Directed Palladium-Catalyzed Oxidative C–H Arylation of (Hetero)arenes with Arylboronic Acids by Using TEMPO

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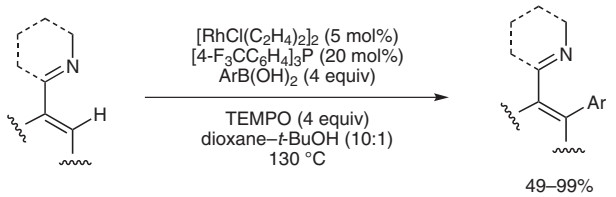
Abstract: Oxidative coupling of three different arenes and a thiophene derivative with various arylboronic acids with $Pd(OAc)_2$ and the commercially available 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical (TEMPO) as an oxidant are reported. A 2-pyridyl group on the substrates serves as *ortho*-directing group to mediate the C–H arylation. Mechanistic studies are provided.

Key words: biaryls, boronic acids, C–H arylation, nitroxides, palladium

Biaryls are an important class of compounds which are often used as ligands in asymmetric synthesis.[1] Moreover, they occur in various natural products[2] and are also valuable building blocks for the construction of organic materials.[3,4] Biaryls have been predominantly prepared by metal-catalyzed cross-coupling reactions of aryl halides and aryl metal compounds.[1] More recently, many research groups have focused on the direct arylation of arenes and heteroarenes without preactivation of one[5] or two[6] of the coupling partners. In most of these reports, Pd catalysts have been used for arene activation, but various other metals have been successfully employed as well.[5] Most of the Pd-catalyzed processes use aryl halides as the activated coupling partner for C–H arylation.[5] Aryl- and alkylboronic acids[7] have also been applied as coupling partners by Murai,[8] Sames,[9] Shi,[10] and Yu.[11] We have recently developed a Rh-catalyzed directed C–H arylation of various arenes with boronic acids by using TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl radical) as an oxidant (Scheme 1).[12,13]

This process is useful since TEMPO and many arylboronic acids are commercially available. Based on these results we initiated a program on the direct C–H arylation of arenes with arylboronic acids by using Pd catalysts and TEMPO as an external oxidant. This study was driven by the fact that Pd catalysts are cheaper than Rh catalysts. In the present letter we disclose our first results on Pd-catalyzed aryl–aryl bond-forming reactions with arylboronic acids as coupling partners in combination with TEMPO as an environmentally benign oxidant. To the best of our knowledge, TEMPO has not been used as an external oxidant in Pd-catalyzed direct C–H arylations of arenes with aryl- or alkylboronic acids.[14]



Scheme 1 Rhodium-catalyzed directed C–H arylation

Initial studies were performed with arene **1**, bearing the *ortho*-directing 2-pyridyl group,[15] and phenylboronic acid (4 equiv) by using various Pd catalysts (10 mol%) in the presence of excess TEMPO (4 equiv) under different conditions to give **2a** (Table 1). As a side product the bisarylated arene **3a** was identified in all reactions performed.

The influence of the solvent with $Pd(OAc)_2$ as a catalyst was investigated first. Reactions were conducted at 50 °C for five days. The C–H arylation in propionic acid was slow and **2a** was isolated in only 20% yield along with traces of **3a** (Table 1, entry 1). Pleasingly, the yield could be improved upon switching to acetic acid as a solvent under otherwise identical conditions (57%, entry 2). No base was required for this reaction. The C–H arylation in DMSO and DMF were low yielding (entries 3 and 4). An acceptable result was achieved in dimethylacetamide (DMA, entry 5). After having identified acetic acid as best solvent we varied the catalyst; $(C_3H_5PdCl)_2$ and $Pd(acac)_2$ showed lower activities as compared to $Pd(OAc)_2$ (entries 6 and 7). Phosphine and sulfoxide ligands turned out to be detrimental to the C–H arylation (entries 8 and 9). The more electrophilic $Pd(CF_3CO_2)_2$ showed a moderate activity (entry 10). Importantly, upon using KF (4 equiv) as an additive with $Pd(OAc)_2$ as a catalyst, reaction time could be decreased without affecting the yield to a large extent (entry 11). Decreasing or increasing the reaction temperature did not improve the yield (entries 12–15). We also tried to run the reaction by using a substoichiometric amount of TEMPO (10 mol%) with oxygen (9.8692×10^{-6} Pa) as a terminal oxidant.[12] However, only traces of the products were formed.

Under the optimized conditions other arylboronic acids were tested in the arylation of **1**.[16] As expected, the tolyl derivative $4\text{-}MeC_6H_4B(OH)_2$ provided a similar result (Table 1, entry 17). The reaction with $4\text{-}FC_6H_4B(OH)_2$ provided selectively the monoarylated product **2b** in 55% yield (entry 16). However, heteroarylboronic acids such as 2-thienyl and 2-furylboronic acid did not undergo direct C–H-arylation under the optimized conditions.

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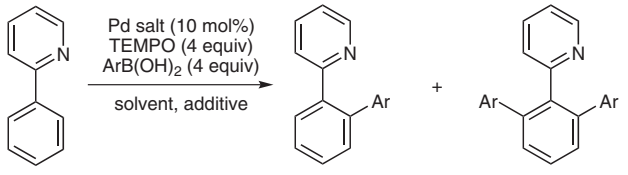
Table 1 Palladium-Catalyzed Directed C–H Arylation under Different Conditions



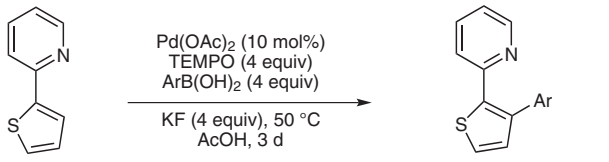
1

2a Ar = Ph
2b Ar = 4–FC_6H_4
2c Ar = Tol

3a Ar = Ph
3b Ar = 4–FC_6H_4
3c Ar = Tol

Entry	Pd catalyst	Solvent	Temp (°C)	Time (d)	Yield (%)[a] **2a/3a**
1	$Pd(OAc)_2$	$EtCO_2H$	50	5	22/1
2	$Pd(OAc)_2$	AcOH	50	5	57/7
3	$Pd(OAc)_2$	DMSO	50	5	25/1
4	$Pd(OAc)_2$	DMF	50	7	13/1
5	$Pd(OAc)_2$	DMA	50	7	49/4
6	$(C_3H_5PdCl)_2$	AcOH	50	5	25/5
7	$Pd(acac)_2$	AcOH	50	6	35/3
8	$Pd(PPh_3)_2(OAc)_2$	AcOH	50	6	20/3
9	$(PhSOCH_2)_2Pd(OAc)_2$	AcOH	50	7	37/3
10	$Pd(CF_3CO_2)_2$	AcOH	50	6	46/7
11[b]	$Pd(OAc)_2$	AcOH	50	3	52/9
12	$Pd(OAc)_2$	AcOH	30	5	33/2
13	$Pd(OAc)_2$	AcOH	40	5	37/5
14	$Pd(OAc)_2$	AcOH	70	6	38/4
15	$Pd(OAc)_2$	AcOH	100	6	28/1
16[b]	$Pd(OAc)_2$	AcOH	50	3	55 (**2b**)/–(**3b**)
17[b]	$Pd(OAc)_2$	AcOH	50	3	49 (**2c**)/8 (**3c**)

[a] Isolated yield.
[b] KF (4 equiv) was added.



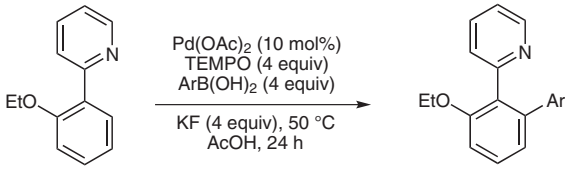
4

5a Ar = Ph 46%
5b Ar = 3–ClC_6H_4 46%
5c Ar = Tol 45%

Scheme 2 Palladium-catalyzed directed C–H arylation of **4**

The 2-pyridyl-substituted thiophene derivative **4** could also be arylated under the same conditions (Scheme 2).[16] Products **5a**–**c** were obtained in 45–46% yield.

We continued our studies with arene **6**, which was identified as an efficient substrate for our Rh-catalyzed C–H arylations.[12] As compared to the transformations of **1** or **4**, we found that reaction with **6** is far faster, and product **7a** was isolated in 74% yield after 24 hours' reaction time (Scheme 3). Increasing the reaction time did not further improve the yield. With substrate **6** efficient arylation could also be achieved by using 2 equivalents of $PhB(OH)_2$ (64%) or by using 2 equivalents of TEMPO (57%).[16]



6

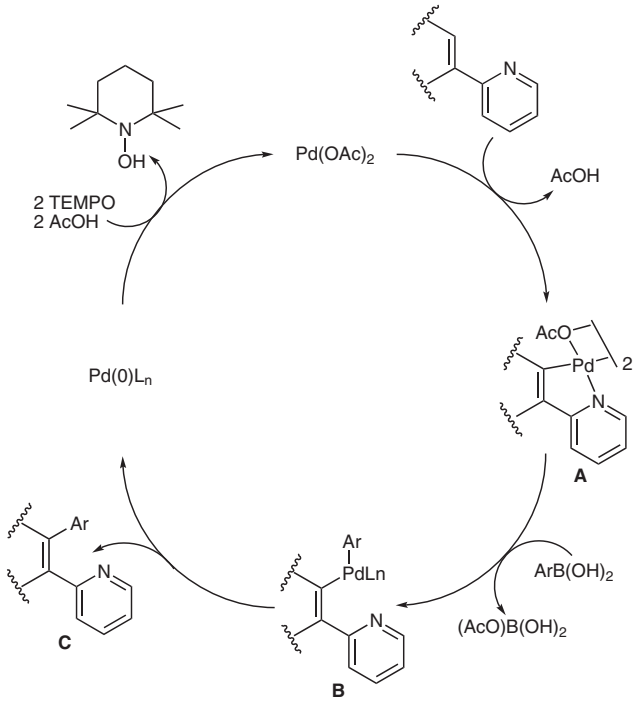
7a Ar = Ph 74%
7b Ar = Tol 54%
7c Ar = PMP 24%
7d Ar = 4–FC_6H_4 41%
7e Ar = 3–ClC_6H_4 65%
7f Ar = 4–vinylC_6H_4 23%

Scheme 3 Palladium-catalyzed directed C–H arylation of **6**

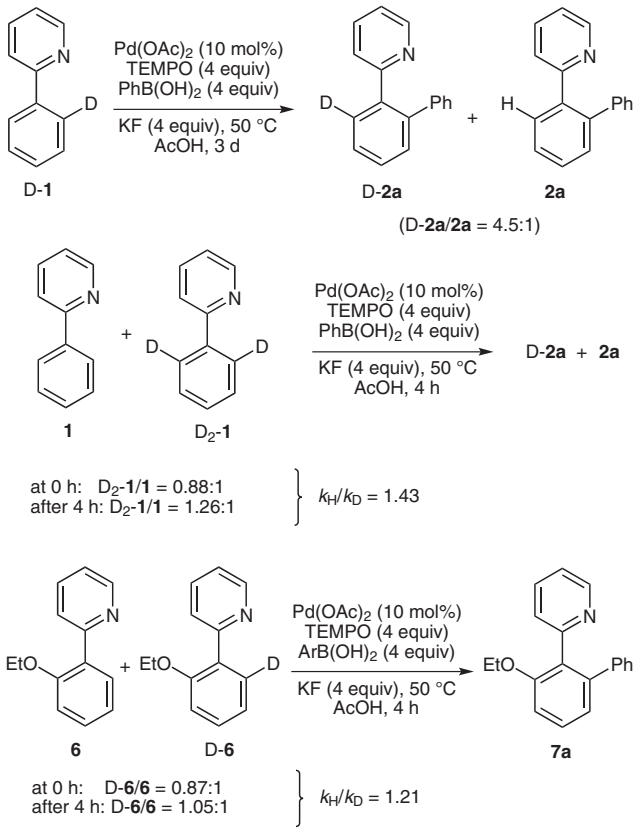
Good yields in the arylation of **6** were obtained with 4-$MeC_6H_4B(OH)_2$ (→ **7b**, 54%) and 3-$ClC_6H_4B(OH)_2$ (→ **7e**, 65%). Electronic effects at the boronic acid moiety strongly influenced the reaction outcome. The electron-poor *para*-fluoro boronic acid [4-$FC_6H_4B(OH)_2$] delivered **7d** in 41% yield, whereas only a moderate yield was obtained with the electron-rich 4-$MeOC_6H_4B(OH)_2$ (→ **7c**, 24%). The C–H arylation with 4-vinyl-$C_6H_4B(OH)_2$ occurred in a low yield (→ **7f**, 23%).

We suggest the following mechanism for the Pd-catalyzed direct C–H arylation (Scheme 4). In acetic acid as solvent the active catalyst is supposed to be $Pd(OAc)_2$ which undergoes pyridyl-directed C–H arylation to give **A** (see discussion below). Transmetalation with an arylboronic acid leads to **B** which subsequently undergoes reductive elimination to afford product **C** and a Pd(0) species. The Pd(0) species is then oxidized with 2 equivalents of TEMPO to give after reaction with acetic acid $Pd(OAc)_2$ and TEMPOH.

The C–H activation may either occur via electrophilic aromatic substitution[5] or via a concerted proton transfer–metalation pathway.[17,18] For substrate **1** we decided to study the primary kinetic isotope effect and also the intermolecular kinetic isotope effect. Thus, compound D-**1** was reacted under optimized conditions with $PhB(OH)_2$ and TEMPO to give **2a** and the deuterated compound D-**2a** in a ratio of 1:4.5, as determined by mass spectrometry (Scheme 5).[19,20] This result indicates that the reaction of **1** with $PhB(OH)_2$ seems to occur via a concerted proton transfer–metalation pathway mechanism.[17,18] Moreover, we studied the intermolecular kinetic isotope effect. To this end, **1** and D_2-**1**[21] (ratio 1:0.88) were reacted with $PhB(OH)_2$ for 4 hours (low conversion). An isotope effect of 1.43 was calculated based on the ratio of unreacted starting material (MS analysis). The smaller intermolecular kinetic isotope effect indicated that complexation of



Scheme 4 Suggested mechanism for Pd-directed C–H arylation with TEMPO as external oxidant



Scheme 5 Kinetic isotope effect for the reaction with D-**1**, **1**/D_2-**1** and **6**/D-**6**

the Pd catalyst with the pyridyl group is to a large extend irreversible (ligand exchange slower than C–H activation).

We also looked at the intermolecular kinetic isotope effect for the more nucleophilic substrate **6**. To this end, a mixture of **6** and D-**6** (0.87:1) was reacted under the optimized conditions with $PhB(OH)_2$ for 4 hours. The MS analysis of the remaining starting material revealed an intermolecular kinetic isotope effect of 1.21. Since **6** is more reactive than **1** we assume that complexation of **6** is also irreversible under the applied conditions. Hence, the experimentally determined intermolecular kinetic isotope effect does not allow any conclusion on the mechanism of the C–H activation step for that substrate.

In conclusion, we presented $Pd(OAc)_2$-catalyzed C–H arylations of four different arenes with readily available arylboronic acids as coupling partners. Commercially available environmentally benign TEMPO was used as a terminal oxidant. The pyridyl group served as directing group to mediate the C–H arylation.

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(16) **General Experimental Procedure**
The corresponding boronic acid (1.00 mmol), TEMPO (156 mg, 1.00 mmol), KF (58 mg, 1.0 mmol), $Pd(OAc)_2$ (5.6 mg, 25 μmol), the pyridine derivative (0.25 mmol), and AcOH (1 mL) were stirred in a sealed tube at 50 °C for 24 h or 72 h, respectively. Water (3 mL) and brine (1 mL) were added and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and the volatiles were removed under reduced pressure. The residue was purified by flash chromatography.

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(19) **Determination of the Kinetic Isotope Effects**
According to the general experimental procedure with 2-(2-deuterophenyl)pyridine (D-**1**, 39 mg, 0.25 mmol) and phenylboronic acid (122 mg, 1.00 mmol) for 72 h. Flash chromatography (pentane–EtOAc, 20:1 → 10:1) gave a mixture of **2a** and D-**2a** as a yellow oil (17 mg, 65%). The isotope effect was determined by integration of the ESI-HRMS data in consideration of the isotope pattern of **2a**. The deuterated species D-**2a** and compound **2a** were obtained in a ratio of 4.5:1. According to GP 1 with 2-ethoxy-2-phenylpyridine (**6**, 10 mg, 50 μmol), 2-(2-ethoxy-6-deuterophenyl)pyridine (D-**6**, 10 mg, 50 μmol) and phenylboronic acid (24 mg, 0.2 mmol) for 4 h. The ratios of D-**6** to **6** (0.87:1) were determined before the reaction (0 h) and after a reaction time of 4 h (1.05:1) by integration of the corresponding ESI-HRMS data in consideration of the isotope pattern of **6**. The kinetic isotope effect was calculated to be 1.21.

(20) As a side product the doubly arylated product is always formed (<15% with respect to the monoarylated compound). We assume that the primary kinetic isotope effect for the second arylation and the first arylation should be similar. Therefore, the measured value of 4.5 is slightly too high since **2a** is consumed faster than D-**2a**. However, the error should be smaller than 12%. Hence the primary kinetic isotope effect for the first arylation is about 4.0–4.5 to 1.

(21) **2-(2,6-Dideuterophenyl)pyridine (D_2-1) and 2-(2,6-Dibromophenyl)pyridine**
2-(2-Bromophenyl)pyridine[22] (466 mg, 2.0 mmol), $Cu(OAc)_2$ (363 mg, 2.0 mmol), and 1,1,2,2-tetra-bromoethane were heated in a sealed reaction tube at 130 °C for 24 h.[23] Dichloromethane (10 mL) and Na_2S (aq sat., 10 mL) were added. The mixture was filtered over Celite and the filtrate was washed with brine (2 × 10 mL). The combined organic layers were dried over $MgSO_4$ and the volatiles were removed under reduced pressure. The residue was purified by flash chromatography (pentane–MTBE, 20:1).

2-(2-Bromo-6-deuterophenyl)pyridine
To a solution of 2-(2,6-dibromophenyl)pyridine (313 mg, 1.0 mmol) in THF (20 mL) at –78 °C was added dropwise *n*-BuLi (1.68 M solution in hexanes, 0.60 mL, 1.00 mmol).[23] The mixture was stirred for 30 min. Then, D_2O (2.0 mL) was added and stirring was continued for additional 30 min. The mixture was allowed to warm to r.t., and EtOAc (10 mL) and brine (20 mL) were added. The mixture was extracted with EtOAc (3 × 20 mL), dried over $MgSO_4$, and the volatiles were removed under reduced pressure. The residue was purified by flash chromatography (pentane–MTBE, 50:1) and the product was obtained as a yellow oil (0.181 g, 0.68 mmol, 77%). The product was used without any further characterization.

2-(2,6-Dideuterophenyl)pyridine (D_2-1)
To a solution of 2-(2-bromo-6-deuterophenyl)pyridine (160 mg, 0.68 mmol) in THF (10 mL) at –78 °C was added dropwise *n*-BuLi (1.68 M solution in hexanes, 0.4 mL, 0.68 mmol).[23] The mixture was stirred for 30 min. Then, D_2O (1.0 mL) was added and stirring was continued for additional 30 min. The mixture was allowed to warm to r.t., and EtOAc (5 mL) and brine (10 mL) were added. The mixture was extracted with EtOAc (3 × 10 mL), dried over $MgSO_4$, and the volatiles were removed under reduced pressure. The residue was purified by flash chromatography (pentane–MTBE, 50:1) and the product was obtained as a colorless oil (0.104 g, 0.66 mmol, 97%, 88 atom% D). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.68 (d, *J* = 4.78 Hz, 1 H, aryl-H), 7.69 (d, *J* = 3.52 Hz, 2 H, aryl-H), 7.42 (m, 3 H, aryl-H), 7.19 (m, 1 H, aryl-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.4 (C), 149.7 (C-H), 139.3 (C), 136.7 (CH), 129.0 (CH), 128.7 (CH), 126.6 (*J* = 23 Hz, CD), 122.1 (CH), 120.5 (CH). ESI-HRMS: *m/z* calcd for $C_{11}H_7D_2N$ $[M + H]^+$: 157.0933; found: 157.0939.

2-(2-Ethoxy-6-deuterophenyl)pyridine (D-6)
2-(2-Ethoxyphenyl)pyridine (**6**, 93 mg, 0.47 mmol), NBS (0.10 g, 0.56 mmol) and $Pd(OAc)_2$ (5.4 mg, 24 mol) in MeCN (10 mL) were heated in a reaction tube at 120 °C for 10 h.[22] The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (pentane–MTBE, 10:1). Crude 2-(2-bromo-6-ethoxy-phenyl)pyridine was obtained as a pale yellow oil (96 mg) and used for the next reaction without any further characterization. To a solution of crude 2-(2-bromo-6-ethoxyphenyl)pyridine (86 mg, 0.31 mmol) in THF (10 mL) at –78 °C was added dropwise *n*-BuLi (1.3 M solution in hexanes, 0.48 mL, 0.62 mmol).[23] The mixture was allowed to warm to –40 °C and stirred for 30 min. Then, D_2O (0.5 mL) was added and stirring was continued for additional 30 min. The mixture was allowed to warm to r.t., and EtOAc (5 mL) was added. The organic layer was washed with brine, dried over $MgSO_4$, and the volatiles were removed under reduced pressure. The crude product was purified by flash chromatography (pentane–MTBE, 20:1) and D-**6** was obtained as a pale yellow oil (43 mg, 46% over two steps, 94 atom% D determined via ESI-MS). IR (neat): 3036, 2980, 2933, 2881, 2363, 2341, 1578, 1474, 1452, 1421, 1391, 1285, 1250, 1190, 1138, 1111, 1088, 1040, 1026, 990, 924, 874, 812, 795, 746, 733, 679, 611, 552 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.68 (m, 1 H, aryl-H), 7.88 (m, 1 H, aryl-

H), 7.66 (m, 1 H, aryl-H), 7.32 (m, 1 H, aryl-H), 7.16 (m, 1 H, aryl-H), 7.05 (m, 1 H, aryl-H), 6.96 (m, 1 H, aryl-H), 4.07 (q, J = 6.9 Hz, 2 H, CH_2), 1.36 (t, J = 6.9 Hz, 2 H, CH_3). ^{13}C NMR (600 MHz, $CDCl_3$): δ = 156.3 (C), 156.0 (C), 149.3 (CH), 135.4 (CH), 130.8 (C), 129.7 (CH), 129.0 (C), 125.1 (CH), 121.5 (CH), 120.9 (CH), 112.5 (CH), 64.1 (CH_2), 14.8 (CH_3). $^1H\{^1H\}$ 1D-TOCSY (600 MHz, $CDCl_3$): $\delta(^1H)_{irr}/\delta(^1H)_{res}$ = 6.96/7.32, 7.05; 8.68/7.88, 7.66, 7.16. $^1H,^1H$ GCOSY (600 MHz, $CDCl_3$): $\delta(^1H)/\delta(^1H)$ = 8.86/7.16; 7.88/7.66; 7.66/7.88, 7.16; 7.32/7.05, 6.96; 7.16/8.68, 7.66; 7.05/7.32; 6.96/7.32. $^1H,^{13}C$ GHSQC (600 MHz, $CDCl_3$): $\delta(^1H)/\delta(^{13}C)$ = 149.3/8.68; 135.4/7.66; 129.7/7.32; 125.1/7.88; 121.5/7.16; 120.9/7.05; 112.5/6.96; 64.1/4.07; 14.8/1.36. $^1H,^{13}C$ GHMBC (600 MHz, $CDCl_3$): $\delta(^1H)/\delta(^{13}C)$ = 156.3/7.80, 7.32, 7.05, 6.96, 4.07; 156.0/7.868, 7.88, 7.66; 149.3/7.66, 7.16; 135.4/8.68, 7.88, 7.80, 7.52; 129.7/7.05; 129.0/7.88, 7.32, 7.05, 6.96; 125.1/8.68, 7.66, 7.16; 121.5/8.68, 7.88, 7.66; 120.9/6.96; 112.5/7.32, 7.05; 64.1/1.35; 14.8/4.05. ESI-HRMS: *m/z* calcd for $C_{13}H_{12}DNO$ $[M + H]^+$: 201.1133; found: 201.1129.

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