Article

Ag₂O/squaramide cocatalyzed asymmetric interrupted Barton-Zard reaction of 8-nitroimidazo[1,2-*a*]pyridines

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ABSTRACT

Imidazo[1,2-*a*]pyridines are present in numerous biologically active compounds as the core structural motif. Herein, we report an asymmetric interrupted Barton-Zard reaction of electron-deficient imidazo [1,2-*a*]pyridines with α-substituted isocyanoacetates. The reaction enables the dearomatization of 8-nitroimidazo[1,2-*a*]pyridines and hence offers straightforward access to an array of optically active highly functionalized imidazo[1,2-*a*]pyridine derivatives that possess three contiguous stereogenic centers in good yields (up to 98%) with high stereoselectivities (>19:1 dr, >99% ee). It is worth noting that the catalytic system consisting of a chiral squaramide and silver oxide displays remarkable reactivity and stereoselectivity, and a gram-scale reaction is compatible with the catalyst loading of 0.5 mol%. In addition, the synthetic potential of this method was showcased by versatile transformations of the product.

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1. Introduction

Imidazo[1,2-*a*]pyridine is a unique heteroaromatic skeleton, which is ubiquitous in luminescent materials, natural products, and biologically active compounds [1–5]. In particular, many optically active imidazo[1,2-*a*]pyridine derivatives are found in pharmacologically important molecules (Fig. 1) [6–8]. In addition, imidazo[1,2-*a*]pyridine derivatives are also widely used in organic synthesis. For example, the Birman group [9,10] developed an acyl transfer catalyst based on a 2,3-dihydroimidazo[1,2-*a*]pyridine backbone for the kinetic resolution of alcohols. Furthermore, Andersson and co-workers [11] developed a series of chiral P,N-ligands based on this framework, which showed high reactivity and excellent enantioselectivities in Ir-catalyzed hydrogenations and Pd-catalyzed intermolecular Heck reactions. Although a variety of synthetic methods have been developed for the synthesis of this important framework [12–20], most optically active imidazo[1,2-*a*]pyridine derivatives rely on the use of enantioenriched starting materials or chiral-resolution techniques [21–24]. Accordingly, the development of efficient synthesis of optically active imidazo[1,2-*a*]pyridines is highly desirable [25–27].

Catalytic asymmetric dearomatization (CADA) reaction has attracted enormous attention because of its potential to access enantioenriched three-dimensional molecules from readily available planar aromatic compounds [28–37]. However, the CADA reaction of imidazo[1,2-*a*]pyridines remains underdeveloped. To the best of our knowledge, the only example was reported by Glorius and co-workers [38], where asymmetric hydrogenation of imidazo[1,2-*a*]pyridines was realized by using a ruthenium/N-heterocyclic carbene (NHC) catalyst, leading to chiral tetrahydroimidazo[1,2-*a*]pyridine derivatives (Scheme 1a).

We recently reported a silver/phosphine complex-catalyzed interrupted Barton-Zard reaction of 3-nitroindoles with α-substituted isocyanoacetates [39]. Although imidazo[1,2-*a*]pyridines are known as electron-rich 10π-electron aromatic compounds and are generally used as nucleophiles, we envisioned that introducing an electron-withdrawing nitro group might make them electrophiles suitable for interrupted Barton-Zard reaction with α-substituted isocyanoacetates. Recently, we realized this design plan by identifying an efficient catalytic system consisting of Ag₂O and a chiral squaramide, where phosphine ligand was not necessary (Scheme 1b). Herein, we report the details of this study.

2. Experimental

Unless stated otherwise, the title reactions were carried out in flame-dried glassware under a dry argon atmosphere. All solvents

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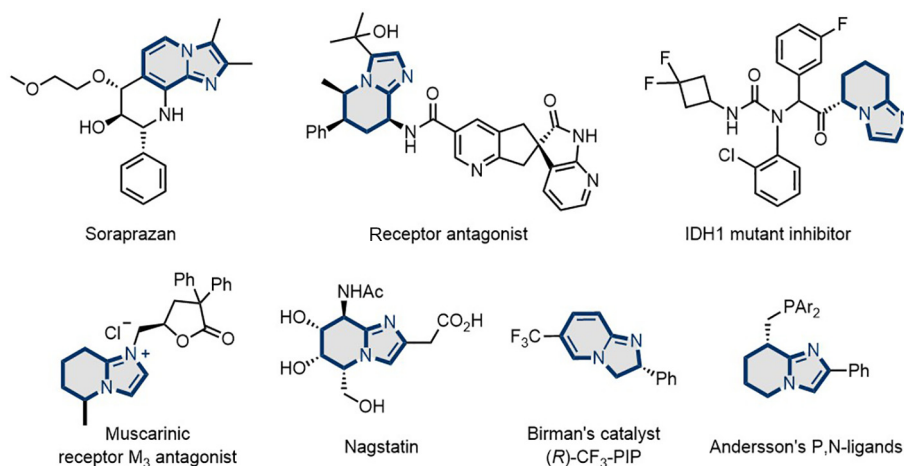 *E-mail addresses:* yaofeng_yuan@fzu.edu.cn (Y.-F. Yuan), slyou@sioc.ac.cn (S.-L. You).
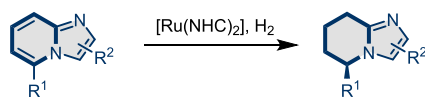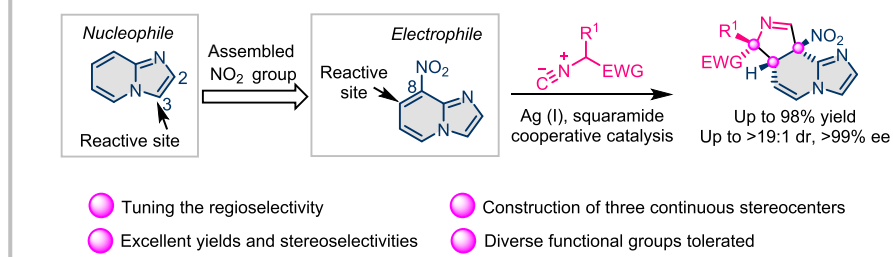
Fig. 1. (Color online) Optically active molecules derived from imidazo[1,2-a]pyridine.

Scheme 1. (Color online) Interrupted Barton-Zard reaction of imidazo[1,2-a]pyridine derivatives. (a) Previous work for asymmetric hydrogenation of imidazo[1,2-a]pyridine derivatives. (b) This work for CADA of imidazo[1,2-a]pyridine derivatives.

were purified and dried according to standard methods prior to use. The ligands **L1**–**L7**, and catalysts **C1**–**C5** were prepared following known procedures. The squaramide **C6**–**C10** were purchased from Daicel Chiral Technologies (China).

^{1}H and ^{13}C NMR spectra were recorded on a Varian instrument (400 and 100 MHz; 600 and 151 MHz, respectively) or an Agilent instrument (400 and 100 MHz) or a Bruker instrument (400 and 100 MHz) and internally referenced to tetramethylsilane signal or residual protio solvent signals. ^{19}F NMR spectra were recorded on an Agilent instrument (376 MHz) or a Bruker instrument (376 MHz) and internally referenced to CFCl$_3$. Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br = broad singlet, coupling constant (s) in Hz, integration). Data for ^{13}C NMR and ^{19}F NMR are reported in terms of chemical shift (δ, ppm). High resolution ESI mass spectra were recorded on a JEOL AccuTOF LC-plus 4G instrument. Enantiomeric excess values were determined by HPLC analysis on a chiral stationary phase on Waters 2489 UV/Visible detector, Waters 1525 binary HPLC pump and Waters 2707 auto sampler or supercritical fluid chromatogra-

phy (SFC) analysis using Waters UPC2 instruments. Optical rotations were measured in CHCl$_3$ or CH$_2$Cl$_2$ on a Rudolph AutopolI/ II/III or Rudolph APVI polarimeter with a sodium lamp of wavelength 589 nm, and reported as follows: $[\alpha]_D^T$ (c g/100 mL, solvent). IR spectra were obtained on Bruker Tensor 27 instruments with Bruker Platinum ATR accessory. X-Ray crystallographic analyses were performed on a Bruker APEX2 at 293 K.

The synthetic routes and characterization data for starting materials and products are shown in Supplementary materials (online).

3. Results and discussion

Initial studies were performed by employing 8-nitro-imidazo [1,2-a]pyridine (**1a**) and α-phenyl isocyanoacetate (**2a**) as the substrates (Table 1). The previous optimal catalytic system for interrupted Barton-Zard reaction of 3-nitroindoles that consists of Ag$_2$O (5 mol%) and cinchonine-derived amino-phosphine **L1** (5 mol%) was first examined in Et$_2$O at room temperature (rt)

Table 1
Optimization studies of silver/phosphine catalytic system.[a]
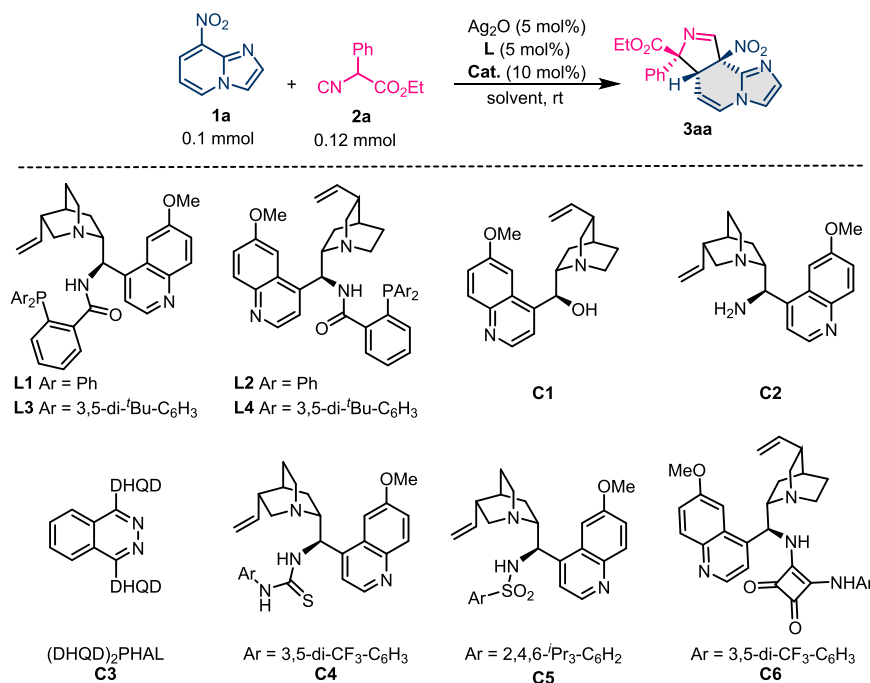
| Entry	L	Cat.	Solvent	Time (h)	Yield (%)[b]	dr[c]	ee (%)[d]
1	L1	-	Et$_2$O	17	51	1.5:1	62
2	L2	-	Et$_2$O	17	56	2.4:1	53
3	L3	-	Et$_2$O	10	93	2:1	94
4	L4	-	Et$_2$O	10	97	3.5:1	95
5	L4	-	Toluene	8	>95	4:1	97
6	L4	-	THF	8	>95	3:1	96
7	L4	-	Dioxane	8	>95	4:1	98
8	L4	C1	Dioxane	24	>95	4.2:1	97
9	L4	C2	Dioxane	24	97	3.6:1	97
10	L4	C3	Dioxane	5.5	>95	3.8:1	98
11	L4	C4	Dioxane	24	82	4.6:1	29
12	L4	C5	Dioxane	5.5	>95	3.8:1	98
13	L4	C6	Dioxane	24	94	4.6:1	88
14	-	C6	Dioxane	5	>95	3.8:1	93
15[e]	-	C6	Dioxane	48	80	5.5:1	85

a) Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), Ag$_2$O (5 mol%), **L** (5 mol%), and organocatalyst (10 mol%) in solvent (2 mL) at room temperature (rt) under argon atmosphere. b) NMR yield of **3aa** using CH$_2$Br$_2$ as an internal standard. c) Determined by ^{1}H NMR of the crude reaction mixture. d) Determined by HPLC analysis. e) Without Ag$_2$O. **L**, ligand; THF, tetrahydrofuran; dr, diastereomeric ratio; and ee, enantiomeric excess.

[39–41]. Gratifyingly, the target reaction proceeded well, delivering the dearomatized product **3aa** in 51% NMR yield with moderate diastereo- and enantioselectivities (1.5:1 dr, 62% ee; entry 1, Table 1). Further investigations on the performance of chiral amino-phosphine ligands (Table 1, entries 2–4, see the Supplementary materials (online) for details) showed that the sterically bulky ligand **L4** stood out as the optimal one, affording **3aa** in 97% NMR yield with 95% ee and 3.5:1 dr (Table 1, entry 4). Subsequently, in combination with **L4**, other reaction parameters including solvent, silver salt, additives, and temperature were screened systematically, but the diastereoselectivity was not improved (Table 1, entries 5–7, see the Supplementary materials (online) for details). To improve the diastereoselectivity, we explored synergistic catalysis by adding an organocatalyst (**C1**–**C6**) (Table 1, entries 8–13). Interestingly, when squaramide **C6** (10 mol%) was used, **3aa** was obtained in comparable yield (94%) and stereoselectivity (4.6:1

dr and 88% ee) but with opposite absolute configuration (entry 13). Control experiments showed that the desired reaction could be promoted by the combination of Ag$_2$O (5 mol%) and squaramide **C6** (10 mol%) in the absence of phosphine ligand **L4**, giving **3aa** in quantitative yield with 93% ee and 3.8:1 dr (Table 1, entry 14). It should be noted that using **C6** alone led to good stereochemical control but largely retarded reactivity (Table 1, entry 15).

Encouraged by these results, other chiral squaramides (**C7**–**C10**) were further evaluated, and they were found to greatly affect both the reaction efficiency and stereoselectivity (Table 2, entries 1–5). Among the tested catalysts, **C10** delivered the best yield and stereoselectivity (97% NMR yield, 15:1 dr, 99% ee, entry 5, Table 2). Both Ag$_2$O and squaramide **C10** are critical for achieving high yield and stereoselectivity through control experiments (Table 2, entries 6 and 7). After the investigation of catalyst loading, substrate concentration, and solvent (Table 2, entries 8 and 9, see the

Table 2
Optimization studies of silver/squaramide catalytic system.[a]
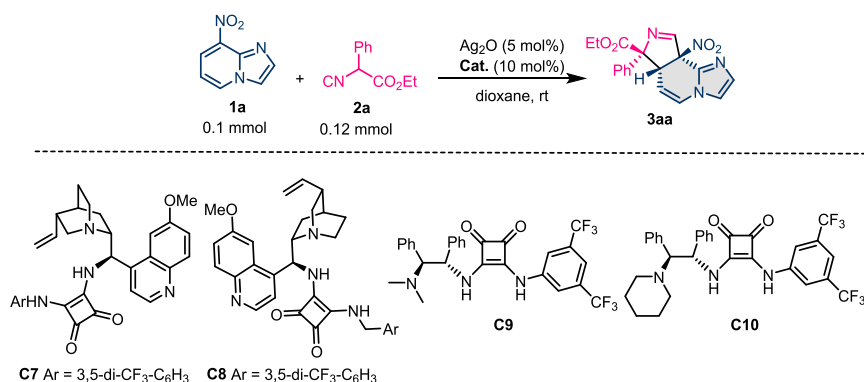
Entry	Ag$_2$O	**Cat.**	Time (h)	Yield (%)[b]	dr[c]	ee (%)[d]
1	Ag$_2$O	**C6**	5	>95	3.8:1	93
2	Ag$_2$O	**C7**	5	>95	5.1:1	86
3	Ag$_2$O	**C8**	1.5	>95	8:1	97
4	Ag$_2$O	**C9**	1.5	>95	10:1	98
5	Ag$_2$O	**C10**	1	97	15:1	99
6	-	**C10**	16	Trace	-	-
7	Ag$_2$O	-	16	Trace	-	-
8[e]	Ag$_2$O	**C10**	18	89	15:1	>99
9[e,f]	Ag$_2$O	**C10**	2	>95	15:1	>99

a) Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), Ag$_2$O (5 mol%), and squaramide catalyst (10 mol%) in dioxane (2 mL) at rt under argon atmosphere. b) NMR yield of **3aa** using CH$_2$Br$_2$ as an internal standard. c) Determined by ^{1}H NMR of the crude reaction mixture. d) Determined by HPLC analysis. e) Ag$_2$O (1 mol%) and **C10** (1 mol%) were used. f) 0.5 mL dioxane was used.

Supplementary materials (online) for details), the optimized conditions were established using Ag$_2$O (1 mol%) and squaramide **C10** (1 mol%) in dioxane (0.2 mol/L for **1a**) at rt. The desired product **3aa** was delivered in quantitative yield with >99% ee and 15:1 dr (Table 2, entry 9).

With the optimized conditions in hand (Table 2, entry 9), we then explored a variety of α-substituted isocyanoacetates **2** (Scheme 2). First, variation of the ester moiety of α-phenyl isocyanoacetates was investigated. The results showed that alkyl isocyanoacetates participated in this reaction efficiently to afford the corresponding adducts **3aa**–**3ac** in excellent yields and stereoselectivities. The relative and absolute configurations of **3ab** were unambiguously assigned by X-ray crystallographic analysis of the enantiomerically pure sample. The configurations of other adducts **3** were then assigned by analogy. Further examination of the substituent effect of isocyanoacetates revealed that most α-aryl isocyanoacetates bearing either an electron-donating or electron-withdrawing group on the *para*- or *meta*-position of the phenyl ring gave the desired adducts **3ad**–**3ak** in good to excellent yields (85%–98%) with excellent stereoselectivities (>19:1 dr, >99% ee). It should be noted that the reaction of *ortho*-tolyl derived isocyanoacetate afforded dearomatized product **3af** in 96% yield and 99% ee, albeit with decreased dr value (5:1 dr), presumably due to the steric hindrance of the substrate. Isocyanoacetates bearing β-naphthyl or heterocyclic rings were also tolerable, leading to the corresponding adducts in comparable yields (89%–96%) with excellent diastereo- and enantioselectivities (**3al**–**3an**, 13:1–>19:1 dr, >99% ee). Notably, switching the ester group to amide lowered the enantioselectivity (**3ao**, **3ap**, 78%–85% ee). In contrast to the previous reports [42–46], less reactive α-alkyl-substituted isocyanoacetates were also reliable partners in this reaction, affording the corresponding products **3aq**–**3at** in excellent enantioselectivity (86%–>99% ee). However, in the case of α-alkyl

group-(methyl and cyclohexanemethylene) substituted isocyanoacetates, the diastereoselectivity of the corresponding adduct significantly decreased (3:1 dr).

Next, the substrate scope of 8-nitro-imidazo[1,2-*a*]pyridines **1** was evaluated (Scheme 3). Generally, all of the 8-nitro-imidazo [1,2-*a*]pyridine substrates examined were readily converted into the corresponding products **3ba**–**3ka** in uniformly good yields (82%–98%) with excellent stereoselectivities (10:1–19:1 dr, 98%–>99% ee). It should be emphasized that the substituents with different electronic nature at the C6-position of the pyridine ring did not have obvious effects on the results of the dearomatization reaction. Excellent reactivity and selectivity were also observed for the substrate bearing a phenyl substituent in the C2-position of the imidazole ring. Furthermore, when an additional phenyl or cyclohexyl ring was fused to the pyridine ring of the substrates, the reactions provided tetracyclic products **3ma** and **3na** in comparable yields (74%–94%) with high stereochemical outcomes (9:1–16:1 dr, 97% ee).

To illustrate the synthetic potential of the current protocol, a gram-scale reaction of **1a** and **2b** was performed with 0.5 mol% of Ag$_2$O and **C10** (Scheme 4), and product **3ab** was obtained in 92% yield (1.25 g) with 16:1 dr and >99% ee.

To further exploit the utility of the reaction, the transformations of product **3ab** were investigated (Scheme 5). The denitronation reaction was realized by subjecting **3ab** to DBU in dichloromethane (DCM), furnishing product **4** in 92% yield with >99% ee. Gratifyingly, tetrahydroimidazo[1,2-*a*]pyridine **5** could be afforded in 83% yield with >99% ee and >19:1 dr by Pd/C-catalyzed hydrogenation of **3ab**. In addition, the imine moiety of **3ab** could be selectively reduced by NaBH$_3$CN/AcOH, delivering amine **6** in 67% yield with >99% ee and >19:1 dr. When compound **6** was treated with DBU at rt, the aromatization reaction occurred to give tricyclic imidazo[1,2-*a*]pyridine **7** in 91% yield with >99% ee. Treating com-
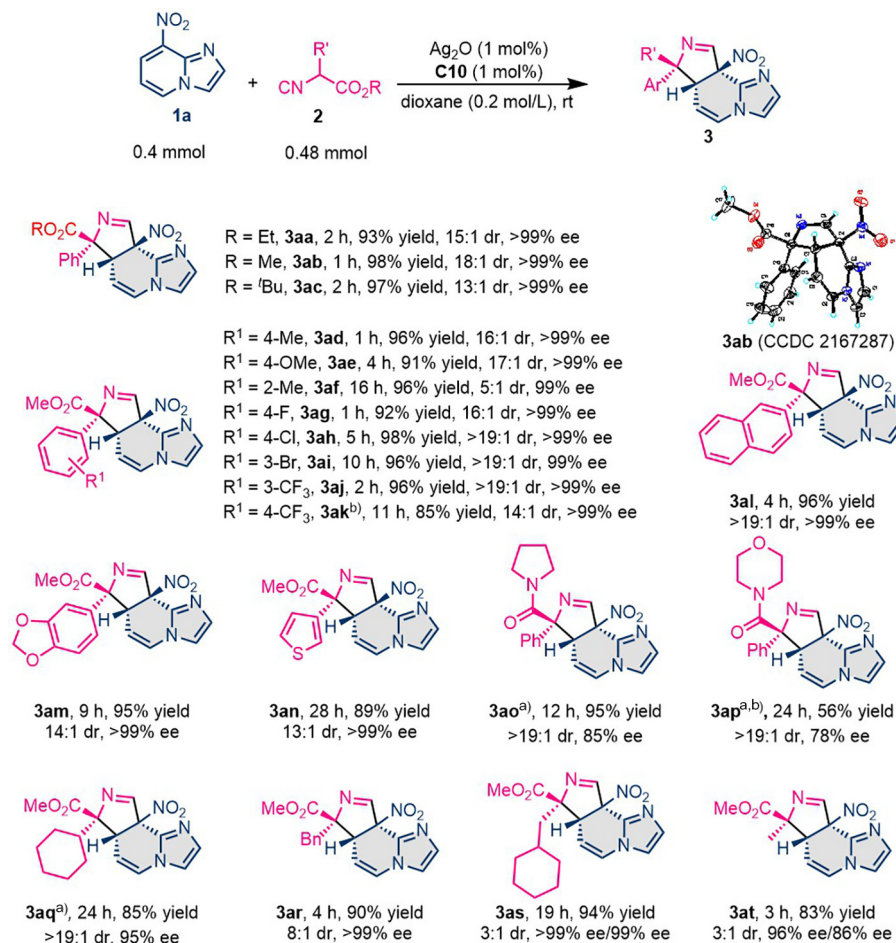
Scheme 2. (Color online) Substrate scope for α-substituted isocyanoacetates. Reaction conditions: **1a** (0.4 mmol), **2** (0.48 mmol), Ag$_2$O (1 mol%), and **C10** (1 mol%) in dioxane (2 mL) at rt under argon atmosphere. a) Ag$_2$O (2 mol% to **1a**) and **C10** (2 mol% to **1a**) at 50 °C were conducted. b) **1a** (0.48 mmol) and **2** (0.4 mmol) were used.
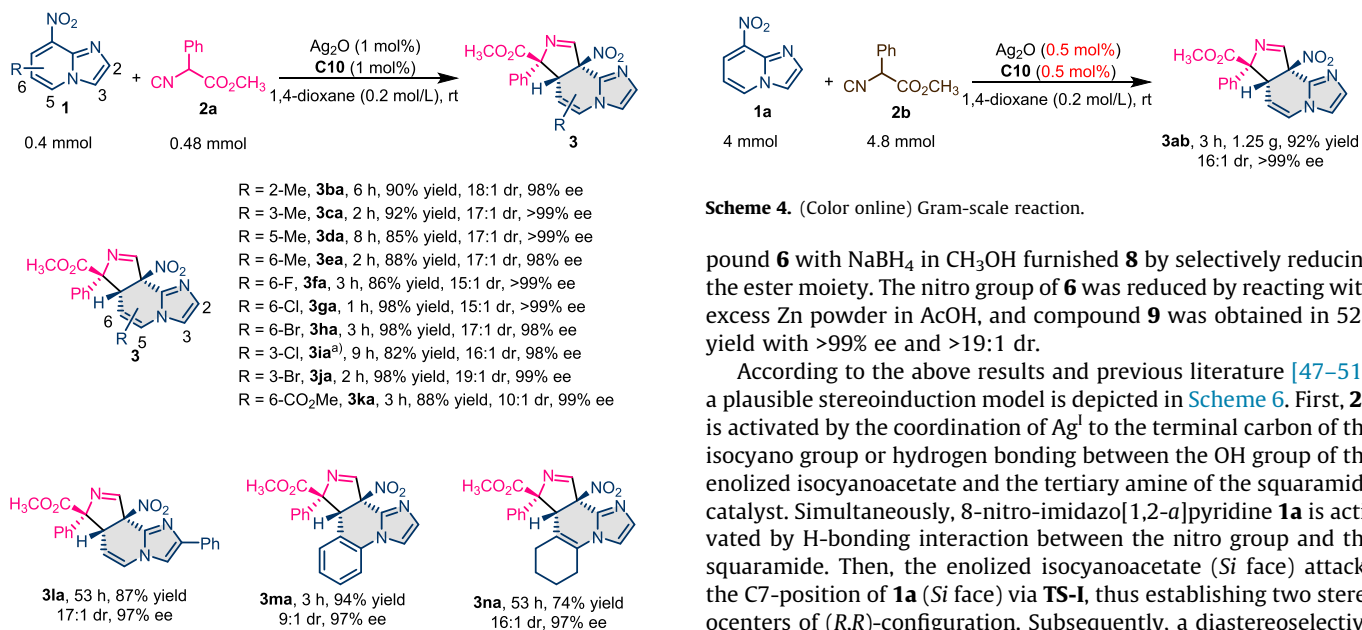

Scheme 3. (Color online) Substrate scope for imidazo[1,2-*a*]pyridines. Reaction conditions: **1** (0.4 mmol), **2a** (0.48 mmol), Ag$_2$O (1 mol%), and **C10** (1 mol%) in dioxane (2 mL) at rt under argon atmosphere. a) Ag$_2$O (2 mol% to **1**) and **C10** (2 mol% to **1**) at 50 °C were conducted.


Scheme 4. (Color online) Gram-scale reaction.

pound **6** with NaBH$_4$ in CH$_3$OH furnished **8** by selectively reducing the ester moiety. The nitro group of **6** was reduced by reacting with excess Zn powder in AcOH, and compound **9** was obtained in 52% yield with >99% ee and >19:1 dr.

According to the above results and previous literature [47–51], a plausible stereoinduction model is depicted in Scheme 6. First, **2b** is activated by the coordination of Ag^I to the terminal carbon of the isocyano group or hydrogen bonding between the OH group of the enolized isocyanoacetate and the tertiary amine of the squaramide catalyst. Simultaneously, 8-nitro-imidazo[1,2-*a*]pyridine **1a** is activated by H-bonding interaction between the nitro group and the squaramide. Then, the enolized isocyanoacetate (*Si* face) attacks the C7-position of **1a** (*Si* face) via **TS-I**, thus establishing two stereocenters of (*R,R*)-configuration. Subsequently, a diastereoselective intramolecular cyclization proceeds between the C8-position of **1a** (*Si* face) and the terminal carbon of the isocyanide group of **2b** via **TS-II**, forging the third stereogenic center of (*S*)-configuration in the product **3ab**.
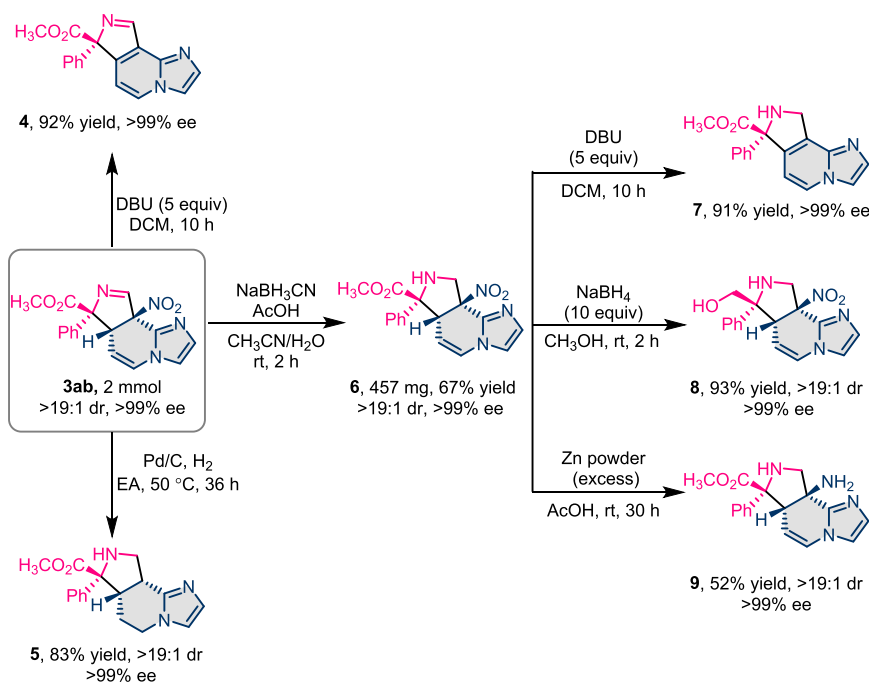
Scheme 5. (Color online) Transformations of **3ab**.
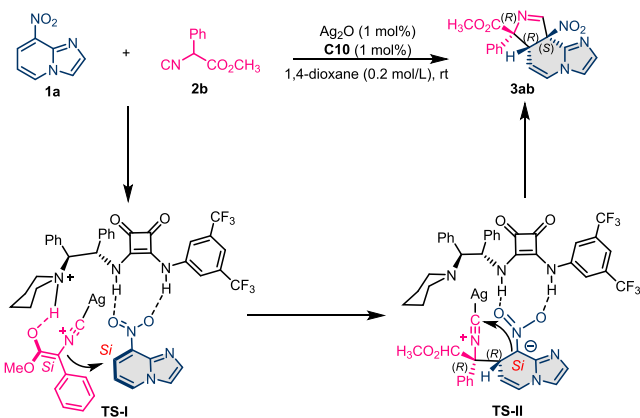
Scheme 6. (Color online) Proposed stereo-induction model.

4. Conclusion

We have developed an efficient diastereo- and enantioselective synthesis of highly functionalized imidazo[1,2-*a*]pyridine derivatives possessing three contiguous stereogenic centers through an interrupted Barton-Zard reaction of 8-nitroimidazo[1,2-*a*]pyridine and α-substituted isocyanoacetates by a Ag$_2$O/squaramide cooperative catalytic system. The protocol features operational simplicity, mild reaction conditions, and wide substrate scope. The loading of Ag$_2$O and squaramide can be lowered to 0.5 mol% without deleterious influence on the reaction outcomes. Meanwhile, the products readily undergo various transformations, further showcasing the synthetic potential of this method.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgments

Author contributions

Qian Wan carried out the experiments and drafted the manuscript. Chao Zheng, Yao-Feng Yuan, and Shu-Li You revised the manuscript. Shu-Li You and Yao-Feng Yuan supervised the whole study. All of the authors discussed the results and commented on the manuscript.

Appendix A. Supplementary materials

Supplementary materials to this article can be found online at https://doi.org/10.1016/j.scib.2022.07.019.

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