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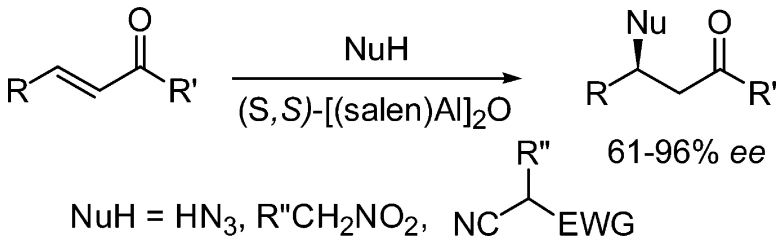


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# Highly Enantioselective Conjugate Additions to α,β-Unsaturated Ketones Catalyzed by a (Salen)Al Complex

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***Abstract:*** Chiral (salen)Al complex **1a** catalyzes the highly enantioselective conjugate addition of carbon- and nitrogen-based nucleophiles to acyclic α,β-unsaturated ketones. This methodology is tolerant of substantial variation of the ketone structure, providing access to a wide range of useful chiral building blocks in high yield and enantiomeric excess. Synthetic manipulations of the conjugate addition products are demonstrated, including the straightforward preparation of β-amino ketones and highly enantioenriched carbo- and heterocyclic compounds.

## Introduction

The conjugate addition of nucleophiles to electron-deficient olefins represents one of the best-established and versatile bond-construction strategies in organic chemistry. Such reactions often result in generation of new stereocenters, and accordingly 1,4-additions have a long and important history in asymmetric catalysis. In 1975, Wynberg and co-workers reported the seminal discovery of Cinchona-alkaloid-catalyzed enantioselective addition of cyclic ketoesters to methyl vinyl ketone,[1] and research in asymmetric catalysis of conjugate addition reactions has received increasing attention ever since.[2] Early work in this field led to significant advances, although the reactions were mostly narrow in substrate scope and restricted to a particular combination of nucleophile and electrophile type. More recently, several catalyst systems have been identified that exhibit a significantly higher degree of generality with respect to one, or both, of the reaction components. For example, Hayashi and co-workers have demonstrated that (binap)rhodium complexes promote the enantioselective conjugate addition of organoboron and organometallic reagents to a range of structurally diverse electron-deficient olefins, including cyclic and acyclic α,β-unsaturated ketones, esters, amides, phosphonates, and nitro compounds.[3] The research groups of Feringa and Hoveyda have developed novel phosphorus-centered ligands for highly enantioselective copper-catalyzed additions of diorganozinc reagents to several important electrophile classes.[4,5] The binol(metal) catalysts studied by Shibasaki and co-workers promote a variety of enantioselective conjugate additions to α,β-unsaturated ketones, acid imidazolides, and *N*-acylpyrroles. High enantioselectivities have been achieved with a range of nucleophilic partners, including malonates, nitro compounds, *O*-alkylhydroxylamines, and hydroperoxides.[6] Metal−bis(oxazoline) complexes have been shown to activate substrates capable of two-point binding in a number of diverse conjugate addition applications.[7] The use of chiral amines to activate enals and enones toward nucleophilic attack through the intermediacy of iminium ions has emerged recently as a highly general strategy and forms the basis for the enantioselective conjugate addition of electron-rich arenes, nitroalkanes, and β-dicarbonyl compounds.[8]

(1) Wynberg, H.; Helder, R. *Tetrahedron Lett.* **1975**, 4057−4060. (b) Hermann, K.; Wynberg, H. *J. Org. Chem.* **1979**, *44*, 2238−2244.
(2) For a review, see: Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033−8061.
(3) For a review, see: Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169−196.
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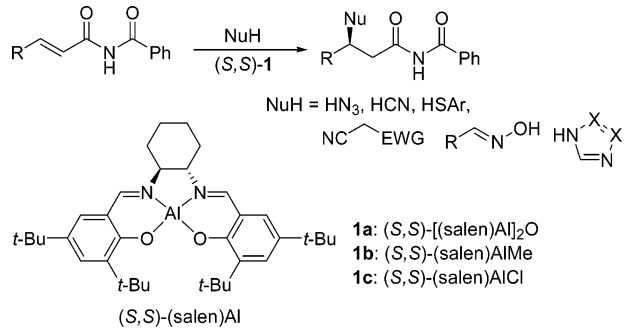
(6) For conjugate addition of β-dicarbonyl compounds to cyclic enones, see: (a) Sasai, H.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1994**, *116*, 1571−1572. (b) Sasai, H.; Arai, T.; Satow, Y.; Houk, K. N.; Shibasaki, M. *J. Am. Chem. Soc.* **1995**, *117*, 6194−6198. (c) Arai, T.; Sasai, H.; Aoe, K.; Okamura, K.; Date, T.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 104−106. (d) Majima, K.; Takita, R.; Okada, A.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 15837−15845. For hydroperoxide epoxidation of enones and acid imidazolides, see: (e) Nemoto, T.; Ohshima, T.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2725−2732 and references therein. (f) Nemoto, T.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 9474−9475. For conjugate addition of nitroalkanes to chalcones, see: (g) Funabashi, K.; Saida, Y.; Kanai, M.; Sasai, H.; Shibasaki, M. *Tetrahedron Lett.* **1998**, *39*, 7557−7558. For conjugate addition of *O*-alkylhydroxylamines to enones, see: (h) Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 16178−16179. For conjugate additions to *N*-acylpyrroles, see: (i) Kinoshita, T.; Okada, S.; Park, S.-R.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4680−4684. (j) Natsunaga, S.; Kinoshita, T.; Okada, S.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 7559−7570.
(7) For the Mukaiyama Michael reaction, see: (a) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325−335 and references therein. For conjugate addition of electron-rich aryl groups, see: (b) Jensen, K. B.; Thorhauge, J.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 160−163. (c) Zhou, J.; Tang, Y. *J. Am. Chem. Soc.* **2002**, *124*, 9030−9031. (d) Evans, D. A.; Scheidt, K. A.; Fandrick, K. R.; Lam, H. W.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 10780−10781. For conjugate addition of carbamates, see: (e) Palumo, C.; Oiarbide, M.; Halder, R.; Kelso, M.; Gómez-Bengoa, E.; García, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 9188−9189. (f) Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **1998**, *120*, 6615−6616. (g) Sibi, M. P.; Liu, M. *Org. Lett.* **2000**, *2*, 3393−3396. (h) Sibi, M. P.; Prabagaran, N.; Ghorpade, S. G.; Jasperse, C. P. *J. Am. Chem. Soc.* **2003**, *125*, 11796−11797.

***Scheme 1.*** Asymmetric Conjugate Additions to α,β-Unsaturated Imides Catalyzed by **1**




Our own efforts in the area of conjugate addition chemistry have revealed that (salen)aluminum complexes catalyze the efficient enantioselective 1,4-addition of a variety of weakly acidic species, including hydrazoic acid, cyanide, thiols, nitrogen heterocycles, and oximes, to α,β-unsaturated imides (Scheme 1).[9] Secondary imides, and particularly *N*-benzoyl imides, proved to be uniquely effective electrophiles among carboxylic acid derivatives, suggesting that the special features of this functional group (e.g., the N−H bond and/or the potential for two-point binding to a metal center) might be tied intrinsically to reactivity and high enantioselectivity with the (salen)-aluminum catalysts. We report here that imides are in fact not unique substrates for this conjugate addition chemistry, with the discovery that simple α,β-unsaturated ketones undergo highly enantioselective and exceptionally efficient conjugate addition of carbon and nitrogen nucleophiles catalyzed by complex **1a**. This observation indicates that simple one-point binding of an electrophile is sufficient for high enantioselectivity in reactions catalyzed by (salen)aluminum complexes.[10] In addition to expanding the generality of these catalysts significantly in conjugate addition chemistry, this result is an advance of practical importance: a wide range of acyclic enones undergo highly selective conjugate addition, providing access to useful bifunctional building blocks for organic synthesis.

## Results and Discussion

**I. Enantioselective Conjugate Additions of Carbon-Centered Nucleophiles.** The enantioselective addition of stabilized carbon-centered nucleophiles to enones has been an actively pursued problem in asymmetric catalysis since the inception of the field, and a variety of structurally diverse catalysts have been developed to fulfill this purpose.[11] Despite these efforts, significant challenges remain, particularly with respect to electrophile scope. Whereas additions to cyclic enone substrates arguably constitute a solved problem for asymmetric catalysis due to the elegant heterobimetallic catalysts developed by Shibasaki,[6a−d] highly enantioselective conjugate addition to acyclic enones remains an area of active investigation. In particular, catalyst systems that exhibit generality with respect to the ketone structure are rare. In this regard, the organocatalytic addition of cyclic 1,3-dicarbonyl compounds reported recently by Jørgensen constitutes the state-of-the-art system.[8c]

**(a) Conjugate Addition of Nitriles.** The addition of methyl cyanoacetate to 4-phenyl-3-buten-2-one was chosen as a model system for our investigation. A systematic optimization of the reaction parameters revealed that the optimal conditions for conjugate additions to enone substrates are virtually identical to those previously reported for imide substrates; oxo-bridged dimer **1a** is the most active catalyst,[12] and cyclohexane provides the highest enantioselectivity of the solvents examined.[13] However, the behavior of enones differed from that of imides in two significant respects. First, addition of *tert*-butyl alcohol was not necessary to accomplish complete conversion of ketone substrates, although this additive was crucial to obtaining high yield in the reactions of imides. Second, the catalyst loadings needed for efficient reaction of ketone substrates were approximately 5-fold lower than those required for imides. Thus, using 1.0 mol % catalyst and unpurified commercial reagents, without the use of inert atmosphere techniques, the conjugate addition product **2a** was obtained in excellent yield (91%) and enantiomeric excess (93%) after 16 h at 23 °C. Adduct **2a** results from the addition of methyl cyanoacetate to the *re* face of the enone, consistent with results obtained previously with imide electrophiles.

The reaction displays impressive generality with respect to the enone β-substituent, with substrates bearing aryl, heteroaryl, and alkyl groups undergoing highly enantioselective conjugate addition (Table 1). Furthermore, although methyl ketones generally provide the best results, *n*-butyl, phenyl, and isopropyl ketones are all useful substrates (products **2e**−**2g**, respectively). As seen previously in conjugate additions to imides, methyl cyanoacetate is not a uniquely effective nucleophile. Other electron-deficient nitriles, such as malononitrile and benzenesulfonylacetonitrile, may also be used successfully (products **2h** and **2i**, respectively). In reactions of methyl phenylcyanoacetate, two stereocenters, including an all-carbon-substituted quaternary center, are generated with high diastereo- and enantioselectivity (Scheme 2). The relative configuration of **2j** was established unambiguously by X-ray crystallography.

(8) For conjugate addition of β-dicarbonyl compounds, see: (a) Yamaguchi, M.; Shiraishi, T.; Hirama, M. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1173−1175. (b) Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 661−665. (c) Halland, N.; Hansen, T.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4955−4957. For conjugate addition of nitroalkanes, see: (d) Hanessian, S.; Pham, V. *Org. Lett.* **2000**, *2*, 2975−2978. (e) Halland, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 8331−8338. For conjugate addition of electron-rich aryl groups, see: (f) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370−4371. (g) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172−1173. (h) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 7894−7895. For the Mukaiyama Michael reaction, see: (i) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192−1194.

(9) (a) Myers, J. K.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 8959−5960. (b) Sammis, G. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *125*, 4442−4443. (c) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *125*, 11204−11205. (d) Vanderwal, C. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 14724−14725. (e) Chen, Q.; Delmonte, A. G.; Gandelman, M. A.; Jacobsen, E. N. Unpublished results.

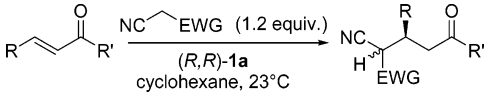
(10) (a) Salen-Red-Al-catalyzed Michael additions to cyclic ketones have been described: Jha, S. C.; Joshi, N. N. *Tetrahedron: Asymmetry* **2001**, *12*, 2463−2466. (b) Catalyst **1c** has been employed in enantioselective conjugate additions of indoles to 1-aryl-3-buten-2-ones: Bandini, M.; Fagioli, M.; Melchiorre, P.; Melloni, A.; Umani-Ronchi, A. *Tetrahedron Lett.* **2003**, *44*, 5843−5846.

(11) For a review, see: Yamaguchi, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 3, Chapter 31.2.

(12) (Salen)aluminum complexes **1a**−**c** (10 mol % Al loading) were tested as catalysts for the addition of methyl cyanoacetate to 4-phenyl-3-buten-2-one (0.2 M cyclohexane, 23 °C, 6.5 h). **1a**: 93% conversion, 94% ee. **1b**: 61% conversion, 94% ee. **1c**: <2% conversion.

(13) Various solvents were tested for the addition of methyl cyanoacetate to 4-phenyl-3-buten-2-one (5 mol % **1a**, 0.2 M solvent, 23 °C, 14 h). In general, highest yields and enantioselectivities were observed in solvents having low dielectric constants. Diethyl ether: 96% conversion, 90% ee. Toluene: 97% conversion, 89% ee. Tetrahydrofuran: 87% conversion, 88% ee. Dichloromethane: 60% conversion, 62% ee.

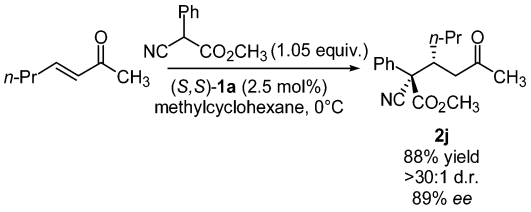
***Table 1.*** Asymmetric Conjugate Additions of Nitriles to α,β-Unsaturated Ketones Catalyzed by **1a**




| product | R | R′ | EWG | **1a** (mol %) | yield (%)[a] | ee (%)[b] |
|---|---|---|---|---|---|---|
| **2a** | Ph | $CH_3$ | $CO_2CH_3$ | 1.0 | 91 | 93[c] |
| **2b** | 2-thienyl | $CH_3$ | $CO_2CH_3$ | 1.0 | 93 | 90 |
| **2c** | *n*-Pr | $CH_3$ | $CO_2CH_3$ | 1.0 | 86 | 89[d] |
| **2d** | $CH_2CH_2OBn$ | $CH_3$ | $CO_2CH_3$ | 1.0 | 90 | 83 |
| **2e** | Ph | *n*-Bu | $CO_2CH_3$ | 1.0 | 91 | 82 |
| **2f** | Ph | Ph | $CO_2CH_3$ | 5.0 | 91 | 87 |
| **2g** | Ph | *i*-Pr | $CO_2CH_3$ | 5.0 | 85 | 75 |
| **2h** | *n*-Pr | $CH_3$ | CN | 0.25 | 76 | 94[d] |
| **2i** | *n*-Pr | $CH_3$ | $SO_2Ph$ | 1.0 | 91[e] | 96[f] |

[a] Isolated yield after purification. [b] Determined by HPLC using commercially available chiral columns, unless otherwise noted. The % ee reflects the 3*R*/3*S* or 3*S*/3*R* ratio. Products **2a**−**2g** and **2i** are isolated as mixtures of diastereomers (1.0−3.0:1 diastereomeric ratio). [c] Absolute configuration determined by correlation to known compound (see Supporting Information for details). [d] Enantiomeric excess determined by GC after derivatization (see Supporting Information for details). [e] With 1.2 equiv of 3-hepten-2-one. [f] Absolute configuration determined by X-ray crystallography.

***Scheme 2.*** Enantio- and Diastereoselective Conjugate Addition of Methyl Phenylcyanoacetate

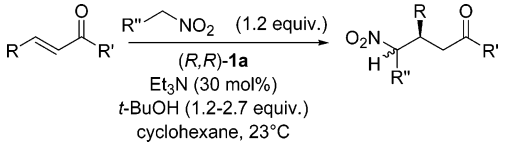



**(b) Conjugate Addition of Nitroalkanes.** The versatility of the nitro group in organic synthesis renders the conjugate addition of nitroalkanes to α,β-unsaturated carbonyl compounds an attractive method for accessing a number of interesting classes of bifunctional compounds. To date, success in the development of enantioselective variants of this transformation has been limited; current catalyst systems capable of this transformation are limited by narrow scope or modest enantioselectivity.[14] Nitromethane and nitroethane were found to undergo highly enantioselective conjugate addition to a variety of β-aryl-substituted enones in the presence of 5−7.5 mol % **1a** (Table 2).[15] In contrast to the addition of nitrile nucleophiles (see above), which requires no Brønsted base additive, the use of triethylamine (30 mol %) was necessary to promote the addition of nitroalkanes. In addition, the presence of *tert*-butyl alcohol (1.2−2.7 equiv) was required in order to achieve efficient catalysis. The results with nitroalkanes represent the sole examples identified thus far where enones are effective substrates in (salen)Al-catalyzed conjugate additions while conjugated imides are not. This is most likely due to the incompatibility of the mildly acidic N−H group of the imide with the basic reaction conditions required for nitroalkane additions.

(14) High (>90%) enantioselectivities for this transformation have been limited to chalcone derivatives and cyclic substrates. See refs 6g and 8d and: Bakó, P.; Bojor, Z.; Töke, L. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3651−3655. Jørgensen and co-workers (ref 8e) have reported conjugate additions of nitroalkanes to α,β-unsaturated methyl ketones, providing the products in 50−99% yield and 49−86% ee.

(15) Enones bearing β-alkyl substituents were found to undergo moderately enantioselective conjugate additions, but poor yields were obtained due to slow reaction rates. For example, addition of nitromethane to 3-hexen-2-one proceeded in 75% ee and 31% yield after 72 h using 7.5 mol % **1a**.

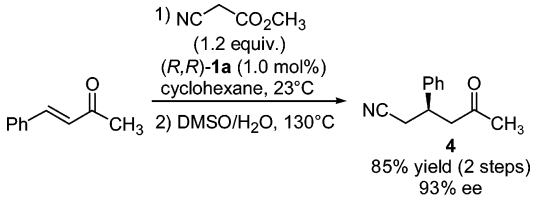
***Table 2.*** Enantioselective Conjugate Additions of Nitroalkanes Catalyzed by **1a**



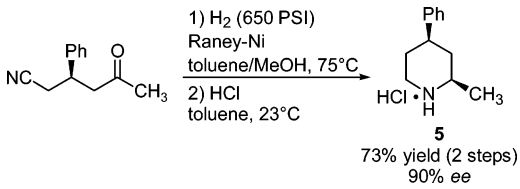

| product | R | R′ | R″ | **1a** (mol %) | yield (%)[a] | ee (%)[b] |
|---|---|---|---|---|---|---|
| **3a** | Ph | $CH_3$ | H | 7.5 | 90 | 95 |
| **3b** | 4-$MeOC_6H_4$ | $CH_3$ | H | 7.5 | 80 | 93 |
| **3c** | 4-$MeC_6H_4$ | $CH_3$ | H | 5 | 70 | 93 |
| **3d** | 4-$BrC_6H_4$ | $CH_3$ | H | 7.5 | 85 | 92 |
| **3e** | Ph | *n*-Bu | H | 7.5 | 72 | 92 |
| **3f** | Ph | *i*-Pr | H | 7.5 | 76 | 88 |
| **3g** | Ph | $CH_3$ | $CH_3$ | 10 | 90[c,d] | 92/91[e] |
| **3h** | 4-$BrC_6H_4$ | $CH_3$ | $CH_3$ | 7.5 | 75[c] | 93/92[e] |

[a] Isolated yield after chromatography. [b] Determined by HPLC or GC using commercially available chiral columns. [c] Product obtained as a 1.1:1 mixture of diastereomers. [d] (*S*,*S*)-**1a** was used. [e] The ee of each diastereomer (major/minor).

***Scheme 3.*** Krapcho Decarboxylation of Enantioenriched Cyanoacetate




***Scheme 4.*** Preparation of Enantioenriched 2,4-*cis*-Disubstituted Piperidine




**(c) Synthetic Manipulations of the Conjugate Addition Products.** The enantioenriched γ-cyanoketone products obtained with this new methodology are useful materials for further synthetic manipulation. Krapcho decarboxylation[16] of adduct **2a** occurred smoothly to provide **4**, the product of formal acetonitrile conjugate addition, in good yield (85% yield over two steps from 4-phenyl-3-buten-2-one), and without compromise of enantiopurity (Scheme 3).

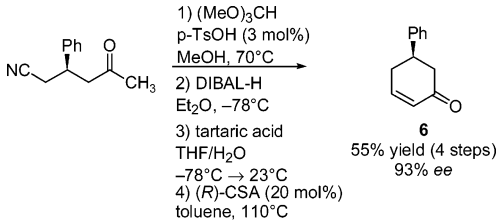
The versatility of the nitrile functional group permits the use of **4** as a precursor to several cyclic compounds of interest. Thus, Raney nickel-catalyzed hydrogenation results in formation of the *cis*-2,4-disubstituted piperidine **5** as a single diastereomer, the relative stereochemistry of which was established by X-ray crystallography (Scheme 4). Such products have previously been prepared in enantioenriched form by alkylation of chiral bicyclic lactams;[17] this new approach provides a versatile method to access this class of compounds by asymmetric catalysis.

Alternatively, cyanoketone **4** can be converted to 5-phenyl-3-cyclohexen-1-one by reduction of the nitrile to the corresponding aldehyde and intramolecular aldol condensation. Such chiral cyclohexenones serve as useful building blocks for the

(16) Krapcho, A. P. *Synthesis* **1982**, 805−822 and 893−913.

(17) Dwyer, M. P.; Lamar, J. E.; Meyers, A. I. *Tetrahedron Lett.* **1999**, *40*, 8965−8968.

***Scheme 5.*** Preparation of 5-Phenyl-3-cyclohexen-1-one by Aldol Condensation

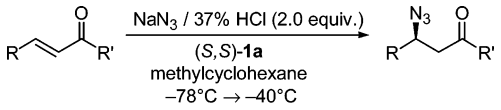



synthesis of highly substituted cyclohexanes through transformations governed by cyclic stereocontrol.[18,19] The preparation of cyclohexenone **6** was commenced by protection of ketone **4** as the dimethyl ketal. Diisobutylaluminum hydride reduction was followed by workup with aqueous tartaric acid, accomplishing hydrolysis of the resulting imine and the labile ketal. Aldol condensation was achieved using catalytic camphorsulfonic acid in refluxing toluene, yielding the desired product without deterioration of enantiopurity and in good yield over the four-step sequence.

**II. Enantioselective Conjugate Addition of Hydrazoic Acid.** The asymmetric catalytic conjugate addition of hydrazoic acid to enones represents a straightforward approach to the enantioselective synthesis of $\beta$-amino ketones. A variety of catalytic methods, including the asymmetric conjugate addition of nitrogen-centered nucleophiles,[20] have been developed for the enantioselective synthesis of $\beta$-amino acid derivatives. In contrast, Shibasaki's recent report of enantioselective 1,4-addition of *O*-alkyl hydroxylamines to aryl-substituted enones stands as the only example of the highly efficient preparation of $\beta$-amino ketones by asymmetric catalytic conjugate addition.[6h] Alternatively, $\beta$-amino ketones have been accessed by enantioselective additions of ketones or enol ether derivatives to imines.[21] The Mannich approach has proven successful for the addition of acetone or hydroxy ketones to aryl- or carbonyl-substituted imines, but the enantioselectivities are generally moderate for imines bearing simple unbranched aliphatic substituents. Accordingly, with an interest in establishing a useful complement to the Mannich reaction, our attention was focused particularly on conjugate additions of azide to $\beta$-alkyl-substituted enones.

**(a) Reaction Optimization and Scope.** To avoid the pregeneration and storage of quantities of hydrazoic acid, we sought to devise a practical method for generating the reagent in situ.[22]

***Table 3.*** Asymmetric Conjugate Addition of Hydrazoic Acid to $\alpha,\beta$-Unsaturated Ketones Catalyzed by **1a**




| product | R | R′ | **1a** (mol %) | yield (%)[a] | ee (%)[b] |
|---|---|---|---|---|---|
| **7a** | *n*-Pr | $CH_3$ | 2.5 | 88[c] | 94 |
| **7b** | *i*-Pr | $CH_3$ | 2.5 | 81 | 94 |
| **7c** | $CH_2CH_2OBn$ | $CH_3$ | 2.5 | 96 | 85 |
| **7d** | $C(CH_3)_2CH_2CH_2CN$ | $CH_3$ | 5.0 | 72[d] | 84 |
| **7e** | *n*-Pr | *n*-Bu | 5.0 | 88 | 89[e] |
| **7f** | *n*-Pr | Ph | 5.0 | 90 | 77 |
| **7g** | *n*-Pr | *i*-Pr | 5.0 | 97 | 61[e] |

[a] Isolated yield after purification. [b] Determined by HPLC using commercially available columns or by GC ($\gamma$-TA column), unless otherwise noted. [c] Absolute configuration determined by correlation (see Supporting Information for details). [d] Reaction carried out at −30 °C. [e] Determined by HPLC after derivatization (see Supporting Information for details).

We found that the use of sodium azide, an inexpensive and easily handled hydrazoic acid precursor, in combination with concentrated aqueous hydrochloric acid, provided the best results. In the presence of 2.5−5.0 mol % **1a** in methylcyclohexane at −40 °C, $\beta$-azido ketone products were obtained in high enantioselectivity and yield. Substantial variation of the ketone structure was tolerated within the context of enones bearing alkyl $\beta$-substituents.[23] As observed previously in the conjugate addition of azide to imide derivatives,[9a] enones bearing aryl $\beta$-substituents exhibited poor reactivity.[24]

**(b) Synthetic Manipulations of $\beta$-Azido Ketones.** The enantioenriched azides **7** are readily converted to suitably protected $\beta$-amino ketones. For example, hydrogenation of **7a** and in situ protection as the *tert*-butyl carbamate yielded **8** in 94% ee and 79% yield over two steps from 3-hepten-2-one.[25] The reactivity of the azide functional group in [3 + 2] dipolar cycloaddition chemistry could also be exploited for the synthesis of nitrogen-containing heterocycles.[26] Azido ketone **7a** underwent thermal cycloaddition with activated alkynes, or highly regioselective copper-catalyzed cycloaddition with terminal alkynes,[27] to provide triazoles **9a** and **9b** without detectable racemization. Product **7d**, which bears a tethered nitrile group, underwent cyclization to form bicyclic tetrazole **10** under thermal conditions.

## Conclusions and Outlook

We have demonstrated a substantial expansion of the substrate scope of (salen)aluminum-catalyzed asymmetric conjugate addition reactions to include acyclic $\alpha,\beta$-unsaturated ketones. Both carbon- and nitrogen-centered nucleophiles were shown to participate in conjugate additions with high enantioselectivity for a range of enone structures. The products of this new methodology are useful synthetic intermediates; moreover, the

(18) (a) Carvone, a naturally occurring 5-substituted 3-cyclohexen-1-one, has been used as a starting material for the synthesis of complex natural products. For examples, see: Srikrishna, A.; Satyanarayana, G. *Org. Lett.* **2004**, *6*, 3143−3144 and references therein. (b) For a recent example of the application of synthetic 3-cyclohexen-1-ones in natural product synthesis, see: Miyashita, M.; Sasaki, M.; Hattoria, I.; Sakai, M.; Tanino, K. *Science* **2004**, *305*, 495−499.

(19) Several diastereoselective approaches to this class of compounds have been developed: (a) Schwarz, J. B.; Devine, P. N.; Meyers, A. I. *Tetrahedron* **1997**, *53*, 8795−8806. (b) Schwarz, J. B.; Meyers, A. I. *J. Org. Chem.* **1998**, *63*, 1732−1735. (c) Hikichi, S.; Hareau, G. P.-J.; Sato, F. *Tetrahedron Lett.* **1997**, *38*, 8299−8302. (d) Sarakinos, G.; Corey, E. J. *Org. Lett.* **1999**, *1*, 811−814. (e) Hareau, G. P.-J.; Koiwa, M.; Hikichi, S.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 3640−3650. (f) Naasz, R.; Arnold, L. A.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 927−930 (catalytic kinetic resolution approach).

(20) See refs 7e−h, 9a, and: Guerin, D. J.; Miller, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 2134−2136.

(21) For an example of the synthesis of $\beta$-amino ketones by asymmetric Mannich reaction, see: List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336−9337.

(22) For the in situ generation of hydrazoic acid from azidotrimethylsilane and carboxylic acids, see: Guerin, D. J.; Horstmann, T. E.; Miller, S. J. *Org. Lett.* **1999**, *1*, 1107−1109.

(23) The conjugate addition of hydrazoic acid to cyclic enones catalyzed by **1a** proceeds with low enantioselectivity. 3-Azidocyclohexanone and 3-azidocycloheptanone are obtained in 8 and 14% ee, respectively (5 mol % **1a**, methylcyclohexane, −40 °C).

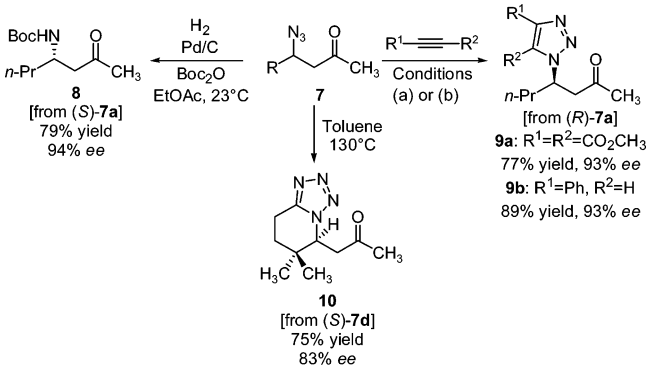
(24) The conjugate addition of hydrazoic acid to 4-phenyl-3-buten-2-one proceeds to 14% conversion in 79% ee after 14 h (5 mol % **1a**, methylcyclohexane, −45 °C).

(25) Saito, S.; Nakajima, H.; Inaba, M.; Moriwake, T. *Tetrahedron Lett.* **1989**, *30*, 837−838.

(26) For a prior demonstration of this approach to enantioenriched triazoles, see ref 20.

(27) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596−2599.

***Scheme 6.*** Synthetic Manipulations of Enantioenriched β-Azido Ketones[a]




[a] Reaction conditions: (a) toluene, 110 °C; (b) $CuSO_4$ (1 mol %), sodium ascorbate (10 mol %), ethanol/water, 23 °C.

knowledge that simple one-point binding of carbonyl compounds to **1a** is sufficient for high enantioselectivity in catalytic processes may serve as a useful starting point for the development of new methodology. Current investigations are underway to gain mechanistic insight into the catalyst system[28] and to continue to delineate its scope.

## Experimental Section

Complete experimental procedures for all substrates are provided as Supporting Information.

**Catalyst 1a.** In a flame-dried round-bottomed flask equipped with a stir bar and reflux condenser, (*S*,*S*)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine (1.79 g, 3.28 mmol) was suspended in acetonitrile (10 mL) and toluene (3.3 mL). Trimethylaluminum (1.64 mL, 2.0 M solution in toluene, 3.28 mmol, 1.00 equiv) was added dropwise by syringe at 23 °C. The mixture was stirred at 23 °C for 30 min, and then heated to reflux and stirred for 5 h. After the mixture was cooled to 23 °C, water (59 μL, 3.28 mmol, 1.00 equiv) was added by syringe. The resulting mixture was heated to reflux and stirred for 15 h. After it was cooled to 23 °C, acetonitrile (25 mL) was added and the mixture filtered through Celite and washed with acetonitrile (total volume of 200 mL). The filtrate was discarded and the Celite washed with dichloromethane (total volume of 125 mL). The filtrate was concentrated in vacuo, yielding the aluminum complex **1a** as a pale yellow solid in 85% yield (1.61 g, 1.40 mmol).

**General Procedure for the Conjugate Addition of Nitriles to Enones: (*S*)-2-Cyano-5-oxo-3-phenylhexanoic Acid Methyl Ester (2a).** Methyl cyanoacetate (529 μL, 6.0 mmol, 1.2 equiv) was added to a solution of 4-phenyl-3-buten-2-one (731 mg, 5.0 mmol) and (*R*,*R*)-**1a** (57.7 mg, 0.05 mmol, 1.0 mol %) in cyclohexane (25.0 mL). The solution was stirred at 23 °C for 16 h, and then the solvent was removed in vacuo and the residue purified by chromatography on silica (20% ethyl acetate in hexanes). Residual methyl cyanoacetate after chromatography was removed by gentle heating in vacuo. The product was obtained as a colorless oil in 91% yield (1.23 g) and 93% ee, as determined by chiral HPLC [(*S*,*S*)-Whelk-01, 14% ethanol/hexanes, 1.4 mL/min, 220 nm, $t_r$(min) = 9.6 min, $t_r$(maj) = 11.2 min]. $\alpha^{25}_D = -29°$ ($c$ = 1.45, $CHCl_3$).

*CAUTION!* Hydrazoic acid is a highly toxic and potentially explosive compound and should be handled with great care in a well-ventilated fume hood.

General Procedure for the Conjugate Addition of Hydrazoic Acid to Enones: (*R*)-4-Azidoheptan-2-one (5a): Hydrochloric acid (164 μL, 37% aqueous, 2.0 mmol, 2.0 equiv) was added dropwise to a suspension of sodium azide (130 mg, 2.0 mmol, 2.0 equiv) in methylcyclohexane (5.0 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 10 min, and then warmed to 23 °C and stirred for 1.5 h. The resulting orange heterogeneous mixture was cooled to −78 °C, and 3-hepten-2-one (132 μL, 1.0 mmol) and then catalyst (*S*,*S*)-1a (28.8 mg, 0.025 mmol, 2.5 mol %) were added sequentially. The mixture was warmed to −40 °C and stirred for 24 h. After the mixture was warmed to 23 °C, ether (15 mL) was added. The solution was washed twice with 1 M aqueous sodium hydroxide (10 mL each), then passed through a short silica plug, eluting with 1:1 hexanes/ether. The solution was concentrated carefully in vacuo, yielding the product as a colorless oil, in 88% yield (136 mg) and 94% ee, as determined by chiral GC [γ-TA, 100 °C isothermal, $t_r$(min) = 9.7 min, $t_r$(maj) = 13.0 min]. $\alpha^{25}_D = -28°$ ($c$ = 1.31, $CHCl_3$).

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**Supporting Information Available:** Complete experimental procedures and characterization data (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(28) The heterogeneity of the reaction mixtures in the enone conjugate addition reactions has limited our ability to carry out accurate kinetic analyses of these processes. However, studies on closely related additions to α,β-unsaturated imides catalyzed by **1a** point to a cooperative mechanism wherein the catalyst activates both nucleophile and electrophile. See ref 9e and: Sammis, G. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 9928−9929.