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Asymmetric Transfer Hydrogenation in Water with a Supported Noyori–Ikariya Catalyst

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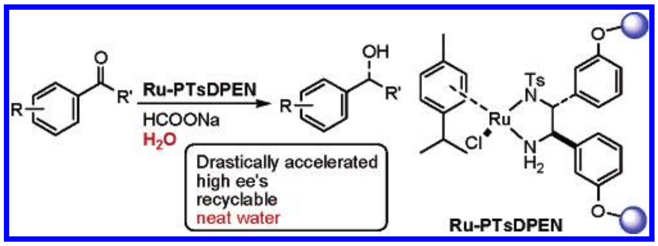
ABSTRACT



The poly(ethylene glycol)-supported ruthenium precatalyst shown above is highly effective for asymmetric transfer hydrogenation of unfunctionalized aromatic ketones by HCOONa in neat water, affording fast rates, good to excellent enantioselectivities, and outstanding reusability.

Asymmetric transfer hydrogenation of ketones has recently emerged as an alternative method to asymmetric hydrogenation for the production of chiral alcohols due to its operational simplicity and the easy availability of reductants.[1] Among the various chiral catalysts reported, the most notable is the ruthenium catalyst Ru-TsDPEN (TsDPEN= *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine) developed by Noyori, Ikariya, Hashiguchi, and co-workers.[2] This catalyst and related variants have since been applied by Noyori, Ikariya, and others to a wide range of prochiral ketones and imines, leading to good to excellent ees in 2-propanol and the $HCOOH-NEt_3$ azeotropic mixture, which have been used almost exclusively as hydrogen donor as well as solvent for the ruthenium catalyst.[3−6] In terms of catalyst activity and reusability, there is still room for improvement, however.

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(1) For recent reviews, see: (a) Blaser, H.-U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103−151. (b) Everaere, K.; Mortreux, A.; Carpentier, J.-F. *Adv. Synth. Catal.* **2003**, *345*, 67−77. (c) Saluzzo, C.; Lemaire, M. *Adv. Synth. Catal.* **2002**, *344*, 915−928. (d) Fan, Q. H.; Li, Y. M.; Chan, A. S. C. *Chem. Rev.* **2002**, *102*, 3385−3466. (e) Palmer, M. J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045−2061. (f) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97−102.

(2) Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562−7563.

(3)) (a) Hamada, T.; Torri, T.; Izawa, K.; Ikariya, T. *Tetrahedron* **2004**, *60*, 7411−7417. (b) Watanabe, M.; Murata, K.; Ikariya, T. *J. Org. Chem.* **2002**, *67*, 1712−1715. (c) Okano, K.; Murata, K.; Ikariya, T. *Tetrahedron Lett.* **2000**, *41*, 9277−9280. (d) Murata, K.; Okano, K.; Miyagi, M.; Iwane, H.; Noyori, R.; Ikariya, T. *Org. Lett.* **1999**, *1*, 1119−1121. (e) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738−8739. (f) Hashiguchi, S.; Fujii, A.; Haack, K.-J.; Matsumura, K.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 288−290. (g) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T. Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916−4917. (h) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521−2522.

(4) For some recent examples, see: (a) Hannedouche, J.; Clarkson, G. J.; Wills, M. *J. Am. Chem. Soc.* **2004**, *126*, 986−987. (b) Geldbach, T. J.; Dyson, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 8114−8115. (c) Sterk, D.; Stephan, M. S.; Mohar, B. *Tetrahedron Lett.* **2004**, *45*, 535−537. (d) Pasto, M.; Riera, A.; Pericas, M. A. *Eur. J. Org. Chem.* **2002**, 2337−2341. (e) Maj, A. M.; Pietrusiewicz, K. M.; Suisse, I.; Agbossou, F.; Mortreux, A. *J. Organomet. Chem.* **2001**, *626*, 157−160. (f) Petra, D. G. I.; Kamer, P. C. J.; Spek, A. L.; Schoemaker, H. E.; van Leeuwen, P. W. N. M. *J. Org. Chem.* **2000**, *65*, 3010−3017. (g) Mizugaki, T.; Kanayama, Y.; Ebitani, K.; Kaneda, K. *J. Org. Chem.* **1998**, *63*, 2378−2381. (h) Palmer, M.; Walsgrove, T.; Wills, M. *J. Org. Chem.* **1997**, *62*, 5226−5228.

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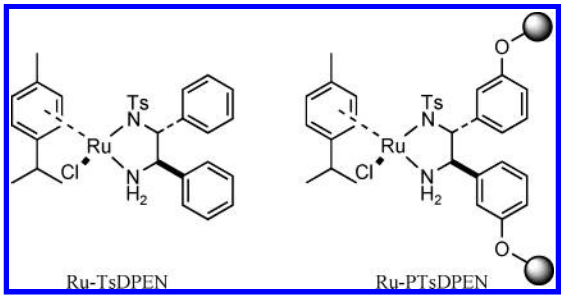
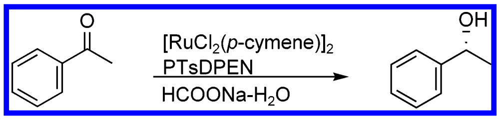
Herein we report that, when carried out in water, the ketone reduction can be drastically accelerated with the additional benefit of very easy catalyst recycle.



As with most other homogeneous catalysts, the Noyori−Ikariya Ru-TsDPEN catalyst cannot be easily separated from products. To address the challenge, various immobilized TsDPEN and related ligands have been reported. However, few have been demonstrated to be both effective and recyclable, and none appears to be more active than TsDPEN itself.[5,6] As part of a program aimed at developing supported chiral diamines,[7] we recently reported that the poly(ethylene glycol)-supported TsDPEN, PTsDPEN, is effective in the Ru(II)-catalyzed asymmetric reduction of unfunctionalized aromatic ketones by HCOOH−NEt$_3$; however, catalyst recycle appears to be possible only when some water is present as a cosolvent.[7a] In its absence, much reduced conversions and ees were observed. We now disclose that water is in fact an excellent solvent for the Ru−PTsDPEN-catalyzed reaction with HCOONa as a reductant. Very recently, we have shown that the unmodified Ru−TsDPEN is also highly effective for ketone reduction by HCOONa in water;[8] however, recycle of the catalyst proved to be difficult due to the catalyst being soluble in common solvents, which renders catalyst separation by extraction impossible.

We set out by examining the asymmetric transfer hydrogenation of acetophenone to 1-phenylethanol. The precatalyst was generated by reacting the polymer-supported ligand PTsDPEN with [RuCl$_2$(*p*-cymene)]$_2$ in water at 40 °C for 1 h with no need for additional base.[9,10] The transfer hydrogenation started with the introduction of 5 equiv of HCOONa (2.5 M) and acetophenone (0.5 M). To our delight, the reaction proceeded to give a 99% conversion at a substrate/catalyst (S/C) ratio of 100 and 40 °C in 1 h, furnishing (*R*)-1-phenylethanol in 92% ee (entry 1, Table 1). In comparison with the HCOOH−Et$_3$N azeotrope solvent using similarly prepared catalyst[11] or using the Ru−TsDPEN catalyst,[10] the current system affords a reduced ee, but a much faster rate. This is evident from the time−conversion diagram shown in Figure 1. With the azeotrope as both reductant and solvent, the Ru−PTsDPEN catalyst produced an ee of 93% and a conversion of 96% in 22 h, while the Ru−TsDPEN catalyst furnished a 97% ee and a 98% conversion in 16 h. There appears to be an induction period for both catalysts in the azeotrope, and it is longer for the PEG-supported one.

Table 1. Asymmetric Transfer Hydrogenation of Acetophenone under Various Conditions[a]



entry	S/C	[HCOONa] (M)	temp (°C)	time (h)	conversion[b] (%)	ee[b] (%)
1	100	2.5	40	1	99	92
2	100	2.5	22	8	>99	93
3	100	1.0	40	4	>99	89
4	100	5.0	40	1	>99	93
5[c]	100	2.5	22	8	>99	94
6	1000	5.0	40	12	>99	89
7[d]	1000	5.0	40	44	>99	89
8[e]	1000	5.0	40	44	36	75
9[f]	1000		40	12	34	89[g]

[a] For detailed procedures, see ref 9. [b] Determined by GC. The alcohol configuration was *R* and was determined by comparison of GC retention time or sign of optical rotation with literature data. [c] Sodium dodecyl sulfate (4 mol %) was added. [d] Performed in CH$_2$Cl$_2$−H$_2$O (1:1). [e] Performed in toluene−H$_2$O (1:1). [f] According to Wills's procedure, in ^{i}PrOH with (1*R*,2*S*)-(+)-amino-2-indanol as a ligand.[4h] [g] (*S*)-Isomer formed.

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(5) For examples of supported TsDPEN and related diamines, see: (a) Liu, P. N.; Gu, P. M.; Wang, F.; Tu, Y. Q. *Org. Lett.* **2004**, *6*, 169−172. (b) Itsuno, S.; Tsuji, A.; Takahashi, M. *Tetrahedron Lett.* **2003**, *44*, 3825−3828. (c) Chen, Y.-C.; Wu, T.-F.; Deng, J.-G.; Liu, H.; Jiang, Y.-Z.; Choi, M. C. K.; Chan, A. S. C. *Chem. Commun.* **2001**, 1488−1489. (d) Touchard, F.; Fache, F.; Lemaire, M. *Eur. J. Org. Chem.* **2000**, 3787−3792. (e) Bayston, D. J.; Travers, C. B.; Polywka, M. E. C. *Tetrahedron: Asymmetry* **1998**, *9*, 2015−2018. (f) ter Halle, R.; Schulz, E.; Lemaire, M. *Synlett* **1997**, 1257−1258.

(6) For literature about aqueous-phase asymmetric transfer hydrogenation of ketones, see: (a) Ma, Y. P.; Liu, H.; Chen, L.; Cui, X.; Zhu, J.; Deng, J. G. *Org. Lett.* **2003**, *5*, 2103−2106. (b) Himeda, Y.; Onozawa-Komatsuzaki, N.; Sugihara, H.; Arakawa, H.; Kasuga, K. *J. Mol. Catal. A: Chem.* **2003**, *195*, 95−100. (c) Rhyoo, H. Y.; Park, H. J.; Suh, W. H.; Chung, Y. K. *Tetrahedron Lett.* **2002**, *43*, 269−272. (d) Rhyoo, H. Y.; Park, H. J.; Chung, Y. K. *Chem. Commun.* **2001**, 2064−2065. (e) Thorpe, T.; Blacker, J.; Brown, S. M.; Bubert, C.; Crosby, J.; Fitzjohn, S.; Muxworthy, J. P.; Williams, J. M. J. *Tetrahedron Lett.* **2001**, *42*, 4041−4043. (f) Bubert, C.; Blacker, J.; Brown, S. M.; Crosby, J.; Fitsjohn, S.; Muxworthy, J. P.; Thorpe, T.; Williams, J. M. *Tetrahedron Lett.* **2001**, *42*, 4037−4039. (g) Ogo, S.; Makihara, N.; and Watanabe, Y. *Organometallics* **1999**, *18*, 5470−5474.

(7) (a) Li, X. G.; Chen, W. P.; Hems, W.; King, F.; Xiao, J. L. *Tetrahedron Lett.* **2004**, *45*, 951−953. (b) Li, X. G.; Chen, W. P.; Hems, W.; King, F.; Xiao, J. L. *Org. Lett.* **2003**, *5*, 4559−4561.

(8) Wu, X. F.; Li, X. G.; Hems, W.; King, F.; Xiao, J. L. *Org. Biomol. Chem.* **2004**, *2*, 1818−1821.

(9) **General Procedure.** [RuCl$_2$(*p*-cymene)]$_2$ (3.1 mg, 0.005 mmol) and PTsDPEN[7a] (50 mg, 0.012 mmol) were dissolved in 2 mL of water. After the solution was stirred at 40 °C for 1 h, HCO$_2$Na (340 mg, 5 mmol) and acetophenone (120 mg, 1.0 mmol) were added to the solution. Following degassing three times, the solution was allowed to react at 40 °C for a certain period of time. After the solution was cooled to room temperature, the organic compounds were extracted with Et$_2$O (6 mL). The conversion and enantioselectivity were determined by GC analysis (Chrompack Chirasil-Dex CB (25 m × 0.25 mm) column). In the case of recycle (10 equiv of HCO$_2$Na was used in the first run), following each reduction the aqueous phase was extracted with ether (2 × 3 mL) by using a syringe, and the new reduction was started by introducing another portion of acetophenone (120 mg) along with 1 equiv of HCOOH (0.1 mL, 10 M). There was no significant decrease in the reaction rates in the first 11 runs; however, the 14th run gave a 87% conversion in 48 h.

(10) Haack, K.-J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 285−288.

(11) Catalyst was prepared in a way similar to that given in ref 9 except CH$_2$Cl$_2$ instead of water was used as solvent at rt for 30 min. The reduction was started following removal of CH$_2$Cl$_2$ and then introduction of the azeotrope.

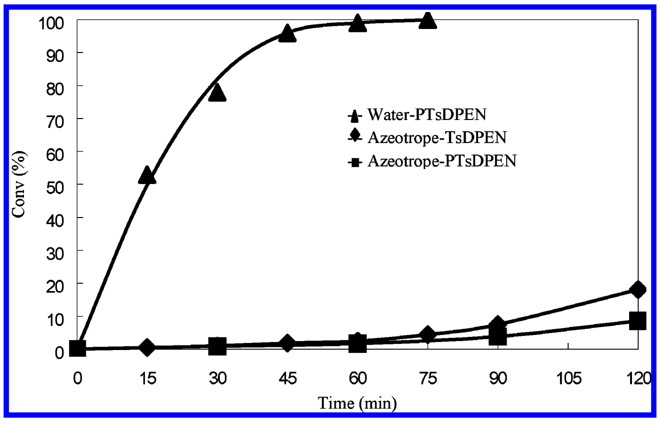
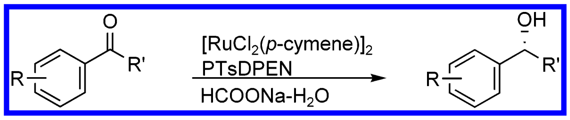


Figure 1. Conversion−time diagram for the reduction of acetophenone (0.5 M) in HCOONa−water with Ru−PTsDPEN[9] and in $HCOOH-NEt_3$ with Ru−TsDPEN[10] and Ru−PTsDPEN[11] at 40 °C.

Table 1 also shows the effect of other variables on the reaction. Thus, lowering the temperature to 22 °C yielded a slightly higher ee at a longer time. The reaction is also affected by the concentration of the formate, with a lower concentration yielding a slower reduction and a lower ee (entries 1, 3, and 4), but it does not appear to be much affected by adding a surfactant (entry 5). Similar observations have been made with the ruthenium catalysts containing proline amides[6c] and a water-soluble, sulfonated TsDPEN.[6a] However, surfactants have proved to be important with these catalysts, particularly in the case of the latter. In our case, PEG itself can serve as a phase-transfer catalyst,[12,15] facilitating the transfer of ketones to water. The reaction was also feasible at a higher S/C ratio of 1000, though a prolonged reaction time was necessary (entry 6). The benefit of using neat water as the solvent is further seen in entries 7 and 8, where dichloromethane and toluene were introduced into the aqueous solution, respectively, creating a biphasic system in both cases. The presence of the organic solvents brought about a much slower reaction and, unexpectedly, resulted in a significant reduction in ee in the case of toluene. Although the decrease in rates may be ascribed to substrate diffusion control, a homogeneous mixture of H_2O-CH_3CN led to a similar, slow reaction. The advantage of the current system over one of the most active asymmetric transfer catalysts, a complex similar to Ru−TsDPEN but containing a β-amino alcohol ligand, is seen by comparing entries 9 and 6.[4h]

Table 2. Asymmetric Transfer Hydrogenation of Ketones with Ru−PTsDPEN by HCOONa in Water[a]



ketone[b]	temp (°C)	time (h)	conversion[c] (%)	ee[c] (%)
Acp	22	8	>99	93
Acp	40	1	99 (98)	92
2′-chloro-acp	22	13	>99	91
2′-chloro-acp	40	1.5	100 (99)	85
4′-chloro-acp	22	13	>99 (98)	90
4′-trifluoromethyl-acp	22	12	>99 (91)	85
3′-methoxy-acp	22	18	98 (97)	90
4′-methyl-acp	22	18	>99 (99)	86
1′-acetonaphthone	22	36	85 (91)	88
2′-acetonaphthone	22	36	>99	94
2′-acetonaphthone	40	8	88 (87)	92
2-acetylfuran	22	18	98 (87)	91
1-indanone	22	18	>99	93
1-indanone	40	3	100 (98)	92
1-tetralone	22	18	>99	94
1-tetralone	40	3	98 (97)	92

[a] Reactions were performed at the temperatures indicated, using 1 mmol of ketone, 5 equiv of HCOONa, and a S/C ratio of 100 in 2 mL of water. [b] Acp = acetophenone. [c] Determined by GC equipped with a chiral column. Numbers in brackets refer to isolated yields for reactions performed at 40 °C (for details, see Supporting Information). The alcohol configuration was *R*.

Encouraged by the results, the reduction was extended to other nonfunctionalized aromatic ketones. Table 2 summarizes the results obtained. As can be seen, various ketones, including 2-substituted, electron-rich, and electron-deficient variants, were reduced with good to excellent ee values using HCOONa as the reductant and neat water as the solvent. At the room temperature of 22 °C, the reactions took longer times to complete than at 40 °C but gave slightly higher ees. As in the case of acetophenone, a most notable feature of these reactions is their rates, which are much faster than those observed with the same Ru−PTsDPEN catalyst in the $HCOOH-NEt_3$ azeotrope. Thus, for example, when carried out in the azeotrope at 50 °C at S/C = 100 (1 M substrate), the reduction of 4′-methylacetophenone with Ru−PTsDPEN led to a conversion of 75% in 30 h and an ee value of 88%.[7a] In sharp contrast, when switched to aqueous HCOONa, the same catalyst afforded a conversion of 99% and an ee of 86% in 18 h at a lower temperature of 22 °C. Another remarkable example is seen in the reduction of 1-indanone with Ru−PTsDPEN, which led to a 71% conversion and 88% ee in 25 h at 50 °C in $HCOOH-NEt_3$,[7a] but a complete reaction with an increased ee of 92% in 3 h at 40 °C in water.

The PEG-supported TsDPEN was designed to facilitate catalyst/product separation. However, as indicated above, when the reduction was carried out in the $HCOOH-NEt_3$ azeotrope, catalyst recycle led quickly to loss of catalyst

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(12) Dickerson, T. J.; Reed, N. N.; Janda, K. D. *Chem. Rev.* **2002**, *102*, 3325−3344.

(13) (a) Kobayashi, S. *Adv. Synth. Catal.* **2002**, *344*, 219. (b) Joo, F. *Aqueous Organometallic Catalysis*; Kluwer: Dordrecht, 2001. (c) Li, C. J.; Chan, T. H. *Organic Reactions in Aqueous Media*; Wiley: New York, 1997.

(14) For recent mechanistic studies, see: (a) Koike, T.; Ikariya, T. *Adv. Synth. Catal.* **2004**, *346*, 37−41. (b) Brandt, P.; Roth. P.; Andersson, P. G. *J. Org. Chem.* **2004**, *69*, 4885−4890 and references therein. (c) Casey, C. P.; Johnson, J. B. *J. Org. Chem.* **2003**, *68*, 1998−2001. (d) Noyori, R.; Yamakawa, M.; Hashiguchi, S. *J. Org. Chem.* **2001**, *66*, 7931−7944.

(15) Starks, C. M.; Liotta, C. L.; Halpern, M. *Phase-Transfer Catalysis*; Chapman & Hall: London, 1994; Chapter 4.

activity and enantioselectivity, presumably due to the decomposition of active Ru−PTsDEPEN complexes.[7a] In the aqueous-phase reaction, the ruthenium catalyst is certainly more stable. In fact, the reduction with Ru−PTsDEPEN can be run in water in the open air without much compromise in conversion and ee (95% conversion and 91% ee in 1.5 h with S/C = 100 and 5 equiv of HCOONa).

With a stable catalyst system in hand, separation and recycle of the catalyst becomes much easier to perform. Thus, in the end of a reduction, a solvent of low polarity such as diethyl ether can be added to precipitate the Ru(II)−PTsDPEN catalyst.[12] In the particular case of acetophenone reduction, we measured the leached ruthenium; ICP analysis showed that 0.4 mol % ruthenium had leached into the organic phase (diethyl ether).

A demonstration of the excellent recyclability of the catalyst is shown in Figure 2. As can be seen, the immobilized catalyst can be reused more than 10 times with no loss in enantioselectivity. Toward the end of the recycle (runs 12−14), longer reaction times were necessary to deliver the observed conversions. This decrease in catalytic activity is most likely due to catalyst loss during solvent extraction rather than its decomposition, as the ees remained literally unchanged even at the 14th run. To the best of our knowledge, this represents the most efficient catalyst system in transfer hydrogenation in terms of catalyst recyclability and activity[5,6] and a novel example of water-accelerated reactions in aqueous catalysis.[13]

In conclusion, this work demonstrates that the Ru−PTsDPEN catalyst is highly effective for the asymmetric transfer hydrogenation of ketones by formate in water, in which it is stable, recyclable, and capable of delivering good to excellent enantioselectivities. A most interesting question arising from the work is how water stabilizes the ruthenium catalyst and accelerates the reaction.[14] This and the possible application of the catalytic system to other reactions are being explored in our lab.

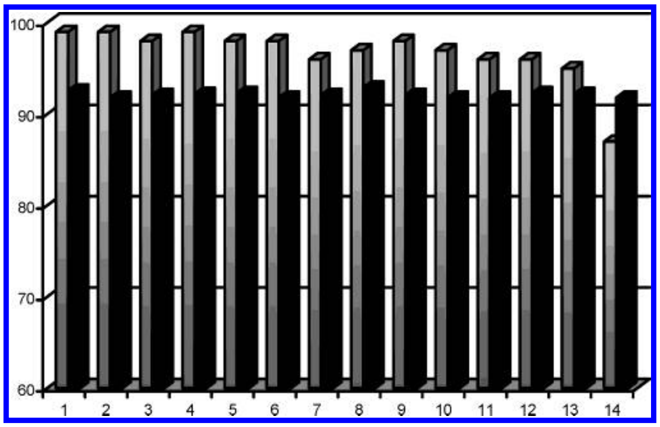

Figure 2. Conversions (grey bar) and ees (black bar) (%) against number of runs in the reduction of acetophenone by HCOONa with Ru−PTsDPEN in water at 40 °C.[9]

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Supporting Information Available: Experimental procedures for the hydrogenation of aromatic ketones and catalyst recycle and ^{1}H and ^{13}C NMR data, GC retention times, and isolated yields for the alcohol products. This material is available free of charge via the Internet at http://pubs.acs.org.

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