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Two-Step Access to β-Substituted *o*-Hydroxyphenyl Ethyl Ketones from 4-Chromanone and its Application in Preparation of a Silica-Supported Cobalt(II) Salen Complex

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Abstract: The *o*-hydroxyphenyl ethyl ketone skeleton is prevalent in many biologically active natural products and active pharmaceutical ingredients. Herein, a two-step protocol has been developed for synthesis of various β-substituted *o*-hydroxyphenyl ethyl ketones. A base-mediated ring opening of 4-chromanone was used to introduce the β-ethoxyl *o*-hydroxyphenyl ethyl ketone intermediary, followed by nucleophile substitution under $BF_3 \cdot Et_2O$ assisted conditions to give the desired β-carbon, nitrogen, or thiol substituted *o*-hydroxyphenyl ethyl ketones. With the aid of this protocol, a silica-supported cobalt(II) salen complex was successfully prepared and its structure was confirmed by FTIR, ^{13}C MAS NMR, UV-Vis absorption, and XPS spectra. The immobilized cobalt(II) salen catalyst not only displayed comparable catalytic activity in the synthesis of several heterocycles including 1,3-oxazolidine, benzimidazole, and benzoxazole as compared with their homogeneous counterparts, but also could be recycled for several times without obvious loss of its catalytic activity.

Keywords: β-Substituted *o*-hydroxyphenyl ethyl ketones; Supported cobalt(II) salen complex; 4-Chromanone; Nucleophiles; Heterocycles

Introduction

Several biologically active natural products and active pharmaceutical ingredients feature a peculiar *o*-hydroxyphenyl ethyl ketone skeleton (Figure 1). For example, Phloridzin, a naturally occurring compound extracted from the bark of pear, apple, cherry and other fruit trees, is a non-selective SGLT inhibitor and a Na^+/K^+-ATPase inhibitor.[1] Methylene-bis-aspidinol isolated from the leaves of Mallotus oppositifolius, has exhibited trypanocidal activity against *Trypanosoma brucei brucei* trypomastigotes similar to drug pentamidine.[2] Flavaspidic acid AB isolated from the rhizomes of Dryopteris crassirhizoma has been shown to exhibit radical scavenging and antibacterial activity.[3] Malabaricone C has been recently found to be a suitable candidate in the treatment and prevention of obesity as a sphingomyelin synthase inhibitor.[4] Therefore, the construction of molecules with *o*-hydroxyphenyl ethyl ketone framework has attracted the interest of the chemistry community.

O-hydroxyphenyl ethyl ketones are typically prepared by the Fries rearrangement of phenol ester albeit in some cases, with moderate regioselectivity

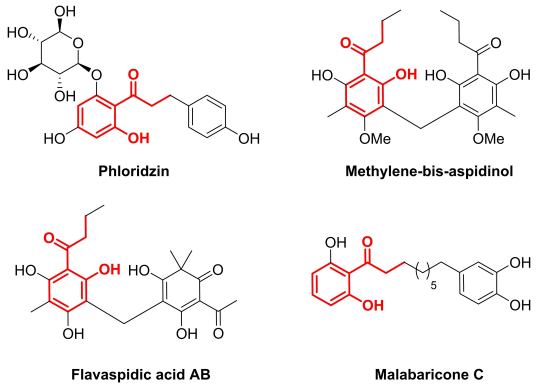
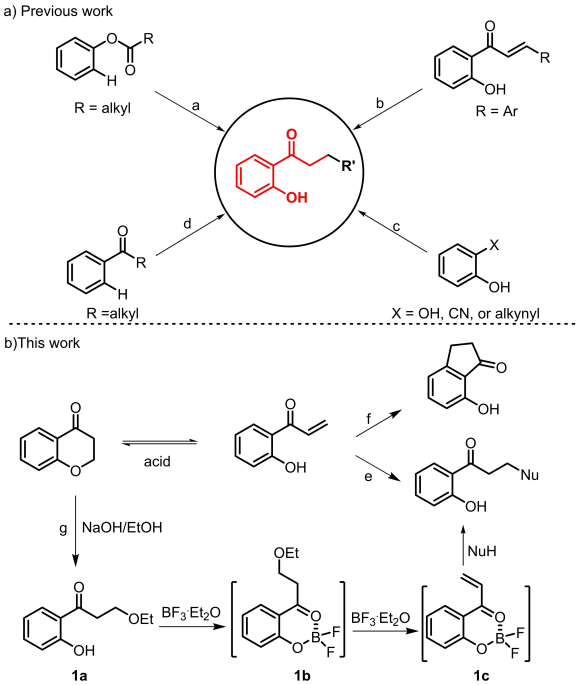


Figure 1. Representative bioactive molecules containing 2-hydroxyphenyl alkyl ketones.

(Scheme 1a).[5] The condensation of *o*-acetylphenol with aromatic aldehyde followed by noble-metal-catalysed hydrogenation provided an alternative way to generate *β*-aryl *o*-hydroxyphenyl ethyl ketones (Scheme 1b).[6] In addition the hydroacylation of salicylaldehyde with olefins,[7] oxidation of *o*-hydroxybenzyl alcohols,[8] electrophilic addition of *o*-hydroxybenzamide or its congeners with organometallic compounds,[9] hydration of *o*-ethynylphenols[10] (Scheme 1c) and C–H hydroxylation aryl alkyl ketone (Scheme 1d),[11] have also been used to synthesize some specific *o*-hydroxyphenyl ethyl ketones. From the view of generation of molecular diversity, the



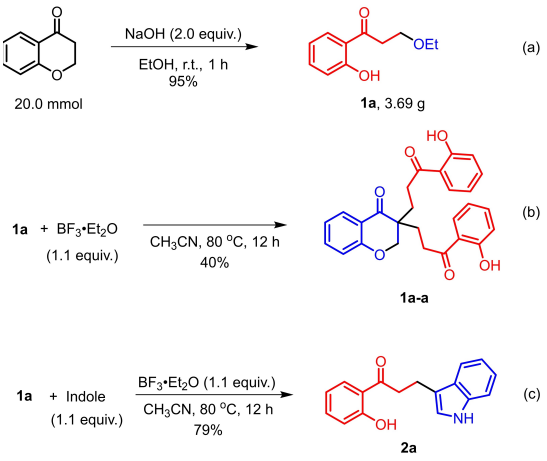
Scheme 1. General methods to furnish the *o*-hydroxyphenyl ethyl ketone skeleton.

Michael addition of *o*-hydroxyphenyl vinyl ketone with a nucleophile is greatly appealing to furnish *o*-hydroxyphenyl ethyl ketones because of the structural diversity of nucleophile (Scheme 1e). However, the lack of simple, cost-effective, and scalable method to prepare *o*-hydroxyphenyl vinyl ketone[12] and its high reactivity to undergo intramolecular cyclization (Scheme 1f) hamper its utilization.[13]

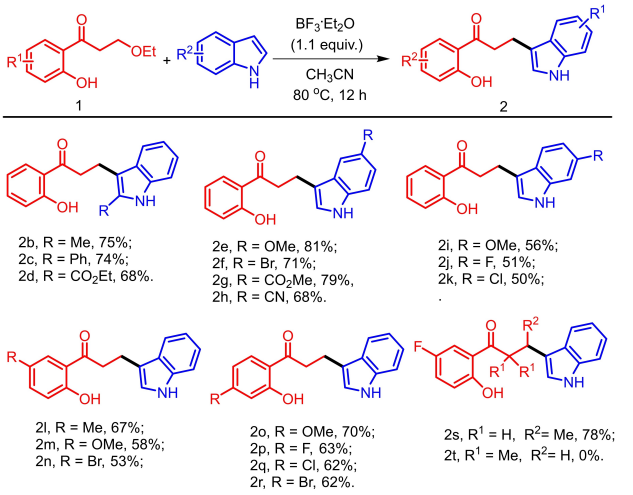
The ring-opening reactions of heterocycles have gained a great prominence, as it not only opens avenues for the creation of structurally novel molecules with multiple functional groups but also enriches the connotation of heterocyclic reactivities. Generally the destruction of heterocycles can be classified into three major categories: (i) the ring opening of highly strained heterocycles, such as aziridines, epoxyethanes etc.;[14] (ii) the gas evolution induced ring opening of medium-sized heterocycles such as denitrogenation of triazoles, decarboxylation of carbamate etc.;[15] (iii) the ring opening of heterocycles containing labile fragments such as acetal, benzyl ether etc.[16] 4-Chromanone was commercially available and also easily prepared by the tandem oxa-Michael addition/cyclization of phenol and acrylonitrile[17] or by tandem adol condensation/oxa-Michael addition of *o*-acetylphenol and paraformaldehyde.[18] The 4-chromanone was labile under either acidic or basic conditions.[19] The direct electrophilic ring opening of 4-chromanone with a nucleophile would be an ideal route to synthesize various *β*-substituted *o*-hydroxyphenyl ethyl ketones. However, it suffered from intramolecular cyclization (Scheme 1f).[19a,b] Herein, we report our results on an effective two-step protocol that allows synthesis of *β*-substituted *o*-hydroxyphenyl ethyl ketones starting from 4-chromanone and consisting in i) the base promoted ring opening of 4-chromanone to give *β*-ethoxyl *o*-hydroxyphenyl ethyl ketone **1 a** and ii) a $BF_3{\cdot}Et_2O$ mediated substitution through the in situ generation of boron difluoride complex **1 b**[20] followed by releasing one molecular ethanol to form boron difluoride complex **1 c**[21] that undergoes intermolecular Michael addition to provide the desired *β*-substituted *o*-hydroxyphenyl ethyl ketones (Scheme 1g). Notably, the first step can be scalable while the second step features a broad substrate scope, in which various C-, N-, and S-based nucleophiles can be employed. With the aid of this two-step protocol, a novel method to prepare silica-supported cobalt(II) salen complexes has also been developed, and the resulting heterogeneous system showed excellent catalytic activities in the oxidative synthesis of several heterocycles.

Results and Discussion

Initially, a base promoted electrophilic ring-opening reaction with EtOH was explored. As shown in Scheme 2a, the NaOH promoted ring opening of 4-



Scheme 2. The synthesis of *β*-indolyl *o*-hydroxyphenyl ethyl ketone.

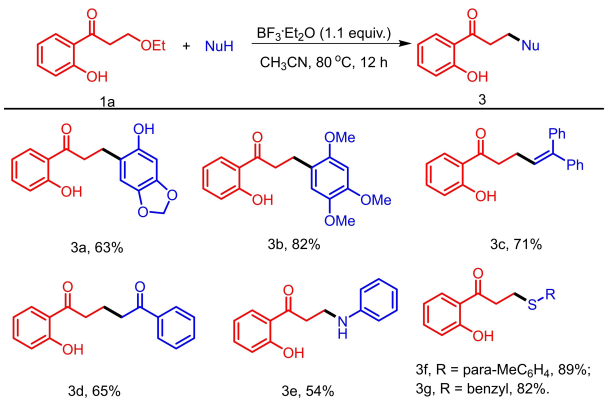


Scheme 3. Substrate scope of $BF_3 \cdot Et_2O$ promoted reactions of*β*-ethoxyl *o*-hydroxyphenyl ethyl ketones and indoles.

chromanone was undemanding. The *β*-ethoxyl *o*-hydroxyphenyl ethyl ketone **1a** could be obtained in 95% yield in a gram scale. With compound **1a** in hand, we started to explore the substitution of **1a** with a nucleophile. Indole is a well-known privileged structure occurring in numerous natural products such as alkaloids, peptides and it is also a natural carbon-based nuclophile. Thus the simple indole was chosen to react with **1a**. However, the reaction was distressing. In the presence of a common acid such as PTSA, TfOH, $ZnCl_2$, and $Sc(OTf)_3$ as catalyst, the desired product was obtained in a poor yield due to the poor chemoselectivity detected by TLC (Table S1 in the supporting information). *O*-hydroxyacetophenone can react with $BF_3 \cdot Et_2O$ to form boron difluoride acetylphenolate chelate easily.[20] Therefore, we envisioned that the solid skeleton of boron difluoride complex might be helpful to suppress aforementioned intramolecular cyclization. Accordingly, we tried to prepare boron difluoride complex **1b**, but unfortunately, only the formation of compound **1a** could be observed (Scheme 2b). Then, the direct addition of 1.1 equivalent of $BF_3 \cdot Et_2O$ to the mixture of **1a** and indole through the generation of **1b** in situ was investigated. To our delight, the desired *β*-indolyl *o*-hydroxyphenyl ethyl ketone **2a** was obtained in a good 79% yield (Scheme 2c).

The substrate scope was then explored. As shown in Scheme 3, there was no significant electronic effect on indole for this reaction. Both electron-rich and electron-deficient indole participated in the reaction smoothly, affording the desired products in the yields of 50–81% under identical conditions. The scope of the reaction with respect to *β*-ethoxyl *o*-hydroxyphenyl ethyl ketone **1a** was next investigated. **1a** featuring an alkyl, alkoxy, or halogen on the aromatic ring reacted readily with indole to deliver *β*-indoly *o*-hydroxyphenyl ethyl ketones **2** in good yields. The strong electron-deficient *β*-ethoxyl 2-hydroxy-5-nitrophenyl ethyl ketone did not give the desired product, indicating the electronic influence on the reaction. The reaction was sensitive to the substituents at the alpha position of **1a**. *β*-ethoxyl *o*-hydroxyphenyl propyl ketone furnished the product (**2s**) in a high yield. But, the *α*-dimethyl *β*-ethoxyl *o*-hydroxyphenyl ethyl ketone could not be employed in this reaction (**2t**), implied **1c** was the reaction intermediate.

Besides indole, other nucleophiles were also explored as a reaction partner. As shown in Scheme 4, electron-rich arenes such as sesamol, and 1,2,4-trimethoxybenzene, or electron-rich alkene such as 1,1-diphenylethylene were all applicable in this reaction (**3a–c**). Surprisingly, the pyrrole could not be



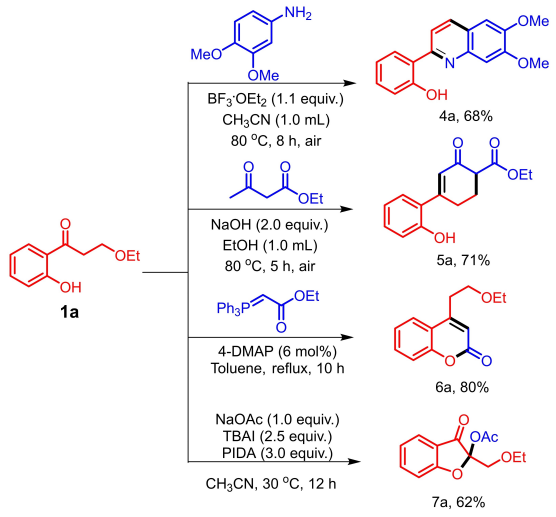
Scheme 4. The substitution reactions of **1a** with other nucleophiles.

employed in this protocol and only complex mixtures were obtained under standard reaction conditions, although it is a typical electron-rich heteroarene. The acetophenone, a Csp^3-based nucleophile afforded the desired 1,5-dicarbonyl compound in 65% yield (**3 d**). The nitrogen-based nucleophile, aniline, participated in the reaction smoothly affording the desired product **3 e** in 54% yield. It is worth mentioning that **3 e** has been proved to be a potential antimicrobial agent.[22] Although a three-component Mannich reaction of formaldehyde, 2-hydroxyacetophenone and aniline has been reported to synthesize **3 e**, the yield is rather low (less than 40%).[23] The reactions of **1 a** and sulfur-based nucleophiles, such as *p*-toluenethiol and benzyl mercaptan, proceeded also smoothly, giving products **3 f** and **3 g** in 89% and 82% yields, respectively.

It was noted that the *β*-ethoxyl *o*-hydroxyphenyl ethyl ketone contained several functional groups, which could also act as a biselectrophile, a 1,4-donor-acceptor, or a bisnucleophile to participate in synthesis of substituted quinolone, cyclohexenone, coumarin, and 3-benzofuranone (Scheme 5).

To demonstrate the applicability of synthetic strategy, a silica-immobilized cobalt(II) salen complex was prepared through $BF_3 \cdot Et_2O$ promoted substitution of *β*-ethoxyl *o*-hydroxyphenyl ethyl ketone **1 a** with sulfhydryl functionalized silica gel followed by condensation with ethylenediamine that coordinated with Co-$(OAc)_2 \cdot H_2O$ to furnish the heterogeneous catalyst (Figure 2).

The FTIR spectra were collected to evaluate the above process. As shown in Figure 3a, the HMS-SH showed a characteristic peak of –SH group at 2439 cm^{-1}.[24] After it reacted with **1 a** promoted by $BF_3 \cdot Et_2O$, that peak disappeared, while it was accom-



Scheme 5. Synthesis of cyclic compounds from **1 a**.

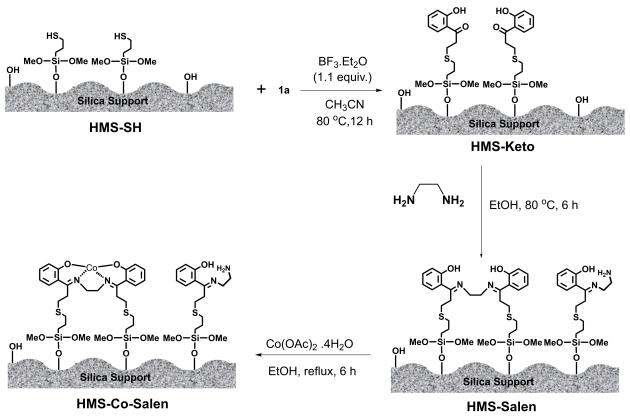


Figure 2. Schematic diagram of the procedure to immobilize salen-type cobalt(II) schiff base complex.

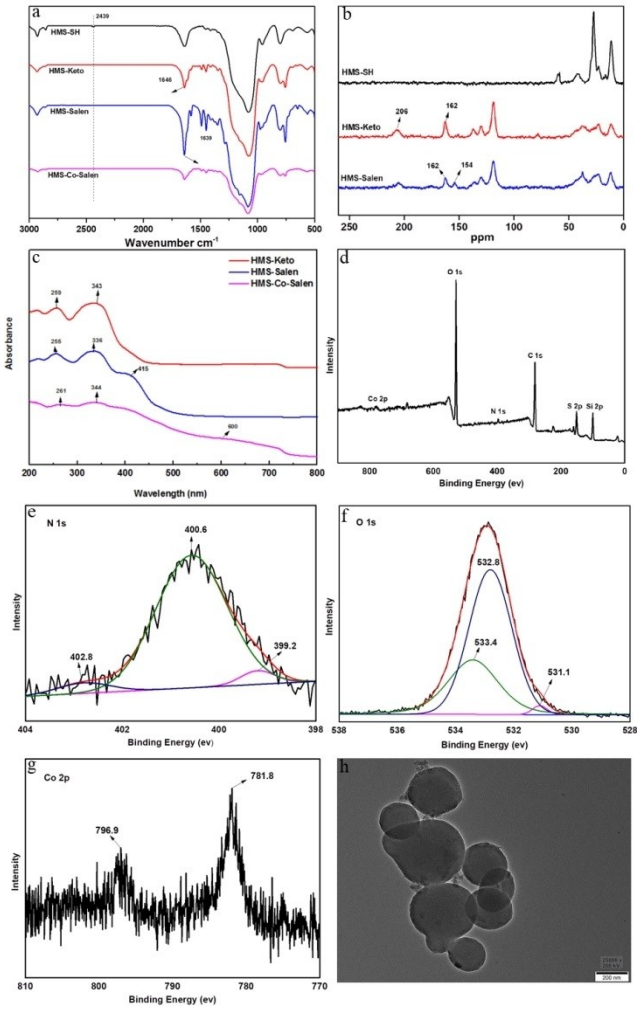
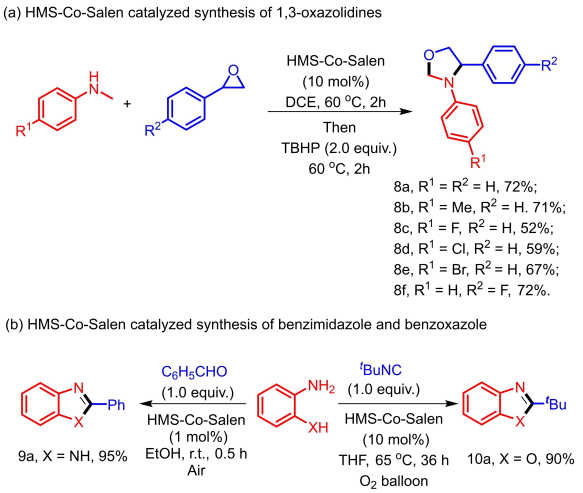


Figure 3. Catalyst characterization. (a) FTIR spectra, (b) ^{13}C MAS NMR spectra, (c) UV-Vis absorbtion spectra, (d–g) XPS spectra, (h) TEM image of the HMS-Co-Salen.

panied by the presence of the characteristic peaks of phenyl group (1400 cm^{-1} to 1600 cm^{-1}) and C=O group (1646 cm^{-1}), proving the successful immobilization of salicylaldehyde fragment.[25] The appearance of characteristic peak of C=N group at 1639 cm^{-1} in the FTIR spectrum of HMS-Salen implied the formation of the salen ligand.[26] The FTIR spectrum of HMS-Co-Salen slightly shifted toward bluer wavelengths compared with HMS-Salen, suggesting the coordination of salen ligand with cobalt salt.[27] This process was also confirmed by the ^{13}C MAS NMR spectra. As shown in Figure 3b, the peaks of HMS-Keto at 162 ppm and 206 ppm could be assigned to the aromatic carbon connected with the hydroxyl group and carbonyl carbon, respectively. After HMS-Keto reacted with ethylenediamine, a peak at 154 ppm appeared, indicative of the formation of C=N bond. In the ^{13}C MAS NMR spectrum of HMS-Salen, the peak at 206 ppm still existed suggesting the incomplete conversion of HMS-Keto. The elemental analysis showed that the loading of salen ligand was 0.42 mmol/g (Table S2). In the UV-Vis absorbtion spectrum of HMS-Salen (Figure 3c), there was an obvious absorption band at 415 nm, which was the characteristic absorption peak of schiff base.[28] After HMS-Salen coordinated with cobalt, a new absorption peak at 600 nm appeared, which was attributed to the d-d electron transition of metal. The surface composition and chemical state were then investigated using X-ray photoelectron spectroscopy (XPS). The wide survey spectrum of HMS-Co-Salen (Figure 3d) showed that all of the essential elements could be detected, consistent with the result of EDX elemental maps (Figure S1). The N 1s spectrum clearly evidenced the presence of nitrogen atoms with three kinds of chemical environments: the peaks at 399.2 and 400.8 eV were attributed to C=N···Co and C=N groups, respectively, while the peak at 402.8 eV was attributed to $–NH_2$ (Figure 3e).[29] These results indicated that the cobalt ion mainly coordinated with salen ligand instead of the ONN tridentate pincer type schiff base ligand (Figure 2). In the spectrum of O 1s (Figure 3f), besides two predominant peaks (533.4 eV for O–Si and 532.8 eV for O–H), there was a small peak at 531.1 eV, which was attributed to O–Co group.[30] The Co 2p XPS profile (Figure 3g) displayed two main peaks centered at 781.8 and 796.9 eV, which were assigned to the Co 2p 3/2 orbital energy level and Co 2p 1/2 orbital energy level, indicative of the existence of Co(II) species.[31] The loading of Co(II) measured by ICP-AAS was 0.21 mmol/g. TEM images showed that the morphologies of HMS-SH and HMS-Keto were spherical sponge-like (Figure S2a, b). However, the morphology of HMS-Salen changed towards to amorphous form (Figure S2c). The HMS-Co-Salen was mainly composed of block-shaped particles and a few spherical particles (Figure 3h). It should be noted that the specific surface areas (BET) of HMS-Keto was almost one half that of HMS-SH although their morphologies were similar (Table S3). The specific surface areas of HMS-Co-Salen was 605 $m^2 g^{-1}$ similar to that of HMS-Keto.

The catalytic activity of HMS-Co-Salen was evaluated in the representative cobalt(II)-catalysed oxidative cyclization reactions. As shown in Scheme 6a, The HMS-Co-Salen catalysed tandem C–N and C–O bond formation of N-methylanilines with styrene oxides in the presence of TBHP *via* a one-pot sequence of S_N2 ring opening of the epoxide, C–H functionalization and cyclization furnished 1,3-oxazolidines in yields of 52–72%, which was comparable with the reported homogeneous protocol[32] and represented the first heterogeneous catalytic system to synthesis of 1,3-oxazolidines from N-methylanilines and styrene. The HMS-Co-Salen catalyst could be recovered by filtration after the reaction and reused for 9 consecutive cycles without obvious loss of activity (Figure S3). More importantly, there was no leached cobalt detected by ICP-AAS in the filtrate. The comparison between the fresh and recoverable catalysts in Co 2p XPS profile and FTIR spectrum had shown no obvious differences (Figure S4). In addition, the HMS-Co-Salen catalyst could also used in aerobic oxidative synthesis of benzimidazole and benzoxazole (Scheme 6b). It is worth mentioning that the HMS-Co-Salen featured a long alkyl chain which made the Co-salen complex more flexible compared with conventional heterogenerous Co-salen complexes prepared by chemical grafting that might account for its high catalytic activities in above oxidative cyclization reactions.[33]



Scheme 6. Synthesis of heterocycles catalyzed by the immobilized salen-type cobalt(II) schiff base complex.

Conclusion

We had developed a two-step protocol whereby 4-chromanone underwent ring destruction with ethanol under basic condition to give *β*-ethoxyl *o*-hydroxyphenyl ethyl ketone that reacted effectively with a nucleophile to deliver the target *β*-substituted *o*-hydroxyphenyl ethyl ketones. Various nucleophiles including indole, 1,2,4-trimethoxybenzene, 1,1-diphenylethylene, acetophenone, *p*-toluenethiol, and benzyl mercaptan all participated smothly in the substitution reaction. In addition, this protocol was applicable to prepare the silica-immobilized cobalt salen complex, which showed excellent catalytic activities in synthesis of 1,3-oxazolidine, benzimidazole, and benzoxazole.

Experimental Section

General procedure for the synthesis of 1a:chroman-4-one (2.96 g, 20 mmol) was mixed with ethanol (100 mL) in a 250 mL of round bottomed flask equipped with magnetic stirring. NaOH (1.60 g, 40 mmol) was added to the system after 4-chromanone dissolved completely. The mixture was then stirred at room temperature for 1.5 h. After completion of the reaction monitored by TLC the mixture was neutralized with HCl (1 M/L). The solvents were removed under vacuum and the aqueous phase was extracted by ethyl acetate (30 mL × 3). The combined organic phase was washed with brine (30 mL) and dried over Na_2SO_4. After removing volatile components, the organic residue was subjected to an isolation with silica column chromatography (eluting solution: petroleum ether/ethyl acetate = 20/1 (v/v)). A light yellow transparent liquid was obtained (3.69 g, 95% yield).

General procedure for the reaction of 1a and indole: In a 10 mL of V-type flask equipped with triangle magnetic stirring, **1a** (0.3 mmol) and indole (0.3 mmol) were dissolved in CH_3CN (1 mL), then $BE_3 \cdot Et_2O$ (1.1 equiv., 0.33 mmol) was added. The mixture was stirred at 80 °C for 12 h. After the reaction was completed, the mixture was cooled to room temperature, and the product was obtained by isolation through preparative thin-layer chromatography (eluting solution: petroleum ether/ethyl acetate = 8/1 (v/v)). Tests for other nucleophiles were all performed with an analogous procedure.

The procedure for synthesis of substituted quinolone 4a: In a 10 mL of V-type flask equipped with triangle magnetic stirring, **1a** (0.3 mmol) and 4-aminoveratrole (0.3 mmol) were dissolved in CH_3CN (1.0 mL), then $BE_3 \cdot Et_2O$ (1.1 equiv., 0.33 mmol) was added. The mixture was stirred at 80 °C for 8 h. After the reaction was completed, the mixture was cooled to room temperature, and the product was obtained (57.4 mg, 68% yield) by isolation by preparative thin-layer chromatography (eluting solution: petroleum ether/ethyl acetate = 2/1 (v/v)).

The procedure for synthesis of substituted cyclohexenone 5a: In a 10 mL of V-type flask equipped with triangle magnetic stirring, **1a** (0.3 mmol), ethyl acetoacetate (0.6 mmol), and NaOH (0.6 mmol) were added in EtOH (1 mL). The mixture was stirred at 80 °C for 5 h. After the reaction was completed, the mixture was cooled to room temperature, and the product was obtained (55.4 mg, 71% yield) by isolation with preparative thin-layer chromatography (eluting solution: petroleum ether/ethyl acetate = 6/1 (v/v)).

The procedure for synthesis of substituted coumarin 6a: In a 10 mL of V-type flask equipped with triangle magnetic stirring, **1a** (0.3 mmol), $Ph_3P\text{-}CHCO_2Et$ (0.45 mmol), and 4-DMAP (0.018 mmol) were added in toluene (1.0 mL). The mixture was refluxing for 10 h. After the reaction was completed, the mixture was cooled to room temperature, and the product was obtained (52.3 mg, 80% yield) by isolation with preparative thin-layer chromatography (eluting solution: petroleum ether/ethyl acetate = 4/1 (v/v)).

The procedure for synthesis of substituted coumarin 7a: In a 10 mL of V-type flask equipped with triangle magnetic stirring, **1a** (0.3 mmol), $PhI(OAc)_2$ (0.9 mmol), Bu_4NI (0.75 mmol), and NaOAc (0.3 mmol) were added in CH_3CN (1.0 mL). The mixture was stirred at 30 °C for 12 h. After the reaction was completed, the mixture was cooled to room temperature, and the product was obtained (46.5 mg, 62%) by isolation with preparative thin-layer chromatography (eluting solution: petroleum ether/ethyl acetate = 5/1 (v/v)).

The procedure for synthesis of heterogeneous HMS-Co-Salen: In a 100 mL of round bottomed flask equipped with triangle magnetic stirring, 1-hexadecylamine (13 mmol, 3.2 g) was dissolved in $EtOH/H_2O$ (50 ml, V/V = 7/9), tetraethyl orthosilicate (39 mmol, 8.3 g) and trimethoxysilylpropanethiol (10 mmol, 1.97 g) were added in sequence at room temperature. After stirring for 20 h at room temperature, a large amount of white solid was obtained and then filtered. Soxhlet extraction was carried out for 72 h to remove impurities. The material was dried under vacuum, affording an organic/inorganic hybrid material,[28] which was named HMS-SH. Next, HMS-SH (2 mmol, 0.92 g) and compound **2a** (2 mmol, 0.39 g) were added to the flask, followed by $BF_3 \cdot Et_2O$ (2.2 mmol, 0.31 g), which were reacted in acetonitrile at 80 °C for 12 h. The solid was filtered out, washed with ethanol and distilled water, and then dried under vacuum conditions to give HMS-Keto. After that, HMS-Keto was reacted with ethylenediamine (0.5 mmol, 0.03 g) in ethanol solution at 80 °C for 6 h. After filtration, the HMS-Salen was obtained by washing with ethanol and drying under vacuum conditions. Finally, the obtained HMS-Salen and $Co(OAc) \cdot 4H_2O$ (0.25 mmol, 0.07 g) were refluxed in ethanol solution for 6 h, followed by filtration, washing with ethanol and distilled water, and drying in vacuum drying oven for 24 h to give HMS-Co-Salen.

General procedure for the reaction of *N*-methylaniline and styrene oxide: In a 10 mL of V-type flask equipped with triangle magnetic stirring, N-methylaniline (0.3 mmol), styrene oxide (0.6 mmol) and HMS-Co-Salen (0.03 mmol) were added in DCE (2 mL). The mixture was stirred at 60 °C for 2 h, and then TBHP (0.6 mmol) was added to the mixture. The mixture was stirred at 60 °C for additional 2 h and then cooled to room temperature. The product was obtained by preparative thin-layer chromatography (eluting solution: petroleum ether/ethyl acetate = 10/1 (v/v)).

The procedure for the reaction of *o*-phenylenediamine and benzaldehyde: In a 10 mL of V-type flask equipped with triangle magnetic stirring, *o*-phenylenediamine (0.2 mmol,

21.6 mg), benzaldehyde (0.2 mmol, 21.2 mg) and HMS-Co-Salen (0.002 mmol, 9.6 mg) were added in EtOH (1 mL). The mixture was stirred at room temperature for 0.5 h. After the reaction was completed, the mixture was cooled to room temperature and the product was obtained (36.9 mg, 95% yield) by isolation with preparative thin-layer chromatography (eluting solution: petroleum ether/ethyl acetate = 5/1 (v/v)).

The procedure for the reaction of 2-aminophenol and *tert*-butyl isocyanide: In a 10 mL of V-type flask equipped with triangle magnetic stirring and oxygen balloon, 2-aminophenol (0.3 mmol, 32.7 mg), tert-butyl isocyanide (0.3 mmol, 24.9 mg) and HMS-Co-Salen (0.03 mmol, 142.8 mg) were added in THF (6 mL), the mixture was stirred at 65 °C for 24 h. The mixture was cooled to room temperature, and the product was obtained (47.3 mg, 90% yield) by isolation with preparative thin-layer chromatography (eluting solution: petroleum ether/ethyl acetate = 5/1 (v/v)).

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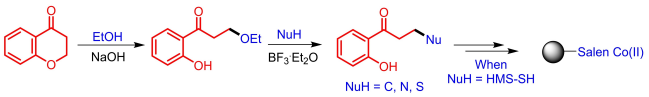
RESEARCH ARTICLE

Two-Step Access to *β*-Substituted *o*-Hydroxyphenyl Ethyl Ketones from 4-Chromanone and its Application in Preparation of a Silica-Supported Cobalt(II) Salen Complex



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