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Divergent Synthesis of Enantioenriched β-Functional Amines via Desymmetrization of *meso*-Aziridines with Isocyanides

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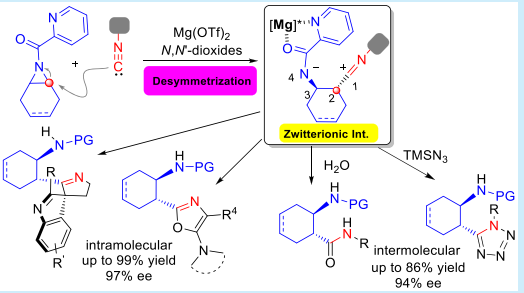
Supporting Information

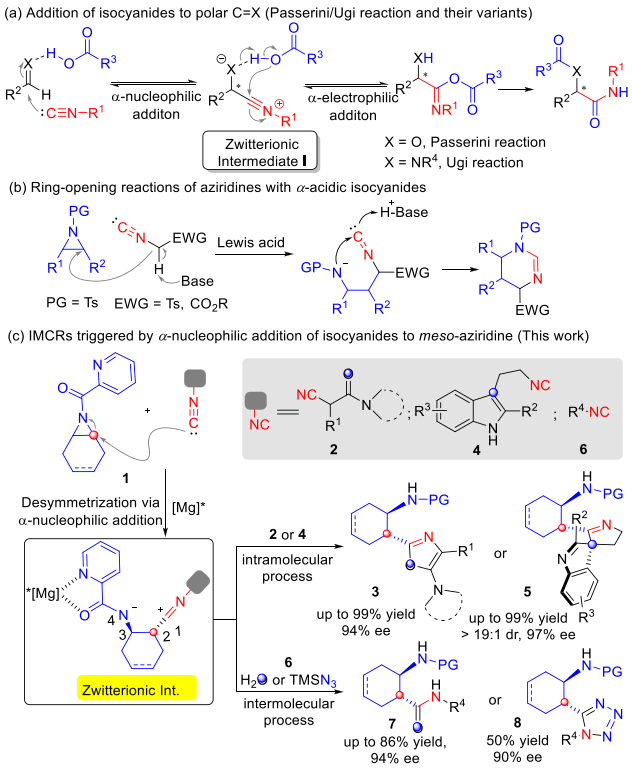
ABSTRACT: A highly enantioselective ring-opening desymmetrization of *meso*-aziridines with isocyanides was achieved in the presence of a chiral *N,N′*-dioxide/$Mg(OTf)_2$ complex. The in situ generated chiral 1,4-zwitterionic intermediates were successfully trapped by intramolecular oxygen- and carbon-based nucleophiles or exogenous H_2O and $TMSN_3$, enabling a collective synthesis of various chiral vicinal amino-oxazoles, spiroindolines, β-amino amides, and tetrazole derivative in moderate to high yields with excellent enantioselectivities.



Benefitting from the unique reactivity profile of the isocyanide functional group, isocyanides have attracted considerable interest in the past several decades.[1,2] In particular, isocyanide-based multicomponent reactions (IMCRs)[2] represent one of the most facile and efficient methods for diversity-oriented synthesis of highly valuable molecules. Comparably, the development of asymmetric versions of such IMCRs was lagging. In the past decades, many research groups studied this area, and an array of enantioselective reactions including the Passerini reaction,[3] Ugi reaction,[4] and their variants[5−7] (Scheme 1a) have been achieved in the presence of organocatalysts or chiral Lewis acid catalysts. In this process, both simple isocyanides and functionalized isocyanides were involved, affording diverse products with high enantioselectivity. Despite such impressive achievements, the electrophiles involved in the initial addition of isocyanides are mainly limited to polar C═X bonds[3−6] along with several sporadic examples of polar C═C or C≡C bonds.[4e,7]

Asymmetric desymmetrization[8−14] of *meso*-aziridines with many nucleophiles including nitrogen,[9] halogen,[10] sulfur,[11] phosphorus,[12] carbon,[13] and others[14] has been extensively studied because it furnishes useful chiral β-functional amine derivatives with vicinal stereocenters in a single step. Recently, the ring-opening reaction of aziridines with α-acidic isocyanides has also been developed.[15] As shown in Scheme 1b, the reaction usually proceeded via Lewis acid promoted S_N2-type ring opening of aziridines with an α-carbanion of the isocyanides under basic conditions. These elegant works in conjunction with our previous works on isocyanides[4e,7a,b] led us to assume that ring opening of *meso*-aziridines with an isocyanide functional group would be possible as well. As depicted in Scheme 1c, in the presence of a proper chiral catalyst, the nucleophilic ring-opening reaction of *meso*-aziridines with isocyanides could provide a new type of chiral 1,4-zwitterionic intermediate, which may be trapped by a second nucleophile. If this hypothesis works well, it will dramatically extend the application scope of IMCRs. However,

Scheme 1. Isocyanide-Based Multicomponent Reactions



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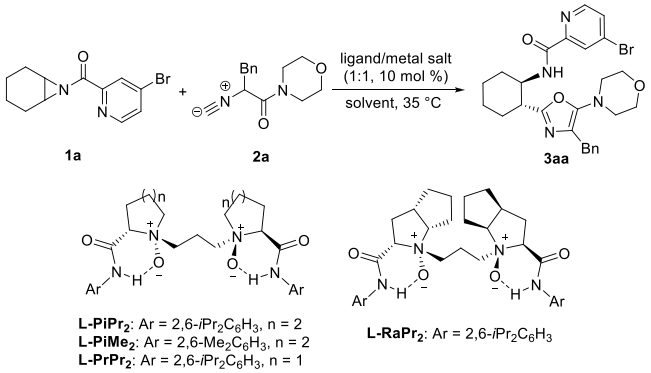
to the best of our knowledge, only a single example of this type of reaction was established, furnishing the racemic β-amino amide compound via S_N1-type ring opening.[16] Herein, we accomplished a direct asymmetric nucleophilic ring opening of *meso*-aziridines with α-isocyanoacetamides or 2-isocyanoethylindoles catalyzed by a chiral *N,N′*-dioxide/$Mg(OTf)_2$ complex.[17] The in situ generated zwitterionic intermediates were subsequently captured by the oxygen of amide or C3 position of indole in isocyanides, affording various vicinal amino-oxazoles and spiroindolines in moderate to good yields and high enantioselectivities. Moreover, exogenous H_2O and $TMSN_3$ were found to be suitable as intermolecular nucleophilic components when simple isocyanides were employed, and the corresponding chiral β-amino amides and tetrazole were obtained with good results.

To assess our hypothesis, the desymmetrization of *meso*-aziridine **1a** with α-isocyanoacetamide **2a** were selected as the model reaction to optimize the reaction conditions (Table 1).[18] We were pleased to find that the complex of $Mg(OTf)_2$[19]

Table 1. Optimization of the Reaction Conditions.[a]



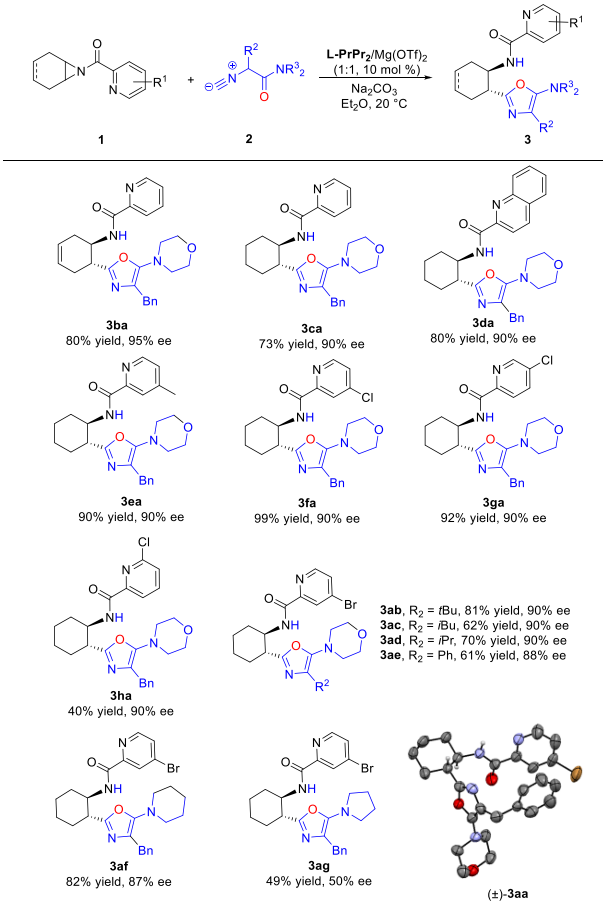
entry	metal salt	ligand	solvent	yield[b] (%)	ee[c] (%)
1	$Mg(OTf)_2$	**L-PiMe$_2$**	CH_2Cl_2	23	11
2	$Mg(OTf)_2$	**L-PiPr$_2$**	CH_2Cl_2	15	38
3	$Mg(OTf)_2$	**L-PrPr$_2$**	CH_2Cl_2	40	78
4	$Mg(OTf)_2$	**L-RaPr$_2$**	CH_2Cl_2	19	67
5	$Mg(OTf)_2$	**L-PrPr$_2$**	Et_2O	59	87
6[d]	$Mg(OTf)_2$	**L-PrPr$_2$**	Et_2O	61	92
7[d,e]	$Mg(OTf)_2$	**L-PrPr$_2$**	Et_2O	95	90

[a]The reactions were performed with ligand/metal salt (1:1, 10 mol %), **1a** (0.10 mmol), and **2a** (0.10 mmol) in the solvent (1.0 mL) under N_2 at 35 °C for 24 h. [b]Isolated yield. [c]Determined by chiral HPLC analysis on a chiral stationary phase. [d]At 20 °C for 48 h. [e]With **2a** (0.15 mmol), Na_2CO_3 (0.10 mmol).

with **L-PiMe$_2$** promoted the reaction smoothly in slightly higher reactivity (Table 1, 23% yield, 11% ee, entry 1). The following survey of ligands coordinating with $Mg(OTf)_2$ showed that the backbone of ligands had a significant influence on the enantioselectivity.[20] L-Proline-derived **L-PrPr$_2$** was superior to **L-PiPr$_2$** and L-ramipril-derived **L-RaPr$_2$** in terms of efficiency, delivering the desired product in 40% yield and 78% ee (Table 1, entry 3 vs entries 2 and 4). In addition, it was found that the solvent had a considerable effect on both the reactivity and enantioselectivity. Better results (59% yield and 87% ee) were obtained when the reaction was carried out Et_2O as the solvent (entry 5). Performing the reaction at 20 °C resulted in a yield of 61% with higher enantioselectivity (entry 6, 92% ee vs 87% ee). Finally, the yield was further improved to 95% with a slightly decreased ee value (90% ee) by utilizing Na_2CO_3 as an additive (other bases were also examined; for details, see the SI) and fixing the ratio of *meso*-aziridine **1a** and isocyanide **2a** to 1:1.5 (entry 7).

With the optimized reaction conditions in hand, the substrate scope was examined. As shown in Table 2, a series

Table 2. Substrates Scope of *meso*-Aziridines and α-Isocyanoacetamides[a]



[a]Performed with **L-PrPr$_2$**/$Mg(OTf)_2$ (1:1, 10 mol %), **1** (0.10 mmol), **2** (0.15 mmol), and Na_2CO_3 (0.10 mmol) in Et_2O (1.0 mL) under N_2 at 20 °C for 48 h.

of aziridines and α-isocyanoacetamides were investigated. The aziridine **1b** bearing an unsaturated six-membered ring afforded the corresponding product **3ba** in 80% yield with 95% ee. A screening of the protecting group of aziridine showed that both the position and electronic property of the substituents on the *N*-2-picolinoyl group of aziridines only affected the yields (**3ca**−**3fa**, 73−99% yield, 90% ee). With the chloro group closing to the *N*-atom on the pyridine ring, the yields of the corresponding products were diminished significantly but the enantioselectivity was maintained (**3fa**−**3ha**). Then various α-substituted isocyanides were examined. To our delight, isocyanides **2b**−**2e** with different alkyl or phenyl substituents on the α-position of isocyanoacetamides were applicable as well, giving the corresponding products **3ab**−**3ae** in 61−81% yield and 88−90% ee. Changing the morpholine unit of isocyanide **2a** to piperidine or pyrrolidine moiety led to decreased yield and enantiomeric excess (82% yield and 87% ee for **3af**; 49% yield and 50% ee for **3ag**). The

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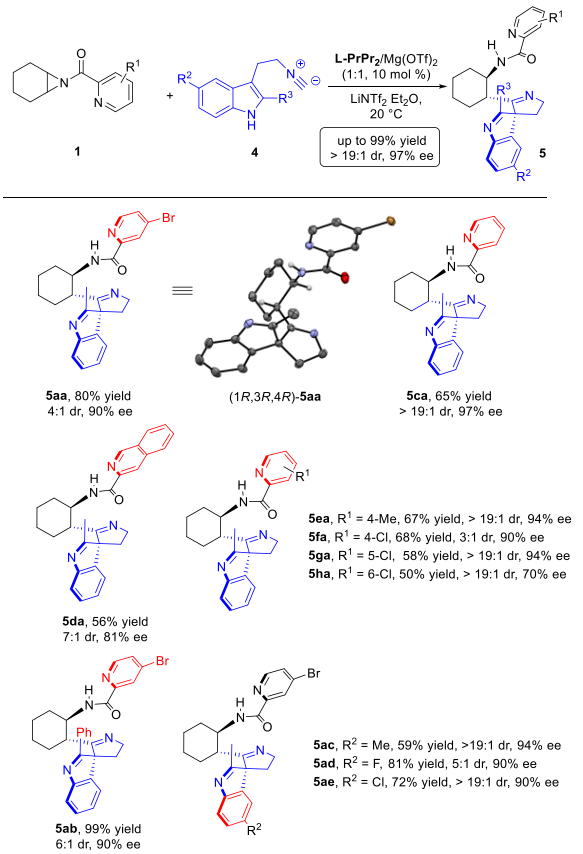
structure of adduct (±)-**3aa** was confirmed by X-ray single-crystal analysis.

Encouraged by these results, we tried to apply the desymmetrization of *meso*-aziridine to the synthesis of the enantiomerically enriched polycyclic spiroindolines by using C2-methyl-substituted 2-isocyanoethylindoles as nucleophiles. As expected, the vicinal amino spiroindoline product could be obtained successfully under the investigated conditions with $Mg(OTf)_2$/**L-PrPr$_2$** complex (Table 3, **5aa**, 80% yield, 4:1 dr

Table 3. Substrates Scope of *meso*-Aziridines and 2-Isocyanoethylindoles[a]

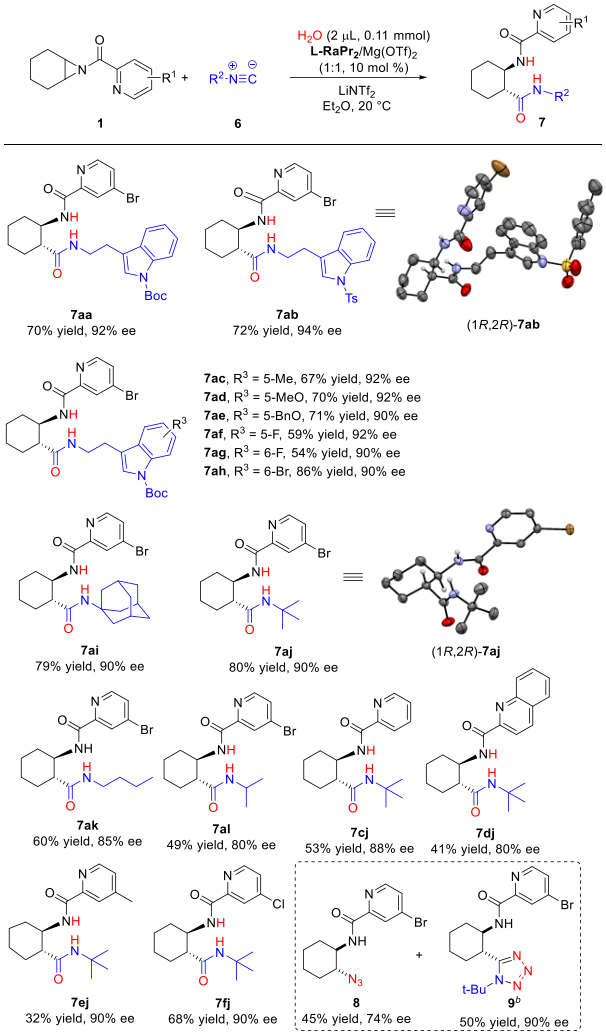


[a]Performed with **L-PrPr$_2$**/$Mg(OTf)_2$ (1:1, 10 mol %), **1** (0.10 mmol), **4** (0.15 mmol), and $LiNTf_2$ (0.03 mmol) in Et_2O (1.0 mL) under N_2 at 20 °C for 48 h.

and 90% ee). Along with the exploration for the protecting group of aziridines, a range of vicinal amino spiroindolines were obtained (**5ca**−**5fa**). The position of the chloro group on the pyridine ring also affected the reactivities and enantioselectivities (50−68% yield, 70−94% ee, **5fa**−**5ha**). Then the substrates with different substitutions on the indole unit were inspected. The phenyl group at the C2 position of the indole supplied the desired polycyclic spiroindole **5ab** in high yield and enantioselectivity (99% yield, 6:1 dr, 90% ee). Isocyanides with electron-donating and electron-withdrawing substituents at the C5 position of indole were suitable in the current system, yielding the expected products with a slightly lower yield with high ee (**5ac**−**5ae**, 59−81% yield, 90−94% ee). The absolute configuration of the major isomer of product **5aa** was determined to be (1*R*,3*R*,4*R*) by X-ray single-crystal analysis.

Interestingly, when *N*-Boc-protected 2-isocyanoethylindole **6a** was employed as the substrate, the vicinal amino amide was afforded instead of spiroindolines products. In this case,[21] ubiquitous H_2O captured the chiral 1,4-zwitterionic intermediate to deliver the amino amide product **7aa**, and further optimization suggested that good results (70% yield and 92% ee) were obtained with addition of H_2O (2 μL) under slightly modified conditions (Table 4, footnote a).[22] By changing the

Table 4. Substrates Scope of *meso*-Aziridines and Isocyanides[a]



[a]Performed with **L-RaPr$_2$**/$Mg(OTf)_2$ (1:1, 10 mol %), **1** (0.10 mmol), **6** (0.15 mmol), H_2O (2 μL, 0.11 mmol), and $LiNTf_2$ (0.03 mmol) in Et_2O (1.0 mL) under N_2 at 20 °C for 48 h. [b]With **1a** (0.10 mmol), *tert*-butyl isocyanide (0.30 mmol), and $TMSN_3$ (0.10 mmol) in CH_2Cl_2 (1.0 mL) under N_2 at 30 °C for 48 h.

N-protected group from a Boc to a tosyl group, both the yield and ee value were increased (**7ab** vs **7aa**). Examination of substitutions on the indole ring with $Mg(OTf)_2$/**L-RaPr$_2$** complex as the catalyst suggested that both electron-donating and electron-withdrawing groups at the C5 position could be compatible in the current system, producing the corresponding vicinal amino amides **7ac**−**7af** in good yields with excellent enantioselectivities (59−71% yield, 90−92% ee, Table 4). Substrates with a halogen atom at the C6 position also afforded

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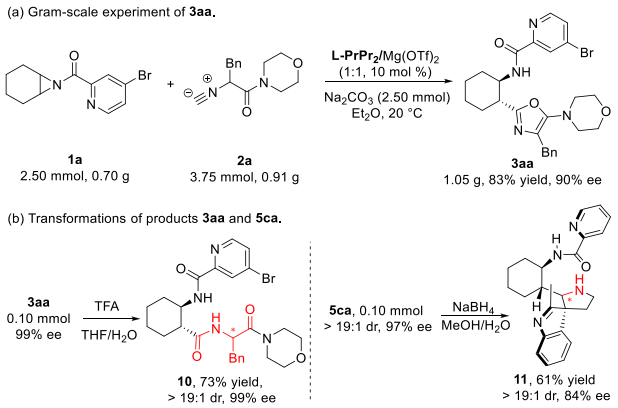
the desired products **7ag** and **7ah** in good yields with slightly decreased enantioselectivities (90% ee). To further extend the substrates, simple isocyanides **6i**–**6l** were applied to obtain prospective β-amino amides. As shown in Table 4, with diminishing steric hindrance of isocyanides, the yields and enantioselectivities declined significantly (**7ai**–**7al**, 49–80% yield, 80–90% ee). Lastly, aziridines with different protecting groups were examined to provide the desired products **7cj**–**7fj** (32–68% yield, 80–90% ee). Except for water, it was found that $TMSN_3$ could serve as the second nucleophile as well.[23] However, the direct ring-opening product **8** with $TMSN_3$ was afforded as the major product. Further optimization indicated that increasing the amount of isocyanide (3 equiv) was beneficial to the ring-opening pathway with isocyanide, and the corresponding product **9** could be obtained in 50% yield and 90% ee along with 45% yield of compound **8** in 74% ee.

To show the synthetic utility of the methodology, a gram-scale synthesis of **3aa** was performed. As shown in Scheme 2a,

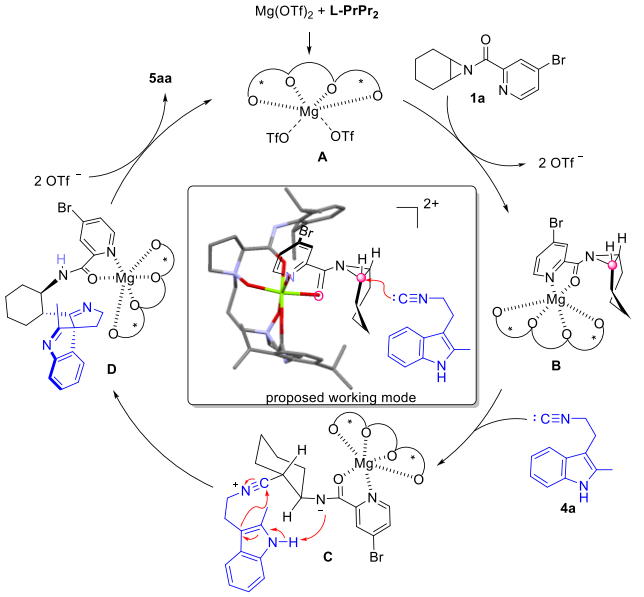
Scheme 2. (a) Gram-Scale Experiment of 3aa; (b) Transformations of Products 3aa and 5ca



2.50 mmol of **1a** reacted smoothly with 3.75 mmol of **2a** under the optimized reaction conditions, and the desired product **3aa** was delivered in 83% yield (1.05 g) with 90% ee value. Next, simple derivatizations of the products were conducted. The vicinal amino-oxazoles **3aa** could be easily hydrolyzed to form **10** in 73% yield without loss of enantioselectivity. Reduction of **5ca** in the presence of $NaBH_4$ afforded the spirocyclic indoline **11** in moderate yield and enantioselectivity.

Based on the structures of $Mg(OTf)_2$/**L-RaPr$_2$** and $Mg(OTf)_2$/**L-PrEt$_2$**,[24] a possible catalytic cycle along with a proposed working mode are provided in Scheme 3. At first, coordination of $Mg(OTf)_2$/**L-PrPr$_2$** complex **A** to *meso*-aziridine **1a** leads to intermediate **B**, in which aziridine **1a** binds to the metal center with the aromatic nitrogen and oxygen of the carbonyl group in a bidentate manner. The cyclohexyl ring of aziridine prefers to locate downward to prevent the steric hindrance with the top-right amide of the ligand, and nucleophilic attack of the isocyanide from the back side of the aziridine ring is favored,[9c,24b] furnishing the nitrilium intermediate *anti*-**C**, which the nitrilium group and amide anion are on the opposite side of the ring. Then, *anti*-**C** undergoes intramolecular proton transfer and is captured by the C3 position on the indole ring from the *Re* face, establishing a new stereogenic center and affording the desired product **5aa** with (1*R*,3*R*,4*R*) configuration as the major isomer.

Scheme 3. Proposed Catalytic Cycle



In conclusion, we developed a highly efficient desymmetrization of *meso*-aziridines by means of ring-opening with isocyanides by using a chiral *N*,*N*′-dioxide/$Mg(OTf)_2$ complex catalytic system. Isocyanoacetamides, 2-isocyanoethylindoles, and simple isocyanides were all well tolerated, enabling the collective synthesis of the corresponding vicinal amino-oxazoles, spiroindolines, β-amino amides, and tetrazole in moderate to good yields and high enantioselectivities. A plausible catalytic cycle and working mode were proposed to elucidate the process of the reaction and the origin of chiral control. Further development of asymmetric isocyanide-based multicomponent reaction is ongoing in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02242.

Experimental procedures, full spectroscopic data for all new compounds, and copies of ^{1}H, $^{13}C\{^{1}H\}$, and $^{19}F\{^{1}H\}$ NMR and HPLC spectra (PDF)

Accession Codes

CCDC 1909099, 1909103, 1921288, and 1921801 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.

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Notes

The authors declare no competing financial interest.

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