Published in final edited form as:

Angew Chem Int Ed Engl. 2016 February 18; 55(8): 2856–2860. doi:10.1002/anie.201510808.

Enantioselective C–H Olefination *via* Kinetic Resolution**

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Abstract

Significant progress has been made in the development of enantioselective C–H activation reactions via desymmetrization in the past decade. However, the requirement for the presence of two chemically identical prochiral C–H bonds represents an inherent limitation in scope. Here, we report the first example of kinetic resolution *via* Pd(II)-catalyzed enantioselective C–H activation and C–C bond formation, significantly expanding the scope of enantioselective C–H activation reactions.

Graphical Abstract

A Pd(II)-catalyzed enantioselective C–H olefination of racemic α -hydroxy and α -amino phenylacetic acids *via* kinetic resolution has been developed using mono-*N*-protected amino acid (MPAA) ligands as chiral ligands. In contrast to the classical kinetic resolution *via* recrystallization with chiral salts or asymmetric acylation, this approach adds complexity to the substrates by installing a synthetically valuable olefin unit leading to a novel class of chiral mandelic acid and phenylglycine derivatives.

Keywords

enantioselective catalysis; C–H activation; palladium; kinetic resolution; mandelic acid

Development of enantioselective C–H activation reactions is a significant and challenging task in catalysis and organic synthesis as they offer new disconnections for asymmetric synthesis.^[1] Among various approaches,^[2–7] the Pd-catalyzed desymmetrization of

**We gratefully acknowledge The Scripps Research Institute for financial support. This work is supported by the NIH (NIGMS, 2R01GM084019).

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Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201510808>

prochiral C–H bonds has emerged as a promising avenue that can lead to a wide range of enantioselective carbon-carbon^[8,9] and carbon-heteroatom bond forming reactions.^[10] However, desymmetrization is only suitable for substrates containing two prochiral C–H bonds, thus limiting the structural diversity that can be accessed by this approach. For example, the previously reported enantioselective Pd(II)-catalyzed C–H olefination of diphenylacetic acids using mono-*N*-protected amino acid (MPAA) ligands cannot be applied to the preparation of important chiral derivatives of mandelic acids and phenylglycines (Fig. 1a).^[8b]

Enantiopure α -hydroxy and α -amino phenylacetic acids, also known as mandelic acids and phenylglycines respectively, are important structural motifs found in many pharmaceuticals and biologically active compounds, such as antibiotics cefamandole, cephalexin and vancomycin.^[11] Enantioenriched mandelic acid and phenylglycine derivatives can also be utilized as catalysts, as well as chiral building blocks in organic synthesis.^[12] As a consequence, asymmetric syntheses of these two families of compounds have received enormous attention.^[13,14] An early example of asymmetric hydroxylation of benzylic C–H bonds of chiral epoxides^[15] and a recent development of enantioselective C–H iodination using Pd(II)/MPAA catalysts demonstrate the feasibility of achieving kinetic resolution^[16] *via* C–H hydroxylation and iodination. Herein, we report a Pd(II)-catalyzed enantioselective C–H olefination of α -hydroxy and α -amino phenylacetic acids through kinetic resolution to afford enantiomerically enriched olefinated mandelic acids and phenylglycines (Fig. 1b). The remaining starting materials are further enantioselectively olefinated using chiral MPAA ligands with the opposite configuration to give the other enantiomer in high enantiomeric purity. Notably, these chiral molecules are not accessible through desymmetrization of prochiral C–H bonds or other asymmetric methods.^[13,14] To the best of our knowledge, this is the first example of kinetic resolution *via* C–H activation and C–C bond formation.

We commenced our studies by exploring the enantioselective C–H olefination/kinetic resolution of racemic pivaloyl (Piv) protected 3-chloromandelic acid **1a** with methyl acrylate as the coupling partner (see Supporting Information for screening of *O*-protecting group). It was found that in the presence of Boc-L-Ala-OH (**L1**) as the ligand, the enantioselective C–H olefination of *rac*-**1a** under aerobic conditions afforded the desired product **2a₁** with 89% ee at 18% conversion, corresponding to a selectivity factor (*s*)^[17] of 21 (Table 1, entry 1). Encouraged by this promising result, we screened a variety of Boc protected amino acid ligands with different side chains (**L1–L6**). The *s*-factors were gradually improved with the increase of the steric bulk on the side chains (Table 1, entries 1–6). In particular, both Boc-L-Tle-OH (**L5**) and Boc-L-Thr(*t*-Bu)-OH (**L6**) gave superior *s*-factors of 38 (entries 5 and 6). As the hydroxyl group on threonine (H-L-Thr-OH) could provide a valuable handle for structural modifications, this amino acid was selected as the ligand backbone for further tuning. Firstly, we investigated the effect of different *N*-protecting groups. While Fmoc-L-Thr(*t*-Bu)-OH (**L8**) provided similar *s*-factor to **L6** albeit with much lower reactivity (entry 7, *s* = 37), Ac-L-Thr(*t*-Bu)-OH (**L7**) resulted in a marked decrease in the *s*-factor value (entry 8, *s* = 26). Based on these results, a number of different hydroxyl protecting groups on Boc-L-Thr-OH were investigated. Ether protecting groups such as benzyl (Bn) and trityl (Trt) led to a slight decrease in selectivity (entries 9 and 10). Gratifyingly, acyl protecting

groups such as Piv and benzoyl (Bz) significantly improved the selectivity with Boc-L-Thr(Bz)-OH (**L12**) gave the best *s*-factor of 54 (entries 11 and 12). When the temperature was raised to 40 °C, the reaction was greatly accelerated, albeit with a slightly decreased *s*-factor value (entry 13). With extended reaction time, the loading of Pd(OAc)₂ could be reduced to 5 mol% without significantly affecting the selectivity (entry 14). Besides, a decrease in the amount of olefin to 0.4 equivalent improved the ee of olefinated product to 93% with a decreased conversion of 40% (entry 15).

With the optimized reaction conditions in hand, we investigated the substrate scope of the protocol. The enantioselective C–H olefination of *rac*-**1a** with different olefin coupling partners were carried out (Table 2). The reaction worked well with a wide range of electron-deficient olefins (entries 1–7). Acrylates were excellent coupling partners, affording the corresponding olefinated products **2a1–2a3** with *s*-factor values ranging from 46 to 54 (entries 1–3). Vinyl amides and vinyl phosphates were well tolerated (entries 4 and 5, *s* = 56 and 52, respectively). Alkyl vinyl ketones were also compatible with this kinetic resolution reaction, although a slightly longer reaction time was required (entry 6, *s* = 52). Coupling with the less reactive styrene also proceeded smoothly to give the olefinated product **2a7** in 90% ee (entry 7, *s* = 48).

Importantly, a wide range of substituted mandelic acid substrates were successfully olefinated with synthetically useful *s*-factor values. The reaction of substrates bearing both electron- withdrawing (CF₃, F, Cl) and electron-donating (Me, Ph, OMe, and OPiv) gave the corresponding products with *s*-factor values ranging from 20 to 50 (entries 8–17). All the *meta*-substituted substrates were regioselectively olefinated at the para position of the 3-substituents (entries 8–11). The chlorine atom in products **2a1–2a7**, **2h** and **2j** can potentially serve as a useful handle for subsequent synthetic elaboration. 3,4-Disubstituted substrates were also compatible with this protocol (entries 16 and 17, *s* = 50 and 28, respectively). The unsubstituted substrate also provided the desired product in 39% yield with 91% ee (entry 18, *s* = 23). Although the *s*-factor values obtained with *para*-substituted and unsubstituted substrates were somewhat lower, the enantiomeric purities of the desired products were still satisfactory (entries 12–15 and 18). Notably, high enantiomeric purity of starting material could be obtained when the conversion was slightly above 50%. For example, 3-chloromandelic acid (**1a**) was recovered in 95% ee at 52% conversion (entry 19). Moreover, subjecting the recovered starting material **1a** with 46% isolated yield and 87% ee (entry 1) to enantioselective C–H olefination conditions using the MPAA ligand with the opposite configuration afforded the chiral product **2a1'** in 99% ee (Scheme 1), demonstrating the feasibility of obtaining both enantiomers of the olefinated mandelic acids through this approach. More importantly, the removal of Piv protecting group can be accomplished under alkaline conditions in high yields without any loss of stereochemical purity (see Supporting Information for the cleavage of Piv group), rendering this reaction a practical method for the synthesis of chiral mandelic acid derivatives.

We next turned our attention to the kinetic resolution of racemic phenylglycine derivatives. Considering the potential bis-dentate coordination of the substrate with Pd(II) center could interfere with the ligand, our initial effort focused on the identification of an appropriate *N*-protecting group. Indeed, when using Boc and Ac as the protecting group, the kinetic

resolution reaction provided the olefinated products in good yields but with very poor enantioselectivities. We were pleased to find that Piv protected 3-chlorophenylglycine **3a** was successfully olefinated at elevated temperature (40 °C) to give **4a** with high selectivity (Table 3, entry 1, $s = 51$). Both electron-withdrawing (Cl, F) and electron-donating (OMe) substituents on the aryl ring were well tolerated, furnishing the olefinated products with good s -factor values (entries 2–4). Notably, the kinetic resolution of racemic phenylglycine **3e** gave exclusively the mono-olefinated product **4e₁** with synthetically useful selectivity (entry 5, $s = 41$). The reaction also worked well with the less reactive styrene to give the olefinated product **4e₂** with high s -factor value (entry 6, $s = 39$).

The absolute configuration of **2f** determined by X-ray crystallography analysis as (*S*)^[18] promoted us to propose a stereomodel to rationalize the origin of the selectivity. According to previous extensive structural and computational studies,^[8a,19] we proposed two possible transition states **TS_S** and **TS_R** (Fig. 2b). In both **TS_S** and **TS_R**, Pd is coordinated with the MPAA ligand and the substrate in a square-planar coordination. The side chain of amino acid points upward, which pushes Boc downward below the Pd coordination plane to avoid steric repulsion. In the C–H activation step, transition state **TS_R** is expected to be disfavored than **TS_S** due to the steric repulsion between Boc and OPiv in **TS_R**, which is consistent with the faster formation of the product with *S* configuration. This could also explain why a better selectivity factor was achieved when using bulky pivaloyl group as *O*-protecting group of mandelic acids.

In conclusion, Pd(II)-catalyzed enantioselective C–H olefination of α -hydroxy and α -amino phenylacetic acids *via* kinetic resolution has been achieved using a mono-*N*-protected amino acid (MPAA) ligand, filling a important gap in enantioselective C–H activation reactions. To the best of our knowledge, this development represents the first example of kinetic resolution *via* C–H activation/C–C bond formation,^[20] providing a new approach for making C–C bond asymmetrically.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. a) Giri R, Shi BF, Engle KM, Mangel N, Yu JQ. Chem Soc Rev. 2009; 38:3242–3272. [PubMed: 19847354] b) Davies HML, Manning JR. Nature. 2008; 451:417–424. [PubMed: 18216847] c) Doyle MP, Duffy R, Ratnikov M, Zhou L. Chem Rev. 2010; 110:704–724. [PubMed: 19785457]
2. For examples of enantioselective Rh-catalyzed C–H amination, see: Liang C, Robert-Peillard F, Fruit C, Müller P, Dodd RH, Dauban P. Angew Chem Int Ed. 2006; 45:4641–4644. Reddy RP, Davies HML. Org Lett. 2006; 8:5013–5016. [PubMed: 17048831] Zalatan DN, Du Bois J. J Am Chem Soc. 2008; 130:9220–9221. [PubMed: 18582043]
3. For an example of enantioselective Ru-catalyzed C–H amination, see: Milczek E, Boudet N, Blakey S. Angew Chem Int Ed. 2008; 47:6825–6828.
4. For an example of Ru-catalyzed atropselective alkylation in moderate ees, see: Kakiuchi F, Le Gendre P, Yamada A, Ohtaki H, Murai S. Tetrahedron: Asymmetry. 2000; 11:2647–2651.
5. For examples of C–H activation followed by enantioselective addition to olefins, see: Mikami K, Hatano M, Terada M. Chem Lett. 1999; 55–56. Thalji RK, Ellman JA, Bergman RG. J Am Chem Soc. 2004; 126:7192–7193. [PubMed: 15186153] Hyster TK, Knörr L, Ward TR, Rovis T. Science.

- 2012; 338:500–503. [PubMed: 23112327] Ye B, Cramer N. *Science*. 2012; 338:504–506. [PubMed: 23112328]
6. For examples of enantioselective Ir(I)-catalyzed C–H activation, see: Pan S, Endo K, Shibata T. *Org Lett*. 2011; 13:4692–4695. [PubMed: 21812393] Pan S, Matsuo Y, Endo K, Shibata T. *Tetrahedron*. 2012; 68:9009–9015. Shibata T, Shizuno T. *Angew Chem Int Ed*. 2014; 53:5410–5413.
7. For an example of enantioselective Rh-catalyzed silylation, see: Lee T, Wilson TW, Berg R, Ryberg P, Hartwig JF. *J Am Chem Soc*. 2015; 137:6742–6745. [PubMed: 25948056]
8. For examples of enantioselective Pd(II)-catalyzed C–H activation/C–C bond formation, see: Shi BF, Mangel N, Zhang YH, Yu JQ. *Angew Chem Int Ed*. 2008; 47:4882–4886. Shi BF, Zhang YH, Lam JK, Wang DH, Yu JQ. *J Am Chem Soc*. 2010; 132:460–461. [PubMed: 20017549] Wasa M, Engle KM, Lin DW, Yoo EJ, Yu JQ. *J Am Chem Soc*. 2011; 133:19598–19601. [PubMed: 22059375] Gao D-W, Shi Y-C, Gu Q, Zhao Z-L, You S-L. *J Am Chem Soc*. 2013; 135:86–89. [PubMed: 23253097] Pi C, Li Y, Cui X, Zhang H, Han Y, Wu Y. *Chem Sci*. 2013; 4:2675–2679. Xiao KJ, Lin DW, Miura M, Zhu RY, Gong W, Wasa M, Yu JQ. *J Am Chem Soc*. 2014; 136:8138–8142. [PubMed: 24815880] Pi C, Cui X, Liu X, Guo M, Zhang H, Wu Y. *Org Lett*. 2014; 16:5164–5167. [PubMed: 25247387] Chan KSL, Fu H, Yu JQ. *J Am Chem Soc*. 2015; 137:2042–2046. [PubMed: 25581489] Du ZJ, Guan J, Wu GJ, Xu P, Gao LX, Han FS. *J Am Chem Soc*. 2015; 137:632–635. [PubMed: 25569141] Yan SB, Zhang S, Duan WL. *Org Lett*. 2015; 17:2458–2461. [PubMed: 25937267] For an example of Pd-catalyzed atropselective arylation, see: Yamaguchi K, Yamaguchi J, Studer A, Itami K. *Chem Sci*. 2012; 3:2165–2169.
9. For examples of enantioselective Pd(0)-catalyzed C–H activation/C–C bond formation, see: Albicker MR, Cramer N. *Angew Chem Int Ed*. 2009; 48:9139–9142. Renaudat A, Jean-Gérard L, Jazzar R, Kefalidis CE, Clot E, Baudoin O. *Angew Chem Int Ed*. 2010; 49:7261–7265. Anas S, Cordi A, Kagan HB. *Chem Comm*. 2011; 47:11483–11485. [PubMed: 21927738] Nakanishi M, Katayev D, Besnard C, Kündig EP. *Angew Chem Int Ed*. 2011; 50:7438–7441. Saget T, Lemouzy SJ, Cramer N. *Angew Chem Int Ed*. 2012; 51:2238–2242. Nakanishi M, Katayev D, Besnard C, Kündig EP. *Chimia*. 2012; 66:241–243. [PubMed: 22613159] Martin N, Pierre C, Davi M, Jazzar R, Baudoin O. *Chem Eur J*. 2012; 18:4480–4484. [PubMed: 22407525]
10. For examples of enantioselective Pd(II)-catalyzed C–H activation/C–X bond formation, see: Cheng XF, Li Y, Su YM, Yin F, Wang JY, Sheng J, Vora HU, Wang XS, Yu JQ. *J Am Chem Soc*. 2013; 135:1236–1239. [PubMed: 23305171] Chu L, Wang XC, Moore CE, Rheingold AL, Yu JQ. *J Am Chem Soc*. 2013; 135:16344–16347. [PubMed: 24151991]
11. a) Tremblay LW, Xu H, Blanchard JS. *Biochemistry*. 2010; 49:9685–9687. [PubMed: 20961112] b) Spencer JL, Flynn EH, Roeske RW, Siu FY, Chauvette RR. *J Med Chem*. 1966; 9:746–750. [PubMed: 5182352] c) Gump DW. *Rev Infect Dis*. 1981; 3:289–292. [PubMed: 7020046]
12. a) Momiyama N, Yamamoto H. *J Am Chem Soc*. 2005; 127:1080–1081. [PubMed: 15669829] b) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*. Wiley; New York: 1995. c) Coppola, GM., Schuster, FH. *α -Hydroxy Acids in Enantioselective Synthesis*. VCH; Weinheim, Germany: 1997.
13. For selected examples on asymmetric synthesis of mandelic acid derivatives, see: Zhuang W, Jørgensen KA. *J Am Chem Soc*. 2000; 122:12517–12522. Tang L, Deng L. *J Am Chem Soc*. 2002; 124:2870–2871. [PubMed: 11902867] Radosevich AT, Musich C, Toste FD. *J Am Chem Soc*. 2005; 127:1090–1091. [PubMed: 15669834] Maier TC, Fu GC. *J Am Chem Soc*. 2006; 128:4594–4595. [PubMed: 16594695] Weng SS, Shen MW, Kao JQ, Munot YS, Chen CT. *Proc Natl Acad Sci U S A*. 2006; 103:3522–3527. [PubMed: 16501046] Zhu SF, Cai Y, Mao HX, Xie JH, Zhou QL. *Nat Chem*. 2010; 2:546–551. [PubMed: 20571572] Wang P, Tao WJ, Sun XL, Liao S, Tang Y. *J Am Chem Soc*. 2013; 135:16849–16852. [PubMed: 24161001] Enders D, Stöckel B, Rembiak A. *Chem Commun*. 2014; 50:4489–4491.
14. For selected examples on asymmetric synthesis of phenylglycine derivatives, see: Krueger CA, Kuntz KW, Dzierba CD, Wirschn WG, Gleason JD, Snapper ML, Hoveyda AH. *J Am Chem Soc*. 1999; 121:4284–4285. Sigman MS, Vachal P, Jacobsen EN. *Angew Chem Int Ed*. 2000; 39:1279–1281. Saaby S, Fang X, Gathergood N, Jørgensen KA. *Angew Chem Int Ed*. 2000; 39:4114–4116. Shirakawa S, Berger R, Leighton JL. *J Am Chem Soc*. 2005; 127:2858–2859. [PubMed: 15740114] Beenen MA, Weix DJ, Ellman JA. *J Am Chem Soc*. 2006; 128:6304–6305. [PubMed: 16683780] Shang G, Yang Q, Zhang X. *Angew Chem Int Ed*. 2006; 45:6360–6362. Li G, Liang Y, Antilla JC. *J Am Chem Soc*. 2007; 129:5830–5831. [PubMed: 17428058] Lee EC, Fu GC. *J Am*

- Chem Soc. 2007; 129:12066–12067. [PubMed: 17877350] Dai H, Lu X. Org Lett. 2007; 9:3077–3080. [PubMed: 17608432]
15. Larrow JF, Jacobsen EN. J Am Chem Soc. 1994; 116:12129–12130.
16. Chu L, Xiao KJ, Yu JQ. Science. 2014; 346:451–455. [PubMed: 25342799] For a Pd-catalyzed atropselective C–H iodination via kinetic resolution in modest selectivity, see: Gao DW, Gu Q, You SL. ACS Catal. 2014; 4:2741–2745.
17. The selectivity factor (s) = (rate of fast-reacting enantiomer) / (rate of slow-reacting enantiomer) = $\ln[(1-c)(1-ee)]/\ln[(1-c)(1+ee)]$ where c is the conversion and ee is the enantiomeric excess of the remaining starting material. Kagan HG, Fiaud JC. Top Stereochem. 1988; 18:249–340.
18. CCDC 1438150 (2f) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.
19. a) Musaev DG, Kaledin A, Shi BF, Yu JQ. J Am Chem Soc. 2012; 134:1690–1698. [PubMed: 22148424] b) Baxter RD, Sale D, Engle KM, Yu JQ, Blackmond DG. J Am Chem Soc. 2012; 134:4600–4606. [PubMed: 22324814] c) Cheng GJ, Yang YF, Liu P, Chen P, Sun TY, Li G, Zhang X, Houk KN, Yu JQ, Wu YD. J Am Chem Soc. 2014; 136:894–897. [PubMed: 24410499] d) Cheng GJ, Chen P, Sun TY, Zhang X, Yu JQ, Wu YD. Chem Eur J. 2015; 21:11180–1188. [PubMed: 26186414]
20. For selected examples on kinetic resolution with carbon-carbon bond formation, see: Tanaka K, Fu GC. J Am Chem Soc. 2003; 125:8078–8079. [PubMed: 12837058] Bandini M, Cozzi PG, Melchiorre P, Umami-Ronchi A. Angew Chem Int Ed. 2004; 43:84–87. Mao B, Ji Y, fañanàs-Mastral M, Caroli G, Meetsma A, Feringa BL. Angew Chem Int Ed. 2012; 51:3168–3173. Chen L, Luo S, Li J, Li X, Cheng JP. Org Biomol Chem. 2010; 8:2627–2632. [PubMed: 20358094]

a Desymmetrization of prochiral C–H bonds (previous work) **b Enantioselective C–H olefination via kinetic resolution (this work)**

Figure 1.
Enantioselective C–H activation reactions.

Scheme 1.

Enantioselective C–H olefination of the recovered starting material.

Table 1

Screening of MPAA ligands.^[a]

Entry	L	ligand	Conv[%]/b]	ee[%]/c]		s
				1a	2a1	
1	L1	Boc-L-Ala-OH	18	19	89	21
2	L2	Boc-L-Leu-OH	35	47	87	22
3	L3	Boc-L-Phe-OH	42	63	86	25
4	L4	Boc-L-Val-OH	46	74	86	29
5	L5	Boc-L-Tle-OH	47	79	88	38
6	L6	Boc-L-Thr(<i>t</i> -Bu)-OH	45	74	89	38
7	L7	Fmoc-L-Thr(<i>t</i> -Bu)-OH	24	29	93	37
8	L8	Ac-L-Thr(<i>t</i> -Bu)-OH	52	88	80	26
9	L9	Boc-L-Thr(Bn)-OH	34	47	90	30
10	L10	Boc-L-Thr(Trt)-OH	49	81	84	29
11	L11	Boc-L-Thr(Piv)-OH	48	82	90	48
12	L12	Boc-L-Thr(Bz)-OH	49	87	90	54
13[d]	L12	Boc-L-Thr(Bz)-OH	46	77	89	40
14[e]	L12	Boc-L-Thr(Bz)-OH	45	75	91	48
15[f]	L12	Boc-L-Thr(Bz)-OH	40	62	93	51

^[a] Reaction conditions: *rac*-1a (0.2 mmol), methyl acrylate (0.6 equiv), Pd(OAc)₂ (10 mol%), ligand (30 mol%), KHCO₃ (2.0 equiv), *t*-AmylOH (1.0 mL), O₂ (1 atm), 30 °C, 24 h.

^[b] Calculated conversion, c = eeSM / (eeSM + eePR).

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 $[\alpha]_D^{25}$ Determined by chiral HPLC analysis. $[\alpha]_D^{25}$ At 40 °C, 12 h. $[\alpha]_D^{25}$ Using Pd(OAc)₂ (5 mol%), **L12** (15 mol%), 48 h. $[\alpha]_D^{25}$ Using 0.4 equiv of methyl acrylate.

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Table 2

Enantioselective C–H olefination/ kinetic resolution of mandelic acids.^[a]

Entry	<i>rac</i> -1	X	R	time [h]	conv ^[b] (yield, %) ^[c]	ee ^[d] [%]	
						1	2
1	1a	3-Cl	CO ₂ Me	24	49 (45)	87	90
2	1a	3-Cl	CO ₂ Et	24	48 (46)	83	90
3	1a	3-Cl	CO ₂ Bn	24	45 (41) ^[e]	73	91
4	1a	3-Cl	CONMe ₂	24	46 (43) ^[e]	77	92
5	1a	3-Cl	PO(OEt) ₂	24	47 (42)	80	91
6	1a	3-Cl	COMe	36	42 (39)	67	92
7	1a	3-Cl	Ph	24	48 (46)	82	90
8	1b	3-CF ₃	CO ₂ Me	48	38 (35)	58	93
9	1c	3-Me	CO ₂ Me	24	44 (43)	70	89
10	1d	3-Ph	CO ₂ Me	24	42 (41)	64	90
11	1e	3-OPiv	CO ₂ Me	24	41 (40)	65	92
12	1f	4-CF ₃	CO ₂ Me	60	43 (38) ^[f]	65	92
13	1g	4-F	CO ₂ Me	60	42 (37) ^[f]	61	90
14	1h	4-Cl	CO ₂ Me	60	41 (35) ^[f]	59	90
15	1i	4-OMe	CO ₂ Me	48	45 (41) ^[f]	67	86
16	1j	3,4-Cl ₂	CO ₂ Me	48	49 (40)	86	89
17	1k	3-OMe-4-OPiv	CO ₂ Me	48	47 (43)	75	85
18	1l	H	CO ₂ Me	24	43 (39) ^[f]	64	91
19	1a	3-Cl	CO ₂ Me	27	52 (48)	95	86

^[a]Reaction conditions: *rac*-1 (0.2 mmol), olefin (0.6 equiv), Pd(OAc)₂ (10 mol%), **L12** (30 mol%), KHCO₃ (2.0 equiv), *t*-AmylOH (1.0 mL), O₂ (1 atm), 30 °C, 24–60 h.

/e/ To simplify separation, the crude olefinated product was methylated using TMSCH₂N₂.

//f/ Conversion determined by crude ¹H-NMR.

/d/ Determined by chiral HPLC analysis.

/c/ Isolated yield of the olefinated product.

/b/ Calculated conversion, $c = ee_{SM} / (ee_{SM} + ee_{PR})$.

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Table 3

Enantioselective C–H olefination/ kinetic resolution of phenylglycines.^[a]

Entry	<i>rac</i> -3	X	R	time [h]	conv ^[b] (yield, %)	ee ^[c] [%] ^[d]			
						3	4	3	4
1	3a	3-Cl	CO ₂ Me	48	47 (41)	79	91	51	
2	3b	4-Cl	CO ₂ Me	72	48 (43)	83	90	49	
3	3c	4-F	CO ₂ Me	72	45 (38)	72	88	34	
4	3d	4-OMe	CO ₂ Me	48	45 (40)	70	87	30	
5	3e	H	CO ₂ Me	10	47 (45)	79	89	41	
6	3a	H	Ph	10	48 (44)	81	88	39	

^[a] Reaction conditions: *rac*-3 (0.2 mmol), olefin (0.6 equiv), Pd(OAc)₂ (10 mol%), **L12** (30 mol%), KHCO₃ (2.0 equiv), *t*-AmylOH (1.0 mL), O₂ (1 atm), 40 °C, 10–72 h.^[b] Calculated conversion, c = eeSM / (eeSM + eePR).^[c] Isolated yield of the olefinated product.^[d] Determined by chiral HPLC analysis.