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Enantioselective Conjugate Addition of *N*,*N*-Dialkylhydrazones to α-Hydroxy Enones[‡]

David Monge,[§] Eloísa Martín-Zamora,[§] Juan Vázquez,[§] Manuel Alcarazo,[†] Eleuterio Álvarez,[†] Rosario Fernández,*[,§] and José M. Lassaletta*[,†]

Instituto de Investigaciones Químicas (CSIC-US), Américo Vespucio 49,
E-41092 Seville, Spain, and Departamento de Química Orgánica, US, Seville, Spain

ffernan@us.es; jmlassa@iiq.csic.es

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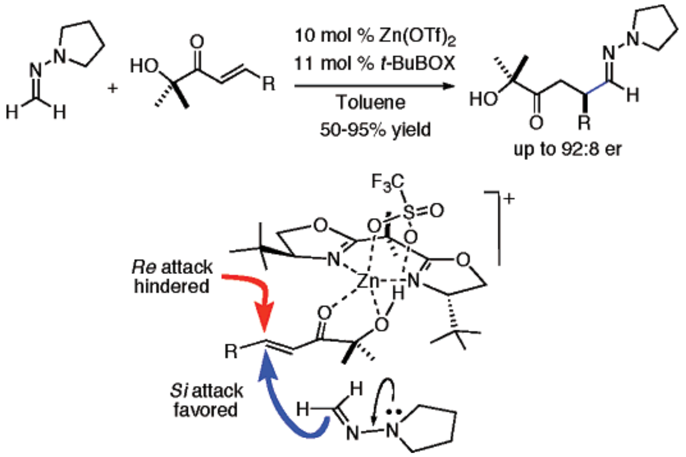
ABSTRACT



The activation of α-hydroxy enones by the $Zn(OTf)_2$/^{t}BuBOX catalyst enables the enantioselective conjugate addition of 1-methyleneaminopyrrolidine as a neutral d^1 synthon. Experimental evidence supports a stereochemical model where a triflate ligand controls the geometry of the catalyst–substrate complex by means of a OH–OTf hydrogen bond. The synthesis of *β*-cyano acids illustrates the potential of the methodology.

The conjugate addition of carbon nucleophiles to α,*β*-unsaturated carbonyl compounds is one of the most fundamental C−C bond forming processes in organic synthesis.[1] In particular, the addition of a formyl anion equivalent has a singular synthetic value due to the versatility of the expected products (1,4-dicarbonyl compounds). Some years ago, we reported on the enhanced aza-enamine character of *formaldehyde* hydrazones **1** and their utility as formyl anion and cyanide equivalents.[2] Using reagents derived from (*S*)-1-amino-2-(methoxymethyl) pyrrolidine (SAMP) or related auxiliaries, spontaneous or Lewis acid mediated diastereoselective additions to a variety of Michael acceptors[3] and carbonyl compounds[4] were developed (Scheme 1).

As a major predictable difficulty, formaldehyde hydrazones **1** exhibit a high tendency to form strong complexes with

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[†] Instituto de Investigaciones Químicas (CSIC-US).

[§] Departamento de Química Orgánica.

[‡] Dedicated to Professor Miguel Yus on the occasion of his 60th birthday.

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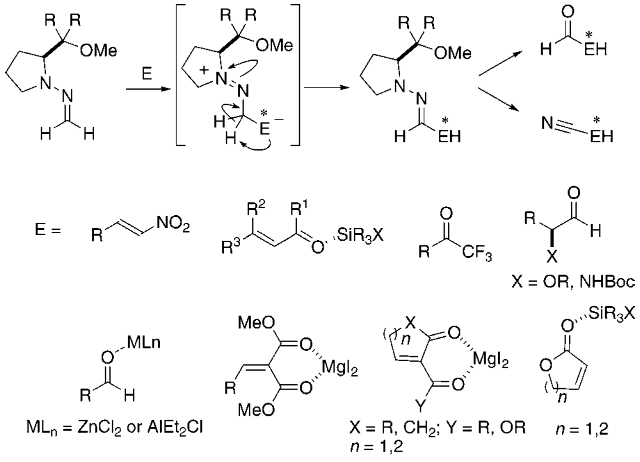
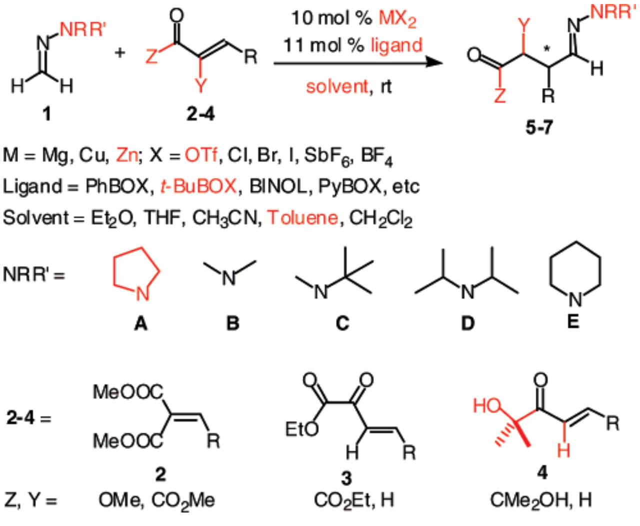
Scheme 1. Aza-enamine Reactivity of Formaldehyde *N*,*N*-Dialkylhydrazones



Scheme 2. Optimization of the Addition of **1** to Enoate Surrogates **2**−**4**[a]



[a] The best choices are marked in red.

most Lewis acids, often leading to decomposition or dimerization.[3d,4c] It was envisaged that the introduction of a suitable achiral template in the substrate would be helpful to avoid deactivation of the Lewis acid, providing also a more rigid substrate−catalyst complex. Thus, alkylidene malonates **2**, alkylidene glyoxylates **3**,[5] and α-hydroxy enones **4**[6] were tested as potential enoate surrogates (Scheme 2). Several screenings were performed to identify the best structure of reagent **1**, the precatalyst, the solvent, and the chiral ligand. It was concluded that 1-methyleneaminopyrrolidine **1A**[7] provides the best results considering combined reactivity and selectivity. Reagents **1B**, **1C**, or **1D** based in acyclic dialkylamino groups afforded lower ee's, and longer reaction times were required for completion. Only piperidine-containing reagent **1E** gave similar ee's; however, 2 equiv of the reagent was required, and the yields were lower. Several metal triflates with PhBOX as the ligand[8] were initially used as the catalysts in the addition reaction of **1A** to **2**−**4**. Fast, clean, and high-yielding reactions to adducts **5**−**7** were observed by using Mg(OTf)$_2$, but racemic products were observed in all cases. With Cu(OTf)$_2$, ee's up to 30% were obtained from alkylidene malonates **2**, but an equimolecular amount of the catalysts was necessary for consumption of the starting material. On the other hand, excellent reactivity was observed using Zn(OTf)$_2$-based catalysts for all substrates. However, addition products from alkylidene malonates **2** were racemic, and those derived from alkylidene glyoxylates **3** showed low ee's and were rather unstable. Finally, the addition of **1A** to α-hydroxy enone **4a** (R = PhCH$_2$CH$_2$) at rt in Et$_2$O afforded adduct **7a** in 90% yield and a noticeable 21% ee as a first encouraging result. Further improvement (95% yield, 64% ee at rt) was achieved by using *t*BuBOX as the ligand and toluene as the solvent. The Zn counteranion proved to be essential for the rate and enantioselectivity of the reaction: the results collected with X = Cl, Br, I, BF$_4$, and SbF$_6$ (slow reactions and low ee's) were in sharp contrast with those observed with Zn(OTf)$_2$.

Under the optimized conditions, **1A** was added to a variety of aliphatic α-hydroxy enones **4a**−**g** (Table 1). The reactions showed in all cases an abnormal dependence of the enantioselectivity with the temperature: the selectivities observed at rt were improved by cooling to 5−10 °C, but the ee's dropped at lower temperatures.[9] The results summarized in Table 1 indicate a uniform behavior for the synthesis of adducts **7a**−**g**, obtained in good yields and ee's. On the other hand, aromatic substrates **4** (R = Ar) showed very low reactivities under these conditions.

Adducts **7** are versatile 1,4-dicarbonyl intermediates that can be transformed into several bifunctional compounds by racemization-free cleavage of the hydrazone[10] and/or release

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(7) As for related enamines, the pyrrolidine ring in **1A** confers a higher nucleophilicity to the aza-enamine system. See refs 3 and 4.

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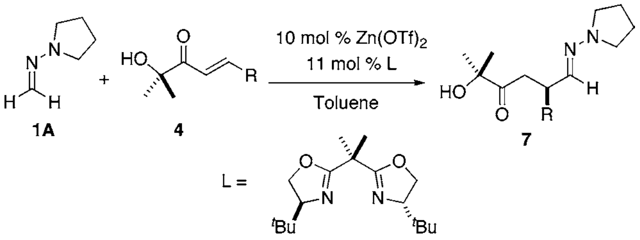
(9) For a similar case and analysis, see: Sibi, M. P.; Gorikunti, U.; Liu, M. *Tetrahedron* **2002**, *58*, 8357−8363 and references therein.

(10) Enders, D.; Wortmann, L.; Peters, R. *Acc. Chem. Res.* **2000**, *33*, 157−169.

Table 1. Nucleophilic Addition of **1A** to α-Hydroxy Enones **4a**−**g**

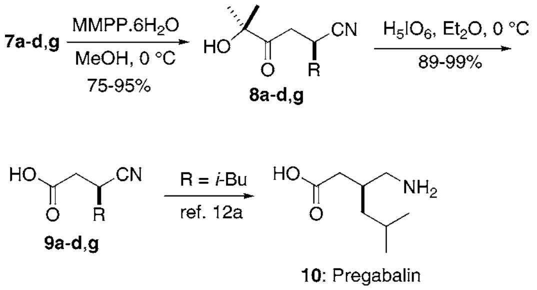


4	R	**7**	*T* (h)	*t* (°C)	yield (%)[a]	er[b]	conf.
4a	CH_2CH_2Ph	**7a**	41	5	78	86:14	(*S*)
4b	*i*-Bu	**7b**	26	10	95	90:10	(*S*)
4c	Cy	**7c**	72	10	73	91:9	(*R*)
4d	*n*-C_5H_{11}	**7d**	27	10	85	92:8	(*S*)
4e	Me	**7e**	17	5	93	83:17	(*S*)
4f	*t*-Bu	**7f**	168	5	50	91:9	(*R*)
4g	*i*-Pr	**7g**	27	10	75	91:9	(*R*)

[a] Isolated yield after column chromatography. [b] Determined by HPLC on chiral stationary phases.

of the 2-hydroxy-2-propyl group.[6] For instance, the oxidative cleavage of the hydrazone by magnesium monoperoxyphtalate (MMPP)[11] readily afforded nitriles **8** (Scheme 3).

Scheme 3. Synthesis of *β*-Cyano Acids **9**



Further oxidation by periodic acid led to cyano acids **9** in good overall yields. These compounds are direct precursors of *γ*-amino butyric acids (GABAs), which are relevant bioactive compounds. In particular, the formal synthesis of pregabalin **10**,[12] an anticonvulsant drug used for treatment of neuropathic pain,[13] is accomplished from **9b** according to a known procedure.[12a]

The absolute (*S*) configuration of **7b** was determined by chemical correlation of nitrile **9b**.[12a,d] The absolute configurations of other adducts **7** were assigned by analogy assuming a uniform reaction pathway. The sense of the selectivity observed in the nucleophilic additions to substrates **4** activated by Cu(II)-based catalysts[6] is the same as that observed with $Zn(OTf)_2$/*t*-BuBOX, in spite of the different coordination geometries expected [square-planar for Cu(II); tetragonal, trigonal pyramidal, or octahedral for Zn(II)]. On the other hand, the intriguing effect by the counteranion in the selectivity suggests that at least one of the triflate ligands remains coordinated to Zn in the active catalyst−substrate complex. To confirm this hypothesis, we unsuccessfully tried to crystallize a **4**/$Zn(OTf)_2$/*t*-BuBOX complex for X-ray analysis. Nevertheless, the diaquo complex [Zn(*t*-BuBOX)-$(H_2O)_2$TfO]$^+$TfO$^-$ **11** was crystallized instead, and its structure was determined by X-ray diffractometry (Figure 1).[9]

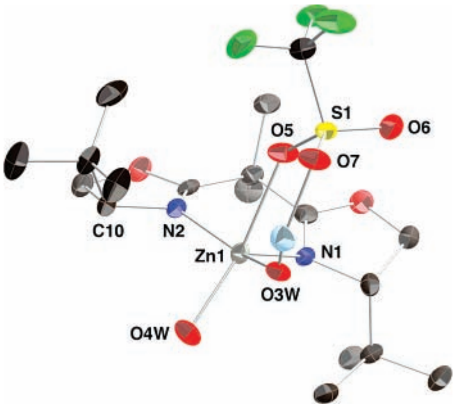


Figure 1. ORTEP drawing of the cation [Zn(*t*-Bu-BOX)$(H_2O)_2$-TfO]$^+$ of complex **11**. Most H atoms and the TfO$^-$ counteranion are omitted for clarity. Selected bond distances (Å) and angles (deg): OH−OTf 1.874; Zn−O(5) 2.358; O(5)−S 1.450; O(6)−S 1.426; O(7)−S 1.441; O(4W)−Zn−N(2)−C(10) 41.9.

This structure served as a template to predict the geometry of the catalyst−substrate complex. Accordingly, a distorted trigonal bipyramidal geometry is envisaged by replacing the two water molecules of **11** with the hydroxy enone **4**, with its orientation fixed by a stabilizing OH−OTf hydrogen bond. The low dihedral O(4W)−Zn−N(2)−C(10) angle of 41.9° places the *re* face of **4** in a zone occupied by a bulky *t*-Bu group, leaving the less-hindered *si* face available for the

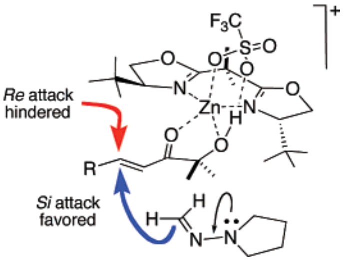


Figure 2. Stereochemical model for the catalyst−substrate complex.

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attack of the nucleophile (Figure 2). This situation resembles the model proposed for Cu(II) complexes[6c] and justifies the essential role played by the triflate counteranion.

In conclusion, we have developed the catalytic asymmetric conjugate addition of 1-methyleneaminopyrrolidine **1A** to α-hydroxy enones as enoate surrogates, leading to 1,4-dicarbonyl compounds. These results expand the synthetic perspectives of reagents **1** as neutral formyl anions and cyanide equivalents in the field of asymmetric catalysis.

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Supporting Information Available: Crystallographic data for **11** and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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