Efficient, Scalable Syntheses of Linker Molecules for Metal-Organic Frameworks

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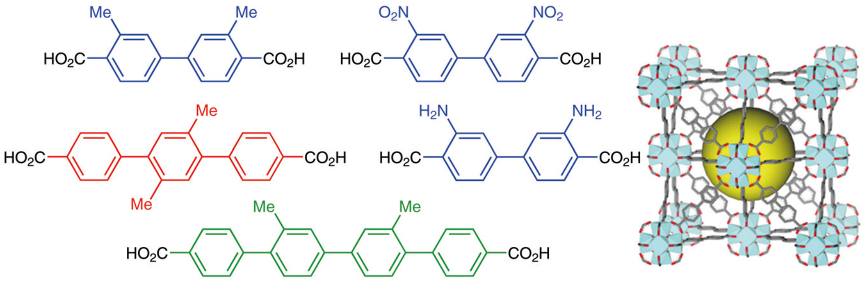
Dedicated to Professor K. Peter C. Vollhardt on the occasion of his 69th birthday and 25 years of service to SYNLETT



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Abstract Efficient synthesis protocols for five linkers of immediate interest for use in metal-organic frameworks (MOFs) are presented. The importance of scalable, cost-effective, high-yield processes with simple purifications and few steps is emphasized. The protocols allow for the efficient synthesis of biphenyl-, terphenyl-, and quaterphenyl-based linkers. Four of the linkers have been structurally characterized.

Keywords metal-organic frameworks, ligands, biaryls, coupling, materials science

Metal-organic frameworks (MOFs) are a class of crystalline, porous materials that consist of metal atoms or clusters as cornerstones, often termed connectors, linked by organic molecules, so-called linkers, via functional groups with coordination abilities, such as carboxylic acids.[1,2]

MOFs have gained much attention over the last two decades, due to their flexible pore topology and structural diversity, which is explored with respect to applications in gas storage and separation,[3–5] catalysis,[6,7] medicine,[8] and chemical sensing,[9] amongst other. Our group was the first to report the ubiquitous, thermally robust zirconium-based MOF UiO-66 and UiO-67 (Figure 1).[10–12]

Due to the nature of MOFs certain criteria for linkers and their syntheses need to be fulfilled. Rather than being final products, the linkers serve as synthetic intermediates in MOF chemistry. As thorough explorations of a MOF may consume considerable amounts of material, efficient and easily scalable syntheses of the linkers are desired, if a MOF is to find its way to practical applications.[13–15]

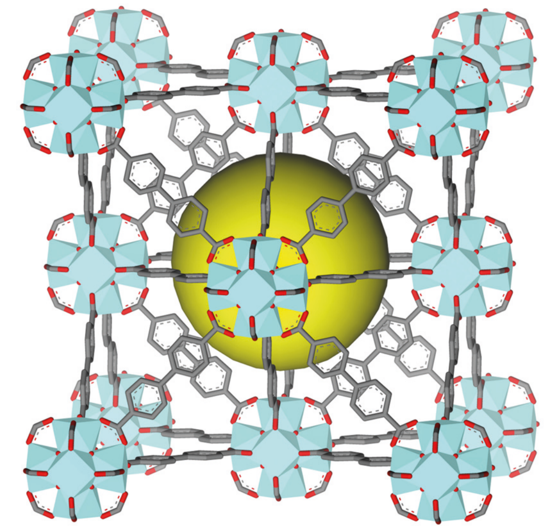
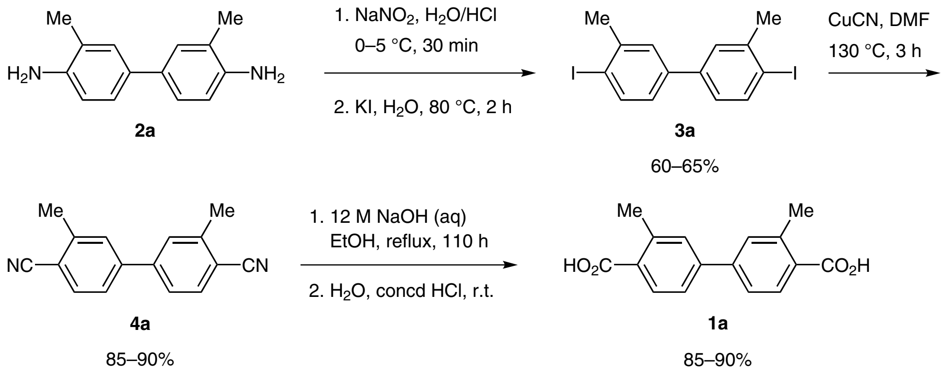


Figure 1 The zirconium-based MOF UiO-67 consists of hexanuclear zirconium oxo clusters that are interconnected by biphenyl-4,4′-dicarboxylate linkers[10]

There is a need to develop linkers which contain functional groups that become available for substrate interaction in the pores of the MOF, that is, not coordinating to the inorganic connector.[16,17] Added linker functionality is motivated by the opportunity it offers to alter the adsorption properties,[18] pore topology,[19] and stability of the MOF.[20–23] Functional linkers also provide valuable sites for postsynthetic functionalization, an important feature of MOFs,[24–27] as was early demonstrated on UiO-66 derivatives by us.[28] In particular, amino-functionalized MOFs attract attention because of their potential for CO_2 capture, activation, and sequestration.[3,24,29,30] Frequently used linkers may be commercially available, but at high prices and with limited choices of added functionality. This creates an in-house demand for linker synthesis in MOF research groups.[23,31]



Scheme 1 The synthesis of 3,3′-dimethylbiphenyl-4,4′-dicarboxylic acid (**1a**)

In this work we present the efficient, multigram syntheses of the linkers 3,3′-dimethylbiphenyl-4,4′-dicarboxylic acid (**1a**), 3,3′-dinitrobiphenyl-4,4′-dicarboxylic acid (**1b**), and 2′,5′-dimethyl-[1,1′:4′,1″-terphenyl]-4,4″-dicarboxylic acid (**1d**) scaled up to 5–10 g quantities, as well as the syntheses of the linkers 3,3′-diaminobiphenyl-4,4′-dicarboxylic acid (**1c**) and 2′,3″-dimethyl-[1,1′:4′,1″:4″,1‴-quaterphenyl]-4,4‴-dicarboxylic acid (**1e**) on a somewhat smaller scale. The reason for including **1c** and **1e** in this letter is the fact that they are conveniently derived from key intermediates in the syntheses of **1a** and **1b**.

The dicarboxylic acid **1a** is an interesting linker for biphenyl-based MOF because the added methyl groups enhance the solubility of the biphenyl system compared with the unfunctionalized biphenyl-4,4′-dicarboxylic acid, which is used as standard linker for the synthesis of UiO-67. The enhanced solubility leads to reduced solvent consumption in the MOF synthesis.

A three-step procedure (Scheme 1) starting from commercially available 3,3′-dimethylbenzidine (**2a**) furnished **1a**. In this route, 3,3′-dimethylbiphenyl-4,4′-dinitrile (**4a**) serves as a key intermediate and immediate precursor to **1a**. Attempts to prepare **4a** from 3,3′-dimethylbenzidine through a double Sandmeyer cyanation always resulted in low yields and difficult purification procedures; low yields have also been previously reported for the synthesis of **4a** by the Sandmeyer reaction.[32]

Instead, the Rosenmund–von Braun cyanation of 4,4′-diiodo-3,3′-dimethylbiphenyl (**3a**) provided **4a** in excellent yields and high purity in quantities up to 10 grams. The diiodide **3a** was synthesized from 3,3′-dimethylbenzidine according to Serre et al.[33]

The final hydrolysis of **4a** to **1a** was performed over several days in a mixture of aqueous 12 M NaOH and ethanol at reflux. The disodium salt of **1a** crystallized during the course of the reaction, and this allowed the facile isolation of the free diacid **1a** without contamination from the copious quantities of NaCl which would be formed by direct acidification of the reaction mixture with HCl. The hydrolysis was also conducted on up to 10 gram scale with high yields and purity. The structure of **1a** based on the X-ray diffraction analysis was determined (Figure 2).

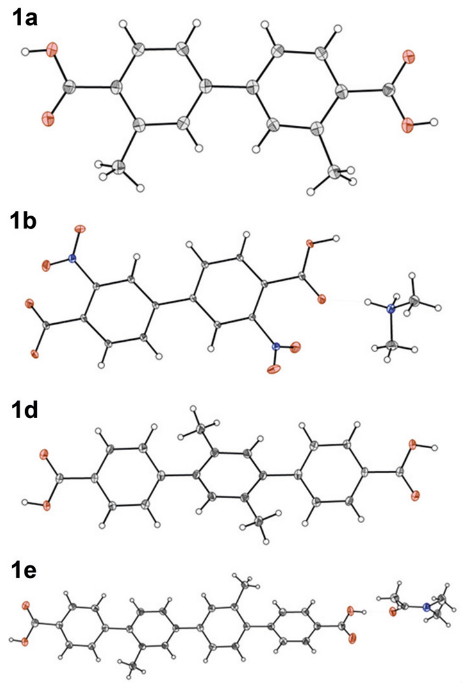
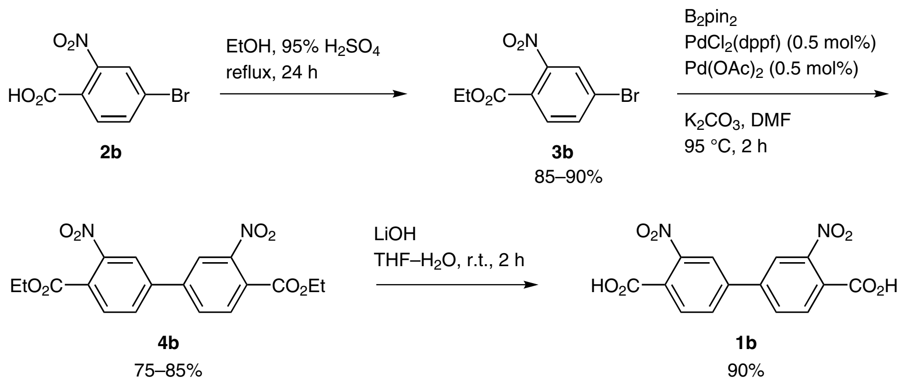


Figure 2 ORTEP plots of the molecular structures of **1a**, **1b** (as its dimethylammonium salt), **1d**, and **1e** (as dimethylacetamide solvate) as determined by X-ray crystallography. Ellipsoids are shown at 50% probability

Our procedure represents a considerable improvement over existing ones to prepare **1a**. The existing methods reported by Yaghi et al.[34] and Serre et al.[33] were also tested by us. While the former lacks some experimental details, severe limitations were found in the latter method when attempts to scale up the process were made. For example, the synthesis of the key intermediate and diacid precursor diethyl 3,3′-dimethylbiphenyl-4,4′-dicarboxylate (**5a**) neces-



Scheme 2 The synthesis of 3,3′-dinitrobiphenyl-4,4′-dicarboxylic acid (**1b**)

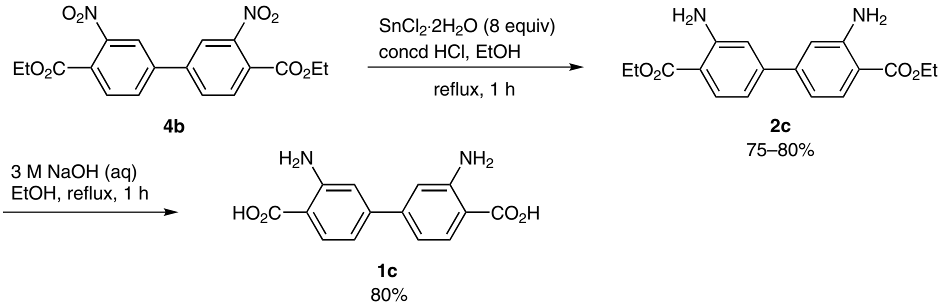
sitated large quantities of *n*-butyllithium and ethyl chloroformate and required purification by column chromatography.

Linker **1b** was synthesized by a different route (Scheme 2). The lack of a suitable, inexpensive biphenyl-based starting material necessitated the construction of the biphenyl system through catalytic coupling chemistry. A procedure described by Bräse[35] was adapted for the key intermediate diethyl 3,3′-dinitrobiphenyl-4,4′-dicarboxylate (**4b**). The precursor, ethyl 4-bromo-2-nitrobenzoate (**3b**), was obtained through the esterification of commercially available 4-bromo-2-nitrobenzoic acid (**2b**).

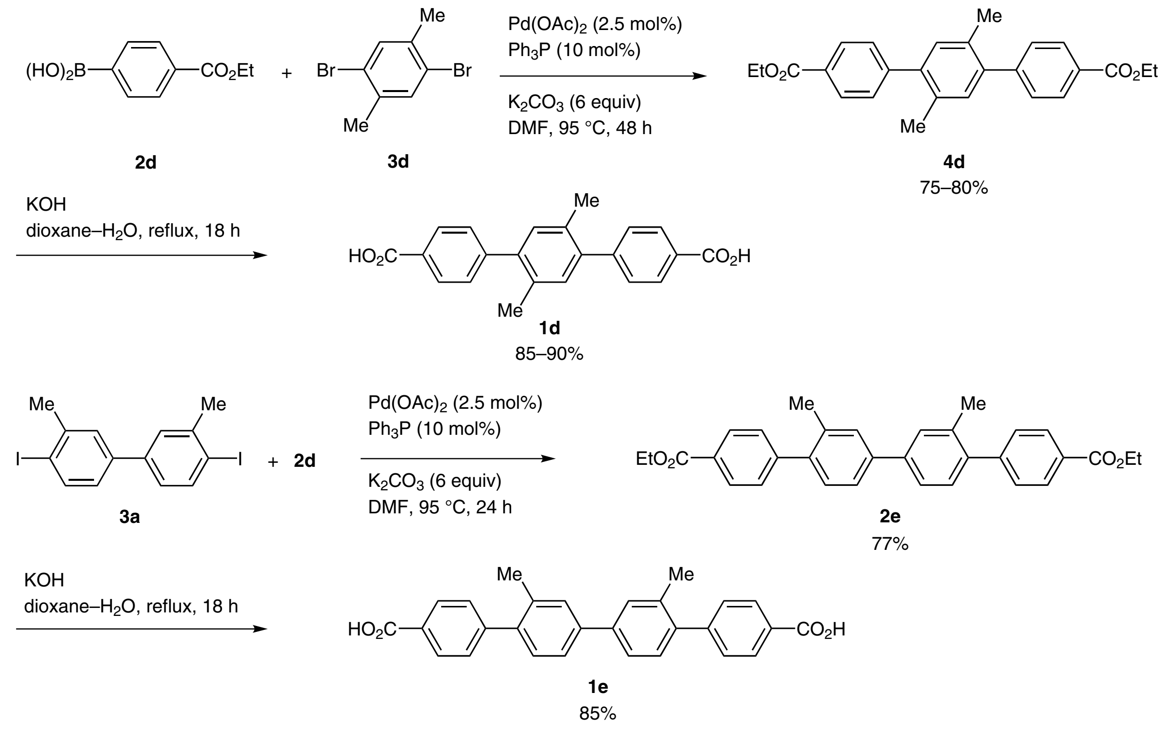
While the coupling reaction proceeded well for **2b** following the procedure established by Bräse, it was found necessary to modify the procedure in order to facilitate larger-scale preparations of **4b**. The rather expensive catalyst $PdCl_2$(dppf) is originally used with a loading of 4 mol%, which is rather unacceptable at the desired scale (minimum 10 grams). We find that the catalyst loading can be decreased to 0.5 mol% with the addition of an extra 0.5 mol% of the relatively inexpensive $Pd(OAc)_2$. The reaction was performed in DMF at 95 °C and was complete in as little as two hours with minimal formation of byproducts. This reaction has been scaled to >15 grams, and the yields are consistently high, in the range of 75–85%. Finally, **1b** was obtained in high purity and high yields by hydrolysis of **4b** with aqueous LiOH in THF at room temperature in >6 gram scale. The X-ray crystal structure of **1b**, in the form of its dimethylammonium salt, was also obtained (Figure 2).

A major motivation for choosing **1b** as a target for a linker synthesis is that the nitro groups may be readily reduced to form amino groups that offer a host of possibilities for further manipulation and exploration. Most notably, amine-functionalized MOF linkers have the potential to interact with CO_2, as addressed in the introduction. Accordingly, **1c** has now been synthesized starting with the reduction of **4b** with $SnCl_2{\cdot}2H_2O$. The product, diethyl 3,3′-diaminobiphenyl-4,4′-dicarboxylate (**2c**), is then subjected to hydrolysis to furnish **1c** (Scheme 3). At this time, the synthesis of **1c** has been explored only on a smaller scale (< 0.5 g) than the syntheses of **1a** and **1b**. We expect that an efficient scalable synthesis will soon be in place.

By using a methodology that is analogous to that described for the biphenyl linkers, we find that it is possible to construct even longer linkers, namely terphenyl- and quaterphenyl-based systems. Thus, the two linkers **1d** and **1e**[36] were synthesized according to Scheme 4, involving a double Suzuki coupling of aromatic dihalides with 4-ethoxycarbonylphenylboronic acid (**2d**), to construct the diethyl ester precursors of **1d** and **1e**, namely diethyl 2′,5′-dimethyl-



Scheme 3 The synthesis of 3,3′-diaminobiphenyl-4,4′-dicarboxylic acid (**1c**)



Scheme 4 The synthesis routes for **1d** and **1e**

[1,1′:4′,1″-terphenyl]-4,4″-dicarboxylate (**4d**) and diethyl 2′,3″-dimethyl-[1,1′:4′,1″:4″,1‴-quaterphenyl]-4,4‴-dicarboxylate (**2e**[36]), respectively.

In the case of **1d**, the commercially available 1,4-dibromo-2,5-dimethylbenzene (**3d**) is the substrate for the double coupling reaction, whereas in the case of **1e**, the diiodide **3a** (which already serves as an intermediate for the synthesis of **1a**) is the starting material. Both coupling procedures proceed with good yields for gram-scale reactions, and column chromatography is again avoided as a purification method in both cases. In both coupling reactions inexpensive Pd(OAc)$_2$ is used as palladium source, but the drawbacks are rather high catalyst loadings (2.5 mol%) and long reaction times (24–48 h). Both **4d** and **2e** are easily hydrolyzed to the corresponding diacids in good yields, and it was possible to obtain the crystal structure of both these linkers.

The molecular structures of **1a**, **1b**, **1d**, and **1e** as determined by single-crystal X-ray crystallography are shown as ORTEP plots in Figure 2.[37] Bond distances are in accordance with the reported structures.[38] Neighboring aromatic planes are rotated by 12.7° (**1a**), 10.3° (**1b**), 35.6° (**1d**), 43.8°, 24.6°, and 45.8° (**1e**) with respect to each other. Further details concerning molecular structures, packing interactions (involving H-bonding networks and π stacking interactions) may be found in the cif files, available as Supporting Information.

In this letter the syntheses of five linkers for metal-organic frameworks have been described and discussed. Each synthesis has been optimized to be easy scalable in terms of the complexity of each synthesis route, the methods for purification, and the cost of starting materials. The strategies established may be applied in synthesis of other functionalized linkers based on the biphenyl, terphenyl, or quaterphenyl moieties. The successful use of these linkers in MOF synthesis will be presented elsewhere.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1381039.

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(36) **Synthesis of Diethyl 2′,3″-Dimethyl-[1,1′:4′,1″:4″,1‴-quaterphenyl]-4,4‴-dicarboxylate (2e)**

To a 100 mL Schlenk flask were added **3a** (3.21 g, 7.39 mmol, 1.0 equiv), **2d** (3.76 g, 19.4 mmol, 2.6 equiv), K_2CO_3 (6.15 g, 44.5 mmol, 6.0 equiv), $Pd(OAc)_2$ (0.039 g, 0.180 mmol, 0.0240 equiv), Ph_3P (0.195 g, 0.740 mmol, 0.100 equiv), and DMF (55 mL). The pale yellow suspension was flushed with argon for 30 min, before it was heated at 95 °C for 24 h under argon. The reaction mixture, which had turned black/dark brown, was cooled to r.t. and poured into a mixture of ice and H_2O (ca. 300 mL). The brown solid was filtered and washed with H_2O, then dried at r.t. for 3 h, before it was dissolved in CH_2Cl_2 (300 mL). The solution was washed with 3 M HCl (aq, 200 mL) and brine (200 mL) and dried with Na_2SO_4, before it was filtered through celite. The celite was washed with additional CH_2Cl_2 (10 × 30 mL). Removal of the solvent under reduced pressure yielded a pale brown solid which was recrystallized from MeCN. This gave **2e** as a colorless solid. Yield 2.73 g, 5.71 mmol, 77%, mp (MeCN): 151–152 °C. ^1H NMR (600 MHz, $CDCl_3$): $\delta = 8.12$ (d, $J = 7.8$ Hz, 4 H), 7.56 (d, $J = 1.8$ Hz, 2 H), 7.53 (dd, $J^o = 7.8$ Hz, $J^m = 1.8$ Hz, 2 H), 7.45 (d, $J = 7.8$ Hz, 4 H), 7.33 (d, $J = 7.8$ Hz, 2 H), 4.42 (q, $J = 7.2$ Hz, 4 H), 2.36 (s, 6 H), 1.43 (t, $J = 7.2$ Hz, 6 H). ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 166.5$ (C), 146.2 (C), 140.2 (C), 140.1 (C), 135.7 (C), 130.1 (CH), 129.4 (CH), 129.3 (CH), 129.2 (CH), 129.1 (C), 124.6 (CH), 61.0 (CH_2), 20.6 (CH_3), 14.4 (CH_3). IR (KBr): 1714.7, 1606.4, 1284.2, 1102.1, 776.9 cm^{-1}. MS (EI, CH_2Cl_2): $m/z = 478$ (100) $[M]^+$, 433 (12) $[M^+ - OEt]$, 194 (6). HRMS (CH_2Cl_2): m/z calcd for $C_{32}H_{30}O_4$: 478.214410 (–3.4 ppm); found: 478.212763.

Synthesis of 2′,3″-Dimethyl-[1,1′:4′,1″:4″,1‴-quaterphenyl]-4,4‴-dicarboxylic Acid (1e)

A suspension of **2e** (2.08 g, 4.34 mmol, 1.0 equiv) and KOH (1.30 g, 23.2 mmol, 5.3 equiv) in a mixture of 1,4-dioxane (25 mL) and H_2O (30 mL) was heated at reflux for 18 h. After cooling to r.t., the solvent was removed under reduced pressure. H_2O (150 mL) was added to the resulting solid. The mixture was heated at reflux until the solid dissolved, and the solution was filtered while hot to remove insoluble impurities. Concentrated HCl (37%) was then added to the hot solution until pH = 1 with the formation of a colorless solid. After cooling to r.t., the solid was filtered and washed several times with H_2O, before it was air-dried overnight. The solid was then crushed to a powder, suspended in H_2O (200 mL) and stirred at r.t. for 1 h. Filtration, followed by washing with H_2O and drying at 100 °C for 24 h, gave **1e** as colorless solid. Yield 1.57 g, 3.71 mmol, 85%; mp (H_2O): >310 °C. ^1H NMR (400 MHz, DMSO-d_6): $\delta = 13.01$ (br s, 2 H, CO_2H), 8.02 (d, $J = 8.0$ Hz, 4 H), 7.70 (d, $J = 2.0$ Hz, 2 H), 7.63 (dd, $J^o = 8.0$ Hz, $J^m = 2.0$ Hz, 2 H), 7.53 (d, $J = 8.0$ Hz, 4 H), 7.33 (d, $J = 8.0$ Hz, 2 H), 2.33 (s, 6 H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 167.2$ (C), 145.4 (C), 139.5 (C), 139.1 (C), 135.4 (C), 130.1

(CH), 129.4 (CH), 129.3 (CH), 129.2 (CH), 128.8 (C), 124.3 (CH), 20.3 (CH_3). IR (KBr): 2927.2, 1681.0, 1607.6, 1431.0, 1297.5, 1320.2 cm^{-1}. MS (EI, DMSO): *m/z* = 422 (100) $[M]^+$, 378 (7) $[M^+ - CO_2]$. HRMS (DMSO): *m/z* calcd for $C_{16}H_{14}O_4$: 422.151809 (2.8 ppm); found: 422.150624.

(37) CCDC 1053020-1053023 contain the supplementary crystallographic data for **1a**, **1b**, **1d**, and **1e**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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