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Simplifying Pyridoxal: Practical Methods for Amino Acid Dynamic Kinetic Resolution

Albert E. Felten, Gangguo Zhu, and Zachary D. Aron*

Department of Chemistry, Indiana University, 800 East Kirkwood Avenue, Bloomington, Indiana 47405-7102

zaron@indiana.edu

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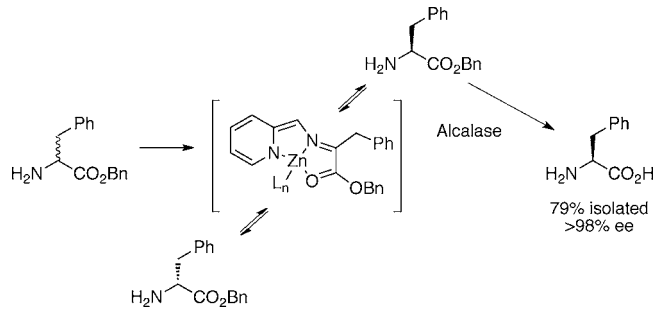
ABSTRACT



Metal complexes of picolinaldehyde are identified as low-cost and environmentally benign catalysts, providing high reaction rates and turnovers for the racemization of amino acids. These pyridoxal surrogates demonstrate activity toward a variety of amino acid esters. Applications to chemoenzymatic dynamic kinetic resolutions provide access to amino acids in high yields and with excellent enantioselectivities, demonstrating their compatibility with protease-mediated transformations.

Chiral amines are critical components of pharmaceuticals, catalysts, and functional biomaterials.[1−3] Despite advances in enantioselective synthesis, the majority of amines continue to be manufactured in racemic form, requiring a subsequent resolution to access pure material.[1] An attractive strategy to improve material throughput would use dynamic kinetic resolutions that combine amine racemization catalysts with resolving agents to convert racemic mixtures to single antipodes.[4] Unfortunately, amine racemization remains a significant challenge, with harsh conditions, high loadings, toxic metals, restricted substrate scopes, and prohibitive costs limiting practical applications.[5−7]

Biomimetic catalysts would provide an attractive alternative for amine racemization. The primary inspiration for amine racemization is the enzyme cofactor pyridoxal-5′-

(1) For a review on the industrial synthesis of chiral amines, see: Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Kesseler, M.; Sturmer, R.; Zelinski, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 788.

(2) For select examples of chiral amines in catalysis, see: (a) Mukhejee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569. (b) Desimoni, G.; Faita, G.; Jorgensen, K. A. *Chem. Rev.* **2006**, *106*, 3561–3651.

(3) For select examples of chiral amines in functional materials, see: (a) Puiggali, J.; Subirana, J. A. *J. Pept. Sci.* **2005**, *11*, 247–249. (b) Xie, D.; Park, J.-G.; Faddah, M.; Zhao, J.; Khanijoun, H. K. *J. Biomater. Appl.* **2006**, *21*, 147–165. (c) Broyer, R. M.; Quaker, G. M.; Maynard, H. D. *J. Am. Chem. Soc.* **2007**, *130*, 1041–1047.

(4) Griengl, H.; Faber, K.; Steinreiber, J. *Chem.—Eur. J.* **2008**, *14*, 8060–8072.

(5) (a) Reetz, M. T.; Schimossek, K. *Chimia* **1996**, *50*, 668–669. (b) Parvulescu, A.; De Vos, D.; Jacobs, P. *Chem. Commun.* **2005**, 5307–5309. (c) Paetzold, J.; Backvall, J. E. *J. Am. Chem. Soc.* **2005**, *127*, 17620–17621. (d) Blacker, A. J.; Stirling, M. J.; Page, M. I. *Org. Process Res. Dev.* **2007**, *11*, 642–648. (e) Gastaldi, S.; Escoubet, S.; Vanthuyne, N.; Gil, G.; Bertrand, M. P. *Org. Lett.* **2007**, *9*, 837–839.

(6) (a) Olivard, J.; Metzler, D. E.; Snell, E. E. *J. Biol. Chem.* **1952**, *199*, 669–674. (b) Clark, J. C.; Phillipps, G. H.; Steer, M. R. *J. Chem. Soc., Perkin Trans. 1* **1976**, 475–481. (c) Tabushi, I.; Kuroda, Y.; Yamada, M. *Tetrahedron Lett.* **1987**, *28*, 5695–5698. (d) Battacharya, A.; Araullo-Mcadams, C.; Meier, M. B. *Synth. Commun.* **1994**, *24*, 2449–2459. (e) Liu, L.; Breslow, R. *Tetrahedron Lett.* **2001**, *42*, 2775–2777. (f) Zimmermann, V.; Beller, M.; Kragl, U. *Org. Process Res. Dev.* **2006**, *10*, 622–627.

(7) Servi, S.; Tessaro, D.; Pedrocchi-Fantoni, G. *Coord. Chem. Rev.* **2008**, *252*, 715–726.

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phosphate (PLP), which uses Schiff base and quinonoid formation to racemize amino acids under mild conditions (Figure 1).[6a,d,8] Analogues such as pyridoxal, salicylaldehyde,

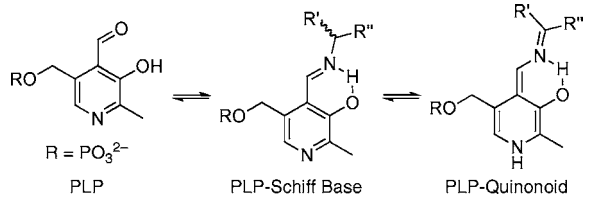
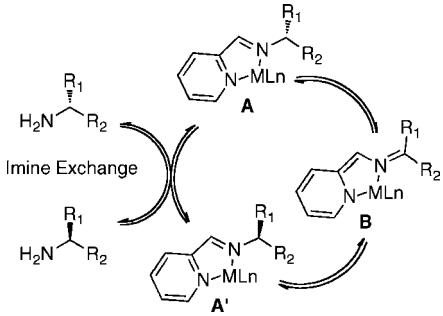


Figure 1. Pyridoxal-5′-phosphate (PLP)-mediated amino acid racemization.

and 3,5-dinitrosalicylaldehyde have been used in dynamic kinetic resolutions, but low activity and/or prohibitive costs limit their utility.[6] We report that simple metal complexes of picolinaldehyde efficiently catalyze amino acid ester racemization under conditions compatible with enzymatic resolution. Our reactions facilitate dynamic kinetic resolutions of amino acids and provide an inexpensive and green alternative to existing methods. This observation is particularly noteworthy since monosubstituted pyridines have not previously been reported to catalytically activate amines.[9−11]

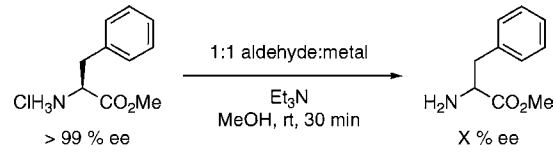
Our rationale for using picolinaldehyde metal complexes was based on the hypothesis that metal binding would facilitate Schiff base formation in a manner analogous to the 3-hydroxyl group of pyridoxal-5′-phosphate (PLP; see Figure 1).[12,13] These complexes are particularly attractive as cation binding is anticipated to enhance reactivity through coordination to the pyridine nitrogen, stabilizing the electron-rich quinonoid tautomer **B** (Scheme 1).[9]

Scheme 1. Picolinaldehyde-Catalyzed Amine Racemization



Initial studies established picolinaldehyde metal chelates as amino acid racemization catalysts (Table 1). Optimization

Table 1. Effect of Metal on the Racemization of Phe(OMe)[a]



entry	metal/aldehyde	X^b	TON[c]
1	$AgNO_3$/picolinaldehyde	99.2	0.4
2	$Ti(OiPr)_4$/picolinaldehyde	99.1	0.45
3	$Co(AcAc)_3$/picolinaldehyde	95.6	2.3
4	$Cu(OTf)_2$/picolinaldehyde	88.9	5.9
5	$Y(OTf)_3$/picolinaldehyde	67.3	19.8
6	$Ni(AcAc)_2$/picolinaldehyde	46.8	38.0
7	$FeSO_4$/picolinaldehyde	33.4	54.8
8	$Ca(OTf)_2$/picolinaldehyde	29.9	60.6
9	**$Zn(OTf)_2$/picolinaldehyde**	**27.0**	**65.4**
10[d]	$Zn(OTf)_2$/picolinaldehyde[d]	30.2[d]	57.9[d]
11	$ZnCl_2$/picolinaldehyde	25.7	68.0
12	$ZnClO_4$/picolinaldehyde	24.2	71.0
13	$Zn(OAc)_2$/picolinlaldehyde	22.2	75.2
14	$Zn(OTf)_2$/4-pyridinecarboxaldehyde	98.3	0.6
15	$Zn(OTf)_2$/pyridoxal	58.3	27.2

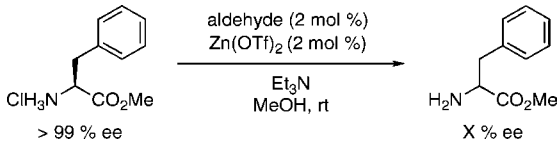
[a] Reactions were run for 30 min at 0.5 M at room temperature, using 0.02 equiv of aldehyde and 0.02 equiv of $Zn(OTf)_2$. [b] As determined by HPLC. [c] TON was determined from reactions halted at 30 min.[14,15] [d] Reaction was run using free Phe(OMe) in the presence of 1 equiv of trifluoroacetic acid.

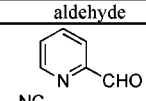
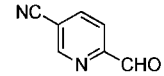
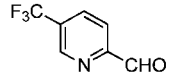
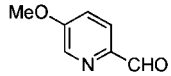
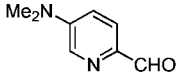
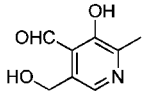
efforts revealed that amine racemization occurs fastest in protic solvents and in the presence of ammonium salts, which are necessary for promoting Schiff base exchange. Under optimal conditions, complexes of $Zn(OTf)_2$ and picolinaldehyde proved highly effective, racemizing Phe(OMe) at rates 4-fold faster than $Zn(OTf)_2$/pyridoxal (Table 2, entries 1 and 6). Consistent with our hypothesis, complexes of 4-pyridinecarboxaldehyde that lack the ability to effectively chelate metals are largely inactive (Table 1, entry 14).

The racemization of Phe(OMe) with various multivalent cations (select examples shown, Table 1) demonstrated distinctive trends. Among metal salts, dicationic species with small atomic radii are most effective,[16] whereas the counterion has little effect when incorporated on the metal or as

(8) Eliot, A. C.; Kirsch, J. F. *Annu. Rev. Biochem.* **2004**, *73*, 383–415.
(9) Several reports exist that describe monosubstituted pyridines acting as stoichiometric PLP analogues; however, no catalytic examples have been described (see ref 10).
(10) (a) Maley, J. R.; Bruice, T. C. *J. Am. Chem. Soc.* **1968**, *90*, 2843. (b) Bachmann, S.; Knudsen, K. R.; Jorgensen, K. A. *Org. Biomol. Chem.* **2004**, *2*, 2044–2049.
(11) (a) Casella, L.; Gullotti, M. *Inorg. Chem.* **1983**, *22*, 2259–2266. (b) Casella, L.; Guillotte, M. *Inorg. Chem.* **1986**, *25*, 1293–1303. (c) Chavez-Gil, T. E.; Yasaka, M.; Senokuchi, T.; Sumimoto, M.; Kurosaki, H.; Goto, M. *Chem. Commun.* **2001**, 2388–2389.
(12) (a) Nitschke, J. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 3073. (b) Schultz, D.; Nitschke, J. R. *Angew. Chem., Int. Ed.* **2006**, *45*, 2453–2456. (c) Schultz, D.; Nitschke, J. R. *J. Am. Chem. Soc.* **2006**, *128*, 9887–9892.
(13) (a) Crugeiras, J.; Rios, A.; Riverios, E.; Richard, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 15815–15824. (b) Crugeiras, J.; Rios, A.; Riveiros, E.; Amyes, T. L.; Richard, J. P. *J. Am. Chem. Soc.* **2008**, *130*, 2041–2050. (c) Toth, K.; Richard, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 3013–3021. (d) Auld, D. S.; Bruice, T. C. *J. Am. Chem. Soc.* **1967**, *89*, 2083–2089.
(14) TON was defined as the number of successful catalyst/substrate interactions per mol of catalysts that occurred within the time span of the given reaction. These numbers were calculated using the following equation derived from methods described by Carpenter:[15] $TON(T) = [\ln(100/ee)]/(cat)$ where ee = ee of substrate at given time T, and (cat) = loading of the catalyst relative to substrate.
(15) Carpenter, B. K. *Determination of Organic Reaction Mechanisms*; Wiley & Sons: New York, 1984; pp 35−37.
(16) Shannon, R. D.; Prewitt, C. T. *Acta Crystallogr.* **1969**, *B25*, 925–946.

Table 2. Effect of Aldehyde Electronics on the Racemization of Phe(OMe)[a]



entry	aldehyde	X[b]	TON[c]	TOF (min^{-1})[d]
1		27.0 ± 1.2 29.9 ± 3.9[e]	65.6 ± 2.3 60.6 ± 6.3[e]	3.32 ± 0.27 2.15 ± 0.22[e]
2		95.9 ± 2.3 50.6 ± 1.4[e]	2.1 ± 1.2 34.0 ± 1.4[e]	0.071 ± 0.018 1.28 ± 0.07[e]
3		86.8 ± 1.3	7.1 ± 0.8	0.21 ± 0.02
4		10.0 ± 0.9	111.3 ± 4.3	4.21 ± 0.31
5		21.3 ± 2.9	77.7 ± 7.1	2.70 ± 0.26
6		58.3 ± 6.8	27.2 ± 5.7	0.82 ± 0.19

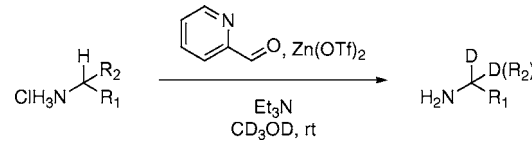
[a] Reactions were run for 30 min at 0.5 M at room temperature, using 0.02 equiv of aldehyde and 0.02 equiv of $Zn(OTf)_2$. [b] As determined by HPLC. [c] TON was determined from reactions halted at 30 min.[14,15] [d] TOF was determined from TON determined at five time points, run in triplicate for each reaction (5−65% conversion). [e] Reactions were run using $Ca(OTf)_2$ in lieu of $Zn(OTf)_2$.

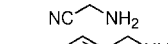
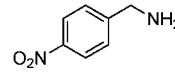
an exogenous salt (Table 1, entries 9−13). This result is surprising considering that the Schiff base changes from an L2- to an LX-type ligand upon deprotonation (Scheme 1). The lack of salt effects suggests that the active species does not incorporate these counterions into the metal ligand sphere.

Our studies found that incorporation of either σ- or π-electron-withdrawing substituents on picolinaldehyde slowed the reaction rate, whereas electron-rich substituents accelerated racemization (Table 2). This observation was unexpected as electron-poor substituents on the aldehyde were anticipated to accelerate Schiff base exchange by increasing imine electrophilicity and to facilitate proton transfer by stabilizing the electron-rich quinonoid intermediate. This phenomenon was examined further by performing Phe(OMe) racemization in the presence of either $Zn(OTf)_2$ or $Ca(OTf)_2$ with both 5-cyanopicolinaldehyde and picolinaldehyde (Table 2, entries 1 and 2). In the case of picolinaldehyde, little change in reaction rate was observed, whereas with 5-cyanopicolinaldehyde, the use of $Ca(OTf)_2$ resulted in a 20-fold rate increase over reactions with $Zn(OTf)_2$. The unusual trends in pyridine substitution and catalysis, coupled with the observation that different metals affect substituted pyridines in different ways, may reflect variations in the metal-binding properties of the substituted pyridines. Accordingly, electron-poor pyridines would act as weaker σ-donors to disfavor metal binding and thus inhibit the formation of catalytically active complexes.

To improve our understanding of catalyst structure and explore reaction scope, we have examined amine activation with a variety of substrates. These experiments measured catalytic activity in the context of deuterium incorporation to allow simple substrates such as Gly(OMe) to be directly assessed (Table 3). Among amino acids, less sterically

Table 3. Deuterium Incorporation of Selected Amines[a]



entry	compound	% conversion	k_{obs} ($x10^{-3}$ min^{-1})[b]
1	Phe(O*t*Bu)	45.2 ± 7.9	12.6 ± 2.8
2	Phe(OMe)	32.5 ± 1.3	8.0 ± 0.4
3	Gly(OMe)	90.2 ± 1.3	46.6 ± 4.3
4	Ala(OMe)	18.2 ± 3.6	4.1 ± 0.8
5	Met(OMe)	58.5 ± 4.2	18.2 ± 2.0
6	Leu(OMe)	59.9 ± 1.3	18.8 ± 0.8
7	Val(OMe)	7.75 ± 0.81	1.8 ± 0.3
8		29.6 ± 6.9	7.3 ± 2.0
9		2.19 ± 0.43	0.4 ± 0.1

[a] Reactions were run for 30 min at 0.5 M at room temperature, using 0.02 equiv of aldehyde and 0.02 equiv of $Zn(OTf)_2$, with % conversions determined by ^1H NMR. [b] The value of k_{obs} was determined from time courses run in triplicate and analyzed as pseudo-first-order.

hindered substrates have proven to be more reactive, with Gly(OMe) incorporating deuterium fastest and Val(OMe) incorporating it slowest (Table 3, entries 3 and 7). These results suggest that either Schiff base exchange is rate-limiting or that steric congestion around the catalyst impairs deprotonation. In contrast, reactions are largely insensitive to the ester substituent, with methyl and *t*-butyl esters incorporating deuterium at similar rates (Table 3, entries 1 and 2). The presence of the carboxylate appears to play a significant role in mediating catalyst activity, with minimal deuterium incorporation seen with *p*-nitrobenzyl amine (Table 3, entry 9) and relatively slow incorporation in the case of the sterically unencumbered cyanomethyl amine (Table 3, entry 8). The high reactivity of carboxylate-containing substrates suggests that the carboxylate is directly bound to the cation, with the insensitivity toward ester substitution suggesting that the carbonyl oxygen provides the coordination (Figure 2).

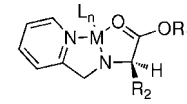
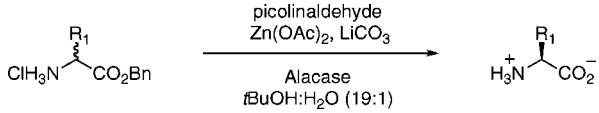
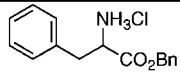
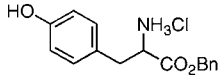
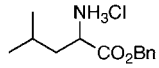
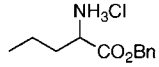
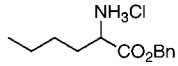


Figure 2. Proposed three-coordinate metal/substrate complex.

To examine our system in the context of chemoenzymatic dynamic kinetic resolutions, we examined the reactions of a variety of amino acid esters in the presence of both Alcalase and picolinaldehyde metal complexes (Table 4). Wang and co-workers have previously established that Alcalase, an inexpensive and readily available proteolytic enzyme mixture,[17] was an effective resolving agent for pyridoxal-catalyzed dynamic kinetic resolutions.[17c] Our development of picolinaldehyde-catalyzed dynamic kinetic resolutions required several changes to our racemization conditions. Since protic acid is generated, lithium carbonate was introduced to buffer the reaction and maintain enzyme activity. Product racemization is avoided by running reactions in a mixture of *t*-butanol and water, which results in the precipitation of amino acid products. Under optimal conditions, highly enantioenriched products can be directly accessed by a simple filtration. Aromatic as well as straight- and γ-branched-chain amino acids are resolved in good yields with high enantiopurity, whereas β-branched amino acids are poorly resolved by Alcalase (data not shown).

Table 4. Dynamic Kinetic Resolutions of Amino Acid Esters[a]



entry	amino acid ester	% yield of amino acid[b]	% ee[c]
1		79	>98
2		63	>98
3		77	>98
4		89	64 ± 1.2
5		75	>98

[a] Reactions were run for 4 h at 0.2 M at room temperature, using 0.1 equiv of aldehyde, 0.05 equiv of $Zn(OTf)_2$, 0.6 equiv of $LiCO_3$, and 1 mL/mmol alcalase solution. [b] Isolated amino acid. [c] As determined by HPLC.

In summary, a simple biomimetic catalyst has been introduced that mediates low-cost and environmentally friendly racemizations of amino acids. Applications to dynamic kinetic resolutions are described and demonstrate the compatibility of our catalyst with chemoenzymatic strategies. The key advantage of this study is that it provides a readily available amino acid racemization catalyst which is capable of interacting with a diverse array of substrates. Future efforts will explore the utility of these simple pyridoxal analogues in a variety of transformations.

Acknowledgment. We acknowledge the financial support of Indiana University.

Supporting Information Available: Experimental procedures describing the synthesis of 4-dimethylaminopicolinaldehyde, general procedures for transformations depicted in Tables 1−4, and tables providing raw data from which Tables 1−4 were generated. This material is available free of charge via the Internet at http://pubs.acs.org.

OL100319B

(17) (a) Chen, S.-T.; Wang, K.-T.; Wong, C.-H. *J. Chem. Soc., Chem. Commun.* **1986**, 1514–1516. (b) Kijima, T.; Ohshima, K.; Kise, H. *J. Chem. Technol. Biotechnol.* **1994**, *59*, 61–65. (c) Chen, S.-T.; Huang, W.-H.; Wang, K.-T. *J. Org. Chem.* **1994**, *59*, 7580–7581. (d) Chen, S.-T.; Wang, K.-T. *J. Chin. Chem. Soc.* **1999**, *46*, 301–311.