

Synthetic Methods

Synthesis of Chiral Triarylmethanes Bearing All-Carbon Quaternary Stereocenters: Catalytic Asymmetric Oxidative Cross-Coupling of 2,2-Diarylacetonitriles and (Hetero)arenes

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Abstract: A direct and enantioselective oxidative cross-coupling of racemic 2,2-diarylacetonitriles with electron-rich (hetero)arenes has been described, which allows for efficient construction of triarylmethanes bearing all-carbon quaternary stereocenters with excellent chemo- and enantioselectivity. The reaction has an excellent functional group tolerance, and exhibits a broad scope with respect to both 2,2-diarylacetonitrile and (hetero)arene components. The rich chemistry of the cyano group allows for facile synthesis of other valuable chiral triarylmethanes bearing all-carbon quaternary centers that are otherwise difficult to access.

Triarylmethanes are important structural motifs in medicinal chemistry, materials science, and organic synthesis.^[1] However, catalytic asymmetric synthesis of these molecules has been a longstanding challenge owing to the lack of sufficient steric difference between the aryl rings.^[2] Since the pioneering work by Yu and co-workers,^[3] a couple of delicate strategies for enantioselective preparation of triarylmethanes bearing tertiary stereocenters have been disclosed.^[4-6] However, asymmetric construction of triarylmethanes containing allcarbon quaternary stereocenters remains underexplored, presumably because of the inherently unfavorable steric hindrance.^[7] In this context, Sun developed an elegant enantioselective arylation of 1,1-diaryl tertiary alcohol or 1,1-diarylalkene moieties with heteroarenes, in which prefunctionlization of the substrate is indispensable (Scheme 1 A).^[8]

Nitriles are common structural features spread across bioactive natural products and synthetic pharmaceuticals. In addition, nitrile moieties can also serve as valuable building blocks because of their robust transformable properties.^[9] Existing studies on enantioselective construction of cyanosubstituted all-carbon quaternary stereocenters predominantly adopted α -nitrile carbanion chemistry involving the cyano-bearing component as a nucleophile (Scheme 1 B).^[10,11] In contrast, asymmetric oxidative coupling of two different

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A) Asymmetric construction of triaryl-substituted all-carbon quaternary center (Ref. [8])



· prefunctionalized alcohol or alkene as substrate

B) Asymmetric construction of cyano-substituted all-carbon quaternary center (Ref. [10])

$$\begin{array}{c} \mathsf{CN} \\ \mathsf{R} \xrightarrow{\mathsf{CN}} \mathsf{Ar} \end{array} \xrightarrow{\mathsf{base}} \begin{bmatrix} \mathsf{CN} \\ \mathsf{R} \xrightarrow{\mathsf{L}} \mathsf{Ar} \end{bmatrix} \xrightarrow{\mathsf{E}^{+}} \overset{\mathsf{CN}}{\mathsf{R} \xrightarrow{\mathsf{L}} \mathsf{E}} \\ \mathsf{R} \xrightarrow{\mathsf{L}} \mathsf{E} \\ \mathsf{Ar} \end{array} \overset{\mathsf{CN}}{\underset{\mathsf{Ar}}{\overset{\mathsf{CN}}{\overset{\mathsf{CN}}}} = \mathsf{electrophile} \end{array}$$

• cyano-bearing component as nucleophile via α-nirtile anion

C) Oxidative coupling for triaryl-cyano substituted all-carbon quaternary center (this work)

 $\begin{array}{c} CN\\ Ar^{1} \stackrel{f_{n}}{\downarrow_{n+1}} + H - Ar^{3} \end{array} \xrightarrow{ \begin{array}{c} \text{asymmetric} \\ \text{oxidative coupling} \\ Ar^{1} \stackrel{f_{n+1}}{\downarrow_{n+2}} \end{array} Ar^{1} \stackrel{f_{n+1}}{\downarrow_{n+2}} Ar^{3} \end{array}$

no prefunctionalization of substrates

• umpolung reactivity of cyano-bearing component as electrophile

versatile chemical reactivities of CN for further diversification

Scheme 1. Overview of enantioselective construction of triaryl-substituted and cyano-substituted all-carbon quaternary centers.

C-H components for quaternary all-carbon center formation has remained understudied.^[12-14] Herein, we report a direct and asymmetric oxidative cross-coupling of racemic 2,2diarylacetonitriles with a range of electron-rich (hetero)arenes for efficient construction of triaryl-cyano-substituted allcarbon quaternary stereocenters (Scheme 1 C). Further manipulation of the nitrile moiety affords a platform to access other valuable chiral triarylmethanes bearing allcarbon quaternary centers that are otherwise difficult to access.

Asymmetric cross-coupling of the racemic 2,2-diarylacetonitrile **1a** with the indole **2a** was initially selected as a model reaction for optimization (Table 1). Common oxidants for benzylic C–H bond cleavage, such as Ag₂O, PhI(OAc)₂, and MnO₂, proved to be futile (entry 1). When DDQ was used as an oxidant, expected product **3a** was isolated in 9% yield with 30% *ee*, though the majority of **1a** was recovered (entry 2). The low conversion might be ascribed to two factors: 1) DDQ competitively reacts with **1a** and **2a**; 2) oxidation of **1a** with DDQ might be a reversible process. Next, a range of additives were examined, and aluminum oxide (activated, basic) was identified to be the best candidate, providing **3a** in 77% yield with 58% *ee* (entries 3–6). Chiral phosphoric acid catalysts were extensively screened,^[15] and the C₂-symmetric imidodi-

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93% ee

99% ee 93% ee 98% ee

98% ee

95% ee

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[a] Reaction conditions: To 1a (0.1 mmol) in CH₂Cl₂ (3.0 mL) was successively added DDQ (0.1 mmol), additive (40 mg), C (3 mol%), and 2a (0.12 mmol) at -78 °C for 12 h. [b] Yield of isolated product. [c] Determined by chiral-phase HPLC analysis. [d] Ag_2O , PhI(OAc)₂, and MnO_2 as oxidant. [e] Dichloroethane as solvent at -40 °C. [f] Diethyl ether as solvent. [g] Acetone as solvent. n.d. = not determined. M.S. = molecular

phosphoric acid C10 furnished highest level of enantiofacial discrimination (entries 6-15).^[15d] Optimization of the solvents identified CH_2Cl_2 to be optimal (entries 16–18).

With the optimized reaction conditions in hand, the scope of the enantioselective oxidative cross-coupling of racemic 2,2-diarylacetonitriles (1) with 2a was explored (Scheme 2). In general, the diversely functionalized 2,2-diarylacetonitriles 1a-l and 1o-s, bearing a wide range of electronically varied aryl groups with different substitution patterns, were compatible with the reaction, providing the respective triarylmethanes 3a-31 and 3o-3s in 72-93% yields with up to 99% ee.^[16] Potential oxidation of ortho-positions of phenols to 1,2benzoquinones was not observed. Moreover, the polyarene naphthalene substituted 1m and thiophene substituted 1n proved to be suitable coupling partners.

The substituent effect of indoles was next evaluated (Scheme 3). A broad range of indoles, bearing either electrondonating or electron-withdrawing groups at different positions (C4, C5, C6, and C7) on the aryl rings, participated in the oxidative cross-coupling with 1a smoothly, affording the



72% 84% ee

Scheme 2. Scope with respect to 2,2-diarylacetonitriles.

Scheme 3. Scope with respect to the indole components. [a] C3 (3 mol%) as catalyst.

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75%, 90% ee

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r r These are not the final page numbers! Besides indole moieties, other (hetero)arenes were also evaluated (Scheme 4). Electron-rich arenes such as the 1naphthol **5b** and phenol **5c** as well as 2-substituted pyrrole **5a** were identified to be competent coupling partners.^[17,18] Aside



Scheme 4. Other (hetero)arene components. [a] **C2** (3 mol%) used. [b] **C4** (3 mol%) used. [c] **C5** (3 mol%) used.

from 2,2-diarylacetonitriles, the 2,2-diarylacetate **7** also proved to be suitable electrophilic component, as demonstrated by the formation of the triaryl-substituted acetate **8** in 53 % yield with 85 % *ee* (Scheme 5). While the reaction scope was not exclusively explored, these results provide a proof-of-concept for the modularity of the method for asymmetric access to diversely functionalized triaryl-substituted all-carbon quaternary stereocenters.



Scheme 5. Oxidative cross-coupling with 2,2-diarylacetate.

The synthetic applications of the method were next illustrated (Scheme 6). The removable/convertible feature of the phenolic hydroxy group was verified. The hydroxy moiety was removed through triflation followed by Pdcatalyzed hydrogenation, as demonstrated by the conversion of 3c into 9 in 90% yield (Scheme 6a). In addition, the hydroxy group in **3a** can also undergo triflation followed by Pd-catalyzed cross-coupling reaction, furnishing the biaryl 10 in high efficiency (Scheme 6b). The nitrile group can be converted into an array of valuable functionality. For example, nitriles can be reduced by DIBAL-H to aldehydes, as demonstrated by the transformation of 3a into 11 in good yield and with complete retention of stereochemistry (Scheme 6c). Alternatively, hydrolysis of the nitrile proceeded smoothly using tert-amyl alcohol under basic conditions, yielding the corresponding amide 12 in 92% ee (Scheme 6d). Notably, no obvious enantiopurity erosion has been observed in these transformations, thus demonstrating the reliability of the method in practical preparation of diversely functional-



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Scheme 6. Transformations of cross-coupling products.

ized chiral triarylmethanes bearing all-carbon quaternary centers.

A series of control experiments were conducted to gain further insights into the mechanism (Scheme 7). The racemic 2,2-diarylacetonitrile **1a** was oxidized by DDQ, giving the δ -CN-δ-phenyl-substituted p-quinone methide (QM) 13 in 90% yield along with DDQH₂ (2,3-dichloro-5,6-dicyanohydroquinone; Scheme 7 a). Subjecting 13 to standard oxidative crosscoupling conditions without DDQ provided 3a with comparable ee value to that observed in the single-operation process, thus indicating the intermediacy of p-QM 13 (Scheme 7b). The asymmetric oxidative coupling was then performed stepwise to understand the reaction details (Scheme 7 c). Once the oxidation of **1a** by DDQ was complete, as monitored by TLC analysis, C10 and 2a were added to the reaction mixture. Surprisingly, 3a was only isolated in 6% yield, and 1a was recovered in 86% yield, indicating the reversibility of the oxidation process. No reaction was observed for 13 and $DDQH_2$ (Scheme 7 d). No reaction was observed for the methyl-protected substrate 14, implying the importance of the hydroxy moiety in p-QM intermediate generation (Scheme 7e). Based on the above results, a plausible mechanism is suggested (Scheme 7 f). 1a is oxidized by DDQ in a reversible process, furnishing intermediate 17, which might be stable in reaction system. Al₂O₃ might promote irreversible collapse of 17, affording DDQH₂ along with p-QM 13 for subsequent enantioselective 1,6-conjugate addition, though the origin of this curious but useful effect has not been clear.^[19] Asymmetric 1,6-conjugate addition was not influenced by stoichiometric DDQH₂ (Scheme 7g). The Nmethyl-protected indole 18 was found to be a less competent coupling partner than 2a, thus suggesting the importance of

(a)

(f)



Scheme 7. Mechanistic studies.

the N-H moiety, presumably as a hydrogen-bond donor (Scheme 7h). Based on the above analysis, a plausible tight transition state is proposed, in which chiral phosphoric acid acts as a bifunctional role for activation of both coupling partners and remote stereocontrol by hydrogen bonding (Scheme 7 i). The proposed pseudo-intramolecular mode is in agreement with the observed excellent remote stereocontrol.

In summary, a direct and enantioselective oxidative cross-coupling of racemic 2,2diarylacetonitriles with (hetero)arenes has been described, allowing efficient construc-

(b) tion of triarylmethanes bearing all-carbon quaternary stereocenters with excellent chemo- and enantioselectivities. The
 (c) single-operation reaction has an excellent

- functional-group tolerance and exhibits a broad scope with respect to both 2,2-
- (d) a broad scope with respect to both 2,2diarylacetonitrile and (hetero)arene components. The rich chemistry of the cyano group allows facile synthesis of other valuable chiral triarylmethanes bearing all-carbon
- (e) quaternary centers that are otherwise difficult to access.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric catalysis · nitrile · oxidative C-H functionalization ·

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