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## Rhodium(III)-Catalyzed Heteroannulations of 3-Sulfolene Derivatives via C(sp<sup>2</sup>)-H Activation. Access to Pyridine *ortho*-Quinodimethane Precursors

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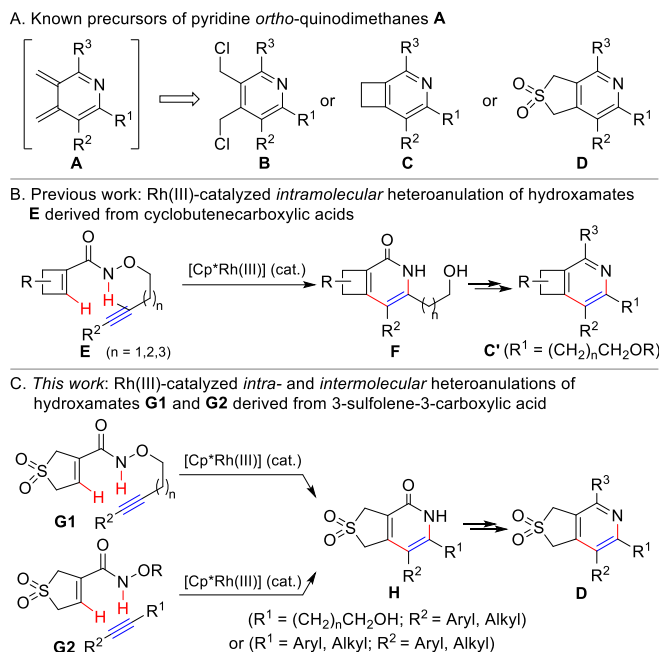
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**Abstract:** Hydroxamates derived from 3-sulfolene-3-carboxylic acid can be involved in intra- and intermolecular rhodium(III)-catalyzed heteroannulations with alkynes proceeding via C(sp<sup>2</sup>)-H bond activation. These transformations allow a straightforward access to diversely substituted pyridones, and to pyridines fused to a sulfolene ring after functional group transformations. Subsequent cheletropic elimination of sulfur dioxide can be achieved under microwave irradiation to generate pyridine *ortho*-quinodimethanes. These results demonstrate that the scope of rhodium(III)-catalyzed C(sp<sup>2</sup>)-H functionalizations can be extended to sulfolenes, a yet unexplored class of alkenes in these latter transformations, thereby affording access to valuable classes of heterocyclic products.

### Introduction

*Ortho*-quinodimethanes are useful reactive intermediates which can be generated *in situ* and involved in [4+2]-cycloadditions to construct complex polycyclic architectures.<sup>[1]</sup> By contrast, the heterocyclic analogs of *ortho*-quinodimethanes have so far found a more limited use in synthesis.<sup>[2-5]</sup> Considering the particular case of pyridine *ortho*-quinodimethanes which enable access to (tetrahydro)isoquinolines after [4+2]-cycloadditions, the generation of intermediates **A** has been usually achieved by reductive dehalogenation of 3,4-bis(chloromethyl)pyridines **B**,<sup>[3]</sup> by electrocyclic ring-opening of cyclobuta[*c*]pyridines **C**,<sup>[4]</sup> or by cheletropic elimination of sulfur dioxide from 1,3-dihydrothieno-[3,4-*c*]pyridine 2,2-dioxides **D**<sup>[5]</sup> (thereafter referred to as "pyridine-sulfolenes") (Scheme 1A). With the goal of developing efficient synthetic routes toward precursors of pyridine *ortho*-quinodimethanes **A**, the construction of the nitrogen heterocycle in compounds **C** and **D** by a transition metal-catalyzed heteroannulation, *via* C(sp<sup>2</sup>)-H activation, emerges as an attractive strategy.<sup>[6]</sup> In this context, we previously reported that *O*-( $\omega$ -alkynyl) hydroxamates **E**, derived from cyclobutene-carboxylic acids, undergo efficient intramolecular rhodium(III)-catalyzed heteroannulations leading to substituted cyclobuta[*c*]pyridones **F**. However, our efforts have so far been vain to implement intermolecular heteroannulations of cyclobutenyl hydroxamates with alkynes, thereby limiting the application of the method to the synthesis of cyclobuta[*c*]pyridines **C'** possessing an  $\omega$ -hydroxyalkyl chain at the  $\alpha$  position of the pyridine nitrogen atom (Scheme 1B).<sup>[7]</sup> To overcome this limitation, pyridine-sulfolenes **D** were targeted as alternative precursors of pyridine *ortho*-quinodimethanes **A**. Pyridine-sulfolenes **D** themselves also constitute interesting heterocyclic targets since the cyclic sulfone can behave as an isostere of the cyclopentane ring possessing both hydrogen bond acceptor and hydrophobic properties.<sup>[8,9]</sup> The preparation of pyridine-sulfolenes **D** has previously been achieved from functionalized pyridines **B** by treatment with sodium sulfide followed by oxidation of the resulting cyclic thioether to the sulfone.<sup>[5]</sup> Therefore, the possibility to construct the nitrogen heterocycle of pyridine-sulfolenes **D** by a transition metal-catalyzed heteroannulation

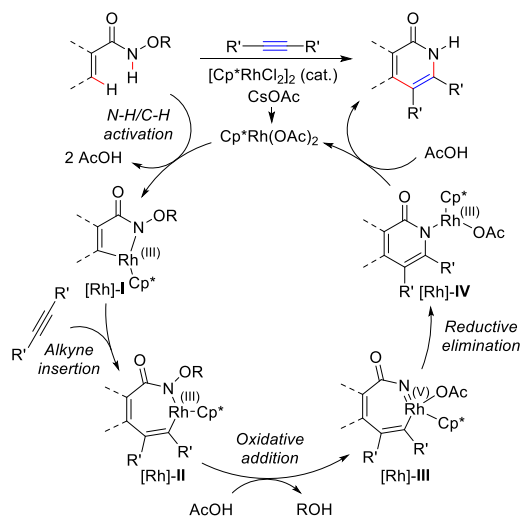
process from 3-sulfolene-3-carboxylic acid derivatives, a yet unexplored class of substrates in vinylic C(sp<sup>2</sup>)-H bonds functionalizations,<sup>[10]</sup> was deemed of interest. Herein, we report our results on the development of both intra- and intermolecular rhodium(III)-catalyzed hetero-annulations involving hydroxamates **G1** and **G2** derived from 3-sulfolene-3-carboxylic acid and their application to the synthesis of pyridone- and pyridine-sulfolenes, respectively **H** and **D**, for the subsequent generation of pyridine *ortho*-quinodimethanes **A** (Scheme 1C).



**Scheme 1.** Application of rhodium(III)-catalyzed heteroannulations to the synthesis of pyridine *ortho*-quinodimethane precursors.

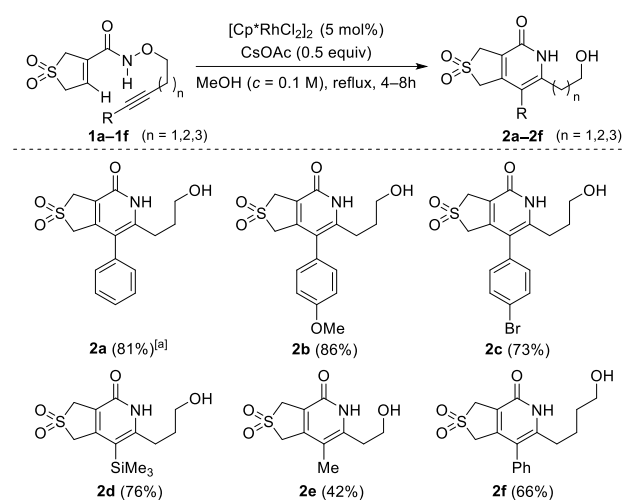
## Results and Discussion

The rhodium(III)-catalyzed oxidative heteroannulation of amides and hydroxamates with alkynes, proceeding *via* C(sp<sup>2</sup>)-H functionalization, constitutes a powerful synthetic tool to construct diversely substituted isoquinolones/pyridones.<sup>[11,12]</sup> In the case of hydroxamates, the N–O bond which is cleaved during the C–H bond activation/annulation process acts as an “internal” oxidant and allows access to heterocycles with a free N–H bond. Under classical conditions using [Cp\*RhCl<sub>2</sub>]<sub>2</sub> (cat.) and CsOAc, the *in situ* generated active catalyst Cp\*Rh(OAc)<sub>2</sub> undergoes ligand exchange with the substrate (N–H activation) and C–H activation occurs through a concerted metalation-deprotonation mechanism to generate [Rh]-I. After migratory insertion of the alkyne, the [Rh]-II complex evolves by oxidative addition of the N–O bond, assisted by AcOH, which leads to the imido-Rh(V) complex [Rh]-III. Reductive elimination and ligand exchange on [Rh]-IV, delivers the heterocyclic product and regenerates the active catalyst (Scheme 2).<sup>[11–13]</sup>



**Scheme 2.** General mechanism of the Rh(III)-catalyzed heteroannulation of hydroxamates with alkynes proceeding via C(sp<sup>2</sup>)-H activation.

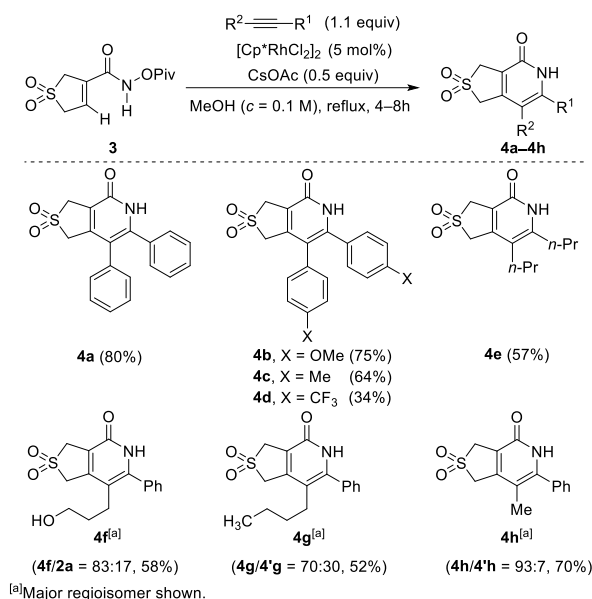
In the absence of any previous report on the involvement of 3-sulfolene-3-carboxylic acid derivatives in C(sp<sup>2</sup>)-H bond functionalizations, to our knowledge, and based on our previous experience with cyclobutenecarboxylic acid derivatives,<sup>[7]</sup> the feasibility of the rhodium(III)-catalyzed intramolecular heteroannulation of the O-(ω-alkynyl) hydroxamate derivatives<sup>[12c]</sup> was first investigated. The requisite substrates **1a-1f** were prepared by condensation of the readily available 3-sulfolene-3-carboxylic acid<sup>[14]</sup> with diversely substituted O-(ω-alkynyl) hydroxylamines. In the presence of [Cp\*RhCl<sub>2</sub>]<sub>2</sub> (5 mol%) and CsOAc (0.5 equiv) (MeOH, reflux, 4–8h), the intramolecular heteroannulation of sulfolenyl-hydroxamate **1a**, proceeding with vinylic C(sp<sup>2</sup>)-H and N-H bonds functionalization and concomitant N-O bond cleavage (redox-neutral process),<sup>[12]</sup> afforded the desired sulfolenyl-pyridone **2a** in 81% yield. Pyridones **2b** (86%) and **2c** (73%), possessing a methoxy group or a bromine atom at the *para* position of the aromatic ring, were both obtained in good yields. The triple bond in the starting hydroxamate could be substituted by a trimethylsilyl substituent or a methyl group, as illustrated with the formation of sulfolene-pyridones **2d** (76%) and **2e** (42%). The lower isolated yield of **2e** was ascribed to its low solubility in usual organic solvents and not to the shorter tether between the oxygen atom and the triple bond compared to substrates **1a-1d**. The intramolecular hetero-annulation of **1f**, in which the length of the tether was increased by one methylene unit compared to **1a**, delivered pyridone **2f** possessing a 4-hydroxybutyl chain in 66% yield (Scheme 3).



<sup>[a]</sup> Experiment carried out at 1.8 mmol scale.

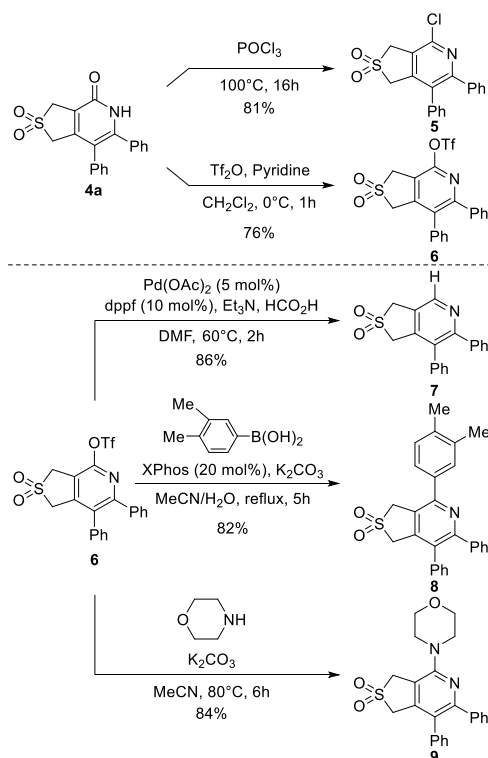
**Scheme 3.** Rhodium(III)-catalyzed intramolecular heteroannulation of hydroxamates **1a-1f** derived from 3-sulfolene-3-carboxylic acid.

The feasibility of the intermolecular heteroannulation was then evaluated. The known high reactivity of O-pivaloyl hydroxamates in redox-neutral heteroannulations proceeding via C(sp<sup>2</sup>)-H activation,<sup>[12a,b]</sup> led us to select substrate **3** which was treated with a slight excess of diphenylacetylene (1.1 equiv) in the presence of [Cp\*RhCl<sub>2</sub>]<sub>2</sub> (5 mol%) and CsOAc (0.5 equiv) (MeOH, reflux). The intermolecular heteroannulation proceeded smoothly and delivered the desired sulfolene-pyridone **4a** in 80% isolated yield (Scheme 4). Thus, intra- and intermolecular rhodium(III)-catalyzed heteroannulations of sulfolenyl hydroxamates could be achieved under equally mild conditions which are compatible with the sulfolene ring and do not trigger extrusion of SO<sub>2</sub>.<sup>[9]</sup> The scope of the intermolecular version was explored with substrate **3** and different alkynes. As previously observed in similar transformations,<sup>[11,12]</sup> tolanes bearing electron-donating substituents at the *para* position of the aromatic group were more reactive partners than those possessing an electron-withdrawing group, as reflected by the isolated yields of sulfolene-pyridones **4b** (75%) and **4c** (64%), compared to **4d** (34%). A symmetrical alkyne substituted by alkyl groups such as 4-octyne was also tolerated and delivered pyridone **4e** (57%). Unsymmetrical alkynes bearing a phenyl and an alkyl group were screened as partners and, in agreement with previous reports, the major isomers were those in which the aromatic ring is preferentially located at the adjacent position of the nitrogen atom.<sup>[11,12]</sup> A moderate regiocontrol was observed for 5-phenylpen-4-yn-1-ol which led to a 83:17 mixture of sulfolene-pyridones **4f** and **2a** (58%). The minor regioisomer **2a** corresponds to the one arising from the intramolecular heteroannulation of **1a**, thereby illustrating the complementary regioselectivities of the intra- and intermolecular heteroannulations.<sup>[12c]</sup> With 1-phenyl-1-hexyne as partner, a mixture of sulfolene-pyridones **4g/4'g** (52%) was formed with a lower regiocontrol (**4g/4'g** = 70:30) than in the previous example. A much better regioselectivity was observed with 1-phenyl-1-propyne, possessing the less hindered methyl group on the alkyne, which produced sulfolene-pyridones **4h/4'h** (**4h/4'h** = 93:7) in 70% yield (Scheme 4).



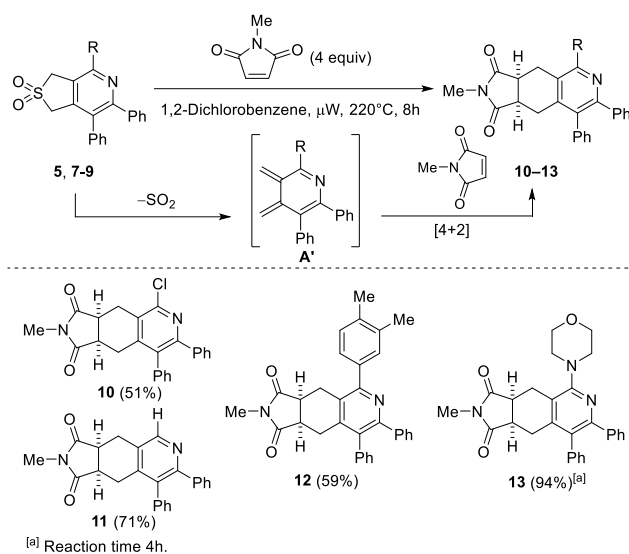
**Scheme 4.** Rhodium(III)-catalyzed intermolecular heteroannulation of hydroxamate **3** with different alkynes. Piv = CO<sub>t</sub>-Bu.

Sulfolene-pyridone **4a** was then selected as substrate to investigate the access to diversely substituted sulfolene-pyridines. Heating pyridone **4a** in neat POCl<sub>3</sub> (100°C, 6h) led to sulfolene-chloropyridine **5** in 81% yield. Treatment of **4a** with triflic anhydride in the presence of pyridine produced triflate **6** (76%) which was used as a platform compound to access other sulfolene-pyridines. Reductive cleavage of the C–O bond in **6** was achieved under palladium-catalyzed conditions, in the presence of triethylammonium formate as the reducing agent,<sup>[15]</sup> to provide tetrasubstituted pyridine **7** (86%). Heteroaromatic triflate **6** was also involved in a Suzuki-Miyaura cross-coupling with 3,4-dimethylphenylboronic acid, using XPhos as the ligand,<sup>[16]</sup> to produce the highly substituted sulfolene-pyridine **8** (82%). A nucleophilic aromatic substitution of **6** with morpholine afforded the sulfolene-aminopyridine **9** in 84% yield (Scheme 5).



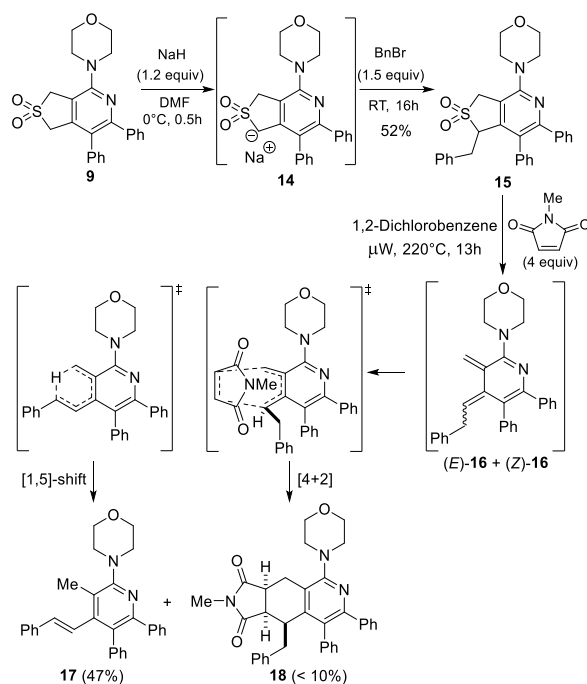
**Scheme 5.** Synthesis of sulfolene-pyridines **5–9** from pyridone **4a**. Tf = CF<sub>3</sub>SO<sub>2</sub>, DMF = HCONMe<sub>2</sub>, dppf = 1,1-bis-(diphenylphosphino)ferrocene, XPhos = 2-(dicyclohexylphosphino)-2',4',6'-triisopropyl-1,1'-biphenyl.

The cheletropic elimination of sulfur dioxide from pyridine-sulfolenes of type **D** has been previously reported and achieved by thermolysis in decalin at 250°C.<sup>[5]</sup> In the case of sulfolene-pyridines **5**, **7–9**, this operation was conveniently achieved by heating in 1,2-dichlorobenzene at 220°C, under microwave irradiation, in the presence of an excess of *N*-methylmaleimide (4 equiv). Under these conditions, the *in situ* generated pyridine *ortho*-quinodimethanes **A'** underwent [4+2]-cycloaddition with *N*-methylmaleimide leading to the corresponding tricyclic compounds **10–13** (51–94%) (Scheme 6). Tetrahydroisoquinoline **10**, which is derived from the chloropyridine substrate **5**, was isolated with the lowest yield (51%) among the four tricyclic adducts **10–13** synthesized. Replacing the electron-withdrawing chlorine atom by a hydrogen atom resulted in an improved yield of the tricyclic adduct **11** (71%) from the corresponding substrate **7**. Only a marginal improvement of the yield was noted in the case of **12** (59%) possessing the 3,4-dimethylphenyl substituent. By contrast, the presence of a strongly electron-releasing amino substituent had a tremendous impact on the yield of the corresponding tricyclic adduct **13** (94%) but also on the efficiency of the whole process which was complete after 4h at 220°C. In the case of substrate **9**, the mesomeric-donor amino substituent probably contributes to the stabilization of the *ortho*-quinodimethane intermediate thereby compensating, to some extent, the loss of aromaticity associated with the formation of these latter reactive species (Scheme 6).



**Scheme 6.** Generation of pyridine *ortho*-quinodimethanes from pyridines **5**, **7–9** and [4+2]-cycloaddition with *N*-methylmaleimide leading to tricyclic compounds **10–13**.  $\mu\text{W}$  = microwave irradiation.

Taking advantage of the acidity of the protons adjacent to the sulfonyl group, a substituent can be introduced on the five-membered ring of pyridine-sulfolenes **D**. When compound **9** was treated with NaH and benzyl bromide (DMF, 0°C to RT, 16h), an alkylation took place leading to sulfolene-pyridine **15** (52%) as a single regioisomer, in agreement with previous literature results.<sup>[5]</sup> Indeed, deprotonation of substrate **9** by the base preferentially leads to the sulfonyl carbanion **14** which is best stabilized by resonance (with charge delocalization up to the nitrogen bond of the pyridine nucleus). When sulfolene-pyridine **15** was heated at 220°C under microwave irradiation in the presence of an excess of *N*-methylmaleimide, a mixture of two compounds **17** and **18** was formed. The pentasubstituted pyridine **17**, possessing a (*E*)-styryl group, was identified as the major product and isolated in 47% yield. The tricyclic compound **18** expected from the Diels-Alder reaction was formed as a minor product (< 10%) albeit as a single diastereomer. Thermal extrusion of SO<sub>2</sub> from sulfolene **15** can potentially generate the corresponding isomeric *ortho*-quinodimethanes (*E*)-**16** and (*Z*)-**16**. In the ring-opening of structurally related benzocyclobutenes,<sup>[7,17]</sup> an electron-donating substituent such as the benzyl group prefers an outward mode of rotation and the (*E*)-*ortho*-quinodimethane is observed. In the case of the cheletropic elimination of SO<sub>2</sub> from substrate **15**, a similar preference may however be counteracted by the steric interaction between the benzyl group and the phenyl substituent at the heteroaromatic *peri* position. The *ortho*-quinodimethane (*Z*)-**16** would evolve by a [1,5]-hydrogen shift and generate the pentasubstituted pyridine **17**.<sup>[5]</sup> An *endo* selective Diels-Alder cycloaddition between *ortho*-quinodimethane (*E*)-**16** and *N*-methylmaleimide would account for the formation of the minor tricyclic compound **18** (Scheme 7).



**Scheme 7.** Alkylation of sulfolene **9** and cheletropic elimination of sulfur dioxide from sulfolene-pyridine **15**.

## Conclusion

In summary, hydroxamates derived from 3-sulfolene-3-carboxylic acid were identified as a new class of substrates in both intra- and intermolecular rhodium(III)-catalyzed oxidative heteroannulations with alkynes. These transformations, which proceed under mild conditions, are compatible with the sulfolene moiety and provide a convenient access to diversely substituted sulfolene-pyridones. Their transformation into polysubstituted sulfolene-pyridines was readily achieved by simple derivatization reactions and subsequent generation of pyridine *ortho*-quinodimethanes by cheletropic extrusion of sulfur dioxide was conveniently triggered by heating under microwave irradiation. These results have paved the way for further developments including the search for alternative catalytic systems to effect similar and other heteroannulations involving sulfolene derivatives.

**Keywords:** Annulation • C–H activation • Pyridines • Rhodium • Sulfur heterocycles

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