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Direct Formation of Tethered Ru(II) Catalysts Using Arene Exchange

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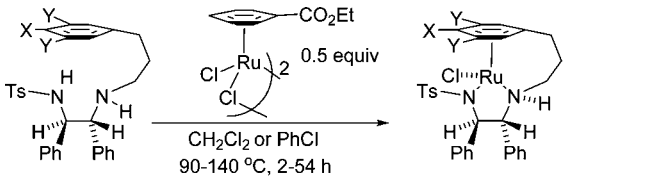
ABSTRACT



6a (X = Y = H)
6b (X = OMe, Y = H)
6c (X = H, Y = OMe)

2 (n = 1) DCM, 90 °C, 54 h, 53%
4 (X = OMe, Y = H) DCM, 90 °C, 54 h, 43%
9 (X = H, Y = OMe) DCM, 90 °C, 49 h, 48%

An 'arene exchange' approach has been successfully applied for the first time to the synthesis of Ru(II)-based 'tethered' reduction catalysts directly from their ligands in one step. This provides an alternative method for the formation of known complexes, and a route to a series of novel complexes. The novel complexes are highly active in both asymmetric transfer and pressure hydrogenation of ketones.

Complexes of type **1**–**3** have been widely adopted in academic and industrial research as enantioselective catalysts for the reduction of C=O and C=N bonds. Noyori et al. first reported the synthesis and use of complexes of type **1**,[1−3] which catalyze the asymmetric reduction of ketones[1] and imines[2] in high ee using either hydrogen gas[4] (asymmetric pressure hydrogenation, APH) or a reagent such as formic acid, sodium acetate, or isopropanol (asymmetric transfer hydrogenation, ATH).[1−3]

We reported[5−7] the synthesis and applications of 'tethered' complexes of type **2** which exhibit increased reactivity relative to **1**. First Ikariya, and later this group,

(1) (a) Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562–7563. (b) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521–2522. (c) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738–8739. (d) Haack, K. J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem.* **1997**, *109*, 297–300. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 285–288. (e) Alonso, D. A.; Brandt, P.; Nordin, S. J. M.; Andersson, P. G. *J. Am. Chem. Soc.* **1999**, *121*, 9580–9588.

(2) (a) Wills, M. In *Modern Reduction Methods*; Andersson, P. G., Munslow, I. J., Eds.; Wiley-VCH: Weinheim, 2008; Chapter 11, pp 271–296. (b) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916–4917. (c) Williams, G. D.; Wade, C. E.; Wills, M. *Chem. Commun.* **2005**, 4735–4737. (d) Sun, X.; Manos, G.; Blacker, J.; Martin, J.; Gavriilidis, A. *Org. Process Res. Dev.* **2004**, *8*, 909–914. (e) Åberg, J. B.; Samec, A. M.; Bäckvall, J.-E. *Chem. Commun.* **2006**, 2771–2773. (h) Casey, C. P.; Clark, T. B.; Guzei, I. A. *J. Am. Chem. Soc.* **2007**, *129*, 11821–11827.

(3) (a) Takamura, H.; Ando, J.; Abe, T.; Murata, T.; Kadota, I.; Uemura, D. *Tetrahedron Lett.* **2008**, *49*, 4626–4629. (b) Fu, R.; Chen, J.; Guo, L.-C.; Ye, J.-L.; Ruan, Y.-P.; Huang, P.-Q. *Org. Lett.* **2009**, *11*, 5242–5245. (c) Kumarasway, G.; Ramakrishna, G.; Naresh, P.; Jagadeesh, B.; Sridhar, B. *J. Org. Chem.* **2009**, *74*, 8468–8471. (d) Zhang, B.; Xu, M.-H.; Lin, G. Q. *Org. Lett.* **2009**, *11*, 4712–4715. (e) Bradley, P. A.; Carroll, R. L.; Lecouturier, Y. C.; Moore, R.; Noeureuil, P.; Patel, B.; Snow, J.; Wheeler, S. *Org. Process Res. Dev.* **2010**, *14*, 1326–1336. (f) Ding, Z.; Yang, J.; Wang, T.; Shen, Z.; Zhang, Y. *Chem. Commun.* **2009**, 571–573. (g) Carpenter, I.; Clarke, M. L. *Synlett* **2011**, 65–68. (h) Kumaraswamy, G.; Ramakrishna, G.; Sridhar, B. *Tetrahedron Lett.* **2011**, *52*, 1778–1782.

(4) (a) Ohkuma, T.; Utsumi, N.; Tsutsumi, K.; Murata, K.; Sandoval, C.; Noyori, R. *J. Am. Chem. Soc.* **2006**, *128*, 8724–8725. (b) Sandoval, C. A.; Ohkuma, T.; Utsumi, N.; Tsutsumi, K.; Murara, K.; Noyori, R. *Chem.—Asian. J.* **2006**, *1*–*2*, 102–110. (c) Ohkuma, T.; Tsutsumi, K.; Utsumi, N.; Arai, N.; Noyori, R.; Murata, K. *Org. Lett.* **2007**, *9*, 255–257. (d) Ohkuma, T.; Utsumi, N.; Watanabe, M.; Tsutsumi, K.; Arai, N.; K. Murata, K. *Org. Lett.* **2007**, *9*, 2565–2567. (e) Ito, M.; Endo, Y.; Ikariya, T. *Organometallics* **2008**, *27*, 6053–6055. (f) Li, C. Q.; Wang, C.; Villa-Marcos, B.; Xiao, J. L. *J. Am. Chem. Soc.* **2008**, *130*, 14450–14451.

(5) (a) Soni, R.; Cheung, F. K.; Clarkson, G. C.; Martins, J. E. D.; Graham, M. A.; Wills, M. *Org. Biomol. Chem.* **2011**, *9*, 3290–3294. (b) Hayes, A. M.; Morris, D. J.; Clarkson, G. J.; Wills, M. *J. Am. Chem. Soc.* **2005**, *127*, 7318–7319.

(6) (a) Soni, R.; Collinson, J.-M.; Clarkson, G. C.; Wills, M. *Org. Lett.* **2011**, *13*, 4304–4307. (b) Cheung, F. K.; Lin, C.; Minissi, F.; Lorente Crivillé, A.; Graham, M. A.; Fox, D. J.; Wills, M. *Org. Lett.* **2007**, *9*, 4659–4662.

(7) Jolley, K. E.; Zanotti-Gerosa, A.; Hancock, F.; Dyke, A.; Grainger, D. M.; Medlock, J. A.; Nedden, H. G.; Le Paih, J. J. M.; Roseblade, S. J.; Seger, A.; Sivakumar, V.; Morris, D. J.; Wills, M. *Adv. Synth. Catal.* **2012**, *354*, 2545–2555.

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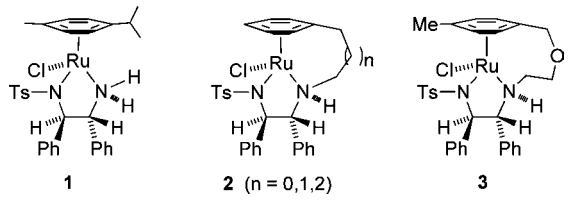
independently reported the synthesis and applications of 'ether-tethered' complex **3**.[8]



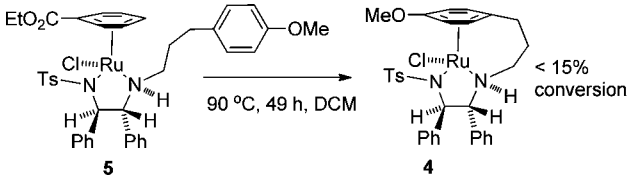
1 **2** (n = 0,1,2) **3**

Although complexes **2** and **3** are excellent catalysts, their syntheses require multistep processes; our original route to **2** ($n = 0-2$)[5a,b] required (i) Birch reduction of an alcohol, (ii) oxidation to an aldehyde, (iii) reductive coupling with a diamine, (iv) complexation with $RuCl_3$, and (v) conversion of the dimer to a monomer. Improved synthetic approaches to **2** ($n = 1$)[7,8a] require conversion of the alcohol from step (i) to the tosylate, triflate, or mesylate and coupling with the diamine component, and also combine the last two stages into one. In alternative approaches, a [4 + 2] cycloaddition may be employed to form the required diene.[8,9] Hence, although efficient, the majority of current synthetic approaches (one exception being the synthesis of **3** by Ikariya et al.[8a]) require the intermediacy of a 1,4-cyclohexadiene intermediate containing a TsDPEN unit.

An appealing alternative approach to the synthesis of tethered complexes would be a direct 'arene substitution' in which the arene on the tether displaces another η^6-arene from Ru(II).[10] This may have an advantage in certain cases for example when the Birch reduction is difficult to achieve.[10d] or in cases where a large excess of diene is required for efficient complexation. The majority of related literature examples of this process involve ligands attached to a metal through a phosphine, typically conducted at ca. 120−130 °C, in a solvent such as chlorobenzene. η^6-Arenes containing an electron-withdrawing function are generally favored as leaving groups. However there appear to be only *two* reported examples of η^6-arene substitutions of complexes initially complexed through a *nitrogen* atom.[10b,c]

Given the precedents we attempted to form tethered Ru(II)/TsDPEN complexes using an intramolecular arene displacement. When an electron-rich ring was used to displace an electron-poor one,[10−12] i.e. biasing the system toward the tethered product, less than 15% of the required complex (*R*,*R*)-**4** was formed from **5** upon heating in DCM at 90 °C after 49 h (Scheme 1, product observed by NMR and not isolated) accompanied by extensive decomposition.

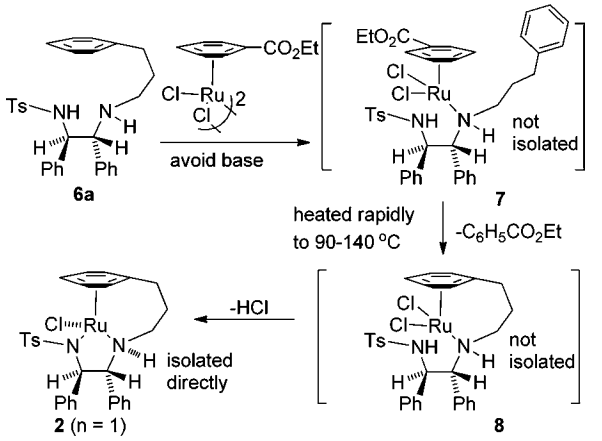
Scheme 1. Attempted Approach to Catalyst **4**



5 **4**

The formation of complexes such as **5** from the Ru(II) dimer precursor (e.g., $[Ru(C_6H_5CO_2Et)Cl_2]_2$) and a TsDPEN-derived ligand generally requires the addition of a base such as triethylamine and temperatures in the range of 80 °C in *i*PrOH, which are below those typically required for η^6-arene displacement.

Scheme 2. Direct Complexation Approach to Tethered Catalyst **2** ($n = 1$)



6a **7** **2** (n = 1) **8**

We proposed that through omission of the base and by *rapid heating* of ligand **6a** and precursor complex, the η^6-arene ring substitution could outpace diamine complexation, i.e via formation of intermediates **7** and **8** rather than **5**, and hence lead to direct formation of tethered complexes (Scheme 2). In the event these conditions worked well and provided a new route to both **2** ($n = 1$) and the new complexes (*R*,*R*)-**4** and (*R*,*R*)-**9** (Scheme 3) through direct combination of the

(8) (a) Touge, T.; Hakamata, T.; Nara, H.; Kobayashi, T.; Sayo, N.; Saito, T.; Kayaki, Y.; Ikariya, T. *J. Am. Chem. Soc.* **2011**, *133*, 14960–14963. (b) Parekh, V.; Ramsden, J. A.; Wills, M. *Catal. Sci. Technol.* **2012**, *2*, 406–414.

(9) Cheung, F. K.; Hayes, A. M.; Morris, D. J.; Wills, M. *Org. Biomol. Chem.* **2007**, *5*, 1093–1103.

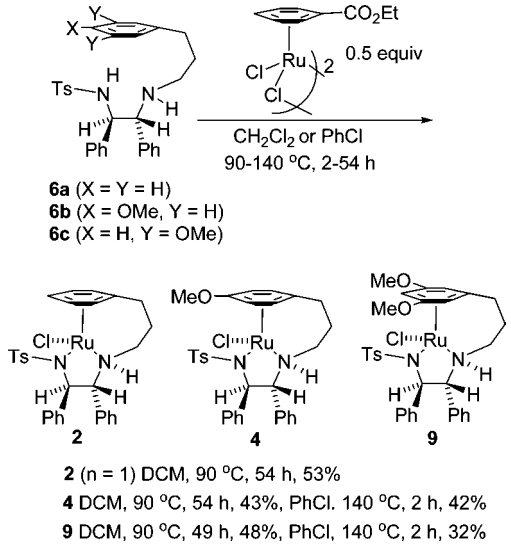
(10) (a) Adams, J. R.; Bennett, M. A. *Adv. Organomet. Chem.* **2006**, *54*, 293–331. (b) Melchart, M.; Habtemariam, A.; Novakova, O.; Moggach, S. A.; Fabbiani, F. P. A.; Parsons, S.; Brabec, V.; Sadler, P. J. *Inorg. Chem.* **2007**, *46*, 8950–8962. (c) Ito, M.; Komatso, H.; Endo, Y.; Ikariya, T. *Chem. Lett.* **2009**, *38*, 98–99. (d) Bennett, M. A.; Huang, T.-N.; Matheson, T. W.; Smith, A. K.; Ittell, S.; Nickerson, W. *Inorg. Synth.* **1982**, *21*, 74–78.

(11) Naphthalene has also been reported to be an efficient 'leaving group' for arene substitution in Ru(II) complexes. Kündig, E. P.; Monnier, F. R. *Adv. Synth. Catal.* **2004**, *346*, 901–905.

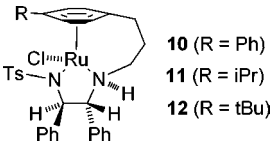
(12) For the synthesis of $[Ru(C_6H_5CO_2Et)Cl_2]_2$) and its precursor diene, see: (a) Emerman, S. I.; Meinwald, J. *J. Org. Chem.* **1956**, *21*, 375. (b) Rigby, J. H.; Balasubramanian, N. *J. Org. Chem.* **1989**, *54*, 224–228. (c) Agudo, R.; Roiban, G.-D.; Reetz, M. T. *ChemBioChem* **2012**, *13*, 1465–1473. (d) Mashima, K.; Kusano, K.-H.; Sato, N.; Matsumura, Y.-I.; Nozaki, K.; Kumobayashi, H.; Sayo, N.; Hori, Y.; T. Ishizaki, T.; Akutagawa, S. Takaya, H. *J. Org. Chem.* **1994**, *59*, 3064–3076. (e) Therrien, B.; Ward, T. R.; Pilkinton, M.; Hoffmann, C.; Gilardoni, F.; Weber, J. *Organometallics* **1998**, *17*, 330–337. (f) Bennett, M. A.; Smith, A. K. *J. Chem. Soc., Dalton Trans.* **1974**, 233–241.

precursor dimer with ligands **6a**–**c** in DCM or chlorobenzene at 90–140 °C for 2–54 h. The use of an electron-rich ring in the substituting ligand appears to be advantageous and may lead to the formation of a more stable complex as a result of the increased electron density in the new η^6-arene ring.[10d,13]

Scheme 3. Synthesis of **2** (n = 1) and Electron-Rich Tethered Catalysts (R,R)-**4** and (R,R)-**9** via Direct η^6-Arene Substitution (isolated yields)



The X-ray crystallographic structures of both (R,R)-**4** and (R,R)-**9** were obtained (see Supporting Information (SI)).[14] These served to confirm both that their structures were correct and also that the relative stereochemistry of the Ru(II) center relative to the diamine backbone matched that previously observed for complexes of this type.[1,5] The arene substitution reaction is slower at lower temperatures, but additional impurities are formed at higher temperatures; therefore, careful control of the conditions is required (see SI for full details). In DCM at 90 °C a reaction time of 40–50 h is typically required. In chlorobenzene (following initial combination of reagents in DCM) the reaction at 90 °C is faster than that in DCM. The reaction can be carried out in the presence of a mild inorganic base; however a stronger base is unfavorable and leads to lower yields of product, as predicted (see SI). Complexes **10**–**12** were also prepared by this route, each as mixtures of diastereoisomers as has been observed previously for related complexes.[5b,7] For the novel electron-rich examples (R,R)-**4** and (R,R)-**9**, this method represents a highly efficient approach which appears well suited to the formation of tethered catalysts containing electron-rich arene rings.



The importance of the higher temperature at an early stage of the complexation was highlighted by stirring **6b** and $[Ru(C_6H_5CO_2Et)Cl_2]_2$ in DCM at RT. This was found to form only the unproductive complex **5** (see SI) and none of the tethered complex (R,R)-**4**. In further tests we found that $[RuCl_2(1,4\text{-}(EtO_2C)_2C_6H_4)]_2$ worked well in the substitution; however, $[RuCl_2(1,4\text{-}(EtO_2C)(CH_3)C_6H_4)]_2$ and $[RuCl_2(p\text{-cymene})]_2$ did not, highlighting the importance of the use of an electron-withdrawing group on the initial η^6-arene ring.[10]

The novel electron-rich complexes (R,R)-**4** and (R,R)-**9** are highly active in the ATH and APH of ketones.[5–8] Selected results for reduction of ketones **13**–**32** (Figure 1) are given in Tables 1 (ATH) and 2 (APH), and further details are in the SI. In the ATH tests shorter reaction times were observed at 60 °C compared to 28 °C (SI) with only marginal loss of enantioselectivity; therefore, the substrate screen was conducted at the higher temperature. Most of the substrates containing aromatic rings adjacent to the ketone, other than *ortho*-substituted rings, were reduced in consistently high ee using (R,R)-**4**. Fused-ring and α-substituted ketones were particularly good substrates. In most cases (R,R)-**9** gave products in lower ee than (R,R)-**4**; however, in several cases it was comparable and in the case of acetylcyclohexane, superior. The latter result may arise from an increased steric hindrance in the transition state as has previously been documented.[6b]

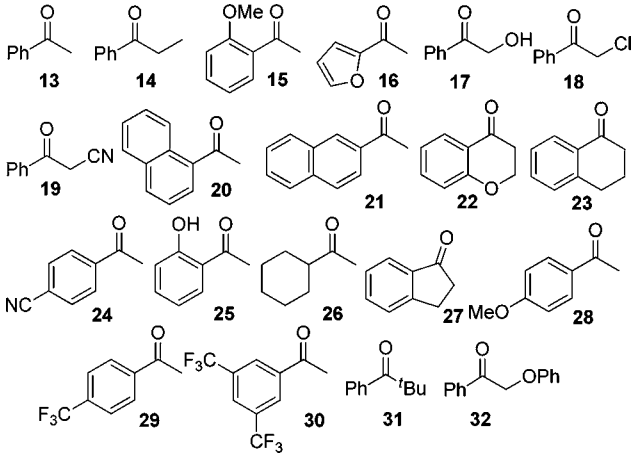


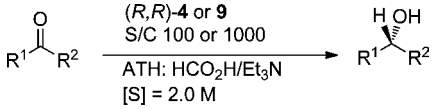
Figure 1. Ketone substrates used in ATH and APH reactions.

Although not listed, an imine was reduced in moderate ee (up to 76% ee) but full conversion using catalyst (R,R)-**9** (see SI). In the case of the APH reductions a similar pattern

(13) (a) Soleimannejad, J.; White, C. *Organometallics* **2005**, *24*, 2538–2541. (b) Soleimannejad, J.; Sisson, A.; White, C. *Inorg. Chim. Acta* **2003**, *352*, 121–128.

(14) The full structural data for ((R,R)-**4**; CCDC913682, (R,R)-**8**; CCDC 923077) can be obtained free of charge from the Cambridge Crystallographic Centre via www.ccdc.cam.ac.uk/data_request/cif.

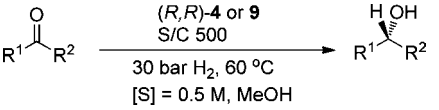
Table 1. ATH Reductions of Ketones



substrate	catalyst	s/c	temp/ °C	*t*/ h	conv %[a]	ee %[a]
13	**4**	1000	60	2	100	96 (*R*)
13	**4**	100	28	4.5	99	97 (*R*)
13	**9**	1000	60	4	100	89 (*R*)
13	**9**	100	28	8	99	91 (*R*)
14	**4**	1000	60	3.5	100	97 (*R*)
14	**9**	1000	60	5	100	88 (*R*)
15	**4**	1000	60	1.5	100	96 (*R*)
16	**4**	1000	60	2	100	98 (*R*)
16	**9**	1000	60	3	99	96 (*R*)
17	**4**	1000	60	2	100	98 (*S*)
17	**9**	1000	60	2	100	95 (*S*)
18	**4**	1000	60	1	99	97 (*S*)
18	**9**	1000	60	2	99	94 (*S*)
19	**4**	1000	60	1	100	98 (*R*)
19	**9**	1000	60	2	99	93 (*R*)
20	**4**	1000	60	3	100	99 (*R*)
21	**4**	1000	60	2	100	94 (*R*)
22	**4**	1000	60	3	100	99 (*R*)[b]
22	**9**	1000	60	3	100	>99 (*R*)[b]
23	**4**	1000	60	5	99	99 (*R*)
23	**9**	1000	60	5	100	99 (*R*)
24	**4**	1000	60	1.5	99	88 (*R*)
25	**4**	1000	60	3	100	99 (*R*)
25	**9**	1000	60	7	100	96 (*R*)
26	**4**	1000	60	5	100	37 (*S*)[c]
26	**9**	1000	60	6	100	73 (*S*)[c]
26	**9**	100	28	21.5	99	74 (*S*)

[a] Conv % and ee % calculated by chiral GC analysis unless otherwise indicated. [b] ee % calculated by chiral HPLC analysis. [c] ee % calculated for acetate derivative.

Table 2. APH Reductions of Ketones[a]



substrate	catalyst	*t*/h	conv %	ee %
13	**4**	16	100	94 (*R*)
13	**9**	16	100	84 (*R*)
14	**4**	16	70	84 (*R*)
17	**4**	24	100	91 (*S*)
17	**9**	24	94	88 (*S*)
22	**4**	24	98	>99 (*R*)
22	**9**	24	100	99 (*R*)
23	**4**	48	100	99 (*R*)
23	**9**	48	60	99 (*R*)
26	**4**	48	99	37 (*S*)
26	**9**	48	40	81 (*S*)
27	**4**	48	95	98 (*R*)
27	**9**	48	72	95 (*R*)
28	**4**	16	100	94 (*R*)
28	**9**	16	100	80 (*R*)
29	**4**	16	98	92 (*R*)
29	**9**	16	99	74 (*R*)
30	**4**	24	100	82 (*R*)
31	**4**	48	32	80 (*R*)
32	**4**	24	100	95 (*S*)

[a] Conv % and ee % calculated as for Table 1.

of results was obtained (Table 2). Following initial screening it was found that an s/c of 500 and a temperature of 60 °C represented convenient reaction conditions.[7,8] The results of the ATH and APH experiments suggest that the methoxy-substituted complexes catalyze ketone reduction through a broadly identical mechanism similar to that of the known tethered and untethered catalysts.[1]

In summary, a concise route to synthetically valuable tethered Ru(II)/TsDPEN catalysts for ATH and APH reactions is described. The direct 'arene exchange' process works efficiently under specific conditions, and the new complexes prepared by this route are effective for the asymmetric transfer and pressure hydrogenation of a range of ketones. We are continuing to establish the potential of this novel method.

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Supporting Information Available. Full experimental details, analytical data, and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.