Asymmetric Catalysis Hot Paper

How to cite:
International Edition: doi.org/10.1002/anie.202107767
German Edition: doi.org/10.1002/ange.202107767

Silver-Catalyzed Asymmetric Dearomatization of Electron-Deficient Heteroarenes via Interrupted Barton–Zard Reaction

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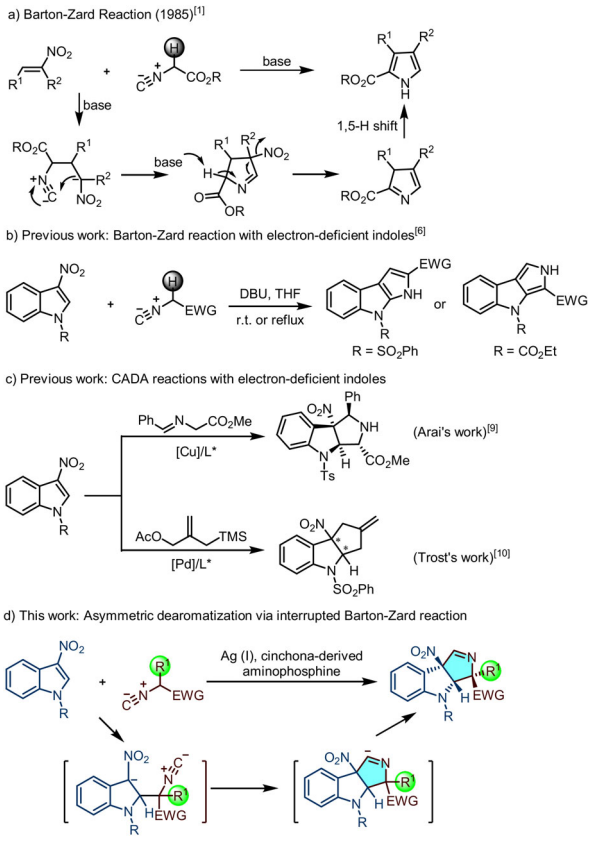
Abstract: *Herein we report a catalytic asymmetric dearomatization reaction of electron-deficient heteroarenes with α-substituted isocyanoacetates through an interrupted Barton–Zard reaction. A range of optically active pyrrolo[3,4-b]indole derivatives was obtained in good yields (up to 97%) with high stereoselectivities (up to >20:1 dr and 97% ee), using a catalytic system consisting of a cinchona-derived amino-phosphine and silver oxide. This reaction features wide substrate scope and mild conditions, and provides a new strategy for developing asymmetric dearomatization reactions.*

The Barton–Zard reaction[1] is an important method for the preparation of 3,4-disubstituted pyrrole-2-carboxylates from readily available isocyanoacetates and dipolarophiles including electron-deficient alkenes,[2] alkynes,[3] and certain nitroarenes[4] (Scheme 1a). The nitro group acts as an activating group in the initial nucleophilic addition and a leaving group for the final formation of the pyrrole ring. This method has been extensively applied in the synthesis of biologically active pyrroles, porphyrins and dipyrromethene dyes.[5] Particularly, the Barton–Zard reaction of 3-nitroindoles with isocyanoacetates has been utilized in the synthesis of various isoindole derivatives. Gribble and co-workers reported elegant examples in which both pyrrolo[2,3-*b*]indoles and pyrrolo[3,4-*b*]indoles could be afforded. The regioselectivity of the reactions could be fine-tuned by the N-protecting groups (Scheme 1b).[6]

Catalytic asymmetric dearomatization (CADA) reactions represent a class of attractive methods to access enantioenriched three-dimensional molecules from readily available planar aromatic compounds.[7] Compared with the well-studied reactions involving electron-rich heteroarenes, the CADA reactions of electron-deficient heteroarenes remain relatively limited.[8] In 2014, the Arai group pioneered a dearomative formal [3+2] cyclization reaction of electron-deficient indoles with imino esters catalyzed by a chiral Cu complex (Scheme 1c).[9] Almost at the same time, the Trost group reported a Pd-catalyzed asymmetric dearomative



Scheme 1. Catalytic asymmetric dearomatization reaction via interrupted Barton–Zard reaction.

cyclization reaction of nitroarenes with trimethylenemethane.[10] Since then, various cyclization modes have been applied for the dearomatization of 3-nitroindoles and related electron-deficient arenes.[11] Encouraged by these successes, we envisioned that if an additional α-substituent is introduced to the isocyanoacetates, the Barton–Zard reaction of 3-nitroindoles might be interrupted after the dearomative cycloaddition, since the final aromatization via the extrusion of HNO_2 is inhibited. This strategy provides a facile protocol for the construction of chiral pyrrolo[3,4-*b*]indole skeleton, which is found as core scaffold in many natural products and pharmacologically active molecules.[12] Recently, we have developed such a highly efficient interrupted Barton–Zard reaction of 3-nitroindoles and related electron-deficient hetereoarenes with α-substituted isocyanoacetates. The stereoselectivity issue is tackled by a catalyst system consisting of a cinchona-derived amino-phosphine and silver oxide. Pyrrolo[3,4-*b*]indole derivatives bearing three contiguous stereogenic centers are obtained in good to excellent yields

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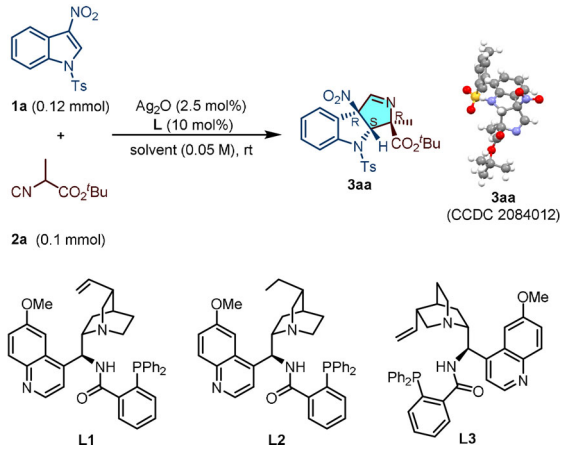
and high stereoselectivity. Herein, we report the results from this study.

The initial studies were carried out using 3-nitroindole (**1a**) and α-methyl isocyanoacetate (**2a**) as model substrates, and the combination of silver oxide and chiral amino-phosphine ligand **L1** as the catalyst in DCM at room temperature (Table 1). This catalytic system has been widely applied in the asymmetric transformations of isocyanoacetates.[13] Gratifyingly, the target reaction proceeded well, delivering the dearomative product **3aa** in excellent yield with moderate diastereoselectivity and promising enantioselectivity (92% NMR yield, 3:1 dr, 88% *ee*; entry 1). The absolute configuration of the major diastereoisomer **3aa** was determined by single-crystal X-ray diffraction analysis.

Further investigations of chiral amino-phosphine ligands showed that **L1** was the optimal one in terms of enantio- and diastereoselectivity (entries 1–3). Subsequently, the examination of solvents (entries 4–8, see the Supporting Information for more details) showed that the stereoselectivity of the reaction could be improved by using Et_2O (9:1 dr, 93% *ee*). Remarkably, the loading of amino-phosphine **L1** can be lowered to 2.5 mol% without any notable influence on reactivity and stereoselectivity (entry 9). Further lowering the loadings of Ag_2O and amino phosphine **L1** to 1 mol% led to significant decrease in both diastereoselectivity and enantioselectivity with a longer reaction time (see the Supporting Information for more details). Control experiments proved that both Ag_2O and amino-phosphine ligand are critical for achieving high yield and stereoselectivity. As determined by NMR analysis, the yield of **3aa** decreased to 74% in the absence of amino-phosphine ligand, and no reaction occurred without Ag_2O (entries 10 and 11). After the investigation on temperature and reactant concentration (see the Supporting Information for more details), the optimized conditions were established using Ag_2O (2.5 mol%) and amino phosphine **L1** (2.5 mol%) in Et_2O (0.025 M for **2a**) at room temperature. The desired product **3aa** was delivered in 90% yield with 94% *ee* and 10:1 dr (entry 12).

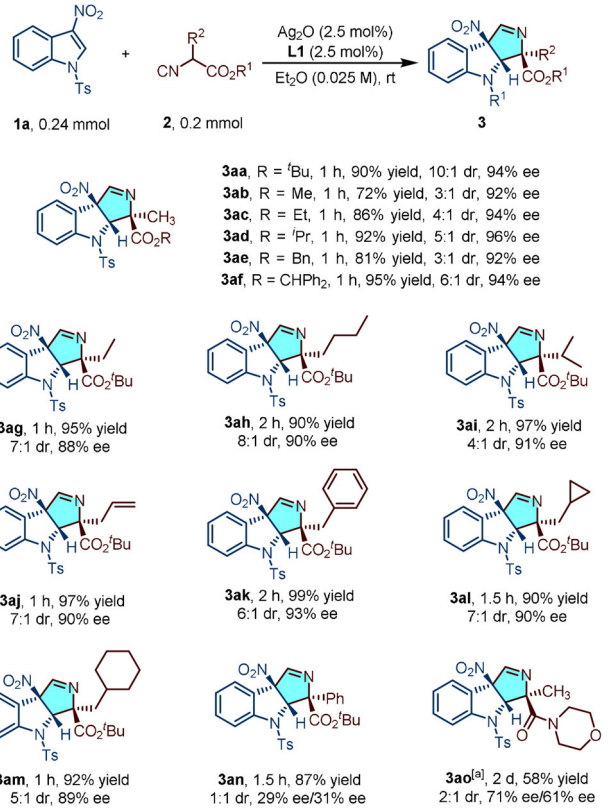
With the optimized reaction conditions in hands (Table 1, entry 12), we next studied the scope of α-substituted isocyanoacetates **2** with 3-nitroindole **1a** (Scheme 2). Firstly, the variation of the ester moiety of α-methyl isocyanoacetates (**2a**–**2f**) was investigated and all tested esters (methyl, ethyl, isopropyl, tert-butyl, benzyl, dibenzhydryl) could be tolerated to afford **3aa**–**3af** in moderate to good diastereoselectivities (3:1–10:1 dr) and excellent enantioselectivities (92–96% *ee*). Interestingly, the diastereoselectivity of this process increases when α-methyl isocyanoacetates bearing sterically more hindered ester group are used. We are pleased to find that

Table 1: Optimization of reaction conditions.[a]



Entry	Ag salt	L	Solvent	*t*	Yield[b]	dr[c]	*ee*[d]
1	Ag_2O	**L1**	DCM	1 h	92%	3:1	88%
2	Ag_2O	**L2**	DCM	1 h	92%	2:1	80%
3	Ag_2O	**L3**	DCM	1 h	97%	2:1	79%
4	Ag_2O	**L1**	DCE	1 h	96%	3:1	85%
5	Ag_2O	**L1**	toluene	1 h	95%	7:1	93%
6	Ag_2O	**L1**	dixone	1 h	99%	4:1	89%
7	Ag_2O	**L1**	THF	1 h	99%	5:1	93%
8	Ag_2O	**L1**	Et_2O	1 h	93%	9:1	93%
9[e]	Ag_2O	**L1**	Et_2O	1 h	95%	10:1	93%
10	Ag_2O	–	Et_2O	17 h	74%	2:1	–
11[e]	–	**L1**	Et_2O	17 h	trace	–	–
12[e,f]	Ag_2O	**L1**	Et_2O	1 h	97% (90%)[g]	10:1	94%

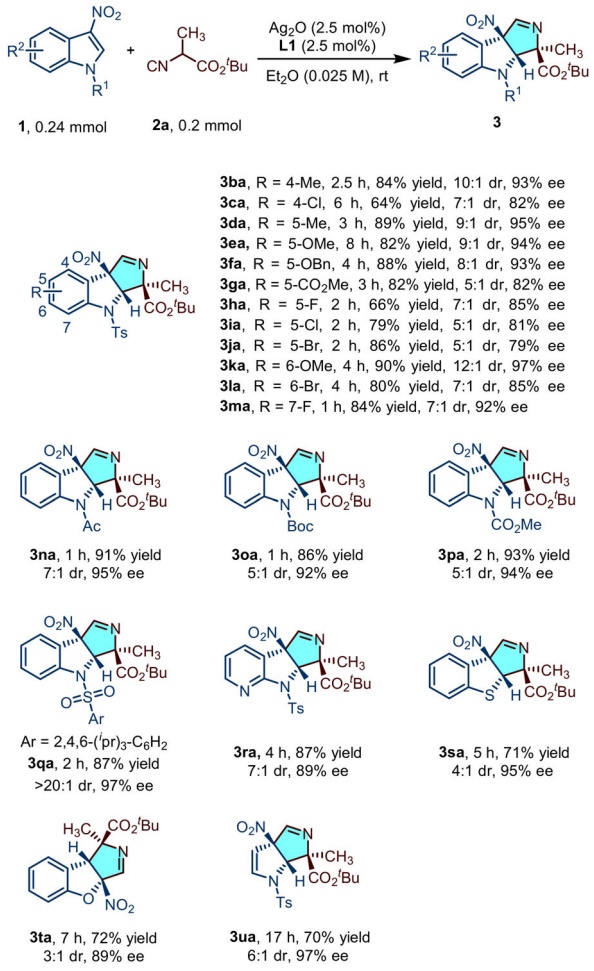
[a] Reaction conditions: **1a** (0.12 mmol), **2a** (0.1 mmol), Ag_2O (2.5 mol%) and **L** (10 mol%) in solvent (2.0 mL) at rt under argon atmosphere. [b] NMR yield of **3aa** using CH_2Br_2 as an internal standard. [c] Determined by ^1H NMR of the crude reaction mixture. [d] Determined by HPLC analysis. [e] **L1** (2.5 mol%) was used. [f] Et_2O (4.0 mL) was used. [g] Isolated yield of **3aa** with both diastereoisomers under the following conditions: **1a** (0.24 mmol), **2a** (0.2 mmol), Ag_2O (2.5 mol%) and **L** (2.5 mol%) in Et_2O (8.0 mL).



Scheme 2. Substrate scope for α-substituted isocyanoacetates. Reaction conditions: **1a** (0.24 mmol), **2a** (0.2 mmol), Ag_2O (2.5 mol%) and **L1** (2.5 mol%) in Et_2O (8.0 mL) at rt under argon atmosphere. [a] Reaction at 50°C.

products **3ag**–**3am** bearing different alkyl substituents (ethyl, *n*-butyl, isopropyl, allyl, benzyl, cyclopropanemethylene, cyclohexanemethylene) on the α-position of tert-butyl isocyanoacetates were obtained in excellent yields (90–99%), with good diastereoselectivities (4:1–8:1 dr) and enantioselectivities (88–93% *ee*). However, it is notable that α-phenyl isocyanoacetate **2n** was a less suitable substrate, affording the corresponding product **3an** with poor stereoselectivity (1:1 dr, 29% *ee*/31% *ee*). A diminished reactivity was observed for α-methyl isocyanoacetamide **2o**, delivering product **3ao** in 58% yield with moderate stereoselectivity (2:1 dr, 71% *ee*/61% *ee*) at 50 °C in two days.

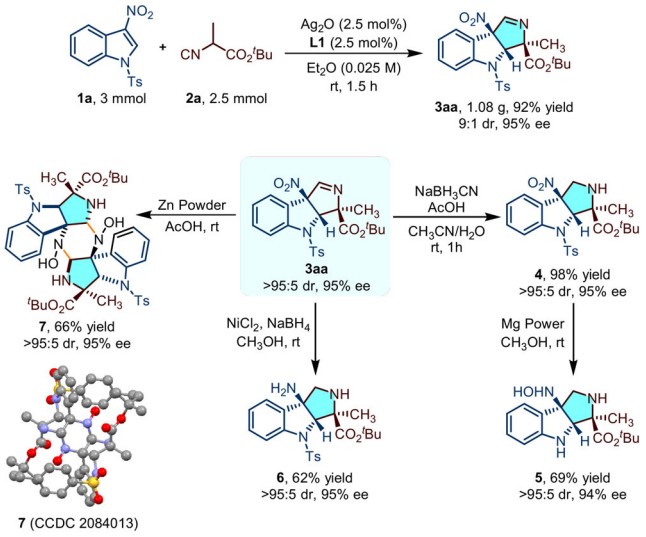
Subsequently, the scope of electron-deficient arenes was explored (Scheme 3). It was found that 3-nitroindoles bearing substituents with varied electronic properties (Me, OMe, OBn, CO_2Me, and halogen atom) at the different position of the indole ring were converted to the corresponding products **3ba**–**3ma** smoothly in good yields (64–90%) and good to excellent diastereo- and enantio-selectivities (5:1–12:1 dr, 79–97% *ee*). It is worth mentioning that stereoselectivity for the reactions of the 3-nitroindoles bearing electron-donating substituents is generally better than those with electron-withdrawing substituents. Then we paid our attention to the



Scheme 3. Substrate scope for electron-deficient heteroarenes. Reaction conditions: **1a** (0.24 mmol), **2a** (0.2 mmol), Ag_2O (2.5 mol%) and **L1** (2.5 mol%) in Et_2O (8.0 mL) at rt under argon atmosphere.

groups on N-1 of 3-nitroindoles, and it was found that various electron-withdrawing groups on N-1 could be accommodated by the reaction (**3na**–**3qa**, 86–93% yield, 5:1- > 20:1 dr, 92–97% *ee*). When sterically more demanding 2,4,6-(^{i}Pr)$_3$-substituted arylsulfonyl group was introduced, **3qa** was obtained in 87% yield, with much improved stereoselectivity (> 20:1 dr, 97% *ee*). To further extend the scope, the reactions of other electron-deficient heteroarenes were investigated. When 7-aza-nitroindole was subjected to the standard conditions, the desired product **3ra** was obtained with good yield (87%) and stereoselectivity (7:1 dr, 89% *ee*). The 3-nitrobenzothiophene and 2-nitrobenzofuran also performed well in this reaction to give products **3sa**–**3ta** with reasonable yields (71–72%), and diastereo- and enantio-selectivities (3:1–4:1 dr, 89–95% *ee*). 5-Membered aromatic heterocycle, such as pyrrole, was also well tolerated, affording the compound **3ua** in moderate yield (70%) with good diastereoselectivity (6:1 dr) and excellent enantioselectivity (97% *ee*).

The synthetic potential of the current protocol was showcased by a gram-scale reaction and several transformations of product **3aa**. As shown in Scheme 4, **3aa** was

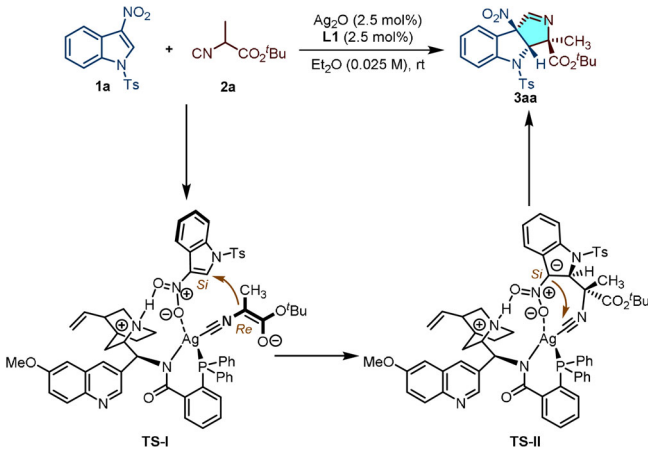


Scheme 4. Gram-scale reaction and transformations of **3aa**.

obtained in 92% yield, 9:1 dr, and 95% *ee*, by treating 3-nitroindole **1a** (3.0 mmol) and α-methyl tert-butyl isocyanoacetate **2a** (2.5 mmol) in the presence of 2.5 mol% Ag_2O and 2.5 mol% **L1**. The imine group of **3aa** was efficiently reduced by $NaBH_3CN$/AcOH, delivering product **4** in 98% yield. Moreover, the treatment of compound **4** by Mg/CH_3OH resulted in the reduction of the nitro group to hydroxylamine accompanied by the removal of the Ts group. The reduction of the nitro group and imine of **3aa** proceeded smoothly by $NiCl_2$/$NaBH_4$, providing **6** in 62% yield. Interestingly, the intermolecular reductive dimerization of **3aa** was observed in the presence of Zn/AcOH, leading to product **7** in 66% yield. The structure and relative stereochemistry of this compound were unambiguously determined by X-ray crystallographic analysis. Notably, during all these above transformations,

products could be obtained as a single diastereoisomer and the enantiomeric purity was retained.

According to the above results and literature reports,[5i,13g] a plausible mechanism and stereo-induction model are proposed with the reaction of 3-nitroindole **1a** and α-methyl tert-butyl isocyanoacetate **2a** as an example (Scheme 5). First



Scheme 5. Proposed stereo-induction model.

both **1a** and **2a** can be activated by the Ag_2O-cinchona complex via coordination and/or hydrogen bonding. This highly pre-organized precursor allows the selective nucleophilic attack of the α-carbon of **2a** (*Re*-face) to the C2-position of **1a** (*Si*-face) through **TS-I**, thus establishing the absolute configuration of the first two stereogenic centers. The subsequent cyclization is highly diastereoselective due to the conformational restriction of the forming five-membered ring. The nucleophile attack of the C3-position of **1a** (*Si*-face) to the terminal carbon of the isocyanide group of **2a** occurs via **TS-II**, leading to the final product **3aa**.

In conclusion, we have successfully developed an Ag-catalyzed asymmetric dearomatization reaction of electron-deficient nitroheteroarenes with α-substituted isocyanoacetates through the interrupted Barton–Zard reaction. A catalytic system consisting of a cinchona-derived aminophosphine and silver oxide displays high efficiency and excellent stereo-control. This strategy provides a facile protocol for the asymmetric construction of optically active pyrrolo[3,4-*b*]indole fragment featuring with wide substrate scope, mild reaction conditions and operationally simple procedure.

Acknowledgements

We thank MOST (2016YFA0202900) and NSFC (21772023, 21821002, and 21961132002) for financial support.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: asymmetric catalysis · Barton–Zard · dearomatization · indole · isocyanoacetate

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[14] Deposition Numbers 2084012 (for **3aa**), and 2084013 (for **7**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

Manuscript received: June 10, 2021
Accepted manuscript online: July 1, 2021
Version of record online: ■■ ■■, ■■■■

Communications

Asymmetric Catalysis

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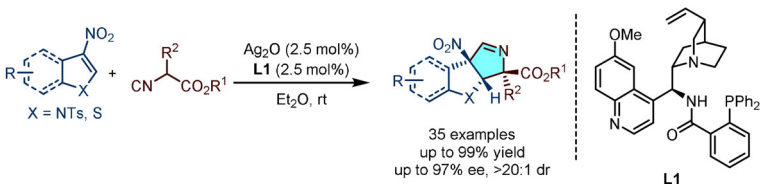
Silver-Catalyzed Asymmetric Dearomatization of Electron-Deficient Heteroarenes via Interrupted Barton–Zard Reaction



Catalytic asymmetric dearomatization reaction of electron-deficient heteroarenes with α-substituted isocyanoacetate ester through an interrupted Barton–Zard reaction is reported. A range of optically active pyrrolo[3,4-*b*]indole derivatives was obtained in good reactivity (up to 99% yield) with high stereoselectivities (up to >20:1 dr, 97% *ee*) in the presence of 2.5 mol% Ag_2O and amino-phosphine **L1**.