ORGANIC
LETTERS

2013
Vol. 15, No. 10
2334–2337

# Synthesis of 2-Aminophenols and Heterocycles by Ru-Catalyzed C–H Mono- and Dihydroxylation

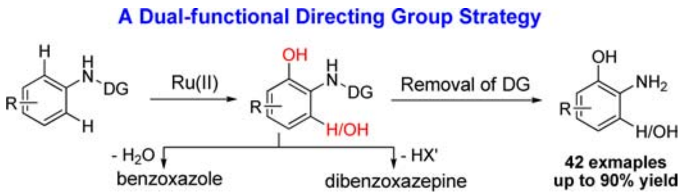
**Xinglin Yang,[†] Gang Shan,[†] and Yu Rao***

*MOE Key Laboratory of Protein Sciences, Department of Pharmacology and Pharmaceutical Sciences, School of Medicine and School of Life Sciences, Tsinghua University, Beijing 100084, China*

*yrao@mail.tsinghua.edu.cn*

**Received February 15, 2013**

## ABSTRACT



**A novel and efficient synthesis of 2-aminophenols, 2-aminobenzene-1,3-diols, and heterocycles through Ru-catalyzed C–H mono- and dihydroxylation of anilides has been developed with a new directing group strategy. The reaction demonstrates excellent reactivity, regioselectivity, good functional group tolerance, and high yields.**

2-Aminophenol and 2-aminobenzene-1,3-diol derivatives[1] are highly valuable building blocks for synthesis, medicinal chemistry, and materials science. By far the most prevalent strategies for preparing 2-aminophenol and 2-aminobenzene-1,3-diol are using the classic sequential nitration–reduction protocols.[2] However, these methods usually suffer from one or more serious limitations including poor regioselectivity, harsh reaction conditions, low yields, and tedious reaction procedures. Therefore, the development of a general, mild, and practical approach to 2-aminophenol and 2-aminobenzene-1,3-diol derivatives still remains an important challenge.

Direct functionalization of C–H bonds by a transition metal has emerged as a powerful method for organic synthesis in recent years.[3] Since in most cases of C–H activation the existing functional group within a substrate is unsuitable to achieve efficient intramolecular delivery of a catalyst or reagent, various directing groups (DGs) have been widely used to achieve the desired regioselectivity.[4] In multistep synthesis, those DGs need to be removed for further chemical manipulations. However, some DGs are nonremovable and deprotections of many special DGs require quite harsh conditions, which will seriously limit the scope and practicality of those methodologies. Hence, in comparison with common directing group approaches, a double-functional DG strategy which can serve as not only a readily cleavable coordinating group but also an essential structural component for complex molecule synthesis would be highly desirable.

---

[†] These authors contributed equally.

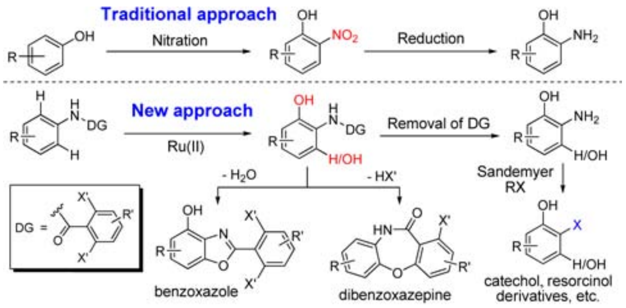
(1) (a) Tyman, J. H. P. *Synthetic and Natural Phenols*; Elsevier: New York, 1996. (b) Rappoport, Z. *The Chemistry of Phenols*; Wiley-VCH: Weinheim, 2003. (c) Hartwig, J. F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley-Interscience: New York, 2002; Vol. 1, p 1097. (d) Fiegel, H.; Voges, H. W.; Hamamoto, T.; Umemura, S.; Iwata, T.; Miki, H.; Fujita, Y.; Buysch, H. J.; Garbe, D.; Paulus, W. *Phenol Derivatives in Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH: New York, 2002.

(2) (a) McComas, C. C. et al. , PCT Int. Appl., 2011106992, 09 Sep 2011. (b) Rodgers, J. D. et al. , PCT Int. Appl., 2010135650, 25 Nov 2010. (c) Smith, C.; Ali, A.; Chen, L.; Hammond, M.; Anderson, M.; Chen, Y.; Eveland, S.; Guo, Q.; Hyland, S.; Milot, D.; Sparrow, C.; Wright, S.; Sinclair, P. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 346.

(3) For general reviews on transition-metal-catalyzed C–H activation of arenes, see: (a) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (b) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439. (c) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (d) Yu, J. Q.; Giri, R.; Chen, X. *Org. Biomol. Chem.* **2006**, *4*, 4041. (e) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (f) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (g) Daugulis, O.; Do, H. Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (h) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (i) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (j) Xu, L.-M.; Li, B.-J.; Yang, Z.; Shi, Z. J. *Chem. Soc. Rev.* **2010**, *39*, 712.

(4) For a review about removable directing groups in organic synthesis: Rousseau, G.; Breit, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 2450.

10.1021/ol400437a



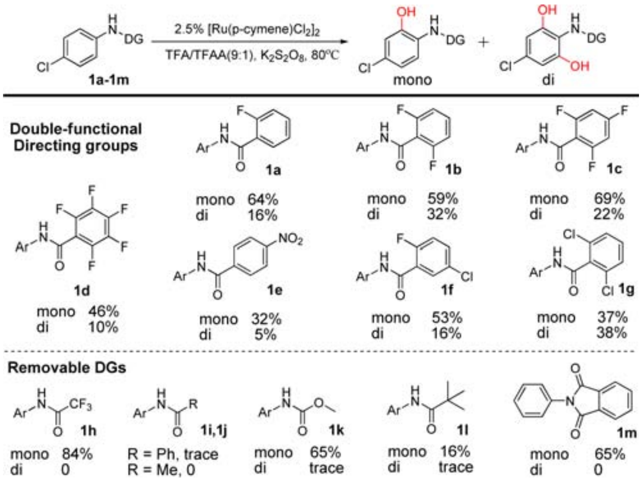
Advantages: 1) Good regioselectivity; 2) fewer steps, milder conditions, higher yields;
3) Broad scope for both mono- and dihydroxylation reactions;
4) A dual-functional DG strategy (removable and usable for synthesis);

**Figure 1.** A new strategy for 2-aminophenol and heterocycle synthesis.

Recently, Ru(II) catalysts have been successfully employed in C−H hydroxylation of benzoates, benzamides, and ketones[5,6] through weak coordination.[7] In our continuous studies of developing new methods for functionalized 2-aminophenol and heterocycle synthesis, we envisioned that an *ortho*-substituted benzoyl group might serve as an ideal double-functional DG in Ru(II)-catalyzed regioselective C−H hydroxylation of anilides and the ensuing heterocycle synthesis with the following presumptions. (1) Compared with a benzoate ester (a very weak coordinating group), a benzamide group having stronger coordinating ability may feasibly facilitate both the *ortho*-selective C−H mono- and dihydroxylation[8] reaction of anilides under suitable conditions to provide 2-aminophenol and 2-aminobenzene-1,3-diol derivatives. (2) Besides removal from hydroxylated products, the directing group (*ortho*-substituted benzoyl part) itself can be further utilized in the synthesis of heterocycles such as dibenzoxazepines and benzoxazoles. Herein we report the first example of the synthesis of 2-aminophenols and heterocycles through Ru(II)-catalyzed C−H mono- and dihydroxylation of anilides with a double-functional DG strategy (Figure 1).

At the beginning of our investigations, we explored different *ortho*-substituted benzoyl groups, including 2-fluorobenzoyl, 2,6-difluorobenzoyl, 2,6-dichlorobenzoyl, 2.4,6-trifluorobenzoyl, pentafluorobenzoyl, etc., as potential directing groups under previously reported hydroxylation reaction conditions. It was found that all these DGs (**1a**−**1g**) were efficient in providing the desired monohydroxylation products. To our delight, three benzoyl groups including **1b**, **1c**, and **1g** showed promising results, producing both mono- and dihydroxylation products in significant amounts respectively (Scheme 1). In parallel, a variety of common removable DGs were used as comparison tests. Among them, trifluoroacetyl **1h**, methyl carbamate **1k**, and imide **1m** groups can provide monohydroxylation products, but none or only a trace amount of the corresponding dihydroxylation products can be observed with these DGs (**1h**−**1m**) by LC-MS analysis.

**Scheme 1.** Screening of Various Directing Groups



Based on the preliminary results of these DGs, compound **1b** containing a 2,6-difluorobenzoyl group was selected for further model study. Then, as shown in Table 1, optimization of the mono- and dihydroxylation of **1b** was performed. After an extensive testing including varied co-oxidants, the ratio of TFA/TFAA, additives, etc., it was noticed that co-oxidant $K_2S_2O_8$[9] was generally superior over other oxidants with a remarkably higher level of efficiency. Interestingly, when $(NH_4)_2S_2O_8$ was used, only dihydroxylation product **1b″** can be observed (entry 10). It was found that a ratio of TFA/TFAA of ∼3:1 is most suitable for the reaction and the amount of co-oxidants is the dominating factor for mono- or dihydroxylation selectivity. For instance, the monohydroxylation reaction will proceed to completion to provide **1b′** with 1.2 equiv of $K_2S_2O_8$ (entry 13). In contrast, when higher amounts of

---

(5) Yang, Y.; Lin, Y.; Rao, Y. *Org. Lett.* **2012**, *14*, 2874.

(6) For Ru-catalyzed C−H oxygenation with amide, ketone as a directing group: (a) Thirunavukkarasu, V. S.; Hubrich, J.; Ackermann, L. *Org. Lett.* **2012**, *14*, 4210. (b) Thirunavukkarasu, V. S.; Ackermann, L. *Org. Lett.* **2012**, *14*, 6206. (c) Yang, F.; Ackermann, L. *Org. Lett.* **2013**, *15*, 718.

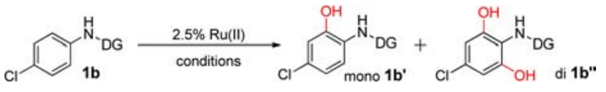
(7) For C−H activation through weak coordinations, see: (a) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788. (b) Wang, D.-H.; Wu, D.-F.; Yu, J.-Q. *Org. Lett.* **2006**, *8*, 3387. (c) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 6097. (d) Dai, H.-X.; Stepan, A. F.; Plummer, M. S.; Zhang, Y.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 7222. (e) Giri, R.; Chen, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 2122.

(8) For some representative examples of Pd-catalyzed C−H oxygenation, see: (a) Dick, A. R.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 12790. (b) Kalyani, D.; Sanford, M. S. *Org. Lett.* **2005**, *7*, 4149. (c) Zhang, Y.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 14654. (d) Powers, D. C.; Xiao, D. Y.; Geibel, M. A. L.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 14530. (e) Emmert, M. H.; Cook, A. K.; Xie, Y. J.; Sanford, M. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 9409. (f) Huang, C.; Ghavtadze, N.; Chattopadhyay, B.; Gevorgyan, V. *J. Am. Chem. Soc.* **2011**, *133*, 17630. (g) Shan, G.; Yang, X.; Ma, L.; Rao, Y. *Angew. Chem., Int. Ed.* **2012**, *52*, 13070. (h) Mo, F.; Trzepkowski, L.; Dong, G. *Angew. Chem., Int. Ed.* **2012**, *52*, 13075.

(9) For bystanding persulfate and $F^+$ oxidants, see: (a) Engle, K. M.; Mei, T.-S.; Wang, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2011**, *50*, 1478. (b) Wang, X.; Lu, Y.; Dai, H. X.; Yu, J. Q. *J. Am. Chem. Soc.* **2010**, *132*, 12203. (c) Vickers, C.; Mei, T.-S.; Yu, J.-Q. *Org. Lett.* **2010**, *12*, 2511. (d) Mei, T.-S.; Wang, X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 10806. (e) Wang, X.; Leow, D.; Yu., J. *J. Am. Chem. Soc.* **2011**, *133*, 13864.

$K_2S_2O_8$ (3.0−4.0 equiv) were used, dihydroxylation product **1b″** became the major product (entry 17). We found that 2.5% equiv amount of [Ru(*p*-cymene)$Cl_2$]$_2$ was enough to effectively promote the reaction. A control reaction showed that omission of the Ru catalyst resulted in complete inactivity of this catalytic system. Typically both mono- and dihydroxylation reaction will proceed to completion within 12 h at 70−90 °C with 1.2 or 3.0 equiv of $K_2S_2O_8$ respectively. To the best of our knowledge, this represents the first example of Ru(II) catalyzed mono- and dihydroxylation of anilides.

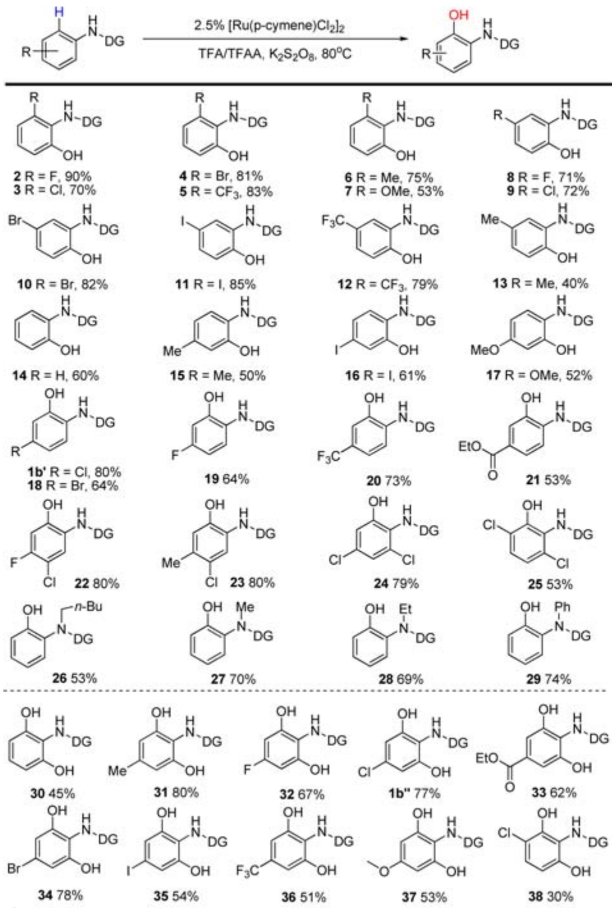
**Table 1.** Optimization of the Reaction Conditions



| entry | catalyst | oxidant | conditions | mono[a] | di[a] |
|---|---|---|---|---|---|
| 1 | [ RuCl$_2$(p-cymene)]$_2$ | $K_2S_2O_8$(2.0eq) | TCA/TCAA/3:1,80°C,12h | 8 | 0 |
| 2 | [ RuCl$_2$(p-cymene)]$_2$ | $K_2S_2O_8$(2.0eq) | TFA/DCE/1:1, 80°C, 12h | 34 | 3 |
| 3 | [ RuCl$_2$(p-cymene)]$_2$ | $K_2S_2O_8$(2.0eq) | TFA, 80°C, 11h | 67 | 10 |
| 4 | [ RuCl$_2$(p-cymene)]$_2$ | $K_2S_2O_8$(2.0eq) | TFA/TFAA/9:1, 80°C, 11h | 70 | 16 |
| 5 | [ RuCl$_2$(p-cymene)]$_2$ | $K_2S_2O_8$(2.0eq) | TFA/TFAA/3:1, 80°C, 11h | 59 | 32[b] |
| 6 | [ RuCl$_2$(p-cymene)]$_2$ | $K_2S_2O_8$(2.0eq) | TFA/TFAA/1:1, 80°C, 11h | 64 | 27 |
| 7 | [ RuCl$_2$(p-cymene)]$_2$ | $K_2S_2O_8$(2.0eq) | TFA/TFAA/1:3, 80°C,11h | 42 | 12 |
| 8 | [ RuCl$_2$(p-cymene)]$_2$ | PhI(TFA)$_2$(2.0eq) | TFA/TFAA/3:1, 80°C, 7h | 6 | 10 |
| 9 | [ RuCl$_2$(p-cymene)]$_2$ | PhI(OAc)$_2$(2.0eq) | TFA/TFAA/3:1, 80°C, 7h | 9 | 9 |
| 10 | [ RuCl$_2$(p-cymene)]$_2$ | $(NH_4)_2S_2O_8$(2.0eq) | TFA/TFAA/3:1, 80°C, 4h | 0 | 30 |
| 11 | RuCl$_2$(PPh$_3$)$_3$[c] | $K_2S_2O_8$(2.0eq) | TFA/TFAA/3:1, 80°C, 12h | 52 | 25 |
| 12 | [ RuCl$_2$(p-cymene)]$_2$ | $K_2S_2O_8$(1.0eq) | TFA/TFAA/3:1, 80°C, 13h | 78 | 5 |
| 13 | [ RuCl$_2$(p-cymene)]$_2$ | $K_2S_2O_8$(1.2eq) | TFA/TFAA/3:1, 80°C, 13h | 83 | 11 |
| 14 | [ RuCl$_2$(p-cymene)]$_2$ | $K_2S_2O_8$(1.5eq) | TFA/TFAA/3:1, 80°C, 13h | 66 | 20 |
| 15 | [ RuCl$_2$(p-cymene)]$_2$ | $K_2S_2O_8$(3.0eq) | TFA/TFAA/3:1, 80°C, 13h | 25 | 49 |
| 16 | [ RuCl$_2$(p-cymene)]$_2$ | $K_2S_2O_8$(4.0eq) | TFA/TFAA/3:1, 80°C, 13h | 0 | 45[b] |
| 17 | [ RuCl$_2$(p-cymene)]$_2$[c] | $K_2S_2O_8$(3.0eq) | TFA/TFAA/3:1, 80°C, 12h | 0 | 77[b] |

[a] Conversion ratio by LC-MS. [b] Isolated yield. [c] Ru catalyst (5%); DG = 2,6-difluorobenzoyl.

With the optimal conditions in hand, we next set out to explore the scope for this new hydroxylation reaction. As displayed in Figure 2, a variety of anilides were smoothly transformed into the corresponding monohydroxylated products in good to excellent yields. The scope of the substituents was found to be very broad. The *ortho*-, *meta*-, and *para*-substituted aryl groups, as well as the electron-withdrawing and -donating functional groups (halides, $CF_3$, ester, methyl, methoxyl, etc.) were well tolerated. For example, satisfactory yields were observed with substrates which contain strong electron-withdrawing groups, such as F and $CF_3$ (**2**, **5**, **8**, **12**, **19**, **20**), especially for **22** and **24** which have two electron-withdrawing groups. All *meta*-substituted substrates gave only one regioisomeric product (such as **8**−**13**) due to steric discrimination. It is noteworthy to point out that the synthesis of **25** is very challenging due to high steric hindrance and the electron-poor property of the precursor compound. Besides secondary benzamides, we were delighted to find that tertiary benzamides can also be successfully converted to the desired *ortho*-hydroxylated products (**26**−**29**). In addition, the scope of C−H dihydroxylation via this transformation was tested as well. As shown in Figure 2, we were pleased to find that the desired dihydroxylation compounds (**30**−**38**) can be smoothly prepared in satisfactory yields by using 3.0−4.0 equiv of $K_2S_2O_8$. It is notable that all of the reactions demonstrated excellent regioselectivity and reactivity. Moreover, all dihydroxylation and most monohydroxylation products either are very difficult or need extra, tedious steps to be prepared with traditional methods.



[a] Isolated yield; DG = 2,6-difluorobenzoyl

**Figure 2.** Subtrate scope of C−H mono- and dihydroxylation.

To prove both the practicality and effectiveness of this method in the large-scale synthesis, we prepared mono- and dihydroxylation products **4**, **5**, **1b′**, **1b″**, **1h**, and **34** on a gram-scale under the optimized conditions in good yields (Figure 3). It was found the large-scale reactions can be smoothly promoted with a very small amount of the Ru(II) catalyst loading (1% for mono- and 2% for dihydroxylation). Remarkably, we were very pleased to observe that even 0.1% [Ru(p-cymene)$Cl_2$]$_2$ can efficiently catalyze the synthesis of compound **4** in a yield of 54%. *It is noteworthy that this protocol was conducted without the need for air- or moisture-proof conditions.* In comparison with conventional approaches, the current method is advantageous for rapid access to these types of molecules because of its operational simplicity and broad availability of starting materials.

To verify the synthetic utility of the new directing groups, two types of important heterocycles were prepared with mono- and dihydroxylation products containing

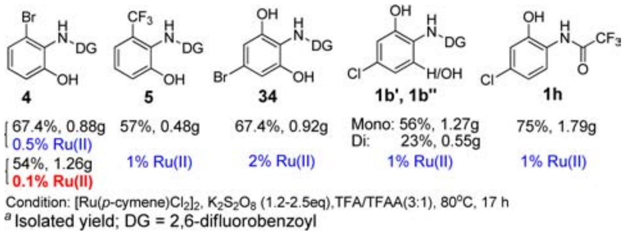
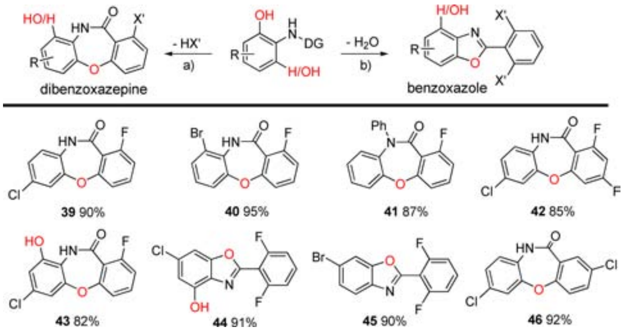


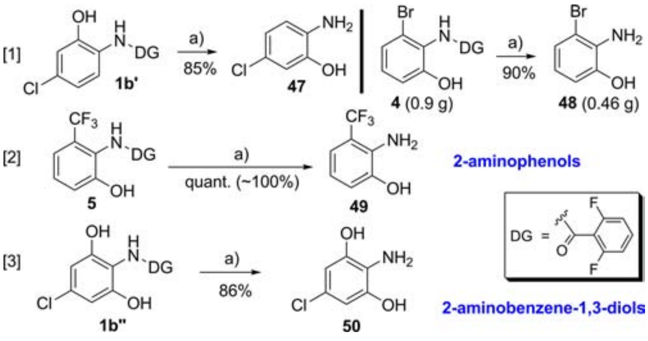
**Figure 3.** Gram-scale synthesis.

**Scheme 2.** Synthesis of Dibenzoxazepine and Benzoxazole[a]



[a] Conditions: (a) $K_2CO_3$ or NaOH, DMF or acetone, 100 °C, 2–3 h; (b) p-TsOH·$H_2O$, p-xylene, 140 °C, 12 h; isolated yield.

**Scheme 3.** Removal of Directing Group[a]



[a] Conditions: (a) $NH_2NH_2 \cdot xH_2O$, 100 °C, 3–4 h.

DGs. As illustrated in Scheme 2, a variety of dibenzoxazepines (**39**–**43**, **46**) and benzoxazoles (**44**, **45**) were readily synthesized with corresponding mono- and dihydroxylation compounds via nucleophilic aromatic substitution and intramolecular dehydration respectively. It is worth mentioning that **43** and **44** containing a free hydroxy group are challenging heterocycles by traditional synthetic approaches. Moreover, the halides from DGs can be further utilized for ensuing chemical manipulations. For example, 2′,4′-fluoride atoms from **42** can readily undergo nucleophilic aromatic substitution to construct a wide range of carbon–carbon and carbon–heteroatom bonds. Using known transformations,[10] **46** can be further transformed into new Cl-containing analogues of representative antidepressant drugs Ioxapine and Amoxapine. Considering the easy availability of the building blocks, this method potentially can provide a convenient approach to novel dibenzoxazepine and benzoxazole analogues for early drug discovery.

Finally, we showed that this amide directing group can be easily removed from both mono- and dihydroxylation products to provide corresponding 2-aminophenols **47**–**49** and 2-aminobenzene-1,3-diol **50** in good to excellent yields (Scheme 3). It should be pointed out that catechols and resorcinols can be readily accessed from these products by Sandemyer reactions.

In summary, a unique and practical directing group strategy has been developed for the synthesis of a broad range of 2-aminophenols and 2-aminobenzene-1,3-diols by Ru-catalyzed C–H mono- and dihydroxylation of easily accessible anilides. The reaction demonstrates excellent reactivity, regioselectivity, good functional group tolerance, and high yields. The synthetic utilities of DGs have been well demonstrated in the facial removal of DGs and ensuing synthesis of heterocycles. Further studies into developing new directing group strategies and the scope of this reaction are in progress in our laboratory.

**Acknowledgment.** This work was supported by the national '973' grant from the Ministry of Science and Technology (Grant No. 2011CB965300), National Natural Science Foundation of China (Grant No. 21142008), and Tsinghua University 985 Phase II funds and Tsinghua University Initiative Scientific Research Program. We thank Mrs. L. Ma for her help in our studies.

**Supporting Information Available.** Experimental procedures and characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

---

[10] Smits, R.; Herman, D. L.; Stegink, B.; Bakker, R. A.; de Esch, I. J. P.; Leurs, R. *J. Med. Chem.* **2006**, *49*, 4512.

The authors declare no competing financial interest.