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COMMUNICATION

Rhodium(I)-Catalyzed Mono-Selective C–H Alkylation of Benzenesulfonamides with Terminal Alkenes

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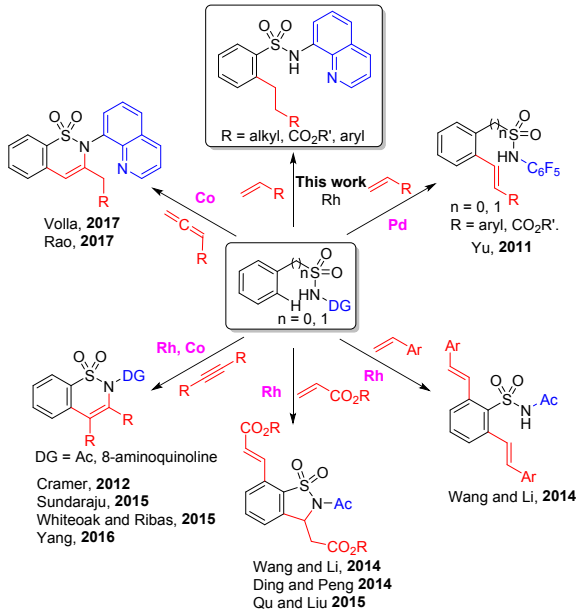
The Rh(I)-catalyzed *ortho*-alkylation of benzenesulfonamides with alkenes with the aid of an 8-aminoquinoline group is reported. The reaction is applicable to a variety of benzenesulfonamide derivatives and various alkenes. Curiously, unactivated 1-alkenes were more reactive than activated alkenes. Deuterium labeling experiments indicate that an unusual 1,2-H shift mechanism to generate a carbene rhodium intermediate is involved.

Sulfonamide derivatives are frequent components of the biologically active structural motifs due to their extensive chemical and biological activities as drugs, such as azosemide, celecoxib, and sulfamethoxazole.[1-3] In the family of sulfonamide derivatives, sultams also show high biological activities.[3] Because of this, various research groups have focused on the synthesis of sultams from sulfonamides via C–H activation.[4] In 2012, Cramer reported the Rh-catalyzed oxidative annulation of *N*-acylated benzenesulfonamides with internal alkynes to afford benzosultam derivatives (Scheme 1).[4a] Similarly, the Co-catalyzed synthesis of benzosultams from benzenesulfonamides and alkynes was independently reported by Sundararaju,[4b] Whiteoak and Ribas,[4c] and Yang.[4d] Recently, Volla[4e] and Rao[4f] independently reported the annulation of benzenesulfonamides with allenes to give sultam derivatives. However, the simple *ortho*-C–H functionalization of sulfonamides with alkenes has not been extensively explored.[5] To the best of our knowledge, only two examples of the *ortho*-C–H alkenylation of benzenesulfonamides have been reported to date. In 2011, Yu reported the Pd-catalyzed *ortho*-alkenylation of *N*-perfluoroaryl-substituted sulfonamides.[5a] A complementary report by Wang and Li described the $[RhCp^*Cl_2]_2$-catalyzed double *ortho*-alkenylation of sulfonamides,[5b] in which the authors showed that the double alkenylation product was formed only when styrene derivatives were used, whereas a simultaneous cyclization proceeded along with alkenylation in the case of α,β-unsaturated esters. Almost the same time, a similar transformation using α,β-unsaturated esters was reported by Ding and Peng.[5c] Mono-selective alkenylation reaction with α,β-unsaturated esters was reported when *ortho*-substituted benzenesulfonamides were used as a substrate.[5d] The reaction of benzenesulfonamides that contain no *ortho*-substitutient on the aryl ring consistently provided double C–H activated product. To the best of our knowledge, interms of alkylation C–H mono-alkylation of benzenesulfonamides with alkenes has not been explored. Thus, a much more selective C–H alkylation of sulfonamides would be highly desirable.



Scheme 1 Literature reports and this work on the C–H functionalization of benzenesulfonamides with unsaturated hydrocarbons.

In the growing field of chelation-assisted C–H functionalization,[6] we previously reported the Rh-catalyzed alkylation of aromatic carboxamides with various alkene coupling partners[7] by taking advantage of an 8-aminoquinoline moiety as a directing group, which was first introduced by Daugulis for Pd-catalyzed C–H arylation reactions.[8] We also recently reported the Rh-catalyzed C8-alkylation of naphthylamides with alkenes with the aid of a picolinamide moiety as a directing group.[9] Having a continuous interest in Rh-catalyzed C–H activation, and the difficulty in controlling the alkylation of sulfonamides prompted us to

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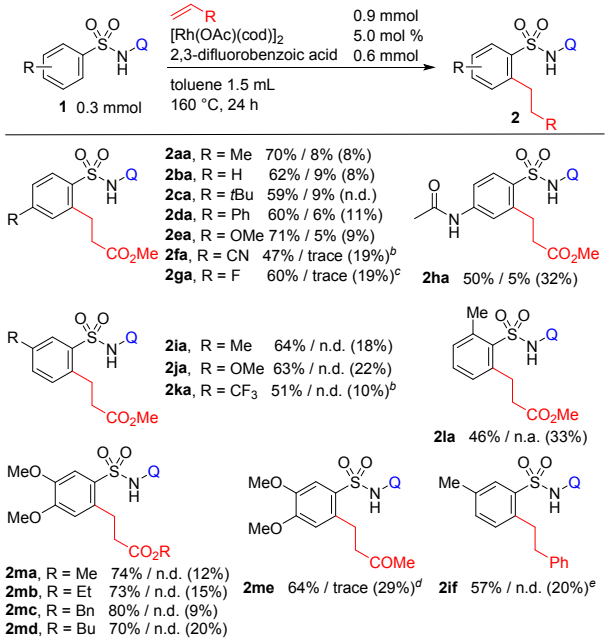
examine the mono-selective linear *ortho*-alkylation of benzenesulfonamides. Herein, we report the first example of the Rh(I)-catalyzed C–H alkylation of benzenesulfonamides with alkenes (Scheme 1). Curiously, it was found that the mechanism for the present reaction is different from that for C–H alkylation of carboxamides with alkenes.

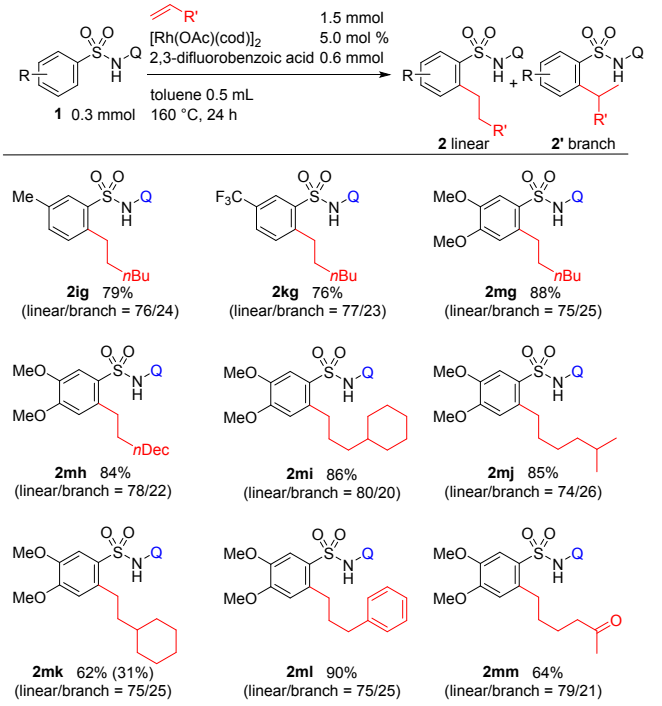
Table 1 Substrate scope for sulfonamides with activated alkenes[a]



[a]Isolated yield of alkylated product **2**/side product **3** (bis-alkylated product). Recovered starting materials are given in parentheses. [b]10 Mol % catalyst and 5 equiv of methyl acrylate were used. [c]Methyl acrylate (4 equiv) was used. [d]Methyl vinyl ketone (5 equiv) was used. [e]Styrene (4 equiv) and the acid additive (3 equiv) were used for 48 h; A mixture of alkylated and alkenylated product formed in a ratio of 86:14

We began our studies by investigating the reaction of the sulfonamide **1a** with methyl acrylate by varying the reaction parameters with the goal of selectively producing the mono-alkylation product **2aa** (see SI). After extensive screening we found that when **1a** was reacted with 3 equivalents of methyl acrylate in the presence of $[Rh(OAc)(cod)]_2$ (5.0 mol%) and 2,3-difluorobenzoic acid (2.0 equiv) at 160 °C for 24 h, the desired product **2aa** formed in 70% isolated yield along with the double C–H activated side product **3aa** in 8% yield (see SI). With the optimized reaction conditions in hand, the scope of the reaction of sulfonamide derivatives with methyl acrylate as a coupling partner was examined (Table 1). Benzenesulfonamide **1b** gave the product **2ba** in 62%, along with 9% of bis-alkylated product. *Para*-substituted benzenesulfonamides **1c-h** also afforded the desired products in moderate to good yields (47%-71%), along with traces of the double C–H activated side product. It should be noted that 4-acetamidobenezene sulfonamide **1h** selectively gave **2ha** with the acetamido group remaining intact. Particularly, electron-deficient sulfonamides, such as **1f** and **1g** showed poor reactivity under the optimized reaction conditions. Hence, the use of a higher catalyst loading and/or an excess amount of the alkene produced the desired products **2fa** and **2ga** in good yields. The reaction of *meta*-substituted aryl sulfonamides, **1i-k** with methyl acrylate selectively gave the corresponding mono-alkylation products **2ja**-**2ka** in which the alkylation took place only at the less-hindered C–H bond, irrespective of the electronic nature of the substituents. The *ortho*-substituted arylsulfonamide **1l** gave the alkylated product **2la** only in moderate yield (46% yield), which could be due to steric repulsion between the *ortho*-methyl group and the sulfonamide moiety. Therefore, mono-selective alkylation products were obtained in a high degree of selectivity in the case of *para*-substituted sulfonamides (**2aa**-**2ha**). The applicability of other alkenes for this C–H alkylation of sulfonamides were tested by using **1m** as a model substrate. Ethyl acrylate, benzyl acylate, and butyl acrylate all gave the desired products **2mb**-**md** in high yields. Even methyl vinyl ketone was reactive, giving a good yield of the alkylated product **2me**.[8c] However, when styrene was used, the corresponding alkylated product **2if** was formed in only a moderate yield, accompanied by the alkenylated product, in a ratio of 86:14.

Table 2 Substrate scope for sulfonamide with unactivated alkenes[a]

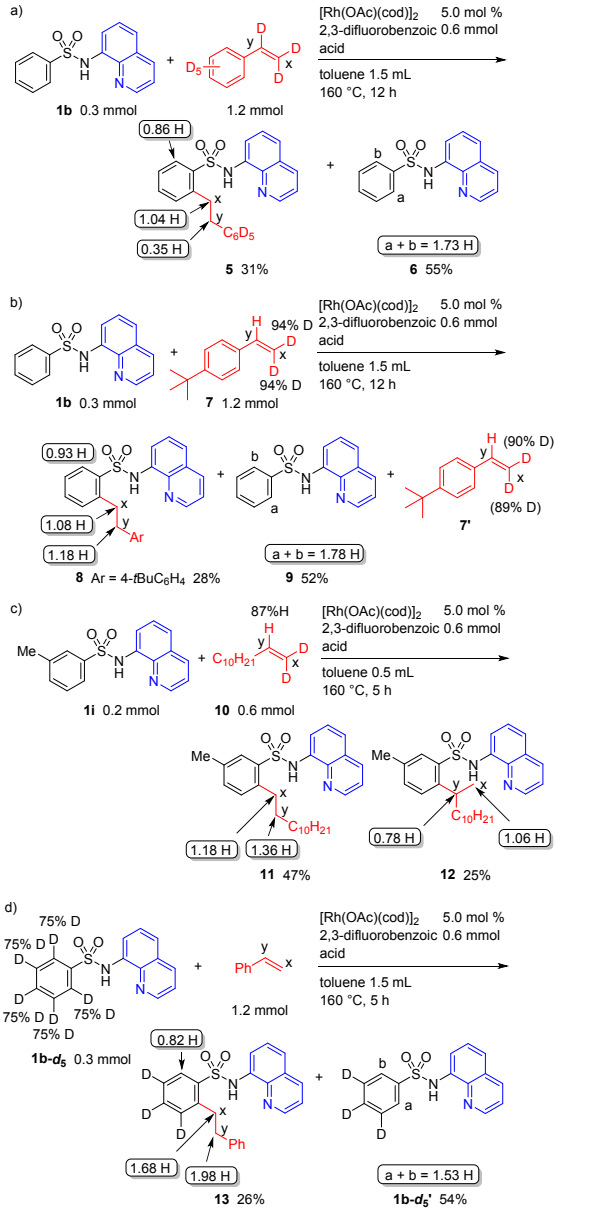


[a]Isolated yield of the product was given. The ratio of linear and branch isomer was calculated from a crude NMR and given in parentheses. Recovered starting material is given in parentheses.

Unactivated 1-alkenes also can be used as a coupling partner (Table 2). It is noteworthy that the reactivity of unactivated alkenes was even higher than that of acrylates and styrene. Sulfonamides **1i**, **1m**, and even the electron withdrawing group substituted sulfonamide **1k** reacted smoothly with 1-hexene to afford the products in very good yields. 1-Undecene, allylcyclohexane, 5-methylhex-1-ene, vinylcyclohexane, allylbenzene, and hex-5-en-2-one afforded the desired product **2mh**, **2mi**, **2mj**, **2mk**, **2ml**, and **2mm** respectively, in good to excellent yields.

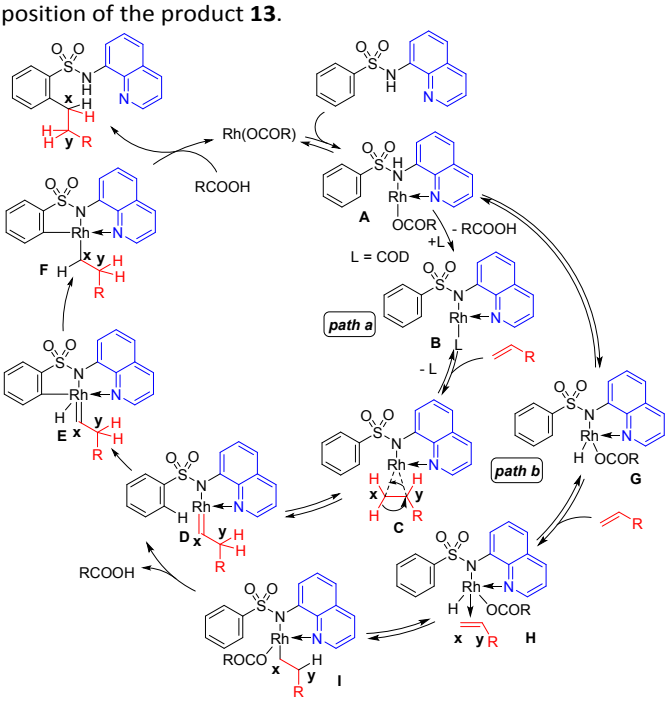
To gain the mechanistic insights into the alkylation reaction, deuterium labelling studies were carried out using deuterated alkenes (Scheme 2). In the reaction of sulfonamide **1b** with styrene-d_8, the product **5** was obtained, in which nearly one proton had been incorporated in the x-position of the product,

which may have originated from the *ortho*-C–H proton of sulfonamide (Scheme 2a). This result is consistent with our previous finding for Rh-catalyzed C–H alkylation reactions with alkenes.[6n,7c,7e,7g,9] However, in the y-position of product **5**, more D incorporation (1.65 D) was observed (0.35 H) than at the x-position, which would only be possible if the D atom had shifted from the x-position to the y-position.[7e]



Scheme 2 Deuterium labelling experiments.

To examine this observation further, deuterated styrene derivative **7** in which only the x-position is deuterated was used (Scheme 2b). The reaction of **1b** with **7** gave **8**, with the deuterium content at the y-position increased, clearly suggesting that a D atom had shifted from the x-position to the y-position. In the recovered starting materials **6** and **9**, D-incorporation was observed at the *ortho*-C–H bond, which indicates that the C–H activation step is reversible. In addition, only negligible H/D exchange was detected in the recovered alkene **7'**. Similarly, the alkylation reaction of **1i** with the x,x'-deuterated alkene **10** gave linear product **11**, in which, a significant amount of D-incorporation (0.64 D) was observed at y-position (1.36 H) in linear product **11** which indicates that the similar mechanism was followed even in unactivated 1-alkene system (Scheme 2c). To verify the incorporation of the *ortho*-C–H bond of the benzenesulfonamide to the x-position of the product, reactions of the deuterated sulfonamide **1b-*d*$_5$** with styrene were also performed (Scheme 2d). Although the D-content is low in the product because of the fast H/D exchange that occurred during the reaction at the *ortho*-position of the starting amide (see SI), a D atom was found only at the x-position of the product **13**.



Scheme 3 Plausible catalytic cycle

We proposed a possible reaction mechanism based on the above deuterium studies (Scheme 3). The first step involves the complexation between Rh(I) and a bidentate sulfonamide to form complex **A**, followed by the release of the carboxylic acid to give Rh complex **B** (path a).[10] Coordination of an alkene to **B** generates **C**, in which a 1,2-hydrogen shift from the x-position to the y-position proceeds to produce a rhodium carbene complex **D** (a shift of one of the deuterium atoms from the x-position to the y-position was observed, as shown in Scheme 2a-c).[11] Oxidative addition of the *ortho*-C–H bond to a Rh center in **D** gives the five-membered rhodacycle complex **E**, which undergoes a 1,2-hydride shift to afford complex **F**.[12,13] Reductive elimination followed by protonation gives the desired alkylated product with the regeneration of Rh(I). In Scheme 2a, the incorporation of a H atom (0.35H) at the y-position of the product **5** was observed. However, if the reactions were to proceed completely through path a, no H atom would be incorporated at the y-position. This result prompted us to consider the possibility that an alternative catalytic cycle is also operative (path b in Scheme 3),[7g,9] in which the oxidative addition of the N–H bond in **A** to a rhodium center proceeds to form the metallacyle **G**.[14] The coordination of an alkene to **G** followed by the insertion of an alkene into a H-Rh bond in **H** gives complex **I**. The successive release of the carboxylic acid from **I** generates the carbene intermediate **D**. The involvement of other minor path cannot rule out completely.

We report herein the first example of the Rh-catalyzed, mono-selective C–H alkylation of benzenesulfonamides with alkenes by taking advantage of a bidentate chelating system. Several alkenes, including acrylate esters, methyl vinyl ketone, styrene, and even unactivated 1-alkenes can be used as an alkylating coupling partner. Deuterium studies revealed that the reaction proceeds through an unusual catalytic cycle, in which a carbene intermediate appears to be generated along with a 1,2-hydrogen shift of the x-hydrogen of an alkene to the y-position, as evidenced by deuterium labelling experiments (Scheme 2a-c). Furthermore, to truly understand the unusual 1,2-H-shifting mechanism for this reaction, DFT studies along with further attempts to isolate reaction intermediates are ongoing in our laboratory.

Conflicts of interest

"There are no conflicts to declare".

Acknowledgements

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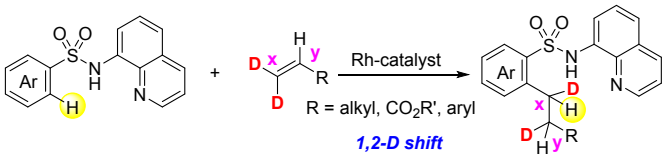

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