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Beneficial effect of carboxylic acid additives on the Pd-catalyzed intramolecular N-arylation of 2-amino-3-(2-chlorophenylsulfonyl)pyrroles

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ABSTRACT

Carboxylic acid additives have been shown to significantly improve the yield of the Pd-catalyzed intramolecular N-arylation of 2-aminopyrroles containing a 2-chlorophenylsulfonyl group at the 3-position to give a novel tricyclic ring system. Pivalic and phenylacetic acid provided the best yield enhancement, while acetic acid showed moderate enhancement. Other acids showed limited to no enhancement or even a detrimental effect on the reaction.

Introduction

The transition metal-catalyzed coupling of an amine with an aryl halide (or pseudohalide) has become the premier method for preparation of substituted aromatic and heteroaromatic amine derivatives.[1] These so called Buchwald–Hartwig reactions are typically conducted using a metal catalyst (often Pd), along with a ligand (often a phosphine), and a base, which deprotonates the amine at some point during the reaction.

Over a year ago now, Buchwald and co-workers described the beneficial effect of acetic acid on the Pd-catalyzed intermolecular N-arylation of some 2-aminothiazoles.[2] Although no exact mechanism for the beneficial effect was proposed, it was shown that the acid led to an enhancement of the activity of the Pd catalyst complex [formed from $Pd(OAc)_2$]. That was apparently the first example of a carboxylic acid additive being used to promote a transition metal-catalyzed N-arylation reaction. Surprisingly, though, we have not seen any subsequent examples of this in the literature. On the other hand, carboxylic acid additives are used extensively to promote transition metal-catalyzed C–H activation reactions (i.e., Heck reactions) of aromatics,[3–7] alkenes,[8,9] and alkanes.[10] In this case, mechanistic studies suggest that the carboxylate anion, formed under the basic conditions of the reaction, plays a supporting role in deprotonation of the carbon that is ultimately arylated, and this deprotonation occurs simultaneously with the metallation of that carbon (concerted metallation–deprotonation pathway).[11–14] Other than Heck reactions, there has been a recent report of acetic acid serving as a beneficial additive in a Pd-catalyzed Hiyama coupling,[15] although those authors only speculated that the acid served to reduce the base-promoted hydrolysis of the mesylate electrophile used in the reaction.

Previously, we have described both intermolecular[16] and intramolecular[17] N-arylation reactions of certain 2-aminopyrroles catalyzed by Pd complexes. Most recently, we have been exploring an intramolecular N-arylation approach to a novel tricyclic pyrrolo[3,2-*b*]benzo[1,4]thiazine ring system, again from 2-aminopyrroles. We initially found this reaction to proceed quite sluggishly when using our previously employed conditions for Pd-catalyzed intramolecular N-arylation, perhaps as we were employing an aryl chloride as a coupling partner in this case. Being aware of Buchwald's finding that acetic acid can be of benefit to Pd-catalyzed N-arylation reactions, we decided to explore the use of this additive. To our delight, the addition of acetic acid led to significant improvements in yields when using our otherwise standard conditions. Upon further exploring this effect, we found that a few other carboxylic acids also provided a beneficial effect, with some (such as pivalic and phenylacetic acid) generally providing higher yields than acetic acid, while other acids showed no benefit or even appeared to hinder the reaction. Herein, we wish to describe these findings, which further substantiate the potential benefit of carboxylic acid additives on Pd-catalyzed N-arylation reactions.

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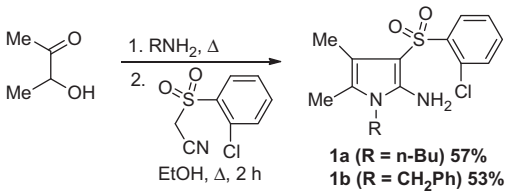


Scheme 1. Synthesis of 2-aminopyrroles (**1a**–**b**).

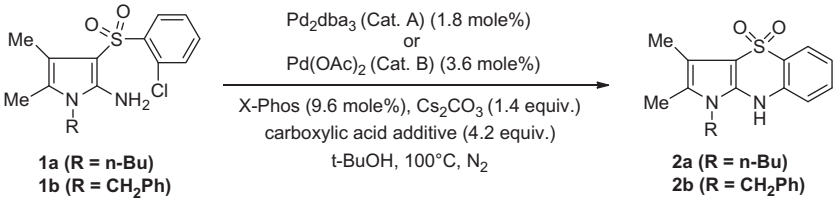
Results and discussion

As shown in Scheme 1, the 2-aminopyrroles (**1a**–**b**) used in this study were prepared by the solvent-free reaction of acetoin with a primary amine, followed by reaction of the intermediate α-aminoketone with (2-chlorophenyl)sulfonylacetonitrile in refluxing EtOH.[17] Although 2-aminopyrroles have been prepared with phenylsulfones at the 3-position,[18] these appear to be the first ortho-halogenated derivatives.[19]

The Pd-catalyzed cyclization of 2-aminopyrroles **1a**–**b** is illustrated in Table 1, along with the yield data. Cyclization of **1a** (with R = *n*-Bu) using our previously described conditions for N-arylation of other 2-aminopyrroles [Pd_2dba_3 (Catalyst A), X-Phos, Cs_2CO_3, *t*-BuOH, 100 °C] gave only a 7% isolated yield of novel tricyclic **2a** after heating for 18 h and recrystallizing the crude product from MeOH (our standard isolation protocol due to the insoluble nature of the tricyclic products) (entry 1, Table 1). However, with the addition of various carboxylic acids (4.2 M equiv) to the otherwise identical reaction, isolated yields ranging from 29–53% were obtained, with phenylacetic and pivalic acid giving the highest yields (both 53%, entries 3 and 4), acetic acid giving 34% yield (entry 2), and benzoic acid giving 29% yield (entry 5).[20] In contrast, no product was obtained when 2-nitrobenzoic acid,[5] 2-picolinic acid,[21] or succinic acid (a diacid) were used as additives (entries 6–8). This could be due to the potentially stronger ligating effects of these acids, which may disrupt the catalyst activity. This could also be due to the greater relative acidity of these other acids (especially 2-nitrobenzoic and 2-picolinic acid), which may decrease the ability of their conjugate bases to effectively promote the concerted metallation–deprotonation pathway (if operable in this case),[7,13] although 2-nitrobenzoic acid has been shown to be better than acetic acid at enhancing a Pd-catalyzed Heck reaction using Ag_2O as base.[5]

With these favorable results in hand for the 18 h reaction, we wanted to see if the use of the acid additive would allow the reaction to be accomplished in a shorter time. Moving forward, we kept the amount of additive used in this study constant at the original

Table 1
Yields for Pd-catalyzed cyclization of 2-aminopyrroles **1a**–**b** to tricyclics **2a**–**b** using various carboxylic acid additives



Entry	Starting 2-aminopyrrole	Pd catalyst	Carboxylic acid additive	Time (h)	%Yield of tricyclic[a] (isolated)
1	**1a**	A	—	18	7
2	**1a**	A	Acetic	18	34
3	**1a**	A	Phenylacetic	18	53
4	**1a**	A	Pivalic	18	53
5	**1a**	A	Benzoic	18	29
6	**1a**	A	2-Nitrobenzoic	18	0
7	**1a**	A	2-Picolinic	18	0
8	**1a**	A	Succinic[b]	18	0
9	**1a**	A	—	3	0
10	**1a**	A	Acetic	3	0
11	**1a**	A	Phenylacetic	3	26
12	**1a**	A	Pivalic	3	30
13	**1a**	A	Benzoic	3	0
14	**1b**	A	—	3	0
15	**1b**	A	Acetic	3	49[c]
16	**1b**	A	Benzoic	3	20
17	**1b**	A	Phenylacetic	3	37
18	**1b**	A	Pivalic	3	53
19	**1a**	B	—	3	0
20	**1a**	B	Acetic	3	51
21	**1a**	B	Phenylacetic	3	61
22	**1a**	B	Pivalic	3	54
23	**1a**	B	Benzoic	3	0
24	**1b**	B	—	3	58
25[d]	**1b**	B	—	0.5	41
26[d]	**1b**	B	Acetic	0.5	81
27[d]	**1b**	B	Phenylacetic	0.5	84
28[d]	**1b**	B	Pivalic	0.5	83
29[d]	**1b**	B	Benzoic	0.5	0[e]

[a] Yield of pure product after recrystallization from MeOH.
[b] 2.1 M equiv used.
[c] The yield was 50% when K_2CO_3 was used as base.
[d] K_2CO_3 used as base.
[e] Reaction was performed three times with consistent results.

4.2 equiv (3 equiv based on the carbonate base). For comparison, Buchwald and coworkers used just 3 mol % of acetic acid in their N-arylation of 2-aminothiazoles,[2] although others have used as much as 10 M equiv of acid additive for Heck reactions.[8]

With a shorter reaction time of 3 h, tricyclic **2a** was not isolated when the acid additive was omitted (entry 9). However, with the addition of phenylacetic (entry 11) or pivalic acid (entry 12), yields of 26 and 36%, respectively, were obtained. In contrast to the 18 h reaction, no product could be isolated when acetic or benzoic acid was used (entries 10 and 13). Thus, phenylacetic and pivalic acid appear to be the most active of the acid additives employed for the cyclization of **1a**. The better activity of pivalic acid compared to acetic acid for this reaction is consistent with a number of reports on the variable activity of different carboxylic acid additives for Heck reactions, which often show pivalic acid to be superior.[7,9,13] On the other hand, we could find no reference to phenylacetic acid being used as an additive in a transition metal-catalyzed coupling reaction.

Next, we examined the cyclization of benzyl-substituted pyrrole **1b**, starting with a 3 h reaction time. Tricyclic **2b** was also not isolated when the acid additive was omitted (entry 14). However, with the addition of acetic, phenylacetic, pivalic, or benzoic acid, **2b** was obtained in yields ranging from 20–53% (entries 15–18), with pivalic acid again giving the highest yield (53%, entry 18). Thus, in contrast to the cyclization of *n*-Bu pyrrole **1a** at 3 h, the cyclization of benzyl pyrrole **1b** at 3 h was promoted by acetic and benzoic acid, although these again did not perform as well as pivalic acid. Also, in contrast to the cyclization of *n*-Bu pyrrole **1a**, a higher yield of tricyclic was obtained when using acetic acid (entry 15) compared to phenylacetic acid (entry 17), a result that does not fit the general trend observed in this study. Consistently, though, no tricyclic product was isolated when 2-nitrobenzoic, 2-picolinic, or succinic acid were used in the attempted cyclization of **1b** (data not shown).

Next, we examined the cyclization when using $Pd(OAc)_2$ (Catalyst B) as the Pd source, using the equivalent amount of catalyst based on Pd and keeping all other conditions the same. A 3 h reaction of *n*-Bu pyrrole **1a** under these conditions and without acid additive gave no isolated product (entry 19). However, when acetic, phenylacetic, or pivalic acid were added, product **2a** was obtained in good yields ranging from 51–61% (entries 20–22), with phenylacetic giving the highest yield in this case (entry 21). Thus, pivalic and phenylacetic acid promoted the cyclization of **1a** in 3 h regardless of which catalyst was used, but acetic acid only promoted the reaction when $Pd(OAc)_2$ was used. Benzoic acid, on the other hand, failed to promote the cyclization of **1a** at 3 h regardless of which catalyst (A or B) was used (entries 13 and 23). These results further suggest that pivalic and phenylacetic acid are the most active of the acid additives used in this study, that acetic acid is a slightly less active, and that benzoic acid is considerably less active.

Upon cyclization of benzyl pyrrole **1b** at 3 h using $Pd(OAc)_2$, tricyclic product **2b** was surprisingly obtained in 58% yield even when without an acid additive (entry 24). This was in stark contrast to the analogous reaction using Pd_2dba_3, which gave no isolated product (entry 14). This is also in contrast to the analogous reaction of butyl pyrrole **1a** using $Pd(OAc)_2$, which gave no product at 3 h when the acid was omitted (entry 19). As a side note, these results thus clearly show that the cyclization of the benzyl pyrrole **1b** is more efficient than **1a**, and that $Pd(OAc)_2$ is a better Pd source for this cyclization. The enhanced reactivity of **1b**, which has the aromatic-containing R group, may be another example of the 'aromatic effect' which has been observed with some transition metal-catalyzed reactions.[22]

With a reaction time of 30 min, the cyclization of **1b** using $Pd(OAc)_2$ and no acid additive still gave a reasonable 41% yield (entry 25). However, the yield was substantially increased to 81–84% with the addition of acetic, phenylacetic, or pivalic acid (entries 26–28). Surprisingly though, no product could be isolated when benzoic acid was used as the additive (entry 29) (this reaction was performed three times; TLC analysis showed only trace amounts of the tricyclic each time). Thus, benzoic acid clearly showed a detrimental effect to the 30 min reaction using $Pd(OAc)_2$ as catalyst. This negative result is difficult to explain, especially considering that benzoic acid showed moderate beneficial effects in reactions using Pd_2dba_3 as catalyst (with longer reaction times; entries 5 and 16). Also, several substituted benzoic acids have reportedly shown beneficial effects in Heck reactions.[5]

Conclusion

In conclusion, we have found that the Pd-catalyzed intramolecular N-arylation of 2-aminopyrroles containing a 2-chlorophenylsulfone at the 3-position is significantly enhanced by the addition of certain carboxylic acid additives. Pivalic and phenylacetic acids, both aliphatic acids, were the best of the acid additives evaluated, while acetic acid showed, in general, a lower beneficial effect. Benzoic acid showed only a modest enhancement of the reaction when using Pd_2dba_3 as catalyst, but clearly showed a detrimental effect when using $Pd(OAc)_2$ and a short reaction time. The three other carboxylic acids tested under our conditions, which were mostly more acidic than the active acids, showed no beneficial effect, or even a detrimental effect, compared to the use of no additive. This work supports Buchwald's original finding that a carboxylic acid additive can promote the Pd-catalyzed N-arylation reaction, and shows that pivalic acid and phenylacetic acid (a more easily handled free-flowing solid acid) may potentially be more active as an additive for the N-arylation reaction than acetic acid. Finally, although carboxylic acid additives are now routinely used for Heck reactions, this appears to be just the second report of their use for Buchwald–Hartwig reactions. Further work is thus still needed to determine the generality of the effect, the precise role of the acid additive, and the optimal amount of acid additive to be used in the reaction.

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19. *Data for butyl pyrrole **1a**:* coarse light yellow crystals, mp 135–136 °C (MeOH). IR (cm^{-1}): 3443, 3346, 2959, 2934, 2865, 1622 (s), 1544, 1492, 1449, 1275 (s),

1137 (s), 1095, 1035, 750, 709, 669, 578, 562. ^{1}H NMR (300 MHz, DMSO-d_6): 0.88 (t, 3H), 1.27 (m, 2H), 1.48 (m, 2H), 1.62 (s, 3H), 1.92 (s, 3H), 3.66 (t, 2H), 5.68 (s, 2H), 7.50–7.57 (m, 3H), 8.07 (d, J = 7.4 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): 8.8, 9.3, 13.7, 19.3, 31.0, 41.4, 92.3, 108.7, 118.5, 127.3, 129.5, 131.7, 131.7, 133.4, 141.2, 144.7. Anal. Calcd for $C_{16}H_{21}ClN_2O_2S$ (340.87): C, 56.38; H, 6.21; N, 8.22. Found: C, 56.36; H, 6.22; N, 8.10. Data for benzyl pyrrole **1b**: light yellow crystals/cubes, mp 164–166.5 °C (MeOH). IR (cm^{-1}): 3409, 3329, 3083, 3004, 2947, 2917, 1607, 1536, 1485, 1449, 1292, 1280 (s), 1142, 1117, 1097 (s), 1035, 769, 728 (s), 707, 692. ^{1}H NMR (300 MHz, DMSO-d_6): 1.64 (s, 3H), 1.78 (s, 3H), 5.02 (s, 2H), 5.85 (s, 2H), 7.02-7.04 (m, 2H), 7.23-7.35 (m, 3H), 7.52–7.60 (m, 3H), 8.12 (m, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): 8.8, 9.3, 44.7, 92.5, 109.1, 109.5, 118.8, 126.0, 127.0, 127.4, 128.5, 129.6, 131.7, 133.5, 137.4, 141.1, 145.3. Anal. calcd for $C_{19}H_{19}ClN_2O_2S$ (374.88): C, 60.87; H, 5.11; N, 7.47. Found: C, 60.76; H, 5.09; N, 7.34.

20. *General procedure for cyclization:* To a 100 mL flask were added (in open air) the 2-aminopyrrole (0.6 mmol), palladium catalyst [0.0108 mmol/1.8 mol % of Pd_2dba_3 or 0.0216 mmol/3.6 mol % of $Pd(OAc)_2$], X-Phos ligand (0.0575 mmol, 9.6 mol %), cesium or potassium carbonate (0.84 mmol, 1.4 molar equiv), *tert*-butanol (7 mL), and, finally, the acid additive (2.52 mmol, 4.2 molar equiv). The mixture was then stirred at reflux at 100 °C (oil bath temperature) under N_2 for the indicated time (Table 1). The reaction was then cooled and diluted with excess water to give a crude solid that was filtered and recrystallized from MeOH (with standing overnight in the cold box) to give product (yields for pure products given in Table 1). The yield was recorded as zero when no product was obtained from the recrystallization. In these cases, TLC generally showed that only a trace amount of product, with starting pyrrole being the major component. Data for butyl tricyclic **2a**: off white/tan fibrous needles, mp 249–251 °C (MeOH). IR (cm^{-1}): 3267, 3190, 3139, 2955, 2930, 2873, 1603, 1552 (s), 1486, 1242 (s), 1135, 1091 (s), 1049, 759 (s). ^{1}H NMR (300 MHz, DMSO-d_6): 0.89 (t, 3H), 1.29 (m, 2H), 1.55 (m, 2H), 2.12 (s, 3H), 2.13 (s, 3H), 3.94 (t, 2H), 7.13 (t, 1H), 7.39 (d, J = 8.1 Hz, 1H), 7.50 (m, 1H), 7.82 (d, J = 8.1 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): 8.7, 9.5, 13.6, 19.2, 31.8, 42.1, 98.8, 107.0, 117.0, 120.6, 121.2, 122.8, 123.6, 131.4, 131.5, 135.6. Anal. Calcd for $C_{16}H_{20}N_2O_2S$ (304.41): C, 63.13; H, 6.62; N, 9.20. Found: C, 63.19; H, 6.55; N, 9.10. Data for benzyl tricyclic **2b**: off white matted solid, mp 288–291 °C (MeOH). IR (cm^{-1}): 3284, 3195, 3143, 2955, 2937, 1602, 1550 (s), 1482, 1243 (s), 1167, 1094 (s), 1052, 767, 730, 694. ^{1}H NMR (300 MHz, DMSO-d_6): 1.98 (s, 3H), 2.16 (s, 3H), 5.30 (s, 2H), 6.98 (d, J = 7.4 Hz, 2H), 7.15 (t, 1H), 7.25–7.37 (m, 4H), 7.48 (dd, J = 1.4, 7.0 Hz, 1H), 7.85 (dd, J = 1.2, 8.1 Hz, 1H), 10.67 (s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): 8.8, 9.5, 45.4, 99.0, 107.7, 117.0, 120.9, 121.7, 122.9, 123.7, 125.8, 127.3, 128.8, 131.6, 132.2, 135.6, 137.2. Anal. Calcd for $C_{19}H_{18}N_2O_2S$ (338.42): C, 67.43; H, 5.36; N, 8.28. Found: C, 67.17; H, 5.31; N, 8.07.

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