Silver-Mediated Oxidative C−H/P−H Functionalization: An Efficient Route for the Synthesis of Benzo[b]phosphole Oxides

Yun-Rong Chen and Wei-Liang Duan*

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

S *Supporting Information*

ABSTRACT: A Ag-mediated C−H/P−H functionalization reaction of arylphosphine oxides with internal alkynes was described for the direct preparation of benzo[b]-phosphole oxides with a high yield. An unusual aryl migration on the P-atom derived from a C−P bond cleavage and a new C−P bond formation was also observed and demonstrated to proceed via the radical process.
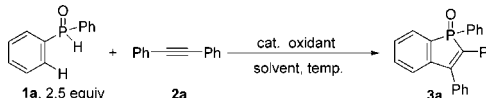
Phosphorus-containing heterocycles have wide applications in organic synthesis, medicinal chemistry, and material industries.[1] Among these compounds, benzo[b]phospholes have recently received considerable attention because of their inherent physical and optical properties, which allow the development of new classes of optoelectrochemical materials.[2] Previous reports have revealed methods for the synthesis of indoles, benzofurans, and benzothiophene heterocycles. Yet, methods for the synthesis of benzo[b]phospholes are lacking. Most reported routes start from o-halide-substituted aryl alkynes, followed by phosphination and cyclization reactions via multiple steps.[3] Therefore, the development of new, efficient methods for the synthesis of benzo[b]phosphole oxides would be highly appealing and essential.

During the past decade, C−H bond functionalization reactions have been extensively investigated to build diverse complex molecules, including various heterocyclic compounds in more efficient ways compared with conventional synthetic methods based on functional group transformation.[4] Typical examples include the synthesis of indoles from the reaction of aniline derivatives with alkynes catalyzed by Pd or Rh,[5] the construction of pyrroles from the reactions of enamines with ketones catalyzed by Rh,[6] and the synthesis of hexamember N- or O-containing heterocycles from the reaction of carboxylic amides or acids with alkynes and alkenes catalyzed by transition metals.[7] However, only a few studies are reported on the synthesis of P-containing heterocycles through the C−H functionalization pathway.[8] In this study, we describe a Ag-mediated C−H/P−H functionalization reaction of disubstituted phosphine oxides with alkynes to synthesize conveniently and directly high yields of benzo[b]-phosphole oxides.

Diphenylphosphine oxide was first reacted with diphenylacetylene under the catalysis of transition metals. The initial assumption is to utilize the coordination ability of the P-atom toward transition metals for the formation and functionalization of possible metallcycle intermediates via ortho C−H bond activation.[9] The use of Rh or Pd catalysts in the presence of Ag_2CO_3 as the oxidant facilitates the reaction smoothly, producing the desired phosphorus heterocycle **3a** in good yields (Table 1, entries 1 and 2). Furthermore, checking the background reaction revealed that this reaction is prompted merely by Ag_2CO_3 (entry 3).[10] For this process, examination of various silver salts indicated that Ag_2O is optimal (entries 3−7). Other metal oxidants, such as copper acetate or iron chloride, did not show activity (entries 8 and 9). Solvent screening disclosed that dimethylformamide (DMF) is optimal (entries 10−16).

Table 1. Silver-Mediated Oxidative Cyclization of Diphenylphosphine Oxide with Diphenylacetylene[11]

entry	catalyst (mol %)	oxidant (equiv)	solvent	temp (°C)/ time (h)	yield (%)[a]
1	Cp*RhCl$_2$ (2.5)	Ag$_2$CO$_3$ (3.0)	DMF	120/1	85
2	Pd(OAc)$_2$ (5.0)	Ag$_2$CO$_3$ (3.0)	DMF	120/1	77
3	−	Ag$_2$CO$_3$ (3.0)	DMF	120/1	70
4	−	Ag$_2$O (2.0)	DMF	120/1	85
5	−	AgNO$_3$ (4.0)	DMF	120/1	62
6	−	AgOAc (6.0)	DMF	120/1	85
7	−	AgOTf (6.0)	DMF	120/1	0
8[b]	−	Cu(OAc)$_2$ (2.0)	DMF	120/1	0
9[b]	−	FeCl$_3$ (4.0)	DMF	120/1	0
10[c]	−	**Ag$_2$O (1.5)**	**DMF**	**100/8**	**94**
11[c]	−	Ag$_2$O (1.5)	CH$_3$CN	100/8	89
12[c]	−	Ag$_2$O (1.5)	dioxane	100/8	23
13[c]	−	Ag$_2$O (1.5)	toluene	100/8	21
14[c]	−	Ag$_2$O (1.5)	DCE	100/8	22
15[c]	−	Ag$_2$O (1.5)	t-AmOH	100/8	32
16[c]	−	Ag$_2$O (1.5)	AcOH	100/8	74
17[c]	Ag$_2$O (20)	NaBrO$_3$ (1.5)	DMF	100/8	22
18[c]	Ag$_2$O (20)	CAN (2.0)	DMF	100/8	23
19[c]	Ag$_2$O (20)	1 atm of O$_2$	DMF	100/8	0

[a]Isolated yield. [b]2.0 equiv of diphenylphosphine oxide used. [c]1.5 equiv of diphenylphosphine oxide used.

Finally, attempts to use catalytic amounts of Ag₂O in the presence of stoichiometric amounts of oxidants, such as sodium bromate, CAN, and O₂, have not been successful (entries 17–19).

With the optimum conditions in hand, the current method was applied for various substrates, and the results are shown in Table 2. Monophenylphosphine oxides bearing various substituted

Table 2. Silver-Mediated Oxidative Cyclization of Phosphine Oxides with Diphenylacetylene

[a]Isolated yield. [b]2.5 equiv of diarylphosphine oxide and Ag₂O used.

groups, such as *tert*-butyl, cyclohexyl, and ethyloxy, can be coupled with diphenylacetylene to afford the corresponding products in moderate to good yields (Table 2, entries 1–4). An optically pure phenylphosphinate having a (−)-menthol group can also be converted to the phosphorus heterocycle, albeit with obvious loss of enantiomeric excess (entry 5). In addition, phosphine oxides having various electron-rich or -poor substituted aryl groups were examined with diphenylacetylene **2a**. In particular, aside from the desired products being generated, a series of compounds with aryl migration on the P-atom was also observed (entries 6–10), and the structures of the phosphorus heterocycles in entry 6 were confirmed by X-ray crystal diffraction analysis.[12] This aryl migration is derived from a C−P bond cleavage and a new C−P bond formation process, which have not been reported to date.[13] Table 3 summarizes the reaction of diphenylphosphine oxide with various disubstituted alkynes. Both diaryl- and dialkyl-substituted alkynes reacted with diphenylphosphine oxide smoothly with good yields (Table 3, entries 1–2). For the unsymmetrically disubstituted alkynes, a phosphorus atom was installed at the less hindered position of alkynes preferentially (entries 3–5).[14] In addition, ethyl 3-phenylpropiolate and 3-phenylpropynenitrile are also suitable acceptors to extend the applicability of the current method (entries 6–7). During our studies, Yang et al. described that metal nitrates can be used as the oxidant to regenerate the active Ag(I) catalyst from Ag(0).[8e] Their impressive work inspired us to

Table 3. Silver-Mediated Oxidative Cyclization of Diphenylphosphine Oxide with Disubstituted Acetylenes[15]


[a]The number outside of parentheses is isolated yield for the reaction carried out through Method A, and the number in parentheses is isolated yield for the reaction carried out through Method B. [b]The reaction was conducted at 110 °C. [c]The structure of the product was confirmed by X-ray crystal diffraction analysis.[12]

apply this strategy in the current reaction. The investigation of several metal nitrates revealed that the use of 1 equiv of zinc nitrate in the presence of 5 mol % Ag₂O promoted the coupling reaction of phosphine oxides with alkynes, furnishing the phosphorus heterocycles in moderate to good yields (Table 3).[15]

To obtain more insights about the mechanism of the current reaction, a series of experiments were conducted. First, competition reactions between diphenylacetylene **2a** and dipropylacetylene **2b** with diphenylphosphine oxide were carried out. The results indicated that **2a** reacts with diphenylphosphine oxide faster than **2b** (Scheme 1). This finding can be attributed to

Scheme 1. Intermolecular Competition Experiments with Diphenylphosphine Oxide
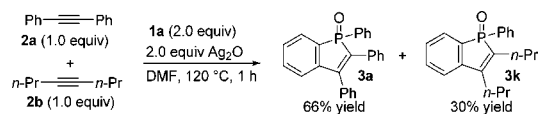

the fact that **2a** is more electron deficient than **2b**. With regard to aryl migration, phosphine oxides with two aryl moieties were examined, and the phenyl group on the phosphorus atom was functionalized at a rate similar to the 4-fluorophenyl ring case but slightly faster than the rate for the 4-methoxylphenyl group (Scheme 2). The kinetic isotope effect was examined through the reaction of deuterated diphenylphosphine oxide with **2a**, and $K_H/K_D = 1.05$ was observed (Scheme 3). This result indicated

## Scheme 2. Intramolecular Competition Experiments with Unsymmetric Diarylphosphine Oxides
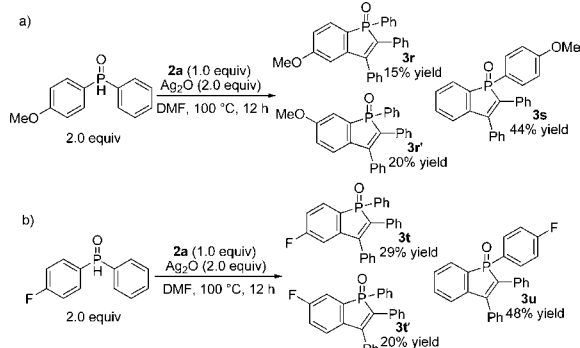
that the C–H bond cleavage on the aryl ring of the phosphine oxide is not involved in the rate-limiting step.[16]

## Scheme 3. Experiments with Isotopically Labeled Compounds
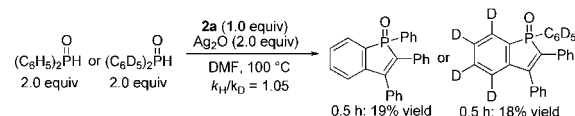
Given that aryl migration is often observed in radical reactions,[13] we proposed a tentative mechanism for the current system (Scheme 4). First, a phosphorus radical is generated from

Scheme 4. Proposed Reaction Pathways
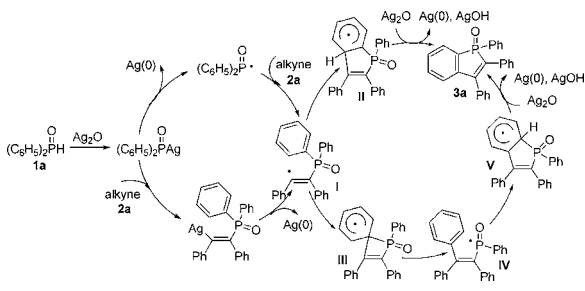
silver diphenylphosphine oxide,[17] and then the radical addition to the alkyne affords an alkenyl radical **I**. Alternatively, **I** also might be generated through the addition of silver diphenylphosphine oxide to alkyne, followed by a silver-induced formation of an alkenyl radical step.[8e,18] Next, the intramolecular addition of the alkenyl radical **I** to the aryl ring at the *ortho* position of the phosphorus atom, followed by the oxidation with Ag$_2$O and the removal of a proton, affords the phosphorus heterocycle **3a**. For the formation of the aryl migration product, the alkenyl radical **I** attacks the aryl ring at the carbon atom directly attached to the phosphorus atom,[13c,d] followed by the C–P bond cleavage, furnishing a phosphorus radical **IV**. Subsequently, radical phosphination on the aryl group that lies at the *cis*-position of the phosphorus atom, in the presence of Ag$_2$O as the oxidant, affords the phosphorus heterocycle with the aryl migration.

To further prove this mechanism, compounds **4a** and **4b** were prepared and examined under the radical cyclization conditions or the current reaction conditions, respectively. The same phosphorus heterocycle **3a** was obtained in both cases (Scheme 5). These results indicated that the steps from intermediate **I** to **II**

Scheme 5. Intramolecular Cyclization Reactions of 4a and 4b
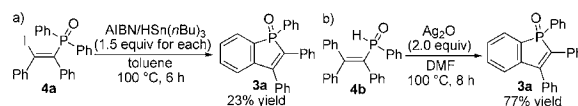
and **3a** or from intermediate **IV** to **3a** are feasible via the radical process. Moreover, the P-centered radicals can be generated from the reaction of disubstituted phosphine oxides with Mn(OAc)$_3$.[19] Thus, the current reaction was carried out with Mn(OAc)$_3$ as the oxidant. Two types of benzo[*b*]phosphole oxides, along with the involvement of aryl migration, were isolated in good yields (Scheme 6), which further support the proposed mechanism in Scheme 4.

Scheme 6. Oxidative Cyclization of Diarylphosphine Oxides Mediated by Mn(OAc)$_3$
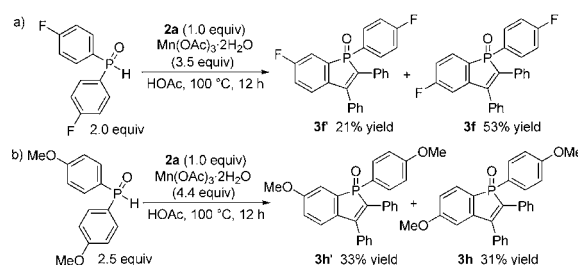
To demonstrate the utility of the current protocol,[20] the reactions of diynes with diphenylphosphine oxide were conducted for the one-step synthesis of the bis(benzo[*b*]-phosphole oxides) (Scheme 7),[21] which has been suggested to

Scheme 7. Applications for the Synthesis of Bis(benzo[*b*]phosphole oxides) 6a and 6b
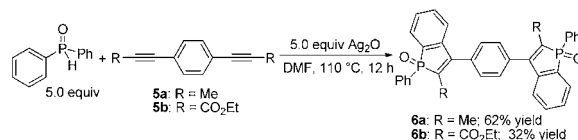
have potential applications in organic electronics.[3a] In addition, the absorption/emission spectra of the obtained benzo[*b*]-phosphole oxides were measured in CH$_2$Cl$_2$, and all the examined compounds showed fluorescence with 0.6–14.5% quantum yields (see the Supporting Information (SI)).

In summary, we have described a Ag-mediated oxidative C–H/P–H functionalization reaction of disubstituted phosphine oxides with internal alkynes, furnishing the benzo[*b*]phosphole oxides with high yields in a simple, efficient way. An unusual aryl migration/cyclization on the P-atom has also been observed and proposed via the radical pathway. Further extension of the current method and application of the obtained P-compounds as the ligand in catalysis will be pursued.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

wlduan@mail.sioc.ac.cn

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

REFERENCES

(1) (a) *Phosphorus Heterocycles II*; Bansal, R. K., Ed.; Topics in Heterocyclic Chemistry; Springer, Berlin, 2010; Vol. 21. (b) *Phosphorus Ligands in Asymmetric Catalysis: Synthesis and Applications*; Börner, A., Ed.; Wiley-VCH: Weinheim, 2008; Vols. *1−3*. (c) *Phosphorus Compounds: Advanced Tools in Catalysis and Material Sciences*; Peruzzini, M., Gonsalvi, L., Ed.; Springer: Berlin, 2011.

(2) Reviews on phospholes: (a) Matano, Y.; Imahori, H. *Org. Biomol. Chem.* 2009, 7, 1258. (b) Mathey, F. *Acc. Chem. Res.* 2004, 37, 954.

(3) (a) Tsuji, H.; Sato, K.; Ilies, L.; Itoh, Y.; Sato, Y.; Nakamura, E. *Org. Lett.* 2008, 10, 2263. (b) Sanji, T.; Shiraishi, K.; Kashiwabara, T.; Tanaka, M. *Org. Lett.* 2008, 10, 2689. (c) Fukazawa, A.; Ichihashi, Y.; Kosaka, Y.; Yamaguchi, S. *Chem.—Asian J.* 2009, 4, 1729. (d) Hayashi, Y.; Matano, Y.; Suda, K.; Kimura, Y.; Nakao, Y.; Imahori, H. *Chem.—Eur. J.* 2012, 18, 15972.

(4) For selected reviews on the synthesis of heterocycles through the C−H bond activation strategy, see: (a) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* 2009, 48, 5094. (b) Gutekunst, W. R.; Baran, P. S. *Chem. Soc. Rev.* 2011, 40, 1976. (c) Stokes, B. J.; Briver, T. G. *Eur. J. Org. Chem.* 2011, 4071. (d) Mei, T.-S.; Kou, L.; Ma, S.; Engle, K. M.; Yu, J.-Q. *Synthesis* 2012, 44, 1778. (e) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* 2012, 51, 8960. (f) Wencel-Delord, J.; Glorius, F. *Nat. Chem.* 2012, 5, 369. (g) Yoshikai, N.; Wei, Y. *Asian J. Org. Chem.* 2013, 2, 466.

(5) For selected examples, see: (a) Würtz, S.; Rakshit, S.; Neumann, J. J.; Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed.* 2008, 47, 7230. (b) Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. N.; Fagnou, K. *J. Am. Chem. Soc.* 2008, 130, 16474. (c) Shi, Z.; Zhang, C.; Li, S.; Pan, D.; Ding, S.; Cui, Y.; Jiao, N. *Angew. Chem., Int. Ed.* 2009, 48, 4572. (d) Bernini, R.; Fabrizi, G.; Sferrazza, A.; Cacchi, S. *Angew. Chem., Int. Ed.* 2009, 48, 8078. (e) Yu, W.; Du, Y.; Zhao, K. *Org. Lett.* 2009, 11, 2417. (f) Stuart, D. R.; Alsabeh, P.; Kuhn, M.; Fagnou, K. *J. Am. Chem. Soc.* 2010, 132, 18326. (g) Chen, J.; Song, G.; Pan, C.-L.; Li, X. *Org. Lett.* 2010, 12, 5426. (h) Guan, Z.-H.; Yan, Z.-Y.; Ren, Z.-H.; Liu, X.-Y.; Liang, Y.-M. *Chem. Commun.* 2010, 46, 2823. (i) Huestis, M. P.; Chan, L.; Stuart, D. R.; Fagnou, K. *Angew. Chem., Int. Ed.* 2011, 50, 1338. (j) Wei, Y.; Deb, I.; Yoshikai, N. *J. Am. Chem. Soc.* 2012, 134, 9098. (k) Shi, Z.; Glorius, F. *Angew. Chem., Int. Ed.* 2012, 51, 9220.

(6) For selected examples, see: (a) Rakshit, S.; Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* 2010, 132, 9585. (b) Zhao, M.; Wang, F.; Li, X. *Org. Lett.* 2012, 14, 1412. (c) Wang, L.; Ackermann, L. *Org. Lett.* 2013, 15, 176. (d) Shi, Z.; Suri, M.; Glorius, F. *Angew. Chem., Int. Ed.* 2013, 52, 4892.

(7) For selected examples, see: (a) Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* 2008, 130, 14058. (b) Lu, Y.; Wang, D.-H.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* 2010, 132, 5916. (c) Guimond, N.; Gouliaras, C.; Fagnou, K. *J. Am. Chem. Soc.* 2010, 132, 6908. (d) Su, Y.; Zhao, M.; Han, K.; Song, G.; Li, X. *Org. Lett.* 2010, 12, 5462. (e) Song, G.; Chen, D.; Pan, C.-L.; Crabtree, R. H.; Li, X. *J. Org. Chem.* 2010, 75, 7487. (f) Lu, Y.; Leow, D.; Wang, X.; Engle, K. M.; Yu, J.-Q. *Chem. Sci.* 2011, 2, 967. (g) Ackermann, L.; Lygin, A. V.; Hofmann, N. *Angew. Chem., Int. Ed.* 2011, 50, 6379. (h) Guimond, N.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* 2011, 133, 6449. (i) Ma, W.; Graczyk, K.; Ackermann, L. *Org. Lett.* 2012, 14, 6318. (j) Deponti, M.; Kozhushkov, S. I.; Yufit, D. S.; Ackermann, L. *Org. Biomol. Chem.* 2013, 11, 142. (k) Cheng, X.-F.; Li, Y.; Su, Y.-M.; Yin, F.; Wang, J.-Y.; Sheng, J.; Vora, H. U.; Wang, X.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* 2013, 135, 1236.

(8) (a) Kuninobu, Y.; Yoshida, T.; Takai, K. *J. Org. Chem.* 2011, 76, 7370. (b) Hou, C.; Ren, Y.; Lang, R.; Hu, X.; Xia, C.; Li, F. *Chem. Commun.* 2012, 48, 5181. (c) Wang, C.-B.; Bian, Y.-J.; Mao, X.-R.; Huang, Z.-Z. *J. Org. Chem.* 2012, 77, 7706. (d) Wang, H.; Li, X.; Wu, F.; Wan, B. *Synthesis* 2012, 44, 941. (e) Sun, M.; Wang, H.-L.; Ting, Q.-P.; Yang, S.-D. *Angew. Chem., Int. Ed.* 2013, 52, 3972. (f) Feng, C.-G.; Ye, M.; Xiao, K.-J.; Li, S.; Yu, J.-Q. *J. Am. Chem. Soc.* 2013, 135, 9322.

(9) For reviews on orthometalation of C−H bond, see: (a) Albrecht, M. *Chem. Rev.* 2010, 110, 576. (b) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* 2010, 110, 624. (c) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* 2012, 41, 3651. For reviews on application of phosphine oxides in metal-catalyzed reactions, see: (d) Dubrovina, N. V.; Börner, A. *Angew. Chem., Int. Ed.* 2004, 43, 5883. (e) Shaikh, T. M.; Weng, C.-M.; Hong, F.-E. *Coord. Chem. Rev.* 2012, 256, 771.

(10) For recent examples of the synthesis of heterocycles through silver-mediated oxidative cyclization processes, see: (a) He, C.; Guo, S.; Ke, J.; Hao, J.; Xu, H.; Chen, H.; Lei, A. *J. Am. Chem. Soc.* 2012, 134, 5766. (b) He, C.; Hao, J.; Xu, H.; Mo, Y.; Liu, H.; Han, J.; Lei, A. *Chem. Commun.* 2012, 48, 11073.

(11) The use of 1 equiv of arylphosphine oxides afforded the products in relatively low yields (around 50%). It may be due to the presence of oxidation side reactions of the arylphosphine oxides into the arylphosphinic acids by silver oxidants.

(12) For X-ray crystal data, see SI for details.

(13) For reviews on radical aryl migration reactions, see: (a) Studer, A.; Bossart, M. *Tetrahedron* 2001, 57, 9649. (b) Bowman, W. R.; Storey, J. M. D. *Chem. Soc. Rev.* 2007, 36, 1803. For examples of intramolecular radical arylation of phosphinates with the C−P bond cleavage, see: (c) Clive, D. L. J.; Kang, S. *Tetrahedron Lett.* 2000, 41, 1315. (d) Clive, D. L. J.; Kang, S. *J. Org. Chem.* 2001, 66, 6083.

(14) An alternative explanation for the observed regioselectivity is that the formed alkenyl radicals can be better stabilized by the adjacent aryl groups than the alkyl groups.

(15) For the related experimental data in Table 1 by Method B, see SI for details.

(16) For a review on the interpretation of deuterium kinetic isotope effects in C−H bond functionalization, see: Simmons, E. M.; Hartwig, J. F. *Angew. Chem., Int. Ed.* 2012, 51, 3066.

(17) Hunt, B. B.; Saunders, B. C. *J. Chem. Soc.* 1957, 2413.

(18) For examples of Ag-promoted generation of the trifluoromethyl radical and nitro radical, see: (a) Ye, Y. D.; Lee, S. H.; Sanford, M. S. *Org. Lett.* 2011, 13, 5464. (b) Maity, S.; Manna, S.; Rana, S.; Naveen, T.; Mallick, A.; Maiti, D. *J. Am. Chem. Soc.* 2013, 135, 3355.

(19) For a review on the use of manganese(III) acetate in organic synthesis, see: (a) Demir, A. S.; Emrullahoglu, M. *Curr. Org. Synth.* 2007, 4, 321. For selected examples, see: (b) Tayama, O.; Nakano, A.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* 2004, 69, 5494. (c) Kagayama, T.; Nakano, A.; Sakaguchi, S.; Ishii, Y. *Org. Lett.* 2006, 8, 407. (d) Mu, X.-J.; Zou, J.-P.; Qian, Q.-F.; Zhang, W. *Org. Lett.* 2006, 8, 5291. (e) Pan, X.-Q.; Zou, J.-P.; Zhang, G.-L.; Zhang, W. *Chem. Commun.* 2010, 46, 1721. (f) Zhou, J.; Zhang, Z.-G.; Zou, J.-P.; Zhang, W. *Eur. J. Org. Chem.* 2011, 3412. (g) Pan, X.-Q.; Wang, L.; Zou, J.-P.; Zhang, W. *Chem. Commun.* 2011, 47, 7875. (h) Wang, G.-W.; Wang, C.-Z.; Zou, J.-P. *J. Org. Chem.* 2011, 76, 6088.

(20) For applications of the obtained products and its derivatives as the catalysts in the asymmetric double aldol reaction and gold-catalyzed cyclization reaction, see the SI for details.

(21) **6a** and **6b** may be generated as a mixture of diastereomers. The ratios cannot be determined due to the overlap in the NMR spectra.