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Synthesis of amino acids and peptides with bulky side chains *via* ligand-enabled carboxylate-directed γ -C(sp³)-H arylation†

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Amino acids and peptides with bulky side chains are of significant importance in organic synthesis and modern medicinal chemistry. The efficient synthesis of these molecules with full enantiocontrol and high diversity remains challenging. Herein we report a Pd-catalyzed ligand-enabled γ -C(sp³)-H arylation of *tert*-leucine and its derived peptides without using an external directing group (DG) *via* a less favored six-membered palladacycle. Structurally diverse bulky side chain amino acids and peptides were accessed in a step-economic fashion and the reaction could be conducted on a gram scale with retention of chirality. The resulting amino acids can be used as chiral ligands in Co(III)-catalyzed enantioselective C(sp³)-H amidation. It is worth noting that the weakly coordinating carboxylate DG outcompetes the strongly coordinating bidentate DG of the peptide backbone, providing the products of γ -C(sp³)-H arylation of Tle residue exclusively. This protocol represents the first example of late stage C(sp³)-H functionalization of peptides using a weakly coordinating directing group.

Introduction

Amino acids with bulky side chains are important structural motifs in a broad range of natural products and pharmaceuticals.¹ For example, Saxagliptin is a highly potent dipeptidyl peptidase IV Inhibitor for the treatment of type 2 diabetes.^{1a} Asunaprevir is a new generation highly potent hepatitis C virus protease inhibitor in phase III clinical trials (Fig. 1a).^{1b} More recently, amino acids with bulky side chains have been recognized as efficient chiral ligands for enantioselective C-H functionalization *via* either an outer-sphere (Fig. 1b)²⁻⁵ or an inner-sphere pathway (Fig. 1c).^{6,7} A series of phthalimide protected amino acid derivatives were first realized as efficient ligands for dirhodium(II) complexes for enantioselective C-H insertion of carbenoid by Hashimoto and co-workers (Fig. 1b).³ Although the optimal catalyst might vary depending on the reactions, the sterically bulky *tert*-leucine (Tle) derived catalyst Rh₂(S-PTTL)₄ generally gives the best enantiocontrol.³ It has also been realized that apart from the steric bulk of amino acid side chains, the type of phthalimide protecting group also plays crucial roles in asymmetric induction.²⁻⁴ Müller and Dauban reported that a 1,8-naphthoyl-protected Tle derived catalyst Rh₂(S-NTTL)₄ (ref. 4a) was the optimum catalyst that allows highly diastereoselective intermolecular C-H amination.^{4b} The Davies group synthesized sterically bulky adamantly-derived Rh₂(S-PTAD)₄ and Rh₂(S-TCPTAD)₄ for

asymmetric carbenoid C-H insertion.⁵ More recently, phthalimide protected bulky side chain amino acids have also been realized as popular chiral ligands in group 9 Cp^{*}M(III)-catalyzed C-H activation.⁶⁻⁸ Cramer and co-workers reported that a strong cooperative effect between the chiral Cp^x Ir(III)/Rh(II) and Phth-Tle enabled the enantioselective C-H functionalization of phosphine oxides.⁶ Bulky side chain amino acids also show remarkable activity in Cp^{*}Co(II)-catalyzed C-H activation. Matsunaga reported the enantioselective C(sp³)-H amidation of thiomides catalyzed by achiral Cp^{*}Co(II) and di-N-protected (S)-H₂-BHTL.⁷ It was found that both of the steric bulk of the side chains and the structure of the protecting groups can significantly influence the asymmetric induction and reactivity. However, the limited availability of sterically bulky amino acids has hampered further development of asymmetric C-H activation reactions. Thus, the development of a novel strategy to diversely access chiral amino acids with bulky side chains would be highly desirable.

Undoubtedly, the direct functionalization of commercially available, sterically bulky *tert*-leucine would offer expeditious access of amino acids with increased steric bulk,⁹ which might find broad applications in asymmetric reactions. Although the direct functionalization of aliphatic carboxylic acid derivatives using covalently attached external directing groups (DGs) has been well investigated,¹⁰ the direct transformation of aliphatic C-H bonds of carboxylic acids without using an exogenous DG remains challenging, largely due to low reactivity resulted from the weak directing ability of carboxyl groups.¹¹ Recently, Pd-catalyzed β -C(sp³)-H functionalization of free carboxylic acids through a kinetically favored five-membered palladacycle has been reported by Yu¹² and others.¹³ Remote C(sp³)-H

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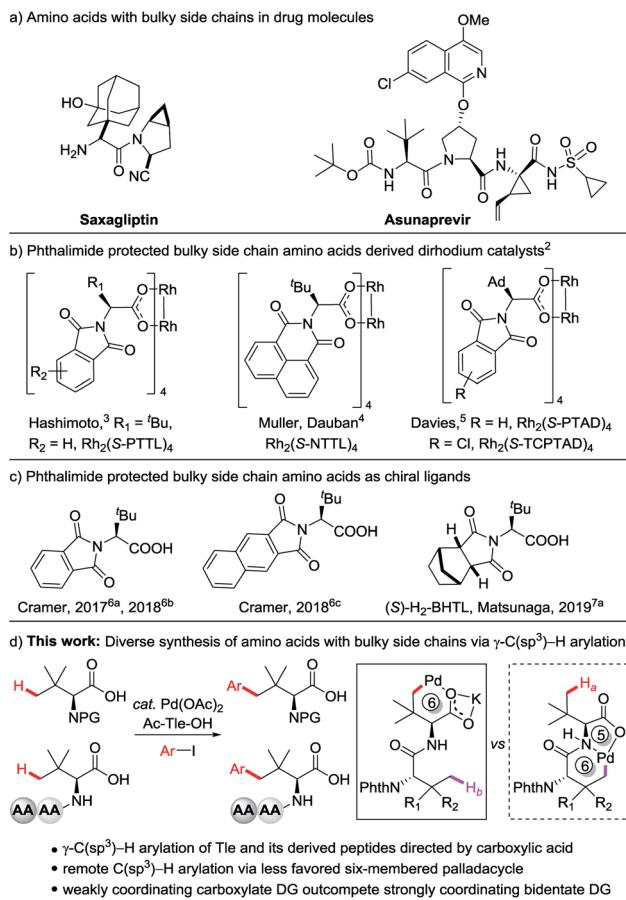


Fig. 1 The importance of amino acids with bulky side chains and our synthetic strategy: (a) amino acids with bulky side chains in drug molecules; (b) phthalimide protected bulky side chain amino acids derived dirhodium catalysts; (c) phthalimide protected bulky side chain amino acids as chiral ligands; (d) this work: diverse synthesis of amino acids with bulky side chains via γ -C(sp³)-H arylation.

functionalization using a weakly coordinating carboxylate DG *via* a six-membered palladacycle remains undeveloped.¹⁴ Herein we report a palladium-catalyzed carboxylate-directed γ -C(sp³)-H arylation to synthesize a wide range of large steric hindrance amino acids through a thermodynamically less stable six-membered palladacycle. γ -C(sp³)-H arylation of Tle-derived peptides is also feasible. It is worth noting that the weakly coordinating carboxylate DG outcompetes the strongly coordinating bidentate DG of the peptide backbone,¹⁵ providing the products of γ -C(sp³)-H arylation of Tle residue exclusively (Fig. 1d).

Results and discussion

We initiated our studies by exploring the reaction of Phth-Tle-OH 1 and 1-iodo-4-methoxybenzene 2a. After screening a series of mono-N-protected amino acid ligands, we were delighted to find that the use of Ac-Tle-OH as a ligand gave the arylation product 3a in 15% yield (Table S1,[†] entry 6).¹⁶ We hypothesize that the sterically bulky side chain of Ac-Tle-OH plays an important role in promoting the reaction. The subsequent investigation of additives led to an exciting finding that Ag₃PO₄ could promote the reaction, giving the

arylation product 3a in 40% yield (Table S3,[†] entry 6). Silver phosphate might play a dual role, functioning as both a halide scavenger and a heteronuclear active species to facilitate C-H cleavage.¹⁷ Further investigation of reaction temperature revealed that the reaction could be conducted at 70 °C (Table S4,[†] entry 4, 46%). Monoarylation product 3a could be obtained in 56% yield with 15% diarylation product 3a' when using 3 equivalents of 2a (Table S5,[†] entry 3). When D-Ac-Tle-OH was used as the ligand, identical results were obtained (Table S5,[†] entry 6, 3a, 57%; 3a', 14%). We finalized the conditions for the γ -selective arylation of 1 with 2a as follows (reaction conditions A): 10 mol% Pd(OAc)₂, 30 mol% Ac-Tle-OH, 1.0 equiv. K₂CO₃, and 1.0 equiv. Ag₃PO₄, with HFIP as the solvent at 70 °C for 24 h under air.

With the optimized reaction conditions in hand, we first turned to the evaluation of the scope of aryl iodides (Fig. 2). Both electron-withdrawing and electron-donating groups afforded the desired products in good yields under the optimized conditions. Electron-withdrawing groups, such as acetyl (2b and 2f), methoxycarbonyl (2c and 2i), and formyl (2d and 2g), at either the *para* or the *meta* position of the aryl iodides, are well tolerated. Multiple substituted aryl iodides (2j–2m) were also compatible with the reaction conditions, giving the desired products in moderate yields. Notably, β -C-H arylation of Phth-Ala-OH also proceeded smoothly under the optimized reaction conditions, giving the β -arylation product in 51% yield (see the ESI[†]).

Recently, transition metal-catalyzed C-H activation has emerged as one of the most powerful strategies for the late-stage modification of structurally complex peptides.^{18,19} However, C(sp³)-H functionalization of peptides has been largely relied on

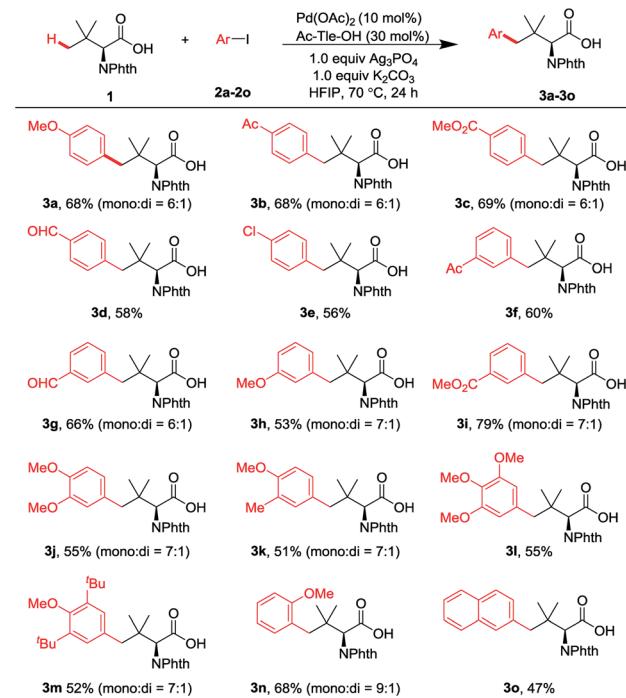


Fig. 2 Scope of aryl iodides for Pd-catalyzed γ -C(sp³)-H arylation. Reaction conditions A: 1 (0.3 mmol), 2 (0.9 mmol), Pd(OAc)₂ (0.03 mmol), Ac-Tle-OH (0.09 mmol), Ag₃PO₄ (0.3 mmol), K₂CO₃ (0.3 mmol), HFIP (3 mL), 70 °C, air, 24 h, and isolated yield.

the use of strong bidentate DGs¹⁹ or the biscoordination of the peptide backbone.¹⁵ We were pleased to find that this protocol is feasible with peptides under slightly modified conditions (reaction conditions B: Ag_2SO_4 was used instead of Ag_3PO_4 , Table S2†). Dipeptides containing glycine (**4a**), cyclohexaneglycine (**4b**), and leucine (**4c**) reacted smoothly with **2c** to give the arylation products in moderate yields. Yu and coworkers have reported C–H activation of N-terminal amino acids in peptides directed by the N,O - or N,N -biscoordination of the peptide backbone.¹⁵ Remarkably, the weakly coordinating carboxylate DG outcompetes the strongly

coordinating bidentate DG of the peptide backbone and reacted selectively with the $\gamma\text{-C}(\text{sp}^3)\text{-H}$ bond of Tle residue (Fig. 3b, **5d–5h**). Notably, tripeptides were also tolerated, albeit in low yield (**5g**, 34%; **5h**, 23%), which might be due to the competitive coordination of the N,N -biscoordination. The unconventional selectivity might originate from the favorable formation of a six-membered palladacycle over its 5,6-fused bicyclic counterpart (Fig. 3b, **Int-A1** vs. **Int-B1**; **Int-A2** vs. **Int-B2**). When *N*-Phth-Ala-Tle-OH (**4i**), a dipeptide bearing an alanine residue at the N-terminus, was used as the substrate, arylation occurred selectively at β -methyl of the N-

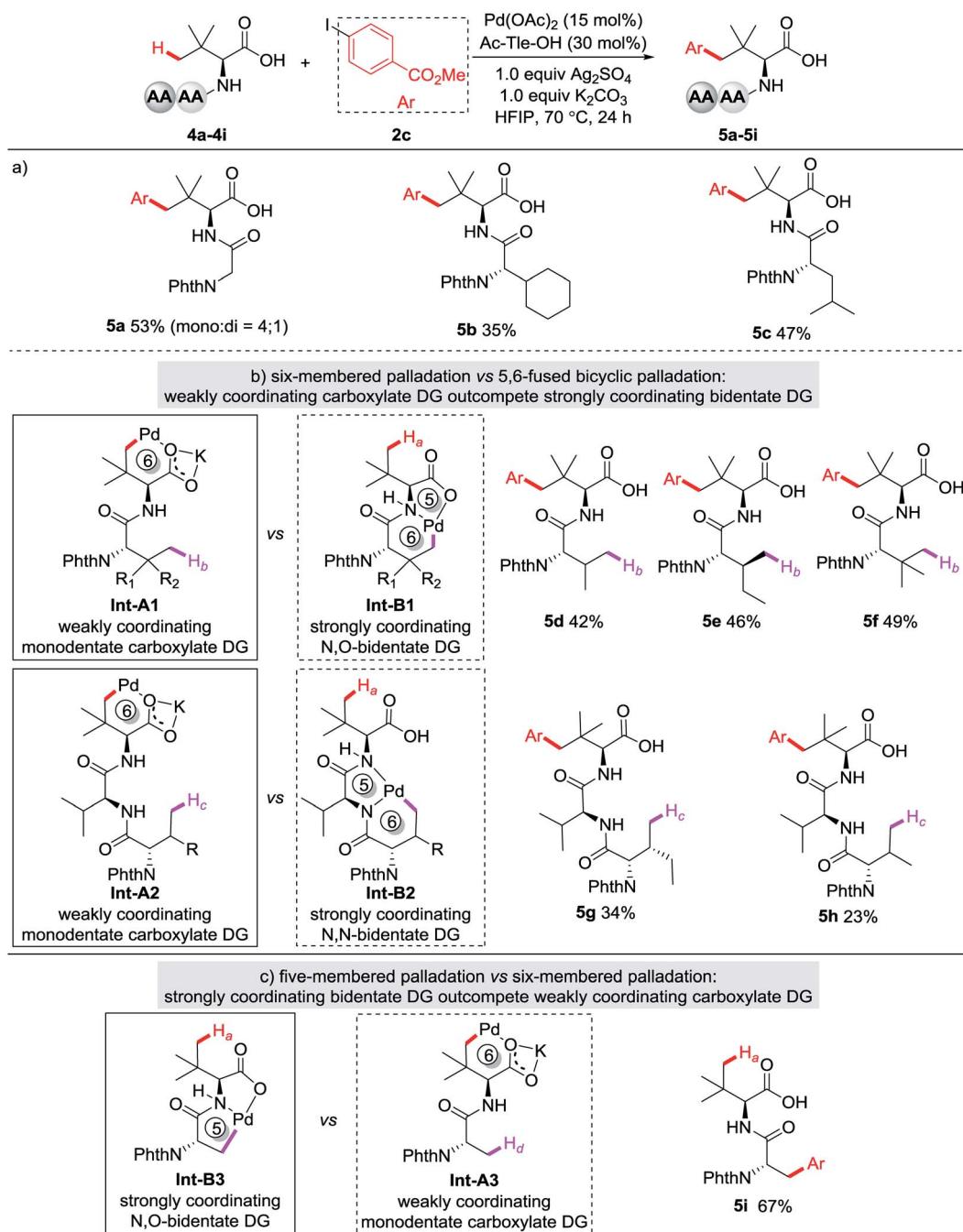


Fig. 3 Scope of different types of peptides (a–c) for Pd-catalyzed $\gamma\text{-C}(\text{sp}^3)\text{-H}$ arylation. Reaction conditions B: **4** (0.1 mmol), **2c** (0.3 mmol), $\text{Pd}(\text{OAc})_2$ (0.015 mmol), Ac-Tle-OH (0.03 mmol), Ag_2SO_4 (0.1 mmol), K_2CO_3 (0.1 mol), HFIP (1 mL), 70°C , air, 24 h, and isolated yield.

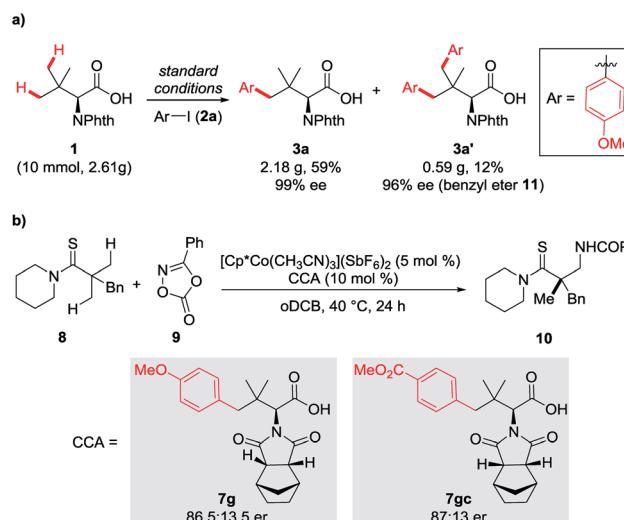


terminus. This selectivity is consistent with Yu's report,^{15a} where the formation of a five-membered palladacycle *via* N,O-bicoordination is favored compared to a six-membered one *via* a monodentate carboxylate DG (Fig. 3c, **Int-B3** vs. **Int-A3**).

Considering that different phthalimide protecting groups have deep influences on asymmetric reactions,³⁻⁷ the compatibility of this protocol with diverse phthalimides would be in high demand. Thus, we examined whether other protecting groups could be applicable to carboxylate-directed γ -C(sp³)-H arylation. To our delight, various phthalimides were compatible with this reaction as shown in Fig. 4. The arylation products 7 were obtained in moderate to high yields. In particular, several types of phthalimides that have been used in asymmetric C-H activation,³⁻⁷ such as 1,8-naphthoyl (**7e**), **7g**, tetrachlorophthaloyl (**7h**), and 2,3-naphthoyl (**7i**), were all tolerated. Succinimide protected Tle (**6j**) also reacted smoothly to give the desired product **7j** in 59% yield. Moreover, Ac-Tle-OH can also react to give the desire product **7kc**, albeit in very low yield (22%, mono : di = 3 : 1). Unfortunately, the alkoxy carbonyl protecting groups, such as Boc, Fmoc, and Cbz, were incompatible with this protocol.

To demonstrate the practicality of this protocol, gram-scale synthesis of **3a** was conducted (Scheme 1a). A 10 mmol-scale reaction of **1** and **2a** was performed, delivering **3a** in 59% yield (2.18 g) and **3a'** in 12% yield (0.59 g) without erosion of optical purity, which is the prerequisite and necessary condition for application as chiral ligands.

The utility of this protocol was further demonstrated by using the resulting bulky side chain amino acids as chiral ligands. Preliminary investigations of Co(III)-catalyzed C(sp³)-H amidation of thioamide **8** with dioxazolone **9** disclosed that **7g** and **7gc** are



Scheme 1 (a) Gram-scale synthesis of bulky side chain amino acids. (b) Co(III)-catalyzed enantioselective C(sp³)-H amidation of thioamide.

highly efficient, giving good enantiocontrol (Scheme 1b, **7g**, 86.5:13.5 er; **7gc**, 87:13 er; (S)-H2-BHTL, 87:13 er^{7a}). These results indicate that the modified amino acids have high potential in asymmetric reactions, especially considering that two sites, the protecting group motif and the aryl skeleton, could be easily and diversely modified.

Conclusions

In conclusion, a Pd-catalyzed carboxylate-directed γ -C(sp³)-H arylation for the diverse synthesis of bulky side chain amino acids and peptides was developed. Notably, this protocol represents the first example of late stage C(sp³)-H functionalization of peptides using a weakly coordinating directing group. The resulting amino acids with bulky side chains have been successfully applied as chiral ligands in asymmetric C(sp³)-H activation. Studies on further applications of these bulky branched chain amino acids in asymmetric synthesis are currently ongoing.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 (a) D. J. Augeri, J. A. Robl, D. A. Betebenner, D. R. Magnin, A. Khanna, J. G. Robertson, A. Wang, L. M. Simpkins,

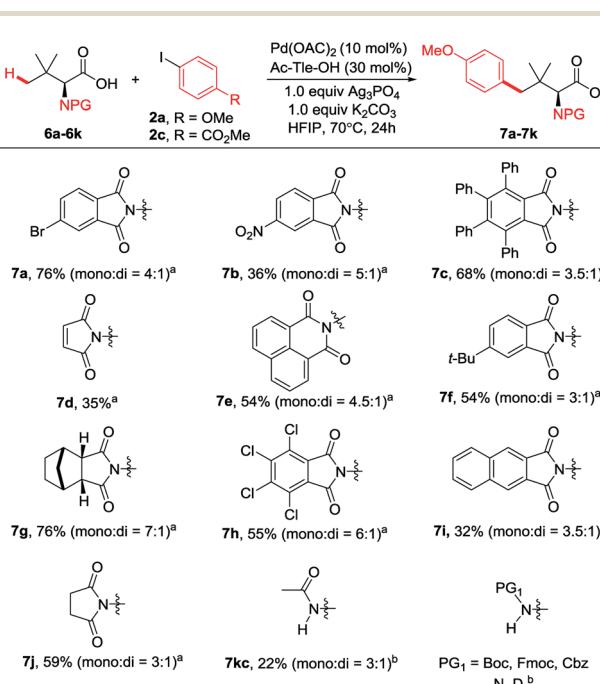


Fig. 4 Scope of protecting groups for Pd-catalyzed C-H arylation.
^aReaction conditions A: **2a** (0.9 mmol) was used as the arylation reagent.
^bReaction conditions B: **2c** (0.9 mmol) was used as the arylation reagent. N. D. = no detected.





P. Taunk, Q. Huang, S.-P. Han, B. Abboe-Offei, M. Cap, L. Xin, L. Tao, E. Tozzo, G. E. Welzel, D. M. Egan, J. Marcinkeviciene, S. Y. Chang, S. A. Biller, M. S. Kirby, R. A. Parker and L. G. Hamann, *J. Med. Chem.*, 2005, **48**, 5025–5037; (b) P. M. Scola, L.-Q. Sun, A. X. Wang, J. Chen, N. Sin, B. L. Venables, S.-Y. Sit, Y. Chen, A. Cocuzza, D. M. Bilder, S. V. D'Andrea, B. Zheng, P. Hewawasam, Y. Tu, J. Friberg, P. Falk, D. Hernandez, S. Levine, C. Chen, F. Yu, A. K. Sheaffer, G. Zhai, D. Barry, J. O. Knipe, Y.-H. Han, R. Schartman, M. Donoso, K. Mosure, M. W. Sinz, T. Zvyaga, A. C. Good, R. Rajamani, K. Kish, J. Tredup, H. E. Klei, Q. Gao, L. Mueller, R. J. Colonna, D. M. Grasela, S. P. Adams, J. Loy, P. C. Levesque, H. Sun, H. Shi, L. Sun, W. Warner, D. Li, J. Zhu, N. A. Meanwell and F. McPhee, *J. Med. Chem.*, 2014, **57**, 1730–1752.

2 (a) H. M. L. Davies and R. E. J. Beckwith, *Chem. Rev.*, 2003, **103**, 2861–2904; (b) M. P. Doyle, R. Duffy, M. Ratnikov and L. Zhou, *Chem. Rev.*, 2010, **110**, 704; (c) H. M. L. Davies and D. Morton, *Chem. Soc. Rev.*, 2011, **40**, 1857.

3 (a) M. Astada and S. Hashimoto, *Tetrahedron Lett.*, 1998, **39**, 79–82; (b) T. Takahashi, H. Tsutsui, M. Tamura, S. Kitagaki, M. Nakajima and S. Hashimoto, *Chem. Commun.*, 2001, **17**, 1604–1605; (c) H. Saito, H. Oishi, S. Kitagaki, S. Nakamura, M. Anada and S. Hashimoto, *Org. Lett.*, 2002, **4**, 3887–3890; (d) K. Minami, H. Saito, H. Tsutsui, H. Nambu, M. Anada and S. Hashimoto, *Adv. Synth. Catal.*, 2005, **347**, 1483–1487.

4 (a) P. Müller, Y. Allenbach and E. Robert, *Tetrahedron: Asymmetry*, 2003, **14**, 779–785; (b) C. Liang, F. Robert-Peillard, C. Fruit, P. Müller, R. H. Dodd and P. Dauban, *Angew. Chem., Int. Ed.*, 2006, **45**, 4641–4644.

5 (a) R. P. Reddy, G. H. Lee and H. M. L. Davies, *Org. Lett.*, 2006, **8**, 3437–3440; (b) K. Liao, T. C. Pickel, V. Boyarskikh, J. Bacsa, D. G. Musaev and H. M. L. Davies, *Nature*, 2017, **551**, 609–613.

6 (a) Y.-S. Jang, M. Dieckmann and N. Cramer, *Angew. Chem., Int. Ed.*, 2017, **56**, 15088–15092; (b) Y.-S. Jang, Ł. Woźniak, J. Pedroni and N. Cramer, *Angew. Chem., Int. Ed.*, 2018, **57**, 12901–12905; (c) Y. Sun and N. Cramer, *Angew. Chem., Int. Ed.*, 2018, **57**, 15539–15543.

7 (a) S. Fukagawa, Y. Kato, R. Tanaka, M. Kojima, T. Yoshino and S. Matsunaga, *Angew. Chem., Int. Ed.*, 2018, **131**, 1165–1169; (b) W. Wang, M. M. Lorion, J. Shah, A. R. Kapdi and L. Ackermann, *Angew. Chem., Int. Ed.*, 2018, **57**, 14700–14717.

8 For early reports on the use of mono-protected amino acids as chiral ligands in C–H activation, see: (a) B.-F. Shi, N. Maugel, Y.-H. Zhang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2008, **47**, 4882–4886; (b) B.-F. Shi, Y.-H. Zhang, J. K. Lam, D.-H. Wang and J.-Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 460–461; (c) D.-W. Gao, Y.-C. Shi, Q. Gu, Z.-L. Zhao and S.-L. You, *J. Am. Chem. Soc.*, 2013, **135**, 86–89; (d) D.-W. Gao, Q. Yin, Q. Gu and S.-L. You, *J. Am. Chem. Soc.*, 2014, **136**, 4841.

9 (a) G. He, B. Wang, W. A. Nack and G. Chen, *Acc. Chem. Res.*, 2016, **49**, 635–645; (b) X. Lu, B. Xiao, R. Shang and L. Liu, *Chin. Chem. Lett.*, 2016, **27**, 305–311.

10 For selected reviews on C(sp³)–H bond activation: (a) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147–1169; (b) O. Baudoin, *Chem. Soc. Rev.*, 2011, **40**, 4902; (c) G. Rouquet and N. Chatani, *Angew. Chem., Int. Ed.*, 2013, **52**, 11726–11743; (d) O. Daugulis, J. Roane and L. D. Tran, *Acc. Chem. Res.*, 2015, **4**, 1053–1064; (e) J. He, M. Wasa, K. S. L. Chan, Q. Shao and J.-Q. Yu, *Chem. Rev.*, 2017, **117**, 8754–8786; (f) J. C. K. Chu and T. Rovis, *Angew. Chem., Int. Ed.*, 2017, **57**, 62–101; (g) Q. Zhang and B.-F. Shi, *Chin. J. Chem.*, 2019, **48**, 5094; (h) C. He, W. G. Whitehurst and M. J. Guant, *Chem.*, 2019, **5**, 1031–1058.

11 (a) K. M. Engle, T.-S. Mei, M. Wasa and J.-Q. Yu, *Acc. Chem. Res.*, 2012, **45**, 788–802; (b) G.-F. Shi and Y.-H. Zhang, *Adv. Synth. Catal.*, 2014, **356**, 1419–1442; (c) M. P. Drapeau and L. J. Goofsen, *Chem.-Eur. J.*, 2016, **22**, 18654–18677.

12 (a) R. Giri, N. Maugel, J.-J. Li, D.-H. Wang, S. P. Breazzano, L. B. Saunders and J.-Q. Yu, *J. Am. Chem. Soc.*, 2007, **129**, 3510–3511; (b) G. Chen, Z. Zhuang, G.-C. Li, T. G. Saint-Denis, Y. Hsiao, C. L. Joe and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2017, **129**, 1506–1509; (c) L. Hu, P.-X. Shen, Q. Shao, K. Hong, J. X. Qiao and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2019, **58**, 2134–2138.

13 (a) K. K. Ghosh and M. van Gemmeren, *Chem.-Eur. J.*, 2017, **23**, 17697–17700; (b) Y. Zhu, X. Chen, C. Yuan, G. Li, J. Zhang and Y. Zhao, *Nat. Commun.*, 2017, **8**, 14904.

14 During the submission of this manuscript, elegant work on γ -C(sp³)–H arylation of free aliphatic acid was reported; however, this protocol was incompatible with Tle and peptides. P. Dolui, J. Das, H. B. Chandrashekhar, S. S. Anjana and D. Maiti, *Angew. Chem., Int. Ed.*, 2019, **58**, 13773–13777.

15 (a) W. Gong, G. Zhang, T. Liu, R. Giri and J.-Q. Yu, *J. Am. Chem. Soc.*, 2014, **136**, 16940–16946; (b) T. Liu, J. X. Qiao, M. A. Poss and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2017, **56**, 10924–10927; (c) A. F. M. Noisier, J. García, I. A. Ionuț and F. Albericio, *Angew. Chem.*, 2016, **129**, 320–324; (d) J. Tang, Y. He, H. Chen, W. Sheng and H. Wang, *Chem. Sci.*, 2017, **8**, 4565–4570.

16 (a) K. M. Engle and J.-Q. Yu, *J. Org. Chem.*, 2013, **78**, 8927–8955; (b) K. M. Engle, *Pure Appl. Chem.*, 2016, **88**, 119–138.

17 K. L. Bay, Y.-F. Yang and K. N. Houk, *J. Organomet. Chem.*, 2018, **864**, 19–25.

18 (a) W. Wang, M. M. Lorion, O. Martinazzoli and L. Ackermann, *Angew. Chem., Int. Ed.*, 2018, **57**, 10554–10558; (b) K. Chen and B.-F. Shi, *Sci. Bull.*, 2018, **63**, 1238–1240; (c) A. F. M. Noisier and M. A. Brimble, *Chem. Rev.*, 2014, **114**, 8775–8806.

19 (a) E. Hernando, J. Villalva, Á. M. Martínez, I. Alonso, N. Rodríguez, R. Gómez Arrayás and J. C. Carretero, *ACS Catal.*, 2016, **6**, 6868–6882; (b) W. Wang, M. M. Lorion, O. Martinazzoli and L. Ackermann, *Angew. Chem., Int. Ed.*, 2018, **57**, 10554–10558; (c) X. Zhang, G. Lu, M. Sun, M. Mahankali, Y. Ma, M. Zhang, W. Hua, Y. Hu, Q. Wang, J. Chen, G. He, X. Qi, W. Shen, P. Liu and G. Chen, *Nat. Chem.*, 2018, **10**, 540–548; (d) B.-B. Zhan, Y. Li, J.-W. Xu, X.-L. Nie, J. Fan, L. Jin and B.-F. Shi, *Angew. Chem., Int. Ed.*, 2018, **57**, 5858–5862.