Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2023, **21**, 3691

Brønsted acid-catalyzed C6 functionalization of 2,3-disubstituted indoles for construction of cyano-substituted all-carbon quaternary centers†

Wen-Jun Huang, [a,b] Li-Xia Liu, [b] Yong-Gui Zhou, [b] Bo Wu *[b] and Guo-Fang Jiang *[a]

Received 16th March 2023,
Accepted 6th April 2023

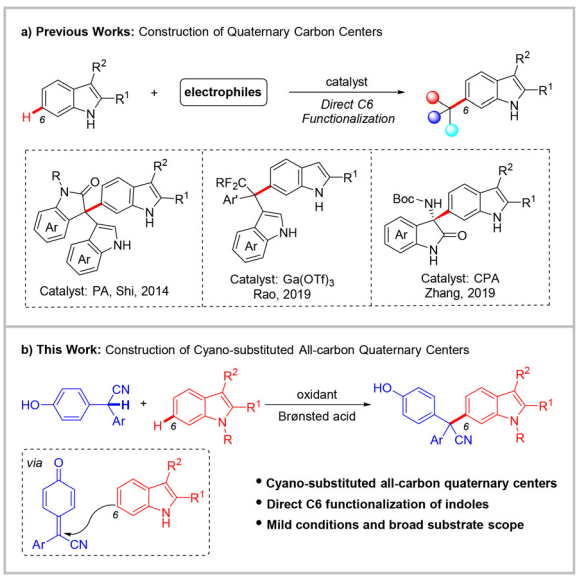
DOI: 10.1039/d3ob00412k

rsc.li/obc

We report a Brønsted acid-catalyzed C6 functionalization of 2,3-disubstituted indoles with 2,2-diarylacetonitriles for efficient construction of cyano-substituted all-carbon quaternary centers with excellent yields. The synthetic utility was demonstrated by the conversion of the cyano-group which enables the divergent preparation of aldehydes, primary amines and amides. Control experiments suggested that this process involves C–H oxidation of 2,2-diarylacetonitriles to *in situ* generate *δ*,*δ*-disubstituted *p*-quinone methide intermediates. This protocol provides an efficient method for C6 functionalization of 2,3-disubstituted indoles to construct all-carbon quaternary centers.

Introduction

Indoles are crucial and prevalent structural units in a myriad of natural products, pharmaceuticals and materials.[1] From the standpoint of medicinal chemistry, indole has always been a popular subject of research for scientists due to its excellent antiviral, anti-inflammatory, anticarcinogenic, and antioxidant properties.[1f] The C–H functionalization of indoles is a facile and straightforward strategy for synthesizing indole derivatives with diverse and complex structures, and has been thoroughly investigated.[2] Owing to the inherently nucleophilic properties, the C–H functionalization of indoles at the remote C6-position becomes challenging. As chemists devoted continuous efforts for C6 functionalization of indoles, several directly catalytic protocols have been developed to construct tertiary carbon centers[3] and quaternary carbon centers.[4] Brønsted acid-catalyzed, Lewis acid-catalyzed and rhodium-catalyzed direct C6 functionalizations of indoles were disclosed for the formation of tertiary carbon centers. Quaternary carbon centers are present in various biologically active natural products and drugs,[5] and their construction has attracted extensive attention. Due to the intrinsic steric hindrance, the access to quaternary carbon centers still encounters difficulties.[6] There are only three reports on the direct catalytic C6 functionalization of indoles to construct quaternary carbon centers. In 2014, Shi and co-workers devised phosphoric acid-catalyzed direct C6 functionalization of 2,3-disubstituted indoles with 3-indolylmethanols, delivering bisindolyl-oxindoles containing all-carbon quaternary centers (Scheme 1a).[4a] Subsequently, gallium triflate-catalyzed C6 functionalization of 2-substituted indoles with trifluoro-methylated 3-indolylmethanols to access trifluoromethylated 3,6′-bis(indolyl)methanes bearing all-



Scheme 1 Direct C6 functionalization of indoles for forming quaternary carbon centers.

[a]*Advanced Catalytic Engineer Research Center of Ministry of Education, College of Chemistry and Chemical Engineering, Hunan University, Changsha 410082, P.R. China. E-mail: gfjiang@hnu.edu.cn*
[b]*State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 457 Zhongshan Road, Dalian, Liaoning 116023, P. R. China. E-mail: bowu@dicp.ac.cn*

† Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d3ob00412k

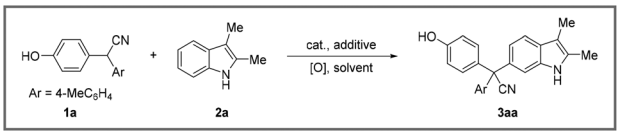
carbon quaternary centers was reported by Rao's group (Scheme 1a).[4b] Zhang and co-workers developed chiral phosphonic acid-catalyzed direct C6 functionalization of 2,3-disubstituted indoles with *N*-Boc ketimines for enantioselective synthesis of quaternary carbon centers containing a nitrogen atom (Scheme 1a).[4c] Although progress has been made in this field, the development of new catalytic direct C6 functionalization of indoles to synthesize all-carbon quaternary centers remains highly desirable.

δ,*δ*-Disubstituted *para*-quinone methides (*p*-QMs) have been recognized as important synthons for the formation of all-carbon quaternary centers owing to the intrinsically strong electrophilic characteristics.[7–11] The approaches to generate *δ*,*δ*-disubstituted *p*-QMs include Brønsted acid-catalyzed dehydration of *p*-hydroxybenzyl alcohols[8,9] and oxidant mediated C–H oxidation of diarylmethanes bearing electron-withdrawing groups.[10,11b] Owing to our interest in C6 functionalization of 2,3-disubstituted indoles,[3d,12] we conceived the catalytic direct C6 functionalization of 2,3-disubstituted indoles with *δ*,*δ*-disubstituted *p*-QMs which were *in situ* generated from 2,2-diarylacetonitriles under oxidative conditions. The electron-withdrawing cyano group of 2,2-diarylacetonitrile would tune the molecular electron-density distribution, and the stability of the resulting *p*-QMs might be enhanced by reducing their polymerizability.[7b] In addition, nitrile moieties can also serve as valuable building blocks because of their diverse transformation performance.[13] Herein, we report a Brønsted acid-catalyzed direct C6 functionalization of 2,3-disubstituted indoles with 2,2-diarylacetonitriles for efficient construction of cyano-substituted all-carbon quaternary centers (Scheme 1b). Control experiments suggested that the reaction involves C–H oxidation of 2,2-diarylacetonitriles to *in situ* generate *δ*,*δ*-disubstituted *p*-QM intermediates. The synthetic utility was demonstrated by the convenient transformation of cyano-substituted products to valuable compounds including aldehydes, primary amines and amides.

Results and discussion

Initially, we began our study with the reaction of 2,2-diarylacetonitrile **1a** and 2,3-dimethylindole **2a** using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as an oxidant, silica gel as an additive, and *p*-toluenesulfonic acid monohydrate as a catalyst in dichloromethane at 30 °C. The desired C6 functionalization product **3aa** was obtained in 74% isolated yield and C5 or C7 functionalization was not observed (Table 1, entry 1). The reason might be that C6-alkylation is more thermodynamically favorable.[3c] Considering that suitable additives would be conducive to promoting the oxidation,[10c] a series of additives were investigated. Additives 4 Å MS and florisil were futile when DDQ was used as an oxidant (entries 2 and 3). The reaction provided product **3aa** in 85% yield with basic aluminum oxide serving as the best additive (entry 4). In addition, the reaction could not take place in the absence of an additive (entry 5). The screening of oxidants showed that DDQ remained the optimal one (entries 4 and 6–8). Next, a variety of acid catalysts were tested. The results revealed that the acid catalyst played a significant role in this C6 functionalization. The C6 functionalization with a racemic phosphoric acid catalyst produced the product in good yield (entry 10). Lewis acids including scandium trifluoromethanesulfonate and copper trifluoromethanesulfonate could not catalyze this reaction well (entries 11 and 12). *p*-Toluenesulfonic acid monohydrate was selected as the best catalyst from the perspective of cost-effectiveness. Various solvents were investigated (entries 4 and 13–16). We found that chloro solvents are superior to other solvents, and dichloromethane served as the most favorable solvent. To further improve the reactivity, the ratios of **1a**, **2a** and DDQ were examined. The ratio of 1.2 equivalents of **1a** and 1.1 equivalents of DDQ was the best choice for the efficient synthesis of the target compound **3aa** (entry 17).

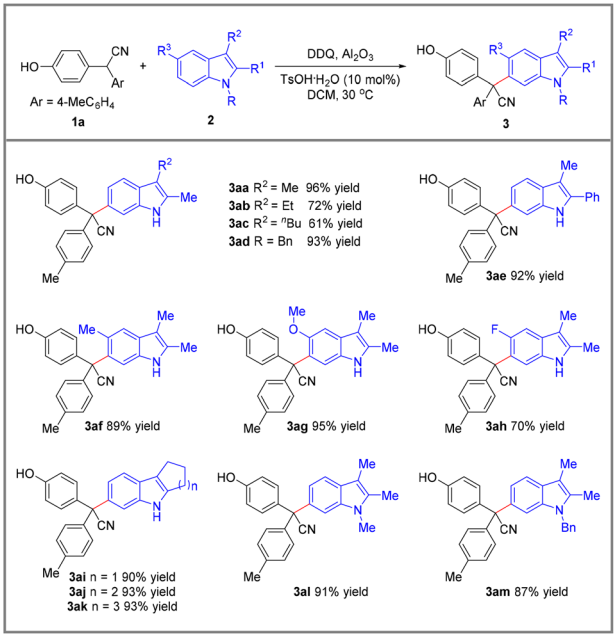
Table 1 Optimization of the reaction conditions



Entry[a]	Additive	[O]	Catalyst	Solvent	Yield[b](%)
1	Silica gel	DDQ	$TsOH{\cdot}H_2O$	DCM	74
2	4 Å MS	DDQ	$TsOH{\cdot}H_2O$	DCM	—
3	Florisil	DDQ	$TsOH{\cdot}H_2O$	DCM	—
4	Al_2O_3	DDQ	$TsOH{\cdot}H_2O$	DCM	85
5	—	DDQ	$TsOH{\cdot}H_2O$	DCM	—
6	Al_2O_3	BQ	$TsOH{\cdot}H_2O$	DCM	—
7	Al_2O_3	MnO_2	$TsOH{\cdot}H_2O$	DCM	—
8	Al_2O_3	DIB	$TsOH{\cdot}H_2O$	DCM	—
9	Al_2O_3	DDQ	$(PhO)_2PO_2H$	DCM	74
10	Al_2O_3	DDQ	PA	DCM	86
11	Al_2O_3	DDQ	$Sc(OTf)_3$	DCM	54
12	Al_2O_3	DDQ	$Cu(OTf)_2$	DCM	14
13	Al_2O_3	DDQ	$TsOH{\cdot}H_2O$	Toluene	52
14	Al_2O_3	DDQ	$TsOH{\cdot}H_2O$	MeCN	16
15	Al_2O_3	DDQ	$TsOH{\cdot}H_2O$	THF	<5
16	Al_2O_3	DDQ	$TsOH{\cdot}H_2O$	DCE	81
17[c]	Al_2O_3	DDQ	$TsOH{\cdot}H_2O$	DCM	89
18[d]	Al_2O_3	DDQ	$TsOH{\cdot}H_2O$	DCM	96

[a] Conditions: **1a** (0.10 mmol), additive (40.0 mg), oxidant (0.10 mmol), solvent (2.0 mL), 3 hours, 30 °C. Then **2a** (0.12 mmol), catalyst (10 mol%), 1 hour. [b] Isolated yield. [c] **1a** (0.12 mmol), **2a** (0.10 mmol), DDQ (0.11 mmol). [d] **1a** (0.24 mmol), **2a** (0.20 mmol), Al_2O_3 (base, 80.0 mg), DDQ (0.22 mmol).

With the optimal conditions in hand, we next set out to explore the scope and generality of this Brønsted acid-catalyzed C6 functionalization of indoles. Initially, the influence of the substituents on indole derivatives **2** was tested (Scheme 2). Different substituents at the C2 or C3 position of the pyrrole ring were well tolerated, affording **3aa–3ae** in moderate to high yields. Meanwhile, introducing methyl (**3af**) or methoxyl (**3ag**) as the C5 substituent on the benzene ring of indole afforded the corresponding products in high yields. The product **3ah** was obtained in 70% yield when the C5 substituent of indole was the electron-withdrawing fluoro group. The ring-fused indoles performed well, affording the desired products (**3ai–**

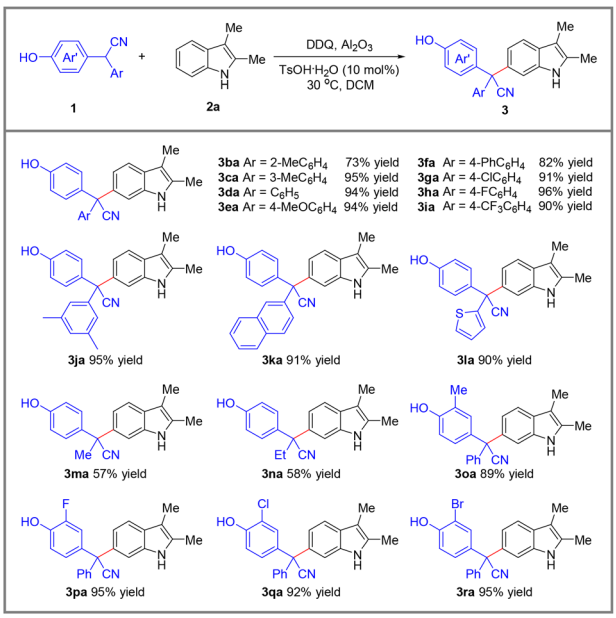


Scheme 2 Substrate scope of 2,3-disubstituted indoles. Reaction conditions: **1a** (0.24 mmol), Al_2O_3 (basic, 80.0 mg), DDQ (0.22 mmol), DCM (2.0 mL), 3 hours. Then **2** (0.20 mmol), $TsOH{\cdot}H_2O$ (10 mol%), 15 minutes–6 hours.

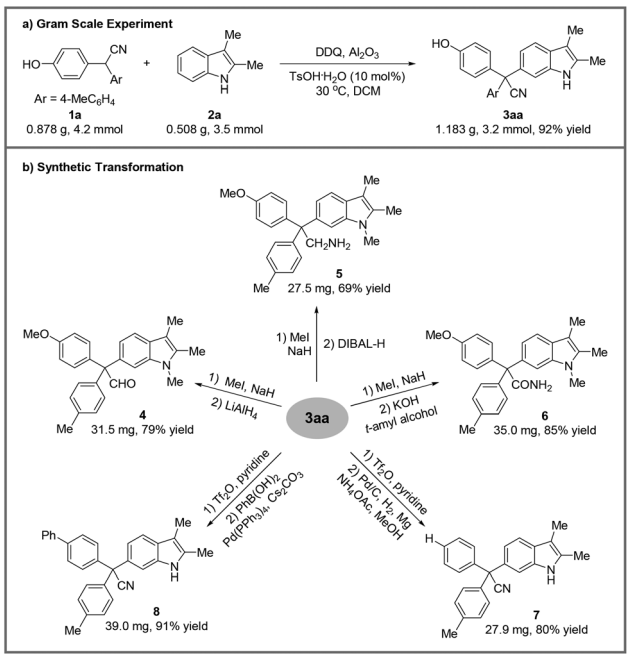
3ak) in favorable yields. Moreover, *N*-protected indoles could also exhibit pleasing results (**3al**, **3am**).

Next, we evaluated the substrate scope of 2,2-diarylacetonitriles. As depicted in Scheme 3, a plethora of 2,2-diarylacetonitriles were suitable reaction partners, giving the desired products in moderate to good yields. The *meta*-methyl substituted 2,2-diarylacetonitrile (**3ca**) was superior to the *ortho*-methyl substituted 2,2-diarylacetonitrile (**3ba**) in view of the yield for this process, which might be caused by steric hindrance. Various electron-donating and electron-withdrawing substituents on the *para*-position of the aryl ring of 2,2-diarylacetonitriles, including 4-methoxy, 4-phenyl, halogen and 4-trifluoromethyl, were acceptable for this protocol. 3,5-Dimethyl phenyl (**1j**) and 2-naphthyl (**1k**) substituted 2,2-diarylacetonitriles underwent the reaction efficiently under the standard conditions. Moreover, the corresponding product **3la** was also isolated in high yield when heteroaryl substituted 2,2-diarylacetonitrile was used. Additionally, alkyl substituted substrates such as 2-(4-hydroxyphenyl)propanenitrile (**1m**) and 2-(4-hydroxyphenyl)-butyronitrile (**1n**) resulted in 57% and 58% yields, respectively. Phenolic moieties bearing electronically varied substituents at the *ortho*-position were well tolerated, affording the desired products in excellent yields (**3oa**–**3ra**). In addition to 2,2-diarylacetonitriles, we also tried *δ*-phenyl and *δ*-trifluoromethyl substituted diarylmethanes. Unfortunately, the reaction failed to provide the target products, which might be caused by steric hindrance and electronic properties.

To demonstrate the practical nature of the present catalytic approach, a gram-scale preparation and further chemical transformations of compound **3aa** were performed (Scheme 4). Under the standard reaction conditions, amplifying the model reaction to a 4.2 mmol scale straightforwardly gave the product **3aa** in 92% yield without a marginal loss of efficiency (Scheme 4a). Furthermore, in light of the fact that nitrile moieties can serve as valuable building blocks in the syntheses of



Scheme 3 Substrate scope of 2,2-diarylacetonitrile. Reaction conditions: **1** (0.24 mmol), Al_2O_3 (basic, 80.0 mg), DDQ (0.22 mmol), DCM (2.0 mL), 2–5 hours. Then **2a** (0.20 mmol), $TsOH{\cdot}H_2O$ (10 mol%), 20 minutes–24 hours.



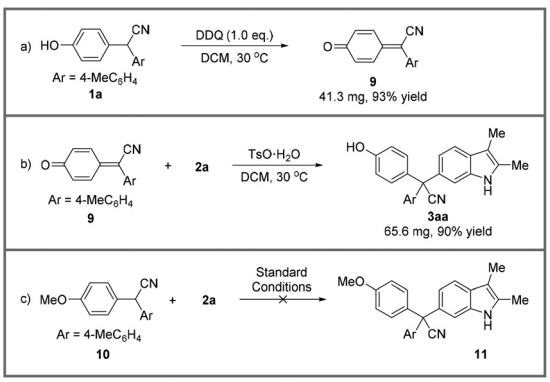
Scheme 4 Gram scale experiment and synthetic transformation.

pharmaceuticals and heterocyclics,[13] transformation experiments were performed on the cyano group (Scheme 4b). Compound **3aa** was methylated with methyl iodide and reduced with lithium aluminum hydride to give the corresponding aldehyde **4**. The methylated **3aa** could undergo reduction in the presence of diisobutylaluminum hydride, giving the corresponding primary amine **5**. Alternatively, for methylated **3aa**, hydrolysis of the cyano-group proceeded smoothly using potassium hydroxide in *tert*-amylalcohol, providing the corresponding amide **6** in 85% yield. Compound **3aa** was treated with trifluoro-methanesulfonic anhydride, followed by Pd/C hydrogenolysis to give the hydroxy group-free product **7**. Palladium-catalyzed cross-coupling reaction of trifluoromethylsulfonylated **3aa** with phenyl boronic acid could provide the Suzuki–Miyaura coupling product **8** with high efficiency.

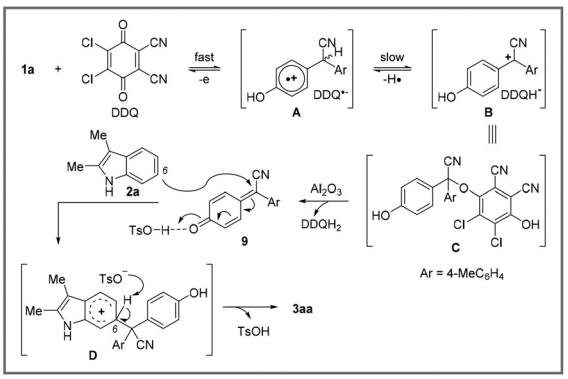
To gain further insights into the mechanism, some control experiments were performed (Scheme 5). The 2,2-diarylacetonitrile **1a** could be oxidized by DDQ, giving the active intermediate *p*-QM **9** in 93% yield (Scheme 5a). Subjecting **9** to the standard reaction conditions without DDQ provided the product **3aa** in comparable yield which was observed in the single-operation process, thus suggesting the formation of *p*-QM intermediate **9** (Scheme 5b). Product **11** was not detected when methyl-protected substrate **10** was used under the standard conditions (Scheme 5c), which indicated that the presence of a free phenolic hydroxyl group in 2,2-diarylacetonitrile is crucial for the formation of the key *p*-QM intermediate.

Based on the above results and literature reports,[10] a plausible mechanism is proposed (Scheme 6). 2,2-Diarylacetonitrile **1a** is reversibly oxidized by DDQ to provide intermediate **B**. Basic Al_2O_3 might be able to adsorb the byproduct $DDQH_2$, which is generated during the oxidation process, and promote the conversion of intermediate **B** to the stable *δ,δ*-disubstituted *p*-QM **9**. Subsequently, Brønsted acid-catalyzed C6 functionalization of 2,3-dimethylindole with *δ,δ*-disubstituted *p*-QM **9** would take place, giving the desired product **3aa**.

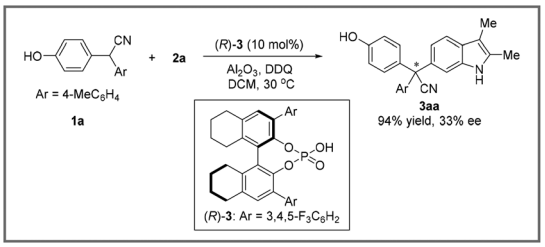
Finally, we also explored chiral phosphoric acid-catalyzed C6 functionalization of 2,3-disubstituted indoles with *δ,δ*-disubstituted *p*-QMs from 2,2-diarylacetonitrile. The desired chiral product could be obtained in 94% yield albeit in moderate 33% ee (Scheme 7, for details, see the ESI†). This could be ascribed to remote activation which might not be beneficial for the control of enantioselectivity.



Scheme 5 Control experiments.



Scheme 6 Plausible mechanism.



Scheme 7 Preliminary investigation on the catalytic asymmetric version.

Conclusions

In summary, we successfully developed Brønsted acid-catalyzed C6 functionalization of 2,3-disubstituted indoles with 2,2-diarylacetonitriles for efficient construction of cyano-substituted all-carbon quaternary centers. This process features excellent yields, broad substrate scope and mild reaction conditions. Furthermore, the cyano-substituted products could be conveniently transformed to other valuable compounds including aldehydes, primary amines and amides. Control experiments suggested that the reaction involves C–H oxidation of 2,2-diarylacetonitriles to *in situ* generated *δ,δ*-disubstituted *p*-QM intermediates. The asymmetric C6 functionalization of 2,3-disubstituted indoles with 2,2-diarylacetonitroles has encountered great challenges possibly owing to remote activation. Further efforts are currently underway toward the asymmetric version of this reaction.

Conflicts of interest

The authors declare no competing financial interest.

Acknowledgements

Financial support from the National Natural Science Foundation of China (21871255) is acknowledged.

References

1 (*a*) W. Gul and M. T. Hamann, Indole Alkaloid Marine Natural Products: An Established Source of Cancer Drug Leads with Considerable Promise for the Control of Parasitic, Neurological and Other Diseases, *Life Sci.*, 2005, **78**, 442–453; (*b*) A. J. Kochanowska-Karamyan and M. T. Hamann, Marine Indole Alkaloids: Potential New Drug Leads for the Control of Depression and Anxiety, *Chem. Rev.*, 2010, **110**, 4489–4497; (*c*) D. F. Taber and P. K. Tirunahari, Indole Synthesis: a Review and Proposed Classification, *Tetrahedron*, 2011, **67**, 7195–7210; (*d*) M. Ishikura, T. Abe, T. Choshi and S. Hibino, Simple Indole Alkaloids and Those with a Non-Rearranged Monoterpenoid Unit, *Nat. Prod. Rep.*, 2013, **30**, 694–752; (*e*) R. D. Taylor, M. MacCoss and A. D. G. Lawson, Rings in Drugs, *J. Med. Chem.*, 2014, **57**, 5845–5859; (*f*) M.-Z. Zhang, Q. Chen and G.-F. Yang, A Review on Recent Developments of Indole-Containing Antiviral Agents, *Eur. J. Med. Chem.*, 2015, **89**, 421–441.

2 For literature on indole functionalization, see: (*a*) S. Cacchi and G. Fabrizi, Synthesis and Functionalization of Indoles Through Palladium-Catalyzed Reactions, *Chem. Rev.*, 2005, **105**, 2873–2920; (*b*) M. Bandini and A. Eichholzer, Catalytic Functionalization of Indoles in a New Dimension, *Angew. Chem., Int. Ed.*, 2009, **48**, 9608–9644; (*c*) G. Bartoli, G. Bencivenni and R. Dalpozzo, Organocatalytic Strategies for the Asymmetric Functionalization of Indoles, *Chem. Soc. Rev.*, 2010, **39**, 4449–4465; (*d*) A. H. Sandtorv, Transition Metal-Catalyzed C-H Activation of Indoles, *Adv. Synth. Catal.*, 2015, **357**, 2403–2435; (*e*) J. A. Leitch, Y. Bhonoah and C. G. Frost, Beyond C2 and C3: Transition-Metal-Catalyzed C-H Functionalization of Indole, *ACS Catal.*, 2017, **7**, 5618–5627; (*f*) Y. Yang and Z. Shi, Regioselective Direct Arylation of Indoles on the Benzenoid Moiety, *Chem. Commun.*, 2018, **54**, 1676–1685; (*g*) T. Abe, S. Aoyama, M. Ohmura, M. Taniguchi and K. Yamada, Revisiting Furodiindolines: One-Pot Synthesis of Furodiindolines Using Indole 2,3-Epoxide Surrogates and Their Synthetic Applications, *Org. Lett.*, 2019, **21**, 3367–3371; (*h*) S. Liu, F. Zhao, X. Chen, G.-J. Deng and H. Huang, Aerobic Oxidative Functionalization of Indoles, *Adv. Synth. Catal.*, 2020, **362**, 3795–3823; (*i*) K. Urbina, D. Tresp, K. Sipps and K. Szostak, Recent Advances in Metal-Catalyzed Functionalization of Indoles, *Adv. Synth. Catal.*, 2021, **363**, 2723–2739; (*j*) P. Bhattacharjee and U. Bora, Organocatalytic Dimensions to the C-H Functionalization of the Carbocyclic Core in Indoles: a Review Update, *Org. Chem. Front.*, 2021, **8**, 2343–2365.

3 For C6 functionalization of indoles to form tertiary carbon centers, see: (*a*) H. Liu, C. Zheng and S.-L. You, Catalytic C6 Functionalization of 2,3-Disubstituted Indoles by Scandium Triflate, *J. Org. Chem.*, 2014, **79**, 1047–1054; (*b*) Q. Wu, G.-L. Li, S. Yang, X.-Q. Shi, T.-A. Huang, X.-H. Du and Y. Chen, A Chemo- and Regioselective C6-Functionalization of 2,3-Disubstituted Indoles: Highly Efficient Synthesis of Diarylindol-6-ylmethanes, *Org. Biomol. Chem.*, 2019, **17**, 3462–3470; (*c*) J. Yan, Z. Zhang, M. Chen, Z. Lin and J. Sun, A Study of the Reactivity of (*Aza*-)Quinone Methides in Selective C6-Alkylations of Indoles, *ChemCatChem*, 2020, **12**, 5053–5057; (*d*) W.-J. Huang, Y.-Y. Ma, L.-X. Liu, B. Wu, G.-F. Jiang and Y.-G. Zhou, Chiral Phosphoric Acid-Catalyzed C6 Functionalization of 2,3-Disubstituted Indoles for Synthesis of Hetero-triarylmethanes, *Org. Lett.*, 2021, **23**, 2393–2398; (*e*) L. Kong, X. Han, H. Chen, H. Sun, Y. Lan and X. Li, Rhodium(II)-Catalyzed Regioselective Remote C-H Alkylation of Protic Indoles, *ACS Catal.*, 2021, **11**, 4929–4935; (*f*) Y.-Y. Zhang, L. Li, X.-Z. Zhang and J.-B. Peng, Brønsted Acid Catalyzed Remote C6 Functionalization of 2,3-Disubstituted Indoles with β,γ-Unsaturated α-Ketoester, *Front. Chem.*, DOI: **10.3389/fchem.2022.992398**.

4 For C6 functionalization of indoles to form quaternary carbon centers, see: (*a*) L.-J. Zhou, Y.-C. Zhang, J.-J. Zhao, F. Shi and S.-J. Tu, Organocatalytic Arylation of 3-Indolylmethanols via Chemo- and Regiospecific C6-Functionalization of Indoles, *J. Org. Chem.*, 2014, **79**, 10390–10398; (*b*) Y. Ling, D. An, Y. Zhou and W. Rao, Ga$(OTf)_3$-C atalyzed Temperature-Controlled Regioselective Friedel-Crafts Alkylation of Trifluoromethylated 3-Indolylmethanols with 2-Substituted Indoles: Divergent Synthesis of Trifluoromethylated Unsymmetrical 3,3′-and 3,6′-Bis(indolyl)methanes, *Org. Lett.*, 2019, **21**, 3396–3401; (*c*) J. Zhou, G.-D. Zhu, L. Wang, F.-X. Tan, W. Jiang, Z.-G. Ma, J.-C. Kang, S.-H. Hou and S.-Y. Zhang, Remote C6-Enantioselective C-H Functionalization of 2,3-Disubstituted Indoles through the Dual H-Bonds and π–π Interaction Strategy Enabled by CPAs, *Org. Lett.*, 2019, **21**, 8662–8666.

5 (*a*) T. Ling and F. Rivas, All-Carbon Quaternary Centers in Natural Products and Medicinal Chemistry: Recent Advances, *Tetrahedron*, 2016, **72**, 6729–6777; (*b*) D. J. Newman and G. M. Cragg, Natural Products as Sources of New Drugs from 1981 to 2014, *J. Nat. Prod.*, 2016, **79**, 629–661; (*c*) W. Chen and H. Zhang, Asymmetric Construction of All-Carbon Quaternary Stereocenters in the Total Synthesis of Natural Products, *Sci. China: Chem.*, 2016, **59**, 1065–1078; (*d*) Z. Xin, H. Wang, H. He and S. Gao, Recent Advances in the Total Synthesis of Natural Products Bearing the Contiguous All-Carbon Quaternary Stereocenters, *Tetrahedron Lett.*, 2021, **71**, 153029.

6 For reviews on forming quaternary carbon centers, see: (*a*) J. Christoffers and A. Mann, Enantioselective Construction of Quaternary Stereocenters, *Angew. Chem.,*

Int. Ed., 2001, **40**, 4024–4591; (*b*) I. Denissova and L. Barriault, Stereoselective Formation of Quaternary Carbon Centers and Related Functions, *Tetrahedron*, 2003, **59**, 10105–10146; (*c*) P. G. Cozzi, R. Hilgraf and N. Zimmermann, Enantioselective Catalytic Formation of Quaternary Stereogenic Centers, *Eur. J. Org. Chem.*, 2007, 5969–5994; (*d*) M. Bella and T. Casperi, Organocatalytic Formation of Quaternary Stereocenters, *Synthesis*, 2009, 1583–1614; (*e*) A. C. B. Burtoloso, Catalytic Enantioselective α-Arylation of Carbonyl Compounds, *Synlett*, 2009, 320–327; (*f*) C. Hawner and A. Alexakis, Metal-Catalyzed Asymmetric Conjugate Addition Reaction: Formation of Quaternary Stereocenters, *Chem. Commun.*, 2010, **46**, 7295–7306; (*g*) J. P. Das and I. Marek, Enantioselective Synthesis of All-Carbon Quaternary Stereogenic Centers in Acyclic Systems, *Chem. Commun.*, 2011, **47**, 4593–4623.

7 For reviews on forming all-carbon quaternary carbon centers by *p*-QMs, see: (*a*) L. Wang, N. Wang, Y. Qi, S. Sun, X. Liu, W. Li and L. Lei, Synthesis of Sterically Hindered α-Aminonitriles through 1,6-*Aza*-conjugate Addition of Anilines to δ-Cyano Substituted *para*-Quinone Methides, *Chin. J. Org. Chem.*, 2020, **40**, 3934–3943; (*b*) Y. Qi, F. Zhang, L. Wang, A. Feng, R. Zhu, S. Sun, W. Li and L. Liu, δ-Cyano Substituted *para*-Quinone Methides Enable Access to Unsymmetric Tri- and Tetraaryl-methanes Containing All-Carbon Quaternary Stereocenters, *Org. Biomol. Chem.*, 2020, **18**, 3522–3526; (*c*) Y. Zhu, H. Wang, G. Wang, Z. Wang, Z. Liu and L. Liu, Enantioselective Construction of Single and Vicinal All-Carbon Quaternary Stereocenters through Ion-Pair-Catalyzed 1,6-Conjugate Addition, *Org. Lett.*, 2021, **23**, 7248–7253.

8 (*a*) Z. Wang, Y. F. Wong and J. Sun, Catalytic Asymmetric 1,6-Conjugate Additionof *para*-Quinone Methides Formationof All-Carbon Quaternary Stereocenters, *Angew. Chem., Int. Ed.*, 2015, **54**, 13711–13714; (*b*) X. Li, M. Duan, Z. Deng, Q. Shao, M. Chen, G. Zhu, K. N. Houk and J. Sun, Catalytic Enantioselective Synthesis of Chiral Tetraarylmethanes, *Nat. Catal.*, 2020, **3**, 1010–1019.

9 (*a*) M. Chen and J. Sun, How Understanding the Role of an Additive Can Lead to an Improved Synthetic Protocol without an Additive: Organocatalytic Synthesis of Chiral Diarylmethyl Alkynes, *Angew. Chem., Int. Ed.*, 2017, **56**, 11966–11970; (*b*) M. Chen, D. Qian and J. Sun, Organocatalytic Enantiocon-vergent Synthesis of Tetrasubstituted Allenes via, Asymmetric 1,8-Addition to aza-para-Quinone Methides, *Org. Lett.*, 2019, **21**, 8127–8131; (*c*) L. Zhang, Y. Han, A. Huang, P. Zhang, P. Li and W. Li, Organocatalytic Remote Stereocontrolled 1,8-Additions of Thiazolones to Propargylic *Aza-p*-Quinone Methides, *Org. Lett.*, 2019, **21**, 7415–7419; (*d*) Z. Han, Y. Zang, C. Liu, W. Guo, H. Huang and J. Sun, Enantioselective Synthesis of Triarylmethanes *via*, Organocatalytic Transfer Hydrogenation of para-Quinone Methides, *Chem. Commun.*, 2022, **58**, 7128–7131.

10 (*a*) Z. Wang, Y. Zhu, X. Pan, G. Wang and L. Liu, Synthesis of Chiral Triarylmethanes Bearing All-Carbon Quaternary Stereocenters Catalytic Asymmetric Oxidative Cross-Coupling of 2,2-Diaryl-acetonitriles and (Hetero)arenes, *Angew. Chem., Int. Ed.*, 2020, **59**, 3053–3057; (*b*) X. Pan, Z. Wang, L. Kan, Y. Mao, Y. Zhua and L. Liu, Cross-Dehydrogenative Coupling Enables Enantioselective Access to CF_3-Substituted All Carbon Quaternary Stereocenters, *Chem. Sci.*, 2020, **11**, 2414–2419; (*c*) X. Liu, C. Zhao, R. Zhu and L. Liu, Construction of Vicinal Quaternary Carbon Stereocenters Through Diastereo- and Enantioselective Oxidative 1,6-Conjugate Addition, *Angew. Chem., Int. Ed.*, 2021, **60**, 18499–18503; (*d*) Z. Li, Y. Li, X. Li, M. Wu, M.-L. He and J. Sun, Organocatalytic Asymmetric Formal Oxidative Coupling for the Construction of All-Aryl Quaternary Stereocenters, *Chem. Sci.*, 2021, **12**, 11793–11798.

11 (*a*) T. Pan, P. Shi, B. Chen, D.-G. Zhou, Y.-L. Zeng, W.-D. Chu, L. He, Q.-Z. Liu and C.-A. Fan, CuH-Catalyzed Asymmetric 1,6-Conjugate Reduction of *p*-Quinone Methides: Enantioselective Synthesis of Triarylmethanes and 1,1,2-Triarylethanes, *Org. Lett.*, 2019, **21**, 6397–6402; (*b*) Y. Mao, Z. Wang, G. Wang, R. Zhao, L. Kan, X. Pan and L. Liu, Redox Deracemization of Tertiary Stereocenters Adjacent to an Electron-Withdrawing Group, *ACS Catal.*, 2020, **10**, 7785–7791.

12 (*a*) X.-W. Wang, W.-J. Huang, H. Wang, B. Wu and Y.-G. Zhou, Chiral-Phosphoric-Acid-Catalyzed C6-Selective Pictet-Spengler Reactions for Construction of Polycyclic Indoles Containing Spiro Quaternary Stereocenters, *Org. Lett.*, 2022, **24**, 1727–1731; (*b*) W.-J. Huang, Z.-P. Chen, L.-X. Liu, Y.-G. Zhou, B. Wu and G.-F. Jiang, A Facile Synthesis of Pyrrolo[2,3-*j*]phenanthridines *via* Thecascade Reaction of Indoleanilines and Aldehydes, *J. Heterocycl. Chem.*, 2022, **59**, 1116–1122.

13 (*a*) K. Friedrich and K. Wallenfels, *The Chemistry of the Cyano Group*, Wiley-Interscience, New York, 1970; (*b*) A. J. Fatiadi, *Preparation and synthetic applications of cyano compounds*, John Wiley & Sons Ltd, 1983, 2, 1057–1303; (*c*) V. Y. Kukushkin and A. J. L. Pombeiro, Additions to Metal-Activated Organonitriles, *Chem. Rev.*, 2002, **102**, 1771–1802; (*d*) N. Otto and T. Opatz, Heterocycles from α-Aminonitriles, *Chem. – Eur. J.*, 2014, **20**, 13064–13077; (*e*) Y. Gao, Z. X. Iao, L. Liu and P. Huang, Direct Reductive Cyanation of A 2-Pyrrolidinone Chiral Building Block Bearing An Unprotected Hydroxyl Group: A Stereoselective Synthesis of *N*-Methyl-2-*epi*-bulgecinine, *Chin. J. Org. Chem.*, 2017, **37**, 1189–1197.

