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Dynamic kinetic resolution (DKR) using immobilized amine nucleophiles

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Abstract—The first example of a dynamic kinetic resolution (DKR) using immobilized amine nucleophiles is described. This approach utilizes a nucleophilic amine attached to a solid phase resin via an organic spacer. The optical purities of the N-substituted α-amino ester products are superior to the solution phase DKR with diastereomeric ratios ranging from 11:1 to 18:1 and chemical yields between 66% and 98%.

During the last decade, there has been tremendous interest in using polymeric supports for the preparation of small molecules including polypeptides,[1] oligosaccharides,[2] and nucleic acids[3] using both soluble and insoluble resin beads. Several excellent reviews have been published describing these approaches.[4] Despite the enormous impact of this approach on the chemical community, a relatively small number of polymer-supported asymmetric reactions have been reported. These examples utilize cycloaddition reactions with resin-supported dienophiles or dipolarophiles,[5,6] Diels–Alder reactions of *N*-crotyl oxazolidinones,[7] 1,3-dipolar cycloaddition reactions using mesitonitrile oxide,[8] and photochemical [2 + 2] cycloadditions.[9] More recently, the preparation of structurally diverse and chirally defined 1,3-oxazolidines has been described.[10] To the best of our knowledge, there have been no reports of polymer-supported kinetic resolutions[11] or dynamic kinetic resolutions.[12] This paper describes the first example of a dynamic kinetic resolution using immobilized amine nucleophiles.

The DKR reaction in this study was modeled after an earlier system useful for the preparation of N-substituted α-amino acid derivatives using α-bromo-(*R*)-pantolactonyl esters and various amines.[13] In our approach, polymer-supported amines were employed as nucleophiles and substituted α-bromo-(*R*)-pantolactonyl esters were used as electrophiles (Fig. 1). Preparation of the substituted α-bromo-(*R*)-pantolactonyl ester derivatives is outlined in Scheme 1.[13b,d] The resin-bound amines (**4a**–**c**) were prepared by coupling Fmoc-protected amino alkanoic acids to MBHA poly(chloromethylstyrene) supports using standard solid phase protocols. Nucleophilic resins with 1, 3, and 10 carbon spacers were prepared.

Reaction of **1** (2.5 equiv) with **4a** produced negative Kaiser and TNBS tests after 2 days (Scheme 1) indicating

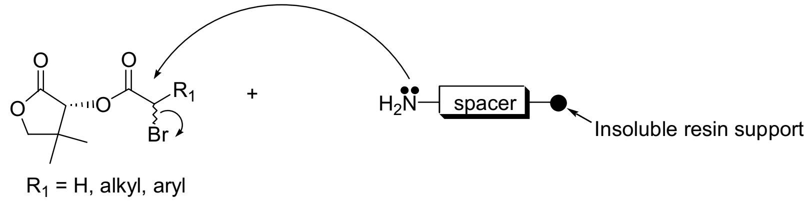

Figure 1.

Keywords: Solid phase; Dynamic kinetic resolution; Resin-bound amine; Immobilized amine.

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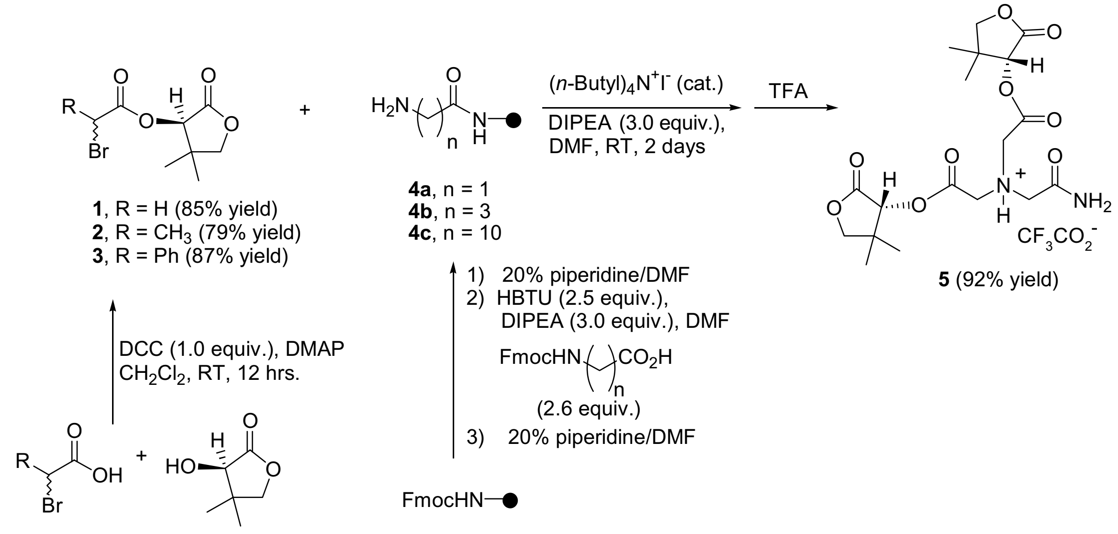


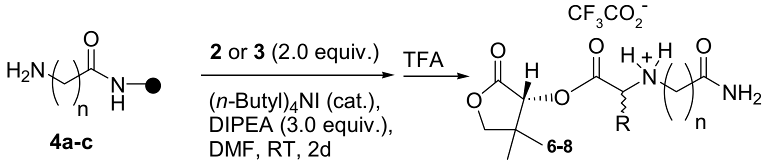
Scheme 1.

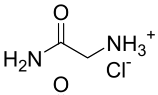
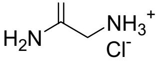
that all of the amines on the resin bead had reacted. Removal of the substrate from the resin by treatment with TFA and characterization by NMR and mass spectrometry confirmed formation of dialkylated product **5** in 92% isolated yield. No trace of the monoalkylated product was detected. This result suggested that while DKR using immobilized amine nucleophiles was feasible, selective formation of mono- and bis-alkylation products may be difficult to control. However, DKR performed with α-substituted esters **2** and **3** furnished only monoalkylated products (Table 1). The exclusive formation of monoalkylated products is attributed to the fact that the secondary amine of products **6–8** is sterically hindered and not prone to reaction with another equivalent of electrophile.

The size of the α-substituent influences the diastereomeric ratios in the formation of products **6–8**. For instance, **6a** ($R = CH_3$) is formed as a 14:1 diastereomeric ratio while **6b** (R = Ph) is produced as an 18:1 diastereomeric ratio. This trend is also observed as the length of the organic spacer between the amino group and the resin increases (Table 1, entries 3–6).

Typical DKR using α-substituted (*R*)-pantolactonyl esters has been shown to favor formation of N-substituted α-amino-(*R*)-pantolactonyl esters with the (*S*,*R*) configuration.[13a] The stereochemical configuration of the major diastereomer in our DKR using immobilized amine nucleophiles was determined by comparing the ^{1}H NMR of products **6–8** with the same products pre-

Table 1. DKR using immobilized amine nucleophiles

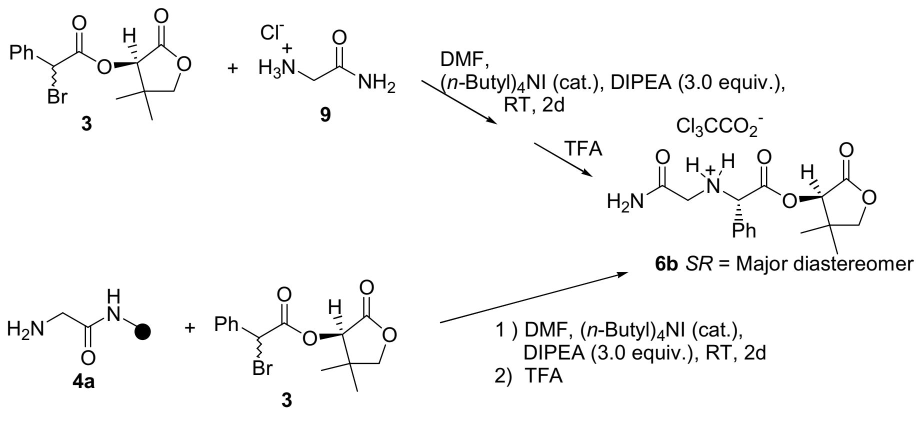


Entry	Nucleophile	Substrate	Product	% Yield[a]	Dr (*S*,*R*/*R*,*R*)[b]
1	**4a** (*n* = 1)	**2**	**6a** ($R = CH_3$, *n* = 1)	66	14:1
2	**4a** (*n* = 1)	**3**	**6b** (R = Ph, *n* = 1)	91	18:1
3	**4b** (*n* = 3)	**2**	**7a** ($R = CH_3$, *n* = 3)	89	11:1
4	**4b** (*n* = 3)	**3**	**7b** (R = Ph, *n* = 3)	84	15:1
5	**4c** (*n* = 10)	**2**	**8a** ($R = CH_3$, *n* = 3)	>95	10:1
6	**4c** (*n* = 10)	**3**	**8b** (R = Ph, *n* = 3)	>95	15:1
7	**9**[c]; 	**2**	**6a** ($R = CH_3$, *n* = 1)	95	3:1
8	**9**[c]; 	**3**	**6b** (R = Ph, *n* = 1)	92	4:1

[a] Yields are reported as crude yields.

[b] Diastereomeric ratios (*S*,*R*/*R*,*R*) were determined using 360 MHz ^{1}H NMR.

[c] Typical DKR conditions; substrate was *not* immobilized on resin during DKR.

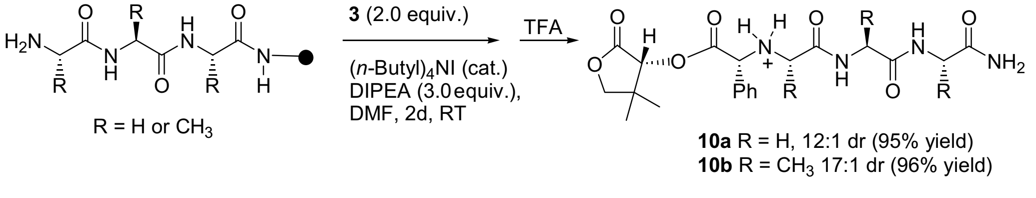


Scheme 2.

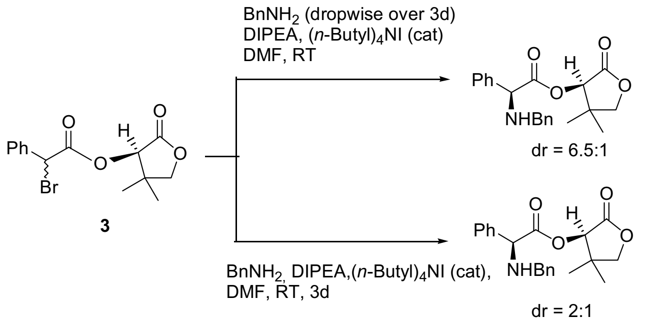
pared via traditional DKR as outlined in Scheme 2. Comparison of the NMR spectra indicated that the major diastereomer from DKR using resin-bound amines possessed the (*S*,*R*) configuration, consistent with typical DKR.

The diastereoselectivities of DKR using resin-supported amines are unexpectedly high when compared to typical DKR. For instance, reaction of electrophiles **2** or **3** with glycinamide hydrochloride **9** under typical DKR conditions furnished compounds **6a** and **6b** in only 3:1 and 4:1 diastereomeric ratio (Table 1, entries 7 and 8). In contrast, DKR using an immobilized amine nucleophile (**4a**) with substrate **2** or **3** produced **6a** (R = CH$_3$) and **6b** (R = Ph) as a 14:1 and 18:1 diastereomeric ratio, respectively. This marked increase in diastereoselectivity was initially attributed to the fact that the resin-bound amine is sterically more demanding than the primary amine in a typical DKR. However, the fact that resin-bound amines with 3 and 10 carbon flexible spacers (**4b** and **4c**) yielded **7a/7b** and **8a/8b** with nearly identical optical purities (Table 1, entries 3–6) was surprising given that as the spacer length increases, the amine is further from the resin bead and steric effects from the bead would be significantly reduced. A plausible explanation for this is that the flexible carbon spacer was not adopting an extended conformation. With this in mind, DKR using immobilized amines with rigid polyglycine and polyalanine tripeptide spacers was performed (Scheme 3). However, these spacers furnished **10a/10b** in a 12:1 and 17:1 diastereomeric ratio, respectively, confirming that steric effects from the resin bead were not responsible for the increase in diastereoselectivity when using immobilized amine nucleophiles.

A typical DKR involves a product-forming reaction between two diastereomeric starting materials however, a key element of the DKR is that these starting materials readily interconvert and this interconversion is much faster than the product-forming reaction. In our case, reaction of the immobilized amine with substrates **1**–**3** constitutes the product-forming reaction while, epimerization of **1**–**3** occurs by reaction with tetra-*N*-butyl ammonium iodide. DKR using an immobilized amine nucleophile is a heterogeneous reaction as the polymer support is insoluble in DMF while a traditional DKR is homogeneous in nature. However, the epimerization reaction is homogeneous in both cases. Given that the rate of a heterogeneous product-forming reaction (S_N2) is expected to be considerably slower than that of a homogeneous reaction, it is plausible that the observed increase in diastereoselectivity associated with the immobilized amine nucleophiles may be a result of this fact. A related hypothesis centers on the fact that the concentration of resin-bound amine is comparatively low, resulting in a decreased rate for the product-forming reaction relative to a typical DKR. This decreased rate would allow for a more efficient epimerization process and increased diastereoselectivities. To explore this possibility, a syringe pump addition experiment was performed to simulate the low concentration of the resin-bound amine in the DKR reaction (Scheme 4). In this experiment, substrate **3** was dissolved in dry DMF with DIPEA (1.3 equiv), *n*-butyl ammonium iodide (cat.), and benzylamine (1.1 equiv) was added via syringe pump over 3 days. This experiment furnished the desired N-substituted α-amino-(*R*)-pantolactone ester in a 6.5:1 diastereomeric ratio and quantitative yield. The identical experiment performed without a syringe pump



Scheme 3.



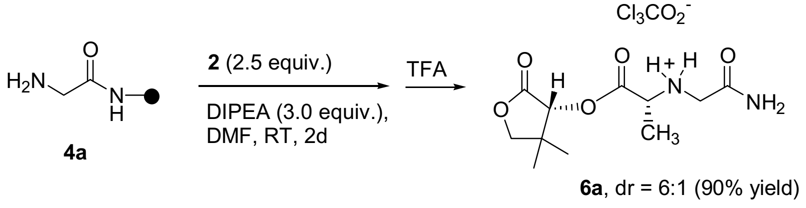
Scheme 4.

addition of benzylamine produced a 2:1 diastereomeric ratio, indicating that the low concentration of amine nucleophile is contributing to the unusually high diastereoselectivity observed in the DKR using immobilized amine nucleophiles. Unfortunately, this experiment does not preclude the possibility that multiple amines may interact in a co-operative manner within the confines of the resin. Furthermore, this experiment does not elucidate the relative rate difference between a heterogeneous DKR and a homogeneous DKR.

Much like in the typical DKR, a catalytic amount of *n*-alkyl ammonium iodide is essential for high diastereoselectivity in the SP–DKR. Reaction of immobilized amine **4a** with **2** furnished **6a** as a 14:1 diastereomeric ratio (Table 1, entry 1). However, when the reaction is performed in the absence of tetra-*n*-butyl ammonium iodide, **6a** is produced as a 6:1 diastereomeric ratio (Scheme 5). Since the catalytic iodide ion epimerizes the α-bromo-(*R*)-pantolactonyl ester, this result implies that a fast interconversion between the (*R*,*R*) and (*S*,*R*) diastereomers of **2** is still important when using immobilized amine nucleophiles. Furthermore, the epimerization is still faster than that of the heterogeneous product-forming reaction.

In summary, we propose that the mechanism for the DKR using immobilized amine nucleophiles (Fig. 2) is very similar to that of the solution phase DKR. One of the most unusual features of the typical DKR is that one major product is formed in greater than 50% yield, despite the fact that the α-bromo-(*R*)-pantolactonyl ester is a racemate ($S,R/R,R = 1{:}1$). This is explained in that one of the α-bromo-(*R*)-pantolactonyl esters undergoes S_N2 reaction faster than the other and the slower reacting diastereomer is epimerized to the faster one in situ. As the major diastereomer from the DKR using resin-bound amines is (*S*,*R*), we conclude that the (*R*,*R*) diastereomer is the faster reacting diastereomer and this is due to formation of an intermolecular hydrogen bond that facilitates delivery of the amine nucleophile.[13b] It is likely that the transition states for the faster and slower reacting diastereomers in the SP–DKR are similar to those of a typical DKR as outlined in Figure 2.

We have demonstrated the first example of a DKR using immobilized amine nucleophiles. Relative to traditional DKR, the diastereoselectivities are superior ranging from 11:1 to 18:1 dr with product yields nearly quantitative in most cases. Our results suggest that the unusually high diastereoselectivities are not attributed to steric effects from the resin but the fact that this is a heterogeneous reaction and the concentration of the immobilized amine nucleophile on the resin is low. This



Scheme 5.

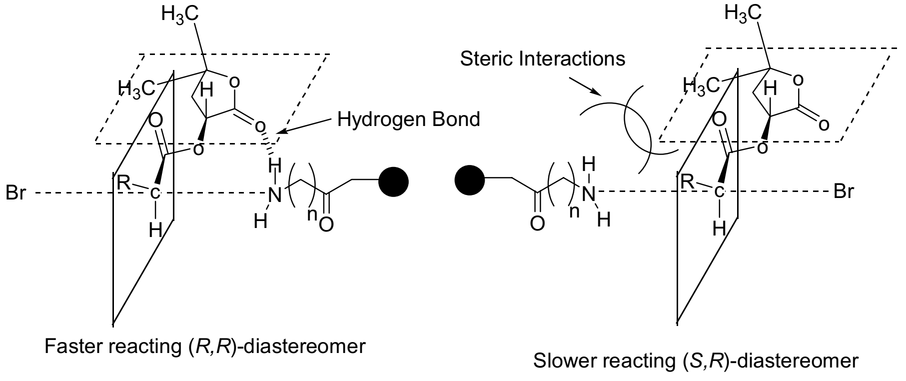


Figure 2. Proposed transition states for substrates **2** and **3**.

approach constitutes a useful method for preparing N-substituted α-amino acid derivatives with high optical purities using solid phase synthesis. The scope of this reaction and applications are currently being explored.

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