Tetrahedron 71 (2015) 8511–8516

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Rh(III)-catalyzed aldehyde C–H bond functionalization of salicylaldehydes with arylboronic acids

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ARTICLE INFO

Article history:
Received 13 July 2015
Received in revised form 18 September 2015
Accepted 22 September 2015
Available online 25 September 2015

Keywords:
C–H activation
Rh(III) catalysis
Salicylaldehydes
2-Hydroxybenzophenones
Divergent synthesis

ABSTRACT

A Rh(III)-catalyzed aldehyde C–H bond functionalization of salicylaldehydes with arylboronic acids has been developed, with features of mild reaction condition and high efficiency. Furthermore, the functionalized 2-hydroxybenzophenone could be subject to divergent synthesis of heterocycles.

1. Introduction

2-Hydroxybenzophenones are important building blocks in synthetic chemistry owing to their high reactivity, particular in the fields of medicinal chemistry. Due to its prevalence in biologically active products and synthetic molecules, great efforts have been devoted to the synthesis of molecules with the 2-hydroxybenzophenone skeleton, and representative examples are shown in Fig. 1. These molecules exhibiting a variety of biological activities, and acted as selective inhibitors of human immunodeficiency virus type 1 reverse transcriptase,[1] antispasmodic agents,[2] inhibitors of transforming growth factor-kinase.[3] Therefore, there are many methods reported toward construction of these molecules. The classical approach relies on Fries rearrangement of phenyl ester which is derived from phenol.[4] There also are transition-metal-catalyzed transformations for access to these compounds. For example, Chen reported a Pd-catalyzed cross coupling of salicylaldehyde and diaryliodonium salts for synthesis of 2-hydroxybenzophenones.[5] Meanwhile, Xu also developed a Pd-catalyzed oxidative coupling of salicylaldehyde with arylboronic acids.[6] Recently, Li reported a Rh-catalyzed rearrangement of 2-aryloxybenzaldehyde for transforming to 2-hydroxybenzophenones.[7] Interestingly, Rao and Dong independently reported the Pd-catalyzed ketone-directed hydroxylation of arenes for synthesis of 2-acylphenols.[8]

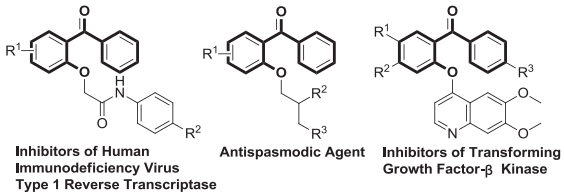

Fig. 1. Biologically active products containing 2-hydroxybenzophenone skeleton.

Recently, Rh(III)-catalyzed functionalization of aryl C–H bond has enjoyed tremendous advance owing to their wide applications to the rapid assembly of various complex molecular structures, particular in the fields of medicinal chemistry.[9] In particular, the Rh(III)-catalyzed C–H functionalization of aldehyde has been paid attention. For example, Miura explored the Rh(III)-catalyzed oxidative coupling between salicylaldehydes and internal alkynes, demonstrating the flexible reactivity of aldehyde in C–H functionalization.[10] Inspired by this, Glorius,[11] Radhakrishnan[12] and Li[13] reported that Rh(III)-catalyzed oxidative coupling of salicylaldehydes with electron deficient olefins, diazabicyclic olefins and TIPS-EBX, respectively. In continuation of our interest in Rh(III)-catalyzed C–H functionalization for biologically interesting small molecule synthesis,[14] herein we report a Rh(III)-catalyzed aldehyde C–H bond functionalization of salicylaldehydes with arylboronic acids. Moreover, the functionalized 2-hydroxybenzophenones

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http://dx.doi.org/10.1016/j.tet.2015.09.053
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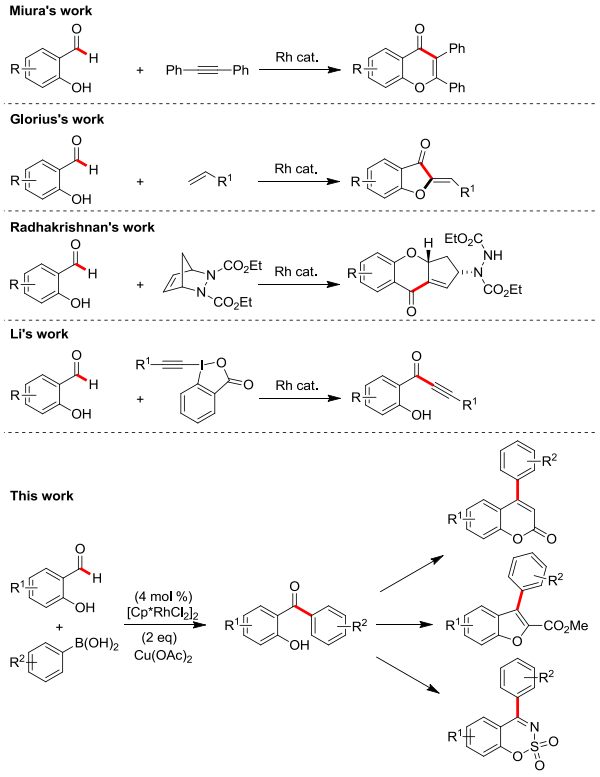
could be subject to various transformations to access divergent compounds (Scheme 1).



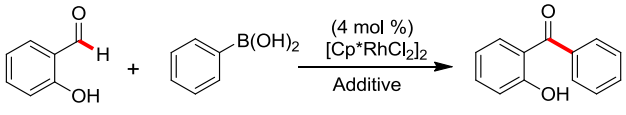
Scheme 1. Rh(III)-catalyzed aldehyde C–H functionalization of salicylaldehydes.

2. Results and discussions

We commenced our study by investigating the coupling of salicylaldehyde **1a** and phenylboronic acid **2a** using $[Cp^*RhCl_2]_2$ as catalyst. When the reaction was conducted in DMF at 80 °C without additives, the Rh(III) catalyzed C–H functionalized product was not observed (Table 1, entry 1). Gratifyingly, equivalent addition of $Cu(OAc)_2$ led to the formation of 2-hydroxybenzophenone **3a** in 98% yield (Table 1, entry 2). This encouraged us to screen the additives, and we found other additives, such as AgOAc, Ag_2O and $K_2S_2O_8$ were inferior (Table 1, entries 3–5). When the solvent was changed to CH_3CN, the reaction afforded trace product when $Cu(OAc)_2$ was used as additive (entry 6). Surprisingly, the combination of CH_3CN and Ag_2O gave the product in 85% yield (entry 7). Further survey of solvents revealed that MeOH, t-amyl alcohol, trifluoroethanol (TFE) and dioxane were not optimal to produce trace products (entries 8–11). Moreover, when the temperature was decreased to 40 °C, the reaction would give the product in a slightly lower yield (entry 12, 76%).

With the optimized reaction condition in hand, we next expanded the scope of this Rh(III)-catalyzed aldehyde functionalization using a variety of salicylaldehydes and arylboronic acids. As depicted in Table 2, various *para*-substituted arylboronic acids with valuable functional groups like bromo, chloro, methoxy, methyl, cyano, hydroxy, phenyl, could react smoothly with **1a** in this process to furnish the products (**3b**–**3h**) in excellent yields, thus offering ample opportunity for further derivatization. The

Table 1
Optimization of reaction conditions[a]

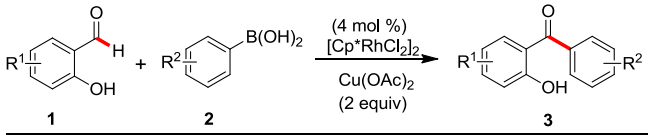


1a 2a 3a

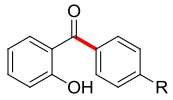
Entry	Additive	Solvent	T [°C]	Yield [%][b]
1	None	DMF	80	0
2	$Cu(OAc)_2$	DMF	80	98
3	AgOAc	DMF	80	Trace
4	Ag_2O	DMF	80	Trace
5	$K_2S_2O_8$	DMF	80	Trace
6	$Cu(OAc)_2$	CH_3CN	60	Trace
7	Ag_2O	CH_3CN	60	85
8	$Cu(OAc)_2$	MeOH	60	Trace
9	$Cu(OAc)_2$	*t*-Amyl alcohol	80	Trace
10	$Cu(OAc)_2$	TFE	60	Trace
11	$Cu(OAc)_2$	Dioxane	80	Trace
12	$Cu(OAc)_2$	DMF	40	76

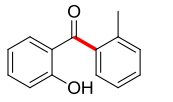
[a] Reaction conditions: 1a (0.2 mmol), 2a (0.4 mmol), $[Cp^*RhCl_2]_2$ (4 mol %), additives (2 equiv), solvent (2 mL).
[b] Yields of isolated products.

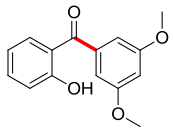
Table 2
Rh(III)-catalyzed aldehyde functionalization of salicylaldehydes[a]

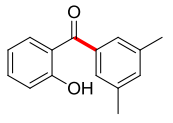


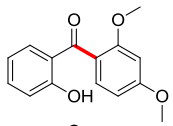
1 2 3

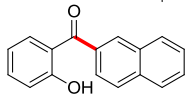

3a, R = H, 98%
3b, R = Br, 93%
3c, R = Cl, 98%
3d, R = OCH_3, 70%
3e, R = Me, 76%
3f, R=CN, 84%
3g, R=OH, 45%
3h, R=Ph, 43%

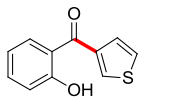

3i, 84%

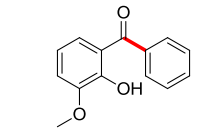

3j, 61%

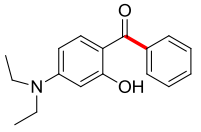

3k, 98%

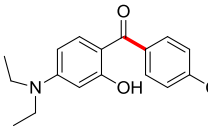

3l, 44%

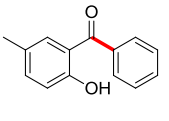

3m, 98%

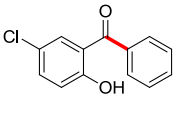

3n, 38%

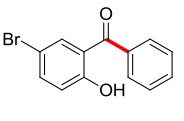

3o, 86%

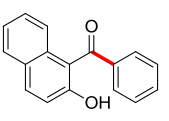

3p, 70%

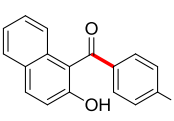

3q, 62%


3r, 98%


3s, 98%


3t, 91%


3u, 94%


3v, 81%

[a] Reaction Conditions: **1** (0.2 mmol), **2** (0.4 mmol), $[Cp^*RhCl_2]_2$ (4 mol %), $Cu(OAc)_2$ (2 equiv), DMF (2 mL), 80 °C, 8 h.