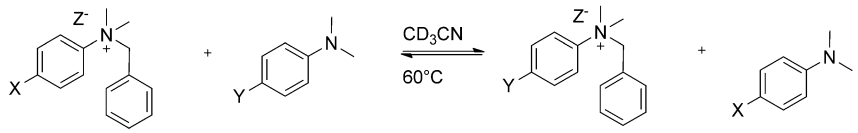
As in the case of quaternary allyl ammonium salts discussed above, the mechanism of the exchange of the tertiary amine moiety between quaternary *N*-benzyl-*N*,*N*-dimethylanilinium salts and a tertiary amine takes place following two mechanistic pathways both of S_N2 type as outlined in Scheme 3:

i) an indirect pathway (Scheme 3a) involving 1) the nucleophilic attack of a bromide anion at the CH_2 carbon of the benzyl group of the quaternary *N*-benzyl-*N*,*N*-dimethylanilinium cation (**IX**) to liberate the *N*,*N*-dimethylaniline (**II**) and benzylbromide (**X**), 2) subsequent reaction of **X** with the introduced tertiary amine **VI** giving the exchange product **XI** in a reversible process.

ii) a direct pathway (Scheme 3b) whereby the tertiary amine **VI** introduced reacts directly at the CH_2 carbon of the benzyl group of **IX** to provide the exchange product **XI**.

As in the previous case, for the allyl anilinium quaternary cations, the much slower reaction observed when PF_6^- or OTf^- were used as counteranions as compared to bromide indicates that the exchange processes studied here occur mainly through the indirect pathway (Scheme 3a) via intermediate benzyl bromide/halide, with negligible if any participation of the direct pathway (Scheme 3b). Thus, the exchange rate is much slower for (benzyl) **5a**-PF_6+**4b** than for **5a**-Br+**4b**, and the change from bromide to PF_6^- slows down the rate much more for the benzylic cations than for the comparable allyl cations (compare (benzyl) **5a**-PF_6+**4b** 215 times slower than **5a**-Br+**4b**; (allyl) **1a**-PF_6+**4b** 40 times slower than **1a**-Br+**4b**).

Table 3. Kinetic and thermodynamic parameters for the exchange reaction between the *N*-benzyl-*N*,*N*-anilinium salts **5a**–**5c** and the *N*,*N*-dimethylaniline-type aromatic tertiary amines **4a**–**4c** (1:1) at 20 mM concentration in CD_3CN at 60 °C. In this table only the organic cation is indicated; all anions are bromide.



5a-Br; X= H, Z = Br
5a-OTf; X= H, Z = OTf
5a-PF_6; X= H, Z = OMe
5b-Br; X= Me, Z = Br
5b-OTf; X= Me, Z = OTf
5b-PF_6; X= Me Z = OMe
5c-Br ; X = OMe, Z = Br

4a; Y = H
4b; Y = Me
4c; Y = OMe

Entry	Starting compounds	[a]	Compound distribution [%][b]						k[c]	$t_{1/2}$ [h]		K_b[d]	K_c[e]
			5a	**4b**	**5b**	**4a**	**a**	**b**					
1	**5a**+**4b**	f_b	6	32	23	30	9	n.a.[f]	6.66	1.5		4.6	4.3
		f_c	6	34	23	29	6	2	12.3	0.9			
	5b+**4a**	r_b	7	20	25	35	13	n.a.[f]	2.72	1.8			
		r_c	7	20	21	39	10	3	5.83	1.2			
			5a	**4c**	**5c**	**4a**	**a**	**b**					
2	**5a**+**4c**	f_b	6	10	33	41	10	n.a.[f]	5.40	2.0		22.0	23.7
		f_c	6	8	34	42	7	2	10.7	1.1			
	5c+**4a**	r_b	4	14	29	44	8	n.a.[f]	2.31	1.5			
		r_c	5	13	29	45	6	2	2.90	1.1			

[a] f_b, forward reaction in the absence of catalyst; f_c, forward reaction in the presence of TBAI (1 equiv) as catalyst; r_b, reverse reaction in the absence of catalyst; r_c, reverse reaction in the presence of TBAI (1 equiv) as catalyst. [b] Proportion [%] of the different compounds: **a** = benzyl bromide, **b** = benzyl iodide. Error on ^{1}H NMR spectroscopy signal integration, ≈4%. [c] k, rate constant [10^{-3} M^{-1} s^{-1}]. [d] K_b, equilibrium constant of the blank reaction. [e] K_c, equilibrium constant of the catalyzed reaction. [f] n.a., not applicable.

Exchange Processes between *N*-Allyl- and *N*-Benzylpyridinium Salts and Pyridine Components by Means of S_N2 and S_N2' Nucleophilic Substitution Processes

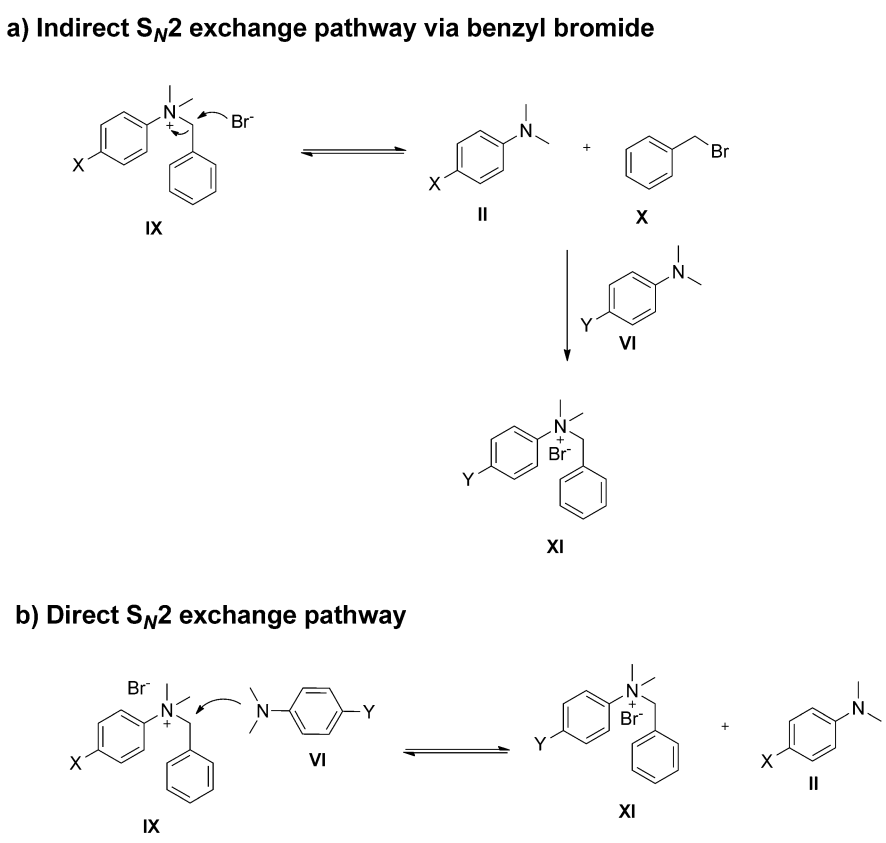
To further extend the range of DCLs generated by nucleophilic substitution processes of S_N2 and S_N2' types, we investigated the exchange reactions between the *N*-benzyl- and *N*-allylpyridinium salts **6a**–**6f** and pyridine derivatives **7a**–**7d**. Initial exploration of solvents and temperatures (see the Supporting Information) led to the use of microwave irradiation at 150 °C (300 W) for 60 min in [D_3]acetonitrile, which provided the best reaction conditions. The composition of the final solutions and the corresponding equilibrium constants (K_{eq}) are listed in Table 4.

In terms of exchange mechanisms and on the basis of the discussions above concerning both the quaternary allyl- and benzylanilinium compounds, the reactions of Table 4 involving the *N*-benzylpyridinium bromides may be considered to occur through an S_N2 pathway with direct attack of the bromide anion on the benzylic CH_2 center and formation of benzyl bromide, which then reacts further with the added pyridine, in analogy to the discussion above (Scheme 3a).

The ability of pyridinium salts and pyridine derivatives to undergo interconversion was followed by considering the effect of *ortho* and *para* substitution on pyridine derivatives. The component exchange between **6a** and 2-methylpyridine resulted in the starting compounds **6a** (26%), 2-methylpyridine (38%), and exchange products 1-benzyl-2-methylpyridinium bromide (12%), pyridine (17%), and benzylbromide (7%). Owing to steric hindrance at the *ortho* position in 2-methylpyridine, only a small amount of the exchange product was obtained, together with a significant amount of liberated benzylbromide. Therefore, for the following investigations, only *para*-substituted pyridine derivatives (**7a**–**d**) were used, which gave the results shown in Table 4. The interconversion between **6a** and **7b** (Figure 4 and Table 4, entry 1) and the reverse reaction under the conditions mentioned above gave the exchange products **6b** (35%) and **7a** (33%) with a trace amount of benzylbromide (2%).

Next, the reaction of the pyridinium salt **6a** and pyridine **7c** (bearing the electron-donating dimethylamino group in the *para* position) under the same conditions afforded **6c** (50%) and **7a** (50%) (Table 4, entry 2). The full conversion indicated that this reaction would not be reversible. Indeed, similar treatment of (**6c**+**7a**) did not provide the exchange products, which confirmed that this process was irreversible. In contrast, exchange between **6a** and **7d** afforded **6d** and **7a** and was reversible (Table 4, entry 3) and thus at thermodynamic equilibrium.

The exchange of the pyridine component of allylpyridinium salts was investigated by combining the *N*-allylpyridinium bromide **6e** and pyridine **7b**. The reaction yielded **6f** and **7a** in



Scheme 3. Pathways for exchange of the tertiary amine moiety between *N*-benzyl-*N*,*N*-dimethylanilinium bromide and an aromatic tertiary amine by means of an S_N2 mechanism.

30 and 29% proportions together with 3% free allyl bromide (Table 4, entry 4). The reversibility was studied by starting with **6f** and **7a**, which afforded products **6e** (11%) and **7b** (16%) in a mixture of a similar composition to that obtained in the forward process, thus indicating thermodynamic equilibrium. In line with the discussion above, the mechanism of the exchange involving the *N*-allylpyridinium salts may in principle occur by S_N2 as well as by direct or indirect S_N2' pathways with attack of the pyridine component either at the α- or at the γ-carbon atom of the allyl group of the pyridinium cation (see discussion above and Scheme 2).

Finally, cross-exchange between *N*-benzyl and *N*-allylpyridinium salts involving nucleophilic substitution interconversion by both S_N2' and S_N2 pathways was investigated by combining **6b** and **6e**. The desired products **6f** (16%) and **6a** (9%) were observed together with significant amounts of other released components as shown in Table 5. This reaction was shown to be reversible by mixing **6f** and **6a**, which gave products **6e** (6%) and **6b** (14%). The forward reaction was also conducted for 90 min and afforded a similar distribution as for 30 min, which indicated that equilibrium was reached after 30 min. The reverse reaction was slower and equilibrium was not reached after 90 min.

Generation of Libraries of Dynamic Ionic Liquids (DILs)

Ionic liquids have attracted high interest and acquired much importance in many areas of chemistry.[27] They usually involve organic quaternary cations, in particular, imidazolium and pyridinium derivatives.[25] We thus were interested in the possibility of generating dynamic libraries of ionic liquids, which might have specific properties not presented by those based on "static" constituents. Considering the results obtained for the pyridinium salts, in particular **6e** and **6f**, we performed some experiments aimed at the generation of dynamic libraries of ionic liquids.

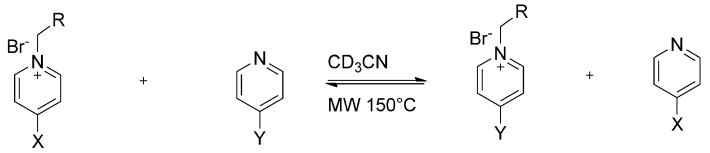
With this in mind, we have investigated the exchange reaction of pyridinium salts with derivatives of pyridine in the absence of added molecular solvent by taking into account that **6e** and **6f** are known to be ionic liquids.[25] Combining **6e** and **7b** in a ratio of 1:2 afforded **6f** (11%) and **7a** (19%) as the exchange products (Scheme 4a) together with some free allyl bromide (8%). However, the reaction medium became colored, which indicated that some decomposition had taken place.

Of special interest is the generation of a DIL library by component exchange in the solid state, that is, from solid constituents. Thus, starting from a mixture of the two solid precursors **6e** and **6b**, in the absence of solvent, and heated by microwave irradiation, a very viscous ionic liquid was obtained with the composition **6e** (18%), **6b** (35%), **6f** (17%), and **6a** (30%) (Scheme 4b). These results, although limited at this stage, demonstrate that DIL libraries may, in principle, be generated from solid materials. One may point out that such a passage from the solid to the liquid phase also raises the question as to whether it may be accompanied by a component selection, that is, whether component exchange and selection would lead to those constituents that provide the ionic liquid presenting the lowest solidification temperature.

As it seems that no ionic liquids based on anilinium salts have been reported, the exchange reaction between **5b**-Br and **1c**-Br was tried in the absence of solvent. Only decomposition of the components was observed after heating.

Finally, we also investigated the nucleophilic substitution exchange of ionic-liquid constituents derived from imidazole derivatives under the same conditions as those used for the pyridinium salts. However, the imidazolium salts used were highly

Table 4. Component exchange between the *N*-benzylpyridinium salts (**6a–f**) and the pyridines (**7a–d**) in CD_3CN under microwave irradiation (300 W) at 150 °C for 60 min.



6a R = Ph; X = H
6b R = Ph; X = Me
6c R = Ph; X = NMe_2
6d R = Ph; X = $C(Me)_3$
6e R = $CH{=}CH_2$; X = H
6f R = $CH{=}CH_2$; X = Me

7a Y = H
7b Y = Me
7c Y = NMe_2
7d Y = $C(Me)_3$

Entry	Starting compounds	[a]	Compound distribution [%][b]					K_{eq}
			6a	**7b**	**6b**	**7a**	**a**	
1	**6a**+**7b**	f	14	16	35	33	2	5.16
	6b+**7a**	r	14	16	35	33	2	
			6a	**7c**	**6c**	**7a**	**a**	
2	**6a**+**7c**	f	–[c]	–[c]	50	50	–[c]	n.d.[d]
	6c+**7a**	r	–[c]	–[c]	50	50	–[c]	
			6a	**7d**	**6d**	**7a**	**a**	
3	**6a**+**7d**	f	13	15	36	33	3	6.23
	6d+**7a**	r	12	16	35	35	2	
			6e	**7b**	**6f**	**7a**	**b**	
4	**6e**+**7b**	f	16	22	30	29	3	3.99
	6f+**7a**	r	11	16	34	35	4	

[a] f, forward reaction; r, reverse reaction. [b] Proportion [%] of the different compounds. **a** = benzyl bromide and **b** = allyl bromide. Error on ^{1}H NMR spectroscopy signal integration, ≈4%. [c] Compound not observed. [d] n.d., not determined.

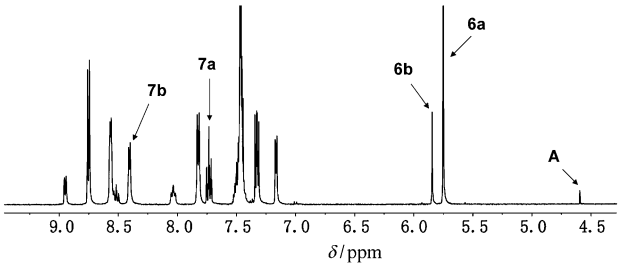


Figure 4. ^{1}H NMR spectrum of the distribution of constituents obtained by component exchange between **6a** (14%) and **7b** (16%) to give products **6b** (35%) and **7a** (33%) at equilibrium. The characteristic $-CH_2-$Ph signals are indicated for **6a**, **6b**, and benzylbromide (**A**), 4-methylpyridine (**7b**), and pyridine (**7a**).

Table 5. Reversible component cross-exchange between *N*-benzyl- (**6a**, **6b**) and *N*-allyl- (**6e**, **6f**) pyridinium bromides in CD_3CN using microwave irradiation (300 W) at 150 °C.

Reaction	*t* [min]	[a]	Compound distribution [%][b]				
			6e	**6b**	**6f**	**6a**	**7a/7b/a/b**
6b+**6e**	30	f	16	27	12	9	13:5:6:11
	90	f	16	25	15	12	13:4:5:10
6f+**6a**	30	r	6	14	25	17	16:3:10:9
	90	r	9	17	25	18	14:3:7:8

[a] f, Forward reaction; r, reverse reaction. [b] Proportion [%] of the different compounds. **7a** = pyridine, **7b** = 4-methylpyridine, **a** = benzyl bromide, and **b** = allyl bromide. Error on ^{1}H NMR spectroscopy signal integration, ≈4%.

stable and not able to exchange with other components (see the Supporting Information for more details).

Conclusion

The results described here extend dynamic covalent chemistry to both a new class of constituents, quaternary ammonium salts, and a new class of dynamic reactions, nucleophilic substitutions. They are thus of interest whenever processes implementing such compounds and transformations are pursued. They also suggest further exploration, for instance, towards exchanges and DCLs based on other nucleophilic substitution reactions (e.g., R–X/R′–Y) or towards other classes of compounds such as quaternary phosphonium salts,[39] or also towards other types of applications such as the generation of dynamic ionic liquid phases, thus pushing further the realm of dynamic structural diversity and functional complexity.

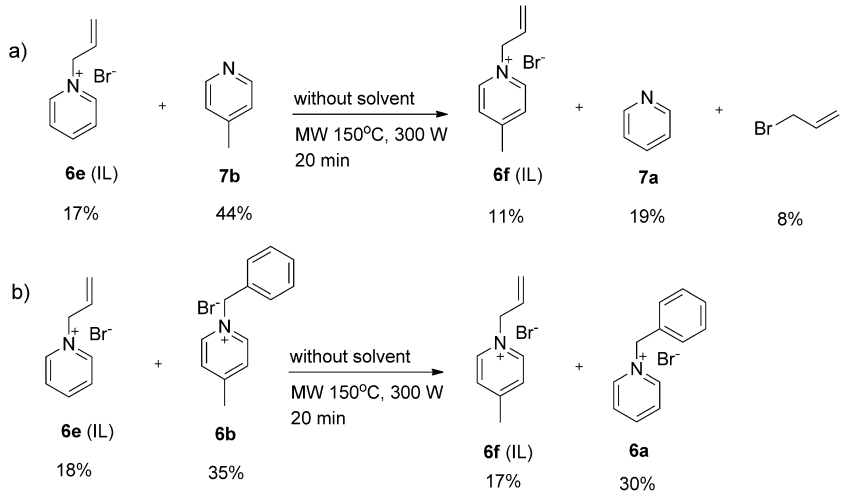
Experimental Section

General Aspects

All reagents and solvents were purchased at the highest commercial quality and used without further purification. Reagents: diethylaniline (99.5%), *p*-anisidine (99%), 4-bromo-*N*,*N*-dimethylaniline (97%), *N*,*N*,4-trimethylaniline (99%), *N*-ethylmethylamine (98%), *N*,*N*-dimethylbenzylamine (99%), *N*,*N*-dimethyl ethanolamine (99.5%), allyl bromide (99%), allyl iodide (98%), potassium hexafluorophosphate (98%), potassium trifluoromethanesulfonate (98%), 4-picoline (99%), 4-dimethylaminopyridine (99%), and TEAI (98%) were purchased from Sigma–Aldrich. *N*,*N*-Dimethylaniline (99%) was purchased from Alfa Aesar. Triethylamine (99%) was purchased from Riedel-de Haën. Benzylbromide (99.5%) and pyridine (99%) were purchased from Acros Organics. 4-(*tert*-Butylamino)-pyridine (99%) and TBAI (98%) were purchased from Janssen Chimica. Deuterated solvents were purchased from Euriso-TOP and used without further purification. Column chromatography (CC): Gedurun silica gel 60 (230–400 mesh, 40–63 μm, Merck). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer; referenced to the solvent; δ in ppm, *J* in Hz. M.p.: Büchi B-540 apparatus. Microwave irradiation was performed on the apparatus from CEM Innovators in Microwave Technology. High-resolution (HR) MS: Bruker Micro TOF mass spectrometer; in *m/z* (rel.%).

General Procedure for the Quaternary Ammonium Salt and Tertiary Amine Exchange

Stock solutions (0.5 mL) of ammonium salt (60 or 180 mM), tertiary amine (60 or 180 mM), TEAI (60 mM), and TBAI stock solution



Scheme 4. Exchange reaction between a) **6e** and **7b** and b) **6e** and **6b** in the absence of molecular solvent under microwave irradiation at 150 °C for 20 min.

(180 mM) were prepared in the desired solvent. For the uncatalyzed reaction, 200 μL of each solution was added to a NMR spectroscopy tube followed by solvent (200 μL) to adjust to a final volume of 600 μL. For the catalyzed reaction, iodide stock solution (200 μL) was added to a NMR spectroscopy tube, followed by the addition of each solution (200 μL). The 60 mM stock solution was used for the final solution of 20 mM and the 180 mM stock solution was used for the final solution of 60 mM.

General Procedure for *N*-Benzyl-*N*,*N*-dimethylanilinium Salts and Tertiary Amines Exchange

Stock solutions (0.5 mL) of *N*-benzyl-*N*,*N*-dimethylanilinium salts (60 mM), tertiary amine (60 mM), and TBAI (60 mM) in CD_3CN were prepared. Then, each stock solution (200 μL) was added to a NMR spectroscopy tube to obtain a final volume of 600 μL. The final solution was 20 mM in each component.

General Procedure for Exchange between Pyridinium Salts and Pyridine Derivatives using Microwave Irradiation

Stock solutions (500 μL) of pyridinium salt (40 mM) and tertiary amine or the derivative of pyridine (40 mM) in CD_3CN were prepared. Then, each stock solution (400 μL) was added to a microwave tube to give a final volume of 800 μL.

General Procedure for Kinetic and Thermodynamic Measurement of Exchange Reactions between Quaternary Ammonium Salts and Tertiary Amines

The concentrations of each component were determined by integration of the *N*-allyl-*N*,*N*-dimethylanilinium salts $CH_2{=}CH_2{-}Ph$, *N*-benzyl-*N*,*N*-dimethylanilinium salts $-CH_2$-Ph, tertiary amine $-N(CH_3)_2$, allyl bromide $CH_2{=}CH_2{-}Br$, and benzyl bromide $Br{-}CH_2{-}Ph$ ^{1}H NMR spectroscopy signals as a function of time. The reaction rate constants were calculated from plots of reactant concentration versus time during the first 10% of the reaction, for which $[A]_0 = [B]_0$.[28] It was found that [A] and [B] reacted in a 1:1 stoichiometric ratio over this timescale. The plot of 1/[A] (or 1/[B]) versus time was linear. This is consistent with an overall second-order reaction at the beginning of the reaction, and first order in [A] and [B], respectively. The half-lives ($t_{1/2}$) of the reactions were determined by integration of the decreasing ^{1}H NMR spectroscopy signals of the starting material as a function of time and taken to be the time at which the starting material was reduced to 50% with respect to the equilibrium value. The equilibrium constants were obtained from the amounts of reactants and products according to Equation (1):

$$K_{eq} = [C][D]/[A][B] \quad (1)$$

Synthesis and Characterization

N-Allyl-N,N-*dimethylbenzenaminium bromide (1 a-Br)*[26a]

The oil bath was preheated to 100 °C. Then dimethylaniline (0.38 mL, 3.0 mmol) was mixed with allylbromide (1.56 mL, 18.0 mmol) and heated at reflux for 2 h. The white precipitate appeared as the reaction progressed, eventually becoming a pink solid. The reaction mixture was allowed to cool to room temperature. Then, the mixture was washed by diethyl ether and dried under vacuum for 4 h to afford **1 a**-Br as a white solid (0.55 g, 76% yield). M.p. not determined; hygroscopic white solid. ^{1}H NMR (400 MHz, CD_3CN): $\delta = 7.82$ (d, $J = 8.1$ Hz, 2H), 7.60 (m, 3H), 5.59 (m, 2H), 5.52 (m, 1H), 4.55 (dd, $J = 1.8$ Hz, 2H), 3.58 ppm (s, 6H).

N-Allyl-N,N,*4-trimethylbenzenaminium (1 b-Br)*[26b]

4,*N*,*N*-Trimethylaniline (0.87 mL, 6.0 mmol) and allylbromide (1.0 mL, 12.0 mmol) were combined in acetone. The solution was heated at reflux for 4 h and then the solvent was removed by evaporation. The product was dried under vacuum to afford **1 b**-Br as a yellow liquid (1.235 g, 81% yield). M.p. not determined; liquid at room temperature. ^{1}H NMR (400 MHz, CD_3CN): $\delta = 7.68$ (d, $J = 8.7$ Hz, 2H), 7.41 (d, $J = 8.7$ Hz, 2H), 5.59 (m, 2H), 5.51 (m, 1H), 4.52 (br, 2H), 3.55 (s, 6H), 2.39 ppm (s, 3H).

N-Allyl-4-methoxy-N,N-*dimethylbenzenaminium bromide (1 c-Br)*[29]

4-Methoxy-*N*,*N*-dimethylaniline (**4 c**) (0.4533 g, 3.0 mmol) was combined with allylbromide (0.78 mL, 9.0 mmol). The reaction was stirred at 40 °C for 10 min and the white solid precipitated as the reaction went on. The product was washed with diethyl ether and dried under vacuum for 4 h to afford **1 c**-Br as a white solid (0.6052, 74% yield). M.p. 139 °C (Ref. [29]: 141–142 °C); ^{1}H NMR (400 MHz, CD_3CN): $\delta = 7.82$ (d, $J = 8$ Hz, 2H), 7.04 (d, $J = 9.3$ Hz, 2H), 5.79 (d, $J = 16.9$ Hz, 1H), 5.44 (m, 2H), 5.08 (d, $J = 6.8$ Hz, 2H), 3.90 (s, 6H), 3.83 ppm (s, 3H).

N-Allyl-4-bromo-N,N-*dimethylbenzenaminium bromide (1 d-Br)*[30]

Prepared in 25% yield as a white solid analogous to the route described for **1 c**. M.p. 148 °C (Ref. [30]: 151–152 °C); ^{1}H NMR

(400 MHz, CD_3CN): $\delta = 7.79$ (d, $J = 9.4$ Hz, 2H), 7.68 (d, $J = 9.2$ Hz, 2H), 5.61 (m, 3H), 4.42 (d, $J = 6.3$ Hz, 2H), 3.52 ppm (s, 6H).

***N-Allyl*-N,N-*dimethylbenzenaminium iodide* (*1a*-*I*)[30]**

To a stirred solution of dimethylaniline (0.38 mL, 3.0 mmol) was added allyl iodide (0.82 mL, 9.0 mmol), and the solution was heated at 30 °C overnight. The solution became yellow as the reaction went on. The solvent was removed by evaporation and dried under vacuum for 3 h to obtain a dark brown solid (0.860 g, 99% yield). M.p. 87–88 °C (Ref. [30]: 87–88 °C); ^{1}H NMR (400 MHz, CD_3CN): $\delta = 7.75$ (d, $J = 8.2$ Hz, 2H), 7.61 (m, 3H), 5.59 (m, 3H), 4.44 (d, $J = 5.6$, 2H), 3.53 ppm (s, 6H).

***N-Allyl*-N,N,*4-trimethylbenzenaminium iodide* (*1b*-*I*).**

Prepared in 90% yield as an orange liquid by a route analogous to that described for **1e**-Br. M.p. not determined; liquid at room temperature. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.76$ (d, $J = 7.4$, 2H), 7.42 (d, $J = 8.8$ Hz, 2H), 5.87 (d, $J = 16$ Hz, 1H), 5.58 (d, $J = 10$ Hz, 1H), 5.49 (m, 1H), 5.07 (d, $J = 7.4$ Hz, 2H), 3.93 (s, 6H), 2.44 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.0$, 54.6, 71.1, 120.8, 124.8, 129.9, 131.4, 141.3 ppm; ESI-MS: *m/z* calcd (%) for $C_{12}H_{18}N^+$: 176.143 [M^+]; found 176.142 (100); HR-ESI-MS: *m/z* calcd (%) for $C_{12}H_{17}IN^+$: 302.0400 [M^+]; found: 302.0369 (100).

***N-Allyl*-N,N-*diethylbenzenaminium bromide* (*1e*-*Br*)[31]**

Diethylaniline (0.48 mL, 3.0 mmol) and allyl bromide (0.78 mL, 9.0 mmol) were combined and kept stirring at 50 °C for 48 h. The white solid was precipitated then washed with diethyl ether. The product was dried under vacuum to obtain a white solid (0.702, 87% yield). M.p. 144–146 °C; ^{1}H NMR (400 MHz, CD_3CN): $\delta = 7.72$ (br, 2H), 7.63 (m, 3H), 5.69 (m, 3H), 4.38 (d, $J = 7.1$ Hz, 2H), 3.81 (m, 4H), 1.10 ppm (t, $J = 7.1$ Hz, 6H).

***N-Allyl*-N,N-*diethylbenzenaminium iodide* (*1e*-*I*)**

Prepared in 98% yield as a white solid by a route analogous to that described for **1e**-Br. M.p. 105–106 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.96$ (d, $J = 8.5$, 2H), 7.65 (t, $J = 7.8$ Hz, 2H), 7.54 (t, $J = 7.4$ Hz, 1H), 5.62–5.79 (m, 3H), 4.65 (d, $J = 5.9$ Hz, 2H), 4.20 (dt, $J = 7.3$, 2H), 4.07 (dt, $J = 7.2$ Hz, 2H), 1.22 ppm (t, $J = 7.0$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 8.8$, 58.0, 63.3, 122.7, 124.2, 129.4, 130.8, 131.3, 141.4 ppm; ESI-MS: *m/z* calcd (%) for $C_{13}H_{20}N^+$: 190.159 [M^+]; found: 190.158 (100); HR-ESI-MS: *m/z* calcd (%) for $C_{13}H_{19}IN^+$: 302.0557 [M^+]; found: 316.0529 (100).

***N-Allyl*-N,N-*dimethylbenzenaminium hexafluorophosphate* (*1a*-PF_6).**

N-Allyl-*N*,*N*-dimethylbenzenaminium bromide (**1a**-Br) (0.072 g, 0.3 mmol) was dissolved in water (1 mL) and combined with a saturated solution of potassium hexafluorophosphate in water. A white solid immediately precipitated. The compound was extracted with dichloromethane and dried with magnesium sulfate. The solvent was removed by evaporation to afford a pink solid and was then recrystallized by dichloromethane/diethyl ether to afford **1a**-PF_6 (0.08 g, 87% yield; m.p. 88–90 °C). The compound was tested with silver nitrate ($AgNO_3$) to demonstrate the absence of bromide ions. ^{1}H NMR (400 MHz, CD_3CN): $\delta = 7.57$–7.70 (m, 5H), 5.49–5.65 (m, 3H), 4.32 (d, $J = 6.1$, 2H), 3.48 ppm (s, 6H); ^{13}C NMR (100 MHz, CD_3CN): $\delta = 54.6$, 72.6, 121.9, 125.9, 129.7, 131.5, 131.7 ppm; HR-ESI-MS: *m/z* calcd (%) for $C_{11}H_{16}N^+$: 162.1280 [M^+]; found: 162.1277 (100).

***N-Allyl*-N,N,*4-trimethylbenzenaminium hexafluorophosphate* (*1b*-PF_6).**

Prepared in 80% yield as a white solid by a route analogous to that described for **1a**-PF_6. ^{1}H NMR (400 MHz, CD_3CN): $\delta = 7.55$ (d, $J = 8.6$ Hz, 2H), 7.43 (d, $J = 8.4$ Hz, 2H), 5.49–5.65 (m, 3H), 4.29 (d, $J = 6.5$ Hz, 2H), 3.45 (s, 6H), 2.40 ppm (s, 3H); ^{13}C NMR (100 MHz, CD_3CN): $\delta = 20.9$, 54.6, 72.5, 121.6, 126.0, 129.6, 131.8 ppm; HR-ESI-MS: *m/z* calcd (%) for $C_{12}H_{18}N^+$: 176.1441 [M^+]; found: 176.1434 (100).

***N*,N,N-*Triethylprop-2-en-1-aminium bromide* (*3a*-*Br*)[32,33]**

Prepared in 92% yield as a white hygroscopic solid by a route analogous to that described for **1a**-Br. ^{1}H NMR (400 MHz, CD_3CN): $\delta =$ 5.93 (m, 1H), 5.68 (d, $J = 12.1$ Hz, 1H), 5.65 (d, $J = 5.4$ Hz, 1H), 3.76 (d, $J = 7.0$ Hz, 2H), 3.19 (q, $J = 7.2$ Hz, 6H), 1.25 ppm (tt, $J = 1.2$ Hz, 9H).

***N*,N-*Diethyl*-N-*methylprop-2-en-1-aminium bromide* (*3b*-*Br*)**

Prepared in 73% yield as a yellow solid by a route analogous to that described for **1a**-Br. ^{1}H NMR (400 MHz, CD_3CN): $\delta = 5.97$ (m, 1H), 5.69 (d, $J = 11.6$ Hz, 1H), 5.66 (d, $J = 4.6$ Hz, 1H), 3.85 (d, $J =$ 7.5 Hz, 2H), 3.27 (q, $J = 7.24$ Hz, 4H), 2.89 (s, 3H), 1.28 ppm (tt, $J =$ 1.5 Hz, 6H); ^{13}C NMR (100 MHz, CD_3CN): $\delta = 8.2$, 47.7, 57.1, 63.7, 125.9, 129.0 ppm; ESI-MS: *m/z* calcd (%) for $C_8H_{18}N^+$: 128.143 [M^+]; found: 128.145 (100); HR-ESI-MS: *m/z* calcd (%) for $C_{16}H_{36}BrN_2^+$: 335.2056 [M^+]; found: 335.2053 (100).

***N-Benzyl*-N,N-*dimethylprop-2-en-1-aminium bromide* (*3c*-*Br*)[31]**

Prepared in 30% yield as a white hygroscopic solid by a route analogous to that described for **1a**-Br. ^{1}H NMR (400 MHz, CD_3CN): $\delta =$ 7.54 (m, 5H), 6.08 (m, 1H), 5.72 (d, $J = 9.8$ Hz, 1H), 5.70 (d, $J =$ 16.9 Hz, 1H), 4.51 (s, 2H), 3.97 (d, $J = 7.4$ Hz, 2H), 2.94 ppm (s, 6H).

***N*,N-*Diethyl*-N-*(2-hydroxyethyl)prop-2-en-1-aminium bromide* (*3d*-*Br*)[34]**

Prepared in 72% yield as a white solid by a route analogous to that described for **1a**-Br. ^{1}H NMR (400 MHz, CD_3CN): $\delta = 6.04$ (m, 1H), 5.7 (d, $J = 6.2$ Hz, 1H), 5.67 (br, 1H), 4.03 (d, $J = 7.7$ Hz, 2H), 3.97 (m, 2H), 3.41 (t, $J = 4.9$ Hz, 2H), 3.08 ppm (s, 6H).

***N*,N,N-*Triethylprop-2-en-1-aminium iodide* (*3a*-*I*)[32,33]**

Prepared in 92% yield as a yellow solid by a route analogous to that described for **1a**-Br. ^{1}H NMR (400 MHz, CD_3CN): $\delta = 5.93$ (m, 1H), 5.68 (d, $J = 12.8$ Hz, 1H), 5.65 (d, $J = 6.8$ Hz, 1H), 3.76 (d, $J =$ 7.3 Hz, 2H), 3.19 (q, $J = 7.5$, 6H), 1.25 ppm (tt, $J = 1.96$ Hz, 9H).

***4-Methoxy*-N,N-*dimethylaniline* (*4c*)[35]**

A 50 mL round-bottomed flask equipped with a reflux condenser was charged with 4-methoxyaniline (1.51 g, 12.26 mmol), TBAI (0.316 g, 0.856 mmol), potassium hydroxide (1.644 g, 29.2 mmol), benzene (14 mL), and water (2 mL). After 10 min, iodomethane (0.78 mL, 12.58 mmol) was added dropwise over 2 min and stirred at room temperature for 7 h. Then, additional TBAI (0.156 g, 0.42 mmol), potassium hydroxide (0.726 g, 12.92 mmol) and iodomethane (0.14 mL) were added and stirred at room temperature

for 11 h. The organic layer was separated and washed with a portion (10 mL) of water, saturated sodium carbonate, and brine, and dried over anhydrous sodium sulfate. Filtration and solvent removal under vacuum gave a dark yellow oil. The crude product was purified by chromatography (silica gel) using 5% ethyl acetate/pentane as an eluent to afford a yellow solid (0.953 g, 51% yield). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.92$ (d, $J = 8.9$ Hz, 2H), 6.82 (d, $J = 9.2$ Hz, 2H), 3.82 (s, 3H), 2.92 ppm (s, 6H).

N-Benzyl-N,N-*dimethylbenzenaminium bromide (5a-Br)*[20]

Dimethylaniline (0.70 mL, 5.5 mmol) and benzylbromide (0.59 mL, 5.0 mmol) were combined in dry benzene and stirred at room temperature for 24 h. A white solid precipitated in the solution. The compound was washed with diethyl ether and dried under vacuum for 4 h to afford white solids (0.288 g, 20%). M.p. 148–149 °C (Ref. [20]: 149–151 °C); ^{1}H NMR (400 MHz, CD_3CN): $\delta = 7.57$–7.67 (m, 5H), 7.46 (t, $J = 8$ Hz, 1H), 7.32 (t, $J = 8$ Hz, 2H), 7.07 (d, $J = 7.7$ Hz, 2H), 4.93 (s, 2H), 3.55 ppm (s, 6H).

N-Benzyl-N,N,*4-trimethylbenzenaminium bromide (5b-Br)*[20]

Prepared in 40% yield as a white solid by a route analogous to that described for **5a**-Br. M.p. 183–184 °C; ^{1}H NMR (400 MHz, CD_3CN): $\delta = 7.52$ (d, $J = 8.9$ Hz, 2H), 7.46 (t, $J = 7.6$ Hz, 1H), 7.38 (d, $J = 8.7$ Hz, 2H), 7.32 (t, $J = 8.3$ Hz, 2H), 7.08 (d, $J = 7.6$ Hz, 2H), 4.92 (s, 2H), 3.52 (s, 6H), 2.40 ppm (s, 3H).

N-Benzyl-4-methoxy-N,N-*dimethylbenzenaminium bromide (5c-Br)*[20]

Prepared in 25% yield as a white solid by a route analogous to that described for **5a**. M.p. 148–149 °C; ^{1}H NMR (400 MHz, CD_3CN): $\delta = 7.44$–7.56 (m, 3H), 7.34 (t, $J = 8.4$ Hz, 2H), 7.05–7.08 (m, 4H), 4.87 (s, 2H), 3.85 (s, 3H), 3.50 ppm (s, 6H).

1-Benzylpyridin-1-ium bromide (6a)[36]

A solution of pyridine (0.4 mL, 5 mmol) and benzylbromide (0.59 mL, 5 mmol) in dry toluene (20 mL) was stirred at room temperature for 24 h. After filtration, the solid was washed with diethyl ether to give **6a** as a white solid (1.052, 84% yield). M.p. 66–70 °C; ^{1}H NMR (400 MHz, CD_3CN): $\delta = 8.91$ (t, $J = 5.5$ Hz, 2H), 8.51 (t, $J = 8.0$ Hz, 1H), 8.03 (t, $J = 6.8$ Hz, 2H), 7.46–7.51 (m, 5H), 5.82 ppm (d, $J = 3.0$ Hz, 2H).

1-Benzyl-4-methylpyridin-1-ium bromide (6b)[37]

A solution of 4-picoline (0.68 mL, 7 mmol) and benzylbromide (0.83, 7 mmol) in acetonitrile (1 mL) was stirred at 45 °C for 3 h. The precipitate formed was washed with diethyl ether and dried under vacuum to give **6b** as a white crystal (1.665 g, 80%). M.p. 159–160 °C; ^{1}H NMR (400 MHz, CD_3CN): $\delta = 8.70$ (br, 2H), 7.82 (d, $J = 6.3$ Hz, 2H), 7.46 (s, 5H), 5.72 (s, 2H), 2.61 ppm (s, 3H).

1-Benzyl-4-(dimethylamino)pyridin-1-ium bromide (6c)[38]

Prepared in 92% yield as a white solid by a route analogous to that described in the literature. M.p. 216–217 °C; ^{1}H NMR (400 MHz, CD_3CN): $\delta = 8.06$ (d, $J = 7.9$ Hz, 2H), 7.40–7.46 (m, 3H), 7.34–7.37 (m, 2H), 6.85 (d, $J = 8.0$ Hz, 2H), 5.30 (s, 2H), 3.16 ppm (s, 6H).

*1-Benzyl-4-(*tert*-butyl)pyridin-1-ium bromide (6d)*[38]

Prepared in 73% yield as a white solid by a route analogous to that described for **6b**. M.p. 163 °C; ^{1}H NMR (400 MHz, CD_3CN): $\delta = 8.87$ (d, $J = 6.5$ Hz, 2H), 8.01 (d, $J = 6.7$ Hz, 2H), 7.43–7.53 (m, 5H), 5.78 (s, 2H), 1.37 ppm (s, 9H).

1-Allylpyridin-1-ium bromide (6e)[25]

A solution of pyridine (0.81, 10 mmol) and allylbromide (1.1 mL, 10 mmol) in acetonitrile (10 mL) was stirred at 50 °C overnight. The crude product was concentrated and dried under vacuum to obtain a light brown solid (1.8902 g, 95% yield). M.p. 92–94 °C; ^{1}H NMR (400 MHz, CD_3CN): $\delta = 8.89$ (d, $J = 6.3$ Hz, 2H), 8.54 (t, $J = 8.1$ Hz, 1H), 8.06 (t, $J = 6.8$ Hz, 2H), 6.09–6.20 (m, 1H), 5.52 (d, $J = 14$ Hz, 2H), 5.28 ppm (d, $J = 6.6$ Hz, 2H).

1-Allyl-4-methylpyridin-1-ium bromide (6f)[37]

Prepared in 96% yield as a brown solid by a route analogous to that described for **6e**. M.p. 76–78 °C; ^{1}H NMR (400 MHz, CD_3CN): $\delta = 8.78$ (d, $J = 6.5$ Hz, 2H), 7.86 (d, $J = 6.2$ Hz, 2H), 6.08–6.18 (m, 1H), 5.48 (d, $J = 13.8$ Hz, 2H), 5.24 (d, $J = 6.5$ Hz, 2H), 2.63 ppm (s, 3H).

Acknowledgements

S.K. thanks the Khon Kaen University (Thailand) and the Franco-Thai scholarship program for a doctoral fellowship. We also thank the ERC (Advanced Research Grant SUPRADAPT 290585) for financial support.

Keywords: amines · ammonium salts · combinatorial chemistry · nucleophilic substitution · reversible reactions

[1] a) J.-M. Lehn, *Chem. Soc. Rev.* **2007**, *36*, 151–160; b) P. T. Corbett, J. Leclaire, L. Vial, K. R. West, J.-L. Wietor, J. K. M. Sanders, S. Otto, *Chem. Rev.* **2006**, *106*, 3652–3711; c) Y. Jin, C. Yu, R. J. Denman, W. Zhang, *Chem. Soc. Rev.* **2013**, *42*, 6634–6654; d) S. Ladame, *Org. Biomol. Chem.* **2008**, *6*, 219–226; e) S. J. Rowan, S. J. Cantrill, G. R. L. Cousins, J. K. M. Sanders, J. F. Stoddart, *Angew. Chem. Int. Ed.* **2002**, *41*, 898–952; *Angew. Chem.* **2002**, *114*, 938–993.

[2] a) J.-M. Lehn, *Chem. Eur. J.* **1999**, *5*, 2455–2463; b) C. Saiz, P. Wipf, E. Manta, G. Mahler, *Org. Lett.* **2009**, *11*, 3170–3173.

[3] a) I. Huc, J.-M. Lehn, *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 2106–2110; b) J. R. Nitschke, J.-M. Lehn, *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 11970–11974; c) R. Nguyen, I. Huc, *Chem. Commun.* **2003**, 942–943; d) P. Wipf, S. G. Mahler, K. Okumura, *Org. Lett.* **2005**, *7*, 4483–4486.

[4] a) O. Ramström, J.-M. Lehn, *ChemBioChem* **2000**, *1*, 41–48; b) S. Otto, R. L. E. Furlan, J. K. M. Sanders, *J. Am. Chem. Soc.* **2000**, *122*, 12063–12064; c) H. Hioki, W. C. Still, *J. Org. Chem.* **1998**, *63*, 904–905.

[5] a) C. Brändli, T. R. Ward, *Helv. Chim. Acta* **1998**, *81*, 1616–1621; b) K. C. Nicolaou, R. Hughes, S. Y. Cho, N. Winssinger, C. Smethurst, H. Labischinski, R. Endermann, *Angew. Chem. Int. Ed.* **2000**, *39*, 3823–3828; *Angew. Chem.* **2000**, *112*, 3981–3986.

[6] a) N. Wilhelms, S. Kulchat, J.-M. Lehn, *Helv. Chim. Acta* **2012**, *95*, 2635–2651; b) M. Ciaccia, R. Cacciapaglia, P. Mencarelli, L. Mandolini, S. D. Stefano, *Chem. Sci.* **2013**, *4*, 2253–2261; c) M. Ciaccia, S. Pilati, R. Cacciapaglia, L. Mandolini, S. D. Stefano, *Org. Biomol. Chem.* **2014**, *12*, 3282–3287.

[7] S. Kulchat, K. Meguellati, J.-M. Lehn, *Helv. Chim. Acta* **2014**, *97*, 1219–1236.

[8] a) I. Nakazawa, S. Suda, M. Masuda, M. Asai, T. Shimizu, *Chem. Commun.* **2000**, 881–882; b) L. M. Greig, A. M. Z. Slawin, M. H. Smith, D. Philp, *Tetrahedron* **2007**, *63*, 2391–2403.

[9] P. G. Swann, R. A. Casanova, A. Desai, M. M. Frauenhoff, M. Urbancic, U. Slomczynska, A. J. Hopfinger, G. C. Le Breton, D. L. Venton, *Pept. Sci.* **1996**, *40*, 617 – 625.
[10] a) P. J. Boul, P. Reutenauer, J.-M. Lehn, *Org. Lett.* **2005**, *7*, 15 – 18; b) P. Reutenauer, E. Buhler, P. J. Boul, S. J. Candau, J.-M. Lehn, *Chem. Eur. J.* **2009**, *15*, 1893 – 1900; c) P. Reutenauer, P. J. Boul, J.-M. Lehn, *Eur. J. Org. Chem.* **2009**, 1691 – 1697; d) N. Roy, J.-M. Lehn, *Chem. Asian J.* **2011**, *6*, 2419 – 2425.
[11] a) J.-M. Lehn, *Prog. Polym. Sci.* **2005**, *30*, 814 – 831; b) J. Lehn, *Aust. J. Chem.* **2010**, *63*, 611 – 623; c) D. Zhao, J. S. Moore, *J. Am. Chem. Soc.* **2002**, *124*, 9996 – 9997; d) R. J. Williams, A. M. Smith, R. Collins, N. Hodson, A. K. Das, R. V. Ulijn, *Nat. Nanotechnol.* **2009**, *4*, 19 – 24; e) S. Otto, *Nat. Nanotechnol.* **2009**, *4*, 13 – 14; f) R. Nguyen, E. Buhler, N. Giuseppone, *Macromolecules* **2009**, *42*, 5913 – 5915; g) N. Roy, E. Buhler, J.-M. Lehn, *Polym. Int.* **2014**, *63*, 1400 – 1405; h) J. Li, P. Nowak, S. Otto, *J. Am. Chem. Soc.* **2013**, *135*, 9222 – 9239; i) N. Giuseppone, *Acc. Chem. Res.* **2012**, *45*, 2178 – 2188; j) H. Otsuka, *Polym. J.* **2013**, *45*, 879 – 891; k) C. Wang, Z. Wang, X. Zhang, *Acc. Chem. Res.* **2012**, *45*, 608 – 618; l) A.-J. Avestro, M. E. Belowich, J. F. Stoddart, *Chem. Soc. Rev.* **2012**, *41*, 5881 – 5895; m) A. Ciesielski, P. Samorì, *Nanoscale* **2011**, *3*, 1397 – 1410; n) T. Maeda, H. Otsuka, A. Takahara, *Prog. Polym. Sci.* **2009**, *34*, 581 – 604; o) A. L. Korich, P. M. Iovine, *Dalton Trans.* **2010**, *39*, 1423 – 1431.
[12] a) O. Ramström, J.-M. Lehn, *Nat. Rev. Drug Discovery* **2002**, *1*, 26 – 36; b) O. Ramström, S. Lohmann, T. Bunyapaiboonsri, J.-M. Lehn, *Chem. Eur. J.* **2004**, *10*, 1711 – 1715; c) T. Hotchkiss, H. B. Kramer, K. J. Doores, D. P. Gamblin, N. J. Oldham, B. G. Davis, *Chem. Commun.* **2005**, 4264 – 4266; d) G. Nasr, E. Petit, C. T. Supuran, J.-Y. Winum, M. Barboiu, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6014 – 6017; e) D. E. Scott, G. J. Dawes, M. Ando, C. Abell, A. Ciulli, *ChemBioChem* **2009**, *10*, 2772 – 2779; f) R. Caraballo, H. Dong, J. P. Ribeiro, J. Jiménez-Barbero, O. Ramström, *Angew. Chem. Int. Ed.* **2010**, *49*, 589 – 593; *Angew. Chem.* **2010**, *122*, 599 – 603; g) M. Hochgürtel, J.-M. Lehn in *Fragm.-Based Approaches Drug Discov.* (Eds.: W. Jahnke, D. A. Erlanson), Wiley-VCH, **2006**, pp. 341 – 364; h) O. Ramström, J.-M. Lehn, in *Compr. Med. Chem. II* (Ed.: J. B. T. J. Triggle), Elsevier, Oxford, **2007**, pp. 959 – 976.
[13] a) E. Wedekind, *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 3791 – 3796; b) E. Wedekind, *Z. Phys. Chem.* **1903**, *45*, 235 – 248.
[14] a) E. Havinga, *Chem. Weekbl.* **1941**, *38*, 642 – 644; b) E. Havinga, *Biochim. Biophys. Acta* **1954**, *13*, 171 – 174.
[15] a) R. G. Kostyanovsky, V. R. Kostyanovsky, G. K. Kadorkina, K. A. Lyssenko, *Mendeleev Commun.* **2001**, *11*, 1 – 5. This paper also gives a detailed and precious description of the historical developments concerning the studies on these optically active quaternary allylammonium compounds: b) V. Y. Torbeev, K. A. Lyssenko, O. N. Kharybin, M. Y. Antipin, R. G. Kostyanovsky, *J. Phys. Chem. B* **2003**, *107*, 13523 – 13531.
[16] R. G. Kostyanovsky, K. A. Lyssenko, O. N. Krutius, V. R. Kostyanovsky, *Mendeleev Commun.* **2009**, *19*, 19 – 20.
[17] a) M. J. O'Donnell, W. D. Bennett, S. Wu, *J. Am. Chem. Soc.* **1989**, *111*, 2353 – 2355; b) O. Marianacci, G. Micheletti, L. Bernardi, F. Fini, M. Fochi, D. Pettersen, V. Sgarzani, A. Ricci, *Chem. Eur. J.* **2007**, *13*, 8338 – 8351; c) T. Ooi, K. Maruoka, *Angew. Chem. Int. Ed.* **2007**, *46*, 4222 – 4266; *Angew. Chem.* **2007**, *119*, 4300 – 4345.
[18] a) J. Ding, D. W. Armstrong, *Chirality* **2005**, *17*, 281 – 292; b) J. Feder-Kubis, M. Kubicki, J. Pernak, *Tetrahedron: Asymmetry* **2010**, *21*, 2709 – 2718; c) S. Zhang, Y. Huang, H. Jing, W. Yao, P. Yan, *Green Chem.* **2009**, *11*, 935 – 938; d) J. Pernak, J. Feder-Kubis, *Chem. Eur. J.* **2005**, *11*, 4441 – 4449.
[19] D. A. Lenev, K. A. Lyssenko, R. G. Kostyanovsky, *Mendeleev Commun.* **2004**, *14*, 312 – 314.
[20] F. G. Bordwell, D. L. Hughes, *J. Am. Chem. Soc.* **1986**, *108*, 7300 – 7309.
[21] I. Lee, Y. K. Park, C. Huh, H. W. Lee, *J. Phys. Org. Chem.* **1994**, *7*, 555 – 560.
[22] a) H. M. Yau, A. K. Croft, J. B. Harper, *Chem. Commun.* **2012**, *48*, 8937 – 8939; b) E. E. L. Tanner, H. M. Yau, R. R. Hawker, A. K. Croft, J. B. Harper, *Org. Biomol. Chem.* **2013**, *11*, 6170 – 6175; c) H. M. Yau, A. G. Howe, J. M. Hook, A. K. Croft, J. B. Harper, *Org. Biomol. Chem.* **2009**, *7*, 3572 – 3575.
[23] a) M.-L. Bennasar, J.-M. Jiménez, B. Vidal, B. A. Sufi, J. Bosch, *J. Org. Chem.* **1999**, *64*, 9605 – 9612; b) S. Yamada, C. Morita, *J. Am. Chem. Soc.* **2002**, *124*, 8184 – 8185; c) D. L. Comins, S. P. Joseph, R. R. Goehring, *J. Am. Chem. Soc.* **1994**, *116*, 4719 – 4728; d) J. T. Kuethe, D. L. Comins, *J. Org. Chem.* **2004**, *69*, 5219 – 5231; e) A. B. Charette, M. Grenon, A. Lemire, M. Pourashraf, J. Martel, *J. Am. Chem. Soc.* **2001**, *123*, 11829 – 11830.
[24] K. Patel, O. Š. Miljanić, J. F. Stoddart, *Chem. Commun.* **2008**, 1853 – 1855.
[25] N. Jiang, Y. Pu, R. Samuel, A. J. Ragauskas, *Green Chem.* **2009**, *11*, 1762 – 1766.
[26] a) H. Katayama, *Chem. Pharm. Bull.* **1978**, *26*, 2027 – 2035; b) H. Katayama, N. Takatsu, *Chem. Pharm. Bull.* **1981**, *29*, 2465 – 2477.
[27] a) M. Freemantle, *An Introduction to Ionic Liquids*, The Royal Society Of Chemistry, Cambridge, **2010**; b) A. M. Scurto, W. Leitner, *Chem. Commun.* **2006**, 3681 – 3683; c) K. J. Fraser, E. I. Izgorodina, M. Forsyth, J. L. Scott, D. R. MacFarlane, *Chem. Commun.* **2007**, 3817 – 3819; d) S. Yazaki, M. Funahashi, J. Kagimoto, H. Ohno, T. Kato, *J. Am. Chem. Soc.* **2010**, *132*, 7702 – 7708; e) R. Balasubramanian, W. Wang, R. W. Murray, *J. Am. Chem. Soc.* **2006**, *128*, 9994 – 9995; f) R. Sheldon, *Chem. Commun.* **2001**, 2399 – 2407.
[28] K. J. Hall, T. I. Quickenden, D. W. Watts, *J. Chem. Educ.* **1976**, *53*, 493.
[29] S. J. A. Grove, J. Kaur, A. W. Muir, E. Pow, G. J. Tarver, M.-Q. Zhang, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 193 – 196.
[30] M. Finkelstein, R. C. Petersen, S. D. Ross, *J. Am. Chem. Soc.* **1959**, *81*, 2361 – 2364.
[31] S. D. Venkataramu, G. D. Macdonell, W. R. Purdum, G. A. Dilbeck, K. D. Berlin, *J. Org. Chem.* **1977**, *42*, 2195 – 2200.
[32] R. S. Underhill, G. Liu, *Chem. Mater.* **2000**, *12*, 3633 – 3641.
[33] F. M. Menger, U. V. Venkataram, *J. Am. Chem. Soc.* **1986**, *108*, 2980 – 2984.
[34] R. R. Ravu, Y.-L. Chen, M. R. Jacob, X. Pan, A. K. Agarwal, S. I. Khan, J. Heitman, A. M. Clark, X.-C. Li, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4828 – 4831.
[35] J. P. Dinnocenzo, S. B. Karki, J. P. Jones, *J. Am. Chem. Soc.* **1993**, *115*, 7111 – 7116.
[36] D. Passarella, R. Favia, A. Giardini, G. Lesma, M. Martinelli, A. Silvani, B. Danieli, S. M. N. Efange, D. C. Mash, *Bioorg. Med. Chem.* **2003**, *11*, 1007 – 1014.
[37] I. Y. Chernyshov, V. V. Levin, A. D. Dilman, P. A. Belyakov, M. I. Struchkova, V. A. Tartakovsky, *Russ. Chem. Bull.* **2010**, *59*, 2102 – 2107.
[38] T. Chang, H. Jing, L. Jin, W. Qiu, *J. Mol. Catal. A* **2007**, *264*, 241 – 247.
[39] A. A. Bredikhin, R. M. Eliseenkova, Z. A. Bredikhina, A. B. Dobrynin, R. G. Kostyanovsky, *Chirality* **2009**, *21*, 637 – 641.

Manuscript received: June 11, 2015
Accepted Article published: July 25, 2015
Final Article published: August 19, 2015