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Formation of α -chiral centers by asymmetric β -C(sp³)-H arylation, alkenylation, and alkynylation

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Abstract

The enzymatic β -C–H hydroxylation of the feedstock chemical isobutyric acid has enabled the asymmetric synthesis of a wide variety of polyketides. The analogous transition metal catalyzed enantioselective β -C–H functionalization of isobutyric acid-derived substrates should provide a versatile method for constructing useful building blocks with enantioenriched α -chiral centers from this abundant C-4 skeleton. However, the desymmetrization of ubiquitous isopropyl moieties by organometallic catalysts has remained an unanswered challenge. Herein, we report the design of chiral mono-protected aminomethyl oxazoline (MPAO) ligands that enable desymmetrization of isopropyl groups *via* palladium insertion into the C(sp³)-H bonds of one of the prochiral methyl groups. We detail the enantioselective β -arylation, -alkenylation and -alkynylation of isobutyric acid/2-amino-isobutyric acid derivatives, which may serve as a platform for the construction of α -chiral centers.

C–H activation reactions enable the use of minimally functionalized bulk chemicals as building blocks for the synthesis of complex molecules, thereby shortening synthetic sequences, reducing waste, and improving the sustainability of chemical synthesis. In order for the logic of C–H activation to be fully realized in the synthesis of chiral molecules, enantioselective C–H activation reactions — whereby stereochemistry is controlled in the C–H cleavage step by a metal catalyst — must be developed (1). The biosynthetic pathways to a myriad of natural products proceed through the enantioselective β -C–H hydroxylation of isobutyric acid (2, 3); further, this process has been adapted for the industrial preparation of the Roche ester, which has served as an invaluable source of α -center chirality in the

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Supplementary Materials:

Supplementary Text

Fig. S1

Tables S1 to S13

NMR Spectra

HPLC Traces

X-Ray Crystallographic Data

References (34–42)

synthesis of complex molecules (4–7; Fig. 1A). Inspired by the bulk preparation of the Roche ester and the central role of α -chiral centers in retrosynthetic analysis (8), our group has long sought to develop methodologies that desymmetrize the isopropyl group of isobutyric acid derivatives through transition metal catalyzed C–H functionalization, in turn expanding the existing chiral pool (Fig. 1B).

Although enantioselective β -methylene C–H arylation has recently been realized (9), desymmetrization of isopropyl groups is a fundamentally different challenge. This challenge is reflected in an analysis of the steric environment associated with respective C–H insertion intermediates **I** and **II** (Fig. 1C). In methylene C–H activation (**I**), steric differentiation between a bulky alkyl group and a methylene C–H bond is required, whereas in the desymmetrization of isopropyl moieties (**II**) the α -hydrogen atom must be differentiated from a relatively small α -methyl substituent. Moreover, the prochiral center (the α -carbon) in isopropyl desymmetrization is too far away to interact directly with the ligated transition metal catalyst, making asymmetric induction considerably more challenging.

To date, intermolecular desymmetrization of α -dialkyl groups has only been possible with cyclopropane, cyclobutane or substrates containing large α -substituents, which serve to amplify the chiral recognition in the transition state (10–13). Related studies on desymmetrization of α -dialkyl groups *via* C–H activation from other laboratories have been limited to intramolecular Pd(0)-catalyzed C–H arylations (14–22). An inspiring formal enantioselective intermolecular β -arylation of isobutyric esters has been demonstrated with moderate enantioselectivity (67:33 to 77:23 er) (23). In this reaction, α -lithiation precedes α -palladation, which is followed by β -hydride elimination to give the corresponding olefin intermediate. Subsequent enantioselective carbopalladation of the double bond, rather than chiral recognition of geminal methyl groups, is responsible for chiral induction.

Herein we report the design of chiral mono-protected aminomethyl oxazoline (MPAO) ligands that enable Pd(II)-catalyzed enantioselective β -arylation, -alkenylation, and -alkynylation of isobutyric amides (Fig. 1B). The remaining α -methyl group can then undergo further C–H functionalizations to afford greater product diversity. Using a chiral benzoyl-protected aminomethyl oxazoline ligand, desymmetrization of 2-aminoisobutyric acid-derived amide (**3**) is also showcased to provide straightforward access to a wide range of enantioenriched α,α -dialkyl α -amino acids that may be used as building blocks for peptide based drug synthesis (24, 25). Systematic ligand modification suggests that the additional interaction of the chiral center on the oxazoline ring with the substrate is crucial to the successful desymmetrization of isopropyl groups.

Our early efforts to desymmetrize isopropyl groups of isobutyric acid-derived substrates focused on the use of chiral auxiliaries (10, 11). These studies, through isolation of well-defined chiral C–H insertion intermediates and computational analysis (26, 27), improved our understanding of how chiral differentiation of α -gem-dimethyl groups could potentially be achieved (Fig. 1C). The difficulty of desymmetrizing the gem-dimethyl groups in isobutyric acid-derived substrates is demonstrated by the fact that even when employing a bulky oxazoline as a chiral auxiliary, no diastereoselectivity is obtained (10). Furthermore, desymmetrization of α -dimethyl groups using a chiral amino acid-derived ligands is only

successful (90:10 er) when the α -hydrogen atom is replaced by an extremely bulky α -*tert*-butyl group (12). The use of chiral phosphoric acid ligands has also failed to enantioselectively differentiate the gem-dimethyl groups in isobutyric acid-derived substrates (28–31).

Our recent development of bidentate chiral acetyl-protected aminoethyl quinoline (APAQ, **L1**) ligands for enantioselective methylene C–H activation prompted us to test whether these ligands would prove useful for the desymmetrization of isopropyl groups in isobutyric acid-derived amides (9). With isobutyric amide substrate **1**, **L1** gave nearly racemic products (Fig. 2A). Furthermore, extensive modification of APAQ ligands did not lead to a noticeable improvement in enantiomeric ratio (er). This result highlights the difference between the desymmetrization of isopropyl groups and enantioselective methylene C–H activation. To amplify steric interactions between substrate and catalyst, we replaced the quinoline motif with oxazoline, thereby enabling introduction of additional chiral bias to the catalyst. Ligand **L2** — consisting of an achiral oxazoline moiety, a bulky isopropyl stereocenter (derived from valine), and an *N*-acetyl-protected amine — failed to achieve significant stereoinduction. Further, the chiral oxazoline ligand **L3** derived from *N*-acetyl glycine — and consequently lacking a stereocenter on the ligand backbone — also failed to afford enantioenriched products. Intriguingly, the combination of the two chiral centers at C-4 on the oxazoline and the side chain in **L22** afforded a promising er of 85:15. Increasing the steric bulkiness on the side chain (i.e. from isopropyl to *tert*-butyl, **L23**) further improved the selectivity to 98:2 er (For extensive optimizations of chiral ligands, Pd source, additives, and reaction concentrations, see tables S1–S5). The synergistic effect of the mutual relationship between these two stereocenters is evident from the complete loss of enantioselectivity when the absolute stereochemistry of one of the chiral centers is reversed as in **L24**. Although full rationalizations of the observed asymmetric induction require extensive computational and kinetic analysis, the absolute configuration of the product and the observed influence of each chiral center on the effectiveness of the ligands are consistent with the steric interactions indicated in the C–H insertion intermediate **III** (Fig. 1C). We propose that the *N*-acetyl group on the coordinating nitrogen is oriented on the top face of the palladium square plane due to steric repulsion from the chiral center on the side chain. The 4-benzyl group on the oxazoline ring further shields the top face of intermediate **III**. These combined steric interactions may reinforce the orientation of the α -methyl group in **III** thereby establishing the stereochemistry of the C–H cleavage step.

With the optimized chiral ligand and conditions in hand, we screened the enantioselective β -C–H arylation of isobutyric amide **1** with a wide range of aryl iodides (Fig. 2B). A range of para-substituents on the aryl iodides from electron-donating (OMe, NBnBoc) to electron-withdrawing (halides, CF₃, keto and nitro) groups are tolerated, providing enantioselectivity up to 98:2 er (**2a–q**). The scope of *meta*-substituted aryl iodides is also broad, and enantiomeric ratios greater than 94:6 (**2r–ab**) were obtained. The above scope of *ortho*-, *meta*- and para-substituted aryl iodides features either halogens (as in **21–2n**, **2u–2w** and **2ah**) or reactive groups (phosphonate moiety as in **2i** and aldehyde functionality as in **2aa** and **2ae**) that can serve as useful synthetic handles for subsequent chemical manipulation. A number of heteroaryl iodides, including thiophene, benzothiophene and indole moieties are

also compatible, affording products with high enantioselectivity in synthetically useful yields (**2al–ap**). The simplicity of deprotecting the amide auxiliary using $\text{BF}_3 \cdot \text{Et}_2\text{O}$ was also demonstrated with product **2q** without erosion in enantioselectivity (see supplementary materials for experimental details).

The unique pharmacological and conformational properties of α,α -disubstituted α -amino acids display in peptide drug molecules (24, 25) prompted us to apply these conditions to *N*-phthaloyl-protected 2-amino-isobutyric acid derivatives (Fig. 2C). However, the analogous amide substrate prepared by condensing the *N*-Phth-protected-2-aminoisobutyric acid with 2,3,5,6-tetrafluoro-4-(trifluoromethyl)aniline is not reactive under these conditions, presumably due to the steric bulkiness of this substrate which may prevent coordination. To reduce the steric hindrance of the substrate, we prepared the *N*-methoxy amide **3** of *N*-phthaloyl-protected 2-amino-isobutyric acid (32, 33; Fig. 2C). Although **3** showed substantial decomposition under the conditions established for substrate **1**, we were able to find milder conditions that allowed the β -arylation to proceed at 35 °C. Although ligand **L23** gave satisfactory enantioselectivity (91:9 er), the yield remained low despite extensive optimizations (ca. 40% yield). We next elected to screen MPAO ligands. Whereas modification of the oxazoline ring and the amino acid side chain afforded only moderate improvement in yields (see supplementary materials for experimental details), replacement of the *N*-acetyl moiety by an *ortho*-difluorobenzoyl group (**L41**) increased the yield of **4a** to 75% while maintaining high enantioselectivity (Fig. 2C, 96:4 er). C–H coupling with a variety of aryl iodides afforded difficult-to-access enantioenriched α,α -disubstituted α -amino acids containing chiral α -quaternary centers (**4a–f**, for coupling with a wide range of aryl iodides, see Fig. S1 in supplementary materials). The facile conversion of the *N*-methoxy amide auxiliary to an ester renders this method easy to use (32). On gram scale, both the *N*-methoxy amide auxiliary and the phth protecting group were removed and converted the Fmoc-protected amino acid as a building block for peptide synthesis (See supplementary materials).

One potential advantage of an organometallic approach to enantioselective functionalizations of $\text{C}(\text{sp}^3)\text{-H}$ bonds is that the metallated intermediate can undergo reactivity with various coupling partners. Unfortunately, Pd-catalyzed enantioselective $\text{C}(\text{sp}^3)\text{-H}$ activation reactions have been limited to arylation thus far. To fully realize the potential of asymmetric metal insertion processes, we next developed enantioselective C–H alkenylation, and alkynylation reactions of **1**. β -Styrenylation of amide **1** using chiral ligand **L23** afforded 88:12 er (Fig. 3). The use of **L30** containing an additional chiral center at C-5 improved the enantioselectivity to 94:6 er. A number of (*E*)-styrenyl iodides are compatible coupling partners (**5a–s**) including the disubstituted (*E*)-styrenyl iodide (**5t**). The use of other simple (*E*)-alkenyl iodides also gave good enantioselectivity, albeit in lower yields (**5u**, **5v**). Upon minor alteration of reaction conditions, **L30** has also allowed the enantioselective β -alkynylation to proceed in 94.5:5.5 er (**6**). To further broaden the diversity of the chiral centers accessed through these three enantioselective transformations, we also performed subsequent diverse β -functionalizations of the remaining methyl group including arylation (**7a–f**), alkynylation (**8**), alkylation (**9**), bromination (**10**), and borylation (**11**) (Fig. 4). Thus

the sequential C–H functionalizations of the isopropyl groups with a wide range of coupling partners afford a myriad of α -chiral carboxylic acids.

Our success in the steric differentiation of a hydrogen atom and a relatively small methyl group by an organometallic catalyst provides invaluable insight for the further development of desymmetrizing enantioselective C–H activation reactions. The enantioselective β -C–H activation reactions reported herein provide a versatile platform for constructing α -chiral centers in asymmetric synthesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We gratefully acknowledge The Scripps Research Institute, the NIH (NIGMS, 2R01GM084019) and Bristol-Myers Squibb for their financial support. Tyler Gordon Saint-Denis, Marcus E. Farmers and Anh Tran are thanked for editorial assistance. J.-Q. Y. conceived the concept. Q.-F. W. developed the chiral ligands, optimized the reaction conditions and surveyed the substrate scope. P.-X. S. performed the sequential C–H functionalization reactions. J. H., X.-B. W., F. Z., Q. S. optimized the chiral ligands. R.-Y. Z. performed the C–H bromination reaction. C. M., J. X. Q., M. A. P. scaled up the C–H activation reaction for the preparation of β -arylated 2-amino-isobutyric acids. J.-Q. Y. directed the project. Additional data supporting the conclusions are in supplementary material. Metrical parameters for the structures of **L23** and **4c** are available free of charge from the Cambridge Crystallographic Data Centre under reference number CCDC- 1518967 and CCDC- 1518968, respectively.

References and Notes

1. Giri R, Shi BF, Engle KM, Mangel N, Yu JQ. *Chem Soc Rev*. 2009; 38:3242–3272. [PubMed: 19847354]
2. Goodhue CT, Schaeffer JR. *Biotechnol Bioeng*. 1971; 13:203–214. [PubMed: 5580680]
3. Hasegawa J, Ogura M, Hamaguchi S, Shimazaki M, Kawaharada H, Watanabe K. *J Ferment Technol*. 1981; 59:203–208.
4. Bode JW, Fraefel N, Muri D, Carreira EM. *Angew Chem Int Ed*. 2001; 40:2082–2085.
5. Paterson I, Britton R, Delgado O, Meyer A, Poullennec KG. *Angew Chem Int Ed*. 2004; 43:4629–4633.
6. Lawhorn BG, Boga SB, Wolkenberg SE, Colby DA, Gauss CM, Swingle MR, Amable L, Honkanen RE, Boger DL. *J Am Chem Soc*. 2006; 128:16720–16732. [PubMed: 17177422]
7. Feng J, Kasun ZA, Krische MJ. *J Am Chem Soc*. 2016; 138:5467–5478. [PubMed: 27113543]
8. Corey, EJ., Kürti, L., editors. *Enantioselective Chemical Synthesis: Methods, Logic and Practice*. Direct Book Publishing; Dallas, TX: 2010.
9. Chen G, Gong W, Zhuang Z, Andrä MS, Chen Y-Q, Hong X, Yang Y-F, Liu T, Houk KN, Yu J-Q. *Science*. 2016; 353:1023–1027. [PubMed: 27701111]
10. Giri R, Chen X, Yu JQ. *Angew Chem Int Ed*. 2005; 44:2112–2115.
11. Giri R, Liang J, Lei JG, Li JJ, Wang DH, Chen X, Naggar IC, Guo C, Foxman BM, Yu JQ. *Angew Chem Int Ed*. 2005; 44:7420–7424.
12. Xiao KJ, Lin DW, Miura M, Zhu RY, Gong W, Wasa M, Yu JQ. *J Am Chem Soc*. 2014; 136:8138–8142. [PubMed: 24815880]
13. He C, Gaunt M. *Angew Chem Int Ed*. 2015; 54:15840–15844.
14. Nakanishi M, Katayev D, Besnard C, Kündig EP. *Angew Chem Int Ed*. 2011; 50:7438–7441.
15. Anas S, Cordi A, Kagan HB. *Chem Comm (Camb)*. 2011; 47:11483–11485.
16. Martin N, Pierre C, Davi M, Jazzar R, Baudoin O. *Chem Eur J*. 2012; 18:4480–4484. [PubMed: 22407525]
17. Saget T, Lemouzy SJ, Cramer N. *Angew Chem Int Ed*. 2012; 51:2238–2242.

18. Larionov E, Nakanishi M, Katayev D, Besnard C, Kündig EP. *Chem Sci.* 2013; 4:1995–2005.
19. Holstein PM, Vogler M, Larini P, Pilet G, Clot E, Baudoin O. *ACS Catal.* 2015; 5:4300–4308.
20. Murai M, Takeshima H, Morita H, Kuninobu Y, Takai K. *J Org Chem.* 2015; 80:5407–5414. [PubMed: 25961415]
21. Yang L, Melot R, Neuburger M, Baudoin O. *Chem Sci.* advance article.
22. Holstein PM, Dailier D, Vantourout J, Shaya J, Millet A, Baudoin O. *Angew Chem Int Ed.* 2016; 55:2805–2809.
23. Renaudat A, Jean-Gérard L, Jazzar R, Kefalidis CE, Clot E, Baudoin O. *Angew Chem Int Ed.* 2010; 49:7261–7265.
24. Venkatraman J, Shankaramma SC, Balaram P. *Chem Rev.* 2001; 101:3131–3152. [PubMed: 11710065]
25. Sagan S, Karoyan P, Lequin O, Chassaing G, Lavielle S. *Curr Med Chem.* 2004; 11:2799–2822. [PubMed: 15544477]
26. Musaev DG, Kaledinm AL, Shi BF, Yu JQ. *J Am Chem Soc.* 2012; 134:1690–1698. [PubMed: 22148424]
27. Giri R, Lan Y, Liu P, Houk KN, Yu JQ. *J Am Chem Soc.* 2012; 134:14118–14126. [PubMed: 22830301]
28. Engle KM, Yu JQ. *J Org Chem.* 2013; 78:8927–8955. [PubMed: 23565982]
29. Yan SB, Zhang S, Duan WL. *Org Lett.* 2015; 17:2458–2461. [PubMed: 25937267]
30. Jain P, Verma P, Xia G, Yu JQ. *Nat Chem.* 2016; 134:14118–14126.
31. Wang H, Tong HR, He G, Chen G. *Angew Chem Int Ed.* 2016; 55:15387–15391.
32. Chen G, Shigenari T, Jain P, Zhang Z, Jin Z, He J, Li S, Mapelli C, Miller MM, Poss MA, Scola PM, Yeung KS, Yu JQ. *J Am Chem Soc.* 2015; 137:3338–3351. [PubMed: 25697780]
33. Zhu RY, Farmer ME, Chen YQ, Yu JQ. *Angew Chem Int Ed.* 2016; 55:10578–10599.
34. Wasa M, Engle KM, Yu JQ. Pd(II)-catalyzed olefination of $\text{sp}^3\text{C-H}$ bonds. *J Am Chem Soc.* 2010; 132:3680–3681. [PubMed: 20187642]
35. Li K, Tan G, Huang J, Song F, You J. Iron-catalyzed oxidative C–H/C–H cross-coupling: an efficient route to α -quaternary α -amino acid derivatives. *Angew Chem Int Ed.* 2013; 52:12942–12945.
36. Nakamura M, Hatakeyama T, Hara K, Nakamura E. Enantioselective synthesis of α -substituted ketones by asymmetric addition of chiral zinc enamides to 1-alkenes. *J Am Chem Soc.* 2003; 125:6362–6363. [PubMed: 12785764]
37. Reetz MT, Drewes MW, Schmitz A. Stereoselective synthesis of β -Amino alcohols from optically active α -amino acids. *Angew Chem Int Ed.* 1987; 26:1141–1143.
38. Wu Y, Liu J, Li X, Chan ASC. Vanadium-catalyzed asymmetric oxidation of sulfides using schiff base ligands derived from β -amino alcohols with two stereogenic centers. *Eur J Org Chem.* 2009:2607–2610.
39. Sun X, Chen Y, Wu N, Kang CS, Song HA, Jin S, Fu Y, Bryant H, Frank JA, Chong HS. *RSC Adv.* 2015; 5:94571–94581. [PubMed: 26989478]
40. Kazmierczak M, Koroniak H. *J Fluorine Chem.* 2012; 139:23–27.
41. Lee JY, Miller JJ, Hamilton SS, Sigman MS. Stereochemical diversity in chiral ligand design: discovery and optimization of catalysts for the enantioselective addition of allylic halides to aldehydes. *Org Lett.* 2005; 7:1837–1839. [PubMed: 15844919]
42. Nerdel F, John U. Untersuchungen in der reihe der hydratropasäure, v. mitteil.: optisch aktive m- und p- substituierte homohydratropasäuren. *Chem Ber.* 1956; 89:1945–1950.

One Sentence Summary

Pd-catalyzed enantioselective C–H arylation, alkenylation, and alkynylation of isobutyric acid/2-amino-isobutyric acid derivatives enables the construction of α -tertiary and α -quaternary centers from bulk chemicals.

A Enzymatic approach **B Organometallic approach** **C Challenges in chiral differentiation**

β -Methylene C-H
Activation

α -gem-Dimethyl C-H
Activation

Steric Interactions in the Intermediate

Fig. 1. Construction of α -chiral centers via C-H activation

(A) Enzymatic approach. (B) Organometallic approach. (C) Challenges in chiral differentiation. DG, directing group; Me, methyl group; *t*-Bu, *tert*-butyl group; CoA, Coenzyme A; R, alkyl or aryl group; pin, pinacolato group.

Fig. 2. Enantioselective C–H arylation of isobutyric acid and 2-aminoisobutyric acid
(A) Ligand optimization. (B) Arylation of isobutyric acid. (C) Arylation of 2-aminoisobutyric acid. For each entry number (in boldface), data are reported as isolated yield. See supplementary materials for experimental details. *10 mol% Pd(OAc)₂, 20 mol% **L30**, Ar-I, Ag₂CO₃, toluene, 50 °C, 72 h. ArF, 4-(CF₃)C₆F₄; *p*-Tol-I, *para*-tolyl iodide; equiv., equivalent; Et, ethyl group; Ph, phenyl group; Ac, acetyl group; Ar(Het), (hetero)aryl group; TBS, *tert*-butyldimethylsilyl group; Bn, benzyl group; Boc, *tert*-butoxycarbonyl group; Ts, tosyl group; Phth, phthalimido group; HFIP, hexafluoro-2-propanol.

Fig. 3. Enantioselective C–H alkenylation and alkynylation of isobutyric acid

For each entry number (in boldface), data are reported as isolated yield. See supplementary materials for experimental details. * 10 mol% Pd(MeCN)₂CH₂ was used instead of Pd(OAc)₂. NaOAc was used as the additive. TIPS, triisopropylsilyl group.

Fig. 4. Diverse functionalizations of the remaining methyl group

For each entry number (in boldface), data are reported as isolated yield. See supplementary materials for experimental details. Reagents and conditions: (a) 10 mol% Cu(OAc)₂, NHEtPh, Ag₂CO₃, toluene, 100 °C (b) H₂O₂, aq. buffer (pH = 7), THF, rt.