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Diastereoselective Synthesis of Indanes and Tetralins via Intramolecular Friedel–Crafts Reaction

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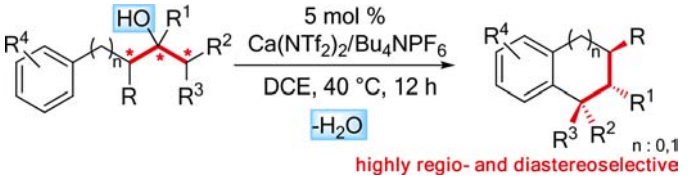
ABSTRACT



An easy access to tetralin and indane skeletons has been developed using a diastereoselective intramolecular Friedel–Crafts alkylation. Treatment of diastereomeric mixtures of benzyl carbinols with a catalytic amount of $Ca(NTf_2)_2/Bu_4NPF_6$ yields the respective tetralin or indane in good yields with high levels of regio- and diastereoselectivity.

Tetralin and indane ring structures are present in a wide range of natural products and pharmaceuticals.[1] A variety of synthetic methods to synthesize these skeletons have been explored.[2] Although intramolecular Friedel–Crafts reactions of benzyl carbinols mediated by stoichiometric amounts of Lewis and Brønsted acids (e.g., $SnCl_4$, $BF_3 \cdot Et_2O$, and CF_3CO_2H) have been described,[3] no catalytic version of this reaction is known to date. Recently, we developed a $Ca(NTf_2)_2/Bu_4NPF_6$ based catalyst system[4] for the intermolecular alkylation of electron-rich arenes using secondary and tertiary benzylic, allylic, and propargylic alcohols as environmentally benign alkylating agents under very mild rt conditions.[5] Hence, we became interested in the possibility of extending the aforementioned protocol to the intramolecular Friedel–Crafts[6] reaction of benzyl carbinols. The reaction starts with a dehydration of the hydroxyl function yielding a carbocationic species **I** (s. Scheme 1), a process which our calcium catalyst has proven to promote particularly efficiently. This initially formed carbocation **I** might cyclize directly with the arene moiety. Alternatively, a prior rearrangement, either by a

† These authors contributed equally.

(1) For examples of tetralins in medicinal chemistry, see: (a) Perrone, R.; Berardi, F.; Colabufo, N. A.; Leopoldo, M.; Tortorella, V.; Fiorentini, F.; Olgiati, V.; Ghiglieri, A.; Govoni, S. *J. Med. Chem.* **1995**, *38*, 943. (b) Brewster, W. K.; Nichols, D. E.; Riggs, R. M.; Mottola, D. M.; Lovenberg, T. W.; Lewis, M. H.; Mailman, R. B. *J. Med. Chem.* **1990**, *33*, 1756. For examples of indanes in medicinal chemistry, see: (c) Gross, M. F.; Beaudoin, S.; McNaughton-Smith, G.; Amato, G. S.; Castle, N. A.; Huang, C.; Zou, A.; Yu, W. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2849.

(2) (a) Xie, K.; Wang, S.; Li, P.; Li, X. *Tetrahedron Lett.* **2010**, *51*, 4466. (b) Youn, S. W.; Pastine, S. J.; Sames, D. *Org. Lett.* **2004**, *6*, 581. (c) Li, G.; Xiao, Q.; Li, C.; Wang, X.; Yin, D. *Tetrahedron Lett.* **2011**, *52*, 6827. (d) Sánchez-Larios, E.; Gravel, M. *J. Org. Chem.* **2009**, *74*, 7536. (e) Chua, P. J.; Tan, B.; Yang, L.; Zeng, X.; Zhu, D.; Zhong, G. *Chem. Commun.* **2010**, *46*, 7611.

(3) (a) Khalaf, A. A.; Roberts, R. M. *J. Org. Chem.* **1972**, *37*, 4227. (b) Roblin, R. O.; Marston, D., Jr.; Bogert, T. *J. Am. Chem. Soc.* **1935**, *57*, 151. (c) Bright, S. T.; Coxon, J. M.; Steel, P. J. *J. Org. Chem.* **1990**, *55*, 1338. (d) Banik, B. K.; Ghosh, S.; Ghatak, U. R. *Tetrahedron* **1988**, *44*, 6947. (e) Axon, B. W.; Davis, R. B.; Woodgate, P. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2956. (f) Nasipuri, D.; De Dalai, I. *J. Chem. Soc., Perkin Trans. 1* **1976**, 19. (g) Bogert, M. T.; Davidson, D.; Apfelbaum, P. M. *J. Am. Chem. Soc.* **1934**, *56*, 959. (h) Barrow, C. J.; Bright, S. T.; Coxon, J. M.; Steel, P. J. *J. Org. Chem.* **1989**, *54*, 2542. (i) Barclay, L. R. C.; Ginn, B. A.; Milligan, C. E. *Can. J. Chem.* **1964**, *42*, 579. (j) Ganeshpure, P. A.; Stevenson, R. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1681. (k) Corey, E. J.; Luo, G.; Lin, L. S. *Tetrahedron Lett.* **1998**, *39*, 2001. (l) Nagumo, S.; Miyoshi, I.; Akita, H.; Kawahara, N. *Tetrahedron Lett.* **2002**, *43*, 2224. (m) Ziegler, F.; Schwartz, J. A. *J. Org. Chem.* **1978**, *43*, 985. (n) Mühlthau, F.; Bach, T. *Synthesis* **2005**, *19*, 3428. (o) Khalaf, A. A.; Roberts, R. M. *J. Org. Chem.* **1969**, *34*, 3571. (p) Lednicer, D.; Emmert, D. E.; Lyster, S. C.; Duncan, G. W. *J. Med. Chem.* **1969**, *12*, 881. (q) Bonnet-Delpon, D.; Cambillau, C.; Charpentier-Morize, M.; Jacquot, R.; Mesureur, D.; Ourevitch, M. *J. Org. Chem.* **1988**, *53*, 754. (r) Angle, S. R.; Louie, M. S. *Tetrahedron Lett.* **1989**, *30*, 5741. (s) Blum, R.; Giovannini, E.; Hengartner, U.; Vallat, G. *Helv. Chim. Acta* **2002**, *85*, 1827–1840.

(4) (a) Haubenreisser, S.; Niggemann, M. *Adv. Synth. Catal.* **2011**, *353*, 469. (b) Meyer, V. J.; Niggemann, M. *Eur. J. Org. Chem.* **2011**, 3671. (c) Meyer, V. J.; Niggemann, M. *Chem.—Eur. J.* **2012**, *18*, 4687. (d) Niggemann, M.; Bisek, N. *Chem.—Eur. J.* **2010**, *16*, 11246. (e) Niggemann, M.; Diba, A. K.; Begouin, J.-M.; M. *Tetrahedron Lett.* **2012**, *53*, 6629.

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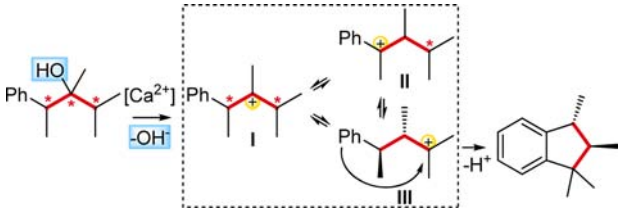
Scheme 1. Rearrangements of Initially Formed Carbocation **I**



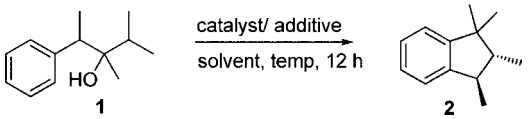
hydride shift or an elimination−reprotonation sequence, might lead to the related carbenium ions **II** and **III**, which in turn can cyclize to give the regioisomeric products. Most interestingly, throughout this process, residual stereocenters in the starting material can be reset to the thermodynamically most favorable *trans*-configuration in **III** before the final cyclization, thus giving rise to diastereomerically pure products even when diastereomeric mixtures are used as starting materials. Opposed to the considerable number of reported direct cyclization reactions of benzyl carbinols,[3h−q] only a handful of examples which involve a prior rearrangement are reported,[3a−g] even though such a rearrangement ring-closure cascade represents a powerful tool to access diastereomerically pure compounds from easily accessible benzyl carbinols.

With these considerations in mind we conducted our initial investigation using benzyl carbinol **1** as a model compound for the screening of a broad spectrum of reaction conditions (Table 1). When **1** was treated with 5 mol % $Ca(NTf_2)_2/Bu_4NPF_6$ in 1,2-dichloroethane (DCE) at rt, the indane **2** was obtained in very low yield (Table 1, entry 1; 10% yield after 12 h) but with complete control of diastereo- and regioselectivity. As expected, the relative stereochemistry was determined to be *trans* by NOE experiments. Intrigued by this preliminary result, we sought to establish reaction conditions in order to improve the yield. To our delight, after 1 h at 80 °C, the desired product **2** was obtained in almost quantitative yield (entry 2). At lower temperature, the reaction rate is reduced and conversion ceases after 12 h (entry 3). The reaction was performed in the presence of molecular sieves to exclude hydrolysis of the catalyst by water generated in the deoxygenation process. However, no influence on the yield was observed. Comparison with other catalyst systems (entries 5, 7, 9, 11, 13) clearly demonstrates the superior activity of the $Ca(NTf_2)_2/Bu_4NPF_6$ system for the intramolecular Friedel−Crafts cyclization. As already mentioned in previous publications,[4a,5,7] the hexafluorophosphate salt is required to form the highly reactive and much more soluble $CaNTf_2PF_6$ species via an anion exchange reaction.[4a] In the presence of 5 or 10 mol % of the superacid $HNTf_2$ (entry 14) the product **2** was obtained in good but considerably lower yield than under calcium catalysis. Interestingly, under acidic conditions the presence of the additive caused the reaction to cease. Among others, such as Bu_4NSbF_6 or Bu_4NBF_4, the initially screened Bu_4NPF_6 was the best additive to promote the process (see Supporting Information (SI)). The reaction rate was significantly lower in other solvents such as toluene, nitromethane, and diethyl ether. Under the thus optimized reaction conditions a series of different benzyl carbinols were cyclized (see Table 2). The synthesis of the cyclization precursors was accomplished by the addition of the appropriate Grignard reagent (methyl-, benzyl-, or isopropylmagnesiumchloride) to the corresponding ketone, yielding the respective carbinol with varying degrees of stereoselectivity. Due to the envisioned redistribution of stereocenters during the ring closure, the stereoselectivity was not further analyzed at this stage.

When the α-position was substituted by an ethyl group as in **3**, instead of the methyl group in **1**, the related indane compound was obtained in good yield and again with full *trans* diastereoselectivity (entry 1).

The presence of the additional phenyl group in **5** has no influence on diastereoselectivity and yield (entry 2). Here, in addition, the phenyl group at the reactive carbocationic

Table 1. Catalyst Screening for the Intramolecular Friedel−Crafts Reaction

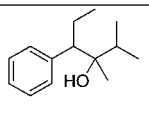
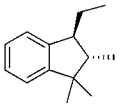
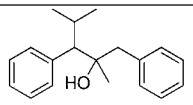
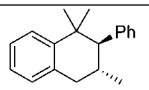
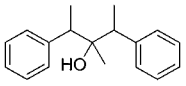
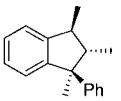
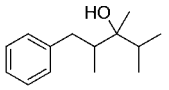
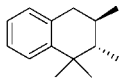
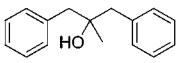
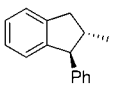
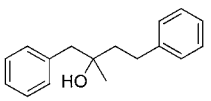
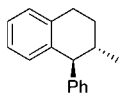
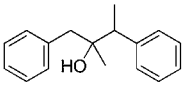
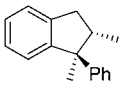
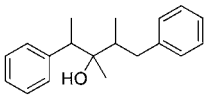
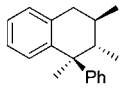
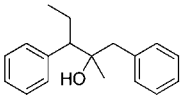
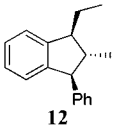
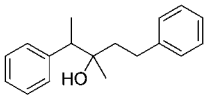
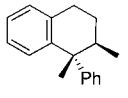
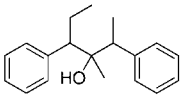
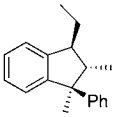
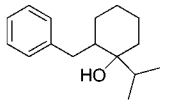
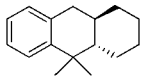
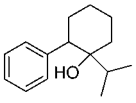
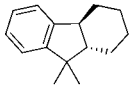
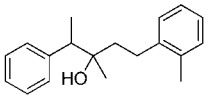
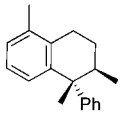
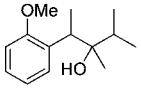
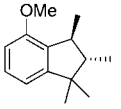
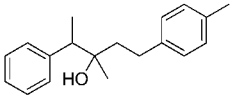
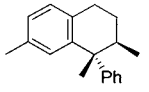
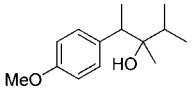
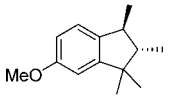
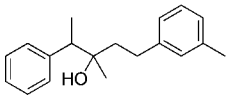
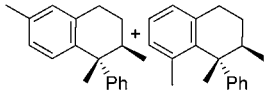
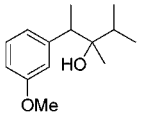
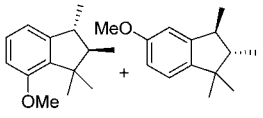
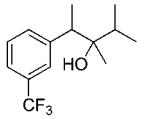
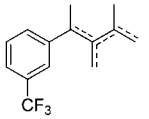


entry[a]	catalyst	additive	temp (°C)	solvent	yield (%)[b]
1	$Ca(NTf_2)_2$	Bu_4NPF_6	rt	DCE	10
2	$Ca(NTf_2)_2$	Bu_4NPF_6	80	DCE	quant[c]
3	$Ca(NTf_2)_2$	Bu_4NPF_6	40	DCE	quant
4	$Ca(NTf_2)_2$	–	40	DCE	0
5	$Ca(OTf_2)_2$	Bu_4NPF_6	40	DCE	0
6	$Ca(OTf_2)_2$	–	40	DCE	0
7	$Ba(NTf_2)_2$	Bu_4NPF_6	40	DCE	0
8	$Ba(NTf_2)_2$	–	40	DCE	0
9	$Ag(NTf)_2$	Bu_4NPF_6	40	DCE	0
10	$Ag(NTf)_2$	–	40	DCE	13
11	$Sc(OTf)_2$	Bu_4NPF_6	40	DCE	22[d]
12	$Sc(OTf)_2$	–	40	DCE	0
13	$HNTf_2$	Bu_4NPF_6	40	DCE	0
14	$HNTf_2$	–	40	DCE	75[d,e]
15	$Ca(NTf_2)_2$	Bu_4NPF_6	40	DCM	quant
16	$Ca(NTf_2)_2$	Bu_4NPF_6	40	Et_2O	8
17	$Ca(NTf_2)_2$	Bu_4NPF_6	40	toluene	12
18	$Ca(NTf_2)_2$	Bu_4NPF_6	40	$MeNO_2$	91

[a] Reaction conditions: The alcohol (0.25 mmol) was dissolved in 0.75 mL of solvent, catalyst (5 mol %) and additive (5 mol %) were added, and the reaction mixture was stirred for 12 h at the indicated temperature. [b] Isolated yield. [c] Yield of **2** after 1 h. [d] 79% yield at 80 °C after 12 h. [e] 49% yield with 10 mol % of $HNTf_2$ at 40 °C after 12 h.

(5) Niggemann, M.; Meel, M. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 1.
(6) (a) Womack, G. B.; Angeles, J. G.; Fanelli, V. E.; Heyer, C. A. *J. Org. Chem.* **2007**, *72*, 7046. (b) Ho, T. L.; Lee, K.-Y.; Chen, C.-K. *J. Org. Chem.* **1997**, *62*, 3365. (c) Suzuki, T.; Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.* **1997**, *119*, 6774. (d) Cai, Q.; Zhao, Z.-A.; You, S.- L.; T. *Angew. Chem., Int. Ed.* **2009**, *48*, 7428. (e) Poulsen, T. B.; Jørgensen, K. A. *Chem. Rev.* **2008**, *108*, 2903. (f) You, S.-L.; Cai, Q.; Zeng, M. *Chem. Soc. Rev.* **2009**, *38*, 2190.
(7) Qui, H.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 409.

Table 2. Catalytic Cyclization of Diastereomeric Mixtures of Benzyl Carbinols

entry[a]	substrate	product	yield[b]	entry[a]	substrate	product	yield[b]
1	 **3**	 **4**	70	11	 **23**	 **24**	60[f,g]
2	 **5**	 **6**	60[c]	12	 **25**	 **26**	96[h]
3	 **7**	 **8**	80[c]	13	 **27**	 **28**	91[i]
4	 **9**	 **10**	85[c]	14	 **29**	 **30**	70[d]
5	 **11**	 **12**	61[c]	15	 **31**	 **32**	70
6	 **13**	 **14**	72[c]	16	 **33**	 **34**	81[j]
7	 **15**	 **16**	77[e]	17	 **35**	 **36**	70
8	 **17**	 **18**	76[f]	18	 **37**	 **38**	80
9	 **19**	 **20**	75[f]	19	 **39**	 67/33 **40**	81
10	 **21**	 30/70 **22**	76[f]	20	 **41**	 **42**	73

[a] Reaction conditions: 5 mol % $Ca(NTf_2)_2/Bu_4NPF_6$ were added to the benzyl carbinol (0.25 mmol) in 0.75 mL of DCE and stirred at 40 °C for 20 h. [b] Isolated yield. [c] Reaction at 80 °C. [d] Mixture 70/30 of *trans*/*cis* diastereomers. [e] The reaction was conducted at 80 °C for 20 h or at 40 °C for 48 h. [f] Reaction at 80 °C for 2 h. [g] Mixture 60/40 of *trans*/*cis* diastereomers. [h] Mixture 90/10 of *trans*/*cis* diastereomers. [i] Mixture 77/23 of *trans*/*cis* diastereomers. [j] Mixture 85/15 of *trans*/*cis* diastereomers.

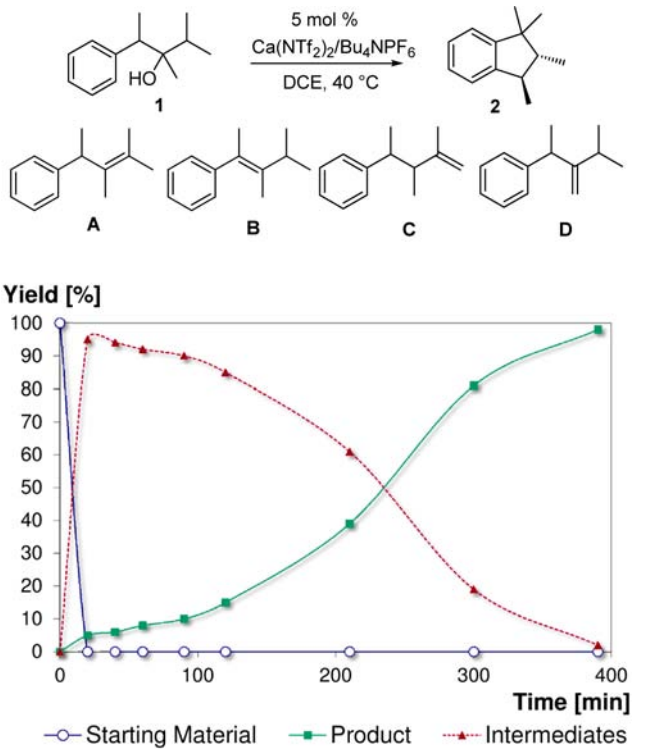
center is oriented as such that it adopts a *trans*-configuration after ring closure. The stereoselectivity in the reactions of benzyl carbinols **7** and **9** is governed by the same preorientation of the phenyl moiety at the carbocationic position. When the formation of regioisomers was prone to occur, the selectivity of the cyclization was generally high.

Compound **9** shows a preference for closure at the more stable tertiary benzylic carbon over closure at its secondary benzylic carbon. The related substrate **11** prefers to close at the less stabilized secondary position, presumably attributed to higher steric repulsion induced by the ethyl group at the tertiary benzylic carbon. Nevertheless, only one out of the three possible diastereomers of **11** was obtained, once again with an all-*trans*-configuration. The regioselectivity was once more exclusive in the cyclization of benzyl carbinol **13**, with steric factors again determining the closure at the benzyl carbon with the methyl substituent. Interestingly, substrate **23**, with an isopropyl substitutent in the α-position, afforded the related six-membered ring. In this case, intramolecular alkylation at the tertiary carbon resulting in the corresponding tetralin is favored over ring closure at the benzylic secondary carbon affording the indane. To investigate the hypothesis that the formation of six-membered rings is generally preferred, we tested a range of substrates in which the reaction of the initially formed carbocation would yield the respective indanes. In all cases (entries 12−19) solely the tetralins were obtained, again always with a high level of *trans* stereoselectivity. The diastereoselectivity was found to be reduced in some cases of tetralin formation (entries 11−14, 16), which might be attributed to the higher flexibility of the cation-bearing carbon chain prior to, and during, the closure of six-membered rings, thus being able to accommodate more than one relative configuration of the residual stereocenters (cf. mechanistic considerations *v.i.*).

To complete the evaluation of scope and limitation of the calcium catalyzed reaction, we investigated the influence of substituents in the arene. Substrates that incorporate an electron-donating methoxy or methyl substituent in the *meta*-position to the site of electrophilic attack on the aromatic ring (entries 8/9, 17/18) react readily to the corresponding indanes or tetralins in good yield and *trans* stereoselectivity. The cyclization of *m*-methoxy and *m*-methyl carbinols **21** or **39** produced a mixture of two relative *trans*-indanes/tetralins, the regioisomer with the substituent in the *meta*-position being predominant. The cyclization of deactivated arenes, such as **41** bearing an electron-withdrawing group, failed, and only a mixture of different olefins **42** was obtained. The same result was obtained for a substrate with a bromide substituent in the *para*-position (not shown).

Preliminary mechanistic investigations were undertaken to gain deeper insight into the stereoselectivity inducing rearrangements prior to the ring closure. Therefore, the distribution of species in the reaction mixture at different reaction times was analyzed (Scheme 2). After ~20 min the starting material **1** is completely converted to different equilibrating species and a small amount of the final product **2**. The intermediates were separated by semipreparative HPLC and identified as **A**, **B**, and traces of **C** and **D**. It is only after 210 min that the concentration of the final product starts to rise. Conversion of the intermediates to the final product is complete after ~6 h. Hence, the first reaction step, the dehydration of the benzyl carbinol by coordination of the calcium catalyst, is comparatively fast. Thereafter, in various deprotonation reprotonation

Scheme 2. Mechanistic Investigations



sequences the double bond isomers **A**−**D** equilibrate for some time until the residual stereocenters have adopted a relative configuration that is favorable for ring closure. That accomplished, once the reactive carbocationic center is formed at a suitable position, ring closure occurs. Thereby, all stereocenters settle into an all-*trans*-configuration.

In summary, we have developed the first catalytic benzyl carbinol cyclization in the presence of a combination of 5 mol % $Ca(NTf_2)_2$ and 5 mol % Bu_4NPF_6 that provides indanes and tetralins in good to high yields with high levels of regio- and diastereoselectivity. The regioselectivity of the cyclizations was found to be governed by subtle changes of the substitution pattern in the reactive carbocationic intermediates, where multiple isomeric ring closures are possible. Cylization to the six-membered tetralins was generally preferred over indane formation. The reaction was found to proceed via an equilibrating mixture of different achiral olefin intermediates after an initial calcium catalyzed dehydration. A ring closure is only encouraged by a single relative configuration of the residual stereocenters, thus determining the high diastereoselectivity. Hence, via this highly elegant self-organizing process diastereomerically pure compounds are accessed from readily available diastereomeric mixtures of benzyl carbinols.

Supporting Information Available. Complete experimental details and compound characterization data, as well as copies of ^{1}H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.