

**Regioselective Access to Sultam Motifs through Cobalt-Catalyzed Annulation of Aryl Sulfonamides and Alkynes using an 8-Aminoquinoline Directing Group**

PLANAS, Oriol, WHITEOAK, Christopher <<http://orcid.org/0000-0003-1501-5582>>, COMPANY, Anna and RIBAS, Xavi

Available from Sheffield Hallam University Research Archive (SHURA) at:

<https://shura.shu.ac.uk/11768/>

---

This document is the Accepted Version [AM]

**Citation:**

PLANAS, Oriol, WHITEOAK, Christopher, COMPANY, Anna and RIBAS, Xavi (2015). Regioselective Access to Sultam Motifs through Cobalt-Catalyzed Annulation of Aryl Sulfonamides and Alkynes using an 8-Aminoquinoline Directing Group. *Advanced Synthesis & Catalysis*, 357 (18), 4003-4012. [Article]

---

**Copyright and re-use policy**

See <http://shura.shu.ac.uk/information.html>

# Regioselective Access to Sultam Motifs through Cobalt-Catalyzed Annulation of Aryl Sulfonamides and Alkynes using an 8-Aminoquinoline Directing Group

Oriol Planas,<sup>a</sup> Christopher J. Whiteoak,<sup>a\*</sup> Anna Company<sup>a</sup> and Xavi Ribas<sup>a\*</sup>

<sup>a</sup> QBIS-CAT Research Group, Institut de Química Computacional i Catàlisi (IQCC) and Departament de Química, Universitat de Girona, Campus Montilivi, E17071 Girona, Catalonia-Spain.  
Tel: (+34) 683 37 69 23; e-mail: [xavi.ribas@udg.edu](mailto:xavi.ribas@udg.edu), [christopher.whiteoak@udg.edu](mailto:christopher.whiteoak@udg.edu)

Received: ((will be filled in by the editorial staff))



Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/adsc.201#####>.

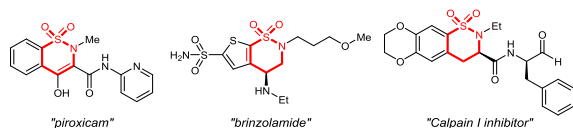
**Abstract.** The use of cobalt as catalyst in direct C-H activation protocols as a replacement for more expensive second row transition metals is currently attracting significant attention. Herein we disclose a facile cobalt-catalyzed C-H functionalization route towards sultam motifs through annulation of easily prepared aryl sulfonamides and alkynes using 8-aminoquinoline as a directing group. The reaction shows broad substrate scope with products obtained in a highly regioselective manner in good to excellent isolated yields.

Mechanistic insights suggest the formation of a Co(III)-aryl key species *via* arene C-H activation during the annulation reaction.

**Keywords:** Alkyne; Cobalt; C-H activation; Annulation; Regioselectivity, Sulfonamides, Sultams

## Introduction

Direct C-H bond functionalization has revolutionized synthetic methodology providing new facile synthetic routes to access molecules which would otherwise require preparation through complex, time-consuming synthetic procedures.<sup>[1]</sup> Sulfonamides have become an important motif in pharmaceutical drugs.<sup>[2]</sup> In particular, cyclic sulfonamide motifs (sultams) have found use as anti-inflammatory drugs (piroxicam), carbonic anhydrase inhibitors used to lower intraocular pressure in patients with open-angle glaucoma or ocular hypertension (brinzolamide) and Calpain I inhibitors in cell signalling dysfunctions (Scheme 1).<sup>[3]</sup> A number of synthetic protocols towards sultams have been reported, although to date the majority of these methodologies start from elaborated precursors.<sup>[4]</sup> The development of a simple metal-mediated C-H bond functionalization protocol starting from easily synthesized starting materials would provide a very appealing route towards the realization of sultam motifs.



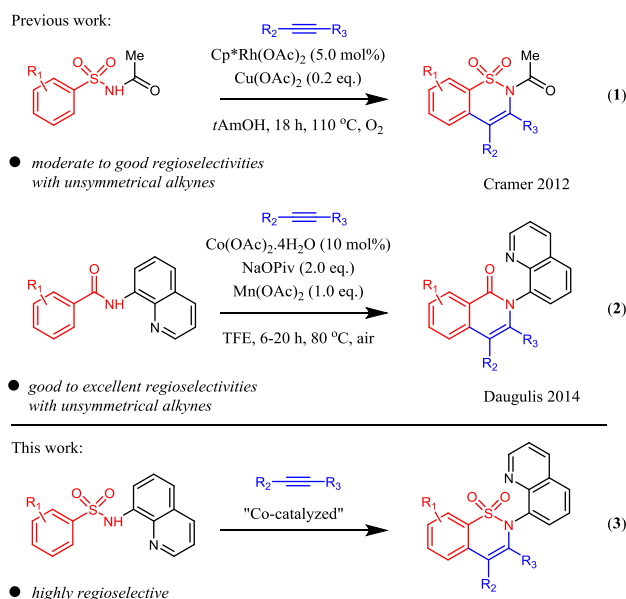
**Scheme 1.** Examples of pharmaceutical drugs containing cyclic sulfonamide (sultam) motifs.

Historically, most C-H coupling protocols have been based on relatively expensive precious transition-metals, for example Ru, Rh, Pd and Ir. More recently, attention has turned to the use of more abundant, cheaper first row transition metals, such as Fe,<sup>[5]</sup> Co,<sup>[6]</sup> Cu<sup>[7]</sup> and Ni.<sup>[8]</sup>

The use of alkynes in annulation reactions has become a very powerful tool for the construction of cyclic compounds. In particular, protocols using Rh,<sup>[9]</sup> Ru,<sup>[10]</sup> Cu,<sup>[11]</sup> Pd<sup>[12]</sup> and Ni<sup>[13]</sup> have been reported for the preparation of a variety of heterocyclic compounds. In terms of the use of these annulation reactions for the realization of sultams, in 2012 Cramer and co-workers reported on a Rh-catalyzed protocol starting from aryl sulfonamides incorporating an acyl directing group (Scheme 2.1).<sup>[14]</sup> The catalyst system displayed a broad substrate scope, furnishing a range of sultam products in good to excellent yields. The limitation of this protocol was that when unsymmetrical alkynes were employed as coupling partners, both possible regioisomers were formed, with only moderate regioselectivities in some cases.

More recently, Daugulis and co-workers have shown that using Co-catalysis, alkynes can be annulated with aryl carboxyamides containing an 8-aminoquinoline directing group (Scheme 2.2).<sup>[15]</sup> The 8-aminoquinoline moiety has been shown to be a privileged directing group for a number of metal-catalyzed conversions.<sup>[15]</sup> In this example the regioselectivities obtained using comparable

unsymmetrical alkynes were considerably higher than for the Rh-catalyzed formation of sultams. For example, when 1-propynylbenzene was employed as coupling partner using the Rh-catalyzed protocol, both possible regioisomers were obtained in a 2:1 ratio, whereas in the Co-catalyzed example the regioselectivity is significantly enhanced at 14:1. With these precedents in mind we decided to investigate the possibility of realizing a Co-catalyzed aryl sulfonamide annulation with alkynes (Scheme 2.3), seeking improved regioselective control compared with the previously described Rh-catalyzed protocol and to showcase the potential of using Co in annulation reactions.



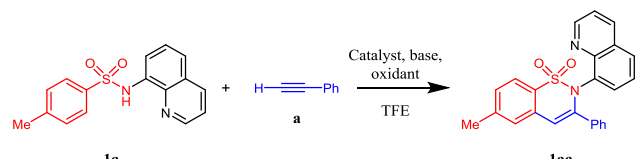
**Scheme 2.** (1) Previously reported Rh-catalyzed annulation of alkynes to aryl sulfonamides forming functionalized sultam motifs and (2) Co-catalyzed annulation of alkynes to aryl carboxamides. (3) Co-catalyzed annulation of aryl sulfonamides and alkynes forming functionalized sultam motifs reported herein.

## Results and Discussion

Initially, we attempted the annulation of the aryl sulfonamide derived from *p*-toluenesulfonyl chloride and 8-aminoquinoline, **1a**, with phenylacetylene, **a**, in a variety of solvents using a catalytic system comprising of Co(OAc)<sub>2</sub> (20 mol%), KOAc (2 equiv.) and Mn(OAc)<sub>2</sub> (1 equiv.) at 100 °C for 24 hours under an atmosphere of air. The observation of 22% of the desired aryl sultam product, **1aa**, using trifluoroethanol (TFE; found to be the optimal solvent, see Supporting Information for solvent optimization) (Table 1, entry 1) prompted us to further optimize the synthetic protocol in terms of Co source, oxidant and base using this solvent.<sup>[16]</sup>

A number of commonly used oxidants for cross-coupling protocols were investigated using Co(OAc)<sub>2</sub>

**Table 1.** Optimization of reaction conditions.<sup>[a]</sup>

				
Entry	Catalyst	Oxidant	Base	1aa [%] <sup>[b]</sup>
1	Co(OAc) <sub>2</sub>	Mn(OAc) <sub>2</sub>	KOAc	22
2	Co(OAc) <sub>2</sub>	Benzoquinone	KOAc	<1
3	Co(OAc) <sub>2</sub>	Ag <sub>2</sub> O	KOAc	6
4	Co(OAc) <sub>2</sub>	AgNO <sub>3</sub>	KOAc	50
5	Co(OAc) <sub>2</sub>	PhI(OAc) <sub>2</sub>	KOAc	12
6	Co(OAc) <sub>2</sub>	Mn(OAc) <sub>3</sub> ·2H <sub>2</sub> O	KOAc	62
7	Co(OAc) <sub>2</sub>	O <sub>2</sub>	KOAc	3
8 <sup>[c]</sup>	Co(OAc) <sub>2</sub>	-	KOAc	<1
9	Co(OAc) <sub>2</sub>	Mn(OAc) <sub>3</sub> ·2H <sub>2</sub> O	Na <sub>2</sub> CO <sub>3</sub>	22
10	Co(OAc) <sub>2</sub>	Mn(OAc) <sub>3</sub> ·2H <sub>2</sub> O	K <sub>2</sub> CO <sub>3</sub>	7
11	Co(OAc) <sub>2</sub>	Mn(OAc) <sub>3</sub> ·2H <sub>2</sub> O	Cs <sub>2</sub> CO <sub>3</sub>	4
12	<b>Co(OAc)<sub>2</sub></b>	<b>Mn(OAc)<sub>3</sub>·2H<sub>2</sub>O</b>	<b>NaOPiv·H<sub>2</sub>O</b>	<b>91(90<sup>[d]</sup>)</b>
13	Co(OAc) <sub>2</sub>	Mn(OAc) <sub>3</sub> ·2H <sub>2</sub> O	CsOPiv	78
14	Co(OAc) <sub>2</sub>	Mn(OAc) <sub>3</sub> ·2H <sub>2</sub> O	NaOAc·H <sub>2</sub> O	67
15	Co(OAc) <sub>2</sub>	Mn(OAc) <sub>3</sub> ·2H <sub>2</sub> O	CsOAc	69
16	-	Mn(OAc) <sub>3</sub> ·2H <sub>2</sub> O	NaOPiv·H <sub>2</sub> O	0
17	CoCl <sub>2</sub>	Mn(OAc) <sub>3</sub> ·2H <sub>2</sub> O	NaOPiv·H <sub>2</sub> O	90
18	CoBr <sub>2</sub>	Mn(OAc) <sub>3</sub> ·2H <sub>2</sub> O	NaOPiv·H <sub>2</sub> O	88
19	Co(NO <sub>3</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	Mn(OAc) <sub>3</sub> ·2H <sub>2</sub> O	NaOPiv·H <sub>2</sub> O	81
20	Co(Cp) <sub>2</sub>	Mn(OAc) <sub>3</sub> ·2H <sub>2</sub> O	NaOPiv·H <sub>2</sub> O	<1
21	Co(acac) <sub>2</sub>	Mn(OAc) <sub>3</sub> ·2H <sub>2</sub> O	NaOPiv·H <sub>2</sub> O	28
22	Co(acac) <sub>3</sub>	Mn(OAc) <sub>3</sub> ·2H <sub>2</sub> O	NaOPiv·H <sub>2</sub> O	17
23	Co(OTf) <sub>2</sub> (MeCN) <sub>2</sub>	Mn(OAc) <sub>3</sub> ·2H <sub>2</sub> O	NaOPiv·H <sub>2</sub> O	31
24	Co(OAc) <sub>2</sub> ·4H <sub>2</sub> O	Mn(OAc) <sub>3</sub> ·2H <sub>2</sub> O	NaOPiv·H <sub>2</sub> O	90
25	CoCl <sub>2</sub> ·6H <sub>2</sub> O	Mn(OAc) <sub>3</sub> ·2H <sub>2</sub> O	NaOPiv·H <sub>2</sub> O	87

<sup>[a]</sup> Reaction conditions: aryl sulfonamide (**1a**) (0.17 mmol), ethynylbenzene (**a**) (2.0 equiv.), Co source (20 mol%), oxidant (1.0 equiv.), base (2.0 equiv.), 2.0 mL TFE (trifluoroethanol) at 100 °C, under air for 24 h.

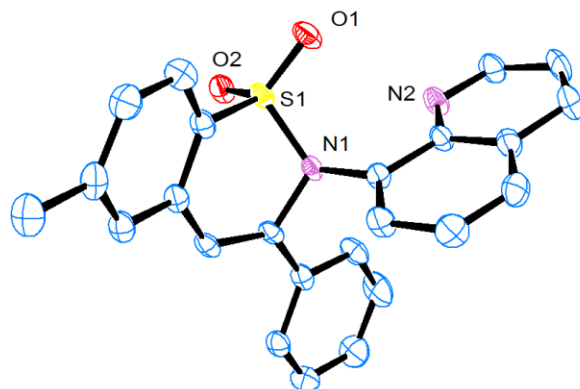
<sup>[b]</sup> Yield calculated by <sup>1</sup>H NMR analysis of crude reaction mixture using mesitylene as internal standard.

<sup>[c]</sup> Reaction prepared and performed under a N<sub>2</sub> atmosphere.

<sup>[d]</sup> At 100 °C for 16 h.

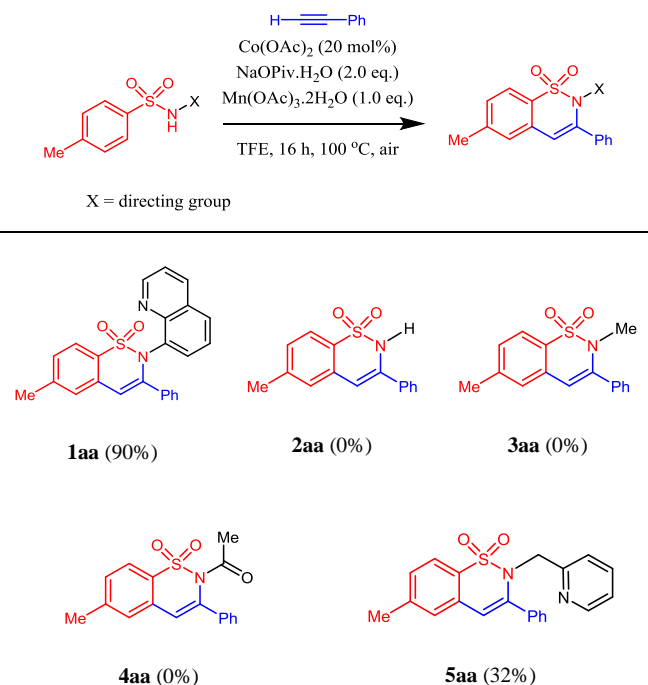
and KOAc (Table 1, entries 1-7). It was found that the optimal oxidant of those tested was Mn(OAc)<sub>3</sub>·2H<sub>2</sub>O, which furnished a 62% yield of **1aa** (Table 1, entry 6). Importantly it was found that the addition of an oxidant is of significant importance as in its absence and under a nitrogen atmosphere, no product formation was observed (Table 1, entry 8). Thereafter, optimization of the base was studied (Table 1, entries 9-15), whereby it was found that a yield of 91% of product **1aa** could be obtained when using NaOPiv·H<sub>2</sub>O (Table 1, entry 12). Finally the Co source was optimized (Table 1, entries 17-22), where it was found that Co(OAc)<sub>2</sub> was the optimal Co source (Table 1, entry 12). It was also observed that there is little difference between the use of anhydrous and hydrated Co sources (see for example table 1, entries 17 and 25; CoCl<sub>2</sub> and CoCl<sub>2</sub>·4H<sub>2</sub>O or table 1,

entries 12 and 24;  $\text{Co}(\text{OAc})_2$  and  $\text{Co}(\text{OAc})_2 \cdot 6\text{H}_2\text{O}$ ), indicating tolerance of the catalyst system to the presence of water. In the absence of Co the reaction did not proceed at all and the starting aryl sulfonamide, **1a**, could be fully recovered (Table 1, entry 16). Final optimization of the reaction time and temperature set the preferred experimental conditions at 100 °C and 16 hours for further substrate scoping (See Supporting Information). These reaction conditions are similar to those identified by Daugulis



**Figure 1.** X-ray structure obtained for compound **1aa**, hydrogen atoms omitted for clarity. For full details see Supporting Information.

**Table 2.** Screening of aryl sulfonamides (**1a-5a**) with/without different directing groups (X) using optimized reaction conditions.<sup>[a,b]</sup>



<sup>[a]</sup> Reaction conditions: aryl sulfonamide (**1a-5a**) (0.17 mmol), alkyne (**a**) (2.0 equiv.),  $\text{Co}(\text{OAc})_2$  (20 mol%),  $\text{Mn}(\text{OAc})_3\cdot 2\text{H}_2\text{O}$  (1.0 equiv.),  $\text{NaOPiv}\cdot\text{H}_2\text{O}$  (2.0 equiv.), 2.0 mL TFE (trifluoroethanol) at 100 °C, under air for 16 h.

<sup>[b]</sup> Yield calculated by  $^1\text{H}$  NMR analysis of crude reaction mixture using mesitylene as internal standard.

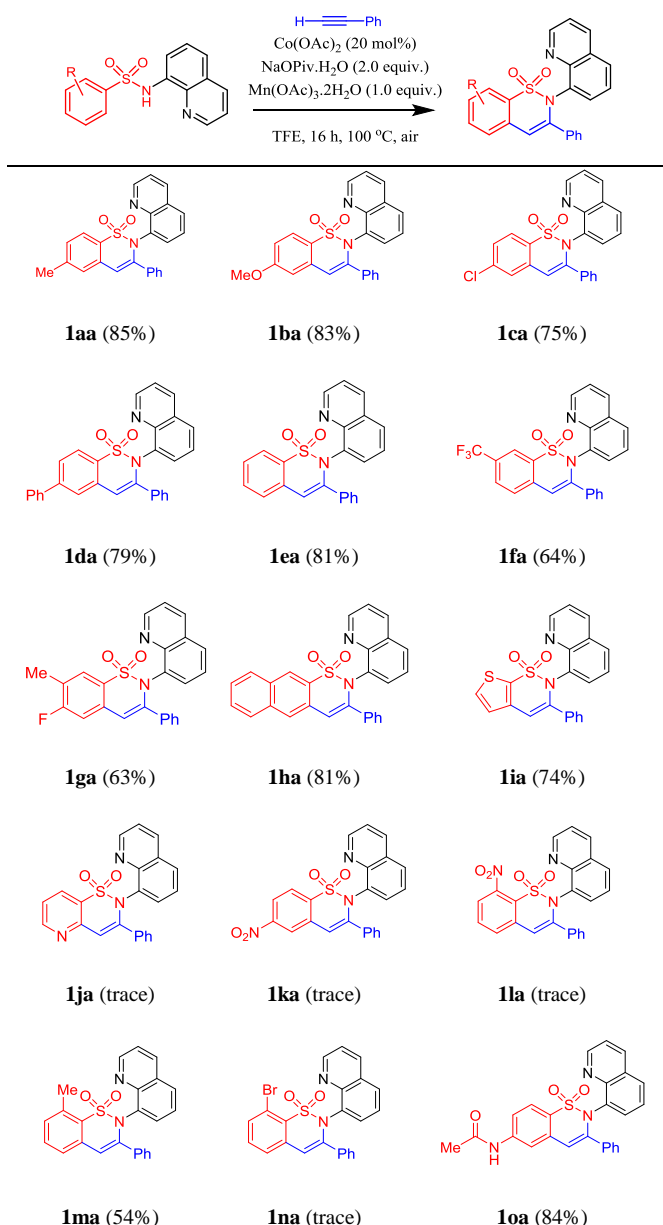
and co-workers for the Co-catalyzed conversion of aryl carboxamide substrates,<sup>[6]</sup> except for the clear beneficial use of  $\text{Mn}(\text{OAc})_3$  instead of  $\text{Mn}(\text{OAc})_2$  with our sulfonamide substrates. Detailed inspection of the  $^1\text{H}$  NMR of the final product confirmed the presence of a single regioisomer. The absolute configuration of **1aa** was established from the structure obtained from X-ray crystallography studies (Figure 1).

With these optimal reaction conditions in hand, we investigated the importance of the 8-aminoquinoline directing group. The results obtained (Table 2) show that the 8-aminoquinoline directing group gives superior yields compared to when no directing group is used (0%) or when acetyl (0%) and pyridyl (32%; single regioisomer) directing groups are present under these conditions. The absence of activity when using the acetyl directing group is in sharp contrast to the Rh-catalyzed protocol reported by Cramer and co-workers.<sup>[14]</sup>

Next, the scope of the newly optimized protocol was proved using different aryl sulfonamide derivatives, which were easily prepared from 8-aminoquinoline and the requisite sulfonyl chloride. These studies furnished functionalized sultam motifs in good to excellent yields (Table 3). In all cases the crude reaction mixtures displayed three well defined species when analyzed by TLC, corresponding to starting aryl sulfonamide, residual alkyne and sultam product. The product isolated after column chromatography was found to contain only a single regioisomer. Trace amounts of other regioisomers were only observed in the formation of **1da** and **1ga** (see Supporting Information). The highest yields were obtained with derivatives containing electron-donating groups (up to 85% isolated yield), whilst those containing electron-withdrawing substituents furnished lower yields (eg. **1fa** was obtained in only 64% yield and **1ka**, **1la**, **1na** were obtained in only trace amounts). We were also able to obtain the sultam containing a thiophene moiety (**1ia**), although only traces of sultam product were obtained when the pyridine derivative was employed (**1ja**), demonstrating some limitations to the substrate scope. When the substituents are present in the ortho-position to the sulfonamide reduced yields are obtained, likely as a result of the blocking of one of the C-H bonds to activation (for example see **1aa** and **1ma** whereby changing the position of the methyl group decreases the isolated yield from 85% to 54% respectively).

Substrates that failed to give satisfactory product yields were then included in poisoning experiments in order to see if the substrate was inhibiting the reaction or if the reaction rate was comparatively slower with these substrates. One equivalent of **1j**, **1k**, **1l** and **1n** were included in reactions for the conversion of **1a** to **1aa** (see Supporting Information for details). It was found that indeed in all cases these substrates are poisoning the catalyst system, resulting in decreased yields of **1aa**. This type of poisoning has

**Table 3.** Scope of Co-catalyzed coupling of phenylacetylene (**a**) to aryl sulfonamide derivatives (**1a-1m**) forming functionalized sultam motifs.<sup>[a,b]</sup>

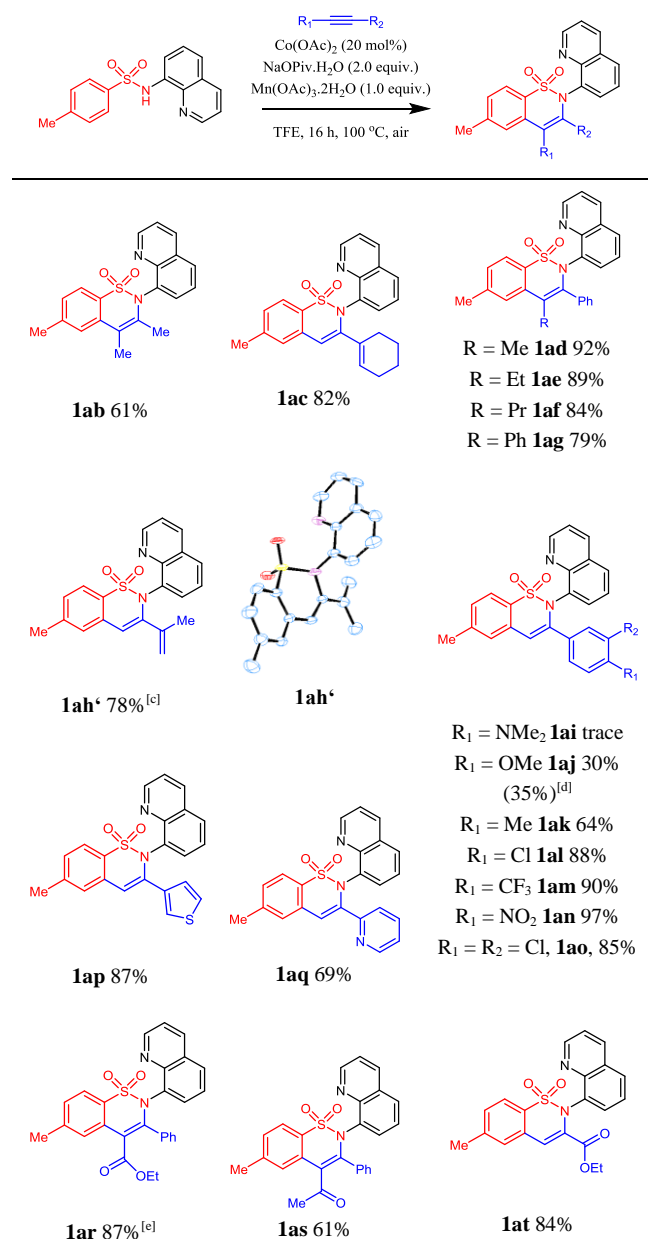


<sup>[a]</sup> Reaction conditions: aryl sulfonamide (**1a-1k**) (0.35 mmol), alkyne (**a**) (2.0 equiv.),  $\text{Co}(\text{OAc})_2$  (20 mol%),  $\text{Mn}(\text{OAc})_3\cdot 2\text{H}_2\text{O}$  (1.0 equiv.),  $\text{NaOPiv}\cdot\text{H}_2\text{O}$  (2.0 equiv.), 2.0 mL TFE (trifluoroethanol) at 100 °C, under air for 16 h.  
<sup>[b]</sup> Isolated yields obtained after purification by column chromatography.

recently been described by Glorius and co-workers.<sup>[17]</sup> We propose that the poisoning observed in our studies arises from poorly reversible coordination of the Co to the substrate.

Following scoping with substituted aryl sulfonamides, we turned our attention to the use of differently substituted alkynes (Table 4). Again the catalyst system displayed broad substrate tolerance for a variety of functional groups and again high regioselectivities were observed as confirmed by the presence of only one species in the  $^1\text{H}$  NMR in most cases. When an ester substituent was present in the alkyne (**1ar**) both possible regioisomers were

**Table 4.** Scope of Co-catalyzed coupling of substituted alkynes (**b-t**) to aryl sulfonamide (**1a**) forming functionalized sultam motifs.<sup>[a,b]</sup>



<sup>[a]</sup> Reaction conditions: aryl sulfonamide **1a** (0.35 mmol), acetylene derivatives (**b-s**) (2.0 equiv.),  $\text{Co}(\text{OAc})_2$  (20 mol%),  $\text{Mn}(\text{OAc})_3\cdot 2\text{H}_2\text{O}$  (1.0 equiv.),  $\text{NaOPiv}\cdot\text{H}_2\text{O}$  (2.0 equiv.), 2.0 mL TFE (trifluoroethanol) at 100 °C, under air for 16 h.

<sup>[b]</sup> Isolated yields obtained after purification by column chromatography.

<sup>[c]</sup> Product derived from 3-chloro-3-methylbut-1-yne.

<sup>[d]</sup> Reaction at 100 °C for 40 h.

<sup>[e]</sup> Combined yield of both regioisomers. Regioisomers obtained in a ratio of 3:1; major regioisomer depicted (See Supporting Information for X-ray crystal structure obtained).

identified (the TLC displayed a single spot for a combination of the two regioisomers). The major regioisomer could be separated from the minor



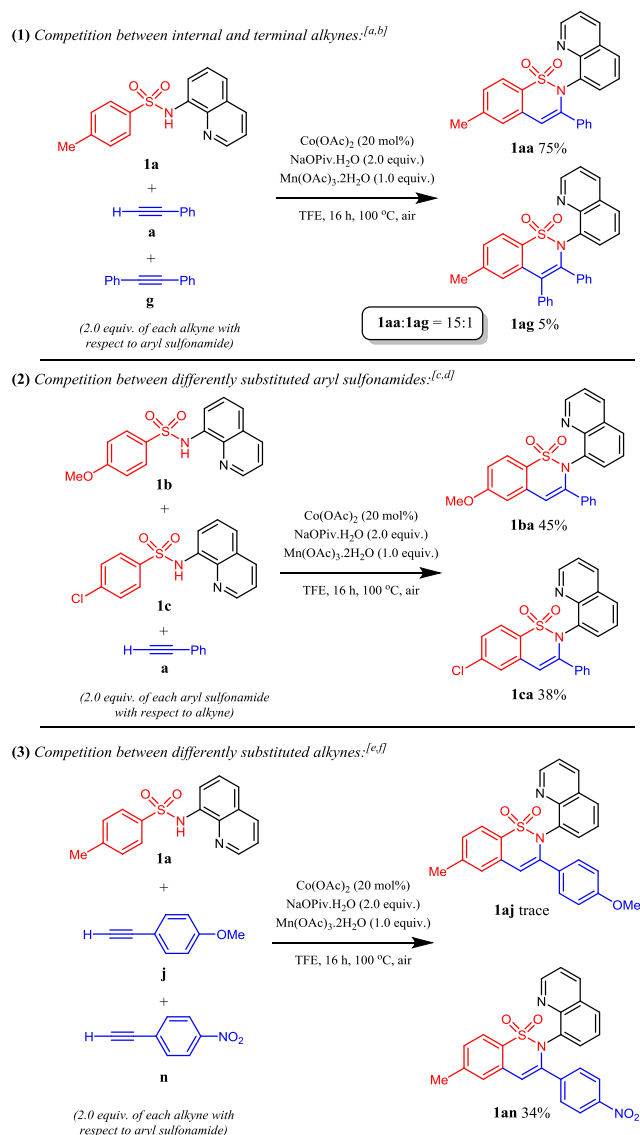
regioisomer by recrystallization and was fully characterized (See Supporting Information). Unexpectedly, when using 3-chloro-3-methylbut-1-yne as substrate (**h**), the product whereby hydrogen chloride had been eliminated was obtained (**1ah'**). When electron-donating substituents are present on the aryl group of phenylacetylene the reaction resulted in low or trace yields (trace amounts and 30% for **1ai** and **1aj** respectively). In the case of **1aj**, even after an extended reaction time the yield was not significantly improved.

The effectiveness of this transformation was further checked by performing a gram-scale reaction to obtain **1aa** and **1al**, furnishing 64 % (0.87 g) and 61% (0.89 g), respectively (see Supporting Information).

In order to further compare the reactivities of the substrates under the optimized protocol, we performed intermolecular competition reactions (Scheme 3). When two equivalents of both a terminal (**a**) and internal (**g**) alkyne were included it was found that insertion of the terminal alkyne was significantly favored, resulting in a product ratio of 15:1 for terminal and internal alkyne insertion respectively (Scheme 3.1). Thereafter we also ran competition reactions using differently substituted aryl sulfonamide and phenylacetylene substrates (Scheme 3.2 and 3.3 respectively). As expected, in agreement with the results obtained from the substrate scoping, reaction with electron-donating aryl sulfonamides (methoxy, **1b**) was found to be slightly favored over electron-withdrawing (chloro, **1c**) aryl sulfonamides. Likewise, insertion of the *p*-nitro phenylacetylene (**n**) was favored over *p*-methoxy phenylacetylene (**j**). The latter competition reaction only yielded 34% of the *p*-nitro product (**1an**), whereas in the absence of the competing *p*-methoxy phenylacetylene during substrate scoping we obtained 97% isolated yield. This result suggests that the *p*-methoxy phenylacetylene is inhibiting the reaction to some extent. This inhibition is similar to the result obtained by Ackermann and co-workers during their intermolecular competition reactions.<sup>[6r]</sup>

We also performed a range of deuterium exchange reactions (Scheme 4). We found that when the reaction was performed in D<sub>4</sub>-methanol the final sultam product was 78% deuterated on the sultam motif (Scheme 4.1). Likewise, when deuterated phenylacetylene was used as substrate we observed 66% of <sup>1</sup>H incorporation into the sultam product (Scheme 4.2). These results indicate that the proton/deuterium of the terminal alkyne likely exchanges with the solvent under the basic reaction conditions.

Additionally, we performed a reaction in the absence of alkyne in D<sub>4</sub>-methanol (Scheme 4.3). At the end of the reaction we observed a low inclusion of deuterium in the starting sulfonamide, suggesting the deuterio-demetalation of a putative aryl-Co intermediate species (see Supporting Information). This is further supported by the Kinetic Isotope

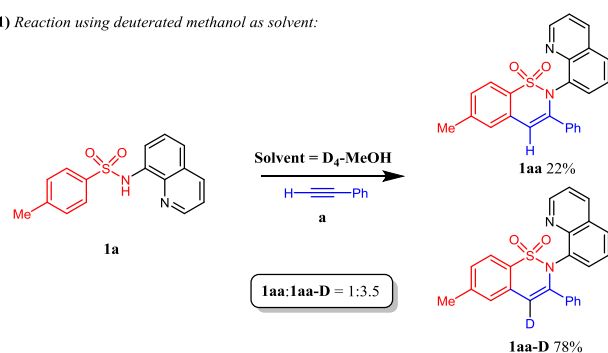


**Scheme 3.** Intermolecular competition reactions under optimized reaction conditions; yields calculated by <sup>1</sup>H NMR analysis of crude reaction mixture using mesitylene as internal standard. <sup>[a]</sup> Aryl sulfonamide **1a** (0.35 mmol), phenylacetylene derivatives (2.0 equiv. of **a** and 2.0 equiv. of **g**), 2.0 mL TFE. <sup>[b]</sup> Yields based on **1a**. <sup>[c]</sup> Aryl sulfonamide **1b** and **1c** (0.70 mmol of each), phenylacetylene derivatives (0.35 mmol, 0.25 equiv. of **a** with respect to combined aryl sulfonamide), 2.0 mL TFE. <sup>[d]</sup> Yields based on **a**. <sup>[e]</sup> Aryl sulfonamide **1a** (0.35 mmol), phenylacetylene derivatives (2.0 equiv. of **j** and 2.0 equiv. of **n**), 2.0 mL TFE. <sup>[f]</sup> Yields based on **1a**.

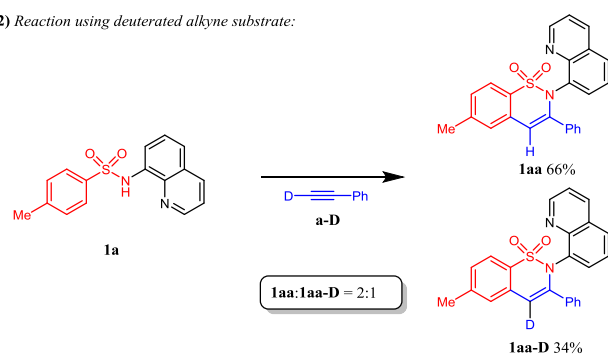
Effect (KIE) calculated when including both **1e** and **D5-1e** in the reaction (Scheme 4.4). The value obtained is consistent with C-H activation being the rate determining step in the reaction.

The exact mechanisms of Co-catalyzed C-H activation protocols are still not fully understood. Recently, Niu, Song and co-workers identified the presence of radicals using EPR spectroscopy in their Co-catalyzed alcohol coupling protocol.<sup>[6m]</sup> This was further evidenced by the lack of activity when the

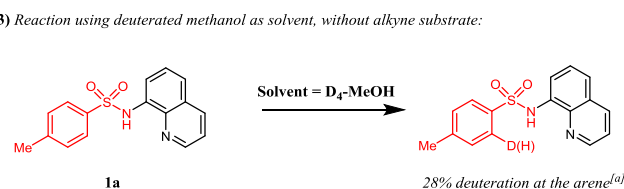
(1) Reaction using deuterated methanol as solvent:



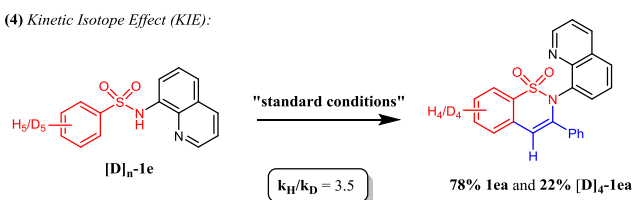
(2) Reaction using deuterated alkyne substrate:



(3) Reaction using deuterated methanol as solvent, without alkyne substrate:



(4) Kinetic Isotope Effect (KIE):

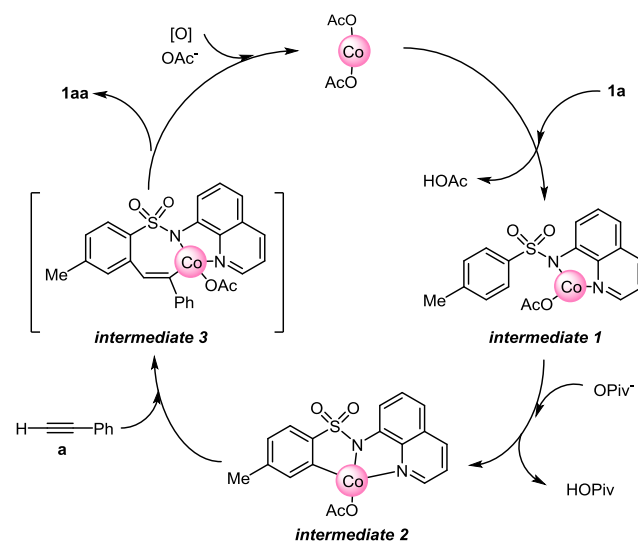


**Scheme 4.** Deuterium labelling experiments: Reaction conditions: aryl sulfonamide **1a** (0.35 mmol), phenylacetylene (**a**) (2.0 equiv.),  $Co(OAc)_2$  (20 mol%),  $Mn(OAc)_3 \cdot 2H_2O$  (1.0 equiv.),  $NaOPiv \cdot H_2O$  (2.0 equiv.), 2.0 mL solvent at 100 °C, under air for 16 h. KIE experiment: 0.17 mmol of both **1e** and **D<sub>5</sub>-1e**, phenylacetylene (**a**) (2.0 equiv.),  $Co(OAc)_2$  (20 mol%),  $Mn(OAc)_3 \cdot 2H_2O$  (1.0 equiv.),  $NaOPiv \cdot H_2O$  (2.0 equiv.), 2.0 mL solvent at 100 °C, under air for 16 h. Yields reported are percentage of isolated compounds obtained after purification by column chromatography. <sup>[a]</sup> See supporting information for full details.

radical scavenger 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) was included (see Supporting Information). We therefore included several different radical scavengers (TEMPO, BHT, AIBN and  $P(OEt)_3$ ) in our reactions and found that activity was almost completely inhibited in agreement with this previous work, suggesting that our reaction likely

proceeds through radical intermediates in some steps of the mechanism.

We propose a mechanism (Scheme 5) in which initially the  $Co(OAc)_2$  chelates to the quinoline directing group and to the sulfonamide of the substrate, **1a**, (Intermediate 1) releasing one equivalent of acetic acid. The aminoquinoline coordination environment favours the stabilization of high-valent Co species; we therefore propose that once coordinated to the aryl sulfonamide substrate the Co(II) undergoes oxidation to Co(III) using oxygen as the terminal oxidant. Indeed our studies show that the presence of oxygen is highly beneficial for the process to proceed (see Supporting Information). Subsequently, this high-valent Co(III) intermediate can then activate the aryl C-H bond through a Concerted Metallation Deprotonation (CMD) type process as a result of its higher electrophilicity of Co(III) compared with Co(II), giving rise to Intermediate 2, although at this point other activation processes cannot be completely discarded.<sup>[18]</sup> An analogous Co(III) species was isolated and characterized by Daugulis and co-workers using Co(II) precursors for their analogous aryl carboxamide substrates.<sup>[6t]</sup> KIE experiments indicate that this challenging C-H activation event is the rate determining step of the reaction (Scheme 4.4). Subsequently, insertion of the alkyne, **a**, into the Co(III)-aryl bond results in the transient Intermediate 3. Finally, elimination of Co(I), which is then reoxidized to  $Co(OAc)_2$ , provides the desired sultam product, **1aa**. As suggested by the radical scavenger experiments described above, some steps of the catalytic cycle may involve radical intermediates. We propose that the improved regioselectivity when using Co catalysts compared with the Rh catalyst reported by Cramer for sultam formation arises from the steric effect of the  $Cp^*$  ligand affecting the direction of the alkyne insertion into the Rh(III)-aryl bond.



**Scheme 5.** Proposed mechanistic cycle.

Finally, we attempted to upgrade the products obtained by removing the 8-aminoquinoline directing group (See Supporting Information for details), although to date we have not been successful. The removal of 8-aminoquinoline directing group has been reported to be possible using ammonia if the annulated product contains carbonyl functionalities at either side of the 8-aminoquinoline, in similarity to the final step of the Gabriel synthesis of amines.<sup>[6n,19]</sup> If two adjacent carbonyl functionalities are not present, the directing group can be removed using cerium(IV) ammonium nitrate (CAN) only if the 5-methoxy-8-aminoquinoline is used.<sup>[20]</sup> However, the CAN strategy does not always work using this elaborated directing group<sup>[21]</sup> as well as in our compounds. We also attempted a H<sub>2</sub>:Pd(0)/C reduction, but only the pyridinic moiety of the 8-aminoquinoline was reduced to afford **1aaH<sub>4</sub>** (see Supporting Information). We also tried reduction with a stronger reducing agent such as SmI<sub>2</sub>, but a complex mixture products was obtained. Our next goal is to develop a facile methodology for the 8-aminoquinoline directing group removal or extrapolate the reported reactivity to be used with more easily removable directing groups.

## Conclusion

In summary, we have reported on a new Co-catalyzed protocol for the synthesis of sultam motifs starting from easily prepared aryl sulfonamides and alkynes. The protocol permits the use of a broad range of substituted aryl sulfonamides and alkynes, as well as displaying excellent regioselectivities compared with the previously reported Rh-catalyzed protocol, where moderate regioselectivity was found.<sup>[14]</sup> This protocol demonstrates the increasing potential of Co to replace more expensive second row transition metals as a result of favorable reactivities and selectivities.<sup>[22]</sup>

## Experimental Section

### General considerations

All reagents and solvents were purchased from Sigma Aldrich, Fisher Scientific or Fluorochem and used without further purification. Aryl sulfonamide (**2a**) was purchased from Sigma Aldrich, all other substrates were synthesized as described in the Supporting Information. <sup>1</sup>H and <sup>13</sup>C {<sup>1</sup>H} NMR spectra were recorded on Bruker AV-300 or Bruker DPX 400 MHz spectrometers and referenced to the residual deuterated solvent signals. High Resolution Mass Spectra (HRMS) were recorded by the Serveis Tècnics of the University of Girona on a Bruker MicroTOF-Q IITM instrument using an ESI ionization source. IR Spectra (FTIR) were recorded on a FT-IR Alpha spectrometer from Bruker with a PLATINUM-ATR attachment using OPUS software to process the data.

### Typical optimized procedure for synthesis of sultam compounds:

Aryl sulfonamide (0.35 mmol), Co(OAc)<sub>2</sub> (12.4 mg, 20 mol%, 0.07 mmol), NaOPiv·H<sub>2</sub>O (86.8 mg, 2.0 equiv., 0.70 mmol), Mn(OAc)<sub>3</sub>·2H<sub>2</sub>O (94.0 mg, 1.0 equiv., 0.7

mmol), alkyne substrate (2.0 equiv., 0.70 mmol) and 2 mL of trifluoroethanol were added to a glass vial under air and the vial was subsequently sealed. The resulting mixture was stirred at 100 °C for 16 h and thereafter cooled to room temperature. The solvent was removed and the product purified using column chromatography (Silica gel: dichloromethane). After purification the product was dried under reduced pressure.

Full characterization data obtained (including original <sup>1</sup>H, <sup>13</sup>C {<sup>1</sup>H} and COSY NMR spectra for all sultam products) can be found in the Supporting Information. Crystallographic data for compounds **1aa** (CCDC-1407285), **1ah'** (CCDC-1407286), **1ar** (CCDC-1411541) and **1aaH<sub>4</sub>** (CCDC-1407287) can be obtained free of charge from the Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).

## Acknowledgements

We acknowledge financial support from the ERC for the Starting Grant Project ERC-2011-StG-277801 to X.R. and MINECO of Spain for CTQ2013-43012-P to X.R. and A.C., and a RyC contract to A.C.. We thank the MEC for a FPU PhD grant to O.P. X.R. also thanks ICREA for an ICREA-Acadèmia award. We are also grateful to X. Fontrodona (X-ray crystallography), Dr. L. Gómez (HRMS) and STR-UdG.

## References

- [1] a) C-H Activation, J.-Q. Yu, Z. Shi, Eds., Vol. 292, Springer-Verlag; Berlin, Germany: **2010**; b) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2012**, *51*, 8960; c) J. Wencel-Delord, F. Glorius, *Nature Chem.* **2013**, *5*, 369; d) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147; e) K. Godula, D. Sames, *Science* **2006**, *312*, 67; f) J. J. Mousseau, A. B. Charrette, *Acc. Chem. Res.* **2013**, *46*, 412; g) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2009**, *48*, 5094; h) A. E. Shilov, G. B. Shul'pin, *Chem. Rev.* **1997**, *97*, 2879; i) C. Jia, T. Kitamura, Y. Fujiwara, *Acc. Chem. Res.* **2001**, *34*, 633; j) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215; h) C-H and C-X Bond Functionalization: Transition Metal Mediation, X. Ribas, Ed. RSC Catalysis, Series No. 11, **2013**.
- [2] S. S. Shah, G. Rivera, M. Ashfaq, *Mini. Rev. Med. Chem.* **2013**, *13*, 70.
- [3] a) J. G. Lombardino, E. H. Wiseman, W. McIlamore, J. *Med. Chem.* **1971**, *14*, 1171; b) L. De Santis, *Surv. Ophthalmol.* **2000**, *44*, S119; c) G. J. Wells, M. Tao, K. A. Josef, R. J. Bihovsky, *Med. Chem.* **2001**, *44*, 3488.
- [4] For some examples of current methods for the synthesis of sultams see: a) V. A. Rassadin, D. S. Grosheva, A. A. Tomashevskii, V. V. Sokolov, *Chem. Heterocycl. Compd.* **2013**, *49*, 39; b) K. C. Majumdar, *RSC Adv.*, **2011**, *1*, 1152; c) S. Merten, R. Fröhlich, O. Kataeva, P. Metz, *Adv. Synth. Catal.* **2005**, *347*, 754; d) X.-Y. Liu, C.-H. Li, C.-M. Che, *Org. Lett.* **2006**, *8*, 2707; e) M. Jiménez-Hopkins, P. R. Hanson, *Org. Lett.* **2008**, *10*,

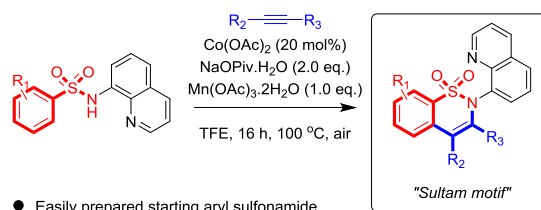


- 2223; f) K. Kaneko, T. Yoshino, S. Matsunaga, M. Kanai, *Org. Lett.* **2013**, *15*, 2502.
- [5] For examples see, X. Sun, J. Li, X. Huang, C. Sun, *Curr. Inorg. Chem.* **2012**, *2*, 64.
- [6] For recent examples see: a) Z. Ding, N. Yoshikai, *Angew. Chem. Int. Ed.* **2013**, *52*, 8574; b) P.-S. Lee, N. Yoshikai, *Angew. Chem. Int. Ed.* **2013**, *52*, 1240; c) B. Wu, M. Santra, N. Yoshikai, *Angew. Chem. Int. Ed.* **2014**, *53*, 7543; d) T. Andou, Y. Saga, H. Komai, S. Matsunaga, M. Kanai, *Angew. Chem. Int. Ed.* **2013**, *52*, 3213; e) H. Ikemoto, T. Yoshino, K. Sakata, S. Matsunaga, M. Kanai, *J. Am. Chem. Soc.* **2014**, *136*, 5424; f) B. Sun, T. Yoshino, S. Matsunaga, M. Kanai, *Adv. Synth. Catal.* **2014**, *356*, 1491; g) T. Yoshino, H. Ikemoto, S. Matsunaga, M. Kanai, *Angew. Chem. Int. Ed.* **2013**, *52*, 2207; h) W. Song, L. Ackermann, *Angew. Chem. Int. Ed.* **2012**, *51*, 8251; i) J. Li, L. Ackermann, *Chem. Eur. J.* **2015**, *21*, 5718; j) J. Li, L. Ackermann, *Angew. Chem. Int. Ed.* **2015**, *54*, 3635; k) W. Ma, L. Ackermann, *ACS Catal.* **2015**, *5*, 2822; l) L. Ackermann, *J. Org. Chem.* **2014**, *79*, 8948; m) B. Punji, W. Song, G. A. Shevchenko, L. Ackermann, *Chem. Eur. J.* **2013**, *19*, 10605; n) A. B. Pawar, S. Chang, *Org. Lett.* **2015**, *17*, 660; o) D. Zhao, J. H. Kim, L. Stegemann, C. A. Strasser, F. Glorius, *Angew. Chem. Int. Ed.* **2015**, *54*, 4508; p) T. Gensch, S. Vásquez-Céspedes, D.-G. Yu, F. Glorius, *Org. Lett.* **2015**, *17*, 3714; q) D.-G. Yu, T. Gensch, F. de Azambuja, S. Vásquez-Céspedes, F. Glorius, *J. Am. Chem. Soc.* **2014**, *136*, 17722; r) L.-B. Zhang, X.-Q. Hao, S.-K. Zhang, Z.-J. Liu, X.-X. Zheng, J.-F. Gong, J.-L. Niu, M.-P. Song, *Angew. Chem. Int. Ed.* **2015**, *54*, 272; s) L. Grigorjeva, O. Daugulis, *Org. Lett.* **2014**, *16*, 4688; t) L. Grigorjeva, O. Daugulis, *Angew. Chem. Int. Ed.* **2014**, *53*, 10209; u) X. Wu, K. Yang, Y. Zhao, H. Sun, G. Li, H. Ge, *Nat. Commun.* **2015**, *6*, 6462; v) L.-B. Zhang, X.-Q. Hao, Z.-J. Liu, X.-X. Zheng, S.-K. Zhang, J.-L. Niu, M.-P. Song, *Angew. Chem. Int. Ed.* **2015**, *54*, 10012; w) J. R. Hummel, J. A. Ellman, *J. Am. Chem. Soc.* **2015**, *137*, 490.
- [7] For an overview see: a) A. Casitas, X. Ribas, *Chem. Sci.* **2013**, *4*, 2301; b) C. Zhang, C. Tang, N. Jiao, *Chem. Soc. Rev.* **2012**, *41*, 3464; c) A. E. Wendlandt, A. M. Suess, S. S. Stahl, *Angew. Chem. Int. Ed.* **2011**, *50*, 11062; d) I. P. Beletskaya, A. V. Cheprakov, *Coord. Chem. Rev.* **2004**, *248*, 2337.
- [8] For an overview see: S. Z. Tasker, E. A. Standley, T. F. Jamison, *Nature* **2014**, *509*, 299.
- [9] See for example: a) N. Umeda, H. Tsurugi, T. Satoh, M. Miura, *Angew. Chem. Int. Ed.* **2008**, *47*, 4019; b) K. Ueura, T. Satoh, M. Miura, *J. Org. Chem.* **2007**, *72*, 5362; c) D. R. Stuart, P. Alsabeh, M. Kuhn, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 18326; d) K. Ueura, T. Satoh, M. Miura, *Org. Lett.* **2007**, *9*, 1407; e) D. R. Stuart, M. Bertrand-Laperle, K. M. N. Burgess, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 16474; f) M. P. Huestis, L. Chan, D. R. Stuart, K. Fagnou, *Angew. Chem. Int. Ed.* **2011**, *50*, 1338; g) K. Morimoto, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2010**, *12*, 2068; h) N. Guimond, K. Fagnou, *J. Am. Chem. Soc.* **2009**, *131*, 12050; i) S. Rakshit, F.W. Patureau, F. Glorius, *J. Am. Chem. Soc.* **2010**, *132*, 9585; j) T. K. Hyster, T. Rovis, *J. Am. Chem. Soc.* **2010**, *132*, 10565; k) G. Song, D. Chen, C.-L. Pan, R. H. Crabtree, X. Li, *J. Org. Chem.* **2010**, *75*, 7487.
- [10] See for example: a) C.-Y. Wu, M. Hu, Y. Liu, R.-J. Song, Y. Lei, B.-X. Tang, R.-J. Li, J.-H. Li, *Chem. Commun.* **2012**, *48*, 3197; b) L. Ackermann, A. V. Lygin, N. Hofmann, *Angew. Chem. Int. Ed.* **2011**, *50*, 6379; c) L. Ackermann, *Acc. Chem. Res.* **2014**, *47*, 281; d) B. Li, N. Wang, Y. Liang, S. Xu, B. Wang, *Org. Lett.* **2013**, *15*, 136.
- [11] See for example: R. Bernini, G. Fabrizi, A. Sferrazza, S. Cacchi, *Angew. Chem. Int. Ed.* **2009**, *48*, 8078.
- [12] See for example : a) J. Wu, X. Cui, X. Mi, Y. Li, Y. Wu, *Chem. Commun.* **2010**, *46*, 6771; b) Z. Shi, S. Ding, Y. Cui, N. Jiao, *Angew. Chem. Int. Ed.* **2009**, *48*, 7895; c) R. C. Larock, *Top. Organomet. Chem.* **2005**, *14*, 147.
- [13] See for example: a) Y. Kajita, S. Matsubara, T. Kurahashi, *J. Am. Chem. Soc.* **2008**, *130*, 6058; b) C.-C. Liu, K. Parthasarathy, C.-H. Cheng, *Org. Lett.* **2010**, *12*, 3518.
- [14] M. V. Pham, B. Ye, N. Cramer, *Angew. Chem. Int. Ed.* **2012**, *51*, 10610.
- [15] For an overview of conversions utilizing 8-aminoquinoline directing groups see: a) M. Corbet, F. De Campo, *Angew. Chem. Int. Ed.* **2013**, *52*, 9896; b) O. Daugulis, J. Roane, L. D. Tran, *Acc. Chem. Res.* **2015**, *48*, 1053.
- [16] For examples of the benefits of using fluorinated solvents see: I. A. Shuklov, N. V. Dubrovina, A. Börner, *Synthesis*, **2007**, *19*, 2925.
- [17] K. D. Collins, F. Glorius, *Acc. Chem. Res.* **2015**, *48*, 619.
- [18] Organometallic Mechanisms and Catalysis, J. K. Kochi, Ed. Academic Press, London, **1978**.
- [19] X. Wu, Y. Zhao, H. Ge, *J. Am. Chem. Soc.* **2015**, *137*, 4924.
- [20] a) L. Grigorjeva, O. Daugulis, *Org. Lett.* **2014**, *16*, 4684; b) G. He, S.-Y. Zhang, W. A. Nack, Q. Li, G. Chen, *Angew. Chem. Int. Ed.* **2013**, *52*, 11124.
- [21] J. Dong, F. Wang, J. You, *Org. Lett.* **2014**, *16*, 2884.
- [22] For example, Kanai and co-workers have recently described the unique reactivity of [Cp\*Co(III)] over [Cp\*Rh(III)] for the direct dehydrative C-H allylation with non-activated allyl alcohols, thus providing an excellent example the potential advantages of the use of Co over Rh; Y. Suzuki, B. Sun, K. Sakata, T. Yoshino, S. Matsunaga, M. Kanai, *Angew. Chem. Int. Ed.* **2015**, *54*, 9944.

Regioselective Access to Sultam Motifs through Cobalt-Catalyzed Annulation of Aryl Sulfonamides and Alkynes using an 8-Aminoquinoline Directing Group

*Adv. Synth. Catal.* **2015**, Volume, Page – Page

Oriol Planas, Christopher J. Whiteoak,\* Anna Company and Xavi Ribas\*



- Easily prepared starting aryl sulfonamide
- Directing group C-H activation approach
- 31 examples obtained in up to 97% isolated yield
- Highly regioselective