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Cu/Pd dual catalyzed stereoselective construction of vicinal tri- and tetrasubstituted stereocenters connected to chiral α-arylacetonitriles

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Herein, we report an optimized Pd/Cu bimetallic catalyst that facilitates the stereoselective allylic alkylation of secondary and tertiary nitriles under mild conditions. This method affords homoallylic nitriles with adjacent tri- and tetrasubstituted stereocenters. Using both racemic and enantioselective catalysts, the system exhibits high regio- and enantioselectivity (ee up to 91%). Mechanistic studies and DFT calculations highlight the key synergistic roles of Pd and Cu in controlling both reactivity and enantioselectivity.

Introduction

Recent research has highlighted the critical importance of the three-dimensional structure of bioactive molecules, and many drugs containing a chiral quaternary center are derived from natural products (see Fig. 1(A)).[1] However, the synthesis of structures with tetrasubstituted stereocenters remains a major challenge.[2] In recent studies, α-cyanocarbanionic metal complexes have emerged as promising nucleophilic intermediates, valuable for their high reactivity and the versatility in nitrile functionalization.[3] However, the stereoselective functionalization of chiral metalated nitriles is hindered by racemization issues. Unique among these are *N*-metalated ketenimines (*N*-MKI), which, due to their axial chirality, act as effective α,α-disubstituted nucleophiles that facilitate the formation of highly congested stereocenters. Prominent contributions from Denmark,[4] List,[5] Leighton,[6] Feng[7] and Nakamura[8] have established methods for generating single stereocenters *via* *N*-MKI reactions with electrophiles, leading to chiral nitrile derivatives. Additionally, studies by Waser[9] and Agbossou-Niedercorn[10] have leveraged both *N*- and *C*-metalated forms of α-cyanocarbanion to produce chiral nitriles with high enantiomeric excesses through intra- or intermolecular processes. Despite progress, the asymmetric synthesis of vicinal stereocenters using chiral metalated nitriles remains largely unexplored.

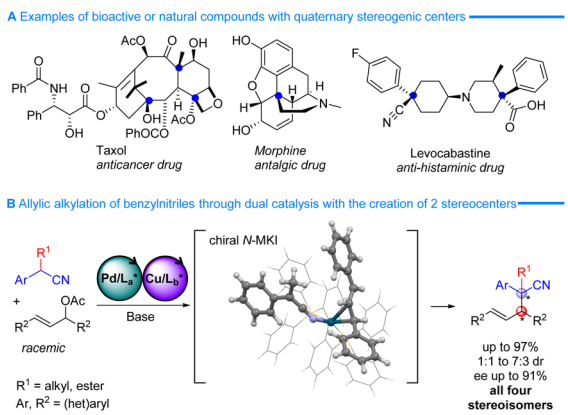

Fig. 1 Asymmetric allylic alkylation of racemic benzylnitriles.

To date, only Leighton[6] and Shibasaki[11] have achieved enantioselective functionalization of racemic nitriles, *via* imine intermediates, yielding chiral aminonitriles. This area holds substantial promise for advancing stereoselective synthesis. Consequently, the development of widely applicable methods for the racemic or enantioselective synthesis of α-alkyl-α-arylacetonitriles from accessible precursors remains a significant unmet challenge. Recently, great strides in transition metal-catalyzed coupling reactions have paved the way for the catalytic construction of enantiopure molecules, particularly through synergistic dual catalysis and its asymmetric variants.[12] During such a process, redox compatibility between the two metal catalysts and balanced kinetics between the two catalytic cycles, avoiding premature termination or unwanted side reactions, play a key role. Among dual-transition metal systems, palladium-based catalysts stand out for their exceptional

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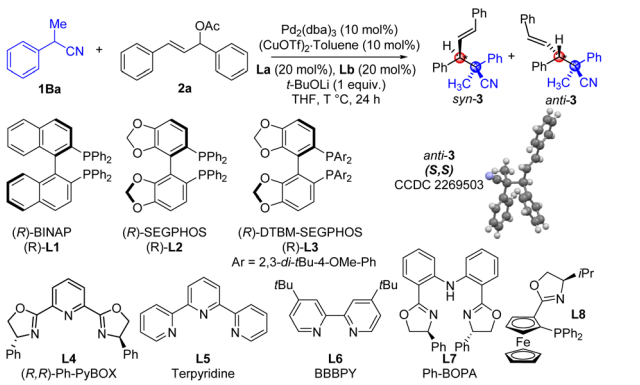
compatibility, especially with copper, which effectively activates nucleophiles in cooperative catalysis.[12b] This combination has enabled groundbreaking reactions, including C(sp^3)–C(sp^2) couplings involving chiral enolate or enamine intermediates. These reactions successfully form adjacent tertiary or quaternary stereocenters, a milestone achieved by multiple research groups.[12d,13] However, successful C(sp^3)–C(sp^3) couplings remain rare, with only one reported case involving a tertiary C(sp^3) nitrile and a secondary C(sp^3) substrate *via* Rh/Pd dual catalysis in asymmetric allylic alkylation.[14] While this reaction exhibits exceptional stereochemical precision, achieving up to 99% enantiomeric excess, it generates only a single stereogenic center. An outstanding challenge in this field is the enantioselective construction of vicinal stereocenters from racemic nitriles, as no methods have been developed despite the broad potential of chiral metalated nitriles. Addressing this gap, our team has achieved the first enantioselective C–C coupling from racemic benzyl nitrile substrates. Using a Pd/Cu dual-catalyzed allylic alkylation of tertiary nitriles, we have established an efficient approach to construct adjacent tertiary and quaternary stereocenters. This innovative method not only enriches the stereoselective synthesis toolkit, but also unlocks new possibilities for the construction of original structurally diverse homoallylic nitriles (Fig. 1(B)).

Results and discussion

To evaluate the viability of allylic alkylation, we used racemic α-methyl-α-phenylacetonitrile **1Ba** and 1,3-diphenylallyl acetate **2a** as model substrates (Table 1). The symmetrical nature of **2a** facilitated regioselectivity during the η^3-palladation phase. Our first priority was to identify an optimal combination of catalyst, ligand, base, solvent, and temperature.[15] We first explored the racemic synthesis of α,α′-dialkyl-α-arylacetonitrile **3**, using *rac*-BINAP as a bidentate phosphine ligand, $Pd_2(dba)_3$ and $(CuOTf)_2$·toluene as catalysts, and *t*-BuOLi as the base. The reaction in THF at 50 °C afforded the desired original quaternary-center-containing product **3** (entry 1) in 97% yield as a 1 : 1 diastereomeric mixture. Notably, no diastereomeric excess was detected.[16] It is worth noting that gram-scale synthesis (7.62 mmol of **1Ba**) maintained efficiency (82% yield). Control experiments underscored the indispensable role of palladium and copper. Omitting palladium, yielded no product (entry 2), while copper absence led to a reduced 41% yield (entry 3). Even at −20 °C (entry 4), the reaction was efficient (96%), suggesting promising conditions for enantioselective investigations. Various bases were also tested, but no improvements were noted (see SI, Table S2). Encouraged by these results, we then pursued an asymmetric variant to generate two adjacent C(sp^3) stereocenters. Screening of chiral bisphosphine ligands (entries 5–8) identified (*R*)-DTBM-SEGPHOS as the most effective, providing >99% yield and enantiomeric ratios up to 69% ee. Preparative HPLC resolved all four stereoisomers of **3**, and ECD analysis assigned peaks 1 and 3 to the *syn*-**3** diastereomers [(2*S*,3*R*) and (2*R*,3*S*)] and peaks 2 and 4 to the *anti*-**3** diastereomers [(2*R*,3*R*) and (2*S*,3*S*)]. X-ray crystallography unequivocally confirmed the structure of *anti*-**3** (2*S*,3*S*) (CCDC 2269503). Notably, excluding the copper catalyst decreased both yield and enantiomeric excess (entry 9), affirming its critical role, while the chiral Pd complex dictated enantioselectivity. Subsequently, we introduced the copper-specific ligand (*R*,*R*)-Ph-PyBOX (**L4**) (entry 10), pre-stirring each ligand with its respective metal. To our delight, the quaternary-center-containing nitrile **3** was obtained with a 70% yield and a notable enantiomeric excess (ee_{syn}) of 91%, though with a low diastereomeric ratio of 1 : 1, suggesting a unique synergistic effect from Pd/Cu dual catalysis. Interestingly, omitting the copper catalyst proved highly detrimental (entry 11).

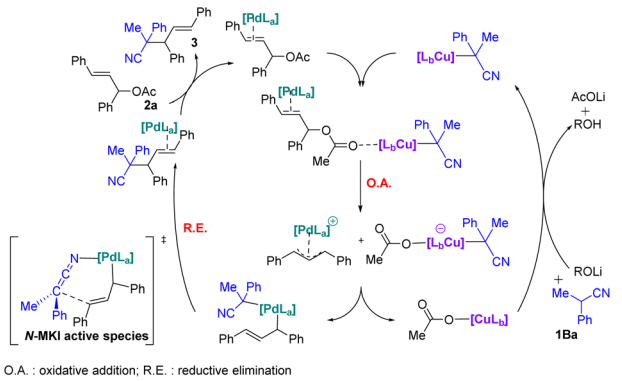
Additional tests using various chiral ligands (entries 12–15) showed a slight erosion in both yield and enantioselectivity. Further investigation into metal counterions and bases revealed that a lithium-based additive positively impacted

Table 1 Optimization of allylic alkylation in asymmetric conditions[a]



Entry	L*a*	L*b*	*T* °C	Yield[b] (%)	ee_{syn}	ee_{anti}	dr
1[d,e]	*rac*-**L1**	—	50	97(82)[c]	0	0	1 : 1
2[d,e,f]	*rac*-**L1**	—	50	N.R.[i]	—	—	—
3[d,e,h]	*rac*-**L1**	—	50	41	0	0	1 : 1
4[e]	*rac*-**L1**	—	−20	96(87)[c]	0	0	1 : 1
5[e]	(*R*)-**L1**	—	−20	97	34	37	6 : 4
6[e]	(*S*)-**L1**	—	−20	96	−39	−42	6 : 4
7[e]	(*R*)-**L2**	—	−20	82	34	37	6 : 4
8[e]	(*S*)-**L2**	—	−20	88	−47	−53	6 : 4
7[e]	(*R*)-**L3**	—	−20	>99	69	45	1 : 1
8[e]	(*S*)-**L3**	—	−20	>99	−64	−38	1 : 1
9[e,g]	(*R*)-**L3**	—	−20	39	62	48	1 : 1
10	(*R*)-**L3**	**L4**	−20	70	91	74	1 : 1
11[g]	(*R*)-**L3**	**L4**	−20	44	58	39	1 : 1
12	(*R*)-**L3**	**L5**	−20	41	66	69	7 : 3
13	(*R*)-**L3**	**L6**	−20	31	62	65	6 : 4
14	(*R*)-**L3**	**L7**	−20	32	50	46	6 : 4
15	(*R*)-**L3**	**L8**	−20	26	0	0	N.D.[j]

[a] Reaction conditions: **1Ba** (0.2 mmol), **2a** (0.4 mmol, 2 equiv.), [Pd] (10 mol%), $(CuOTf)_2$·toluene (10 mol%), *rac*-BINAP (40 mol%), base (1 equiv.), solvent (0.1 M) for 24 h. [b] NMR yields using 1,3,5-trimethoxybenzene as an internal standard; the dr was determined by ^{1}H NMR; the ee was determined by HPLC or SFC analysis on a chiral stationary phase. [c] Isolated yield on gram scale synthesis. [d] Reaction performed at 50 °C for 6 h. [e] Using 40 mol% of L*a*. [f] Without palladium catalyst. [g] Without copper catalyst. [h] Without base. [i] N.R.: no reaction. [j] N.D.: Not determined or conversion below 10%.



Scheme 1 Proposed reaction mechanism.

enantioselectivity (see SI, Table S5). Attempts to improve reaction efficiency by employing alternative palladium and copper sources were unsuccessful (see SI, Tables S3 and S4).[17] In our specific model, computational studies have revealed that the *C*-coordination of the cyanoalkyl anion to Cu or Pd complexes is preferred over *N*-coordination, though Me and Ph substituents on the anionic carbon attenuate this preference (see SI, Table S7).

In the absence of Cu, the lowest energy transition state for reductive elimination is a 7-membered ring with η^1-allyl and a *N*-metalated anion (see SI, Fig. S2). However, the oxidative addition exhibits a higher activation energy, and is the rate-determining step (see SI, Fig. S1), explaining the poor stereoselectivity in absence of Cu, as this step is not responsible for C–C bond formation. The coordination of a Cu(I) complex to the OAc termination of the Pd complex (see Scheme 1, O.A.) significantly lowers the oxidative addition barrier, with no effect on reductive elimination. In the presence of Cu, the rate-determining step is the reductive elimination process (Scheme 1, R.E.), which occurs within a Pd-only complex. Copper additives activate the reaction by facilitating oxidative addition, and also increase stereoselectivity since the rate-determining step is the C–C bond formation. This hypothesis is sustained by the optimization of the reaction intermediate leading to reductive elimination, namely the Pd(allyl)(ketenimine) complex (see SI, Fig. S3). The most stable configuration corresponds to the formation of 3*R* diastereomers. The orthogonal arrangement of the ketenimine and allyl chains in this structure is responsible of the poor diastereoselectivity.

Under optimized racemic conditions at 50 °C, a series of secondary and tertiary α-alkyl-α-(het)aryl acetonitriles **1A–F** were reacted with 1,3-diphenylallyl acetate **2a** to explore substrate scope. Despite varying nucleophilic partners, diastereoselectivity remained consistently low, indicating minimal stereochemical control from the nitriles.[18] Efforts to increase steric hindrance on the nitrile moiety failed to improve

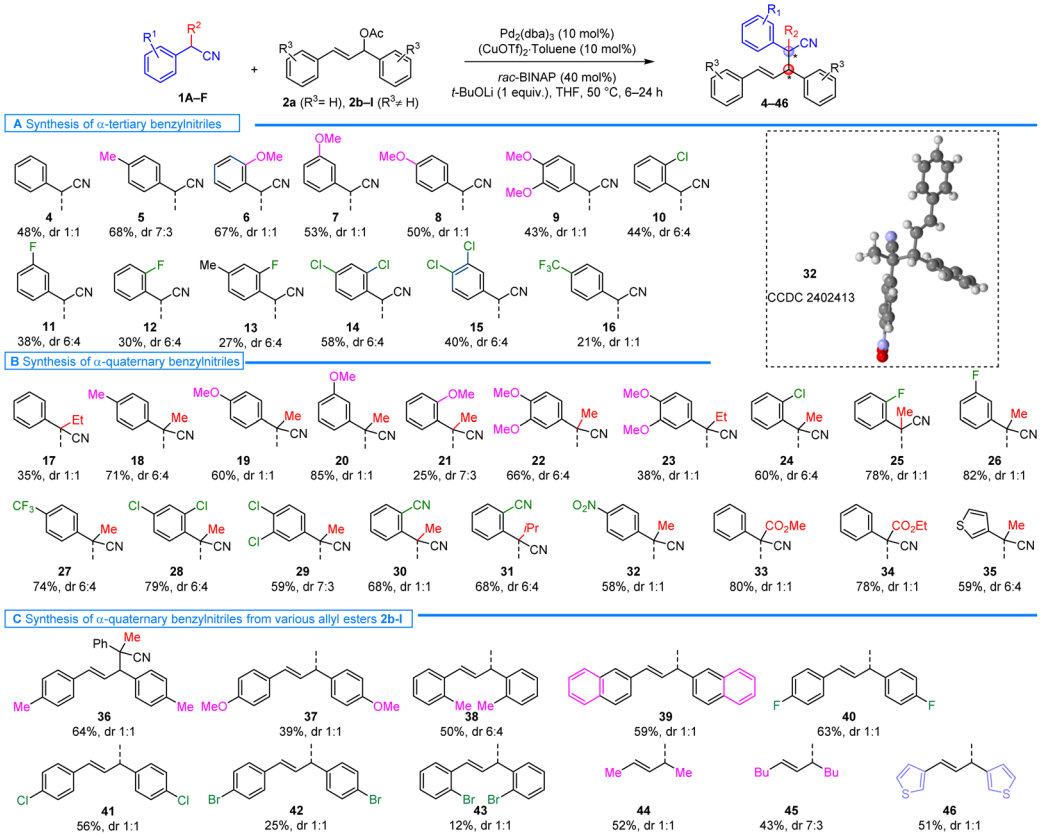


Fig. 2 Substrate scope of the allylic alkylation of benzyl nitriles **1A–F** under racemic conditions: **1A–F** (0.25 mmol, 1.0 equiv.), **2a–l** (1.2 equiv.), $Pd_2(dba)_3$ (10 mol%), *rac*-BINAP (40 mol%), $(CuOTf)_2$·toluene (10 mol%), *t*-BuOLi (1 equiv.), 50 °C, THF, 6–24 h. Yield of isolated benzylnitriles. dr determined on the crude reaction mixture by ^{1}H NMR analysis.

selectivity and often compromised substrate stability or reactivity. Subsequently, several new α-tertiary benzyl nitriles (**4–16**) were obtained (Fig. 2(A)). Electron-donating substituents (*e.g.*, Me, MeO) on the phenyl ring improved yields, whereas electron-withdrawing groups (Cl, F, CF_3) were tolerated but led to lower efficiencies, with compound **16** exhibiting particularly poor conversion. In the case of α-quaternary benzylnitriles (Fig. 2(B)), yields improved slightly, particularly in the presence of an electron-donating group (**18–24**), except for the sterically hindered ortho-substituted derivative (**21**). However, bulkier α-alkyl chain (R^2 = ethyl or isopropyl, *e.g.*, compounds **17**, and **23**), reduced yields, due to reactivity loss except for compound **31** which gave a good 68% yield. Conversely, benzylnitriles with electron-withdrawing substituents (Cl, F, CF_3, CN, NO_2: **24–32**) showed enhanced yields. The nitro derivative (**32**) was structurally confirmed *via* X-ray analysis (CCDC 2402413). Substituting R^2 with ester groups (**33**, R = CO_2Me, **34**, R = CO_2Et) facilitated complexation with copper, achieving high yields of 80% and 78%, respectively for compounds **33**, and **34**. The reaction was also successful with a thiophene moiety (**35**), a relevant pharmacophore. Further exploration of 1,3-di(het) aryl allylic ester precursors **2b–l** demonstrated that both electron-donating and electron-withdrawing groups were compatible electrophiles (Fig. 2(C), **36–43**, **46**). Substituting the aryl moiety with an alkyl group yielded the α-quaternary benzylnitrile derivatives (**44**, **45**), albeit with moderate efficiency. To exploit the synthetic potential of this dual metal catalyzed reaction, we explored asymmetric allylic alkylation using chiral Pd/Cu catalysts, an unprecedented approach in the literature (Fig. 3).

Under optimized enantioselective conditions (*cf.* Table 1, entry 10), nitriles **1A–D** were evaluated to identify factors affecting yield and efficiency (Fig. 3(A)). Substitution on the aryl ring significantly influenced enantioselectivity. Electron-donating groups (**4**, **6–8**) yielded distinct enantiomeric ratios compared to electron-withdrawing ones (**12**, **14**, **15**). For α-quaternary benzylnitriles (**17**, **21**, **25**, **30**, **31**), ortho-positioned electron-withdrawing groups (F or CN) enhanced yield and enantiomeric excess (Fig. 3(B)). Additionally, we systematically assessed the impact of chiral catalyst configurations, identifying $Pd_2(dba)_3$·(*R*)-DTBM-SEGPHOS and $(CuOTf)_2$·toluene·(*R*,*R*)-Ph-ByBOX as the optimal combination (Fig. 3(C)). This catalyst system effectively converted racemic symmetrical 1,3-disubstituted allyl acetate **2a** with tertiary benzyl nitrile **1Ba** into enantioenriched α,α-disubstituted quaternary benzylnitrile **3**, achieving full stereodivergence.[12b] A minor negative non-linear effect was observed, likely due to the aggregation of chiral complex (see SI, Table S6).

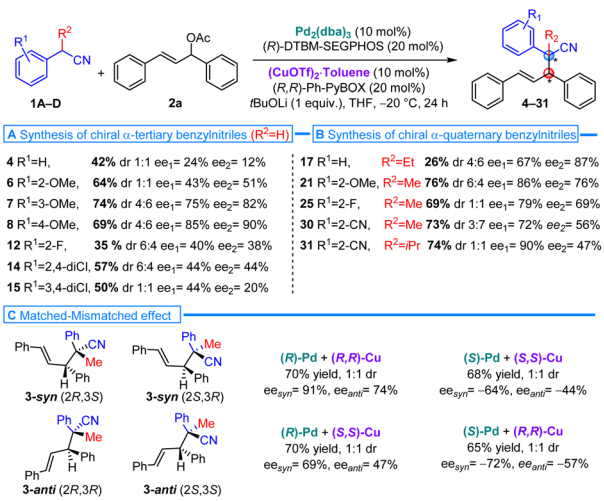


Fig. 3 Catalytic asymmetric allylic alkylation of **1A–D**. Conditions: **1A–D** (1.0 equiv.), **2a** (1.2 equiv.), $Pd_2(dba)_3$ (10 mol%), (*R*)-DTBM-SEGPHOS (20 mol%), $(CuOTf)_2$·toluene (10 mol%), (*R*,*R*)-Ph-PyBOX (20 mol%), *t*-BuOLi (1 equiv.). NMR yields using 1,3,5-trimethoxybenzene as an internal standard.

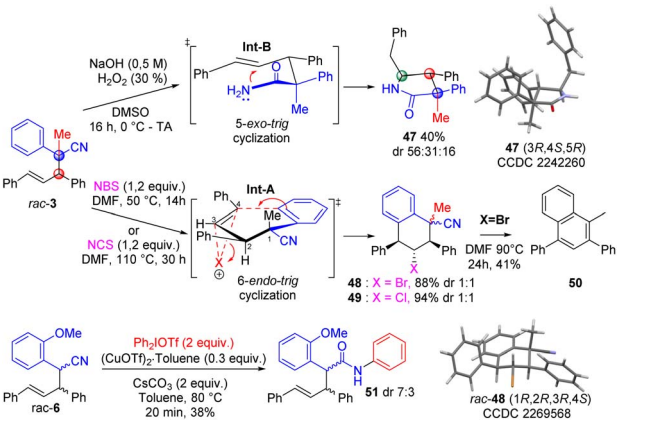


Fig. 4 Products derivatization from nitriles **3** and **6**.

To illustrate the synthetic utility of this methodology, transformations of nitrile-containing compounds were probed (Fig. 4). α-Quaternary benzylnitrile *rac*-**3** was efficiently transformed into lactam **47** *via* alkaline peroxide hydrolysis, followed by 5-*exo*-*trig*-cyclization (Fig. 4, **Int-A**). This novel 5-benzylpyrrolidin-2-one **47** was obtained as a mixture of three diastereomers (dr 56 : 31 : 16), with the structure of one isomer confirmed by X-ray crystallography (CCDC 2242260). Treatment of *rac*-**3** with NBS or NCS led to the formation of bicycles **48** and **49**, each with four contiguous stereocenters. These products, obtained as only two diastereomers, resulted from a 6-*endo*-*trig* cyclization of the electron-rich phenyl ring onto the bridged halonium ion. These two diastereomers are formed by the preferential equatorial positioning of the phenyl group at C2, directing halonium ion formation to the opposite face (Fig. 4, **Int-B**). Heating the brominated derivative in DMF yielded the naphthalene compound **50** in 41% yield.[19] Finally, nitrile *rac*-**6** was successfully converted to an aryl amide (*e.g.*, cmpd **51**) using diaryliodonium salts under copper catalysis.[20]

Conclusions

In summary, we have developed an enantioselective approach for constructing original homoallylic nitriles with vicinal stereogenic centers *via* an allylic alkylation process. This method leverages a dual catalytic system, wherein a palladium

catalyst governs the configuration of the electrophilic carbon in an allylic acetate, while a copper catalyst dictates the stereochemistry of the nucleophilic carbon through an *N*-MKI active species. This strategy originally provides vicinal quaternary and tertiary stereogenic centers bearing nitrile, yielding products with high efficiency (up to 99%) and enantiomeric excesses up to 91%. Accessing all four stereoisomers highlights the independent stereocontrol over both nucleophilic and electrophilic centers. The reaction is scalable while maintaining excellent yield. Computational studies have revealed the critical role of the copper catalyst and demonstrated that poor diastereoselectivity stems from the orthogonal arrangement of the ketenimine and allyl chains within the reaction intermediate. Ongoing post-functionalization efforts suggest broader synthetic applications of the catalytic construction of original chiral homoallylic benzyl nitriles.

Author contributions

L. M. and H. S. performed the experiments and collected the data. H. G. and F. H. performed the DFT calculations. N. V. conducted the ECD and VCD studies. L. R. and C. W. performed the SFC study and P. R. the crystallography. I. G. conceived the concept, I. G. and C. N. directed the project and co-authored the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

CCDC 2242260, 2269503, 2269568, 2281305 and 2402413 (**49**/**3-anti**/**50-dia2**/**50-dia-1**/**35**, respectively) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge *via* the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

Experimental details, characterization data, NMR spectra, and DFT details and crystallo-graphic data (PDF), and Electronic and vibrational circular dichroism (ECD and VCD) study (PDF). See DOI: **https://doi.org/10.1039/d5ra04516a**.

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15 Other palladium precursors and achiral bisphosphine ligands have also demonstrated efficiency in this transformation (see the SI).

16 See SI for electronic and vibrational circular dichroism (ECD and VCD) study.

17 Several organic solvents, including DCM, DMF, and toluene, were also tested; however, no improvement in yield or enantioselectivity was observed.

18 (*a*) See SI for a detailed DFT analysis and discussion regarding the control of diastereoselectivity.; (*b*) Due to the limited diastereoselectivity observed, the use of non-symmetric allyl substrates is ruled out to prevent the formation of a complex mixture of products.

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