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ABSTRACT

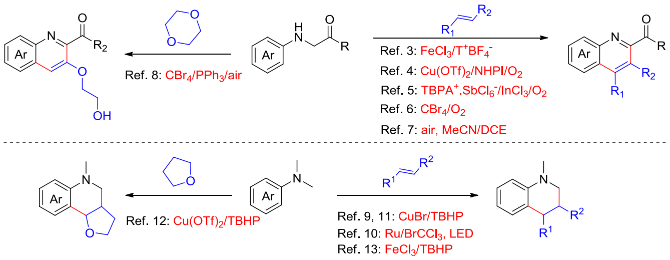
A simple and efficient cobalt-catalyzed aerobic oxidative dehydrogenative Povarov reaction of tertiary anilines with dihydrofuran has been developed for the synthesis of hexahydrofuro[3,2-*c*]quinolines. The one-electron-oxidation involved reaction is performed under mild conditions and only requires simple cobalt salts as a catalyst and dioxygen as a terminal oxidant.

Diels-Alder reaction is one of the most atom-economic and efficient synthetic routes for constructing 6-membered rings. Tetrahydroquinoline derivatives are an important class of natural products, which exhibit both biological and pharmaceutical activities in various fields.[1-13] First discovered in 1963, the Povarov reaction comprises a formal [4+2] cycloaddition of imines derived from aromatic amines and electron-rich olefins.[1] Since then, this *imino*-Diels-Alder reaction has become a powerful synthetic tool to form tetrahydroquinoline motifs.[2]

Recently, oxidative dehydrogenative Povarov reaction of secondary amines has been well developed (Scheme 1, top). In 2011, an oxidative Povarov/aromatization tandem reaction of glycine derivatives with alkenes using $FeCl_3$ as the catalyst and 2,2,6,6-tetramethylpiperidin-1-yl)oxy oxoammonium salt as the oxidant was first reported by Mancheño et al.[3] After that, some aerobic catalytic systems, such as $Cu(OTf)_2$/NHPI/O_2,[4] $TBPA^+ \cdot SbCl_6^-/O_2$[5], CBr_4/O_2,[6] and even auto-oxidation,[7] have been achieved in this transformation. Since 2015, we also developed an aerobic double-oxidative dehydrogenative (DOD) cyclization strategy of glycine derivatives with dioxane for the synthesis of complex quinoline motifs.[8]

Meanwhile, the oxidative dehydrogenative Povarov reaction of tertiary amines was realized too (Scheme 1, bottom). In 2014, Seidel et al reported an oxidative Povarov reaction of *N*-aryl tetrahydroisoquinolines with enamides under CuBr/TBHP conditions.[9] In the next year, Xu et al demonstrated a similar process using visible light photoredox catalysis.[10] In 2009, 2 examples of oxidative *aza*-Diels-Alder reaction of tertiary anilines with dihydrofuran have been mentioned by Zhang et al using CuBr/TBHP catalytic system.[11] Last year, liu et al described a $Cu(OTf)_2$/TBHP catalyzed double-oxidative dehydrogenative (DOD) Povarov reaction between tertiary anilines and tetrahydrofuran.[12] In this year, Guan et al presented a $FeCl_3$/TBHP promoted dehydrogenative Povarov reaction of tertiary anilines and enamides for the synthesis of tetrahydroquinolines with amido-substituted quaternary carbon centers.[13] Although these examples have achieved notable progress in this area, stoichiometric or more amounts of chemical oxidants were always necessary in these reactions. Therefore, the development of new methods using low-cost catalyst with molecular oxygen as terminal oxidant for the dehydrogenative [4+2] cycloaddition of tertiary amines is still highly desired.

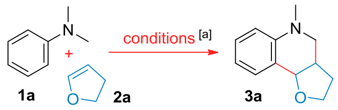
Scheme 1. Oxidative Dehydrogenative Povarov Reaction of Amines



Herein, in this paper, we report a cobalt-catalyzed[14] aerobic oxidative dehydrogenative [4+2] cycloaddition reaction of tertiary anilines with dihydrofuran for the synthesis of hexahydrofuro[3,2-*c*]quinolines.[15]

Our initial investigations focused on the reaction between *N*, *N*-dimethylaniline **1a** and dihydrofuran (**2**) in combination with various inexpensive first-row transition metal salts as the catalysts in acetonitrile at room temperature under aerobic conditions (Scheme 2, entries 1-9). After screening of metal catalysts, Co(II) Perchlorate was found to be the most effective for implementation of the present transformation (Scheme 2, entry 8). Screening of temperature suggested that 50°C was the best choice for the transformation (Scheme 2, entries 8, 10-12). The solvent effect was also explored, with acetonitrile being identified as the optimal solvent (Scheme 2, entries 13-16). The catalyst loading was varied too, and 10 mol % gave the best result (Scheme 2, entries 11, 17 and 18). Finally, changing the air atmosphere to pure oxygen atmosphere resulted in an improvement of the efficiency (Scheme 2, entry 19). After various reaction parameters were screened, the best results were found to be $Co(ClO_4)_2 \cdot 6H_2O$ (10 mol %) in MeCN at 50°C under oxygen atmosphere (Scheme 2, entry 19). Under these reaction conditions, a 61% yield of hexahydrofuroquinoline **3a** was obtained after 48 h.

Scheme 2. Screening of Reaction Conditions



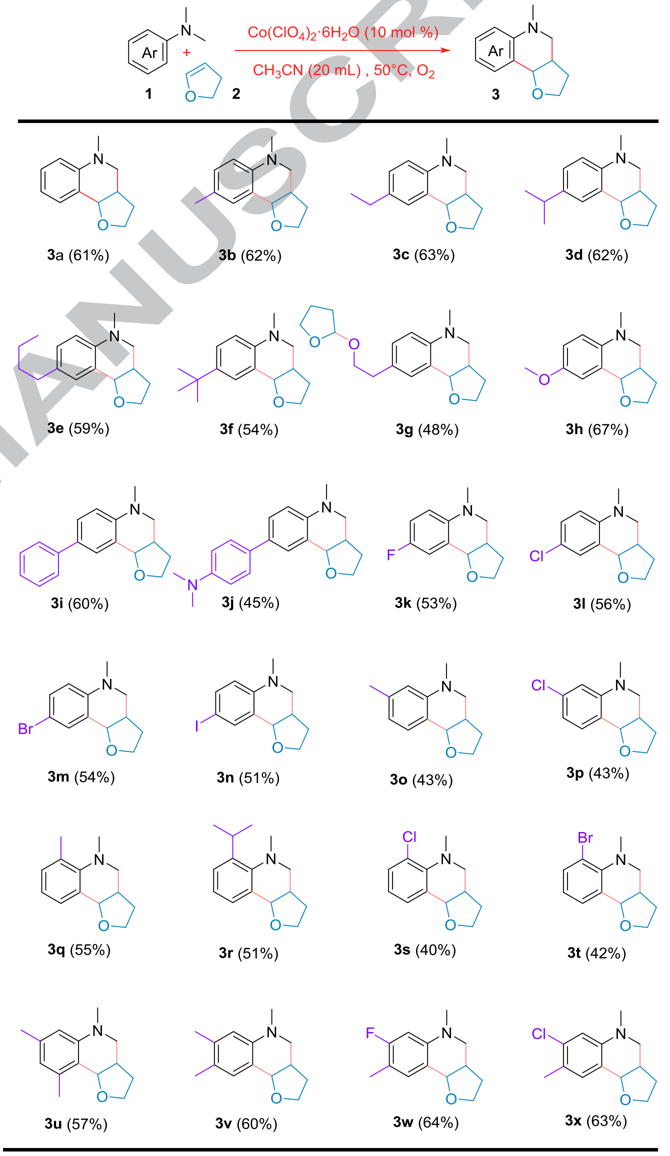
Entry	Catalyst	Temperature	Solvent	Loading	Atmosphere	**3a** (yield %)[b]
1	$CuCl_2$	rt	CH_3CN	10 mol %	air	45
1	CuCl	rt	CH_3CN	10 mol %	air	20
3	$FeCl_3$	rt	CH_3CN	10 mol %	air	0
4	$FeCl_2$	rt	CH_3CN	10 mol %	air	0
5	$CoCl_2 \cdot 6H_2O$	rt	CH_3CN	10 mol %	air	16
6	$CoBr_2 \cdot XH_2O$	rt	CH_3CN	10 mol %	air	35
7	$Co(NO_3)_2 \cdot 6H_2O$	rt	CH_3CN	10 mol %	air	10
8	$Co(ClO_4)_2 \cdot 6H_2O$	rt	CH_3CN	10 mol %	air	48
9	$Co(acac)_3$	rt	CH_3CN	10 mol %	air	0
10	$Co(ClO_4)_2 \cdot 6H_2O$	40 °C	CH_3CN	10 mol %	air	50
11	$Co(ClO_4)_2 \cdot 6H_2O$	50 °C	CH_3CN	10 mol %	air	59
12	$Co(ClO_4)_2 \cdot 6H_2O$	60 °C	CH_3CN	10 mol %	air	33
13	$Co(ClO_4)_2 \cdot 6H_2O$	50 °C	$(CH_2Cl)_2$	10 mol %	air	20
14	$Co(ClO_4)_2 \cdot 6H_2O$	50 °C	CH_3NO_2	10 mol %	air	10
15	$Co(ClO_4)_2 \cdot 6H_2O$	50 °C	THF	10 mol %	air	30
16	$Co(ClO_4)_2 \cdot 6H_2O$	50 °C	-	10 mol %	air	40
17	$Co(ClO_4)_2 \cdot 6H_2O$	50 °C	CH_3CN	15 mol %	air	55
18	$Co(ClO_4)_2 \cdot 6H_2O$	50 °C	CH_3CN	5 mol %	air	30
19	$Co(ClO_4)_2 \cdot 6H_2O$	50 °C	CH_3CN	10 mol %	O_2	**61**

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (10 mmol), solvent (20 mL), O_2, 50°C, 48 h. [b] Yields of the isolated product.

With the optimized reaction conditions in hand, we then evaluated the scope of the reactions of various tertiary anilines with dihydrofuran. As shown in Scheme 3, tertiary anilines with a variety of substituents at *para* position including methyl, ethyl, *iso*-propyl, butyl, *tert*-butyl, methoxyl, phenyl, and *N*, *N*-dimethylphenyl generated the desired products in good to high yields (Scheme 3, **3a-3j**). The reaction is tolerant to fluoro, chloro, bromo and iodo substituents on the aromatic ring of anilines, and the corresponding target products were obtained in good yields (Scheme 3, **3k-3n**). These halogen substituted examples enable potential applications in further functionalization. Tertiary anilines with *meta*-, or *ortho*-substituent groups on the aryl ring gave the desired quinolines in satisfactory yields too (Scheme 3, **3o-3t**). In addition, substrates bearing multiple substituents also worked well (Scheme 3, **3u-3x**).

To develop a more general and useful method, we found this simple cobalt/O_2 catalyst system is also efficient for the oxidative dehydrogenative [4+2] cyclization of *N*,*N*-dimethylaniline with electron deficient olefin maleimide (**4**).[16] Moreover, using *N*-phenyl 1,2,3,4-tetrahydroisoquinoline (**6**) and dihydrofuran (**2**) as substrates, polycyclic tetrahydroquinolines (**7**) can be achieved under the standard reaction conditions.[9,10] These 2 kinds of ring-fused tetrahydroquinolines are valuable precursors of many bioactive molecules and are widely used building blocks in organic synthesis.[9,10]

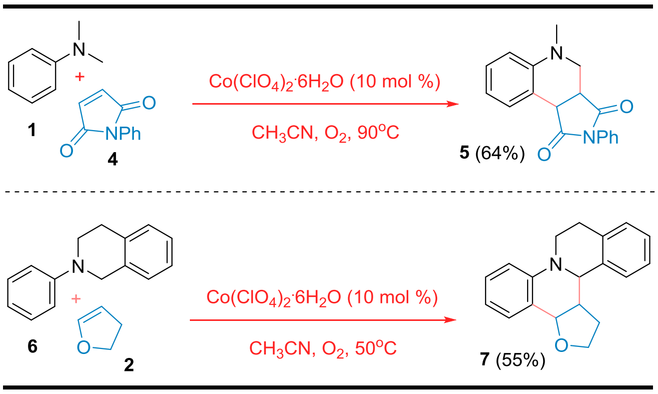
Scheme 3. Co(II) catalyzed aerobic oxidative Povarov reaction for the Syntheses of hexahydrofuro[3,2-c]quinolines



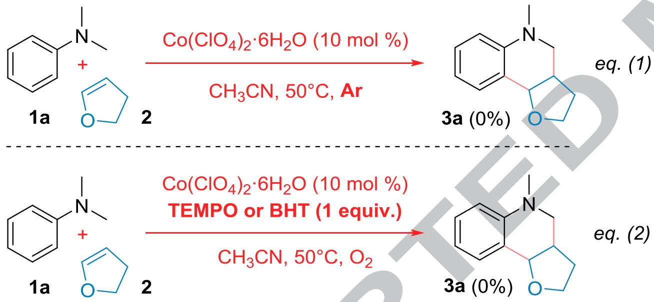
[a] Reaction conditions: **1** (1.0 mmol), **2** (10 mmol), CH_3CN (20 mL), O_2, 50°C, 48 h. [b] Yield of the isolated product.

Some control experiments were carried out in order to reveal the mechanism of this transformation (Scheme 5). Firstly, the reaction of **1a** with **2** in the absence of molecular oxygen (argon atmosphere) furnished no product [*Eq. (1)*], indicating that dioxygen is definitely crucial for the reaction. Secondly, no reaction occurred when a stoichiometric amount of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) or butylated hydroxytoluene (BHT) was employed in the standard reaction as radical scavenger [*Eq. (2)*]. This result suggested that the present reaction includes a radical process. To account for the aforementioned results, a proposed mechanism for the cobalt-catalyzed dehydrogenative [4+2] cyclization of tertiary anilines **1** with dihydrofuran **2** is shown in Scheme 6. First, a cobalt(III) peroxide radical generated by a combination of molecular oxygen with cobalt(II) might abstract a hydrogen atom of **1** to form radical intermediate **A**. The iminium type intermediate **B** could then be formed through a single electron transfer (SET) from **A**. Subsequently, cycloaddition of **B** with **2** results in the desired product **3** (path A). Path B was also possible because electron-deficient maleimide (**4**) was suitable substrate for this transformation too.

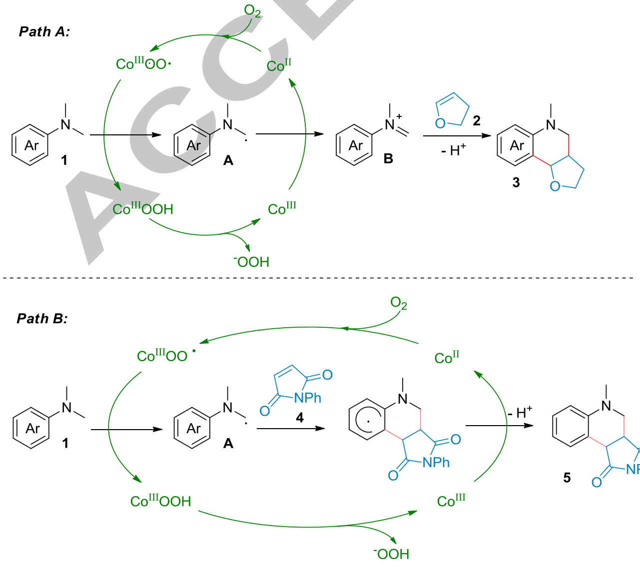
Scheme 4. Other applications



Scheme 5. Control experiments



Scheme 6. Proposed mechanism



In summary, we have demonstrated a cobalt-catalyzed, aerobic oxidative dehydrogenative formal [4+2] reaction of *N*,*N*-dimethylanilines with dihydrofuran. The reaction proceeds through cobalt-catalyzed dehydrogenation of tertiary amines followed by nucleophilic addition/intramolecular cyclization with dihydrofuran to afford hexahydrofuroquinoline motifs in good yields. The use of low-cost simple cobalt salts as the catalyst and molecular oxygen as the oxidant makes this transformation sustainable and practical.

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References and notes

1. (a) Povarov, L.-S.; Mikhailov, B.-M. *Izv. Akad. Nauk SSSR Otd. Khim. Nauk*. **1963**, 953–956; (b) Povarov, L.-S.; Grigos, V.-I.; Mikhailov, B.-M. *Izv. Akad. Nauk SSSR Otd. Khim. Nauk*. **1963**, 2039–2041; (c) Povarov, L.-S. *Russian. Chem. Rev.* **1967**, *36*, 656–670.
2. Recent review, see: Kouznetsov, V.-V. *Tetrahedron*. **2009**, *65*, 2721–2750.
3. Richter, H.; Mancheño, O. G. *Org. Lett.* **2011**, *13*, 6066–6069.
4. Xie, Z. Y.; Jia, J.; Liu, X. G.; Liu, L. *Adv. Synth. Catal.* **2016**, *358*, 919-925.
5. Jia, X.; Peng, F.; Qing, C.; Huo, C.; Wang, X. *Org. Lett.* **2012**, *14*, 4030-4033.
6. Huo, C.; Xie, H.; Wu, M.; Jia, X.; Wang. X.; Chen, F.; Tang, J. *Chem. Eur. J.* **2015**, *21*, 5723−5726.
7. Huo, C.; Yuan, Y.; Wu, M.; Jia, X.; Wang, X., Chen, F.; Tang, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 13544–13547.
8. Huo, C.; Xie, H.; Chen, F.; Tang, J.; Wang, Y. *Adv. Synth. Catal*. **2016**, *358*, 724–730.
9. Min, C.; Sanchawala, A.; Seidel, D. *Org. Lett.* **2014**, *16*, 2756−2759.
10. Xu, G.-Q.; Li, C.-G.; Liu, M.-Q.; Cao, J. Luo, Y.-C.; Xu, P.-F. *Chem. Commun.* **2016**, *52*, 1190-1193.
11. Huang, L.-H.; Zhang, H.-B.; Zhang, Y.-H. *Org. Lett.* **2009**, *11*, 3730–3733.
12. Kawade, R.-K.; Huple, D. B.; Lin, R.-J.; Liu, R.-S. *Chem. Commun.* **2015**, *51*, 6625-6628.
13. Zhao, M.-N.; Yu, L.; Hui, R.-R.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *ACS Catal.* **2016**, *6*, 3473–3477.
14. Recent review, see: (a) Moselage, M.; Li, J.; Ackermann, L. *ACS Catal.* **2016**, *6*, 498–525. Recent examples, see: (b) Shang, X. J.; Liu, Z. Q. *Tetrahedron Lett.* **2015**, *56*, 482-484; (c) Ozkal, E.; Cacherat, B.; Morandi, B. *ACS Catal.* **2015**, *5*, 6458–6462; (d) Villanueva, O.; Weldy, N. M.; Blakey, S. B.; MacBeth, C. E. *Chem. Sci.* **2015**, *6*, 6672-6675; (e) Kong, L. H.; Yu, S. G.; Zhou, X. k.; Li, X. G. *Org. Lett.* **2016**, *18*, 588–591.
15. (a) Reddy, S. B. V.; Grewal, H. *Tetrahedron Lett.* **2011**, *52*, 761-763; (b) Chen, R. F.; Qian, C. T. *Synthetic Communication.* **2002**, *32*, 2543–2548.
16. (a) Song, Z. Q.; Antonchick, A. P. *Tetrahedron Lett.* DOI: 10.1016/j.tet.2016.04.052; (b) Yadav, A. K.; Yadav, L. D. S. *Tetrahedron Lett.* **2016**, *57*, 1489–1491; (c) Tang, J.; Grampp, G.; Liu, Y.; Wang, B.-X.; Tao, F.-F.; Wang, L.-J.; Liang, X.-Z.; Xiao, H.-Q.; Shen, Y.-M. *J. Org. Chem.* **2015**, *80*, 2724−2732; (d) Liang, Z.-W.; Xu, S.; Tian, W.-Y.; Zhang, R.-H. *Beilstein. J. Org. Chem.* **2015**, *11*, 425–430; (e) Nishino, M.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2011**, *76*, 6447–6451.For selected reviews, see: Ford, A.; Miel, H.; Ring, A.; Slattery, C. N.; Maguire, A. R.; McKervey, M. A. *Chem. Rev.* **2015**, *115*, 9981−10080.

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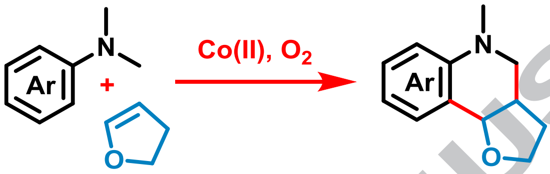

Highlights

Cobalt-catalyzed aerobic oxidative dehydrogenative Povarov reaction was developed.

Hexahydrofuro[3,2-*c*]quinolines were synthesized efficiently.

One-electron-oxidation involved reaction mechanism was proposed.