Organic LETTERS

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Cobalt Catalyzed C−H and N−H Bond Annulation of Sulfonamide with Terminal and Internal Alkynes

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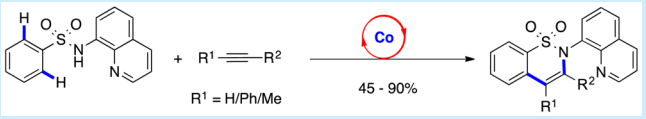
Supporting Information

ABSTRACT: Chelate assisted cobalt catalyzed C−H and N−H annulation of aryl sulfonamide with terminal and internal alkynes is reported. Very high regioselectivity and excellent functional group tolerance were achieved using oxygen as a co-oxidant. The reaction is scalable under mild conditions.



Functional groups such as sulfonamide, sulfonylurea, and naturally unavailable cyclic sultam are common motifs in many drugs and medicinal compounds and play a significant role in their bioactivity.[1] Common drugs such as glibenclamide, sultiame, and COX-II inhibitors Piroxicam, Ampiroxiam, and Celecoxib possess a sulfonyl moiety, which displays potential activity across a variety of biological targets (Figure 1).[2]

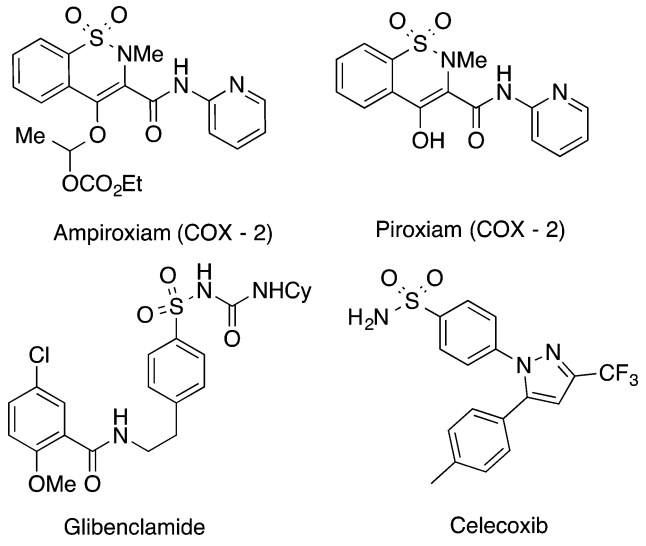


Figure 1. Drugs featuring biologically active benzosultam and sulfonamide motif.

Straightforward synthesis of these structural motifs in particular for annulated benzosultam are relatively rare. Very few examples have been reported of C−H bond functionalization[3] using sulfonamide as a directing group,[4] unlike in traditional methods which require multistep synthesis or the prefunctionalization of arene.[5] Recently, noble metals such as Pd^{II}, Rh^{III}, and Ru^{II} have been utilized for the preparation of sultam derivatives using sulfonamide as a directing group.[4] To the best of our knowledge, utilization of a cheap, abundant base metal as a catalyst for the functionalization of sulfonamide has not been reported in the literature. Furthermore, the reported catalytic systems based on noble metal catalysts are efficient with internal alkynes, but lack in reactivity with terminal alkynes.[4d] The concept of utilizing a bidentate directing group for chelate assisted C−H bond functionalization was first introduced by Daugulis[6] and later explored by Chatani[7] and others[8] for various C−C and C−X bond formations with various transition metals.[9] Very recently, Daugulis showed an elegant method for the annulation of benzamide[10a] using a simple, commercially available cobalt(II) precursor along with a carboxylate base and Mn(III) as a cocatalyst under mild conditions.[10] In continuation of our constant effort on the utilization of first row, late transition metals as a catalyst[11,12] for C−H bond functionalization,[13] we herein report the first cobalt catalyzed C−H bond annulation of sulfonamide via C−H and N−H activation with terminal and internal alkynes.

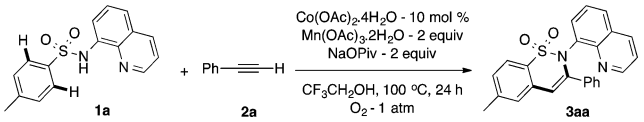
We began our investigation by screening various cobalt precursors; among them, cobalt(II) acetate gave a good yield with sulfonamide **1a** and phenyl acetylene **2a** using trifluoroethanol as a solvent under 1 atm of oxygen at 100 °C for 24 h (Table 1, entries 1−4). Changing the solvent from trifluoroethanol to *tert*-amyl alcohol completely stopped the reaction (entry 5). Control experiments revealed that [Co], [Mn], and NaOPiv were necessary to obtain the annulated product in good yield (entries 6−8). Changing the base from NaOPiv to AgOPiv did not improve the yield (entry 9). A similar yield was obtained when the reaction was carried out at a slightly lower temperature for 36 h, whereas a drop in yield was observed when the reaction was performed under air.

With the optimized conditions in hand, the scope for various substituted sulfonamides featuring 8-aminoquinoline is presented in Table 2. Electron-rich substrates gave good to excellent yields, whereas electron-deficient substrates gave moderate yields (**3ba**−**3fa**). Sulfonamides containing a *meta*-substituent gave a mixture of C6 and C2 functionalized regioisomers in a 1.7:1 ratio (**3ga**). The sterically hindered substituent did not give any annulated product, even at high temperature (**1i**). When sulfonamide **1j** was employed, no sign

Received: October 30, 2015

DOI: 10.1021/acs.orglett.5b03142
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Optimization of Cobalt Catalyzed Annulation of Sulfonamide[a]



entry	conditions	yield (%)[b]
1	standard conditions	70
2	$CoBr_2$ (10 mol %) as [Co] source	50
3	$CoCl_2{\cdot}6H_2O$ (10 mol %) as [Co] source	55
4	$Co(acac)_3$ as a [Co] source	10
5	tAmOH was used as a solvent	n.r.
6	without [Co] cat.	n.r.
7	without Mn(III)	n.r.
8	without NaOPiv	n.r.
9	AgOPiv instead of NaOPiv	35
10	at 80 °C for 24 h	60
11	at 80 °C for 36 h	70
12	performed under air instead of O_2	50

[a]Standard reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), $Co(OAc)_2{\cdot}4H_2O$ (0.03 mmol), NaOPiv (0.6 mmol), $Mn(OAc)_3{\cdot}2H_2O$ (0.6 mmol), CF_3CH_2OH (0.2 M), O_2 (1 atm), 100 °C. [b]Isolated yield; Q = quinoline.

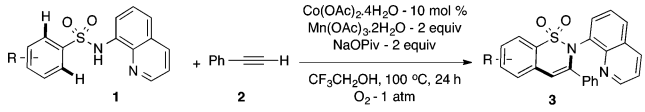
of product formation was observed, which may be due to difficulty in the formation of a six-membered metallocycle, or it may indicate that the presence of an acidic C−H proton between SO_2− and Ph− terminating the reaction completely. Nevertheless, the currently developed cobalt catalytic system seems to be the best catalyst for the annulation of sulfonamides especially with terminal alkynes with very high regioselectivity.

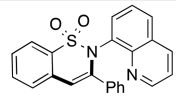
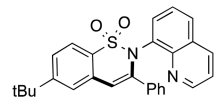
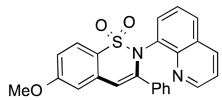
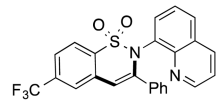
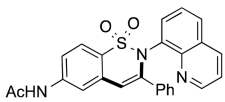
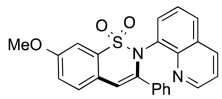
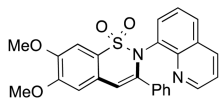
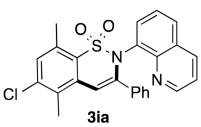
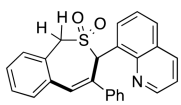
Next, we investigated the scope of various terminal and internal alkynes (Scheme 1). Electron-rich and -deficient 3- and 4-substituted phenyl acetylenes underwent the reaction smoothly with good yields as a single regioisomer (Scheme 1, **4cb**−**4ce**). Aliphatic terminal alkynes including cyclopropyl- and cyclopentyl-substituted alkynes, which are known to be less reactive for annulation, expedited product formation in a facile manner along with the small amount of β-substituted compound as a minor isomer (Scheme 1, **4cf**−**4ci**). Terminal alkynes with phenyl or larger substituents give a single regioisomer whereas a smaller substituent gives a mixture of regioisomers, which may possibly be due to steric factors.

Furthermore, we undertook the challenge of employing functionalized terminal alkynes **2j**−**k** under optimized reaction conditions with **1c** and the annulation progressed smoothly in good yield (Scheme 1, **4cj**−**4ck**). The reaction can also be extended to other internal alkynes. Symmetrical alkynes such as diaryl- and dialkyl-substituted acetylenes were efficiently used for cyclization in good yield (Scheme 1, **4cl**−**4cm**). Unsymmetrical alkyne **2n** was exposed to our reaction conditions, and it gave a highly regioselective product in moderate yield.

A gram scale reaction was performed with the objective of evaluating the feasibility of this catalytic process by exercising **1c** (1.0 g, 2.93 mmol) and **2a** (644 μL, 5.86 mmol) using 10 mol % of [Co], 2 equiv of NaOPiv, and 2 equiv of $Mn(OAc)_3{\cdot}2H_2O$ in trifluoroethanol at 100 °C for 24 h, which gave **3ca** in 85% yield (Scheme 2). Intermolecular competition experiments were performed using 8-aminoquinoline protected benzamide and sulfonamide with phenyl acetylene **2a** under our optimized conditions favoring annulation with a benzamide over sulfonamide, confirming the ease of cyclometalation with a

Table 2. Scope of Sulfonamides[a]



entry	R	product **3**	yield (%)[b]
1	H	 **3ba**	60
2	4-^{t}Bu	 **3ca**	84
3	4-OMe	 **3da**	70
4	4-CF_3	 **3ea**	45
5	4-AcNH-	 **3fa**	60
6	3-OMe	 **3ga**	90 (1.7:1)[c]
7	3,4-$(OMe)_2$	 **3ha**	90
8	2,5-Me-4-Cl-	 **3ia**	0
9	-	 **3ja**	0

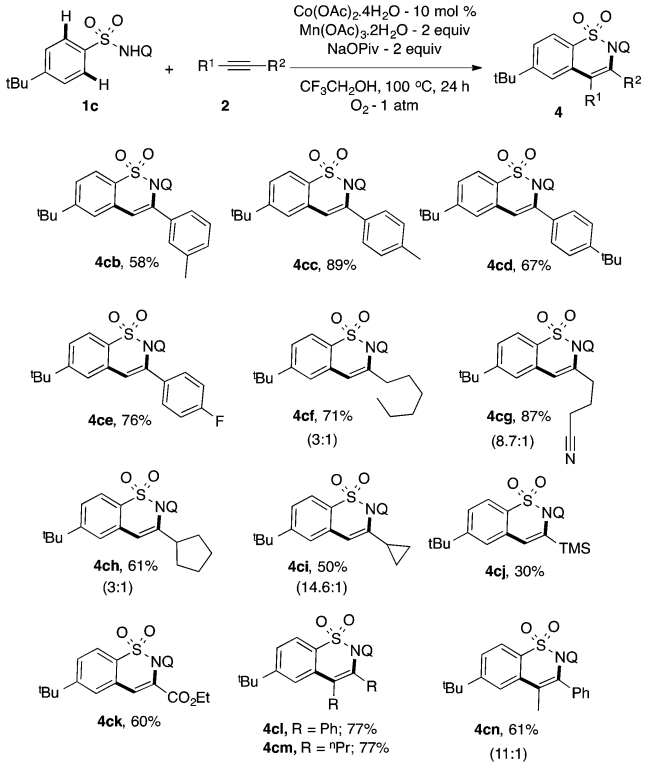
[a]Standard reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), $Co(OAc)_2{\cdot}4H_2O$ (0.03 mmol), NaOPiv (0.6 mmol), $Mn(OAc)_3{\cdot}2H_2O$ (0.6 mmol), CF_3CH_2OH (0.2 M), O_2 (1 atm), 100 °C. [b]Isolated yield. [c]Mixture of regioisomer (C6/C2) obtained in 1.7:1 ratio.

benzamide over an attenuated sulfonamide (Scheme 3a). In addition, we conducted a competitive reaction with electron-rich and -poor terminal alkynes with **1c**, which somewhat favors toward electron-rich alkynes in a 1.4:1 ratio of **4cc** and **4ce**, suggesting that the cyclometalation is possibly irreversible in nature (Scheme 3b).

Given the efficacy of the versatile cobalt catalyzed C−H annulation of sulfonamides, a plausible mechanism was proposed based on our experimental observations and relevant reports with cobalt(II) (Scheme 4).[10a] Initial coordination of 8-

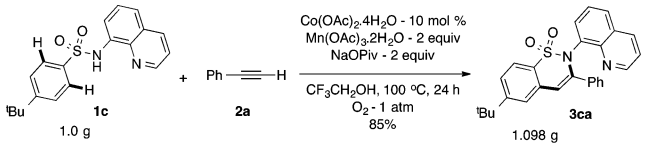
DOI: 10.1021/acs.orglett.5b03142
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Scope of Alkynes[a]

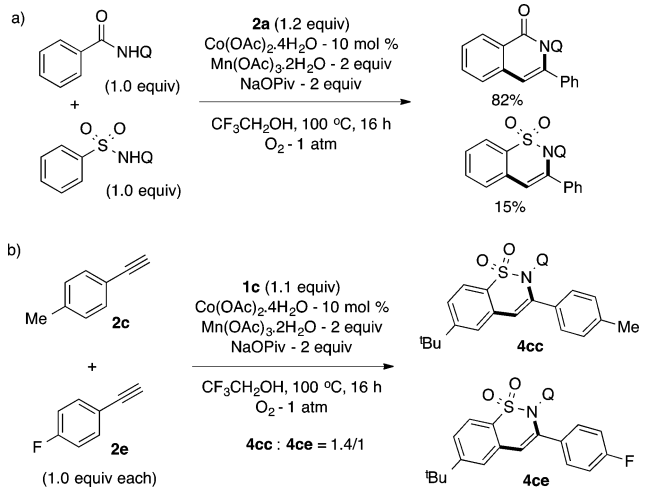


[a]All reactions were carried out under Oxygen (1 atm) with **1c** (0.3 mmol), **2** (0.6 mmol), $Co(OAc)_2{\cdot}4H_2O$ (0.03 mmol), NaOPiv (0.6 mmol), $Mn(OAc)_3{\cdot}2H_2O$ (0.6 mmol) in CF_3CH_2OH (0.2 M) at 100 °C for 24 h; Q = quinoline.

Scheme 2. Gram Scale Synthesis of 3ca

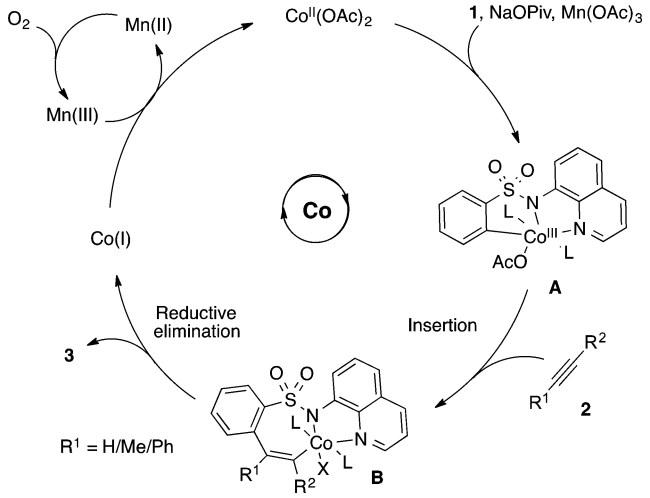


Scheme 3. Intermolecular Competitive Experiments



aminoquinoline followed by base assisted C−H bond functionalization led to complex **A** which further coordinated with alkyne **2** followed by insertion, which led to intermediate

Scheme 4. Proposed Mechanism



B. Reductive elimination of **B** led to **3** and regenerated the active catalyst upon oxidation of Co(I) using a Mn(III) cocatalyst. Nevertheless, the possibility of proceeding via a radical pathway cannot be overlooked at this stage.

In conclusion, we have developed an unprecedented cobalt catalyzed C−H/N−H annulation of sulfonamide with various terminal alkynes and internal alkynes via bidentate chelate assisted C−H bond activation. The annulation reaction possibly involved a Co(II)/Co(III) catalytic system and O_2 as a terminal oxidant along with Mn(III) a cocatalyst. We have shown excellent regioselectivity in particular, with terminal alkynes in good yield. Further studies probing the reaction mechanism and stoichiometric experiments are currently in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03142.

Experimental details and complete spectra of all newly synthesized compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support provided by the Indian Institute of Technology Kanpur through initiation grant (IITK/CHM/20130187) and DAE-BRNS (BRNS/CHM/2014110) for the young scientist research fund award to B.S. is gratefully acknowledged. D.K. wishes to thank IITK for her fellowship.

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DOI: 10.1021/acs.orglett.5b03142
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