An Environmentally Benign Procedure for the Synthesis of Aryl and Arylvinyl Nitriles Assisted by Microwave in Ionic Liquid

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Abstract: Aryl and arylvinyl nitriles have been prepared in good yields from the corresponding bromides with potassium hexacyanoferrate(II) using palladium-catalyzed reactions in ionic liquid under microwave irradiation.

Key words: palladium, potassium hexacyanoferrate(II), microwave, ionic liquid

Aryl nitriles are of considerable interest as integral part of dyes, herbicides, natural products and pharmaceuticals.[1] In organic synthesis, nitriles are important intermediates for further transformations into other functional groups. In medicinal chemistry, nitriles are very useful as they can be transformed into a variety of biologically important structures such as tetrazoles, triazoles, oxazoles, thiazoles, oxazolidinones. An elegant method for the preparation of benzonitriles is the transition-metal-catalyzed cyanation of aryl halides.[2,3] Among them, the palladium-catalyzed coupling reaction has attracted widespread interest,[4–7] and has been the topic of several investigations.

Palladium-based cyanations have garnered most of the attention due to their functional group tolerance, air stability and high catalytic activity. However, most of the work has concentrated on the inconvenient traditional cyanide sources. Alkali cyanides are highly poisonous, zinc cyanide leads to stoichiometric waste of heavy metal salts and trimethylsilyl cyanide is sensitive to moisture and can easily liberate hydrogen cyanide, which is also true for acetone cyanohydrin. Although potassium hexacyanoferrate(II) ($K_4[Fe(CN)_6]$) has been rediscovered as a non-toxic cyanide source by Beller,[8] separating products from the reaction system and recycling the palladium catalyst system are other challenges.

Ionic liquids have been developed as new clean reaction medium over recent years[9] because of their special property and the Rosenmund–von Braun reaction has been attempted to carry out in ionic liquid.[10] Moreover, microwave-assisted synthesis has been accepted for reducing reaction time.[11] To further improve and expand more easy and safe tools for cyanation reactions, non-toxic palladium-catalyzed cyanation in ionic liquid under microwave irradiation can still attract current interest. Herein, we wish to report our study on the cyanation of aryl and arylvinyl bromides with $K_4[Fe(CN)_6]$ in ionic liquid ($[BMIm]BF_4$)[12] under microwave irradiation (Scheme 1).

$$\text{R–Br} + K_4[Fe(CN)_6] \xrightarrow[Na_2CO_3,\ [BMIm]BF_4,\ MW]{PdCl_2,\ DMEDA} \text{R–CN}$$

R = aryl, arylvinyl

Scheme 1

As a starting point for the development of our cyanation system, the reaction of 4-bromobiphenyl with $K_4[Fe(CN)_6]\cdot 3H_2O$ was investigated. Variation of reaction parameters on this model reaction is shown in Table 1. The reaction was first attempted using 0.5 mmol of 4-bromobiphenyl, 0.2 equivalent of $K_4[Fe(CN)_6]\cdot 3H_2O$, 1.0 equivalent of Na_2CO_3 and 2.5 mol% of $PdCl_2$ as the catalyst in $[BMIm]BF_4$ under microwave promotion. It provided a 39% yield of 4-cyanobiphenyl within 16 minutes (Table 1, entry 1). Other Pd catalysts, such as $Pd(OAc)_2$, Pd/C (5%), $Pd_2(dba)_3$ have also been employed in this reaction and none of them gave a higher yield than $PdCl_2$. Using anhydrous $K_4[Fe(CN)_6]$[13] as cyanide source led to some improvement of yield (Table 1, entry 5). To our surprise, addition of 10 mol% of DMEDA (*N*,*N*′-di-

Table 1 Cyanation of 4-Bromobiphenyl under Microwave[14] Promotion[a]

Entry	Pd catalyst (2.5%)	Ligand (10%)	Cyanide source	Yield (%)[b]
1	$PdCl_2$	—	$K_4[Fe(CN)_6]\cdot 3H_2O$	39
2	$Pd(OAc)_2$	—	$K_4[Fe(CN)_6]\cdot 3H_2O$	<5
3	$Pd_2(dba)_3$	—	$K_4[Fe(CN)_6]\cdot 3H_2O$	No reaction
4	Pd/C (5%)	—	$K_4[Fe(CN)_6]\cdot 3H_2O$	16
5	$PdCl_2$	—	$K_4[Fe(CN)_6]$	53
6	$PdCl_2$	DMEDA	$K_4[Fe(CN)_6]$	84
7	$PdCl_2$	Proline	$K_4[Fe(CN)_6]$	43
8	$PdCl_2$	PPh_3	$K_4[Fe(CN)_6]$	<10

[a] General conditions: 4-bromobiphenyl (0.5 mmol), cyanide source (0.1 mmol), $[BMIm]BF_4$ (3.0 ml), Na_2CO_3 (0.5 mmol), 16 min.
[b] Isolated yields.

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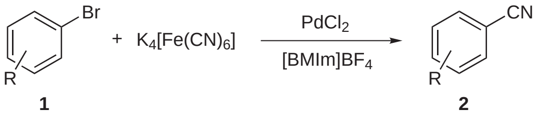
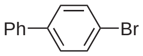
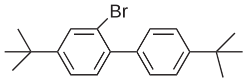
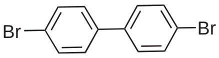
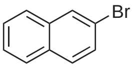
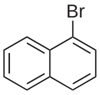
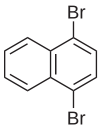
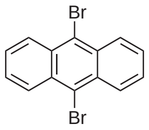
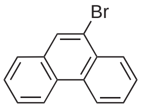
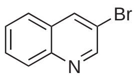
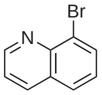
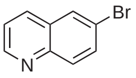
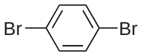
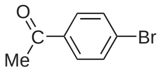
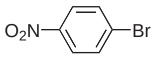
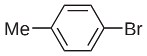
Table 2 Cyanation of Various Aryl and Quinoline Bromides under Microwave Promotion[a]



Entry	Ar–Br	Product	Time (min)	Yield (%)[b]
1		**2a**	16	84
2		**2b**	39	44
3[c]		**2c**[d]	24	73
4		**2d**	33.5	76
5		**2e**	33	80
6[c]		**2f**[d]	34	78
7[c]		**2g**[d]	30.5	64
8		**2h**	14	79
9		**2i**	16	70
10		**2j**	22	67
11		**2k**	20	84
12[c]		**2l**[d]	14	55
13		**2m**	18	56
14		**2n**	14	50
15		**2o**	30	No reaction

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[a] General conditions: anhyd $K_4[Fe(CN)_6]$ (0.05 mmol), Na_2CO_3 (0.25 mmol), aryl bromide (0.25 mmol), $PdCl_2$ (0.00625 mmol, 2.5 mol%), DMEDA (0.025 mmol), $[BMIm]BF_4$ (1.5 mL).

[b] Isolated yields. All products were identified by NMR and MS.

[c] 2.0 Equiv of anhyd $K_4[Fe(CN)_6]$ were used.

[d] Dicyano product.

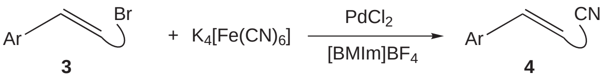
methylethylenediamine) as a ligand to the reaction increased the yield of desired product greatly (84%, Table 1, entry 6). The use of other ligands, such as PPh_3 and proline, did not bring about good results (Table 1, entries 7 and 8). On the basis of the above optimization efforts, the combination of 0.5 mmol of 4-bromobiphenyl, 0.2 equivalents of $K_4[Fe(CN)_6]$, 2.5 mol% of $PdCl_2$, 1.0 equivalent of Na_2CO_3 and 10 mol% of DMEDA in $[BMIm]BF_4$ under microwave irradiation gave the best result.

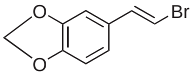
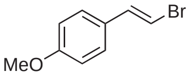
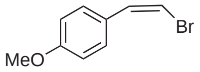
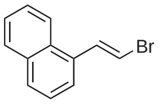
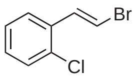
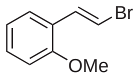
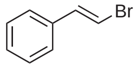
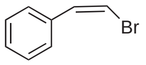
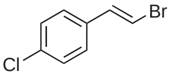
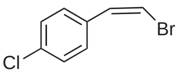
Having optimized the conditions, we explored the scope of this method. Various aryl bromides are converted to the corresponding nitriles using these conditions. The results are presented in Table 2. A number of biphenyl and fused ring aryl bromides worked well in this procedure (Table 2, entries 1–8). For 1,4-dibromobenzene, 4,4′-dibromobiphenyl, 1,4-dibromonaphthalene and 9,10-dibromoanthracene, both halogen substituents were replaced by cyanides (Table 2, entries 3, 6, 7 and 12).

The cyanation of N-heteroaryl bromides was also successful. Quinoline bromides gave the corresponding nitriles in good yields (Table 2, entries 9–11). Thus, the aryl bromides with extensive conjugated system gave satisfactory results in our reaction system. Simple ring aryl bromides with electron-withdrawing substituents were cyanated in moderate yields (Table 2, entries 12–14). Disappointingly, an attempt to convert electron-donating substrate such as 1-bromo-4-methylbenzene to the corresponding nitrile was unsuccessful (Table 2, entry 15).

Since α,β-unsaturated nitriles also have featured as intermediates in several natural product syntheses[15] and are particularly valuable as precursors to substituted nitriles by conjugate additions,[16] we turned our attention to expanding cyanation of arylvinyl bromides with $K_4[Fe(CN)_6]$ under the same catalyst system. The investigation was successful and the results are summarized in Table 3. Various arylvinyl bromides bearing electron-donating substituent underwent a smooth reaction in this process and gave excellent results in terms of stereo-

Table 3 Cyanation of Various Arylvinyl Bromides under Microwave Promotion[a]



Entry	Ar–Br	Product	Time (min)	Yield (%)[b] (*E*/*Z*)[c]
1		**4a**	38	41 (*E*)
2		**4b**	33.5	55 (*E*)
3		**4c**	40	36 (*Z*)
4		**4d**	12	76 (*E*)
5		**4e**	20	31 (*E*)
6		**4f**	32	47 (*E*)
7		**4g**	24	74 (*E*/*Z* = 8:1)
8		**4h**	22	71 (*E*/*Z* = 1:2)
9		**4i**	16	65 (*E*/*Z* = 17:1)
10		**4j**	18	63 (*E*/*Z* = 1:4)

[a] Reagents: anhyd $K_4[Fe(CN)_6]$ (0.05 mmol), Na_2CO_3 (0.25 mmol), arylvinyl bromide (0.25 mmol), $PdCl_2$ (0.00625 mmol, 2.5 mol%), DMEDA (0.025 mmol), $[BMIm]BF_4$ (1.5 mL).

[b] Isolated yields. All products were identified by NMR and MS.

[c] Determined by ^1H NMR.

selectivity (Table 3, entries 1–4). For example, compound **3d**, as an extensive conjugated system, showed optimal stereoselectivity and good yield of product (Table 3, entry 4). Moreover, the reaction had perfect stereoselectivity in cases of substituents in *ortho*-position (Table 3, entries 5 and 6). Compared to this situation, β-bromostyrene and β-bromo-4-chlorostyrene have also been allowed to react with $K_4[Fe(CN)_6]$ and afforded good yields of the corresponding nitriles, as a pair of *E* and *Z* isomers (Table 3, entries 7–10).

Catalyst recycling studies were also performed (Table 4). After extraction with ethyl acetate–petroleum ether = 8:1 to separate the product from the system, the resulting $[BMIm]BF_4$ was pumped under reduced pressure for several minutes and reused for the next reaction directly. The resulting $[BMIm]BF_4$ containing Pd catalyst could be reused successfully five times without reduction of its catalytic activity.

Table 4 Recycle of Ionic Liquid Reaction Medium under Microwave Promotion[a]

Isolated yield (%)				
Run 1	Run 2	Run 3	Run 4	Run 5
84	86	84	88	84

[a] Reagents: $PdCl_2$ (0.0125 mmol, 2.5 mol%), DMEDA (0.05 mmol), $[BMIm]BF_4$ (3 mL), 4-bromobiphenyl (0.5 mmol), anhyd $K_4[Fe(CN)_6]$ (0.1 mmol), Na_2CO_3 (0.5 mmol), 16 min.

Finally, the reactions under conventional heating conditions were carried out (Table 5). As can be seen, the cyanation of 4-bromobiphenyl led to a 49% yield in DMA and gave poor yield of product in $[BMIm]BF_4$ for 24 hours (Table 5, entries 1 and 2). Moreover, the reaction in DMA under microwave irradiation could not afford any improvement in product yield (Table 5, entry 3). In contrast, the cyanation of 4-bromobiphenyl was dramatically speeded-up under microwave irradiation in $[BMIm]BF_4$ (16 min) and high yield was obtained (84%, Table 5, entry 4). It provided clear evidence that microwave irradiation could reduce reaction time significantly and promote the cyanation reaction in ionic liquid effectively.

In summary, we have demonstrated the successful development of an environmentally benign procedure[17] for the synthesis of aryl and arylvinyl nitriles[18] using anhydrous $K_4[Fe(CN)_6]$ in ionic liquid under microwave irradiation. The cyanide source is non-toxic and inexpensive. The solvent is 'green', harmless and readily available. The microwave heating reduces reaction times greatly and the catalyst system can be easily separated from the product and reused several times.

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References and Notes

(1) (a) Larock, R. C. *Comprehensive Organic Transformations*; VCH: New York, **1989**, 819. (b) Grundmann, C. In *Houben-Weyl: Methoden der organischen Chemie*, 4th ed., Vol. E5; Falbe, J., Ed.; Thieme: Stuttgart, **1985**, 1313.

(2) For the nickel-catalyzed cyanation of aryl halides, see: (a) Cassar, L. *J. Organomet. Chem.* **1973**, *54*, 57. (b) Cassar, L.; Foà, M.; Montanari, F.; Marinelli, G. P. *J. Organomet. Chem.* **1979**, *173*, 335. (c) Sakakibara, Y.; Okuda, F.; Shimoyabashi, A.; Kirino, K.; Sakai, M.; Uchino, N.; Takagi, K. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1985. (d) Sakakibara, Y.; Ido, Y.; Sasaki, K.; Sakai, M.; Uchino, N. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2776. (e) Rock, M.-H.; Merhold, A. WO 98/37058, **1998**.

(3) For the palladium-catalyzed cyanation of aryl halides, see: (a) Takagi, K.; Okamoto, T.; Sakakibara, Y.; Oka, S. *Chem. Lett.* **1973**, 471. (b) Sekiya, A.; Ishikawa, N. *Chem. Lett.* **1975**, 277. (c) Takagi, K.; Okamoto, T.; Sakakibara, Y.; Ohno, A.; Oka, S.; Hayama, N. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3298. (d) Takagi, K.; Okamoto, T.; Sakakibara, Y.; Ohno, A.; Oka, S.; Hayama, N. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3177. (e) Dalton, J. R.; Regen, S. L. *J. Org. Chem.* **1979**, *44*, 4443. (f) Akita, Y.; Shimazaki, M.; Ohta, A. *Synthesis* **1981**, 974. (g) Chatani, N.; Hanafusa, T. *J. Org. Chem.* **1986**, *51*, 4714. (h) Takagi, K.; Sasaki, K.; Sakakibara, Y. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1118. (i) Anderson, Y.; Långström, B. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1395. (j) Okano, T.; Kiji, J.; Toyooka, Y. *Chem. Lett.* **1998**, 425. (k) Anderson, B. A.; Bell, E. C.; Ginah, F. O.; Harn, N. K.; Pagh, L. M.; Wepsiec, J. P. *J. Org. Chem.* **1998**, *63*, 8224. (l) Maligres, P. E.; Waters, M. S.; Fleitz, F.; Askin, D. *Tetrahedron Lett.* **1999**, *40*, 8193. (m) Jin, F.; Confalone, P. N. *Tetrahedron Lett.* **2000**, *41*, 3271.

Table 5 Cyanation of 4-Bromobiphenyl[a]

Entry	Solvent	Conventional heating	Microwave irradiation	Time	Yield (%)[b]
1	DMA	160 °C	–	24 h	49
2	$[BMIm]BF_4$	160 °C	–	24 h	<5
3	DMA	–	120 W	16 min	34
4	$[BMIm]BF_4$	–	120 W	16 min	84

[a] Reagents: $PdCl_2$ (0.0125 mmol, 2.5 mol%), DMEDA (0.05 mmol), solvent (3 mL), 4-bromobiphenyl (0.5 mmol), anhyd $K_4[Fe(CN)_6]$ (0.1 mmol), Na_2CO_3 (0.5 mmol).

[b] Isolated yields.

(4) Sundermeier, M.; Zapf, A.; Beller, M. *Eur. J. Inorg. Chem.* **2003**, 3513.

(5) (a) Okano, M.; Amano, M.; Takagi, K. *Tetrahedron Lett.* **1998**, *39*, 3001. (b) Ramnauth, J.; Bhardwaj, N.; Renton, P.; Rhakit, S.; Maddafird, S. *Synlett* **2003**, 2237. (c) Tschaen, D. M.; Desmond, R.; King, A. O.; Forin, M. C.; Pipik, B.; King, S.; Verhoeven, T. R. *Synth. Commun.* **1994**, *24*, 887. (d) Marcantonio, K. M.; Frey, L. F.; Liu, Y.; Chen, Y.; Strine, J.; Phenix, B.; Wallace, D. J.; Chen, C.-Y. *Org. Lett.* **2004**, *6*, 3723. (e) Maligres, P. E.; Waters, M. S.; Fleitz, F.; Askin, D. *Tetrahedron Lett.* **1999**, *40*, 8193. (f) Jiang, B.; Kan, Y.; Zhang, A. *Tetrahedron* **2001**, *57*, 1581.

(6) (a) Chidambaram, R. *Tetrahedron Lett.* **2004**, *45*, 1441. (b) Jin, F.; Confalone, P. N. *Tetrahedron Lett.* **2000**, *41*, 3271. (c) Okano, T.; Iwahara, M.; Kiji, J. *Synlett* **1998**, 243. (d) Stazi, F.; Palmisano, G.; Turconi, M.; Santagostino, M. *Tetrahedron Lett.* **2005**, *46*, 1815. (e) Hatsuda, M.; Seki, M. *Tetrahedron Lett.* **2005**, *46*, 1849. (f) Grossman, O.; Gelman, D. *Org. Lett.* **2006**, *8*, 1189.

(7) (a) Okano, T.; Kiji, J.; Toyooka, Y. *Chem. Lett.* **1998**, 425. (b) Cassar, L.; Foa, M. *J. Organomet. Chem.* **1979**, *173*, 335. (c) Sundermeier, M.; Zapf, A.; Beller, M. *Angew. Chem. Int. Ed.* **2003**, *42*, 1661. (d) Sundermeier, M.; Mutyala, S.; Zapf, A.; Spannenberg, A.; Beller, M. *J. Organomet. Chem.* **2003**, *684*, 50. (e) Yang, C.; Williams, J. M. *Org. Lett.* **2004**, *6*, 2837.

(8) (a) First use of potassium ferrocyanide in this capacity (uncatalyzed reaction): Merz, V.; Weith, W. *Ber. Dtsch. Chem. Ges.* **1877**, 10746. (b) Schareina, T.; Zapf, A.; Beller, M. *Chem. Commun.* **2004**, *12*, 1388. (c) Schareina, T.; Zapt, A.; Beller, M. *J. Organomet. Chem.* **2004**, *689*, 4576. (d) Schareina, T.; Zapf, A.; Beller, M. *Tetrahedron Lett.* **2005**, *46*, 2585. (e) Weissman, S. A.; Zewge, D.; Chen, C. *J. Org. Chem.* **2005**, *70*, 1508.

(9) (a) Wasserscheid, P.; Welton, T. *Ionic Liquids in Synthesis*; Wiley-VCH: Weinheim, **2002**. (b) Liao, M. C.; Duan, X. H.; Liang, Y. M. *Tetrahedron Lett.* **2005**, *46*, 3469.

(10) Wu, J. X.; Beck, B.; Ren, R. X. *Tetrahedron Lett.* **2002**, *43*, 387.

(11) (a) Leadbeater, N. E.; Torenius, H. M.; Tye, H. *Tetrahedron* **2003**, *59*, 2253. (b) Cai, L.; Liu, X.; Tao, X.; Shen, D. *Synth. Commun.* **2004**, *34*, 1215. (c) Srivastava, R. R.; Collibee, S. E. *Tetrahedron Lett.* **2004**, *45*, 8895. (d) Arvela, R. K.; Leadbeater, N. E. *J. Org. Chem.* **2003**, *68*, 9122. (e) Arvela, R. K.; Leadbeater, N. E.; Torenius, H. M.; Tye, H. *Org. Biomol. Chem.* **2003**, *1*, 1119. (f) Alterman, M.; Hallberg, A. *J. Org. Chem.* **2000**, *65*, 7984.

(12) As the ionic liquid, [BMIm]BF_4 was chosen because it was not only most easily manipulated at r.t., but one can be sure to be able to separate the product from the solvent completely via simple extraction with a conventional organic solvent and reused.

(13) $K_4[Fe(CN)_6]\cdot 3H_2O$ is ground to a fine powder and dried under vacuum (ca. 2 mbar) at 80 °C overnight.

(14) Microwave experiments were conducted using a CEM Discover Synthesis Unit (CEM Corp., Matthews, NC). The machine consists of a continuous focused microwave power delivery system with operator selectable power output from 0–300 W.

(15) For recent examples, see: (a) Ho, T.-L.; Su, C.-Y. *J. Org. Chem.* **2000**, *65*, 3566. (b) Williams, G. M.; Roughley, S. D.; Davies, J. E.; Holmes, A. B. *J. Am. Chem. Soc.* **1999**, *121*, 4900. (c) Carless, H. A. J.; Dove, Y. *Tetrahedron: Asymmetry* **1996**, *7*, 649.

(16) (a) Fleming, F. F.; Pu, Y.; Tercek, F. *J. Org. Chem.* **1997**, *62*, 4883. (b) Fleming, F. F.; Hussain, Z.; Weaver, D.; Norman, R. E. *J. Org. Chem.* **1997**, *62*, 1305. (c) Fleming, F. F.; Pak, J. J. *J. Org. Chem.* **1995**, *60*, 4299.

(17) **General Procedure for the Cyanation of Aryl and Arylvinyl Bromides under Microwave Promotion.** [BMIm]BF_4 (1.5 mL) was placed into a 10-mL glass microwave tube and to this was added anhyd $K_4[Fe(CN)_6]$ (0.05 mmol), Na_2CO_3 (0.25 mmol), substrate (0.25 mmol), $PdCl_2$ (2.5 mol%), and DMEDA (10 mol%). After sealing the tube, the mixture was exposed to microwave irradiation (a maximum microwave power of 120 W, a temperature threshold of 200 °C and a pressure threshold of 200 psi) for the requisite time. After the reaction mixture was cooled, the product was extracted from the system by washing the ionic liquid repeatedly with EtOAc–PE = 8:1 (4 × 3 mL). Finally, the product was isolated by flash chromatography on silica gel using EtOAc–PE as mobile phase.

(18) Compound **2a**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.72–7.65$ (m, 4 H), 7.60–7.56 (m, 2 H), 7.51–7.41 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 145.5$, 139.0, 132.5, 129.0, 128.6, 127.6, 127.1, 118.9, 110.7 ppm. MS: $m/z = 179$ [M$^+$], 151, 76.

Compound **2c**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.81–7.78$ (m, 4 H), 7.71 (d, $J = 8.7$ Hz, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 143.4$, 132.8, 127.9, 118.4, 112.3 ppm. MS: $m/z = 204$ [M$^+$], 153, 126, 76.

Compound **4d**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.22$ (d, $J = 16.5$ Hz, 1 H), 8.03 (d, $J = 8.1$ Hz, 1 H), 7.95–7.87 (m, 2 H), 7.67–7.46 (m, 4 H), 5.96 (d, $J = 16.5$ Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 147.8$, 133.5, 131.5, 130.8, 130.6, 128.8, 127.3, 126.5, 125.3, 124.6, 122.7, 118.2, 98.7 ppm. MS: $m/z = 179$ [M$^+$], 152, 76.