Chemo-selective Aziridination and Oxyamination of Alkenes with Nano-cobalt catalyst

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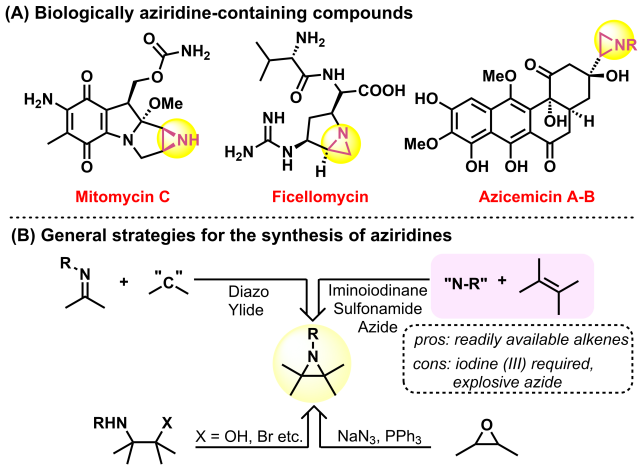
Supporting Information Placeholder

ABSTRACT: Aziridine synthesis from readily available alkene has been a long-standing point of interest for organic chemists, owing to their widely existence in bioactive compounds and plentiful synthetic derivatizations. Herein, a nano-cobalt catalyzed chemo-selective aziridination/oxyamination reaction from alkene and hydroxylamine was developed under room temperature, this system proceeds without external oxidant and exhibits mild, efficient, atom-economic and recyclable characters, which makes this discovery more practical and fascinating. Late-stage aziridinations of drug-derived olefins and diversified synthetic transformation of the aziridine product further expanded the utility of this method. Moreover, this novel methodology represents a rare example of alkene difunctionalization under nano-catalyst, which bridges the gap between homo- and heterogeneous catalysis. Finally, mechanistic studies including deuterium-labeled experiment and Hammet analysis were conducted, and a potential mechanism was proposed accordingly.

INTRODUCTION

Aziridines, the smallest nitrogen-containing heterocycle, are valuable synthetic building blocks in organic synthesis.[1] The aziridine structural motifs are frequently found in bioactive natural products as well as pharmaceuticals,[2] especially antibiotic and antitumor compounds such as Mitomycin C, Ficellomycin, and Azicemicin A-B (Scheme 1, A). Therefore, much efforts have been devoted to the synthesis of aziridines (Scheme 1, B).[1b, 2b, 3] The general routes to the preparation of aziridines include 1) diazo carbene/ylide addition to imine; 2) nitrogen transfer to alkene; 3) intramolecular cyclization of 1,2-aminoalcohol or β-halide amine; 4) the ring opening of epoxide by azide nucleophile and subsequent Staudinger reaction. Among these approaches, the generation of aziridine from alkene has drawn most attention since alkenes are bulk chemicals from petroleum industry. During the recent decades, transition-metal catalyzed alkene aziridination has witnessed significant progresses,[4] representative nitrogen



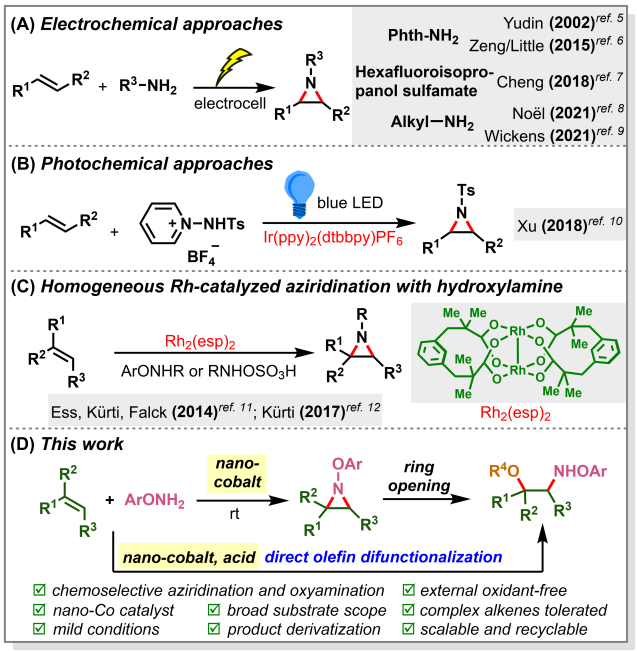
Scheme 1. The aziridine motifs in representative bio-active compounds and the general strategies for the synthesis of aziridines.

transfer reagents include iminoiodinane, sulfonamide, azides, or amine with hypervalent iodine oxidant, which usually form metal-nitrene to implement the aziridination process. However, the necessity of iodine (III) oxidants and explosive azide prevented this protocol to become a sustainable and atom-efficient aziridine synthesis method.

The state-of-the-art olefin aziridinations try to avoid the use of hypervalent iodine oxidant and azide by seeking for new nitrogen transfer reagents (Scheme 2). Along with the development of electrosynthesis, several aziridination reactions with primary amine have been reported under electrochemical oxidation (Scheme 2, A). By employing *N*-aminophthalimide (Phth-NH_2), Yudin,[5] Zeng and Little[6] both realized the aziridine synthesis from simple olefins with either divided or undivided cell. In 2018, Cheng developed an elegant aziridination of steric hindered tri-substituted alkenes using hexafluoroisopropanol sulfamate under electrochemical conditions.[7] Very recently, groundbreaking reports led by Noël,[8] and Wickens[9] revealed that primary alkyl amine was able to serve as the nitrogen precursor, and electrogenerated (di)cation was demonstrated as the crucial intermediate. Besides electrochemical approaches, photoredox catalysis was proved feasible for olefin aziridination reaction as well (Scheme 2, B). Xu and coworkers disclosed a visible light induced iridium catalyzed aziridine synthesis

with *N*-Tosyl 1-aminopyridinium salt through radical process.[10] Together with the advancement achieved through electro- and photocatalysis, the field of homogeneous transition metal catalyzed aziridination has also gained significant developments (Scheme 2, C). A very important breakthrough by Ess, Kürti, and Falck in 2014 showed *O*-(2,4-dinitrophenyl) hydroxylamine (DPH) was an excellent nitrogen transfer reagent under $Rh_2(esp)_2$ catalysis, various olefins underwent aziridination successfully without external oxidants.[11] With the same Rh catalyst, Kürti further expanded the *N*-reagent to hydroxylamine-*O*-sulfonic acids in 2017.[12]

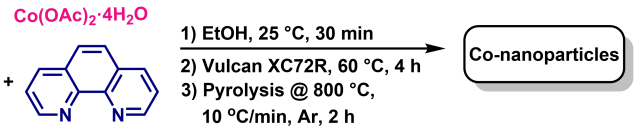
Based on our previous work on cobalt nanoparticles catalyzed transformations[13] and nitrogen incorporation into small molecules,[14] we are keen to seek heterogenous systems for aziridine synthesis and further bridges the gap between homo- and heterogeneous catalysis, also to fill the voids in olefin aziridination with simple amines since non-noble metal based heterogeneous catalysts have not been employed. Herein, we wish to report our recent result on nano-cobalt catalyzed olefin aziridination with commercially available *O*-aryl hydroxylamine as the nitrogen transfer reagent (Scheme 2, D). Compared to the aforementioned methods, our findings use cobalt instead of expensive, toxic Ir/Rh catalysts and avoid the apparatus set-up needed in electro- or photo-chemical approaches. Moreover, a one-step alkene oxyamination with the same nano-cobalt catalyst have been realized selectively.



Scheme 2. Olefin aziridinations with new nitrogen transfer reagents.

RESULTS AND DISCUSSION

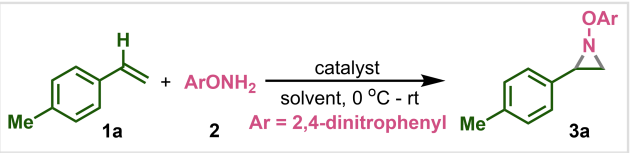
Preparation of Catalysts. The nano-cobalt catalysts were prepared according to our previous work with minor modifications (Scheme 3).[13a, b] Cobalt acetate tetrahydrate and 1,10-phenanthroline were stirred in ethanol for 20 minutes at room temperature to form a homogeneous cobalt complex, commercially available Vulcan XC72R carbon was added as the support and then the mixture was stirred at 60 °C for 4 hours. The solvent was removed in vacuo, and the residue was grinded to fine powder, transferred to a quartz boat and then placed in a tube furnace under argon. The sample was heated to 800 °C at a rate of 10 °C/min, held at 800 °C for 2 hours, and cooled to room temperature. During the whole process argon was constantly passed through the furnace. The obtained cobalt nanoparticles are named as Co-phen(2)@C-800, where 2 denoted the molar ratio of ligand to cobalt.



Scheme 3. Preparation of nano-cobalt catalyst.

Optimization of Reaction Conditions. We commenced our study by using 4-methylstyrene (**1a**) and *O*-(2,4-dinitrophenyl) hydroxylamine (**2**, DPH) as the model substrates (Table 1). Initially, solvent screening was conducted with Co-phen(2)@C-800 catalyst at room temperature (the reaction vials were fist placed in ice bath and warmed up to rt with stirring for 12 hours), while trifluoroethanol (TFE) and hexafluoroisopropanol (HFIP) only showed moderate activity, MeCN afforded 72% yield of the aziridine product **3a** (entries 1-3). It was found alcohol solvents were beneficial to this reaction, and the best result was obtained in methanol with 83% yield (entries 4-5). Similar results were attained when the reaction atmosphere was changed from air to oxygen or argon (entries 6-7). To distinguish the heterogeneous catalyst system from its homogeneous precursors, a few control experiments were carried out. The reaction did not take place when no catalyst was used, and employing $Co(OAc)_2{\cdot}4H_2O$ alone or its physical mixture with 1,10-phenanthroline both failed to generate product **3a**, moreover, the non-pyrolyzed Co-phen(2)@C also did not work for this transformation (entries 8-11). These interesting results triggered us to identify the inherent composition of the nano-cobalt catalyst, and to apply this nano-cobalt system for broader aziridine synthesis.

Table 1. Reaction conditions optimization [a]

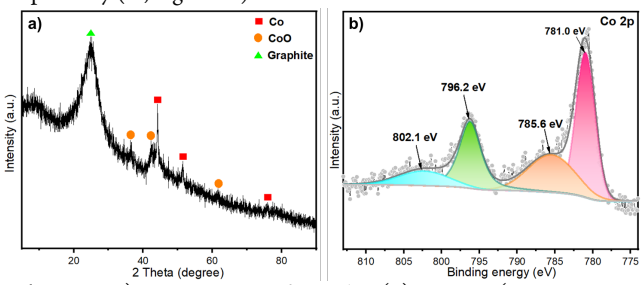


entry	catalyst	solvent	yield (%)
1	Co-phen(2)@C-800	TFE	44
2	Co-phen(2)@C-800	HFIP	56
3	Co-phen(2)@C-800	MeCN	72
4	Co-phen(2)@C-800	*i*PrOH	80
5	**Co-phen(2)@C-800**	**MeOH**	**83**
6[b]	Co-phen(2)@C-800	MeOH	78
7[c]	Co-phen(2)@C-800	MeOH	77
8	no catalyst	MeOH	0
9	$Co(OAc)_2{\cdot}4H_2O$	MeOH	0
10	$Co(OAc)_2{\cdot}4H_2O$ + 1,10-phen	MeOH	0
11	non-pyrolyzed Co-phen(2)@C	MeOH	0

[a] Reaction conditions: **1a** (0.1 mmol), **2** (0.15 mmol), catalyst (10 mg), solvent (1 mL), 0 °C-rt, air, isolated yield. [b] Under O_2. [c] Under Ar.

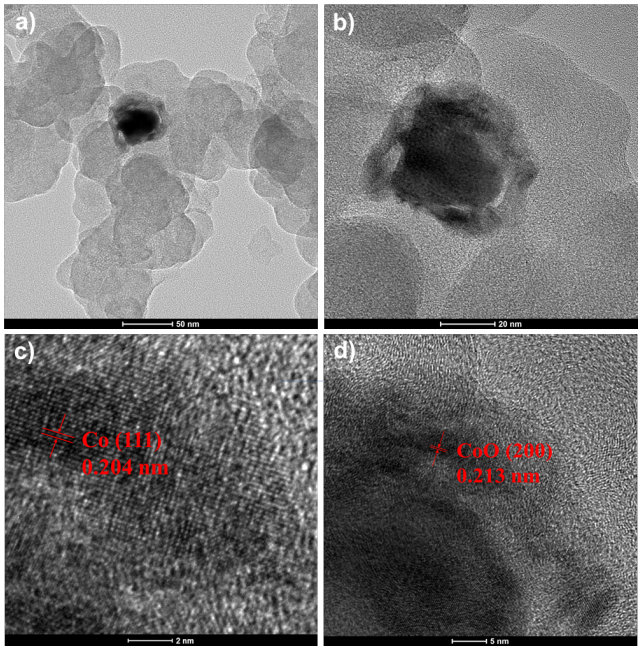
Characterization of the Optimal Catalyst. To understand the superior activity of Co-phen(2)@C-800, detailed structural characterization of this material was next performed. The cobalt content of the Co-phen(2)@C-800 determined by ICP-OES was 1.93 wt% (3 mol% to **1a**), which was a relatively low catalyst loading, especially for non-noble catalyst. The X-ray diffraction (XRD) powder pattern of the optimal catalyst showed two sharp peaks at 2Θ = 44.2° and 51.5°, and weak reflections at 2Θ = 36.5°, 42.4° and 61.5°, the former signals are identical to the metallic Co according to Powder Diffraction File (PDF No. 15-0806) database and the latter confirms the presence of CoO (PDF No. 43-1004) (Scheme 4, a). To further understand the catalyst

surface, X-ray photoelectron spectroscopy (XPS) was conducted (Scheme 4, b). The sample exhibited binding energy of 781.0 eV and 796.2 eV for Co $2p_{3/2}$ and Co $2p_{1/2}$ respectively, and satellite peaks at 785.6 eV and 802.1 eV, which are characteristic for oxidic Co especially Co^{2+} according to literature reports.[15] In nitrogen 1s region, three peaks are observed with binding energy around 399.3 eV, 401.0 eV and 403.3 eV, which are assigned to pyridinic N, pyrrolic N, and N-oxide species, respectively (SI, Figure S1).



Scheme 4. a) XRD spectra of Co-phen(2)@C-800 (assignment according to PDF No. 15-0806, 43-1004); b) XPS Co 2p spectra of Co-phen(2)@C-800.

Subsequently, transmission electron microscopy (TEM) analysis was conducted on the optimal catalyst. Annular bright field (ABF) analysis showed that the cobalt nanoparticles possess core-shell structure and are surrounded by graphitic layers (Scheme 5, a and b), the size of cobalt nanoparticles ranged from 20-50 nm (SI, Figure S2). From the HRTEM images, we clearly observed the lattice spacing of 0.204 nm of the core which is consistent with Co (111) plane, and 0.213 nm of the shell, which is consistent with CoO (200) plane (Scheme 5, c and d). These observations, together with XRD and XPS results, suggested a Co@CoO core-shell structure that is responsible for the catalytic activity.



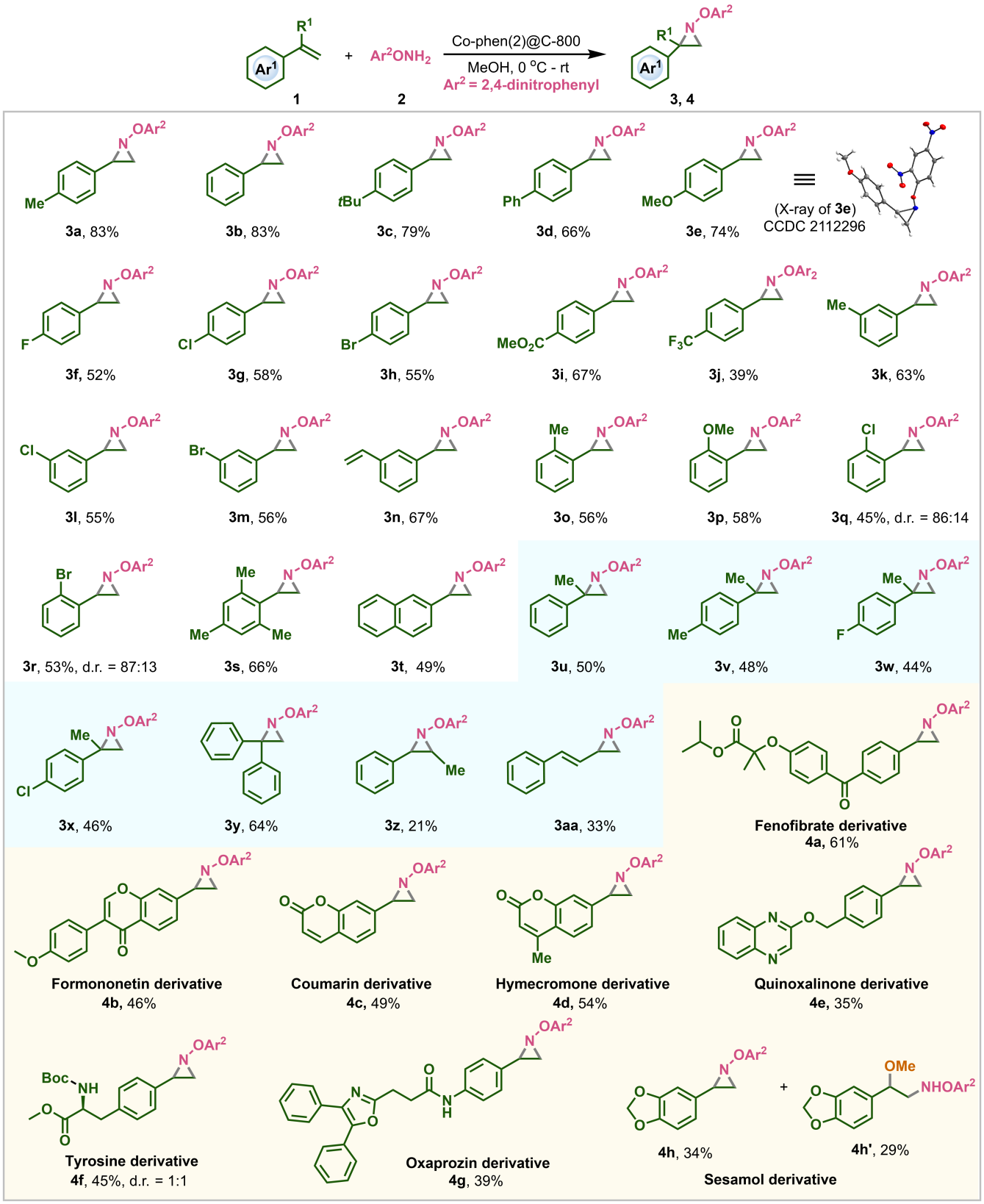
Scheme 5. TEM and HRTEM images of Co-phen(2)@C-800.

Substrate Scope. A series of alkenes were next investigated under the optimal conditions (Table 2). Apart from styrene (**3b**), various *para*-substituted styrene derivatives (*t*Bu, Ph, OMe, F, Cl, Br, CO_2Me, CF_3) showed moderate to good efficiencies (**3c-3j**), and the structure of **3e** was further confirmed by single-crystal X-ray diffraction (CCDC 2112296). *Meta*- and *ortho*-substituted styrene analogues all exhibited good compatibility to generate corresponding aziridine (**3k-3r**), regardless of electronic effect and steric effect. However, it should be noted diastereomers were observed in two cases in the presence of large substituent at *ortho*-position (**3q**, **3r**). Besides, 2,4,6-trimethylstyrene (**3s**) and 2-vinylnaphthalene (**3t**) were amenable to this transformation as well. In addition to mono-substituted olefin, we were eager to apply this practical system to 1,1- or 1,2-disubstituted olefins and more. Gratifyingly, α-methylstyrene and its derivatives (*p*-Me, *p*-F, *p*-Cl), and 1,1-diphenylethylene all resulted in corresponding multi-substituted aziridines smoothly (**3u-3y**), even 1,2-disubstituted olefin (β-methylstyrene) was tolerated, albeit with relatively low yield due to poor substrate conversion (**3z**). Notably, non-styrene type olefin such as 1,3-diene was proved feasible for the aziridination reaction as well (**3aa**), which further expanded the substrate types of this new methodology.

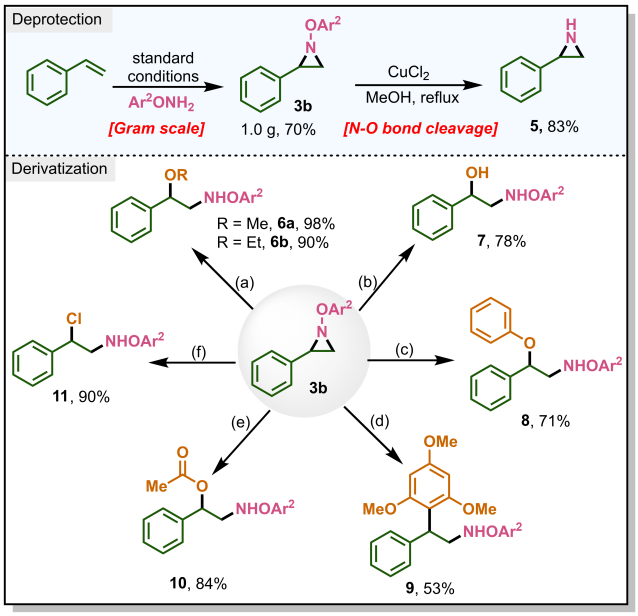
Late-stage Aziridination of Olefins. In light of the widely existence of aziridine structural motif in bioactive compounds and pharmaceuticals, the late-stage olefin aziridination would provide an efficient, concise and atom-economic route to the synthesis of these important molecules, which also avoided the pre-generated aziridine being destroyed in subsequent synthesis steps due to its high reactivity. Encouraged by the results obtained in hand, the nano-Co catalyzed late-stage aziridination of complex olefins were investigated (Table 2). The dyslipidemia-treating drug fenofibrate, and the isoflavone natural product formononetin derived olefins were successfully converted to corresponding aziridine in 61% and 46% yield, respectively (**4a**, **4b**). In both examples the ketone groups stayed intact and were not transformed into oxime ethers in the presence of hydroxylamine **2**. The coumarin, hymecromone and quinoxalinone derivatives were eligible candidates for this transformation as well (**4c-4e**). Furthermore, the amino acid tyrosine, and the anti-inflammatory drug oxaprozin derived olefins were fully compatible with the standard conditions (**4f**, **4g**). It is worth mentioning that the sesamol derived olefin delivered both aziridine product (**4h**) and ring opening oxyamination product (**4h'**), with 63% total yield and a ratio of 1.15:1, which promoted us to further study the direct olefin difunctionalization under nano cobalt catalysis (*vide infra*).

Scale-up Experiment, Deprotection and Derivatization of Aziridines. Based on the above results, more explorations were conducted in order to demonstrate the practicability of this transformation (Scheme 6, top). The gram-scale aziridination of styrene afforded **3b** in 70% yield, which is comparable to previous millimole-scale result. We are also delighted to discover that with $CuCl_2$ in reflux methanol, the N-O bond cleavage of **3b** occurred smoothly to yield the N-H aziridine **5** with 83% yield, which provided a feasible deprotection method for *N*-aroxyl aziridine. With plenty of compound **3b** in hand from the scale-up reaction, versatile derivatizations employing aziridine as the synthetic building block were carried out to showcase the utility of this novel methodology (Scheme 6, bottom). The ring opening of aziridine by different nucleophiles worked effectively, several oxyaminated products were formed with alcohol, water or phenol as oxygen nucleophile (**6**-**8**). Moreover, the carbo-amination, amino-acetoxylation and chloro-amination compounds were gained from aziridine **3b** successfully (**9**-**11**).

Table 2. Olefin aziridination substrate scope under nano cobalt catalysis[a]



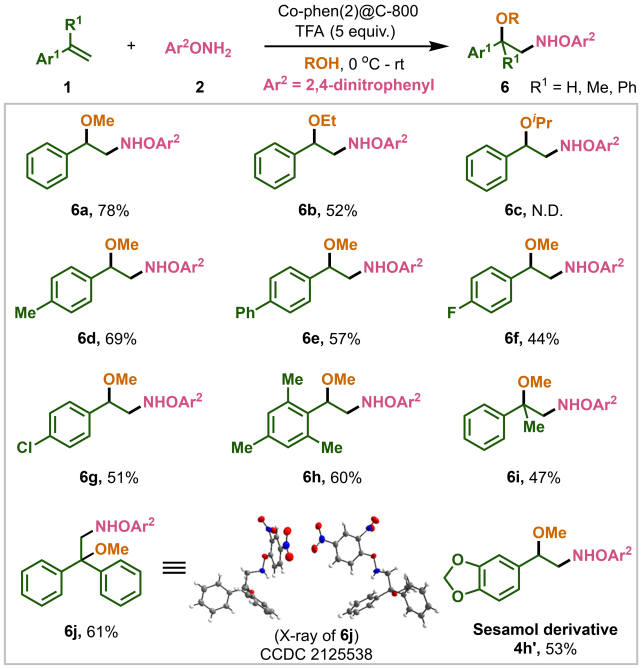
[a]Reaction conditions: olefins (**1**, 0.1 mmol), *O*-(2,4-dinitrophenyl) hydroxylamine (**2**, 0.15 mmol), Co-phen(2)@C-800 (10 mg), MeOH (1 mL), 0 °C-rt, 8-12 h, air, isolated yield.



Scheme 6. Scale-up experiment, deprotection and derivatization of aziridines. (a) TFA (2 equiv.), MeOH or EtOH, rt; (b) H_2O (1.5 equiv.), $BF_3{\cdot}Et_2O$ (20 mol%), MeCN, rt; (c) phenol (1.5 equiv.), $Sc(OTf)_3$ (5 mol%), DCM, rt; (d) 1,3,5-trimethoxybenzene (1.5 equiv.), $Zn(OTf)_2$ (5 mol%), $Sc(OTf)_3$ (5 mol%), DCE, 0 °C-rt; (e) HOAc (1.5 equiv.), $Sc(OTf)_3$ (5 mol %), DCM, rt; (f) HCl (aq.) (3 equiv.), DCM, rt.

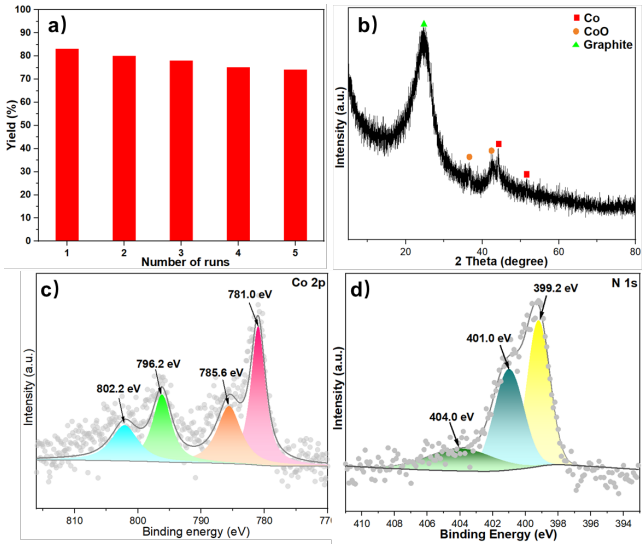
Direct Oxyamination of Alkenes by Nano-cobalt. The alkene difunctionalization reaction represents a rapid and efficient way to build molecular complexity, which introduces different functionalities across the alkene double bond. Despite immense progresses have been witnessed in alkene difunctionalizations over the past years,[16] heterogeneous catalysts especially nano-catalysts were rarely employed.[17] Inspired by the above results, we speculate that the aziridine ring-opening by alcohol could facilitate a direct alkene oxyamination catalyzed by nano cobalt. A few rapid screenings revealed that the addition of trifluoroacetic acid to former standard conditions was amenable to promote alkene oxyamination efficiently, and the substrate scope was examined subsequently (Table 3). The target oxyamination products were formed smoothly with methanol and ethanol as the solvent, while *i*PrOH did not afford any product, only with the formation of aziridine product (**6a**-**6c**). Next, a series of alkenes with electron-donating and withdrawing groups were found well-tolerated with methanol as the solvent (**6d**-**6h**), and the difunctionalization was also applied to 1,1-disubstituted olefins to form products containing quaternary carbon center (**6i**, **6j**), the structure of **6j** was confirmed by single-crystal X-ray diffraction (CCDC 2125538, as a pair of isomers). The one-step oxyamination of bioactive compound was also proved feasible with sesamol derivative which gave 53% yield (**4h'**).

Table 3. Nano-cobalt catalyzed direct oxyamination of olefins[a]



[a] Reaction conditions: olefins (**1**, 0.1 mmol), *O*-(2,4-dinitrophenyl) hydroxylamine (**2**, 0.15 mmol), Co-phen(2)@C-800 (10 mg), TFA (0.5 mmol, 5 equiv.), alcohol (1 mL), 0 °C-rt, 12 h, air, isolated yield.

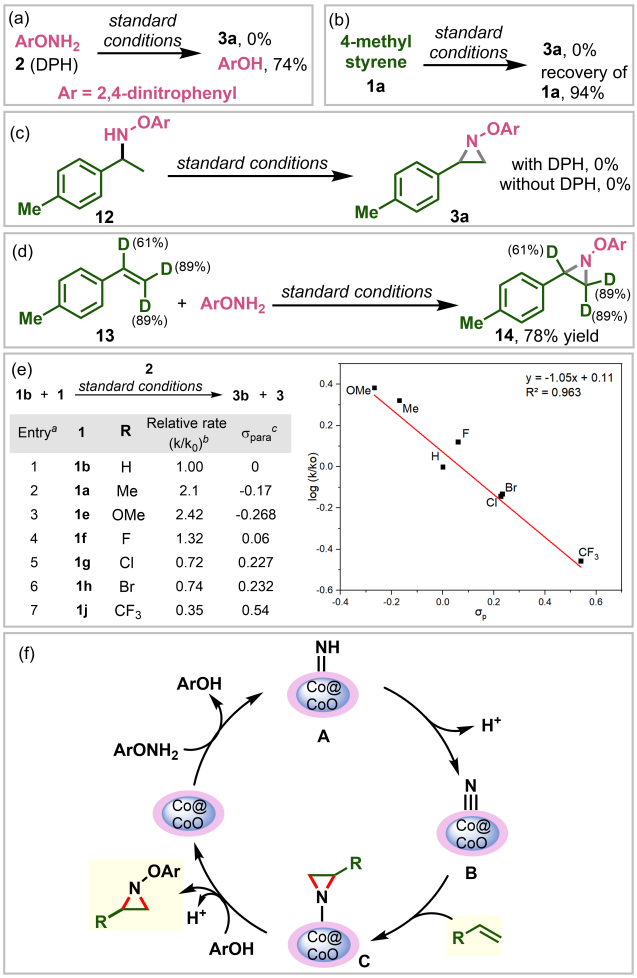
Recyclability, Mechanistic Studies and Proposed Mechanism. The catalyst recyclability and stability are notable advantages of heterogeneous catalysis over homogeneous catalysis. In our scenario, the recycling experiment was performed with styrene as the substrate, and after five runs the yield was attained with 74%, which is comparable to the fresh catalyst (Scheme 7, a). The slightly diminished activity could be ascribed to the decrease of crystallinity as can be seen from XRD of the recycled sample (Scheme 7, b). The XPS analysis of the reused catalyst after five runs did not show obvious changes compared with the fresh catalyst (Scheme 7, c and d), which indicated the stability of the cobalt and nitrogen species on the catalyst surface during the reactions.



Scheme 7. a) Recycling experiment; b) XRD spectra; c) XPS Co 2p spectra; d) XPS N 1s spectra of the recycled catalyst.

Finally, mechanistic explorations were conducted to illustrate the possible reaction pathway. It was found that *O*-(2,4-dinitrophenyl) hydroxylamine (DPH) underwent decomposition to 2,4-dinitrophenol with 74% yield in the absence of 4-methylstyrene (Scheme 8, a), while 4-methylstyrene was recovered in 94% yield in the absence of DPH under the standard conditions (Scheme 8, b), which implied the reaction may be initiated by the interaction of catalyst with DPH. The FTIR spectroscopy of the recycled catalyst from scheme 8a hinted the presence of cobalt imido or cobalt nitride species.[18] In order to verify the possible hydroamination intermediate pathway, compound **12** was prepared and subjected to the optimal conditions, however, **3a** was not

formed no matter with or without DPH, which ruled out the tandem hydroamination/intramolecular cyclization route (Scheme 8, c). Deuterated experiment employing 4-methylstyrene-d_3 (**13**) as substrate afforded the product **14** with 78% yield, all deuterium stayed intact and no hydrogen-deuterium exchange was found (Scheme 8, d). The Hammet plot analysis was conducted by competition experiments of **1b** and *para*-substituted styrenes, the plots correlated linearly with σ_P = -1.05, this negative slope pointed to an electrophilic active species in the aziridine formation (Scheme 8, e). On the basis of above result and literature,[11,19] a possible mechanistic pathway was proposed (Scheme 8, f). Under the Co@CoO core-shell nanocatalyst, DPH first released ArOH to generate cobalt imido species **A**. The key intermediate, electrophilic cobalt terminal nitride **B** was formed through deprotonation of **A**. Another possible evidence of the cobalt terminal nitride is that the reaction failed to provide any products when using *N*-Me-DPH. Subsequent trapping of **B** by olefin afforded the cobalt aziridino species **C**, which was attacked by ArOH to yield the final product.



Entry[a]	1	R	Relative rate (k/k_0)[b]	σ_{para}[c]
1	1b	H	1.00	0
2	1a	Me	2.1	-0.17
3	1e	OMe	2.42	-0.268
4	1f	F	1.32	0.06
5	1g	Cl	0.72	0.227
6	1h	Br	0.74	0.232
7	1j	CF_3	0.35	0.54

Scheme 8. (a)-(d) Mechanistic experiments; (e) Hammett plot experiment and the Hammet plot of log(k/k$_0$) against σ_P; (f) the proposed mechanism. [a] Reaction conditions: styrene (**1b**, 0.1 mmol); *para*-substituted styrene (**1**, 0.1 mmol), *O*-(2,4-dinitrophenyl) hydroxylamine (**2**, 0.15 mmol), Co-phen(2)@C-800 (10 mg), MeOH (1 mL), 0 °C-rt, 5 h. [b]Relative rate is calculated by the ratio of **3**/**3b** in ^{1}H NMR. [c] Hammett constant.

CONCLUSIONS

In summary, we have developed a heterogeneous non-noble metal-based Co@CoO core-shell catalyst that is capable of realizing olefin aziridination with hydroxylamine, which is a distinct approach compared with existing electro-/photo-chemical and homogeneous rhodium systems with unconventional nitrogen transfer reagent. This new protocol is easily-operated, highly efficient, oxidant-free and carried out at room temperature. A series of styrene derivatives and diene performed well to demonstrate the broad scope, and various natural product or drug-derived olefins underwent the late-stage aziridinations smoothly, which is hardly seen in aforementioned reports. Notably, various ring opening reactions of aziridine afforded the formal alkene oxyamination, carboamination, and aminochlorination products, and the alkene oxyamination was further exhibited chemo-selectively with nano-Co catalyst in a one-step fashion, which represented a rare example employing nano-catalyst to realize olefin difunctionalization. Based on XRD, XPS, TEM characterizations and mechanistic studies, the possible catalytic center and its involvement with substrates were illustrated in the proposed mechanism, more detailed mechanistic research are in progress and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

Additional experimental details, materials, methods, and ^{1}H, ^{13}C ,^{19}F NMR spectra for all compounds. The Supporting Information is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interests.

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