Advanced Synthesis & Catalysis

Accepted Article

Title: Rh(III)-Catalyzed Aldehydic C–H Functionalization Reaction between Salicylaldehydes and Sulfoxonium Ylides

Authors: Guo-Dong Xu, Kenneth Huang, and Zhi-Zhen Huang

To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201900276

Link to VoR: http://dx.doi.org/10.1002/adsc.201900276

10.1002/adsc.201900276

COMMUNICATION

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Rh(III)-Catalyzed Aldehydic C–H Functionalization Reaction between Salicylaldehydes and Sulfoxonium Ylides

Guo-Dong Xu,[a] Kenneth L. Huang,[b] and Zhi-Zhen Huang*,[a]

[a] Department of Chemistry, Zhejiang University, Hangzhou 310058, P.R. China
E-mail: huangzhizhen@zju.edu.cn
[b] School of Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta, GA 30332, USA

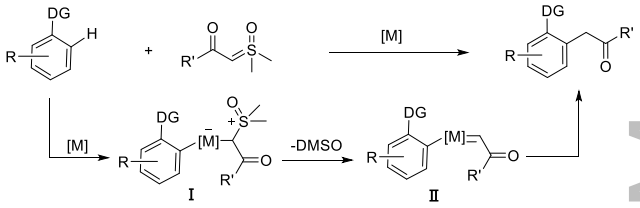
Received: ((will be filled in by the editorial staff))

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

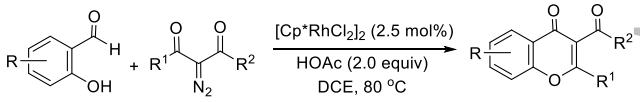
Abstract: A novel aldehydic C-H functionalization reaction between salicylaldehydes and sulfoxonium ylides has been developed under rhodium(III) catalysis, affording coupling products in moderate to good yields. A plausible mechanism involving aldehydic C(sp^2)-H activation by rhodium(III) and rhodium(III) catalyzed carbene insertion is also proposed. It was also found that the aldehydic C-H functionalization followed by dehydrative cyclization was able to produce flavonoids in one-pot.

Keywords: aldehydic C-H activation; rhodium(III) catalyzed; salicylaldehydes; sulfoxonium ylides; carbene insertion

Over the past decades, transition-metal-catalyzed C-H activations following by migration insertions of metal carbenes resulted from carbene precursors have been emerged as a powerful strategy for the formations of carbon-carbon bonds.[1] Among the employed carbene precursors, diazo compounds are used most widely. Later sulfoxonium and sulfonium ylides are found to be good carbene precursors, which are safer than diazo compounds.[2,3] Recently, sulfoxonium ylides as carbene precursors were applied into C-H functionalization under the catalysis of Rh(III),[3a-p] Ru(II),[3q-r] and Co(III)[3s] (Scheme 1). For example, in 2017, Aïssa et al. reported that under rhodium(III) catalysis, a cross-coupling reaction between *α*-carbonyl sulfoxonium ylides and aromatic C-H bonds in 2-arylpyridines performed smoothly to give corresponding *α*-arylated ketones.[3a] On the other hand, among various C-H functionalizations, aldehydic C-H functionalizations are becoming an important strategy in constructing carbon-carbon bonds.[4] However, the study on the aldehydic C-H functionalizations through insertions of metal carbenes is rarely disclosed.[5] In 2016, Yao and co-workers disclosed a Rh(III)-catalyzed annulation between salicylaldehydes and diazo compounds to give chromone derivatives (Scheme 2).[5a] To the best of our knowledge, the report on an aldehydic C-H functionalization reaction using a sulfoxonium or sulfonium ylide as a carbene precursor remains unknown so far. Thus, we carried out the investigation on aldehydic C-H functionalization reaction between salicylaldehydes and sulfoxonium ylides under rhodium(III) catalysis.



Scheme 1. C-H Functionalization Using Sulfoxonium Ylides as Carbene Precursors.



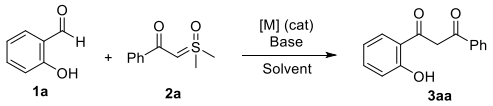
Scheme 2. Yao's Work on Aldehydic C-H Functionalization with Diazo Compounds.

Initially, the exploration and optimization of an aldehydic C-H functionalization reaction of salicylaldehyde **1a** with sulfoxonium ylide **2a** was carried out. When $[RhCp^*(MeCN)_3](SbF_6)_2$ (2.5 mol %) and NaOAc were employed as a transition-metal catalyst and a base respectively, we were pleased to find that the C-H functionalization reaction occured in DCE at 90 °C, affording the desired coupling product **3aa** in a yield of 67% (entry 1, Table 1). Using $[Cp^*RhCl_2]_2$ instead of $[RhCp^*(MeCN)_3](SbF_6)_2$ resulted in the increase of the yield to 90% (entry 2, Table 1). The other transition-metal catalysts, such as $[Cp^*IrCl_2]_2$, $Pd(OAc)_2$ and $[Ru(p\text{-cymene})Cl_2]_2$ were probed as well. The experimental results indicated that they

10.1002/adsc.201900276

were less effective than $[Cp^*RhCl_2]_2$ (compare entry 1 with entries 2-5, Table 1; also see the supporting information (SI)). When $[Cp^*RhCl_2]_2/AgSbF_6$ was employed as a catalyst system, **3aa** was obtained in a low yield (entry 6, Table 1). Using NaOEt, CsOAc or Ag_2CO_3 as bases led to lower yields as compared to NaOAc (compare entry 2 with entries 7-9, Table 1; also see the SI). When other solvents such as ethyl acetate, MeCN, toluene or dioxane were used instead of DCE, the yields of **3aa** were decreased remarkabley (entries 12-14, Table 1; also see SI). Thus, it can be concluded that the optimized reaction should be performed under the catalysis of $[Cp^*RhCl_2]_2$ (2.5 mol %) in the presence of NaOAc (2.0 equiv.) at 90 °C in DCE.

Table 1. Optimization of the Aldehydic C-H Functionalization Reaction between Salicylaldehyde **1a** and Sulfoxonium Ylide **2a**.[a]

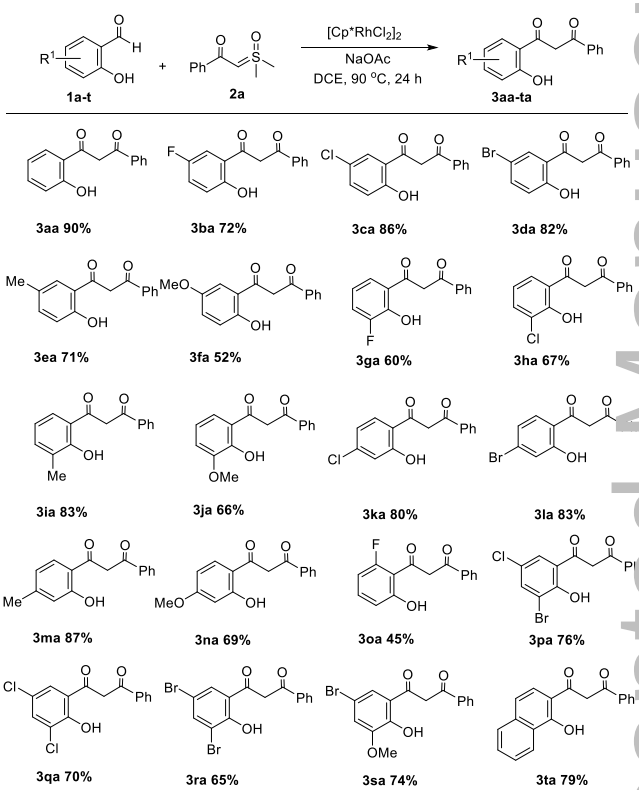


Entry	[M]	Base	Solvent	Yield(%)[b]
1	$[Cp^*Rh(MeCN)_3](SbF_6)_2$	NaOAc	DCE	67
2	$[Cp^*RhCl_2]_2$	NaOAc	DCE	90
3	$[Cp^*IrCl_2]_2$	NaOAc	DCE	0
4	[Ru(*p*-cymene)Cl_2]$_2$	NaOAc	DCE	0
5	$Pd(OAc)_2$[c]	NaOAc	DCE	0
6	$[Cp^*RhCl_2]_2/AgSbF_6$[d]	NaOAc	DCE	40
7	$[Cp^*RhCl_2]_2$	NaOEt	DCE	0
8	$[Cp^*RhCl_2]_2$	CsOAc	DCE	80
9	$[Cp^*RhCl_2]_2$	Ag_2CO_3	DCE	61
10	$[Cp^*RhCl_2]_2$	--	DCE	0
11	--	NaOAc	DCE	0
12	$[Cp^*RhCl_2]_2$	NaOAc	ethyl acetate	68
13	$[Cp^*RhCl_2]_2$	NaOAc	MeCN	28
14	$[Cp^*RhCl_2]_2$	NaOAc	dioxane	0

[a] Reaction conditions: **1a** (0.10 mmol), **2a** (0.12 mmol), [M] (2.5 mol %), base (2.0 equiv.), solvent (2.0 mL), 90 °C, for 24 h in a sealed tube. [b] Isolated yields. [c] $Pd(OAc)_2$ (10 mol %). [d] $AgSbF_6$ (10 mol %).

With the optimized conditions in the hand, the scope of salicylaldehydes **1** in the aldehydic C-H functionalization reaction was investigated. We found that a series of salicylaldehydes **1a-s** were able to undergo the reaction with sulfoxonium ylide **2a** to give the corresponding coupling products **3aa-sa** in moderate to good yields (Table 2). In view of the yields of **3ba-fa**, the salicylaldehydes **1b-d** bearing electron-withdrawing groups at the 5-position of benzene rings seem to be more beneficial to the reaction as compared to those **1e-f** bearing electron-donating groups at the 5-position of benzene rings. No matter substituents are at the 3-position of benzene salicylaldehydes **1g-j** or at the 4-position of benzene rings in salicylaldehydes **1k-n**, no matter they are electron-withdrawing groups or electron-donating groups, the reaction proceeded smoothly to afford the corresponding coupling products **3ga-ja** or **3ka-na** in satisfactory yields. However, 4-nitro substituted salicylaldehyde led to a poor yield (20%) of corresponding product. Salicylaldehydes **1p-r** bearing two electron-withdrawing groups also performed the coupling reaction well with sulfoxonium ylide **2a** to give the desired products **3pa-ra** in satisfactory yields. 1-Hydroxy-2-naphthaldehyde **1t** as an expansion of aromatic counterparts from salicylaldehydes also undergo the reaction expediently to afford **3ta** in a 79% yield.

Table 2. The Scope of Salicylaldehydes **1** in the Aldehydic C-H Functionalization Reaction with Sulfoxonium Ylide **2a**.[a]

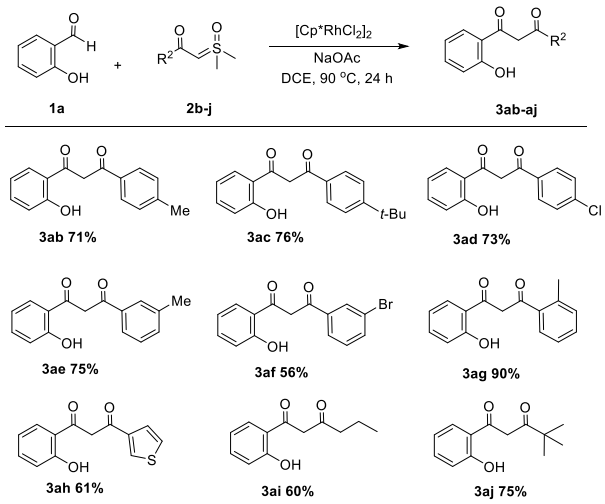


[a] Reaction conditions: **1a** (0.10 mmol), **2** (0.12 mmol), $[Cp^*RhCl_2]_2$ (2.5 mmol %), NaOAc (2.0 equiv.), DCE (2.0 mL), 90 °C, for 24 h. Isolated yields.

After various salicylaldehydes **1a-s** were examined in the C-H functionalization reaction, the scope of sulfoxonium ylides **2** was also studied (Table 3). It was found that under rhodium(III) catalysis, diverse sulfoxonium ylides **2b-j** were able to undergo the aldehydic C-H functionalization reaction expediently with salicylaldehyde **1a** in the presence of sodium acetate under the optimized conditions. The sulfoxonium ylides **2b-g** bearing either electron-donating groups or electron-withdrawing groups on benzene rings resulted in the desired coupling

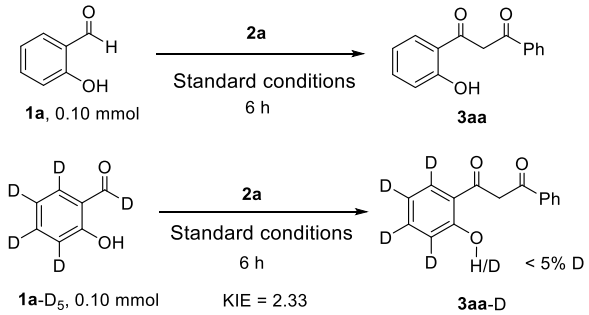
products **3ab-ag** with up to 90% yield. When the phenyl group in sulfoxonium ylide **2a** were switched to thienyl or alkyl group, the reaction still performed smoothly to give the corresponding product **3ah** or **3ai-aj** respectively.

Table 3. The Scope of Sulfoxonium Ylides **2** in the Aldehydic C-H Functionalization Reaction with Salicylaldehyde **1a**. [a]



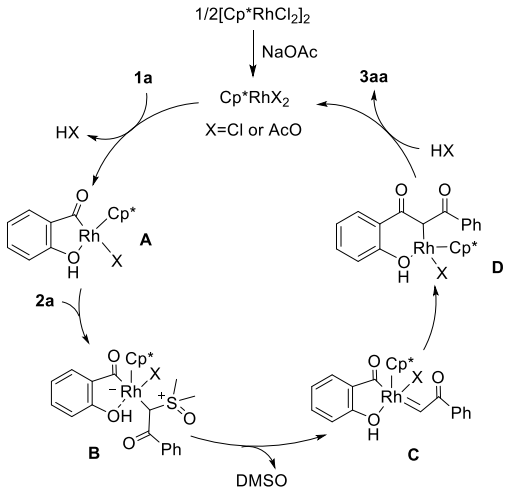
[a] Reaction conditions: **1a** (0.10 mmol), **2** (0.12 mmol), $[Cp^*RhCl_2]_2$ (2.5 mmol %), NaOAc (2.0 equiv.), DCE (2.0 mL), 90 °C, for 24 h. Isolated yields.

To gain insight into the mechanistic pathway of the aldehydic C-H functionalization reaction, a kinetic isotopic experiment was conducted under the standard conditions. Two parallel reactions using equimolar amounts of salicylaldehyde **1a** and deuterated salicylaldehyde **1a**-D_5 were performed respectively (Scheme 3). The value of the kinetic isotope effect (KIE) is 2.33, and the KIE result suggests that the aldehydic C(sp^2)-H functionalization may be a rate-determining step in the coupling reaction.



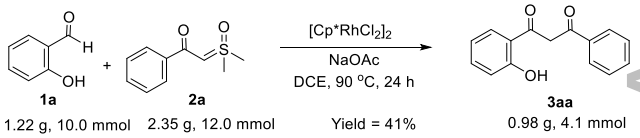
Scheme 3. Kinetic Isotope Effect Study

On the basis of precedent literatures,[3e,5a] a plausible mechanism for the reaction between salicylaldehyde **1a** and sulfoxonium ylide **2a** is proposed as shown in Scheme 4. First, under the direction of hydroxyl group, $[Cp^*RhX_2]$ activates the C(sp^2)-H bond of aldehydic group in salicylaldehyde **1a** to form a five-membered rhodacyclic intermediate **A**. Next, sulfoxonium ylide **2a** reacts with the rhodacycle intermidiate **A** to form a betaine intermediate **B**. DMSO breaking away from the intermidiate **B** leads to rhodium(III) carbene species **C**. Then, a migratory insertion of carbene group into the C(sp^2)-Rh bond in the intermidiate **C** affords a six-membered rhodacycle intermediate **D**. Finally, protonolysis of the intermediate **D** results in the coupling product **3aa** with regenerating active $[Cp^*RhX_2]$.



Scheme 4. Plausible Mechanism for the Aldehydic C-H Functionalization Reaction.

To demonstrate the scalability and practicality of the aldehydic C-H functionalization reaction, a gram-scale reaction was performed under rhodium(III) catalysis. The exprimental result shew that the reaction of salicylaldehyde **1a** (1.22 g) with sulfoxonium ylide **2a** (2.35 g) proceeded readily to give the desired coupling product **3aa** (0.96 g) under the optimized conditions (Scheme 5).

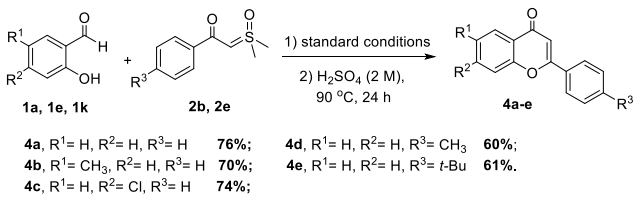


Scheme 5. The Aldehydic C-H Functionalization Reaction on a Gram-Scale

The coupling products **3** in this work are important building blocks for the synthesis of flavonoids. So we performed the aldehydic C-H functionalization reaction followed by intramolecular cyclization in one-pot. After the reaction of salicylaldehydes **1a**, **1e**,

10.1002/adsc.201900276

or **1k** with sulfoxonium ylides **2b**, or **2e** finished under the above standard conditions, it was found that a successive dehydration for an intramolecular cyclization could be performed smoothly at the same temperature by adding aqueous sulfuric acid, affording corresponding flavonoids **4a-e** in satisfactory yields respectively (Scheme 6).



Scheme 6. Aldehydic C–H Functionalization Followed by Dehydrative Cyclization for the Synthesis of Flavonoids in One-pot.

In conclusion, we have developed an aldehydic C-H functionalization reaction of salicylaldehydes **1** with sulfoxonium ylides **2** by rhodium(III) catalysis and in the presence of sodium acetate. It was found that various functional groups in salicylaldehydes **1** and sulfoxonium ylides **2** are compatible with the reaction, affording corresponding coupling products **3** in moderate to good yields. A plausible mechanism involving aldehydic C(sp^2)-H activation by rhodium(III) and rhodium(III)-catalyzed carbene insertion is also proposed. Moreover, salicylaldehydes **1** and sulfoxonium ylides **2** were able to undergo the C-H functionalization followed by dehydrative cyclization in one-pot to produce corresponding flavonoids **4**.

Experimental Section

General procedure for the aldehydic C-H functionalization reaction: The reaction mixture of salicylaldehyde **1** (0.10 mmol), sulfoxonium ylide **2** (0.12 mmol), $[Cp^*RhCl_2]_2$ (1.5 mg, 0.0025 mmol, 2.5 mol %) and NaOAc (16.4 mg, 0.20 mmol) in DCE (2.0 mL) was stirred at 90 °C for 24 h. Then, the mixture was evaporated under reduced pressure, and the residue was purified by column chromatography (silica gel, ethyl acetate/ petroleum ether = 1/20 as eluent) to give desired coupling product **3**.

Acknowledgements

The financial support from National Natural Science Foundation of China (No. 21372195) is gratefully acknowledged.

References

[1] Some reviews on C-H functionalizations by metal carbene insertions: a) H. M. L. Davies, R. E. J. Beckwith, *Chem. Rev*. **2003**, *103*, 2861-2903; b) H. M. L. Davies, J. R. Manning, *Nature* **2008**, *451*, 417-424; c) Z. Liu, J. Wang, *J. Org. Chem.* **2013**, *78*, 10024-10030; d) A. Caballero, M. M. Díaz-Requejo, M. R. Fructos, A. Olmos, J. Urbano, P. J. Pérez, *Dalton Trans.* **2015**, *44*, 20295-20307; e) F. Hu, Y. Xia, C. Ma, Y. Zhang, J. Wang, *Chem. Commun.* **2015**, *51*, 7986-7995.

[2] a) A. C. B. Burtoloso, R. M. P. Dias, I. A. Leonarczyk, *Eur. J. Org. Chem.* **2013**, 5005-5016; b) J. D. Neuhaus, R. Oost, J. Merad, N. Maulide, *Top. Curr. Chem.* **2018**, *376*, 15

[3] a) M. Barday, C. Janot, N. R. Halcovitch, J. Muir, C. Aïssa, *Angew. Chem., Int. Ed.* **2017**, *56*, 13117-13121; b) Y. Xu, X. Zhou, G. Zheng, X. Li, *Org. Lett.* **2017**, *19*, 5256-5259; c) X. Wu, H. Xiong, S. Sun, J. Cheng, *Org. Lett.* **2018**, *20*, 1396-1399; d) P. Hu, Y. Zhang, Y. Xu, S. Yang, B. Liu, X. Li, *Org. Lett.* **2018**, *20*, 2160-2163; e) K. S. Halskov, M. R. Witten, G. L. Hoang, B. Q. Mercado, J. A. Ellman, *Org. Lett.*. **2018**, *20*, 2464-2467; f) Y. Xu, G. Zheng, X. Yang, X. Li, *Chem. Commun.* **2018**, *54*, 670-673; g) C. Zhou, F. Fang, Y. Cheng, Y. Li, H. Liu, Y. Zhou, *Adv. Synth. Catal.* **2018**, *360*, 2546-2551; h) G. Chen, X. Zhang, R. Jia, X. Fan, *Adv. Synth. Catal.* **2018**, *360*, 3781-3787. i) C. You, C. Pi, Y. Wu, X. Cui, *Adv. Synth. Catal.* **2018**, *360*, 4068-4072; j) H. Oh, S. Han, A. K. Pandey, S. H. Han, N. K. Mishra, S. Kim, R. Chun, H. S. Kim, J. Park, I. S. Kim, *J. Org. Chem.* **2018**, *83*, 4070-4077. k) G. L. Hoang, A. D. Streit, J. A. Ellman, *J. Org. Chem.* **2018**, *83*, 15347-15360; l) G. Zheng, M. Tian, Y. Xu, X. Chen, X. Li, *Org. Chem. Front.* **2018**, *5*, 998-1002; m) P. Hu, Y. Zhang, B. Liu, X. Li, *Org. Chem. Front.* **2018**, *5*, 3263-3266; n) R. Yang, X. Wu, S. Sun, J.-T. Yu, J. Cheng, *Synthesis* **2018**, *50*, 3487-3492; o) G. L. Hoang, J. A. Ellamn, *Tetrahedron* **2018**, *74*, 3318-3324; p) J. Zu, S. Sun, J. Cheng, *Tetrahedron Lett.* **2018**, *59*, 2284-2287, q) H. Xie, J. Lan, J. Gui, F. Chen, H. Jiang, W. Zeng, *Adv. Synth. Catal.* **2018**, *360*, 3534-3543; r) X. Shi, R. Wang, X. Zeng, Y. Zhang, H. Hu, C. Xie, M. Wang, *Adv. Synth. Catal*. **2018**, *360*, 4049-4053; s) S. Ji, K. Yan, B. Li, B. Wang, *Org. Lett.* **2018**, *20*, 5981-5984.

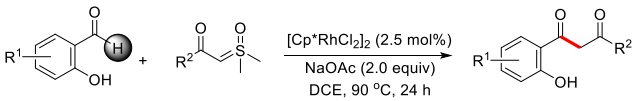
[4] Some papers on aldehydic C-H functionalizations: a) C.-H. Jun, E.-A. Jo, J.-W. Park, *Eur. J. Org. Chem.* **2007**, 1869-1881; b) M. C. Willis, *Chem. Rev.* **2010**, *110*, 725-748; c) Z. Shi, N. Schröder, F. Glorius, *Angew. Chem., Int. Ed.* **2012**, *51*, 8092-8096; d) M. V. Delius, C. M. Le, V. M. Dong, *J. Am. Chem. Soc.* **2012**, *134*, 15022-15032; e) J. Yang, N. Yoshikai, *Angew. Chem., Int. Ed.* **2016**, *55*, 2870-2874; *Angew. Chem.* **2016**, *128*, 2920-2924; f) M. Holmes, L. A. Schwartz, M. J. Krische, *Chem. Rev.* **2018**, *118*, 6026-6052.

[5] a) P. S. Sun, S. Gao, C. Yang, S. Guo, A. Lin, H. Yao, *Org. Lett.* **2016**, 18, 646 4-6467; b) G.-D. Xu, Z.-Z. Huang, *New J. Chem.* **2018**, *42*, 18358-18362.

10.1002/adsc.201900276

COMMUNICATION

Rh(III)-Catalyzed Aldehydic C-H Functionalization Reaction between Salicylaldehydes and Sulfoxonium Ylides



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

Guo-Dong Xu, Kenneth L. Huang, and Zhi-Zhen Huang*