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Heteroannulation Enabled by a Bimetallic Rh(III)/Ag(I) Relay Catalysis: Application in Total Synthesis of Aristolactams BII

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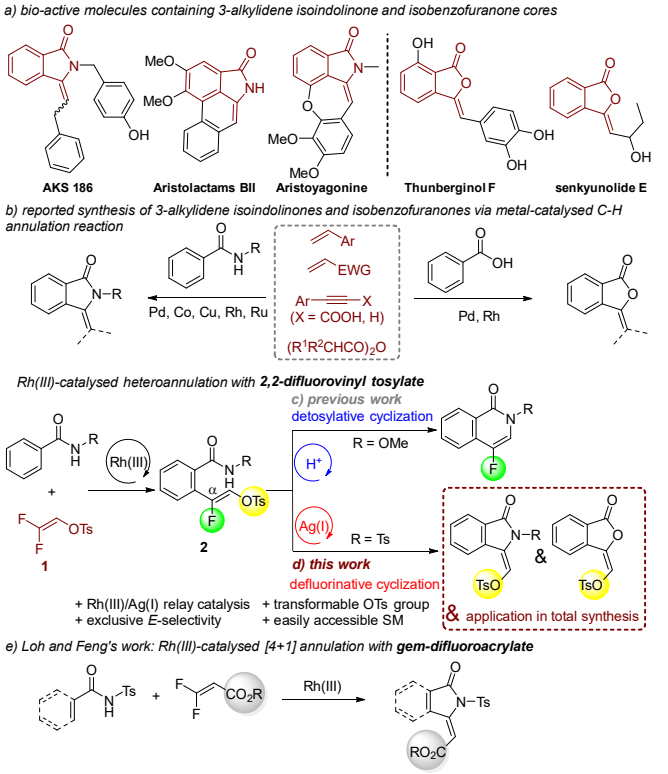
A redox-neutral bimetallic Rh(III)/Ag(I) relay catalysis allowed the efficient construction of 3-alkylidene isoindolinones and 3-alkylidene isobenzofuranones. The Rh(III) catalyst was responsible for the C-H monofluoroalkenylation reaction, whereas the Ag(I) salt was an activator for the follow-up cyclization. The methodology developed was applied as a key step to the rapid total synthesis of natural product aristolactam BII.

Isoindolinones and isobenzofuranones are important heterocyclic compounds possessing diverse biological properties.[1] Among them, the 3-alkylidene isoindolinones and 3-alkylidene isobenzofuranones bearing an exocyclic double bond are of particular interest and have received considerable attention (Scheme 1a).[2] Traditionally, the synthesis of these two heterocyclic scaffolds relied on reactions of heavily pre-functionalized substrates.[3] Recently, with the development of organometallic chemistry, the transition-metal-catalysed C-H annulation reaction provided a simple while flexible strategy for their synthesis from easily accessible starting materials.[4] For examples, with benzamides or benzoic acids as substrates, the oxidative annulation reactions with activated alkenes,[5] terminal alkynes[6a,6c-e] or arylpropiolic acids[6b,6f] were known to be effective for their construction (Scheme 1b). The use of carboxylic anhydrides as coupling partner further broadened the scope to the corresponding alkyl-substituted heterocycles (Scheme 1 b).[7] Although elegant and useful, limitations such as dependence on high reaction temperatures,[5c,6a-d,7] employment of stoichiometric amount of oxidants[5a,6a,6c,6e,6f] and/or unsatisfactory stereospecificities[7a] still remain. Of note, the synthesis of heteroatom-substituted 3-alkylidene isoindolinones or 3-alkylidene isobenzofuranones via C-H activation strategy remains under-explored,[6a] although the heteroatom substituent is expected to offer ample opportunities for further decoration of the products.



Scheme 1. Representative bio-active 3-alkylidene isoindolinones and 3-alkylidene isobenzofuranones and their synthesis.

Recently, our group reported the use of 2,2-difluorovinyl tosylate **1** in Rh(III)-catalysed C-H activation reactions for the diverse synthesis of several types of fluorinated heterocycles.[8] With *N*-OMe benzamide as substrate, the coupling reaction generated a monofluoroalkene intermediate **2** with the retention of the OTs functionality. By acidic hydrolysis of OTs, we were able to realize the intramolecular cyclization to furnish a six-membered fluorinated isoquinolin-1(2*H*)-one product (Scheme 1c). We envisioned there might be an opportunity for 5-exo cyclization by taking advantage of the reactivity of monofluoroalkene.[9] Specifically, the inductive

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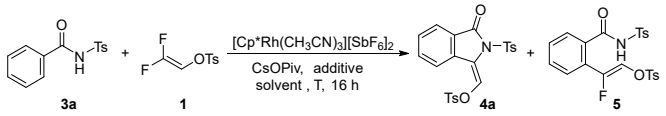
effect of fluorine atom and its mesomeric p-π-interaction with alkene in **2** would render the α position susceptible to nucleophilic attack.[10] In light of our continuing interest in combining C-H activation with catalyst relay for one-pot multi-bonds forming reactions,[11] we report herein our realization of a bimetallic Rh(III)/Ag(I) based relay catalysis for the redox-neutral heteroannulation of benzamides or benzoic acids with 2,2- difluorovinyl tosylate **1** for the synthesis of OTs-substituted 3-alkylidene isoindolinones and 3-alkylidene isobenzofuranones, respectively (Scheme 1d). The Rh(III) catalyst was responsible for the C-H monofluoroalkenylation reaction, whereas the Ag(I) salt was an activator for the follow-up cyclization. The manipulations of the OTs group allowed the diverse synthesis of several isoindolinone derivatives. In addition, the protocol developed was applied as a key step to the synthesis of natural product aristolactams BII. During the investigation of this project, Loh and Feng reported a Rh(III)-catalysed [4+1] cyclization by using *gem*-difluoroacrylate as coupling partner.[12a] With two-fold C-F bonds cleavage, the reaction allowed a redox-neutral construction of ester substituted 5-methylene-1H-pyrrol-2(5*H*)-ones and isoindolin-1-ones (Scheme 1e).

Table 1. Reaction optimization.[a]

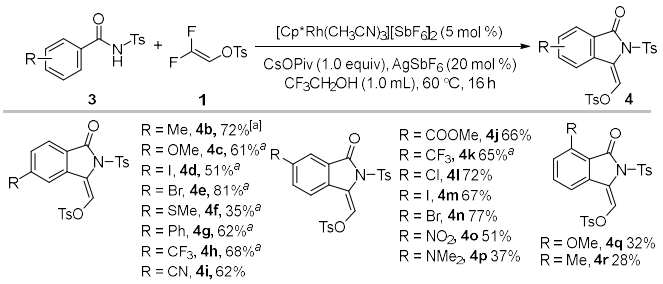


entry	additive (x mol %)	T (°C)	yield of **4a**	yield of **5**
1	-	45	n.d	86%
2	AgOAc (50)	45	70%	n.d
3	$Cu(OTf)_2$ (50)	45	n.d.	34%
4	$AuCl(PPh_3)$ (50)	45	n.d.	n.d.
5	$AgSbF_6$ (50)	45	75%	n.d.
6	AgOTf (50)	45	78%	n.d.
7	$AgSbF_6$ (50)	60	90%	n.d.
8	**$AgSbF_6$ (20)**	**60**	**83%**	**n.d.**
9	AgOTf (20)	60	77%	n.d.

[a]**3a** (0.2 mmol), **1** (1.5 equiv), $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ (5 mol %), CsOPiv (1.0 equiv), additive (x mol %), CF_3CH_2OH (1.0 mL), T, 16 h, isolated yield.

We initiated our study by reacting *N*-tosylbenzamide **3a** with **1** under the catalysis of $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ (5 mol %). With CsOPiv as base in CF_3CH_2OH at 45 °C, the reaction provided an open-chain monofluoroalkenylated product **5** in 86% yield, with no cyclization product found (Table 1, entry 1). We envisioned the addition of π-acid to activate the fluoroalkene might induce a one-pot cyclization. Indeed, the use of AgOAc (50 mol %) as additive promoted the expected defluorinative cyclization to give OTs-substituted 3-alkylidene isoindolinones **4a** in 70% yield (entry 2). $Cu(OTf)_2$ and $AuCl(PPh_3)$ were proven to be ineffective for the reaction (entries 3 and 4). Further screening demonstrated that $AgSbF_6$ and AgOTf showed superior reactivity (entries 5 and 6). An excellent yield of 90% was obtained when the reaction temperature was increased to 60 °C (entry 7). Gratifyingly, the loading of Ag(I) could be lowered to 20 mol %, with a good isolated yield of 83% being assured (entry 8). It should be noted only one stereoisomer was formed and the geometry of the double bond was determined to be *E* based on X-ray crystallography analysis.[13]

Table 2. Synthesis of 3-alkylidene isoindolinones.

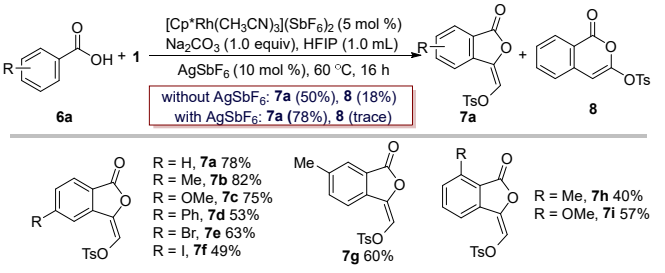


[a]AgOTf (20 mol %) was used instead of $AgSbF_6$.

The generality and limitation of the reaction were then investigated. As shown in Table 2, a variety of differently substituted *N*-tosylbenzamides were subjected. It was found that the commonly encountered functional groups, regardless of their electronic properities, including methyl (**4b**), methoxy (**4c**), chloro (**4l**), bromide (**4e**, **4n**), iodine (**4d**, **4m**), phenyl (**4g**), trifluoromethyl (**4h**, **4k**), ester (**4j**), cyanide (**4i**) and nitro (**4o**) were well tolerated. Methylthiol (**4f**) and dimethylamino (**4p**) groups, which would potentially poison both of the catalysts also survived, although lower yields were obtained. The *meta*-subsituted substrates delivered only one regioisomer, with the reaction occurring at the less sterically hindered positions (**4j-4p**). Unfortunately, the *ortho*-substitutent (**4q**, **4r**) residing in close proximity to the directing group retarded the reaction.

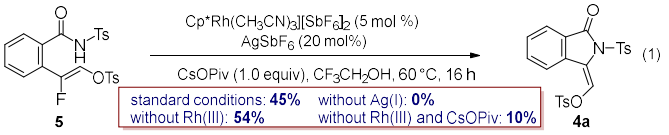
With the stereoselective synthesis of OTs-substituted 3-alkylidene isoindolinones established, we set to explore the analogous reaction by using benzoic acids as substrates. In this case, the reaction of benzoic acid **6a** with **1** under the catalysis of $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ directly provided the cyclization product **7a** in 50% yield,[13] together with 18% of six-membered heterocycle isochromen-1-one **8** (Table 3). With the addition of $AgSbF_6$ (10 mol %), the formation of **8** was suppressed and an improved yield of **7a** (78%) was obtained. The scope of this reaction was also quite decent. *Para*- and *meta*-substituted benzoic acids underwent smooth cyclization to give the corresponding 3-alkylidene isobenzofuranones **7** in moderate to good yields. The survival of halide functional group (Br and I)

Table 3. Synthesis of 3-alkylidene isobenzofuranones.

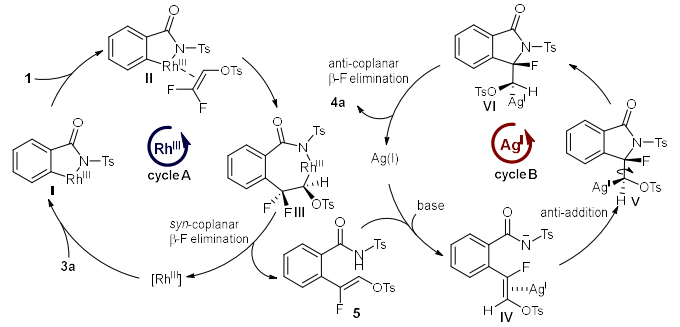


provides additional handles for further decoration of the products. Of note, *ortho*-substitutents (**7h**, **7i**) were also tolerated to give acceptable yields.

To gain mechanistic insight into the relay catalysis, control experiments were conducted. Staring from monofluoroalkene **5**, the reaction under the standard reaction conditions provided the cyclization product **4a** in 45% yield, confirming that **5** was an intermediate for the relay catalysis (eq 1). While the absence of Rh(III) catalyst provided a higher yield of 54%, the omission of $AgSbF_6$ gave no **4a** at all, indicating Ag(I) was the catalyst for the cyclization. In addition, the yield dropped dramatically when CsOPiv was removed. Taking together, these results concluded that both Ag(I) and base play crucial role in the cyclization reaction.

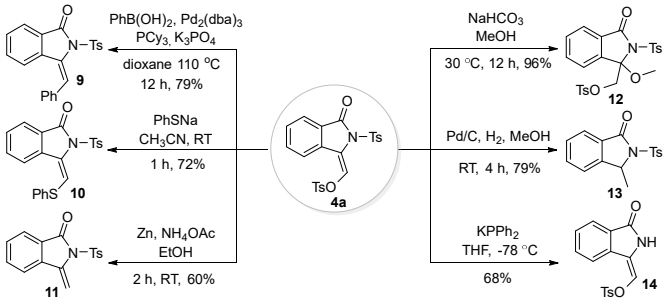


A reaction mechanism was proposed to account for the reaction outcome. Initially, Rh(III)-catalysed C-H activation under the assistance of *N*-Ts group generates intermediate **I** (Scheme 2). The coordination of **1** is followed by a regioselective olefin insertion to give **III**. A syn-coplanar β-F elimination provides the *Z* type monofluoroalkenylation product **5** with good stereoselectivity.[8] We reasoned Ag(I) may act as a π acid to activate the olefin, thereby facilitating the intramolecular cyclization reaction. Thus, the anti-addition to the double bond resulted in a 5-exo cyclization to give **V**. The selective attack at the α position of the F atom could be explained by the low-lying LUMO with large coefficient at this position.[10] Thereafter, an anti-coplanar β-F elimination led to the stereospecific formation of *Z* type 3-alkylidene isoindolidone product **4a**.



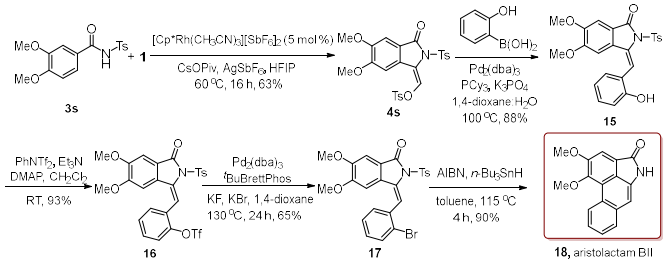
Scheme 2. Mechanistic proposal.

The synthetic utilities of the formed 3-alkylidene isoindolidones were evidenced by the facile transformation of **4a** into a diverse array of isoindolidone derivatives (Scheme 3). For examples, the Suzuki-Miyaura coupling of the C-OTs bond with phenylboronic acid[14] allowed the efficient synthesis of *E*-type phenylmethylene isoindolidone **9**. The substitution of OTs group with benzenethiolate was accomplished by reacting **4a** with sodium benzenethiolate in CH_3CN. Moreover, the OTs group could be reduced with zinc in EtOH. Interestingly, a hemiaminal ether **12** was formed via the hydromethoxylation of the exocyclic double bond while stirring the methanol solution of **4a** in the presence of $NaHCO_3$. Full reduction of the double bond and the OTs group was fulfilled by catalytic hydrogenation with Pd/C. Finally, the *N*-tosyl group could be selectively removed upon the treatment with $KPPh_2$.[15]



Scheme 3. Derivatization of **4a**.

Aristolactams belong to a large family of natural products which have been used as folk medicines in Eastern Asian.[16] Among them, aristolactam BII was found to be able to inhibit T and B lymphocyte proliferation and exhibit cytotoxic activity.[17] The total synthesis of aristolactam BII has been described by several research groups.[18] By using our methodology as key reaction, this natural product was rapidly constructed (Scheme 4). Thus, starting from benzamide **3s**, the Rh(III)/Ag(I)-based relay catalysis in HFIP produced **4s** in 63% yield with excellent regio- and stereo-selectivity. The Suzuki-Miyaura coupling with (2-hydroxyphenyl)boronic acid led to the successful introduction of 2-hydroxylphenyl group to the scaffolds. After protected with trifluoromethylsulfonyl, compound **15** was converted to bromide **17** via OTf-bromo exchange under the catalysis of palladium.[19] The treatment of **17** with AIBN and *n*-Bu_3SnH, led to the debromocyclization and deprotection of the tosyl group,[18c] providing the target molecule aristolactam BII in 90% yield. It is worthy mention our synthetic route represents the shortest one so far for the synthesis of aristolactam BII.[20]



Scheme 4. Total synthesis of natural product aristolactam BII.

In conclusion, by taking advantage of the intriguing reactivity of difluorovinyl tosylate, we have realized the efficient synthesis of 3-alkylidene isoindolinones and 3-alkylidene isobenzofuranones via a Rh(III)/Ag(I) relay catalysis. The methodology developed was applied to the rapid total synthesis of aristolactam BII. Further explorations of *gem*-difluoroalkene in relay catalysis are ongoing in our laboratory.

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