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

ORGANIC LETTERS XXXX Vol. XX, No. XX 000–000

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Received February 15, 2013



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 derivatives¹ 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.

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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 benzovl 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 orthoselective C-H mono- and dihydroxylation⁸ 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).

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At the beginning of our investigations, we explored different ortho-substituted benzoyl groups, including 2-fluorobenzoyl, 2,6-difluorobenzoyl, 2,6-dichlorobenzoyl, 2.4,6trifluorobenzoyl, 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 monohydroxvlation products. To our delight, three benzovl 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.

2.5% [Ru(p-cymene)Cl₂] TFA/TFAA(9:1), K₂S₂O₈, 80°C 1a-1m mono di Double-functional Directing groups 59% 32% 69% 22% mono 64% 16% mono di mono di 1e c 1g 1d 46% 10% mono di mono 53% 16% 37% 38% mono di mono di 32% 5% Removable DGs _CF₃ ∥ 0 0 0 11 1h 1i,1j 1k ć 1m 16% trace 65% trace 65% 0 mono 84% di 0 mono R = Ph, trace R = Me, 0 mono mono

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 cooxidants, the ratio of TFA/TFAA, additives, etc., it was noticed that co-oxidant K₂S₂O₈⁹ was generally superior over other oxidants with a remarkably higher level of efficiency. Interestingly, when (NH₄)₂S₂O₈ was used, only dihydroxylation product 1b" can be observed (entry 10). It was found that a ratio of TFA/TFAA of \sim 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

Scheme 1. Screening of Various Directing Groups

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 $K_2S_2O_8$ (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	[RuCl2(p-cymene)]2	K ₂ S ₂ O 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 ₂ S ₂ O 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 ₂ S ₂ O 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, CF₃, 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 electronpoor 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.



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 monoand 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)Cl₂]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.

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 47-49and 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

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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 \cdot H₂O, *p*-xylene, 140 °C, 12 h; isolated yield.

Scheme 3. Removal of Directing Group^a



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.

The authors declare no competing financial interest.