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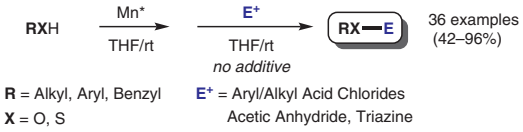
Highly Active Manganese-Mediated Acylation of Alcohols with Acid Chlorides or Anhydrides

Seong-Ryu Joo
Young-Jin Youn
Young-Ran Hwang
Seung-Hoi Kim*

Department of Chemistry, Dankook University,
119 Anseo Cheonan, 31116, Republic of Korea
kimsemail@dankook.ac.kr



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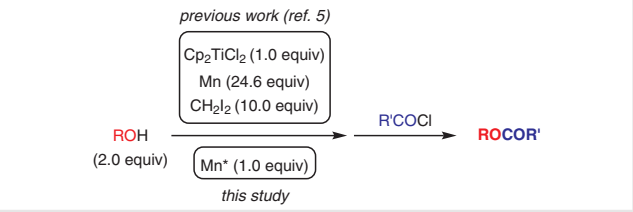
Abstract To explore further the practical uses of highly active manganese (Mn*), a variety of alcohols were treated with Mn*, and the resulting complexes were coupled with acid chlorides and/or acetic anhydride in the absence of any extra catalyst. The subsequent reactions took place smoothly under mild conditions, providing the corresponding O-acylation products in good to excellent isolated yields.

Key words active manganese, manganese catalysis, acylation, alcohols, thiols, esters

The ester moiety is a characteristic subunit of many natural and synthetic products that show a wide range of biological activities. In addition, it plays a significant role as a building block in syntheses of fine organic compounds and industrial products.[1] Because of the significance of ester functionalities in organic compounds, a variety of synthetic methods have been reported that provide efficient routes to these moieties. In this regard, transesterifications and acylations of alcohols have been considered to be the most accessible protocols. In general, these strategies have been accomplished by acid- or base-catalyzed reactions of alcohols with carboxylic acids, anhydrides, or acid chlorides.[2] Along with these protocols, metal complex-mediated acylations of alcohols have also been frequently used, even though they retain some disadvantages, such as harsh reaction conditions, toxicity, and laborious workup.[3]

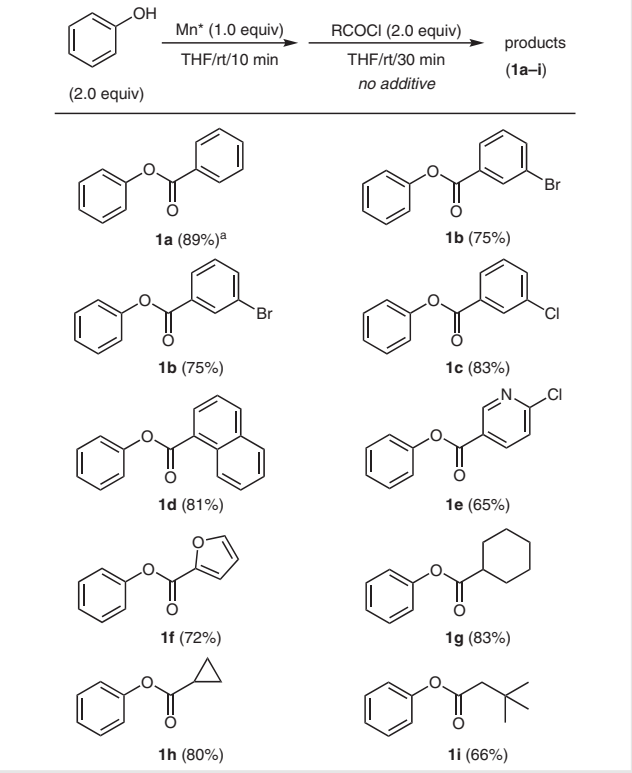
In our continuing studies to develop a broad-spectrum of applications of highly active metals, we recently obtained an unprecedented result in a reaction of highly active zinc with iodophenols when we observed the formation of esters by the reaction of highly active zinc (Zn*), 3- or 4-iodophenol, and an acid chloride.[4] Interestingly, as previously reported, various metal complexes have been successfully used in the O-acylation of alcohols. On the basis of these observations, we immediately sought to explore the possibility of highly active metal-mediated O-acylation of alcohols. The Collado group recently published an interesting report on a metal-promoted O-acylation of alcohols and phenol by using a large excess of Mn dust in the presence of Cp_2TiCl_2 as a promoter.[5] More importantly, the presence of CH_2I_2 was crucial for completion of the transesterification (Scheme 1). Prompted by this outcome, we first selected highly active manganese (Mn*) as a metal catalyst to investigate our strategy.



Scheme 1 O-Acylation of alcohols

An initial attempt was conducted by using commercially available phenol with highly active manganese, prepared by the reported procedure.[6] Phenol (2.0 equiv) was treated with one equivalent of Mn* at room temperature in THF. Upon the addition of the phenol to the THF solution of Mn*, bubbling was observed in the reaction flask. Once the bubbling ceased, neat benzoyl chloride (2.0 equiv) was added to the flask at room temperature. The subsequent coupling reaction was exothermic. It is of significance that the reaction proceeded smoothly in the absence of any extra catalyst at room temperature and was complete in 30 minutes. The spectroscopic properties of the product, phenyl benzoate (**1a**), were identical to those described in the literature.[7] With this promising result in hand, we used other aroyl chlorides, including bulky 1-naphthoyl chloride, in our re-

action system to give the corresponding esters **1b–d** in moderate to good yields (Scheme 2). Hetaroyl chlorides also coupled well under the same conditions, providing esters **1e** and **1f** in good yields. Furthermore, to generalize our system, we selected cyclic and noncyclic alkanoyl chlorides as coupling substrates in this process and obtained the corresponding products **1g–i** in good yields.



Scheme 2 Mn*-mediated O-acylations of phenol (reported yields are the isolated yields based on phenol)

Next, we attempted to apply our system to other phenol derivatives (Figure 1). Cresols were treated under the same conditions (1.0 equiv of Mn* and 2.0 equiv of alcohol), and subsequently coupled with 2.0 equivalent of an aroyl chloride or isovaleroyl chloride. As expected, the corresponding O-acylated products **2a–d** were successfully obtained in good to excellent isolated yields. It is of interest that the C–I bond, which is available for further elaboration, remained intact in product **2e**. Moreover, the desired coupling product **2f** was obtained by using 7-hydroxycoumarin. Likewise, both 4-hydroxycoumarin and 4-hydroxypyrone underwent O-acylation in a comparable fashion to yield the corresponding esters **2g** and **2h** in moderate yields. Acylation of 7-hydroxybenzoquinone gave 1,4-dioxo-1,4-dihydronaphthalen-2-yl benzoate (**2i**) in a diminished yield.

On the basis of these results, we next turned our attention an expansion of the scope of the alcohol, because benzyl benzoates, the expected products from our protocol, are

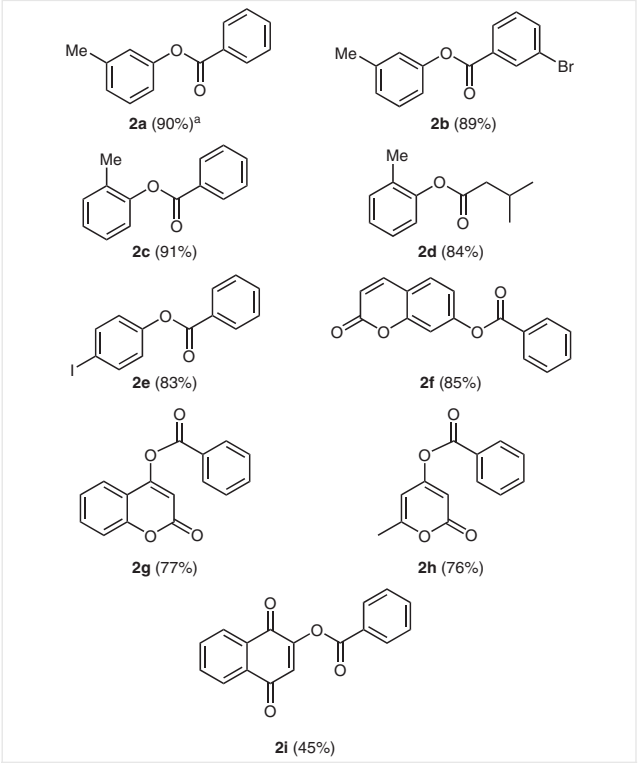


Figure 1 Mn*-mediated O-acylations of aryl alcohols (reported yields are the isolated yields based on the alcohol)

frequently found in the pharmaceutical and agrochemical industries.[8] To our great delight, benzyl alcohols proved to be effective substrates for our protocol, giving the corresponding O-acylated products under the same conditions as used before (Figure 2). Reactions of benzyl alcohols, including substituted benzyl alcohols, with aroyl chlorides gave the corresponding benzyl benzoates **3a–f** in good yields, al-

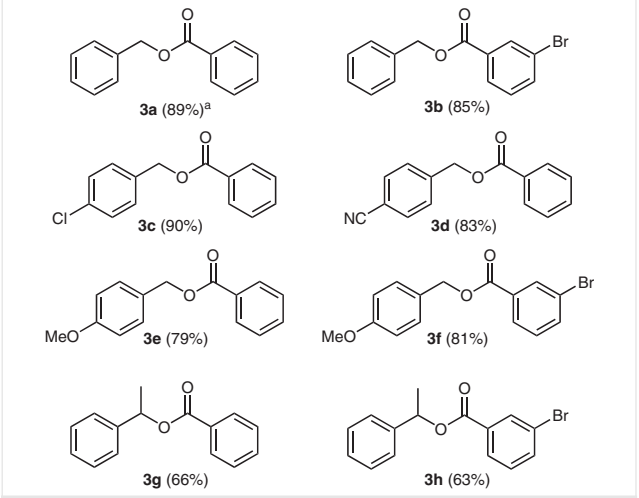


Figure 2 Mn*-mediated O-acylations of benzyl alcohols (reported yields are the isolated yields based on the alcohol)

though less heat was evolved during the reaction of Mn* with benzyl alcohols compared with the case of phenols. With the sterically demanding 1-phenylethanol, a general steric effect was observed and products **3g** and **3h** were obtained in lower isolated yields.

Having obtained a better understanding of the reactivity of our approach, we examined the substrate scope of the O-acylation with alkyl and cycloalkyl alcohols. To address this aim, we chose cyclohexanol as a model substrate. As previously, treatment of the alcohols with Mn* was carried out at room temperature in THF, and then the appropriate acid chlorides were subsequently added to the flask. The corresponding esters **4a–e** were obtained in moderate to good yields (Figure 3). Primary alcohols bearing longer carbon chains, double bonds, or aryl rings similarly gave the corresponding esters **4f–j**. However, a tertiary alcohol provided the desired ester **4k** in a relatively poor isolated yield of 40%.

Taking into account the results obtained thus far, we considered that O-acylation of alcohols by acetic anhydride instead of acid chlorides would be a more challenging subject as an alternative route.[9] Consequently, our next set of experiments focused on establishing the use of Mn*/acid anhydrides in the construction of ester derivatives. To meet this challenge, we attempted a Mn*-mediated O-acetylation of a variety of alcohols with acetic anhydride. Most of alcohols that were previously used in this study, including phenols and benzyl, alkyl, and allylic alcohols were tested. This attempt was successful, and gave the corresponding acetylated products **5a–n** in good yields. Once again, it should be emphasized that the reaction proceeded efficiently at room temperature without any extra catalyst. Acetylation was carried out at room temperature for one hour. The results are shown in Figure 4.

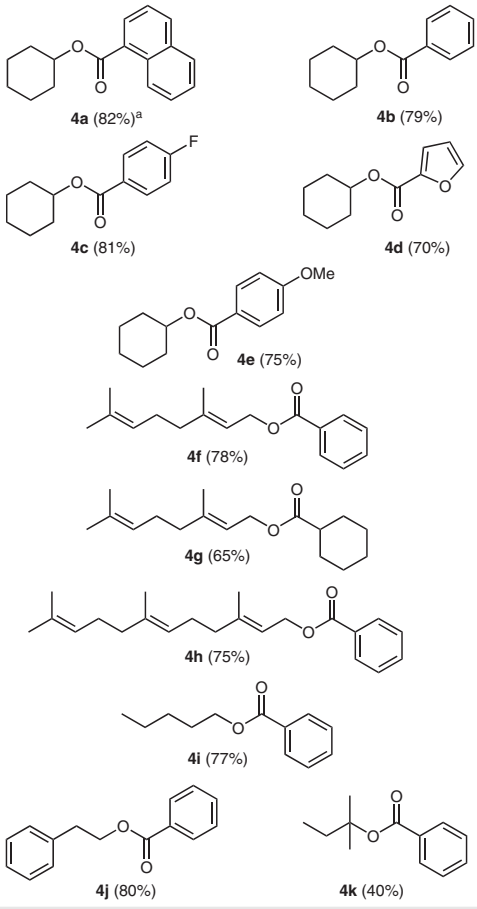


Figure 3 Mn*-mediated O-acylations of alkanols (reported yields are the isolated yields based on the alcohol)

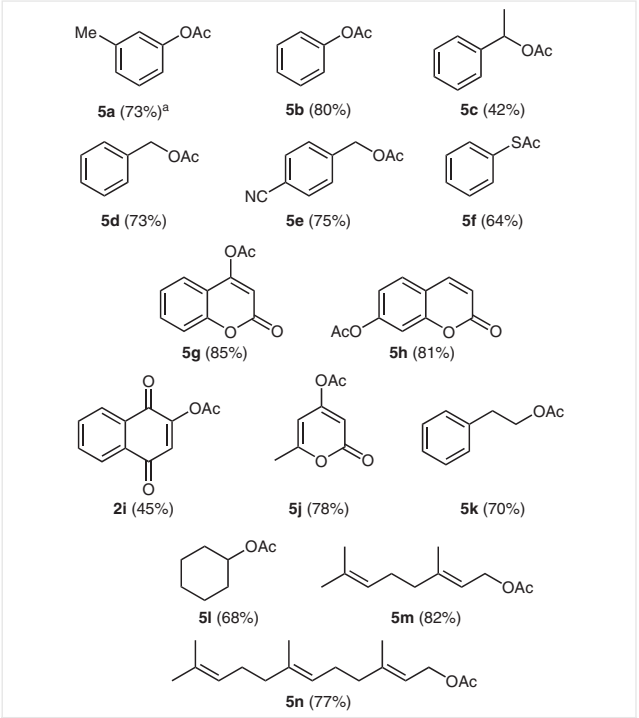
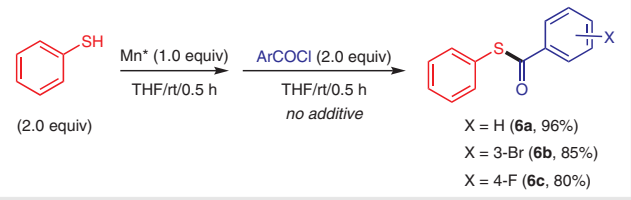


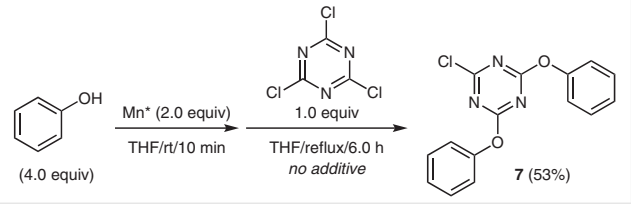
Figure 4 Mn*-mediated acetylation of alcohols with acetic anhydride (reported yields are the isolated yields based on the alcohol)

Next, the S-acylation of benzenethiol was investigated to extend the scope of our system further. As shown in Scheme 3, the same conditions were employed in the reaction of 2.0 equivalents of benzenethiol with one equivalent of highly active manganese. The resulting manganese complex was subsequently treated with various aroyl chlorides at room temperature. Once again, it is worth mentioning that no catalyst was required for completion of the coupling reaction. The corresponding thioesters **6a–c** were efficiently obtained in good to excellent isolated yields.



Scheme 3 Acylations of benzenethiol

To demonstrate the practicality and robustness of this method, we applied our approach to the reaction with 2,4,6-trichloro-1,3,5-triazine (TCT), an efficient reagent for further transformations in organic synthesis. Under the conditions shown in Scheme 4, the whole procedure proceeded smoothly to give product **7** exclusively in 53% isolated yield, even at an elevated temperature and with an extended reaction time.



Scheme 4 Reaction with TCT

In conclusion, we have demonstrated another application of highly active manganese (Mn*) in organic synthesis: catalyst-free Mn*-mediated O- and S-acylations of alcohols and thiols, respectively, with acid chlorides or acetic anhydride under mild conditions.[10] In addition, it should be noted that, unlike a previous method,[3] our method uses an environmentally friendly metal (Mn*) and has an easy work-up procedure. Although the exact role of the highly active manganese is unclear at this time, this approach can provide an alternative and simple route to O-acylation of alcohols or S-acylation of thiols. Further studies to elucidate the reactivity of highly active manganese are currently underway in our laboratory.

Acknowledgment

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(4) Unpublished results from our laboratory; Zn* (1.0 equiv) reacted with 3- or 4-iodophenol (1.0 equiv), and the resulting complex was coupled with acid chlorides to give the corresponding phenyl benzoate esters instead of the expected Negishi ketone products.

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(10) **Phenyl 3-Chlorobenzoate (1c); Typical Procedure**
A 25 mL flask was charged with lithium (0.07 g, 9.68 mmol), naphthalene (0.19 g, 1.48 mmol), anhyd MnI_2 (1.45 g,

4.71 mmol), and freshly distilled THF (10 mL) under argon pressure, and the mixture was stirred for 1 h at r.t. To the resulting slurry, containing 2.5 mmol of highly active manganese, was added PhOH (0.47 g, 5.0 mmol) and the resulting mixture was stirred at r.t. for 10 min. Neat 3-chlorobenzoyl chloride (0.88 g, 5.0 mmol) was then added to the flask, and the mixture was stirred at r.t. for 30 min. The reaction was then quenched with 3 M aq HCl, and the mixture was extracted with Et_2O (3 × 10 mL). The organic layers were combined and washed with sat. aq $NaHCO_3$ (3 × 10 mL), sat. aq $Na_2S_2O_3$ (3 × 10 mL), and brine (3 × 10 mL), then dried ($MgSO_4$). Column chromatography (silica gel, 1% EtOAc–hexanes) gave a pale-yellow solid; yield: 0.96 g (83%); mp 60–63 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.19 (br s, 1 H), 8.10 (d, *J* = 8.0 Hz, 1 H), 7.64 (d, *J* = 8.0 Hz, 1 H), 7.50–7.45 (m, 3 H), 7.32 (t, *J* = 7.5 Hz, 1 H), 7.24 (d, *J* = 7.5 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.0, 150.7, 134.8, 133.6, 131.3, 130.2, 130.0, 129.6, 128.3, 126.2, 121.6. HRMS: *m/z* [M^+] calcd for $C_{13}H_9ClO_2$: 232.0291; Found: 232.0280.