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Convenient method for the kinetic resolution of β-aminoalcohols

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Abstract—A variety of easily removable protecting groups were tested in the kinetic resolution of *N*-protected β-aminoalcohols using chiral catalysts derived from *N*-4′-pyridinyl-α-methyl proline. The trifluoroacetyl group was the most promising protecting group as it gave the highest selectivities with all alcohols tested and can easily be removed without loss of enantiomeric excess. This strategy constitutes a convenient method for the kinetic resolution of β-aminoalcohols.

Kinetic resolution (KR) is a method of choice to recover one pure enantiomer from a racemic mixture.[1] Enzymatic methods are well established for the kinetic resolution of alcohols[2] and the last decade has also witnessed the development of nonenzymatic methods using nucleophilic chiral catalysts as acylating agents.[3–16] Recently, we have reported a family of chiral catalysts based on a *N*-4′-pyridinyl-α-methyl proline derivative **1** (Fig. 1) for the KR of racemic alcohols.[17] These catalysts are easily prepared in only two steps and offer diversity by changing the nature of the R group on the proline moiety. We have also shown that when **1** is linked onto a polymeric support, high enantioselectivities can still be obtained even after several uses of the catalyst.[18] This new family of both solution and solid-phase catalysts was in particular screened for the KR of β-aminoalcohols where the amine was protected by a (4-dimethylamino)benzoyl group. Although this amide group provides high enantioselectivities, it requires strong acidic conditions (6 M HCl) to be cleaved.[5a] Here, we report the kinetic resolution of racemic mixture of β-aminoalcohols *N*-protected with easily removable protecting groups.

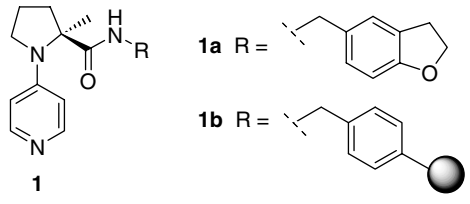

Figure 1.

To start our survey of different protecting groups, we selected (±)-*cis*-1-amino-2-indanol **2** and *N*-protecting groups bearing a carbonyl moiety next to the amine as we believe that this electron-donor group is crucial to obtain high enantioselectivities.[17b] *N*-Protected aminoindanols **2a**–**f** were synthesized using standard procedures and resolved in the presence of isobutyric anhydride and 5 mol % of solution-phase catalyst **1a**[17b] or Merrifield resin-supported catalyst **1b**[18] (Table 1).

From a general point of view, there is a good correlation between selectivities obtained with catalysts in solution and supported on a resin. In our previous work, aminoalcohol **2a** was resolved with high enantioselectivities when protected by a *N*-(4-dimethylamino)benzoyl group (Table 1, entries 1-2). Carbamate derivatives such as **2b** (Cbz) or **2c** (Boc), and pentafluorophenoyl compound **2e** gave lower selectivities (*S* up to 3.8) than phthalimide derivative **2d** ($S = 6.9$ in solution). Higher enantioselectivities both in solution and solid-phase were obtained

Keywords: Kinetic resolution; β-Aminoalcohols; Nonenzymatic nucleophilic catalysts; Enantioselective acylations; Trifluoroacetamides.
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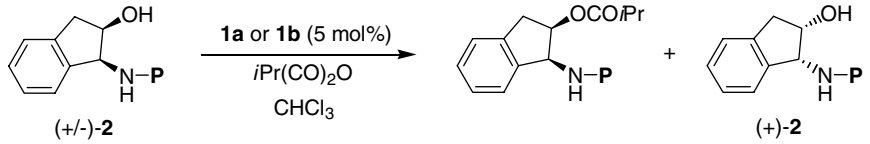
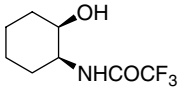
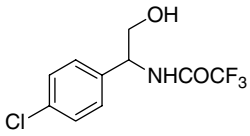
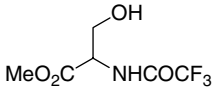
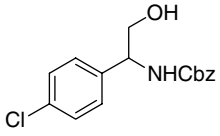
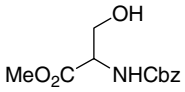
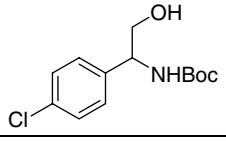
Table 1. Kinetic resolution of *N*-protected *cis*-1-amino-2-indanols **2** with catalysts **1a** or **1b**[a]



Entry	Alcohol	–P	Catalyst	% Conv.[b]	% ee[c]	Selectivity[d]
1	**2a**	$-COC_6H_4$-*p*NMe_2	**1a**	74	99	9.0
2			**1b**	72	97	8.3
3	**2b**	–Cbz	**1a**	49	10	1.3
4			**1b**	40	6	1.3
5	**2c**	–Boc	**1a**	77	83	3.8
6			**1b**	72	60	2.7
7	**2d**	–Phth	**1a**	61	79	6.9
8			**1b**	56	29	2.1
9	**2e**	$-COC_6F_5$	**1a**	51	35	2.8
10	**2f**	$-COCF_3$	**1a**	64[e]	92	9.4
11			**1b**	69[e]	84	5.3

[a] Conditions: aminoalcohol **2** (1 equiv, 0.05 mmol), catalyst **1a** or **1b** (5 mol %), isobutyric anhydride (0.7 equiv for **1a** and 1.2 equiv for **1b**), $CHCl_3$, rt, 16 h.
[b] % Conversion = 100 × ee(recovered alcohol)/[ee(recovered alcohol) + ee(ester formed)].[1]
[c] Enantiomeric excess of the recovered alcohol, determined by HPLC (chiralpak AD column).
[d] The selectivity index (*S*) represents the ratio of rate constants for the more reactive to the less reactive enantiomer.[1]
[e] Determined by ^{19}F NMR (400 MHz) from the ratio of ester formed to recover alcohol.

Table 2. Kinetic resolution of various *N*-protected aminoalcohols with catalyst **1a** or **1b**[a]

Entry	Alcohol		Catalyst	% Conv.[b]	% ee[c]	Selectivity[d]
1	**3a**		**1a**	68[e]	97[f]	10.0
2			**1b**	72[e]	97[f]	8.0
3	**4a**		**1a**	69[e]	97[f]	9.5
4			**1b**	81[e]	97[f]	5.2
5	**5a**		**1a**	71[e]	82[f]	4.6
6			**1b**	72[e]	60[f]	2.7
7	**4b**		**1a**	62	55	3.3
8			**1b**	38	13	1.7
9	**5b**		**1a**	56	13	1.4
10			**1b**	45	7	1.3
11	**4c**		**1a**	63	23	1.6

[a] Conditions: aminoalcohol (1 equiv, 0.05 mmol), catalyst **1a** or **1b** (5 mol %), isobutyric anhydride (0.7 equiv for **1a** and 1.2 equiv for **1b**), $CHCl_3$, rt, 16 h.
[b] % Conversion = 100 × ee(recovered alcohol)/[ee(recovered alcohol) + ee(ester formed)].[1]
[c] Enantiomeric excess of the recovered alcohol, determined by HPLC (chiralpak AD column).
[d] The selectivity index (*S*) represents the ratio of rate constants for the more reactive to the less reactive enantiomer.[1]
[e] Determined by ^{19}F NMR (400 MHz) from the ratio of ester formed to recover alcohol.
[f] Determined by ^{1}H and ^{19}F NMR (750 MHz) using (*R*)-(−)-(9-anthryl)-2,2,2-trifluoroethanol as chiral derivatizing agent.

with **2f** bearing a trifluoroacetyl group as *N*-protective group (*S* up to 9.4). The advantage of trifluoroacetamides is in the ease of formation and in the ease of cleavage of the amide bond. Deprotection of (+)-**2f** was thus carried out in a 2.0 M solution of ammonia in methanol affording (+)-*cis*-1-amino-2-indanol without loss of enantiomeric excess.[19]

In order to establish whether the trifluoroacetyl group could represent a general protecting group for the kinetic resolution of aminoalcohols, this study has been extended to structurally different alcohols **3**–**5** (Table 2). As in previous work, KR studies gave comparable results with solution or solid-supported catalyst for all *N*-protected aminoalcohols. Selectivities obtained with catalyst **1a** were generally slightly better but supported-catalyst **1b** does have the advantage of being easy to recycle and reuse. The trifluoroacetyl group consistently gives better results (Table 2, entries 1–6) than the Cbz and Boc derivatives (entries 7–11) for a range of protected aminoalcohols, matching results obtained with the *cis*-1-amino-2-indanol series. These results form a platform for further studies but indicate that kinetic resolution is possible with a more easily removed protecting group.

In conclusion, we have studied the kinetic resolution of different *N*-protected β-aminoalcohols in the presence of a solution phase or a solid-supported *N*-4′pyridinyl-α-methyl proline derived catalyst. The trifluoroacetyl group represents the most promising *N*-protecting group, giving the highest selectivities with all alcohols tested. The advantages of this protecting group are in its quantitative formation and also in its ease of cleavage without loss of enantioselectivity. We envisage further use of the trifluoroacetyl group for the kinetic resolution of a wide library of structurally different aminoalcohols.

Acknowledgement

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19. Procedure for trifluoroacetamide cleavage: *N*-(CF_3CO)-protected (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol **2f** (0.05 mmol) was stirred at room temperature in 1.5 ml of a 2 M ammonia in methanol solution until completion (2 days). Solvent was removed and (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol was purified on a silica gel column (ethyl acetate then methanol). The optical rotation of recovered alcohol is $[\alpha]_D^{20}$ +62.2 (*c* 0.4, chloroform). In the literature (99% ee/GLC, Aldrich): $[\alpha]_D^{22}$ +63 (*c* 0.2, chloroform).