


 Cite this: *RSC Adv.*, 2021, **11**, 164

Mn(II)-Catalysed *ortho*-alkenylation of aromatic amines and its application in reproductive diseases†

 Jinfei Yang,^{‡*} Xiaolong Wu,[‡] Banghua Yang, Yirong Liu, Rui Cheng, Zijun Gong and Fei Sun*

A Mn(II)-catalysed *ortho*-alkenylation of aromatic amines and its application in reproductive diseases were developed. The use of MnCl₂ was critical for the *ortho*-alkenylation of aromatic amines. The general applicability of this procedure was highlighted by the synthesis of 27 vinylanilines, with good regioselectivities. The value of our approach in practical applications was investigated by studying the effects of one of the compounds **3m** on 8 week-old adult male rats with azoospermia as a mammalian model. The results show that a small amount of sperm will gradually be produced in the epididymis and testes by treatment of 8 week-old adult male rats with azoospermia with 1 mg kg⁻¹ **3m** after two weeks, while treatment with 10 mg kg⁻¹ **3m** led to obvious sperm production. Notably, if we increase the dose to 100 mg kg⁻¹, there will be a lot of sperm production in the epididymis and testes after two weeks of treatment. The results of this study will be of great significance in research on drugs for treating azoospermia and oligospermia diseases.

Received 2nd December 2020

Accepted 7th December 2020

DOI: 10.1039/d0ra10172a

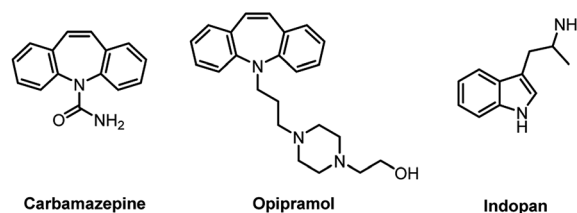
rsc.li/rsc-advances

Alkenyl arylamines are very important intermediates for the synthesis of drug molecules, such as carbamazepine,¹ opipramol,² and indopan³ (Scheme 1). *O*-Alkenyl arylamines have attracted much attention because of their widespread presence in a variety of heterocycles including indoles, quinolines and cinnolines, which are key structural units for many biologically important compounds.⁴ Moreover, they have also been used as synthetic intermediates in several total synthetic methods.⁵ Therefore, it is of great significance to carry out the *ortho*-alkenylation reaction of aromatic amines. But it is not an easily accessible process under normal Friedel–Crafts conditions due to the coordination of the Lewis acid with the nitrogen atom of amino group, which leads to the deactivation of the aromatic ring.⁶ To overcome this challenge, chemists began to try other methods to achieve *ortho*-alkenylation of aromatic amines. Subsequently, several related *ortho*-alkenylation of aromatic amines with phenylacetylene was reported in the literature.^{4a,7} However, the *ortho*-alkenylation of aromatic amines catalyzed by base metals has not yet been developed, especially manganese. Therefore, it is still very important to develop a Mn-catalyzed *ortho*-alkenylation reaction of aromatic amines. Notably, there have been more C–H bond functionalization reactions catalyzed by monovalent manganese in recent years, but few of them were catalyzed by divalent manganese.⁸

Ackermann's research group reported several Mn(II)-catalyzed *ortho*-functionalization reactions of arylamides.⁹ In addition, a Mn(II)-catalysed dehydrogenative annulation of *N*-aryl anilines with alkenes or alkynes was reported by our group last year.¹⁰

Herein, we report an example of Mn(II)-catalysed *ortho*-alkenylation of aromatic amines and its application in reproductive diseases (Scheme 2). In our previous work, divalent manganese is easily oxidized to tetravalent manganese by K₂S₂O₈.¹⁰ This work, we hypothesis the *ortho*-alkenylation product of aromatic amine will be generated after the oxidant was removed in the system. Based on this hypothesis, we tried a series of manganese catalysts.

We began by treating *N*-benzylaniline and phenylacetylene with toluene as a solvent. Initially, we attempted using various Mn(II) catalysts to catalyse the *ortho*-alkenylation of aromatic amines at 120 °C, *i.e.*, MnO, MnSO₄, Mn(OAc)₂, and Mn(acac)₂, as detected by GC analysis, while 73% and 61% yields were observed when MnBr₂ and MnI₂ were used as catalysts (Table 1, entries 1–7). Fortunately, a 80% yield of *N*-benzyl-2-(1-



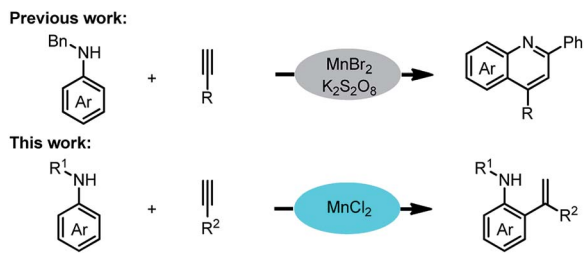
Scheme 1 Drug molecules containing alkenyl arylamine skeleton.

Medical School, Institute of Reproductive Medicine, Nantong University, Nantong 226019, China. E-mail: jfyang@ntu.edu.cn; sunfei@ntu.edu.cn

† Electronic supplementary information (ESI) available. See DOI: 10.1039/d0ra10172a

‡ J.-F. Y. and X.-L. W. contributed equally to this work.





Scheme 2 Proposed strategy.

phenylvinyl)aniline was obtained when using MnCl_2 . To improve the reaction efficiency, different solvents, including *N,N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), acetonitrile (CH_3CN), 1,4-dioxane, tetrahydrofuran (THF), 1,2-dichloroethane (DCE), *p*-xylene, mesitylene and *n*-hexane were tested (Table 1, entries 8–16). The optimal reaction solvent was found to be toluene. To increase conversion to the *N*-benzyl-2-(1-phenylvinyl)aniline, we examined a wide range of reaction temperatures (Table 1, entries 17–22). The results show that 120 °C was the optimum temperature, and the corresponding *N*-

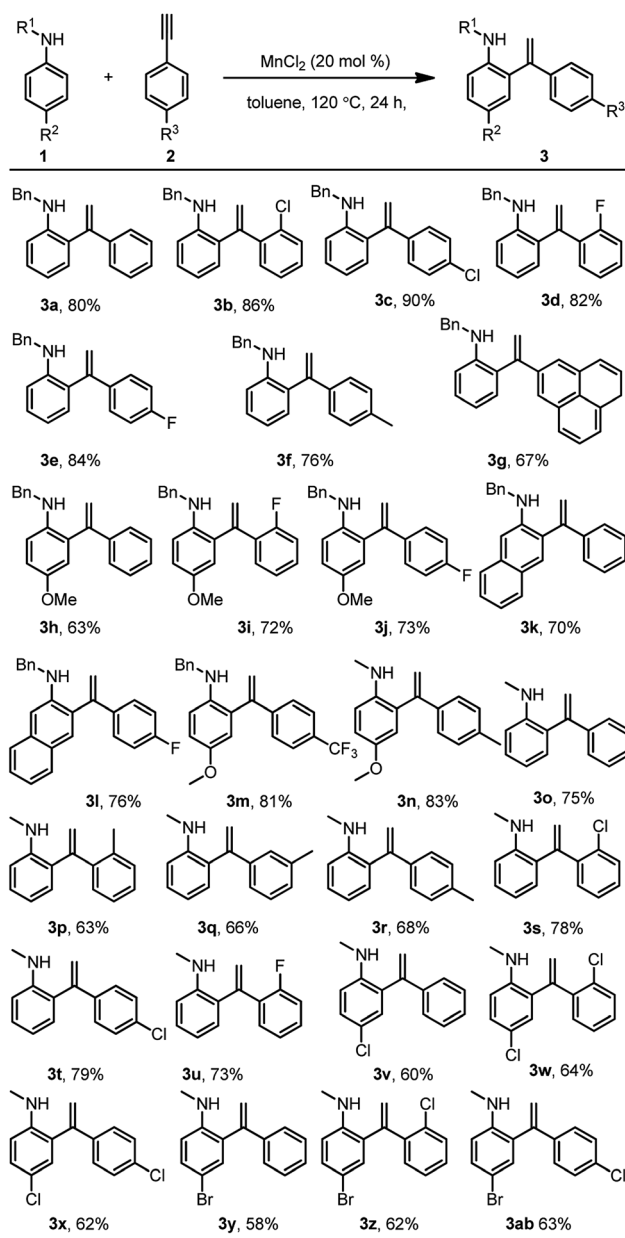
Table 1 Effects of catalyst, temperature, and solvent. *N*-Benzylaniline (0.2 mmol), phenylacetylene (0.4 mmol), catalyst (0.04 mmol), solvent (2.0 mL), at 120 °C for 24 h

Entry	Catalyst	Solvent	<i>T</i> (°C)	Yield 3a ^b (%)
1	$\text{Mn}(\text{OAc})_2$	Toluene	120	20
2	MnO	Toluene	120	0
3	MnSO_4	Toluene	120	0
4	$\text{Mn}(\text{acac})_2$	Toluene	120	50
5	MnBr_2	Toluene	120	73
6	MnI_2	Toluene	120	61
7	MnCl_2	Toluene	120	80
8	MnCl_2	DMF	120	0
9	MnCl_2	DMSO	120	0
10	MnCl_2	CH_3CN	120	3
11	MnCl_2	Dioxane	120	28
12	MnCl_2	THF	120	14
13	MnCl_2	DCE	120	26
14	MnCl_2	<i>p</i> -Xylene	120	50
15	MnCl_2	Mesitylene	120	52
16	MnCl_2	<i>n</i> -Hexane	120	10
17	MnCl_2	Toluene	80	12
18	MnCl_2	Toluene	90	29
19	MnCl_2	Toluene	100	51
20	MnCl_2	Toluene	110	63
21	MnCl_2	Toluene	130	70
22	MnCl_2	Toluene	140	63
23 ^c	None	Toluene	120	0

^a The reactions were carried out in sealed tubes. ^b Yields were determined by GC analysis. ^c Without MnCl_2 .

benzyl-2-(1-phenylvinyl)aniline was obtained the best yield. It is worth noting that more cyclization products were formed when the temperature is raised to 130 °C. Therefore, temperature is another key factor that drives the reaction forward. Notably, the addition of oxidant will terminate this reaction (see the ESI Table 1† for details). These results therefore support our initial hypothesis that the *ortho*-alkenylation product of aromatic amine will be generated after the oxidant was removed.

With the optimum reaction conditions in hand, a series of aromatic amine were investigated for extending the substrate scope (Scheme 3). This Mn(II)-catalysed *ortho*-alkenylation of aromatic amines shows good functional group tolerance.



Scheme 3 Reaction conditions: substrate 1 (0.2 mmol), aryl acetylene (0.4 mmol), MnCl_2 (0.04 mmol), toluene (2.0 mL), at 120 °C for 24 h, and isolated yields for products.

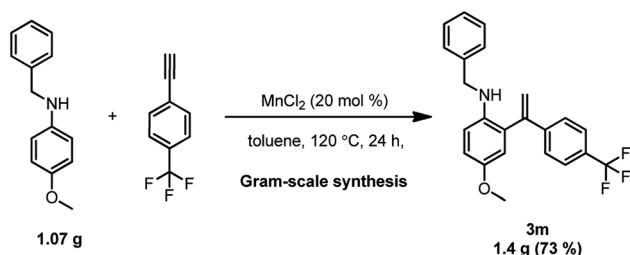


Aromatic amine with electron-neutral or electron-donating groups such as alkyl, phenyl, and methoxy on the aryl rings all gave the corresponding *ortho*-olefination products with high selectivities and in good yields. Aryls containing an electron-withdrawing group such as chloro, and bromo were also tolerated and afforded the corresponding *ortho*-olefination products **3v–3ab** in moderate yields with highly *ortho*-selectivities. Moreover, the reaction of aromatic amine containing naphthyl of the aromatic rings also gave the corresponding *ortho*-olefination products **3k** and **3l** in good yields. Unfortunately, it does not give good yields for *meta*-substituted aromatic amines.

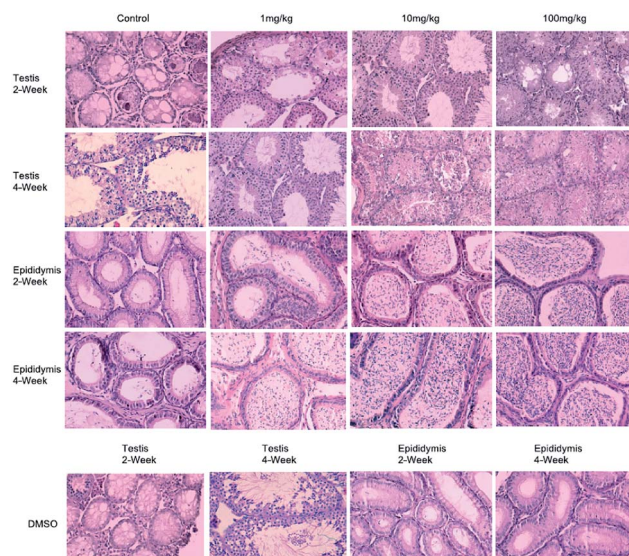
In addition, aryl acetylene with electron-neutral or electron donating groups such as alkyl and anthryl on the aryl rings all gave the corresponding *ortho*-olefination products with high selectivities and in good yields. Aryls containing an electron-withdrawing group such as fluoro, chloro, bromo and trifluoromethyl were also tolerated and afforded the corresponding *ortho*-olefination products **3b–3e**, **3i**, **3j**, **3l**, **3m**, **3s–3u**, **3w** and **3z** in moderate to good yields. More importantly, retention of the fluorine, chlorine, and bromine atoms in the products makes the products of considerable use in organic transformations.

The synthetic utility of the current method was tested by performing a gram-scale *ortho*-alkenylation of aromatic amines under the optimum conditions. The target *N*-benzyl-4-methoxy-2-(1-(4-(trifluoromethyl)phenyl)vinyl)aniline **3m** was obtained in 73% yield (Scheme 4).

Azoospermia is the medical condition of a man whose semen contains no sperm.¹¹ Pre- and post-testicular azoospermia are frequently correctible, while testicular azoospermia is usually permanent.¹² In humans, azoospermia affects about 1% of the male population and may be seen in up to 20% of male infertility situations in Canada.¹³ However, there is no specific drugs for azoospermia currently on the market. The empirical drug commonly used in clinical practice is clomiphene.¹⁴ Clomiphene is a non-steroidal drug with a chemical structure similar to diethylstilbestrol. Its mechanism of action may be that the molecule competitively occupies the ER, thereby blocking the negative feedback effect of circulating endogenous estradiol, leading to increased secretion of GnRH released by the hypothalamus, stimulating the secretion of FSH and LH, and promoting spermatogenesis. Although it has been widely used by clinicians, clinical studies show that long-term use of clomiphene may increase the risk of cancer. Therefore, it is necessary to develop a safer drug that can replace clomiphene. Given that the structure of the **3m** is similar to clomiphene, we envision that **3m** may also have the effect of promoting spermatogenesis.



Scheme 4 Gram-scale synthesis.



Scheme 5 Biological activity evaluation test in spermatogenesis.

To verify the potential of **3m** in promoting spermatogenesis, we study the effects of **3m**, with 8 week-old adult male rats with azoospermia as a mammalian model (Scheme 5). The test results show that a small amount of sperm will gradually be produced in the epididymis and testis by treatment of 8 week-old adult male rats with azoospermia with 1 mg kg^{-1} **3m** after two weeks later, and treatment with 10 mg kg^{-1} **3m** led to obvious sperm production. To our delight, a lot of sperm will be produced in the epididymis and testis after four weeks. Notably, if we increase its dose to 100 mg kg^{-1} , there will be a lot of sperm production in the epididymis and testis after two weeks of treatment. In addition, to exclude the influence of DMSO, we made a group of control test, and the test results showed that the sperm number has no change in epididymis and testis. So DMSO has no effect on spermatogenesis. Accordingly, we have discovered a drug molecule that can effectively promote spermatogenesis. The results of this study will be of great significance in research on drugs for treating azoospermia and oligospermia diseases.

Additional experiments were performed to gain a better understanding of the roles of MnCl_2 in the *ortho*-alkenylation of aromatic amines. Control experiments showed that the absence of MnCl_2 shut down the reaction (Table 1, entry 23). These results imply that MnCl_2 is essential to this reaction. We propose the catalytic cycle shown in the ESI.† Phenylacetylene and aromatic amine first undergoes ligand coordination with the metal center, and subsequent electrophilic addition with aromatic amine provides an intermediate A, and then the target product is obtained through proton migration, with regeneration of the catalytic Mn(II) (see the ESI Fig. 1† for details).

Conclusions

In summary, we have developed a highly efficient Mn(II) -catalysed *ortho*-alkenylation of aromatic amines and its application in reproductive diseases. This method is safer, more



convenient, and more economical than traditional strategies. It is compatible with a range of functional groups and is suitable for gram-scale reactions. The value of our approach in practical applications was shown by studying the effects of treatment with **3m**, with 8 week-old adult male rats with azoospermia as a mammalian model. The test results show that **3m** significantly affect spermatogenesis. The results of this study will be of great significance in research on drugs for treating azoospermia and oligospermia diseases. Further investigations of the drug molecular mechanism of action, and other reaction types are underway in our laboratory.

Ethical statement

All animal procedures were performed in accordance with the Guidelines for Care and Use of Laboratory Animals of Nantong University and Experiments were approved by the Animal Ethics Committee (approval no. 20171220-005).

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the National Key Research and Development Program of China (2018YFC1003500 to F. S.), the High Level Talent Foundation of "Six Talent Peaks" in Jiangsu Province (131219631004 to J. Y.) for financial support.

Notes and references

- (a) S. J. Nevitt, A. G. Marson, J. Weston and C. Smith Tudur, *Cochrane Database Syst. Rev.*, 2018, **8**, CD001769; (b) N. Kaniwa and Y. Saito, *J. Hum. Genet.*, 2013, **58**, 317–326; (c) L. Liu, T. Zheng, M. J. Morris, C. Wallengren, A. L. Clarke, C. A. Reid, S. Petrou and T. J. O'Brien, *J. Pharmacol. Exp. Ther.*, 2006, **319**, 790–798; (d) A. Tateno, K. Sawada, I. Takahashi and Y. Hujiiwara, *Pediatr. Neurol.*, 2006, **35**, 131–134.
- (a) H. J. Möller, H. P. Volz, I. W. Reimann and K. D. Stoll, *J. Clin. Psychopharmacol.*, 2001, **21**, 59–65; (b) M. Hanner, F. F. Moebius, A. Flandorfer, H. G. Knaus, J. Striessnig, E. Kempner and H. Glossmann, *Proc. Natl. Acad. Sci. U. S. A.*, 1996, **93**, 8072–8077.
- (a) J. Wilcox, *J. Psychoact. Drugs*, 2012, **44**, 274–276; (b) F. Nagai, R. Nonaka and K. H. K. Satoh, *Eur. J. Pharmacol.*, 2007, **559**, 32–137; (c) X. M. Huang, M. P. Johnson and D. E. Nichols, *Eur. J. Pharmacol.*, 1991, **200**, 187–190.
- (a) A. Chatupheeraphat, M. Rueping and M. Magre, *Org. Lett.*, 2019, **21**, 9153–9157; (b) L. G. Qiang and N. H. Baine, *J. Org. Chem.*, 1988, **53**, 4218–4222; (c) C. Hausch and G. Helmkamp, *J. Am. Chem. Soc.*, 1951, **73**, 3080–3082; (d) C. Hausch, D. G. Crosby, M. Sadoski, A. Leo and D. Percival, *J. Am. Chem. Soc.*, 1951, **73**, 704–706.
- (a) J. B. Jiang, D. P. Hesson, B. A. Dusak, D. L. Dexter, G. J. Kang and E. Hamel, *J. Med. Chem.*, 1990, **33**, 1721–1728; (b) R. Smith and T. Livinghouse, *J. Org. Chem.*, 1983, **48**, 1554–1555; (c) P. D. Magnus and N. L. Sear, *Tetrahedron*, 1984, **40**, 2795–2797.
- T. Sugawara, *J. Synth. Org. Chem., Jpn.*, 1978, **36**, 480.
- A. Arienti, F. Bigi, R. Maggi, E. Marzi, P. Moggi, M. Rastelli, G. Sartori and F. Tarantola, *Tetrahedron*, 1997, **53**, 3795–3804.
- (a) S. Waiba and B. Maji, *ChemCatChem*, 2020, **12**, 1891–1902; (b) Y. Hu and C. Wang, *ChemCatChem*, 2019, **11**, 1167–1174; (c) X. Yang and C. Wang, *Chem.-Asian J.*, 2018, **13**, 2307–2315; (d) Y. Hu, B. Zhou and C. Wang, *Acc. Chem. Res.*, 2018, **51**, 816–827; (e) Q. Lu, S. Cembellín Santos, S. Greßies, S. Singha, C. Daniliuc and F. Glorius, *Angew. Chem., Int. Ed.*, 2018, **57**, 1399–1403; (f) C. Zhu, J. L. Schwarz, S. Cembellín, S. Greßies and F. Glorius, *Angew. Chem., Int. Ed.*, 2018, **57**, 437–441; (g) Q. Lu, S. Greßies, S. Cembellín, F. J. R. Klauck, C. G. Daniliuc and F. Glorius, *Angew. Chem., Int. Ed.*, 2017, **56**, 12778–12782; (h) Q. Lu, S. Greßies, F. J. R. Klauck and F. Glorius, *Angew. Chem., Int. Ed.*, 2017, **56**, 6660–6664.
- (a) Z. Shen, H. Huang, C. Zhu, S. Warratz and L. Ackermann, *Org. Lett.*, 2019, **21**, 571–574; (b) C. Zhu, J. C. A. Oliveira, Z. Shen, H. Huang and L. Ackermann, *ACS Catal.*, 2018, **8**, 4402–4407; (c) W. Liu, G. Cera, J. C. A. Oliveira, Z. Shen and L. Ackermann, *Chem.-Eur. J.*, 2017, **23**, 11524–11528.
- C. Wang, J. Yang, X. Meng, Y. Sun, X. Man, J. Li and F. Sun, *Dalton Trans.*, 2019, **48**, 4474–4478.
- (a) H. Wang, R. Zhao, C. Guo, S. Jiang, J. Yang, Y. Xu, Y. Liu, L. Fan, W. Xiong, J. Ma, S. Peng, Z. Zeng, Y. Zhou, X. Li, Z. Li, X. Li, D. C. Schmitt, M. Tan, G. Li and M. Zhou, *Sci. Rep.*, 2016, **6**, 21776; (b) N. Sermondade, C. Faure, L. Fezeu, A. G. Shayeb, J. P. Bonde, T. K. Jensen, M. Van Wely, J. Cao, A. C. Martini, M. Eskandar, *et al.*, *Hum. Reprod. Update*, 2013, **19**, 221–231; (c) B. M. Berookhim and P. N. Schlegel, *Urol. Clin. North Am.*, 2014, **41**, 97–113.
- Male Infertility Best Practice Policy Committee of the American Urological Association; Practice Committee of the American Society for Reproductive Medicine. *Infertility: report on evaluation of the azoospermic male*. American Urological Association, American Society for Reproductive Medicine, 2001.
- K. Jarvi, K. Lo, A. Fischer, J. Grantmyre, A. Zini, V. Chow and V. Mak, *Can. Urol. Assoc. J.*, 2010, **4**, 163–167.
- S. Yilmaz, N. Y. Sezer, İ. M. Gönenc, S. E. İlhan and E. Yilmaz, *Cytotechnology*, 2018, **70**, 489–495.

