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Cite this: *Chem. Sci.*, 2022, **13**, 170

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Organocatalytic enantioselective S_N1-type dehydrative nucleophilic substitution: access to bis(indolyl)methanes bearing quaternary carbon stereocenters†

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Received 18th September 2021
Accepted 18th November 2021

DOI: 10.1039/d1sc05174a

rsc.li/chemical-science

A highly general and straightforward approach to access chiral bis(indolyl)methanes (BIMs) bearing quaternary stereocenters has been realized *via* enantioconvergent dehydrative nucleophilic substitution. A broad range of 3,3′-, 3,2′- and 3,1′-BIMs were obtained under mild conditions with excellent efficiency and enantioselectivity (80 examples, up to 98% yield and >99 : 1 *er*). By utilizing racemic 3-indolyl tertiary alcohols as precursors of alkyl electrophiles and indoles as C–H nucleophiles, this organocatalytic strategy avoids pre-activation of substrates and produces water as the only by-product. Mechanistic studies suggest a formal S_N1-type pathway enabled by chiral phosphoric acid catalysis. The practicability of the obtained enantioenriched BIMs was further demonstrated by versatile transformation and high antimicrobial activities (**3al**, MIC: 1 μg mL^{-1}).

Introduction

Quaternary carbon stereocenters are frequently found in numerous natural products, pharmaceuticals and biologically active compounds.[1] The catalytic and enantioselective construction of these stereocenters pose a long-standing challenge, especially in acyclic systems.[2] In the past decade, various elegant approaches have been developed to address this challenge.[3] Among them, catalytic enantioconvergent substitution reactions of racemic tertiary alkyl electrophiles have always been considered as an efficient and versatile approach to access quaternary stereocenters (Fig. 1a, left).[4] However, these reactions generally require a good leaving groups (LG = halides, OAc, OTf, *etc.*) to promote carbon–carbon bond formation. A representative example is the work of Jacobsen, who developed a pioneering enantioconvergent catalytic S_N1 reaction of propargyl acetates using allyl silane as a nucleophile.[4k] From the viewpoint of synthetic simplicity and efficiency, the dehydrative nucleophilic substitution of readily available tertiary alcohols (LG = OH) with C–H nucleophiles represents a straightforward and economical means for constructing quaternary carbon stereocenters (Fig. 1a, right).[5] Despite its attractive potential, this type of reaction has been applied less and enantioselective examples of such process remain rare.[6–8] Towards this end, Sun[8] and coworkers have elegantly developed formal dehydrative S_N1 substitutions of 1,1-diaryl tertiary alcohols for the highly enantioselective formation of acyclic all-carbon quaternary stereocenters, but a directing group was needed.

Bis(indolyl)methanes (BIMs) are privileged structural motifs in natural products and bioactive molecules with significant antibacterial, anticancer, and anti-inflammatory activities (Scheme 1a).[9] Therefore, the development of efficient approaches for BIMs have drawn much attention from the synthetic community. However, these established methods are mainly focused on the construction of symmetrical BIMs bearing tertiary stereocenters,[10,11] and the asymmetric synthesis of enantioenriched BIMs bearing quaternary carbon centers

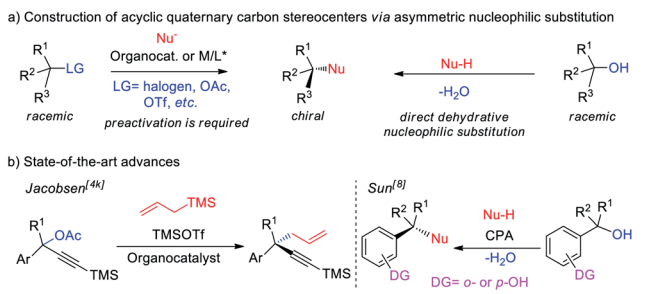

Fig. 1 Synthetic strategies to all-carbon quaternary stereogenic center.

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† Electronic supplementary information (ESI) available. CCDC 2101620, 2101638 and 2101639. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1sc05174a

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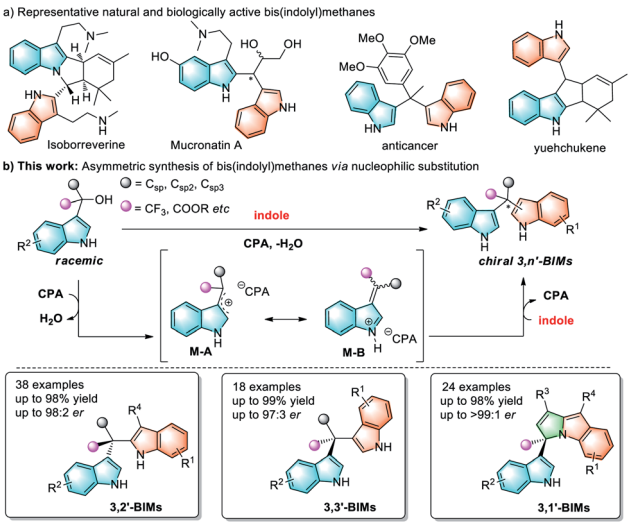


Scheme 1 Representative bis(indolyl)methanes (BIMs) in our current work.

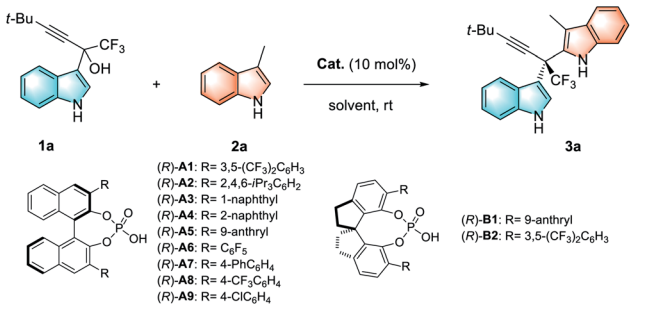
still remain less explored.[12,13] Moreover, existing synthetic methods are largely limited to symmetrical and unsymmetrical 3,3′-BIMs. In contrast, other types of BIMs (such as 3,1′-, 3,2′- and 3,*n*′-BIMs) received less attention and their asymmetric synthesis using the same strategy has remained unstudied, although these BIMs exhibit potential biological activities and deserve special attention as well. Therefore, a broadly applicable synthetic strategy for a wide variety of chiral BIMs would be of high importance.

Given the significance of both the dehydrative nucleophilic substitution and bis(indolyl)methanes (BIMs), herein we report the direct S_N1-type dehydrative nucleophilic substitution of racemic 3′-indolyl tertiary alcohols with various indole nucleophiles catalyzed by chiral phosphoric acids, providing various BIMs bearing quaternary stereogenic carbon centers with good to excellent enantioselectivities; remarkably, we establish a unified strategy for the first time to enable the asymmetric synthesis of a wide range of enantioenriched 3,3′-, 3,2′- and 3,1′-BIMs under mild conditions (Scheme 1b). We further illustrate that the BIM products could be transformed into other valuable enantioenriched molecules bearing all-carbon quaternary centers such as chiral triarylmethanes that are difficult to access. Moreover, preliminary biological activities demonstrate that these chiral BIMs are potential antibacterial agents with MIC (minimum inhibitory concentration) of up to 1 μg mL^{-1} against *Bacillus subtilis*.

Results and discussion

To initiate our investigation, racemic α-indolyl-α-trifluoromethyl propargylic alcohol **1a** was selected as the model substrate in consideration of the privileged role of the CF_3 group in medicinal chemistry[14,15] and the versatile alkynyl handle for further diversification.[16] Moreover, we envisioned that the Brønsted acid catalyst[17] could activate the tertiary alkyl alcohol **1a** *via* dehydration to form the corresponding tertiary carbocation intermediate, which is stabilized by its iminium type resonance form. Furthermore, the chiral Brønsted acid catalyst is expected to achieve efficient chiral induction through ion-pair or hydrogen-bonding with the corresponding carbocation and indole nucleophile simultaneously, to deliver the desired all-carbon quaternary stereocenter. To test this hypothesis, BINOL-derived chiral phosphoric acid (*R*)-**A1** was initially employed as the catalyst to promote the reaction of **1a** with 3-methylindole **2a**, and the reaction proceeded smoothly to afford 3,2′-bis(indolyl)methane **3a** in 90% yield with 64 : 36 *er* (Table 1, entry 1). Next, a series of BINOL- and SPINOL-derived chiral phosphoric acid catalysts were examined to improve the enantioselectivities (Table 1, entries 1–11). We were pleased to find that catalyst (*R*)-**A6** bearing a perfluorophenyl substituent at the 3,3′-position of the BINOL backbone showed a significant increase in enantioselectivity (91 : 9 *er*) with 90% yield (Table 1, entry 6). Interestingly, the catalyst loading was successfully reduced to 5 mol% without any loss in chemical efficiency and enantioselectivity (entry 12). Various solvents, reaction temperatures, concentrations and additives were further investigated in the presence of 5 mol% (*R*)-**A6** (Table 1, entries 13–16. For details, see the ESI†). Finally, the highest yield (92%)

Table 1 Optimization of reaction conditions[a]



Entry	Catalyst	Solvent (× mL)	Time	Yield[b] (%)	*er*[c]
1	(*R*)-**A1**	DCM (1)	20 h	90	64 : 36
2	(*R*)-**A2**	DCM (1)	72 h	Trace	—
3	(*R*)-**A3**	DCM (1)	20 h	90	56 : 44
4	(*R*)-**A4**	DCM (1)	20 h	88	61 : 39
5	(*R*)-**A5**	DCM (1)	72 h	Trace	—
6	(*R*)-**A6**	DCM (1)	20 h	90	91 : 9
7	(*R*)-**A7**	DCM (1)	20 h	68	53 : 47
8	(*R*)-**A8**	DCM (1)	20 h	65	65 : 35
9	(*R*)-**A9**	DCM (1)	20 h	53	64 : 36
10	(*R*)-**B1**	DCM (1)	72 h	Trace	—
11	(*R*)-**B2**	DCM (1)	72 h	Trace	—
12[d]	(*R*)-**A6**	DCM (1)	20 h	90	91 : 9
13[d]	(*R*)-**A6**	DCM (3)	24 h	89	93 : 7
14[d,e]	(*R*)-**A6**	DCM (3)	20 h	90	94 : 6
15[d,e,f]	(*R*)-**A6**	DCM (3)	5 d	92	95 : 5
16[d,e,f,g]	(*R*)-**A6**	DCM (3)	5 d	92	96 : 4

[a] Unless otherwise specified, all reactions were carried out with the catalyst (10 mol%), **1a** (0.10 mmol) and **2a** (0.12 mmol) in DCM (× mL) at room temperature. [b] Isolated yield of **3a**. [c] Determined by chiral-phase HPLC analysis. [d] Catalyst (5 mol%) was used. [e] $MgSO_4$ (35 mg) was used. [f] Performed at 10 °C. [g] **1a** : **2a** (1 : 1) was used.

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and the best enantioselectivity (96 : 4 *er*) were achieved when the reaction was catalyzed by 5 mol% (*R*)-**A6** in DCM (3 mL) at 10 °C with $MgSO_4$ (35 mg) as the additive (Table 1, entry 16).

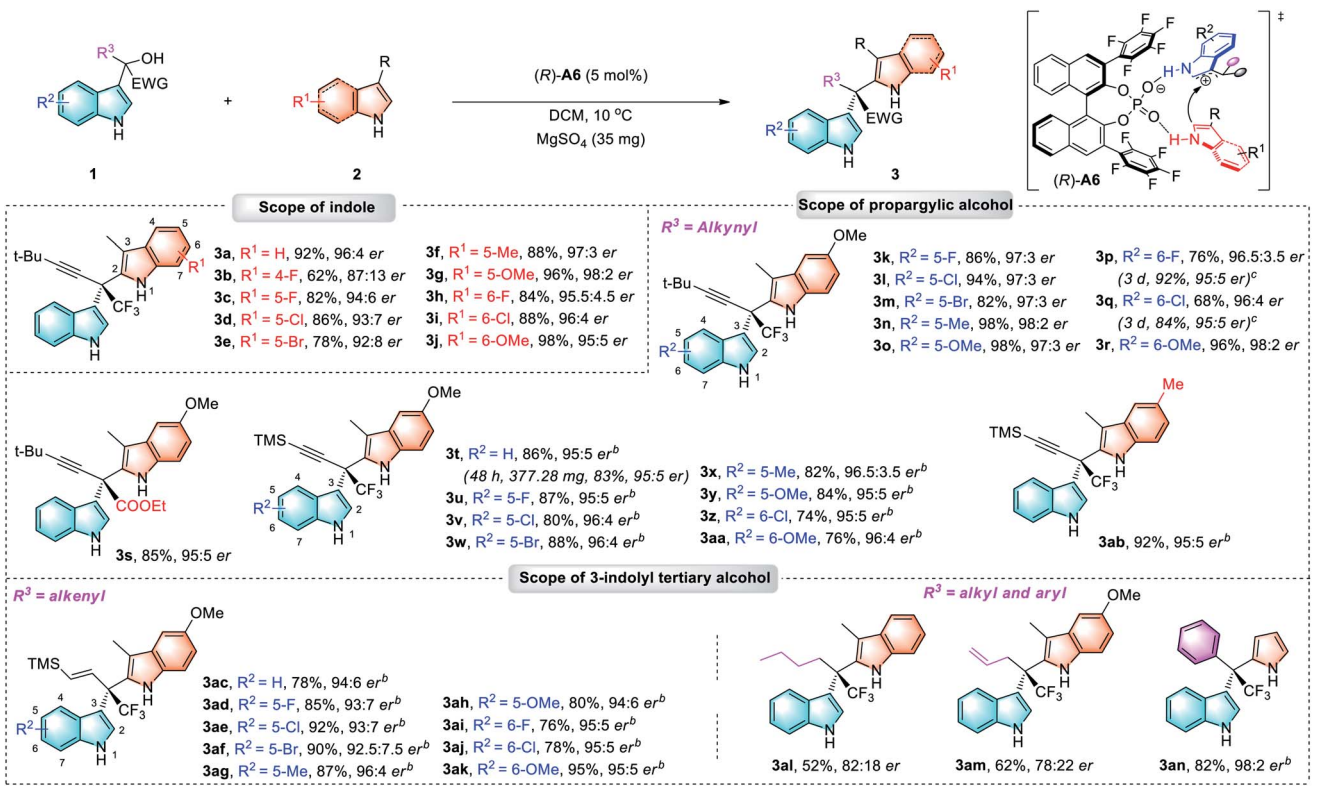
Having established the optimal reaction conditions, we then proceed to examine the reaction scope (Tables 2–4). First, we evaluated the method for the synthesis of chiral 3,2′-BIMs bearing all-carbon quaternary stereocenters. As illustrated in Table 2, a broad range of 3-methylindoles **2** bearing either electron-donating or -withdrawing groups at different positions of the indole ring (C4, C5 and C6) participated in this reaction, furnishing corresponding 3,2′-BIMs (**3a–3j**) in 62–98% yields with 87 : 13–98 : 2 *er*s. Next, various α-indolyl propargylic alcohols **1** bearing substituents on the indolyl moiety were investigated, and excellent enantioselectivities (95 : 5–98 : 2 *er*s) were obtained for the corresponding 3,2′-BIMs (**3k–3ab**).

Notably, α-ethoxycarbonyl substituted propargylic alcohol was used to produce **3s** in 85% yield and 95 : 5 *er*. In addition, a scale-up reaction for the synthesis of **3t** was also successfully performed with similar results. To our delight, the R^3 group of **1** could be expanded from alkyne to various alkenyl, alkyl and aryl functionalities. When racemic allyl alcohols were employed, alkenyl substituent products **3ac–3ak** were afforded in up to 95% yield and 96 : 4 *er*, while moderate yields and enantioselectivities were observed for alkyl-substituted tertiary alcohols. Finally, triarylmethane **3an** could also be obtained with high yield and excellent enantioselectivity (98 : 2 er). The absolute configuration of **3t** was determined to be *R* based by X-ray crystallographic analysis after derivatization, and those of other chiral 3,2′-BIMs were assigned analogously.[18]

As a significant extension of this asymmetric catalytic method, we then turned our attention to the construction of more challenging chiral 3,3′-BIMs which have two similar indole rings. To our disappointment, the optimal catalyst (*R*)-**A6** for chiral 3,2′-BIMs failed to deliver chiral 3,3′-BIM products with good enantioselectivity (Table S2 in the ESI†). After slight modification of the reaction conditions (see ESI for details†), the highest enantioselectivity of 97 : 3 *er* with 92% yield was achieved when the reaction was catalyzed by spirocyclic phosphoric acid (*R*)-**B1** (10 mol%) in DCM at room temperature (**5a**, Table 3). Next, the scope of the enantioenriched 3,3′-BIMs was investigated. As shown in Table 3, various substituted groups on the indole **4** could be well tolerated (**5a–5g**, 80%–98% yields, 92 : 8–97 : 3 *er*s). Similarly, this process was applicable to a wide range of tertiary alcohols **1** bearing various R^2/R^3 substituents, which afforded products **5h–5r** in generally high yields (62%–96%), and moderate to excellent enantioselectivities (70 : 30–97 : 3 *er*s). A single crystal X-ray analysis of **5i** established the absolute configuration of the 3,3′-BIM products.[18]

During the investigation of the nucleophilic substitution reaction of 3-methylindole **2a** with α-indolyl propargylic alcohol

Table 2 Substrate scope for the synthesis of acyclic chiral 3,2′-BIMs[a]



[a] Unless otherwise specified, all reactions were carried out with the catalyst (5 mol%), **1** (0.10 mmol), **2** (0.10 mmol) and $MgSO_4$ (35 mg) in DCM (3 mL) at 10 °C for 12–288 h. [b] Carried out with the catalyst (10 mol%), **1** (0.10 mmol), **2** (0.12 mmol) and $MgSO_4$ (25 mg) in DCM (1 mL) at rt. [c] Carried out with the catalyst (10 mol%), **1** (0.10 mmol), **2** (0.10 mmol) and $MgSO_4$ (35 mg) in DCM (3 mL) at rt.

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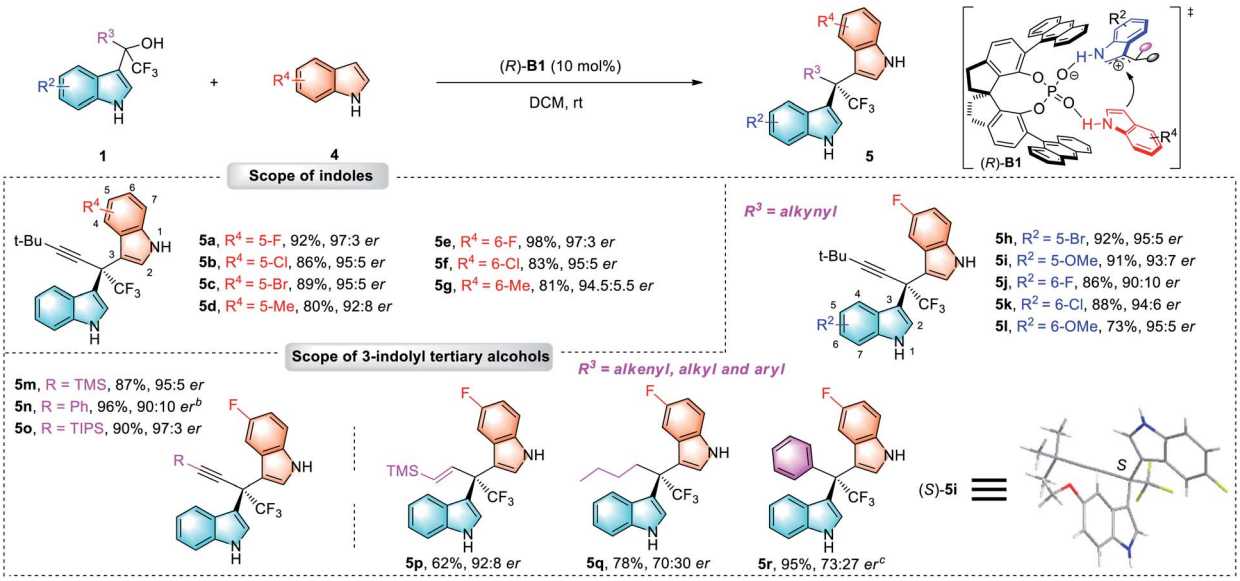
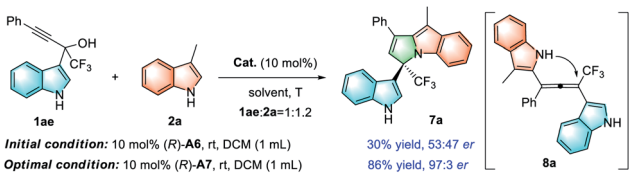
Table 3 Substrate scope for the synthesis of acyclic chiral 3,3′-BIMs[a]



[a] Unless otherwise specified, all reactions were carried out with the catalyst (10 mol%), **1** (0.10 mmol) and **4** (0.12 mmol) in DCM (1 mL) at room temperature for 10–240 h. [b] Carried out with the catalyst (5 mol%), **1** (0.10 mmol) and **4** (0.12 mmol) in DCM (1 mL) at rt. [c] Carried out with catalyst (*R*)-**A6** (10 mol%), **1** (0.10 mmol) and **4** (0.12 mmol) in toluene (1 mL) at 80 °C.

1ae, an unexpected cyclic 3,1′-BIM **7a** was isolated in 30% yield with 53 : 47 *er* under the standard conditions shown in Table 2, which was proposed to be formed through the intramolecular hydroamination of the allene intermediate **8a** (Scheme 2). Encouraged by this interesting result, we next turned our attention to improve the enantioselectivity of this reaction. After optimization (see the ESI for details†), 3,1′-BIM **7a** could be afforded in 86% yield and 97 : 3 *er* when the reaction was performed at room temperature with (*R*)-**A7** as the catalyst (Table 4, **7a**).

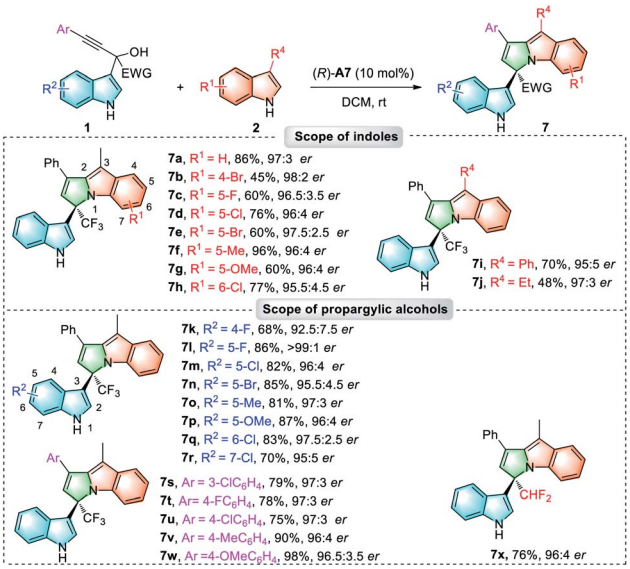
Next, the scope of cyclic 3,1′-BIMs was explored. As shown in Table 4, various indoles **2** with different R^1/R^4 substituents produced the desired 3,1′-BIMs **7a–7j** in 45%–96% yields with 95 : 5–98 : 2 *er*s. Different substituents including halogens, methyl and methoxyl on the phenyl ring of the indolyl moiety were all compatible, giving **7k–7w** in 68%–98% yields with an excellent stereocontrol (92.5 : 7.5–>99 : 1 *er*s). Besides, when α–CHF_2-substituted propargylic alcohol was subjected to this process, the corresponding 3,1′-BIM **7x** was obtained in 76% yield with 96 : 4 *er*. The absolute configurations of these 3,1′-BIMs were assigned based on the X-ray crystal structure of compound **18** (derivated from **7a**, Scheme 4).[18]



Scheme 2 Model reaction employed for condition optimization.

To gain some insights into the mechanism, a series of control experiments were performed. First, the products with opposite chirality can be isolated in a similar yield after subjecting racemic **1a** to the chiral (*R*)- or (*S*)-phosphoric acid catalyst **A6** (Scheme 3a). Using the same (*R*)-**A6** catalyst, both (+)-**1a** and (−)-**1a** reacted with **2a** to deliver product (+)-**3a** with

Table 4 Substrate scope for the synthesis of cyclic chiral 3,1′-BIMs[a]



[a] Unless otherwise specified, all reactions were carried out with the catalyst (10 mol%), **1** (0.10 mmol) and **2** (0.12 mmol) in DCM (1 mL) at room temperature for 10–96 h.

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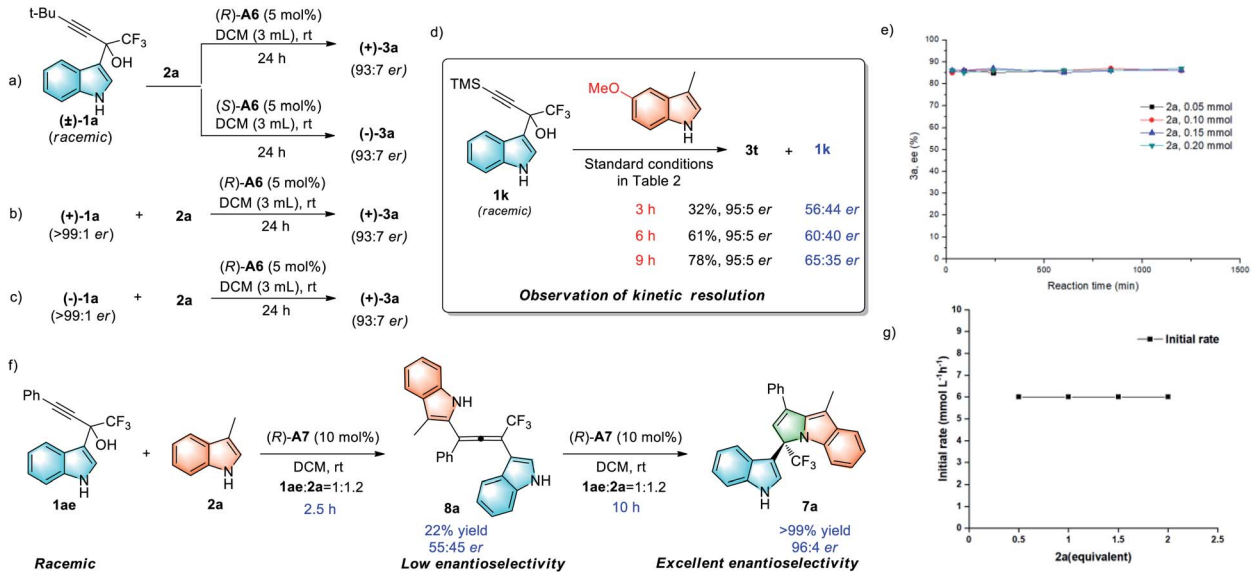
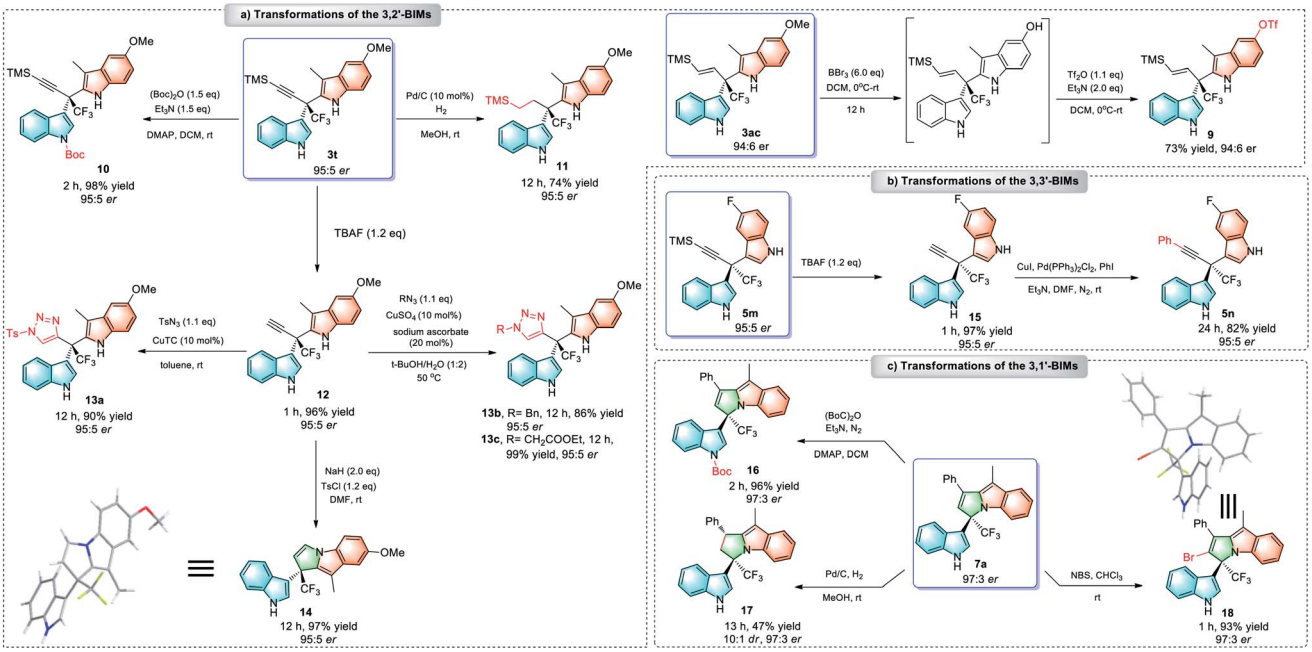


Scheme 3 Control experiments and mechanistic studies.

the same configuration (Schemes 3b and 3c). Based on these results, an enantiospecific mechanism could be ruled out. Moreover, under the standard conditions, substrate **1k** was observed to undergo a partial kinetic resolution process (Scheme 3d). However, variations in the initial concentrations of **2a** (with the same initial concentration of **1a**) produce good consistency in the reaction rate, which shows that the reaction is zeroth-order for **2a**, and it has no rate dependence on the initial concentration of the nucleophile **2a** (Scheme 3g). Meanwhile, reactions carried out with different initial concentrations of **2a** produce good overlay in the enantiomeric excess data of product **3a**, indicating no catalyst decomposition or product inhibition in this process (Scheme 3e). When taken together, these experimental results excluded the S_N2 mechanism coupled with dynamic kinetic resolution.

To explore the origin of the excellent stereocontrol in the formation of chiral cyclic 3,1′-BIMs, control experiments were carried out using **1ae** and **2a** under the standard reaction conditions (Scheme 3f). After 2.5 hours, the allene intermediate **8a** can be isolated in 22% yield with low enantioselectivity (55 : 45 *er*). Subjecting **8a** to the standard conditions provided **7a** with comparable yield and enantioselectivity (96 : 4 *er*) to



Scheme 4 Synthetic transformations of compounds **3ac**, **3t**, **5m** and **7a**.

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Table 5 The antimicrobial activities of the synthetic compounds against various bacteria[a]

	MIC (μg mL^{-1})		
Compound	*Escherichia coli*	Bacillus subtilis	Methicillin-resistant Staphylococcus aureus
3l	64	4	16
3o	8	4	16
3u	16	2	16
3y	>64	8	>64
3ad	64	2	16
3ah	64	8	>64
3al	>64	1	2
5m	>64	4	4
7a	64	4	16
7g	64	8	16
Ampicillin	2	2	—
Vancomyci	—	—	1

[a] MIC values were obtained by the microdilution method following CLSI standards and are given in μg mL^{-1}.

those observed in the one-pot as shown process in Table 4 (see the ESI for details†), thus indicating that hydroamination of the alkene intermediate is the enantiodetermining step (Scheme 3f, right).

Next, ten randomly selected chiral BIMs (**3l**, **3o**, **3u**, **3y**, **3ad**, **3ah**, **3al**, **5m**, **7a** and **7g**) were evaluated for their antimicrobial activities with the FDA-approved broad-spectrum antimicrobial drug ampicillin or vancomycin as the positive control. We first screened their antibacterial activities against *escherichia coli* and *bacillus subtilis* with ampicillin as the positive control. As shown in Table 5, 3,2′-BIMs **3o** and **3u** exhibited antibacterial effects towards *escherichia coli*. Meanwhile, all selected compounds showed remarkable antibacterial activities against *bacillus subtilis* (MIC: 1–8 μg mL^{-1}). Notably, 3,2′-BIM **3al** bearing a butyl group was 2 times more potent than ampicillin with a MIC value of 1 μg mL^{-1}. We further examined their antibacterial potency against methicillin-resistant *staphylococcus aureus* (MRSA) using vancomycin as the reference. To our delight, most of these compounds showed impressive antibacterial effects against MRSA (MIC: 2–16 μg mL^{-1}), especially compounds **3al** and **5m** (MIC: 2–4 μg mL^{-1}). These preliminary antibacterial tests indicated that enantioenriched BIMs might be developed as novel antibacterial agents.

To illustrate the synthetic utilities of this new methodology, we have also tried to transform these 3,*n*′-BIM products into a variety of useful enantioenriched compounds with quaternary stereocenters. In the case of **3ac**, its methoxyl group can be smoothly converted into triflate (**9**) in good yield without loss of enantiomeric purity, which provides more possibilities for further functionalization. For 3,2′-BIM **3t**, regioselective protection of the indole NH moiety provided **10**; hydrogenation of the alkyne afforded α-alkyl BIM **11**; removal of the TMS group generated terminal alkyne **12**, which underwent either a Cu-catalyzed azide–alkyne cycloaddition (CuAAC) to deliver triarylmethanes **13a–13c**, or an intramolecular cyclization to give **14** with a pyrrolo[*1,2-a*]indole scaffold (Scheme 4a). Furthermore, 3,3′-BIM **5m** with the TMS-protected alkyne moiety can be transformed into aryl alkyne **15** through desilylation followed by Sonogashira coupling (Scheme 4b). The synthetic utility of 3,1′-BIM **7a** was also demonstrated by N–H protection, selective hydrogenation and bromination (Scheme 4c).

Conclusions

In conclusion, we have developed an enantioselective S_N1-type dehydration nucleophilic substitution of racemic tertiary alcohols with various substitution patterns (C_{sp}, C_{sp}^2 and C_{sp}^3). Under chiral phosphoric acid catalysis, a wide range of readily available racemic 3-indolyl tertiary alcohols were attacked by indoles to produce acyclic bis(indolyl)methanes (3,2′-BIMs and 3,3′-BIMs) and cyclic 3,1′-BIMs bearing quaternary stereogenic centers with high efficiencies and enantioselectivities (80 examples, up to 98% yield and >99 : 1 *er*). The rich chemistry of the indolyl, alkynyl, and other functional groups in the obtained BIMs allows for facile transformation into valuable chiral compounds bearing quaternary centers that are otherwise difficult to access. Mechanism investigations exclude the S_N2 mechanism and suggest a formal S_N1-type pathway enabled by CPA catalysts. Preliminary biological evaluation demonstrated that these enantioenriched BIMs exhibited impressive preliminary antibacterial activities, and notably **3al** is 2 times more potent than ampicillin against *bacillus subtilis* with a MIC value of 1 μg mL^{-1}. This strategy not only provides an efficient and unified method for accessing valuable chiral BIMs, but also opens opportunities for asymmetric dehydrative cross-coupling reactions employing tertiary alcohols as competent electrophiles without pre-activation.

Data availability

The ESI† include experimental detail, HPLC data, NMR data and HRMS data.

Author contributions

W.-R. Zhu and Q. Su conceived the project, performed the experiments, and wrote the manuscript. X.-Y. Deng, T. Zhong, and J.-T. Yi. Carried out experiments and prepared the ESI.† J.-S. Liu performed the experiments of antimicrobial activities. J. Weng, S.-S. Meng, and G. Lu analyzed the results. G. Lu, and J. Weng conceived and directed the project and wrote the paper. All authors contributed to discussions.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was financially supported by the National Natural Science Foundation of China (No. 81972824), Guangdong Basic and Applied Basic Research Foundation (No 2020A1515011513

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and 2020A1515010684), Guangdong Provincial Key Laboratory of Chiral Molecule and Drug Discovery (No 2019B030301005), and National Engineering and Technology Research Center for New Drug Druggability Evaluation (Seed Program of Guangdong Province, No 2017B090903004). We are grateful to Prof. Ming Lu and Shu-Ting Li (SYSU) for their help in the single crystal preparation. We are also thankful to Prof. Ge Zhang (SYSU) for her help in the evaluation of antimicrobial activities, and to Prof. Hong-Gen Wang (SYSU) for helpful discussion.

Notes and references

1 (*a*) D. J. Newman and G. M. Cragg, *J. Nat. Prod.*, 2016, **79**, 629–661; (*b*) C. Li, S. S. Ragab, G. Liu and W. Tang, *Nat. Prod. Rep.*, 2020, **37**, 276–292.

2 For selected reviews, see:(*a*) K. Fuji, *Chem. Rev.*, 2002, **93**, 2037–2066; (*b*) J. P. Das and I. Marek, *Chem. Commun.*, 2011, **47**, 4593–4623; (*c*) K. W. Quasdorf and L. E. Overman, *Nature*, 2014, **516**, 181–191; (*d*) J. Feng, M. Holmes and M. J. Krische, *Chem. Rev.*, 2017, **117**, 12564–12580.

3 For selected recent reviews, see:(*a*) X.-P. Zeng, Z.-Y. Cao, Y.-H. Wang, F. Zhou and J. Zhou, *Chem. Rev.*, 2016, **116**, 7330–7396; (*b*) X. Zhang and C.-H. Tan, *Chem*, 2021, **7**, 1451–1486; (*c*) J. Sietmann and J. M. Wiest, *Angew. Chem., Int. Ed.*, 2020, **59**, 6964–6974; For some recent examples, see:(*d*) T.-S. Mei, H. H. Patel and M. S. Sigman, *Nature*, 2014, **508**, 340–344; (*e*) S. Krautwald, D. Sarlah, M. A. Schafroth and E. M. Carreira, *Science*, 2013, **340**, 1065–1068; (*f*) B. W. H. Turnbull and P. A. Evans, *J. Am. Chem. Soc.*, 2015, **137**, 6156–6159; (*g*) Z. Wang, Y. Zhu, X. Pan, G. Wang and L. Liu, *Angew. Chem., Int. Ed.*, 2020, **59**, 3053–3057; (*h*) D. Ma, C. B. Miao and J. Sun, *J. Am. Chem. Soc.*, 2019, **141**, 13783–13787; (*i*) V. Lanke and I. Marek, *J. Am. Chem. Soc.*, 2020, **142**, 5543–5548; (*j*) M. Isomura, D. A. Petrone and E. M. Carreira, *J. Am. Chem. Soc.*, 2021, **143**, 3323–3329; (*k*) S. Liu, Y. Tanabe, S. Kuriyama, K. Sakata and Y. Nishibayashi, *Angew. Chem., Int. Ed.*, 2021, **60**, 11231–11236; (*l*) K. Liao, Y. Gong, R.-Y. Zhu, C. Wang, F. Zhou and J. Zhou, *Angew. Chem., Int. Ed.*, 2021, **60**, 8488–8493.

4 For selected reviews, see:(*a*) C. H. Ding and X. L. Hou, *Chem. Rev.*, 2011, **111**, 1914–1937; (*b*) W. Xue, X. Jia, X. Wang, X. Tao, Z. Yin and H. Gong, *Chem. Soc. Rev.*, 2021, **50**, 4162–4184; For selected examples, see:(*c*) B. M. Trost and C. Jiang, *J. Am. Chem. Soc.*, 2001, **123**, 12907–12908; (*d*) S. Ma, X. Han, S. Krishnan, S. C. Virgil and B. M. Stoltz, *Angew. Chem., Int. Ed.*, 2009, **48**, 8037–8041; (*e*) P. Zhang, H. Le, R. E. Kyne and J. P. Morken, *J. Am. Chem. Soc.*, 2011, **133**, 9716–9719; (*f*) P. A. Evans, S. Oliver and J. Chae, *J. Am. Chem. Soc.*, 2012, **134**, 19314–19317; (*g*) H. Zhang, L. Hong, H. Kang and R. Wang, *J. Am. Chem. Soc.*, 2013, **135**, 14098–14101; (*h*) A. Khan, L. Yang, J. Xu, L. Y. Jin and Y. J. Zhang, *Angew. Chem., Int. Ed.*, 2014, **53**, 11257–11260; (*i*) K. Tsuchida, Y. Senda, K. Nakajima and Y. Nishibayashi, *Angew. Chem., Int. Ed.*, 2016, **55**, 9728–9732; (*j*) X. Liu, P. Wang, L. Bai, D. Li, L. Wang, D. Yang and R. Wang, *ACS Catal.*, 2018, **8**, 10888–10894; (*k*) A. E. Wendlandt, P. Vangal and E. N. Jacobsen, *Nature*, 2018, **556**, 447–451; (*l*) X. Zhang, R. Ren, S. M. Tan, D. Tan, R. Lee and C.-H. Tan, *Science*, 2019, **363**, 400–404; (*m*) V. Lanke and I. Marek, *Chem. Sci.*, 2020, **11**, 9378–9385; (*n*) Z. Wang, Z.-P. Yang and G. C. Fu, *Nat. Chem.*, 2021, **13**, 236–242.

5 For selected reviews on the dehydrative nucleophilic substitution, see:(*a*) R. Kumar and E. V. Van der Eycken, *Chem. Soc. Rev.*, 2013, **42**, 1121–1146; (*b*) J. Moran, M. Dryzhakov and E. Richmond, *Synthesis*, 2016, **48**, 935–959; (*c*) S. O'Neill, J. Rodriguez and M. A. Walczak, *Chem.–Asian J.*, 2018, **13**, 2978–2990; (*d*) S. Estopina-Duran and J. E. Taylor, *Chem.–Eur. J.*, 2021, **27**, 106–120; (*e*) A. Gualandi, G. Rodeghiero and P. G. Cozzi, *Asian J. Org. Chem.*, 2018, **7**, 1957–1981.

6 For selected examples on the synthesis of tertiary stereocenters *via* asymmetric dehydrative nucleophilic substitution, see:(*a*) P. G. Cozzi, F. Benfatti and L. Zoli, *Angew. Chem., Int. Ed.*, 2009, **48**, 1313–1316; (*b*) B. Xu, Z.-L. Guo, W.-Y. Jin, Z.-P. Wang, Y.-G. Peng and Q.-X. Guo, *Angew. Chem., Int. Ed.*, 2012, **51**, 1059–1062; (*c*) Z. Lai, Z. Wang and J. Sun, *Org. Lett.*, 2015, **17**, 6058–6061; (*d*) S. Tanaka and M. Kitamura, *Chem. Rec.*, 2021, **21**, 1385–1397.

7 For selected examples on the synthesis of quaternary stereocenters in cyclic systems *via* asymmetric dehydrative nucleophilic substitution, see:(*a*) C. Guo, J. Song, J. Z. Huang, P. H. Chen, S. W. Luo and L. Z. Gong, *Angew. Chem., Int. Ed.*, 2012, **51**, 1046–1050; (*b*) Y. Liu, H. H. Zhang, Y. C. Zhang, Y. Jiang, F. Shi and S. J. Tu, *Chem. Commun.*, 2014, **50**, 12054–12057; (*c*) C. Ma, F. Jiang, F.-T. Sheng, Y. Jiao, G.-J. Mei and F. Shi, *Angew. Chem., Int. Ed.*, 2019, **58**, 3014–3020; (*d*) L. Song, Q. X. Guo, X. C. Li, J. Tian and Y. G. Peng, *Angew. Chem., Int. Ed.*, 2012, **51**, 1899–1902.

8 For selected examples on the synthesis of quaternary stereocenters in acyclic systems *via* asymmetric dehydrative nucleophilic substitution, see:(*a*) Z. Wang, Y. F. Wong and J. Sun, *Angew. Chem., Int. Ed.*, 2015, **54**, 13711–13714; (*b*) W. Zhao, Z. Wang, B. Chu and J. Sun, *Angew. Chem., Int. Ed.*, 2015, **54**, 1910–1913; (*c*) X. Li, M. Duan, Z. Deng, Q. Shao, M. Chen, G. Zhu, K. N. Houk and J. Sun, *Nat. Catal.*, 2020, **3**, 1010–1019.

9 (*a*) X. He, S. Hu, K. Liu, Y. Guo, J. Xu and S. Shao, *Org. Lett.*, 2006, **8**, 333–336; (*b*) H. J. Kim, H. Lee, J. H. Lee, D. H. Choi, J. H. Jung and J. S. Kim, *Chem. Commun.*, 2011, **47**, 10918–10920; (*c*) R. Bell, S. Carmeli and N. Sar, *J. Nat. Prod.*, 1994, **57**, 1587–1590; (*d*) G. Bifulco, I. Bruno, L. Minale, R. Riccio, A. Calignano and C. Debitus, *J. Nat. Prod.*, 1994, **57**, 1294–1299; (*e*) G. Bifulco, I. Bruno, R. Riccio, J. Lavayre and G. Bourdy, *J. Nat. Prod.*, 1995, **58**, 1254–1260; (*f*) N. Ichite, M. B. Chougule, T. Jackson, S. V. Fulzele, S. Safe and M. Singh, *Clin. Cancer Res.*, 2009, **15**, 543–552; (*g*) M. Shiri, M. A. Zolfigol, H. G. Kruger and Z. Tanbakouchian, *Chem. Rev.*, 2010, **110**, 2250–2293; (*h*) M. Marrelli, X. Cachet, F. Conforti, R. Sirianni, A. Chimento, V. Pezzi, S. Michel, G. A. Statti and F. Menichini, *Nat. Prod. Res.*, 2013, **27**, 2039–2045; (*i*) S. Roy, R. Gajbhiye, M. Mandal, C. Pal,

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A. Meyyapan, J. Mukherjee and P. Jaisankar, *Med. Chem. Res.*, 2014, **23**, 1371–1377; (*j*) M. M. Queiroz, E. F. Queiroz, M. L. Zeraik, S. N. Ebrahimi, L. Marcourt, M. Cuendet, I. Castro-Gamboa, M. Hamburger, V. da Silva Bolzani and J.-L. Wolfender, *J. Nat. Prod.*, 2014, **77**, 650–656; (*k*) I. Syahrul, T. Muhammad and I. Nor Hadiani, *Curr. Med. Chem.*, 2015, **22**, 4412–4433.

10 For selected examples on the construction of symmetrical BIMs: see:(*a*) T. Tsuchimoto and M. Kanbara, *Org. Lett.*, 2011, **13**, 912–915; (*b*) T. Mehrabi and A. Ariafard, *Chem. Commun.*, 2016, **52**, 9422–9425; (*c*) F. Ling, L. Xiao, L. Fang, C. Feng, Z. Xie, Y. Lv and W. Zhong, *Org. Biomol. Chem.*, 2018, **16**, 9274–9278; (*d*) E. B. McLean, F. M. Cutolo, O. J. Cassidy, D. J. Burns and A.-L. Lee, *Org. Lett.*, 2020, **22**, 6977–6981; (*e*) J. Nie, G.-W. Zhang, L. Wang, A. Fu, Y. Zheng and J.-A. Ma, *Chem. Commun.*, 2009, 2356–2358; (*f*) S. Sasaki, Y. Ikekame, M. Tanayama, T. Yamauchi and K. Higashiyama, *Synlett*, 2012, **23**, 2699–2703; (*g*) Y. Wang, Y. Yuan, C.-H. Xing and L. Lu, *Tetrahedron Lett.*, 2014, **55**, 1045–1048; (*h*) W. E. Noland, H. V. Kumar, G. C. Flick, C. L. Aspros, J. H. Yoon, A. C. Wilt, N. Dehkordi, S. Thao, A. K. Schneerer, S. Gao and K. J. Tritch, *Tetrahedron*, 2017, **73**, 3913–3922; (*i*) V. K. Pandey and P. Anbarasan, *J. Org. Chem.*, 2017, **82**, 12328–12336; (*j*) Y.-M. Ren, M.-D. Xu and X. Wang, *Catalysts*, 2017, **7**, 300–306; (*k*) A. Muthukumar, G. N. Rao and G. Sekar, *Org. Biomol. Chem.*, 2019, **17**, 3921–3933; (*l*) Z. Wu, G. Wang, S. Yuan, D. Wu, W. Liu, B. Ma, S. Bi, H. Zhan and X. Chen, *Green Chem.*, 2019, **21**, 3542–3546; (*m*) J. Qiao, S. Gao, L. Wang, J. Wei, N. Li and X. Xu, *J. Organomet. Chem.*, 2020, **906**, 121039–121046; (*n*) Y. Ling, D. An, Y. Zhou and W. Rao, *Org. Lett.*, 2019, **21**, 3396–3401; (*o*) A. A. More and A. M. Szpilman, *Org. Lett.*, 2020, **22**, 3759–3764.

11 For selected examples on the construction of chiral BIMs bearing tertiary stereocenters, see:(*a*) M. H. Zhuo, Y. J. Jiang, Y. S. Fan, Y. Gao, S. Liu and S. Zhang, *Org. Lett.*, 2014, **16**, 1096–1099; (*b*) H.-Q. Wang, M.-M. Xu, Y. Wan, Y.-J. Mao, G.-J. Mei and F. Shi, *Adv. Synth. Catal.*, 2018, **360**, 1850–1860; (*c*) C. Yue, F. Na, X. Fang, Y. Cao and J. C. Antilla, *Angew. Chem., Int. Ed.*, 2018, **57**, 11004–11008.

12 For selected examples on the synthesis of chiral BIMs bearing cyclic quaternary stereogenic carbon centers, see:(*a*) X.-X. Sun, B.-X. Du, H.-H. Zhang, L. Ji and F. Shi, *ChemCatChem*, 2015, **7**, 1211–1221; (*b*) M.-H. Zhuo, G.-F. Liu, S.-L. Song, D. An, J. Gao, L. Zheng and S. Zhang, *Adv. Synth. Catal.*, 2016, **358**, 808–815.

13 For selected examples on the synthesis of chiral BIMs bearing acyclic quaternary stereogenic carbon centers, see:(*a*) Y. Zhang, S.-X. Zhang, L.-N. Fu and Q.-X. Guo, *ChemCatChem*, 2017, **9**, 3107–3110; (*b*) X.-K. Guan, H. Zhang, J.-G. Gao, D.-Y. Sun, X.-S. Qin, G.-F. Jiang, G.-L. Zhang and S. Zhang, *J. Org. Chem.*, 2019, **84**, 12562–12572.

14 (*a*) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320–330; (*b*) X. H. He, Y. L. Ji, C. Peng and B. Han, *Adv. Synth. Catal.*, 2019, **361**, 1923–1957.

15 For our recent related work, see:(*a*) W.-J. Huang, Q. Chen, N. Lin, X.-W. Long, W.-G. Pan, Y.-S. Xiong, J. Weng and G. Lu, *Org. Chem. Front.*, 2017, **4**, 472–482; (*b*) W.-R. Zhu, Q. Chen, N. Lin, K.-B. Chen, Z.-W. Zhang, G. Fang, J. Weng and G. Lu, *Org. Chem. Front.*, 2018, **5**, 1375–1380; (*c*) W.-R. Zhu, K. Liu, J. Weng, W.-H. Huang, W.-J. Huang, Q. Chen, N. Lin and G. Lu, *Org. Lett.*, 2020, **22**, 5014–5019; (*d*) W.-R. Zhu, Q. Su, H.-J. Diao, E.-X. Wang, F. Wu, Y.-L. Zhao, J. Weng and G. Lu, *Org. Lett.*, 2020, **22**, 6873–6878; (*e*) W.-R. Zhu, Q. Su, N. Lin, Q. Chen, Z.-W. Zhang, J. Weng and G. Lu, *Org. Chem. Front.*, 2020, **7**, 3452–3458.

16 For selected reviews, see:(*a*) B. M. Trost and C.-J. Li, *Modern Alkyne Chemistry: Catalytic and Atom-Economic Transformations*, Wiley, New York, 2014; (*b*) I.-T. Trotuș, T. Zimmermann and F. Schüth, *Chem. Rev.*, 2014, **114**, 1761–1782; (*c*) H. Schobert, *Chem. Rev.*, 2014, **114**, 1743–1760; (*d*) R. Chinchilla and C. Nájera, *Chem. Rev.*, 2014, **114**, 1783–1826.

17 For selected reviews, see:(*a*) T. Akiyama, *Chem. Rev.*, 2007, **107**, 5744–5758; (*b*) M. Terada, *Chem. Commun.*, 2008, 4097–4112; (*c*) D. Parmar, E. Sugiono, S. Raja and M. Rueping, *Chem. Rev.*, 2014, **114**, 9047–9153; (*d*) T. James, M. van Gemmeren and B. List, *Chem. Rev.*, 2015, **115**, 9388–9409. For selected examples, see:(*e*) D. Uraguchi and M. Terada, *J. Am. Chem. Soc.*, 2004, **126**, 5356–5357; (*f*) T. Akiyama, J. Itoh, K. Yokota and K. Fuchibe, *Angew. Chem., Int. Ed.*, 2004, **43**, 1566–1568; (*g*) F. Jiang, K.-W. Chen, P. Wu, Y.-C. Zhang, Y. Jiao and F. Shi, *Angew. Chem., Int. Ed.*, 2019, **58**, 15104–15110; (*h*) S.-S. Meng, P. Yu, Y.-Z. Yu, Y. Liang, K. N. Houk and W.-H. Zheng, *J. Am. Chem. Soc.*, 2020, **142**, 8506–8513.

18 (*a*) ESI.†; (*b*) X. Ou, X. Li, H. Rong, L. Yu and M. Lu, *Chem. Commun.*, 2020, **56**, 9950–9953.