Highly Active Manganese to C—O Cross-Coupling Reaction for the Synthesis of *N*-Hydroxyphthalimide Esters

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Since the first report of the direct preparation of highly active manganese (Mn*) and its application in organic chemistry has been reported,[1] this protocol along with transmetallation methodology has been widely utilized for the preparation of organomanganese reagents.[2] To date, most of the successful experiments using Mn* focused on the construction of C—C bond via cross-coupling reactions. Very recently, we reported a somewhat different type of Mn* application to cross-coupling reactions, resulting in C—O bond formation.[3] In the study, highly active manganese played a role as a reaction promoter to provide the corresponding esters from the reactions of normal alcohols with acid chlorides. Albeit the mechanistic details of this transformation were not investigated in that study, the reaction could be presumably completed via a manganese alkoxide-like intermediate.

Prompted by this observation, we decided to perform a further study on the diversification of highly active manganese in C—O cross-coupling reactions. To address this issue, *N*-hydroxyphthalimide (NHPI) was among the best candidate to execute our strategy, since NHPI is a slightly different type of hydroxyl-group-containing compound from the alcohols used in our previous research.[3] More interestingly, NHPI has proved to be an efficient and broadly applicable radical precursor in cross-dehydrogenative coupling (CDC) reactions.[4] Therefore, we assumed that the utilization of NHPI in our reaction system could be very useful to determine the role of highly active manganese (*i.e.,* radical versus metal alkoxide source). Secondly, the application of NHPI in the CDC strategy with aldehydes and alcohols has been intensively developed to provide facile protocols for the preparation of *N*-hydroxyimide esters,[5,6] which could be the resulting products from our C—O coupling reaction strategy. In addition, these active esters have often been used in amidation and peptide synthesis as valuable coupling intermediates.[5,7] Therefore, we anticipated that our strategy would provide an alternative synthetic tool for the synthesis of *N*-hydroxyimide esters.

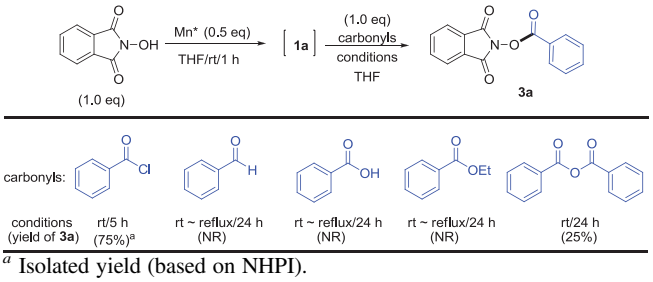
Based on this assumption, our initial set of experiment involved reacting highly active manganese with NHPI, and then the obtained complex was subjected to coupling with carbonyl compounds.

Since our first goal was to find out the best coupling partner, we decided to carry out the screening test with various carbonyls. As described in Table 1, NHPI was initially treated with Mn* in THF at room temperature, resulting in the formation of a dark solution (**1a**). Next, an appropriate carbonyl compound (1.0 equiv) was added to the solution (**1a**). To our delight, the expected *N*-hydroxyphthalimide ester, 1,3-dioxoisoindolin-2-yl benzoate (**3a**), was obtained from the reaction of benzoyl chloride in 75% isolated yield. With the expectation of forming **3a** by using an aldehyde or a carboxylic acid as a coupling partner, both benzaldehyde and benzoic acid were also examined in the system. Unfortunately, no coupling reaction took place. Compared with the positive outcome delivered by benzoyl chloride, benzoic anhydride turned out to be less effective in our system, but it still gave rise to the corresponding product **3a** with a diminished yield (25%). For fine tuning of the ratio of Mn* to NHPI, additional tests using 1.0 equiv of Mn*/1.0 equiv of NHPI/1.0 equiv. of benzoyl chloride, and 1.0 equiv. of Mn*/1.5 equiv of NHPI/1.0 equiv of benzoyl chloride were carried out. However, no improvement in terms of isolated yield was observed. A mixture of unidentified products was obtained instead.

In addition to the preliminary tests with the carbonyls above, various coupling partners such as acid anhydrides and sulfonyl chlorides, were employed to elucidate the applicability of our system and the results are described in Scheme 1.

The coupling of **1a** with acetic anhydride led to the formation of the corresponding product, 1,3-dioxoisoindolin-2-yl acetate (**2a**), in a relatively lower yield (24%). The result obtained from utilizing trifluoroacetic anhydride (**2b**, 29% isolated yield) was not very different. Furthermore, to explore O—S bond formation, both benzene sulfonyl chloride and *p*-toluenesulfonyl chloride were reacted with **1a** under the same conditions. To our great delight, the corresponding products, 1,3-dioxoisoindolin-2-yl benzenesulfonate (**2c**) and 1,3-dioxoisoindolin-2-yl 4-methylbenzenesulfonate (**2d**)

Table 1. Screening for coupling partners.

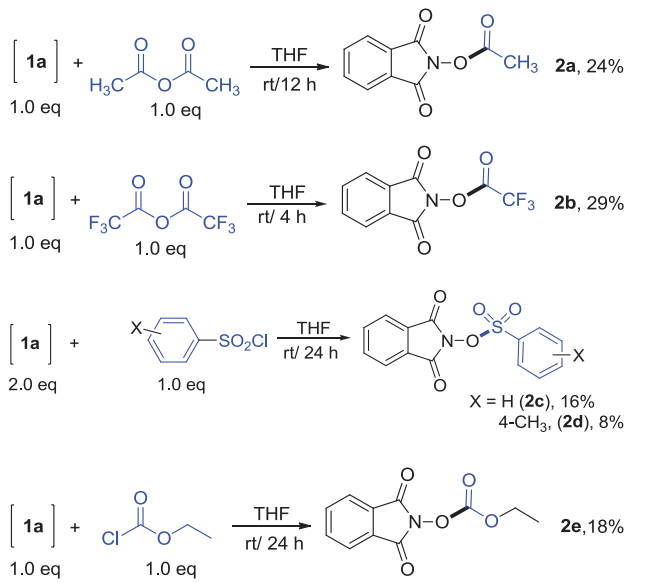


[a] Isolated yield (based on NHPI).

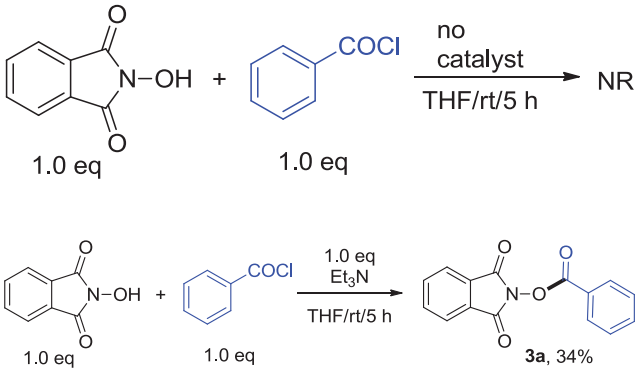
were successfully produced, but in severely reduced isolated yields (16% and 8%, respectively). Additionally, ethyl chloroformate was also reacted with **1a**, resulting in a partially satisfied outcome (**2e**, 18%).

On the basis of all of the outcomes above, it could be inferred that acid chlorides would be the most suitable substrates to couple with **1a,** giving rise to the corresponding coupling products in terms of isolated yield.

Next, two control experiments were also performed to explore the role of Mn*. As shown in Scheme 2, NHPI was reacted with benzoyl chloride in the absence of any catalyst in THF at room temperature, resulting in no reaction. To address an oxide-type coupling procedure, a typical Et_3N-catalyzed coupling reaction of **1a** with benzoyl chloride was carried out providing **3a** in 34% isolated yield. The use of other organic bases such as DBU and $(n\text{-Bu})_2NH$ also provided **3a** in the range of 40–45% isolated yields. Based upon these results, it could be perceived that the presence of the phthalimide *N*-oxide-like intermediate (**1a)** was critical for the effective completion of C—O bond forming even though there is no obvious evidence, and highly active manganese was a suitable reagent for producing the intermediate **1a**.



Scheme 1. Coupling of **1a** with anhydrides and sulfonyl chlorides.

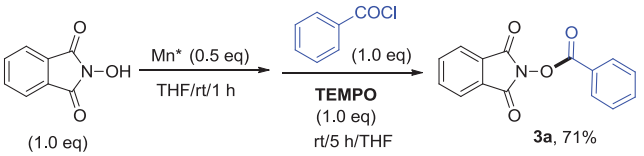


Scheme 2. Controlled reactions searching for the role of Mn*.

To gain further insight into the presence of potential radical species, phthalimide *N*-oxy (PINO), a brief control experiment was set up in the following manner (Scheme 3). Since this radical species has been reported and considered to be a reaction intermediate in previous similar studies,[4] the test would enable us to determine whether radical species existed in our system. When the coupling reaction of **1a** with benzoyl chloride was carried out in the presence of a radical scavenger 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO, 1.0 equiv) under the same conditions used before, smooth progress was indicated, furnishing the desired product (**3a**) with a slightly reduced isolated yield (71%). Considering the results obtained thus far, even though detailed mechanistic studies have not performed, we inferred that our reaction system worked via a manganese alkoxide-like intermediate rather than a radical pathway.

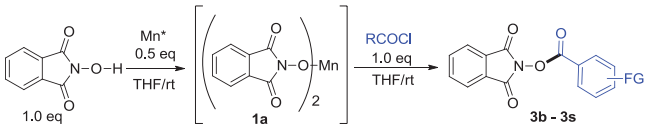
With the above observations in hand, we began to examine the scope of this strategy to develop a novel synthetic pathway for the preparation of *N*-hydroxyphthalimide esters using a variety of acid chlorides. The results are summarized in Table 2.

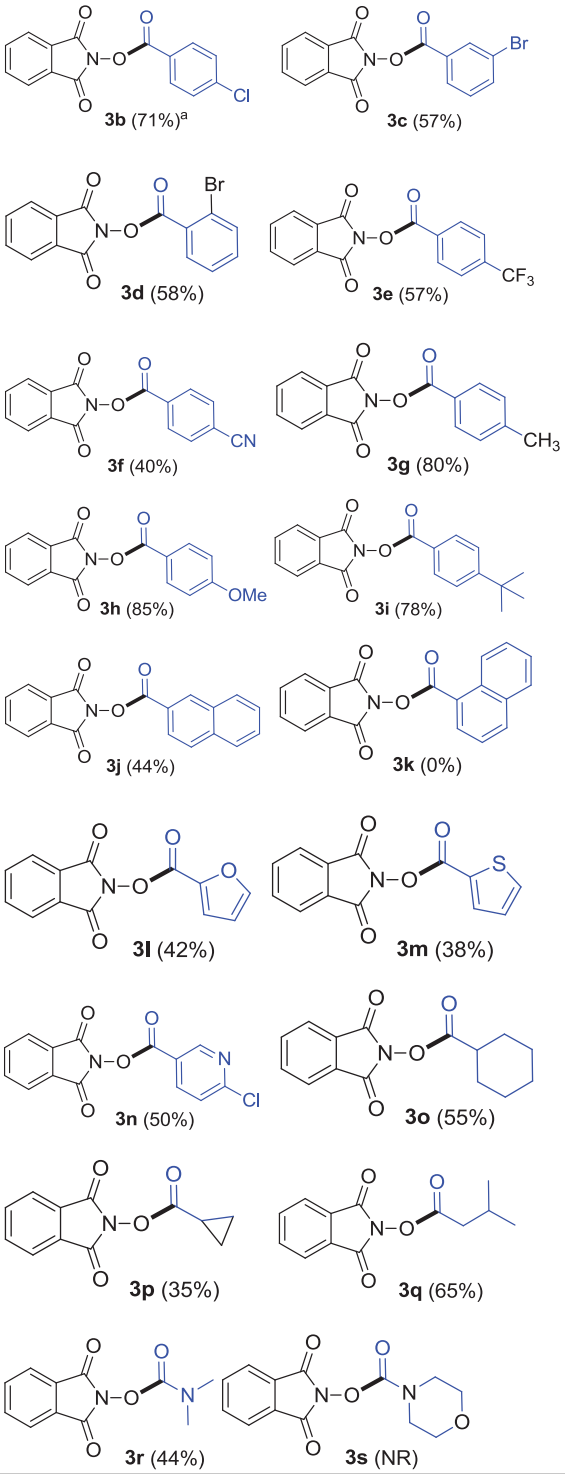
The coupling reactions with halobenzoyl chlorides were examined first, generating the desired esters (**3b-d**, Table 2) with moderate isolated yields. Next attempts were conducted with electron-rich and electron-deficient aryl acid chlorides. As depicted below, coupling with aryl acid chlorides bearing electron-donating groups such as methyl, methoxy, and *t*-butyl moieties produced the corresponding products (**3g-i**, Table 2) in higher yields (78–85%) than that (**3e** and **3f**, 57 and 40%, respectively) of electron-withdrawing groups. The following two reactions (entries 9 and 10, Table 2) clearly showed a steric effect on the coupling reaction. A mixture of indistinguishable products was obtained from the reaction with 1-naphthanoyl chloride



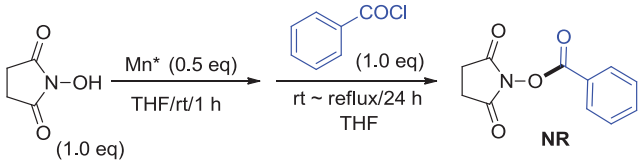
Scheme 3. Control reaction with TEMPO.

Table 2. Scope of the reaction of **1a** with acid chlorides.





[a] Isolated yield (based on acid chloride).



Scheme 4. Reaction with *N*-hydroxysuccimide.

under the conditions used whereas 2-naphthanoyl chloride reacted well with **1a** affording **3j** in 44% isolated yield. Heteroaromatic carbonyl chlorides were additionally proven to be suitable partners for our system. For examples, 2-furoyl chloride, 2-thiophenecarbonyl chloride, and 6-chloronicotinoyl chloride were efficiently coupled with **1a** to produce the corresponding *N*-hydroxyimide esters (**3l**, **3m**, and **3n**, Table 2) in 38–50% yields.

The coupling reaction with acid chlorides was then expanded to alkyl acid chlorides. As expected, all the reactions of cyclic and non-cyclic acid chlorides took place successfully at room temperature furnishing the corresponding esters (**3o–q**, Table 2) in moderate yields. The applicability of **1a** was further examined by the reaction with carbamoyl chlorides (entries 18 and 19, Table 2). Unlike the previous cyclic acid chlorides, it was found that no coupling reaction was observed with a sterically demanded 4-morpholinecarbonyl chloride. On the other hand, dimethylcarbamoyl chloride gave rise to the coupling product **3r** in 44% isolated yield.

Encouraged by the results described above, the same reaction environment was adapted to the coupling of *N*-hydroxysuccinimide (NHSI) with acid chlorides. Unfortunately, the expected *N*-hydroxysuccinimide esters were not generated even at various reaction conditions such as prolonged reaction time, elevated temperature, and various molar ratios. Instead, a mixture of the 1,4-halohydrines generated from the ring-opening of tetrahydrofuran was exclusively obtained (Scheme 4).[8]

In conclusion, we have demonstrated the first example of a highly active manganese-mediated C—O cross-coupling reaction of readily available NHPI with a variety of acid chlorides under mild conditions. The resulting products, *N*-hydroxyphthalimide esters, were successfully obtained from the reaction of acid chlorides and NHPI in the presence of Mn* under mild conditions, whereas no reaction occurred when utilizing NHSI. A concise mechanistic study showed that the formation of a manganese alkoxide-like intermediate could be responsible for producing coupling products. Further applications of this strategy are currently underway in our laboratory.

Experiment

A typical preparation of highly active manganese (Mn*): In a 25 mL round-bottom flask, lithium (9.68 mmol), naphthalene (1.48 mmol), and anhydrous manganese iodide (4.71 mmol) were placed under argon pressure. Next, freshly distilled THF (10 mL) was added into the flask,

then the mixture was allowed to stir at room temperature for 3 h. The resulting black solution containing highly active manganese was ready for use.

Representative procedure: (a) Preparation of bis(1,-3-dioxoisoindolin-2-yloxy)manganese (**1a**): In 25 mL of round-bottomed flask containing 1.5 mmol of active manganese in THF was added 0.49 g (3.0 mmol) of *N*-hydroxyphthalimide at room temperature. The resulting mixture was stirred at room temperature for 1.0 h, then settled down at room temperature. The top layer was cannulated into a 25 mL of flask. (b) Cross-coupling reaction of **1a** with 4-methoxybenzoyl chloride; To a 25 mL of flask containing 3 mL (0.5 M in THF, 1.5 mmol) bis(1,-3-dioxoisoindolin-2-yloxy)manganese (**1a**) was added 0.51 g (3.0 mmol) of 4-methoxybenzoyl chloride. The resulting mixture was stirred at room temperature for 3.0 h. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with ether (10 mL × 3). The combined organic layers were washed with saturated $Na_2S_2O_3$ solutions and brine and dried over $MgSO_4$. Column chromatography with 5% ethyl acetate/95% Hexanes afforded 1.26 g of **3 h** (85%) as a pale yellow solid (m.p. 76–78 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): 8.16 (dt, J = 2.8, 2.1 Hz, 2H), 7.42 (t, 8.4 Hz, 2H), 7.20 (d, 6.3 Hz, 2H), 6.98 (dt, J = 2.8, 2.1 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): 180.30, 164.94, 163.90, 133.00, 132.30, 129.44, 125.73, 121.82, 113.85, 59.60 ppm. HRMS; calcd for $C_{16}H_{11}NO_5$ 297.0637, found 297.0721.

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References

1. S.-H. Kim, M. V. Hanson, R. D. Rieke, *Tetrahedron Lett.* **1996**, *37*, 2197.
2. (a) S.-H. Kim, R. D. Rieke, *J. Org. Chem.* **2000**, *65*, 2322. (b) S.-H. Kim, R. D. Rieke, *Tetrahedron Lett.* **1997**, *38*, 993. (c) S.-H. Kim, R. D. Rieke, *J. Org. Chem.* **1998**, *63*, 6766. (d) S.-H. Kim, R. D. Rieke, *J. Org. Chem.* **1998**, *63*, 5235. (e) R. D. Rieke, S.-H. Kim, X. Wu, *J. Org. Chem.* **1997**, *62*, 6921.
3. S.-R. Joo, Y.-J. Youn, Y. R. Hwang, S.-H. Kim, *Synlett* **2017**, *28*, 2665.
4. (a) X. Zhu, Z. He, Q. Y. Li, X.-J. Wang, *RSC Adv.* **2017**, *7*, 25171. (b) S. Samanta, R. R. Donthiri, C. Ravi, S. Adimurthy, *J. Org. Chem.* **2016**, *81*, 3457. (c) S. Tsujimoto, S. Sakaguchi, Y. Ishii, *Tetrahedron Lett.* **2003**, *44*, 5601. (d) G. Yang, T. Ma, J. Xu, *J. Am. Chem. Soc.* **2004**, *126*, 10542. (e) F. Recupero, C. Punta, *Chem. Rev.* **2007**, *107*, 3800. (f) J. M. Lee, E. J. Park, S. H. Cho, S. Chang, *J. Am. Chem. Soc.* **2008**, *130*, 7824. (g) A. S. Patil, D.-L. Mo, H.-Y. Wang, D. S. Mueller, L. L. Anderson, *Angew. Chem. Int. Ed.* **2012**, *51*, 7799. (h) R. Ghosh, B. Olofsson, *Org. Lett.* **2014**, *16*, 1830.
5. For recent examples on *N*-hydroxyimide ester synthesis by CDC, see; (a) Z. Guo, X. Jiang, C. Jin, J. Zhou, B. Sun, W. Su, *Synlett* **2017**, *28*, 1321. (b) X. Xu, P. Li, Y. Huang, C. Tong, Y. Yan, Y. Xie, *Tetrahedron Lett.* **2017**, *58*, 1742. (c) Y. Lv, K. Sun, W. Pu, S. Mao, G. Li, J. Niu, Q. Chen, T. Wang, *RSC Adv.* **2016**, *6*, 93486. (d) M. Dinda, C. Bose, T. Ghosh, S. Maity, *RSC Adv.* **2015**, *5*, 44928. (e) B. Tan, N. Toda, C. F. Barbas III. , *Angew. Chem. Int. Ed.* **2012**, *51*, 12538. (f) H. Yao, Y. Tang, K. Yamato, *Tetrahedron Lett.* **2012**, *53*, 5094. (g) N. Wang, R. Liu, Q. Xu, X. Liang, *Chem. Lett.* **2006**, *35*, 566. (h) A. Schulze, A. Giannis, *Adv. Synth. Catal.* **2004**, *346*, 252. (i) I. B. Krylov, V. A. Vi□, A. O. Teren□ev, J. Beilstein, *Org. Chem.* **2015**, *11*, 92. (j) I. B. Krylov, A. O. Terentev, V. P. Timofeev, B. N. Shelimov, R. A. Novikov, V. M. Merkulova, G. I. Nikishin, *Adv. Synth. Catal.* **2014**, *356*, 2266. (k) S. K. Rout, S. Guin, K. K. Ghara, A. Banerjee, B. K. Patel, *Org. Lett.* **2012**, *14*, 3982.
6. For *N*-hydroxyimide ester synthesis by traditional method, see; (a) M. Kim, K.-J. Han, *Synth. Commun.* **2009**, *39*, 4467. (b) E. Grochowski, J. Jurczak, *Synthesis* **1977**, *1977*, 277. (c) H. Ogura, T. Kobayashi, K. Shimizu, K. Kawabe, K. Takeda, *Tetrahedron Lett.* **1979**, *20*, 4745. (d) K. Kim, K. Y. Ko, *J. Chem. Soc. Chem. Commun.* **1985**, 473. (e) P. Pöchlauer, W. Hendel, *Tetrahedron* **1998**, *54*, 3489.
7. (a) T. Qin, J. Cornella, C. Li, L. R. Malins, J. T. Edwards, S. Kawamura, B. D. Maxwell, M. D. Eastgate, P. S. Baran, *Science* **2016**, *352*, 801. (b) K. M. M. Huihui, J. A. Caputo, Z. Melchor, A. M. Olivares, A. M. Spiewak, K. A. Johnson, T. A. DiBenedetto, S. Kim, L. K. G. Ackerman, D. J. Weix, *J. Am. Chem. Soc.* **2016**, *138*, 5016. (c) G. Wang, Q.-Y. Yu, J. Wang, S. Wang, S.-Y. Chen, X.-Q. Yu, *RSC Adv.* **2013**, *3*, 21306. (d) M. J. Schnermann, L. E. Overman, *Angew. Chem. Int. Ed.* **2012**, *51*, 9576. (e) G. Pratsch, G. L. Lackner, L. E. Overman, *J. Org. Chem.* **2015**, *80*, 6025.
8. For a recent example showing THF-ring opening, see; M. J. Duran-Pena, J. M. Botubol-Ares, J. R. Hanson, R. Hernandez-Galan, I. G. Collado, *Eur. J. Org. Chem.* **2016**, *3584*.

