Palladium-Catalyzed Domino Cyclization (5-exo/3-exo), Ring-Expansion by Palladium Rearrangement, and Aromatization: An Expedient Synthesis of 4-Arylnicotinates from Morita–Baylis–Hillman Adducts

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Abstract: Various 4-arylnicotinate derivatives were synthesized via a palladium-catalyzed cascade reaction of N-(2-bromoallyl)-N-cinnamyltosylamides in a one-pot procedure in good yields. The reaction involves a domino 5-exo/3-exo carbopalladation, ring-expansion by palladium rearrangement, and an aromatization process.

Keywords: 4-arylnicotinates; Morita–Baylis–Hillman adducts; palladium; palladium rearrangement; pyridines

Polysubstituted pyridines are an important class of compounds due to their abundance in biologically important natural substances and their usefulness as synthetic intermediates in organic synthesis. Especially, the synthesis of functionalized pyridines with a carboxylic acid moiety at the 3-position (nicotinic acid derivatives) has received much attention due to their biological importance. The Morita–Baylis–Hillman (MBH) adducts have been used for the synthesis of various biologically important substances and synthetic intermediates. Various efficient protocols for the synthesis of pyridine and quinoline derivatives from the MBH adducts have also been developed by us and other groups.

In 2008, we reported the synthesis of 6-oxacyclopropa[α]indenes via a palladium-catalyzed sequential 5-exo carbopalladation and C(sp³)-H activation from modified MBH adduct bearing a 2-bromoaryl moiety, as shown in Scheme 1. The alkypalladium inter-

Scheme 1. Synthetic rationale of methyl nicotinate 2a.
mediate does not have a suitable β-hydrogen atom and activates the proton near to the oxygen atom of the dihydrobenzofuran ring to form a cyclopropane ring. Later, we observed a similar 5-exo carbopalladation of modified MBH adducts in their palladium-cat-
ylized domino reactions.\[b,c\] In 1992, the 2010 Nobel prize laureate Negishi and his co-workers rationalized that palladium-catalyzed cyclizations of 2-halo-1,6-
dienes occur as sequences of 5-exo/3-exo carbopallada-
dations with subsequent palladium rearrangement of the cyclopropylcarbinyl-palladium intermediate in which the β-H elimination is suppressed.\[6a\] Later, such a domino 5-exo/3-exo carbopalladation accompa-
nying a palladium rearrangement process was studied by many research groups including those of Steven-
son,\[6b\] de Meijere,\[6c–e\] and Ahn.\[6f\] Similar n-exo(n=6 or 4)/3-exo carbopalladation and palladium rearrange-
ments have also been reported.\[7\] Such a tandem 5-
exo/3-exo cyclization accompanying ring-expansion process was also observed in a radical reaction of a propargyl ether of an MBH adduct\[8a\] and bis-vinyl ethers.\[8b\] In these respects, we envisioned that 3,4,5-
trisubstituted pyidine derivative 2a could be syn-
thesized from 1a via a palladium-catalyzed domino cycli-
zation (5-exo/3-exo), ring-expansion by palladium rear-
arrangement, and an aromatization process, as shown in Scheme 1.

The starting material 1a was prepared readily from the MBH adduct of benzaldehyde and methyl acry-
late by a simple three-step process, that is a sequential bromination, substitution with tosylamide, and 2-bro-
moallylation (see the Supporting Information). With 1a in our hand, a brief screening of the reaction con-
ditions was carried out for the synthesis of methyl nic-
tinate 2a, and the results are summarized in Table 1. When we carried out the reaction in the presence of Et3N (entries 1–3), 1,4,5,6-tetrahydropyridine 3a was produced as a major product along with a trace amount of 1,2,5,6-tetrahydropyridine 3a′ (<4%).\[6a\] The reaction in the presence of K2CO3 afforded a low yield of 2a (10%), but the major product was still 3a (entry 4). In order to facilitate the elimination of p-
toluenesulfonic acid from 3a or 3a′, we examined the reaction with Cs2CO3 (entry 5), and 2a was obtained in good yield (65%). The reaction in refluxing CH3CN was not efficient even in the presence of Cs2CO3 for a long time (entry 6).

The mechanism for the formation of 2a could be proposed in detail, as shown in Scheme 2. An oxidative addition of the C–Br bond of 1a to Pd(0) and a subsequent 5-exo carbopalladation gave an alkylpalladium intermediate I. Because the intermediate I has no suitable β-hydrogen atom that can be eliminated, a sequential 3-exo carbopalladation occurred to afford an alkylpalladium intermediate II. The pres-
ence of an ester group can stabilize both alkylpalladi-
um intermediates I and II by chelation\[19\] and this

![Table 1. A brief optimization of reaction conditions.\[a\]](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Time [h]</th>
<th>2a [%]</th>
<th>3a [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et3N[b]</td>
<td>DMF[d]</td>
<td>20</td>
<td>0</td>
<td>54[d]</td>
</tr>
<tr>
<td>2</td>
<td>Et3N[b]</td>
<td>DMF[d]</td>
<td>3</td>
<td>0</td>
<td>72[d]</td>
</tr>
<tr>
<td>3</td>
<td>Et3N[b]</td>
<td>DMF[d]</td>
<td>3</td>
<td>&lt;5</td>
<td>76[d]</td>
</tr>
<tr>
<td>4</td>
<td>K2CO3[c]</td>
<td>DMF[d]</td>
<td>3</td>
<td>10</td>
<td>74[d]</td>
</tr>
<tr>
<td>5</td>
<td>Cs2CO3[c]</td>
<td>DMF[d]</td>
<td>3</td>
<td>65</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Cs2CO3[c]</td>
<td>CH3CN[f]</td>
<td>10</td>
<td>12</td>
<td>70[d]</td>
</tr>
</tbody>
</table>

\[a\] Conditions: substrate 1a (0.5 mmol), Pd(OAc)2 (5 mol%), PPh3 (10 mol%), 120°C.
\[b\] 2.0 equiv.
\[c\] 2.5 equiv.
\[d\] At 70°C.
\[e\] NaI (1.0 equiv.) was added.
\[f\] Reflux.
\[g\] 3a was isolated in 4%.
\[h\] Trace amount of 3a′ was observed but not isolated.

![Scheme 2. A plausible reaction mechanism.](image)
porting Information), and examined the synthesis of 4-arylnicotinates. As summarized in Table 2, various 4-arylnicotinates 2b–l were synthesized in moderate to good yields (41–75%) in a one-pot procedure under the optimized palladium-catalyzed reaction conditions.

As a next experiment, we examined the reaction of n-pentyl derivative 1m in order to prepare 4-pentylnicotinate 2m, as shown in Scheme 3. However, the reaction of 1m under the optimized condition using Cs₂CO₃ in DMF showed the formation of 3m/3mᵢ in low yield along with many intractable side products. The reaction of 1m under the influence of Et₃N afforded 3m (70%) along with a low yield of 3mᵢ (13%). A desired 4-pentylnicotinate 2m was not formed during the reaction at all. Thus the conversion of 3m to 2m was examined under various conditions; however, we failed to obtain 2m even under conditions employing an excess amount DBU (5.0 equiv.) in refluxing toluene (vide infra). The proton at the 4-position of 3m is less acidic than those of the corresponding 4-aryl derivatives producing 2a–l, and this might be the reason for the failure. It is noteworthy that the 3-exo carbopalladation/palladium rearrangement process occurred at the intermediate stage I–m to give 3m/3mᵢ preferentially rather than the β-H elimination to form 3-hex-1-enylpyrrolidine derivative 4.

In order to synthesize 4-styrylnicotinate 2n we examined the reaction of 1n, as shown in Scheme 4. The one-pot synthesis of 2n was carried out under the optimized condition in the presence of Cs₂CO₃; however, the yield of 2n was moderate (47%). Thus we examined a two-step process, the synthesis of tetrahydropyridine and the following aromatization. The tetrahydropyridine 3n was obtained in good yield (72%) along with 3nᵢ (11%) when we carried out the reaction in the presence of Et₃N. The intermediate 3n could be converted to 2n under the influence of DBU (5.0 equiv.) in refluxing toluene in good yield (64%). However, the overall yield of 2n using a two-step process was similar to that of the one-pot reaction. A consecutive 4-exo carbopalladation at the intermediate stage II–n to a tricyclic compound 5 cannot occur.

### Table 2. Synthesis of various 4-arylnicotinates.

<table>
<thead>
<tr>
<th>Ar</th>
<th>COOR</th>
<th>Pd(OAc)₂ (5 mol%)</th>
<th>PPH₃ (10 mol%)</th>
<th>Cs₂CO₃ (2.5 equiv.)</th>
<th>DMF, 120 °C, 3 h</th>
<th>ROOC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ts</td>
<td>Br</td>
<td>1a–l</td>
<td></td>
<td></td>
<td></td>
<td>2a–l</td>
</tr>
</tbody>
</table>

### Scheme 3. Attempted synthesis of 4-pentylnicotinate 2m.

because the alkylpalladium and styryl moieties are positioned in a trans-relationship.

In order to synthesize 5-arylmethyl- or 5-alkynicotinates, we examined a palladium-catalyzed Heck reaction of 3a and cross-metathesis (CM) reaction, as shown in Scheme 5. The Heck reaction of 3a with 2-bromonaphthalene was carried out under the influence of K₂CO₃, because compound 3a could be converted into 2a in the presence of Cs₂CO₃. In this way, a tetrahydropyridine 3o was obtained in good yield (78%) along with a trace amount of pyridine 2o (3%). The tetrahydropyridine 3o could be converted to 2o in good yield (71%) by treatment with Cs₂CO₃ in DMF at 120°C for 3 h. However, a trial for the conversion of methylene derivative 3a to hexylidene derivative 6 by a CM reaction with 1-hexene failed in the presence of a second generation Grubbs catalyst.[12]

2-Arylnicotinate 2p could also be synthesized from N-(2-bromoallyl)-substituted aza-MBH adduct 1o, as shown in Scheme 6. The synthesis of 1,2,5,6-tetrahydropyridine 3p' was reported by us a few years ago.[8d] At that time, the aromatization of 3p' afforded only a low yield of 2p (22%). Thus we reexamined a one-pot synthesis of 2p from 1o in the presence of Cs₂CO₃ in DMF. At the early stage of the reaction compound 3p' was formed as a major product along with a trace amount of 2p; however, a prolonged heating of the reaction mixture caused a severe decomposition of 3p' without an increase of 2p. To our delight, the aromatization of 3p' was efficiently conducted with DBU to produce 2p in moderate yield (59%), as for the conversion of 3n to 2n (vide supra, Scheme 4). It is interesting to note that 3p' has been formed as the sole product, as compared to the formation of 3a and 3a' in a mixture from 1a (vide supra, Scheme 2). As shown in Scheme 6, the first 5-exo carbopalladation might occur selectively towards the re-face of the double bond of 1o to form the intermediate IV, presumably due to the electronic repulsion between the ester and N-sulfonyl groups. The intermediate IV was converted to VI, and a subsequent syn β-H elimination produced 3p'.

As a next examination, we carried out the reaction of 1p bearing a nitrile group instead of an ester, as shown in Scheme 7. A severe decomposition was observed under the conditions employing Cs₂CO₃ in DMF at 120°C, while the use of Et₃N at low temperature (90°C) showed very sluggish reactivity. Only a low yield of tetrahydropyridine 3q (22%) was ob-

Scheme 4. Synthesis of 4-styrylnicotinate 2n.

Scheme 5. Heck reaction of 3a and an extension of side chain.
tained along with a tosylamide derivative (24%) when we carried out the reaction under the influence of Et₃N at 120 °C. As we noted above, the ester moiety of 1a might facilitate 5-exo carbopalladation by stabilizing the alkylpalladium intermediate I; however, such a directing and/or stabilizing effect is not present in the corresponding intermediate I-p for the nitrile derivative, and this would be the reason for the low yield of 3q.

In order to obtain 3-acetylpyridine 2r the reaction of an acetyl derivative 1q was examined, as shown in Scheme 8. Initially, we examined a one-pot synthesis of 2r in the presence of Cs₂CO₃ in DMF at 120 °C; however, we failed to obtain 2r in a reasonable yield. Monitoring of the reaction progress showed a rapid formation of tetrahydropyridine 3r as a major product along with a trace amount of 2r. However, the amount of 2r was not increased even after a prolonged heating. Thus, we prepared 3r in the presence of Et₃N and examined the aromatization of 3r to 2r. As in the case of the styryl derivative (Scheme 4) an aromatization of 3r to 2r was carried out in the presence of DBU in toluene, and 2r could be obtained in moderate yield (64%).

As a last entry, we examined the synthesis of 5-alkynicotinate 2s, as shown in Scheme 9. As noted above in Scheme 5, an attempted synthesis of 5-alkynicotinate using the cross-metathesis protocol failed. Thus, we prepared compound 1r with 1,2-dibromo-
hex-2-ene, which was prepared from trans-2-hexenal in three steps.[6b] The one-pot synthesis of 5-butylnicotinate 2r was successfully carried out under the optimized conditions in reasonable yield (46%).

In summary, we have disclosed an efficient synthesis of various nicotinate derivatives from suitably modified Morita–Baylis–Hillman (MBH) adducts via a palladium-catalyzed reaction involving domino 5-exo/3-exo carbopalladations, ring-expansion by palladium rearrangement, and an aromatization process.

**Experimental Section**

**Typical Experimental Procedure for the Pd-Catalyzed Synthesis of Methyl 4-Phenyl-5-methylnicotinate (2a)**

A mixture of 1a (232 mg, 0.5 mmol), Pd(OAc)2 (6 mg, 5 mol%), PPh3 (13 mg, 10 mol%) and Cs2CO3 (408 mg, 2.5 equiv.) in DMF (1.5 mL) was heated to 120 °C for 3 h. The reaction mixture was poured into dilute HCl solution and extracted with diethyl ether. The organic solvent was removed by evaporation, and the residue was purified by flash column chromatography (hexanes/ether, 3:1) to afford 2a as a pale yellow solid; yield: 125 mg (65%); mp 48–49°C; 1H NMR (CDCl3, 300 MHz): δ = 2.11 (s, 3H), 3.62 (s, 3H), 7.15–7.17 (m, 2H), 7.36–7.48 (m, 3H), 8.62 (br s, 1H), 8.92 (br s, 1H); 13C NMR (CDCl3, 75 MHz): δ = 17.27, 52.07, 126.39, 127.59, 127.77, 128.23, 132.11, 137.44, 148.39, 149.69, 153.26, 166.84; ESI-MS: m/z = 228 [M+H]+; anal. calcld. for C16H14NO2: C 73.99, H 5.77, N 6.16; found: C 74.13, H 5.89, N 6.01.

Scheme 9. Synthesis of 5-butylnicotinate 2s.

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### References


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