

NHC-Catalyzed/Titanium(IV)—Mediated Highly Diastereo- and Enantioselective Dimerization of Enals

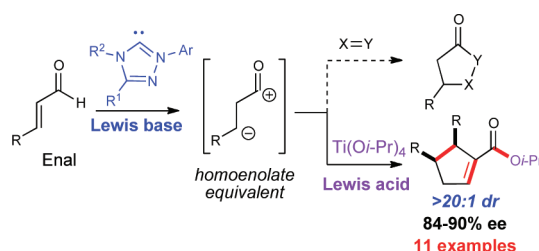
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Received December 22, 2010

ABSTRACT



An NHC-catalyzed, diastereo- and enantioselective dimerization of enals has been developed. The use of $\text{Ti}(\text{O}i\text{-Pr})_4$ is a key element for the reactivity and selectivity of this process. The cyclopentenones are obtained with high levels of diastereo- and enantioselectivity and their synthetic utility is demonstrated by functionalization of the product alkene.

The field of N-heterocyclic carbene (NHC) catalysis has undergone explosive growth over the past decade.¹ In addition to a pyruvate decarboxylase-type of acyl anion reactivity,^{2,3} these unique Lewis base catalysts can induce unusual homoenolate reactions that (a) create nucleophilic character at the β -position of an enal and (b) involve a

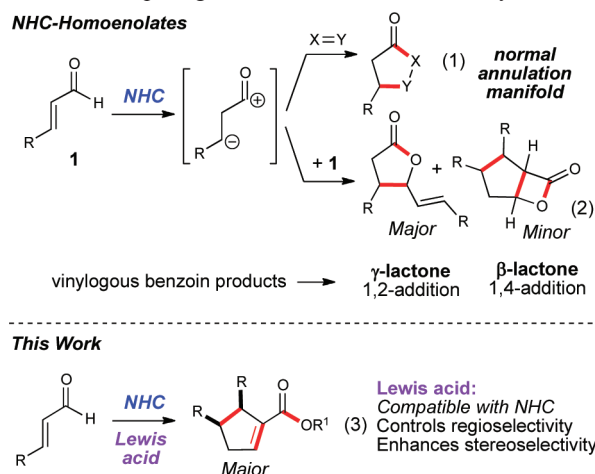
terminal acylation event to release the azolium catalyst.^{4,5} We have been focused on developing new carbene catalyzed reactions and specifically with regard to homoenolates, engaging these nucleophiles with reactive partners to generate new formal [M + N] cycloaddition processes. In our continuing investigations of different X=Y systems (such as azo compounds and azomethine imines, Scheme 1,

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Scheme 1. Competing NHC Homoenoate Pathways



eq 1) that could be successful reaction partners in these carbene-catalyzed processes, we have encountered what can be viewed as a “vinylogous benzoin” limitation.⁶ Similarly, for NHC-generated homoenoate reactions, many times the most reactive electrophile present is the homoenoate precursor, or enal **1**. Consequently, the major product can be the γ -lactone product when the $X=Y$ reactant does not possess the optimal reactivity (Scheme 1, eq 2, major product).

While successful new homoenoate reactions have been realized by judicious choice of electrophile to circumvent the vinylogous benzoin pathway, we have also been investigating alternative strategies to engage NHC-homoenolates in more general reactions.⁷ An interesting minor product that we have observed in these homoenoate type reactions is the β -lactone product, resulting from the 1,4-addition of the homoenoate (Scheme 1, eq 2, minor product).⁸ This alternate dimerization pathway competes with the more standard 1,2-addition which leads to γ -lactones. Prior to the disclosure of our 1,4-addition observation, both Nair and Bode reported variations of this manifold combining enals and chalcones (Nair)⁹ or a

reactive oxo-butenate (Bode)¹⁰ to produce cyclopentenones after an unusual room temperature decarboxylation.¹¹

Even with the numerous reports of NHC-homoenoate reactions, the factors governing the partitioning between these competing 1,2- vs 1,4-addition pathways are currently not well understood. Additionally, efficient conjugate addition reactions of NHC-derived homoenolates to enals have remained difficult to accomplish efficiently. Our recent success employing Lewis acids with NHC catalysis promoted us to investigate this reaction using a NHC/Lewis acid approach to control the regio- and enantioselectivity outcome.¹² To the best of our knowledge, these are the first examples of a highly diastereo- and enantioselective dimerization of these reactive unsaturated carbonyl systems using cooperative catalysis NHC/Lewis acid conditions.

Our studies to explore this carbene/Lewis acid possibility began by combining cinnamaldehyde (**1a**) in THF with a stoichiometric amount of Lewis acid (1 equiv) in the presence of azolium salt **A** (20 mol %) and DBU at 60 °C. Several metal alkoxides were initially tested in this reaction, but most of them provided the γ -butyrolactones (1,2 addition) or led to the decomposition of the starting material.¹³ After extensive investigation, we discovered that the use of $Ti(Oi-Pr)_4$ afforded compound **2** as a sole diastereoisomer as detected by NMR spectroscopy (Table 1, entry 1). The evaluation of several of the available chiral azolium salts revealed that phenylalanine-derived azolium **C** and tryptophan-derived azolium **E**¹⁴ provided the highest levels of enantioselectivity (entries 3 and 5). *Importantly, performing the reaction in the absence of $Ti(Oi-Pr)_4$ did not afford any of **2**, which confirmed the essential role of the Lewis acid in this process (entry 6).* At this stage, the efficiency and selectivity of the transformation (58% yield, 66% ee) was encouraging, but not synthetically viable. Lowering the temperature to improve the enantioselectivity resulted in a mixture of desired **2** and an intermediate β -hydroxyester (**16**, Scheme 2), which was observed by ¹H NMR spectroscopy. We anticipated that the full elimination of water to yield compound **2**¹⁵ could be promoted

(4) For a review of Lewis base catalysis, see: Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560–1638. For a review of NHC-generated homoenoate methodology, see: Nair, V.; Vellalath, S.; Babu, B. P. *Chem. Soc. Rev.* **2008**, *37*, 2691–2698.

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(6) For the benzoin reaction, the acyl anion generated in situ adds to the starting material benzaldehyde, thereby typically producing dimeric products.

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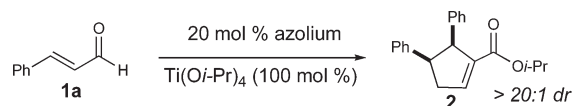
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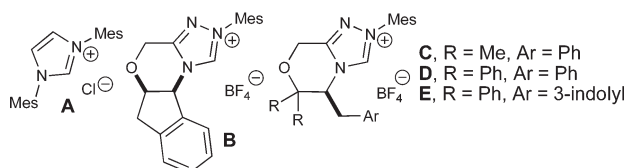
(13) Numerous metal alkoxides were examined including $Mg(Oi-Pr)_2$, $Ba(Oi-Pr)_2$, and $Sr(Oi-Pr)_2$.

(14) Maki, B. E.; Chan, A.; Scheidt, K. A. *Synthesis* **2008**, 1306–1315.

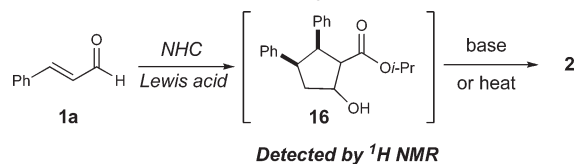
(15) The absolute and relative stereochemistry of compounds **2** was determined by X-ray crystallography of a related derivative (see Supporting Information) and additional assignments made by analogy.

Table 1. Optimization of Reaction Conditions

entry	azolium	conditions ^a	yield (%) ^b	ee (%) ^c
1	A	0.2 M THF, 40 mol % DBU, 60 °C	63	—
2	B	0.2 M THF, 40 mol % DBU, 60 °C	0	—
3	C	0.2 M THF, 40 mol % DBU, 60 °C	28	66
4	D	0.2 M THF, 40 mol % DBU, 60 °C	45	40
5	E	0.2 M THF, 40 mol % DBU, 60 °C	58	66
6 ^d	E	0.2 M THF, 40 mol % DBU, 60 °C	0	—
7 ^e	E^f	0.75 M toluene, 20 mol % TBD, 23 °C	61	90



^a All reactions performed on 0.38 mmol scale. ^b Isolated yield. ^c Enantiomeric excess determined by HPLC with a chiral stationary phase. Diastereomeric ratio determined by ¹H NMR spectroscopy (500 MHz) of unpurified reaction mixture. ^d Reaction performed without Ti(Oi-Pr)₄. ^e 1.0 equiv of TBD added after 12 h. ^f 10 mol % azolium salt and 20 mol % TBD.

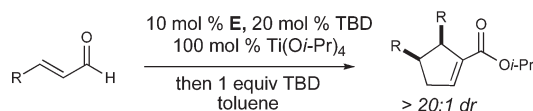
Scheme 2. ¹H NMR Detection of β -Hydroxyl Intermediate

after consumption of the enal starting material by the addition of excess base. After a short survey of bases and temperature profiles (not shown) a significant improvement in enantioselectivity and yield was obtained when the reaction was conducted in toluene with 1,5,7-triazabicyclo-[4.4.0]dec-5-ene (TBD) as the base and 10 mol % of triazolium salt **E** (entry 7). One key to the high yield of **2** was the addition of an equivalent of TBD after consumption of the enal.¹⁶ Finally, decreasing the amount of Lewis acid to substoichiometric levels (e.g., 20 mol %, not shown) resulted in lower yields and enantioselectivities.

We next evaluated the substrate scope of differentially substituted aryl enals using the chiral triazolium salt **E** (Table 2).¹⁷ Both electron-donating and -withdrawing substituents were tolerated at the *para* position, yielding the cyclopentene in 59–61% yield and up to 90% ee.

(16) Increasing the loading of the base at the beginning of the reaction (e.g., 120 mol %) resulted in <100% conversion with an effective stalling of the process.

(17) The two side products observed in these reactions are; mainly (E)-isopropyl 3-aryl-acrylate (see ref 14), and the γ -lactone (1,2-addition).

Table 2. Substrate Scope

entry	R	yield (%) ^a	ee (%) ^b
1	Ph	61(2)	90
2	<i>p</i> -Br-C ₆ H ₄	61(3)	90
3	<i>p</i> -Cl-C ₆ H ₄	59(4)	90
4	<i>m</i> -Cl-C ₆ H ₄	58(5)	84
5	<i>p</i> -OMe-C ₆ H ₄	61(6)	90
6	<i>m</i> -OMe-C ₆ H ₄	60(7)	90
7	<i>p</i> -Me-C ₆ H ₄	61(8)	90
8	<i>m</i> -Me-C ₆ H ₄	62(9)	85
9	1-Naphthyl	59(10)	85
10	2-Naphthyl	63(11)	86
11 ^c	<i>p</i> -CO ₂ Me-C ₆ H ₄	72(12)	84

^a Isolated yield. ^b Enantiomeric excess determined by HPLC with a chiral stationary phase. Diastereomeric ratio determined by ¹H NMR spectroscopy (500 MHz) of unpurified reaction mixture. ^c Lewis acid (2.5 equiv); transesterification to *p*-(CO₂*i*-Pr)-C₆H₄ was observed.

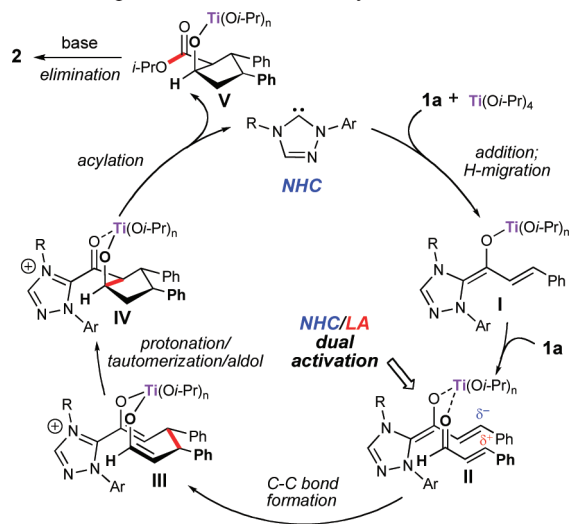
When the *para*-methyl ester substrate was employed, an increase in yield was observed, but the enantioselectivity decreased slightly (entry 11). *Meta*-substituted aryl groups at the β -position and naphthyl-derived enals were also tolerated, but the enantiomeric excess was sometimes lower in these cases. Finally, more sterically demanding substrates such as *ortho*-substituted aryl enals, β -alkyl or α -substituted enals suffered from low yields or no conversion (results not shown).

Our proposed reaction pathway for this dimerization is shown in Scheme 3. The initial coordination of the α,β -unsaturated aldehyde to the titanium(IV) Lewis acid induces the formation of the extended Breslow intermediate **I**. The coordination of a second enal to the aldehyde-titanium(IV) complex increases its reactivity toward conjugate addition and organizes the reactants in space as shown in **II** to promote 1,4-addition over 1,2-addition.¹⁸ Both the homoenolate and the enal are thus poised to react through an *s-cis* conformation, ensuring high *cis* diastereofacial selectivity in the products. Following the C–C bond formation to give intermediate **III**, the bis-enolate undergoes protonation, tautomerization and intramolecular aldol to afford **IV**. The NHC catalyst is then regenerated from acylation of the acyl azolium to give intermediate **V** and the cyclopentene **2** is formed after base-promoted elimination.

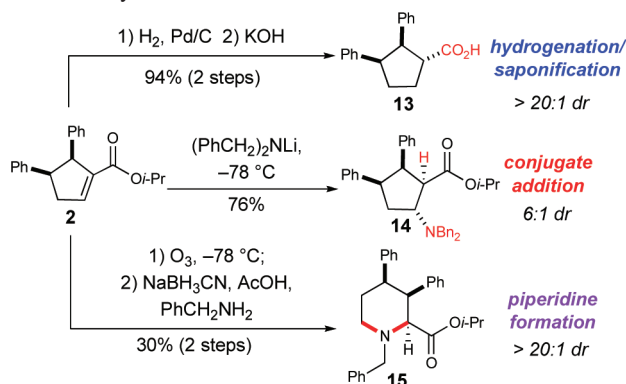
This new carbene/Lewis acid reaction provides α,β -unsaturated esters that can be processed in highly stereoselective synthetic transformations (Scheme 4). For example, the reduction of the endocyclic double bond under hydrogen atmosphere followed by saponification proceeded in

(18) For computational studies supporting an NHC homoenolate conjugate addition pathway, see: Domingo, L. R.; Zaragoza, R. J.; Arnó, M. *Org. Biomol. Chem.* **2010**, *8*, 4884–4891. For discussion of an alternative benzoin/oxy-Cope pathway, see ref 10.

Scheme 3. Proposed Reaction Pathway



Scheme 4. Synthetic Transformation



94% yield over two steps to give the 1,2,3-trisubstituted cyclopentane product **13** as the sole diastereoisomer.¹⁹ We next explored the possibility of introducing nucleophiles by conjugate addition on the α,β -unsaturated ester.

(19) The relative stereochemistry of compound **13** was determined by X-ray crystallography (Advanced Photon Source) of a related derivative (see Supporting Information).

(20) The absolute and relative stereochemistry of compound **14** was determined by X-ray crystallography of a related derivative (see Supporting Information).

(21) For reviews, see: (a) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219–3232. (b) Seebach, D.; Hook, D. F.; Glättli, A. *Biopolymers* **2006**, *84*, 23–37. (c) Horne, W. S.; Gellman, S. H. *Acc. Chem. Res.* **2008**, *41*, 1399–1408. Selected examples: (d) Appella, D. H.; Christianson, L. A.; Klein, D. A.; Powell, D. R.; Huang, X.; Barchi, J. J.; Gellman, S. H. *Nature* **1997**, *387*, 381. (e) Martinek, T. A.; Tóth, G. K.; Vass, E.; Hollósi, M.; Fülöp, F. *Angew. Chem., Int. Ed.* **2002**, *41*, 1718–1721. (f) Choi, S. H.; Guzei, I. A.; Spencer, L. C.; Gellman, S. H. *J. Am. Chem. Soc.* **2009**, *131*, 2917–2924.

Treatment of the cyclopentene with lithium dibenzylamide afforded the protected amine **14** in 76% yield as a 6:1 mixture of diastereoisomers.²⁰ These substituted β -amino esters possess unusual substitution patterns that may be useful in conformationally restricted peptides incorporating β -amino acids.²¹ The ozonolysis of the double bond followed by reductive amination with benzylamine produced the substituted pipercolic ester **15** as a single diastereoisomer.²² Pipercolic acid derivatives are important constituents of biologically active molecules,²³ including immunosuppressants,²⁴ N-methyl-D-aspartic acid (NMDA) antagonists,²⁵ and antibiotics.²⁶

In summary, an NHC-catalyzed, Lewis acid mediated enantioselective dimerization of enals has been developed. The use of $\text{Ti}(\text{O}i\text{-Pr})_4$ promotes a selective 1,4 conjugate addition versus the typical 1,2-addition. The synthetic utility of these cyclopentene compounds produced from carbene catalysis is predominantly a function of the unsaturated ester produced in the reaction. The merging of Lewis acid activation with N-heterocyclic carbene Lewis bases is a powerful new strategy that opens new opportunities for catalytic methodology development.

Acknowledgment. Financial support has been generously provided by the NIH (RO1-NIGMS), Amgen, AstraZeneca, GlaxoSmithKline. D.T.C. is a recipient of GAANN fellowship. B.C.-D. gratefully acknowledges FQRNT (Fonds Québécois de la Recherche sur la Nature et les Technologies) for a postdoctoral fellowship. Use of the APS was supported by the U.S. Department of Energy (Contract No. DE-AC02-06CH11357). Use of the LS-CAT Sector 21 was supported by the Michigan Economic Development Corp. (Grant 085P1000817).

Supporting Information Available. Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(22) The relative stereochemistry of compound **15** was determined by ^1H NMR NOESY experiments (see Supporting Information for details and reference to a related transformation).

(23) For reviews, see: (a) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borchering, D. R. *Tetrahedron* **2003**, *59*, 2953–2989. (b) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701–1729. (c) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781–1813. For a related example, see: (d) Hutchison, A. J.; Williams, M.; Angst, C.; De Jesus, R.; Blanchard, L.; Jackson, R. H.; Wilusz, E. J.; Murphy, D. E.; Bernard, P. S. *J. Med. Chem.* **1989**, *32*, 2171–2178.

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(26) Vanderhaeghe, H.; Janssen, G.; Compennolle, F. *Tetrahedron Lett.* **1971**, *12*, 2687–2688.