Organic LETTERS

Letter

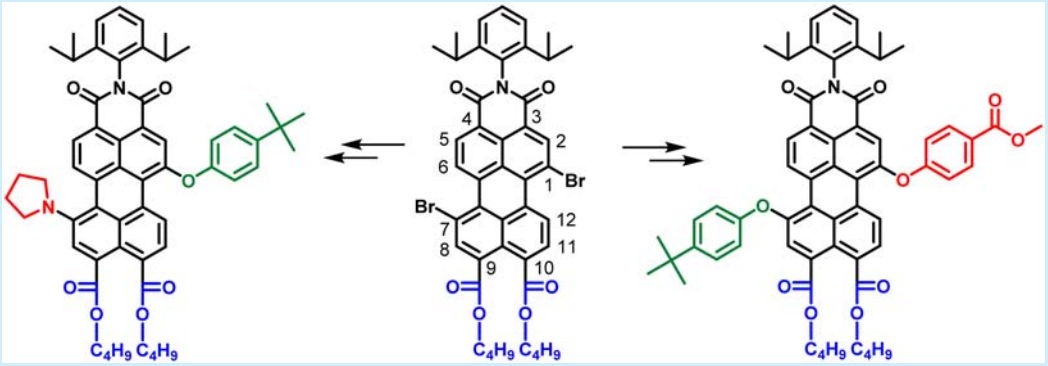
pubs.acs.org/OrgLett

Synthesis of Perylene-3,4,9,10-tetracarboxylic Acid Derivatives Bearing Four Different Substituents at the Perylene Core

Rajeev K. Dubey,*[,†] Nick Westerveld,[†] Stephen J. Eustace,[‡] Ernst J. R. Sudhölter,[†] Ferdinand C. Grozema,[†] and Wolter F. Jager*[,†]

[†]Department of Chemical Engineering and [‡]Department of Biotechnology, Delft University of Technology, Van der Maasweg 9, 2629 HZ, Delft, The Netherlands

Supporting Information



ABSTRACT: Nucleophilic aromatic substitution reactions on 1,7-dibromoperylene-3,4,9,10-tetracarboxylic monoimide dibutylester, using phenol and pyrrolidine reagents, have been exploited to synthesize perylenes with four different substituents at the perylene core. The first substitution is always regiospecific at the imide-activated 7-position. A second substitution reaction does not always replace the bromine at C-1, but may replace a phenol substituent at the highly activated 7-position. Exploiting this reactivity pattern, a "mixed" 1,7-diphenoxy, 1,7-dipyrrolidinyl, and two 1-phenoxy-7-pyrrolidinyl derivatives have been synthesized.

Perylene bisimides (PBIs) form a class of highly valuable organic dyes, which have been investigated thoroughly both in academia and industry. The continuing interest in perylene dyes stems from their outstanding properties, such as chemical robustness, high photo- and thermal stability, and outstanding optoelectronic properties. PBIs are applied as industrial colorants, fluorescent probes, and *n*-type semiconductors in organic electronics and photovoltaics,[1] while applications for singlet fission[2] and artificial photosynthesis[3] are envisaged.

For the more demanding application, as well the realization of complex covalent and supramolecular structures,[4] precise control of the molecular architecture of the perylene derivatives is a prerequisite. In molecular solutions the properties of the individual molecules, which are mainly governed by the positioning of electroactive substituents, is of paramount importance. This is evident for molecular probes, where placement of fluorescence quenching electron donors at the bay positions results in probes with superior properties.[5] The optoelectronic properties of molecular aggregates are the key parameter for applications in which perylene molecules are condensed in solids, gels, or other molecular aggregates. Properties of the individual molecules are relevant, but the topology of the aggregates is the major parameter determining physical properties. Consequently, the exact placements of *all* substituents, even those with subtle steric differences, is relevant. The large influence of molecular packing on material properties has been demonstrated convincingly for n-conducting materials[6] and materials for singlet fission.[7]

Recently, we reported the synthesis of a series of regioisomerically pure 1,7-dibromo perylene-3,4,9,10-tetracarboxylic acid derivatives.[8] For the aromatic nucleophilic substitution reaction (S_NAr)[9] of the bromine atoms, it was observed that perylene bisimides (PBIs) were significantly more reactive than perylene tetraesters (PTEs).[10] Monosubstitution and subsequent attachment of another substituent yielded PBIs[11] and PTEs[6b] with different phenols at the bay positions. Along with the symmetrical 1,7-dibromo perylene-3,4,9,10-tetracarboxylic acid derivatives we also synthesized the nonsymmetrically peri-substituted 1,7-dibromoperylene monoimide diester (**1**), see Figure 1. The bromine atoms in compound **1** are nonequivalent and are expected to have significantly different reactivities, reminiscent to those of PBIs and PTEs.

Received: September 25, 2016
Published: October 25, 2016

DOI: 10.1021/acs.orglett.6b02887
Org. Lett. 2016, 18, 5648−5651

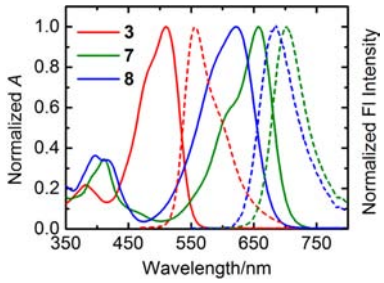


Figure 1. Normalized absorption (solid lines) and emission spectra (dashed lines) of compounds **3**, **7**, and **8** in chloroform.

In this communication we report on the aromatic nucleophilic substitution of the 1,7-bromine atoms in compound **1**. Phenols and pyrrolidine,[12] substituents with strongly different electronic properties, are used as the nucleophiles. Due to the reactivity differences of the 1 and 7 bromine atoms, the substitution reactions are regiospecific, leading to the first efficient synthesis of perylene 3,4,9,10-tetracarboxylic acid derivatives bearing four different substituents. The scope and limitations of this synthetic procedure and the optoelectronic properties of the resulting compounds will be investigated.

The reaction of compound **1** with 1.05 equiv of *tert*-butylphenol using mild conditions produced compound **2**, by a regiospecific and highly efficient substitution at the 7-position. Subsequent reaction with 4-hydroxy methylbenzoate gave substitution at C-1, and compound **3** was obtained in a 64% yield, Scheme 1. To the best of our knowledge, compound **3** is the first perylene tetracarboxylic acid derivate with four different substituents attached to the perylene core.

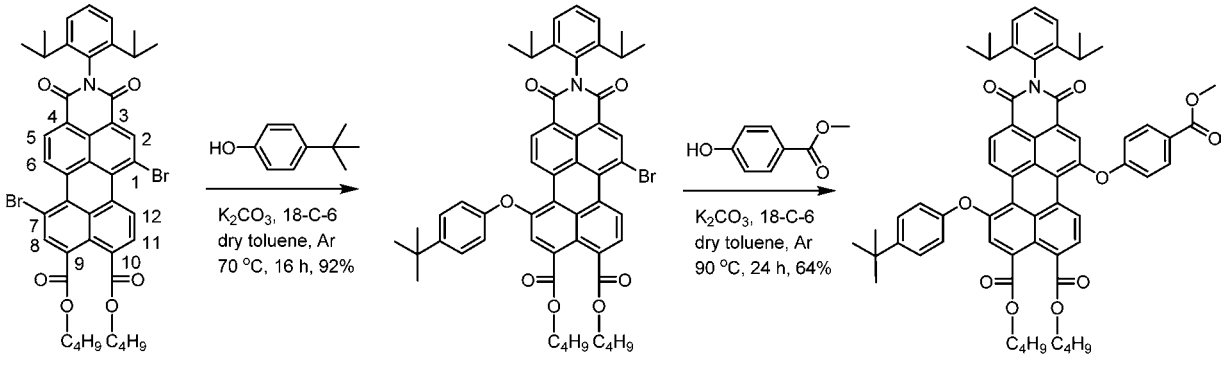
The substitution pattern of compound **2** was confirmed unambiguously by identifying the cross peaks in the $^{1}H-^{1}H$ NOESY spectrum of this compound, see Figure S4. The assignment of the ^{1}H and ^{13}C resonances of compound **2** was unambiguously confirmed by a series of systematic NMR measurements, namely, ^{1}H, ^{13}C-APT, ^{13}C DEPT-135, $^{1}H-^{1}H$ COSY, $^{1}H-^{13}C$ HSQC, and $^{1}H-^{13}C$ HMBC, see Section I of the Supporting Information (SI). The higher reactivity of the bromine atom at position 7 toward a nucleophilic aromatic substitution reaction (S_NAr)[9] is explained from the resonance structures of the "transition states" depicted in Scheme S1. In the state leading to 7-substitution, the negative charge is delocalized on the more electron withdrawing imide side of the molecule, and therefore, this is the most stable transition state.

By reversing the order in which the phenols were added, we anticipated that the complementary regioisomer, with the phenoxy substituents at C-1 and C-7 interchanged compared to compound **3**, could be synthesized. The first reaction, the regiospecific substitution of the bromine atom at position 7 with 4-hydroxy methylbenzoate, produced compound **4** in 89% yield. The subsequent reaction of compound **4** with 1.05 equiv of *tert*-butylphenol, however, yielded a mixture perylenes, from which the *tert*-butylphenoxy substituted compounds **2** and **5** were isolated, Scheme S2 and Figures S23 and S24. This rather unexpected result revealed that *tert*-butylphenol substituted the 4-hydroxyl methylbenzoate group at position 7. This implies that the large difference in reactivity at the positions 1 and 7, which is a pronounced advantage in the first substitution, may hamper the second substitution reaction.

To test reactivity toward other nucleophiles, we reacted compound **1** with pyrrolidine, a highly reactive secondary amine, that is often used to substitute bay halogens in perylene-3,4,9,10-tetracarboxylic acid derivatives.[12] Because pyrrolidine is a stronger nucleophile than phenol, the substitution on compound **1** already took place at 30 °C, yielding the blue-green monosubstituted compound **6** in 89% yield. The dipyrrolidinyl substituted compound **7** could be synthesized from compound **1** in 61% yield, using harsher reaction conditions, Scheme 2. Reaction of compound **6** with *tert*-butylphenol, however, did not yield disubstituted products. In toluene reductive debromination occurred at C-1,[13] Scheme S3 and Figure S25, while the reaction in DMF resulted in a mixture of unidentified decomposition products. Surprisingly, reaction of the 7-*tert*-butylphenoxyl substituted compound **2** with pyrrolidine did not yield disubstituted products either. Instead, compound **6** was formed by a regiospecific substitution of the phenol at position 7,[14] while substitution of the 1-bromine did not take place, Scheme 2.[15]

In order to obtain compounds with both a phenoxyl and a pyrrolidinyl substituent attached to the perylene core, the di-*tert*-butylphenoxyl compound **5** has been reacted with pyrrolidine. This resulted in the formation of compound **8**, by an efficient regiospecific substitution of the *tert*-butylphenoxyl substituent at position 7, Scheme 3. In a similar fashion compound **10**, the 4-hydroxymethylbenzoate analogue of compound **8**, has been obtained, Scheme S4. Compounds **8** and **10**, in addition to compound **3**, are examples of

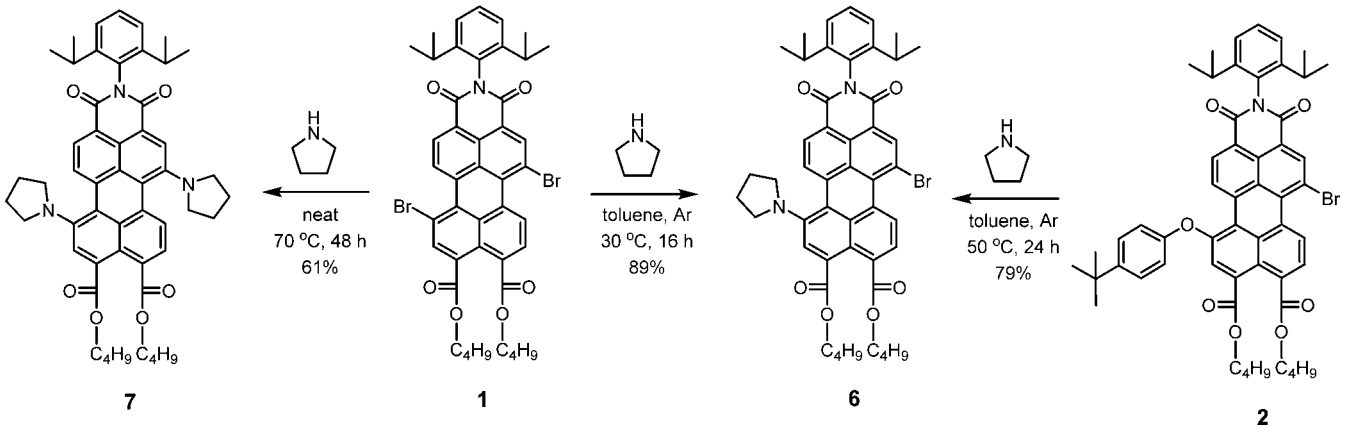
Scheme 1. Synthesis of Compound 3 by Two Subsequent Regiospecific Substitution Reactions Using Different Phenols



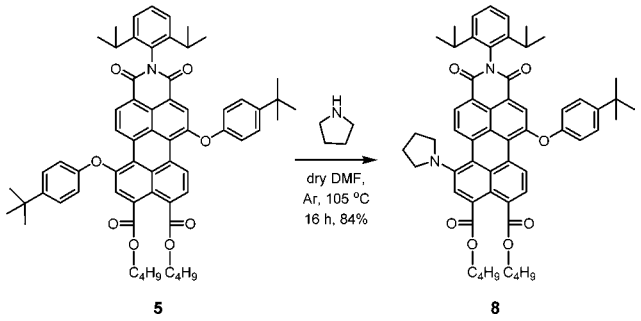
1 **2** **3**

DOI: 10.1021/acs.orglett.6b02887
Org. Lett. 2016, 18, 5648−5651

Scheme 2. Substitution Reactions of Compounds 1 and 2 with Pyrrolidine



Scheme 3. Substitution Reaction of Compound 5 with Pyrrolidine



perylene-3,4,9,10-tetracarboxylic acid derivatives bearing four different substituents at the peri and bay positions. The substitution pattern of compounds **3** and **8** was proven by NMR spectroscopy, see Section I of the SI. Attempts to selectively substitute the 7-substituents of other 1,7-disubstituted compounds were not successful. The reaction of the di 4-*tert*-butylphenol compound **5** with 4-hydroxy methyl benzoate to synthesize the regioisomer of compound **3** and reactions of the dipyrrolidine **7** with phenols to obtain the regiosomers of compounds **8** and **10** failed due to a lack of reactivity.

The outcome of the syntheses described in this work can be rationalized by taking into account the nucleophilicity, leaving group ability, and electron donating capability of the reagents used.[16] For example, the successful synthesis of compound **3** and the failed synthesis of its regioisomer make perfect sense because *tert*-butyl phenol is the stronger nucleophile and 4-hydroxybenzoate ester is the better leaving group. Therefore, *tert*-butyl phenol is able the substitute the 4-hydroxybenzoate ester at the highly activated 7-position in compound **4**, while the substitution of the *tert*-butyl phenol in compound **2** by a 4-hydroxybenzoate ester cannot take place.

The presence of pyrrolidinyl or phenoxy substituents at C7, in compounds **6**, **2**, and **4**, deactivate the bromine atoms at position 1. In the case of the 7-pyrrolidine compound **6**, this prevents substitution of this bromine atom by moderately nucleophilic phenols. For the 7-phenol substituted compounds **2** and **4**, bromine deactivation results in a substitution of the phenol at position 7, when the strongly nucleophilic pyrrolidine is used. In this reaction, the large differences in activation of positions 1 and 7, by the peri imide and ester functionalities, make the 7-phenol the better leaving group.

Steady state absorption and emission spectra, fluorescence lifetimes, and redox potentials were measured from the newly synthesized compounds **3**, **7**, and **8**, Figures 1, S21 and S22 and Table 1. The optical properties of these compounds are

Table 1. Optical and Electrochemical Properties of the Compounds 3, 7, and 8[a]

	λ_{abs} (nm)	ε ($M^{-1}cm^{-1}$)	λ_{em}(nm)	Φ_f	τ_f (ns)	E_{1ox}	E_{2ox}
3	510	39900	556	0.73	4.93	1.04	
7	657	32400	702	0.06	4.11	0.17	0.31
8	622	33200	686	0.08	3.97	0.40	0.90

[a]Optical spectra measured in chloroform. Redox potentials (V vs Fc^+/Fc) measured in dichloromethane.

in between those of the corresponding PBIs[17] and PTEs.[18] The effect of strongly electron-donating pyrrolidinyl substituents on the absorption and emission spectra is clearly visible by successive bathochromic shifts observed going from compound **3** to **8** and **7**. Along with the bathochromic shifts, pyrrolidinyl substituents induce strong decreases in fluorescence quantum yields. Surprisingly, the fluorescence quantum yield is lower for compound **7** than for the corresponding PBI.[19] Another notable observation is the long lifetime of compounds **7** and **8**, around 4 ns. Cyclic voltammetry measurements reveal that the compound **3** is the least electron rich among compounds **3**, **7**, and **8**. This compound shows only one reversible oxidation peak at very high potential, i.e., 1.04 V against ferrocene (Table 1). However, compound **7** is the most electron rich derivative due to the presence of two pyrrolidinyl groups at the bay-positions. It shows two reversible oxidations at very low potentials 0.17 and 0.31 V. Interestingly, compound **8**, which has one phenoxy and one pyrrolidinyl group, displays two oxidations; the first at low potential (0.40) and the second at high potential (0.90 V). The reduction part of the voltammograms was not conclusive, and therefore, we have restricted our discussion to the oxidation potentials.

In conclusion, we have demonstrated that compound **1** is a very useful synthon that enabled us to synthesize perylenes bearing four different substituents. Nucleophilic substitution reactions with phenols and pyrrolidine on compound **1** are always regiospecific and highly efficient reactions, in which the imide-activated bromine at C-7 is substituted. Specific

DOI: 10.1021/acs.orglett.6b02887
Org. Lett. 2016, 18, 5648−5651

substitution of the remaining bromine at C-1 occurs in a limited number of cases only because the imide-activation of C-7 toward nucleophilic substitution is so pronounced that displacement of the substituent at C-7 may compete with the substitution of the bromine at C-1. If the substituent attached at C-7 is a phenol with poor leaving group ability and the nucleophile is another phenol, substitution of the bromine atom at C-1 occurs selectively. If the substituent at C-7 is a phenol and the nucleophile is pyrrolidine, substitution takes place at C-7, displacing the phenol without effecting the bromine at C-1. By exploiting this reactivity pattern, we have synthesized several perylenes with four different substituents; 1,7-diphenoxy compounds bearing different phenols (**3**), 1-phenoxy,7-pyrrolidinyl derivatives (**8** and **10**), and 1,7-dipyrrolidinyl compound (**7**). Optical and electrochemical characterization of these novel molecules demonstrated that the optoelectronic properties of these molecules are primarily influenced by the presence of strongly electron donating pyrrolidine substituent(s). Our current research efforts are focused on further developing regiospecific substitution reactions on compound **1** and examining structure−property relationships of the obtained nonsymmetric bay substituted derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02887.

Conformation of the molecular structure of compounds **2**, **3**, and **8** by 1D and 2D NMR spectroscopy. Experimental section describing the synthesis and characterization of all novel compounds, including ^{1}H and ^{13}C NMR spectra of all new compounds, HR MS spectra of all new compounds, and cyclic voltammograms and fluorescence decay curves of compounds **3**, **7**, and **8** (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: w.f.jager@tudelft.nl.
*E-mail: r.k.dubey@tudelft.nl.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work is in part funded by the research programme of the Foundation for Fundamental Research on Matter (FOM), which is part of The Netherlands Organisation for Scientific Research (NWO).

■ REFERENCES

(1) (a) Huang, C.; Barlow, S.; Marder, S. R. *J. Org. Chem.* **2011**, *76*, 2386−2407. (b) Langhals, H. *Helv. Chim. Acta* **2005**, *88*, 1309−1343. (c) Würthner, F. *Chem. Commun.* **2004**, 1564−1579.

(2) Smith, M. B.; Michl, J. *Chem. Rev.* **2010**, *110*, 6891−6936.

(3) (a) Wasielewski, M. R. *Acc. Chem. Res.* **2009**, *42*, 1910−1921. (b) Blas-Ferrando, V. M.; Ortiz, J.; Ohkubo, K.; Fukuzumi, S.; Fernandez-Lazaro, F.; Sastre-Santos, A. *Chem. Sci.* **2014**, *4*, 4785−4793. (c) Harriman, A. *Chem. Commun.* **2015**, *51*, 11745−11756. (d) Dubey, R. K.; Inan, D.; Sengupta, S.; Sudhölter, E. J. R.; Grozema, F. C.; Jager, W. F. *Chem. Sci.* **2016**, *6*, 3517−3532.

(4) Würthner, F.; Saha-Moller, C. R.; Fimmel, B.; Ogi, S.; Leowanawat, P.; Schmidt, D. *Chem. Rev.* **2016**, *116*, 962−1052.

(5) (a) Aigner, D.; Borisov, S. M.; Petritsch, P.; Klimant, I. *Chem. Commun.* **2013**, *49*, 2139. (b) Dubey, R. K.; Knorr, G.; Westerveld, N.; Jager, W. F. *Org. Biomol. Chem.* **2016**, *14*, 1564−1568.

(6) (a) Vura-Weiss, J.; Ratner, M. A.; Wasielewski, M. R. *J. Am. Chem. Soc.* **2010**, *132*, 1738−1739. (b) Delgado, M. C. R.; Kim, E. G.; Filho, D. A.; Bredas, J. L. *J. Am. Chem. Soc.* **2010**, *132*, 3375−3387. (c) Günbas, D. D.; Chenming, X.; Patwardhan, S.; Fravventura, M. C.; Zhang, H.; Jager, W. F.; Sudhölter, E. J. R.; Siebbeles, L. D. A.; Savenije, T. J.; Shi, J.; Grozema, F. C. *Chem. Commun.* **2014**, *50*, 4955−4958.

(7) (a) Eaton, S. W.; Shoer, L. E.; Karlen, S. D.; Dyar, S. M.; Margulies, E. A.; Veldkamp, B. S.; Ramanan, C.; Hartzler, D. A.; Savikhin, S.; Marks, T. J.; Wasielewski, M. R. *J. Am. Chem. Soc.* **2013**, *135*, 14701−14712. (b) Mirjani, F.; Renaud, N.; Gorczak, N.; Grozema, F. C. *J. Phys. Chem. C* **2014**, *118*, 14192−14199. (c) Renaud, N.; Grozema, F. C. *J. Phys. Chem. Lett.* **2015**, *6*, 360−365.

(8) Sengupta, S.; Dubey, R. K.; Hoek, R. W. M.; van Eeden, S. P. P.; Gunbaş, D. D.; Grozema, F. C.; Sudhölter, E. J. R.; Jager, W. F. *J. Org. Chem.* **2014**, *79*, 6655−6662.

(9) Terrier, F. *Modern Nucleophilic Aromatic Substitution*; Wiley-VCH: Weinheim, Germany, 2013.

(10) The reactivity is reflected by the reaction conditions required. While the reactions with PBIs run smoothly in toluene, the reactions with PTEs have to be performed under more drastic reaction conditions; DMF at elevated temperatures.

(11) Xiao, S.; Li, Y.; Li, Y.; Zhuang, J.; Wang, N.; Liu, H.; Ning, B.; Liu, Y.; Lu, F.; Fan, L.; Yang, C.; Li, Y.; Zhu, D. *J. Phys. Chem. B* **2004**, *108*, 16677−16685.

(12) Zhao, Y.; Wasielewski, M. R. *Tetrahedron Lett.* **1999**, *40*, 7047−7050.

(13) Debromination of 1,7-dibrome PBIs under harsh conditions has been reported; see ref 12 and Lin, M.-J.; Finnel, B.; Radacki, K.; Würthner, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 10847−10850.

(14) Similarly, the formation of compound **6** from compound **4** was also observed in 95% yield using the same reaction conditions.

(15) For a corresponding PBI, the anticipated substitution of the Br atom at C-1 by pyrrolidine has been reported; see: Dubey, R. K.; Niemi, M.; Kaunisto, K.; Stranius, K.; Efimov, A.; Tkachenko, N. V.; Lemmetyinen, H. *Inorg. Chem.* **2013**, *52*, 9761−9773.

(16) The nucleophilicity of phenols, *tert*-butyl phenol, and 4-hydroxy methylbenzoate ester is derived from the Hammett substituent constants σ_p of the para substituents; see: Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165−195.

(17) PBIs with phenols at positions 1 and 7, a phenol and an pyrrolidine and two pyrrolidine substituents are known; see refs 9, 15, and 12.

(18) PTEs with two phenols at positions 1 and 7 are known; see ref 5. Pyrrolidine-substituted PTEs have not been reported.

(19) Dubey, R. K.; Efimov, A.; Lemmetyinen, H. *Chem. Mater.* **2011**, *23*, 778−788.

DOI: 10.1021/acs.orglett.6b02887
Org. Lett. 2016, 18, 5648−5651