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The MPEG Effect: Improving Asymmetric Processes by Simple Additives

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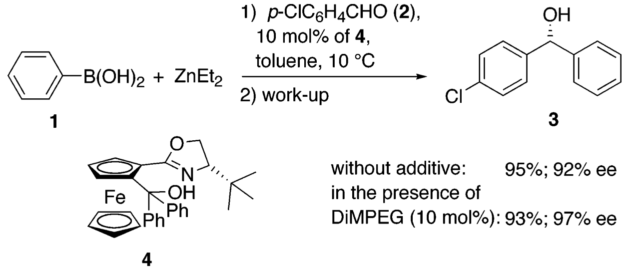
Abstract: Small amounts of simple methoxy poly(ethylene glycol)s (MPEGs) have a beneficial effect on catalyzed asymmetric aryl and alkyl transfer reactions onto aldehydes. The enantiomeric excesses of the products are improved, and this "MPEG effect" allows a reduction of the catalyst loading by a factor of 10.

Efficient catalysts for asymmetric C−C bond formations are difficult to find.[1] Although major progress has recently been made, catalysts yielding products with high enantiomeric excesses at low catalyst loadings (e.g., 1 mol %) are still rare.[2] For the transfer of alkyl, alkenyl, and aryl groups onto aldehydes and imines, organozinc-based systems proved to be most suitable, and since the initial discoveries, many catalysts have been developed that lead to products with excellent enantiomeric excesses in high yields.[3−6] Often, however, 10−20 mol % of the catalyst are required to achieve synthetically useful results. Thus, in terms of catalyst loading, major progress is still most desirable.

Recently, we described catalyzed enantioselective aryl transfer reactions to aldehydes using ferrocene **4** as the catalyst and aryl boronic acids as the aryl source.[5] Two aspects were particularly interesting: First, in most reactions, the enantioselectivies were high, leading to substituted diaryl methanols with >90% ee. Second, to our surprise, we found that the ee values increased when the reactions were performed in the presence of small amounts of DiMPEG (dimethoxy poly(ethylene glycol); Scheme 1).[7−9]

SCHEME 1. Aryl Transfer to Aldehydes Using Boronic Acids



We now wondered about the generality of this "MPEG effect" and hoped that other catalyzed processes could also be improved by the presence of this simple additive. A reduction of the original catalyst loading of 10 mol % to significantly less was considered as the most desirable goal of this study.

Since the increase of enantioselectivity upon DiMPEG addition had so far only been demonstrated in aryl transfer reactions from aryl boronic acids catalyzed by **4**, it was essential to ensure that the effect also occurred in reactions with both other aryl sources and different catalysts. With regard to the first aspect, two systems were studied. One was purely zinc-based and involved the use of mixtures of diphenyl- and diethylzinc.[4] The second utilized triphenylborane as the aryl source and represented a new, previously undescribed aryl transfer method. By applying commercially available DBNE (*N*,*N*-dibutyl norephedrine) as a catalyst, we confirmed that the MPEG effect also occurred with other catalyst systems. The most significant results are summarized in Table 1.

As demonstrated in our previous studies,[4a] the application of ferrocene **4** in the catalyzed phenyl transfer from mixtures of ZnPh$_2$ and ZnEt$_2$ onto aldehyde **5** proceeds well (93% yield) to give the resulting alcohol with excellent enantioselectivity (98% ee). The data in Table 1 (entry 1) reveal that in this system, the addition of 10 mol % DiMPEG does not affect the ee. Although the yield

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(1) (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. (b) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999. (c) *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000.

(2) Recent advances have been summarized in a focused edition on Enantioselective Catalysis: Bolm, C.; Gladysz, J., Eds. *Chem. Rev.* **2003**, *103*, 2761−3400.

(3) For recent reviews, see: (a) Soai, K.; Shibata, T. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; pp 911−922. (b) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757−824.

(4) For selected recent examples, see: (a) Bolm, C.; Hermanns, N.; Hildebrand, J. P.; Muñiz, K. *Angew. Chem.* **2000**, *112*, 3607−3609; *Angew. Chem., Int Ed.* **2000**, *39*, 3465−3467. (b) Bolm, C.; Kesselgruber, M.; Hermanns, N.; Hildebrand, J. P. *Angew. Chem.* **2001**, *113*, 1536−1538; *Angew. Chem., Int Ed.* **2001**, *40*, 1488−1490. (c) For an initial study on the use of ferrocene **4** in aryl transfer reactions using pure ZnPh$_2$ as an aryl source, see: Bolm, C.; Muñiz, K. *Chem. Commun.* **1999**, 1295−1296. (d) Review: Bolm, C.; Hildebrand, J. P.; Muñiz, K.; Hermanns, N. *Angew. Chem.* **2001**, *113*, 3382−3407; *Angew. Chem., Int. Ed.* **2001**, *40*, 3284−3308.

(5) Bolm, C.; Rudolph, J. *J. Am. Chem. Soc.* **2002**, *124*, 14850−14851.

(6) (a) Catalyzed asymmetric aryl-to-imine transfers: Hermanns, N.; Dahmen, S.; Bolm, C.; Bräse, S. *Angew. Chem.* **2002**, *114*, 3844−3846; *Angew. Chem., Int. Ed.* **2002**, *41*, 3692−3694. (b) Enantioselective alkyl-to-imine transfer: Dahmen, S.; Bräse, S. *J. Am. Chem. Soc.* **2002**, *124*, 5940−5941 and references therein.

(7) For example, in the absence of DiMPEG, the addition of 2-bromophenyl boronic acid onto benzaldehyde catalyzed by **4** afforded a product with 73% ee (54% yield). When 10 mol % DiMPEG was added, the ee of the resulting alcohol increased to 88% (58% yield).

(8) For the influence of a*chiral* additives on reactions with organometallic reagents, see: (a) H$_2$O: Ribe, S.; Wipf, P. *Chem. Commun.* **2001**, 299−307. (b) MeOH: Dosa, P. I.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 444−445. (c) Review on additive effects in catalyses: Vogl, E. M.; Gröger, H.; Shibasaki, M. *Angew. Chem.* **1999**, *111*, 1672−1680; *Angew. Chem., Int. Ed.* **1999**, *38*, 1570−1577.

(9) (a) Muñoz-Muñiz, O.; Juaristi, E. *J. Org. Chem.* **2003**, *68*, 3781−3785. (b) For a review on the use of achiral ligands in asymmetric catalyses, see: Walsh, P. J.; Lurain, A. E.; Balsells, J. *Chem. Rev.* **2003**, *103*, 3297−3344. (c) For effects of *chiral* additives in enantioselective reactions with racemic catalysts, see: Mikami, K.; Yamanaka, M. *Chem. Rev.* **2003**, *103*, 3369−3400. (d) For chiral poisoning and asymmetric activations, see: Faller, J. W.; Lavoie, A. R.; Parr, J. *Chem. Rev.* **2003**, *103*, 3345−3367.

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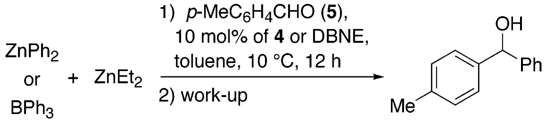
TABLE 1. Asymmetric Phenyl Transfer onto Aldehyde 5 to Give Alcohol 6[a]



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			no additive		DiMPEG (10 mol %) as an additive[e]	
entry	catalyst precursor	aryl source (method)[b]	yield [%][c]	ee [%][d]	yield [%][c]	ee [%][d]
1	**4**	$ZnPh_2/ZnEt_2$ (A)	93	98 (*R*)	75	98 (*R*)
2	DBNE[f]	$ZnPh_2/ZnEt_2$ (A)	81	90 (*S*)	87	95 (*S*)
3	**4**	$BPh_3/ZnEt_2$ (B)	95	93 (*R*)	96	96 (*R*)
4	DBNE[f]	$BPh_3/ZnEt_2$ (B)	85	87 (*S*)	85	93 (*S*)
5	**4**	$ZnPh_2$ (C)	44	77 (*R*)	30−39	78−87 (*R*)
6	DBNE[f]	$ZnPh_2$ (C)	73	62 (*S*)	27−40	20−46 (*S*)

[a] All experiments were performed multiple times to ensure reproducibility. In entries 1−4, the yields and the ee values varied by ±5 and ±1%, respectively. The reactions performed with $ZnPh_2$ and DiMPEG (entries 5 and 6, right columns) were less reproducible, and the yield and ee ranges of six runs are given. [b] Method A: 0.65 equiv of $ZnPh_2$ + 1.3 equiv of $ZnEt_2$. Method B: 1 equiv of BPh_3 + 4.3 equiv of $ZnEt_2$. Method C: 1.5 equiv of $ZnPh_2$. [c] After column chromatography. [d] Enantiomeric ratios were determined by chiral HPLC using a Chiralcel OD column. [e] DiMPEG with M_w = 2500 was used. [f] (1*S*,2*R*)-Enantiomer of DBNE was used. Its antipode gave the enantiomer of **6** and analogous results.

decreases, the ee remains 98%.[10] With DBNE as a catalyst precusor, however, the situation is different. Here, DiMPEG has a mostly positive influence, and both the ee and the yield increase when the reaction is performed in the presence of the additive (Table 1, entry 2). Analogous observations were made with the new aryl transfer system based on the use of mixtures of BPh_3 and $ZnEt_2$. In this case, both the catalysis with ferrocene **4** and the one with DBNE were positively affected by the addition of DiMPEG (Table 1, entries 3 and 4, respectively). Thus, the yield and the ee in the formation of **6** increased when the reactions were performed in the presence of the additive. The results of aryl transfer reactions from pure $ZnPh_2$ in the presence of DiMPEG (Table 1, entries 5 and 6, right columns) were more complex. Compared to reactions performed without the additive, the yields were reduced. However, whereas use of ferrocene **4** as a catalyst precursor gave about equal or better enantioselectivities, application of DBNE afforded alcohol **6** with lower ee. Even though these reactions proved to be difficult in terms of reproducibility, the results were particularly important for the mechanistic interpretation of the DiMPEG effect.

$ZnPh_2$ is known to add to aldehydes even in the absence of a catalyst.[4] If $ZnPh_2$ is mixed with $ZnEt_2$, a new zinc species (most likely a mixed zinc diorganyl such as ZnPhEt) is formed,[4a] and the aryl transfer rate is reduced.[11] Recent DFT calculations revealed that the equilibrium between $ZnEt_2$ and $ZnPh_2$ on one hand and 2 ZnPhEt on the other is virtually thermoneutral (ΔE = 0.2 kJ mol^{-1}).[12]

Thus, under Curtin−Hammet conditions,[13] all three organozinc species are present in solution, with $ZnPh_2$ being the most reactive one.[11,12] As a consequence, in the asymmetric catalysis the aldehyde addition product is formed via two independent routes. The first is catalyzed (by ferrocene **4** or DBNE) and leads to enantiomerically enriched diarylmethanols. The second gives a racemate on an uncatalyzed parallel pathway. The ee of the product will therefore be determined not only by the stereocontrol of the catalyst but also by the ratio of these two reactions. Since the latter is influenced by the concentrations of the aryl zinc species, beneficial effects on the enantioselectivity of the asymmetric aryl transfer reaction could be expected from a shift of the forementioned equilibrium toward the less reactive mixed zinc organyl (by addition of $ZnEt_2$) or a deactivation of a major fraction of the most reactive aryl transfer agent ($ZnPh_2$) by coordination to a another agent (e.g., MPEG in this case). The previous results[4] and the data shown in entries 1−4 of Table 1 support this interpretation. Both the presence of $ZnEt_2$ and the addition of DiMPEG lead to a lower reaction rate (by reducing the quantity of $ZnPh_2$) and give a product with higher ee (by minimizing the uncatalyzed nonasymmetric parallel reaction). The results with pure $ZnPh_2$ (Table 1, entries 5 and 6) are more difficult to interpret. The lower yields in the reactions with DiMPEG follow the proposed scenario and can be regarded as evidence of a reduced availability of the aryl transfer reagent. The decreased ee with DBNE as a catalyst precursor, however, must then be explained by a negative interference of the catalyzed pathway by DiMPEG.[14]

In the equilibrium situation discussed above (and an uncatalyzed parallel reaction leading to racemic product), the catalyst loading is an important factor.[15] Usually, relatively large catalyst quantities are required to guarantee that the major amount of the product stems from the catalyzed pathway. If, however, the uncatalyzed addition reaction is efficiently suppressed, lower catalyst loadings should be applicable. This hypothesis was experimentally confirmed, as revealed by the data presented in Table 2.[16]

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(10) In some cases, the separation of the polyglycols from the product alcohols was somewhat problematic, since in the extractive workup no phase separation of the organic and the aqueous solution was achieved. This problem could easily be solved by addition of brine (10 mL), affording clean product alcohols without traces of the polyglycols.

(11) Kinetic studies by React-IR show a slower aryl transfer from $ZnPh_2/ZnEt_2$ mixtures than from pure $ZnPh_2$. This effect was also found in a related system. Fontes, M.; Verdaguer, X.; Solà, L.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **2004**, *69*, 2532−2543.

(12) Rudolph, J.; Rasmussen, T.; Bolm, C.; Norrby, P.-O. *Angew. Chem.* **2003**, *115*, 3110−3113; *Angew. Chem., Int. Ed.* **2003**, *40*, 3002−3005.

(13) Maskill, H. *The Physical Basis of Organic Compounds*; Oxford University Press: Oxford, 1985; pp 293−295.

(14) In principle, the improvement of the catalytic performance upon addition of MPEG could also be explained by a dissociation of aggregated catalysts. However, since a linear correlation between the ee of a ferrocene of type **4** and that of the product was found in a previous study (Bolm, C.; Muñiz, K.; Hildebrand, J. P. *Org. Lett.* **1999**, *1*, 491−494), we believe that this explanation is less relevant here.

(15) Interestingly, this uncatalyzed pathway also plays a role in the diethylzinc addition to aromatic aldehydes. Although it is known that $ZnEt_2$ does not react with the aldehyde without initial activation, this situation changes when the reaction started. The formed alkoxide can then also become a ligand and thus lead to an undirected alternative pathway.

TABLE 2. Dependence of the Enantioselectivity in the Formation of Diarylmethanol 3 and 1-Phenylpropanol (7) on the Catalyst Loading^a

			no additive		DiMPEG (25 mol %) as an additive^{d,e}	
entry	catalyst loading mol %	product	yield [%]^b	ee [%]^c	yield [%]^b	ee [%]^c
1	10	(*R*)-**3**	95	97	61	97
2	5	(*R*)-**3**	87	95	74	96
3	1	(*R*)-**3**	84	79	71	93
4	0.1	(*R*)-**3**	77	3	72	12
5	10	(*R*)-**7**	92	93	76	94
6	5	(*R*)-**7**	81	93	85	94
7	1	(*R*)-**7**	43	86	79	92
8	0.1	(*R*)-**7**	<5	nd	<10	68

[a] Ferrocene **4** was used as a catalyst precursor in all cases. Reactions affording alcohol **3** (entries 1−4) were carried out with 0.25 mmol of p-ClC_6H_4CHO (**2**), 0.65 equiv of $ZnPh_2$, and 1.3 equiv of $ZnEt_2$ in toluene for 12 h at 10 °C. 1-Phenylpropanol (**7**; entries 5−8) was obtained using the following conditions: 0.25 mmol of benzaldehyde and 1.5 equiv of $ZnEt_2$ in toluene for 12 h at 0 °C. [b] After column chromatography. [c] Enantiomeric ratios of **3** were determined by HPLC using a Chiralcel OB-H column. For the analyses of the enantiomeric ratios of **7**, a Chiralcel OD column was used. [d] DiMPEG with $M_w = 2500$ g/mol was used. [e] Additional experiments showed that the use of 25 or 10 mol % DiMPEG or 10 mol % MonoMPEG ($M_w = 2000$ g/mol) leads to virtually identical results (see also Table 3).

As discussed above, the enantioselective formation of **3** in the presence of 10 mol % ferrocene **4** proceeds well and affords the product with 97% ee in 95% yield. When the catalyst loading is reduced to 5 and 1 mol %, the ee decreases to 95 and 79%, respectively (Table 2, entries 2 and 3). However, this loss of enantioselectivity is significantly lower when 25 mol % DiMPEG is added to the reaction mixture; even with 1 mol % catalyst, 91% ee is achieved (entry 3). If the catalyst amount is further reduced to 0.1 mol % (entry 4), the ee of **3** is low with and without DiMPEG. Interestingly, analogous results were obtained in diethylzinc additions to benzaldehyde (Table 2, entries 5−8).[17] Again, in the presence of 25 mol % DiMPEG, a reduction of the catalyst loading to 1 mol % was possible, and 1-phenylpropanol (**7**) was obtained with >90% ee. Without the additive the enantioselectivity decreases to 86% ee (entry 7). These results demonstrate that the MPEG effect is not only relevant for phenyl transfer reactions but also useful for reducing the catalyst loading (here by a factor of 10) in asymmetric alkylations.

Assuming that the effect of DiMPEG was related to its ability to deactivate Lewis acidic species (such as $ZnPh_2$) by coordination, reactions in the presence of $ZnBr_2$ were performed. Previously, we had found that 10 mol % of this zinc salt led to racemic **3** in the phenyl transfer to aldehyde **2** catalyzed by ferrocene **4**. As the data in Table 3 show, the addition of DiMPEG or monomethoxy poly(ethylene glycol) (MonoMPEG) changed the outcome of the catalysis significantly. Now, relatively large quantities of the zinc salt were tolerated, and reactions performed in the presence of even 50 mol % $ZnBr_2$ led to **3** with 94% ee (Table 3, entry 4). Both Di- as well as MonoMPEG behaved virtually identically. In this context, it should also be noted that large quantities of $ZnBr_2$ (e.g., higher than 50 mol %) do not give a homogeneous solution in toluene even after long periods of sonication. Here also the equilibrium between $ZnBr_2$ and $ZnPh_2$ is important, since $ZnBr_2$ is removed from the reaction mixture by the formation of ZnBrPh due to large amounts of $ZnPh_2$ with respect to the bromide. In the absence of a catalyst, this phenylzinc reagent is expected to react with the carbonyl compound even faster than $ZnPh_2$.

TABLE 3. Enantioselectivities in the Catalyzed Formation of (*R*)-3 in the Presence of Various Amounts of $ZnBr_2$^{a}

		25 mol % DiMPEG as an additive		10 mol % MonoMPEG as an additive	
entry	$ZnBr_2$ [mol %]	yield [%]^b	ee [%]^c	yield [%]^b	ee [%]^c
1	5	85	97	75	97
2	10	86	96	89	97
3	25	80	95	53	95
4	50	66	94	76	94
5	100	57	80	55	80

[a] Ferrocene **4** (10 mol %) was used as a catalyst precursor in all reactions. DiMPEG: $M_w = 2000$ g/mol; MonoMPEG: $M_w = 5000$ g/mol. [b,c] See footnotes of Table 2.

The latter results are relevant for the mechanistic interpretation of the MPEG effect but also noteworthy, since diarylzincs are commonly prepared by transmetalation from aryllithium or aryl Grignard reagents by treatment with zinc dihalides. In this case, various zinc species together with newly formed (Lewis acidic) metal salts are present in the reaction mixture, and all of them can easily interfere with subsequent reactions, thereby rendering the overall process less enantioselective. On the basis of the results presented above, we now assumed that the addition of PEG ethers would suppress these unwanted nonasymmetric pathways by deactivating the (achiral) metal catalysts and preventing their nonenantioselective contribution on the overall process. Preliminary results confirmed this hypothesis. Thus, performing asymmetric aryl transfer reactions catalyzed by **4** in the presence of DiMPEG with arylzinc reagents prepared from $ZnBr_2$ and phenyllithium (followed by filtration through Celite) afforded diarylmethanol **3** with up to 92% ee.[16a,18] Even though the yields in these first attempts were rather low (8−31%), the results are promising, and further optimizations are expected to render this process synthetically useful.

In summary, small amounts of simple PEG ethers can have beneficial effects on catalyzed enantioselective processes with parallel nonasymmetric pathways promoted by achiral Lewis acids. Particularly noteworthy is the fact that this MPEG effect allows a reduction of the catalyst loading and thereby improves the efficiency of an existing asymmetric catalytic process. Finally, a new aryl transfer system based on the use of mixtures of BPh_3 and $ZnEt_2$ was introduced.

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(16) Catalyst loading can also be reduced when a PEG-supported ferrocene is applied as a catalyst. (a) Hermanns, N. Dissertation, RWTH Aachen, Aachen, Germany, 2002. (b) For the synthesis and application of this catalyst, see also: Bolm, C.; Hermanns, N.; Claβen, A.; Muñiz, K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1795−1798.

(17) Without the additive, this reaction has been studied before. For details, see: Bolm, C.; Muñiz-Fernandez, K.; Seger, A.; Raabe, G.; Günther, K. *J. Org. Chem.* **1998**, *63*, 7860−7867.

(18) Rudolph, J.; Bolm, C. Unpublished results.

Experimental Section

Method A. Under an inert atmosphere, in a well-dried reaction vessel (18 mm, 50 mm high) with a Teflon-coated stirring bar, diphenyl zinc (36 mg, 0.16 mmol) is dissolved in toluene (2 mL). After treatment of the mixture with $ZnEt_2$ (33 μL, 0.33 mmol), the solution is stirred for 15−30 min. When required, dimethoxy poly(ethylene glycol) (63 mg, 0.025 mmol, M_w = 2500 g/mol) dissolved in toluene (2 mL) is added. Then, the precatalyst (ferrocene **4**, 12 mg, 0.025 mmol; DBNE, 6.6 mg, 0.025 mmol) is added. After stirring for another 15−30 min at room temperature, the mixture is cooled to 10 °C. Finally, the aldehyde (*p*-Cl-benzaldehyde, 35 mg, 0.25 mmol; *p*-Me-benzaldehyde, 30 mg, 30 μL, 0.25 mmol) is added in one portion. After stirring for 12 h at 10 °C, the reaction mixture is quenched with H_2O (10 mL) and extracted with dichloromethane (3 × 50 mL). The organic layers are combined and dried ($MgSO_4$), and the solvents are removed under reduced pressure. Subsequent purification by flash chromatography (pentane/diethyl ether [85:15]) affords diaryl methanols **3** or **6**.

Method B. In a well-dried reaction vessel (18 mm ∅, 50 mm high) with a Teflon-coated stirring bar, triphenyl borane (60 mg, 0.25 mmol) is dissolved in toluene (2 mL) under an inert atmosphere. After treatment of the mixture with $ZnEt_2$ (110 μL, 1.075 mmol) in one portion, the solution is stirred at room temperature for 15−30 min. When required, dimethoxy poly(ethylene glycol) (63 mg, 0.025 mmol, M_w = 2500 g/mol) dissolved in toluene (2 mL) is added. The protocol continues with the addition of the precatalyst followed by the aldehyde as decribed unter method A.

Method C. Under an inert atmosphere, in a well-dried reaction vessel (18 mm ∅, 50 mm high) with a Teflon-coated stirring bar, diphenyl zinc (82 mg, 0.375 mmol) is dissolved in toluene (2 mL). When required, dimethoxy poly(ethylene glycol) (63 mg, 0.025 mmol, M_w = 2500 g/mol) dissolved in toluene (2 mL) is added. The protocol continues with the addition of the precatalyst followed by the aldehyde as decribed unter method A.

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Supporting Information Available: ^{1}H and ^{13}C NMR analysis and spectra, as well as HPLC conditions for the enantiomeric ratio determinations for products **3**, **6**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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