EDGE ARTICLE

Check for updates

Asymmetric synthesis of aryl/vinyl alkyl carbinol esters *via* Ni-catalyzed reductive arylation/vinylation of 1-chloro-1-alkanol esters†

Deli Sun, [ID] [a] Xianghua Tao,[b] Guobin Ma, [ID] *[b] Jifen Wang*[a] and Yunrong Chen [ID] *[b]

We report herein an asymmetric Ni-catalyzed cross-electrophile coupling approach to prepare enantioenriched aryl/vinyl alkyl carbinol esters through arylation/vinylation of easily accessible racemic 1-chloro-1-alkanol esters with aryl/vinyl electrophiles. The method features a broad substrate scope as demonstrated by more than 60 examples including the challenging chiral allylic esters. It tolerates a wide array of functional groups including alkenyl, carbonyl and free hydroxyl groups that may not survive in conventional carbonyl reduction and addition methods. The synthetic utility of the present work was showcased by facile preparation of a few key intermediates and the modification of chiral drugs and naturally occurring compounds. Finally, we describe an efficient one-pot procedure for this method.

Introduction

Optically pure benzylic and allylic secondary alcohols and their derivatives represent an important class of carbinol structural units that are widely found in natural products and drug molecules (Scheme 1A), and serve as building blocks for diverse organic transformations.[1,2] Therefore, considerable efforts have been devoted to the catalytic asymmetric preparation of these chiral secondary alcohols. A typical strategy is the transformation or resolution of achiral or racemic secondary alcohols through desymmetrization,[3] dynamic kinetic/kinetic resolution,[4] and deracemisation[5] methods. Another strategy is the conversion of other organic compounds into alcohols, such as the classic asymmetric (transfer) hydrogenation of ketones[6] and asymmetric addition of aldehydes.[7] In addition, several impressive advancements of these strategies and other new methods have been achieved recently.[8] The Zhou group developed a delicate method for asymmetric hydrogenation of dialkyl ketones and aliphatic cyclic ketones enabled by iridium catalysis, in which a bulky phosphine ligand was used.[9] Transition metal-catalyzed asymmetric addition[10] and reductive arylation[11] of aldehydes are other powerful methods for the preparation of diaryl carbinols. Just a few days ago, the Xiao group reported a highly enantioselective photoassisted cobalt-catalyzed reductive arylation/vinylation of aldehydes, which efficiently affords

diaryl, aryl/vinyl and aryl/alkyl carbinols.[12] In addition, the use of transition metal-catalyzed carbon–carbon bond coupling protocols that bypass carbonyl additions has received increasing attention in recent years. A very notable development
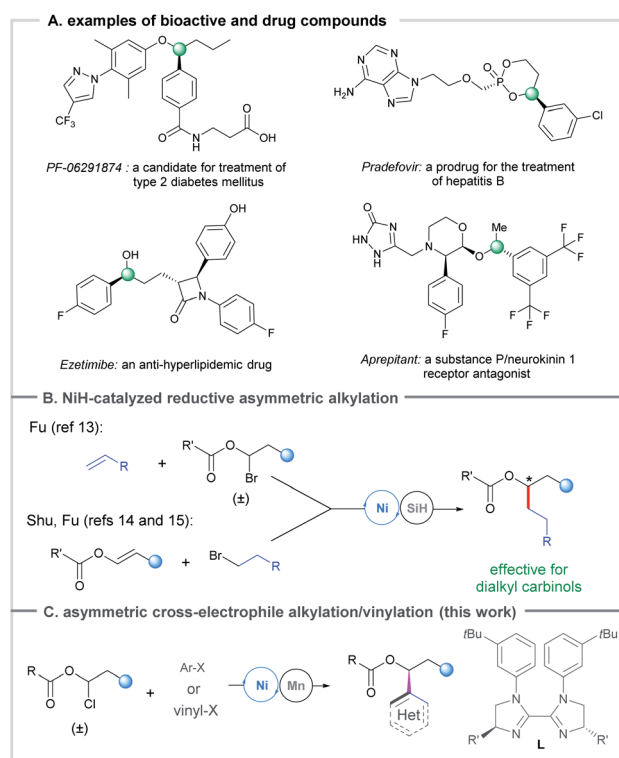
Scheme 1 Ni-catalyzed asymmetric reductive alkylation to access chiral alkyl carbinols and selected examples of bioactive aryl alkyl carbinols.

[a]School of Resources and Environmental Engineering, Shanghai Polytechnic University, 2360 Jinhai Road, Shanghai 201209, P. R. China. E-mail: wangjifen@sspu.edu.cn

[b]Center for Supramolecular Chemistry and Catalysis and Department of Chemistry, College of Sciences, Shanghai University, 99 Shangda Road, Shanghai, 200444 P. R. China. E-mail: yr_chen@shu.edu.cn; maguobin@shu.edu.cn

† Electronic supplementary information (ESI) available. See https://doi.org/10.1039/d2sc02806a

in the field lies in the asymmetric synthesis of enantioenriched dialkyl carbinols based on NiH-catalyzed enantioconvergent coupling of racemic alkyl halides with α-olefins developed by Fu,[13] and hydroalkylation of enol esters with alkyl halides reported by Shu[14] and Fu[15] (Scheme 1B).

In line with the rapid growth of Ni-catalyzed enantioselective cross-electrophile coupling reactions over the past decade,[16,17] we wondered the feasibility of the preparation of chiral secondary alcohols *via* Ni-catalyzed asymmetric cross-coupling of the readily available 1-halo-1-alkanol esters[13,18] with C(sp²)-electrophiles. The Glorius group has demonstrated that a Ni-catalyzed reductive coupling of 1-bromo-1-alkanol ester intermediates with aryl bromides could furnish racemic aryl alkyl carbinols.[18] Herein, we report a strategy of Ni-catalyzed reductive coupling of a diverse set of racemic 1-chloro-1-alkanol esters with aryl and vinyl halides/triflates using a chiral bisimidazoline (BiIm) ligand, affording a facile access to enantioenriched aryl/vinyl alkyl carbinols (Scheme 1C). This method displays a broad substrate scope and excellent functional group compatibility for the efficient preparation of chiral aryl/vinyl alkyl carbinols. The mild conditions are compatible with many sensitive functional groups, *e.g.*, formyl, alkenyl, 2-halopyridinyl and free hydroxyl groups, that are usually not tolerated in carbonyl reduction or addition reactions. Its utility was

showcased by a number of examples of the functionalization and preparation of key intermediates of drug compounds.

Results and discussion

Our investigations commenced with the coupling between racemic 1-chloropropyl 4-methylbenzoate **1** and methyl 4-bromobenzoate (Table 1). After an extensive screening of reaction parameters,[19] reaction under the optimized reaction conditions gave the chiral product **2** in 92% isolated yield and 94% ee, using NiBr₂(DME) as precatalyst, **L1** as ligand and Mn as reductant (entries 1 and 2). Other chiral bisoxazolines or BiIm ligands (**L2–L8**) were also examined (entries 3–9). A trace amount of product was detected without TBAI (tetrabutylammonium iodide) and LiI (entry 10). In the absence of TBAI or LiI, equivalent enantioselectivity with 70% and 20% yields were detected, respectively (entries 11 and 12). This is likely due to a necessary Cl/I exchange to generate more reactive alkyl iodides at low concentration. While LiI is possibly more effective for halide exchange, TBAI may also promote the homogeneity of the reaction. A gram-scale reaction gave the product in high yield without causing the enantioselectivity to deteriorate (entry 13). Finally, **2** was facilely converted into free alcohol **3** in 77% yield with retained enantiomeric excess upon treatment with

---

Table 1 Optimization for the formation of **2**
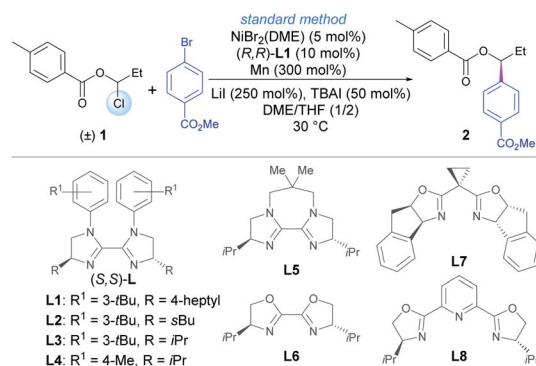
Entry[a]	Deviation from the standard conditions	Yield (%)	ee (%)
1	No changes	95 (92)[b]	94
2	(S,S)-**L1** instead of (R,R)-**L1**	93	−94
3	**L2** instead of (R,R)-**L1**	94	−90
4	**L3** instead of (R,R)-**L1**	95	−89
5	**L4** instead of (R,R)-**L1**	90	−87
6	**L5** instead of (R,R)-**L1**	82	−62
7	**L6** instead of (R,R)-**L1**	36	−54
8	**L7** instead of (R,R)-**L1**	9	−17
9	**L8** instead of (R,R)-**L1**	50	−56
10	Without TBAI and LiI	Trace	-
11	Without TBAI	70	93
12	Without LiI	20	92
13	Gram-scale with 5 mmol of methyl 4-bromobenzoate	85	93

[a] Reactions conducted on a 0.15 mmol scale for 40 h, DME/THF = 1 : 2, NMR yield using 2,5-dimethyl furan as the internal standard, ee was determined by chiral HPLC analysis, DME = 1,2-dimethoxyethane. [b] Isolated yield.

MeONa in MeOH (Scheme S1†).[19] The absolute configuration of alcohol **3** was determined by comparison of the optical rotation with literature data.[20]

With the optimized conditions (Table 1, entry 1) in hand, a set of 1-chloropropyl benzoates decorated with methyl, F and *t*Bu on the phenyl moieties or 2-naphthoate were tested to examine their coupling with methyl 4-bromobenzoate. The resultant chiral benzylic esters **4–8** were obtained in high yields and ees (Scheme 2). Varying the alkyl chain length of the esters did not affect the coupling yields and enantioselectivity as demonstrated by the examples of **9–13**. Of note was the competency of 1-chloropropyl isobutyrate that delivered **14** in high yield and ee, indicating that an alkanoyl ester is also suitable under the reaction conditions. The alkyl chains containing different terminal groups such as *i*Pr (**15**), Ph (**16**), OBz (**18**, **19**), an ester group (**20**), MeS (**21**), Ts (**22**) and a cholic acid derivative (**23**) were all compatible in this method, but a large β group such as *t*Bu significantly affects the yield (**17**).

The scope of aryl halides was examined next for the coupling with **1** (Scheme 3, Part a). A diverse array of electron-poor aryl bromides were highly compatible with the method as exemplified by **24–34**. The functional groups that survived in these transformations included esters, alkene, amides, aldehyde, acetones, sulfone, phosphonate and chloride, which provided opportunities for further synthetic elaboration. Moreover, heteroaryl bromides such as chloro- and trifluormethyl-substituted pyridinyl and pyrimidinyl were successfully incorporated into the products **35–39**, wherein moderate coupling yields and high ees were detected. The applicability of this reaction was

showcased by the introduction of a chiral ester motif to drug frameworks, *e.g.*, fenofibrate (**40**), procanine (**41**) and indomethacine (**42**), affording the coupling products in good yields and high ees.

For electron-neutral and electron-rich arenes, aryl iodides were more appropriate coupling partners for **1** under the standard conditions (Scheme 3, Part b). A wide spectrum of functional groups was tolerated as evidenced by the results of **43–50**. The notable functional groups included ether, thioether, Bpin, chloride, BocNH and free hydroxyl groups. A number of heteroaryl iodides were also examined. While the electron-rich indole iodide also gave a good result (**51**), the electron-deficient 6-iodo-2-methoxyquinoline and 2-chloro- and 2-methoxy 5-iodo-pyridines produced **52–54** in low to moderate yields. In all these cases, high levels of enantioselectivity were constantly obtained. Likewise, the present method was also suitable for the diversification of a natural product, L-phenylalanine, and a drug molecule, clofibrate, furnishing the desired chiral products **55** and **56** in good yields and excellent ees respectively.

To further demonstrate the synthetic utility of this method, we prepared the key structural scaffolds of four biologically active molecules shown in Scheme 3 (Part c). Chiral products **57–60** were obtained in high yields and ees.

We next studied the reaction of **1** with vinyl electrophiles. In this case, vinyl triflates are usually more effective (Scheme 3, Part d). To our delight, **61** bearing 3,6-dihydro-2*H*-thiopyran-4-yl was afforded in 60% yield and 90% ee, using 3,6-dihydro-2*H*-thiopyran-4-yl triflate as a substrate. The vinylation protocol was also suitable for other five to seven membered rings giving
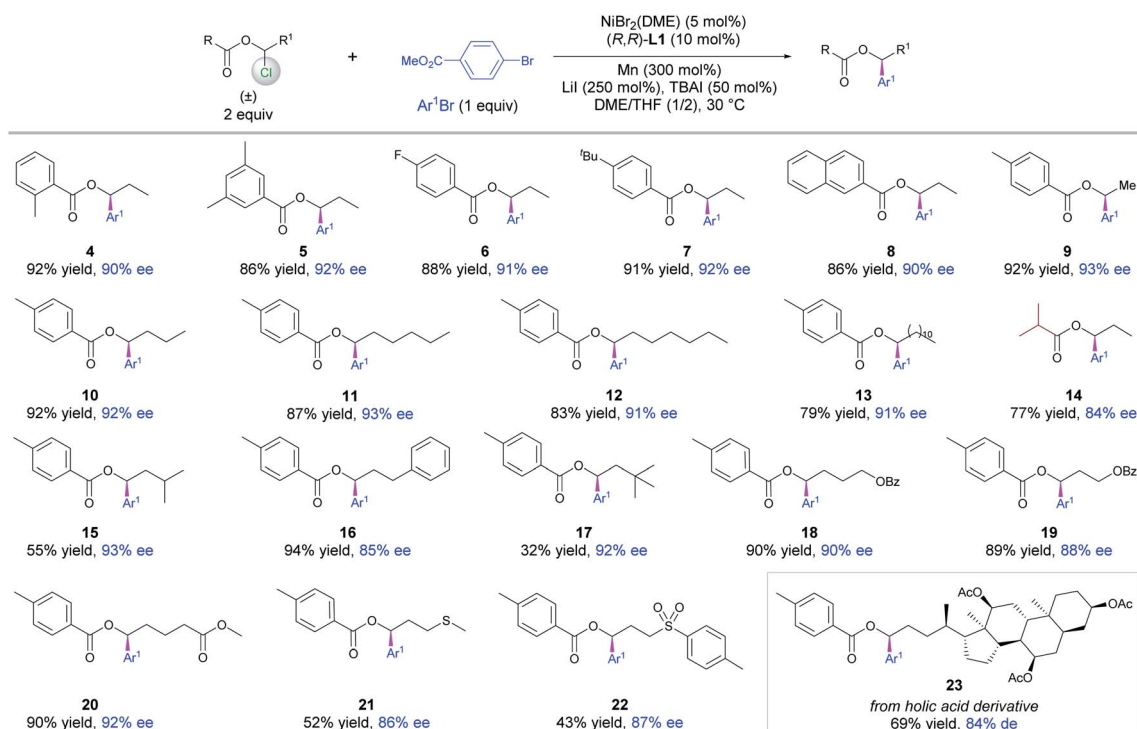
Scheme 2 Scope of 1-chloro-1-alkanol esters. Reactions were conducted on a 0.15 mmol scale for 40 h, and ee was determined by chiral HPLC analysis.
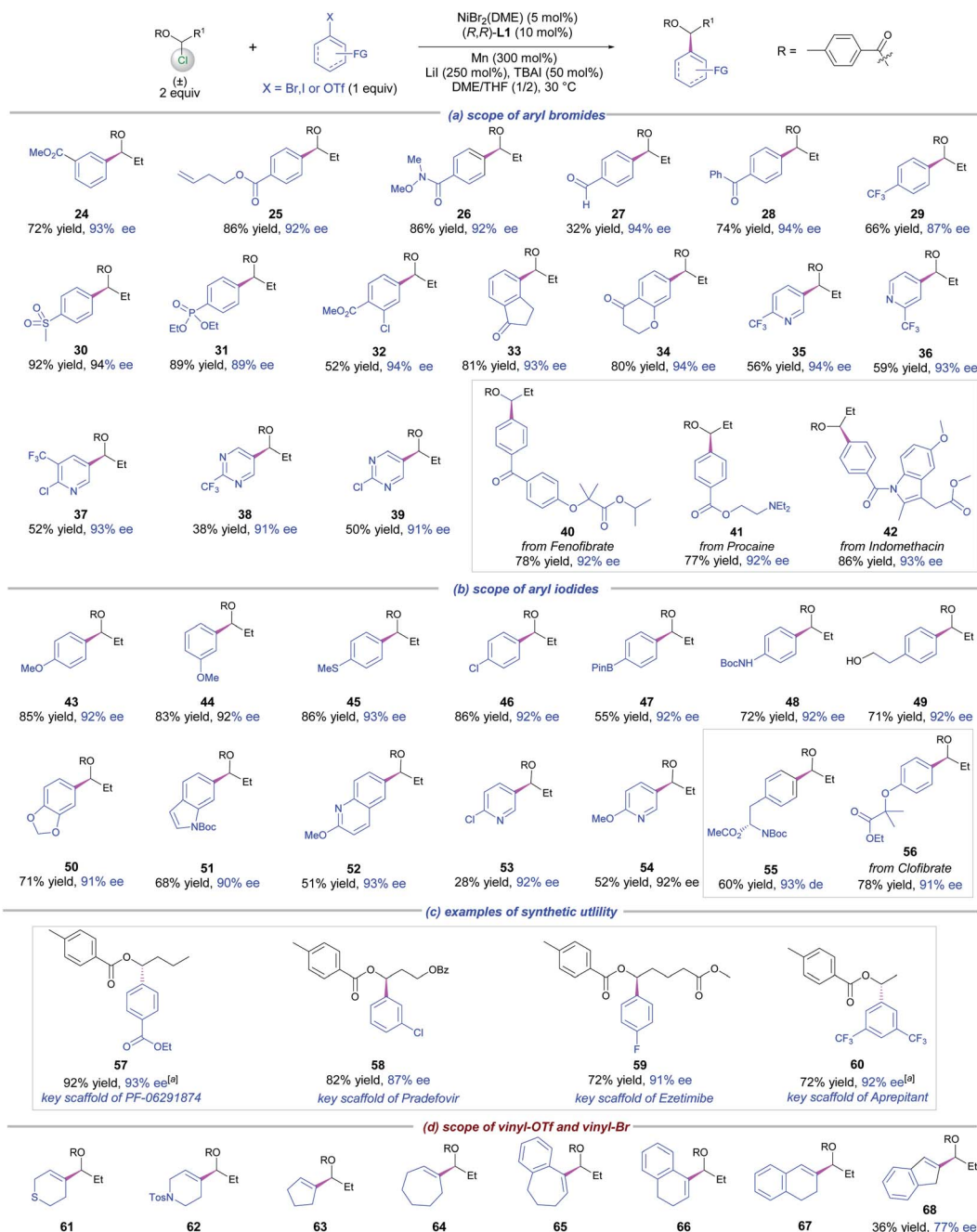
Scheme 3 Scope of aryl/vinyl electrophiles. Reactions conducted on a 0.15 mmol scale for 40 h, ee was determined by chiral HPLC analysis. [a] (*S,S*)-**L1** used as the chiral ligand. [b] With vinyl–OTf. [c] With vinyl–Br.

chiral products **62–67** in moderate to good yields and high enantioselectivities. However, for a 1*H*-inden-2-yl substrate, vinyl bromide gave a better result (**68**). In contrast, a terminal alkenyl bromide such as (*E*)-(4-bromobut-3-en-1-yl)benzene gave a trace amount of product, due to severe homodimerization of the vinyl bromide.

Finally, we found that the reaction conditions of the *in situ* substrate preparation and the coupling reaction are compatible. To our delight, a one-pot procedure afforded the desired product in excellent yield and ee as well, and only two equivalents of acid chloride and aldehyde were used (Scheme 4).[21] The ZnCl2 catalyst

of the former step has almost no influence on the coupling step. Actually, ZnCl2 is a byproduct of some Ni-catalyzed cross-electrophile couplings using organochlorides and zinc.[22]
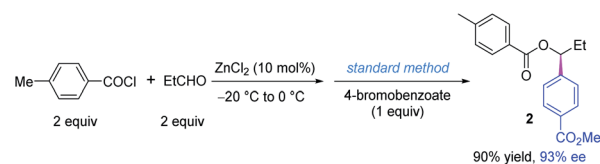
Scheme 4 One-pot reductive arylation.
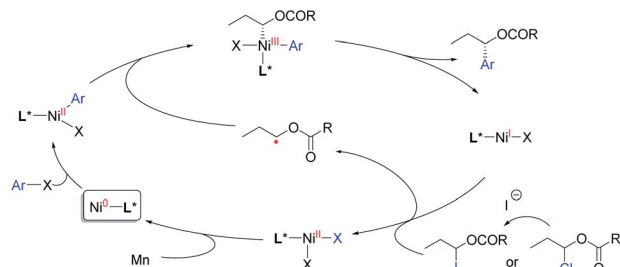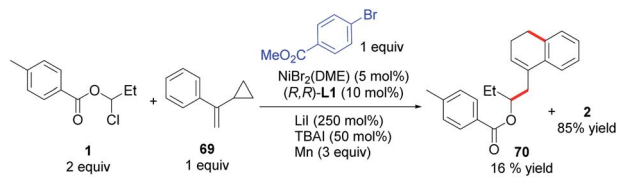
Scheme 5 Radical clock experiment and a working hypothesis of the reaction mechanism.

Based on Weix's study on the Ni-catalyzed arylation of secondary alkyl halides with aryl halides,[23] we propose a radical chain mechanism for this coupling reaction (Scheme 5). The oxidative addition of aryl halide to Ni(0) forms an Ar–Ni(II)–X species, which intercepts an α-oxa carbon radical derived from a 1-Cl/I-1-alkanol ester and then gives an Ar–Ni(III)X–alkyl species. Upon reductive elimination, the chiral product is produced along with a Ni(I)X species. The Ni(I)X is responsible for reduction or halide abstraction of the 1-Cl/I-1-alkanol ester to afford the alkyl radical and Ni(II)X$_2$. Reduction of this Ni(II) to Ni(0) closes the catalytic cycle. The radical nature of the reaction was evidenced by a radical clock experiment, wherein the addition of an alkyl radical derived from **1** to **69** followed by cyclopropyl ring-opening, intramolecular cyclization and hydrogen abstraction affords **70**. Moreover, the reaction of a (dtbbpy)BrNi(II)Ar complex and **1** gave the coupling product (*rac*-**2**) in 36% yield in the absence of reductant (Mn), while the reaction with addition of 3 equiv. of Mn cannot provide a higher yield of the product (see ESI part 5†). This result is consistent with a radical chain mechanism.[24] However, due to the small energy barrier difference between the possible mechanisms, a subtle change of the reaction parameters (*e.g.*, concentration of the catalyst, ligands, and type of substrate) may lead the reaction to proceed *via* a different main pathway. So a sequential reduction (or double oxidative addition, see ESI part 5†) mechanism[24d,25] also cannot be ruled out in these coupling reactions.

Conclusions

In summary, we have developed a method for preparation of enantioenriched aryl/vinyl alkyl carbinols *via* Ni-catalyzed asymmetric reductive cross-coupling between 1-chloro-1-alkanol esters and aryl/vinyl electrophiles. This transformation exhibited a broad substrate scope and tolerated a variety of functional groups, generally furnishing the coupling products in moderate to high yields with high

enantioselectivities. The present work provides a convenient handle for the functionalization and preparation of bioactive and drug molecules and their intermediates. This method adds a new entry to accessing and diversifying chiral secondary benzylic and allylic alcohol derivatives using readily accessible electrophiles.

Data availability

All experimental and characterization data is available in the ESI.†

Author contributions

Conceptualization: D. S., G. M. and Y. C.; investigation: D. S. and X. T.; formal analysis, D. S. and Y. C.; writing – original draft: D. S., J. W. and Y. C.; writing – review & editing: J. W. and Y. C.; supervision: G. M. and J. W.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Notes and references

1 (*a*) G. Wang and M. J. Krische, *J. Am. Chem. Soc.*, 2016, **138**, 8088–8091; (*b*) Y.-M. Siu, J. Roane and M. J. Krische, *J. Am. Chem. Soc.*, 2021, **143**, 10590–10595.

2 (*a*) B. M. Trost and M. L. Crawley, *Chem. Rev.*, 2003, **103**, 2921–2944; (*b*) E. Skucas, M.-Y. Ngai, V. Komanduri and M. J. Krische, *Acc. Chem. Res.*, 2007, **40**, 1394–1401; (*c*) A. Lumbroso, M. L. Cooke and B. Breit, *Angew. Chem., Int. Ed.*, 2013, **52**, 1890–1932; (*d*) A. Gil, F. Albericio and M. Álvarez, *Chem. Rev.*, 2017, **117**, 8420–8446.

3 (*a*) Z. Li, W. Zhang and H. Yamamoto, *Angew. Chem., Int. Ed.*, 2008, **47**, 7520–7522; (*b*) B. Liu, P. Xie, J. Zhao, J. Wang, M. Wang, Y. Jiang, J. Chang and X. Li, *Angew. Chem., Int. Ed.*, 2021, **60**, 8396–8400.

4 (*a*) D. C. Ebner, J. T. Bagdanoff, E. M. Ferreira, R. M. McFadden, D. D. Caspi, R. M. Trend and B. M. Stoltz, *Chem.–Eur. J.*, 2009, **15**, 12978–12992; (*b*) O. Verho and J.-E. Backvall, *J. Am. Chem. Soc.*, 2015, **137**, 3996–4009.

5 (*a*) G. R. A. Adair and J. M. J. Williams, *Chem. Commun.*, 2007, 2608–2609; (*b*) M. M. Musa, F. Hollmann and F. G. Mutti, *Catal. Sci. Technol.*, 2019, **9**, 5487–5503.

6 (*a*) R. Noyori and T. Ohkuma, *Angew. Chem., Int. Ed.*, 2001, **40**, 40–73; (*b*) H. Wang, J. Wen and X. Zhang, *Chem. Rev.*, 2021, **121**, 7530–7567; (*c*) J.-H. Xie and Q.-L. Zhou, in *Asymmetric Hydrogenation and Transfer Hydrogenation*, ed. V. Ratovelomanana-Vidal and P. Phansavath, WILEY-VCH GmbH, 2021, pp. 87–128.

7 S. Suga and M. Kitamura, in *Asymmetric 1,2-addition of organometallics to carbonyl and imine groups; synthetic methods III-catalytic methods: C–C bond formation, comprehensive chirality*, ed. H. Yamamoto and E. M. Carreira, Elsevier Science, Oxford, 2012, pp. 328–342.

8 G. Li, X. Huo, X. Jiang and W. Zhang, *Chem. Soc. Rev.*, 2020, **49**, 2060–2118.

9 F.-H. Zhang, F.-J. Zhang, M.-L. Li, J.-H. Xie and Q.-L. Zhou, *Nat. Catal.*, 2020, **3**, 621–627.

10 X. M.-H. Zhu Dong-Xing, *Chin. J. Org. Chem.*, 2020, **40**, 255–275.

11 (*a*) H.-T. Chang, M. Jeganmohan and C.-H. Cheng, *Chem.– Eur. J.*, 2007, **13**, 4356–4363; (*b*) K. Yabushita, A. Yuasa, K. Nagao and H. Ohmiya, *J. Am. Chem. Soc.*, 2019, **141**, 113–117; (*c*) S. Zhang, S. Perveen, Y. Ouyang, L. Xu, T. Yu, M. Zhao, L. Wang, P. Song and P. Li, *Angew. Chem., Int. Ed.*, 2022, **61**, e202117843; (*d*) Z. Zhu, J. Xiao, M. Li and Z. Shi, *Angew. Chem., Int. Ed.*, 2022, **61**, e202201370.

12 X. Jiang, H. Jiang, Q. Yang, Y. Cheng, L.-Q. Lu, J. A. Tunge and W.-J. Xiao, *J. Am. Chem. Soc.*, 2022, **144**, 8347–8354.

13 Z.-P. Yang and G. C. Fu, *J. Am. Chem. Soc.*, 2020, **142**, 5870–5875.

14 S. Wang, J.-X. Zhang, T.-Y. Zhang, H. Meng, B.-H. Chen and W. Shu, *Nat. Commun.*, 2021, **12**, 2771.

15 X.-X. Wang, L. Yu, X. Lu, Z.-L. Zhang, D.-G. Liu, C. Tian and Y. Fu, *CCS Chem.*, 2022, **4**, 605–615.

16 (*a*) A. H. Cherney, N. T. Kadunce and S. E. Reisman, *J. Am. Chem. Soc.*, 2013, **135**, 7442–7445; (*b*) A. H. Cherney and S. E. Reisman, *J. Am. Chem. Soc.*, 2014, **136**, 14365–14368; (*c*) J. L. Hofstra, A. H. Cherney, C. M. Ordner and S. E. Reisman, *J. Am. Chem. Soc.*, 2018, **140**, 139–142; (*d*) H. Guan, Q. Zhang, P. J. Walsh and J. Mao, *Angew. Chem., Int. Ed.*, 2020, **59**, 5172–5177; (*e*) H.-Y. Tu, F. Wang, L. Huo, Y. Li, S. Zhu, X. Zhao, H. Li, F.-L. Qing and L. Chu, *J. Am. Chem. Soc.*, 2020, **142**, 9604–9611; (*f*) D. Sun, G. Ma, X. Zhao, C. Lei and H. Gong, *Chem. Sci.*, 2021, **12**, 5253–5258; (*g*) P. Zheng, P. Zhou, D. Wang, W. Xu, H. Wang and T. Xu, *Nat. Commun.*, 2021, **12**, 1646.

17 (*a*) Y. Jin and C. Wang, *Synlett*, 2020, **31**, 1843–1850; (*b*) K. E. Poremba, S. E. Dibrell and S. E. Reisman, *ACS Catal.*, 2020, **10**, 8237–8246; (*c*) A. Lipp, S. O. Badir and G. A. Molander, *Angew. Chem., Int. Ed.*, 2021, **60**, 1714–1726; (*d*) S. Zhu, X. Zhao, H. Li and L. Chu, *Chem. Soc. Rev.*, 2021, **50**, 10836–10856.

18 H.-M. Huang, P. Bellotti, J. E. Erchinger, T. O. Paulisch and F. Glorius, *J. Am. Chem. Soc.*, 2022, **144**, 1899–1909.

19 See the ESI† for details.

20 (*a*) M. Rouen, P. Chaumont, G. Barozzino-Consiglio, J. Maddaluno and A. Harrison-Marchand, *Chem.–Eur. J.*, 2018, **24**, 9238–9242; (*b*) Q. Wang, S. Li, C.-J. Hou, T.-T. Chu and X.-P. Hu, *Appl. Organomet. Chem.*, 2019, **33**, e5108.

21 The sequential operation is more efficient, avoiding the loss of 1-chloro-1-alkanol esters (about 50% yield after isolation) in the quench and silica gel chromatography process.

22 (*a*) Y. Ye, H. Chen, J. L. Sessler and H. Gong, *J. Am. Chem. Soc.*, 2019, **141**, 820–824; (*b*) S. Kim, M. J. Goldfogel, M. M. Gilbert and D. J. Weix, *J. Am. Chem. Soc.*, 2020, **142**, 9902–9907.

23 S. Biswas and D. J. Weix, *J. Am. Chem. Soc.*, 2013, **135**, 16192–16197.

24 (*a*) N. D. Schley and G. C. Fu, *J. Am. Chem. Soc.*, 2014, **136**, 16588–16593; (*b*) O. Gutierrez, J. C. Tellis, D. N. Primer, G. A. Molander and M. C. Kozlowski, *J. Am. Chem. Soc.*, 2015, **137**, 4896–4899; (*c*) S. A. Green, S. Vásquez-Céspedes and R. A. Shenvi, *J. Am. Chem. Soc.*, 2018, **140**, 11317–11324; (*d*) X. Wang, G. Ma, Y. Peng, C. E. Pitsch, B. J. Moll, T. D. Ly, X. Wang and H. Gong, *J. Am. Chem. Soc.*, 2018, **140**, 14490–14497.

25 (*a*) A. H. Cherney, N. T. Kadunce and S. E. Reisman, *J. Am. Chem. Soc.*, 2013, **135**, 7442–7445; (*b*) Q. Lin and T. Diao, *J. Am. Chem. Soc.*, 2019, **141**, 17937–17948.