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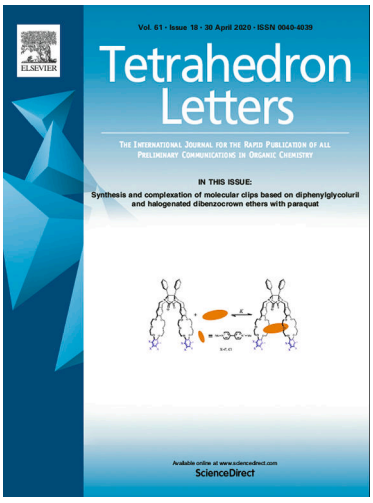

Aerobic Redox Deracemization of α-Aryl Glycine Esters

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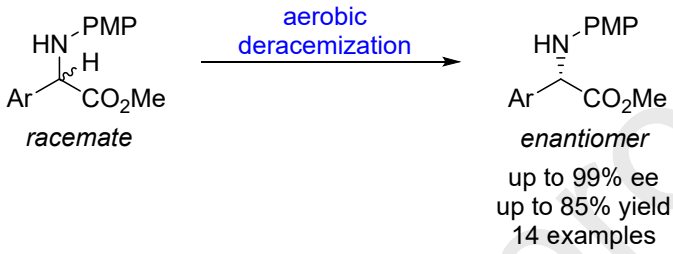

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Aerobic Redox Deracemization of α-Aryl Glycine Esters

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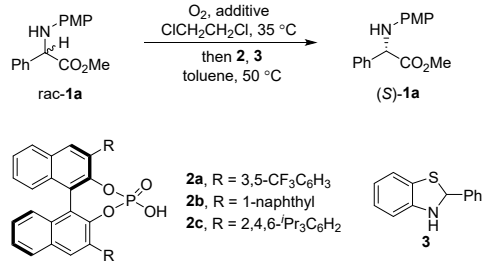
ABSTRACT

An effective redox deracemization of α-aryl glycine esters has been described. The one-pot redox process consisted of copper(II) catalysis using molecular oxygen as terminal oxidant and chiral phosphoric acid catalyzed asymmetric transfer hydrogenation with benzothiazoline as hydride donor. The reaction exhibited good functional group tolerance, providing a range of optically active non-natural α-aryl glycine esters with excellent enantioselectivity.

Conventional enantioselective approaches involving either conversion of achiral reactants to chiral products or differential conversion of stereoisomers of racemic reactants (kinetic resolutions) have attracted extensive interest.[1,2] In contrast, direct and whole transformation of racemic reactants into a single enantiomer of the same molecule, namely deracemization, has remained underexplored, despite conceptual simplicity and potential practical benefits.[3,4] To achieve such thermodynamically disfavored process, the stereochemistry is generally destroyed by oxidation and regenerated by asymmetric reduction.[5] Existing non-enzymatic redox deracemization studies are limited to alcohol, cyclic amine, and cyclic ether moieties.[6-9] Pure chemically catalytic redox deracemization of acyclic amines has remained elusive.[10] In addition, current studies usually require stoichiometric oxidants like NBS, DDQ, and oxopiperidinium salt, thus producing undesired waste. More ideal molecular oxygen as oxidant in terms of economical and ecological factors with H_2O as the only byproduct has not been applied for the process.[11] Given the importance of non-natural α-aryl glycine derivatives in pharmaceutical science, we herein reported a redox deracemization of α-aryl glycine derivatives using molecular oxygen as terminal oxidant.[12,13]

Initially, the redox deracemization of α-phenyl glycine ester rac-**1a** was chosen for optimization using molecular oxygen as

Table 1. Reaction condition optimization.[a]



Entry	Additive	2	Yield[b] (%)	ee[c] (%)
1	—	—	n.o.	n.d.
2	$Cu(OTf)_2$	—	n.o.	n.d.
3	$Cu(OAc)_2$	**2a**	10	21
4	$CuBr_2$	**2a**	46	27
5	$CuCl_2$	**2a**	69	31
6	CuCl	**2a**	16	19
7[d]	$CuCl_2$	**2a**	77	35
8[d]	$CuCl_2$	**2b**	58	67
9[d]	$CuCl_2$	**2c**	82	83
10[d,e]	$CuCl_2$	**2c**	85	91
11[d,e,f]	$CuCl_2$	**2c**	83	88
12[d,e,g]	$CuCl_2$	**2c**	86	90

[a] General conditions: rac-**1a** (0.1 mmol) and additive (10 mol %) in $ClCH_2CH_2Cl$ (2 mL) under 1 atm molecular oxygen at 35 ºC for 18 h, followed by **2** (5 mol %) and **3** (0.12 mmol) in toluene at 50 ºC for 24 h.
[b] Yield of isolated product.
[c] Determined by chiral HPLC analysis.
[d] Oxidation at 50 ºC.
[e] Asymmetric reduction in mesitylene.
[f] 3 Å molecular sieves (20 mg) as additive.
[g] 8 mol% **2c** as catalyst.

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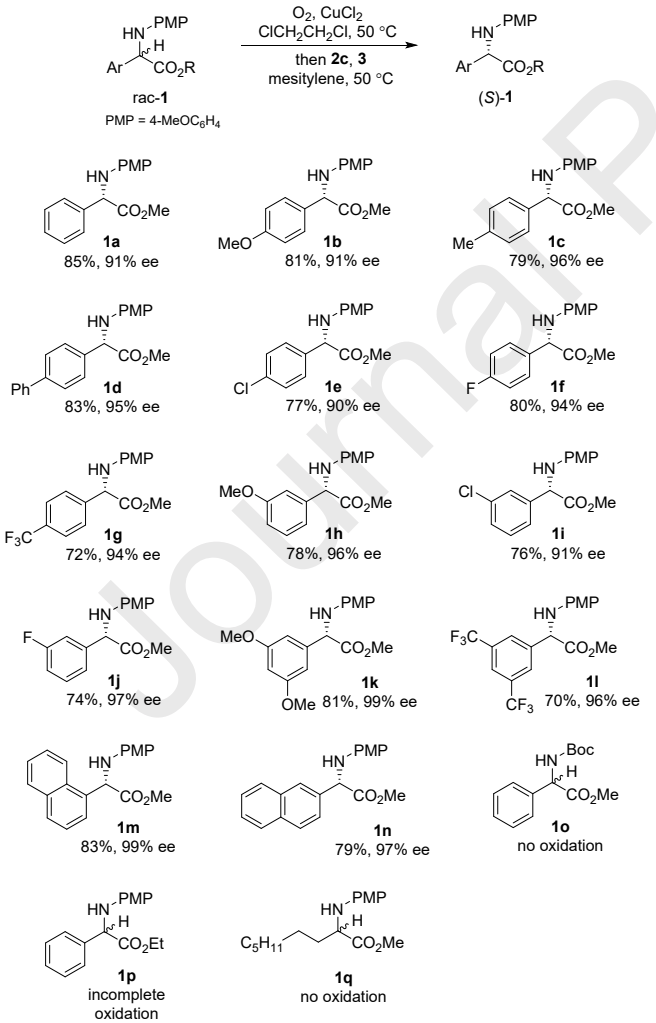
terminal oxidant (Table 1). Chiral phosphoric acid **2a** and benzothiazoline **3** were used for asymmetric transfer hydrogenation.[13d,14,15] Oxidation and asymmetric reduction were conducted in a two-step, one-pot manner to avoid reagent quenching. No oxidation was observed in the presence of sole molecular oxygen (entry 1, Table 1). An extensive investigation of copper additives suggested that efficient aerobic oxidation was achieved in the presence of 10 mol % of $CuCl_2$ at 50 ºC, furnishing desired (*S*)-**1a** in 77% yield with 35% ee (entries 2-7, Table 1). Further optimization of chiral phosphoric acids identified **2c** to be optimal (entries 7-9, Table 1). Performing the asymmetric transfer hydrogen in mesitylene provided (*S*)-**1a** in 85% yield with 91% ee (entry 10, Table 1). The reaction was not sensitive to moisture, and molecular sieves as additive did not afford improvement on ee (entry 11, Table 1). Increasing the loading of phosphoric acid **2c** did not give superior ee (entry 12, Table 1).

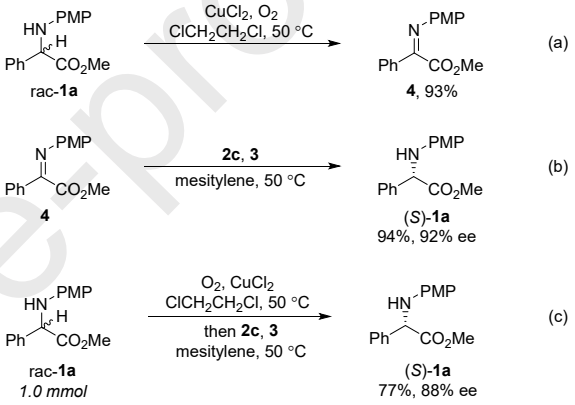
The scope of aerobic one-pot deracemization of α-aryl glycine esters was next investigated (Scheme 1). In general, substrates bearing electronically varied aryl groups at α-position with diverse substituent patterns were effectively deracemized, affording respective **1a**-**1l** with excellent ee (90%-99%). Higher efficiency was observed for substrates bearing an electron-rich α-aryl group. Polyarene substituted glycine esters were also suitable components, as



Scheme 1. Scope of α-aryl glycine esters.

with excellent enantiocontrol. No oxidation was observed for substrate **1o** bearing a Boc (*tert*-butyloxycarbonyl) moiety and **1q** with an α-alkyl substituent. Substrate **1p** containing an ethyl ester afforded an incomplete oxidation under the standard condition.

Control experiments were conducted to understand the preliminary reaction mechanism (Scheme 2). In the presence of catalytic amount of $CuCl_2$ under molecular oxygen atmosphere, α-amino ester rac-**1a** was converted to an intermediate detected by TLC analysis, which was identified as α-imino ester **4** (Scheme 2a). Subjecting **4** to standard conditions in the absence of oxidation elements furnished expected (*S*)-**1a** with comparable ee to that of deracemization process, indicating the intermediacy of α-imino ester **4** (Scheme 2b). The reaction can be scaled up without obvious loss of efficiency and ee, as demonstrated by the effective deracemization of **1a** in 1.0 mmol scale (Scheme 2c).



Scheme 2. Control experiments

In conclusion, an effective redox deracemization of α-aryl glycine esters has been described. The one-pot redox process consisted of $CuCl_2$ catalysis using molecular oxygen as terminal oxidant and chiral phosphoric acid catalyzed asymmetric transfer hydrogenation with benzothiazoline as hydrogen donor. The reaction exhibited good functional group tolerance, providing a range of optically active non-natural α-aryl glycine esters with excellent enantioselectivity.

Acknowledgments

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Supplementary Material

The spectra of the products associated with this manuscript can be found in the supporting information.

References and notes

1. Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis*, vols. I to III (Springer, **1999**).
2. (a) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343,* 5; (b) Vedejs, E.; Jure, M. *Angew. Chem. Int. Ed.* **2005,**

Huerta, F. F.; Minidis, A. B. E.; Backvall, J. E. *Chem. Soc. Rev.* **2001**, *30*, 321; (e) Bhat, V.; Welin, E. R.; Guo, X.; Stoltz, B. M. *Chem. Rev.* **2017**, *117*, 4528; (f) K. S. Petersen, *Asian J. Org. Chem.* **2016**, *5*, 308; (g) Echeverria, P.-G.; Ayad, T.; Phansavath, P.; Ratovelomanana-Vidal, V. *Synthesis* **2016**, *48*, 2523; (h) Gurubrahamam, R.; Cheng, Y.-S.; Huang, W.-Y.; Chen, K. *ChemCatChem*. **2016**, *8*, 86.

3. Deracemization used in this text is the definition in the strict sense, and the only difference between the product and the starting material is that the latter is enantioenriched.
4. (a) Faber, K. *Chem. Eur. J.* **2001**, *7,* 5004; (b) Gruber, C. C.; Lavandera, I.; Faber, K.; Kroutil, W. *Adv. Synth. Catal.* **2006**, *348,* 1789; (c) Turner, N. J. *Curr. Opin. Chem. Biol.* **2010**, *14*, 115;(d) Rachwalski, M.; Vermue, N.; Rutjes, F. P. J. T. *Chem. Soc. Rev.* **2013**, *42,* 9268; (e) Simon, R. C.; Richter, N.; Busto, E.; Kroutil, W. *ACS Catal.* **2014**, *4,* 129.
5. An innovative example of photochemical deracemization of allenes enabled by chiral sensitizer showing different energy transfer efficiencies for two enantiomers, see: (a) Hölzl-Hobmeier, A.; Bauer, A.; Silva, A. V.; Huber, S. M.; Bannwarth, C.; Bach, T. *Nature.* **2018**, *564*, 240; (b) Tröster, A.; Bauer, A.; Jandl, C.; Bach, T. *Angew. Chem. Int. Ed.* **2019**, *58*, 3538.
6. Current deracemization studies rely heavily on enzymatic catalysis with alcohol and amine substrates, see: (a) Voss, C. V.; Gruber, C. C.; Kroutil, W. *Angew. Chem. Int. Ed.* **2008**, *47*, 741; (b) Voss, C. V.; Gruber, C. C.; Faber, K.; Knaus, T.; Macheroux, P.; Kroutil, W. *J. Am. Chem. Soc.* **2008**, *130*, 13969; (c) Dunsmore, C. J.; Carr, R.; Fleming, T.; Turner, N. J. *J. Am. Chem. Soc.* **2006**, *128*, 2224; (d) Ghislieri, D.; Green, A. P.; Pontini, M.; Willies, S. C.; Rowles, I.; Frank, A.; Grogan, G.; Turner, N. J. *J. Am. Chem. Soc.* **2013**, *135*, 10863; (e) Yasukawa, K.; Nakano, S.; Asano, Y. *Angew. Chem. Int. Ed.* **2014**, *53*, 4428; (f) Chen, M.; Han, Y.; Ma, D.; Wang, Y.; Lai, Z.; Sun, J. *Chin. J. Chem.* **2018**, *36*, 587.
7. (a) Shimada, Y.; Miyake, Y.; Matsuzawa, H.; Nishibayashi, Y. *Chem. Asian J.* **2007**, *2*, 393; (b) Adair, G. R. A.; Williams, J. M. J. *Chem. Commun.* **2007**, *25*, 2608; (c) Qu, P.; Kuepfert, M.; Jockusch, S.; Weck, M. *ACS Catal.* **2019**, *9*, 2701.
8. (a) Lackner, A. D.; Samant, A. V.; Toste, F. D. *J. Am. Chem. Soc.* **2013**, *135*, 14090; (b) Ji, Y.; Shi, L.; Chen, M. W.; Feng, G. S.; Zhou, Y. G. *J. Am. Chem. Soc.* **2015**, *137*, 10496; (c) Shin, N. Y.; Ryss, J. M.; Zhang, X.; Miller, S. J.; Knowles, R. R. *Science.* **2019**, *366*, 364.
9. (a) Wan, M.; Sun, S.; Li, Y.; Liu, L. *Angew. Chem. Int. Ed.* **2017**, *56*, 5116; (b) Lu, R.; Li, Y.; Zhao, J.; Li, J.; Wang, S.; Liu, L. *Chem. Commun.* **2018**, *54*, 4445.
10. Zhang, L.; Zhu, R.; Feng, A.; Zhao, C.; Chen, L.; Feng, G.; Liu, L. *Chem. Sci.* **2020**, *11*, 4444.
11. (a) Gulzar, N.; Schweitzer-Chaput, B.; Klussmann, M. *Catal. Sci. Technol.* **2014,** *4*, 2778; (b) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem. Int. Ed.* **2011**, *50*, 11062; (c) Shi, Z.; Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3381.
12. (a) Townsend, C. A.; Brown, A. M. *J. Am. Chem. Soc.* **1983**, *105*, 913; (b) Spencer, J. L.; Flynn, E. H.; Roeske, R. W.; Siu, F. Y.; Chauvette, R. R. *J. Med. Chem.* **1966**, *9*, 746; (c) Rama Rao, A. V.; Gurjar, M. K.; Laxma Reddy, K.; Rao, A. S. *Chem. Rev.* **1995**, *95*, 2135.
13. (a) Shang, G.; Yang, Q.; Zhang, X. *Angew. Chem. Int. Ed.* **2006**, *45*, 6360; (b) Li, G.; Liang, Y.; Antilla, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 5830; (c) Kang, Q.; Zhao, Z. A.; You, S. L. *Adv. Synth. Catal.* **2007**, *349*, 1657; (d) Zhu, C.; Akiyama, T. *Adv. Synth. Catal.* **2010**, *352*, 1846; (e) Mazuela, J.; Antonsson, T.; Johansson, M. J.; Knerr, L.; Marsden, S. P. *Org. Lett.* **2017**, *19*, 5541.
14. (a) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744; (b) Terada, M. *Synthesis.* **2010**, *42*, 1929; (c) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev.* **2014**, *114*, 9047; (d) Čorić, I.; List, B. *Nature.* **2012**, *483*, 315; (e) Hoffmann, S.; Seayad, A. M.; List, B. *Angew. Chem. Int. Ed.* **2005**, *44*, 7424.
15. (a) Zhu, C.; Saito, K.; Yamanaka, M.; Akiyama, T. *Acc. Chem. Res.* **2015**, *48*, 388; (b) Zhu, C.; Falck, J. R. *ChemCatChem.* **2011**, *3*, 1850; (c) Zhu, C.; Akiyama, T. *Org. Lett.* **2009**, *11*, 4180; (d) Henseler, A.; Kato, M.; Mori, K.; Akiyama, T. *Angew. Chem. Int. Ed.* **2011**, *50*, 8180.

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