Organic LETTERS

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Tandem [3 + 2] Cycloaddition/1,4-Addition Reaction of Azomethine Ylides and Aza-*o*-quinone Methides for Asymmetric Synthesis of Imidazolidines

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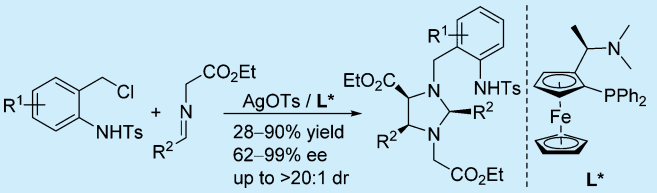
Supporting Information

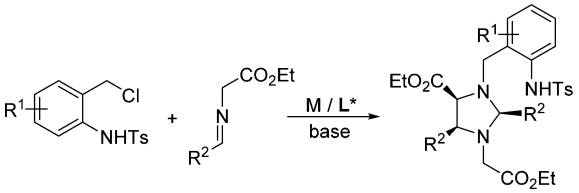
ABSTRACT: An enantioselective synthesis of biologically important imidazolidines has been achieved via a tandem [3 + 2] cycloaddition/1,4-addition reaction of azomethine ylide and aza-*o*-quinone methides. With the use of this tool, various imidazolidine derivatives are obtained in good yields with excellent diastereoselectivities and enantioselectivities.



The transition-metal-catalyzed asymmetric 1,3-dipolar [3 + 2] cycloaddition (1,3-DCs) of azomethine ylides with electron-deficient alkenes has been developed as one of the most powerful and widely used tools for the construction of five-membered nitrogen-containing heterocycles.[1] In sharp contrast, due to the lower reactivity of imines, enantioselective 1,3-DCs of azomethine ylides with carbon−nitrogen double bonds are rare.[2] The key reason for this situation is that the 1,3-DCs of azomethine ylides with imines might be reversible,[2c,3] thus leading to low yields of the imidazolidines. Capturing imidazolidines in situ will be a good strategy to drive the reaction to completion for efficient construction of the chiral imidazolidine skeleton, which constitutes the core structure of many natural products,[4] bioactive compounds,[5] and important catalysts or ligands.[6]

In recent years, aza-*o*-quinone methides (ao-QMs) have attracted much attention. As reactive intermediates,[7] they work as general electrophiles to react with the nucleophile to provide either a [4 + *n*] annulation[8] or 1,4-addition products via stepwise and/or concerted pathways. The 1,4-addition reactions of ao-QMs with Grignard reagent[9] or alcohol[10] were extensively studied. In 1988, a thio etherification of 2-mercaptobenzimidazole with *o*-aminobenzyl halides protected with electron-withdrawing groups under meutral or acidic conditions was reported to give the sulfides.[11] In 2014, Scheidt presented the reaction of benzyl chloride and benzaldehyde in the presence of NHC and DBU to yield the ketone.[12] Rueping reported, in 2015, that CPA catalysts facilitated the generation of ao-QMs from *o*-aminobenzhydryl alcohols, which were alkylated by substituted indole nucleophiles to synthesize triarylmethane derivatives in high yields and enantioselectivities.[8j] We wondered if imidazolidines from 1,3-DCs of azomethine ylides with imines might be captured by ao-QM intermediates, affording biologically important imidazolidine derivatives. Inspired by our previous work on cycloaddition reaction of azomethine ylides[13] and aiming to synthesize biologically interesting imidazolidine derivatives, herein we report a [3 + 2] cycloaddition/1,4-addition sequence of azomethine ylide and ao-QM precursor for synthesis of various imidazolidine derivatives (Scheme 1).

Scheme 1. Tandem [3 + 2] Cycloaddition/1,4-Addition Reaction



In initial studies, the reaction between ao-QM precursor (**1a**) and azomethine ylide precursor (**2a**) was surveyed using Ag(I) salts as the precatalyst and ferrocenylphosphine P−N ligand **L1** as the chiral ligand[14] in the presence of 0.20 mmol of KOH and 0.02 mmol of 18-crown-6 at −30 °C. To our delight, under the catalysis of 10 mol % of AgOTf and 11 mol % of **L1**, the reaction proceeded smoothly in dichloromethane to give the desired product **3aa** possessing three stereocenters as the major product in 72% yield, >20:1 dr, and 90% ee (Table 1, entry 1). The absolute configuration was determined to be (2*S*,4*S*,5*S*) by single-crystal X-ray analysis.[15] Other Ag(I) salts such as $AgNO_3$ and AgOTs could also promote the reaction, providing good yields and excellent enatioselectivities (entries 2 and 3). Among several Ag(I) salts, AgOTs exhibited the best catalytic activity. In this case, the product **3aa** was obtained in 74% yield with 93% ee (entry 3). Next, various chiral ferrocenylphosphine ligands were evaluated. Unfortunately, better results could not be obtained. With the use of **L2**/AgOTs and **L3**/AgOTs as the catalyst, the enantiomeric excesses dropped to 88% and 87%, respectively, although the yields remained good (entries 4 and 5). With the use of **L4**/AgOTs and **L5**/AgOTs as the catalyst,

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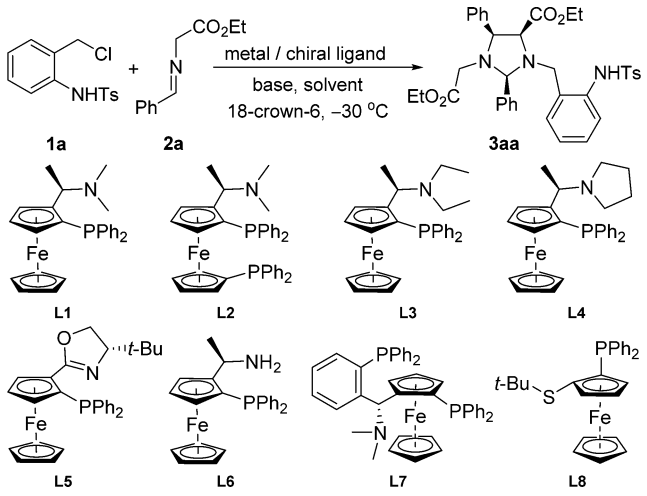
Table 1. Optimization of the Reaction Conditions[a]



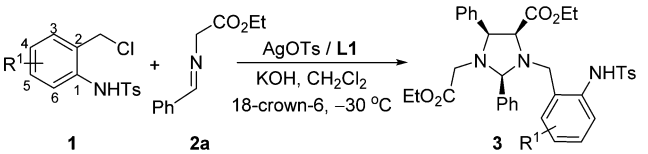
entry	base	metal	ligand	solvent	yield[b] (%)	ee[c] (%)
1	KOH	AgOTf	**L1**	DCM	72	90
2	KOH	$AgNO_3$	**L1**	DCM	75	90
3	KOH	AgOTs	**L1**	DCM	74	93
4	KOH	AgOTs	**L2**	DCM	86	88
5	KOH	AgOTs	**L3**	DCM	75	87
6	KOH	AgOTs	**L4**	DCM	7	27
7	KOH	AgOTs	**L5**	DCM	6	70
8	KOH	AgOTs	**L6**	DCM	trace	
9	KOH	AgOTs	**L7**	DCM	trace	
10	KOH	AgOTs	**L8**	DCM	trace	
11	KF	AgOTs	**L1**	DCM	60	89
12[d]	$CsCO_3$	AgOTs	**L1**	DCM	12	79
13[d]	DIPEA	AgOTs	**L1**	DCM	6	75
14	KOH	AgOTs	**L1**	DCE	86	86
15	KOH	AgOTs	**L1**	$CHCl_3$	trace	
16[e]	KOH	AgOTs	**L1**	DCM	74	93
17[e,f]	KOH	AgOTs	**L1**	DCM	29	89

[a]Unless indicated otherwise, reactions of **1a** (0.10 mmol) and **2a** (0.22 mmol), were carried out at −30 °C in the presence of metal salt (0.01 mmol), chiral ligand (0.011 mmol), base (0.20 mmol), and 18-crown-6 (0.02 mmol) in 1.5 mL of the solvent for 4 h. [b]Isolated yield. [c]Determined by chiral HPLC analysis. The dr is >20:1, determined by ^{1}H NMR analysis. [d]No 18-crown-6. [e]The reaction was conducted at −40 °C. [f]AgOTs (0.005 mmol) and **L1** (0.005 mmol) were used.

only a very small amount of the product was obtained (7 and 6% yield, respectively) (entries 6 and 7). In contrast, the catalysts **L6**/AgOTs, **L7**/AgOTs, and **L8**/AgOTs could only afford traces of the product (entries 8−10). It has been demonstrated that base-promoted in situ generation of ao-QM from **1a** has some effect on catalytic process.[7,8b−d,h] Therefore, with the use of the optimal **L1**/AgOTs as the catalyst, several bases were next screened. However, shifting the base to KF, $CsCO_3$, or *N*,*N*-diisopropylethylamine (DIPEA) led to deterioration of both yield and ee (entries 11−13). The solvent screening revealed that 1,2-dichloroethane (DCE) was compatible with catalysis, giving the product in 86% yield with 86% ee, but $CHCl_3$ did not (entries 14 and 15). Lowering the reaction temperature to −40 °C has no influence on the yield and ee (entry 16). Reducing the catalyst loading to 5 mol % still afforded a 29% yield of product in 89% ee (entry 17). On the basis of the above observations, subsequent reactions were performed at −30 °C using **L1** (10 mol %)/AgOTs (11 mol %) in 1.5 mL of DCM in the presence of KOH (200 mol %) and 18-crown-6 (20 mol %). On a 1 mmol scale, the reaction still worked efficiently for 12 h to provide the product **3aa** in 86% yield with 97% ee (for experimental details, see the Supporting Information).

With the optimal reaction conditions established, the scope of the substrates was then investigated. As shown in Table 2,

Table 2. Substrate Scope of ao-QM Precursors 1[a]



entry	1	R^1	3	yield[b] (%)	ee[c] (%)
1	**1a**	H	**3aa**	74	93
2	**1b**	3-Cl	**3ba**	75	94
3	**1c**	3-F	**3ca**	80	93
4[d]	**1d**	4-F	**3da**	68	99
5	**1e**	5-F	**3ea**	76	92
6	**1f**	3-CH_3	**3fa**	60	90
7[d]	**1g**	4-CH_3	**3ga**	69	99
8	**1h**	5-CH_3	**3ha**	79	95
9[e]	**1i**	6-CH_3	**3ia**	58	93
10	**1j**	4-OMe	**3ja**	69	94

[a]Unless indicated otherwise, reactions of **1** (0.10 mmol) and **2a** (0.22 mmol) were carried out at −30 °C in the presence of AgOTs (0.01 mmol), **L1** (0.011 mmol), KOH (0.20 mmol), and 18-crown-6 (0.02 mmol) in 1.5 mL of DCM for 4 h. [b]Isolated yield. [c]Determined by chiral HPLC analysis. The dr is >20:1, determined by ^{1}H NMR analysis. [d]Reactions were carried out for 5 h. [e]Reaction was carried out for 6 h.

various ao-QM precursors **1** having diverse electron-donating or -withdrawing groups at different positions on the benzene ring performed the reaction to give the corresponding product in moderate to high yields with excellent enantioselectivities (entries 1−10). It is worth mentioning that the reactions of the ao-QM precursors **1d** and **1g** produced the products **3da** and **3ga** with the best enantioselectivities (99% ee), respectively (entries 4 and 7).

As shown in Table 3, the steric and electronic properties of azomethine ylide precursor **2** had a remarkable effect on the catalytic reaction. In general, those azomethine ylides bearing electron-withdrawing substituents on the benzene ring displayed higher reactivities than those with electron-donating substituents on the benzene ring (Table 3, entries 1−6 vs entries 7 and 8), probably because the electron-withdrawing substituents might increase the nucleophilicities of the ylides. Thienyl-substituted iminoesters was also compatible substrates for the reaction, providing the corresponding product in high yield with moderate enantioselectivity (entry 9). Unfortunately, the aliphatic and conjugated azomethine ylides (R^2 = cyclohexyl, *n*-hexyl, *n*-propyl, styryl, and crotyl) were unreactive under the standard reaction conditions.

In order to shed light on the reaction mechanism, a series of control experiments were carried out. The results discounted an ao-QM-induced ylide formation,[16] which proceeded through an addition followed by proton transfer (for a detailed description of the control experiments, see the Supporting Information). The tandem 1,4-addition/[3 + 2] cycloaddition reaction of azomethine ylides and ao-QM precursors was excluded (Scheme 2a). Interestingly, the intermediate **4** was accidentally

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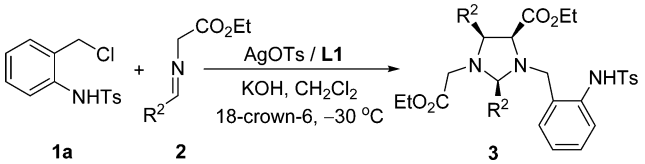
Table 3. Substrate Scope of Azomethine Ylides[a]

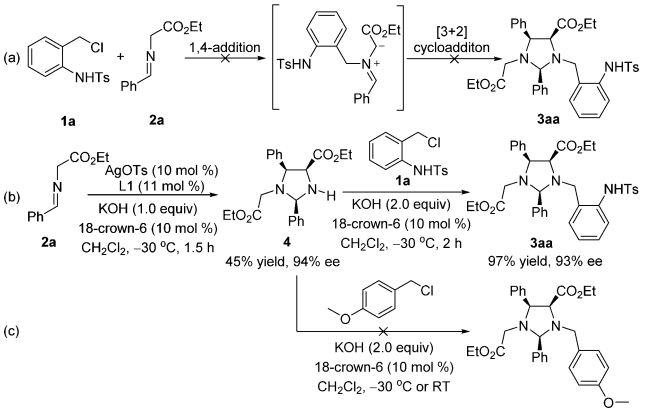


1a 2 3

entry	2	R^2	3	yield[b] (%)	ee[c] (%)
1	**2b**	2-FC_6H_4	**3ab**	85	95[d]
2	**2c**	3-FC_6H_4	**3ac**	76	90
3	**2d**	4-FC_6H_4	**3ad**	82	94
4	**2e**	2-ClC_6H_4	**3ae**	82	92[d]
5	**2f**	3-ClC_6H_4	**3af**	82	85
6	**2g**	4-ClC_6H_4	**3ag**	82	92
7	**2h**	2-$CH_3C_6H_4$	**3ah**	53	62
8	**2i**	4-$CH_3C_6H_4$	**3ai**	85	81
9	**2j**	2-thienyl	**3aj**	90	64[d]
10	**2k**	2-naphthyl	**3ak**	28	91

[a]Unless indicated otherwise, reactions of **1a** (0.10 mmol) and **2** (0.22 mmol), were carried out at −30 °C in the presence of AgOTs (0.01 mmol), **L1** (0.011 mmol), KOH (0.20 mmol), and 18-crown-6 (0.02 mmol) in 1.5 mL of DCM for 4 h. [b]Isolated yield. [c]Determined by chiral HPLC analysis. The dr is >20:1, determined by ^{1}H NMR analysis. [d]Entry 1, dr is 4.3:1; entry 4, dr is 5.6:1; entry 9, dr is 4:1.

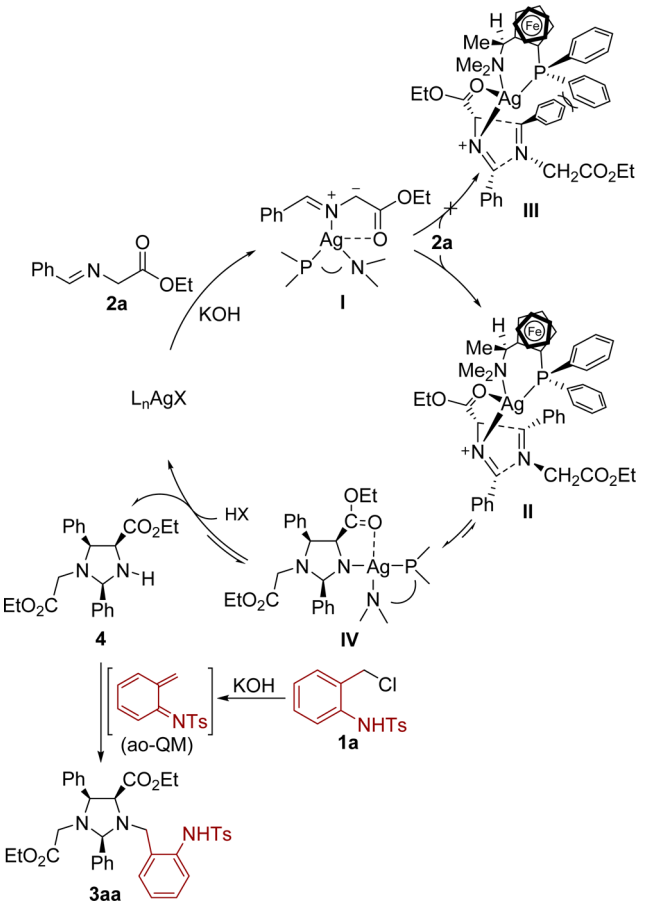
Scheme 2. Tandem 1,4-Addition/[3 + 2] Cycloaddition Reaction



in moderate yield with excellent enantioselectivity (45% yield, 20:1 dr and 94% ee). The intermediate **4** and ao-QM precursor **1a** smoothly underwent 1,4-addition in DCM in the presence of KOH and 18-crown-6, to furnish the imidazolidine **3aa** in 97% yield with nearly the same ee as that of **4** (Scheme 2b). It is worth noting that the product **3aa** through one-pot synthesis had a higher yield (74% yield, Table 1, entry 3) than the yield of the [3 + 2] cycloaddition of azomethine ylides (45% yield). The control experiments with 1-(chloromethyl)-4-methoxybenzene instead of **1a** were performed, producing no desired product (Scheme 2c; see also the Supporting Information). The results showed that a simple amine alkylation of **4** did not occur.

In view of control experiments and literature reports,[1,2,7] a plausible mechanism is proposed in Scheme 3. Treatment of **2a** with a base in the presence of the in situ generated silver complex would lead to the formation of the metalloazomethine ylide **I** as an active species. A regioselective [3 + 2] cycloaddition of azomethine ylides **I** and the second equivalent of Schiff base **2a** then occurs.[2] The transition state **II** is believed

Scheme 3. Plausible Mechanism



to be more thermodynamically stable than **III** because of steric congestion existing in the latter. The high degree of *endo* stereocontrol and excellent diastereofacial discrimination of the transition state **II** generates the imidazolidine complex **IV** as the exclusive intermediate. The intermediate **IV** was protonated to form the intermediate **4**, which was then captured by ao-QM generated in situ from **1a** to accomplish the final product **3aa**.

In conclusion, Ag(I)-catalyzed tandem [3 + 2] cyclization/1,4-addition in the reaction between azomethine ylide and ao-QM has been developed. This asymmetric cycloaddition afforded imidazolidine derivatives with high yields, complete regioselectivities, and excellent diastereo- and enantioselectivities. This tandem reaction involved a carbon−nitrogen bond formation through ao-QM capturing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02512

Experimental procedure, characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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