Anthraquinones

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Practical Synthesis of *p*- and *o*-Amino- and Methoxyphenolic Anthraquinones

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Abstract: *New versatile and selective methods for the syntheses of substituted amino- and methoxyphenolic anthraquinones (**I–IV**) based on fusion of cyanophthalides (**V**) and semiquinone aminals (**VI**, **VII**) under basic conditions are described.*

Amino- and methoxy-anthraquinones and related systems are common structural motifs of natural and designed molecules of biological, medical and industrial importance. Examples of such compounds abound and include the biologically active enediynes[1,2] (e.g. uncialamycin, Figure 1a),[3–6] tetracycline antibiotics[7] (e.g. viridicatumtoxin B),[8–10] and trioxacarcins[11–14] (e.g. DC-45-A2) classes of natural products as well as the brightly colorful compounds alizarin and carminic acid (crimson, cochineal). The former and their analogues are of particular interest as potential ligands, lead compounds and drug candidates while the latter are classic red dyes. And yet methods for their synthesis lack practicality and generality. Here we report practical, versatile and selective methods for the construction of *p*- and *o*-aminophenolic anthraquinones (**I** and **II**, Figure 1a) and *o*- and *p*-methoxyphenolic anthraquinones (**III** and **IV**, Figure 1a). Involving fusion of 3-cyanophthalides (e.g. **V**, Figure 2) with *p*- and *o*-alkoxy semiquinone aminals (**VI** and **VII**, Figure 2) under basic conditions, these methods are currently enabling synthetic efforts toward uncialamycin and its analogs[15] and other biologically active molecules and are expected to find further applications as useful technologies in chemical synthesis, chemical biology, medicinal chemistry, and dye development.

The problematic nature of the existing methods for the construction of *p*-substituted aminophenolic anthraquinones is documented by the isolated examples[4,16] and limited success with complex substrates (see Figure 1b).[17,18] In the latter cases directed toward the total synthesis of dynemycin, Myers[17] and Danishefsky[18] reported formation of undesired products **C**[17] and **D**[17,18] instead of the desired amino anthraquinone advanced intermediates (**E** and thence **F**, Figure 1b) through a Hauser–Kraus type[19–21] reaction from the corresponding cyanophthalide (**A**) and iminoquinones (**B**) (Figure 1b).

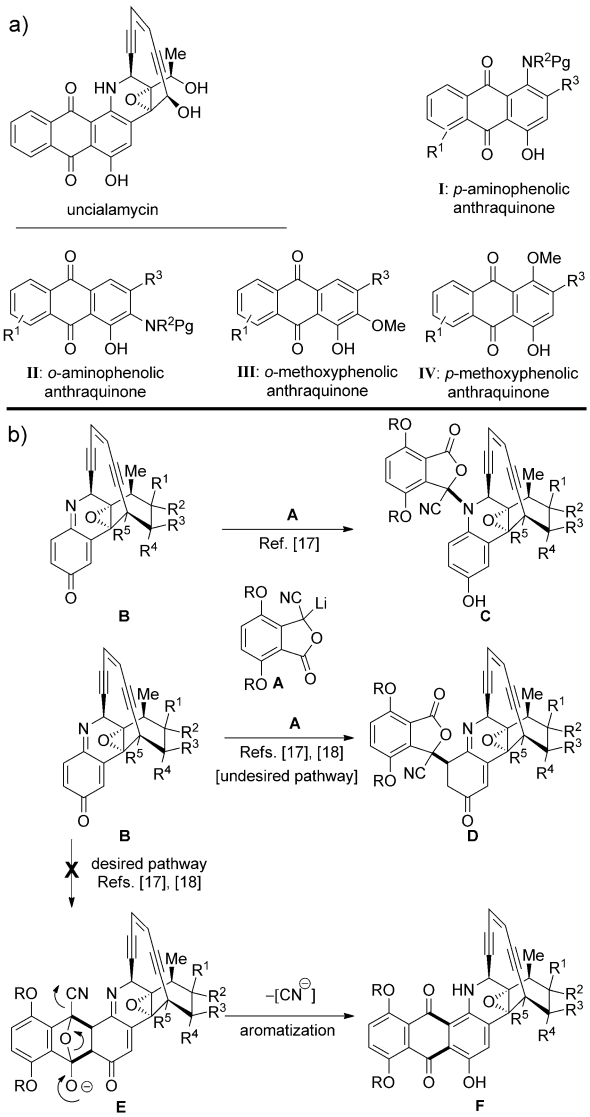

Figure 1. Amino- and methoxyphenolic anthraquinones and related systems. a) Uncialamycin and targeted amino- and methoxy-anthraquinone structures (**I–IV**); b) unsuccessful attempts to construct *p*-substituted aminophenolic anthraquinones. Abbreviations: Pg = protective group; LDA = lithium diisopropylamide; LiHMDS = lithium bis(trimethylsilyl)amide.

Figure 2 depicts the mechanistic rationale for the proposed expanded annulation reaction to form *p*- and *o*-substituted amino- (**I** and **II**, Figure 2, pathways **a** and **c**, respectively) and methoxyphenolic anthraquinones (**III** and **IV**, Figure 2, pathways **d** and **b**, respectively) from the corresponding cyanophthalides (**V**, Figure 2) and *p*- and *o*-

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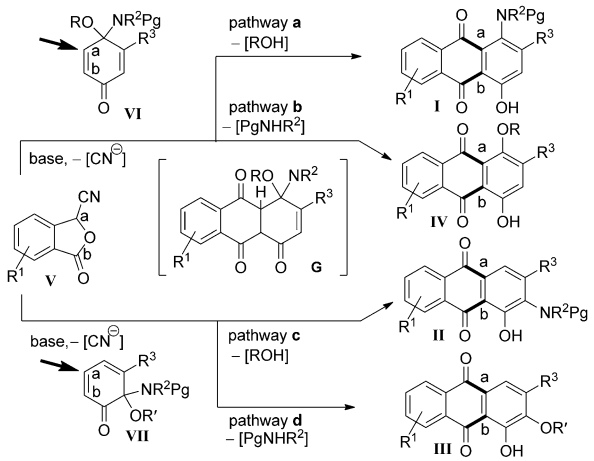

Figure 2. Mechanistic rationale for selective formation of anthraquinones **I**–**IV**.

alkoxy semiquinone aminals (**VI** and **VII**, Figure 2). In order to develop this strategy, we undertook studies to determine the feasibility of the expected carbon–carbon bond forming and breaking reactions and explored the optimization of the required base, conditions, and substrates. Upon extensive experimentation with substrates **1** and **6** (Figure 3) (see Supporting Information (SI) for details), it was found that pathway **a** [**V** + **VI** → **I**, Figure 2] could be achieved smoothly by the use of LiHMDS in THF (or DME) at −78 → 25 °C to afford *p*-aminophenolic anthraquinone **10** as demonstrated in Figure 3 (e.g. **1** + **6** → **10**, 88 % yield). This process is presumed to proceed through intermediate **G** (Figure 2), which preferentially collapses via departure of the methoxy group rather than the amino group to afford the observed product. Exploration of the generality and scope of the reaction using a variety of cyanophthalides **V** (**1**–**5**, Figure 3) and *p*-methoxy semiquinone aminals **VI** (**6**–**9**, Figure 3) employing the above optimized conditions led to a series of novel *p*-aminophenolic anthraquinones **I** (**10**–**17**) in good to excellent yields as shown in Figure 3. Noteworthy is the applicability of this process to the construction of substituted *p*-aminophenolic anthraquinones with additional fused rings in their structures (i.e. compounds **12**, **13**, and **16**, Figure 3).

Attempts to implement a similar strategy for the synthesis of *o*-aminophenolic anthraquinones **II** (pathway **c**, Figure 2) employing cyanophthalides **V** and *o*-methoxy semiquinone aminals (**VII**) under the same optimized conditions at −60 → 25 °C (LiHMDS, THF) led to the targeted *o*-aminophenolic anthraquinones **II** (Figure 2) as only the minor products. Their *o*-methoxyphenolic counterparts (**III**, Figure 2) were the major products in these reactions formed via pathway **d** (Figure 2) as demonstrated in Figure 4a with substrates cyanophthalide **1** and semiquinone **18** (**1** + **18** → **22**, 20 % yield; **21**, 70 % yield). *o*-Methoxyphenolic anthraquinone **21** is presumably formed through intermediate **H** (Figure 4a), whose formation from **18** and collapse to **21** (expulsion of MeN=C=O and CN^-) are shown in Figure 4a. Unexpected and not ideal, this observation prompted us to optimize the process further in order to deliver either product (i.e. **21** or **22**) in high yield. Our results from this study are summarized in

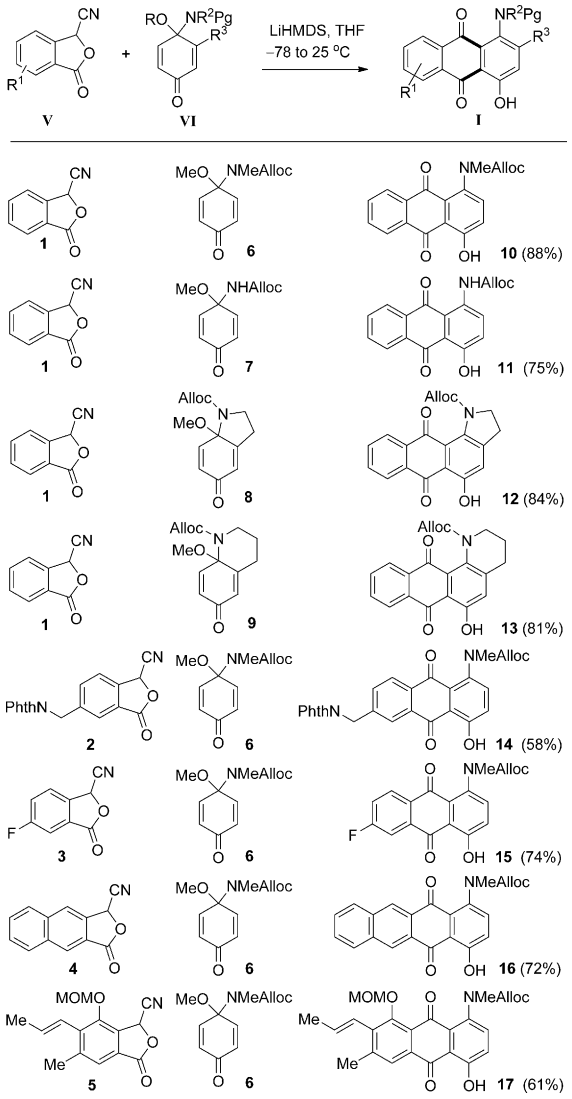

Figure 3. Selective formation of *p*-aminophenolic anthraquinones **I** (**10**–**17**). Abbreviations: Alloc = allyloxycarbonyl; MOM = methoxymethyl; Phth = phthalimide. Reactions were carried out on 0.09–0.2 mmol scale. For preparation of substrates and further details, see the Supporting Information.

Figures 4b and 5, respectively. Thus, employing substrates **1** and **18**, and using LiO*t*Bu, instead of LiHMDS, at lower temperature (i.e. −78 → 25 °C) resulted in the formation of the *o*-methoxyphenolic anthraquinone **21** (85 % yield) as depicted in Figure 4b. This reaction proved of general applicability and scope, accommodating cyanophthalides **V** (e.g. **1**–**3**) and semiquinone aminals **VII** (R^2 = Me) (e.g. **18** and **24**) as substrates, furnishing a variety of *o*-methoxyphenolic anthraquinones **III** (e.g. **21**, **25**–**27**) in good yields as summarized in Figure 4b. It should be noted that the more obvious *o*-dimethoxy semiquinone **29**[21] (Figure 4c) is a fleeting intermediate, undergoing rapid and quantitative self [4+2]-cycloaddition to form dimer **30** upon generation from *o*-methoxyphenol (**28**) at 0 °C through the action of $PhI(OAc)_2$, and therefore, cannot be conveniently used as a precursor to this type of anthraquinones.

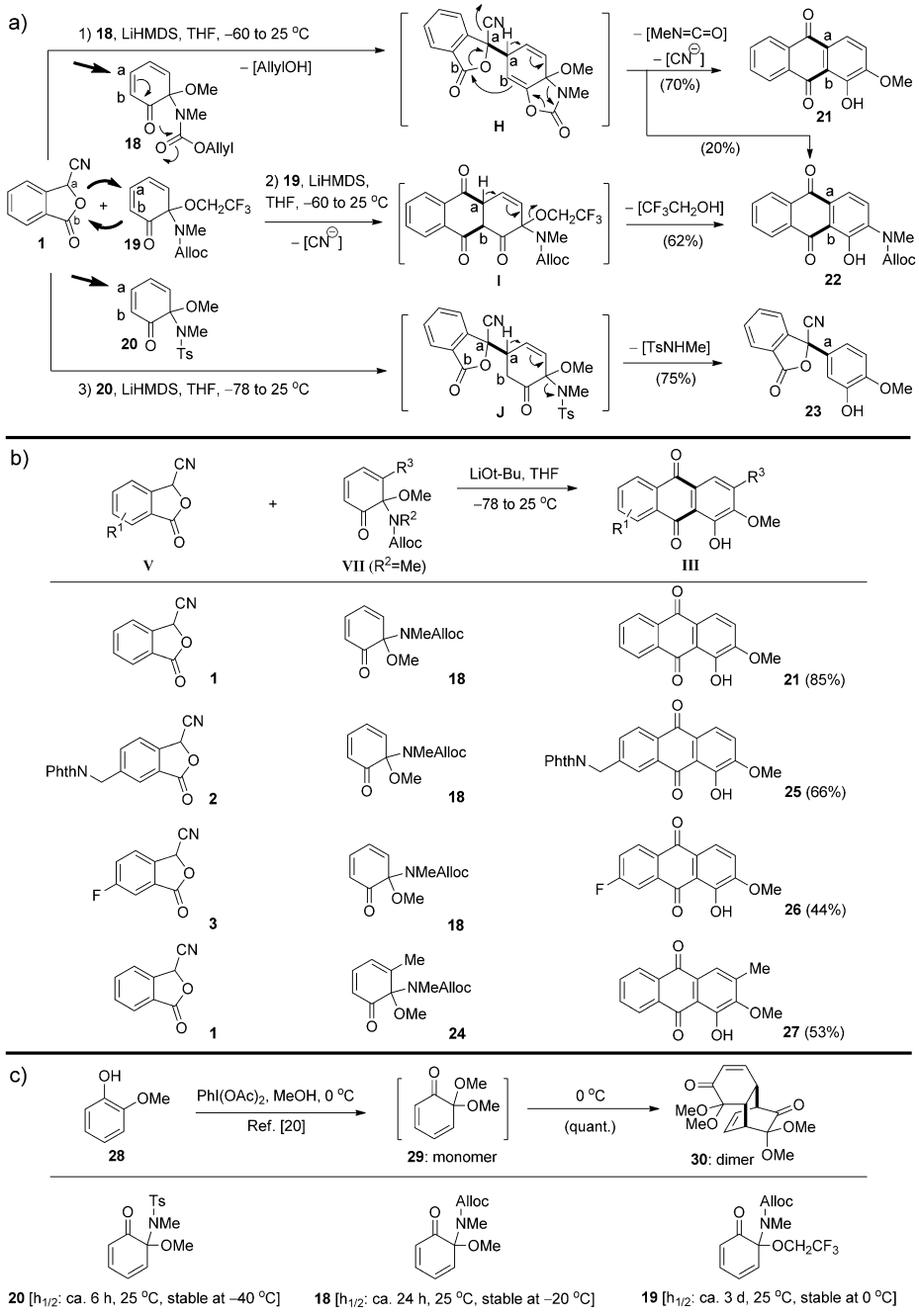

Figure 4. Exploratory studies with *o*-methoxy semiquinone aminals and synthesis of *o*-methoxyphenolic anthraquinones **III**. a) Selective formation of *o*-methoxyphenolic- (**21**), *o*-aminophenolic (**22**) anthraquinones, and *o*-methoxyphenolic tricycle **23**; b) examples of *o*-methoxyphenolic anthraquinones (**21, 25–27**); c) preparation and chemical reactivity of *o*-dimethoxy semiquinone (**29**) and stability of *o*-semiquinone aminals **18–20.** Abbreviation: Ts = tosyl. Reactions were carried out on 0.14–0.2 mmol scale. For preparation of substrates and further details, see the Supporting Information.

In our search for an exclusive pathway to *o*-aminophenolic anthraquinones (**II**, Figure 2), we reasoned that switching the methoxy (OMe) within the semiquinone aminal substrate **18** (Figure 4a) to a better leaving group, such as the trifluoroethoxy (OCH_2CF_3), may override the reactivity of the Alloc group, thus avoiding the formation of species **H** in favor of intermediate **I** (see Figure 4a), an occurrence that would inevitably lead to the desired *o*-aminophenolic anthraquinone **22** (as indicated by the arrows) instead of its methoxy counterpart (**21**, see Figure 4a). Indeed, trifluoroethoxy substrate **19** (Figure 4a, see SI for preparation details) suffered attack from the anion generated from cyanophthalide **1** (LiHMDS, THF, −60→25 °C) to afford, cleanly and exclusively, the targeted anthraquinone **22** (62% yield), presumably through transient intermediate **I** as shown in Figure 4a. Figure 5 shows a number of examples of this reaction (**V** + **VII** → **II**), leading to a variety of *o*-aminophenolic anthraquinones (**22**, **32–36**), employing cyanophthalides **1–5** and *o*-trifluoroethoxy semiquinone aminals **19** and **31**, demonstrating its generality and scope.

Placing a methyl group (Me) at the position adjacent to the *p*-methoxy aminal of semiquinone partners **VI** diverted its annulation reaction with cyanophthalides **V** (e.g. **1**: $R^1 = H$) from pathway **a** to pathway **b**, leading to *p*-methoxyphenolic anthraquinones **IV** (e.g. **1**: R = H, R^3 = Me) through elimination of AllocNHMe, instead of MeOH (LiO*t*Bu, THF, −78→25 °C, 85% yield as the major product with < 5% of the corresponding *p*-aminophenolic anthraquinone) as shown in Figure 2 and 6a. The additional examples of this reaction, shown in Figure 6a (**38–42**), demonstrate its versatility as a means to construct this type of *p*-methoxyphenolic anthraquinones (i.e. **IV**, Figure 2). Interestingly, the selectivity effect of the Me group on the semiquinone partner was reversed back to the *p*-aminophenolic anthraquinone product upon switching the methoxy to the trifluoroethoxy group as shown in Figure 6b (**1** + **43** → **44**, 83% yield). This option provides an avenue for the preparation of *p*-aminophenolic anthraquinones with substitution patterns beyond those shown in Figure 3.

Replacement of the Alloc group on the nitrogen of the *o*-semiquinone aminal **18** (Figure 4a) with a tosylate (*p*-$MeC_6H_4SO_2$) group (i.e. *o*-amino semiquinone **20**) resulted in

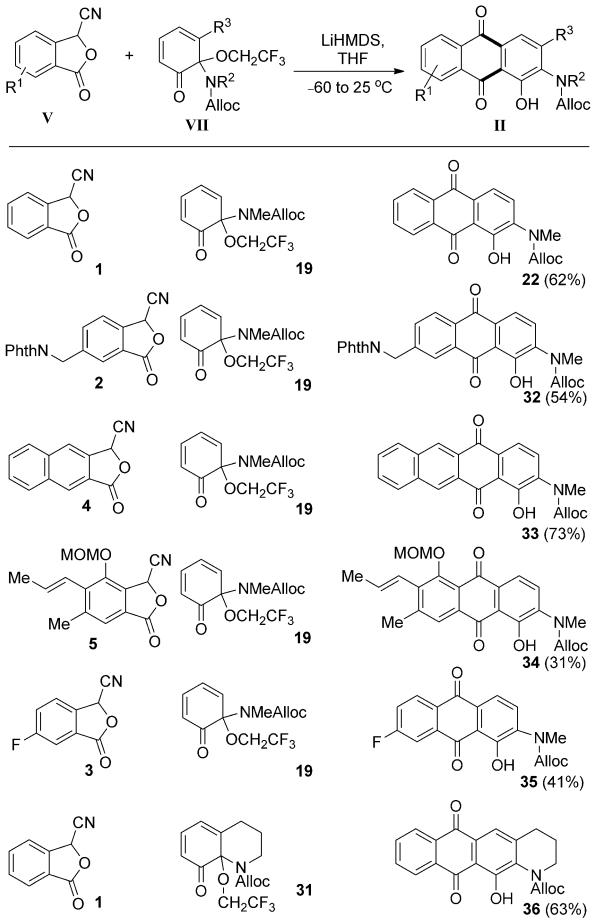

Figure 5. Selective formation of *o*-aminophenolic anthraquinones **II** (**22**, **32**–**36**). Reactions were carried out on 0.023–0.2 mmol scale. For preparation of substrates and further details, see the Supporting Information.

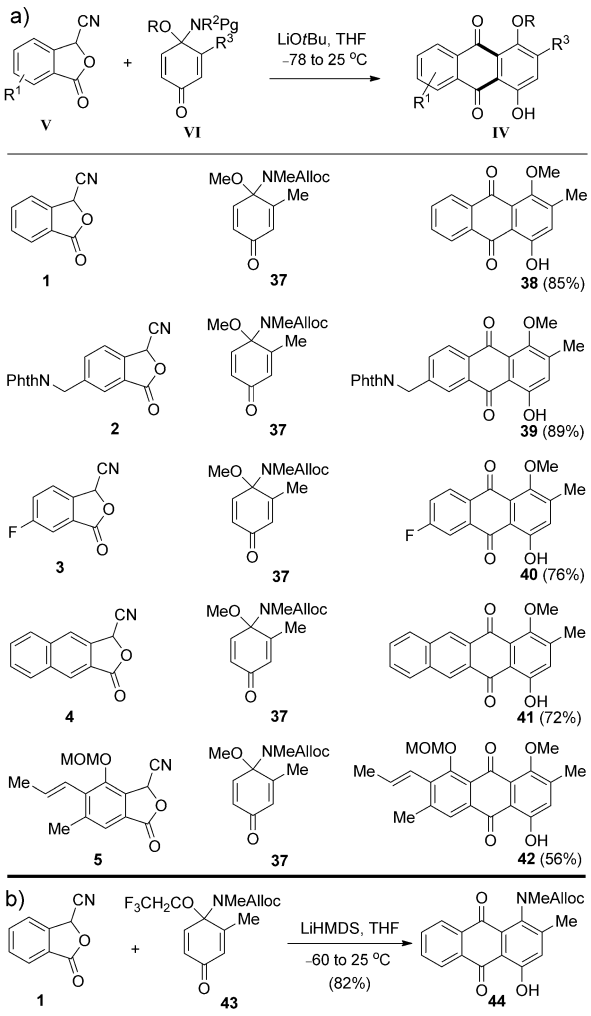

Figure 6. Selective formation of trisubstituted *p*-methoxyphenolic **IV** and *p*-aminophenolic anthraquinones **I**. a) Methyl-substituted *p*-methoxyphenolic anthraquinones (**38**–**42**); b) methyl-substituted *p*-aminophenolic anthraquinone (**44**). Reactions were carried out on 0.08–0.2 mmol scale. For preparation of substrates and further details, see the Supporting Information.

the formation of *o*-methoxyphenolic tricycle **23** (**1** + **20** → **23**, LiHMDS, −78 → 25 °C), presumably formed through intermediated **J**, as the major product (75% yield), together with *o*-methoxyphenolic anthraquinone **21** as a minor product (6% yield, Figure 4a). This finding opens up yet another productive pathway toward novel molecular diversity relevant to biology and medicine. It should be noted that the chemical stabilities of *o*-semiquinone aminals **18**–**20** (Figure 4a) are considerably higher than that of the fleeting *o*-dimethoxy semiquinone (**29**),[22] as summarized in Figure 4c, making the former substrates practical building blocks for chemical synthesis purposes.

The versatility of the developed synthetic technologies was further demonstrated by the preparation and use of *p*-methoxyiodo semiquinone aminal **45** as a partner in the described annulation reaction with cyanophthalide **1** to generate iodo-substituted *p*-aminophenolic anthraquinone **46** and derivatives thereof as shown in Figure 7. Thus, reaction of **1** with **45** under the optimized conditions (LiHMDS, −78 °C → 25 °C) furnished **46** in 81% yield). The latter was successfully employed as a substrate in an array of metal-catalyzed coupling reactions to afford a variety of substituted aminoanthraquinones, including the phenyl- [**47**: $PhB(OH)_2$, $Pd(dppf)Cl_2$ cat., K_3PO_4, 77% yield], methyl- [**48**: $MeB(OH)_2$, Ag_2O, K_3PO_4, $Pd(PPh_3)_4$ cat., 63% yield], acetylenic- [**49**: $PdCl_2(PPh_3)_2$ cat., CuI cat., TMSC≡CH, 66% yield], and carbomethoxy- [**50**: $PdCl_2(PPh_3)_2$ cat., (ethoxyvinyl)tributyltin; then 1.0 M aq. HCl, 61% yield] substituted derivatives shown in Figure 7.

In conclusion, we have developed versatile and selective methods for the practical synthesis of *p*-amino- and *p*-methoxyphenolic anthraquinones and *o*-amino- and *o*-methoxyphenolic anthraquinones from simple and readily available 3-cyanophthalides and *p*-methoxy- and *o*-trifluoromethoxy semiquinone aminals. The described chemistry is expected to find applications in the synthesis of natural and designed molecules relevant to biology and medicine as well as dye and imaging technologies.

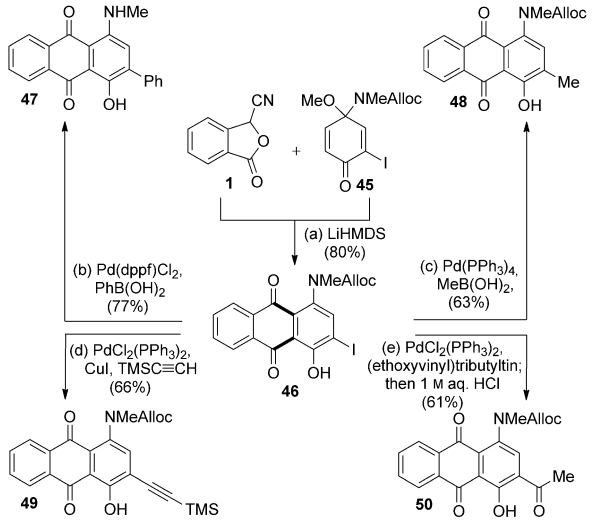

Figure 7. Synthesis of an iodo-substituted *p*-aminophenolic anthraquinone **46** and versatility and scope of the present synthetic method. Reagents and conditions: a) LiHMDS (1.5 equiv), **1** (1.5 equiv), THF, −78 °C, 10 min; then **45** (1.0 equiv), −78 to 25 °C, 1 h, 80%; b) $PdCl_2$(dppf) (0.1 equiv), $PhB(OH)_2$ (1.5 equiv), K_3PO_4 (3.0 equiv), THF, 67 °C, 6 h, 77%; (c) $Pd(PPh_3)_4$ (0.10 equiv), $MeB(OH)_2$ (3.0 equiv), Ag_2O (2.5 equiv), K_2PO_4 (3.0 equiv), THF, 67 °C, 14 h, 63%; (d) $PdCl_2(PPh_3)_2$ (0.2 equiv), CuI (0.4 equiv), Et_3N (4.0 equiv), TMSC≡CH (1.5 equiv), THF, 25 °C, 6 h, 66%; (e) $PdCl_2(PPh_3)_2$ (0.2 equiv), (ethoxyvinyl)tributyltin (2.0 equiv), THF, 67 °C, 6 h; then 1.0 M aq. HCl, 61%. Abbreviation: dppf = 1,1′-bis(diphenylphosphino)ferrocene. For preparation of substrates and further details, see the Supporting Information.

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