Kinetic Resolution

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Recyclable Ligands for the Non-Enzymatic Dynamic Kinetic Resolution of Challenging α-Amino Acids

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Abstract: *Structurally simple and inexpensive chiral tridentate ligands were employed for substantially advancing the purely chemical dynamic kinetic resolution (DKR) of unprotected racemic tailor-made α-amino acids (TM-α-AAs), enabling the first DKR of TM-α-AAs bearing tertiary alkyl chains as well as multiple unprotected functional groups. Owing to the operationally convenient conditions, virtually complete stereoselectivity, and full recyclability of the source of chirality, this method should find wide applications for the preparation of TM-α-AAs, especially on large scale.*

With the complete elucidation of the human genome, as well as the genomes of numerous animals, plants, and bacteria, the broad multidisciplinary area of synthetic biology has rapidly become a subject of major scientific advancements.[1] In particular, engineering genetically modified organisms that depend on tailor-made α-amino acids (TM-α-AAs)[2] is one of the recent breakthroughs in biocontainment research.[3] The development of methods for the synthesis of various TM-α-AAs in enantiomerically pure form is clearly one of the critical components of any effort to understand the proteome and its relation to life, disease, and health.[4] Furthermore, owing to the rapidly growing number of pharmaceutical products that incorporate TM-α-AAs in their structures,[5] the interest in the development of new methods for the preparation of TM-α-AAs in enantiomerically pure form is at an all-time high.[6,7]

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Among various approaches to enantiomerically pure TM-α-AAs,[6–8] the dynamic kinetic resolution (DKR) of racemates is unarguably the most economic solution, especially on a large scale.[9] However, the choice of methods available for such processes is overwhelmingly dominated by biocatalytic procedures,[10] whereas purely chemical methods[11] have been disproportionally underdeveloped and prohibitively expensive.[12] Therefore, to surpass the exceptional efficiency of enzymatic approaches,[10] a purely chemical method should feature an ingenious combination of simple and high-yielding reactions, operationally convenient conditions,[13] as well as inexpensive starting materials and a recyclable source of chirality. As part of our long-term interests in the development of practical methods for the preparation of TM-α-AAs and TM-β-AAs[14,15] and drawing inspiration from work by Chin and co-workers,[16] we have recently been focusing on the development of new types of chiral ligands that are suitable for direct and practically useful DKR reactions of unprotected TM-α-AAs.

In particular, compounds **1** and **2**, which were reported by Chin[16] and co-workers and ourselves,[17] are considered as the best-performing ligands for the direct DKR of unprotected TM-α-AAs (Figure 1). For both types of ligands, DKR

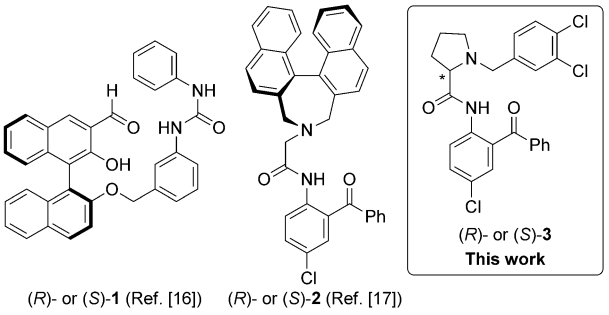

Figure 1. The previously reported ligands **1** and **2**, which contain axially chiral 1,1′-binaphthyl moieties, and the structurally advantageous proline-derived ligands **3**, which were used in this work.

proceeds via the corresponding Schiff base intermediates followed by thermodynamic equilibration of the resulting diastereomers. However, ligands **1** and **2** also share the same shortcomings: 1) They completely fail in the DKR of amino acids with tertiary side chains, and 2) as they are based on axially chiral 1,1′-binaphthyl moieties, they are rather expensive to rival the economic efficiency of enzymatic methods for the large-scale preparation of TM-α-AAs. Continuing our work on modular approaches to chiral ligands,[18] we identi-

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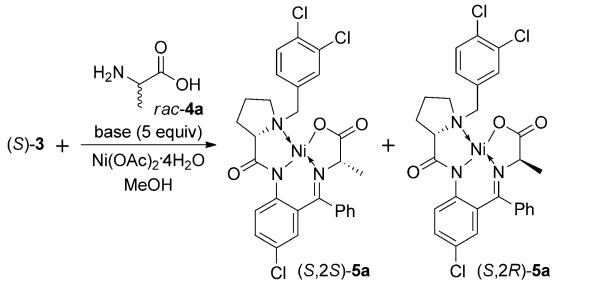
fied the structurally advantageous, proline-derived ligands **3**, which can be readily prepared in both the *S*- and *R*-enantiomeric forms on any scale.[19] In this work, we report that with the fully recyclable ligands **3**, the DKR of unprotected TM-α-AAs proceeds with virtually complete stereoselectivity under operationally simple and convenient reaction conditions. Furthermore, the present method has broad synthetic generality, and can be applied to most challenging, sterically constrained substrates with tertiary side chains. These features, in combination with the very low cost of the recyclable ligands **3**, bode well for their wide application for the practical preparation of enantiomerically pure TM-α-AAs of academic and pharmaceutical importance.

The optimization of the reaction conditions for the DKR of racemic α-AAs with ligand (*S*)-**3** was methodically studied, considering the strengths of bases, polarities of solvents, various Ni^{II} ion sources, the effects of the reaction temperature and time, as well as varying the stoichiometric ratios of all starting materials. Some key experimental data leading to the optimized conditions are presented in Table 1. For the optimization study, we selected racemic alanine (*rac*-**4a**), which bears a sterically and electronically unimposing methyl group. The best conditions that we were able to attain are given in entry 1: Under these conditions, the DKR of *rac*-**4a** led to the formation of a single diastereomer (> 98% d.e.) of (*S*,2*S*)-**5a** in an excellent chemical yield (97%). The strength of the base that catalyzes the intermediate formation of the corresponding Schiff bases as well as the thermodynamic equilibration of the diastereomers (*S*,2*S*)-**5a** and (*S*,2*R*)-**5a** was found to be particularly important. For example, the use of organic bases, such as triethylamine (TEA; entry 2) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; entry 3), for the

Table 1: Optimization of the reaction conditions for the DKR of racemic alanine **4a** using ligand (*S*)-**3**.[a]



Entry	Base	*T* [°C]	*t* [h]	Yield [%][b]	d.r.[c]
1	K_2CO_3	60	3	97	99:1
2	TEA	60	36	13	91:9
3	DBU	60	36	61	96:4
4	Na_2CO_3	60	36	94	96:4
5	K_2CO_3	RT	48	94	99:1
6[d]	K_2CO_3	60	8	85	99:1

[a] Reaction conditions: (*S*)-**3** (0.20 mmol), *rac*-**4a** (0.22 mmol), $Ni(OAc)_2 \cdot 4H_2O$ (0.22 mmol), and base (1 mmol) in methanol (4 mL). [b] Combined yield of isolated (*S*,2*S*)-**5a** and (*S*,2*R*)-**5a**. [c] Determined by HPLC and ^1H NMR analysis of the crude products (*S*,2*S*)-**5a**/(*S*,2*R*)-**5a**. [d] (*S*)-**3** (0.22 mmol), *rac*-**4a** (0.20 mmol), $Ni(OAc)_2 \cdot 4H_2O$ (0.22 mmol), K_2CO_3 (1 mmol) in methanol (4 mL).

DKR of *rac*-**4a** resulted in an unimpressive stereochemical outcome, most likely owing to rather slow reaction rates. An improved chemical yield, but still incomplete diastereoselectivity, was also observed with Na_2CO_3 (entry 4). A near-perfect stereochemical outcome could be obtained at ambient temperature for reactions mediated by K_2CO_3. However, in this case, full thermodynamic control took about 48 hours (entry 5). To achieve better reaction rates, we used a 10% excess of *rac*-**4a**, considering the fact that racemic amino acids are usually relatively inexpensive starting materials. However, in view of a possible situation where the racemate may be rather expensive, the chiral ligand (*S*)-**3** can be used in excess without virtually any effect on the DKR outcome (entry 6). Finally, the major and minor diastereomeric products, (*S*,2*S*)-**5a** and (*S*,2*R*)-**5a**, were isolated in diastereomerically pure form. Their structures were confirmed by ^1H and ^{13}C NMR spectroscopy and mass spectrometry, and their absolute stereochemistry was undoubtedly determined by single-crystal X-ray diffraction (see the Supporting Information for details).

With optimized reaction conditions in hand, we were in a position to carry out a systematic substrate generality study using various types of TM-α-AAs with different steric, functional, and electronic characteristics (for the full substrate scope, which contains 78 examples, see the Supporting Information). Here, we will discuss only the most representative examples (Table 2).

First, we investigated a series of TM-α-AAs containing straight alkyl chains, such as methyl, ethyl, *n*-propyl, and *n*-butyl (Table 1, entries 1 and 2; for all examples, see the Supporting Information). Excellent stereoselectivities were observed in all cases, suggesting that the stereocontrol provided by ligand (*S*)-**3** might handle any TM-α-AA bearing an unbranched alkyl chain. An unusual example in this series is α-AA **4c**, possessing a chloro-substituted phenethyl pharmacophore; its racemate was readily converted into the *S* enantiomer in a practically useful yield (entry 3). Next, we studied a relatively large series (8 examples) of AAs featuring benzyl-type side chains (**4d**–**4f**; entries 4–6). Essentially perfect stereoselectivities were generally observed regardless of the electronic nature or the position of substituents on the aryl ring. The same, nearly complete diastereoselectivities and excellent chemical yields were observed for other types of TM-α-AAs bearing heterocyclic (**4g**, **4h**) or alkene (**4i**) moieties (entries 7–9). With these very inspiring results in hand, we were excited to test more challenging TM-α-AAs with bulky and multifunctional side chains. First, we conducted the DKR of α-branched, valine-type AAs; these reactions produced the desired products **5j** and **5k** with excellent yields and stereoselectivities (entries 10 and 11). Even more gratifying outcomes were obtained for the *tert*-butyl and adamantyl-substituted derivatives **4l** and **4m**, as the diastereomerically pure products **5l** and **5m** were isolated in good yields. It is noteworthy that the results presented in entries 12 and 13 are the first successful DKR reactions of AAs bearing tertiary alkyl groups, underscoring the remarkable performance and potential of ligands **3**.

Phenylglycines represent yet another type of structurally difficult TM-α-AAs owing to both steric and direct electronic

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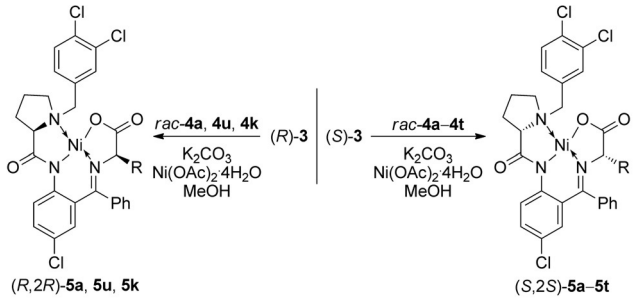
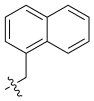
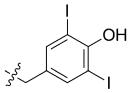
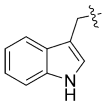
Table 2: Dynamic kinetic resolution of unprotected racemic α-amino acids using chiral ligand (*S*)-**3** or (*R*)-**3**.[a]

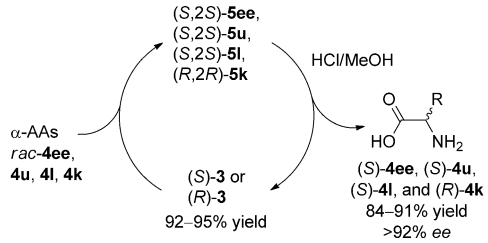


Entry	3	R	4	*T* [°C]	*t* [h]	Yield[b] [%]	d.r.[c]
1	(*S*)-**3**	Me	**4a**	60	3	97	99:1
2	(*S*)-**3**	*n*Bu	**4b**	60	1.5	95	98:2
3	(*S*)-**3**	4-Cl-$C_6H_4CH_2CH_2$	**4c**	RT	72	95	98:2
4	(*S*)-**3**	4-Cl-$C_6H_4CH_2$	**4d**	60	3	99	>99:1
5	(*S*)-**3**		**4e**	RT	72	97	>99:1
6	(*S*)-**3**		**4f**	60	72	98	99:1
7	(*S*)-**3**		**4g**	60	6	99	99:1
8	(*S*)-**3**		**4h**	RT	72	98	>99:1
9	(*S*)-**3**		**4i**	60	6	99	99:1
10	(*S*)-**3**	*i*Bu	**4j**	60	3	90	97:3
11	(*S*)-**3**	Cy	**4k**	RT	72	92	99:1
12	(*S*)-**3**	*t*Bu	**4l**	60	72	83	>99:1
13	(*S*)-**3**	adamant-1-yl	**4m**	60	72	84	>99:1
14	(*S*)-**3**	4-CF_3-C_6H_4	**4n**	RT	18	85	97:3
15	(*S*)-**3**	Ph-C_6H_4	**4o**	RT	72	97	>99:1
16	(*S*)-**3**	2-thienyl	**4p**	RT	24	92	97:3
17	(*S*)-**3**	$CH_2CH_2SCH_3$	**4q**	RT	72	99	99:1
18	(*S*)-**3**	$CH_2CH_2C(O)NH_2$	**4r**	60	1.5	97	>99:1
19	(*S*)-**3**	CH_2CH_2COOH	**4s**	60	2	86	>99:1
20	(*S*)-**3**	CH_2CH_2SH	**4t**	60	4.5	93	99:1
21	(*R*)-**3**	Me	**4a**	RT	72	96	99:1
22	(*R*)-**3**	Bn	**4u**	60	1.5	95	99:1
23	(*R*)-**3**	Cy	**4k**	60	3	96	99:1

[a] Reaction conditions: (*S*)-**3** or (*R*)-**3** (0.2 mmol), *rac*-**4** (0.22 mmol), $Ni(OAc)_2{\cdot}4H_2O$ (0.22 mmol), and K_2CO_3 (1 mmol) in methanol (4 mL). [b] Combined yield of isolated products **5**. [c] Determined by LC-MS analysis of the crude products **5**. Bn = benzyl, Cy = cyclohexyl.

effects of the aromatic ring. Seven differently substituted phenylglycines were subjected to DKR (see the Supporting Information) with two interesting examples presented in entries 14 and 15. In these cases, the best results were obtained at ambient temperature, which was also the case for heteroaromatic analogues, for example, 2-thienyl-substituted **4p** (entry 16). The observed difference is most likely related to the strongly acidifying effect of the aromatic rings on the α-C–H bond, giving better stereochemical outcomes at lower temperatures. The DKR of unprotected polyfunctional α-AAs is of particular interest and synthetic value. To this aim, we selected the series of α-AAs that are shown in entries 17–20. The stereoselectivities observed for the DKR of methionine (**4q**), glutamine (**4r**), glutamic acid (**4s**), and homocysteine (**4t**) were rather exceptional, highlighting the general applicability of ligand (*S*)-**3**. Finally, we examined the DKR reactions of alanine (**4a**), phenylalanine (**4u**), and cyclohexylglycine (**4k**) using ligand (*R*)-**3**. As expected (entries 21–23), excellent results were obtained; these mirrored the data obtained for the reactions of (*S*)-**3**, but enabled the preparation of α*R*-configured TM-α-AAs.

Finally, we prepared the α-AAs (*S*)-**4ee**, (*S*)-**4u**, (*S*)-**4l**, and (*R*)-**4k** in enantiomerically pure form. The diastereomers (*S*,2*S*)-**5ee**, (*S*,2*S*)-**5u**, (*S*,2*S*)-**5l**, and (*R*,2*R*)-**5k** were disassembled under acidic conditions[6d,f,g] (Scheme 1) furnishing the free *S*- and *R*-configured α-AAs along with the stereochemically intact ligands (*S*)-**3** and (*R*)-**3**, which were reused for repetitive DKR reactions.



Scheme 1. Disassembly of diastereomerically pure (*S*,2*S*)-**5ee**, (*S*,2*S*)-**5u**, (*S*,2*S*)-**5l**, and (*R*,2*R*)-**5k**, and isolation of the free target α-AAs (*S*)-**4ee**, (*S*)-**4u**, (*S*)-**4l**, and (*R*)-**4k** along with the recycling and reuse of the chiral ligands (*S*)-**3** and (*R*)-**3**.

In summary, we have developed an advanced, purely chemical approach for the dynamic kinetic resolution of unprotected racemic tailor-made α-amino acids. The substrate scope was found to be remarkably general, and the first DKR of TM-α-AAs bearing tertiary alkyl chains as well as unprotected functional groups was thus developed. Owing to the operationally convenient conditions, virtually complete stereoselectivity, and a fully recyclable source of chirality, this method should find wide application for the preparation of TM-α-AAs, especially on a large scale. Thorough mechanistic studies of the stereocontrol in this reaction and investigations towards the further application of this method for the synthesis of structurally complex derivatives of pharmaceutical importance are currently ongoing and will be reported in due course.

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