Chiral aluminum complexes as catalysts in asymmetric Baeyer-Villiger reactions of cyclobutanones

Carsten Bolm, Oliver Beckmann, and Chiara Palazzi

Abstract: BINOL-aluminum complexes were successfully employed as mediators and catalysts in asymmetric Baeyer-Villiger rearrangements of cyclobutanones. Good enantioselectivies were achieved with only 15 mol% of the chosen chiral Lewis acid. The enantiomeric excesses obtained have never been reached before in such metal-catalyzed Baeyer-Villiger reactions.

Key words: aluminum, asymmetric catalysis, lactones, oxidations, rearrangement.

Resumé : Des complexes d'aluminium-BINOL ont été employés avec succès en tant que médiateurs et catalyseurs dans des réactions de Baeyer-Villiger asymétriques de cyclobutanones. Avec des taux catalytiques pouvant aller jusqu'à seulement 15 mol% en acide de Lewis chiral, il a été possible d'obtenir des excès énantiomériques jamais atteints auparavant dans de tels oxydations de Baeyer-Villiger catalysées par des métaux.

Mots clés : aluminium, catalyse asymétrique, lactones, oxydation, réarrangement.

Introduction

More than 100 years after its discovery, the Baeyer-Villiger oxidation has become a valuable tool in organic synthesis, owing to its tolerance of functional groups, its regioselectivity, and retention of configuration during the migration step (1). However, the search for an asymmetric metal catalysis for this rearrangement is still a challenging task in modern chemistry. The metal systems that have been devised to render the reaction asymmetric either lack a broader scope of substrates and enantioselectivity or exhibit the drawback of relying on stoichiometric amounts of the metal (2).[3] Existing catalytic procedures employ platinum (3) or copper complexes (4), while (over)stoichiometric variants make use of titanium, tin, zinc, or zirconium (5). These approaches have in part provided appreciable results with respect to enantiomeric excesses, but none represent a practical, synthetically useful method. Thus, further development in this field of asymmetric oxygen insertion is still necessary.

In the present report we introduce a novel catalyst involving a BINOL-aluminum promoter, which has already been successfully applied to other reactions (6): the combination of Me_2AlCl with enantiopure BINOL under a dry, inert gas atmosphere furnishes a catalyst, which is able to oxidize cyclobutanones in an enantioselective manner upon addition of a hydroperoxide (Scheme 1).

To the best of our knowledge this is the first example of a main group metal complex that can mediate in substoichiometric amounts asymmetric Baeyer-Villiger oxidations.[4] The γ-butyrolactones formed are valuable intermediates in the synthesis of pharmaceuticals or natural products, particularly when they are obtained in an enantiomerically pure form, and hence there is a notable effort to gain synthetic access to these important building blocks (7).

Results and discussion

In principle, if a bicyclic cyclobutanone derivative such as **1** is oxidized, two regioisomeric lactones may be formed, since the insertion of oxygen can occur on either side of the carbonyl group. Thus, when the racemic bicyclooctanone **1** was used as the substrate, the novel Al-mediated oxidation afforded not only 7-oxabicyclo[4.3.0]nonan-8-one (**2a**), which is the normal predominately formed lactone in common Baeyer-Villiger reactions (1), but also its regioisomer, 8-oxabicyclo[4.3.0]nonan-7-one (**2b**), in fairly large quantity. With (*S*)-BINOL in combination with Me_2AlCl (metal-to-ligand ratio = 1:1, 50 mol%), the products were (+)-(1*R*,6*R*)-**2a** with 34% ee and (+)-(1*R*,6*S*)-**2b** with 96% ee, exhibiting a remarkably low ratio **2a**:**2b** of 2.7 (Table 1, entry 1). Apparently, this transformation represents an example of an enantiodivergent reaction. Hence, the regioisomeric, enantio-

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[3]For reviews on asymmetric metal-mediated Baeyer-Villiger reactions see ref. 2.
[4]The aforementioned nonstoichiometric variants known to date are based on transition metals platinum or copper (3, 4).

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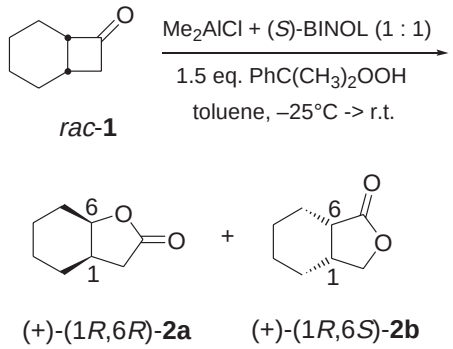
Scheme 1.



merically enriched lactone **2a** is produced chiefly from one enantiomer of the racemic starting material *rac*-**1**, while the substrate antipode gives rise to the other nonracemic regioisomeric product **2b**. Such a behavior has previously been found in biocatalytic Baeyer-Villiger reactions (8) and in the copper-catalyzed Baeyer-Villiger oxidation of the same substrate, *rac*-**1** (4b). Mathematically it was described by Kagan (9).

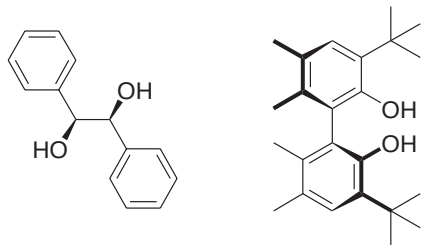
Furthermore, the bicyclic, commercially available ketone *rac*-**3** and the indene-derived cyclobutanone *rac*-**5** each led to two regioisomeric lactones (Table 1, entries 2 and 3). Here, the ratio **a**:**b** of regioisomers had shifted even more in favor of the unusual Baeyer-Villiger product (i.e., toward **4b** and **6b**, respectively). In parallel, the enantiomeric excesses of either lactone are leveling to nearly the same value. In addition, under the applied conditions, the olefinic ketone *rac*-**3** did not seem susceptible to epoxidation according to GC analysis.

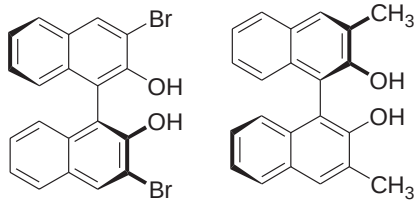
Besides the racemic disubstituted ketones **1**, **3**, and **5**, prochiral 3-monosubstituted cyclobutanones **7**, **9**, **11**, **13**, and **15** were also tested. These are accessible by means of [2+2]-cycloaddition of dichloroketene to an olefin with subsequent dehalogenation (11). The oxidation of 3-phenylcyclobutanone (**7**) yielded the corresponding lactone with 71% ee when 50 mol% of the Al-BINOL mixture was used (Table 1, entry 4). On reducing the catalyst loading to 15 mol%, the ee dropped only slightly to 68%,[5] which is the highest value reached to date in metal-catalyzed Baeyer-Villiger reactions of this substrate (2, 4*d*).

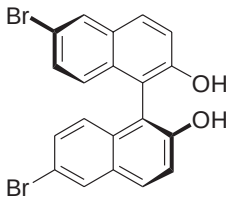
Neither the introduction of a chloro substituent on the arene nor the replacement of the aromatic substituent by an alkyl group at positon C3 had a detrimental effect with respect to the conversion and enantiomeric excess (Table 1, entries 5 and 6). In addition, 3-benzylcyclobutanones, whose lactones are intermediates in syntheses of pharmaceuticals and lignanes (7*e*, 12), proved to be suitable substrates for this (catalytic) asymmetric transformation. Albeit, piperonyl lactone **16** showed a modest ee of 58% in comparison to lactone **14** with 73% ee (Table 1, entries 7 and 8). All oxidations were complete within 12 h. No ketone could be detected by GC analysis and lactones **10** and **14** were isolated after column chromatography in 82 and 87% yield, respectively.

During the evaluation of the new Al-based Baeyer-Villiger system, different metal sources were employed. Aluminum reagents such as $EtAlCl_2$, $AlCl_3$, and $Al(O\text{-}t\text{-}Bu)_3$ in combination with BINOL did not lead to complete oxidation and afforded products with low ee's. Me_3Al with BINOL allowed full conversion but gave a racemate. Solely when dialkyl aluminum chlorides (R_2AlCl with R = Me, Et) were used was the reaction successful. Of the compounds tested, the dimethyl derivative gave somewhat higher enantiomeric excesses than the diethyl metalhalide (e.g., 71 vs. 63% ee for lactone **8** and 68 vs. 54% ee for lactone **10**). The different performances of dialkyl precursors with BINOL as ligand may be indicative of an intricate, oligomeric active species. Since Me_3Al is not an appropriate metal source, even though it readily reacts with diols, a simple mononuclear (BINOL)AlMe structure formed by reaction of BINOL with Me_2AlCl may be excluded as the catalyzing complex, since it should also be expected to be formed from Me_3Al. On the other hand a (BINOL)AlCl species cannot play a decisive role in the enantioselection because of the aforementioned influence of the alkyl rest, i.e., alkyl groups are likely to be still bound to an active aluminum complex. Thus, aluminum catalyst(s) incorporating two or more metal centers and bridging ligands are probable.[6]

A survey of various chiral diols as ligands revealed the binaphthyl scaffold to be the most effective one for achieving



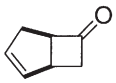
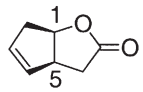
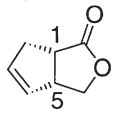
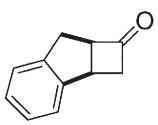
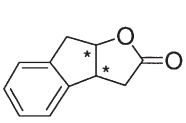
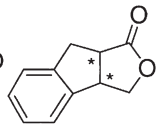
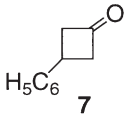
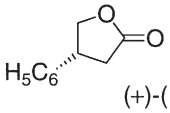
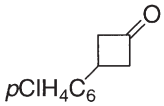
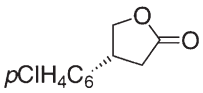
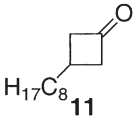
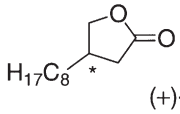
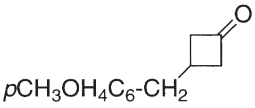
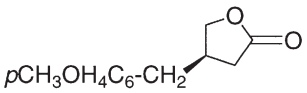
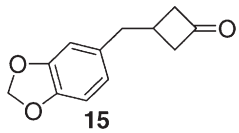
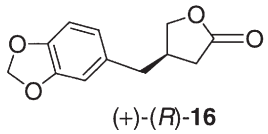




[5] A reduction of catalyst loading to 15 mol% was possible with 4-chlorophenyl cyclobutanone **9** as well (ee dropped from 68 to 57% at full conversion), but not with bicyclooctanone *rac*-**1**. In the latter case full conversion with 25 mol% of BINOL-Al (1:1) could no longer be achieved. However, when 25 mol% of BINOL and 50 mol% of Me_2AlCl were used, the oxidation of *rac*-**1** was still complete, albeit the enantioselectivity deteriorated (**2a**: 5% ee; **2b**: 80% ee).

[6] A similar interpretation was supported by ^{27}Al NMR studies and molecular weight determinations as described in ref. 13.

Table 1. Asymmetric Baeyer-Villiger reaction of various cyclobutanone derivatives mediated by the (*S*)-BINOL-Al system (50 mol%).

Entry	Ketone	Product(s)	ee (%) of product(s)	Ratio of lactones **a**:**b**[a]
1	*rac*-**1**	(+)-(1*R*,6*R*)-**2a** (+)-(1*R*,6*S*)-**2b**	34 (**2a**) 96 (**2b**)	2.7
2	 *rac*-**3**	 (+)-(1*R*,5*S*)-**4a**	 (+)-(1*S*,5*R*)-**4b**	79 (**4a**)[b] 74 (**4b**)	0.8
3	 *rac*-**5**	 **6a**	 **6b**	78 (**6a**) 68 (**6b**)	0.9
4	 **7**	 (+)-(*S*)-**8**	71	–
5	 **9**	 (+)-(*S*)-**10**	68	–
6	 **11**	 (+)-**12**	67	–
7	 **13**	 (+)-(*R*)-**14**	73	–
8	 **15**	 (+)-(*R*)-**16**	58	–

Note: For details see *Experimental*. (*R*)-BINOL as ligand gave the same results yet with inverted absolute configuration of the product.

[a]Calculated from area percentages in the GC.

[b]The ee analysis by chiral GC did not give baseline-separated signals.

enantioselectivity. Me_2AlCl in combination with L-diethyl tartrate, (*R*,*R*)-TADDOL, dianhydro D-mannitol, or D-erythrono lactone was not able to promote an asymmetric oxidation of ketone *rac*-**1** and **7**, and in some cases even failed to afford full conversion to the corresponding lactones. Furthermore, nitrogen-containing diols (salen-type ligands) prevented the ketones from being oxidized, which is consistent with the observed inhibitory effect of additives such as triethylamine, triphenylphosphine oxide, or tetrahydrofuran bearing coordinating sites. Eventually, it was (*S*,*S*)-hydrobenzoin **17**, (*S*)-$BIPHENH_2$ **18** (14*a*), and BINOL and derivatives thereof, in particular **21** (14b), that brought about noticeable enantiomeric excesses with a full conversion.

The test reaction involving 3-phenyl cyclobutanone (**7**) as the substrate and 3,3′-disubstituted BINOLs such as **19**, with two bromo substitutents, or BINOL with two biphenyl or naphthyl moieties, at C3 and C3′ (15), respectively, merely led to racemic lactones if they showed full conversion at all.[7] Only when 3,3′-dimethyl-BINOL ((*R*)-**20**) was used as the ligand, did the oxidation go to completion. Lactone **8** having

[7]We are grateful to Prof. K.A. Jørgensen (Aarhus University) for a kind donation of (*R*)-3,3′-bis(2,5-dimethoxyphenyl)-2,2′-dihydroxy-1,1′-dinaphthyl, which when employed as ligand unfortunately inhibited the Baeyer-Villiger oxidation.

an (*R*)-configuration was achieved with an enantiomeric excess of 40%.[8] However, 6,6′-disubstituted BINOL (*S*)-**21** proved to be the most effective ligand, leading to (*S*)-**8** with 77% ee, which is an even higher enantioselectivity than the one the unsubstituted BINOL ligand induced in the oxidation of **7**.[9] Hence, modifications at this end of the BINOL scaffold with different groups seem to be promising in regards to further improvement of the enantioselectivity. We are currently investigating these BINOL derivatives along with other oxidants and substrates in the aluminum-mediated Baeyer-Villiger oxidation.

Experimental

In a typical procedure, a solution of Me_2AlCl in hexanes (0.10 mL, 1.0 M, 0.10 mmol) was injected to enantiopure BINOL (29 mg, 0.10 mmol; obtained by resolution according to ref. 18) in absolute toluene under argon atmosphere. After stirring for 0.5–1 h at ambient temperature, the ketone (0.20 mmol) was added to the suspension, which within 15 min at room temperature became less turbid. The mixture was cooled down to –25°C before the addition of cumene hydroperoxide (technical grade 80%, 57 mg, 0.30 mmol) and then slowly let warm to room temperature again. After 12 h of stirring the mixture was treated with aq. HCl (0.5 M), then diluted with ether, washed with saturated. aq. $NaHCO_3$ and brine, and finally dried over $MgSO_4$. The obtained solution was directly subjected to GC analysis for the determination of the conversion (calculated from area percentages in the GC) and the ee (using chiral columns). The peak assignments were assured by comparison with chromatograms of ketones and racemic lactones.

For the correlations of optical rotations and absolute configurations, see ref. 10*a* for **2a**, ref. 10*b* for **2b**, ref. 10*c* for **8**, ref. 10*d* for **10**, ref. 7*e* for **14**, and ref. 10*e* for **16**. In ref. 7*a*, (*R*)-configurated 3-pentyl- and 3-hexyl-butyrolactones were shown to have a positive sign of optical rotation. Thus, the absolute configuration of octyl-bearing lactone (+)-**12** is supposed to be (*R*) too.

When isolated yields were to be determined, 1 to 2 mmol of ketone were employed and the product purified by column chromatography on silica gel.

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References

1. (*a*) A. Baeyer and V. Villiger. Ber. Deut. Chem. Ges. **32**, 3625 (1899); (*b*) G. Krow. Org. Reactions, **43**, 251 (1993); (*c*) M. Renz and B. Meunier. Eur. J. Org. Chem. 737 (1999).
2. (*a*) C. Bolm. *In* Advances in catalytic processes. Vol. 2. *Edited by* M.P. Doyle. JAI Press, Greenwich. 1997. p. 43; (*b*) C. Bolm, O. Beckmann, and T.K.K. Luong. *In* Transition metals for organic synthesis. Vol. 2. *Edited by* M. Beller and C. Bolm. Wiley–VCH, Weinheim. 1998. p. 213; (*c*) G. Strukul, Angew. Chem. **110**, 1256 (1998); Angew. Chem. Int. Ed. Engl. **37**, 1198 (1998); (*d*) C. Bolm and O. Beckmann. *In* Comprehensive asymmetric catalysis. *Edited by* E.N. Jacobsen, A. Pfaltz, and H. Yamamoto. Springer, Berlin. 1999. p. 803.
3. (*a*) A. Gusso, C. Baccin, F. Pinna, and G. Strukul. Organometallics, **13**, 3442 (1994); (*b*) G. Strukul, A. Varagnolo, and F. Pinna. J. Mol. Catal. **117**, 413 (1997); (*c*) C. Paneghetti, R. Gavagnin, F. Pinna, and G. Strukul. Organometallics, **18**, 5057 (1999).
4. (*a*) C. Bolm, G. Schlingloff, and K. Weickhardt. Angew. Chem. **106**, 1944 (1994); Angew. Chem. Int. Ed. Engl. **33**, 1848 (1994); (*b*) C. Bolm and G. Schlingloff. J. Chem Soc. Chem. Commun. 1247 (1995); (*c*) C. Bolm, G. Schlingloff, and F. Bienewald. J. Mol. Cat. **117**, 347 (1997); (*d*) C. Bolm, T.K.K. Luong, and G. Schlingloff. Synlett, 1151 (1997); (*e*) C. Bolm, O. Beckmann, and T.K.K. Luong. *In* Asymmetric oxidation reactions: a practical approach. *Edited by* T. Katsuki. Oxford University Press, Oxford. 2001. p. 1476.
5. (*a*) M. Lopp, A. Paju, T. Kanger, and T. Pehk. Tetrahedron Lett. **37**, 7583 (1996); (*b*) T. Kanger, K. Kriis, A. Paju, T. Pehk, and M. Lopp. Tetrahedron: Asymmetry, **9**, 4475 (1998); (*c*) T. Sugimura, Y. Fujiwara, and A. Tai. Tetrahedron Lett. **38**, 6019 (1997); (*d*) T. Shinohara, S. Fujiora, and H. Kotsuki. Heterocycles, **55**, 237 (2001); (*e*) C. Bolm and O. Beckmann. Chirality, **12**, 523 (2000).
6. (*a*) K. Maruoka and H. Yamamoto. *In* Catalytic asymmetric synthesis *Edited by* I. Ojima. VCH, New York. 1993. p. 413; (*b*) T. Ooi and K. Maruoka. *In* Comprehensive asymmetric catalysis. Vol. 3. *Edited by* E.N. Jacobsen, A. Pfaltz, and H. Yamamoto. Springer, Berlin. 1999. p. 1237; (*c*) C. Chapuis and J. Jurczak. Helv. Chim. Acta, **70**, 436 (1987); (*d*) J. Bao, W.D. Wulff, and A.L. Rheingold. J. Am. Chem. Soc. **115**, 3814 (1993); (*e*) H. Urabe, K. Yamashita, K. Suzuki, K. Kobayashi, and F. Sato. J. Org. Chem. **60**, 3576 (1995); (*f*) M.S. Sigman and E.N. Jacobsen. J. Am. Chem. Soc. **120**, 5315 (1998); (*g*) Y. Hamashima, D. Sawada, M. Kanai, and M. Shibasaki. J. Am. Chem. Soc. **121**, 2641 (1999); (*h*) K. Maruoka, T. Itoh, T. Shirasaka, and H. Yamamoto. J. Am. Chem. Soc. **110**, 310 (1988); (*i*) K.B. Simonsen, N. Svenstrup, M. Roberson, and K.A. Jørgensen. Chem. Eur. J. **6**, 123 (2000); (*j*) M. Takamura, Y. Hamashima, H. Usuda, M. Kanai, and M. Shibasaki. Angew. Chem. **112**, 1716 (2000); Angew. Chem. Int. Ed. **39**, 1650 (2000).
7. (*a*) H. Kosugi, K. Tagami, A. Takashi, H. Kanna, and H. Uda. J. Chem. Soc. Perkin Trans. 1, 935 (1989); (*b*) A. Pelter, R.S. Ward, D.M. Jones, and P. Maddocks. J. Chem. Soc. Perkin Trans. 1, 2621 (1993); (*c*) S.S. Canan Koch and A.R. Chamberlin. J. Org. Chem. **58**, 2725 (1993); (*d*) M.P. Doyle, M.N. Protopopova, Q.–L. Zhou, J.W. Bode, S.H. Simonsen, and V. Lynch. J. Org. Chem. **60**, 6654 (1995); (*e*) Shiotani, H. Okada, T. Yamamoto, K. Nakamata, J. Adachi, and H. Nakamoto. Heterocycles, **43**, 113 (1996); (*f*) C. Mazzini, J. Lebreton, V. Alphand, and R. Furstoss. Tetrahedron Lett. **38**, 1195 (1997); (*g*) A. Krief, A. Ronvaux, and A. Tuch. Bull. Soc. Chim. Belg. **106**, 699 (1997); (*h*) K. Hirayama and K. Mori. Eur. J. Org. Chem. 2211 (1999); (*i*) B.M. Trost and Y.H. Rhee. J. Am. Chem. Soc. **121**, 11680 (1999); (*j*) Y. Takaya, T. Senda, H. Kurushima, M. Ogasawara, and T. Hayashi. Tetrahedron: Asymmetry, **10**, 4047 (1999); (*k*) G. Fardella, P. Barbetti, G. Grandolini, I. Chiappini, V. Ambrogi, V. Scarcia, and A.

[8] This is not the first example of sheer BINOL being a superior ligand in comparison to its 3,3′-substituted derivatives, cf.: ref. 16.
[9] For other catalyses exhibiting a marked improvement when, instead of BINOL, 6,6′-dibromo-BINOL was used, see ref. 17.

Furlani Candiani. Eur. J. Med. Chem. **34**, 515 (1999); (*l*) D. Takano, M. Doe, Y. Morimoto, K. Yoshihara, and T. Kinoshita. J. Heterocyclic Chem. **36**, 221 (1999); (*m*) N. Gathergood and K.A. Jørgensen. Chem. Commun. 1869 (1999); (*n*) E.J. Bergner and G. Helmchen. Eur. J. Org. Chem. 419 (2000).

8. V. Alphand, A. Archelas, and R. Furstoss. Tetrahedron Lett. **30**, 3663 (1989).
9. H.B. Kagan. Croatica Chem. Acta, **69**, 669 (1996).
10. (*a*) W.H. Pirkle and P.E. Adams. J. Org. Chem. **45**, 4111 (1980); (*b*) I.J. Jakovac, H.B. Goodbrand, K.P. Lok, and J.B. Jones. J. Am. Chem. Soc. **104**, 4659 (1982); (*c*) G. Helmchen and G. Nill. Angew. Chem. **91**, 66 (1979); Angew. Chem. Int. Ed. Engl. **18**, 65 (1979); (*d*) J.W. Lawston and T.D. Inch. J. Chem. Soc. Perkin Trans. 1, 2629 (1983); (*e*) M. Kuhn and A. von Wartburg. Helv. Chim. Acta, **50**, 1546 (1967).
11. (*a*) L. Ghosez, R. Montaigne, A. Roussel, A. Vanlierde, and P. Mollet. Tetrahedron, **27**, 615 (1971); (*b*) L.R. Krepski and A. Hassner. J. Org. Chem. **43**, 2879 (1978); (*c*) V. Kaiwar, C.B. Reese, E.J. Gray, and S. Neidle. J. Chem. Soc. Perkin Trans. 1, 2281 (1995).
12. R.S. Ward. Tetrahedron, **46**, 5029 (1990).
13. M. Brunner. PhD thesis. RWTH Aachen, Germany. 1995.
14. (*a*) J.B. Alexander, D.S. La, D.R. Cefalo, A.H. Hoveyda, and R.R. Schrock. J. Am. Chem. Soc. **120**, 4041 (1999); (*b*) G.D.Y. Sogah and D.J. Cram. J. Am. Chem. Soc. **101**, 3035 (1979).
15. (*a*) S.S. Zhu, D.R. Cefalo, D.S. La, J.Y. Jamieson, W.M. Davies, A.H. Hoveyda, and R.R. Schrock. J. Am. Chem. Soc. **121**, 8251 (1999); (*b*) K.B. Simonsen, K.V. Gothelf, and K.A. Jørgensen. J. Org. Chem. **63**, 7536 (1998); (*c*) P. Kratky, U. Haslinger, and M. Widhalm. Monatsh. Chem. **129**, 1319 (1998).
16. A. Graven, M. Johannsen, and K.A. Jørgensen. Chem. Commun. 2372 (1996).
17. (*a*) M. Terada, Y. Motoyama, and K. Mikami. Tetrahedron Lett. **35**, 6693 (1994); (*b*) H. Ishitani, M. Keno, and S. Kobayashi. J. Am. Chem. Soc. **119**, 7153 (1997).
18. D. Cai, D.L. Hughes, T.R. Verhoeven, and P.J. Reider. Tetrahedron Lett. **36**, 7991 (1995).