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# Highly Enantioselective Cyclizations of Conjugated Trienes with Low Catalyst Loadings: A Robust Chiral *N*-Heterocyclic Carbene Enabled by Acetic Acid Cocatalyst

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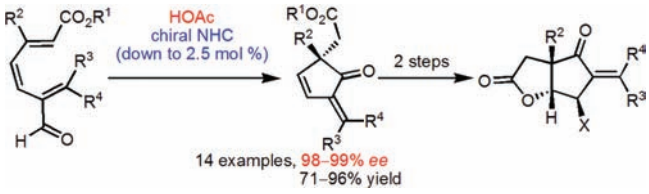
## ABSTRACT




**Densely functionalized cyclopentenones are useful synthetic intermediates. We report herein a new method to synthesize this important class of compounds through a highly enantioselective (98 → 99% *ee*) triene cyclization that is cocatalyzed by acetic acid and a chiral *N*-heterocyclic carbene (NHC). We discovered that acetic acid not only could coexist with NHCs but also could greatly stabilize the active catalyst, which enables a long-lived catalyst with high reactivity and selectivity.**

Selective catalysis of triene cyclizations has long been a challenge for synthetic chemists. The cyclized products contain unique functional groups, and they are often difficult to access by other means. One possible Stetter cyclization product, a densely functionalized cyclopentenone, is of particular importance, since it contains a quaternary stereogenic center and an adjacent conjugated diene. The cyclization product can be easily elaborated to tetrahydrocyclopenta[*b*]furan-dione, a structural motif identified in a variety of natural products and analogs in the ginkgolide family (Scheme 1).[1] However, asymmetric catalysis of this type of transformation on a conjugated triene remained largely unexplored, because the ease of stereochemical control often falls off with increased substrate rigidity and conjugation, such as in the extended 6$\pi$ system under study.

Chiral *N*-heterocyclic carbenes (NHCs) belong to a class of privileged Lewis bases in asymmetric organocatalysis.[2,3] Although a few impressive examples of NHC catalysis with low catalyst loadings have been reported, most intramolecular Stetter cyclizations with activated olefins require relatively high catalyst loadings (≥10 mol %).[4] Therefore,

(1) For selective references for isolation and medicinal chemistry research of ginkgolide family natural products, see: (a) Sakabe, N.; Takada, S.; Okabe, K. *Chem. Commun.* **1967**, 259. (b) Nakanishi, K.; Habaguch, K. *J. Am. Chem. Soc.* **1971**, *93*, 3546. (c) Hu, L. H.; Chen, Z. L.; Xie, Y. Y.; Jiang, Y. Y.; Zhen, H. W. *Biorg. Med. Chem.* **2000**, *8*, 1515.

(2) For reviews of privileged catalysts and Lewis base catalysis, see: (a) Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691. (b) Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560.

(3) For selective reviews of organocatalysis, especially on chiral NHC catalysis, see: (a) Jacobsen, E. N.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20618. (b) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534. (c) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606. (d) de Alaniz, J. R.; Rovis, T. *Synlett* **2009**, 1189. (e) Moore, J. L.; Rovis, T. *Top. Curr. Chem.* **2010**, *291*, 77. (f) Rovis, T.; Vora, H. U. *Aldrichimica Acta* **2011**, *44*, 3. (g) Nair, V.; Vellalath, S.; Babu, B. P. *Chem. Soc. Rev.* **2008**, *37*, 2691. (h) Phillips, E. M.; Chan, A.; Scheidt, K. A. *Aldrichimica Acta* **2009**, *43*, 55. (i) Biju, A. T.; Kuhl, N.; Glorius, F. *Acc. Chem. Res.* **2011**, *44*, 1182. (j) Hirano, K.; Piel, I.; Glorius, F. *Chem. Lett.* **2011**, *40*, 786.

(4) For selective examples of NHC catalysis with low catalyst loadings, see: (a) He, M.; Uc, G. J.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 15088. (b) Rommel, M.; Fukuzumi, T.; Bode, J. W. *J. Am. Chem. Soc.* **2008**, *130*, 17266. (c) Biju, A. T.; Wurz, N. E.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 5970. (d) Bugaut, X.; Liu, F.; Glorius, F. *J. Am. Chem. Soc.* **2011**, *133*, 8130.

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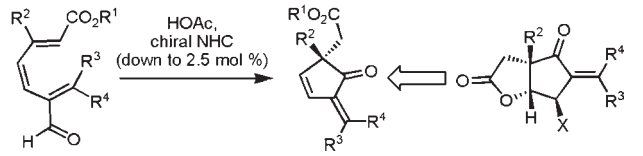
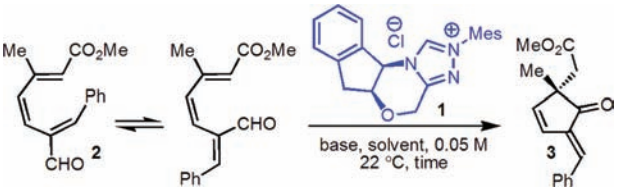
reducing catalyst loading, while preserving catalyst reactivity, has been a major challenge in chiral NHC catalysis. We described here the development of highly enantioselective Stetter cyclizations to densely functionalized cyclopentenones. We discovered that a catalytic amount of external acetic acid could stabilize the active NHC catalyst, which enables efficient reactions with low catalyst loadings (down to 2.5 mol %).

**Scheme 1.** Enantioselective Triene Cyclizations to Densely Functionalized Cyclopentenones




The proposed transformations were explored with a geometrically defined (2*E*,4*Z*,6*E*) triene (**2**).[5] Preliminary catalyst screening with several privileged chiral NHC catalysts revealed that a chiral aminoindanol-derived triazolium catalyst (**1**) was most effective in converting the triene (**2**) to the cyclopentenone (**3**) (Table 1).[6−8] It is important to note that the catalytic efficiency of **1** seemed to depend crucially on the Brønsted base and acid cocatalysts. To our surprise, well-established reaction conditions for intramolecular Stetter cyclizations were ineffective in this system: Catalyst **1** barely achieved a single turnover, in the presence of strong non-nucleophilic bases, including KHMDS and KO*t*-Bu (entries 1−2).[9] Neither organic bases (entries 3−5) nor $K_2CO_3$ (entry 6) could effectively turn over the catalytic cycle. The incomplete conversion under these conditions suggests that the integrity of the catalyst was largely compromised, a finding rarely reported in the literature.

**Table 1.** Correlation of NHC Reactivity with Brønsted Bases and AcOH Cocatalyst




| entry | base (equiv) | solvent | 1 (equiv) | time (h) | yield[a] (%) | final yield[b] (%) | *ee*[c] (%) |
|---|---|---|---|---|---|---|---|
| 1 | KHMDS (0.2) | THF | 0.2 | 7 | 0 | 16 | 95 |
| 2 | KO*t*-Bu (0.2) | THF | 0.2 | 7 | <5 | 17 | 98 |
| 3 | DBU (0.2) | THF | 0.2 | 7 | 0 | 0 | NA |
| 4 | (*i*-Pr)$_2$EtN (0.2) | THF | 0.2 | 7 | 0 | 0 | NA |
| 5 | $Et_3N$ (0.2) | THF | 0.2 | 7 | 0 | 0 | NA |
| 6 | $K_2CO_3$ (0.2) | THF | 0.2 | 7 | 15 | 52 | 95 |
| 7 | NaOAc (0.2) | THF | 0.2 | 5 | 85 | 85 | 97 |
| 8 | NaOBz (0.2) | THF | 0.2 | 7 | 52 | 83 | 97 |
| 9 | NaOAc (0.1) | THF | 0.1 | 7 | 44 | 79 | 97 |
| 10 | NaOAc (0.5) | THF | 0.1 | 7 | 62 | 84 | 97 |
| 11 | NaOAc (1.0) | THF | 0.1 | 7 | 88 | 88 | 97 |
| 12 | NaOAc (1.0) | ether | 0.1 | 2.5 | 96 | 96 | 98 |
| 13[d] | NaOAc (0.5) | ether | 0.05 | 4.0 | 96 | 96 | 99 |
| 14[d] | NaOAc (0.25) | ether | 0.025 | 7.5 | 96 | 96 | 99 |

[a] Yields refer to isolated yields after column chromatography. [b] Final yields are obtained after 48 h, when there is no further conversion. [c] *ee* was determined by chiral HPLC. Absolute stereochemistry was determined by X-ray crystallographic analysis of its derivative. [d] 0.1 equiv of AcOH was applied.

The aforementioned Brønsted bases (entries 1−6) are capable of generating sufficient quantities of NHC through deprotonation. However, the data suggest the decomposition of active catalyst significantly compromises the reaction efficiency (turnover number of **1** < 3.0). For this reason, we explored carboxylates that have a much weaker Brønsted basicity, which emerge as uniquely effective reagents (entries 7−12).[10] A catalytic amount (20 mol % each) of NaOAc and triazolium salt (**1**) (entry 7) cocatalyzed a highly enantioselective reaction with excellent efficiency (97% *ee* and 85% yield within 5 h). Although NaOBz (entries 8) provided a less impressive rate acceleration compared to

(5) For details of substrate synthesis, see Supporting Information.

(6) Absolute stereochemistry of the product was determined by X-ray crystallographic analysis of its derivative.

(7) For a selection of privileged chiral NHCs, see: (a) Enders, D.; Breuer, K.; Teles, J. H. *Helv. Chim. Acta* **1996**, *79*, 1217. (b) Knight, R. L.; Leeper, F. J. *Tetrahedron Lett.* **1997**, *38*, 3611. (c) Dvorak, C. A.; Rawal, V. H. *Tetrahedron Lett.* **1998**, *39*, 2925. (d) Kerr, M. S.; de Alaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298. (e) He, M.; Struble, J. R.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 8418. (f) Mennen, S. M.; Blank, J. T.; Tran-Dube, M. B.; Imbriglio, J. E.; Miller, S. J. *Chem. Commun.* **2005**, 195. (g) Piel, I.; Steinmetz, M.; Hirano, K.; Froehlich, R.; Grimme, S.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 4983.

(8) For a selection of application of Mes-substituted catalyst **1a** in asymmetric catalysis, see: (a) Chiang, P. C.; Kaeobamrung, J.; Bode, J. W. *J. Am. Chem. Soc.* **2007**, *129*, 3520. (b) He, M.; Bode, J. W. *J. Am. Chem. Soc.* **2008**, *130*, 418. (c) Kaeobamrung, J.; Kozlowski, M. C.; Bode, J. W. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20661. (d) Kaeobamrung, J.; Mahatthananchai, J.; Zheng, P. G.; Bode, J. W. *J. Am. Chem. Soc.* **2010**, *132*, 8810. (e) Mahatthananchai, J.; Zheng, P. G.; Bode, J. W. *Angew. Chem., Int. Ed.* **2011**, *50*, 1673. (f) Fang, X. Q.; Jiang, K.; Xing, C.; Hao, L.; Chi, Y. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 1910. (g) Wadamoto, M.; Phillips, E. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 10098. (h) Phillips, E. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 2416. (i) Raup, D. E. A.; Cardinal-David, B.; Holte, D.; Scheidt, K. A. *Nat. Chem.* **2010**, *2*, 766. (j) Cardinal-David, B.; Raup, D. E. A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 5345. (k) Cohen, D. T.; Cardinal-David, B.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 1678. (l) Rong, Z. Q.; Jia, M. Q.; You, S. L. *Org. Lett.* **2011**, *13*, 4080. (m) Zhu, Z. Q.; Zheng, X. L.; Jiang, N. F.; Wan, X.; Xiao, J. C. *Chem. Commun.* **2011**, 8670.

(9) For standard conditions to generate chiral NHCs, see: (a) Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 8876. (b) de Alaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 6284. (c) Reynolds, N. T.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 16406. (d) Liu, Q.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 2552. (e) DiRocco, D. A.; Oberg, K. M.; Dalton, D. M.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 10872. (f) Lathrop, S. P.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 13628. (g) Vora, H. U.; Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 2860. (h) DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2011**, *133*, 10402. (i) Kawanaka, Y.; Phillips, E. M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2009**, *131*, 18028. (j) Jousseaume, T.; Wurz, N. E.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1410.

(10) For a recent example using carboxylates in chiral NHC catalysis, see: Zhao, X. D.; DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2011**, *133*, 12466.

that of NaOAc, the same *ee* was observed in each case. These data suggest that carboxylates are likely involved in the rate-determining step (RDS), but not in the enantioselectivity-determining step, in the catalytic cycle. We subsequently noted a few interesting discoveries: First, increasing the ratio of NaOAc to triazolium salt (**1**) significantly accelerated the reaction (entries 9–11). Since NaOAc is only sparingly soluble in THF, the exact mechanism for rate dependence on the amount of solid NaOAc is unclear. Second, solvent is crucial for reactivity and selectivity. Catalyst **1** is most reactive and selective in diethyl ether (entry 12).[11] Most intriguingly, we discovered that the loading of **1** could be decreased further down to 2.5 mol % without sacrificing the yield and *ee*, as long as a catalytic amount of AcOH was used as the cocatalyst (entries 13–14).

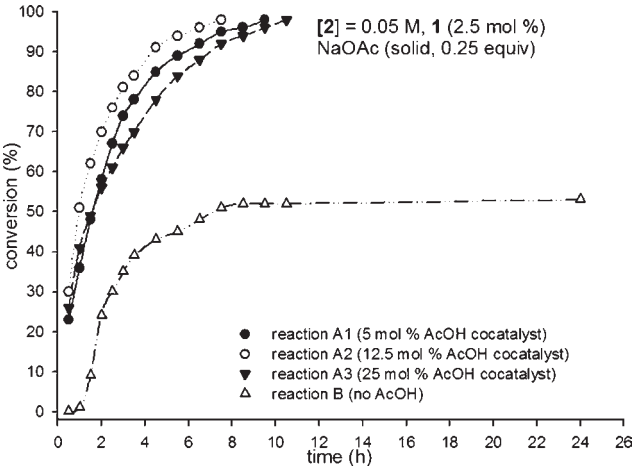
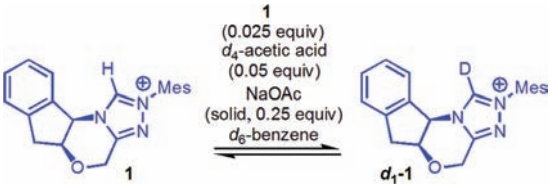



**Figure 1.** Kinetic studies to reveal the crucial role of AcOH to stabilize the active catalyst.

The application of carboxylates as weak Brønsted bases in NHC catalysis is precedented, but not under conditions of low catalyst loadings in the presence of an external acid cocatalyst ($pK_a$ (in water) = 4.75). It is plausible that AcOH confers certain advantages, by either protecting the chiral NHC from decomposition or promoting catalyst turnover. To test this hypothesis, we compared the kinetics of a few model reactions for the AcOH effect. In each case, the loading of chiral NHC was decreased to 2.5 mol % (Figure 1). Interestingly, the initial rates of reactions A1–A3 (with 0.05–0.25 equiv AcOH as the additive) were significantly higher than the one without it (reaction B). Reaction B seemed to have a relatively long induction period (around 1% conversion at 1 h), but its rate increased significantly after 2 h. Although reactions A1–A3 reached full conversion within 10 h, reaction B stopped at around 8 h, failing to reach full conversion even after 24 h (53% yield). The kinetic studies suggest that external AcOH is crucial in preventing catalyst decomposition and maintaining the robustness of catalyst **1**. Although weak Brønsted acids, especially catechols, are sometimes known to be beneficial for NHC catalysis, carboxylic acids with much lower $pK_a$ values are uniquely effective in maintaining the catalyst integrity in this system.[12]

Since the reversibility of catalyst generation could be a safeguard against catalyst decomposition, we hypothesized that the NHC generation could become readily reversible when a catalytic amount of AcOH was used as a cocatalyst. We subsequently designed a hydrogen/deuterium exchange experiment and observed that formyl-H in triazolium salt **1** was readily exchanged with a deuterium of $d_4$-AcOH under synthetically relevant conditions (2.5 mol % of **1**, 0.25 equiv of solid NaOAc, and 0.05 equiv of $d_4$-AcOH in $d_6$-benzene).[13] (Scheme 2)

**Scheme 2.** Reversible NHC Generation under Reaction Conditions




Under optimized conditions, a variety of (2*E*, 4*Z*, 6*E*) trienes with different steric ($R^1$ through $R^3$ substituents) and electronic properties were studied (Table 2). We applied 5 mol % of catalyst **1** for most substrates so that most reactions can complete within 40 h. Electron withdrawing and moderately donating groups on the aromatic region ($R^3$ position) were well tolerated, and cyclopentenones **3** were isolated with excellent yields and *ee*'s (92–96% yield, 98–99% *ee*). The presence of strong electron donating groups retarded the reaction rate (entries 5 and 7), but the isolated yields were minimally affected (75% and 87% yield, 99% *ee*). The introduction of an additional alkyl group ($R^2$) was tolerated (entries 8–10, up to 94% yield, >99% *ee*), and the cyclization efficiency of substrates with large substituents ($R^1$) at the C2 position was maintained as well (entries 11–14).

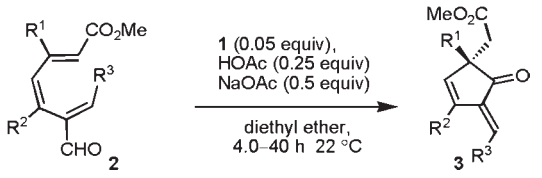
The immediate synthetic application of this reaction discovery becomes apparent after the following two-step transformation (Scheme 3A). Saponification of **3a**, followed by halo-lactonizations, delivered enantiopure bicyclic lactones with three contiguous stereogenic centers (**5a**–**6a**). The bicyclic moiety with the aforementioned stereochemical array can be identified in a variety of natural products and their analogs in the ginkgolide family.[1] The enantiopure bicyclic allylic halides (**5a**–**6a**) are versatile intermediates for further transformations. Isomeric trienes (**7**) also readily participate in an NHC-catalyzed annulation

(11) For a complete solvent effect screen, see Supporting Information.

(12) Phenols and catechols are noneffective in stabilizing the catalyst or assisting the catalyst turnover, when its loading is low (2.5 mol %).

(13) For a hydrogen-deuterium exchange experiment of thiamine in water, see: Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719.

**Table 2.** Substrate Scope of the Cyclization Reaction




| entry | $R^1$ | $R^2$ | $R^3$ | yield (%)[a] | *ee* of **3** (%)[b] |
|---|---|---|---|---|---|
| 1 | Me | H | Ph | 96 | 99 |
| 2 | Me | H | *p*-Br-Ph | 92 | 99 |
| 3 | Me | H | *p*-Cl-Ph | 93 | 98 |
| 4 | Me | H | *p*-Me-Ph | 95 | 99 |
| 5 | Me | H | *p*-OMe-Ph | 75 | 99 |
| 6 | Me | H | *m*-Cl-Ph | 94 | 99 |
| 7 | Me | H | *O*-$CH_2$-*O*-Ph | 87 | >99 |
| 8 | Me | Me | Ph | 80 | >99 |
| 9 | Me | Me | *p*-Br-Ph | 94 | >99 |
| 10 | Me | Me | *m*-Cl-Ph | 94 | >99 |
| 11[c] | Ph | H | Ph | 80 | 99 |
| 12[c] | Ph | H | *p*-Cl-Ph | 82 | >99 |
| 13[c] | Ph | H | *p*-Br-Ph | 71 | 99 |
| 14[c] | Ph | H | *m*-Cl-Ph | 74 | >99 |

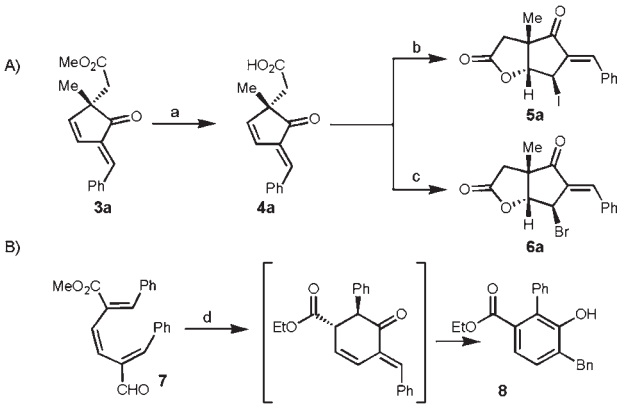
[a] Yields refer to isolated yields after column chromatography. [b] *ee* was determined by chiral HPLC. [c] 10 mol % of **1** was applied.

under the same conditions to deliver a highly functionalized, tetrasubstituted benzenoid **8**, which seems prohibitively difficult to access by other means (Scheme 3B).[14]

In summary, we have developed a highly enantioselective Stetter cyclization of a conjugated triene to access highly functionalized cyclopentenones with low catalyst loadings (down to 2.5 mol %). The substrate scope for this method is general, and the cyclization products are synthetically useful. Through mechanistic studies, we discovered that the AcOH cocatalyst is crucial in preventing active NHC catalyst decomposition and facilitating the NHC

(14) For a detailed synthesis of **7**, see Supporting Information.

**Scheme 3.** Synthetic Application of (A) Chiral Cyclopentanones and (B) This Method in Functionalized Phenol Synthesis[a]




[a] Reagents and conditions: (a) LiOH, THF, 22 °C, 3 h, 95%; (b) *N*-Iodosuccinimide, THF, 0 °C, 1 h, 90%; (c) *N*-Bromosuccinimide, THF, 25 °C, 6 h, 86%; (d) **1** (0.05 equiv), HOAc (0.25 equiv), NaOAc (0.5 equiv), diethyl ether, 25 °C, 6 h, 95%.

turnover. The design and discovery of other robust catalytic systems enabled by cooperative catalysis is underway.

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**Supporting Information Available.** Experimental procedures, characterization data, NMR, HPLC, and X-ray analysis spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.