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Cobalt-Catalyzed Aryl C–H Activation and Highly Regioselective Intermolecular Annulation of Sulfonamides with Allenes

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ABSTRACT: Herein we describe a cobalt-catalyzed C–H activation of aryl and heteroaryl sulfonamides and their intermolecular heteroannulation reaction with allenes, providing a convergent strategy for the synthesis of biologically interesting heterocyclic scaffolds. Carbometallation of allenes proceeds selectively through a Co-alkenyl pathway for a wide range of electron-poor and electron-rich allenes.

Sulfonamides and their cyclic analogues, sultams, are very important structural motifs for drug discovery because of their extensive chemical and biological activities.[1] In particular, benzofused sultams are present in many drugs and pharmaceuticals with a wide range of medicinal properties as exemplified by the activities displayed by Ampiroxicam, Brinzolamide and Calpain **I** inhibitor (Fig 1).[2] Transition-metal catalyzed C–H activation reactions gained considerable attention in the last few decades for promoting a diverse range of annulation reactions for synthesizing a variety of heterocyclic scaffolds.[3,4] Although excellent progress was made in metal-catalyzed directed C-H activation to facilitate a wide range of directing groups, only a few studies have been reported wherein easily available and medicinally important sulfonamide derivatives were used as *ortho* directing groups for sp^2 C–H activation.[5] Cramer in 2012 disclosed an efficient Rh(III)-catalyzed strategy for the synthesis of benzosultams by the *ortho* C–H activation of *N*-acetylated sulfonamides.[6] Among other interesting C–H functionalization methods for the synthesis of benzosultams include the Ni(0)-catalyzed denitrogenative annulation reaction of allenes with 1,2,3,4-benzothiatriazine-1,1(*2H*)-dioxides developed by Murakami.[7]

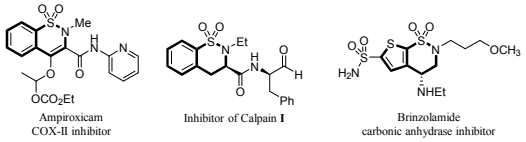

Fig. 1: Biologically active sultams

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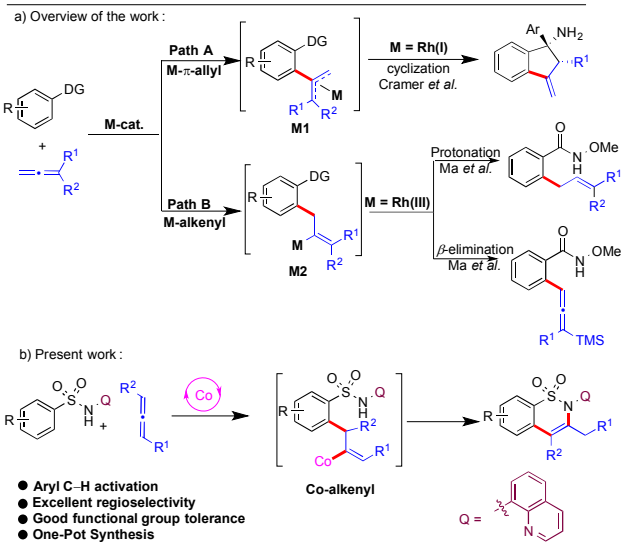
Electronic Supplementary Information (ESI) available: Experimental procedures, characterization of products, ^{1}H and ^{13}C NMR spectra for products, and X-ray crystallographic analysis (CIF file for compound **3a**, **3i**, **3x**) CCDC 1504459 (**3a**), 1504464 (**3i**), 1504460 (**3x**). See DOI: 10.1039/x0xx00000x

Although allenes have been widely employed in metal-catalyzed addition reactions,[8] insertion reactions with allenes via C-H bond functionalization were relatively rare.[9] Insertion of the organometallic intermediate at C2 or C1 of the allene leads to either M-π-allyl **M1** or M-alkenyl intermediate **M2** respectively (Scheme 1a).[10] The resulting organometallic intermediate can undergo different types of reactions such as protonation, cyclization or *β*-elimination. Rh(I)-catalyzed C-H functionalization of ketemines with terminal olefins was illustrated by Cramer and co-workers proceeding through M-π-allyl intermediate **M1** (Scheme 1a, path A).[11] Ma and co-workers demonstrated Rh(III)-catalyzed protonation and *β*-elimination reactions of M-alkenyl species **M2** leading to allylation and allenylation of benzamides (Scheme 1a, path B).[12] Similarly, Krische and co-workers reported cationic Ir-catalyzed prenylation reactions.[13a] However, a cyclization pathway leading to biologically interesting moieties remained unexplored for the M-alkenyl intermediates **M2**.



Scheme 1: Overview of the work

The use of earth-abundant, first-row transition metals for catalyzing various C–H functionalization reactions has emerged as a promising alternative to noble metals.[14] In particular, cobalt-salts

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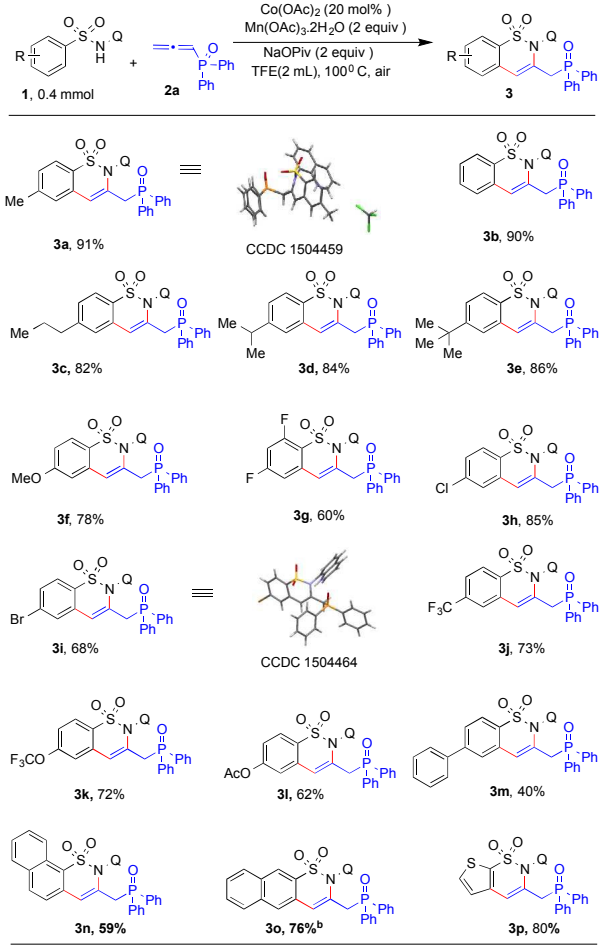
have proven to be exceptionally versatile for promoting these transformations because of their unique reactivity.[15] In a pioneering study, Daugulis and co-workers developed an efficient cobalt(II)-catalyzed bidentate chelation strategy for the C–H activation of benzamides and phosphinic amides.[16]

We have recently reported a cobalt-catalyzed heteroannulation reaction of arylamides and alkenylamides with allenes under mild conditions to access various isoquinolinone and pyridone derivatives.[17] In view of the great potential of aryl fused sultam scaffolds for biological and pharmaceutical studies, we envisaged developing a direct and straight forward method for synthesizing these derivatives, and herein, we report our studies on the regioselective Co-catalyzed intermolecular annulation of arylsulfonamides and allenes (Scheme 1b). Based on the prior success of allene interaction with organometallic intermediates, arylsulfonamide **1** was employed as the substrate. We expected that the bidentate chelator, 8-aminoquinoline pioneered by Daugulis would have the prerequisites for stabilizing the metallacycle intermediate for successful allene insertion.

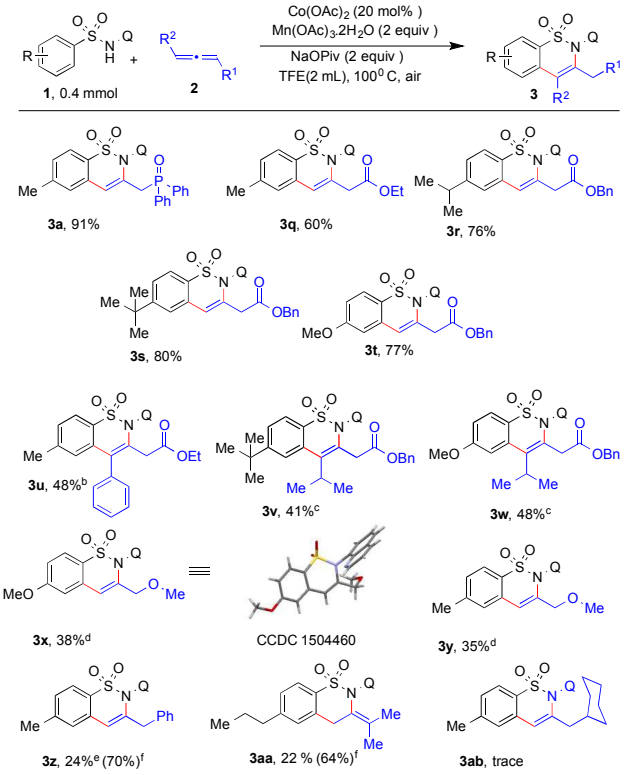
Table 1: Scope of sulfonamides with allenylphosphonate[a]



[a]Reaction conditions: **1** (0.4 mmol), allene **2a** (0.48 mmol), $Co(OAc)_2.4H_2O$ (20 mol %), $Mn(OAc)_3.2H_2O$ (0.8 mmol), $NaOPiv.H_2O$ (0.8 mmol), TFE (4 mL), 36-48 h, 100 ^{0}C, yield of the isolated product, [b]5:1 regioisomers

For the initial investigation, we chose tosylsulfonamide **1a** and allenylphosphonate **2a** as the coupling partners, and the reaction was tested under the conditions which we developed previously for the benzamide C–H activation (20 mol % $Co(acac)_2$, 1.0 equiv. $Mn(OAc)_3.2H_2O$, 2.0 equiv. NaOPiv in TFE at rt). Only traces of the product were formed under these conditions. However, increasing the temperature to 100 ^{o}C from rt led to the selective formation of benzosultam **3a** in 32% yield indicating that the reductive elimination from a seven membered cobaltacycle was faster than the protonation or β-elimination. We are also pleased to observe that the reaction displayed a high regioselectivity for the annulation proceeding through the Co-alkenyl intermediate. This is in line with our previous observation that the carbometallation of electron-poor allenes takes places through a M-alkenyl pathway.[13a] Encouraged by these initial results, we screened different cobalt salts to improve the yield. Indeed, the desired reactivity was achieved when 20 mol % $Co(OAc)_2$ was used along with 2.0 equiv. of $Mn(OAc)_3.2H_2O$ and 2.0 equiv. NaOPiv in TFE at 100 ^{0}C and **3a** was isolated in 91% yield (see Supporting Information for more details). The regioselectivity of **3a** was further confirmed by X-ray crystallography. When 10 mol % of $Co(OAc)_2$ was used instead of 20 mol %, the reaction took longer for completion and the yield decreased to 45%. Omission of either cobalt salt or oxidant completely shuts down the reactivity, illustrating the importance of the combination.

Table 2: Synthesis of benzosultams from different allenes[a]



[a]Reaction conditions: **1** (0.4 mmol), allene **2** (0.8 mmol), $Co(OAc)_2.4H_2O$ (20 mol %), $Mn(OAc)_3.2H_2O$ (0.8 mmol), $NaOPiv.H_2O$ (0.8 mmol), TFE (4 mL), 36-48 h, 100 ^{0}C, isolated yield, [b]2:1 regioisomers, [c]4:1 regioisomers, [d]5:1 regioisomers, [e]10:1 regioisomers, [f]brsm yield.

With these optimized conditions in hand, we probed the substrate scope of the arylsulfonamides **1** with allenylphosphonate **2a**. As shown in Table 1, different functional groups on the arylsulfonamide were tolerated under the standard conditions.

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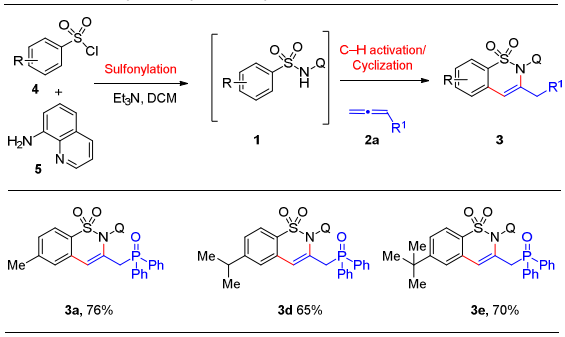
Several valuable functional groups such as methoxy (**3f**), fluoro (**3g**), chloro (**3h**), bromo (**3i**), trifluoro (**3j**), trifluoromethoxy (**3k**), and acetyl (**3l**) are compatible at different position of **1**. In addition, this strategy was further extended to 4-biphenyl and 1-naphthyl sulfonamides to obtain the corresponding products **3m** and **3n** in good yields (40-59%). When 2-naphthylsulfonamide was used, a mixture of 5:1 regioisomers was isolated in 76% yield. In addition, heterocyclic derivatives such as thiophenesulfonamide (**3p**) was also found to be compatible. Unfortunately, 1,1-disubstituted allenylphosphonates (see Supporting Information) failed to undergo the reaction probably because of the increased steric hindrance.

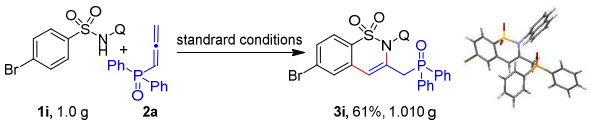
We further tested the scope of different allenes for the cobalt-catalyzed heteroannulation of arylsulfonamides (Table 2). Under the optimized conditions, ethyl and benzyl 2,3-butadienoates served to provide the expected arylsultams (**3q-3t**) in good to excellent yields as a single regioisomeric product. The reaction occurs exclusively at the less substituted double bond of the allene. To our delight, 1,3-disubstituted allenoate provided the corresponding products **3u-3w** in 41-48% (mixture of regioisomers arising from 1,3-hydrogen shift, *vide infra* Scheme 4). Intriguingly, changing the allene partner from electron poor to electron rich allene such as methoxyallene also led to the selective formation of benzosultams **3x** and **3y** in 38% and 35% respectively. The structure and regioselectivity of the **3x** was confirmed by X-ray crystallography. Reaction of sulfonamide **1a** with phenylallene afforded **3z** with the same regioselectivity in 24% yield. Pleasingly, 1,1-dimethylallene under the same reaction conditions furnished the heteroannulated sultam **3aa** without 1,3-hydrogen shift in 22% yield. Surprisingly, no cyclic π-allyl product was observed in these cases.

Table 3: One-pot sequential protocol[a]



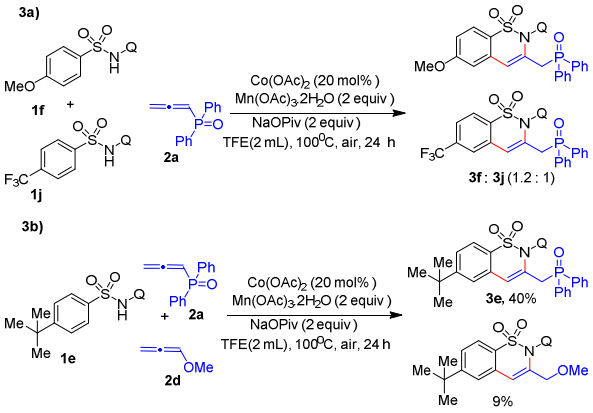
[a]Yield of the isolated product after column chromatography.

To highlight the synthetic applicability of this method further, we set out to develop a one-pot protocol for the sequential amidation of arylsulfonyl chlorides followed by cobalt-catalyzed C–H activation and heteroannulation with allenes. Thus, arylsulfonyl chlorides **4** were treated with 8-aminoquinoline **5** utilizing Et_3N in CH_2Cl_2 and upon completion of the reaction, the mixture was concentrated to dryness. Subjection of the crude sulfonamide **1** to optimized conditions furnished the corresponding sultams **3** in comparable yields (Table 3).



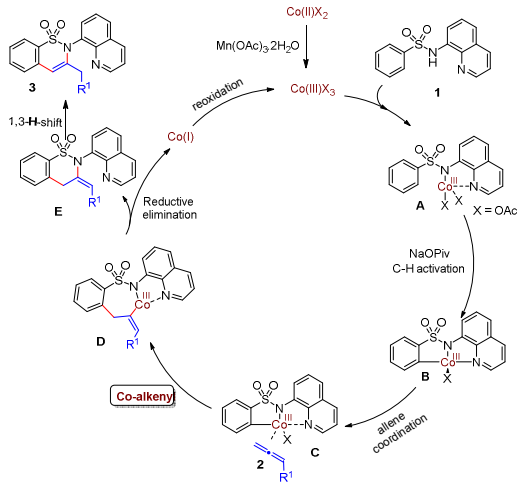
Scheme 2: Gram scale synthesis of sultam

The efficiency of this protocol was further tested by performing a gram-scale reaction to obtain **3i** in 61% yield (Scheme 2). The structure and the regioselectivity of bromoaryl sultam **3i** were confirmed unambiguously by the X-ray crystallography.



Scheme 3: Intermolecular competitive experiments

The mechanism of the reaction was studied utilizing intermolecular competition experiments. When a mixture of 1:1 4-methoxy and 4-trifluoromethyl benzene sulfonamides **1f** and **1j** was treated with allenylphosphonate **2a** under the standard conditions, a 1.2:1 ratio of the products was obtained suggesting that electrophilic cobaltation is unlikely (Scheme 3a). To acquire further understanding, another intermolecular competitive experiment was carried out using a 1:1 mixture of allenylphosphonate **2a** and methoxyallene under standard conditions with *p-tert*-butylbenzenesulfonamide derivative **1e**. A ratio of 4.4:1 was observed, indicating that the migratory insertion of the arylcobalt species proceeds faster with electron-poor allenes (Scheme 3b).



Scheme 4: Proposed reaction mechanism

Based on the above experiments and previous reports on Co-catalyzed C–H bond activation, a plausible mechanism was proposed (Scheme 4). The catalytic cycle begins with the *in situ* generation of Co(III)-species by the oxidation of Co(II) precatalyst. Coordination of 8-aminoquinoline derived sulfonamide **1** to Co(III) forms the intermediate **A**,[13a] which upon base assisted C–H activation leads to the key metallacycle Co(III) intermediate **B**. The formation of the intermediate **B** can be proposed based on ESI-MS (See Supporting Information). The key Co(III)-metalacycle

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intermediate was observed by treating stoichiometric amounts of $Co(OAc)_2$ with arylsulfonamide **1e.** Coordinative insertion of C-Co bond of intermediate **C** with the less-substituted double bond of allene affords seven membered cobaltacycle intermediate **D**. Reductive elimination from **D** gives the cyclic product **E** and regenerates the Co(III) species after oxidation of Co(I) with oxidant. Intermediate **E** undergoes 1,3-hydrogen shift to provide the corresponding final product **3**.

In summary, we developed a novel cobalt(II)-catalyzed chelation assisted *ortho* C–H activation of sulfonamides to furnish the biologically relevant aryl and heteroaryl fused sultams in a highly regioselective manner. The reaction proceeds in air under operationally simple conditions with inexpensive cobalt-salts. Notable features of this transformation include high regioselectivity for the intermolecular annulation proceeding through Co-alkenyl pathway and excellent functional group compatibility. The reaction conditions are amenable to scale up and further development of a one-pot three-component protocol illustrates the practicality of the method.

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