ORGANIC LETTERS

2000
Vol. 2, No. 23
3731−3734

# Asymmetric Synthesis of the Fully Functional Macrolide Core of Salicylihalamide: Remote Control of Olefin Geometry during RCM

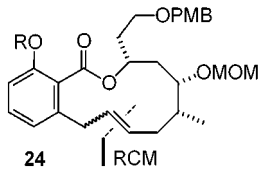
**Alois Fürstner,* Oliver R. Thiel, and Gaetano Blanda**

*Max-Planck-Institut für Kohlenforschung, D-45470 Mülheim/Ruhr, Germany*

*fuerstner@mpi-muelheim.mpg.de*

**Received September 25, 2000**

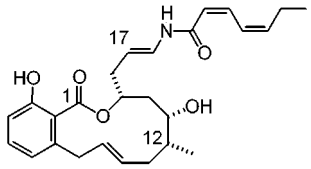
## ABSTRACT




| R | E : Z |
|---|---|
| H | 0 : 100 |
| TBS | 40 : 60 |
| Me | 66 : 34 |

**A catalysis-based approach to the core region 24 of the antitumor agents salicylihalamides A and B is reported. Key steps are two asymmetric hydrogenations of β-keto esters 13 and 16 catalyzed by [(*R*)-BINAP·RuCl$_2$]$_2$·NEt$_3$ and an RCM-based macrocyclization effected by the NHC-containing ruthenium carbene 21. The stereochemical outcome of the latter reaction is controlled by remote substituents on the phenolic OH group of the cyclization precursor 23.**

Bioassay-guided fractionation of the extracts of an unidentified sponge of the *Haliclona* genus collected off the Southwestern Australian coast led to the discovery of salicylihalamides A (**1**) and B (**2**), potent cytotoxic mac-




Salicylihalamide A (**1**): 17(*E*)
Salicylihalamide B (**2**): 17(*Z*)

rolides with a mean GI$_{50}$ concentration of about 15 nM in the NCI's 60 cell line human tumor assay.[1] More importantly, these natural products are unique in the sense that their meangraph profile in this assay shows no significant correlation to that of any other compound contained in the NCI database,[2] suggesting a hitherto unknown mechanism of action. These attractive biological properties render **1** and **2** priority targets for total synthesis and excellent templates for the development and validation of new methodology.

In this context, several procedures for the formation of the rather labile enamide entity of **1** have been reported,[3] while no concise synthesis of the salicylate macrolide segment has been described thus far. As part of our ongoing program on the use of ring closing metathesis (RCM),[4] we have recently outlined an efficient entry into a truncated

(1) Erickson, K. L.; Beutler, J. A.; Cardellina, J. H.; Boyd, M. R. *J. Org. Chem.* **1997**, *62*, 8188.

(2) Since the discovery of salicylihalamide, several closely related cytotoxic agents have been isolated which also combine a salicyclic acid macrolide and a polyunsaturated enamide side chain, cf.: (a) Lobatamides: McKee, T. C.; Galinis, D. L.; Pannell, L. K.; Cardellina, J. H.; Laakso, J.; Ireland, C. M.; Murray, L.; Capon, R. J.; Boyd, M. R. *J. Org. Chem.* **1998**, *63*, 7805. (b) Oximidines: Kim, J. W.; Shin-ya, K.; Furihata, K.; Hayakawa, Y.; Seto, H. *J. Org. Chem.* **1999**, *64*, 153. (c) CJ-12,950 and CJ-13,357: Dekker: K. A.; Aiello, R. J.; Hirai, H.; Inagaki, T.; Sakakibara, T.; Suzuki, Y.; Thompson, J. F.; Yamauchi, Y.; Kojima, N. *J. Antibiot.* **1998**, *51*, 14. (d) Apicularens: Jansen, R.; Kunze, B.; Reichenbach, H.; Höfle, G. *Eur. J. Org. Chem.* **2000**, 913.

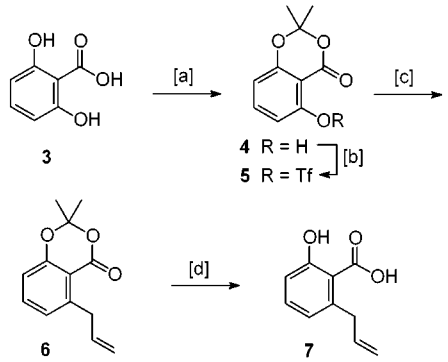
(3) (a) Shen, R.; Porco, J. A. *Org. Lett.* **2000**, *2*, 1333. (b) Snider, B. B.; Song, F. *Org. Lett.* **2000**, *2*, 407. For additional methods for the construction of enamides, see: (c) Hudrlick, P. F.; Hudrlick, A. M.; Rona, R. J.; Misra, R. N.; Withers, G. P. *J. Am. Chem. Soc.* **1977**, *99*, 1993. (d) Alonso, D. A.; Alonso, E.; Nájera, C.; Yus, M. *Synlett* **1997**, 491. (e) Ogawa, T.; Kiji, T.; Hayami, K.; Suzuki, H. *Chem. Lett.* **1991**, 1443. (f) Stefanuti, I.; Smith, S. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2000**, *41*, 3735.

10.1021/ol006646d CCC: $19.00 
**Published on Web 10/27/2000**

version of this core region and have evaluated its biological activity.[5] Described below is an extension of this work which delivers the fully functional macrocycle **24** required for the total synthesis of **1** and **2** and reveals a striking influence of remote functionality on the stereochemical outcome of RCM.

The salicylic acid part is obtained from cheap 2,6-dihydroxybenzoic acid **3** which is converted on a multigram scale into triflate **5** by formation of the isopropylidene derivative **4**[6] and subsequent reaction with triflic anhydride under standard conditions (Scheme 1).[7] This compound can

**Scheme 1**[a]

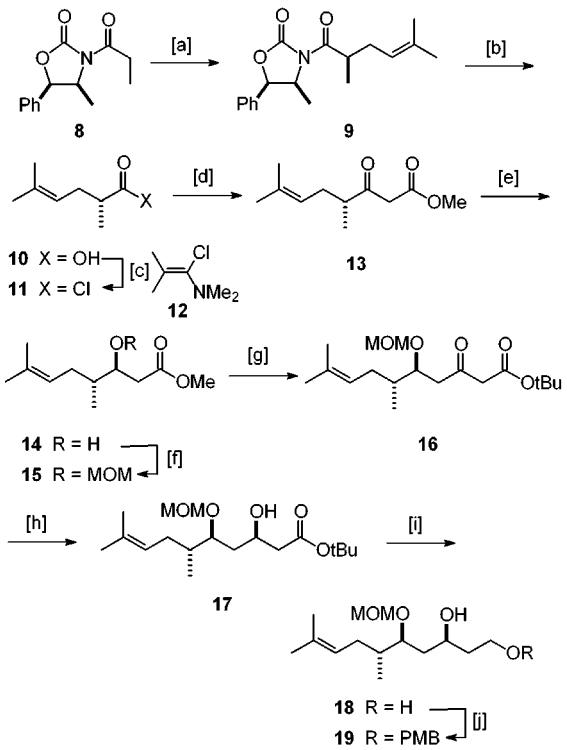



[a] [a] acetone, $SOCl_2$, DMAP, DME, 96%; [b] triflic anhydride, pyridine, 85%; [c] 9-allyl-9-BBN, KOMe, $PdCl_2$(dppf) cat., THF, 83%; [d] $BCl_3$, $CH_2Cl_2$, 96%.

be subjected to allylation in high yield by a modified Suzuki-type reaction[8] according to a procedure previously developed in this laboratory.[9] Specifically, 9-allyl-9-BBN is treated with KOMe to afford a mixture of borate complexes which rapidly transfer the allyl group to the triflate in the presence of catalytic amounts of $PdCl_2$(dppf). Subsequent cleavage of the isopropylidene group of **6** is best achieved with $BCl_3$ in $CH_2Cl_2$ at 0 °C, affording the desired salicyclic acid **7** in almost quantitative yield.

The configuration of the chiral center at C-12 in the aliphatic segment (salicylihalamide numbering) (Scheme 2) is secured by means of an asymmetric alkylation reaction of the oxazolidinone derivative **8** with prenyl bromide.[10]

**Scheme 2**[a]




[a] [a] (i) LiHMDS, THF, −78 °C, 30 min; (ii) dimethylallyl bromide, 0 °C, 16h, 85%; [b] LiOH, $H_2O_2$, THF/$H_2O$, 0 °C, 99%; [c] **12**, $CH_2Cl_2$, 90 min; [d] (i) LDA, methyl acetate, THF, −78 °C, 1 h; (ii) addition of crude **11**, rt, 2 h, 81%; [e] [(*R*)-BINAP·$RuCl_2$]$_2$·$NEt_3$ (0.8 mol %), $H_2$ (4 atm), MeOH, 80 °C, 4 h, 96%; [f] MOMCl, $^iPr_2NEt$, DMAP cat., $CH_2Cl_2$, 40h, 90%; [g] (i) LHMDS, *tert*-butyl acetate, THF, −45 → −30 °C, 90 min; (ii) **15**, −40 → −30 °C, 3 h, 98%; [h] [(*R*)-BINAP·$RuCl_2$]$_2$·$NEt_3$ (1.2 mol %), $H_2$ (80 atm), MeOH, 25 °C, 6.5 h, 93%; [i] $LiAlH_4$, $Et_2O$, 0 °C, 6 h, 98%; [j] (i) NaH, DMF, 75 min; (ii) PMBCl, 90 min, 85%.

Hydrolytic cleavage of the auxiliary affords acid **10**, which is converted into the corresponding acid chloride **11** under strictly neutral conditions using the chloroenamine reagent **12** developed by Ghosez et al.[11] Reaction of crude **11** with the lithium enolate of methyl acetate at low temperature[12] affords the $\beta$-keto ester **13** in 81% yield and sets the stage for a ligand-controlled asymmetric reduction using [(*R*)-BINAP·$RuCl_2$]$_2$·$NEt_3$ as the catalyst ($H_2$, 4 atm; 80 °C) without concomitant hydrogenation of the alkene entity.[13] O-Alkylation of the resulting diastereomerically pure (de ≥ 99%) alcohol **14** with MOMCl, followed by chain extension with lithio *tert*-butyl acetate,[14] delivers $\beta$-keto ester **16** amenable to another double stereodifferentiating hydrogena-

(4) Recent reviews: (a) Fürstner, A. *Angew. Chem.* **2000**, *112*, 3140; *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (c) Schuster, M.; Blechert, S. *Angew. Chem.* **1997**, *109*, 2124; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036. (d) Fürstner, A. *Top. Catal.* **1997**, *4*, 285.

(5) Fürstner, A.; Seidel, G.; Kindler, N. *Tetrahedron* **1999**, *55*, 8215.

(6) Hadfield, A.; Schweitzer, H.; Trova, M. P.; Green, K. *Synth. Commun.* **1994**, *24*, 1025.

(7) (a) Fürstner, A.; Konetzki, I. *Tetrahedron* **1996**, *52*, 15071. (b) Fürstner, A.; Konetzki, I. *J. Org. Chem.* **1998**, *63*, 3072. (c) Fürstner, A.; Nikolakis, K. *Liebigs Ann.* **1996**, 2107.

(8) Review: Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147.

(9) Fürstner, A.; Seidel, G. *Synlett* **1998**, 161.

(10) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

(11) (a) Devos, A.; Remion, J.; Frisque-Hesbain, A.-M.; Colens, A.; Ghosez, L. *J. Chem. Soc., Chem. Commun.* **1979**, 1180. (b) Haveaux, B.; Dekoker, A.; Rens, M.; Sidani, A. R.; Toye, J.; Ghosez, L. *Org. Synth.* **1980**, *59*, 26. (c) For a previous application in total synthesis see: Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1998**, *120*, 2817.

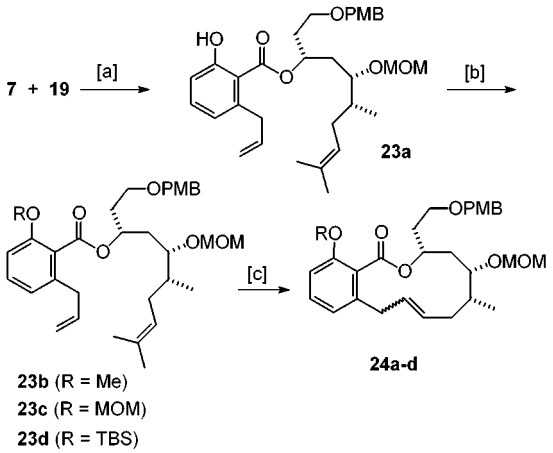
(12) (a) Rathke, M. W.; Deitch, J. *Tetrahedron Lett.* **1971**, 2953. (b) Taber, D. F.; Deker, P. B.; Gaul, M. D. *J. Am. Chem. Soc.* **1987**, *109*, 7488.

(13) (a) Taber, D. F.; Silverberg, L. J. *Tetrahedron Lett.* **1991**, *32*, 4227. (b) Ikariya, T.; Ishii, Y.; Kawano, H.; Arai, T.; Saburi, M.; Yoshikawa, S.; Akutagawa, S. *J. Chem. Soc., Chem. Commun.* **1985**, 922. (c) For a pertinent review see: Noyori, R. *Asymmetric Catalysis in Organic Synthesis*, Wiley: New York, 1994.

(14) Rathke, M. W.; Lindert, A. *J. Am. Chem. Soc.* **1971**, *93*, 2318.

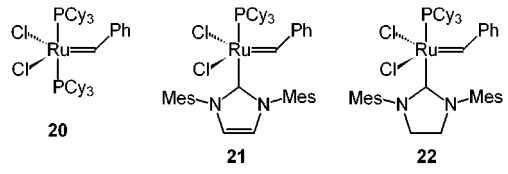
tion reaction. While [(*R*)-BINAP·$RuCl_2$]$_2$·$NEt_3$ as the catalyst again serves this purpose very well, it turns out that optimal results (de > 98%) are obtained under slightly modified conditions by increasing the pressure of $H_2$ to 80 atm but lowering the reaction temperature to 25 °C.[15] Compound **17** is then reduced with $LiAlH_4$, and the resulting diol **18** is converted into the mono-PMB ether derivative **19** by double deprotonation with excess NaH and slow addition of 1 equiv of PMBCl to the resulting dianion; under these conditions, the alkylation of the primary alkoxide was found to be highly favored over the competing protection of the secondary one.[16] Esterification of alcohol **19** with acid **7** under Mitsunobu conditions[17] gives the desired ester **23a** in 88% yield and sets the stage for the crucial metathetic macrocyclization (Scheme 3).

**Scheme 3**[a]




[a] [a] DEAD, $PPh_3$, $Et_2O$, 20 h, 88%; [b] (i) $TMSCH_2N_2$, THF/MeOH (2:1), 46 h, then AcOH, 54% (**23b**); *or* (ii) MOMCl, $^iPr_2NEt$, $CH_2Cl_2$, 18 h, 84% (**23c**); *or* (iii) TBSCl, imidazole, DMF, 24 h, 89% (**23d**); [c] catalyst **21**, see Table 1.

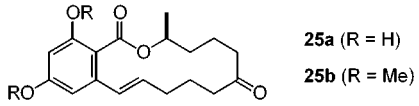
In view of the high degree of substitution on one of the olefinic sites of **23**, it was not surprising to find that the classical Grubbs catalyst **20**[18] fails to afford any cyclized material. Complex **20** is known to be very sensitive toward




the substitution pattern of the alkenes.[19] Gratifyingly, however, exchange of one of the $PCy_3$ ligands by an N-heterocyclic carbene (NHC) helps to overcome this limitation. Thus, compound **21** (Mes = mesityl), its "saturated" analogue **22**, and congeners of this series were recently reported to be superior metathesis catalysts.[20] They have been successfully applied to several handicaped cases beyond the scope of the parent complex **20**, including RCM of highly substituted olefins.[20,21] Therefore, these novel tools hold the promise to effect the macrocyclization of substrate **23** as well.

In fact, diene **23a** is cleanly converted into the desired 12-membered ring **24a** on treatment with catalytic amounts of ruthenium complex **21** in toluene at 80 °C.[22] Surprisingly, however, the product was obtained as a single isomer, which was unambiguously assigned the (*Z*)-configuration on the basis of its high-field NMR spectra.

This outcome was totally unexpected for the following reasons: (i) The vast majority of RCM-based macrocyclizations reported in the literature provide (*E*,*Z*)-mixtures, with the (*E*)-isomer usually being favored.[4] (ii) This general pattern was observed in our previous approach to a truncated salicylihalmide core which has been obtained in an *E*:*Z* ratio of 2.3:1.[5,23] (iii) NHC-containing metathesis catalysts were recently shown to be particularly (*E*)-selective, by enriching the product initially formed in the thermodynamically more favored alkene via subsequent isomerization.[24](iv) Complex **21**, when applied to the total synthesis of zearalenone **25a**, a fungal metabolite closely related to salicylihalamide from the structural point of view, substantiated this notion, giving exclusively the protected (*E*)-isomer **25b** in excellent yield.[25]




In view of this precedence, we speculated which particular conformational constraints within **23a** are responsible for its exclusive cyclization to (*Z*)-**24a**. Possible candidates are the hydrogen bond between the phenolic OH and the COOR group, preventing free rotation in this part of the molecule, or the branches on the aliphatic chain which might force this segment to adopt a strongly preferred conformation.[26]

While addressing these issues, it was noticed that *protection of the seemingly remote phenolic OH group has a*

(15) For precedence see: Harris, C. R.; Kuduk, S. D.; Balog, A.; Savin, K.; Glunz, P. W.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 7050.

(16) See also: (a) McDonald, A. I.; Overman, L. E. *J. Org. Chem.* **1999**, *64*, 1520. (b) Paquette, L. A.; Collado, I.; Purdie, M. *J. Am. Chem. Soc.* **1998**, *120*, 2553.

(17) Review: Mitsunobu, O. *Synthesis* **1981**, 1.

(18) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.

(19) Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310.

(20) These "second generation" metathesis catalysts have been independently and almost simultaneously reported by three groups, cf.: (a) Huang, J.; Stevens, E. D.; Nolan, S. P.; Petersen, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674. (b) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247. (c) Ackermann, L.; Fürstner, A.; Weskamp, T.; Kohl, F. J.; Herrmann, W. A. *Tetrahedron Lett.* **1999**, *40*, 4787. (d) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. (e) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751. (f) Weskamp, T.; Kohl, F. J.; Hieringer, W.; Gleich, D.; Herrmann, W. A. *Angew. Chem.* **1999**, *111*, 2573.

(21) (a) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204. (b) Ackermann, L.; El Tom, D.; Fürstner, A. *Tetrahedron* **2000**, *56*, 2195.

(22) It is important to quench the reaction mixture by addition of ethyl vinyl ether in order to inactivate the catalyst prior to workup.

(23) Fürstner, A.; Kindler, N. *Tetrahedron Lett.* **1996**, *37*, 7005.

(24) Lee, W. C.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 2145.

(25) Fürstner, A.; Thiel, O. R.; Kindler, N.; Bartkowska, B. *J. Org. Chem.*, in press.

*dramatic effect on the stereochemical outcome of the RCM-based macrocyclization* (Table 1).[27] Thus, simple methylation

**Table 1.** RCM-Based Cyclization of **23** to **24**. All Reactions Were Carried Out Using Ruthenium Complex **21** (5 mol %) in Toluene at 80°C unless Stated Otherwise

| entry | substrate | *t* (h) | yield (%) | *E*:*Z* |
|---|---|---|---|---|
| 1 | **23a** | 20 | 69[a] | 0:100 |
| 2 | **23b** | 1.5 | 93 | 66:34 |
| 3 | **23c** | 3 | 91[a] | 68:32 |
| 4 | **23d** | 1 | 91 | 40:60 |

[a] Using 10 mol % of the catalyst.

completely alters the stereochemical bias and leads to the preferred formation of the (*E*)-isomer in excellent yield. A MOM or a TBS group exerts similar effects. The *E*/*Z* ratio did not change during the course of the reaction, nor did we observe any further enrichment in one isomer[24] if purified **24d** was reexposed to 20 mol % of catalyst **22** for 40 h in refluxing $CH_2Cl_2$. These experimental facts indicate that the configuration of the newly formed olefin is substrate- rather than catalyst-controlled even if "second generation" carbene complexes are used. The subtle effects on fairly distant sites of the diene that are difficult to predict on the basis of our present understanding of RCM[28,29] clearly illustrate the need for the development of truly stereoselective metathesis protocols.[30]

In summary, we have developed a concise and high-yielding approach to the fully functional core **24** of the potent antitumor agents salicylihalamides A and B. The synthesis is largely based on catalytic processes,[31] both for the control of the absolute and relative configuration as well as for the preparation of the macrocyclic scaffold. Cleavage of the PMB ether in (*E*)-**24** with DDQ followed by oxidation of the resulting primary alcohol to the corresponding aldehyde sets the stage for the attachment of the enamide side chain according to one of the procedures outlined in the literature.[3] We are actively pursuing the end game of the total synthesis of these highly relevant targets.

**Acknowledgment.** Generous financial support by the Deutsche Forschungsgemeinschaft (Leibniz award to A.F.) and the Fonds der Chemischen Industrie is gratefully acknowledged. We thank Dr. R. Mynott for his help with the unambiguous assignment of the alkene stereochemistry of our RCM products.

**Supporting Information Available:** Full experimental section containing the analytical and spectroscopic data of all new compounds. This material is available free of charge via the Internet at http:pubs.acs.org.

OL006646D

(26) For a pertinent review on how branches on an acyclic compound affect the conformation, see: Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2000**, *39*, 2054 and literature cited therein. We have briefly studied if changing the relative configuration between the Me and the OMOM branch of the cyclization precursor from *anti* to *syn* has an influence on the stereochemical outcome of RCM but found no appreciable effect. Details will be reported in a forthcoming full paper.

(27) For a previous example of the influence of remote substituents on the stereochemical course of RCM, see: (a) Fürstner, A.; Langemann, K. *J. Org. Chem*. **1996**, *61*, 3942. (b) Fürstner, A.; Langemann, K. *Synthesis* **1997**, 792.

(28) We believe that the cyclizations reported herein provide a unique opportunity to reach a better understanding of the transition state of RCM reactions because (i) mechanistically well behaved catalysts are employed, (ii) the substrates have a *defined site of initiation* (the terminal rather than the trisubstituted alkene), and (iii) the strong stereochemical preferences allow to match the results by molecular modeling. Theoretical investigations along these lines are underway.

(29) Another explanaton for the different stereoselectivity in RCM of the O-protected substrates (**23b**−**d**) as compared to the O-unprotected diene **23a** relates to the possible in situ formation of phenolate substituted metathesis catalysts in the latter case. Such compounds are known to be catalytically active (cf: Chang, S.; Jones, L.; Wang, C.; Henling, L. M.; Grubbs, R. H. *Organometallics* **1998**, *17*, 3460). We thank the referee for pointing out this possibility which is presently studied in our laboratory.

(30) Thus far, only macrocyclic (*Z*)-alkenes can be selectively and predicatably formed by metathesis via a new protocol comprising *alkyne* metathesis followed by Lindlar reduction, cf.: (a) Fürstner, A.; Seidel, G. *Angew. Chem.* **1998**, *110*, 1758; *Angew. Chem., Int. Ed.* **1998**, *37*, 1734. (b) Fürstner, A.; Mathes, C.; Lehmann, C. W. *J. Am. Chem. Soc*. **1999**, *121*, 9453. (c) Fürstner, A.; Guth, O.; Rumbo, A.; Seidel, G. *J. Am. Chem. Soc*. **1999**, *121*, 11108. (d) Fürstner, A.; Grela, K. *Angew. Chem*. **2000**, *112*, 1292; *Angew. Chem., Int. Ed.* **2000**, *39*, 1234. (e) Fürstner, A.; Rumbo, A. *J. Org. Chem*. **2000**, *65*, 2608. (f) Fürstner, A.; Seidel, G. *J. Organomet. Chem*. **2000**, *606*, 75. (g) Fürstner, A.; Dierkes, T. *Org. Lett*. **2000**, *2*, 2463.

(31) For a discussion, see: Fürstner, A. *Synlett* **1999**, 1523.