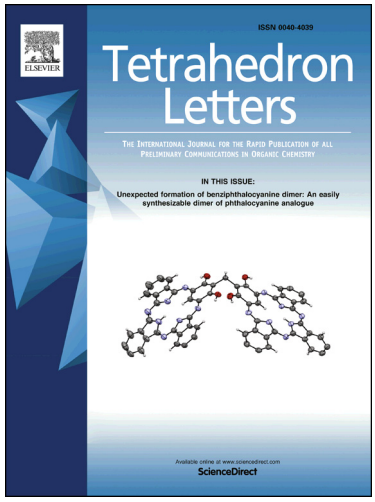

Synthesis of bis-8-hydroxyquinolines *via* an imination or a Suzuki-Miyaura coupling approach

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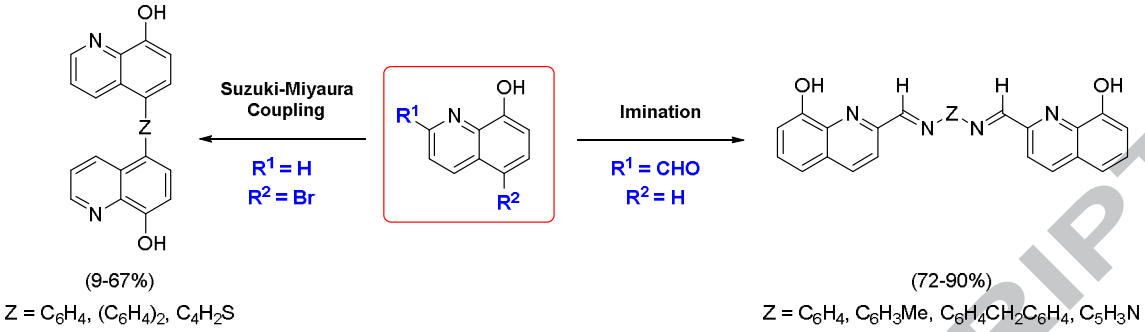
Graphical abstract



(9-67%)

Z = C_6H_4, $(C_6H_4)_2$, C_4H_2S

(72-90%)

Z = C_6H_4, C_6H_3Me, $C_6H_4CH_2C_6H_4$, C_5H_3N

Synthesis of bis-8-hydroxyquinolines *via* an imination or a Suzuki-Miyaura coupling approach

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Abstract

Bis-8-hydroxyquinolines represent an important yet underexplored class of potential ligands for the preparation of various coordination polymers, which can be used in a plethora of applications. In this work, the synthesis of two types of bis-8-hydroxyquinolines, prepared *via* either an imination or a Suzuki-Miyaura coupling approach, as well as their analysis is discussed. Imination was pursued through the condensation of quinolinecarbaldehydes with diamines or aminoquinolines with dialdehydes, and the Suzuki-Miyaura coupling reactions were evaluated using a bromoquinoline substrate and diboronic acids.

Keywords: 8-hydroxyquinoline, imination, Suzuki-Miyaura coupling, NMR, EPR

8-Hydroxyquinolines have attracted a lot of attention due to their excellent electroluminescent properties upon coordination with metals.[1] Elaborating further on the success of 8-hydroxyquinoline complexes in OLED displays, significant effort has been devoted in the last decade to the generation of novel derivatives with improved photometric and thermal properties.[2-4] By designing and developing bis-8-hydroxyquinolines, in which two 8-hydroxyquinoline systems are integrated into one molecular framework, the construction of coordination polymers can be envisioned representing an extended network of metal ions coordinated to multidentate organic molecules. These chemical architectures could then be applied to various areas e.g. chemical catalysis, molecular separation, gas storage, chemical sensing, ion exchange and drug delivery.[5,6] Although not frequently studied, some examples of bis-8-hydroxyquinolines have been described in the literature (Fig. 1).[7-15] Compounds **1** and **2** were previously prepared from 5-chloromethyl-8-hydroxyquinoline *via* nucleophilic substitution using an amine, whereas structures **3** and **4** were synthesized from 2- or 5-substituted 8-

hydroxyquinolinecarbaldehydes through a condensation reaction. This short communication reports on our recent endeavours to prepare similar structures and to extend the list of known examples with novel bis-8-hydroxyquinolines synthesized through imination or Suzuki-Miyaura cross-coupling approaches using 8-hydroxyquinoline-2-carbaldehyde or 5-bromo-8-hydroxyquinoline, respectively.

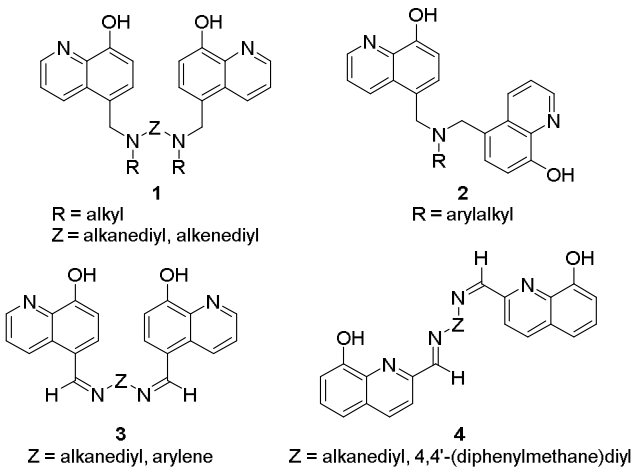
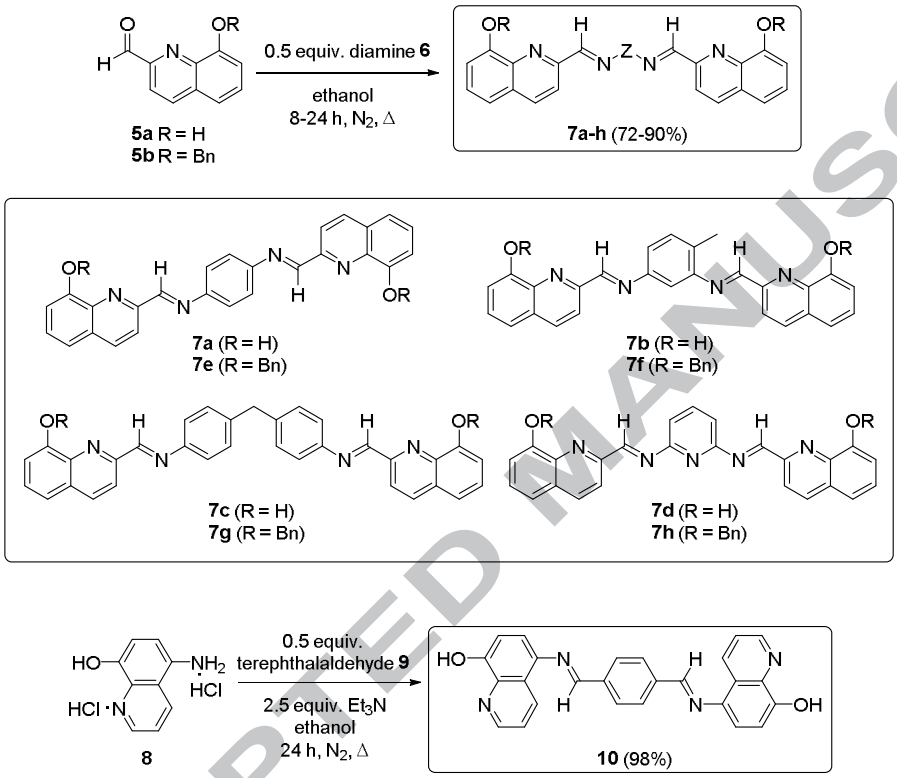


Figure 1. Selected examples of bis-8-hydroxyquinolines **1-4** reported in the literature.[7-15]

The first set of bis-8-hydroxyquinolines **7a-d** was synthesized *via* a condensation reaction between 8-hydroxyquinoline-2-carbaldehyde **5a** (R = H, Scheme 1) and diamines **6** (Table 1). It should be mentioned that derivatives **7a** and **7c** have previously been synthesized,[15,16] whereas structures **7b** and **7d** represent new systems. These iminations took place in ethanol at reflux for 8-24 hours, after which the reaction was cooled to room temperature to obtain bis-imines **7a-d** as pure solids. Full characterization of these compounds was attempted using ^{1}H and ^{13}C NMR spectroscopy ($CDCl_3$ or DMSO-d_6). Surprisingly, for pyridine-containing scaffold **7d** no signals were detected in the ^{1}H and ^{13}C NMR spectra, even though the compound completely dissolved in $CDCl_3$ and DMSO-d_6. To address this problem, NMR spectra were recorded in other deuterated solvents ($(CD_3)_2CO$, ethanol-d_6) and at higher temperatures, however, once again no signals were detected. We suspect that the formation of stabilized unpaired electrons provoked the problem of NMR-silence in molecule **7d**, and therefore, electron paramagnetic resonance (EPR) measurements were performed on all four bis-8-hydroxyquinolines **7a-d**. The obtained spectra revealed a signal at a g-factor of 2.0044 for compounds **7b-d** (Q-band, microwave frequency normalized to 34.09 GHz, Fig. 2). This is a typical value for carbon-centered radicals, and this observation thus provides a possible explanation for the NMR incompatibility of structure **7d**.[17] As the free phenolic group present in compounds **7a-d** could be the source of radical species formation, synthesis of the corresponding *O*-benzyl-protected derivatives **7e-h** was realized *via* the imination of 8-benzyloxyquinoline-2-carbaldehyde **5b**.

Surprisingly, again only for analog **7h** possessing a pyridine linker, no signals were detected in the NMR spectra, pointing to the contribution of the pyridine ring fragment to the NMR-silence of these molecules. Finally, 5-substituted bis-8-hydroxyquinoline **10**[18] was prepared *via* a 'reversed' imination approach (Scheme 1, Table 1). This was accomplished by adding terephthalaldehyde **9** to 5-amino-8-hydroxyquinoline **8** in EtOH in the presence of triethylamine (2.5 equiv.). The solubility of bis-imine **10** in organic solvents (EtOH, EtOAc, $CHCl_3$, DMSO, DMF), however, proved to be low, which could possibly hamper its utility for further applications.



Scheme 1. Synthesis of bis-8-hydroxyquinolines **7a-h** and **10**.

Table 1. Synthesis and solubility of bis-8-hydroxyquinolines **7a-h** and **10**.

Cmpd.	Diamine 6	R	Solubility (DMSO, rt)	Possibility to record ^{1}H NMR spectrum	Yield (%)
7a	*p*-phenylenediamine **6a**	H	yes	yes	90
7b	2,4-diaminotoluene **6b**	H	yes	yes	75
7c	4,4'-methylenedianiline **6c**	H	yes	yes	72
7d	2,6-diaminopyridine **6d**	H	yes	no	85
7e	*p*-phenylenediamine **6a**	Bn	yes	yes	86
7f	2,4-diaminotoluene **6b**	Bn	yes	yes	75
7g	4,4'-methylenedianiline **6c**	Bn	yes	yes	73
7h	2,6-diaminopyridine **6d**	Bn	yes	no	75
10	-	-	partial	yes	98

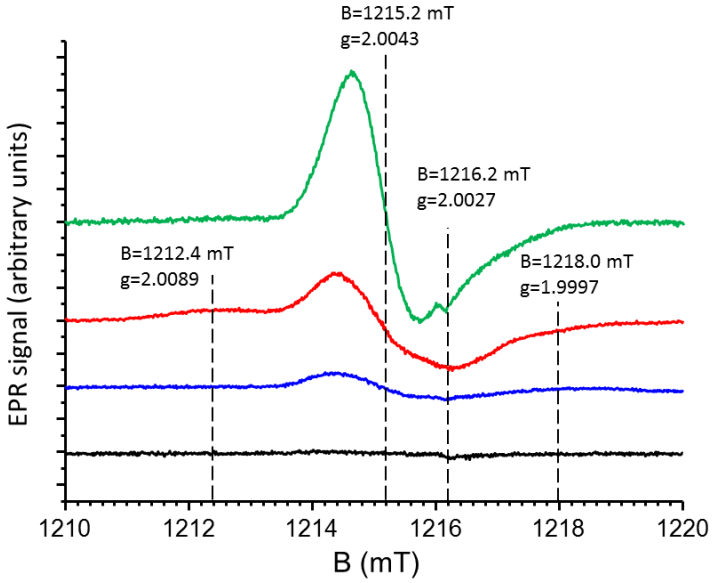
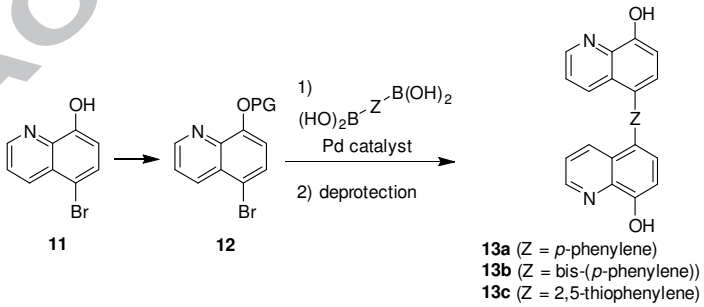


Figure 2. EPR spectra of compounds **7a-d** at 34.09 GHz, recorded at room temperature with 5 mW microwave power (**7a** = black, **7b** = blue, **7c** = red, **7d** = green).

In summary, five bis-8-hydroxyquinolines (**7a-d** and **10**) and four bis-8-benzyloxyquinolines (**7e-h**) were synthesized *via* an imination approach for further investigation as potential scaffolds.

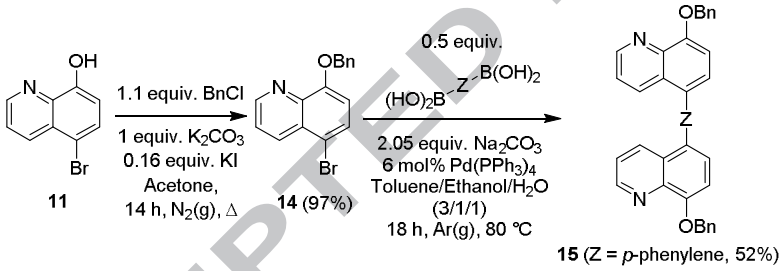
In a second part of this study, the synthesis of bis-8-hydroxyquinolines **13a-c** was contemplated utilizing Suzuki-Miyaura cross coupling methodology (Scheme 2). To that end, the following three-step strategy was applied. In a first step, (i) *O*-protection of 5-bromo-8-hydroxyquinoline **11** with a suitable protecting group (PG) to allow an efficient Suzuki-Miyaura coupling, (ii) addition of a diboronic acid and a palladium catalyst to synthesize the *O*-protected bis-8-hydroxyquinolines, and (iii) deprotection of the aromatic alcohol group to give compounds **13**.



Scheme 2. Synthesis outline *en-route* to bis-8-hydroxquinolines **13a-c**.

In the literature, one method is available for the synthesis of bis-8-hydroxyquinoline **13b** (Z = bis-(*p*-phenylene)).[19] In that approach, the 8-hydroxyquinoline moiety was first *O*-protected with a methyl group, but the yield of the subsequent demethylation reaction was low despite many attempts (yields not reported). Therefore, the methoxymethyl protecting group was introduced instead, which resulted in the synthesis of **13b** (Z = bis-(*p*-phenylene)) in good yields for both the Suzuki-Miyaura coupling and the deprotection step (78% and 91%, respectively).

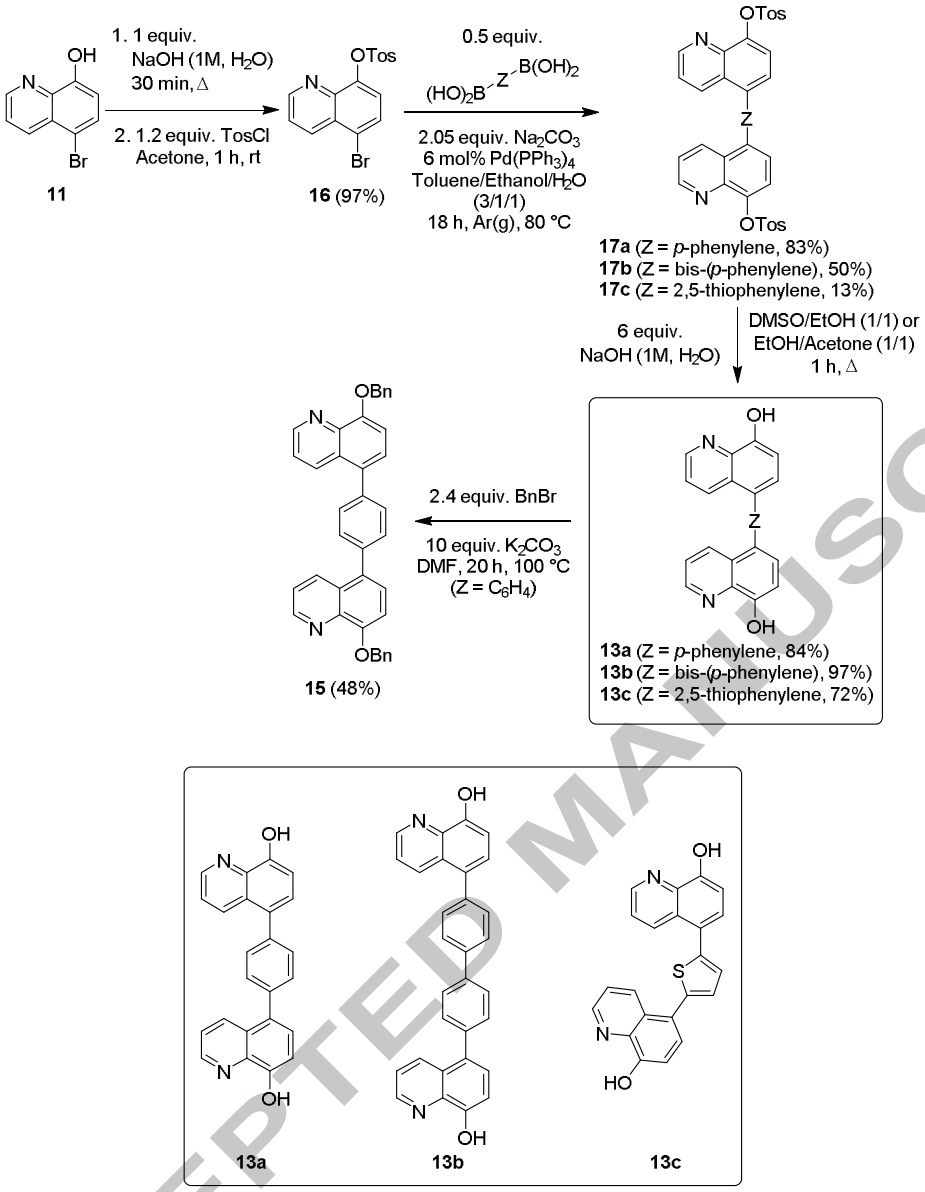
In our first attempt to obtain compound **13a** (Z = 1,4-phenylene, Scheme 2), 5-bromo-8-hydroxyquinoline **11** was efficiently protected with a benzyl group utilizing a previously described method by adding a slight excess of benzyl chloride to 5-bromo-8-hydroxyquinoline **11** in the presence of potassium carbonate and potassium iodide (Scheme 3).[20] Then, the Suzuki-Miyaura coupling reaction was accomplished utilizing 5-bromo-8-benzyloxyquinoline **14**, benzene-1,4-diboronic acid, sodium carbonate and tetrakis(triphenylphosphine)palladium(0), affording dimeric compound **15** in 52% yield after column chromatographic purification (SiO_2). Unfortunately, 5-phenyl-8-benzyloxyquinoline was also formed as a minor side-product. To obtain target molecule **13a**, several attempts were made to remove the benzyl protecting group, utilizing palladium on carbon and 1,4-cyclohexadiene or hydrogen gas, but unfortunately no deprotection of the benzyl group was achieved in these experiments.



Scheme 3. Synthesis of compound **15** *via* 8-benzyloxyquinoline **14**.

This disappointing result led us to explore an alternative route and to instead synthesize tosyl-protected derivative **16** (Scheme 4), since the tosyloxy group could enhance the reactivity of the bromoquinoline in the Suzuki-Miyaura reaction due to its electron-withdrawing properties.[21,22] Furthermore, this protecting group has been reported to be easily removed upon treatment with aqueous sodium hydroxide.[23] For the tosyl protection of 5-bromo-8-hydroxyquinoline **11**, a slightly modified literature procedure was employed.[23,24] Sodium hydroxide was used as a base to abstract the phenolic proton in 5-bromo-8-hydroxyquinoline **11**, after which *para*-toluenesulfonyl chloride was added to afford tosylate **16** in nearly quantitative yield (Scheme 4). The following Suzuki-Miyaura reaction with 1,4-benzenediboronic acid furnished bis-8-tosyloxyquinoline **17a** in 83% yield, which

was considerably better than the same reaction carried out with the benzyl-protected counterpart **14** (52%, Scheme 3). Since the reactions in this pathway proceeded well, this sequence was also used to produce derivatives **17b** and **c** possessing a bis-(*p*-phenylene) and a 2,5-thiophenylene linker, respectively, in 50% and 13% yield after column chromatographic purification (SiO_2). In the final deprotection step, all three tosylates **17a-c** were subjected to hydrolysis with sodium hydroxide, generating bis-8-hydroxyquinolines **13a-c** in 72-97% yield. These three final products **13a-c** were obtained by performing the protecting group removal in different solvent systems (DMSO/EtOH 1/1 for **13a** and **13b** or EtOH/Acetone 1/1 for **13c**), which improved the solubility of the starting products **17a-c** and of sodium hydroxide. In a paper by Cui and co-workers, it has been reported that the solubility of bis-8-hydroxyquinolines such as structure **13b** is very low in organic solvents (THF and CH_2Cl_2).[19] This was confirmed here, as bis-quinolines **13a** and **13b** were shown to be poorly soluble in water and in several organic solvents (EtOAc, DMSO, $CHCl_3$). As a consequence, no NMR spectra could be recorded for these two compounds. Fortunately, thiophenylene-linked structure **13c** was somewhat more soluble and was completely characterized by NMR (DMSO-d_6). To indirectly prove that structure **13a** was effectively formed after the tosyl deprotection step, a derivatisation approach was proposed. This was achieved by adding benzyl bromide (2.4 equiv.) and potassium carbonate (10 equiv.) to hydroxyquinoline **13a**, which generated *O*-benzylated compound **15** (48%, Scheme 4). High temperatures, an extended reaction time and a polar solvent (DMF) were necessary to improve the solubility of compound **13a**. It should be noted that the same compound **15** was previously prepared using the Suzuki-Miyaura coupling approach illustrated in Scheme 3. The ^{1}H and ^{13}C NMR spectra of structures **15** obtained *via* both pathways (Schemes 3 and 4), were identical, indirectly proving that structure **13a** was formed after the deprotection of tosylate **17a**.



Scheme 4. Synthesis of compounds **13a-c** *via* 8-tosyloxyquinoline **16**.

Overall, eight bis-8-hydroxyquinolines (**7a-d**, **10** and **13a-c**) were synthesized *via* an imination or a Suzuki-Miyaura cross coupling approach and represent valuable molecular scaffolds for further studies with respect to metal complexation. Of these eight structures, four have not been reported in the literature (**7b**, **7d**, **13a** and **13c**). The solubility of the compounds obtained through imination of 8-hydroxyquinoline-2-carbaldehyde using diamines (**7a-d**) in organic solvents (EtOH, EtOAc, $CHCl_3$, DMSO, DMF) proved to be superior over the structures obtained *via* imination with terephthalaldehyde and 5-amino-8-hydroxyquinoline (**10**) or *via* Suzuki-Miyaura coupling (**13a-c**). For bis-8-hydroxyquinolines **7d** and **13a**,**b**, no signals were detected upon NMR spectroscopic analysis.

This NMR-silence could be explained by the paramagnetic properties of **7d**, as observed *via* EPR measurements, and by the insolubility of bis-8-hydroxyquinolines **13a,b** in water and organic solvents. In conclusion, soluble bis-8-hydroxyquinolines **7a-d** are much easier to handle, and therefore we suggest that further investigation into the possible applications of the more soluble imines **7a-d** should have priority. Moreover, imines **7a-d** can be easily prepared in only one step in good yields.

References

1 Tang CW, VanSlyke SA. *Appl Phys Lett.* 1987; *51*: 913-915.

2 Jang H, Do L-M, Kim Y, Kim JG, Zyung T, Do Y. *Synth Met.* 2001; *121*: 1669-1670.

3 Matsumura M, Akai T. *J Appl Phys.* 1996; *35*: 5357-5360.

4 Sapochak LS, Padmaperuma A, Washton N, et al. *J Am Chem Soc.* 2001; *123*: 6300-6307.

5 Corma A, García H, Llabrés i Xamena FX. *Chem Rev.* 2010; *110*: 4606-4655.

6 Farha OK, Hupp JT. *Acc Chem Res.* 2010; *43*: 1166-1175.

7 Prajapati NK, Patel AD, Patel JA, Prajapati SP. *Int J Chem Sci.* 2011; *9*: 363-370.

8 Patel AD, Prajapati NK, Patel SP, Patel GR. *Chemica Sin.* 2011; *2*: 130-135.

9 Patel AD, Patel RS, Patel GR. *E-J Chem.* 2010; *7*: 1023-1028.

10 Madonna S, Beclin C, Laras Y, et al. *Eur J Med Chem.* 2010; *45*: 623-638.

11 Jiang P, Huang W, Li J, Zhuang D, Shi J. *J Mater Chem.* 2008; *18*: 3688.

12 Xie J. *Dyes Pigm.* 2003; *59*: 153-162.

13 Chen L, Yan C, Du B-B, Wu K, Zhang L-Y, Yin S-Y, Pan M. *Inorg Chem Commun.* 2014; *47*: 13-16.

14 Arslan T, Öğretir C, Tsiouri M, Plakatouras JC, Hadjiliadis N. *J Coord Chem.* 2007; *60*: 699-710.

15 Nuñez C, Fernandez-Lodeiro J, Dinis M, Larguinho M, Capelo JL, Lodeiro C. *Inorg Chem Commun.* 2011; *14*: 831-835.

16 Reihsig J, Krause HW. *J Prakt Chem.* 1966; *31*: 167-178.

17 Kwong CY, Djurišić AB, Choy WCH, et al. *Mater Sci Eng B.* 2005; *116*: 75-81.

18 Horowitz E, Tryon M, Christensen RG, Perros TP. *J Appl Polym Sci.* 1965; *9*: 2321-2336.

19 Cui Y, Wang S. *J Org Chem.* 2006; *71*: 6485-6496.

20 Shoji E, Miyatake K, Hlil AR, et al. *J Polym Sci, Part A: Polym Chem.* 2003; *41*: 3006-3016.

21 Miyaura N, Suzuki A. *Chem Rev.* 1995; *95*: 2457-2483.

22 Hassan J, Sévignon M, Gozzi C, Schulz E, Lemaire M. *Chem Rev.* 2002; *102*: 1359-1469.

23 Heiskanen JP, Hormi OEO. *Tetrahedron.* 2009; *65*: 518-524.

24 Thinnes CC, Tumber A, Yapp C, et al. *Chem Commun.* 2015; *51*: 15458-15461.

Highlights

- Bis-8-hydroxyquinolines concern underexplored ligands for the preparation of coordination polymers
- Few reports on the synthesis of bis-8-hydroxyquinolines are available
- This work discloses the preparation of bis-8-hydroxyquinolines (via imination or Suzuki-Miyaura coupling) and their analysis