### Tetrahedron Letters 53 (2012) 4347-4350

Contents lists available at SciVerse ScienceDirect

**Tetrahedron Letters** 

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

# Palladium-catalyzed desulfitative addition of sodium sulfinates with $\alpha$ , $\beta$ -unsaturated carbonyl compounds

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#### ARTICLE INFO

Article history: Received 26 April 2012 Revised 30 May 2012 Accepted 5 June 2012 Available online 13 June 2012

Keywords: Addition Desulfination Palladium Sulfinic acids

Transition-metal-catalyzed conjugate addition to electron deficient olefins is a powerful strategy for the construction of new C-C bonds.<sup>1</sup> The use of transition-metal catalysts in combination with an organometallic reagent has been particularly effective in this regard. The commonly used organometallic reagents for conjugate addition reactions are relatively active organolithiums, organomagnesiums, or organozincs catalyzed by copper catalysts.<sup>2</sup> However, this strategy is problematic for 1,4-addition of  $\alpha,\beta$ unsaturated carbonyl compounds due to its sensitivity to the carbonvl functional groups. In recent years, the rhodium-catalyzed conjugate addition of organoboranes,<sup>3</sup> -silicones,<sup>4</sup> and -stannanes<sup>5</sup> with  $\alpha$ ,  $\beta$ -unsaturated carbonyl compounds is as an attractive alternative because of their insensitivity to carbonyl functional groups and the availability of various chiral ligands for rhodium catalysts (Scheme 1, a).<sup>6</sup> This strategy showed good selectivity and the carbonyl groups are well tolerated under the reaction conditions. Recently, Zhao et al. developed a rhodium-catalyzed decarboxylative conjugated addition of benzoic acids to  $\alpha,\beta$ -unsaturated carbonyl compounds (Scheme 1, b).<sup>7</sup> In this transformation, benzoic acids acted as the aryl nucleophiles via releasing of CO<sub>2</sub>.<sup>8</sup> This strategy showed good selectivity and provided an efficient synthetic route for conjugate addition reactions. However, it required ortho-fluoro-substituted benzoic acid substrates and thus limited the scope.

Compared with the widely studied arylboronic acid and carboxylic acid partners, aromatic sulfinic acid sodium salts are rarely used as aryl sources via desulfination. Sulfinic acid sodium salts are relatively stable, easy to handle, and when necessary, are

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A palladium-catalyzed desulfitative conjugate addition of sodium sulfinates with  $\alpha$ , $\beta$ -unsaturated carbonyl compounds is described. The reaction showed very good selectivity and tolerated a wide range of functionalities under an atmosphere of argon.

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accessible preparatively from their corresponding sulfonyl chlorides.<sup>9</sup> Sulfinic acid sodium salts have the potential to serve as the aryl sources for C–C bond forming reactions via releasing SO<sub>2</sub> under relatively mild conditions.<sup>10</sup> However, the current research has been mainly focused on sulfonylation reagents.<sup>11</sup> Research on desulfitative C–C bond formation is rare.<sup>12,13</sup> Very recently, we and others developed various palladium-catalyzed desulfitative Heck-type reactions,<sup>14</sup> addition reactions,<sup>15</sup> and cross-coupling reactions with C–H bonds<sup>16</sup> under relative mild conditions. Various aromatic sulfinic acids were used as aryl sources without the requirement of ortho substituents.<sup>17</sup> In continuing with our



Scheme 1. Various routes for conjugate addition of  $\alpha,\beta$ -unsaturated carbonyl compound.





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#### Table 1

Optimization of the reaction conditions<sup>a</sup>



Entry	Catalyst	Ligand	Additive	Solvent	Yield <sup>b</sup> (%)
1	PdCl <sub>2</sub>	2,2'-Dipyridine	HOAc	1,4-Dioxane	0
2	$Pd_2(dab)_3$	2,2'-Dipyridine	HOAc	1,4-Dioxane	16
3	$Pd(OAc)_2$	2,2'-Dipyridine	HOAc	1,4-Dioxane	23
4	Pd(CH <sub>3</sub> CN) <sub>2</sub> Cl <sub>2</sub>	2,2'-Dipyridine	HOAc	1,4-Dioxane	40
5	$Pd(CF_3CO_2)_2$	2,2'-Dipyridine	HOAc	1,4-Dioxane	50
6	Pd(OH) <sub>2</sub>	2,2'-Dipyridine	HOAc	1,4-Dioxane	58
7	Pd(OH) <sub>2</sub>	1,10-Phen	HOAc	1,4-Dioxane	46
8	Pd(OH) <sub>2</sub>	2,2'-Biquinoline	HOAc	1,4-Dioxane	43
9	Pd(OH) <sub>2</sub>	TMEDA	HOAc	1,4-Dioxane	57
10	Pd(OH) <sub>2</sub>	DMAP	HOAc	1,4-Dioxane	68
11	Pd(OH) <sub>2</sub>	DABCO	HOAc	1,4-Dioxane	70
12	Pd(OH) <sub>2</sub>	DABCO		1,4-Dioxane	10
13	Pd(OH) <sub>2</sub>	DABCO	TFA	1,4-Dioxane	80
14 <sup>c</sup>	Pd(OH) <sub>2</sub>	DABCO	TFA	1,4-Dioxane	94
15 <sup>c</sup>	Pd(OH) <sub>2</sub>	DABCO	TFA	DMF	30
16 <sup>c</sup>	Pd(OH) <sub>2</sub>	DABCO	TFA	Anisole	50
17 <sup>c</sup>	Pd(OH) <sub>2</sub>	DABCO	TFA	Toluene	38
18 <sup>c</sup>	Pd(OH) <sub>2</sub>	DABCO	TFA		50
19 <sup>d</sup>	$Pd(OH)_2$	DABCO	TFA	1,4-Dioxane	35

<sup>a</sup> Conditions: 1a (0.4 mmol), 2a (0.2 mmol), catalyst (5 mol %), ligand (10 mol %), additive (0.4 mL), solvent (0.2 mL), H<sub>2</sub>O (0.2 mL), 120 °C, 20 h under argon unless otherwise noted.
 <sup>b</sup> GC yield based on 2a.
 <sup>c</sup> 0.1 mL TFA was used.

<sup>d</sup> Without water.

## Table 2

Desulfitative addition 1a with various unsaturated compounds<sup>a</sup>

	$1a + R^{1} \frac{1}{2} R^{2} \frac{Pd(C)}{DAB}$	$\begin{array}{c} DH)_{2} \\ DC \\ DC, 20 h \end{array} \xrightarrow{O} p-Tolyl \\ R^{2} \\ R^{1} \\ 3 \end{array}$	
Entry	Substrate <b>2</b>	Product	Yield <sup>b</sup> (%)
1	Ph 2a	3a	80
2	0 2b	3b	87
3	MeO 2c	3c	89
4	<sup>O</sup> <sup>t</sup> Bu 2d	3d	70
5	о Г	Зе	53
6	CI 2f	3f	80
7	Br 2g	3g	79

Table	2	(continued)
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Entry	Substrate 2	Product	Yield <sup>b</sup> (%)
8	CI 2h	3h	55
9	<b>2</b> i	3i	60
10	Ph H 2j	3j	64
11	2k	3k	85

<sup>a</sup> Conditions: **1a** (0.4 mmol), **2** (0.2 mmol), Pd(OH)<sub>2</sub> (5 mol %), DABCO (10 mol %), TFA (0.1 mL), 1,4-dioxane (0.2 mL), H<sub>2</sub>O (0.2 mL), 120 °C, 20 h under argon.

<sup>b</sup> Isolated yield based on **2**.





<sup>a</sup> Conditions: 1 (0.4 mmol), 2a (0.2 mmol), Pd(OH)<sub>2</sub> (5 mol %), DABCO (10 mol %), TFA (0.1 mL), 1,4-dioxane (0.2 mL), H<sub>2</sub>O (0.2 mL), 120 °C, 20 h under argon.
 <sup>b</sup> Isolated yield.

interest in using aromatic sulfinic acids (salts) as the aryl sources, herein we describe a palladium-catalyzed desulfitative conjugate addition of sodium sulfinates with  $\alpha$ , $\beta$ -unsaturated carbonyl compounds (Scheme 1, c).<sup>18</sup>

We began our study by examining the reaction of *p*-toluenesulfinic acid sodium salt (**1a**) with benzylideneacetone (**2a**) in 1,4-dioxane/H<sub>2</sub>O (1:1) by using palladium salt as catalyst and 2,2'-dipyridine as ligand in the presence of excess acetic acid. Various palladium salts were investigated for this transformation. No desired product was observed when PdCl<sub>2</sub> was used as determined by GC and <sup>1</sup>H NMR methods (Table 1, entry 1). The desired product **3a** was obtained in 16% and 23% yields when Pd<sub>2</sub>(dba)<sub>3</sub> and



Scheme 2. Proposed mechanism.

 $Pd(OAc)_2$  were used (entries 2 and 3). The reaction yield can be further improved to 50% when  $Pd(CF_3CO_2)_2$  was employed (entry 5). Among them, Pd(OH)<sub>2</sub> was the most efficient catalyst and the addition product was obtained in 58% yield (entry 6). Various nitrogencontaining ligands were also investigated using Pd(OH)<sub>2</sub> as the catalyst (entries 7-11). Phenanthroline (1,10-Phen), 1,2-bis(dimethylamino)ethane (TMEDA), 4-dimethylaminopyrdine (DMAP) and 1,4-diazabicyclo[2.2.2]octane (DABCO) were efficient ligands for the addition reaction. The acidic additive had an important impact on the reaction yield. Only 10% yield was achieved in the absence of acid additive (entry 12). The replacement of acetic acid with trifluoroacetic acid (TFA) could improve the reaction yield slightly (entry 13). Interestingly, 94% yield was obtained when the amount of TFA was reduced to 0.1 mL (entry 14). The solvent also had a significant impact on the reaction yield. The reaction yield decreased when the reaction was run in other organic solvents or in the absence of water (entries 15-19).

With the optimized reaction conditions in hand, we then explored the scope and generality of this transformation. Various  $\alpha,\beta$ -unsaturated ketones bearing electron-withdrawing and donating substituents on the phenyl ring were investigated (Table 2). (*E*)-4-*p*-Tolylbut-3-en-2-one (**2b**) and (*E*)-4-(4-methoxyphenyl) but-3-en-2-one (**2c**) both smoothly reacted with **1a** and gave the desired conjugate addition products in 87% and 89% yields, respectively (entries 2 and 3). A slightly lower yield was obtained when **2d** reacted with **1a** (entry 4). Halogen substituents such as fluoro, chloro, and bromo were well tolerated under the optimized

reaction conditions and the coupling of (E)-4-(4-bromophenyl)but-3-en-2-one (**2g**) with **1a** gave the product in 79% yield (entry 7). The position of the substituents on the phenyl ring affects the reaction yield significantly. The reaction yields decreased to 55% and 60% when **2h** and **2i** were used as substrates (entries 8 and 9). Notably, the addition of cinnamaldehyde (**2j**) with **1a** afforded the desired product in 64% yield (entry 10). Aryl substituted enone substrate (*E*)-chalcone (**2k**) also smoothly reacted with **1a** and gave the desired product in 85% yield (entry 11).

The reaction results of various arylsulfinic acid sodium salts with benzylideneacetone **2a** are presented in Table 3. A series of functional groups including *tert*-butyl, methoxy, fluoro, chloro, and bromo were tolerated under the optimal reaction conditions, and the desired products were obtained in moderate to good yields (entries 2–6). More bulky substrates such as 2-naphthylsulfinic acid sodium salt (**1h**) also efficiently reacted with **2a** and gave the desired product in 89% yield (entry 7).

A plausible mechanism to rationalize this transformation is illustrated in Scheme 2. Similar to the Pd(II)-catalyzed conjugate addition of arylboronic acids to  $\alpha,\beta$ -unsaturated carbonyl compounds, the proposed mechanism involves the following 5 steps: (1) coordination of aromatic sulfinic acid sodium salts to palladium(II) to give complex **I**; (2) desulfitative reaction of the sulfinic acid to generate the aryl-palladium complex **II**; (3) coordination of the ketone group to form complex **III**; (4) migratory insertion of the C=C bond with aryl-palladium complex to give complex **IV**; (5) protonation of **IV** by the acid to give the final addition product and a palladium(II) species.

In summary, we have demonstrated a palladium-catalyzed desulfitative conjugate addition of sodium sulfinates with  $\alpha$ , $\beta$ -unsaturated ketones (aldehydes). Various aromatic sulfinic acid sodium salts with or without substituents selectively added with  $\alpha$ , $\beta$ -unsaturated ketones and afforded the adducts in good yields. Unlike the decarboxylative coupling reaction, no electronwithdrawing or donating group *ortho* to the sulfinic acid group was necessary to ensure the desulfitative addition. Functional groups such as methyl, methoxy, fluoro, chloro, and bromo were all well tolerated under the optimized reaction conditions. The scope, mechanism, and synthetic applications of this reaction in asymmetric version are under investigation.

### Acknowledgements

This work was supported by the National Natural Science Foundation of China (21172185, 20902076), the Hunan Provincial Natural Science Foundation of China (11JJ1003), the New Century Excellent Talents in University from Ministry of Education of China (NCET-11-0974) and the Scientific Research Foundation for Returned Scholars, Ministry of Education of China (2011-1568).

# Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06. 026.

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