Enantioenriched Amines

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Kinetic Resolution of Nitrogen Heterocycles with a Reusable Polymer-Supported Reagent**

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Enantioenriched N-heterocycles are commonly prepared by resolution of their racemic mixtures.[1] Surprisingly, enzymatic and other catalytic resolutions of these important building blocks are less developed;[2,3] the state of the art remains separations by diastereomeric salt formation or resolution by chromatography on chiral stationary phases.[4] As an alternative, stoichiometric chiral acylating agents can be used for enantioselective amidation of racemic amines. Researchers, including Fu,[5] Mioskowski,[6] Atkinson,[7] and others,[8] have reported progress on such methods but their widespread use has been precluded by restricted substrate scope, inconvenient reaction procedures, and lengthy syntheses of the reagents.

We have recently developed a method for the catalytic kinetic resolution of cyclic secondary amines featuring the in situ generation of chiral *O*-acyl hydroxamic acid **1**.[9] This enantioselective acylating agent is remarkably robust; it can be purified by column chromatography and stored for prolonged periods without decomposition. This suggests that a solid-supported version of **1** could act as an easily handled reagent for the resolution of amines and could be reloaded and reused (Figure 1). In certain contexts, such as the rapid resolution of a chiral amine with minimal reaction optimization, the transfer of specialized acyl groups, or use in a flow process, a reusable chiral reagent would offer advantages over the catalytic system.[10,11]

We now document the synthesis of the robust and reusable polystyrene-supported reagent **9** and its use for the facile resolution of racemic amines. The resolutions are conducted simply by mixing the racemic amine and this reagent (ca. 0.6 equiv), followed by aqueous extraction or column chromatography to separate the acylated product from the enantioenriched recovered amine. The reagent can be reused dozens of times without loss of efficiency or selectivity. This approach is useful for obtaining enantiopure amines from their racemates as well as preparing enantioenriched amides with groups that can be cleaved under mild conditions. In contrast, our catalytic conditions are currently

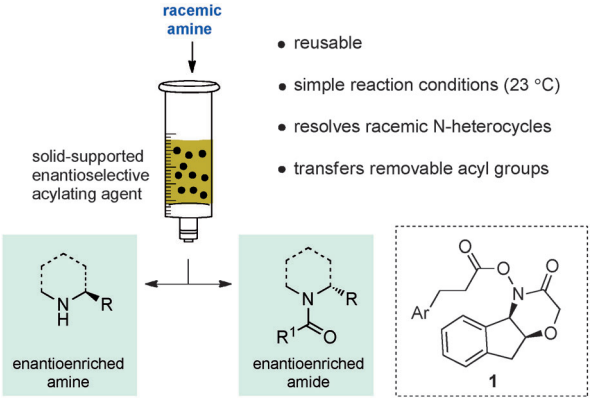

Figure 1. Kinetic resolution of N-heterocycles with a reusable, solid-supported reagent based on chiral stoichiometric reagent **1**.

best suited to the formation of amides that are difficult or impossible to cleave.

The synthesis of solid-supported reagent **9** commenced from bromo-substituted hydroxamic acid **4**, which is available in three steps from inexpensive chiral aminoindanol **2**.[12,13] Heck coupling with benzylacrylate gave **5** in 65% yield.[14] A one-pot procedure consisting of temporary protection of the hydroxamic acid moiety (Ac_2O), reduction of the double bond and the benzyl ester (10% Pd/C, H_2), followed by basic workup (1M LiOH) afforded carboxylic acid **6** in 73% yield. Both enantiomers of hydroxamic acid **6** were prepared and subsequently immobilized onto aminomethyl polystyrene resin **7** using HATU and DMAP. Treatment of the polymer-supported hydroxamic acid **8** with 3-phenylpropionic anhydride generated the desired amine resolving agent **9** (Scheme 1).

We chose racemic 2-ethylpiperidine as a test substrate for resolutions using solid-supported reagent **9**. The best conversions and selectivities were obtained in CH_2Cl_2 owing to the efficient swelling of the resin in this solvent. Optimal conversion of about 60%, which resulted in highly enantioenriched recovered amine, was achieved at 23 °C in 48 h.[15] We also tested various resin loadings, and selected a reagent with 1.0 mmol g^{-1} of transferable acyl groups for the majority of our studies. Resolving N-heterocycles proved to be remarkably easy: 1.0 equiv of the amine was shaken with 0.6–0.7 equiv **9** followed by filtration to recover resin-bound reagent **8**. The resolved amide and unreacted amine were separated by an aqueous extraction or by column chromatography. Reagent **8** was reused by treatment with 3-phenylpropionic anhydride to regenerate **9**. A single batch of **8** has been used for more than 20 cycles across different substrates and acylating agents, and we have not, so far, observed any loss of selectivity or reactivity. This resolution procedure was

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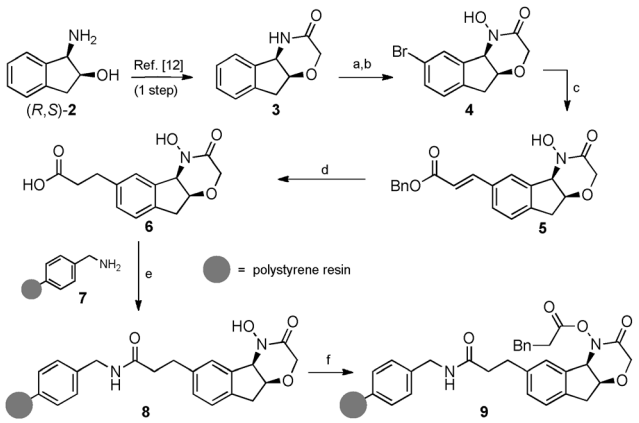
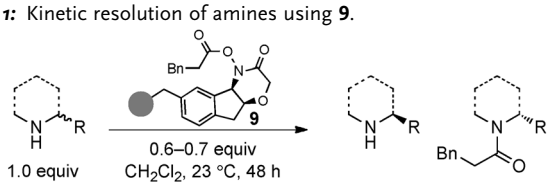
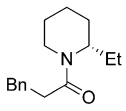
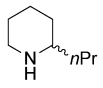
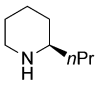
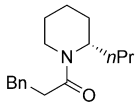
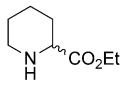
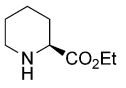
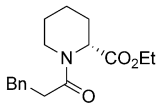
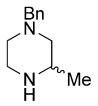
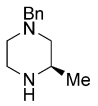
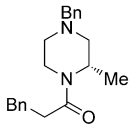
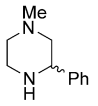
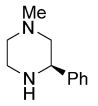
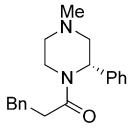
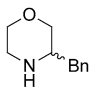
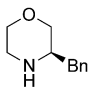
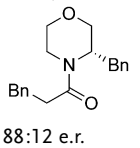
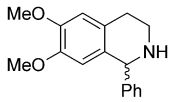
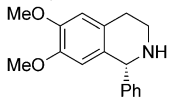
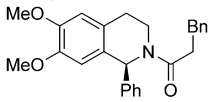
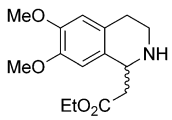
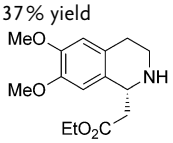
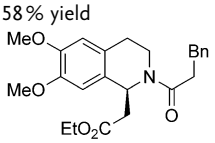
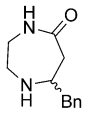
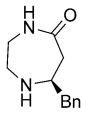
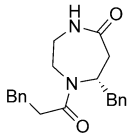


Scheme 1. Preparation of solid-supported amine-resolving agent **9**. Reagents and conditions: a) TFA/H_2SO_4 (3:1) 0 °C, then NBS (1.01 equiv), 80%; b) *N*,*O*-bis(trimethylsilyl)acetamide (1.1 equiv), CH_3CN, 23 °C to 75 °C, then MoO_5·Py·HMPA (MoOPH) (1.2 equiv), CH_2Cl_2, 23 °C, 73%; c) benzylacrylate (1.50 equiv), $Pd(OAc)_2$ (0.10 equiv), P(*o*-tolyl)$_3$ (0.21 equiv), Et_3N (5.00 equiv), CH_3CN, 23 °C to 75 °C, 65%; d) Ac_2O (1.10 equiv), EtOAc, 23 °C to 45 °C, then Pd/C (10 wt%), H_2; then 1 M LiOH, 73%; e) **7**(0.50 equiv), HATU (0.95 equiv), DMAP (1.00 equiv), Hünig's base (3.00 equiv), DMF; f) 3-phenylpropanoic anhydride, DMF, 45 °C. Abbreviations: TFA = trifluoroacetic acid, NBS = *N*-bromosuccinimide, Py = pyridine, HMPA = hexamethylphosphoric acid triamide, HATU = 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate, DMAP = 4-dimethylaminopyridine.

applied to a diverse range of N-heterocycles, including piperidines (Table 1, entries 1–3), piperazines (entries 4 and 5), morpholines (entry 6), tetrahydroisoquinolines (entries 7 and 8), and diazapenones (entry 9), all proceeding with high selectivities and good product recovery.

Table 1: Kinetic resolution of amines using **9**.



Entry	Racemic substrate	Recovered amine	Acylated product
1			
	c = 62%[a] s = 15[b]	98:2 e.r.[c] 19% yield[d]	80:20 e.r.[c] 56% yield[d]
2			
	c = 54% s = 17	93:7 e.r. 21% yield	86:14 e.r. 51% yield
3			
	c = 58% s = 17	96:4 e.r. 32% yield	84:16 e.r. 48% yield
4			
	c = 66% s > 14	> 99:1 e.r. 23% yield	75:25 e.r. 52% yield
5			
	c = 60% s = 13	96:4 e.r. 34% yield	81:19 e.r. 52% yield
6			
	c = 53% s = 20	93:7 e.r. 21% yield	88:12 e.r. 49% yield
7			
	c = 59% s = 23	99:1 e.r. 37% yield	84:16 e.r. 58% yield
8[e]			
		90:10 33% yield	64% yield
9			
	c = 20% s = 19	62:38 e.r. 76% yield	94:6 e.r. 19% yield

[a] Calculated conversion.[16] [b] Selectivity.[16] [c] Enantiomeric ratio determined by SFC or HPLC on a chiral support. [d] Yield of isolated product. [e] Reaction time 96 h; we have focused on the recovered amine in this example (an important precursor of isoquinoline alkaloids).[17]

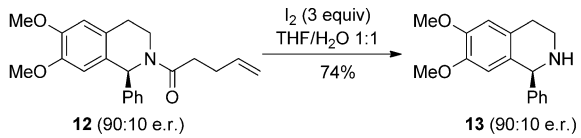
After the resolution, the recovered enantioenriched amine can always be used directly for further manipulations. However, it is often desirable to gain access to both scalemic amines in one single experiment by deprotecting the amide product. This is especially true if the racemic amine is valuable and is essential for the eventual development of dynamic kinetic resolutions.[18] Our initial efforts to cleave the hydrocinnamyl amide under mild conditions using hydrolases[19] or the Schwartz reagent,[20] or under harsher conditions such as reflux with strong acids or bases,[21] were unsuccessful.[22] We therefore sought to identify an easily cleavable, but also readily available, acyl group that could be used in combination with resin **8**.

Several amide-derived protecting groups for amines that are removed under mild conditions have been disclosed.[23]

We selected two examples based on the similarity of the acyl groups to hydrocinnamic acid and the compatibility of the deprotection conditions with our desired substrates. Entwistle reported that 3-(2-nitrophenyl)propanoyl amides can be reduced to the corresponding anilines which undergo spontaneous intramolecular cyclization and releases the amine.[24] Alternatively, the pent-4-enoyl group is rapidly cleaved using iodine.[25] Chiral acylating agents **10** and **11** bearing these groups were easily generated from resin **8** and the corresponding carboxylic acid.

Upon testing these solid-supported reagents with several of our most important substrates, we were pleased to find that the resolutions proceeded under identical conditions to our standard procedure, and with similar efficiencies (Table 2, entries 1–5). With shorter reaction times, which led to lower conversion, highly enantioenriched amides were obtained (entry 2). The use of the removable group and an excess amount of an inexpensive, racemic amine such as 2-ethylpiperidine can be used to easily produce enantioenriched amides (entry 6). Although this approach is less atom-economical, it is a straightforward method to access enantioenriched material from a racemic sample.

Many N-heterocycles, particularly electron-rich tetrahydroisoquinolines, are sensitive to oxidation and epimerization. To confirm that the pent-4-enoyl group can be deprotected without complication in such substrates, we allowed **12** to react with 3 equiv of I_2 in aqueous THF under air, which cleanly afforded the unprotected amine in good yield (Scheme 2). Careful isolation and analysis of the resulting amine product confirmed that neither oxidation nor epimerization occurred during the deprotection.

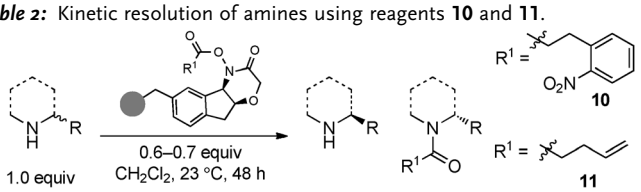


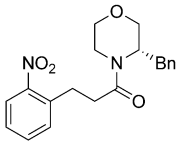
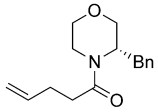
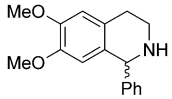
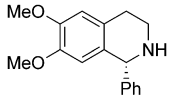
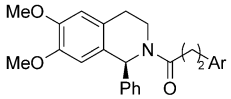
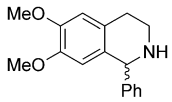
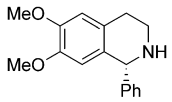
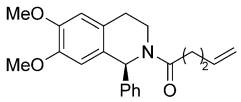
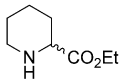
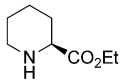
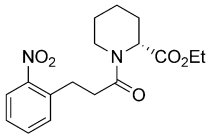
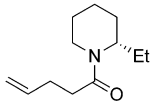
12 (90:10 e.r.) **13** (90:10 e.r.)

Scheme 2. Cleavage of the pent-4-enoyl without racemization.

In summary, we have developed a robust, reusable polymer-bound reagent for the kinetic resolution of a wide range of N-heterocycles. The reagent benefits from brevity of synthesis, high selectivity, robustness, and ease of recovery (more than 20 cycles without erosion of reactivity or selectivity). We have established a simple resolution procedure: shaking the reagent and the amine at room temperature, followed by filtration to separate the reagent from the resolved enantiomers. Importantly, and in contrast to our current catalytic amine resolution, this method allows the facile transfer of acyl groups that can be easily removed from the enantioenriched amide products.

Table 2: Kinetic resolution of amines using reagents **10** and **11**.



Entry	Racemic substrate	Recovered amine	Acylated product
1			
	$c = 47\%$[a] $s = 25$[b]	87:13 e.r.[c] 50% yield[d]	92:8 e.r.[c] 43% yield[d]
2			
	$c = 26\%$[e] $s = 18$	65:35 e.r. 57% yield	93:7 e.r. 21% yield
3			
	$c = 62\%$ $s > 23$	$> 99{:}1$ e.r. 32% yield	80:20 e.r. 61% yield
4			
	$c = 49\%$ $s = 20$	88:12 e.r. 41% yield	90:10 e.r. 44% yield
5			
	$c = 43\%$ $s = 17$	80:20 e.r. 42% yield	90:10 e.r. 40% yield
6[e,f]			
			92:8 er[g]

[a] Calculated conversion.[16] [b] Selectivity.[16] [c] Enantiomeric ratio determined by SFC or HPLC on a chiral support. [d] Yield of isolated product. [e] Reaction time 15 h. [f] Ca. 5 equiv amine was used (unreacted amine was not recovered). [g] 0.3 mmol of the product was obtained.

Experimental Section

Resin-bound reagent **9** (1.00 g, ca. 1.00 mmol g^{-1}, 0.6–0.7 equiv) was swollen in CH_2Cl_2 for 1 h. 6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (380 mg, 1.40 mmol, 1.00 equiv; Table 1, Entry 7) as a solution in CH_2Cl_2 (5 mL) was added to the beads and the mixture was shaken for 48 h. The beads were filtered off and washed with CH_2Cl_2 (7× three times the bead volume). The solution was concentrated under reduced pressure and the amide product and unreacted amine were separated by column chromatography (hexanes/EtOAc 1:1 for the amide; EtOAc/Et_3N 99.9:0.1 for the amine; stationary phase used: silica). Recovered amine 140 mg (37% yield, e.r. = 99:1), acylated product 340 mg (58% yield, e.r. = 84:16). Calculated conversion $c = 59\%$, $s = 23$.

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Communications

Enantioenriched Amines

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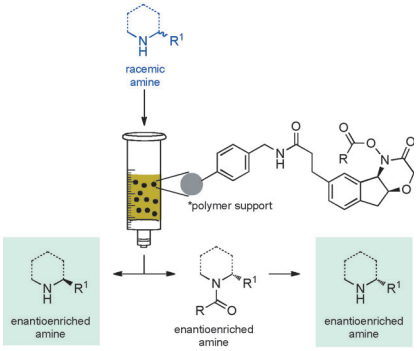
Kinetic Resolution of Nitrogen Heterocycles with a Reusable Polymer-Supported Reagent



Shake it up baby! Simply shaking a polymer-supported reagent and the racemic amine at room temperature kinetically resolves a broad range of N-heterocycles with good selectivity. The polymer-supported reagents are robust, easy to regenerate, and can be reused dozens of times. Cleavable acyl groups can be used to give access to both amine enantiomers in a single resolution.