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Oxirane synthesis from diazocarbonyl compounds via NHC-Ag$^+$ catalysis

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ABSTRACT

A new method was developed to synthesize oxirane products from the reaction of diazocarbonyl substrates with aryl aldehydes by using Ag(I) *N*-heterocyclic carbene complex as the catalyst. A combination of *N*-heterocyclic carbene silver complex (IPrAgCl) with another silver salt (AgOTf) generated the catalytic active IPr-Ag$^+$ intermediate, which then catalyzed the epoxidation reaction.

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Introduction

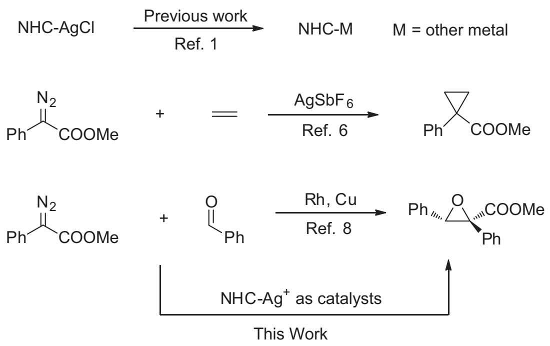
The catalytic role of silver(I) complexes in homogeneous organic reactions was commonly used either as co-catalyst or as Lewis acid,[1] and thus, it has long been considered to be of low catalytic efficiency.[2,3] One famous and early exception to this notion is Arndt–Eistert reaction, which involved a silver carbenoid intermediate in the late step. Nevertheless, this in situ generated silver carbenoid exhibited an atypical intramolecular reactivity (Wolff rearrangement) as compared with dirhodium catalysis.[4]

The first example of intermolecular silver carbenoid chemistry was documented by Dias group in 2003, in which, silver scorpionate catalyst was utilized to catalyze α-diazo esters C–Cl insertion reaction.[5] In 2007, Davies group reported that silver salt ($AgSbF_6$) catalyzed cyclopropanation by using donor/acceptor substituted diazo compounds.[6] In this reaction, silver carbenoid intermediate exhibited a high reactivity and high chemoselectivity, even for the sterically hindered alkenes, which are unreactive under rhodium(II) acetate-catalyzed conditions. Despite these achievements, however, extending this highly reactive silver carbenoid to other types of carbene transfer reactions has never been explored.

Oxirane units are important precursors to a broad range of valuable small molecules and polymers,[7] transition metal(Rh or Cu) mediated [2+1] cycloaddition of a carbene with an aldehyde has been reported to be an important synthetic route for the preparation of the oxirane structure.[8]

Herein we will report a new method of oxirane synthesis from the reaction of diazocarbonyl compounds with aldehydes via NHC-silver catalysis. In the previous research, Ag(I) *N*-heterocyclic carbene complexes (NHC-AgX) were usually employed as the NHC transfer agents, and has seldom been utilized in catalysis.[9] This is the first example, to our knowledge, of employing NHC-Ag$^+$ as catalysts in metal mediated carbene transfer reactions (Scheme 1).

The reaction of methyl phenyldiazoacetate **1a** with electron-rich anisaldehyde **2a** was chosen as the model system for our initial investigation. As shown in Table 1, a mixture of **1a** (0.1 mmol) and 1 mol equiv of **2a** in CH_2Cl_2 was treated with 5 mol % equiv of AgOTf in the condition of 50 mg 4 Å molecular sieves. 24 h later, only trace amounts of oxirane **3a** could be detected, together with



Scheme 1. Metal mediated [2+1] carbene cycloaddition.

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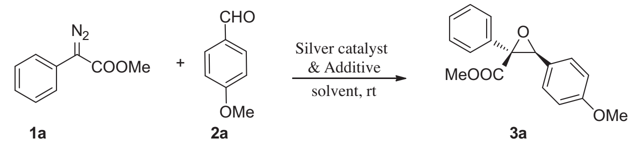
Table 1

Silver mediated epoxidation of phenyldiazoacetate **1a** with anisaldehyde **2a**[a]



	Ag catalyst (mol %)	Additive (mol %)	Solvent/ time (h)	Yield[b] (%)
1	AgOTf (5)	No	DCM/24	<5
2	AgOTf (5)/Ph_3P (5)	No	DCM/8	52
3	AgOTf(5)/Cy_3P (5)	No	DCM/8	57
4	AgOTf (5)/$(C_6F_5)_3P$ (5)	No	DCM/24	<5
5	IPrAgCl (5)	AgOTf (5)	DCM/8	69
6	SIPrAgCl (5)	AgOTf (5)	DCM/8	41
7	ICyAgCl (5)	AgOTf (5)	DCM/8	42
8	IPrAgCl (5)	$AgBF_4$ (5)	DCM/8	39
9	IPrAgCl (5)	$AgSbF_6$ (5)	DCM/8	12
10	IPrAgCl (5)	$AgPF_6$ (5)	DCM/8	26
11	IPrAgCl (5)	$AgNTf_2$ (5)	DCM/8	54
12	IPrAgCl (5)	Ag_2CO_3 (5)	DCM	NR
13	IPrAgCl (5)	$AgClO_4$ (5)	DCM/8	20
14	IPrAgCl (5)	AgOTf (5)	$CHCl_3$/8	58
15	IPrAgCl (5)	AgOTf (5)	DCE/8	52
16	IPrAgCl (5)	AgOTf (5)	Toluene	NR
17	IPrAgCl (5)	AgOTf (5)	Et_2O/8	40
18	IPrAgCl (5)	AgOTf (2.5)	DCM/24	42
19	IPrAgCl (5)	AgOTf (10)	DCM/24	30
20[c]	IPrAgCl (5)	AgOTf (5)	DCM/8	88
21	IPrAgCl (5)	–	DCM	NR

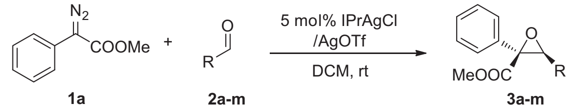
[a] In Table 1 scheme, **3a**'s structure only shows relative configuration. Unless noted, all reactions were carried out on 0.1 mmol scale in 2 mL solvent at rt with the addition of 50 mg 4 Å molecular sieves.

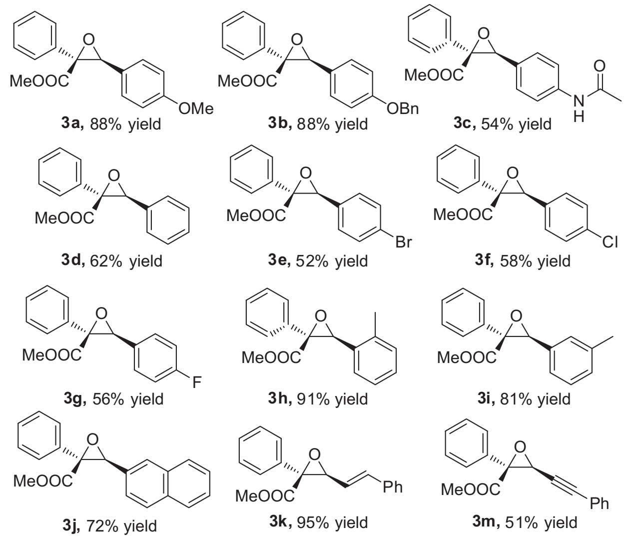
[b] The reaction yields were determined by ^{1}H NMR spectral data.

[c] 2 mol equiv of **1a** was used. NR = No Reaction.

Table 2

NHC-Ag^+ mediated epoxidation reaction of **1a** with various aldehydes.[a, b, c]





3a, 88% yield
3b, 88% yield
3c, 54% yield
3d, 62% yield
3e, 52% yield
3f, 58% yield
3g, 56% yield
3h, 91% yield
3i, 81% yield
3j, 72% yield
3k, 95% yield
3m, 51% yield

[a] Unless noted, all reactions were carried out on 0.1 mmol scale in 2 mL CH_2Cl_2 at rt with the addition of 50 mg 4 Å molecular sieves.

[b] Isolated yields.

[c] Product **3a–m**'s structure only show their relative configuration

the formation of a mixture of carbene dimerization and decomposition products (Table 1, entry 1). When 4 Å molecular sieves were removed, no desired product was obtained. We envisioned that suitable ligand binding would enhance silver carbenoid stability and therefore enhance their reactivity. To our delight, when 5 mol % equiv of Ph_3P was added, **3a**'s yield could be improved to 52% (Table 1, entry 2). Electron rich phosphine ligand Cy_3P performed better than Ph_3P (Table 1, entry 3), while a combination of silver salt with electron deficient $(C_6F_5)_3P$ showed poor reactivity. We considered that σ donating NHC ligand (*N*-heterocyclic carbene) would further improve silver carbenoid reactivity. As shown in Table 1, treating the reaction mixture with 5 mol % equiv of IPrAgCl/AgOTf could provide the desired product **3a** in 69% yield (Table 1, entry 5). Other NHC ligands, such as: SIPrAgCl and ICyAgCl, were also tested, which gave much less yields (Table 1, entry 6–7).

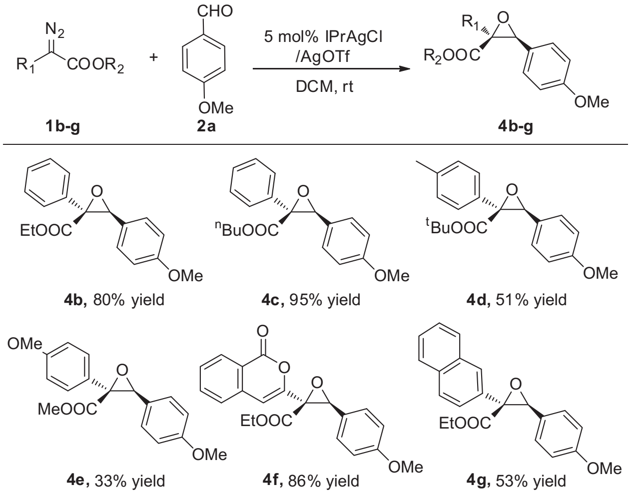
Then, different silver co-catalysts (Table 1, entry 8–13) and solvents (Table 1, entry 14–17) were screened. It was found that $AgBF_4$, $AgSbF_6$, $AgPF_6$, and $AgNTf_2$ gave the desired product in moderate yields. $AgClO_4$ afforded **3a** in a relatively low yield, while Ag_2CO_3 gave no reaction. Further exploration on various solvents was also fruitless. Thus, catalyst IPrAgCl/AgOTf in CH_2Cl_2 was proved to be the best combination (Table 1, entry 5). Improving or lowering the co-catalyst AgOTf's equivalence reduced **3a**'s reaction yield (Table 1, entry 18–19). When **1a**'s amount was improved to 2 equiv, **3a** could be obtained in 88% yield (Table 1, entry 20). In the control experiment, the sole silver catalyst IPrAgCl without silver co-catalyst gave no desired product (Table 1, entry 21).[10]

With the optimal reaction conditions in hand, the substrate scope was explored and a series of oxirane derivatives were synthesized. At first, various aromatic and α, β-unsaturated aldehydes were tested by using methyl phenyldiazoacetate **1a** as the reacting carbene source (Table 2). It has been reported that epoxidation reaction started from the nucleophilic attack of an aldehyde onto metal carbenoid. Therefore, the aldehyde substrate's oxygen nucleophilicity would affect the reaction yield. As shown in Table 1, several *para*-, *ortho*-, and *meta*-substituted benzaldehydes were scrutinized. Both electron-donating and electron-withdrawing benzaldehydes worked very well in this silver carbene [2+1] cycloaddition reaction. Electron rich *p*-alkoxy benzaldehydes afforded **3a** and **3b** in high reaction yields (Table 2, **3a–b**), while *p*-acetoaminobenzaldehyde gave only a moderate yield (Table 2, **3c**). The electron-poor *p*-halo substituted benzaldehydes provided the desired oxiranes in relatively low yields (Table 2, **3e–g**). The *m*- and *o*-substituted benzaldehyde and 2-naphthaldehyde were then tested, which gave **3h**, **3i**, and **3j** in moderate to good yields. α, β-Unsaturated aldehydes were also evaluated. Both vinyl and alkynyl substrates worked very smoothly in this reaction (Table 2, **3k–m**).

Various diazocarbonyl substrates were then explored (Table 3). Both phenyl and vinyl diazocarbonyl substrates reacted smoothly with **2a**, which provided a series of desired oxirane products (Table 3, **4b–g**). Alkyl diazocarbonyl substrate was also tested, but it did not give the desired oxirane product.

In order to elucidate the exact active reaction mediator, we examined the effect of the ligand loading. As compared with the effect of the sole silver salt (5 mol % of AgOTf, Table 1, entry 1) and the combination of AgOTf/Cy_3P (5 mol %, Table 1, entry 3), improving Cy_3P's equivalence to 7 mol % lowered down **3a**'s yield (Scheme 2). Furthermore, only trace amounts of **3a** could be detected in the condition of 5 mol % AgOTf and 10 mol % of Cy_3P. This result, combined with the control experiment (Table 1, entry 21), indicated that IPrAg^+ might be the real active reaction mediator.

Table 3
NHC-Ag$^+$ mediated epoxidation reaction of **2a** with various diazocarbonyl compounds. [a, b, c]



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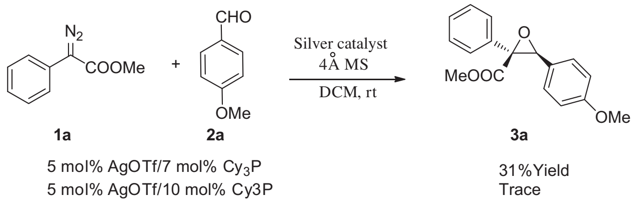
[a] Unless noted, all reactions were carried out on 0.1 mmol scale in 2 mL CH_2Cl_2 at rt with the addition of 50 mg 4 Å molecular sieves.

[b] Isolated yields.

[c] Product **4b–f**'s structure only show relative configuration.



Scheme 2. Effect of Cy_3P loading on the reaction yield.

It was proposed that a carbonyl ylide was generated as the reaction intermediate, which then underwent an intramolecular cyclization to provide the oxirane unit. Trapping this carbonyl ylide intermediate with electron-poor aldehyde would provide 1,3-dioxolane products.[11] As shown in Scheme 3, the reaction of methyl phenyldiazoacetate **1a** with anisaldehyde **2a** and *p*-nitrobenzaldehyde **5** gave 1,3-dioxolane **6** and **6**′ in 65% yield (**6**/**6**′ = 1.4/1), together with 27% yield of **3a**.

In summary, a new method was developed to synthesize oxirane products from the reaction of diazocarbonyl substrates with aryl aldehydes by using Ag(I) *N*-heterocyclic carbene complex as the catalyst. [12] A combination of a *N*-heterocyclic carbene silver complex (IPrAgCl) with another silver salt (AgOTf) would generate the catalytic active IPr-Ag$^+$ intermediate, which then catalyzed the epoxidation reaction. As compared with previous reports, *N*-heterocyclic carbene ligand stabilized the silver catalyst and enhanced its catalytic activity.

Acknowledgments

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Supplementary data

Supplementary data (a brief experimental details, and spectral data for all new products and NOESY spectra for compound **4f**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.03.105.

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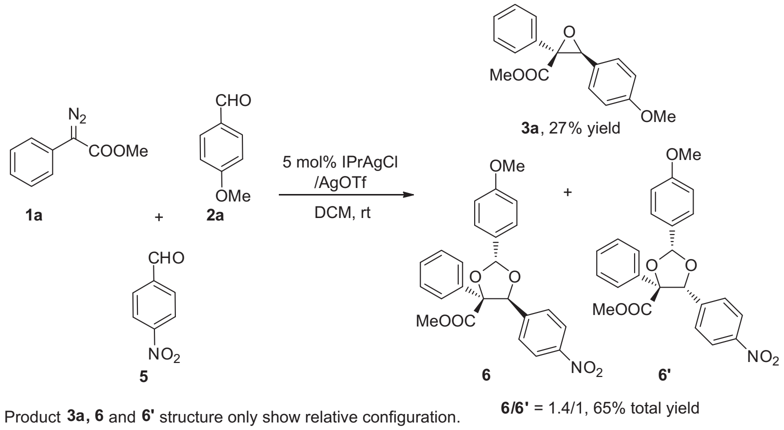

Scheme 3. Trapping the carbonyl ylide with *p*-nitro benzaldehyde to give 1,3-dioxolane.

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10. **3a**'s relative stereochemistry was confirmed by comparing its ^{1}H NMR spectral data with the previous reports and was also deduced from the NOESY spectral data for compound **4f**.

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12. *General procedure for NHC ligated silver catalyzed carbene transfer reaction:* To a solution of IPrAgCl/AgOTf (5 mol %) in dry CH_2Cl_2 (2 mL), was added 100 mg activated 4 Å MS, and was then added diazo ester compound **1a** (0.2 mmol) and anisaldehyde **2a** (0.1 mmol). The reaction was stirred at rt until complete consumption of the starting material with TLC monitoring. Then, the reaction mixture was concentrated in vacuum, and the residue was purified by flash chromatography over silica gel column using hexane/EtOAc (60:1) as the eluent to afford **3a** in 88% yield as a colorless oil. The spectral data of methyl 3-(4-methoxyphenyl)-2-phenyloxirane-2-carboxylate **3a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65–7.62 (m, 2H), 7.41–7.37 (m, 3H), 7.32 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 4.10 (s, 1H), 3.82 (s, 3H), 3.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.3, 159.9, 134.8, 128.7, 128.6, 127.3, 126.2, 125.8, 113.9, 67.1, 65.8, 55.3, 52.2; IR (neat) 2916, 2839, 1734, 1627, 1610, 1508, 1437, 1265, 1165, 739, 698 cm^{-1}.