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First example of chiral *N*-heterocyclic carbenes as catalysts for kinetic resolution

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Chiral *N*-heterocyclic carbenes, which are derived from C_2-symmetric 1,3-bis(1-arylethyl)imidazolium salts, catalyze enantioselective acylation of racemic secondary alcohols.

N-Heterocyclic carbenes (NHC) are efficient catalysts for reactions such as the benzoin condensation[1] and the Stetter reaction.[2] The use of chiral NHC has led to asymmetric benzoin condensation[3,4] and the asymmetric-intramolecular Stetter reaction.[3,5]

In our continuous studies on the NHC-catalysis,[6] we explored the possibilities for an enantioselective acylation of secondary alcohols using chiral NHCs. Non-enzymatic catalysts for the kinetic resolution of racemic secondary alcohols have been extensively studied over the last decade. The development of chiral nucleophilic catalysts is one of the major breakthroughs,[7] yet more selective, general, and easily accessible catalysts are in demand. Recently, the Nolan group[8] and the Hedrick group[9] independently reported the NHC-catalyzed transesterification/acylation reaction. *N*-Heterocyclic carbenes are nucleophilic acylation catalysts and are readily synthesized. We assumed that chiral NHCs have the potential for kinetic resolution catalysis.

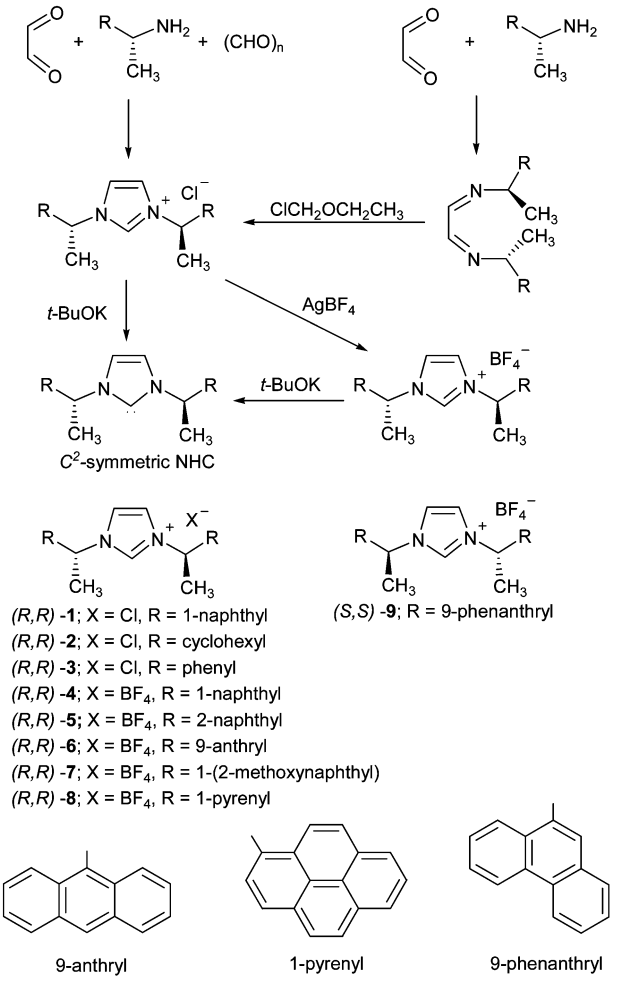
We selected the C_2-symmetric imidazolium salt-derived NHCs as catalysts, since they can be easily prepared from inexpensive materials, namely, chiral amines, glyoxal, and formaldehyde or chloromethyl ethyl ether (Scheme 1).[10]

N-Heterocyclic carbenes were generated *in situ* from imidazolium salts and were used in the reactions. A mixture of catalytic amounts of imidazolium salts (3 mol%) and potassium *tert*-butoxide (*t*-BuOK, 2.5 mol%) in ether was stirred for 30 min, followed by the addition of vinyl acetate and alcohols. The results are summarized in Table 1.

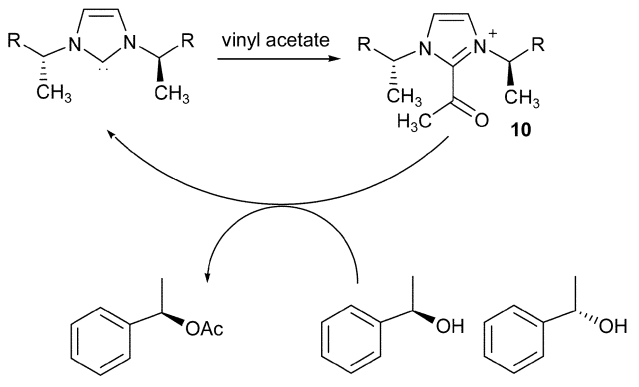
The acylation of 1-(1-naphthyl)ethanol (**11**) using (*R*,*R*)-**1** at room temperature provided acetate **15** in 21% yield with 42% ee (entry 1). The unreacted **11** was recovered in 69% yield with 21% ee. At 0 °C, the selectivity was improved (entry 2). Under the same conditions at room temperature, the acylation of 1-phenylethanol (**12**) provided acetate **16** in 29% yield with 31% ee, and **12** was recovered in 36% yield with 20% ee (entry 4). The catalysts (*R*,*R*)-**2** and (*R*,*R*)-**3** showed less selectivities than (*R*,*R*)-**1** (entries 3, 5). The reaction rate increased when imidazolium tetrafluoroborate (*R*,*R*)-**4**, instead of chloride (*R*,*R*)-**1**, was used in the acylation of **11** (entry 6). Imidazolium salt (*R*,*R*)-**5** has a 2-naphthyl substituent on the *N*-ethyl group and had less selectivity than (*R*,*R*)-**4** that has a 1-naphthyl substituent (entry 8).

These results led us to assume that an aromatic substituent on the *N*-ethyl group of NHC needs to be bulkier than naphthyl in order to achieve a better selectivity. Hence, we examined the reaction using (*R*,*R*)-**6**,**7**,**8** and (*S*,*S*)-**9** that have the aromatic substituents 9-anthryl, 1-(2-methoxynaphthyl), 1-pyrenyl, and 9-phenanthryl, respectively. In contrast, (*R*,*R*)-**6**,**7** had lower selectivities, and the reaction rates were slow. The 9-anthryl- and 1-(2-methoxynaphthyl) groups seem to hinder the attack of alcohol on the carbonyl carbon of intermediate **10** (Scheme 2). (*R*,*R*)-**8** and (*S*,*S*)-**9** showed comparable selectivities to (*R*,*R*)-**4**.

In summary, we have demonstrated for the first time that C_2-symmetric *N*-heterocyclic carbenes catalyze the enantioselective acylation of racemic secondary alcohols. When an *N*-substituent of carbene is a (*R*)-1-arylethyl group, the acylation of 1-arylethanols



Scheme 1 C_2-Symmetric imidazolium salts.



Scheme 2 Enantioselective acylation of secondary alcohols.

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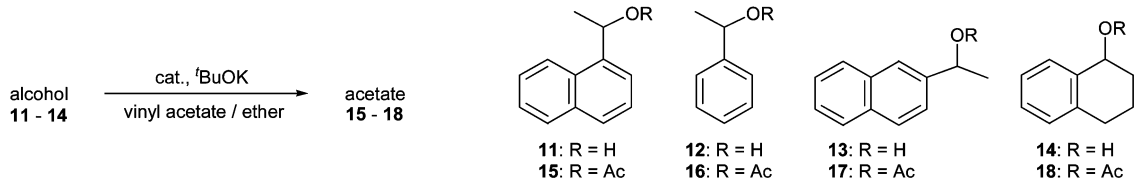
Table 1 Kinetic resolution of secondary alcohols



Entry	Racemic alcohol	Cat.	X	Condition	Resolved alcohol	Acetate yield (%)[a]	Ee (%)[b]	Alcohol yield (%)	Ee (%)[b]
1	**11**	(*R*,*R*)-**1**	Cl	rt, 48 h	**15**	21	42 (*R*)	69	21 (*S*)
2	**11**	(*R*,*R*)-**1**	Cl	0 °C, 48 h	**15**	21	51 (*R*)	79	11 (*S*)
3	**11**	(*R*,*R*)-**2**	Cl	rt, 18 h	**15**	15	19 (*S*)	83	1 (*R*)
4	**12**	(*R*,*R*)-**1**	Cl	rt, 72 h	**16**	29	31 (*R*)	36	20 (*S*)
5	**12**	(*R*,*R*)-**3**	Cl	rt, 72 h	**16**	27	18 (*R*)	74	9 (*S*)
6	**11**	(*R*,*R*)-**4**	BF_4	0 °C, 24 h	**15**	33	45 (*R*)	56	22 (*S*)
7	**11**	(*R*,*R*)-**4**	BF_4	−15 °C, 72 h	**15**	14	58 (*R*)	85	8 (*S*)
8	**11**	(*R*,*R*)-**5**	BF_4	0 °C, 18 h	**15**	43	14 (*R*)	47	14 (*S*)
9	**11**	(*R*,*R*)-**6**	BF_4	0 °C, 48 h	**15**	6	23 (*R*)	80	5 (*S*)
10	**11**	(*R*,*R*)-**7**	BF_4	0 °C, 60 h and then rt, 48 h	**15**	4	13 (*R*)	84	<1
11	**11**	(*R*,*R*)-**8**	BF_4	0 °C, 12 h	**15**	27	49 (*R*)	73	20 (*S*)
12	**11**	(*S*,*S*)-**9**	BF_4	0 °C, 18 h	**15**	37	39 (*S*)	60	23 (*R*)
13	**13**	(*R*,*R*)-**4**	BF_4	0 °C, 18 h	**17**	44	44 (*R*)	49	37 (*S*)
14	**14**	(*R*,*R*)-**4**	BF_4	0 °C, 48 h	**18**	14	9	84	2

[a] Isolated yield. [b] Enantioselectivities were measured by HPLC using a Chiralcel OD column or a Chiralpac AS column.

proceeded with *R*-selectivities, and in the case of a (*S*)-1-arylethyl group, the reaction proceeded with *S*-selectivities. Although the selectivities are not satisfactory, we anticipate that a further design and modification of a carbene structure will lead to the discovery of a practical catalyst for a kinetic resolution.

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