Homogenous Catalysis

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Access to Sultams by Rhodium(III)-Catalyzed Directed C–H Activation**

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The aryl sulfonamide moiety is a very important and ubiquitous functional group which is closely linked to pharmaceutical activity, and plays a significant role as a structural design element in medicinal chemistry.[1] Both primary sulfonamides and sulfonyl ureas are common motifs is drugs as exemplified by celecoxib, brinzolamide, sultiame, and glibenclamide (Figure 1).[2] Acylated sulfonamides, which

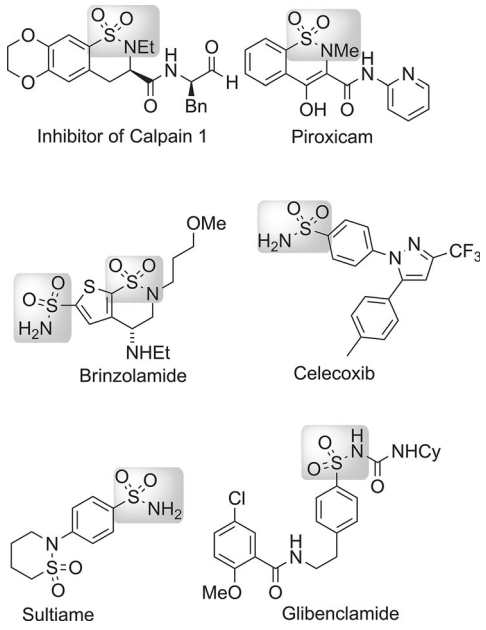
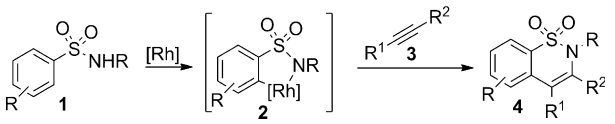


Figure 1. Drugs with a sultam and sulfonamide substructure motif.

are subject to facile deacylation, can be used as prodrugs.[3] Besides aryl sulfonamides, their cyclic analogues, benzosultams, play an important role given their broad biological activities.[4] Piroxicam and brinzolamide demonstrate the utility of annulated sultams.[5]

Reported methods for the synthesis of benzosultams are based on intramolecular cyclizations of elaborated precursors, thus requiring several reaction steps.[6] Intermolecular reactions are much rarer and need prefunctionalized starting materials such as *ortho*-halosulfonamides[7] or benzothiatriazine derivatives.[8] A direct intermolecular and efficient method starting from simple and widely available sulfonamides would not only enable a new set of accessible scaffolds, but also allow additional and late-stage modifications of existing compounds having biological properties.

The activation and subsequent functionalization of aromatic C–H bonds *ortho* to directing groups has evolved rapidly over the past years.[9] In this context, rhodium(III)-catalyzed reactions[10] using a wide range of carbonyl-derived directing groups such as benzamides,[11] acetanilides,[12] imines,[13] ketones,[14] and carboxylic acids[15] were reported, thus illustrating the utility of this reactivity concept. Despite their critical importance, aryl sulfonamides have, to the best of our knowledge, not been explored with rhodium catalysts. Very recently, a single report from Yu and co-workers described the use of perfluoroaryl-substituted sulfonamides as competent directing groups in palladium(II)-catalyzed reactions.[16] Herein, we report a rhodium(III)-catalyzed oxidative C–H activation of simple acylated sulfonamides (**1**) and subsequent addition of internal alkynes (**3**) to give access to the benzosultams **4** (Scheme 1).[17]



Scheme 1. Benzosultams by sulfonamide-directed C–H activations.

At first, we evaluated the influence of different substituents on the sulfonamide nitrogen atom (Table 1). While primary or N-alkylated sulfonamides were completely unreactive (entries 1 and 2), an N-acetyl group was best suited and gave the product **4aa** under optimized reaction conditions in 90% yield (entry 3). The trifluoroacetyl derivative is too labile and undergoes unproductive deacylation (entry 5). A bulky pivaloyl group shuts the reactivity completely down. The defined and highly soluble $[Cp^*Rh(OAc)_2]$ (**A**; $Cp^* = C_5Me_5$) catalyst[18,19] is advantageous compared to the commonly utilized $[\{Cp^*RhCl_2\}_2]$ precatalyst and its in situ alteration methods to give cationic or acetate containing species (entries 6 and 7). 1,2-Dichloroethane and *tert*-amyl alcohol are inferior to toluene as a solvent (entries 8 and 9). The classical Cu^I/Cu^{II} redox couple provides better yields than

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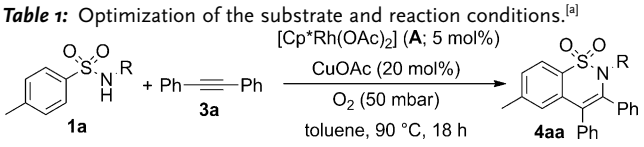
Table 1: Optimization of the substrate and reaction conditions.[a]

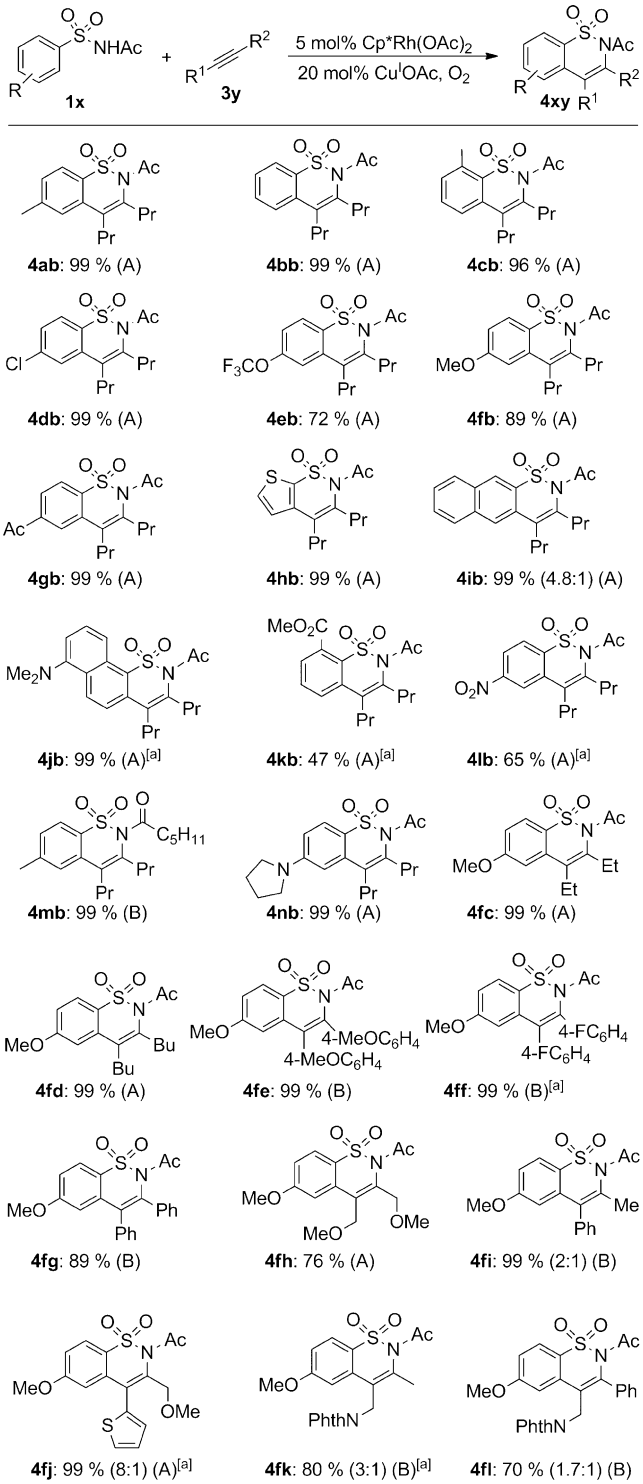


Entry	R	Changes from standard reaction conditions	Conv. [%][b]	Yield [%][b]
1	H	none	< 5	–
2	Bu	none	< 5	–
3	Ac	none	100	90[c]
4	Piv	none	< 5	–
5	Tfa	none	100	0[d]
6	Ac	2.5 mol% $[\{Cp^*RhCl_2\}_2]$ 10 mol% $AgSbF_6$ 40 mol% $Cu(OAc)_2\cdot H_2O$	8	8
7	Ac	2.5 mol% $[\{Cp^*RhCl_2\}_2]$ 2.5 equiv $Cu(OAc)_2\cdot H_2O$	54	54
8	Ac	tAmOH instead of toluene	34	34
9	Ac	DCE instead of toluene	43	43
10	Ac	20 mol% $Cu(OAc)_2\cdot H_2O$	75	52
11	Ac	2.5 equiv $Cu(OAc)_2\cdot H_2O$, no O_2	78	75
12	Ac	*t*BuOOH instead of O_2	13	7
13	Ac	$K_2S_2O_8$ instead of O_2	26	21
14	Ac	1 bar air instead of O_2	70	70
15	Ac	2 equiv AcOH	25	10
16	Ac	2 equiv CsOAc	100	0
17	Ac	2 equiv $NaHCO_3$	93	10

[a] Standard reaction conditions: **1a** (0.10 mmol), **3a** (0.125 mmol), $[Cp^*Rh(OAc)_2]$ (**A**; 5.0 μmol), $Cu^{I}OAc$ (20 μmol), toluene (for final concentration of 0.2 M), O_2 (50 mbar), 90 °C, 18 h. [b] Determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [c] Yield of isolated product. [d] Deacylation. Tfa = trifluoroacetyl

other oxidants such as $K_2S_2O_8$ or $tBuO_2H$ (entries 10–13). However, with stoichiometric as well as catalytic amounts of copper(II) acetate, the reaction stalls and does not go to completion. Closer examination showed that the reaction is sensitive to both free carboxylic acid and additional base (entries 15–17). Acetic acid leads to almost complete inhibition of the reaction. We presume that it stabilizes the complex **A** and that the initial displacement step of acetate from **A** by the substrate is not very favorable. Cesium acetate and sodium bicarbonate decompose **1a** by acetyl cleavage. Catalytic amounts of copper(I) acetate and molecular oxygen as a terminal oxidant minimize the amount of free acetic acid during this redox cycle and improves conversions and yields substantially.

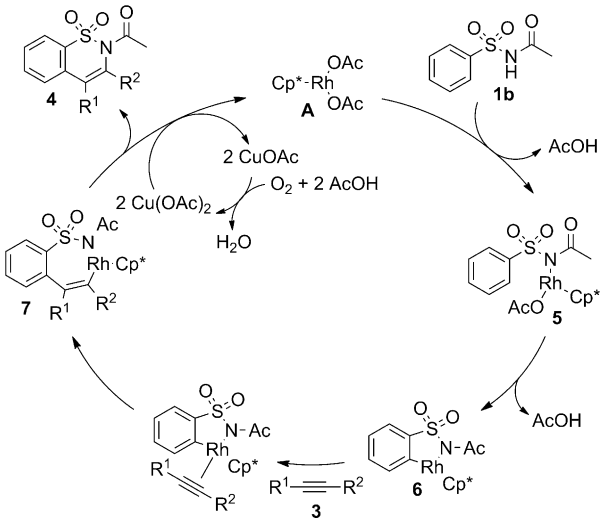
The scope of the reaction is outlined in Scheme 2. The reaction is tolerant of different substitutions on the aromatic substrate. In this respect, electron-rich or electron-poor substituents as well as *ortho* and *meta* substitution are accepted. Heterocycles and condensed aromatic substrates were tested and are compatible. Concerning the scope of the alkynes **3**, we found that the often reluctant dialkyl alkynes work very well when *tert*-amyl alcohol is used as the solvent instead of toluene. Unsymmetrical alkynes display moderate



Scheme 2. Scope of the sultam formation. Conditions A: **1** (0.10 mmol), *t*AmOH (for final concentration of 0.2 M), **3** (1.5 equiv), **A** (5 mol%), Cu(OAc) (20 mol%), 110 °C, 18 h; O_2 (50 mbar). Conditions B: **1** (0.10 mmol), toluene (for final concentration of 0.2 M), **3** (1.5 equiv), **A** (5 mol%), Cu(OAc) (20 mol%), 110 °C, 18 h; O_2 (50 mbar). All yields refer to pure isolated **4**. [a] Reaction performed with 2 × 5 mol% **A**, 40 mol% CuOAc, 0.1 M.

to good regioselectivities, which are somewhat dependent upon the alkyne concentration. Higher concentrations lower the regioselectivity.

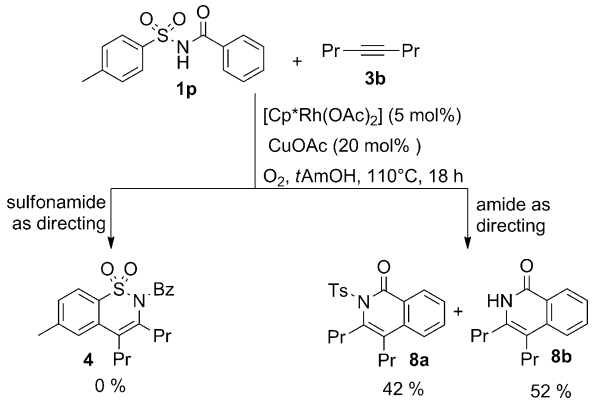
In analogy to amide directing groups, the catalytic cycle of the reaction is initiated by exchanging of one acetate ligands of $[Cp^*Rh(OAc)_2]$ with the an acetylsulfonamide substrate, thus leading to the intermediate **5** with the rhodium(III) bound to the directing group (Scheme 3). Subsequent cyclometalation by an acetate-assisted concerted metalation–deprotonation (CMD) pathway[20] and loss of a second molecule of acetic acid forms **6**. Association of the alkyne and migratory insertion would provide the rhodacycle **7**. Formation of the carbon–nitrogen bond by reductive elimination expels the product **4**. The concomitantly formed rhodium(I) species is oxidized by copper(II) acetate which in turn is reoxidized itself in a coupled cycle by molecular oxygen, thus not increasing the overall acidity of the reaction media.



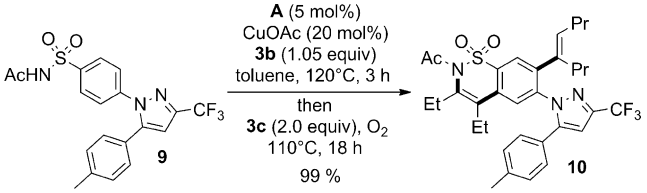
Scheme 3. Presumed catalytic cycle for the cyclization.

To rank the acyl sulfonamide in the context of the established carbonyl-based directing groups, an internal directing group competition of tosyl benzamide (**1p**) was undertaken. Under the established reaction conditions, an exclusive functionalization of the benzamide portion results, thus leading to a mixture of the quinolone **8a** and its detosylated congener **8b** (Scheme 4).[11k] This result confirms that sulfonamides have an attenuated directing group character which might be attributed to a different hybridization (sp^3-hybridized sulfur atom versus sp^2-hybridized carbon atom) and a less favorable alignment for the cyclometalation.

To further highlight the reported reactivity and the different directing group power, we chose to modify the acylated COX-2 inhibitor Celecoxib[21] (**9**) through sequential C–H activation modes (Scheme 5). The pyrazole group[22] exhibits a stronger directing group effect and reacts first. In contrast to previous reports, no stoichiometric amounts of $Cu(OAc)_2$ were required for high conversion in the alkyne hydroarylation reaction. It turned out that the reaction works best in the presence of catalytic amounts of CuOAc under anaerobic conditions.[24] When the first functionalization step is completed, 3-hexyne (**3c**) is added to the reaction mixture,



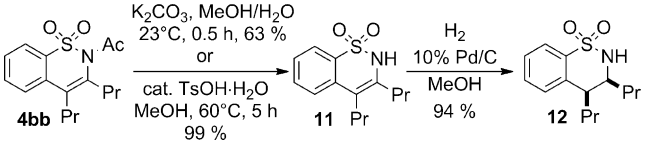
Scheme 4. Activation competition between sulfonamide and amide. Ts = 4-toluenesulfonyl.



Scheme 5. Consecutive C–H functionalizations of the COX-2 inhibitor Celecoxib.

and the nitrogen atmosphere replaced by oxygen, thus delivering the differentially functionalized Celecoxib derivative **10** in 99 % yield.

An advantage of the N-acyl sulfonamide directing group is its relative lability. As already observed as side reaction during the C–H functionalization, it can be removed very fast under mildly basic conditions or, alternatively, by using acid to give **11** (Scheme 6). The double bond of the ensulfonamide can be reduced by palladium-catalyzed hydrogenation to selectively give the saturated derivative **12** as the *cis* diastereomer.



Scheme 6. Deprotection and reduction of sultam **4bb**.

In conclusion, we have established acylated sulfonamides as suitable directing groups for rhodium(III)-catalyzed C–H bond activations. The cyclometalated intermediates readily react with a broad range of internal alkynes and open a rapid and general access to aryl sultams. The significance of aryl sulfonamides as well as aryl sultams as design elements in pharmacologically active substances should render this method attractive for synthetic and medicinal chemistry.

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[24] Omitting the copper source completely results in a very sluggish reaction. Non-oxidative conditions are crucial to limiting the reactivity to the hydroarylation.

Communications

Homogenous Catalysis

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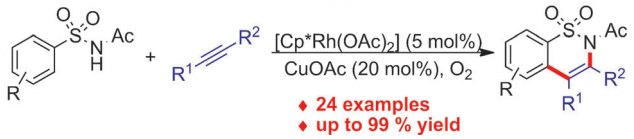
N. Cramer* _____ ■■■■–■■■■

Access to Sultams by Rhodium(III)-Catalyzed Directed C–H Activation



Director's cut: The pharmaceutically relevant sulfonamide group is shown to be a competent directing group for [Cp*Rh(OAc)$_2$]-catalyzed C–H functionalizations. Reactions of the cyclometalated intermediate with internal alkynes provide access to a wide range of sultam derivatives. The reaction is high yielding and works best under aerobic conditions with catalytic amounts of CuOAc as an oxidation mediator. Cp* = C_5Me_5.

