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Palladium-Catalyzed Asymmetric Acetoxylative Cyclization/Acyl Transfer Cascade of Alkyne-Tethered Malononitriles with Carboxylic Acids

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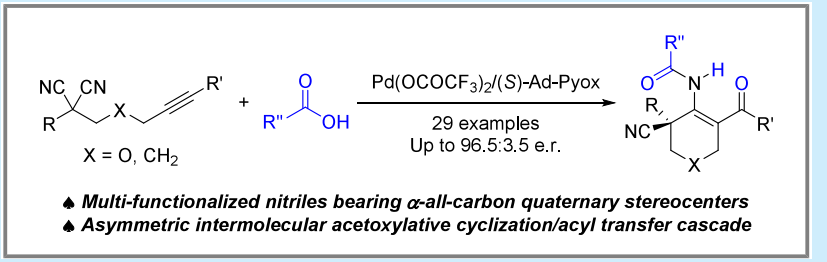

ABSTRACT: Palladium-catalyzed asymmetric intermolecular *trans*-acetoxypalladation/desymmetric cyclization/acyl transfer cascades of alkyne-tethered malononitriles with carboxylic acids have been demonstrated. Such a sequence enables the formation of multifunctionalized nitriles bearing α-all-carbon quaternary stereocenters with a high degree of enantiocontrol with a broad substrate scope. Moreover, synthetic elaborations present these multifunctionalized molecules as promising chiral building blocks. Mechanistic studies illustrate that the cascade process proceeds via a key imine intermediate, and the desymmetric cyclization is the enantio-determining step.

Nitriles occupy a privileged and prominent position in both synthetic and medicinal chemistry.[1] They have been powerful and useful for diverse functional transformations and can be converted into functionalities such as aldehydes, amines, carboxylic acids, amides, etc.[1a] Moreover, nitriles bearing α-all-carbon quaternary stereocenters are prevalent structural motifs in pharmaceuticals and biologically active molecules,[1b,c] which exhibit inhibitory effects on oxidation of the α-carbon of the cyano group and release of cyanide. Therefore, the efficient construction of nitriles bearing α-all-carbon quaternary stereocenters has received widespread attention. Among the existing strategies,[2−5] transition-metal-catalyzed enantioselective desymmetric cyclization of alkyne-tethered malononitriles represents a type of robust approach to the formation of nitriles bearing α-all-carbon quaternary stereocenters.[5a,d,e,g−i] These methods feature a selective desymmetric cyclization of malononitriles via migratory insertion of the prerequisite vinyl−metal intermediate into one cyano group. Generally, there are two ways to afford vinyl−metal intermediates. One is insertion of the aryl−nickel species into the alkynes. Subsequently, the *in situ*-formed vinyl−nickel intermediates undergo a reversible *cis*/*trans* isomerization to facilitate enantioselective nickel-catalyzed *anti*-arylation/desymmetric cyclization of alkyne-tethered malononitriles (Scheme 1a).[5a,g−i] The other is palladium-catalyzed intramolecular nucleopalladation of the alkynes (Scheme 1a).[5d,e] Liu and co-workers reported an elegant palladium-catalyzed asymmetric intramolecular aminopalladation/desymmetric cyclization cascade of alkynylaniline-tethered malononitriles to access α-quaternary carbazolones with excellent enantioselectivities (Scheme 1b).[5d] With a similar strategy, they disclosed a palladium-catalyzed asymmetric cascade reaction of alkynylbenzoate-tethered malononitriles for the synthesis of enantioenriched fused isocoumarins, and this process involved intramolecular oxypalladation (Scheme 1b).[5e] Although great progress has been achieved in the asymmetric intramolecular nucleopalladation/desymmetric cyclization cascade of alkyne-tethered malononitriles, the intramolecular reaction requires the preinstallation of nucleophilic units into substrates, which sets a limit to the scope of substrates to some extent. The intermolecular nucleopalladation/desymmetric cyclization cascade of alkyne-tethered malononitriles may overcome the obstacle. Hence, the development of an asymmetric intermolecular nucleopalladation/desymmetric cyclization cascade of alkyne-tethered malononitriles with nucleophiles is highly desirable.

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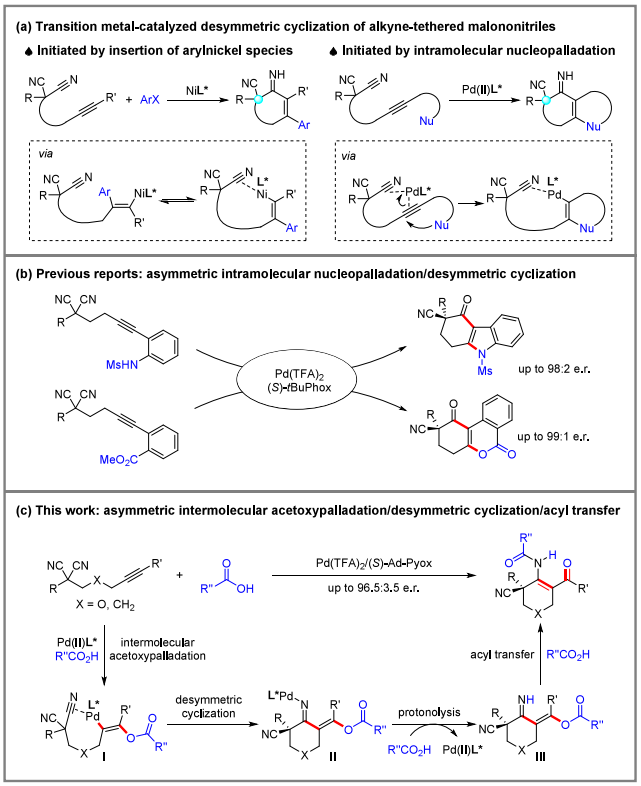
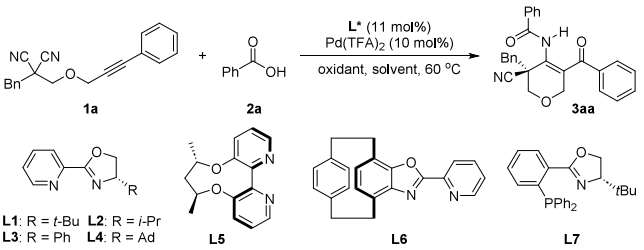
Scheme 1. Construction of Nitriles Bearing α-All-Carbon Quaternary Stereocenters via Transition-Metal-Catalyzed Enantioselective Desymmetric Cyclization of the Alkyne-Tethered Malononitriles



Carboxylic acids have been broadly employed as nucleophiles in *trans*-acetoxypalladation of the alkynes under the activation of Pd(II) catalysts.[6] By virtue of our interest in palladium-catalyzed asymmetric acetoxylative cyclization,[7] we envisioned palladium-catalyzed asymmetric intermolecular acetoxylative cyclization of alkyne-tethered malononitriles with carboxylic acids for the assembly of nitriles bearing α-all-carbon quaternary stereocenters. This palladium-catalyzed reaction of alkyne-tethered malononitriles with carboxylic acids can be conducted through the following pathway. Initially, asymmetric acetoxylative cyclization of the alkyne-tethered malononitrile with the carboxylic acid occurred, which involved intermolecular *trans*-acetoxypalladation, desymmetric cyclization, and protonolysis to give imine intermediate **III** embellished with the enol carboxylic ester moiety. Subsequently, intermediate **III** favored the transfer of an acyl group from the oxygen atom to the nitrogen atom under the acidic condition to provide the multifunctionalized nitrile bearing an α-all-carbon quaternary stereocenter (Scheme 1c). Herein, we disclose a palladium-catalyzed asymmetric intermolecular *trans*-acetoxypalladation/desymmetric cyclization/acyl transfer cascade of alkyne-tethered malononitriles using carboxylic acids as the external nucleophiles. This cascade reaction offers straightforward access to highly enantioselective synthesis of multifunctionalized nitriles bearing α-all-carbon quaternary stereogenic centers.

To begin our investigation, we selected alkyne-tethered malononitrile **1a** and benzoic acid **2a** as the model substrates to perform the reaction in toluene at 60 °C using a $Pd(TFA)_2$/(*S*)-*t*Bu-Pyox (**L1**) catalyst. As expected, target product **3aa** was afforded in 55% yield with 92.5:7.5 er (Table 1, entry 1). It should be noted that we observed palladium black during the reaction, indicating the inactivation of the catalyst. *p*-Benzoquinone (BQ) as an oxidant could ensure the activity of the catalyst and improve the yield to 70% (entry 3). Further evaluation of the solvents revealed that toluene was vital for the reaction. Solvents such as ethyl acetate (EA), 1,2-dichloroethane (DCE), and tetrahydrofuran (THF) yielded inferior data (entries 4−6, respectively). Employing 1,4-dioxane as the solvent, the enantiomer ratio was in accord with that with toluene, but the yield was only 45% (entry 7). To increase the degree of enantiocontrol, a series of *N*,*N*-ligands were screened. Compared with **L1**, both **L2** and **L3** resulted in diminished yields and enantioselectivities (entries 9 and 10, respectively). When the Pyox ligand was decorated with the bulkier 1-adamantyl group (**L4**), the yield of **3aa** was 66% with a slightly increased enantiomer ratio of 94:6 (entry 11). Encouraged by the recent excellent performances of ACBP and COXPY ligands,[7,8] we then examined our own developed C3-ACBP (**L5**) and COXPY (**L6**). **L6** behaved better than **L5**, albeit with moderate results (entries 12 and 13, respectively). With regard to *N*,*P*-ligand **L7**, it did not lead to the desired reaction, with all of substrate **1a** remaining (entry 14). In the end, a survey of the amount of benzoic acid **2a** was conducted. It was found that decreasing or increasing the amount of **2a**

Table 1. Optimization of Reaction Conditions[a]



entry	oxidant	solvent	L*	yield (%)[b]	er[c]
1	–	toluene	**L1**	55	92.5:7.5
2[d]	O_2	toluene	**L1**	59	92.5:7.5
3[e]	BQ	toluene	**L1**	70	93:7
4[e]	BQ	EA	**L1**	54	88.5:11.5
5[e]	BQ	DCE	**L1**	38	67.5:32.5
6[e]	BQ	THF	**L1**	36	88:12
7[e]	BQ	1,4-dioxane	**L1**	45	93:7
8[e]	BQ	DMF	**L1**	<5	–
9[e]	BQ	toluene	**L2**	51	77:23
10[e]	BQ	toluene	**L3**	34	82.5:17.5
11[e]	BQ	toluene	**L4**	66	94:6
12[e]	BQ	toluene	**L5**	25	44:56
13[e]	BQ	toluene	**L6**	45	14.5:85.5
14[e]	BQ	toluene	**L7**	–	–
15[e,f]	BQ	toluene	**L4**	60	94.5:5.5
16[e,g]	BQ	toluene	**L4**	75	93:7
17[e,h]	BQ	toluene	**L4**	66 (63)[i]	94.5:5.5

[a]Reaction conditions: **1a** (0.10 mmol), benzoic acid **2a** (0.70 mmol), $Pd(TFA)_2$ (10 mol %), **L*** (11 mol %), solvent (1.0 mL), 60 °C, 72 h. [b]Yield measured by analysis of ^1H nuclear magnetic resonance spectra, using 1,3,5-trimethoxybenzene as the internal standard. [c]Determined by chiral high-performance liquid chromatography. [d]Under 1 atm of O_2. [e]With 50 mol % BQ. [f]With 0.30 mmol of benzoic acid **2a**. [g]With 1.5 mmol of benzoic acid **2a**. [h]On a 0.20 mmol scale. [i]Isolated yield.

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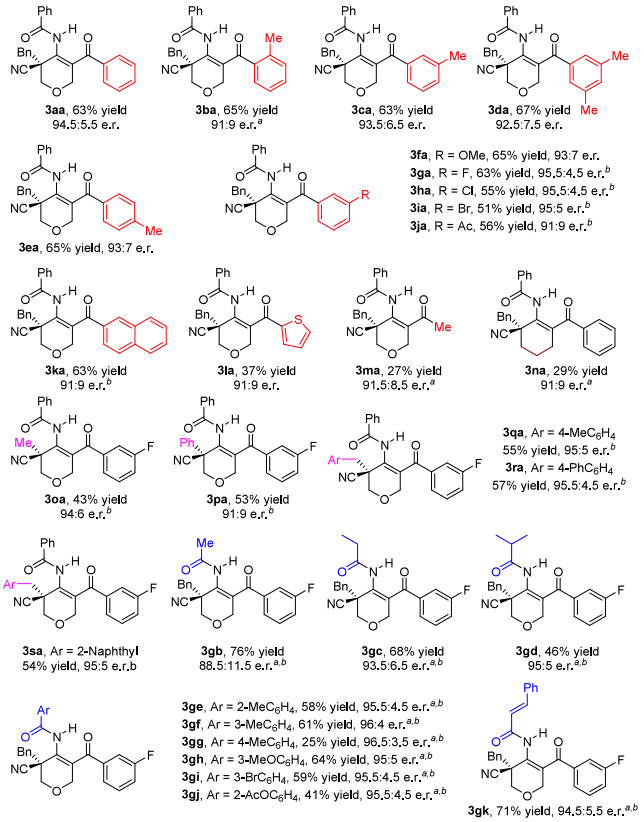
would reduce the yield or the enantiomer ratio (entries 15 and 16), and 7.0 equiv of **2a** proved to be superior. Upon judicious optimization of the reaction parameters, the reaction of **1a** and **2a** with BQ and $Pd(TFA)_2$/(*S*)-Ad-Pyox (**L4**) in toluene at 60 °C provided the best results, affording **3aa** in 63% isolated yield with 94.5:5.5 er (entry 17).

Having established reliable conditions, we explored the universality of this asymmetric acetoxylative cyclization/acyl transfer cascade by using various alkyne-tethered malononitriles **1** with benzoic acid **2a** (Scheme 2). First, the methyl

Scheme 2. Substrate Scope of Alkyne-Tethered Malononitriles 1 and Carboxylic Acids 2[c]



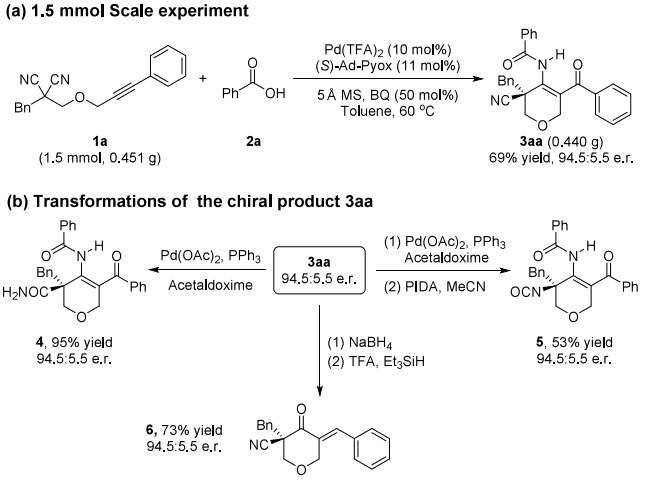
[a]With 50 mg of 5 Å MS. [b]With 5.0 mmol of **2**. [c]Reaction conditions: **1** (0.20 mmol), **2** (1.4 mmol), $Pd(TFA)_2$ (10 mol %), (*S*)-Ad-Pyox (**L4**) (11 mol %), BQ (50 mol %), toluene (2.0 mL), 60 °C, 72 h.

substituent at different positions of the phenyl ring was tested. For *o*-methyl-substituted substrate **1b**, product **3ba** was achieved in 65% yield with 91:9 er by adding 5 Å MS (details in Scheme 4). Alkyne-tethered malononitriles with the methyl substituent at other positions reacted competently and produced comparable outcomes (**3ca**−**3ea**). For the electron-donating methoxy group at the *meta* position of the phenyl ring, it was compatible with the standard conditions, whereas substrates containing electron-withdrawing groups exhibited relatively low reactivities. Fortunately, utilizing 25 equiv of **2a** facilitated the reactions and improved the yields (**3ga**−**3ja**). Remarkably, halogen groups had a positive influence on the enantioselectivities. Moreover, the strategy could also be extended to the methyl-substituted alkyne-tethered malononitrile and the substrate containing a carbon linker, delivering products **3ma** and **3na** with good enantioselectivities. Compared with the benzyl group, the methyl group (**3oa**) and phenyl group (**3pa**) afforded reduced enantioselectivities.

The success described above encouraged us to examine the scope of the carboxylic acids (Scheme 2). Due to the increase in ambient humidity, 5 Å MS was added to the reaction to avoid the formation of hydrolyzed products. Alkyl carboxylic acids could also be applied to the cascade reaction. Notably, the reactivities and enantioselectivities were affected by the steric hindrance of alkyl groups in an opposite fashion. For isobutyric acid **2d** with the more sterically hindered isopropyl group, product **3gd** could be obtained with 95:5 er, albeit in a modest yield of 46%. It was pleasing that a range of aromatic carboxylic acids could be transformed into products with excellent enantiomer ratios (**3ge**−**3gj**). In addition, satisfactory results were furnished by employing *trans*-cinnamic acid **2k** as the nucleophile. In addition, the absolute configuration of chiral product **3gb** was assigned as *R* on the basis of X-ray crystallographic analysis (see the Supporting Information for details), and other products were determined by analogy.

To verify the scalability of the strategy and guarantee the repeatability, a 1.5 mmol scale reaction of **1a** with **2a** was carried out under the conditions with 5 Å MS as a desiccant, giving **3aa** in 69% yield with 94.5:5.5 er consistent with the results on a 0.2 mmol scale (Scheme 3a). Subsequently, the

Scheme 3. Experiment at a 1.5 mmol Scale and Synthetic Transformations



potential for synthetic applications of multifunctionalized molecule **3aa** was investigated (Scheme 3b). Palladium-catalyzed transfer hydration of the cyano group of **3aa** using acetaldoxime as the water donor proceeded smoothly, furnishing primary amide **4** in 95% yield with 94.5:5.5 er. The hydration of the nitrile into the primary amide and (diacetoxyiodo)benzene-promoted Hofmann-type rearrangement of the primary amide afforded isocyanate **5** in 53% yield in two steps with the optical purity maintained. The ketocarbonyl group of **3aa** was easily converted into a hydroxy group with sodium borohydride (low diastereoselectivity), and then treatment of the alcohol intermediate with trifluoroacetic acid and triethylsilane unexpectedly led to α,β-unsaturated ketone product **6** via deoxygenative olefin migration. The configuration of the carbon−carbon double bond of **6** was determined to be *E* by the NOE spectrum (see the Supporting Information for details).

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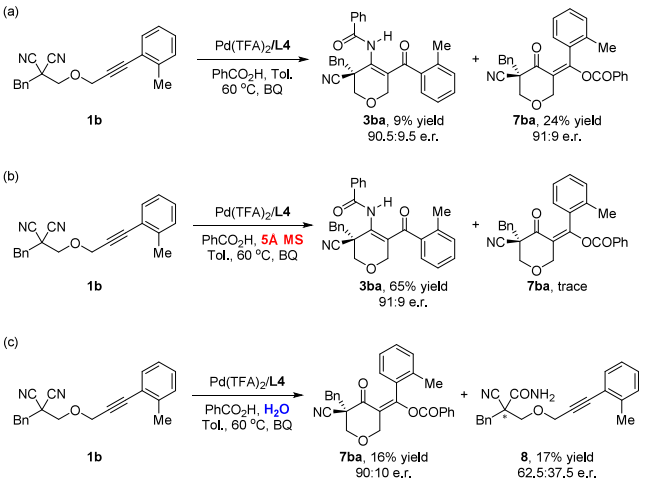
To shed light on the reaction mechanism, control experiments were conducted. When alkyne-tethered malononitrile **1b** was subjected to the reaction with benzoic acid **2a** under the standard conditions, target product **3ba** was isolated in only 9% yield (Scheme 4a). Meanwhile, side product **7ba** from

Scheme 4. Control Experiments

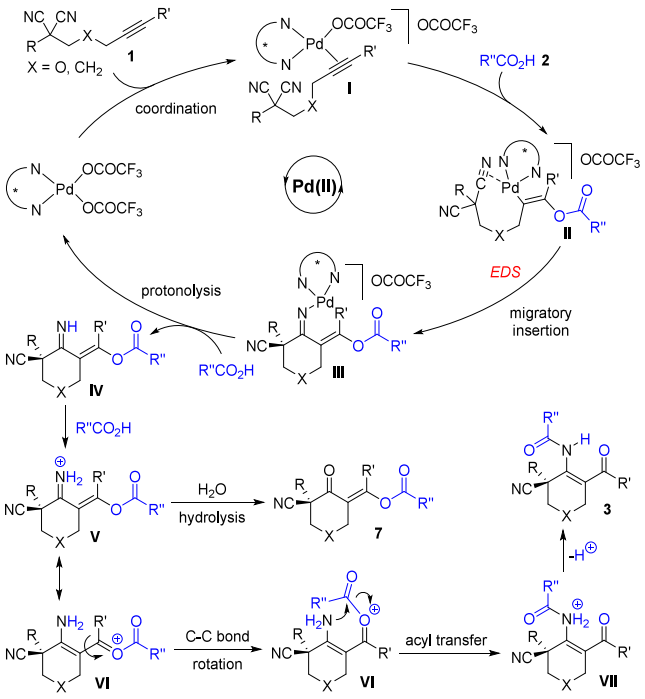


the hydrolysis of the imine was detected and showed an enantiomer ratio similar to that of **3ba**. Upon addition of 5 Å MS, hydrolyzed product **7ba** was distinctly inhibited and **3ba** was produced as the major product (Scheme 4b). Furthermore, the reaction was performed with addition of 10 equiv of water, producing hydrolyzed product **7ba** in 16% yield without the formation of **3ba** (Scheme 4c). Due to the hydrolysis of substrate **1b**, side product **8** was monitored during the reaction. The outcomes described above adequately indicated that the imine was the key intermediate of this cascade reaction and both **3ba** and **7ba** were generated from the imine intermediate with a decided enantiomer ratio.

Supported by the control experiments and previous reports,[5d,e,9,10] the plausible mechanism of the palladium-catalyzed asymmetric acetoxylative cyclization/acyl transfer cascade is proposed in Scheme 5. Initially, coordination of substrate **1** with the chiral Pd(II) catalyst and activation of the alkyne moiety for *trans*-acetoxypalladation delivered vinyl–Pd(II) species **II**. Selective insertion into one cyano group provided intermediate **III**, which was the enantio-determining step of the reaction. Protonolysis of intermediate **III** formed key imine intermediate **IV** and regenerated the Pd(II) catalyst. Imine **IV** was activated by carboxylic acid **2**, followed by tautomerism to furnish intermediate **VI**. Ultimately, intermediate **VI** underwent acyl transfer[9] to afford target product **3**. Meanwhile, imine **IV** might be hydrolyzed to give side product **7**.

In conclusion, we have accomplished a palladium-catalyzed asymmetric intermolecular acetoxylative cyclization/acyl transfer cascade of alkyne-tethered malononitriles with carboxylic acids. The substrate scope for both partners was extensive, and plenty of multifunctionalized nitriles bearing α-all-carbon quaternary stereocenters were synthesized with good to excellent enantiomer ratios. It is noteworthy that the products, including structures of cyano-bearing all-carbon quaternary stereocenters, enamides, and α,β-unsaturated ketones, could serve as chiral building blocks and undergo the diversifying

Scheme 5. Proposed Mechanism



reactions. We anticipate that this work will open new vistas for access to nitriles bearing α-all-carbon quaternary stereocenters.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.4c04865.

Experimental procedures, characterization data, single-crystal X-ray data, and copies of nuclear magnetic resonance and high-performance liquid chromatography spectra (PDF)

Accession Codes

Deposition Number 2385331 contains 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.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Rappoport, Z., Ed. *The Chemistry of the Cyano Group*; Wiley: London, 1970. (b) 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. (c) 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.

(2) For selected examples involving electrophilic functionalization of α-cyanocarbonyls, see: (a) Jautze, S.; Peters, R. Enantioselective Bimetallic Catalysis of Michael Additions Forming Quaternary Stereocenters. *Angew. Chem., Int. Ed.* **2008**, *47*, 9284−9288. (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) Trost, B. M.; Miller, J. R.; Hoffman, C. M., Jr A Highly Enantio- and Diastereoselective Molybdenum-Catalyzed Asymmetric Allylic Alkylation of Cyanoesters. *J. Am. Chem. Soc.* **2011**, *133*, 8165−8167.

(3) For selected examples involving electrophilic functionalization of ketene imines, see: (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) Jiao, Z.; Chee, K. W.; Zhou, J. Palladium-Catalyzed Asymmetric α-Arylation of Alkylnitriles. *J. Am. Chem. Soc.* **2016**, *138*, 16240−16243. (c) Chen, L.; Pu, M.; Li, S.; Sang, X.; Liu, X.; Wu, Y.-D.; Feng, X. Enantioselective Synthesis of Nitriles Containing a Quaternary Carbon Center by Michael Reactions of Silyl Ketene Imines with 1-Acrylpyrazoles. *J. Am. Chem. Soc.* **2021**, *143*, 19091−19098.

(4) For selected examples involving electrophilic α-cyanation of 1,3-dicarbonyls, see: (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) 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.

(5) For selected examples involving chemical catalytic desymmetrization of disubstituted malononitriles, see: (a) Lu, Z.; Hu, X.-D.; Zhang, H.; Zhang, X.-W.; Cai, J.; Usman, M.; Cong, H.; Liu, W.-B. Enantioselective Assembly of Cycloenones with a Nitrile-Containing All-Carbon Quaternary Center from Malononitriles Enabled by Ni Catalysis. *J. Am. Chem. Soc.* **2020**, *142*, 7328−7333. (b) Cai, J.; Bai, L.-G.; Zhang, Y.; Wang, Z.-K.; Yao, F.; Peng, J.-H.; Yan, W.; Wang, Y.; Zheng, C.; Liu, W.-B. Ni-Catalyzed Enantioselective [2+2+2] Cycloaddition of Malononitriles with Alkynes. *Chem.* **2021**, *7*, 799−811. (c) Li, K.; Wei, L.; Sun, M.; Li, B.; Liu, M.; Li, C. Enantioselective Synthesis of Pyridines with All-Carbon Quaternary Carbon Centers *via* Cobalt-Catalyzed Desymmetric [2+2+2] Cycloaddition. *Angew. Chem., Int. Ed.* **2021**, *60*, 20204−20209. (d) Hu, X.-D.; Chen, Z.-H.; Zhao, J.; Sun, R.-Z.; Zhang, H.; Qi, X.; Liu, W.-B. Enantioselective Synthesis of α-All-Carbon Quaternary Center-Containing Carbazolones *via* Amino-palladation/Desymmetrizing Nitrile Addition Cascade. *J. Am. Chem. Soc.* **2021**, *143*, 3734−3740. (e) Zhang, H.; Li, W.; Hu, X.-D.; Liu, W.-B. Enantioselective Synthesis of Fused Isocoumarins *via* Palladium-Catalyzed Annulation of Alkyne-Tethered Malononitriles. *J. Org. Chem.* **2021**, *86*, 10799−10811. (f) Chen, Z.-H.; Sun, R.-Z.; Yao, F.; Hu, X.-D.; Xiang, L.-X.; Cong, H.; Liu, W.-B. Enantioselective Nickel-Catalyzed Reductive Aryl/Alkenyl-Cyano Cyclization Coupling to All-Carbon Quaternary Stereocenters. *J. Am. Chem. Soc.* **2022**, *144*, 4776−4782. (g) Zheng, Y.-Q.; Li, C.-L.; Liu, W.-B.; Yu, Z.-X. DFT Study of Mechanism and Stereochemistry of Nickel-Catalyzed *trans*-Arylative Desymmetrizing Cyclization of Alkyne-Tethered Malononitriles. *J. Org. Chem.* **2022**, *87*, 16079−16083. (h) Liu, W.-M.; Lu, Z.; Wei, Q.; Liu, W.-B. Enantioselective Nickel-Catalyzed Reductive *anti*-Arylative Annulation of Alkyne-Tethered Malononitriles to Construct Quaternary Stereocenters. *Org. Lett.* **2023**, *25*, 1811−1816. (i) Long, J.; Lu, Z.; Li, X.-L.; Xue, P.; Liu, W.-B. Ni-Catalyzed Enantioselective Difunctionalization of Alkynes to Azepine Derivatives Bearing a Quaternary Center and an Unprotected Imine. *Chin. J. Chem.* **2024**, *42*, 873−878. (j) Zheng, Y.; Yang, T.; Chan, K. F.; Lin, Z.; Huang, Z. Cobalt-Catalysed Desymmetrization of Malononitriles *via* Enantioselective Borohydride Reduction. *Nat. Chem.* **2024**, *16*, 1845−1854.

(6) Liu, W.; Chen, P. Palladium-Catalyzed Cyclization of 1,6-Enynes. *Chem. J. Org. Chem.* **2024**, *44*, 2077−2091.

(7) Bai, Y.-Q.; Wang, X.-W.; Wu, B.; Wang, X.-Q.; Liao, R.-Z.; Li, M.; Zhou, Y.-G. Design and Synthesis of Planar-Chiral Oxazole-Pyridine *N,N*-Ligands: Application in Palladium-Catalyzed Asymmetric Acetoxylative Cyclization. *ACS Catal.* **2023**, *13*, 9829−9838.

(8) Gao, X.; Wu, B.; Huang, W.-X.; Chen, M.-W.; Zhou, Y.-G. Enantioselective Palladium-Catalyzed C-H Functionalization of Indoles Using an Axially Chiral 2,2'-Bipyridine Ligand. *Angew. Chem., Int. Ed.* **2015**, *54*, 11956−11960.

(9) (a) Zhao, L.; Lu, X. Pd^{II}-Catalyzed Cyclization of Alkynes Containing Aldehyde, Ketone, or Nitrile Groups Initiated by the Acetoxypalladation of Alkynes. *Angew. Chem., Int. Ed.* **2002**, *41*, 4343−4345. (b) Xia, G.; Han, X.; Lu, X. Palladium(II)-Catalyzed Cyclization Reaction of 2-(Alk-2'-ynyl-oxy)benzoin-triles or 2-(Alk-2'-ynylamino)-benzonitriles: A Facile Way to 2*H*-Chromene and 1,2-Dihydroquinoline Derivatives. *Adv. Synth. Catal.* **2012**, *354*, 2701−2705.

(10) (a) Zhou, C.; Larock, R. C. Synthesis of Aryl Ketones or Ketimines by Palladium-Catalyzed Arene C-H Addition to Nitriles. *J. Org. Chem.* **2006**, *71*, 3551−3558. (b) Dhara, H. N.; Rakshit, A.; Alam, T.; Patel, B. K. Metal-Catalyzed Reactions of Organic Nitriles and Boronic Acids to Access Diverse functionality. *Org. Biomol Chem.* **2022**, *20*, 4243−4277. (c) Rakshit, A.; Dhara, H. N.; Sahoo, A. K.; Patel, B. K. The Renaissance of Organo Nitriles in Organic Synthesis. *Chem. - Asian J.* **2022**, *17*, No. e202200792. (d) Rakshit, A.; Dhara, H. N.; Sahoo, A. K.; Alam, T.; Patel, B. K. Pd(II)-Catalyzed Synthesis of Furo[2,3-*b*]pyridines from β-Ketodinitriles and Alkynes *via* Cyclization and N−H/C Annulation. *Org. Lett.* **2022**, *24*, 3741−3746. (e) Dhara, H. N.; Rakshit, A.; Alam, T.; Sahoo, A. K.; Patel, B. K. Visible-Light-Mediated Solvent-Switched Photosensitizer-Free Synthesis of Polyfunctionalized Quinolines and Pyridines. *Org. Lett.* **2023**, *25*, 471−476. (f) Dhara, H. N.; Das, B.; Barik, D.; Manna, S.; Patel, B. K. Pd(II)-Catalyzed Three-Component Synthesis of Furo[2,3-*d*]-pyrimidines from β-Ketodinitriles, Boronic Acids, and Aldehydes. *Org.*

Lett. **2023**, *25*, 9070−9075. (g) Nath Dhara, H.; Manna, S.; Patel, B. K. A Cascade Synthesis of Furo-Pyrrolo-Pyridines *via* Pd(II)-Catalyzed Dual N−H/C Annulative-Cyclization. *Chem. - Eur. J.* **2025**, *31*, No. e202403470.

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