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HYBRID CATALYSIS OF 8-QUINOLINECARBOXALDEHYDE AND BRØNSTED ACID FOR EFFICIENT RACEMIZATION OF α-AMINO AMIDES AND ITS APPLICATION IN CHEMOENZYMATIC DYNAMIC KINETIC RESOLUTION

Kohsuke Ohmatsu, Mari Kiyokawa, Yuto Shirai, Yuya Nagato, and Takashi Ooi*

Institute of Transformative Bio-Molecules (WPI-ITbM), and Department of Molecular and Macromolecular Chemistry, Graduate School of Engineering, Nagoya University, Nagoya, 464-8601, Japan. tooi@chembio.nagoya-u.ac.jp

Abstract – The combination of 8-quinolinecarboxaldehyde and benzoic acid proved to be an effective catalyst system for the racemization of *N*-unprotected α-aryl- or α-alkyl-substituted α-amino amides. Application of this system to chemoenzymatic dynamic kinetic resolution provided an efficient access to enantiomerically pure *N*-acetyl-α-amino amides in good to high yields.

Inspired by the enzyme cofactor pyridoxal-5′-phosphate (PLP), heteroaromatic or aromatic aldehydes have long been utilized as catalysts for the chemical transformations of amines and amino acid derivatives.[1,2] The unique feature of aldehyde catalysis resides in the reversible formation of a Schiff base with unprotected amine functionality, which causes a considerable increase in α-C−H acidity.[3] In particular, analogs of pyridinecarboxaldehyde or salicylaldehyde are known to be effective for the activation of *N*-unprotected α-amino acid derivatives, facilitating the subsequent deprotonation to generate resonance-stabilized carbanions with the aid of Brønsted bases and/or Lewis acids. Based on this Schiff-base activation strategy, the synthetic potential of using aldehydes as catalysts has been significantly expanded, leading to the development of catalytic α-functionalizations of amino acids and *N*-unprotected amino esters.[4] Another notable aspect of aldehyde catalysis is that it permits smooth racemization of chiral *N*-unprotected α-amino acid derivatives under mild conditions compatible with enzymatic kinetic resolution. For instance, Aron and coworkers reported that 2-pyridinecarboxaldehyde allowed stereorandomization of α-amino esters in protic polar solvents under the influence of zinc acetate and appropriate Brønsted bases. Furthermore, they combined this catalysis with alcalase-catalyzed asymmetric saponification to establish an efficient dynamic kinetic resolution (DKR) as a practical means

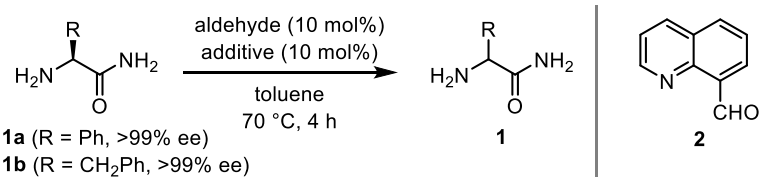
for the preparation of optically active α-amino acid derivatives.[5] Considering the increased α-C−H acidity of α-amino acids upon Schiff-base formation,[6] various α-amino acid derivatives, other than unprotected amino acids and amino esters, would likely be amenable to this mode of aldehyde-catalyzed stereoconvergent reaction systems. However, the use of less acidic substrates, such as α-amino amides, in such systems has been underexplored despite the synthetic versatility of this class of amino acid derivatives.[7-9]

We recently found that 8-quinolinecarboxaldehyde, in cooperation with a suitable acidic cocatalyst, exerted a considerably higher catalytic activity than the combination of pyridinecarboxaldehyde or salicylaldehyde with certain acids, enabling the smooth racemization of α-amino esters without the requirement of any Brønsted base additives in nonpolar solvents.[10] During the course of our studies along this line, we envisioned that our acid-assisted racemization catalysis would be competent for the activation and tautomerization of α-amino amides because of the high coordination aptitude of amide functionality to the acid cocatalyst.[11,12] Herein, we communicate the successful realization of this possibility: aldehyde- and acid-cocatalyzed efficient racemization of *N*-unprotected α-amino amides. We also demonstrate the compatibility of the hybrid catalysis with an enzymatic system through its application in DKR using *Candida antarctica* lipase B (CALB) immobilized on an acrylic resin.

We initially selected L-phenylglycine amide (**1a**) as a model substrate and attempted its racemization reaction in toluene at 40 °C for 24 h in the presence of 8-quinolinecarboxaldehyde (**2**) and zinc acetate dihydrate (Table 1, entry 1). While this catalyst combination was capable of promoting the epimerization of **1a**, the turnover number (TON) was low. Interestingly, switching the acidic cocatalyst from zinc-based Lewis acid to benzoic acid led to a slight increase in TON (entry 2). Subsequent optimizations of the reaction parameters revealed that raising the temperature had a beneficial effect on the reaction efficiency, with TON reaching 6.7 when the racemization was conducted at 70 °C for 4 h. In the cases of employing other Brønsted acids, such as trichloroacetic acid, acetic acid, *p*-toluenesulfonic acid, and trifluoromethanesulfonic acid, as cocatalysts under similar conditions, lower TONs were generally observed (entries 4-7). We then focused on the evaluation of the catalytic performance of different aldehydes. Although 2-pyridinecarboxaldehyde was effective for catalyzing the reaction, its TON was lower than that of **2** (entry 8). In addition, the catalytic activities of 3-pyridine- and 4-pyridinecarboxaldehyde were negligible, suggesting that the mutual spatial arrangement of formyl functionality and pyridine nitrogen was critical for efficiently promoting the epimerization of α-amino amides (entries 9 and 10). The insufficient reactivity of salicylaldehyde also underscored the importance of the structure of the aldehyde catalyst (entry 11). Eventually, the combination of **2** and benzoic acid was identified as the optimal hybrid catalyst system, and the treatment of L-**1a** with this system at 70 °C for 24

h resulted in the quantitative recovery of **1a** in a nearly racemic form (entry 12).[13] Furthermore, α-alkyl-substituted α-amino amides, with less acidic α-proton, were amenable to the present catalytic racemization, as enantiomerically pure phenylalanine amide (**1b**) was completely racemized under identical conditions (entry 13).

Table 1. Catalytic racemization of phenylglycine amide by hybrid catalysis of aldehyde and acidic additive[a]



entry	amino amide	aldehyde	additive	% ee of recovered **1**[b]	TON[c]
1[d,e]	**1a**	**2**	$Zn(OAc)_2 \cdot 2H_2O$	82	2.0
2[d,e]	**1a**	**2**	$PhCO_2H$	78	2.5
3	**1a**	**2**	$PhCO_2H$	51	6.7
4	**1a**	**2**	Cl_3CCO_2H	77	2.6
5	**1a**	**2**	AcOH	68	3.9
6	**1a**	**2**	$TsOH \cdot H_2O$	92	0.8
7	**1a**	**2**	TfOH	60	5.1
8	**1a**	2-pyridinecarboxaldehyde	$PhCO_2H$	58	5.4
9	**1a**	3-pyridinecarboxaldehyde	$PhCO_2H$	91	0.9
10	**1a**	4-pyridinecarboxaldehyde	$PhCO_2H$	88	1.3
11	**1a**	salicylaldehyde	$PhCO_2H$	77	2.6
12[e]	**1a**	**2**	$PhCO_2H$	3	35
13[e]	**1b**	**2**	$PhCO_2H$	<1	>46

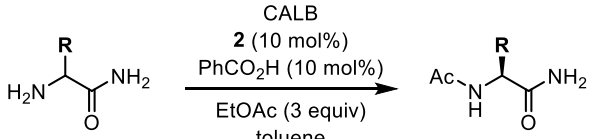
[a] Unless otherwise noted, the reactions were performed with L-**1** (0.1 mmol), **2** (10 mol%), and additive (10 mol%) in toluene (1.0 mL) at 70 °C for 24 h.
[b] Determined by chiral HPLC after conversion to *N*-acetyl amino amide.
[c] TON = [ln(100/ee)]/(cat) where ee = % ee of recovered **1** and (cat) = loading of **2** relative to **1**.
[d] Conducted at 40 ºC. [e] Conducted for 24 h.

We next turned our attention to the application of the **2**/benzoic acid hybrid catalyst system for the DKR of α-amino amides. Taking into account the heating conditions required for the catalytic racemization, we chose the chemoenzymatic approach using immobilized CALB because of its thermal stability and preeminent stereocontrolling ability in the kinetic resolution of chiral amines through asymmetric

N-acylation.[14] Although the DKR of chiral α-amino amides has been elegantly achieved by the combination of the CALB-catalyzed *N*-acylation with Pd/AlO(OH)-catalyzed racemization via reversible dehydrogenation−hydrogenation,[15] the catalysis used for the racemization in this protocol is apparently intolerant of reducible functional groups, such as bromide and alkynes. In contrast, the aldehyde catalysis would exhibit a superior functional-group compatibility.

As an experiment to demonstrate the feasibility of parallel aldehyde-catalyzed racemization and CALB-catalyzed *N*-acylation, we examined the reaction of **1a** with ethyl acetate as an acyl donor under the conditions indicated in Table 2. As expected, the combined use of CALB, aldehyde **2**, and benzoic acid allowed the conversion of racemic phenylglycine amide (**1a**) to *N*-acetyl amide **3a** in high yield with complete enantioselectivity (entry 1). It is noteworthy that racemic phenylalanine amide (**1b**) also

Table 2. Chemoenzymatic dynamic kinetic resolution of α-amino amide[a]



entry	R	3	%yield[b]	% ee[c]
1	Ph	**3a**	87	>99
2[d]	$PhCH_2$	**3b**	88	95
3	4-BrC_6H_4	**3c**	82	>99
4[d]	4-$HC{\equiv}CC_6H_4$	**3d**	72	>99
5	4-MeC_6H_4	**3e**	92	>99
6	4-$MeOC_6H_4$	**3f**	81	>99
7	2-naphthyl	**3g**	63	>99
8	2-MeC_6H_4	**3h**	66	99
9	2-BrC_6H_4	**3i**	75	99

[a] The reactions were performed with **1** (0.2 mmol), CALB (10 mg), **2** (10 mol%), $PhCO_2H$ (10 mol%), and EtOAc (3 equiv) in toluene (2.0 mL) at 70 °C for 24 h.
[b] Isolated yield. [c] Determined by chiral HPLC. [d] Conducted for 48 h.

underwent DKR smoothly to furnish the corresponding amide **3b** albeit with slightly lower enantioselectivity (entry 2). Further exploration of the substrate scope showed that α-amino amides possessing 4-bromo- or 4-ethynylphenyl substituents appeared to be good substrates, affording the enantiomerically pure acetylated products **3c** and **3d** in uniformly good yields (entries 3 and 4). Other

derivatives of racemic phenylglycine amide **1**, such as those with 4-substituted phenyl or fused aromatic side chains, were also converted to *N*-acetylamino amides **3e-3g** with over 99% ee (entries 5-7). Moreover, this system tolerated α-amino amides **1** having sterically demanding *ortho*-substituted phenyl groups, leading to the production of **3h** and **3i** without notable decrease in enantioselectivity (entries 8 and 9).

In conclusion, we demonstrated that the combination of 8-quinolinecarboxaldehyde and benzoic acid enabled the smooth catalytic racemization of *N*-unprotected α-amino amides. Owing to its compatibility with enzymatic transformations as well as various functional groups, the present aldehyde/Brønsted acid hybrid catalyst system allowed the efficient chemoenzymatic DKR for directly converting a range of racemic α-amino amides to the corresponding *N*-acetyl amides of high optical purity. We believe that this study expands the potential utility of the catalysis of heteroaromatic aldehydes, particularly in the context of judicious combination with different modes of catalysis for the development of otherwise difficult asymmetric transformations.

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SUPPORTING INFORMATION

Supplementary data (representative experimental procedures and analytical data for reaction products) associated with this article can be found, in the online version, at URL: https://www.heterocycles.jp/newlibrary/downloads/PDFsi/26827/103/1

REFERENCES AND NOTES

1. E. E. Snell, *Physiol. Rev.*, 1953, **33**, 509; W. Sakami and H. Harrington, *Annu. Rev. Biochem.*, 1963, **32**, 355; A. E. Martell, *Acc. Chem. Res.*, 1989, **22**, 115; K. Fesko and M. Gruber-Khadjawi, *ChemCatChem*, 2013, **5**, 1248; Y. Murakami, J. Kikuchi, Y. Hisaeda, and O. Hayashida, *Chem. Rev.*, 1996, **96**, 721.
2. J. Olivard, D. E. Metzler, and E. E. Snell, *J. Biol. Chem.*, 1952, **199**, 669; J. C. Clark, G. H. Phillipps, and M. R. Steer, *J. Chem. Soc., Perkin Trans. 1*, 1976, 475; I. Tabushi, Y. Kuroda, and M. Yamada, *Tetrahedron Lett.*, 1987, **28**, 5695; A. Bhattacharya, C. Araullo-Mcadams, and M. B. Meier, *Synth. Commun.*, 1994, **24**, 2449; L. Liu and R. Breslow, *Tetrahedron Lett.*, 2001, **42**, 2775; V. Zimmermann, M. Beller, and U. Kragl, *Org. Process Res. Dev.*, 2006, **10**, 622.

3. K. Toth and J. P. Richard, *J. Am. Chem. Soc.*, 2007, **129**, 3013; J. Crugeiras, A. Rios, E. Riveiros, T. L. Amyes, and J. P. Richard, *J. Am. Chem. Soc.*, 2008, **130**, 2041; J. Crugeiras, A. Rios, E. Riveiros, and J. P. Richard, *J. Am. Chem. Soc.*, 2009, **131**, 15815; W. R. Griswold and M. D. Toney, *J. Am. Chem. Soc.*, 2011, **133**, 14823.
4. H. Kuzuhara, N. Watanabe, and M. Ando, *J. Chem. Soc., Chem. Commun.*, 1987, 95; M. Ando, J. Watanabe, and H. Kuzuhara, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 88; Y. Murakami, J. Kikuchi, T. Miyajima, and Y. Hisaeda, *Chem. Lett.*, 1994, **23**, 55; J. T. Koh, L. Delaude, and R. Breslow, *J. Am. Chem. Soc.*, 1994, **116**, 11234; T. Kimura, V. P. Vassilev, G.-J. Shen, and C.-H. Wong, *J. Am. Chem. Soc.*, 1997, **119**, 11734; K. Fesko, M. Uhl, J. Steinreiber, K. Gruber, and H. Griengl, *Angew. Chem. Int. Ed.*, 2010, **49**, 121; P. Fang, M. R. Chaulagain, and Z. D. Aron, *Org. Lett.*, 2012, **14**, 2130; W. Wen, L. Chen, M.-J. Luo, Y. Zhang, Y.-C. Chen, Q. Ouyang, and Q.-X. Guo, *J. Am. Chem. Soc.*, 2018, **140**, 9774; J. Chen, X. Gong, J. Li, Y. Li, J. Ma, C. Hou, G. Zhao, W. Yuan, and B. Zhao, *Science*, 2018, **360**, 1438.
5. A. E. Felten, G. Zhu, and Z. D. Aron, *Org. Lett.*, 2010, **12**, 1916.
6. R. Casasnovas, M. Adrover, J. Ortega-Castro, J. Frau, J. Donoso, and F. Muñoz, *J. Phys. Chem. B*, 2012, **116**, 10665; R. Casasnovas, J. Frau, J. Ortega-Castro, J. Donoso, and F. Muñoz, *J. Phys. Chem. B*, 2013, **117**, 2339.
7. S. Cortes and H. Kohn, *J. Org. Chem.*, 1983, **48**, 2246; C. Guo, I. McAlpine, J. Zhang, D. D. Knighton, S. Kephart, M. C. Johnson, H. Li, D. Bouzida, A. Yang, L. Dong, J. Marakovits, J. Tikhe, P. Richardson, L. C. Guo, R. Kania, M. P. Edwards, E. Kraynov, J. Christensen, J. Piraino, J. Lee, E. Dagostino, C. Del-Carmen, Y.-L. Deng, T. Smeal, and B. W. Murray, *J. Med. Chem.*, 2012, **55**, 4728; T. D. Montgomery and V. H. Rawal, *Org. Lett.*, 2016, **18**, 740; N. Borlinghaus, S. Gergel, and B. M. Nestl, *ACS Catal.*, 2018, **8**, 3727.
8. M. W. van der Meijden, M. Leeman, E. Gelens, W. L. Noorduin, H. Meekes, W. J. P. van Enckevort, B. Kaptein, E. Vlieg, and R. M. Kellogg, *Org. Process Res. Dev.*, 2009, **13**, 1195; P. Wilmink, C. Rougeot, K. Wurst, M. Sanselme, M. van der Meijden, W. Saletra, G. Coquerel, and R. M. Kellogg, *Org. Process Res. Dev.*, 2015, **19**, 302.
9. Y. Asano and S. Yamaguchi, *J. Am. Chem. Soc.*, 2005, **127**, 7696; K. Yasukawa and Y. Asano, *Adv. Synth. Catal.*, 2012, **354**, 3327.
10. Y. Nagato, M. Kiyokawa, Y. Ueki, J. Kikuchi, K. Ohmatsu, M. Terada, and T. Ooi, *Asian J. Org. Chem.*, 2020, **9**, 561.
11. S. Kobayashi, H. Kiyohara, and M. Yamaguchi, *J. Am. Chem. Soc.*, 2011, **133**, 708.
12. N. Kumagai and M. Shibasaki, *Chem. Eur. J.*, 2016, **22**, 15192.
13. The addition of water as a co-solvent accelerated the catalytic racemization of L-**1a**. In contrast,

however, the presence of water led to notable decrease in the yield of *N*-acetyl amide in the chemoenzymatic kinetic resolution probably due to the rapid hydrolysis of ethyl acetate. For details, see the Supporting Information.

14. Y. Kim, J. Park, and M.-J. Kim, *ChemCatChem*, 2011, **3**, 271; C. Ortiz, M. L. Ferreira, O. Barbosa, J. C. S. dos Santos, R. C. Rodrigues, Á. Berenguer-Murcia, L. E. Briand, and R. Fernandez-Lafuente, *Catal. Sci. Technol.*, 2019, **9**, 2380.
15. M.-J. Kim, W.-H. Kim, K. Han, Y. K. Choi, and J. Park, *Org. Lett.*, 2007, **9**, 1157; Y. K. Choi, Y. Kim, K. Han, J. Park, and M.-J. Kim, *J. Org. Chem.*, 2009, **74**, 9543.