Letter

Sequential C#H and C#C Bond Cleavage: Divergent Constructions of Fused N-Heterocycles via Tunable Cascade

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Sequential C–H and C–C Bond Cleavage: Divergent Constructions of Fused *N*-Heterocycles via Tunable Cascade

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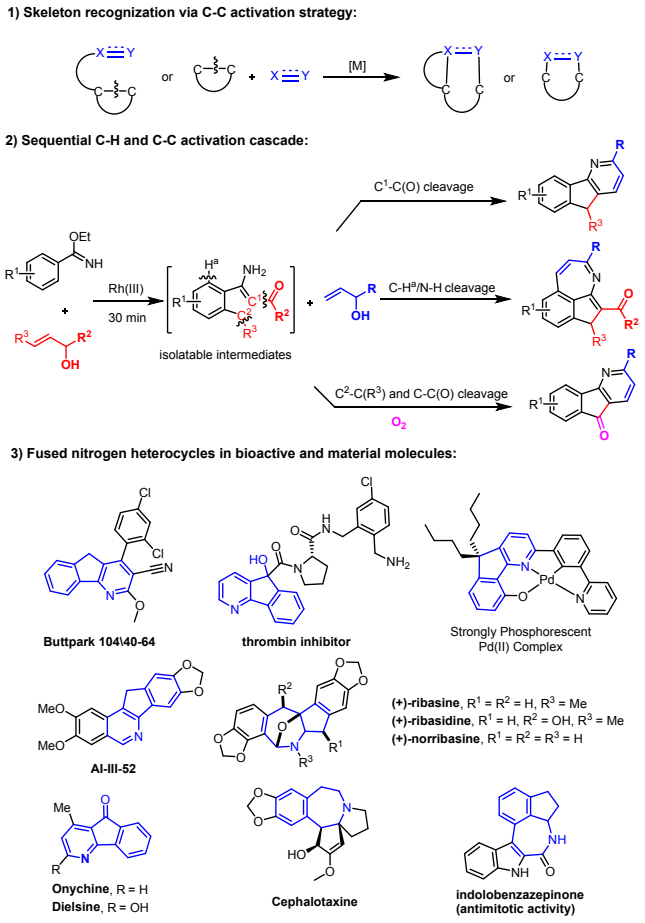
ABSTRACT: Streamlining generation of diverse highly functionalized molecules from abundant feedstocks, holds great synthetic promises and challenges in pharmaceutical and material discovery. Herein, we report a tunable selectivity in multiple cascade reactions for the divergent assembly of fused *N*-heterocycles, comprising sequential activation of C-H and C-C bonds. Isolatable indene type intermediates might be responsible for the generation of densely substituted fused pyridines, azepines and azafluorenones products. The tolerance of strongly coordinating *N*-heterocycles and readily applicable for the late-stage modifications of pharmaceuticals and material molecules precursors, further demonstrated the synthetic robustness of this transformation.

KEYWORDS: *multiple oxidative cascade • C-H and C-C cleavage • tunable selectivity • traceless directing group • fused N-heterocycles.*

In pursuing green processes for the rapid construction of target molecules via economically and environmentally benign routes, catalytic cascade reaction has emerged as a powerful strategy.[1] Fruitful results in the cascade transformations have been achieved, however, the exploration of C-H activation initiated multiple cascade,[2] especially for the precise control of the selectivity in cascade reactions that involved the cleavage and reconstruction of multiple chemical bonds, is still elusive. Moreover, sequential activation of inert C-H and C-C bonds triggered multiple cascade for the divergent constructions of complex molecules, remained underexplored.

Selective transformations of inert C-C bonds[3] have enriched the synthetic arsenal for the constructions of complex skeletons, while typical strategies relied on the use of strained structures or directing groups. In this context, the use of unstrained substrates and traceless directing moiety to facilitate C-C activation cascade, enabling the diversity-oriented synthesis (DOS)[4], would be extremely attractive. Herein, we reported a sequential C-H and C-C cleavage cascade with switchable selectivity, affording to divergent delivery of fused *N*-heterocycles (Scheme 1-2). Significantly, selective C-H and C-C bond activation of acyclic system in this transformation could be well tuned, by the choice of oxidant or solvent.

Fused *N*-heterocycles such as pyridines, azepines and azafluorenones,[5-6] serve as important structural motifs that occurred widely in natural products, pharmaceuticals and functional materials (Scheme 1-3).[7] Notable strategies toward their efficient assembly included condensation of carbonyls with amine precursors and cycloaddition of C-C unsaturated bonds with nitrogen functionalities. However, certain limitations such as multiple steps and troublesome selectivity, were often suffered. Thus, expedient methodologies to efficiently access to these valuable molecular architectures are highly desirable.

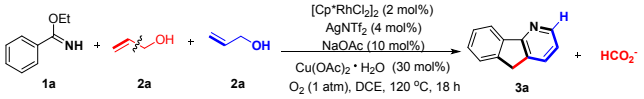


Scheme 1. Sequential activation of C-H and C-C bonds strategy for Fused *N*-heterocycles Synthesis.

We commenced our study by choosing imidate **1a** and allylic alcohols **2a** as the model substrates under metal catalysis (Table 1).[8,9] After extensive screen of catalytic

parameters, we found that with $[Cp^*RhCl_2]_2$[10] and $AgNTf_2$ as the catalyst, NaOAc as the additive, $Cu(OAc)_2•H_2O$ and molecular oxygen as the terminal oxidant, sequential C-H and C-C bond activation to afford fused pyridine **3a** in good yield.[11,12] No desired product **3a** was obtained in the absence of Rh(III) complex, while Pd(II) and Ir(III) complexes showed no catalytic efficiency, $[Ru(p\text{-cymene})Cl_2]_2$ showed relatively lower efficiency. $Cu(OAc)_2•H_2O$ played a critical role, since low conversion of substrate **1a** was observed with AgOAc instead. Moreover, DTBP oxidant totally shut down this reaction. Inferior results were obtained in the absence of either $Cu(OAc)_2•H_2O$ or NaOAc. Additional base or acid exhibited no significant effect to this oxidative cascade. The use of HFIP or *t*-Amyl-OH as the solvent led to moderated yields of the desired product **3a**.

Table 1. Variation of standard conditions.[a]

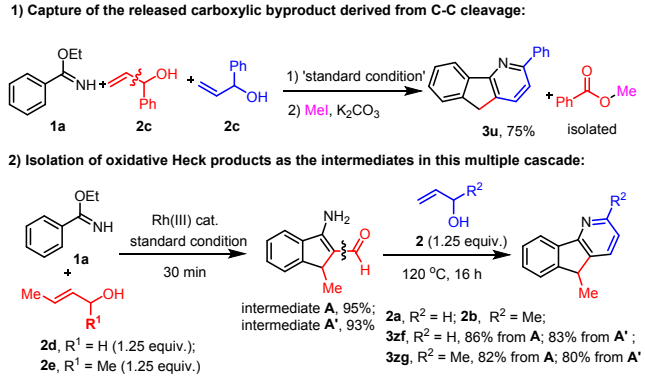


Entry	Variation of standard condition	Yield[b] (%)
1	None	90
2	$PdCl_2$ or $[IrCp^*Cl_2]_2$ instead of $[RhCp^*Cl_2]_2$	n.r.
3	$[Ru(p\text{-cymene})_2Cl_2]_2$ instead of $[RhCp^*Cl_2]_2$	72
4	AgOAc or ^{t}BuOO^{t}Bu instead of $Cu(OAc)_2·H_2O$	< 10 or n.r.
5	Without $Cu(OAc)_2·H_2O$	22
6	Without NaOAc	37
7	Addition of Cs_2CO_3 or PivOH (30 mol%)	88, 76
8	HFIP or ^{t}Amyl-OH as the solvent	81, 77

[a] Standard conditions: **1a** (0.20 mmol), **2a** (0.50 mmol), $[Cp^*RhCl_2]_2$ (2 mol%), $AgNTf_2$ (4 mol%), NaOAc (10 mol%), $Cu(OAc)_2·H_2O$ (30 mol%), DCE (1 mL) under air for 18 h. [b] Isolated yield.

In order to obtain insight into this multiple cascade, some control experiments were conducted (Scheme 2), and the results revealed that: 1) With addition of MeI to this reaction under standard condition, methyl benzoate product was obtained, which might derive from C-C bond cleavage of allylic alcohol moiety; 2) Oxidative Heck product **A** and **A'** were isolated within 30 minutes with **1a** and 1,2-disubstituted olefins **2d**, and further addition of **2a** into this catalytic system led to densely substituted fused pyridines in high yields in one-pot manner. This observation indicated that indene might serve as the key intermediate in this multiple cascade.

With the optimal condition, we next explored the synthetic generality of this C-H/C-C activation cascade, broad substrate scope with great functional group tolerance was observed (Scheme 3). (Pseudo)halides including F (**3b**), Cl (**3c**), Br (**3d**), I (**3e**), CF_3 (**3g**), OTs (**3i**) and OTf (**3k**) could be well tolerated, providing new opportunities for the further diversification. Readily transformable functionality including nitro (**3h**), benzylic chloride (**3l**), ester (**3m**), phenolic hydroxyl (**3j**), amine (**3n**) and ethers (**3o-3p**) were compatible. Methyl (**3q-3t**), ethyl (**3zc**), phenyl (**3u-3x**) and heterocycles including furan (**3zd**) and thiophene (**3ze**) derived allylic alcohols could also serve as suitable substrates in this cascade reaction. However, pyridine and thiozole-derived allyl alcohols delivered moderate yield of the corresponding fused pyridine products. The structure of the obtained fused pyridine was unambiguously confirmed by X-ray analysis (**3x**). Notably, regioselective C-H functionalization took place at steric hindered position (**3y-3z**), probably due to the directing effect of the fluoro and OMe groups.[13] Further investigation revealed that the use of *meta*-Cl benzimidate ester under standard Rh(III) catalysis led to 1:1 regioisomers of fused pyridines; while the reaction took place at less steric hindered C-H position with the use of *meta*-CF_3 benzimidate ester. This sequential C-H and C-C activation cascade could be applied to imidates with two different allylic alcohols (**3zf-3zo**), indene intermediates might be generated with the addition of 1,2-disubstituted allylic alcohols first, and subsequently added mono-substituted allylic alcohols to the reaction systems, various fused pyridines could be obtained.



Scheme 2. Preliminary mechanism studies.

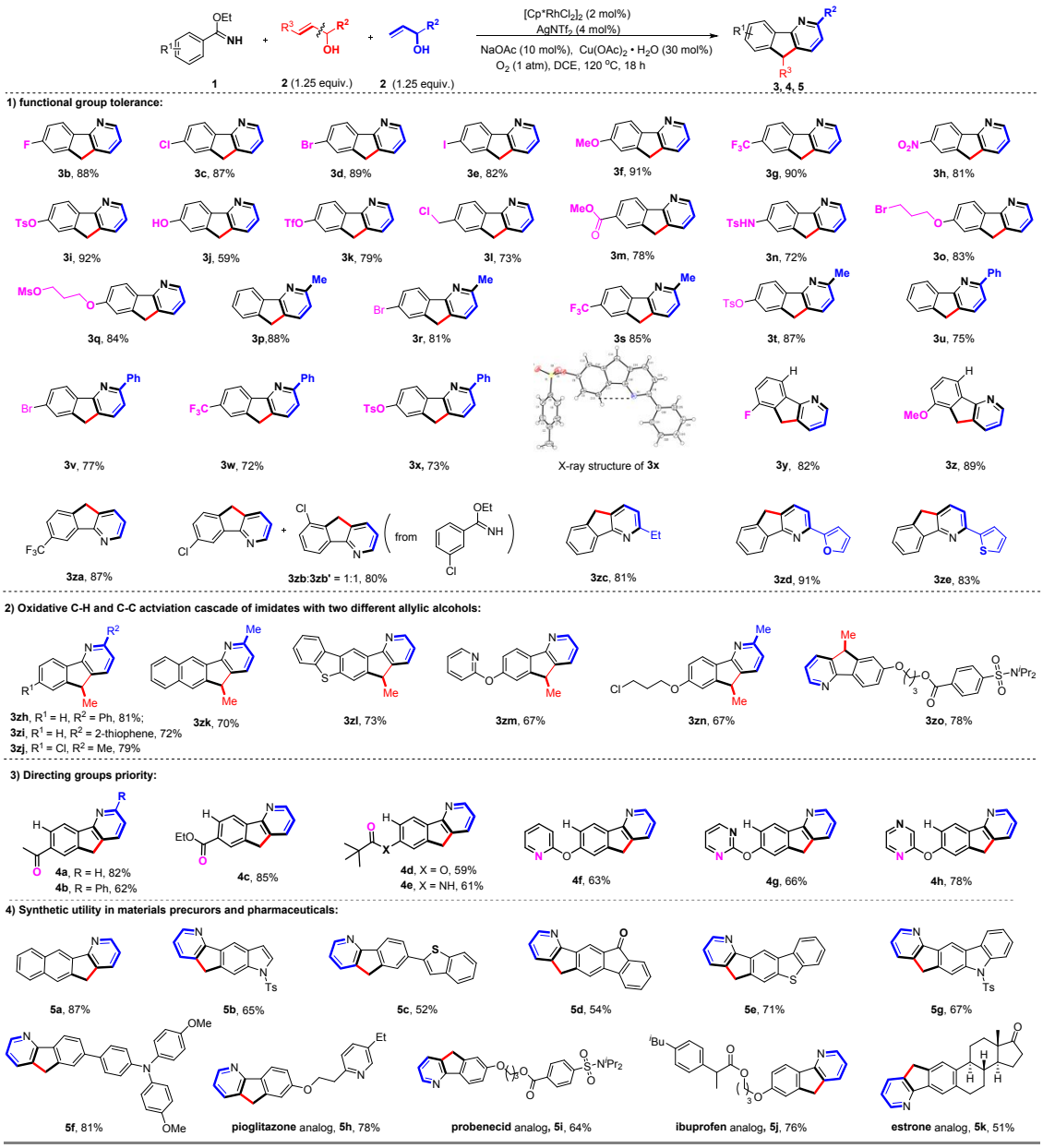
Regioselective C-H functionalization of multiple substituted arenes holds significant utility in the late-stage modification of bioactive molecules and materials. Nevertheless, the search for proper catalytic system for the effective discrimination of specific C-H bond in the complex molecules remained challenging. In this context, Yu, Dai, and Ackermann have developed efficient C-H transformations that could overcome the commonly encountered limitations of C-H activation with strongly coordinating *N*-heterocycles. [14]

We were also intrigued of the directing priority towards multiple functionalized arenes in this C-H functionalization initiated multiple cascade reaction. To our delight, imine functionality outcompete ketone (**4a**, **4b**), carboxlic acid ester (**4c**), phenol ester OPiv (**4d**) and NHPiv (**4e**), leading to the desired products in a selective manner. Significantly, heterocycles that are widely used in materials and pharmaceuticals included pyridine (**4f**), pyrimidine (**4g**) and pyrazine (**4h**), could also be compatible in this transformation.

To further exploration of the synthetic utility of this reaction, we selected fused heterocycles that were frequently used in materials for the diversification. Naphthalene (**5a**), indoles (**5b**), benzothiophene (**5c**), tertiary aromatic amine (**5d**), fluorenone (**5e**), dibenzo[b,d]thiophene (**5f**), carbazole (**5g**), thiophene (**3zi**) derived highly fused heterocycle could be readily accessed, which might provide inspiration into organic optoelectronic materials discovery.[15,16]

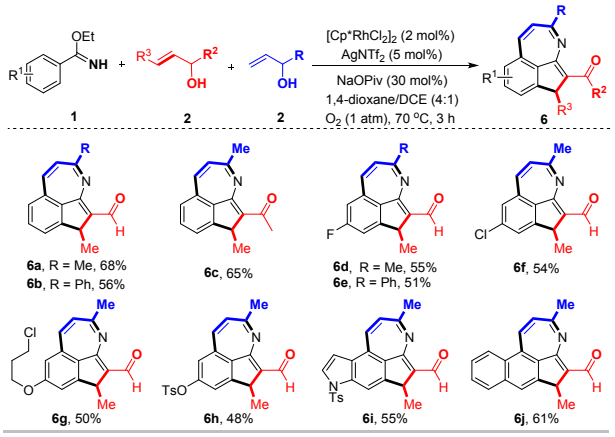
This transformation also enabled late-stage modification of bioactive molecules, including pioglitazone (**5h**), probenecid

(**5i**), ibuprofen (**5j**) and estrone (**5k**), demonstrating their synthetic potential in pharmaceutical discovery.



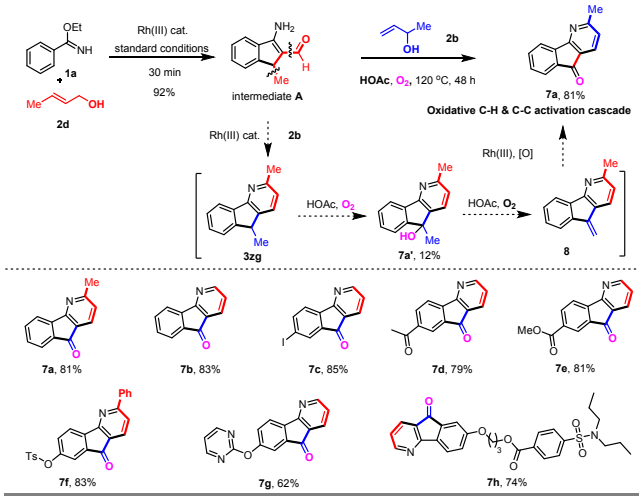
Scheme 3. Sequential C-H and C-C activation for assembly of fused pyridines: 1) functional group tolerance; 2) imidates with two different allylic alcohols; 3) directing groups priority; 4) synthetic utility in material and pharmaceuticals.

Intriguingly, oxidative double C-H Heck cascade reaction of arylimidates with allylic alcohols took place in the absence of Cu(II) salt under lower temperature. Further optimization revealed that with isolatable indenes, which were obtained from imidates with 1,2-disubstituted allylic alcohols under Rh(III) catalysis in 30 minutes; subsequent addition of another mono-substituted allylic alcohol, affording to the densely fused azepines under 70 °C within 3 hours (Scheme 4). Halogens such as F (**6d**), Cl (**6e**), OTs (**6h**) and alkyl chloride (**6g**) could be well compatible, leading to densely substituted azepines. Moreover, fused azepines **(6i, 6j)** were also readily accessible from indole and naphthalene substrates, providing a valuable platform for the rapid construction of molecular libraries of azepines. The moderated efficiency that observed might be contributed to the insufficient directing abilities for the oxidative Heck reaction and partial decomposition of the primary amine moieties.



Scheme 4. Fused azepines synthesis via multiple oxidative C-H Heck reaction using allyl alcohols.

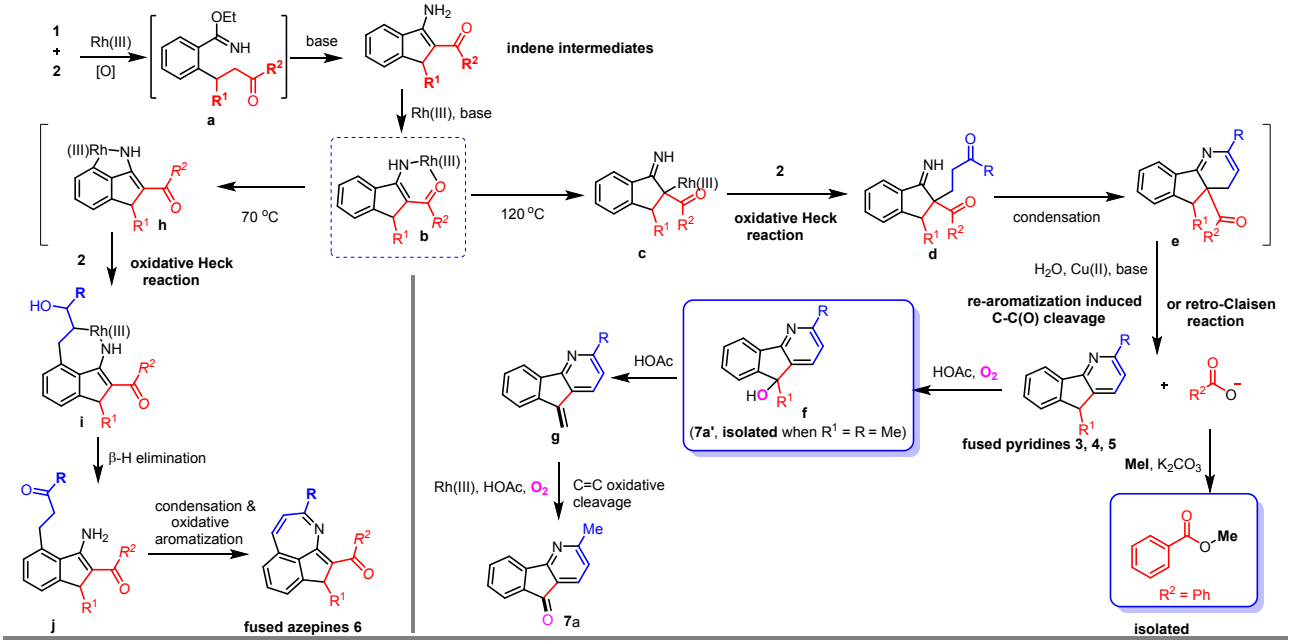
Notably, with isolatable intermediate **A** and further addition of **2b** in HOAc under Rh(III) catalysis, azafluorenone products were obtained (Scheme 5). Readily transformable functional groups including iodo (**7c**), ketone (**7d**), ester (**7e**), OTs (**7f**) and strong coordination nitrogen heterocycles (**7g**) could be compatible. Moreover, late-stage modification of pharmaceuticals such as Probenecid was also operational, demonstrating the synthetic potential of this transformation. Control experiments with fused pyridine **3zg** under standard conditions in HOAc solvent revealed that the azafluorenone product **7a** could be isolated, together with detectable amount of benzylic C-H oxygenated fused pyridine **7a'**. We speculated that a benzylic C-H oxidation followed by dehydration to give the olefin intermediate **8**, and subsequent oxidative cleavage of C-C double bonds might be involved.[17]



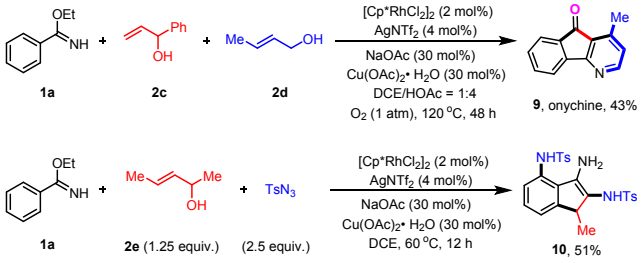
Scheme 5. Azafluorenones synthesis via multiple oxidative C-H/C-C activation cascade.

Considering fused *N*-heterocycles that are widely existed in natural products and pharmaceuticals, we further demonstrate the synthetic application of this transformation for the concise delivery of onychine using our methodology. As depicted in Scheme 6, by using benzimidate ester **1a** and terminal allylic alcohol **2c** under Rh(III) catalysis for 30 minutes, and subsequent addition of the second 1,2-disubstituted allylic alcohol **2d** in HOAc under molecular oxygen atmosphere for 48 hours, onychine could be obtained. The observed moderate efficiency of the overall transformation is probably due to the steric hinderance of the second added 1,2-disubstituted allylic alcohol.

Inspired by Chang's work on catalytic C-H amidation using azides as the amidation reagents,[18] we investigated the reactivity of TsN_3 in this multiple cascade reaction. Intriguingly, with indene intermediate that could be readily



accessed from imidate ester **1a** with allylic alcohol **2e** under Rh(III) catalysis, further addition of TsN_3 under standard condition revealed that a C-H and C-C bond action for the amidation reaction took place, and further efforts toward the optimization and synthetic application of this transformation is in progress.



Scheme 6. Synthetic applications: 1) concise synthesis of Onychine; 2) amidation reaction via C-H and C-C activation cascade.

Scheme 7. Possible mechanism for the sequential C-H and C-C bond activation cascade.

According to precedent literatures and the experimental observations, a tentative mechanism was proposed (Scheme 7): with the assistance of acetate ion, Rh(III) catalyzed C-H activation of imines **1** with alkenes **2** took place, which followed by β-H elimination[8,19] and condensation to give key indene intermediates (eg. al., **A** or **A'**). Subsequent coordination of Rh(III) or Cu(II) to indene intermediates led to two pathways, which might be controlled by the temperature, solvent and Cu(II) salt as a Lewis acid and oxidant[20] (See Supporting Information for details):

1) When the reaction was conducted at 120 °C in the presence of $Cu(OAc)_2 \cdot H_2O$, Rh(III) intermediate **b** might be generated, which followed by oxidative Heck reaction. Further condensation and C-C bond cleavage took place to afford the desired fused pyridines products, together with the release of carboxylic acid derivatives, which could be captured by the addition of MeI, to generate $PhCO_2Me$ (detected by GC-MS). We assumed that re-aromatization or retro-Claisen reaction,[21,22] which might serve as the driving force for the C-C bond cleavage in this process,[20,23] was assisted by water and Cu(II) salt.

2) When the reactions were conducted in the absence of Cu(II) salt under lower temperature, with the assistance of primary amines, regioselective aryl Csp^2-H oxidative Heck reaction took place, which followed by condensation and oxidative aromatization to give the desired fused azepines products **6**.[24]

On the other hand, while under acidic conditions, oxidative hydroxylation of benzylic C-H bond with molecular oxygen led to hydroxylated fused pyridine intermediate (which was isolated as **7a'** when R^1 = R = Me). Upon further dehydration, C-C double bonds were formed, which underwent oxidative cleavage under Rh(III)-catalyzed aerobic oxidation,[17] affording to azafluorenone products **7**.

In summary, we have successfully accomplished an attractive strategy for the modular delivery of densely functionalized fused *N*-heterocycles via sequential C-H and C-C bond cleavage. Significantly, tunable selectivity for the diverse products generation was obtained, which might be contributed to the retro-Claisen type reaction or re-aromatization as the driving force. This methodology features broad substrate scope and great functional group tolerance, and enabled divergent access of building blocks that might be used in organic optoelectronic materials and bioactive molecules. This strategy might provide new insight into C-C bond activation, showcasing the viability of late-stage modification of complex molecules toward a diversity-oriented synthesis.

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Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Experimental procedures and spectra data for all new compounds (PDF)

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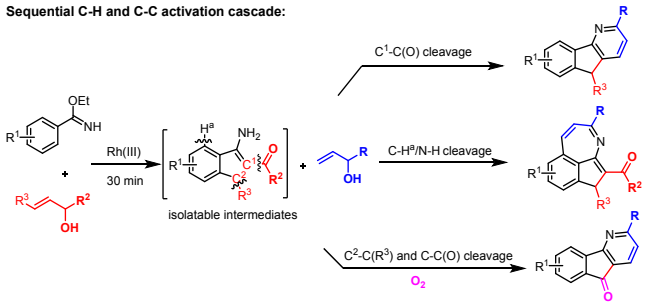
Sequential C-H and C-C activation cascade:
OEt
NH
Rh(III)
30 min
isolatable intermediates
C1-C(O) cleavage
C-Ha/N-H cleavage
C2-C(R3) and C-C(O) cleavage
O2