OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX–XXX

pubs.acs.org/OrgLett

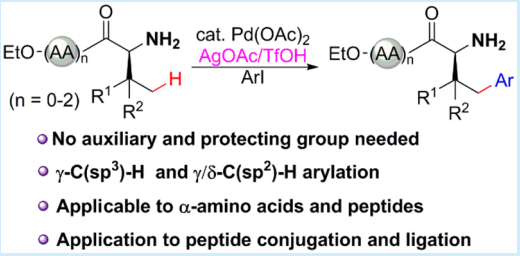
Site-Selective Modification of α-Amino Acids and Oligopeptides via Native Amine-Directed γ-C(sp^3)-H Arylation

Feipeng Yuan, Zhen-Lin Hou, Pranab K. Pramanick, and Bo Yao*

MOE Key Laboratory of Cluster Science, Beijing Key Laboratory of Photoelectronic-Electrophotonic Conversion Materials, School of Chemistry and Chemical Engineering, Beijing Institute of Technology, Beijing 102488, P. R. China

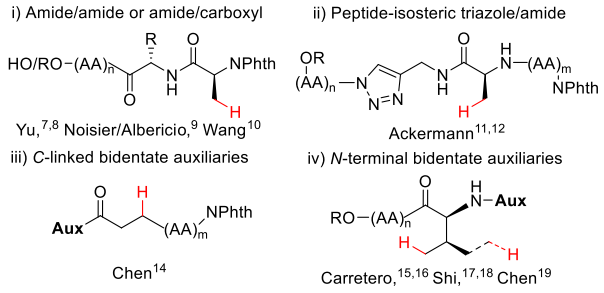
Supporting Information

ABSTRACT: Site-selective modification of chemically and biologically valuable α-amino acids and peptides is of great importance for biochemical study and pharmaceutical development. Few methods based on remote C(sp^3)-H functionalization of aliphatic side-chains of peptides has been disclosed in recent years. In this report, we developed a novel approach for γ-C(sp^3)-H and γ-/δ-C(sp^2)-H arylation of α-amino acids with α-hydrogen by native amine-directed C−H functionalization and further realized the γ-C(sp^3)-H arylation of *N*-terminally unprotected peptides.



Peptides have gained more and more interest as therapeutics in recent years.[1] The postsynthetic modification of bioactive peptides provides one of the most efficient and straightforward approaches for the synthesis of peptide drug candidates. Compared with traditional methods relying on the chemistry of amine, thiol, alcohol, carboxylic acid, and others, the direct functionalization of inert C−H bonds of peptides is much more challenging.[2] Selective C(sp^2)-H functionalization such as arylation,[3] vinylation,[4] allylation,[5] and alkynylation[6] at Trp and Phe residues of peptides has also been developed in the past decade. In contrast, methods based on the remote C(sp^3)-H functionalization of the aliphatic side chains of peptides are rare. Using the backbone functional groups (amide and carboxyl) as bidentate directing groups, Yu developed the β-C(sp^3)-H arylation[7] and alkynylation[8] of peptides at the N-terminus (Scheme 1i), and Noisier/Albericio[9] and Wang[10] later reported intramolecular β-C(sp^3)-H arylation/macrocyclization (Scheme 1i). With the peptide−isosteric triazole and amide as bidentate directing groups, Ackermann developed the β-C(sp^3)-H arylation of peptidomimetics at internal residues[11] and applied this protocol to the BODIPY labeling of peptidomimetics (Scheme 1ii).[12] In addition, 8-aminoquinoline-derived amides were also used to promote β-C(sp^3)-H arylation[13] and macrocyclization (Scheme 1iii).[14] However, all of these transformations required the protection of the N-terminus (NH_2). In particular, auxiliaries were even needed to form powerful directing groups at the N-terminus to promote the γ- or δ-C(sp^3)-H functionalization (Scheme 1iv).[15−19] Although a variety of efficient transformations such as δ-alkylation,[17] γ-silylation,[18] and γ-arylation/macrocyclization[19] have been developed, the additional steps for the preinstallation and the removal of these groups reduce the atom- and step-economy of these methods. Therefore, the use of the native amino group of peptides as the monodentate directing group for γ- or δ-C(sp^3)-H functionalization would be challenging but also appealing.

Scheme 1. Directing Groups for Remote C(sp^3)-H Functionalization of Peptides

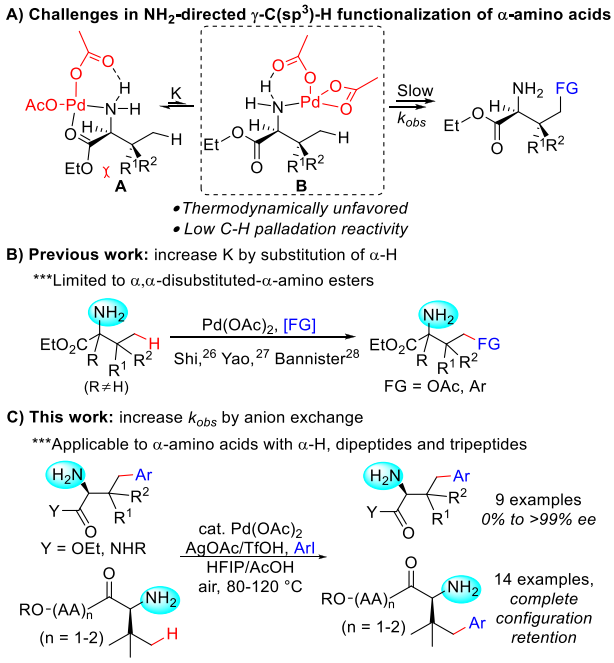


Compared with other N-containing functional groups, free amino groups have been far less utilized as directing groups in transition-catalyzed C−H functionalization.[20,21] Successful examples were mainly restricted to the C(sp^2)-H functionalization of anilines,[22] benzyl amines,[23] and arylethylamines,[24] as well as the C(sp^3)-H functionalization of sterically bulky secondary amines.[25] So far, there have been only three reports on the NH_2-directed γ- or δ-C(sp^3)-H functionalization of primary aliphatic amines and amino esters (Scheme 2B).[26−28] As for the scope of α-amino acids, only α,α-disubstituted α-amino esters were compatible with the conditions. The reaction of α-amino esters having α-hydrogen was met with such problems as low yield and serious racemization.[27] In the meantime, in recent years, transient directing strategies have been developed to solve the problems in the remote C(sp^3)-H functionalization of primary aliphatic amines.[29−31] Although the efficient γ-C(sp^3)-H arylation of α-amino esters with α-hydrogen was enabled by an aldehyde-type transient ligand, the reaction was susceptible to full racemization.[30] In another

Received: October 12, 2019

DOI: 10.1021/acs.orglett.9b03607
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. NH_2-Directed γ-C(sp^3)-H Functionalization of α-Amino Acids and Oligopeptides

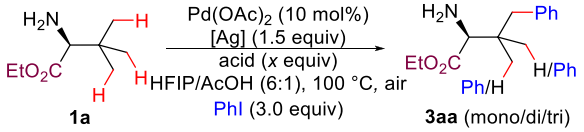


work on CO_2-mediated γ-C(sp^3)-H arylation, ethyl L-valinate underwent monoarylation to give the product with 3.3:1 *dr* and with the retention of the S-configuration of α-stereocenters.[31]

In this context and in continuation with our project on NH_2-directed C−H functionalization,[27] we envisioned that the anion exchange of the key complex **B** with a suitable anion might afford a more reactive complex and thereby improve the reactivity of α-amino esters having α-hydrogen (Scheme 2A). Herein we report a novel method of native amine-directed γ-C(sp^3)-H arylation for the site-selective modification of α-amino acids and oligopeptides (Scheme 2C). The key features and contributions of this work are as follows: (1) The use of TfOH and AgOAc as additives considerably improved the reactivity and led to the first NH_2-directed γ-C(sp^3)-H arylation of α-amino acids containing α-hydrogen. (2) The observation of the complete retention of the α-stereocenter's configuration in α-amino amide led to the development of the first C(sp^3)-H late-stage modification of N-unprotected oligopeptides. (3) The conjugation with the natural product, fluorophore, and the amino acid showcased the synthetic utility of the established method.

The study commenced with conditions optimized for the γ-C(sp^3)-H arylation of ethyl L-*tert*-leucinate **1a** with PhI **2a** by mainly screening anions (Table 1). First, the counteranions of silver additives were examined by performing the reaction with diverse silver salts or oxide in the presence of 10 mol % $Pd(OAc)_2$ in HFIP/AcOH (6/1) at 100 °C (entries 1−6 in Table 1). Among the tested silver additives, AgOTf gave the best result and yielded a mixture of γ-mono- and diarylation products (**3a**) in 55% yield and with a 2.58:1 ratio (entry 6 in Table 1). However, the further addition of 1.0 equiv of TsOH to the reaction with AgOTf led to a poor yield (entry 7 in Table 1). By contrast, the combination of 1.5 equiv of AgOAc with 1.0 equiv of TsOH resulted in a slightly higher yield (59%) and a larger turnover number (TON = 8) (entry 8 in Table 1). Notably, a similar yield and TON were retained when conducting the reaction without AcOH as the cosolvent (entry 9 in Table 1). These results suggested that the higher reactivity was attributed to the effect of anions rather than the acidity. Then, several protic acids with different pK_a values and steric bulks were tested (entries 10−13 in Table 1). Both

Table 1. Conditions Optimization for the γ-Arylation of Ethyl L-*tert*-Leucine Ester with PhI[a]



entry	[Ag]	acid (equiv)	ratio of **3aa**-mono/di/tri[b]	yield (%) (TON)[b]
1	AgOAc		1.22/1/−	39
2	AgTFA		1.35/1/−	44
3[c]	Ag_2CO_3		1.45/1/−	41
4[c]	Ag_2O		1.83/1/−	50
5	$AgNO_3$		n.d.	trace
6	AgOTf		2.58/1/−	55 (7)
7	AgOTf	TsOH (1.0)	1/−/−	15
8	AgOAc	TsOH (1.0)	1.26/1/−	59 (8)
9[d]	AgOAc	TsOH (1.0)	1.92/1/−	58 (8)
10	AgOAc	CF_3CO_2H (1.0)	1/1.3/0.44	49 (9)
11	AgOAc	*o*-NO_2-$C_6H_4CO_2H$ (1.0)	1/0.68/−	64 (9)
12	AgOAc	PivOH (1.0)	1/0.61/0.14	63 (9)
13	AgOAc	TfOH (1.0)	1/0.76/0.13	62 (10)
14[e]	AgOAc	TfOH (1.0)	1/0.81/0.13	77 (12)
15[e]	AgOAc	TfOH (1.2)	1/0.65/0.11	69 (12)
16[e]	AgOAc	**TfOH** (0.8)	1/1.14/0.39	80 (14)[f]
17[g]	AgOAc	TfOH (0.8)	1/0.14/−	23

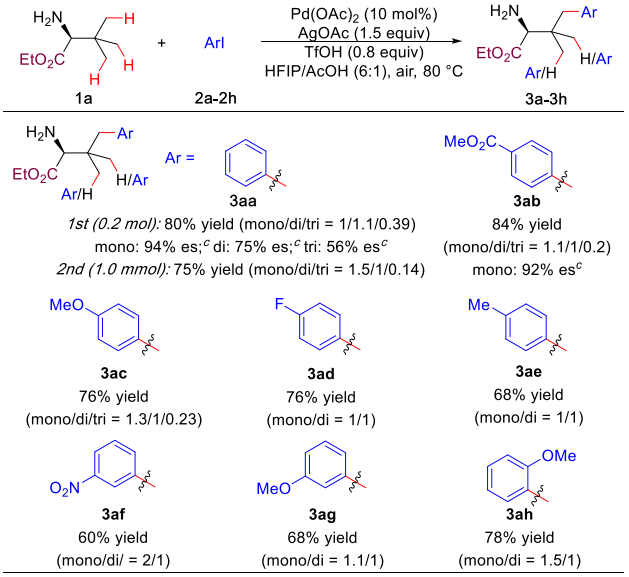
[a]Conditions: **1a** (0.3 mmol), PhI **2a** (0.9 mmol), $Pd(OAc)_2$ (10 mol %), [Ag] (1.5 equiv), acid, HFIP/AcOH (6/1, 3 mL), air, 100 °C, 24 h. [b]Total yield and ratios of mono/di/triarylation products were obtained based on the ^{1}H NMR spectra of crude samples. Turnover numbers (TON) are provided in parentheses. [c]0.75 equiv of Ag_2O or Ag_2CO_3. [d]HFIP (3 mL). [e]80 °C. [f]Isolated yield. [g]60 °C.

DOI: 10.1021/acs.orglett.9b03607
Org. Lett. XXXX, XXX, XXX−XXX

strong acid and sterically bulky acids exhibited a positive effect, and TfOH led to the largest TON (entry 13 in Table 1). To further improve the reactivity and reduce the degradation, we optimized the amount of TfOH and the temperature (entries 14−17) and finally determined the optimal conditions to be ethyl L-*tert*-leucinate **1a** (0.3 mmol), PhI (3.0 equiv), 10 mol % $Pd(OAc)_2$, 1.5 equiv AgOAc, 0.8 equiv TfOH in HFIP/AcOH (6/1 v/v, 3 mL) at 80 °C, air, 24 h (entry 16 in Table 1). The reaction under the optimal conditions afforded a mixture of mono-, di-, and triarylation products in 80% total yield (TON = 14) by flash chromatographic purification without the protection of the amino group. It is worth noting that the yield based on AgOAc was ∼94%.

With the optimal conditions in hand, we first investigated the scope of aryl iodides for the γ-C(sp^3)-H arylation of ethyl L-*tert*-leucinate **1a** (Scheme 3). Both electron-rich and

Scheme 3. Scope of Aryl Iodides in the γ-Arylation of Ethyl L-*tert*-Leucine Ester[a,b]

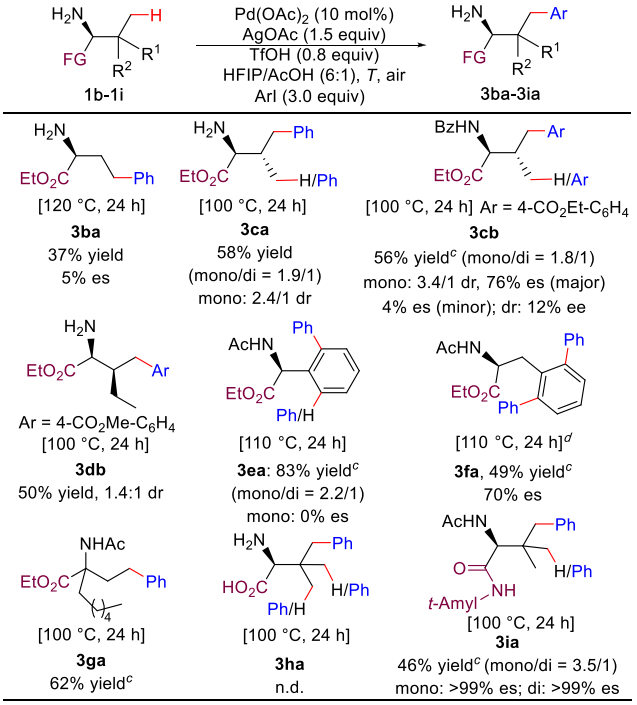


[a]Standard conditions: **1a** (0.3 mmol), ArI (0.9 mmol), $Pd(OAc)_2$ (10 mol %), AgOAc (1.5 equiv), TfOH (0.8 equiv), HFIP/AcOH (6/1, 3 mL), air, 80 °C, 24 h. [b]Yield and ratio of mono-, di-, and triarylation products were based on chromatographic purification. [c]Enantiomeric excess (*ee*) was determined by HPLC analysis of the corresponding acetamides. (See the details in the SI.)

electron-poor aryl groups were successfully installed in the γ-positions, yielding the γ-arylation products in moderate to good yield (**3aa**−**ae**, 60−84% total yield). Meta- and ortho-substituted aryl iodides gave a similar result as para-substituted aryl iodides, indicating that the reaction was not sensitive to steric hindrance. Gratifyingly, the HPLC analysis of the acetamides of the monoarylation products showed that the racemization was largely inhibited (**3aa**-mono: 94% *es*; **3ab**-mono: 92% *es*). However, the *ee* erosion took place as more aryl groups were installed (**3aa**-di: 75% *es*, **3aa**-tri: 56% *es*), suggesting that the racemization process was related to palladium (Scheme 2A).

Then, we continued to investigate the scope of α-amino acids (Scheme 4). The ethyl esters of six α-amino acids were submitted to the optimal conditions. At various temperatures (100−120 °C), these reactions afforded the desired γ-C(sp^3)-H or γ/δ-C(sp^2)-H arylation products in moderate yield

Scheme 4. Scope of α-Amino Acids[a,b]



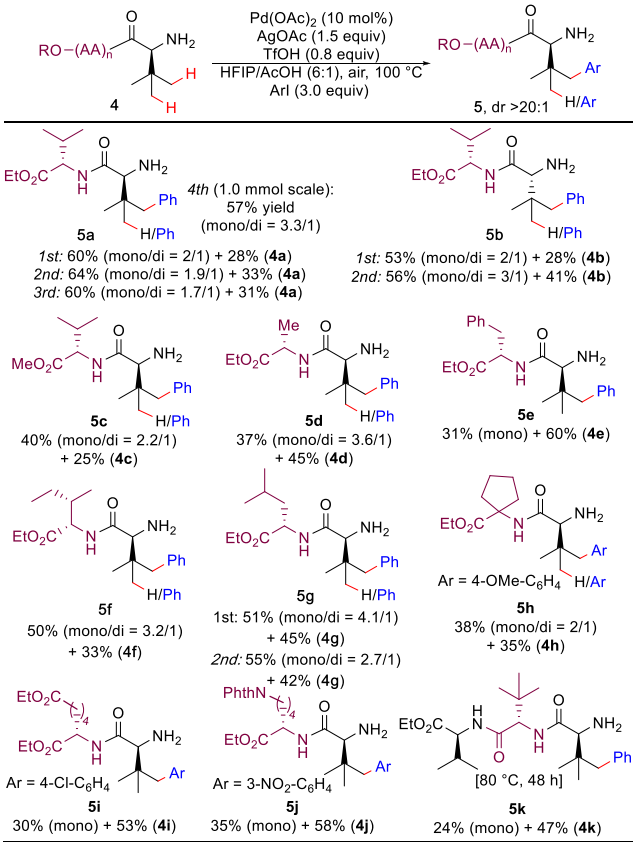
[a]Standard conditions: **1** (0.3 mmol), ArI (0.9 mmol), $Pd(OAc)_2$ (10 mol %), AgOAc (1.5 equiv), TfOH (0.8 equiv), HFIP/AcOH (6/1, 3 mL), air, 100−120 °C, 24 h. [b]*ee* was determined by the HPLC analysis of the acetamides. (See the details in the SI.) [c]Acyl-protection by AcCl or BzCl. [d]AgTFA (1.5 equiv).

(**3ba**−**ga**, 37−83%). The extent of racemization/epimerization varied according to the steric and electronic properties of side-chains: Ethyl (*S*)-2-aminobutanoate **1b** (smallest side-chain) and L-phenylglycinate **1e** (aromatic side-chain) underwent serious racemization to give the products as almost racemic mixtures (**3ba**, 5% *es*; **3ea**, 0% *es*), whereas the reaction of ethyl L-phenylalaninate **1f** (benzylic side-chain) gave the diarylation product in 70% *es*, even under 110 °C. Both the ethyl L-valinate **1c** and L-isoleucinate **1d** yielded the products with moderate *dr* (**3ca**-mono, 2.4 *dr*; **3cb**-mono: 3.4:1 *dr*; **3db**, 1.4:1 *dr*). The *ee* and optical rotation data of **3cb**-mono (two diastereomers) and **3cb**-di showed that the epimerization at the α-stereocenter took place but was slower than the first C−H arylation. Furthermore, free α-amino acid and α-amino amide were also examined. L-*tert*-Leucine **1h** exhibited no reactivity, probably due to the formation of the inactive η^2-Pd(II)−amino acid complex. By contrast, α-amino amide **1i** displayed moderate reactivity, yielding the mono- and diarylation products **3ia** in 46% yield and with 3.5:1 ratio as well as >99% *es*. The inhibition of the racemization in the reaction of **1i** might be attributed to the faster tautomerization of the amide group than the enolization related to α-hydrogen (Scheme 2A).[32]

Inspired by the result above, we wondered if the NH_2-directed γ-C(sp^3)-H arylation method could be applied to the postsynthetic modification of N-terminus unprotected peptides (Scheme 5). Surprisingly, a series of dipeptides (**4a**−**j**) underwent γ-C(sp^3)-H arylation at the N-terminal Tle residues, delivering arylation products in moderate yield with the complete retention of the configuration of all α-stereocenters (**5a**−**j**). A wide range of α-amino acid residues

DOI: 10.1021/acs.orglett.9b03607
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 5. Scope for the γ-C(sp³)-H Arylation of Oligopeptides[a,b]

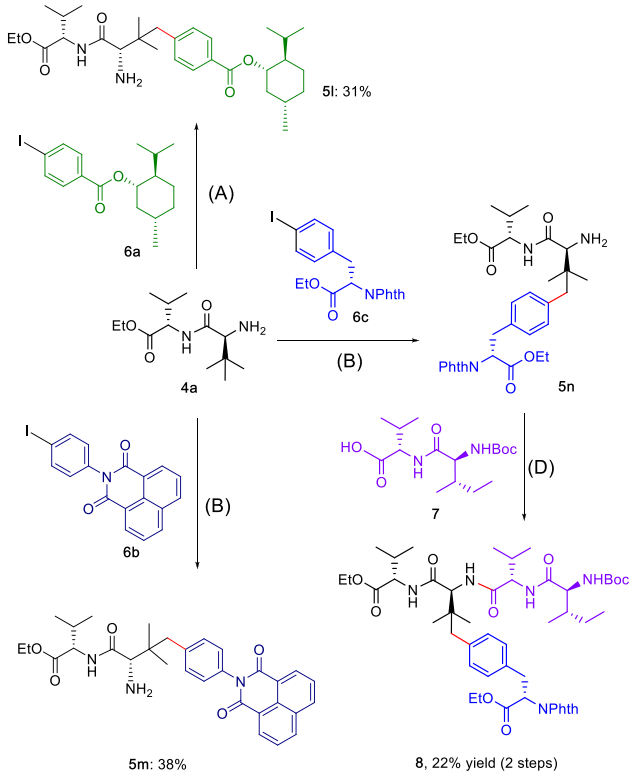


[a]Standard conditions: peptide **4** (0.2 mmol), ArI (0.6 mmol), $Pd(OAc)_2$ (10 mol %), AgOAc (1.5 equiv), TfOH (0.8 equiv), HFIP/AcOH (6/1, v/v, 2 mL), air, 100 °C, 24 h; then, $SOCl_2$ (10 equiv), EtOH (2 mL), reflux, 5 h. [b]Yield and ratio were based on the result of chromatographic purification. (See the details in the SI.)

such as Val (**5a–c**), Ala (**5d**), Phe (**5e**), Ile (**5f**), Leu (**5g**), Tle (**5k**), and other unnatural amino acids (**5h–j**) at the C-terminus were compatible. Functional groups such as carboxamide, carboximide, ester, chloro, ether, nitro, and amino groups were well tolerated, providing opportunities for further transformations of the products and late-stage conjugation with functional molecules. In addition, tripeptide **4k** was also successfully arylated at the N-terminus at 80 °C, delivering the γ-monoarylation product **5k** in 24% yield. Notably, all of these products and unreacted substrates were practically isolated by chromatographic purification without the protection of the amino group. In addition, the excellent repeatability and scale-up reaction also exhibited the practicality of the method.

Finally, the synthetic application of the method for peptide modification was investigated (Scheme 6). With ester and carboximide functional groups as linkers, natural D-(+)-menthol and fluorescent 1,8-naphthalimide were installed to dipeptide **4a** via the C–H arylation method to give the conjugates **5l** and **5m** in 31 and 38% yield, respectively (Scheme 2A,B). In addition, combining the C–H arylation method with the amide formation reaction, a two-fold peptide ligation strategy was established (Scheme 2C,D). The sequential reaction of **4a** with amino acid **6c** and dipeptide **7** afforded the trigeminal peptide **8** in 22% yield (two steps).

Scheme 6. Synthetic Application[a]



[a]Conditions for (A–C): **4a** (0.2 mmol), **6** (0.6 mmol), $Pd(OAc)_2$ (10 mol %), AgOAc (1.5 equiv), TfOH (0.8 equiv), HFIP/AcOH (6/1, 2 mL), 100 °C, air, 24 h. For (D): **5n**, **7** (1.0 equiv), DCC (1.1 equiv), HOBt (1.1 equiv), iPr_2EtN (1.0 equiv), CH_2Cl_2 (5 mL), rt, 12 h.

In conclusion, we have developed a new protocol of native amine-directed C–H functionalization and realized the first NH_2-directed γ-C(sp³)-H arylation of diverse chiral α-amino acids having α-hydrogen. The extent of the racemization of the α-stereocenters was found to be dependent on the properties of side-chains and functional groups at the C-terminus. On the basis of this observation, we further established the first γ-C(sp³)-H arylation of N-terminus unprotected oligopeptides. The synthetic application of this protocol was demonstrated by the conjugation with natural D-(+)-menthol and fluorescent 1,8-naphthalimide as well as the two-fold peptide ligation to prepare a trigeminal peptide. In view of the ubiquitous feature of the L-*tert*-leucine moiety in many peptide-based drugs and chiral ligands, the present method will find applications in the future. Our present project is to develop new protocols of native functional-group-directed C–H functionalization for the selective late-stage modification of complex peptides at diverse residues.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03607.

Detailed experimental procedures, complete optimization table, characterization data of prepared starting materials and products, and copies of ^1H and ^{13}C NMR spectra of these compounds (PDF)

DOI: 10.1021/acs.orglett.9b03607
Org. Lett. XXXX, XXX, XXX–XXX

AUTHOR INFORMATION

Corresponding Author

*E-mail: yaobo@bit.edu.cn

ORCID

Bo Yao: 0000-0002-8709-7989

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We gratefully acknowledge the National Natural Science Foundation of China (21502006), Beijing National Laboratory for Molecular Sciences, and Beijing Institute of Technology (BIT) for financial support. We also thank the Analysis and Testing Centre of BIT for the NMR and HRMS analysis and Yu-Fei Ao at the Institute of Chemistry, Chinese Academy of Sciences (ICCAS) for the HPLC analysis.

REFERENCES

(1) (a) Craik, D. J.; Fairlie, D. P.; Liras, S.; Price, D. *Chem. Biol. Drug Des.* **2013**, *81*, 136−147. (b) Fosgerau, K.; Hoffmann, T. Drug Discov. *Drug Discovery Today* **2015**, *20*, 122−128. (c) Lau, J. L.; Dunn, M. K. *Bioorg. Med. Chem.* **2018**, *26*, 2700−2707.

(2) (a) deGruyter, J. N.; Malins, L. R.; Baran, P. S. *Biochemistry* **2017**, *56*, 3863−3873. (b) Brandhofer, T.; García Mancheño, O. *Eur. J. Org. Chem.* **2018**, *2018*, 6050−6067. (c) Noisier, A. F. M.; Brimble, M. A. *Chem. Rev.* **2014**, *114*, 8775−8806. (d) Sengupta, S.; Mehta, G. *Tetrahedron Lett.* **2017**, *58*, 1357−1372.

(3) (a) Ruiz-Rodriguez, J.; Albericio, F.; Lavilla, R. *Chem. - Eur. J.* **2010**, *16*, 1124−1127. (b) Mendive-Tapia, L.; Preciado, S.; Garcia, J.; Ramon, R.; Kielland, N.; Albericio, F.; Lavilla, R. *Nat. Commun.* **2015**, *6*, 7160. (c) Zhu, Y.; Bauer, M.; Ackermann, L. *Chem. - Eur. J.* **2015**, *21*, 9980−9983. (d) Schischko, A.; Ren, H.; Kaplaneris, N.; Ackermann, L. *Angew. Chem., Int. Ed.* **2017**, *56*, 1576−1580. (e) Reay, A. J.; Hammarback, L. A.; Bray, J. T. W.; Sheridan, T.; Turnbull, D.; Whitwood, A. C.; Fairlamb, I. J. S. *ACS Catal.* **2017**, *7*, 5174−5179.

(4) (a) Bai, Z.; Cai, C.; Yu, Z.; Wang, H. *Angew. Chem., Int. Ed.* **2018**, *57*, 13912−13916. (b) Zheng, Y.; Song, W. *Org. Lett.* **2019**, *21*, 3257−3260.

(5) Lorion, M. M.; Kaplaneris, N.; Son, J.; Kuniyil, R.; Ackermann, L. *Angew. Chem., Int. Ed.* **2019**, *58*, 1684−1688.

(6) (a) Ruan, Z.; Sauermann, N.; Manoni, E.; Ackermann, L. *Angew. Chem., Int. Ed.* **2017**, *56*, 3172−3176. (b) Hansen, M. B.; Hubálek, F.; Skrydstrup, T.; Hoeg-Jensen, T. *Chem. - Eur. J.* **2016**, *22*, 1572−1576. (c) Tolnai, G. L.; Brand, J. P.; Waser, J. *Beilstein J. Org. Chem.* **2016**, *12*, 745−749.

(7) Gong, W.; Zhang, G.; Liu, T.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 16940−16946.

(8) Liu, T.; Qiao, J. X.; Poss, M. A.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2017**, *56*, 10924−10927.

(9) Noisier, A. F. M.; Garcia, J.; Ionut, I. A.; Albericio, F. *Angew. Chem., Int. Ed.* **2017**, *56*, 314−318.

(10) Tang, J.; He, Y.; Chen, H.; Sheng, W.; Wang, H. *Chem. Sci.* **2017**, *8*, 4565−4570.

(11) Bauer, M.; Wang, W.; Lorion, M. M.; Dong, C.; Ackermann, L. *Angew. Chem., Int. Ed.* **2018**, *57*, 203−207.

(12) Wang, W.; Lorion, M. M.; Martinazzoli, O.; Ackermann, L. *Angew. Chem., Int. Ed.* **2018**, *57*, 10554−10558.

(13) Mondal, B.; Roy, B.; Kazmaier, U. *J. Org. Chem.* **2016**, *81*, 11646−11655.

(14) Zhang, X.; Lu, G.; Sun, M.; Mahankali, M.; Ma, Y.; Zhang, M.; Hua, W.; Hu, Y.; Wang, Q.; Chen, J.; He, G.; Qi, X.; Shen, W.; Liu, P.; Chen, G. *Nat. Chem.* **2018**, *10*, 540−548.

(15) Rodriguez, N.; Romero-Revilla, J. A.; Fernandez-Ibanez, M. A.; Carretero, J. C. *Chem. Sci.* **2013**, *4*, 175−179.

(16) Hernando, E.; Villalva, J.; Martínez, Á. M.; Alonso, I.; Rodríguez, N.; Gómez Arrayás, R.; Carretero, J. C. *ACS Catal.* **2016**, *6*, 6868−6882.

(17) Zhan, B. B.; Li, Y.; Xu, J. W.; Nie, X. L.; Fan, J.; Jin, L.; Shi, B. F. *Angew. Chem., Int. Ed.* **2018**, *57*, 5858−5862.

(18) Zhan, B.-B.; Fan, J.; Jin, L.; Shi, B.-F. *ACS Catal.* **2019**, *9*, 3298−3303.

(19) Li, B.; Li, X.; Han, B.; Chen, Z.; Zhang, X.; He, G.; Chen, G. *J. Am. Chem. Soc.* **2019**, *141*, 9401−9407.

(20) (a) He, C.; Whitehurst, W. G.; Gaunt, M. J. *Chem.* **2019**, *5*, 1031−1058. (b) Zhang, M.; Zhang, Y.; Jie, X.; Zhao, H.; Li, G.; Su, W. *Org. Chem. Front.* **2014**, *1*, 843−895.

(21) Selected references on nondirected C(sp^3)-H functionalization of free amines: (a) Lee, M.; Sanford, M. S. *J. Am. Chem. Soc.* **2015**, *137*, 12796−12799. (b) Mbofana, C. T.; Chong, E.; Lawniczak, J.; Sanford, M. S. *Org. Lett.* **2016**, *18*, 4258−4261. (c) Lee, M.; Sanford, M. S. *Org. Lett.* **2017**, *19*, 572−575.

(22) (a) Liang, Z.; Ju, L.; Xie, Y.; Huang, L.; Zhang, Y. *Chem. - Eur. J.* **2012**, *18*, 15816−15821. (b) Suzuki, C.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2013**, *15*, 3990−3993. (c) Boelke, A.; Caspers, L. D.; Nachtsheim, B. J. *Org. Lett.* **2017**, *19*, 5344−5347.

(23) (a) Lazareva, A.; Daugulis, O. *Org. Lett.* **2006**, *8*, 5211−5213. (b) Miura, M.; Feng, C.-G.; Ma, S.; Yu, J.-Q. *Org. Lett.* **2013**, *15*, 5258−5261. (c) Zhang, C. H.; Ding, Y. Z.; Gao, Y. Z.; Li, S. D.; Li, G. *Org. Lett.* **2018**, *20*, 2595−2598.

(24) (a) Orito, K.; Horibata, A.; Nakamura, T.; Ushito, H.; Nagasaki, H.; Yuguchi, M.; Yamashita, S.; Tokuda, M. *J. Am. Chem. Soc.* **2004**, *126*, 14342−14343. (b) Haffemayer, B.; Gulias, M.; Gaunt, M. J. *Chem. Sci.* **2011**, *2*, 312−315.

(25) (a) McNally, A.; Haffemayer, B.; Collins, B. S. L.; Gaunt, M. J. *Nature* **2014**, *510*, 129−133. (b) Calleja, J.; Pla, D.; Gorman, T. W.; Domingo, V.; Haffemayer, B.; Gaunt, M. J. *Nat. Chem.* **2015**, *7*, 1009−1016. (c) He, C.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2015**, *54*, 15840−15844. (d) Willcox, D.; Chappell, B. G. N.; Hogg, K. F.; Calleja, J.; Smalley, A. P.; Gaunt, M. J. *Science* **2016**, *354*, 851−857. (e) Cabrera-Pardo, J. R.; Trowbridge, A.; Nappi, M.; Ozaki, K.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2017**, *56*, 11958−11962.

(26) Chen, K.; Wang, D.; Li, Z. W.; Liu, Z.; Pan, F.; Zhang, Y. F.; Shi, Z. J. *Org. Chem. Front.* **2017**, *4*, 2097−2101.

(27) Pramanick, P. K.; Zhou, Z.; Hou, Z.-L.; Yao, B. *J. Org. Chem.* **2019**, *84*, 5684−5694.

(28) Lin, H.; Pan, X.; Barsamian, A. L.; Kamenecka, T. M.; Bannister, T. D. *ACS Catal.* **2019**, *9*, 4887−4891.

(29) (a) Xu, Y.; Young, M. C.; Wang, C.; Magness, D. M.; Dong, G. *Angew. Chem., Int. Ed.* **2016**, *55*, 9084−9087. (b) Wu, Y.; Chen, Y.-Q.; Liu, T.; Eastgate, M. D.; Yu, J.-Q. *J. Am. Chem. Soc.* **2016**, *138*, 14554−14557. (c) Chen, Y.-Q.; Wang, Z.; Wu, Y.; Wisniewski, S. R.; Qiao, J. X.; Ewing, W. R.; Eastgate, M. D.; Yu, J.-Q. *J. Am. Chem. Soc.* **2018**, *140*, 17884−17894. (d) Liu, Y.; Ge, H. *Nat. Chem.* **2017**, *9*, 26−32. (e) Yada, A.; Liao, W.; Sato, Y.; Murakami, M. *Angew. Chem., Int. Ed.* **2017**, *56*, 1073−1076. (f) St John-Campbell, S.; Ou, A. K.; Bull, J. A. *Chem. - Eur. J.* **2018**, *24*, 17838−17843.

(30) Lin, H.; Wang, C.; Bannister, T. D.; Kamenecka, T. M. *Chem. - Eur. J.* **2018**, *24*, 9535−9541.

(31) Kapoor, M.; Liu, D.; Young, M. C. *J. Am. Chem. Soc.* **2018**, *140*, 6818−6822.

(32) Kapoor, M.; Chand-Thakuri, P.; Young, M. C. *J. Am. Chem. Soc.* **2019**, *141*, 7980−7989.

DOI: 10.1021/acs.orglett.9b03607
Org. Lett. XXXX, XXX, XXX−XXX