Organic LETTERS

Letter

pubs.acs.org/OrgLett

Direct Interconversion of BINOL and H8-BINOL-Based Chiral Brønsted Acids Using Single-Step Red/Ox Manipulations

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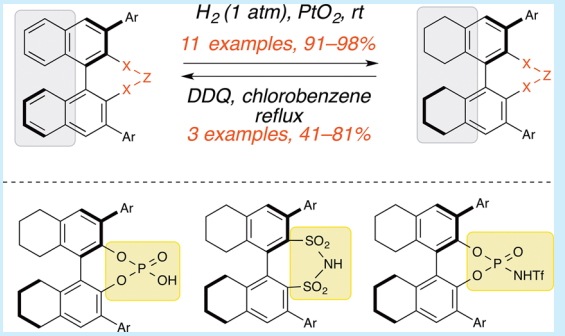
Supporting Information

ABSTRACT: A direct single-step hydrogenation of BINOL-based chiral phosphoric acids, *N*-triflyl phosphoramides, and disulfonimides to the corresponding H8-BINOL Brønsted acids in excellent yields and chemoselectivities is described. In addition, the conditions for the single-step oxidation of H8-BINOL-based Brønsted acids into the corresponding BINOL-based acids have been identified and employed to accomplish these interconversions in 41−81% yield.



In the past decades, chiral organic Brønsted acids have emerged as powerful and broadly applicable catalysts for a variety of asymmetric transformations.[1] In particular, chiral phosphoric acid (CPA) catalysis has received constantly increasing attention in recent years.[2] Since the pioneering work by the Akiyama and Terada groups in 2004 highlighted the utility of BINOL-derived CPA catalysts in asymmetric Mannich reactions,[3] the BINOL scaffold has served as the central element for phosphoric acid-based catalyst design (**1**, Figure 1). The key general features of this scaffold that make it

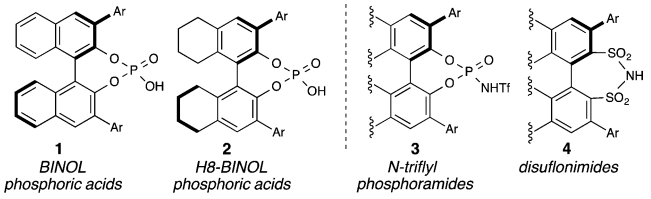


Figure 1. Examples of BINOL and H8-BINOL-based chiral Brønsted acids.

of particular importance not only to CPA catalysis but also to asymmetric catalysis, in general, include its high degree of tunability, conformational rigidity, and C_2 symmetry. In addition to phosphate, other types of functionalities can be appended to the BINOL scaffold to enhance the Brønsted acidity of the catalyst. For example, BINOL-based *N*-triflyl phosphoramides (**3**)[4] and disulfonimides (**4**)[5] have recently been developed as more powerful alternatives to CPAs.[1,2]

Among the other C_2-symmetric scaffolds that have been utilized in CPA catalysis,[6] the related H8-BINOL scaffold **2** is one of the most frequently used alternatives to BINOL.[1,2] H8-BINOL-derived CPAs **2** possess the same key features of their fully aromatic counterparts **1** but possess different solubilities, acidities, and racemization profiles as well as different geometries and bite angles. Although BINOL and H8-BINOL-based catalysts are structurally related, their preparation is achieved via two distinct synthetic sequences each requiring 5−10 steps (Scheme 1). As the optimization of asymmetric reactions often requires the introduction of alternative substituents at the 3 and 3′ positions of CPA, various direct (**5a** and **6a**) and inverse (**5b** and **6b**) coupling methods resulting in arylated BINOL precursors **7** have been developed.

These cross-coupling reactions could be challenging, and alternative strategies (i.e., using the **5b** and **6b** approach instead of **5a** and **6a** coupling) may be required for the construction of H8-BINOL-based **7** with the same 3,3′-substituents as the corresponding BINOL-based **7**. This significantly complicates the catalyst-screening/optimization part of an asymmetric reaction development as the introduction of new structural elements in both H8-BINOL and BINOL-based catalysts may require considerable synthetic efforts. Similarly, various methods exist for the synthesis of BINOL-based disulfonimides from iodide **9**, which could be derived from BINOL or BINAM in five to six steps.[5] Compound **9** can be subjected to Suzuki cross-couplings with boronic acids **6a** to provide functionalized disulfonimides **4a** in one step. To our knowledge, no approach to H8-BINOL-based disulfonimides **4b** has been described to date, and most likely such catalysts would be accessible in a similar number of steps.

Based on our prior experiences in chiral Brønsted acid catalysis,[7] we proposed a more straightforward way to generate H8-BINOL Brønsted acids from the corresponding BINOL-based catalysts (Scheme 1). As the unfunctionalized H8-

Received: June 16, 2015

DOI: 10.1021/acs.orglett.5b01754
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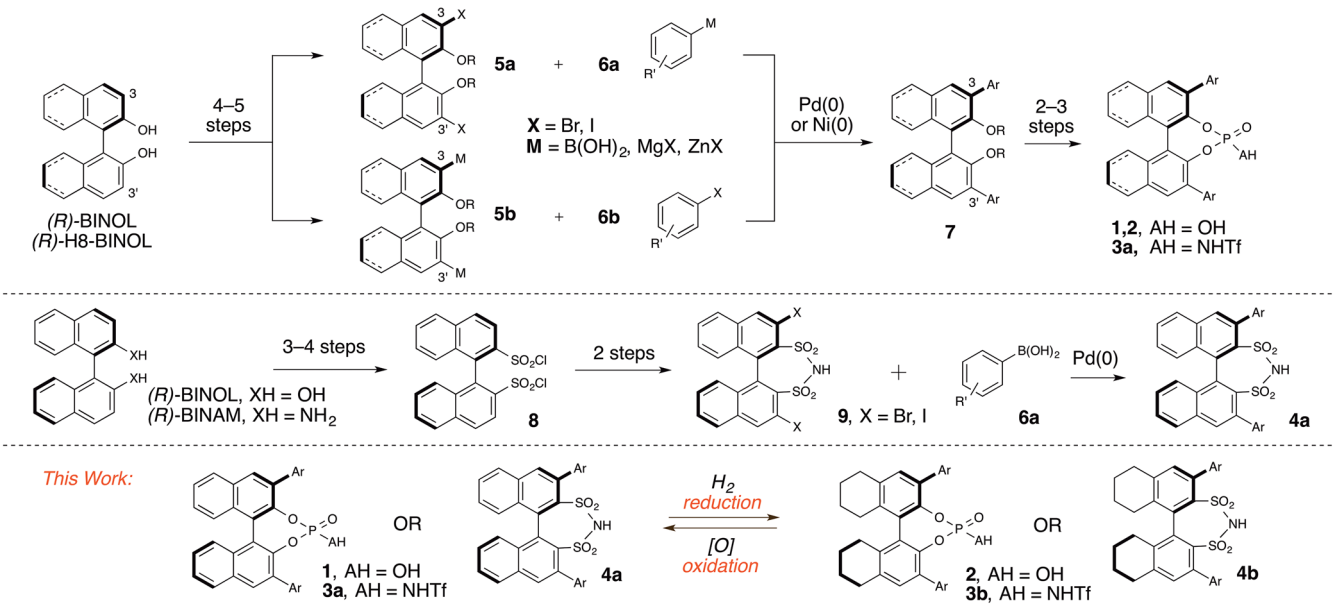
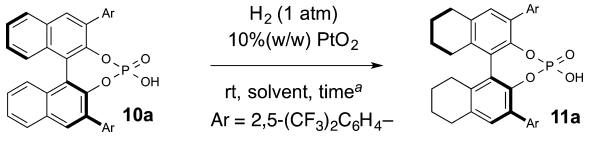
Scheme 1. Strategies for the Synthesis of BINOL and H8-BINOL



BINOL could be prepared by hydrogenation of BINOL without significant racemization,[8] we surmised that a related transformation could be executed with the functionalized phosphoric acids in a single step. Similarly, the reverse transformation could be accomplished if H8-BINOL-based catalysts are exposed to dehydrogenation conditions without affecting the phosphate functionality and the majority of commonly employed 3,3′-substituents. While these single-step transformations can significantly improve the accessibility of Brønsted acid catalysts, such a strategy, to our knowledge, has not been previously explored.

Our studies commenced with investigation of the possibility of hydrogenating phosphoric acid **10a** in the presence of PtO_2, previously employed for the conversion of BINOL into H8-BINOL (Table 1).[9] Considering that BINOL-based CPAs display a wide range of solubilities in organic solvents, various solvent systems were investigated (entries 1−7, Table 1). While **10a** is soluble in acetone, DCM, benzene, or DMF, no reduction was observed at rt after 24 h (entries 1−4). The reaction in EtOAc resulted in the formation of **11a** in 26% after 3 days (entry 5), and no reduction of the phosphate or 3,3′-aryl substituents was noted. The corresponding hydrogenations proceeded significantly faster in the presence of the protic solvents such as AcOH or $MeOH/CH_2Cl_2$ (entries 6 and 7) and were accomplished in quantitative yields. With the optimal hydrogenation conditions in hand, the scope of this transformation was investigated next (Table 2).

Table 1. Proposed Direct Interconversion of BINOL and H8-BINOL-Based Chiral Brønsted Acids



entry	solvent	time, h	yield, %
1	acetone	24	<5%[b]
2	CH_2Cl_2	24	<5%[b]
3	benzene	24	<5%[b]
4	DMF	24	<5%[b]
5	EtOAc	72	26%[c]
6	AcOH	24	98%[d]
7	$MeOH/CH_2Cl_2$	16	98%[d]

[a]The reactions were performed on a 0.013 mmol scale (0.05 M). [b]Determined by ^{1}H NMR. [c]Determined by ^{1}H NMR using 1,2-dichloroethane as the internal standard. [d] Isolated yields.

In order to test the scalability of the hydrogenation, the reduction of 2,4-bis(trifuloromethyl)phenyl-substituted CPA **10a** was repeated (entry 1) on a 1.0 g scale (98% yield). Similarly, the reaction with unsubstituted acid **10b** proceeded selectively without overreduction of the hydrogen phosphate functionality. Importantly, neither **10a** nor **10b** was found to racemize under the reaction conditions (see the Supporting Information).

The acids with electron-withdrawing (entries 3−6) and electron-donating (entries 7−9) substituents in the meta-position were examined next. The reduction of 3,5-bis-(trifluoromethyl)phenyl-substituted acid **10c** and 3,5-bis-(pentafluoro-l_6-sulfanyl)phenyl-substituted acid **10d** proceeded smoothly and selectively in quantitative yield.

Furthermore, while the reduction of 3,5-difluorophenyl-substituted acid **10e** proceeded smoothly, the reduction of 3,5-dichlorophenyl-substituted acid **10f** resulted in a mixture of products due to dechlorination followed by the reduction of resultant phenyl rings. Similar to the prior observations, CPAs containing phenyl groups with bulky *t*-Bu- and *i*-Pr-substituents in *meta*-positions (entries 7 and 8) were selectively reduced to provide the corresponding H8-BINOL acids in excellent yields. However, the 3,3′-aryl substituent diastereomeric overreduction products were obtained for less hindered acid **10i**. To our delight, frequently used in asymmetric catalysis catalysts **10j** and **10k** containing bulky substituents at the *ortho*- and *para*-positions underwent efficient reduction as well (entries 10 and 11). Considering that the corresponding H8-BINOL-based acids **11j** and **11k** require challenging syntheses, the described protocol can be used for a single-step preparation of these catalysts from the commercially available catalysts **10j** and **10k**.

DOI: 10.1021/acs.orglett.5b01754
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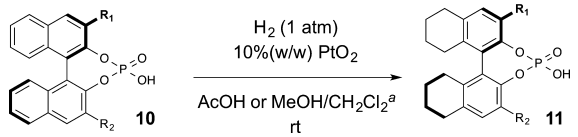
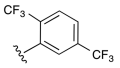
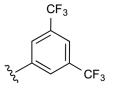
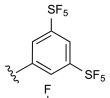
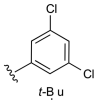
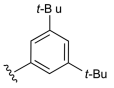
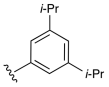
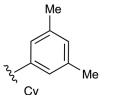
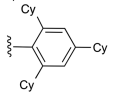
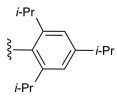
Table 2. Formation of H8-BINOL-Based CPA from BINOL-Based CPAs



entry	substrate	solvent	time, h	yield, %[b]
1	**10a**, R_1, R_2 = 	AcOH	17	>98 (1.0 g)[c]
2	**10b**, R_1, R_2 = H	$MeOH/CH_2Cl_2$ (2:3)	16	>98
3	**10c**, R_1, R_2 = 	$MeOH/CH_2Cl_2$ (1:1)	17	>98[d]
4	**10d**, R_1, R_2 = 	$MeOH/CH_2Cl_2$ (1:1)	17	>98[d]
5	**10e**, R_1, R_2 = 	$MeOH/CH_2Cl_2$ (2:3)	17	>98
6	**10f**, R_1, R_2 = 	$MeOH/CH_2Cl_2$ (2:3)	17	–[e]
7	**10g**, R_1, R_2 = 	$MeOH/CH_2Cl_2$ (2:3)	17	96
8	**10h**, R_1, R_2 = 	$MeOH/CH_2Cl_2$ (2:3)	16	>98
9	**10i**, R_1, R_2 = 	$MeOH/CH_2Cl_2$ (1:1)	17	–[f]
10	**10j**, R_1, R_2 = 	$MeOH/CH_2Cl_2$ (2:3)	17	91[g]
11	**10k**, R_1, R_2 = 	$MeOH/CH_2Cl_2$ (2:3)	17	>98[g]

[a]The reactions were performed on a 0.013 mmol scale (0.04–0.05 M). [b]Isolated yields (average of two runs). [c]The reaction was performed on a 1.29 mmol scale. [d]The reactions were performed on a 0.026 mmol scale. [e]A complex mixture consisting of dechlorination and 3,3′-substituent overreduction products was observed. [f]A complex mixture consisting of 3,3′-substituent overreduction products was observed. [g]20% (w/w) of PtO_2, 0.01 M concentration was used.

The protonation state of the phosphoric acid had a dramatic effect on the rate of hydrogenation in the aforementioned studies. Thus, a filtration through silica gel produced significantly less reactive form of CPA, probably, due to the formation of Na^+ and Ca^{2+} salts that poison the catalyst.[10] On the other hand, washing the CPA with hydrochloric acid prior to reduction was found to improve the rate of hydrogenation in some cases.

To demonstrate that this approach is applicable to the interconversion of other types of Brønsted acids, the formation of H8-BINOL acids **13**–**15** was investigated (Figure 2). The reductions leading to *N*-triflyl phosphoramide **13** and disulfonimide **15** proceeded chemoselectively in excellent yields. However, the formation of the *N*-triflyl thiophosphoramide **14** was not observed, probably due to catalyst poisoning by sulfur. To our knowledge, the synthesis of **15** represents the

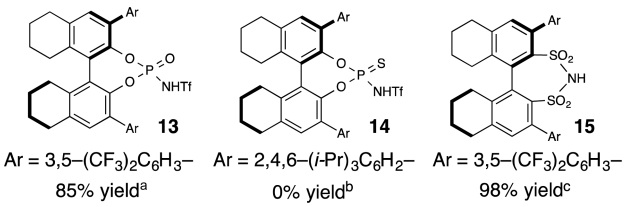
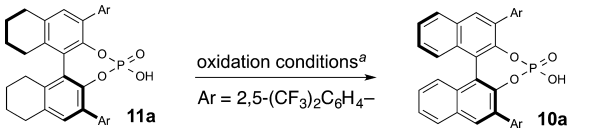


Figure 2. Formation of the other types of H8-BINOL-based chiral Brønsted Acids. Conditions: The reactions were conducted on 0.026 mmol scale in AcOH (0.07 M). The yields represent an average of two runs. (a) Conducted with 5% (w/w) of PtO_2 for 18 h. (b, c) Reactions were conducted with 10% (w/w) of PtO_2 for 16 h.

first synthesis of H8-BINOL-based disulfonimides, and the alternative multistep approach to **15** from H8-BINOL is yet to be developed.

The reverse reaction (i.e., converting H8-BINOL acids to BINOL acids) was investigated next (Table 3). The H8-BINOL

Table 3. Proposed Direct Interconversion of BINOL and H8-BINOL-Based Chiral Brønsted Acid



entry	conditions	conversion, % (yield, %)
1	Pd/C, diglyme, reflux, 14 h	decomposition
2	V_2O_5 (8.8 equiv), AcOH, reflux, 12 h	0
3	V_2O_5 (8.4 equiv), SiO_2, toluene, reflux, 12 h	0
4	DDQ (8 equiv), xylenes, reflux, 18 h	0
5	DDQ (8 equiv), 1,4-dioxane, reflux, 18 h	~25 (n.d.)[b]
6	DDQ (8 equiv), chlorobenzene, reflux, 15 h	>98 (74)[c]

[a]The reactions were performed on a 0.013 mmol scale (0.05 M). [b]Conversion was determined by MS; partial dehydrogenation was noted. [c]Performed on a 0.026 mmol scale.

CPA **11a** was subjected to a variety of oxidants known to convert 1,2,3,4-tetrahydronaphthalenes into the corresponding naphthalenes. While the dehydrogenation with Pd/C in refluxing diglyme[11] resulted in decomposition due to dephosphorylation as well as other pathways (entry 1), the oxidations with V_2O_5[12] did not result in any reaction, and only starting material **11a** was observed (entries 2 and 3). Similarly, the oxidation with DDQ[13] in xylenes at reflux provided no conversion (entry 4), while a similar reaction in 1,4-dioxane resulted in some partial dehydrogenation leading to product **10a** (~25%, entry 5). Finally, the oxidation with DDQ (8 equiv) in refluxing chlorobenzene resulted in clean formation of the desired product **10a** in 74% isolated yield. Similar to the oxidation of **11a**, additional H8-BINOL Brønsted acids (**13** and **15**) were efficiently converted to the corresponding BINOL derivatives **16** and **17** (Figure 3). To our knowledge, these are the most complex derivatives of H8-BINOL that have been successfully dehydrogenated to date.[12b]

In summary, we have developed a new approach that allows a direct reduction of BINOL-based Brønsted acids to the corresponding H8-BINOL-based catalysts. This reduction tolerates various electron-withdrawing and bulky substituents on 3,3′-aromatic rings and could be applied to the selective formation of chiral phosphates, *N*-triflyl phosphoramides, and

DOI: 10.1021/acs.orglett.5b01754
Org. Lett. XXXX, XXX, XXX–XXX

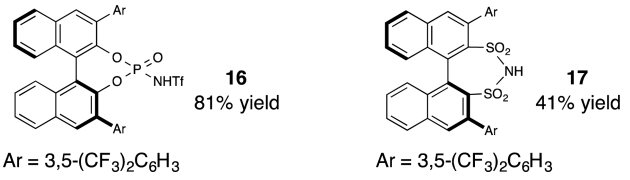


Figure 3. Oxidative formation of BINOL-based chiral Brønsted acids from H8-BINOL based Brønsted acids. Conditions: The reactions were performed on a 0.026 mmol scale with DDQ (8 equiv) in chlorobenzene (**16**) or dichlorobenzene (**17**) (0.05 M) at reflux for 15 h. The yields represent an average of two runs.

disulfonimides. The reverse transformation allowing the oxidation of H8-BINOL-based catalysts into BINOL-based catalysts has also been demonstrated using DDQ as the oxidant. The outlined strategy would allow a rapid diversification of the existing libraries of Brønsted acids and will expand the availability of BINOL and H8-BINOL-based Brønsted acid catalysts for asymmetric transformations.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01754.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work has been supported by the National Science Foundation CAREER Award (CHE-1350060). PN is a Sloan Foundation Fellow.

■ REFERENCES

(1) Selected reviews: (a) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (b) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (c) Yamamoto, H.; Boxer, M. *Chimia* **2007**, *61*, 279.

(2) Selected reviews: (a) Terada, M. *Synthesis* **2010**, *12*, 1929. (b) Zamfir, A.; Schenker, S.; Freund, M.; Tsogoeva, S. B. *Org. Biomol. Chem.* **2010**, *8*, 5262. (c) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev.* **2014**, *114*, 9047.

(3) (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566. (b) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356.

(4) Nakashima, D.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 9626.

(5) (a) Garcia-Garcia, P.; Lay, F.; Rabalakos, C.; List, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 4363−4366. (b) Treskow, M.; Neudorfl, J.; Giernoth, R. *Eur. J. Org. Chem.* **2009**, *2009*, 3693. van Gemmeren, M.; Lay, F.; List, B. *Aldrichimica Acta* **2014**, *47*, 3.

(6) Selected examples of other C_2-symmetric CPAs: SPINOL: (a) Coric, I.; Muller, S.; List, B. *J. Am. Chem. Soc.* **2010**, *132*, 17370. (b) Xu, F.; Huang, D.; Shen, W.; Lin, X.; Wang, Y. *J. Org. Chem.* **2010**, 75, 8677. VINOL and VAPOL: (c) Desai, A. A.; Huang, L.; Wulff, W. D.; Rowland, G. B.; Antilla, J. C. *Synthesis* **2010**, *2010*, 2106. CPAs with multiple chiral axes: (d) Momiyama, N.; Konno, T.; Furiya, Y.; Iwamoto, T.; Terada, M. *J. Am. Chem. Soc.* **2011**, *133*, 19294. (e) Guo, Q.-S.; Du, D.-M.; Xu, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 759.

(7) (a) Sun, Z.; Winschel, G. A.; Borovika, A.; Nagorny, P. *J. Am. Chem. Soc.* **2012**, *134*, 8074. (b) Nagorny, P.; Sun, Z.; Winschel, G. A. *Synlett* **2013**, *24*, 661. (c) Borovika, A.; Nagorny, P. *Tetrahedron* **2013**, *69*, 5719. (d) Mensah, E.; Camasso, N.; Kaplan, W.; Nagorny, P. *Angew. Chem., Int. Ed.* **2013**, *52*, 12932. (e) Borovika, A.; Tang, P.-I.; Klapman, S.; Nagorny, P. *Angew. Chem., Int. Ed.* **2013**, *52*, 13424. (f) Bhattarai, B.; Tay, J.-H.; Nagorny, P. *Chem. Commun.* **2015**, *51*, 5398. (g) Sun, Z.; Winschel, G. A.; Zimmerman, P.; Nagorny, P. *Angew. Chem., Int. Ed.* **2014**, *53*, 11194.

(8) Cram, D. J.; Helgeson, R. C.; Peacock, S. C.; Kaplan, L. J.; Domeier, L. A.; Moreau, P.; Koga, K.; Mayer, J. M.; Chao, Y.; Siegel, M. G.; Hoffman, D. H.; Sogah, G. D. Y. *J. Org. Chem.* **1978**, *43*, 1930.

(9) McDougal, N. T.; Trevellini, W. L.; Rodgen, S. A.; Kliman, L. T.; Schaus, S. E. *Adv. Synth. Catal.* **2004**, *346*, 1231.

(10) Klussmann, M.; Ratjen, L.; Hoffmann, S.; Wakchaure, V.; Goddard, R.; List, B. *Synlett* **2010**, *14*, 2189.

(11) Bergman, J.; Pelcman, B. *Tetrahedron* **1988**, *44*, 5215.

(12) Karki, M.; Araujo, H. C.; Magolan, J. *Synlett* **2013**, *24*, 1675.

(13) Dehydrogenation with quinones: (a) Braude, E. A.; Brook, A. G.; Linstead, R. P. *J. Chem. Soc.* **1954**, 3569. Dehydrogenation of BINAM derivatives: (b) Kano, T.; Tanaka, Y.; Osawa, K.; Yurino, T.; Maruoka, K. *J. Org. Chem.* **2008**, *73*, 7387.

DOI: 10.1021/acs.orglett.5b01754
Org. Lett. XXXX, XXX, XXX−XXX