Natural Products

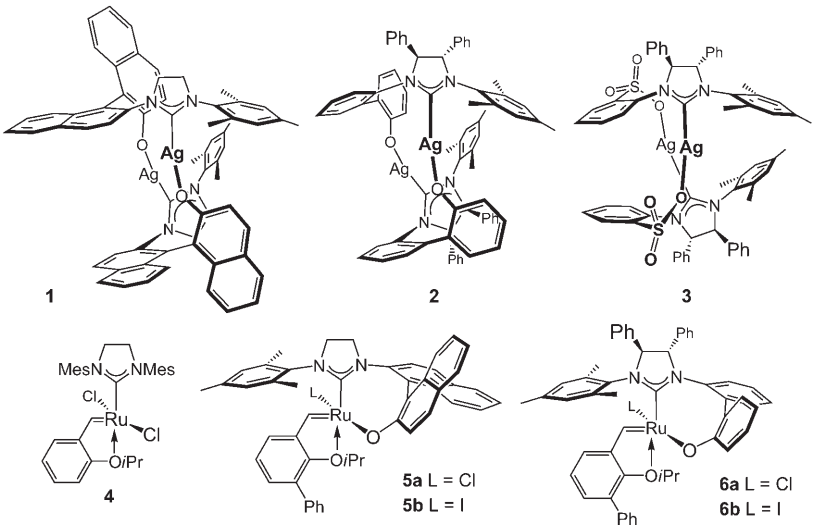
DOI: 10.1002/ange.200700501

Chiral N-Heterocyclic Carbenes in Natural Product Synthesis: Application of Ru-Catalyzed Asymmetric Ring-Opening/Cross-Metathesis and Cu-Catalyzed Allylic Alkylation to Total Synthesis of Baconipyrone C**

*Dennis G. Gillingham and Amir H. Hoveyda**

Natural product synthesis and development of catalysts and methods benefit from a critical relationship.[1] A new process provides access to alternative, and often more efficient, routes—it renders a previously untenable scheme feasible. Total synthesis, an important testing ground for a new catalyst and the transformation that it promotes, is particularly valuable when it necessitates the discovery of a method that might otherwise remain unknown. Herein, we report an enantioselective synthesis of the unusual siphonariid metabolite baconipyrone C.[2] The total synthesis demonstrates the utility of recently developed N-heterocyclic carbene (NHC) complexes (Scheme 1); it provides the first application of Ru-catalyzed asymmetric olefin metathesis.[3–4] Completion of the synthesis necessitated the development of a new protocol for catalytic asymmetric allylic alkylation (AAA) as well—the first with an alkylaluminum reagent.[5,6]

The retrosynthesis for baconipyrone C is presented in Scheme 2. We envisioned that pseudo-C_2-symmetric diketone **I** might be prepared via 1,6-diene **II**; this approach would allow us to investigate whether chiral (NHC)Cu complexes developed for AAA reactions[5,6] provide efficient access to 1,6-diene **II** via **III**. Segment **IV** would be synthesized by reductive cleavage of pyran **V**, secured by asymmetric ring-opening/cross-metathesis (AROM/CM) of **VI**.[3e] The chiral catalyst-based approach in Scheme 2 thus differs fundamentally from the well-established chiral auxiliary-based diastereoselective aldol strategies[7] employed in the only other recorded total synthesis of this target.[8]



Scheme 1. NHC-based complexes examined and utilized for the total synthesis of baconipyrone C.

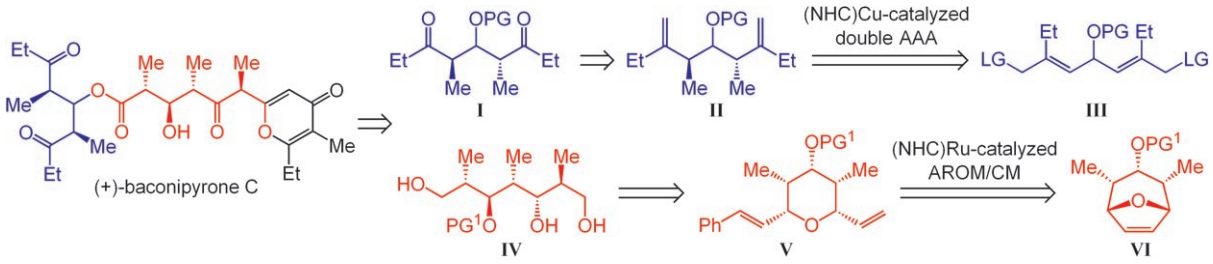
The catalytic double AAA proposed for conversion of **III** to **II** establishes, in a single operation, the two stereogenic centers in **I**, but would present a number of challenges as well. One set of complications is inherent to processes that are promoted by a single chiral catalyst and that involve diastereo- and enantioselective formation of proximal stereogenic centers. The initially established center can strongly influence, often in competition with the chiral catalyst, the sense of stereocontrol in the subsequent bond formation. Thus, as illustrated in Scheme 3, addition of the first Me unit to diene **III** would generate two new stereogenic centers. The first alkylation delivers **VII** (or the corresponding *syn* isomer), wherein the central carbon, unlike **III** or the desired final product **II**, is a stereogenic center. Selective formation of **II** requires that the second alkylation occur preferentially with the *opposite* sense of relative stereochemistry (vs. **III**→**VII**); otherwise, *meso*-**VIII** AAA would be generated. That is, **II** can only be obtained selectively if the chiral catalyst—not the stereogenic centers in **VII**—dictates the course of the second alkylation.

The substitution pattern of the olefins in **III** poses another challenge. This class of olefins represents a difficult and relatively unexplored set of substrates for catalytic AAA,[5] the first examples of which were only recently reported.[9] Existing disclosures do not, however, contain reactions that involve acyclic substrates with a non-aromatic olefin substituent.

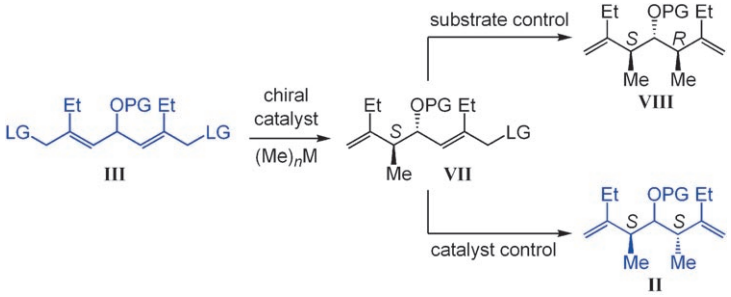
[*] D. G. Gillingham, Prof. A. H. Hoveyda
Department of Chemistry
Merkert Chemistry Center
Boston College
Chestnut Hill, MA 02467 (USA)
Fax: (+1) 617-552-1442
E-mail: amir.hoveyda@bc.edu

[**] We are grateful to the NIH (GM-47480) and NSF (CHE-0213009) for financial support.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



Scheme 2. Retrosynthetic analysis for baconipyrone C. AAA = asymmetric allylic alkylation; AROM/CM = asymmetric ring-opening/cross-metathesis; PG = protecting proup; LG = leaving group.



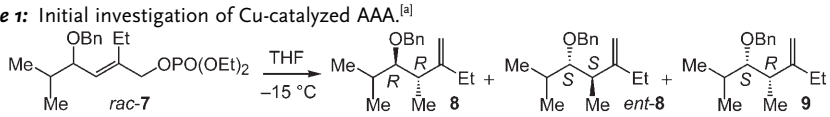
Scheme 3. Catalyst versus substrate control in the catalytic double AAA.

To identify conditions for the catalytic double AAA, we investigated related reactions of *rac*-**7** (Table 1). Protocols involving dialkylzinc reagents, highly effective for AAA of disubstituted and even the sterically congested α-trisubstituted olefins,[3f,6a] miss the mark in this case (Table 1, entries 1–4). We thus turned our attention to the more Lewis acidic and nucleophilic Me_3Al.[10] Reaction with CuCN proved encouraging (entry 5): in contrast to alkylation with Me_2Zn (10% conv. in 24 h, 200 mol% CuCN; entry 1), reaction with Me_3Al proceeds to greater than 98% conversion in 4 h with 15 mol% Cu salt, affording a 9:1 mixture of **8**:**9** (>20:1 $S_N2':S_N2$). The observed diastereoselectivity implies that substrate-controlled alkylation favors formation of the *anti* diastereomer—desirable in the first part of the double AAA but not the second, which, as a result, must be controlled by the chiral catalyst. Next, we probed alkylations in the presence of chiral NHC complexes **1**–**3** (Scheme 1) and commercially available $CuCl_2{\cdot}2H_2O$. Complexes **1**[6a] and **3**,[11] unlike **2**,[3f] (Table 1, entries 6–8) catalyze the desired process in 98% and 94% *ee*, respectively. Chiral NHC–sulfonate **3** is, however, more efficient than NHC–aryloxide **1**.

The observation that NHC complex **3** with $CuCl_2{\cdot}2H_2O$ promotes the reaction beyond 50% conversion to afford **8** in high *ee* suggests that this system can influence the AAA of the slower-reacting enantiomer of **7** (*S*-**7**). As illustrated in Scheme 4, variations in diastereoselectivity (**8**:**9**) and the enantiomeric purity of *anti* diastereomer **8** (Table 1, entries 8–10) shed light on the ability of chiral NHC **3** to control the outcome of the catalytic double AAA. A transformation that proceeds to completion and is fully controlled by the catalyst would be a parallel kinetic resolution[12] that furnishes a 1:1 mixture of **8**:**9**. Specifically, *anti* isomer **8** would be the sole product from AAA of the faster reacting *R*-**7** (conv. ≤50%), and *syn* isomer **9** would be generated exclusively through the remainder of the process (the C–C bond would be formed with the same sense of enantioselectivity in both cases). Any amount of *ent*-**8** formed would be as a result of substrate control. Variations in diastereoselectivity (from 1:1) or lowering of enantioselectivity in the formation of **8** at high conversion would imply loss of catalyst control in alkylation of the slower-reacting *S*-**7**. As the catalytic AAA approaches complete conversion, **8** and **9** are obtained in 1.5:1 ratio and enantiopurity of **8** decreases only slightly (Table 1, entries 8–10), indicating that the Cu complex derived from **3** would be effective in promoting the double AAA.

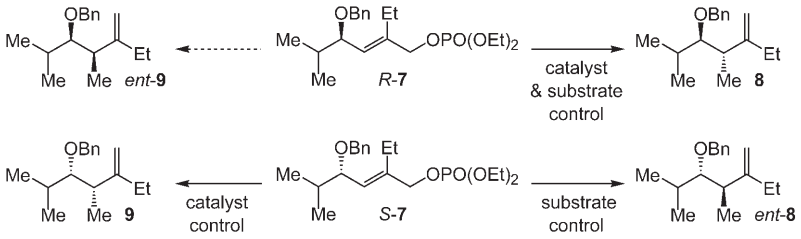
The requisite substrate (**13**) was prepared from commercially available **10** in seven steps with greater than 98% *E* selectivity (Scheme 5).[13] The high stereochemical purity of the trisubsti-

Table 1: Initial investigation of Cu-catalyzed AAA.[a]



Entry	Alkyl metal	Catalyst (mol%)	Conv. [%][b]	*t* [h]	$S_N2':S_N2$[b]	**8**:**9**[b]	e.r. [%] **8**[c]	*ee* [%] **8**[c]
1	Me_2Zn	CuCN (200)	10	24	>20:1	9:1	–	–
2	Me_2Zn	**1** (7.5); $CuCl_2{\cdot}2H_2O$ (15)	<2	24	–	–	–	–
3	Me_2Zn	**2** (7.5); $CuCl_2{\cdot}2H_2O$ (15)	<2	24	–	–	–	–
4	Me_2Zn	**3** (7.5); $CuCl_2{\cdot}2H_2O$ (15)	<2	24	–	–	–	–
5	Me_3Al	CuCN (15)	>98	4	>20:1	9:1	–	–
6	Me_3Al	**1** (7.5); $CuCl_2{\cdot}2H_2O$ (15)	45	24	>20:1	20:1	99:01	98
7	Me_3Al	**2** (7.5); $CuCl_2{\cdot}2H_2O$ (15)	15	24	nd	9:1	nd	nd
8	Me_3Al	**3** (7.5); $CuCl_2{\cdot}2H_2O$ (15)	68	1	>20:1	2.6:1	97:03	94
9	Me_3Al	**3** (7.5); $CuCl_2{\cdot}2H_2O$ (15)	89	4.5	>20:1	1.7:1	95:05	90
10	Me_3Al	**3** (7.5); $CuCl_2{\cdot}2H_2O$ (15)	95	24	>20:1	1.5:1	94.5:5.5	89

[a] Reactions were performed under N_2. [b] Determined by 400-MHz ^1H NMR analyses of unpurified mixtures. [c] Determined by chiral GLC analysis (see the Supporting Information for details). nd = not determined.

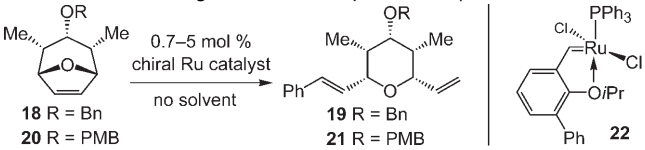


Scheme 4. Product distribution as an indication of catalyst versus substrate control in Cu-catalyzed AAA of *rac*-**7**.

tuted olefins was secured by treatment of commercially available **10** with Br_2, followed by elimination with DBU to afford **11** (>98% *E*) after reduction (DIBAL-H) and protection of the resulting primary alcohol. Conversion of vinyl bromide **11** to **13** was accomplished as shown in Scheme 5.[14] Treatment of **13** with 7.5 mol% **3**, 15 mol% $CuCl_2 \cdot 2H_2O$, and Me_3Al (−15 °C, 16 h) afforded the desired **14** in greater than 98% *ee* and 61% yield. The *meso* diene **15** was isolated in 8% yield along with **16** in 27% yield and 98% *ee*. Alkylation with CuCN (200 mol%) afforded a 1:1.5 mixture of **14**:**15**; thus, in the second alkylation catalyst control overcomes substrate preferences with 8:1 selectivity (**14**:**15**). Formation of **16** (98% *ee* and >98% *de*), arising from an S_N2'/S_N2 sequential alkylation, underlines the higher barrier to the S_N2' mode of reaction (to give **14** and **15**) in the second alkylation. Zirconocene-mediated removal of the allyl group[15] and ozonolytic cleavage of the olefins furnished **17** in greater than 98% *ee* and *de*.

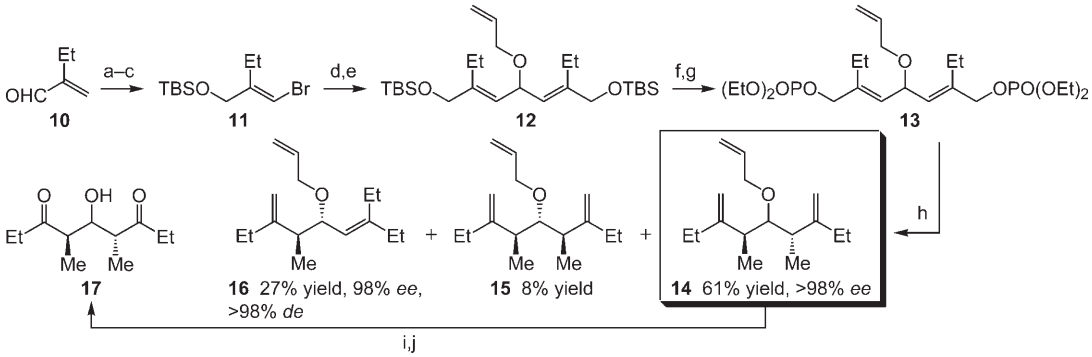
Enantioselective synthesis of the other acyclic segment (see **IV**, Scheme 2) began with Ru-catalyzed AROM/CM of oxabicycle **18**. As reported before, with 5 mol% of chiral complex **5b**[3e] (Scheme 1) and styrene, pyran **19** can be obtained in 55% yield and 80% *ee* (Table 2, entry 1); 5 mol% catalyst loading and 44 h are required for greater than 90% conversion. In search of a more efficient and selective process, we turned to the recently developed chiral carbene **6b**.[3f] Under similar conditions, with complex **6b**, **19** is formed in 81% *ee* but with substantially higher efficiency (Table 2, entry 2): greater than 98% conversion is observed in 15 h (vs. 96% conv. in 44 h with **5b**). The higher activity of **6b**, generated in situ from **22** and NaI,[3f] allows the catalyst loading to be reduced to 2.5 mol% (Table 2, entry 3) without loss of selectivity. The reaction proceeded to greater than 98% conversion even with 0.7 mol% **6b** (Table 2, entry 4), albeit with diminution of selectivity (73% *ee* vs. 81% *ee*). Importantly, the improved activity of Ru catalyst **6b** (vs. **6a**) and the possibility of performing AROM/CM at −15 °C results in enhanced enantioselectivities (88–89% *ee* vs. 73–81% *ee*), lower amounts of oligomeric by-products (derived from **18** or **20**) and higher isolated

Table 2: Initial investigation of Ru-catalyzed AROM/CM.[a]



Entry	Substrate	Catalyst (mol%)	Equiv styrene	*T* [°C]; *t* [h]	Conv. [%][b]; Yield [%][c]	*ee* [%][d]
1	**18**	**5b** (5)	4	22; 44	96; 55	80
2	**18**	**6b** (5)	4	22; 15	>98; 56	81
3	**18**	**2**+**22**+NaI (2.5)	4	22; 14	>98; 44	81
4	**18**	**2**+**22**+NaI (0.7)	4	22; 14	>98; 46	73
5	**18**	**2**+**22**+NaI (2.0)	8	−15; 20	>98; 64	89
6	**20**	**2**+**22**+NaI (2.0)	8	−15; 20	>98; 62	88

[a] Reactions were performed under N_2. [b] Conversions were determined by 400-MHz ^{1}H NMR analyses of unpurified mixtures. [c] Yields of isolated product after purification. [d] Determined by chiral HPLC analysis (see the Supporting Information for details).



Scheme 5. Enantioselective synthesis of diketone fragment **17**. a) Br_2, CH_2Cl_2, 0 °C, 4 h; DBU, THF, 65 °C, 1 h. b) 1.1 equivalents of DIBAl-H, toluene, 0 °C to 22 °C, 1 h; 72% overall yield. c) TBSCl, 5 mol% DMAP, Et_3N, CH_2Cl_2, 4 h; 90% yield. d) 2.1 equivalents of *t*BuLi, THF, −78 °C, 15 min; 0.5 equivalents of HCO_2Et, −78 °C to 22 °C, 45 min. e) NaH, $H_2C{=}CHCH_2Br$, DMF, 22 °C, 12 h; 43% overall yield. f) *n*Bu_4NF, THF, 22 °C, 3 h; 91% yield. g) $(EtO)_2P(O)Cl$, 5 mol% DMAP, Et_3N, CH_2Cl_2, 4 h; 87% yield. h) 7.5 mol% **3**, 15 mol% $CuCl_2 \cdot 2H_2O$, 4 equivalents of Me_3Al, THF, −15 °C, 16 h. i) 1.1 equivalents of $[Cp_2ZrCl_2]$, 2.2 equivalents of *n*BuLi, THF, −78 °C, 1 h; 80% yield. j) O_3, pyridine/CH_2Cl_2, −78 °C, 5 min; PPh_3, 1 h; 65% yield. DBU = 1,8-diazobicyclo[5.4.0]undec-7-ene; DIBAl-H = diisobutylaluminum hydride; TBSCl = *tert*-butyldimethylsilyl chloride; DMAP = 4-dimethylaminopyridine.

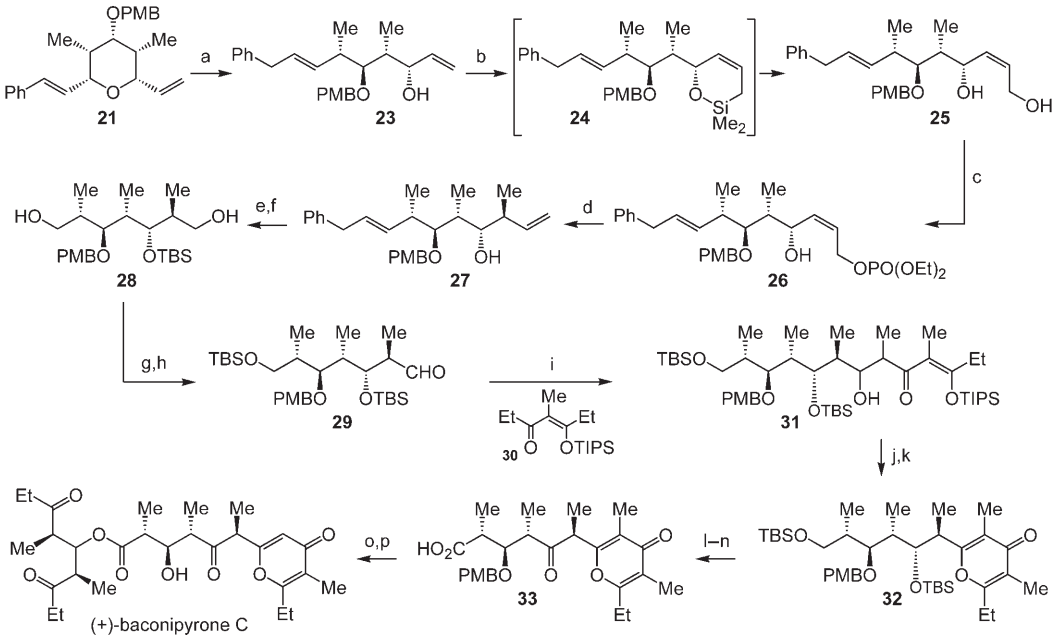
yields (62–64% vs. 44–56%). The Ru-catalyzed AROM/CM is easily carried out on a multigram scale.[16]

The total synthesis was completed as shown in Scheme 6. The precursor to the acyclic γ-pyrone-containing polypropionate segment was unmasked by treatment of **21** with Na/NH_3, providing **23** as a single alkene isomer (<2% conjugated β-alkylstyrene) in 70% yield. Synthesis of **23** proceeded site-selectively: 4-hydroxypyran derived from competitive cleavage of the PMB ether was not detected (<2%), and the acyclic diol corresponding to **23** was isolated as the only by-product (22% yield).[17] Preparation of allylic phosphate **26** (or its *trans* isomer) required access to allylic alcohol **25**. Attempts to synthesize **25** (or its *trans* isomer) through catalytic cross-metathesis[18] of **23** (or its protected derivatives) with various olefin partners and catalysts resulted in less than 20% conversion.[19] An alternative approach, involving catalytic Si-tethered ring-closing metathesis,[20] was therefore pursued. Subjection of **23** to chlorodimethylallylsilane, followed by treatment of the resulting diene with Ru carbene **4**[21] and oxidation of the cyclic product **24** with H_2O_2 and KF furnished *cis* allylic alcohol **25** in 73% yield. Conversion to phosphate **26** and subsequent diastereoselective allylic alkylation with Me_2Zn and CuCN[22] provided **27** in 98% *de* and 75% overall yield. Protection of the secondary alcohol, ozonolytic cleavage, and reductive workup afforded **28** (72% yield).

The primary alcohols of **28** exhibit different rates of reaction when subjected to TBSOTf and 2,6-lutidine (−78°C, CH_2Cl_2). When **28** was treated with 1.2 equivalents of TBSOTf, 50% of desired product was obtained; 30% of the bis(silyl) product was also formed, but the undesired monosilyl product was not detected (<2%). To facilitate selective silylation, substoichiometric amounts of TBSOTf were used and the unreacted starting material was recycled (60% yield after four runs). The remaining primary alcohol was oxidized, affording **29** in 98% yield.

We utilized the aldol addition of an enolate derived from **30** to aldehyde **29** as the first step towards installment of the γ-pyrone moiety. Reactions involving a variety of enolate derivatives were investigated. The lithium enolate obtained from reaction of ketone **30** (>98% *Z*) with LDA proved to be the most efficient in furnishing **31** (88% yield). The mixture of the resulting enol ether isomers (4:1) was subjected to Dess–Martin periodinane and the diketone was treated with DBU to afford γ-pyrone **32** in 64% overall yield for two steps.[23] Removal of the silyl ethers in **32** required the use of TAS-F in DMF[24] (98% yield).[25] Synthesis of carboxylic acid **33** and fragment coupling with **17** was accomplished according to previously reported procedures, delivering (+)-baconipyrone C (unnatural enantiomer).[8]

The present total synthesis is based on bond disconnections rendered feasible by the availability of new chiral Ag-,



Scheme 6. Enantioselective synthesis of fragment **32** and completion of the total synthesis. a) Na, NH_3, *t*BuOH, Et_2O, −78°C, 3 min.; 70% yield. b) 1.2 equivalents of $ClMe_2Si(CH_2(H)C{=}CH_2)$, imidazole, CH_2Cl_2, 22°C, 45 min; 2 mol% **4**, toluene, 22°C, 40 min; H_2O_2, KF, $KHCO_3$, THF/MeOH, 16 h; 73% yield. c) 1.1 equivalents of $(EtO)_2P(O)Cl$, Et_3N, 5 mol% DMAP, CH_2Cl_2, 4 h. d) 4 equivalents of Me_2Zn, 1.5 equivalents of CuCN, THF, −15°C, 22 h; 75% overall yield for two steps. e) 1 equivalent of TBSOTf, 2,6-lutidine, CH_2Cl_2, −78°C, 1 h. f) O_3, CH_2Cl_2/MeOH, −78°C, 10 min; $NaBH_4$, 22°C, 2 h; 72% overall yield for two steps. g) 0.4 equivalents of TBSOTf, 2,6-lutidine, CH_2Cl_2, −78°C; 60% yield after four runs. h) DMP, CH_2Cl_2, 22°C, 30 min; 98% yield. i) 1.1 equivalents of LDA, **30**, THF, −78°C, 2 h; **29**, −78°C, 2 h; 88% yield. j) DMP, CH_2Cl_2, 22°C, 1 h. k) DBU, THF, 60°C, 4 h; 64% overall yield for two steps. l) 8 equivalents of TAS-F, DMF, 4 h; 98% yield. m) $(COCl)_2$, DMSO, −78°C; NEt_3, −30°C, CH_2Cl_2. 2 h. n) $NaClO_2$, Na_2HPO_4, $Me_2C{=}CMe_2$, *t*BuOH, H_2O, 1 h; 61% overall yield for two steps. o) 1 equivalent of **17**, 30 equivalents of 1,3,5-trichlorobenzoyl chloride, 50 equivalents of DMAP, 20 equivalents of Et_3N, toluene, 22°C, 30 min; 68% yield. p) 2 equivalents of DDQ, 10% pH 7 buffer in CH_2Cl_2, 1 h; 90% yield. THF = tetrahydrofuran; TBSOTf = *tert*-butyldimethylsilyl triflate; LDA = lithium diisopropylamine; DMP = Dess–Martin periodinane; DMSO = dimethylsulfoxide; DDQ = 2,3-dichloro-5,6-dicyanoquinone; TAS-F = tris(dimethylamino)sulfonium difluorotrimethylsilicate; TIPS = triisopropylsilyl; PMB = *p*-methoxybenzyl.

Cu-, and Ru-based NHC complexes; it demonstrates the utility of enantioselective (NHC)Ru-catalyzed olefin metathesis and expands that of (NHC)Cu-catalyzed allylic alkylations.[26]

Received: February 4, 2007
Published online: April 5, 2007

Keywords: allylic alkylation · asymmetric catalysis · natural products · N-heterocyclic carbenes · olefin metathesis

[1] For a general discussion of natural product synthesis and asymmetric catalysis, see: A. H. Hoveyda, *Stimulating Concepts in Chemistry* (Eds: F. Vögtle, J. F. Stoddart, M. Shibasaki), Wiley-VCH, Weinheim, **2000**, pp. 145 – 162.

[2] D. C. Manker, D. J. Faulkner, T. J. Stout, J. Clardy, *J. Org. Chem.* **1989**, *54*, 5371 – 5374.

[3] For a review on asymmetric olefin metathesis, see: a) A. H. Hoveyda, *Handbook of Metathesis*, *Vol. 2* (Ed.: R. H. Grubbs), VCH-Wiley, Weinheim, **2003**, pp. 128 – 150; for previous reports on Ru-catalyzed asymmetric olefin metathesis, see: b) T. J. Seiders, D. W. Ward, R. H. Grubbs, *Org. Lett.* **2001**, *3*, 3225 – 3228; c) J. J. Van Veldhuizen, J. S. Kingsbury, S. B. Garber, A. H. Hoveyda, *J. Am. Chem. Soc.* **2002**, *124*, 4954 – 4955; d) J. J. Van Veldhuizen, D. G. Gillingham, S. B. Garber, O. Kataoka, A. H. Hoveyda, *J. Am. Chem. Soc.* **2003**, *125*, 12502 – 12508; e) D. G. Gillingham, O. Kataoka, S. B. Garber, A. H. Hoveyda, *J. Am. Chem. Soc.* **2004**, *126*, 12288 – 12290; f) J. J. Van Veldhuizen, J. E. Campbell, R. E. Giudici, A. H. Hoveyda, *J. Am. Chem. Soc.* **2005**, *127*, 6877 – 6882; g) T. W. Funk, J. M. Berlin, R. H. Grubbs, *J. Am. Chem. Soc.* **2006**, *128*, 1840 – 1846; h) J. M. Berlin, S. D. Goldberg, R. H. Grubbs, *Angew. Chem.* **2006**, *118*, 7753 – 7757; *Angew. Chem. Int. Ed.* **2006**, *45*, 7591 – 7595; i) R. E. Giudici, A. H. Hoveyda, *J. Am. Chem. Soc.* **2007**, in press.

[4] For applications of Mo-catalyzed asymmetric olefin metathesis in natural product synthesis, see: a) S. D. Burke, N. Muller, C. M. Beudry, *Org. Lett.* **1999**, *1*, 9720 – 9721; b) G. S. Weatherhead, G. A. Cortez, R. R. Schrock, A. H. Hoveyda, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5805 – 5809; for a review of applications of catalytic olefin metathesis in natural product synthesis, see: c) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem.* **2005**, *117*, 4564 – 4601; *Angew. Chem. Int. Ed.* **2005**, *44*, 4490 – 4527.

[5] For an overview of recent advances in catalytic asymmetric allylic alkylation reactions, see: H. Yorimitsu, K. Oshima, *Angew. Chem.* **2005**, *117*, 4509 – 4513; *Angew. Chem. Int. Ed.* **2005**, *44*, 4435 – 4439.

[6] For catalytic AAA reactions promoted by chiral NHC-based complexes, see: a) A. O. Larsen, W. Leu, C. Nieto-Oberhuber, J. E. Campbell, A. H. Hoveyda, *J. Am. Chem. Soc.* **2004**, *126*, 11130 – 11131; b) S. Tominaga, Y. Oi, T. Kato, D. K. An, S. Okamoto, *Tetrahedron Lett.* **2004**, *45*, 5585 – 5588; c) reference [2f]; d) S. Okamoto, S. Tominaga, N. Saino, K. Kase, K. Shimoda, *J. Organomet. Chem.* **2005**, *690*, 6001 – 6007; e) Y. Lee, A. H. Hoveyda, *J. Am. Chem. Soc.* **2006**, *128*, 15604 – 15605.

[7] *Modern Aldol Reactions* (Ed.: R. Mahrwald), Wiley-VCH, Weinheim, **2004**.

[8] I. Paterson, D. Y. Chen, J. L. Aceña, A. S. Franklin, *Org. Lett.* **2000**, *2*, 1513 – 1516.

[9] a) C. A. Falciola, K. Tissot-Croset, A. Alexakis, *Angew. Chem.* **2006**, *118*, 6141 – 6144; *Angew. Chem. Int. Ed.* **2006**, *45*, 5995 – 5998; for reactions of activated substrates, see: b) P. J. Goldsmith, S. J. Teat, S. Woodward, *Angew. Chem.* **2005**, *117*, 2275 – 2277; *Angew. Chem. Int. Ed.* **2005**, *44*, 2235 – 2237.

[10] For use of trialkylaluminum reagents in Cu-catalyzed asymmetric conjugate additions, see: M. d'Augustin, L. Palais, A. Alexakis, *Angew. Chem.* **2005**, *117*, 1400 – 1402; *Angew. Chem. Int. Ed.* **2005**, *44*, 1376 – 1378.

[11] M. K. Brown, T. L. May, C. A. Baxter, A. H. Hoveyda, *Angew. Chem.* **2007**, *119*, 1115 – 1118; *Angew. Chem. Int. Ed.* **2007**, *46*, 1097 – 1100.

[12] E. Vedejs, M. Jure, *Angew. Chem.* **2005**, *117*, 4040 – 4069; *Angew. Chem. Int. Ed.* **2005**, *44*, 3974 – 4001.

[13] Preliminary studies indicated that a benzyl ether gives rise to side products during AAA; the alcohol was therefore masked as an allyl ether.

[14] See the Supporting Information for full experimental details involving synthesis of **13**.

[15] H. Ito, T. Taguchi, Y. Hanazawa, *J. Org. Chem.* **1993**, *58*, 774 – 775.

[16] Chiral Mo catalysts (R. R. Schrock, A. H. Hoveyda, *Angew. Chem.* **2003**, *115*, 4740 – 4782; *Angew. Chem. Int. Ed.* **2003**, *42*, 4592 – 4633) provide **19** with lower enantiomeric purity (≤67% *ee*).

[17] Prolonged reaction times led to the formation of the acyclic diol as the exclusive product.

[18] a) S. J. Connon, S. Blechert, *Angew. Chem.* **2003**, *115*, 1944 – 1968; *Angew. Chem. Int. Ed.* **2003**, *42*, 1900 – 1923; b) A. K. Chatterjee, T.-L. Choi, D. P. Sanders, R. H. Grubbs, *J. Am. Chem. Soc.* **2003**, *125*, 11360 – 11370.

[19] Similar observations were made when pyran **21** was used as the substrate.

[20] a) P. A. Evans, J. Cui, S. J. Gharpure, A. Polosukhin, H. Zhang, *J. Am. Chem. Soc.* **2003**, *125*, 14702 – 14703; b) T. R. Hoye, B. M. Elkov, J. Jeon, M. Khoroosi, *Org. Lett.* **2006**, *8*, 3383 – 3386.

[21] S. B. Garber, J. S. Kingsbury, B. L. Gray, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, *122*, 8168 – 8179.

[22] Lower amounts of CuCN (e.g., 20 mol%) led to the formation of substantial amounts of dihydrofuran by-product derived from phosphate displacement by the secondary allylic alcohol. With 1.5 equiv CuCN, about 10% of this by-product is generated.

[23] Previously reported methods for synthesis of γ-pyrones through triketone cyclizations proved to be inefficient; see: a) H. Arimoto, S. Nishiyama, S. Yamamura, *Tetrahedron Lett.* **1990**, *31*, 5619 – 5620; b) T. Lister, M. V. Perkins, *Angew. Chem.* **2006**, *118*, 2622 – 2626; *Angew. Chem. Int. Ed.* **2006**, *45*, 2560 – 2564.

[24] K. A. Scheidt, H. Chen, B. C. Follows, S. R. Chemler, D. Coffey, W. R. Roush, *J. Org. Chem.* **1998**, *63*, 6436 – 6437.

[25] Alternative protocols (e.g., aqueous HOAc, nBu$_4$NF) led to low yields owing to decomposition of starting material and/or product.

[26] The full scope of the Cu-catalyzed AAA with alkylaluminum reagents will be reported in a separate account.

