SCIENCE CHINA
Chemistry

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March 2022 Vol.65 No.3: 546–553
https://doi.org/10.1007/s11426-021-1149-1

Catalytic asymmetric synthesis of chiral azo compounds *via* interrupted Japp-Klingemann reaction with aryldiazonium salts

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Received September 13, 2021; accepted November 2, 2021; published online January 7, 2022

Asymmetric synthesis of enantioenriched azo compounds bearing tetrasubstituted stereocenter was achieved through chiral *N*,*N*′-dioxide/metal Lewis acid promoted interrupted Japp-Klingemann reaction of aryldiazonium tetrafluoroborate salts with nucleophiles under mild conditions. This protocol features wide substrate scope and good functional group compatibility. Azaarene-containing chiral azo compounds were stable enough in Japp-Klingemann reaction condition. The key to success of the reaction was the employment of metal salt/*N*,*N*′-dioxide ligand and the dual-task roles of the base. Moreover, the X-ray crystal structure of Ni(II)/*N*,*N*′-dioxide/substrate complex confirmed that the substrate was activated by bidentate coordination, which shed light on the origin of chiral control of the reaction.

asymmetric synthesis, Japp-Klingemann reaction, chiral azo compounds, aryldiazonium salts, *N*-electrophile

Citation: Wang Y, Yihuo A, Wang L, Dong S, Feng X. Catalytic asymmetric synthesis of chiral azo compounds *via* interrupted Japp-Klingemann reaction with aryldiazonium salts. *Sci China Chem*, 2022, 65: 546–553, https://doi.org/10.1007/s11426-021-1149-1

1 Introduction

The Japp-Klingemann reaction, involving the coupling of aryldiazonium salts and 1,3-dicarbonyl compounds to yield arylhydrazones, is famous for the Fischer indole synthesis as well as for the enantiopure amino acids synthesis [1]. Even though Japp-Klingemann reaction has the potential to be one of the most efficient methods for the synthesis of alkyl azo compounds (Scheme 1a), this strategy has received much less attention for over one hundred years. There are two major reasons: (1) alkyl azo intermediate was unstable under Japp-Klingemann reaction and was prone to undergo hydrolytic scission of the functional group of acyl, carboxyl, ester *etc*., to yield hydrazone derivatives; (2) lack of mature asymmetric catalytic system to harness active aryldiazonium salts because it would extrude of N_2 easily and take place other an array of name reactions, such as Sandmeyer reaction, Pschorr reaction, and Meerwein arylation [2]. Comparing with unstable aryldiazonium salts, diazocarbonyl compounds are relatively stabilized through conjugation with the carbonyl group (Scheme 1b) [3]. There was a facile way to synthesize chiral alkylhydrazone compounds by Feng's group [4] with α-diazoesters as the *N*-electrophile under the influence of chiral *N*,*N*′-dioxide/Sc^{III} catalyst. On the other hand, chemists found that aryldiazonium tetrafluoroborate salts were stable enough to separate and preserve comparing with other halogen salts. This provided a chance to exploit asymmetric interrupted Japp-Klingemann reaction to obtain optical active alkyl azo compounds. Toste and co-workers [5] described that aryldiazonium tetrafluoroborate salts could be controlled by chiral phosphoric acid catalyst in ion pair formation, providing a facile route to chiral alkyl azo compounds through interrupted Japp-Klingemann reaction, which solved the problem of low solubility of aryldiazonium tetrafluoroborate salts (Scheme 1b).

Though the property and potential value of alkyl azo compounds received less attention than aromatic azo compounds which have been widely used in biological systems,

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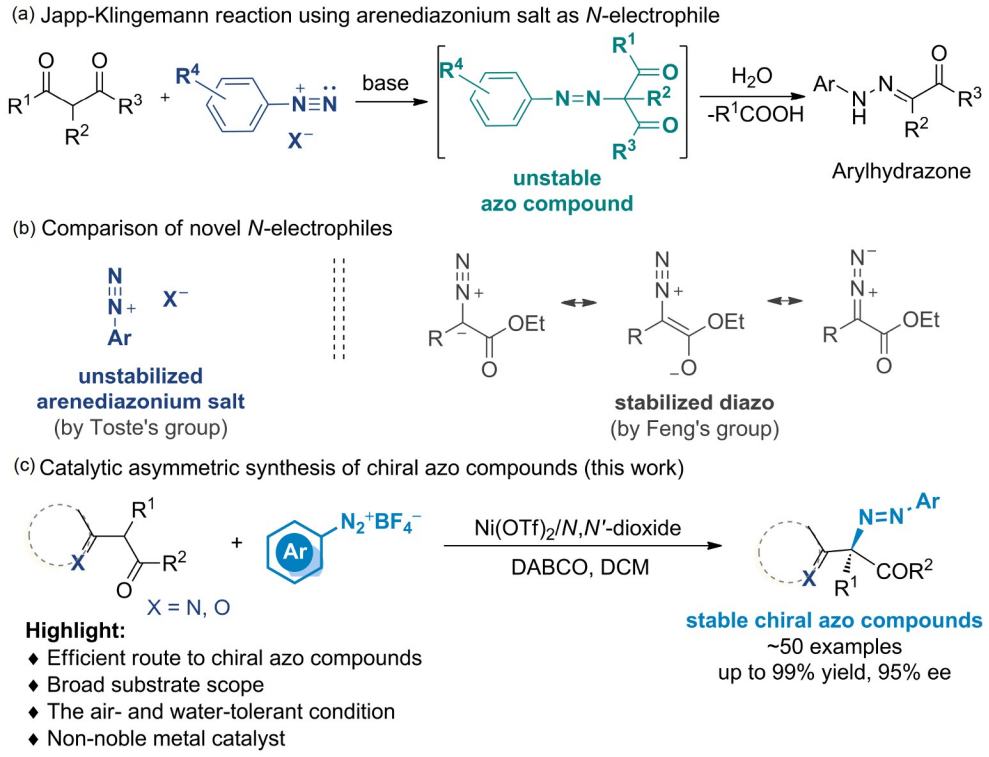


Scheme 1 Catalytic asymmetric synthesis of chiral azo compounds (color online).

industrial applications, and organic synthesis [6], Ar–N=N–R structural motif was found to be very important in developing new azo prodrugs and be easily transform into cyclic diaza compounds, hydrazine derivatives, and non-natural amino acids with a tetra-substituted stereogenic center (Figure 1) [7]. Currently, straightforward routes to challenging chiral aliphatic azo-compounds are scarce [8]. Therefore, developing novel and convenient synthetic methods to obtain stable chiral alkyl azo compounds with variety structure is highly desirable.

Based on our continuous efforts on chiral *N*,*N*′-dioxide/metal complex [9], we hypothesized that chiral *N*,*N*′-dioxide/metal Lewis acid catalyst was a potential promoter for the asymmetric diazenation reaction of carbonyl compounds with aryldiazonium tetrafluoroborate salts as the *N*-electrophiles. Obviously, the keys to success were: (1) preventing metal salt or base breaking aryldiazonium salt down; (2) increasing the solubility of aryldiazonium salt in organic solvents; (3) carrying the reaction under mild conditions to produce azo compounds rather than arylhydrazones.

Herein, we described our experimental results on interrupted Japp-Klingemann reaction to afford a wide range of enantioenriched stable alkyl azo compounds under mild conditions. Chiral *N*,*N*′-dioxide/metal salt complex was eventually identified to be efficient catalyst for the α-amination reaction of azaarylacetamides, azaarylacetate esters or β-ketoamides β-ketoesters with aryldiazonium tetrafluoroborate salts. Experimental studies suggested that 1,4-diazabicyclo[2.2.2]octane (DABCO) has dual-task roles for both deprotonating nucleophile and activating aryldiazonium tetrafluoroborate salt. What is more valuable, the X-ray crystal structure of Ni(II)/*N*,*N*′-dioxide/substrate complex was informative to understand the catalysis mechanism.

2 Results and discussion

In view of the fact that azaarene- and fluorine-containing compounds existed widely in biologically active molecules, pharmaceuticals and agrochemicals [10], we chose 2-(benzo[*d*]thiazol-2-yl)-2-fluoro-*N*,*N*-dimethylacetamide (**1a**) [11] and $PhN_2^+BF_4^-$ (**2a**) as model substrates to optimize the reaction conditions (Table 1). Firstly, different kinds of metal salts were investigated in the presence of (*S*)-2-pipecolinic acid derived **L-PiMe$_3$**. It was found that the first-row metal could promote the reaction smoothly with DABCO as the base in dichloromethane (DCM, entries 1−5). However, no chiral control was observed with $Fe(OTf)_2$. $Ni(OTf)_2$ and $Co(OTf)_2$ provided better enantioselectivities than $Cu(OTf)_2$ and $Zn(OTf)_2$ (86% ee and 84% ee *vs*. 40% ee and 71% ee, respectively). Next, other chiral *N*,*N*′-dioxide ligands were tested with Ni(II) (entries 6−8), and it was indicated that the steric hindrance of amide moiety of the ligands had a significant influence on the reactivity and enantioselectivity. **L-**

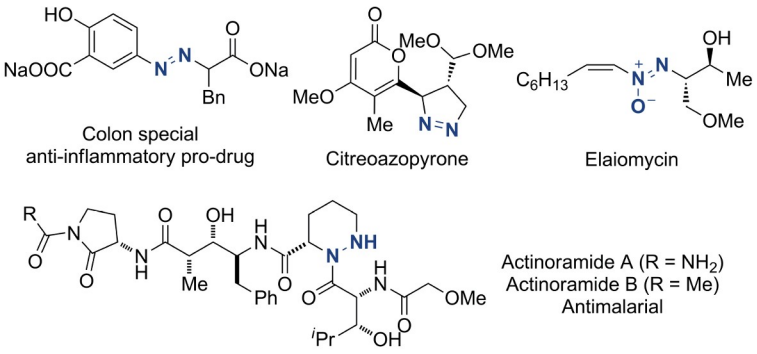
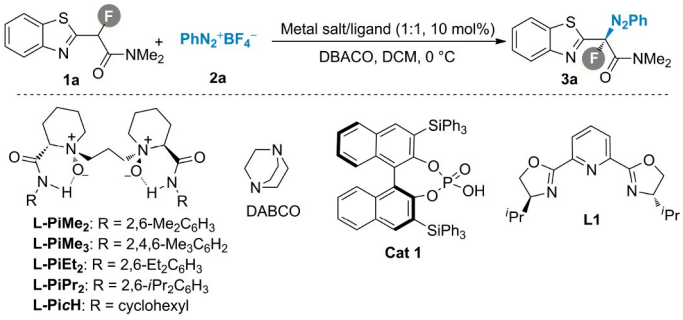


Figure 1 Representative examples of the N-N pharmacophore in pharmaceuticals and natural products (color online).

Table 1 Optimization of the reaction conditions



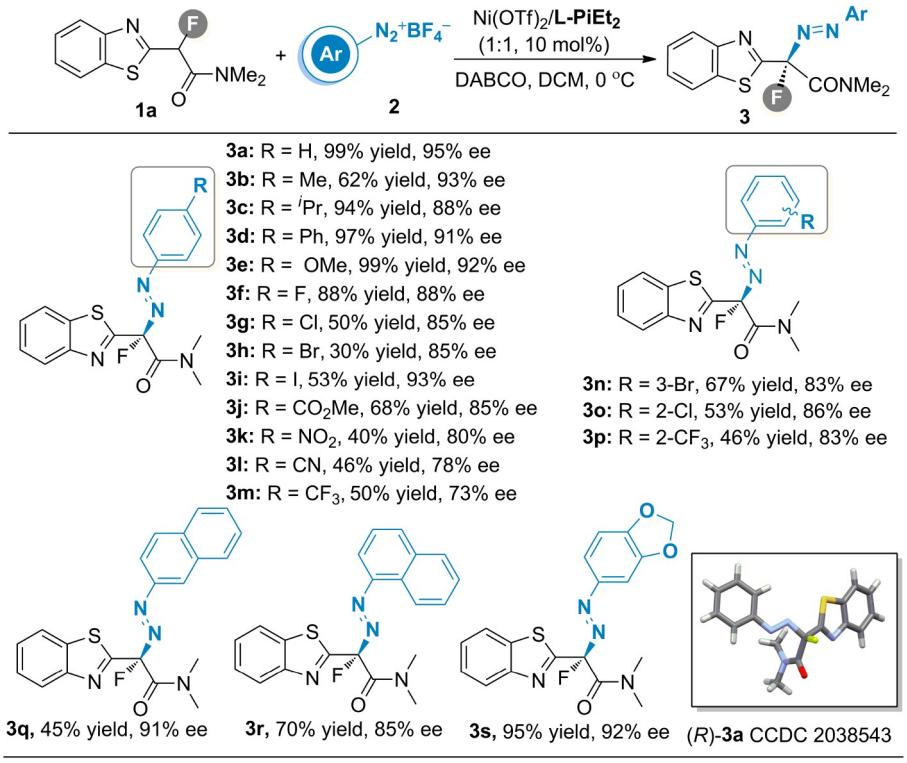
Entry [a]	Metal salt	Ligand	Yield [b] (%)	ee [c] (%)
1	$Fe(OTf)_2$	**L-PiMe$_3$**	35	0
2	$Co(OTf)_2$	**L-PiMe$_3$**	38	84
3	$Ni(OTf)_2$	**L-PiMe$_3$**	38	86
4	$Cu(OTf)_2$	**L-PiMe$_3$**	59	40
5	$Zn(OTf)_2$	**L-PiMe$_3$**	47	71
6	$Ni(OTf)_2$	**L-PiMe$_2$**	58	84
7	$Ni(OTf)_2$	**L-PiEt$_2$**	53	95
8	$Ni(OTf)_2$	**L-PiPr$_2$**	29	79
9 [d]	$Ni(OTf)_2$	**L-PiEt$_2$**	99	95
10 [d]	/	**Cat 1**	21	0
11 [d]	$Ni(OTf)_2$	**L1**	25	3

a) All reactions were performed with **1a** (0.1 mmol), **2a** (0.1 mmol), metal salt/ligand (1:1, 10 mol%), base (1.0 equiv.), in DCM (1.0 mL) at 0 °C for 20 h; b) isolated yield; c) determined by chiral high performance liquid chromatography (HPLC) on a chiral stationary phase; d) the reaction was performed with **1a** (0.18 mmol), **2a** (0.1 mmol), base (1.8 equiv.) for 40 h.

PiEt$_2$ with medium steric hindrance at 2,6-position of aromatic group provided better chiral control (entry 7, 53% yield, 95% ee) than **L-PiMe$_2$** with 2,6-dimethyl substituents or **L-PiPr$_2$** bearing 2,6-^{i}Pr$_2$ groups (entries 6 and 8, 58% yield, 84% ee and 29% yield, 79% ee, respectively). Increasing the amount of substrate **1a** and base led to the desired azo-product **3a** in an increased yield (entry 9). Other reaction parameters, including base, solvent and reaction temperature, were examined as well, but no better results were obtained (see Supporting Information online for more details). The use of other representative chiral catalyst and ligands, such as chiral phosphonic acid **cat 1** and chiral oxazoline ligand **L1**, produced **3a** in low yield and poor enantioselectivity (entries 10 and 11).

With the optimized conditions in hands, we evaluated the generality of this reaction. As shown in Table 2, a series of aryldiazonium tetrafluoroborate salts bearing various *para*-substituted phenyl group reacted with azaarylacetamide **1a** well, delivering the corresponding chiral aryl-alkyl azo compounds with moderate to good yield and high ee value (**3a**–**3m**, 30% to 99% yield, 73% to 95% ee). The electronic property of *para*-substituents on the phenyl ring of **2** dis-

Table 2 Substrate scope of aryldiazonium tetrafluoroborate [a)]



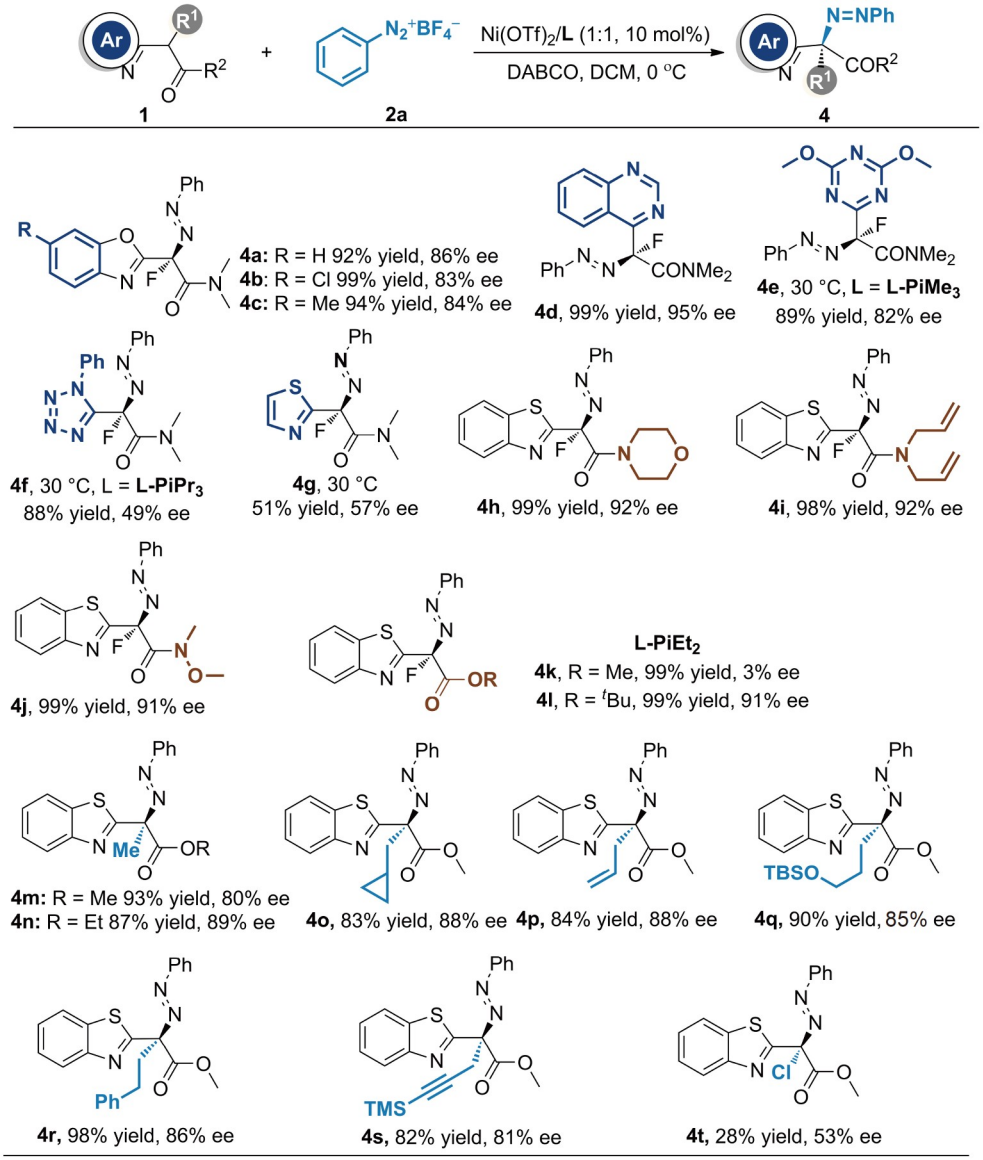
a) All conditions were carried out with **L-PiEt$_2$**/Ni(OTf)$_2$ (1:1, 10 mol%), **1a** (1.8 equiv.), **2**(0.20 mmol) and DABCO (1.8 equiv.) in DCM (2.0 mL) at 0°C for 40 h. Isolated total yield of product **3**. The ee value was determined by HPLC on a chiral stationary phase.

played an obvious effect on the reactivity and enantioselectivity. Generally, the diazonium salts with electron-donating substituents provided higher yield and enantiomeric excess than the ones with electron-withdrawing substituents (**3a**–**3e** *vs*. **3f**–**3m**). Due to the low solubility of halogen-substituted diazonium salts in DCM, lower yields for **3g**–**3i** were obtained. Diazonium salt **2** with other electron-withdrawing groups, such as CO_2Me, NO_2, CN and CF_3, were unstable and prone to decompose during the reaction process, thus resulting in medium yield (**3j**–**3m**, 40%–68% yield, 73%–85% ee). *Ortho*- or *meta*- substituted diazonium salts **2** were converted into the desired products **3n**–**3p** in moderate yield with high optical purity (46%–67% yield, 83%–86% ee). The fused ring substituted ones with 2-naphthyl, 1-naphthyl or piperonyl groups were suitable, affording the expected products **3q**–**3s** with acceptable results (45%–95% yield, 85%–92% ee). The absolute configuration of the product **3a** was determined to be *R* by X-ray crystal diffraction analysis. The stereochemistry of other products was assigned by comparing their CD spectra with that of compound (*R*)-**3a** [12].

The scope of nucleophile was next evaluated under the optimal reaction conditions. A set of α-fluoro nucleophiles bearing benzothiazolyl groups underwent α-amination reaction to generate the targeted products **4a**–**4c** in 92%–99% yield with 83%–86% ee (Table 3). The electronic feature of substituents on benzothiazolyl ring showed a limited influence on the outcomes. α-Fluoro amides with other azo-aromatic rings, for examples 4-quinazolinyl or (2,4-dimethyl)-1,3,5-triazinyl group, delivered the adducts **4d** and **4e** in 99% and 89% yield with 95% ee and 82% ee, respectively. In stark contrast, the reaction of 1-phenyl-1*H*-tetrazole ring and thiazole ring substituted **1** only resulted in moderate results after further condition optimization (**4f**, 88% yield, 49% ee; **4g**, 51% yield, 57% ee). The substituents at amide moiety displayed a trifling impact on the yield and enantioselectivity (**4h**–**4j**, 98%–99% yield, 91%–92% ee). **3l** with a bulky ester group also worked well, and the product **4l** was isolated in 99% yield with 91% ee. Encouraged by aforementioned results, we turned our attention to switch the fluoro substituent to other functional groups in α-azaaryl esters **1**. After slight modification of the reaction conditions, the reaction of **1m** with methyl group provided the corresponding product **4m** in 93% yield and 80% ee in the presence of Ni(II)/**L-Pic*H***. Under such conditions, an array of α-azaaryl esters **1** bearing cyclopropyl, alkenyl, *tert*-butyldimethylsiloxy (OTBS), aryl and alkynyl groups were all tolerated, affording products **4o**–**4s** in good yield (82%–98% yield) with high enantiomeric excess (81%–95% ee). Unfortunately, the reaction of chloro-substituted α-azaaryl esters **1t** was sluggish and **4t** was obtained with poor yield and medium enantiomeric excess.

Moreover, cyclic β-keto amides were tolerated as well in

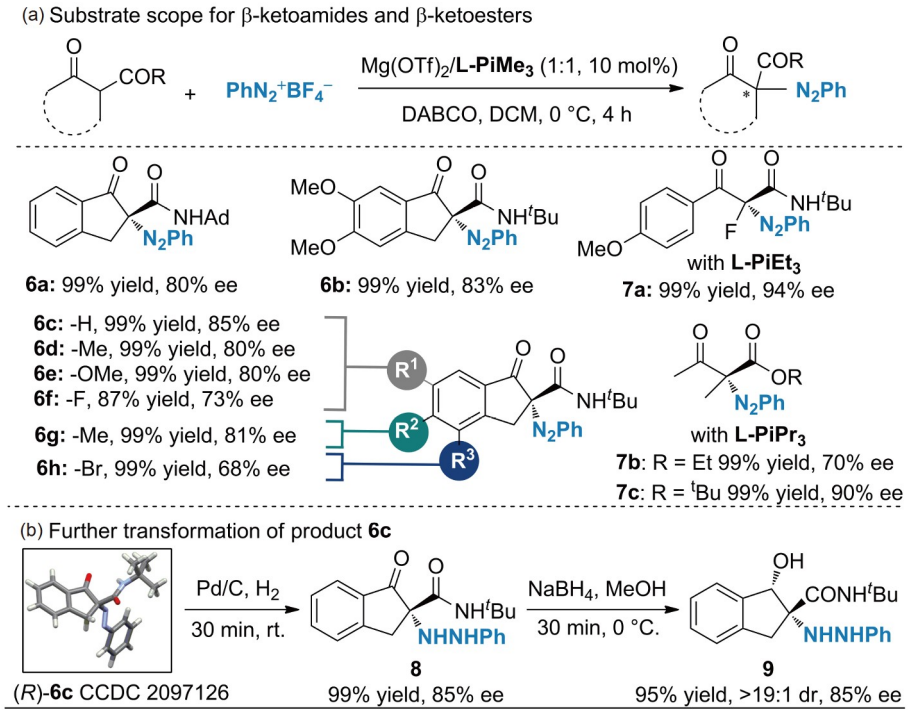
Table 3 Substrate scope of azaaryl acetamides and acetates [a)]



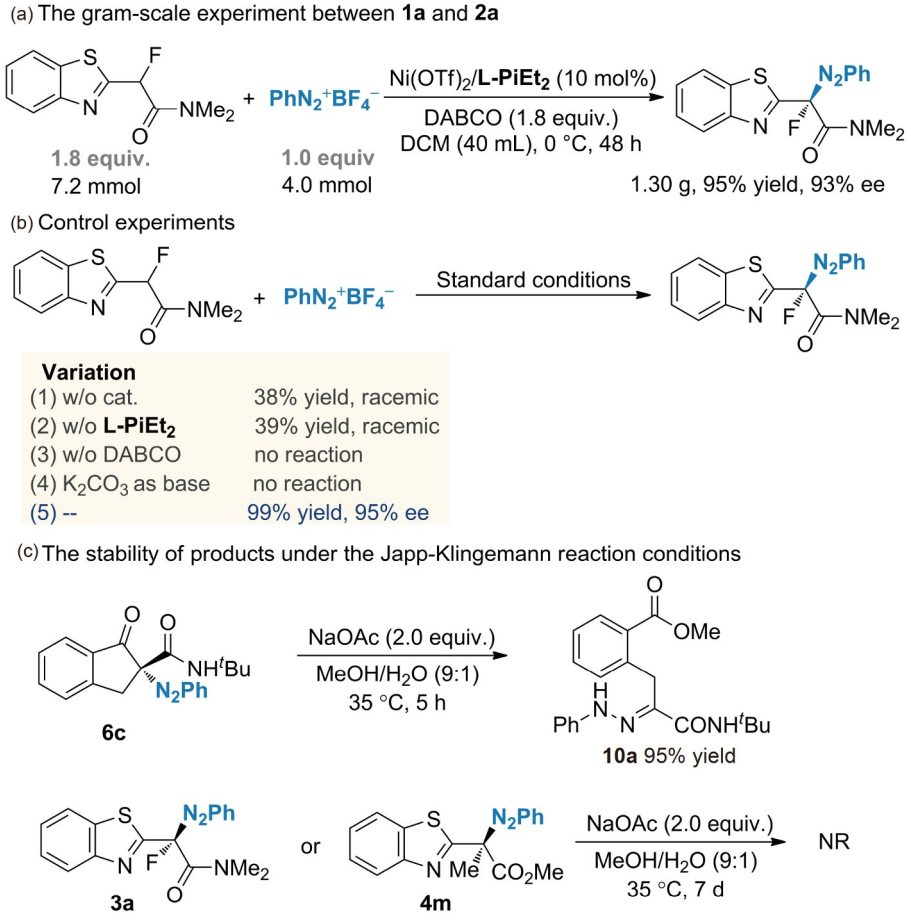
a) Unless otherwise noted, condition A for **4a**–**4j**: **L-PiEt$_2$**/Ni(OTf)$_2$ (1:1, 10 mol%), **1** (1.8 equiv.), **2a** (0.20 mmol) and DABCO (1.8 equiv.) in DCM (2.0 mL) at 0 °C for 40 h. Condition B for **4k-t**: **L-Pic*H***/Ni(OTf)$_2$ (1:1, 10 mol%), **1** (1.0 equiv.), **2a** (0.20 mmol) and DABCO (1.0 equiv.) in DCM (2.0 mL) at 0°C.

the presence of Mg(II)/**L-PiMe$_3$** (for more details, see Supporting Information online, Tables S8 and S9). As illustrated in Scheme 2a, representative examples of β-keto amides were investigated, and most of the reactions proceeded well, providing the related products in high yields with good enantioselectivitives (**6a**–**6e** and **6g**, 99% yield, 80%–85% ee). Slightly decreased enantiomeric excess was given for the β-keto amides with 4-Br and 6-F substituents (**6f**, 87% yield, 73% ee; **6h**, 99% yield, 68% ee). It is worthy of note that the open-chain β-keto amide was amenable to the reaction, and the desired product **7a** was isolated in 99% yield with 94% ee. 2-Methyl-3-oxobutanoate, a common substrate in Japp-Klingemann reaction, was compatible as well in this reaction, delivering the corresponding product **7b** in 99% yield and 70% ee. The absolute configuration of the product **6c** was determined to be *R* by X-ray crystal diffraction analysis [13]. Upon treatment of **6c** with Pd/C, H_2, the chiral hydrazo compound **8** was obtained in 99% yield with maintained ee value. Further transformation of **8** with $NaBH_4$ could give the product **9** with 95% yield and 85% ee, >19:1 dr (Scheme 2b).

To show the synthetic utility of this protocol, a gram-scale reaction was conducted. Substrate **1a** (7.2 mmol) reacted with diazonium salt **2a** (4.0 mmol) under the optimized reaction conditions, providing the product **3a** in 95% yield (1.30 g) with 93% ee (Scheme 3a). To understand the role of each component in the current transformation, several control experiments were carried out (Scheme 3b). When the



Scheme 2 Substrate scope for β-ketoamides and transformation of **6c** (color online).



Scheme 3 Scaled-up reaction and further experimental studies (color online).

reaction was run without Ni(OTf)$_2$/**L-PiEt$_2$**, product **3a** was isolated in 38%, indicating base-promoted background reaction existed. Performing the reaction without chiral ligand **L-PiEt$_2$** resulted into similar results (39% yield), these results implied that a ligand-accelerated catalysis was involved [14]. The reaction did not occur in the absence of DABCO. Different from Toste's work, inorganic base (for an instance, K_2CO_3) could not facilitate the reaction at 0 °C. The role of the base was investigated further. The solution of 4-F substituted diazonium salt **2a** was heterogeneous due to its low solubility in dichloromethane. In contrast, the solution became clear upon the addition of DABCO. We assumed that a soluble species was formed by the nucleophilic addition of DABCO to the diazonium salt [15], which was also confirmed by nuclear magnetic resonance (NMR) spectroscopy and high resolution mass spectrometry (HRMS). This similar structure was postulated by several groups [16]. However, the isolation and characterization of this compound was unsuccessful due to its lability (for more details, see section 11 in Supporting Information online). These results rendered us to conclude that: (1) the activity of Ni(OTf)$_2$/**L-PiEt$_2$** was high enough to outcompete the racemic background; (2) the base acts dual-task roles in the current reaction. In addition, to probe the stability of alkyl azo products under Japp-Klingemann reaction conditions, the products **3a**, **4m** and **6c** were treated with NaOAc in the mixture of methanol and water. It was found that **3a** and **4m** was stable enough, while the product **6c** from cyclic β-keto amides converted into the coresponding hydrazone smoothly with 85% yield. These results indicated that benzothiazolyl ring incresed the stability of product and it's an important discovery to replenish Japp-Klingemann reaction (Scheme 3c).

In order to get more insight into the origin of chiral control, we tried to get the single-crystal of the catalyst/substrate complex. As shown in Figure 2, the X-ray crystal structure of Ni(II)/**L-PiEt$_2$**/**1a** [17] indicated that a slightly distorted octahedral structure was formed, wherein chiral *N*,*N*′-dioxide **L-PiEt$_2$** acted as neutral tetradentate ligand to bind the center metal Ni(II) in a *cis*-α fashion with two oxygen atoms of amides and two oxygen atoms of N−O. Interestingly, (*S*)-isomer of the substrate **1a** coordinated with Ni(II) in bidentate manner with the nitrogen atom of benzothiazolyl ring and oxygen of amide, indicating potentional kinetic resolution and chiral recognization ability of the chiral catalyst [18]. It is worth noting that the crystals of catayst/substrate complex displayed higher catalytic activity than that of *in-situ* formed catalyst (see Supporting Information online, Section 13 for more details). Based on the absolute configuration of product **3a** and control experiments, a catalytic cycle along with possible working mode was provided to elucidate the reaction process and stereoselectivity. Initially, the substrate **1a** ligated to the Ni(II)/**L-PiEt$_2$** catalyst, and intermediate **I** was deprotonated by DABCO to generate the active enolate **II**, which subsequently underwent nucleophilic attack to species **III** generated by the nucleophilic addition of DABCO to the diazonium salt. Arising from the steric hindrance of 2,6-Et$_2$C$_6$H$_3$ moiety, the *Re*-face of enolate **I** was blocked, leaving its *Si*-face available for the approach of diazonium salt **2a**. Therefore, (*R*)-**3a** was generated, which was in agreement with obtained stereoselectivity.

3 Conclusions

In summary, enantioselective α-amination of azaarylacetamide, azaarylacetate esters and β-ketoamides with aryldiazonium salts were realized by chiral *N*,*N*′-dioxide/metal salt as the Lewis acid catalyst and DABCO as the base through interrupted Japp-Klingemann reaction. Experi-

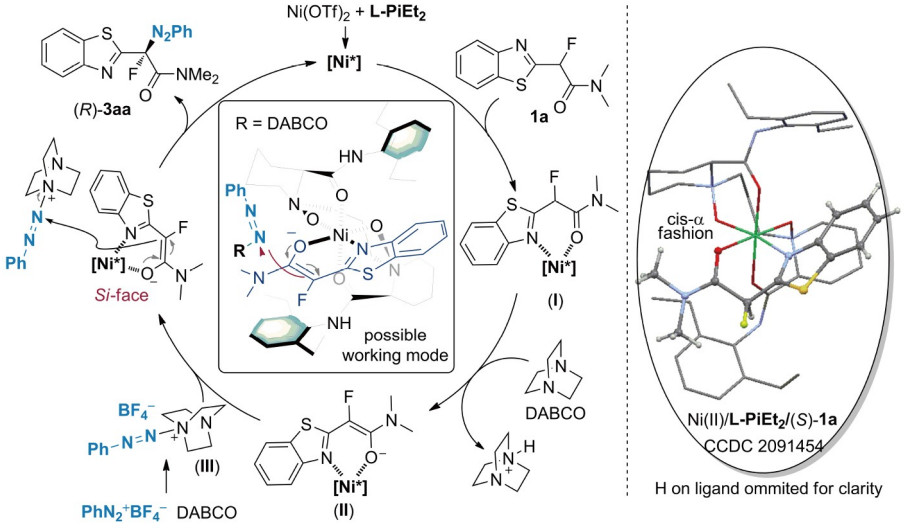


Figure 2 The proposed catalytic cycle (color online).

mental studies suggested that DABCO not only deprotonated nucleophiles, but also interacted with aryldiazonium tetrafluoroborate salt to form soluble species, facilitating the α-amination reaction. Azaarene-containing chiral azo compounds were more stable than others in Japp-Klingemann reaction condition. On the basis of control experiments and X-ray crystal structure of Ni(II)/*N*,*N*′-dioxide/substrate complex, a possible transition state cycle was also proposed to understand the obtained stereochemistry. Further exploration of chiral *N*,*N*′-dioxide/metal complex in other reaction is in progress.

Acknowledgements This work was supported by the National Natural Science Foundation of China (21890723, 21921002).

Conflict of interest The authors declare no conflict of interest.

Supporting information The supporting information is available online at http://chem.scichina.com and http://link.springer.com/journal/11426. The supporting materials are published as submitted, without typesetting or editing. The responsibility for scientific accuracy and content remains entirely with the authors.

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