Enantioselective organocatalytic substitution of α-cyanoacetates on imidoyl chlorides – synthesis of optically active ketimines†

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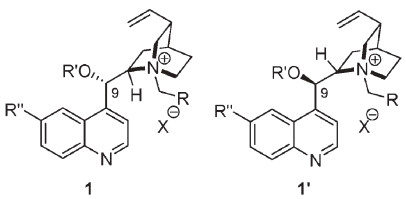
The enantioselective substitution of α-cyanoacetates on imidoyl chlorides under phase-transfer catalytic conditions is presented; a simple quinidine-derived phase-transfer catalyst gives access to the products, highly substituted ketimines, in generally good yields and up to 90% ee.

Imidoyl halides are reactive and versatile chemical compounds which have found wide application in organic synthesis and in the study of chemical reactivity.[1] The halide in these compounds can be replaced by various nucleophiles for functionalization, in which process the imidoyl halide acts as an electrophile equivalent to the imidoyl carbocation. Furthermore, the C=N bond can be used for other processes, *e.g.* alkylation, cyclization and reduction to amines. Among imidoyl halides, trifluoroacetimidoyl chlorides are probably the most interesting as they are important building blocks for the synthesis of functionalized fluorine-containing compounds.[2] Trifluoroacetimidoyl chlorides are easily accessible and can be prepared in a one-step synthesis starting from cheap and commercially available materials.[3]

Up to now, no asymmetric reactions involving these compounds are known, although the optically active products might have considerable synthetic applicability. In this communication, we wish to present our initial investigations towards this goal by performing a substitution at the carbon atom in the imidoyl chlorides using asymmetric phase transfer catalysis.[4] Regarding the choice of a model system for studying this reaction, our interest focused on the use of α-substituted-α-cyanoacetates as the nucleophilic component, considering the synthetic possibilities associated with having both an ester and nitrile functionality attached to the same chiral carbon atom.[5] This reaction leads to the formation of an all-carbon quaternary stereocenter,[6] and furthermore, the products – optically active ketimines – contain functional groups that may be used for successive modifications.

We started our investigation with a preliminary screening of the substituent at the nitrogen atom of the imidoyl chloride and the alcoholic moiety of the ester group of the α-substituted-α-cyanoacetate. This screening (see ESI†) clearly demonstrated that electron-deficient aryl substituents on the imidoyl chloride were a necessity for sufficient reactivity and in particular that mono-nitro substituted aryl groups seemed to afford a good compromise between reactivity and stability. Of the substrates tested, *o*-nitrophenyl was found to be optimal with respect to enantioselectivity. Furthermore, the screening also revealed that bulky ester groups, such as *tert*-butyl, in the α-substituted-α-cyanoacetates gave higher enantioselectivities compared to smaller groups.

On the basis of these results, we decided to perform a catalyst and conditions screening using 2,2,2-trifluoro-*N*-(2-nitrophenyl) acetimidoyl chloride **2a** and *tert*-butyl 2-cyanopentanoate **3a** as the nucleophile. Several phase-transfer catalysts derived from cinchona alkaloids were tested (Fig. 1 and Table 1).



1a : R = Ph; R' = H; R'' = H; X = Cl
1'a : R = Ph; R' = H; R'' = H; X = Br
1b : R = Ph; R' = Bn; R'' = H; X = Br
1c : R = 4-CF_3-C_6H_4; R' = H; R'' = H; X = Br
1d : R = 9-anthracenyl; R' = H; R'' = H; X = Cl
1e : R = 3,5-MeO-C_6H_3; R' = H; R'' = H; X = Br
1f : R = 3,4,5-MeO-C_6H_2; R' = H; R'' = H; X = Br
1g : R = 3,4,5-BnO-C_6H_2; R' = H; R'' = H; X = Br
1h : R = 3,4,5-MeO-C_6H_2; R' = H; R'' = MeO; X = Br
1'h : R = 3,4,5-MeO-C_6H_2; R' = H; R'' = MeO; X = Br

Fig. 1 Catalysts.

Generally, the reaction occurred with excellent conversion after stirring overnight. Commercially available *N*-benzylcinchoninium chloride **1a** and the quasienantiomer *N*-benzylcinchonidinium bromide **1′a** catalyzed the reaction with moderate enantioselectivity (Table 1, entries 1 and 2). Derivatisation of the catalyst motif revealed that the 9-OH functionality had to be unprotected to maintain these levels of enantioinduction (entry 3). Additionally, increasing the size of the substituent R at the nitrogen atom led to a significant improvement in the enantioselectivity (entry 5). An equivalent or even larger increase in the enantioselectivity could also be realized by introducing two or three methoxy groups on the benzyl ring (catalysts **1e** and **1f**, entries 6 and 7). Unfortunately, changing the ether substituents from methyl to benzyl (catalyst **1g**) was unproductive.[7] Finally, we prepared a new catalyst, changing the alkaloid moiety from cinchonine to quinidine (R″ = OMe), and obtained a further increase in the enantiomeric excess of **4a** to 86% ee (catalyst **1h**, entry 11). Temperatures higher or lower than −20 °C afforded decreased enantioinduction and slight changes in the solvent had no significant effect.

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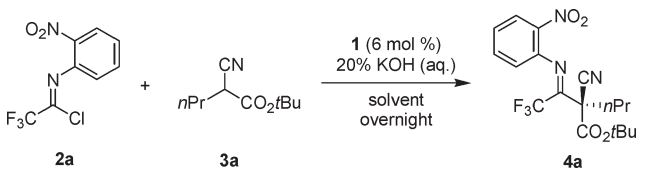
Table 1 Catalyst and conditions screening[a]



2a 3a 4a

Entry	Catalyst	Solvent	T/°C	Conv. (%)[b]	ee (%)[c]
1	**1a**	*o*-Xylene–$CHCl_3$ 7 : 1	−20	95	30
2	**1′a**	*o*-Xylene–$CHCl_3$ 7 : 1	−20	95	−42
3	**1b**	*o*-Xylene–$CHCl_3$ 7 : 1	−20	97	16
4	**1c**	*o*-Xylene–$CHCl_3$ 7 : 1	−20	80	36
5	**1d**	*o*-Xylene–$CHCl_3$ 7 : 1	−20	96	72
6	**1e**	*o*-Xylene–$CHCl_3$ 7 : 1	−20	84	76
7	**1f**	*o*-Xylene–$CHCl_3$ 7 : 1	−20	92	81
8[d]	**1f**	*o*-Xylene–$CHCl_3$ 7 : 1	−30	72	73
9[e]	**1f**	*o*-Xylene–$CHCl_3$ 7 : 1	0	39	73
10	**1g**	*o*-Xylene–$CHCl_3$ 7 : 1	−20	95	71
11	**1h**	*o*-Xylene–$CHCl_3$ 7 : 1	−20	89	86
12	**1′h**	*o*-Xylene–$CHCl_3$ 7 : 1	−20	n. d.	−79
13	**1h**	*m*-Xylene–$CHCl_3$ 7 : 1	−20	n. d.	85
14	**1h**	*o*-Xylene–DCM 7 : 1	−20	n. d.	86

[a] Reaction performed with **3a** (0.1 mmol), **2a** (1.3 equiv.) and catalyst (6 mol%) in 0.66 mL of solvent and 0.33 mL of 20% KOH aqueous solution. [b] Determined from NMR spectroscopy. [c] Determined from HPLC. [d] 50% KOH aqueous solution was used as the base. [e] 40% K_3PO_4 aqueous solution was used as the base.

Using the optimized conditions we studied the generality of the asymmetric substitution on trifluoroacetimidoyl chloride **2a** using a variety of *tert*-butyl α-substituted-α-cyanoacetates as the nucleophile (Table 2). Among these substituents, both simple α-(*primary*-alkyl)- and α-(*sec*-alkyl)-α-cyanoacetates exhibited high enantioselection (entries 1 and 4–8).

Spatial proximity of an aryl-group to the α-carbon atom had a negative effect on the enantioselectivity (entries 2 and 3), and when an α-aryl-α-cyanoacetate was employed, the reaction occurred with low enantioselectivity (entry 9). All reactions afforded the products **4** in good yields, with the exception of those performed with α-(*sec*-alkyl)-α-cyanoacetates (entries 4 and 5). In these cases the reaction was slower and probably the hydrolysis of the imidoyl chloride became competitive with the substitution reaction. The best result was obtained using *tert*-butyl 2-cyano-5-phenylpentanoate **3h** as the nucleophile. The reaction afforded the corresponding ketimine **4h** in 98% yield and 90% ee.

It was possible to obtain compound **4c** as a single enantiomer by recrystallization from EtOAc–hexane. An X-ray crystal structure (Fig. 2) revealed that the absolute configuration of the reaction products was (*S*) and that the imine was formed as the sterically less encumbered (*Z*)-isomer.[8]

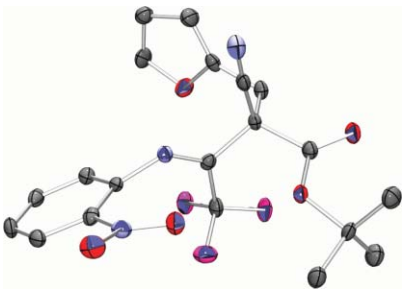
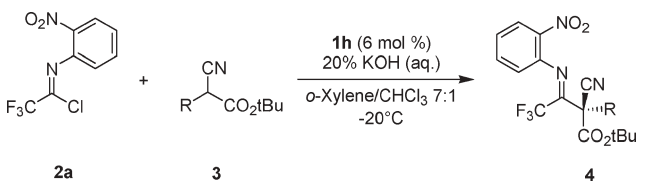


Fig. 2 X-Ray structure of (*S*)-**4c** (ellipsoids drawn at 50% probability).

Table 2 Scope of the reaction[a]



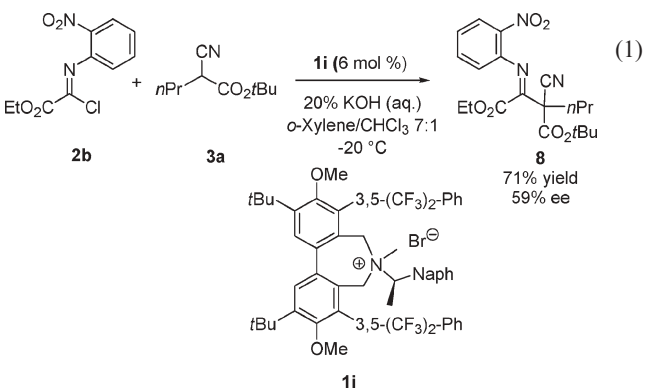
2a 3 4

Entry	R	Substrate	Reaction time	Yield (%)[b]	ee (%)[c]
1	$CH_3CH_2CH_2$	**3a**	18 h	**4a** - 76	86
2	$PhCH_2$	**3b**	17 h	**4b** - 99	62
3	(2-Furanyl)CH_2	**3c**	17 h	**4c** - 70	65 (*S*)[d]
4[e]	Cyclohexyl	**3d**	7 d	**4d** - 30	86
5[e]	$(CH_3)_2CH$	**3e**	7 d	**4e** - 27	90
6	CH_3	**3f**	12 h	**4f** - 90	84
7	$TBSO(CH_2)_5$	**3g**	16 h	**4g** - 95	88
8	$PhCH_2CH_2CH_2$	**3h**	16 h	**4h** - 98	90
9[f]	Ph	**3i**	5 d	**4i** - 78	34

[a] Reaction performed with **3** (0.2 mmol), **2a** (1.3 equiv.) and **1h** (6 mol%) in 1.33 mL of *o*-xylene–$CHCl_3$ 7 : 1 and 0.66 mL of 20% KOH aqueous solution. [b] Isolated yield. [c] Determined from HPLC. [d] Configuration assigned from X-ray crystallography. [e] Reaction performed with 3 equiv. of **2a**. [f] 40% K_3PO_4 aqueous solution used as base.

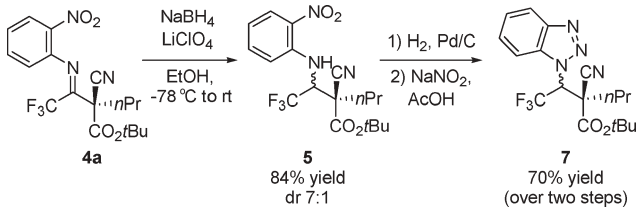
Several synthetic manipulations of the products can be envisioned. For instance, ketimine **4a** was stereoselectively reduced in a substrate-controlled process in high yield and good diastereoselectivity (7 : 1). Subsequent reduction of the nitro-group and treatment with $NaNO_2$ in acidic media led to the formation of the corresponding 1-substituted benzotriazole **7** in good yield (70% over two steps, Scheme 1).

The asymmetric substitution reaction presented here is not limited to the use of trifluoroacetimidoyl chlorides as the electrophilic reaction partner. Preliminary results obtained from the reaction between **3a** and carbethoxyacetimidoyl chloride **2b** in the presence of phase-transfer catalyst **1i** have showed that this methodology can also be used for the synthesis of optically active α-imino esters, such as **8**, with promising selectivities (eqn (1)).



(1)

In summary, we have presented the first example of an asymmetric reaction involving the use of imidoyl halides as the electrophile. The substitution reaction is an effective and practical method for preparing optically active ketimines α-functionalized



Scheme 1 Diastereoselective reduction of the ketimine and benzotriazole formation.

with a quaternary stereocenter. The reaction is catalyzed by a simple and readily accessible catalyst prepared from commercially available and cheap starting materials. The process occurs with generally high yields and with up to 90% ee.

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Notes and references

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8 *Crystal data* for [**4c**]: $C_{20}H_{18}F_3N_3O_5$, M = 437.37, orthorhombic, space group $P2_12_12_1$ (no. 14), a = 8.2352(4), b = 14.0673(5), c = 17.2845(8) Å, V = 2002.36(15) Å^3, T = 100 K, Z = 4, μ(Cu-Kα) = 1.067 mm^{-1}, 8608 reflections collected, 2538 unique (R_{int} = 0.0336) which were used in all calculations. Refinement on F^2, final $R(F)$ = 0.0331, w$R(F^2)$ = 0.0778. Flack parameter is 0.08(14). CCDC 663280. For crystallographic data in CIF or other electronic format, see DOI: 10.1039/b715810f.