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Communication

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Enantioselective Assembly of Cycloenones with a Nitrile-Containing All-Carbon Quaternary Center from Malononitriles Enabled by Ni-Catalysis

Zhiwu Lu,† Xu-Dong Hu,† Hui Zhang, Xiao-Wen Zhang, Jinhui Cai, Muhammad Usman, Hengjiang Cong, and Wen-Bo Liu*

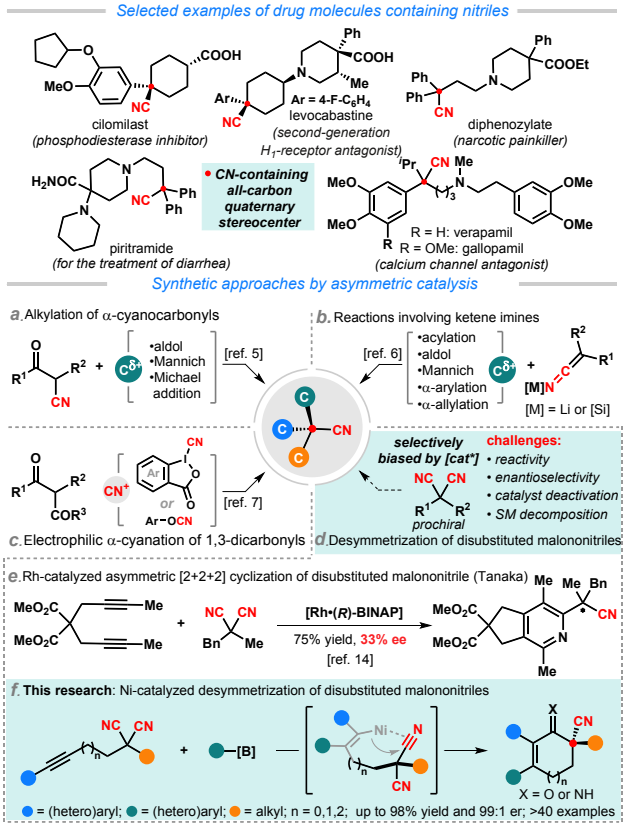
Sauvage Center for Molecule Sciences; Engineering Research Center of Organosilicon Compounds & Materials (Ministry of Education); College of Chemistry and Molecular Sciences, Wuhan University, 299 Bayi Rd, Wuhan 430072, Hubei, China

ABSTRACT: Chiral nitriles are valuable molecules in modern organic synthesis and drug discovery. Selectively differentiating the two nitrile groups of widely available malononitrile derivatives is a straightforward yet underdeveloped route to construct enantioenriched nitriles. Here we report an enantioselective nickel-catalyzed desymmetrization of malononitriles for the generation of nitrile-containing all-carbon quaternary stereocenters. This protocol involves a nickel-catalyzed addition of aryl boronic acids to alkynes followed by a selective nitrile insertion, providing unprecedented access to enantioenriched 5–7-membered α-cyano cycloenones with a fully substituted olefin from a broad range of substrates. The synthetic utility of these nitrile products is demonstrated by gram-scale synthesis and conversion to several useful functional groups.

As an important pharmacophore, the nitrile unit plays an efficacious role in medicines.[1,2] The biocompatible and metabolically stable nitrile functionality facilitates polar interactions, accentuates hydrogen bonding properties, and improves the toxicology profiles of molecules.[2] Indeed, nitrile-containing motifs are increasingly found in pharmaceuticals and active clinical candidates.[1a] Of special importance are those bioactive compounds with the nitrile group contained within an all-carbon quaternary stereocenter (Scheme 1, top), which prevents oxidation at the α-carbon of the nitrile avoiding toxic cyanide release.[3] Moreover, the nitrile is among the most useful functional groups in organic synthesis and can be easily converted to versatile functionalities, such as carboxylic acid, aldehyde, amine, oxazoline, and piperidine, etc.[4] Consequently, elegant catalytic protocols including electrophilic functionalization of α-cyanocarbonyls[5] (Scheme 1a) and ketene imines[6] (Scheme 1b), and α-cyanation of 3-dicarbonyls[7] among others[8] (Scheme 1c), have been reported for the synthesis of enantioenriched all-carbon quaternary stereocenter-containing nitriles.[9]

Desymmetrization reactions have been developed as a powerful tool for accessing all-carbon quaternary centers.[10] Given the readily availability of disubstituted malononitriles, desymmetrization of the two nitriles is a straightforward, cyanide-free yet underdeveloped route to construct enantioenriched nitriles. Stereoselective differentiation of malononitriles is challenging probably due to their coordinating affinity to transition metals[11] and the minuscule steric size[12] of the nitrile group. Moreover, decyanative decomposition of malononitriles in the

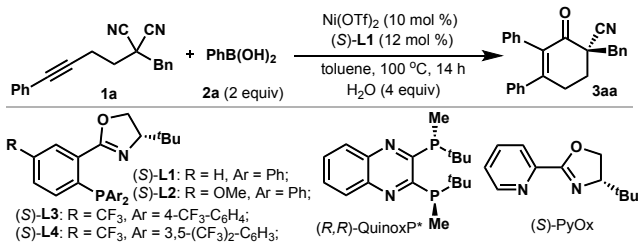
Scheme 1. Selected Examples of Drugs with a Nitrile-Containing Quaternary Center Subunit (Top) and Asymmetric Catalytic Synthetic Strategies (Bottom)



presence of transition-metal catalysts or organometallic reagents would be problematic.[13] Although enantioselective enzymatic hydrolysis of dinitriles has been known for decades,[14] only two examples for chemical catalytic desymmetrization of malononitriles were revealed to date, namely, rhodium-catalyzed [2+2+2] cycloaddition by the Tanaka group (Scheme 1d)[15a] and ruthenium-catalyzed hydration reaction by the Ikariya group.[15b] However, these reports presented limited substrates, resulted in poor enantioselectivities, and necessitated precious transition metal catalyst, further highlighting the challenges associated with the desymmetrization of the two nitrile groups.

In light of these impediments and inspired by the transition-metal-catalyzed alkyne insertion/addition chemistry reported recently by Lam group and others,[16] we envisaged that an intermolecular addition of alkynes and intramolecular cyclization cascade strategy could facilitate the desymmetrization of malononitriles to access the nitrile-containing quaternary centers (Scheme 1e). In this communication, we report a nickel-catalyzed desymmetrization of alkyne-tethered malononitriles **1** with aryl boronic acids **2** under base-free conditions. All-carbon quaternary carbon substituted nitriles **3** were successfully assembled in synthetically useful enantioselectivities and yields.

Table 1. Selected Results of Reaction Optimization



entry[a]	variation	conv (%)[b]	er[c]
1	none	>95 (93)[d]	94:6
2	**L2** instead of **L1**	91	94:6
3	**L3** instead of **L1**	69	91:9
4	**L4** instead of **L1**	43	77:23
5	QuinoxP* instead of **L1**	49	68:32
6	PyOx instead of **L1**	28	53:47
7	80 °C instead of 100 °C ***(standard conditions)***	92 (89)[d]	95:5
8	without H_2O	N.R.	–

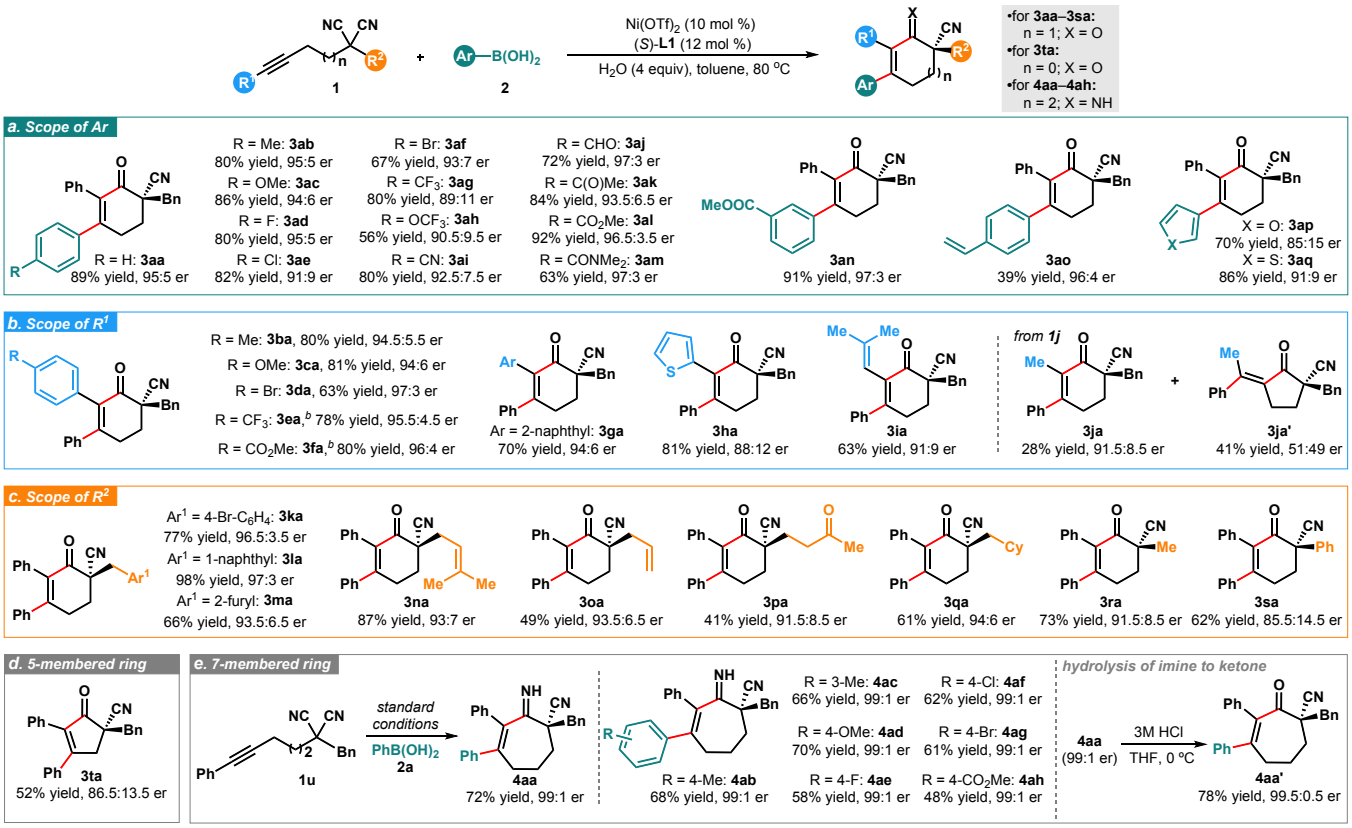
[a]Reactions conducted on a 0.1 mmol scale. [b]NMR yields using 1,3,5-trimethoxybenzene as an internal standard. [c]Determined by HPLC. [d]Isolated yield. N.R. = No reaction.

Outlined in Table 1 are the representative results of the condition optimization (also see Tables S1–S6 in the Supporting Information for details). We were able to access the desired product **3aa** by desymmetrization of malononitrile **1a** in 93% yield with 94:6 er using $Ni(OTf)_2$/phosphinooxazoline (phox, **L1**) as the catalyst (entry 1). Electron-rich phox ligand **L2** performed equally well compared with **L1** (entry 2), whereas electron-poor phox ligands **L3** and **L4** exhibited diminished reactivity and enantioselectivity (entries 3 and 4). Poor yields and er were obtained with the examined bisphosphine or dinitrogen ligands (entries 5 and 6). Finally, lowering the temperature to 80 °C furnished 89% isolated yield and slightly increased enantioselectivity (95:5 er), which was identified as the optimal conditions (entry 7). It should be noted that the addition of water was found crucial with no reaction occurring in its absence (entry 8 and Table S6 in the SI).

The scope of aryl boronic acids was investigated (Table 2a). Electron-donating groups including methyl and methoxy afforded the corresponding products **3ab** and **3ac** in 80–86% yields with 94:6–95:5 er. Aryl boronic acids bearing –F (**3ad**), –Cl (**3ae**), and –Br (**3af**) provided 67–82% yields and 91:9–95:5 er. Gratifyingly, diversity functional groups, such as trifluoromethyl (**3ag**), trifluoromethoxy (**3ah**), cyano (**3ai**), aldehyde (**3aj**), acetyl (**3ak**), ester (**3al**), and amide (**3am**), all delivered the desired quaternary center-containing products with moderate to good er. A *meta*-ester substituted substrate (**2n**) was a viable reaction partner as well, providing excellent yield and er (**3an**, 91% yield and 97:3 er). A terminal alkene-bearing phenyl boronic acid was compatible as well delivering addition product **3ao** with excellent er (96:4) albeit in a reduced yield. Notably, heteroaryl nucleophiles, such as 3-furyl and 3-thienyl boronic acids provided the corresponding products **3ap** and **3aq** in good yields with slightly lower enantioselectivities.

Next, a panel of malononitriles with substituted alkynes were explored (Table 2b). Various substituted (R^1) alkynes including electron-donating (–Me, –OMe) and -withdrawing (–Br, $–CF_3$, $–CO_2Me$) groups containing aromatics were well tolerated and afforded the corresponding products **3ba**–**3fa** in 63–81% yields with 94:6–97:3 er. In general, the reactions of electron-deficient aryl substituted alkynes were sluggish at 80 °C but synthetically useful yields were achieved at an elevated temperature (100 °C). Naphthyl alkyne-derived product **3ga** was obtained in 70% yield with 94:6 er. Remarkably, heteroaryl (thienyl, **1h**) and alkenyl (**1i**) substituted alkynes were also compatible substrates, providing **3ha** and **3ia** in 63–81% yields, albeit with diminished er (88:12–91:9). Changing the substituent R^1 to a methyl group provided a mixture of isomers **3ja** and **3ja'**. Furthermore, we examined the influence of various groups (R^2) at the α-position of the malononitriles (Table 2c). 4-Bromobenzyl (**3ka**), 1-naphthalenylmethyl (**3la**), and 2-furylmethyl (**3ma**) groups were well tolerated resulting in 66–98% yields with 93.5:6.5–97:3 er. The absolute configuration of **3ka** (>99:1 er) was assigned by X-ray analysis after recrystallization. Importantly, allylic (**3na** and **3oa**) and 3-oxobutyl (**3pa**), useful functional groups allowing for downstream versatile transformations, were endured as well. Finally, **3qa** (cyclohexylmethyl), and **3ra** (methyl) are additional examples of aliphatic α-substituted malononitriles, whereas **3sa** (phenyl) represents an aryl-substituted product.

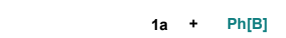
Table 2. Substrate Scope[a]



[a]Reactions conducted under the conditions of entry 7, Table 1. Percentages represent isolated yields. [b]100 °C.

The reaction scope for the asymmetric synthesis of other ring size analogs was also conducted (Table 2d and 2e). Reacting one-carbon truncated **1t** gave cyclopentenone **3ta** in 52% yield with 86.5:13.5 er. Interestingly, seven-membered imines **4**, stable enough for chromatography isolation, were formed in good yields with excellent enantioselectivities (99:1 er) in general. Treatment of malononitrile **1u** and phenyl boronic acid **2a** under the standard conditions delivered cyclohept-2-en-1-imine **4aa** in 72% yield with 99:1 er. Pleasantly, aryl boronic acids substituted with both electron-donating (–Me, –OMe, **4ab**–**4ad**) and electron-withdrawing (–F, –Cl, –Br, –CO_2Me, **4ae**–**4ah**) groups were compatible in this transformation delivering the corresponding products with excellent enantioselectivities (**4ab**–**4ag,** 99:1 er for all). The imine was readily hydrolyzed to the corresponding ketone (**4aa'**) upon treatment with 3M HCl at 0 °C without loss of the er. Attempts to synthesize 8-membered analogs failed, resulting in a complex mixture. It is also worth noting that pyridine-substituted alkynyl malononitrile (**1v**), aryl boronic acids bearing functional groups such as acidic acid (**2r**), free-amide (**2s**), *ortho*-methyl ester (**2t**), unprotected indole- and pyridine-derived boronic acids (**2u** and **2v**), and phenylethenyl boronic acid (**2w**), are not compatible with this desymmetrization process (see Scheme S1 for details).

Table 3. Reactivity of Aryl Boronic Precursors[a]

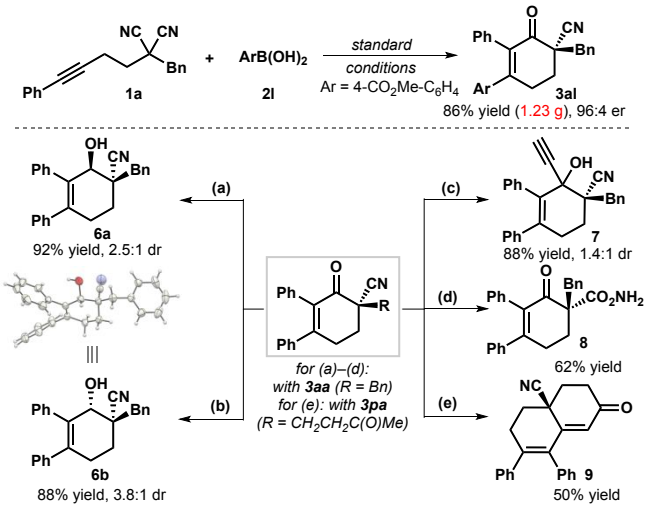


$PhB(OH)_2$ **2a** (2 equiv)	$(PhBO)_3$ **5a** (0.7 equiv)	$PhBF_3K$ **5b** (2 equiv)	PhBpin **5c** (2 equiv)
89% yield, 95:5 er	91% yield, 95:5 er	87% yield, 94.5:5.5 er	N.R. (at 100 °C)

[a]Reactions conducted on a 0.1 mmol scale with isolated yields represented.

Other aryl boronic sources were also interrogated with malononitrile **1a** to further examine the feasibility of this strategy (Table 3). Besides phenyl boronic acid **2a**, the reaction with triphenylboroxin **5a** and phenyl trifluoroborate **5b** resulted in excellent yields and identical enantioselectivities. However, PhBpin **5c** was failed to convert into the desired product, probably due to sluggish transmetalation under base-free conditions.[17]

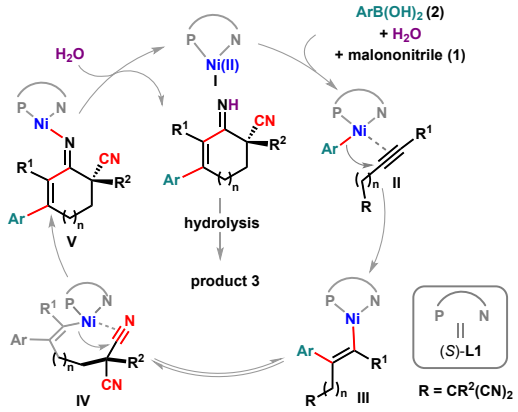
Scheme 2. Gram-scale Synthesis and Products Derivatization



Conditions: (a) Et_2AlCl (1.5 equiv), toluene, 0 °C–rt, 14 h; (b) $NaBH_4$ (2 equiv), THF/MeOH (1:1), rt, 6 h; (c) HCCMgBr (2 equiv), THF, 0 °C–rt, 8 h; (d) $Ni(ClO_4)_2•6H_2O$ (20 mol %), bipyridine (24 mol %), AcOH (10 equiv), toluene, 140 °C, 24 h; (e) AcOH (30 mol %), pyrrolidine (30 mol %), MTBE, 60 °C, 2 h.

The synthetic utility of this methodology was then demonstrated as depicted in Scheme 2. The gram-scale reaction with 3.4 mmol of **1a** furnished the corresponding product **3aa** (1.23 g) smoothly without loss of efficiency (86% yield, 96:4 er). Selective synthesis of *trans* (**6a**) and *cis* (**6b**) diols were achieved by judicious choice of reductants. The addition of ethynylmagnesium bromide to the ketone group of **3aa** formed alcohol **7** with two continuous stereogenic centers. Hydrolysis of the sterically encumbered nitrile group of **3aa** produced amide **8** in 62% yield. With a methylketone-bearing nitrile **3pa**, an aldol condensation furnished bicyclic product **9** with a γ-quaternary center in moderate yield.

Scheme 3. Postulated Catalytic Cycle



Furthermore, a number of experiments were carried out to get insights into the possible mechanistic scenarios (see SI for details). First, the reaction with electron-rich aryl boronic acid (**2c**) is slightly faster than with the electron-deficient one (**2l**, Scheme S2a).[18] Second, competition experiments with methoxy (**1c**) and ester (**1f**) substituted aryl alkynes under the standard conditions showed that the electron-rich alkyne reacts faster (Scheme S2b). Third, parallel experiments with H_2O and D_2O were performed employing $(PhBO)_3$ to avoid the proton scrambling between the phenyl boronic acid and D_2O. Both reactions resulted in similar yields with no obvious kinetic isotopic effect (KIE) observed (Scheme S2c).[19] Additionally, ^{13}C KIE studies[20] of the substrate **1a** at natural abundance were carried out. A significant nitrile carbon ^{13}C KIE was observed by comparing the changes in ^{13}C isotopic composition of the recovered **1a** to the original starting material **1a** (Scheme S2d). A reaction with stoichiometric amount of catalyst was conducted without the addition of water resulted in no product formation (Scheme S3). ^{31}P NMR studies indicated that water may play a role in promoting the transmetalation between the in situ formed nickel complex with aryl boronic acids (Figure S1). Combined with previous mechanistic studies on nickel-catalyzed cross-coupling and addition reactions,[18,21] a putative catalytic cycle was proposed as depicted in Scheme 3. Transmetalation of nickel complex **I** with aryl boronic acid generates aryl-nickel species **II** with the alkyne coordinated in the presence of substrate **1**. Insertion of the alkyne into the C–Ni bond generates *cis*-alkenyl-nickel **III**. Then a reversible *cis*/*trans* isomerization[22] provides *trans*-alkenyl-nickel species **IV**. Addition of **IV** to one of the nitrile groups delivers the iminyl-nickel complex **V**, which is the enantiodifferentiating step in the catalytic cycle. Finally, protonation of **V** releases the active nickel catalyst together with the imine which is further hydrolyzed to yield the cycloenone product **3**.

In conclusion, we have developed a regioselective and enantioselective nickel-catalyzed alkyne addition and cyclization cascade reaction for the synthesis of cycloenones bearing a nitrile-containing all-carbon quaternary center. Utilizing a catalyst derived from commercially available $Ni(OTf)_2$ and phox ligand (**L1**), the desymmetrization of the two nitrile groups of malononitriles was achieved in good yields with moderate to good enantioselectivities. The reaction is scalable and proceeds with a broad range of substrates. Ongoing explorations in our laboratory include investigating the mechanism underlying and utilizing malononitriles as precursors for other value-added molecules their synthetic applications.

ASSOCIATED CONTENT

Detail results of reaction condition optimization (Table S1–S6), synthetic procedures and characterization data for new compounds, HPLC and NMR spectra (PDF); Crystallographic data for **3ka** and **6b** (CIF). These materials are available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*wenboliu@whu.edu.cn

Author Contributions

†These authors contributed equally.

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Wang, Y.; Du, Y.; Huang, N. A survey of the role of nitrile groups in protein-ligand interactions. *Future Med. Chem.* **2018**, *10*, 2713–2728. (b) Sterling, T.; Irwin, J. J. ZINC 15-Ligand Discovery for Everyone. *J. Chem. Inf. Model.* **2015**, *55*, 2324–2337.

(2) (a) Fleming, F. F.; Yao, L.; Ravikumar, P. C.; Funk, L.; Shook, B. C. Nitrile-Containing Pharmaceuticals: Efficacious Roles of the Nitrile Pharmacophore. *J. Med. Chem.* **2010**, *53*, 7902–7917; (b) Michel, J.; Tirado-Rives, J.; Jorgensen, W. L. Energetics of Displacing Water Molecules from Protein Binding Sites: Consequences for Ligand Optimization. *J. Am. Chem. Soc.* **2009**, *131*, 15403–15411.

(3) (a) Tanii, H.; Hashimoto, K. Structure-Toxicity Relationship of Aliphatic Nitriles. *Toxicol. Lett.* **1984**, *22*, 267–272; (b) Ahmed, A. E.; Trieff, N. M. Aliphatic nitriles: metabolism and toxicity. *Prog. Drug Metab.* **1983**, *7*, 229–294.

(4) (a) Fleming, F. F. Nitrile-containing natural products. *Nat. Prod. Rep.* **1999**, *16*, 597–606. (b) Friedrich, K.; Wallenfels, K. *The Chemistry of the Cyano Group*; Wiley-Interscience: New York. 1970. (c) Zhang, Z.; Zhang, X.; Nagib, D. A. Chiral Piperidines from Acyclic Amines via Enantioselective, Radical-Mediated δ C–H Cyanation. *Chem* **2019**, *5*, 3127–3134.

(5) Selected examples: (a) Kuwano, R.; Miyazaki, H.; Ito, Y. Asymmetric Aldol Reaction of 2-Cyanopropionates Catalyzed by a Trans-Chelating Chiral Diphosphine–Rhodium(I) Complex: Highly Enantioselective Construction of Quaternary Chiral Carbon Centers at α-Positions of Nitriles. *J. Organomet. Chem.* **2000**, *603*, 18–29. (b) Kawato, Y.; Takahashi, N.; Kumagai, N.; Shibasaki, M. Catalytic Asymmetric Conjugate Addition of α-Cyanoketones for the Construction of a Quaternary Stereogenic Center. *Org. Lett.* **2010**, *12*, 1484–1487. (c) Mukhopadhyay, S.; Nath, U.; Pan, S. C. Organocatalytic Asymmetric Synthesis of 3,3-Disubstituted 3,4-Dihydro-2-Quinolones. *Adv. Synth. Catal.* **2017**, *359*, 3911-3916. (d) Nakashima, K.; Noda, Y.; Hirashima, S.-i.; Koseki, Y.; Miura, T. Asymmetric Conjugate Addition of α-Cyanoketones to Enones Using Diaminomethylenemalononitrile Organocatalyst. *J. Org. Chem.* **2018**, *83*, 2402–2408. (e) Nagata, K.; Sano, D.; Shimizu, Y.; Miyazaki, M.; Kanemitsu, T.; Itoh, T. Catalytic Asymmetric Alkylation of α-Cyanocarboxylates and Acetoacetates using a Phase-Transfer Catalyst. *Tetrahedron: Asymmetry* **2009**, *20*, 2530–2536. (f) For a decarboxylative alkylation: Yin, L.; Kanai, M.; Shibasaki, M. Nucleophile Generation via Decarboxylation: Asymmetric Construction of Contiguous Trisubstituted and Quaternary Stereocenters through a Cu(I)-Catalyzed Decarboxylative Mannich-Type Reaction. *J. Am. Chem. Soc.* **2009**, *131*, 9610–9611.

(6) (a) Mermerian, A. H.; Fu, G. C. Nucleophile-Catalyzed Asymmetric Acylations of Silyl Ketene Imines: Application to the Enantioselective Synthesis of Verapamil. *Angew. Chem. Int. Ed.* **2005**, *44*, 949–952. (b) Denmark, S. E.; Wilson, T. W.; Burk, M. T.; Heemstra, Jr. J. R. Enantioselective Construction of Quaternary Stereogenic Carbons by the Lewis Base Catalyzed Additions of Silyl Ketene Imines to Aldehydes. *J. Am. Chem. Soc.* **2007**, *129*, 14864–14865. (c) Zhao, J.; Liu, X.; Luo, W.; Xie, M.; Lin, L.; Feng, X. Asymmetric Synthesis of β-Amino Nitriles through a Sc^{III}-Catalyzed Three-Component Mannich Reaction of Silyl Ketene Imines. *Angew. Chem. Int. Ed.* **2013**, *52*, 3473–3477. (d) Zhao, J.; Fang, B.; Luo, W.; Hao, X.; Liu, X.; Lin, L.; Feng, X. Enantioselective Construction of Vicinal Tetrasubstituted Stereocenters by the Mannich Reaction of Silyl Ketene Imines with Isatin-Derived Ketimines. *Angew. Chem. Int. Ed.* **2015**, *54*, 241–244. (e) Turnbull, B.; W. H.; Evans, P. A. Enantioselective Rhodium-Catalyzed Allylic Substitution with a Nitrile Anion: Construction of Acyclic Quaternary Carbon Stereogenic Centers. *J. Am. Chem. Soc.* **2015**, *137*, 6156–6159. (f) Jiao, Z.; Chee, K. W.; Zhou, J. Palladium-Catalyzed Asymmetric α-Arylation of Alkylnitriles. *J. Am. Chem. Soc.* **2016**, *138*, 16240–16243. (g) For a seminal report: Mi, A. Q.; Wang, Z. Y.; Jiang, Y. Z. Asymmetric Catalytic Alkylation of 4-Chlorophenylacetic Acid. *Tetrahedron: Asymmetry*, **1993**, *4*, 1957–1960.

(7) (a) Chowdhury, R.; Schörgenhumer, J.; Novacek, J.; Waser, M. Towards an Asymmetric Organocatalytic α-Cyanation of β-Ketoesters. *Tetrahedron Lett.* **2015**, *56*, 1911–1914; (b) Chen, M.; Huang, Z.-T.; Zheng, Q.-Y. Organic base-promoted enantioselective electrophilic cyanation of β-keto esters by using chiral phase-transfer catalysts. *Org. Biomol. Chem.* **2015**, *13*, 8812–8816. (c) Qiu, J.-S.; Wang, Y.-F.; Qi, G.-R.; Karmaker, P. G.; Yin, H.-Q.; Chen, F.-X. Highly Enantioselective α-Cyanation with 4-Acetylphenyl Cyanate. *Chem. Eur. J.* **2017**, *23*, 1775–1778.

(8) Selected other methods: (a) Wu, Q.; Li, C.; Wang, W.; Wang, H.; Pan, D.; Zheng, P. NHC-Catalyzed Enantioselective Synthesis of Dihydropyran-4-Carbonitriles Bearing All-Carbon Quaternary Centers. *Org. Chem. Front.* **2017**, *4*, 2323–2326. (b) Zhou, Z.; He, Q.; Jiang, Y.; Ouyang, Q.; Du, W.; Chen, Y.-C. Double Thiol-Chiral Brønsted Base Catalysis: Asymmetric Cross Rauhut-Currier Reaction and Sequential [4 + 2] Annulation for Assembly of Different Activated Olefins. *Org. Lett.* **2019**, *21*, 7184–7188. (c) Enders, D.; Zamponi, A.; Raabe, G. Runsink, J. Enantioselective Synthesis of 2-Alkyl-2-cyanocycloalkanones with a Quaternary Stereogenic Center. *Synthesis* **1993**, 725-728. (d) Xiong, Y.; Du, Z.; Chen, H.; Yang, Z.; Tan, Q.; Zhang, C.; Zhu, L.; Lan, Y.; Zhang, M. Well-Designed Phosphine–Urea Ligand for Highly Diastereo- and Enantioselective 1,3-Dipolar Cycloaddition of Methacrylonitrile: A Combined Experimental and Theoretical Study. *J. Am. Chem. Soc.* **2019**, *141*, 961–971. (e) During the preparation of this manuscript, an elegant asymmetric oxidative cross-coupling reaction was reported: Wang, Z.; Zhu, Y.; Pan, X.; Wang, G.; Liu, L. Synthesis of Chiral Triarylmethanes Bearing All-Carbon Quaternary Stereocenters: Catalytic Asymmetric Oxidative Cross-Coupling of 2,2-Diarylacetonitriles and (Hetero)arenes. *Angew. Chem. Int. Ed*. **2020**, *59*, 3053–3057.

(9) For selected reviews of all-carbon quaternary stereocenter synthesis: a) Quasdorf, K. W.; Overman, L. E. Catalytic Enantioselective Synthesis of Quaternary Carbon Stereocentres. *Nature,* **2014**, *516*, 181–191. (b) Liu, Y.; Han, S.-J.; Liu, W.-B.; Stoltz, B. M. Catalytic Enantioselective Construction of Quaternary Stereocenters: Assembly of Key Building Blocks for the Synthesis of Biologically Active Molecules. *Acc. Chem. Res.* **2015**, *48*, 740–751. (c) Minko, Y.; Pasco, M.; Lercher, L.; Botoshansky, M.; Marek, I. Forming All-Carbon Quaternary Stereogenic Centres in Acyclic Systems from Alkynes. *Nature* **2012**, *490*, 522–526. (d) Marek, I.; Minko, Y.; Pasco, M.; Mejuch, T.; Gilboa, N.; Chechik, H.; Das, J. P. All-Carbon Quaternary Stereogenic Centers in Acyclic Systems through the Creation of Several C–C Bonds per Chemical Step. *J. Am. Chem. Soc.* **2014**, *136*, 2682–2694.

(10) Selected reviews of asymmetric desymmetrization: (a) Borissov, A.; Davies, T. Q.; Ellis, S. R.; Fleming, T. A.; Richardson, M. S. W.; Dixon, D. J. Organocatalytic Enantioselective Desymmetrisation. *Chem. Soc. Rev.* **2016**, *45*, 5474–5540. (b) Zeng, X.-P.; Cao, Z.-Y.; Wang, Y.-H.; Zhou, F.; Zhou, J. Catalytic Enantioselective Desymmetrization Reactions to All-Carbon Quaternary Stereocenters. *Chem. Rev.* **2016**, *116*, 7330–7396.

(11) Rach, S. F.; Kühn, F. E. Nitrile Ligated Transition Metal Complexes with Weakly Coordinating Counteranions and Their Catalytic Applications. *Chem. Rev.* **2009**, *109*, 2061–2080.

(12) The CN group is about 8 times smaller than a methyl group based on a comparison of A values for nitrile and methyl groups: Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*, Wiley: New York, **1994**, pp 696.

(13) (a) Mills, L. R.; Graham, J. M.; Patel, P.; Rousseaux, S. A. L. Ni-Catalyzed Reductive Cyanation of Aryl Halides and Phenol Derivatives via Transnitrilation. *J. Am. Chem. Soc.* **2019**, *141*, 19257–19262. (b) Reeves, J. T.; Malapit, C. A.; Buono, F. G.; Sidhu, K. P.; Marsini, M. A.; Sader, C. A.; Fandrick, K. R.; Busacca, C. A.;

Senanayake, C. H. Transnitrilation from Dimethylmalononitrile to Aryl Grignard and Lithium Reagents: A Practical Method for Aryl Nitrile Synthesis. *J. Am. Chem. Soc.* **2015**, *137*, 9481–9488; (c) Alazet, S.; West, M. S.; Patel, P.; Rousseaux, S. A. L. Synthesis of Nitrile-Bearing Quaternary Centers by an Equilibrium-Driven Transnitrilation and Anion-Relay Strategy. *Angew. Chem. Int. Ed.* **2019**, *58*, 10300–10304.

(14) (a) Yokoyama, M.; Sugai, T.; Ohta, H. Asymmetric Hydrolysis of a Disubstituted Malononitrile by the Aid of a Microorganism. *Tetrahedron Asymmetry* **1993**, *4*, 1081–1084. (b) Kashiwagi, M.; Iwasaki, M.; Fuhshuku, K.-i.; Ohta, H.; Sugai, T. Realization of the synthesis of α,α-disubstituted carbamylacetates and cyanoacetates by either enzymatic or chemical functional group transformation, depending upon the substrate specificity of Rhodococcus amidase. *Tetrahedron Asymmetry* **2004**, *15*, 2817–2820. (c) Wang, M.-X. Enantioselective Biotransformations of Nitriles in Organic Synthesis. *Acc. Chem. Res.* **2015**, *48*, 602–611.

(15) (a) Tanaka, K.; Suzuki, N.; Nishida, G. Cationic Rhodium(I)/Modified-BINAP Catalyzed [2+2+2] Cycloaddition of Alkynes with Nitriles. *Eur. J. Org. Chem.* **2006**, *2006*, 3917–3922. (b) Kamezaki, S.; Akiyama, S.; Kayaki, Y.; Kuwata, S.; Ikariya, T. Asymmetric Nitrile-Hydration with Bifunctional Ruthenium Catalysts Bearing Chiral N-Sulfonyldiamine Ligands. *Tetrahedron: Asymmetry* **2010**, *21*, 1169–1172. (c) For a double [2+2+2] cycloaddition, Wada, A.; Noguchi, K.; Hirano, M.; Tanaka, K. Enantioselective Synthesis of C_2-Symmetric Spirobipyridine Ligands through Cationic Rh(I)/Modified-BINAPCatalyzed Double [2 + 2 + 2] Cycloaddition. *Org. Lett.* **2007**, *9*, 1295–1298.

(16) (a) Shimkin, K. W.; Montgomery, J. Synthesis of Tetrasubstituted Alkenes by Tandem Metallacycle Formation/Cross-Electrophile Coupling. *J. Am. Chem. Soc.* **2018**, *140*, 7074–7078. (b) Yap, C.; Lenagh-Snow, G. M. J.; Karad, S. N.; Lewis, W.; Diorazio, L. J.; Lam, H. W. Enantioselective Nickel-Catalyzed Intramolecular Allylic Alkenylations Enabled by Reversible Alkenylnickel E/Z Isomerization. *Angew. Chem. Int. Ed.* **2017**, *56*, 8216–8220. (c) Karad, S. N.; Panchal, H.; Clarke, C.; Lewis, W.; Lam, H. W. Enantioselective Synthesis of Chiral Cyclopent-2-Enones by Nickel Catalyzed Desymmetrization of Malonate Esters. *Angew. Chem. Int. Ed.* **2018**, *57*, 9122–9125. (d) Clarke, C.; Incerti-Pradillos, C. A.; Lam, H. W. Enantioselective Nickel-Catalyzed anti-Carbometallative Cyclizations of Alkynyl Electrophiles Enabled by Reversible Alkenylnickel E/Z Isomerization. *J. Am. Chem. Soc.* **2016**, *138*, 8068–8071. (e) Chen, J.; Han, X.; Lu, X. Enantioselective Synthesis of Tetrahydropyrano[3,4-b]indoles: Palladium(II)-Catalyzed Aminopalladation/1,4-Addition Sequence. *Angew. Chem. Int. Ed.* **2017**, *56*, 14698–14701.

(17) (a) Lennox, A. J. J.; Lloyd-Jones, G. C. Selection of Boron Reagents for Suzuki–Miyaura Coupling. *Chem. Soc. Rev.* **2014**, *43*, 412–443. (b) Zhang, N.; Hoffman, D. J.; Gutsche, N.; Gupta, J.; Percec, V. Comparison of Arylboron-Based Nucleophiles in Ni-Catalyzed Suzuki–Miyaura Cross-Coupling with Aryl Mesylates and Sulfamates. *J. Org. Chem.* **2012**, *77*, 5956–5964. (c) Malapit, C. A.; Bour, J. R.; Brigham, C. E.; Sanford, M. S. Base-Free Nickel-Catalysed Decarbonylative Suzuki–Miyaura Coupling of Acid Fluorides. *Nature* **2018**, *563*, 100–104. (d) Malapit, C. A.; Bour, J. R.; Laursen, S. R.; Sanford, M. S. Mechanism and Scope of Nickel-Catalyzed Decarbonylative Borylation of Carboxylic Acid Fluorides. *J. Am. Chem. Soc.* **2019**, *141*, 17322–17330.

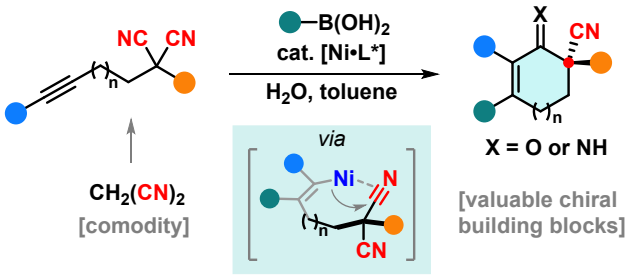
(18) (a) Payard, P.-A.; Perego, L. A.; Ciofini, I.; Grimaud, L. Taming Nickel-Catalyzed Suzuki-Miyaura Coupling: A Mechanistic Focus on Boron-to-Nickel Transmetalation. *ACS Catal.* **2018**, *8*, 4812–4823. (b) Christian, A. H.; Müller, P.; Monfette, S. Nickel Hydroxo Complexes as Intermediates in Nickel-Catalyzed Suzuki–Miyaura Cross-Coupling. *Organometallics,* **2014**, *33*, 2134–2137. (c) For a recent mechanistic study of transmetalation between nickel and organoboronic acids under base-free, see ref. 17d.

(19) Simmons, E. M.; Hartwig, J. F. On the Interpretation of Deuterium Kinetic Isotope Effects in C–H Bond Functionalizations by Transition-Metal Complexes. *Angew. Chem. Int. Ed.* **2012**, *51*, 3066–3072.

(20) Singleton, D. A.; Thomas, A. A. High-Precision Simultaneous Determination of Multiple Small Kinetic Isotope Effects at Natural Abundance. *J. Am. Chem. Soc.* **1995**, *117*, 9357–9358.

(21) Jackson, E. P.; Malik, H. A.; Sormunen, G. J.; Baxter, R. D.; Liu, P.; Wang, H.; Shareef, A.-R.; Montgomery, J. Mechanistic Basis for Regioselection and Regiodivergence in Nickel-Catalyzed Reductive Couplings. *Acc. Chem. Res.* **2015**, *48*, 1736–1745.

(22) Huggins, J. M.; Bergman, R. G. Mechanism, Regiochemistry, and Stereochemistry of the Insertion Reaction of Alkynes with Methyl(2,4-pentanedionato)(triphenylphosphine)nickel. A Cis Insertion That Leads to Trans Kinetic Products. *J. Am. Chem. Soc.* **1981**, *103*, 3002–3011.



• enantioenriched nitrile • all-carbon quaternary center
• base-free • up to 98% yield and 99:1 er • >40 examples