Enantioconvergent Synthesis by Sequential Asymmetric Horner−Wadsworth−Emmons and Palladium-Catalyzed Allylic Substitution Reactions

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Abstract: A new method for enantioconvergent synthesis has been developed. The strategy relies on the combination of an asymmetric Horner−Wadsworth−Emmons (HWE) reaction and a palladium-catalyzed allylic substitution. Different α-oxygen-substituted, racemic aldehydes were initially transformed by asymmetric HWE reactions into mixtures of two major α,β-unsaturated esters, possessing opposite configurations at their allylic stereocenters as well as opposite alkene geometry. Subsequently, these isomeric mixtures of alkenes could be subjected to palladium-catalyzed allylic substitution reactions with carbon, nitrogen, and oxygen nucleophiles. In this latter step, the respective (*E*) and (*Z*) alkene substrate isomers were observed to react with opposite stereospecificity: the (*E*) alkene reacted with retention and the (*Z*) alkene with inversion of stereochemistry with respect to both the allylic stereocenter and the alkene geometry. Thus, a single γ-substituted ester was obtained as the overall product, in high isomeric purity. The method was applied to a synthesis of a subunit of the iejimalides, a group of cytotoxic macrolides.

Introduction

Kinetic resolution[1] of a racemic starting material is a widely used strategy for obtaining chiral molecules in enantiomerically enriched form. One drawback with standard kinetic resolutions is the inherently inefficient material throughput, since a maximum yield of 50% of the desired product can be obtained. Modified strategies which permit more efficient use of the starting material [e.g., dynamic resolution,[2] parallel kinetic resolution (PKR),[3] and deracemization/stereoinversion[4]] have been demonstrated for some substrate types. Many of the methods reported for dynamic resolution rely on a rapid interconversion of the substrate enantiomers via a reversible proton transfer[2d] or an oxidation/reduction sequence.[2e] The concept of parallel kinetic resolution, which recently was introduced by Vedejs,[3a] is based on the simultaneous use of two different reagents which react with opposite enantiomer preference. Applications to different reaction types are emerging. In a deracemization/stereoinversion sequence, on the other hand, a kinetic resolution is followed by an inversion of configuration of either the product or the unreacted starting enantiomer from the first step. Another alternative strategy is to use an enantioconvergent reaction sequence (i.e., conversion of both enantiomers of a racemate to the same chiral end product via isomeric synthetic intermediates).[4,5] Since the first report of the concept by Fischli and co-workers,[5a] several methods, based on different reactions/reaction combinations, have been demonstrated. How-

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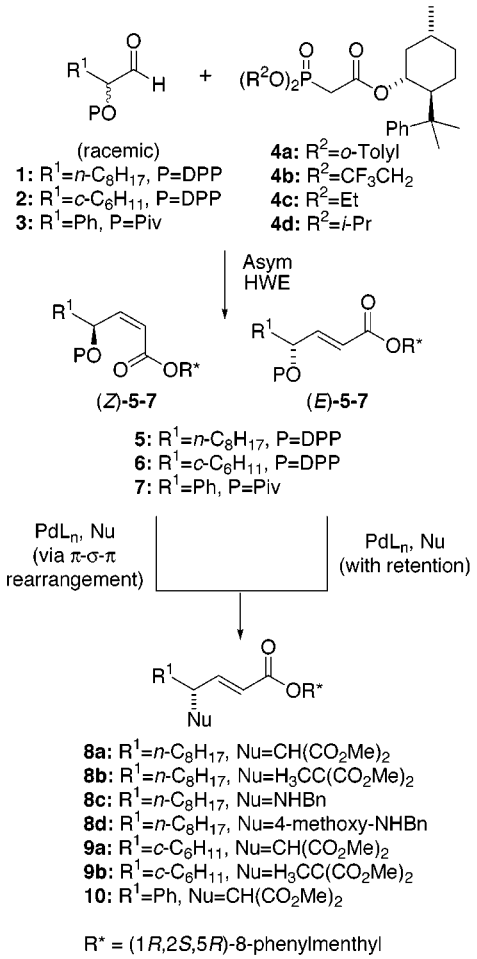
Scheme 1



ever, some of the methods reported require separation and individual manipulation of the respective intermediates formed from the starting enantiomers. In this paper, we report a novel method for enantioconvergent synthesis, which is based on the sequential combination of an asymmetric Horner−Wadsworth−Emmons (HWE) reaction[3d,6] with a palladium-catalyzed allylic nucleophilic substitution.[7] The fact that no separation of the intermediate HWE products is necessary before the stereoconvergent step is an attractive feature of this method.

Results

Our approach is illustrated in Scheme 1. The racemic aldehydes **1**−**3** were available in a few steps from commercially available starting materials (see the Supporting Information).

Table 1. Asymmetric HWE Reactions of Racemic Aldehydes **1**−**3** with Phosphonates **4** To Give Alkenes **5**−**7**[a]

entry	aldehyde (equiv)	phosphonate	product, yield (%)[b]	(*E*):(*Z*) ratio	d.r., (*E*)[c,d]	d.r., (*Z*)[c,d]
1	**1** (2.2)	**4a**	**5**, 96	46:54	94:6	97:3
2	**1** (1.3)	**4a**	**5**, 96	43:57	95:5	98:2
3[f]	**1** (1.1)	**4b**/**4c**[e]	**5**, 63	52:48	94:6	90:10
4	**2** (2.2)	**4a**	**6**, 97	69:31	95:5	>99:1
5	**2** (1.3)	**4a**	**6**, 91	60:40	95:5	>99:1
6	**2** (1.1)	**4a**	**6**, 84	56:44	94:6	>99:1
7	**2** (1.1)	**4b**/**4d**[e]	**6**, 70	60:40	85:15	>99:1
8	**3** (2.2)	**4a**	**7**, 95	41:59	95:5	98:2
9	**3** (1.1)	**4a**	**7**, 96	42:58	97:3	96:4

[a] For reaction conditions, see the Experimental Section and Supporting Information. [b] Isolated combined yield of (*E*)- and (*Z*)-product, judged as ≥95% pure by NMR and TLC. The yield is based on the total amount of phosphonate used. [c] Ratios in crude and isolated products were generally the same, within 1%. [d] In all cases, the absolute configuration of the main product is the one indicated in Scheme 1. [e] 0.5 equiv of each reagent. [f] See ref 3d.

The group P must function well as both a protecting group in the initial asymmetric HWE reaction and then as part of a suitable leaving group in the ensuing palladium-catalyzed allylic substitution. We have found that the $Ph_2P(O)$ (DPP) group works well when R^1 is aliphatic, whereas pivaloyl is a good choice when R^1 is aromatic. Asymmetric HWE reactions with reagents **4** provided alkenes (*Z*)-**5**−**7** and (*E*)-**5**−**7** (Table 1; see also the Supporting Information). Phosphonate **4a** was generally the best choice for obtaining both alkene products with high diastereoselectivities and in excellent yields (entries 1−2, 4−6, 8, and 9). PKR reactions[3d] using a combination of reagents **4b** and **4c** were also tried (entries 3 and 7), but use of reagent **4a** alone gave even better diastereoselectivities. Another interesting observation was that use of close to equimolar amounts of racemic aldehyde and phosphonate still led to excellent diastereoselectivities (entries 2, 5, 6, and 9). Under normal circumstances this phenomenon should only be possible under reaction conditions that allow a dynamic kinetic resolution to take place. This observation could be rationalized from our knowledge that the major diastereomers of the respective (*Z*) and (*E*) products were formed from opposite enantiomers of **1**−**3**.[8] Accordingly, the diastereoselectivities were high even when equimolar amounts of substrate and reagent were used, thus enabling high material throughput with respect to the substrate. The combined yields of (*Z*) and (*E*) product were uniformly high.

In the subsequent step, the mixtures of (*Z*)-**5**−**7** and (*E*)-**5**−**7** were subjected to palladium-catalyzed allylic nucleophilic substitutions. For our initial studies of stereoconvergence, we investigated reactions with representative carbon and nitrogen nucleophiles (sodium dimethyl malonate, sodium dimethyl methylmalonate, benzylamine, and 4-methoxybenzylamine respectively). According to our plan, the reaction should proceed with opposite stereospecificity from the different alkene intermediates: the (*E*)-substrate should react with retention of configuration, whereas the (*Z*)-alkene should, under appropriate conditions, undergo inversion with respect to both the allylic stereocenter and the alkene geometry, via a $\pi-\sigma-\pi$-rearrangement of the intermediate Pd complex.[9] Overall, both substrate isomers should thus be transformed into *the same* stereoisomer of the respective γ-substituted ester (*E*)-**8**−**10**. As shown by

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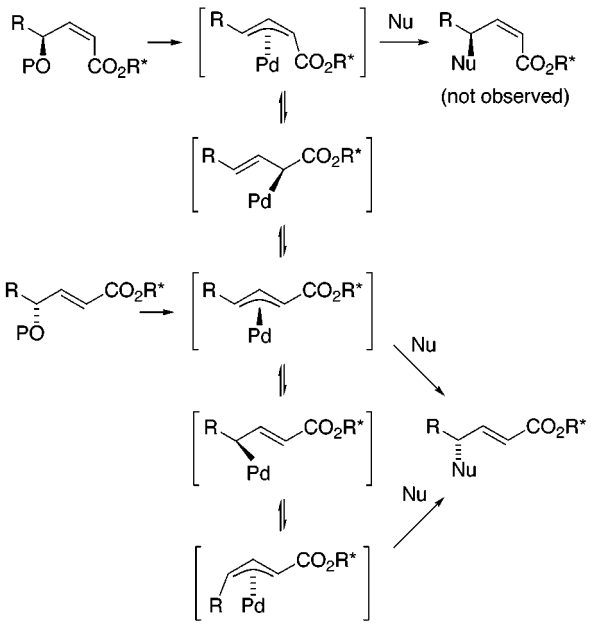
Table 2. Palladium(0)-Catalyzed Reaction of Alkenes **5**−**7** with Nucleophiles[a]

entry	substrate, (*E*):(*Z*)	d.r., (*E*)	d.r., (*Z*)	NuH	product	yield (%)[b]	d.r.[c,d]
1	**5**, 43:57	95:5	98:2	DMM[e]	**8a**	77	90:10
2	**5**, 47:53	95:5	98:2	DMMM[f]	**8b**	79	91:9
3	**5**, 46:54	94:6	97:3	$BnNH_2$	**8c**	83	93:7
4	**5**, 47:53	95:5	98:2	4-MBA[g]	**8d**	88	93:7
5	**6**, 60:40	95:5	>99:1	DMM	**9a**	79	92:8
6	**6**, 60:40	95:5	>99:1	DMMM[f]	**9b**	66	94:6
7	**7**, 46:54	97:3	92:8	DMM	**10**	97	93:7

[a] For reaction conditions, see the Experimental Section and Supporting Information. [b] Isolated yield of product, judged as ≥95% pure by NMR and TLC. In each case, only (*E*)-product was detected. [c] Ratios in crude and isolated products were generally the same, within 1%.[d] In all cases, the absolute configuration of the main product is assigned as indicated in Scheme 1. For details regarding determination of the absolute configurations, see the Supporting Information. [e] Dimethyl malonate. [f] Dimethyl methylmalonate. [g] 4-Methoxybenzylamine.

Scheme 2



the results summarized in Table 2, this plan was realized very well in practice. It is noteworthy that both carbon and nitrogen nucleophiles work well in this context, and that the products were obtained with ≥90:10 diastereoselectivity in good yields, as exclusively (*E*)-isomers even though the allylic substrates **5**−**7** were used as mixtures of geometric and diastereoisomers.

To investigate the influence of the chiral auxiliary in the Pd-catalyzed allylic subtitution, we attempted to cleave the auxiliary in alkene products **5**−**7** to obtain the corresponding methyl ester prior to the Pd reaction. However, several attempts to effect such a transesterification failed to proceed cleanly, presumably due to the steric bulk of the chiral auxiliary.

As seen from Table 2, the diastereomer ratios of products **8**−**10** were slightly decreased compared to those of the substrates **5**−**7**. All of the allowed $\pi-\sigma-\pi$ rearrangements of the intermediate in the Pd-catalyzed step are depicted in Scheme 2.[10] It can be seen that both major isomeric alkenes obtained from the HWE reaction must enter the same dynamic manifold in the Pd-catalyzed substitution. Furthermore, no $\pi-\sigma-\pi$ rearrangement of the intermediate formed from the major substrate isomers can lead to the minor product isomers. The observed slight lowering of the diastereomeric ratios must therefore take place by another process. It is known that crossover between the manifolds can occur slowly, possibly catalyzed by Pd(0).[11] However, use of a minimum amount of Pd catalyst in our study did not completely suppress this unwanted phenomenon.[12]

(10) With a symmetric ligand, other known dynamic processes such as the apparent rotation of the allyl moiety have no effect on the outcome of the reaction.

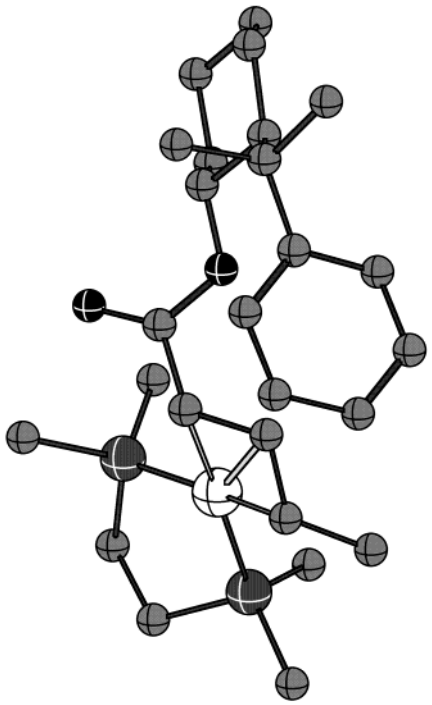


Figure 1. Favored η^3-allyl-Pd intermediate formed from the major substrate isomers, in which the approach of the nucleophile is blocked by the chiral auxiliary. Hydrogens as well as all phenyls except in the auxiliary have been hidden for clarity.

Detailed conformational considerations contribute to an understanding of these results. We have previously shown that the selectivities in Pd-catalyzed allylic alkylations can be rationalized using molecular modeling.[13] Using a recently developed molecular mechanics force field[14] that has been successfully employed in similar systems,[15] we determined the structures of the intermediates depicted in Scheme 2.[16] Interestingly, it was found that a slightly detrimental effect could be expected from the chiral auxiliary. The global minimum for the major isomer is depicted in Figure 1. It can be seen that the phenyl group of the auxiliary fits perfectly above the plane of the allyl moiety, thus blocking the approach of the nucleophile.

(11) (a) Granberg, K. L.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1992**, *114*, 6858 (for previous suggestions of this type of isomerization, see ref 5 in this article). (b) Martin, J. T.; Oslob, J. D.; Åkermark, B.; Norrby, P.-O. *Acta Chem. Scand.* **1995**, *49*, 888. (c) Moreno-Mañas, M.; Morral, L.; Pleixats, R. *J. Org. Chem.* **1998**, *63*, 6160. (d) Amatore, C.; Gamez, S.; Jutand, A.; Meyer, G.; Moreno-Mañas, M.; Morral, L.; Pleixats, R. *Chem. Eur. J.* **2000**, *6*, 3372.

(12) Alternatively, a reversible conjugate addition could cause partial (*Z*)- to (*E*)-isomerization of the substrate, with a corresponding loss of diastereomeric purity.

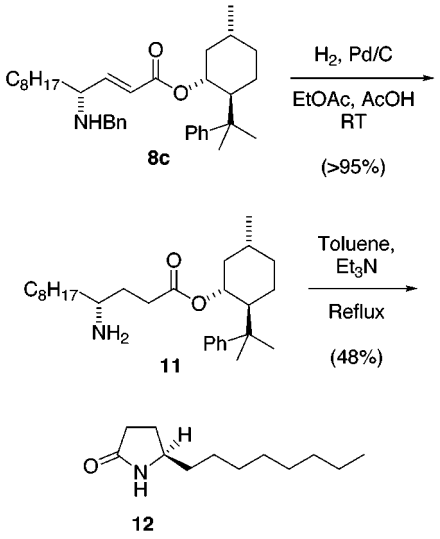
(13) (a) Oslob, J. D.; Åkermark, B.; Helquist, P.; Norrby, P.-O. *Organometallics* **1997**, *16*, 3015. (b) Peña-Cabrera, E.; Norrby, P.-O.; Sjögren, M.; Vitagliano, A.; deFelice, V.; Oslob, J.; Ishii, S.; Åkermark, B.; Helquist, P. *J. Am. Chem. Soc.* **1996**, *118*, 4299.

(14) (a) http://compchem.dfh.dk/PeO/. (b) Hagelin, H.; Åkermark, B.; Norrby, P.-O. *Organometallics* **1999**, *18*, 2884.

(15) Farrell, A. Ph.D. Thesis, University College Dublin, 1999.

(16) The published force field (ref 14) has been updated for use with Maestro v 3.0 from Schrodinger, Inc., www.schrodinger.com. The updated force field is avaliable upon request from Per-Ola Norrby, pon@kemi.dtu.dk.

Scheme 3



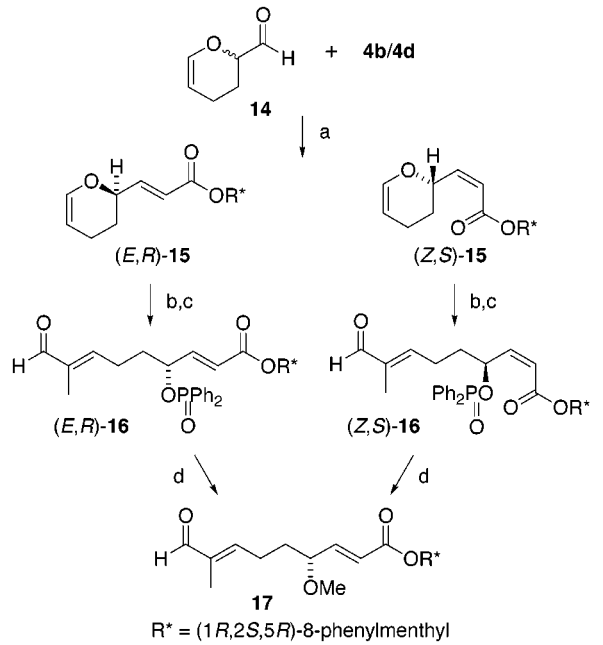
Other conformers in which this blocking is less pronounced are energetically accessible, but the preference of the intermediate for the folded conformation can be expected to lead to a retardation of the reaction. In the intermediate formed from the minor substrate isomers (not illustrated), the approach of the nucleophile is not blocked to the same extent. Thus, the slight lowering of the diastereomeric ratio can be rationalized by an unfavorable kinetic resolution. This conclusion is in line with the observation that the lowering of the diastereomeric ratio is mainly observed in the reactions which show relatively lower yields. In the reaction of substrate **7** (Table 2, entry 7), which yielded 97% product, the decrease in the diastereomeric ratio was insignificant.

As an initial demonstration of synthetic applicability, the chiral auxiliary was cleaved in product **8c** by the sequence depicted in Scheme 3.[3d] Simultaneous reduction of the double bond and debenzylation of **8c** afforded amine **11**, which was further converted into lactam **12**. Not only does this sequence illustrate our enantioconvergent strategy, but it also demonstrates a powerful pathway for obtaining an important class of chiral lactams.

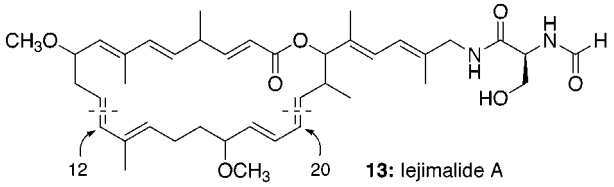
Application to the Synthesis of an Iejimalide Subunit

We have applied this novel strategy to a stereoconvergent synthesis of a subunit of the iejimalides (e.g. iejimalide A, **13**),[17] a group of cytotoxic macrolides. Compound **17**, which is a suitably functionalized building block corresponding to the C12−C20 unit, was prepared as shown in Scheme 4. Racemic aldehyde **14** (acrolein dimer) was first transformed into alkenes (*E*,*R*)-**15**[18] and (*Z*,*S*)-**15**[18] by a PKR.[3d] These intermediates were readily separated by chromatography, and then converted into (*E*,*R*)-**16**[18] and (*Z*,*S*)-**16**,[18] respectively, by oxidative cleavage of the vinyl ether, Wittig chain elongation, and conversion of the formate ester into a DPPO group. Finally, in the key stereoconvergent step, both (*E*,*R*)-**16** and (*Z*,*S*)-**16** could be transformed into the desired iejimalide building block **17**[19] by a Pd-catalyzed allylic substitution using methanol as the nucleophile.[20] It is noteworthy that methanol works well in this context, even though oxygen nucleophiles often perform poorly in intermolecular Pd-catalyzed allylic substitutions, and even though alcohols often function as hydrogen transfer agents in metal-catalyzed reductions.[21] The use of building block **17** in the total synthesis of the iejimalides will be reported in due course.

Scheme 4[a]



[a] Conditions: (a) KHMDS, 18-Crown-6, THF, −78 °C; 50% (*E*,*R*)-**15** (d.r. = 95:5), 42% (*Z*,*S*)-**15** (d.r.= 98:2). (b) (i) Dimethyl dioxirane, K_2CO_3, CH_2Cl_2, 0 °C; (ii) $NaIO_4$, H_2O/THF, room temperature; >95% overall. (c) (i) $Ph_3P{=}C(CH_3)CHO$, toluene, reflux; (ii) $NaHCO_3$, MeOH/H_2O, room temperature; (iii) $ClP(O)Ph_2$, imidazole, CH_2Cl_2/Et_2O, room temperature; (*E*,*R*)-**16**, 34% overall; (*Z*,*S*)-**16**, 28% overall. (d) $Pd_2(dba)_3$, Dppe, MeOH/THF; 66% (d.r. = 94:6) from (*E*,*R*)-**16**, 79% (d.r. > 99:1) from (*Z*,*S*)-**16**.



Conclusions

To summarize, we have demonstrated the possibility of effecting enantioconvergent synthesis by using a combination of an asymmetric HWE reaction and a stereoselective Pd-catalyzed allylic substitution. From a practical viewpoint, it is worth noting that the initial products formed in the HWE step need not be separated before the stereoconvergent step. In the present setting, the overall result is the conversion of a racemic, α-oxygen-substituted aldehyde into a chain-elongated, γ-stereogenic, α,β-unsaturated ester. Initial applications of this strategy in total synthesis have been demonstrated, and additional applications are being studied.

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(18) The descriptors (*R*) and (*S*) refer to the allylic stereocenter.

(19) The major diastereomer of **17** could be obtained isomerically pure after chromatography.

(20) (a) Van der Deen, A.; Van Oeveren, A.; Kellogg, R. M.; Feringa, B. L. *Tetrahedron Lett.* **1999**, *40*, 1755. (b) Hamada, Y; Seto, N.; Takayanagi, Y.; Nakano, T.; Hara, O. *Tetrahedron Lett.* **1999**, *40*, 7791.

(21) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97.

Experimental Section

General Procedure for Asymmetric HWE Reactions. To a solution of phosphonate (1.0 equiv; ca. 0.02 M in THF) and 18-crown-6 (5 equiv), precooled to −78 °C, was added KHMDS (1.0 equiv) under argon. The mixture was stirred for 30 min and then transferred via cannula to a precooled solution of the aldehyde (1.1−2.2 equiv). The reaction was stirred at −78 °C and under argon for 3 h whereafter a 1 M solution of acetic acid in methanol was added. After continued stirring for 5 min phosphate buffer at pH 7 was added, and the mixture was allowed to warm to room temperature. Extraction with EtOAc afforded a crude mixture that was purified by flash chromatography (3−25% EtOAc in hexanes).

General Procedure for Palladium-Catalyzed Allylic Substitution Reactions. To a solution of substrate (1.0 equiv; ca. 0.04 M in THF), $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5−5 mol %), and dppe (6.3−12.5 mol %) in THF was added the nucleophile; the carbon nucleophiles were formed immediately before use, by addition of either DMM or DMMM (6.0 equiv) to NaH (6.0 equiv, 60% dispertion in mineral oil) in THF. The reaction mixture was stirred at room temperature under argon for 1−16 h. Addition of water followed by extraction with Et_2O afforded a crude mixture, which was purified by flash chromatography (5−10% EtOAc in hexanes).

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Note Added in Proof. For a recently reported example of PKR, see: Bertozzi, F.; Crotti, P.; Macchia, F.; Pineschi, M.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 930.

Supporting Information Available: Experimental procedures and characterization data for new compounds and precursors (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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