OL | Organic Letters

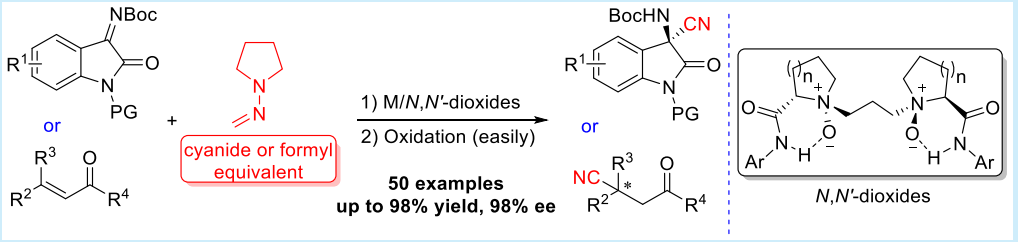
pubs.acs.org/OrgLett Letter

Catalytic Asymmetric Addition Reactions of Formaldehyde *N,N*-Dialkylhydrazone to Synthesize Chiral Nitrile Derivatives

Hang Zhang, Yao Luo, Chenhao Zhu, Shunxi Dong, Xiaohua Liu,* and Xiaoming Feng*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c01857 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



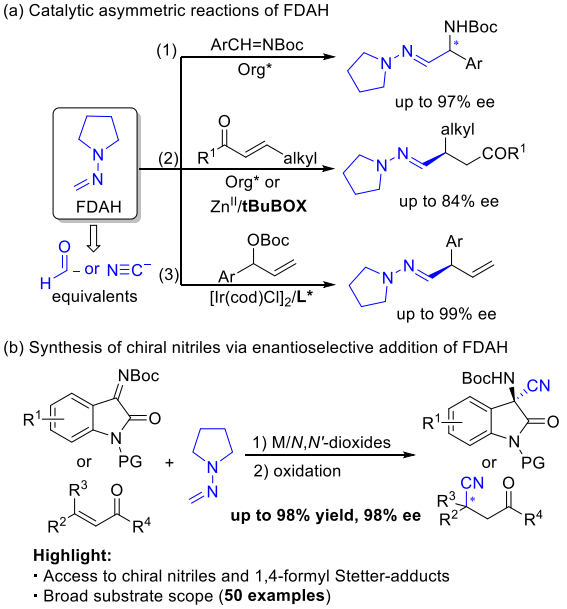
ABSTRACT: A number of nitrile-containing chiral molecules were synthesized via asymmetric nucleophilic addition of formaldehyde *N,N*-dialkylhydrazone as the nitrile equivalent. Chiral *N,N′*-dioxide/metal salt complexes enabled the asymmetric addition reactions to both isatin-derived imines and α,β-unsaturated ketones, generating amino nitriles and 4-oxobutanenitrile derivatives in good yields with high enantioselectivities. This protocol was highlighted by avoiding the use of toxic nitrile reagents, wide substrate scope, and versatile transformations of chiral hydrazone adducts into other valuable molecules.

Downloaded via UPPSALA UNIV on June 13, 2020 at 10:07:26 (UTC).
See https://pubs.acs.org/sharingguidelines for options on how to legitimately share published articles.

Chiral nitrile-containing molecules play a significant role in asymmetric synthesis since they can be readily converted into other valuable optically active functionalized compounds, such as carboxylic acids derivatives, amines, aldehydes, ketones, and heterocycles.[1] Moreover, an array of enantioenriched nitriles have been found in pharmaceutical molecules.[2] During the past several decades, tremendous endeavors have been devoted to the rapid construction of chiral nitriles from both academics and industry researchers.[3,4] Among of various methods established, the addition of cyano reagents to prochiral carbonyl compounds, imines, and alkenes represents one of the most efficient and prevailing strategies.[4] However, most of these methods suffered from the use of highly toxic cyanide reagents as the nitrile source.[4] In light of safety and environmental constraints, the search for low toxic[5] and/or cyanide-free[6] nitrile sources has become a much sought after goal among synthetic chemists. Until now, several well-designed nitrile equivalents have been successfully utilized in a few of organic transformations,[6] including sporadic asymmetric variants.[6b−f,8,9] Nevertheless, there still leaves much room for improvement in terms of type of catalyst, efficiency, and substrate scope.

Benefitting from ready availability and ease of transformation into formyl and cyanide functional groups, formaldehyde *N,N*-dialkylhydrazone (FDAH) has been extensively studied as a distinct and useful neutral synthon by the groups of Enders, Lassaletta, and others.[7−9] Notably, the asymmetric addition of such hydrazone to imines (Scheme 1a-1) and electron-deficient olefins provides an alternative route to enantiomerically enriched Strecker adducts and related

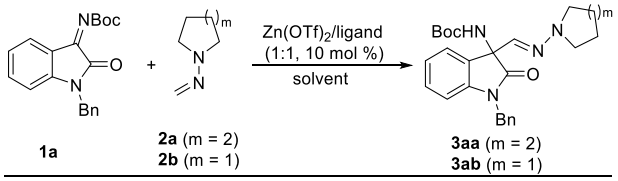
Scheme 1. Catalytic Asymmetric Additions of FDAH

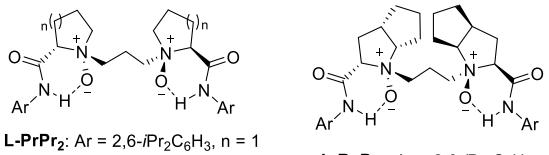


Received: June 2, 2020

© XXXX American Chemical Society

Table 1. Optimization of the Reaction Conditions[a]





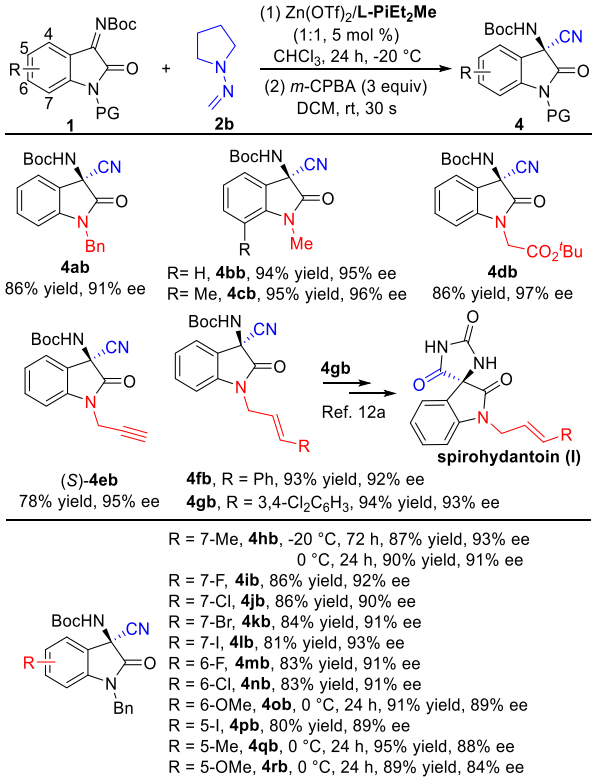
L-PrPr$_2$: Ar = 2,6-*i*Pr$_2$C$_6$H$_3$, n = 1
L-PiPr$_2$: Ar = 2,6-*i*Pr$_2$C$_6$H$_3$, n = 2
L-PiEt$_2$: Ar = 2,6-Et$_2$C$_6$H$_3$, n = 2
L-PiEt$_2$Me: Ar = 2,6-Et$_2$-4-MeC$_6$H$_2$, n = 2
L-PiMe$_3$: Ar = 2,4,6-Me$_3$C$_6$H$_2$, n = 2

L-RaPr$_2$: Ar = 2,6-*i*Pr$_2$C$_6$H$_3$

entry	ligand	yield[b] (%)	ee[c] (%)
1	L-**PrPr$_2$**	97	30
2	L-**RaPr$_2$**	52	20
3	L-**PiPr$_2$**	98	49
4	L-**PiEt$_2$**	98	70
5	L-**PiEt$_2$Me**	98	75
6	L-**PiMe$_3$**	90	74
7[d]	L-**PiEt$_2$Me**	98	79
8[d,e]	L-**PiEt$_2$Me**	98	83
9[d–f]	L-**PiEt$_2$Me**	98	92
10[d–g]	L-**PiEt$_2$Me**	96	92

[a]Reactions were performed with **1a** (0.10 mmol), **2a** (1.5 equiv), 4 Å MS (20 mg), and Zn(OTf)$_2$/ligand (1:1, 10 mol %) in CH_2Cl_2 (0.5 mL) at 30 °C for 24 h. [b]Yield of the isolated product. [c]Determined by chiral HPLC analysis on a chiral stationary phase. [d]$CHCl_3$ (0.5 mL) was used without 4 Å MS. [e]Substrate **2b** was used. [f]At −20 °C. [g]5 mol % catalyst in $CHCl_3$ (0.2 mL).

Scheme 2. Substrate Scope for Isatin-Derived Imines[a]



R = 7-Me, **4hb**, -20 °C, 72 h, 87% yield, 93% ee
0 °C, 24 h, 90% yield, 91% ee
R = 7-F, **4ib**, 86% yield, 92% ee
R = 7-Cl, **4jb**, 86% yield, 90% ee
R = 7-Br, **4kb**, 84% yield, 91% ee
R = 7-I, **4lb**, 81% yield, 93% ee
R = 6-F, **4mb**, 83% yield, 91% ee
R = 6-Cl, **4nb**, 83% yield, 91% ee
R = 6-OMe, **4ob**, 0 °C, 24 h, 91% yield, 89% ee
R = 5-I, **4pb**, 80% yield, 89% ee
R = 5-Me, **4qb**, 0 °C, 24 h, 95% yield, 88% ee
R = 5-OMe, **4rb**, 0 °C, 24 h, 89% yield, 84% ee

[a]Reactions were performed with **1** (0.20 mmol), **2b** (1.5 equiv), and Zn(OTf)$_2$/L-**PiEt$_2$Me** (1:1, 5 mol %) in $CHCl_3$ (0.4 mL) at −20 °C for 24 h; after column separation, *m*-CPBA (85 wt %, 3 equiv) was added to the products **3** in CH_2Cl_2 (2.0 mL).

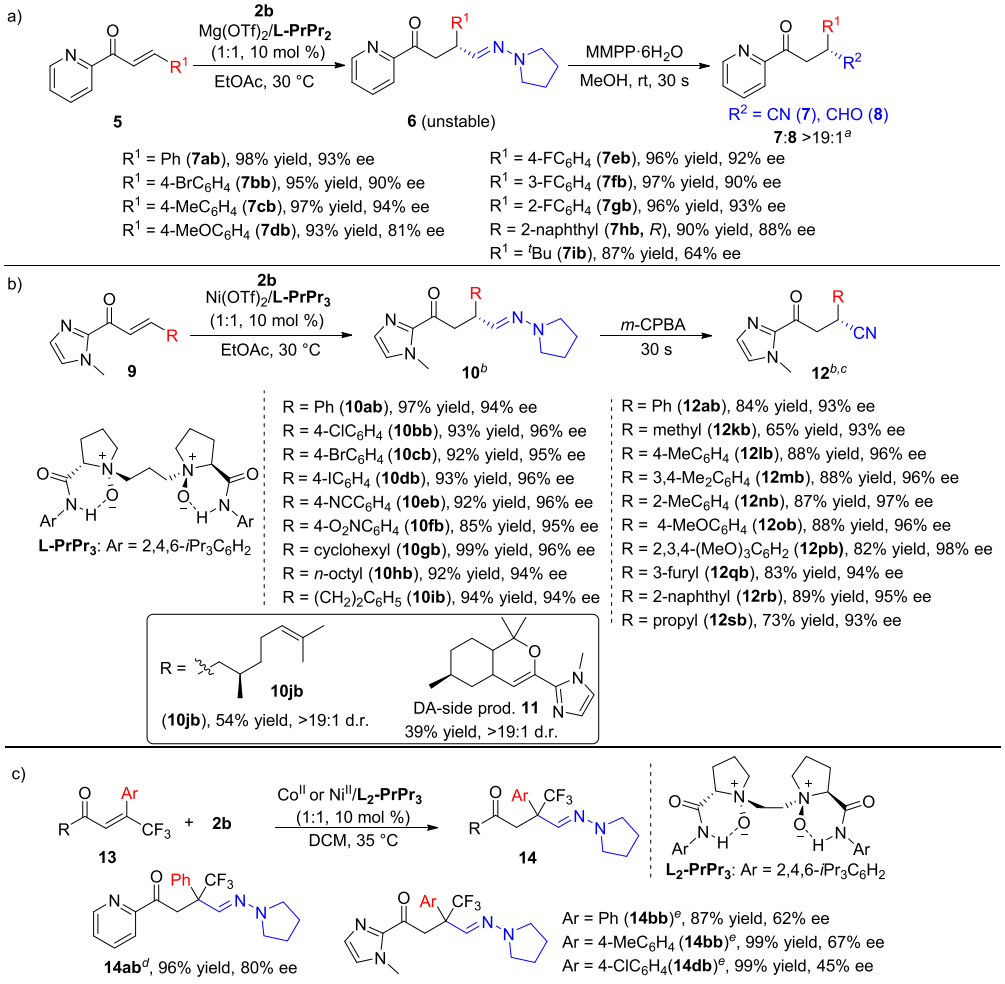
nitriles.[8] Generally, chiral organocatalysts were found to be particularly appropriate for accelerating foregoing reactions.[7d,8] In contrast, asymmetric variants with chiral Lewis acid complexes were rare.[9] In this respect, the group of Lassaletta described the first example wherein Zn(OTf)$_2$/**^{t}BuBOX** was employed as an efficient promoter in asymmetric conjugate addition of FDAH to alkyl-substituted α-hydroxy enones (Scheme 1a-2).[9a] Recently, Carreira and co-workers developed an elegant Iridium-mediated asymmetric allylic substitution with FDAH as a neutral C1-nucleophile (Scheme 1a-3).[9b] As part of our interest in synthesis of chiral nitriles,[10] we envisioned that chiral *N,N′*-dioxide−metal complexes[11] developed by our group have potential to be efficient catalysts in the asymmetic additions of FDAH to imines and electron-deficient olefins for two reasons: (1) The well-defined chiral *N,N′*-dioxide−metal Lewis acid catalysts prefer to coordinate with electrophiles in a bidentate fashion rather than nitrogen atom of FDAH, which was crucial for maintaining the high activity of catalyst and avoiding the decomposition of FDAH.[10e] (2) Outstanding performance has been shown for chiral *N,N′*-dioxide−metal complexes in discriminating prochiral face of various electrophiles.[11c] Herein, we report our achievement in this area. Highly enantioselective addition reactions of formaldehyde *N,N*-dialkylhydrazone with isatin-derived imines and α,β-unsaturated ketones were achieved in the presence of chiral *N,N′*-dioxide complexes of Zn^{II}, Mg^{II}, or Ni^{II} salts. Various enantioenriched nitriles, including amino nitriles and 4-oxobutanenitriles, were afforded in good yields with high enantiomeric excess by subsequent oxidization of the adducts under mild conditions.

First, the addition of formaldehyde *N,N*-dialkylhydrazone **2a** to isatin-derived imine **1a** was selected as the model reaction to optimize the reaction conditions (Table 1). On the basis of the initial investigation,[10e] Zn(OTf)$_2$ was employed as the central metal to examine chiral *N,N′*-dioxide ligands. It was found that L-pipecolic acid derived L-**PiPr$_2$** was superior than L-**PrPr$_2$** derived from L-proline and L-**RaPr$_2$** derived from L-ramipril in terms of enantioselectivity (98% yield, 49% ee, entry 3 vs entries 1 and 2). The substituents at the amide moiety in the ligand displayed an important role on the chiral control, the use of the ligand L-**PiEt$_2$Me** bearing 2,6-diethyl-4-methyl substituent delivered the highest ee value (entry 5 vs entries 4 and 6, 75% ee). When $CHCl_3$ was used as the solvent and no 4 Å MS was added, the product **3aa** was obtained in 98% yield with a slightly higher ee value (entry 7 vs entry 5; 79% ee). Fortunately, switching substrate **2a** having piperidine ring to **2b** with pyrrolidine ring resulted in an increased enantiomeric excess (entry 8, 83% vs 79% ee). In addition, performing the reaction at −20 °C provided a significant improvement for the enantioselectivity of **3ab** (entry 9, 92% ee). Finally, adjustment of the reaction concentration supplied the optimal conditions, and the product **3ab** was isolated in 96% yield, 92% ee at 5 mol % catalyst loading (entry 10). As expected, treatment of adduct **3ab** with *m*-CPBA (3 equiv) delivered the corresponding chiral amino nitrile **4ab** in 90% yield with 91% ee.

With these optimized reaction conditions in hand, various substituted isatin imines **1** were examined. As shown in

https://dx.doi.org/10.1021/acs.orglett.0c01857
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Substrate Scope for Ketones[a]



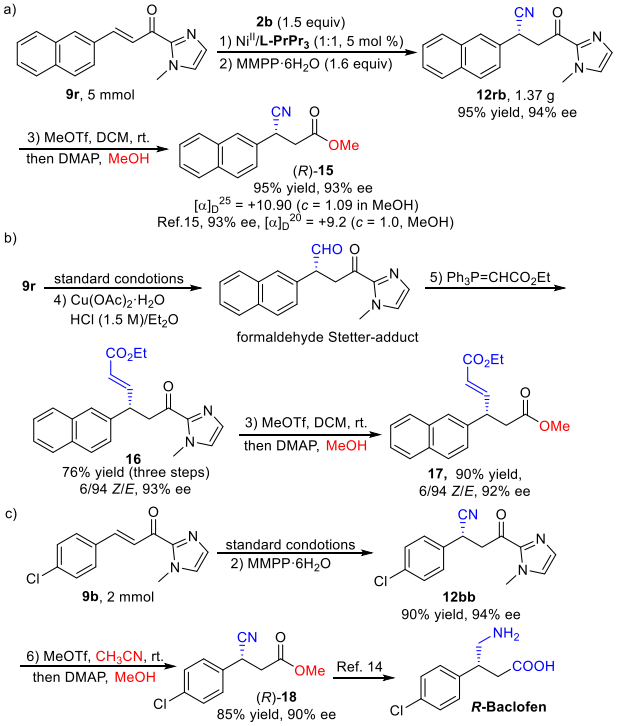
[a]These reactions were performed with **5** (0.20 mmol), **2b** (1.5 equiv), and $Mg(OTf)_2$/L-**PrPr**$_2$ (1:1, 10 mol %) in EtOAc (1.0 mL) at 30 °C for the indicated time. Then MMPP·$6H_2O$ (80 wt %, 204 mg, 1.6 equiv) was used to oxidize isolated product **6** into nitriles **7**. [b]Carried out with **9** (0.20 mmol), **2b** (1.5 equiv), and $Ni(OTf)_2$/L-**PrPr**$_3$ (1:1, 10 mol %) in EtOAc (1.0 mL) at 30 °C. [c]Then *m*-CPBA (85 wt %, 80 mg, 2 equiv) was used in the following oxidation process. [d]Performed with **13a** (0.10 mmol), **2b** (1.5 equiv), and $Co(OTf)_2$/L$_2$-**PrPr**$_3$ (1:1, 10 mol %) in DCM (0.5 mL) at 35 °C for 24 h. [e]Carried out with **13b**−**13d** (0.10 mmol), **2b** (1.5 equiv), and $Ni(OTf)_2$/L$_2$-**PrPr**$_3$ (1:1, 10 mol %) in DCM (0.5 mL) at 35 °C for 48 h.

Scheme 2, the reaction of FDAH **2b** with *N*-Boc imines **1** prepared from different *N*-protected isatin derivatives, such as methyl, $-CH_2CO_2{}^tBu$, propargyl, and allyl groups, occurred well, yielding the corresponding chiral amino nitriles **4bb**−**4gb** in good to high yields (78−95%) with excellent enantioselectivities (92−97% ee). It was worth noting that the product **4gb** (94% yield and 93% ee) could be easily transformed into the spirohydantoin I according to a previous report,[12a] which was potentially useful in the treatment of pain.[12b] The substituents on the phenyl ring of isatin backbones were also investigated. Regardless of the substituent pattern and the electronic property of the aryl moiety, the products **4hb**−**4rb** could be furnished in good results (81−95% yield, 84−93% ee). In addition, the absolute configuration of the product **4eb** was determined to be *S* by X-ray crystal diffraction analysis.

Subsequently, we turned our attention to extend the substrate scope to the α,β-unsaturated carbonyl compounds. Unsaturated acylpyridine **5a** and FDAH **2b** were selected as model reactants, and only moderate ee value was given under the above optimized conditions. Therefore, the reaction parameters were modulated (for details, see the SI). When the reaction was carried out with $Mg(OTf)_2$/L-**PrPr**$_2$ in EtOAc at 30 °C, following an oxidation reaction of the addition product **6ab** by MMPP·$6H_2O$ (magnesium monoperoxyphthalate), the corresponding chiral β-cyano substituted ketone **7ab** was isolated in 98% yield and 93% ee along with a minute amount of β-formyl-substituted ketone **8ab**. Next, different unsaturated acylpyridines **5** were tested (Scheme 3a). It is important to note that the addition products **6**, especially with electron-donating substituents at the β-aryl group, were unstable at room temperature. Thus, these adducts were immediately converted into the stable nitrile adducts **7**. As summarized in Scheme 3a, subjecting β-aromatic substituted enones **5a**−**5g** into the above conditions afforded the desired products **7ab**−**7hb** in high yields and moderate to high enantioselectivities (90−98% yields and 81−94% ee). In addition, the absolute configuration of the product **7hb** was determined to be *R* by X-ray crystal diffraction analysis. In comparison, the reaction of the substrate **5i** with a *tert*-butyl group provided the adduct **7ib** in moderate ee value (64% ee). Encouraged by these results, we attempted to displace unsaturated acylpyridines **5** with α,β-unsaturated 2-acylimida-

https://dx.doi.org/10.1021/acs.orglett.0c01857
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 4. Gram-Scale Experiment and Product Derivatizations



zoles **9**, which could be readily transformed into esters.[13] To our delight, in the presence of $Ni(OTf)_2$/L-**PrPr$_3$** complex, substrates **9a**−**9i** bearing either *β*-aryl or *β*-alkyl groups led to the addition products **10ab**−**10ib** in high yields with excellent enantioselectivities (Scheme 3b, 85−99% yields, 94−96% ee). When the ketone **9j** bearing a chiral substituent was used in this catalytic system, the addition product **10jb** was isolated in excellent diastereoselectivity (>19:1 dr) with 54% yield along with 39% yield of the intramolecular Diels−Alder adduct **11** (>19:1 dr). Since the products **10** with electron-rich aromatic groups or alkyl substituents were not stable, they were readily oxidized into chiral nitriles **12** by using *m*-CPBA as the oxidant. As depicted in Scheme 3b, all of the nitrile products **12** were obtained in moderate to good yields (**12ab**, **12kb**−**12sb**, 65−89% yield) with excellent enantioselectivities (93−98% ee). In addition, sterically congested *β*,*β*-disubstituted *α*,*β*-unsaturated ketones **13a**−**d** were also well tolerated in modified catalytic system, generating the all-carbon quaternary nitrile products **14** in high yields with moderate enantioselectivities (Scheme 3c, **14ab**−**14db**, 87−99% yields, 45−80% ee).

To evaluate the synthetic potential of the catalytic system, a gram-scale synthesis of 4-oxobutanenitrile **12rb** was carried out. As shown in Scheme 4a, 5.0 mmol of **9r** reacted smoothly with 7.5 mmol of **2b** with 5 mol % of the catalyst $Ni(OTf)_2$/L-**PrPr$_3$**, delivering the product **12rb** in 95% yield and 94% ee after a subsequent oxidative transformation. Furthermore, treatment of product **12rb** with MeOTf, followed by DMAP in methanol could furnish synthetic useful intermediate chiral *β*-cyano ester[1c,d,10a] **15** in 95% yield and 93% ee (Scheme 4a). The absolute configuration of **15** was assigned to be *R* by comparing the optical rotation data in reported literature.[14] Additionally, in the presence of copper salt and HCl(1.5 M)/Et_2O, the addition product **10rb** smoothly converted into chiral *β*-formyl substituted carbonyl derivative, which was difficult to access by conventional catalytic Stetter reaction.[15] Moreover, following by a well-established Wittig reaction, the 1,6-dicarbonyl compound **16** was afforded in 76% yield (three steps), 6/94 *Z*/*E*, and 93% ee. With the same procedure shown in Scheme 4a, compound **16** could be transformed into the corresponding ester **17** in 90% yield and 92% ee (Scheme 4b). In addition, the *β*-cyano-substituted ketone **12bb** was also obtained in 90% yield and 94% ee after a subsequent oxidative transformation. Treatment of product **12bb** with MeOTf in acetonitrile, followed by a catalytic amount of DMAP in methanol, could furnish synthetic useful intermediate chiral *β*-cyano ester **18** in 85% yield and 90% ee (Scheme 4c), which could be easily transformed into the drug *R*-Baclofen according to a previous report.[14]

In summary, the catalytic asymmetric addition reactions of formaldehyde *N*,*N*-dialkylhydrazone with isatin imines or *α*,*β*-unsaturated ketones were achieved by using chiral *N*,*N*′-dioxide/metal salt complexes as the catalysts. The corresponding chiral adducts were readily converted into enantioenriched nitrile compounds. This addition/oxidation sequence provided an efficient and practical access to diverse chiral nitriles without having to resort to the use of highly toxic nitrile reagents. In addition, it also gave a convenient way to synthesize the formaldehyde Stetter adduct. Further studies on the exploration of the current method in organic synthesis and extension to other substrates are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01857.

Experimental details, characterization data (copies of ^{1}H, ^{13}C{^{1}H}, ^{19}F{^{1}H} NMR, HPLC, and HRMS data) (PDF)

Accession Codes

CCDC 1982495 and 2007078 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

Xiaohua Liu − *Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, China*; orcid.org/0000-0001-9555-0555; Email: xhliu@scu.edu.cn

Xiaoming Feng − *Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, China*; orcid.org/0000-0003-4507-0478; Email: xmfeng@scu.edu.cn

Authors

Hang Zhang − *Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, China*

Yao Luo − *Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, China*

https://dx.doi.org/10.1021/acs.orglett.0c01857
Org. Lett. XXXX, XXX, XXX−XXX

Chenhao Zhu − *Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, China*

Shunxi Dong − *Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, China;* orcid.org/0000-0002-3018-3085

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c01857

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (Nos. 21801175 and U19A2014) for financial support.

■ REFERENCES

(1) For selected comprehensive books or a review, see: (a) Rappoport, Z. E. *The Chemistry of the Cyano Group*; Wiley, Weinheim, 1971. (b) Larock, R. C.; Yao, T. *Comprehensive Organic Transformations*, 3rd ed.; Wiley, Weinheim, 2018. (c) Malykh, A. G.; Sadaie, M. R. Piracetam and Piracetam-Like Drugs. *Drugs* **2010**, *70*, 287. (d) Silverman, R. B. From Basic Science to Blockbuster Drug: The Discovery of Lyrica. *Angew. Chem., Int. Ed.* **2008**, *47*, 3500.

(2) For selected reviews, see: (a) Lednicer, D.; Mitscher, L. A. *The Organic Chemistry of Drug Synthesis*; Wiley: New York, 1980;. (b) Fleming, F. F. Nitrile-containing Natural Products. *Nat. Prod. Rep.* **1999**, *16*, 597. (c) 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.

(3) (a) Tolman, C. A.; Mckinney, R. J.; Seidel, W. C.; Druliner, J. D.; Stevens, W. R. Homogeneous Nickel-Catalyzed Olefin Hydrocyanation. *Adv. Catal.* **1985**, *33*, 1. (b) Tolman, C. A. Steric and Electronic Effects in Olefin Hydrocyanation at Du Pont: A Scientific and Industrial Success Story. *J. Chem. Educ.* **1986**, *63*, 199.

(4) For selected reviews, see: (a) Enders, D.; Shilvock, J. P. Some Recent Applications of α-Amino Nitrile Chemistry. *Chem. Soc. Rev.* **2000**, *29*, 359. (b) Gawronski, J.; Wascinska, N.; Gajewy, J. Recent Progress in Lewis Base Activation and Control of Stereoselectivity in the Additions of Trimethylsilyl Nucleophiles. *Chem. Rev.* **2008**, *108*, 5227. (c) Khan, N. H.; Kureshy, R. I.; Abdi, S. H. R.; Agrawal, S.; Jasra, R. V. Metal Catalyzed Asymmetric Cyanation Reactions. *Coord. Chem. Rev.* **2008**, *252*, 593. (d) Shibasaki, M.; Kanai, M.; Matsunaga, S.; Kumagai, N. Recent Progress in Asymmetric Bifunctional Catalysis Using Multimetallic Systems. *Acc. Chem. Res.* **2009**, *42*, 1117. (e) Wang, J.; Liu, X. H.; Feng, X. M. Asymmetric Strecker Reactions. *Chem. Rev.* **2011**, *111*, 6947. (f) Kurono, N.; Ohkuma, T. Catalytic Asymmetric Cyanation Reactions. *ACS Catal.* **2016**, *6*, 989.

(5) (a) Gaspar, B.; Carreira, E. M. Mild Cobalt-Catalyzed Hydrocyanation of Olefins with Tosyl Cyanide. *Angew. Chem., Int. Ed.* **2007**, *46*, 4519. (b) Choi, J.; Fu, G. C. Catalytic Asymmetric Synthesis of Secondary Nitriles via Stereoconvergent Negishi Arylations and Alkenylations of Racemic α-Bromonitriles. *J. Am. Chem. Soc.* **2012**, *134*, 9102. (c) Jiao, Z. W.; Chee, K. W.; Zhou, J. R. Palladium-Catalyzed Asymmetric α-Arylation of Alkylnitriles. *J. Am. Chem. Soc.* **2016**, *138*, 16240. (d) Fang, X. J.; Yu, P.; Morandi, B. Catalytic Reversible Alkene-nitrile Interconversion Through Controllable Transfer Hydrocyanation. *Science* **2016**, *351*, 832. (e) Yu, P.; Morandi, B. Nickel-Catalyzed Cyanation of Aryl Chlorides and Triflates Using Butyronitrile: Merging Retro-hydrocyanation with Cross-Coupling. *Angew. Chem., Int. Ed.* **2017**, *56*, 15693. (f) Bhunia, A.; Bergander, K.; Studer, A. Cooperative Palladium/Lewis Acid-Catalyzed Transfer Hydrocyanation of Alkenes and Alkynes Using 1-Methylcyclohexa-2,5-diene-1-carbonitrile. *J. Am. Chem. Soc.* **2018**, *140*, 16353. (g) Orecchia, P.; Yuan, W. M.; Oestreich, M. Transfer Hydrocyanation of α- and α,β-Substituted Styrenes Catalyzed by Boron Lewis Acids. *Angew. Chem., Int. Ed.* **2019**, *58*, 3579.

(6) (a) Fier, P. S.; Maloney, K. M. NHC-Catalyzed Deamination of Primary Sulfonamides: A Platform for Late-Stage Functionalization. *J. Am. Chem. Soc.* **2019**, *141*, 1441. (b) Schuppe, A. W.; Borrajo-Calleja, G. M.; Buchwald, S. L. Enantioselective Olefin Hydrocyanation without Cyanide. *J. Am. Chem. Soc.* **2019**, *141*, 18668. (c) Li, X. X.; You, C.; Yang, J. X.; Li, S. L.; Zhang, D. Q.; Lv, H.; Zhang, X. M. Asymmetric Hydrocyanation of Alkenes without HCN. *Angew. Chem., Int. Ed.* **2019**, *58*, 10928. (d) Betke, T.; Rommelmann, P.; Oike, K.; Asano, Y.; Gröger, H. Cyanide-Free and Broadly Applicable Enantioselective Synthetic Platform for Chiral Nitriles through a Biocatalytic Approach. *Angew. Chem., Int. Ed.* **2017**, *56*, 12361. (e) Guin, J.; Varseev, G.; List, B. Catalytic Asymmetric Protonation of Silyl Ketene Imines. *J. Am. Chem. Soc.* **2013**, *135*, 2100. (f) Enders, D.; Plant, A.; Backhaus, D.; Reinhold, U. Asymmetric Synthesis of α-Substituted Nitriles and Cyanohydrins by Oxidative Cleavage of Chiral Aldehyde Hydrazones with Magnesium Monoperoxyphthalate. *Tetrahedron* **1995**, *51*, 10699.

(7) For representative reviews, see: (a) Enders, D.; Wortmann, L.; Peters, R. Recovery of Carbonyl Compounds from *N,N*-Dialkylhydrazones. *Acc. Chem. Res.* **2000**, *33*, 157. (b) Brehme, R.; Enders, D.; Fernandez, R.; Lassaletta, J. M. Aldehyde *N,N*-Dialkylhydrazones as Neutral Acyl Anion Equivalents: Umpolung of the Imine Reactivity. *Eur. J. Org. Chem.* **2007**, 5629. (c) Lazny, R.; Nodzewska, A. *N,N*-Dialkylhydrazones in Organic Synthesis. From Simple *N,N*-Dimethylhydrazones to Supported Chiral Auxiliaries. *Chem. Rev.* **2010**, *110*, 1386. (d) de Gracia Retamosa, M.; Matador, E.; Monge, D.; Lassaletta, J. M.; Fernandez, R. Hydrazones as Singular Reagents in Asymmetric Organocatalysis. *Chem. - Eur. J.* **2016**, *22*, 13430.

(8) (a) Herrera, R. P.; Monge, D.; Martín-Zamora, E.; Fernández, R.; Lassaletta, J. M. Organocatalytic Conjugate Addition of Formaldehyde *N,N*-Dialkylhydrazones to β,γ-Unsaturated α-Keto Esters. *Org. Lett.* **2007**, *9*, 3303. (b) Dixon, D. J.; Tillman, A. L. Enantioselective Brønsted Acid Catalyzed Addition Reactions of Methyleneaminopyrrolidine to Imines. *Synlett* **2005**, *17*, 2635. (c) Rueping, M.; Sugiono, E.; Theissmann, T.; Kuenkel, A.; Köckritz, A.; Pews-Davtyan, A.; Nemati, N.; Beller, M. An Enantioselective Chiral Brønsted Acid Catalyzed Imino-Azaenamine Reaction. *Org. Lett.* **2007**, *9*, 1065. (d) Hashimoto, T.; Hirose, M.; Maruoka, K. Asymmetric Imino Aza-enamine Reaction Catalyzed by Axially Chiral Dicarboxylic Acid: Use of Arylaldehyde *N,N*-Dialkylhydrazones as Acyl Anion Equivalent. *J. Am. Chem. Soc.* **2008**, *130*, 7556. (e) Hashimoto, T.; Kimura, H.; Maruoka, K. Enantioselective Formal Alkenylations of Imines Catalyzed by Axially Chiral Dicarboxylic Acid Using Vinylogous Aza-Enamines. *Angew. Chem., Int. Ed.* **2010**, *49*, 6844.

(9) The main obstacle to Lewis acid catalysis, as described in previous reports,[7d] lies in the deactivation by the nitrogenated reagent and/or the concurrence of undesired side reactions. (a) Monge, D.; Martín-Zamora, E.; Vázquez, J.; Alcarazo, M.; Álvarez, E.; Fernández, R.; Lassaletta, J. M. Enantioselective Conjugate Addition of *N,N*-Dialkylhydrazones to α-Hydroxy Enones. *Org. Lett.* **2007**, *9*, 2867. (b) Breitler, S.; Carreira, E. M. Formaldehyde *N,N*-Dialkylhydrazones as Neutral Formyl Anion Equivalents in Iridium-Catalyzed Asymmetric Allylic Substitution. *J. Am. Chem. Soc.* **2015**, *137*, 5296.

(10) See some examples: (a) Wang, J.; Li, W.; Liu, Y. B.; Chu, Y. Y.; Lin, L. L.; Liu, X. H.; Feng, X. M. Asymmetric Cyanation of Activated Olefins with Ethyl Cyanoformate Catalyzed by a Modular Titanium Catalyst. *Org. Lett.* **2010**, *12*, 1280. (b) Zhao, J. N.; Liu, X. H.; Luo, W. W.; Xie, M. S.; Lin, L. L.; Feng, X. M. 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. (c) Zhao, J. N.; Fang, B.; Luo, W. W.; Hao, X. Y.; Liu, X. H.; Lin, L. L.; Feng, X. M. 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. (d) Zheng, J. F.; Lin, L. L.; Dai, L.; Tang, Q.; Liu, X.

H.; Feng, X. M. Nickel-Catalyzed Conjugate Addition of Silyl Ketene Imines to In Situ Generated Indol-2-ones: Highly Enantioselective Construction of Vicinal All-Carbon Quaternary Stereocenters. *Angew. Chem., Int. Ed.* **2017**, *56*, 13107. (e) Zhang, H.; Yao, Q.; Cao, W. D.; Ge, S. L.; Xu, J. X.; Liu, X. H.; Feng, X. M. Catalytic Enantioselective Ene-type Reactions of Vinylogous Hydrazone: Construction of α-Methylene-γ-butyrolactone Derivatives. *Chem. Commun.* **2018**, *54*, 12511. (f) Dai, L.; Lin, L. L.; Zheng, J. F.; Zhang, D.; Liu, X. H.; Feng, X. M. *N,N′*-Dioxide/Gd(OTf)$_3$ Complex-Promoted Asymmetric Aldol Reaction of Silyl Ketene Imines with Isatins: Water Plays an Important Role. *Org. Lett.* **2018**, *20*, 5314.

(11) (a) Liu, X. H.; Lin, L. L.; Feng, X. M. Chiral *N,N′*-Dioxides: New Ligands and Organocatalysts for Catalytic Asymmetric Reactions. *Acc. Chem. Res.* **2011**, *44*, 574. (b) Liu, X. H.; Lin, L. L.; Feng, X. M. Chiral *N,N′*-Dioxide Ligands: Synthesis, Coordination Chemistry and Asymmetric Catalysis. *Org. Chem. Front.* **2014**, *1*, 298. (c) Liu, X. H.; Zheng, H. F.; Xia, Y.; Lin, L. L.; Feng, X. M. Asymmetric Cycloaddition and Cyclization Reactions Catalyzed by Chiral *N,N′*-Dioxide-Metal Complexes. *Acc. Chem. Res.* **2017**, *50*, 2621. (d) Liu, X. H.; Dong, S. X.; Lin, L. L.; Feng, X. M. Chiral Amino Acids-Derived Catalysts and Ligands. *Chin. J. Chem.* **2018**, *36*, 791. (e) Wang, Z.; Liu, X. H.; Feng, X. M. Asymmetric Catalysis Enabled by Chiral *N,N′*-Dioxide−Nickel(II) Complexes. *Aldrichimica Acta* **2020**, *53*, 3−10.

(12) (a) Liu, Y. L.; Zhou, J. Organocatalytic Asymmetric Cyanation of Isatin Derived *N*-Boc Ketoimines. *Chem. Commun.* **2013**, *49*, 4421. (b) Horoszok, L.; Leung, C.; Tomaszewski, M.; Walpole, C. *PCT Int. Appl.*. WO 2007091946, 2007.

(13) (a) Lauberteaux, J.; Crévisy, C.; Baslé, O.; Figueiredo, R. M. D.; Mauduit, M.; Campagne, J. Copper-Catalyzed Asymmetric Conjugate Additions of Bis(pinacolato)diboron and Dimethylzinc to Acyl-*N*-methylimidazole Michael Acceptors: A Highly Stereoselective Unified Strategy for 1,3,5,···n (OH, Me) Motif Synthesis. *Org. Lett.* **2019**, *21*, 1872.

(14) Li, X. X.; You, C.; Yang, Y. S.; Yang, Y. H.; Li, P.; Gu, G. X.; Chung, L. W.; Lv, H.; Zhang, X. M. Rhodium-Catalyzed Asymmetric Hydrogenation of β-Cyanocinnamic Esters with the Assistance of a Single Hydrogen Bond in a Precise Position. *Chem. Sci.* **2018**, *9*, 1919.

(15) (a) Zhang, J.; Xing, C.; Tiwari, B.; Chi, Y. R. Catalytic Activation of Carbohydrates as Formaldehyde Equivalents for Stetter Reaction with Enones. *J. Am. Chem. Soc.* **2013**, *135*, 8113. (b) Barco, A.; Benetti, S.; De Risi, C.; Pollini, G. P.; Spalluto, G.; Zanirato, V. 4-Isopropyl-2-oxazolin-5-one Anion as a new Convenient Formyl Anion Equivalent for Conjugate Addition and Aldol Reactions. *Tetrahedron Lett.* **1993**, *34*, 3907. (c) Zhang, S.; Tan, Z. M.; Zhang, H. N.; Liu, J. L.; Xu, W. T.; Xu, K. An Ir-Photoredox-Catalyzed Decarboxylative Michael Addition of Glyoxylic Acid Acetal as a Formyl Equivalent. *Chem. Commun.* **2017**, *53*, 11642. (d) Kuang, Y. L.; Wang, K.; Shi, X. C.; Huang, X. Q.; Meggers, E.; Wu, J. Asymmetric Synthesis of 1,4-Dicarbonyl Compounds from Aldehydes by Hydrogen Atom Transfer Photocatalysis and Chiral Lewis Acid Catalysis. *Angew. Chem., Int. Ed.* **2019**, *58*, 16859.

https://dx.doi.org/10.1021/acs.orglett.0c01857
Org. Lett. XXXX, XXX, XXX−XXX