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Nonenzymatic, Enantioconvergent Dynamic Kinetic Resolution (DKR) of Racemic 2-(1*H*-Pyrrol-1-yl)alkanoic Acids as α-Amino Acid Equivalents

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We report an effective dynamic kinetic resolution (DKR) system of racemic 2-(1*H*-pyrrol-1-yl)alkanoic acids, which consists of a rapid racemization step via an activating substrate and an enantio-discriminating step via catalytic esterification. The combination of pivalic anhydride as an activating agent, bis(α-naphthyl)methanol as an achiral alcohol, (*R*)-BTM as a chiral acyl-transfer catalyst, and Hünig's base converted racemic 2-(1*H*-pyrrol-1-yl)alkanoic acids to the corresponding chiral carboxylates, which can be transformed into chiral α-amino acid derivatives with maintained high enantiopurity.

α-Amino acids have long been considered fundamental moieties in organic chemistry, and the enantio-controlled and catalytic construction of the chiral α-position of α-amino acids has been targeted as an attractive synthetic goal.[1–6]

In order to provide large amounts of chiral α-amino acids from racemic α-amino acids, dynamic kinetic resolution (DKR)[7,8] has been anticipated to be an ideal method. While a wide range of enzymatic DKRs[9–11] for α-amino acid derivatives has been disclosed as reliable methodologies, non-enzymatic DKRs have also emerged as promising approaches during the last decade. However, major examples of the successful non-enzymatic DKR of chiral α-amino acids have involved the catalytic ring-opening alcoholysis of cyclic precursors, such as racemic urethane-protected α-amino acid *N*-carboxyanhydrides (Deng[12]) and racemic 2-phenylazlactones (Seebach,[13] Fu,[14] Berkessel,[15–17] Connon,[18,19] Birman,[20,21] etc.). Note that the DKR systems for racemic 2-phenylazlactones principally allowed production of *N*-benzoyl amino acids with high enantiopurities.

As illustrated in Figure 1, we have reported the effective kinetic resolution (KR) of racemic α-arylpropanoic acids[22] using carboxylic anhydride as the coupling agent, bis(α-naphthyl)-methanol as the achiral alcohol, and benzotetramisole (BTM)[23] as the chiral acyl-transfer catalyst. In this procedure, a racemic mixture of α-arylpropanoic acids was separated into the corresponding chiral carboxylates and the recovered chiral carboxylic acids with high selectivity. A mechanistic study[24] revealed that this enantioselective esterification proceeds through a mixed anhydride (MA), a reactive intermediate formed from the substrate and the coupling reagent, followed by formation of a transition state (TS) with the achiral alcohol and chiral BTM. Furthermore, acceleration of the racemization process in a polar reaction media such as DMF led to the development of the corresponding DKR system for α-arylpropanoic acids.[25]

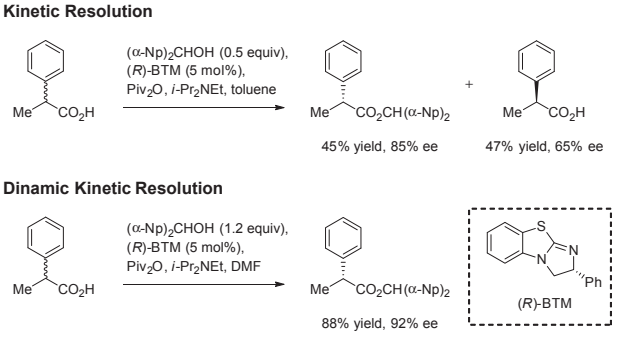


Figure 1. Previous studies of KR/DKR via asymmetric esterification.

Despite the growing number of DKR systems reported to date, there has yet been no example of a catalytic DKR system for protected α-amino acids via direct esterification using acyclic precursors. Moreover, to the best of our knowledge, there are no examples of catalytic DKR systems for any racemic α-nitrogen-containing carboxylic acids. In the present study, we report the first DKR of racemic 2-(1*H*-pyrrol-1-yl)alkanoic acids, which can then be converted to α-amino acids.

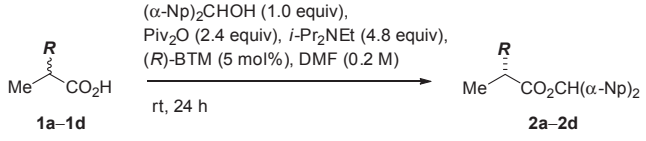
In general, rapid racemization of substrates bearing an amino group at the α-position seemed to be a significant challenge because of the low acidity of α-protons, which results from the presence of very electron-rich amino groups. In order to achieve both rapid racemization of the intermediates and enantioselective esterification, one solution was to modify the α-amino group in an appropriate manner. Thus, a variety of propanoic acids bearing modified α-amino groups were screened using the similar conditions established in our previous study:[25] 1.0 equiv of bis(α-naphthyl)methanol, 2.4 equiv of Piv_2O, 4.8 equiv and *i*-Pr_2NEt, 5 mol % (*R*)-BTM, and DMF (Table 1).

First, *N*-benzoyl alanine (**1a**), *N*-Boc alanine (**1b**), and *N*-Cbz alanine (**1c**) were tested as commonly used substrates containing a protected α-amino group (Entries 1, 2, and 3). We expected DKR to proceed smoothly and only one enantiomeric isomer of the corresponding ester to be obtained in over 50% yield. However, contrary to our expectations, the yields and enantiopurities of the obtained esters **2a**, **2b**, and **2c** were both poor (≤42% yield, ≤10% ee).

Given the similarity in size and aromaticity of these α-substituents to the α-phenyl group, it was anticipated that a promising precursor of an α-amino acid would contain a substituent similar to a benzene ring with a nitrogen atom at the α-position, such as an *N*-heteroaromatic ring. Therefore, racemic 2-(1*H*-pyrrol-1-yl)propanoic acid (**1d**) was next subjected to screening (Entry 4). As we anticipated, the reaction proceeded with high enantioselectivity, and the yield of the major isomer of the corresponding ester exceeded 50% (72% yield, 89% ee), thus the occurrence of the aimed DKR was evident.

Furthermore, other substrates **1e**–**1g** bearing *N*-heteroaromatic rings at the α-position were investigated (Entries 2–4

Table 1. Initial studies of various substrates bearing α-amino groups



1a–1d 2a–2d

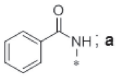
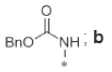
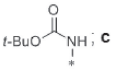
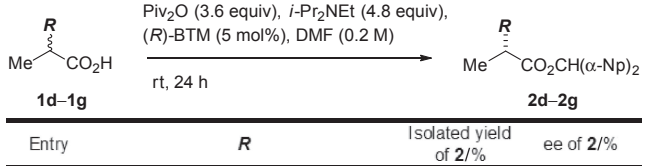
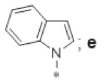
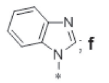
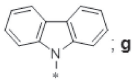
Entry	R	Isolated yield of 2/%	ee of 2/%
1	 ; a	Trace	—
2	 ; b	23	10
3	 ; c	42	7
4	 ; d	72	89

Table 2. Investigations of DKR of α-amino acid derivatives bearing *N*-heteroaromatic rings at the α-position



1d–1g 2d–2g

Entry	R	Isolated yield of 2/%	ee of 2/%
1	 ; d	76	86
2	 ; e	87	91
3	 ; f	71	77
4	 ; g	62	64

in Table 2). Racemic 2-(1*H*-indol-1-yl)propanoic acid (**1e**) also proved to be a promising substrate, providing the corresponding carboxylate **2e** in 87% yield with 91% ee (Entry 2). However, substrates bearing benzimidazole and carbazole substituents provided lower yields and enantioselectivities (Entry 3, 71% yield, 77% ee, and Entry 4, 62% yield, 64% ee). Thus, the screening process indicated that pyrrole and indole rings are suitable for the DKR system (Entries 1 and 2).

As illustrated in Figure 2, 2-(1*H*-pyrrol-1-yl)alkanoic acids are readily prepared via the Clauson–Kaas synthesis,[26,27] which involves refluxing the corresponding α-amino acid with commercially available 2,5-dimethoxytetrahydrofuran,[28,29] while the pyrrole group is chemoselectively degraded by ozonolysis.[30,31] Therefore, the pyrrole group (Table 1, Entry 4) seems to be

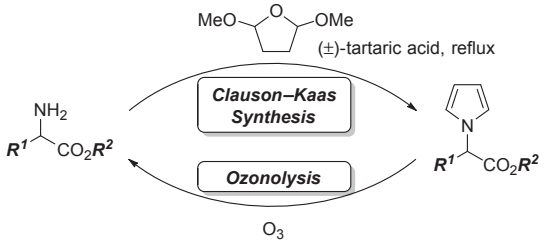
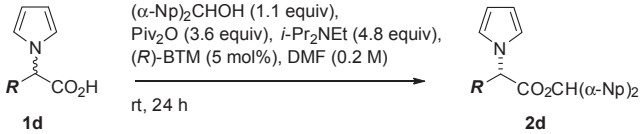
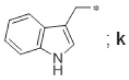
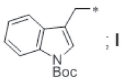
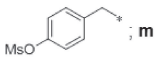
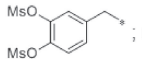


Figure 2. Modification of α-amino groups via Clauson–Kaas synthesis and degradation of pyrrole groups via ozonolysis.

Table 3. Examination of DKR of various racemic 2-(1*H*-pyrrol-1-yl)alkanoic acids



1d 2d
1h–1n 2h–2n

Entry	R	Isolated yield of 2/%	ee of 2/%
1	Me; d	76	86
2	Et; h	67	71
3	Pr; i	64	67
4	Bn; j	81	87
5	 ; k	58	84
6	 ; l	64	86
7	 ; m	80	88
8	 ; n	80	92

sufficiently useful as a protected *N*-terminal group for the preparation of enantiomerically active α-amino acids via DKR.

In order to investigate the utility of α-amino acids in our DKR system, a variety of racemic 2-(1*H*-pyrrol-1-yl)alkanoic acids **1h**–**1n** were prepared from the corresponding α-amino acids via the Clauson–Kaas synthesis (see Supporting Information), and then subjected to DKR (Table 3).

Racemic 2-(1*H*-pyrrol-1-yl)alkanoic acids bearing extended alkyl chains, such as ethyl, propyl, and benzyl, gave reasonable yields and enantiomeric excesses around 70%–80% (Entries 2–4). With racemic carboxylic acids bearing an arylmethyl moiety, which is common to many biogenic α-amino acids, the corresponding esters were obtained with good to high enantioselectivity. In particular, pyrrole substrates derived from phenylalanine[32] (Entry 4), mesylated-tyrosine (Entry 7), and mesylated-DOPA (Entry 8) provided the corresponding esters **2j**, **2m**, and **2n** in over 80% yield with high enantioselectivities (near 90% ee). Furthermore, substrates derived from tryptophan (Entry 5) and Boc-protected tryptophan (Entry 6) also provided the desired enantiomerically active esters **2k** and **2l** in good yields with high selectivities (84% ee and 86% ee, respectively).

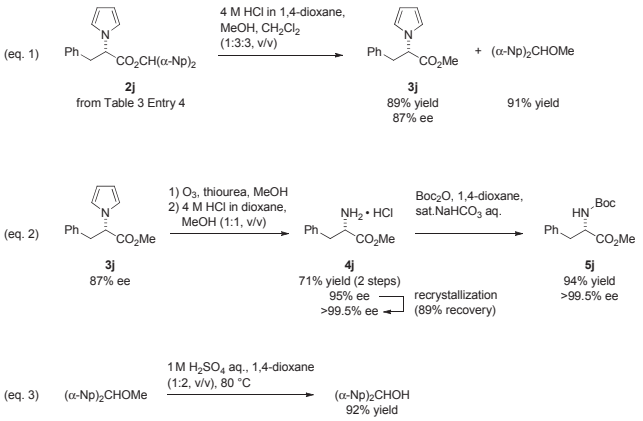


Figure 3. Synthesis of *N*-Boc α-amino acid methyl ester **5j** and recovery of $(\alpha\text{-Np})_2$CHOH.

Note that the present successful development of DKR of various racemic 2-(1*H*-pyrrol-1-yl)alkanoic acids was realized by the preferable rapid racemization of pyrrole substrates under suitable conditions to form a MA using Piv_2O with *i*-Pr_2NEt and BTM in a polar solvent.

With the substrate scope in hand, our attention then turned to demonstrating the derivatization of the enantiomerically active bis(α-naphthyl)methyl carboxylates produced in DKR. In these studies, product **2j** (Table 3, Entry 4; R = Bn, 87% ee) was chosen as a standard substrate.

As shown in Figure 3, the enantiomerically active bis(α-naphthyl)methyl carboxylate **2j** was readily converted to the corresponding *N*-Boc α-amino acid methyl ester **5j** and bis(α-naphthyl)methanol. Prior to the degradation of the pyrrole ring, an ester-exchange reaction of **2j** afforded methyl carboxylate **3j** in 89% yield, while the bis(α-naphthyl)methyl moiety was isolated as bis(α-naphthyl)methyl methyl ether in 91% yield (eq 1). Subsequently, **3j** was subjected to ozonolysis, followed by treatment with HCl in dioxane, to provide **4j** whose ee increased to 95% after solidification in the usual work-up (eq 2, 71% yield in 2 steps). Single recrystallization of the resulting solid afforded enantiomerically pure **4j**. After protection, *N*-Boc phenylalanine methyl ester **5j** was obtained in 94% yield with the retention of high enantiomeric excess (eq 2, >99.5% ee). In addition, the valuable bis(α-naphthyl)methanol was recovered via hydrolysis of bis(α-naphthyl)methyl methyl ether in 92% yield (eq 3).

In summary, we have developed an effective DKR system that provides enantiomerically active 2-(1*H*-pyrrol-1-yl)alkanoic acids from their corresponding racemates. The present series of conversion processes enables the preparation of chiral pyrroles and their derivatives in good yields and high enantiomeric excesses starting from the corresponding racemic 2-(1*H*-pyrrol-1-yl)alkanoic acids.

Supporting Information is available electronically on J-STAGE.

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32 Absolute configuration of the product **2j** in Table 3, Entry 4 was determined as *S* by the chiral HPLC analysis (see Supporting Information).