OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

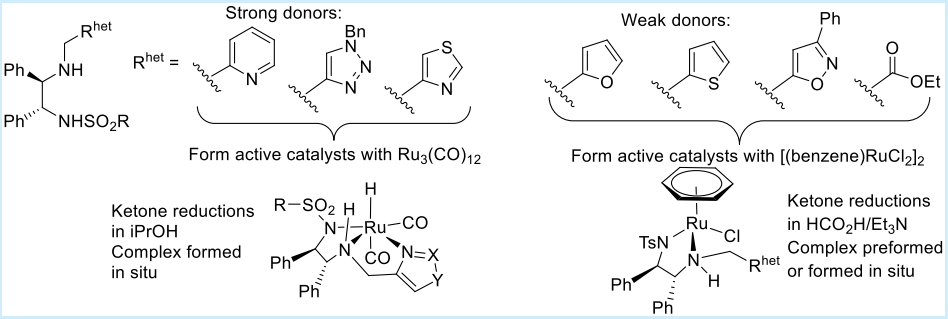
Probing the Effects of Heterocyclic Functionality in [(Benzene)Ru(TsDPENR)Cl] Catalysts for Asymmetric Transfer Hydrogenation

Jonathan Barrios-Rivera,[†] Yingjian Xu,*[,‡] and Martin Wills*[,†]

[†]Department of Chemistry, University of Warwick, Coventry, CV4 7AL, United Kingdom

[‡]GoldenKeys High-Tech Materials Co., Ltd., Building B, Innovation & Entrepreneurship Park, Guian New Area, Guizhou Province 550025, China

Supporting Information



ABSTRACT: A range of TsDPEN catalysts containing heterocyclic groups on the amine nitrogen atom were prepared and evaluated in the asymmetric transfer hydrogenation of ketones. Bidentate and tridentate ligands demonstrated a mutual exclusivity directly related to their function as catalysts. A broad series of ketones were reduced with these new catalysts, permitting the ready identification of an optimal catalyst for each substrate and revealing the subtle effects that changes to nearby donor groups can exhibit.

The [(arene)Ru(TsDPEN)Cl] class of precatalyst (**1**) for asymmetric transfer hydrogenation (ATH) of ketones and imines, first reported by Noyori et al.,[1] are now established reagents for synthetic chemists.[2] Although the parent compounds contain a TsDPEN ligand with a primary amine bound to the Ru(II), it is known that one substituent can be added to the amine atom, i.e., in complexes **2**, without causing lack of activity (Figure 1),[3−13] and in some cases a higher activity, notably to C═N reduction, is observed.[5,6,11−13] Functional groups on the amine atom of TsDPEN can also provide a means for tuning the structures of complexes to particular substrates[6,11−13] and to modify the properties of the complexes, e.g., to improve their water solubility or assist extraction from a mixture.[9,10,14]

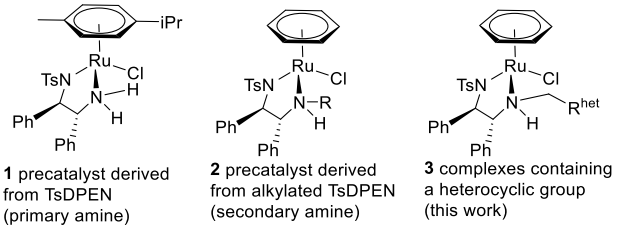


Figure 1. [(Arene)Ru(TsDPEN)Cl] ATH precatalyst derivatives.

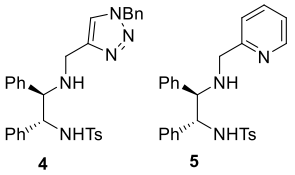


Figure 2. Reported ligands for ATH using $Ru_3(CO)_{12}$.

However, very little work has been reported on the functionalization of Ru/TsDPEN catalysts with heterocyclic functionality on the amine atom, which would offer further possibilities for wider synthetic applications. We previously reported that TsDPEN derivatives **4** and **5**, containing a triazole or pyridine group, respectively, form active complexes for ATH with $Ru_3(CO)_{12}$ which are capable of ATH of ketones in IPA (Figure 2).[15,16] However, these have not been investigated as components of [(arene)Ru(TsDPENR)Cl] precatalysts, and neither has the wider applications of these ligands.

To gain a further understanding of the effect of functionalizing the TsDPEN ligand with a heterocyclic group on catalysis with both [(arene)Ru(TsDPENR)Cl] and

Received: July 8, 2019

DOI: 10.1021/acs.orglett.9b02339
Org. Lett. XXXX, XXX, XXX−XXX

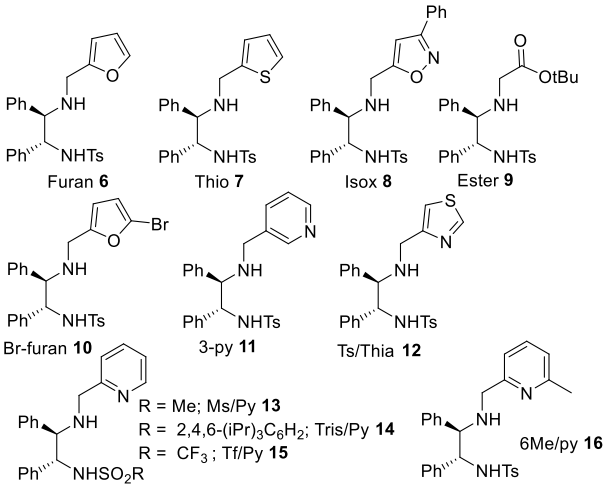


Figure 3. New ligands investigated in this project.

Table 1. Application of Ligands in Figure 3 to ATH of Acetophenone using $Ru_3(CO)_{12}$[a]

ligand	conv (%)	ee (%)[b]
4	98	92
5	87	92
Ts/Thia **12**	90	83
Ms/Py **13**	55	82
Tris/Py **14**	79	73
Tf/Py **15**	95	93
6Me/py **16**	49	76

[a]1 mol % ligand, 0.33 mol % $Ru_3(CO)_{12}$, iPrOH, 80 °C, 48h, [S] = 0.1M. [b]*R*-configuration product formed.

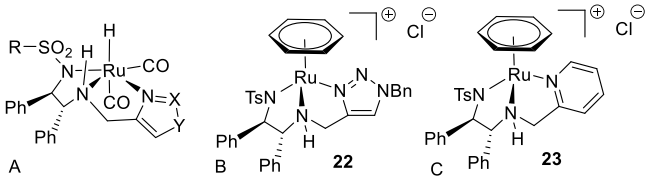


Figure 4. (A) Likely active complex formed between tridentate ligands and $Ru_3(CO)_{12}$.[15,16] (B,C) Inert tridentate complexes **22** and **23** formed by reaction of ligands **4** and **5** respectively with $[(benzene)RuCl_2]_2$.

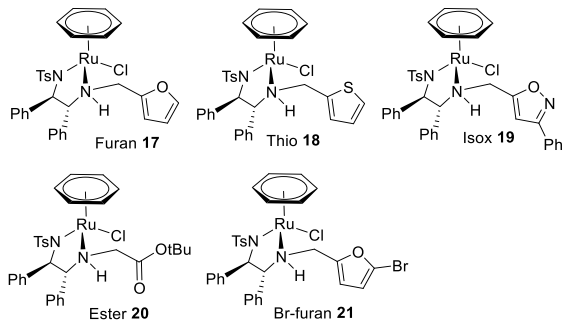


Figure 5. Complexes **17**−**21** prepared from weak donor heterocycle derivatives of TsDPEN and isolated.

$Ru_3(CO)_{12}$, we prepared a diverse series of derivatives (*R*,*R*)-**6**−**16** which contain alternative donor groups (Figure 3). Ligand **6**, **7**, **9**, and **11**−**16** were prepared through the reductive amination of (*R*,*R*)-TsDPEN with the corresponding aldehyde. Ligand **8** was prepared by the cycloaddition of the nitrile oxide PhCNO with a propargyl-substituted TsDPEN. Ligand **10** was prepared by the reaction of TsDPEN with *t*-butylbromoacetate.

Table 2. Application of Catalysts in Figure 5 to ATH of Acetophenone in [(Benzene)Ru(TsDPENR)Cl] Complexes[a]

ligand	[S] (M)	time (h)	conv (%)	ee (%)[b]
Ts/Furan **17**	1	72	95	90
Ts/Thio **18**	1	72	56	93
Ts/Isox **19**	1	72	99	95
Ts/ester **20**	1	95	60	96
Ts/BrFuran **21**	1	86	73	95
Ts/Furan **17**	2	24	99	92
Ts/Thio **18**	2	24	98	92
Ts/Isox **19**	2	72	96	90
Ts/ester **20**	2	156	90	93

[a]1 mol % **17**−**21**, 5:2 HCO_2H/Et_3N, rt. [b]*R*-configuration product formed.

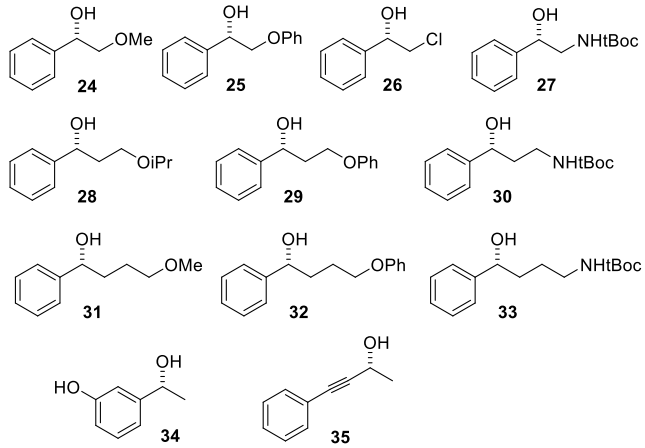


Figure 6. Products of ATH of substituted ketones using **4** or **5**/$Ru_3(CO)_{12}$ and complexes **17**−**20** (Table 3).

We first evaluated the new ligands in the ATH reaction with $Ru_3(CO)_{12}$ (Table 1), along with tests of **4** and **5** as control reactions. We were surprised to find that ligands **6**−**11** did not form active catalysts, whereas all of ligands **12**−**16** did. The unreactive ligands all contain weaker donor atoms (**6**−**10**) or more distal heteroatoms (**11**) and cannot form strong tridentate complexes with $Ru_3(CO)_{12}$. We had previously found that a benzyl group on the TsDPEN was also not an effective catalyst, and these results align with this observation.[15] It can be concluded that, for this application, a ligand requires a third heteroatom containing a strong donor atom which can form a tridentate complex (Figure 4) which acts as the catalyst in the reaction. As previously described, the hydrogen transfer mechanism is likely to involve a bifunctional catalysis mechanism,[15,16] similar to that reported for complex **1**.[17]

Because the results suggested that the non N-donating heterocycles were weak donors, we examined the preparation of derivatives of the catalysts with $[(Benzene)RuCl_2]_2$ in the anticipation that, provided the heterocycle did not coordinate to the metal, that it would not hinder the generation of an active catalyst. The use of benzene as the η^6-ligand in the complex is important, as we have previously found that the use

DOI: 10.1021/acs.orglett.9b02339
Org. Lett. XXXX, XXX, XXX−XXX

Table 3. Application of Catalysts to ATH for the Synthesis of Products 24−35[a]

reduction product/ catalyst	time (h)	conv (%)	yield (%)	ee (%)	*R*/*S*
24/**4**/$Ru_3(CO)_{12}$	nr[b,c]				
24/**5**/$Ru_3(CO)_{12}$	nr[b,c]				
24/Furan **17**	120		84	94	*S*
24/Thio **18**	120		41	91	*S*
24/Isox **19**	144		74	92	*S*
24/Ester **20**	168	82	79	91	*S*
25/**4**/$Ru_3(CO)_{12}$	72	100	94	81	*S*
25/**5**/$Ru_3(CO)_{12}$	72	100	96	53	*S*
25/Furan **17**	72	100	71	92	*S*
25/Thio **18**	120	98	89	94	*S*
25/Isox **19**	96	100	91	90	*S*
25/Ester **20**	144	100	97	92	*S*
26/**4**/$Ru_3(CO)_{12}$	nr[b,c]				
26/**5**/$Ru_3(CO)_{12}$	nr[b,c]				
26/Furan **17**	96	99	91	90	*S*
26/Thio **18**	96	100	79	89	*S*
26/Isox **19**	96	99	87	91	*S*
26/Ester **20**	168	94	86	91	*S*
27/**4**/$Ru_3(CO)_{12}$	72	100	99	97	*S*
27/**5**/$Ru_3(CO)_{12}$	72	100	92	94	*S*
27/Furan **17**	120	100	94	95	*S*
27/Thio **18**	120	100	95	96	*S*
27/Isox **19**	120	100	95	93	*S*
27/Ester **20**	168	98	91	95	*S*
28/**4**/$Ru_3(CO)_{12}$	72	100	95	99	*R*
28/**5**/$Ru_3(CO)_{12}$	72	100	96	99	*R*
28/Furan **17**	120	80	70	89	*R*
28/Thio **18**	132	52	45	92	*R*
28/Isox **19**	120	87	73	94	*R*
28/Ester **20**	168	55	41	96	*R*
29/**4**/$Ru_3(CO)_{12}$	72	100	98	86	*R*
29/**5**/$Ru_3(CO)_{12}$	72	100	96	90	*R*
29/Furan **17**	120	98	94	91	*R*
29/Thio **18**	120	50	41	87	*R*
29/Isox **19**	144	100	93	91	*R*
29/Ester **20**	168	72	70	90	*R*
30/**4**/$Ru_3(CO)_{12}$	72		95	92	*R*
30/**5**/$Ru_3(CO)_{12}$	72		88	91	*R*
30/Furan **17**	120	95	88	91	*R*
30/Thio **18**	120	52	41	91	*R*
30/Isox **19**	144	85	84	92	*R*
30/Ester **20**	144	96	92	96	*R*
31/**4**/$Ru_3(CO)_{12}$	72	99	91	83	*R*
31/**5**/$Ru_3(CO)_{12}$	72	71	66	92	*R*
31/Furan **17**	144	89	70	88	*R*
31/Thio **18**	144	55	49	84	*R*
31/Isox **19**	168	66	57	90	*R*
31/Ester **20**	168	71	66	92	*R*
32/**4**/$Ru_3(CO)_{12}$	72	100	98	90	*R*
32/**5**/$Ru_3(CO)_{12}$	72	95	89	89	*R*
32/Furan **17**	72	93	93	90	*R*
32/Thio **18**	168		61	87	*R*
32/Isox **19**	144	100	96	89	*R*
32/Ester **20**	168	50	48	93	*R*
33/**4**/$Ru_3(CO)_{12}$	72	100	99	92	*R*
33/**5**/$Ru_3(CO)_{12}$	72	100	92	91	*R*
33/Furan **17**	80	100	92	93	*R*
33/Thio **18**	144	55	45	88	*R*
33/Isox **19**	144	77	73	76	*R*
33/Ester **20**	168	50	45	90	*R*
34/**4**/$Ru_3(CO)_{12}$	48	98		94	*R*
34/**5**/$Ru_3(CO)_{12}$	48	99		88	*R*
34/Furan **17**	96	100	81	93	*R*
34/Thio **18**	144	94	74	92	*R*
34/Isox **19**	144	94	86	93	*R*
34/Ester **20**	96	99	87	90	*R*
35/**4**/$Ru_3(CO)_{12}$	nr[b]				
35/**5**/$Ru_3(CO)_{12}$	nr[b]				
35/Furan **17**	96		80	86	*R*
35/Thio **18**	120		57	89	*R*
35/Isox **19**	120		65	86	*R*
35/Ester **20**	120	56	45	84	*R*

[a]Either 5 mol % ligand **4** or **5**, 1.67 mol % $Ru_3(CO)_{12}$, iPrOH, 80 °C, 48h, [S] = 0.1 M or 1 mol % **17**−**20**, 5:2 HCO_2H/Et_3N, DCM,, [S] = 1 M rt. [b]nr = no reduction. [c]Catalyst inhibition observed.

of a more substituted arene in the complex can reduce its activity.[5] In all cases of ligands **6**−**10**, we were pleased to find that complexes, **17**−**21**, respectively, were formed in the reactions (Figure 5), the spectroscopic data for which indicated the formation of [(benzene)Ru(TsDPENR)Cl]. Each of these complexes also proved to be effective at the asymmetric ketone hydrogenation of acetophenone in good ee (Table 2). Ligand **11** did not form a stable complex.

Ligands **4** and **5** were combined with $[(benzene)RuCl_2]_2$, but neither formed an active ATH complex. Analysis of the spectroscopic data for the resulting complexes indicated the formation of tridentate cationic species **22** and **23** instead, both of which were stable and inert (Figure 4). In view of the observations, the formation of complexes with closely related ligands **12**−**16** was not investigated. A recently reported series of TsDPEN-derived, tridentate ligand-containing (arene)Ru-(II) complexes have been demonstrated to be effective ATH catalysts, with reversible formation of one of the Ru−N bonds being important for reactivity.[18]

Having established which structural features of a substituted ligand are essential for formation of specific catalyst types, the application of both systems (specifically ligands **4** and **5** with $Ru_3(CO)_{12}$, and complexes **17**−**20**) was extended to a range of substituted ketone substrates (Figure 6, Table 3). In these examples, due to lower solubility in FA/TEA, the reactions with **17**−**20** were run at [S] = 1 M with DCM as a cosolvent, and the reactions with **4**/**5** employed 5 mol % of the catalyst to ensure full conversion of these more hindered ketones. The range of results allowed the identification of the best catalyst for each substrate. In several cases where ligands **4** and **5** were used, full conversions were observed even though the reaction in IPA is reversible, presumably due to evaporation of the acetone side product at the elevated reaction temperature.[2d]

The furan-substituted catalyst **17** proved to be the most versatile, giving products of good ee for most substrates, although the other catalysts gave products in excellent yield and ee in some cases. For example, for product **26**, catalysts **19** and **20** gave excellent results. For products **27** and **28**, the $Ru_3(CO)_{12}$ system worked very well. Ester-containing catalyst

DOI: 10.1021/acs.orglett.9b02339
Org. Lett. XXXX, XXX, XXX−XXX

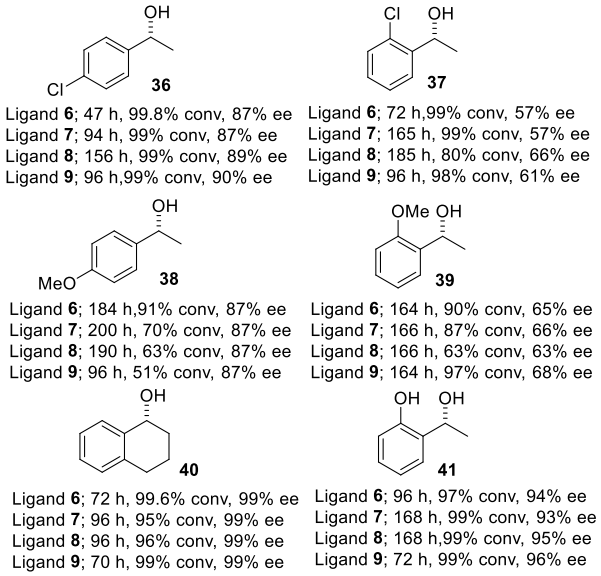


Figure 7. Products of ATH of substituted ketones using in situ-generated complexes **17**–**20**. Conditions: 1 mol % ligand **6**–**9**/0.5 mol % $[(benzene)RuCl_2]_2$, 5:2 FA:TEA, DCM, [S] = 1M, rt.

20 also gave reduction products **30** and **31** in the highest ees. The thiophene-containing catalyst **18** was the least versatile overall but gave one of the best results for product **27**. It was interesting to note that both α-chloro- and α-methoxyacetophenone inhibited the catalysis by **4** and **5**, which was confirmed by a test using a 1:1 mixture of $PhCOCH_2Cl$:PhCOMe in which neither ketone was reduced. This may be due to competing co-ordination of the Ru(II) by the substrate. However, the other heteroatom-substituted reagents were compatible with all the catalysts tested. The attempted reduction of the triple bond-containing ketone **35** was also not successful with **4** or **5**. The alcohols in Figure 7 are novel ATH products in many cases and add to the utility of ATH for the preparation of asymmetric alcohols, hence the catalyst set described herein represents a valuable toolkit for identification of suitable catalysts for ATH of diverse substrates.

In a further demonstration of the value of the new bidentate ligands, it was also found that catalysts **17**–**21** could be formed in situ by combination of the precursor ligands **6**–**9** with $[(benzene)RuCl_2]_2$. The complexes generated in this way proved to be effective for the ATH of simple acetophenone derivatives to give products **36**–**41** (Figure 7, Supporting Information, Table S2) that have previously been reported as substrates for **4**/**5**/$Ru_3(CO)_{12}$.[15,16] The use of the in situ catalysts in these cases gave products in good conversion and ee's similar to those previous reported for ATH catalysis, noting that *ortho*-substituted acetophenone derivatives are challenging substrates that often give lower ee's than less hindered ketones.[1−3,19]

In conclusion, we have established that the selection of the heterocyclic functional group on "TsDPENR" ligands will determine whether they are suited as tridentate ligands in complexes with $Ru_3(CO)_{12}$ or as bidentate ligands in complexes with [(benzene)Ru(TsDPENR)Cl] precatalysts, both of which appear to be mutually exclusive. In both cases, effective catalysts for ATH of a range of functionalized ketones, some reported for the first time, can be generated from each ligand. The complexes can be generated in situ or isolated before use, depending on the class of substate under study.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02339.

Experimental procedures, NMR spectra, HPLC and full table of reductions of **24**–**35** (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: m.wills@warwick.ac.uk
*E-mail: goldenkeys9996@thegoldenkeys.com.cn

ORCID

Martin Wills: 0000-0002-1646-2379

Notes

The authors declare the following competing financial interest(s): Author Y Xu is founder and CEO of the company supporting the work.

■ ACKNOWLEDGMENTS

We thank Warwick University and GoldenKeys High-Tech Material Co., Ltd. for funding (of J.B.-R.) via the Warwick Collaborative Postgraduate Scholarship Scheme. The research data (and/or materials) supporting this publication can be accessed at http://wrap.warwick.ac.uk/.

■ REFERENCES

(1) (a) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97−102. (b) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521−2522.

(2) (a) Wang, D.; Astruc, D. *Chem. Rev.* **2015**, *115*, 6621−6686. (b) Foubelo, F.; Nájera, C.; Yus, M. *Tetrahedron: Asymmetry* **2015**, *26*, 769−790. (c) Milner, L.; Talavera, G.; Nedden, H. *Chem. Oggi.* **2017**, *35*, 37−40. (d) Ikariya, T.; Blacker, A. J. *Acc. Chem. Res.* **2007**, *40*, 1300−1308.

(3) Barrios-Rivera, J.; Xu, Y.; Wills, M. *Org. Biomol. Chem.* **2019**, *17*, 1301−1321.

(4) Koike, T.; Ikariya, T. *Adv. Synth. Catal.* **2004**, *346*, 37−41.

(5) Martins, J. E. D.; Clarkson, G. J.; Wills, M. *Org. Lett.* **2009**, *11*, 847−850.

(6) Martins, J. E. D.; Contreras Redondo, M. A.; Wills, M. *Tetrahedron: Asymmetry* **2010**, *21*, 2258−2264.

(7) Soni, R.; Hall, T. H.; Morris, D. J.; Clarkson, G. J.; Owen, M. R.; Wills, M. *Tetrahedron Lett.* **2015**, *56*, 6397−6401.

(8) Parekh, V.; Ramsden, J. A.; Wills, M. *Catal. Sci. Technol.* **2012**, *2*, 406−414.

(9) Zammit, C. M.; Wills, M. *Tetrahedron: Asymmetry* **2013**, *24*, 844−852.

(10) Shan, W.; Meng, F.; Wu, Y.; Mao, F.; Li, X. *J. Organomet. Chem.* **2011**, *696*, 1687−1690.

(11) Touge, T.; Arai, T. *J. Am. Chem. Soc.* **2016**, *138*, 11299−11305.

(12) Ma, W.; Zhang, J.; Xu, C.; Chen, F.; He, Y.-M.; Fan, Q.-H. *Angew. Chem., Int. Ed.* **2016**, *55*, 12891−12894.

(13) Yang, Z.; Chen, F.; He, Y.; Yang, N.; Fan, Q.-H. *Angew. Chem., Int. Ed.* **2016**, *55*, 13863−13866.

(14) Zimbron, J. M.; Dauphinais, M.; Charette, A. B. *Green Chem.* **2015**, *17*, 3255−3259.

(15) Johnson, T. C.; Totty, W. G.; Wills, M. *Org. Lett.* **2012**, *14*, 5230−5233.

DOI: 10.1021/acs.orglett.9b02339
Org. Lett. XXXX, XXX, XXX−XXX

(16) Darwish, M. O.; Wallace, A.; Clarkson, G. J.; Wills, M. *Tetrahedron Lett.* **2013**, *54*, 4250−4253.
(17) (a) Dub, P. A.; Gordon, J. C. *Dalton Trans* **2016**, *45*, 6756−6781. (b) Dub, P. A.; Ikariya, T. *J. Am. Chem. Soc.* **2013**, *135* (7), 2604−2619. (c) Dub, P. A.; Gordon, J. C. *Nature Rev. Chem.* **2018**, *2*, 396−408.
(18) Dub, P. A.; Matsunami, A.; Kuwata, S.; Kayaki, Y. *J. Am. Chem. Soc.* **2019**, *141* (6), 2661−2677.
(19) Xu, Y.; Alcock, N. W.; Clarkson, G. J.; Docherty, G.; Woodward, G.; Wills, M. *Org. Lett.* **2004**, *6*, 4105−4107.

DOI: 10.1021/acs.orglett.9b02339
Org. Lett. XXXX, XXX, XXX−XXX