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Organocatalytic Conjugate Addition of Formaldehyde *N,N*-Dialkylhydrazones to β,γ-Unsaturated α-Keto Esters

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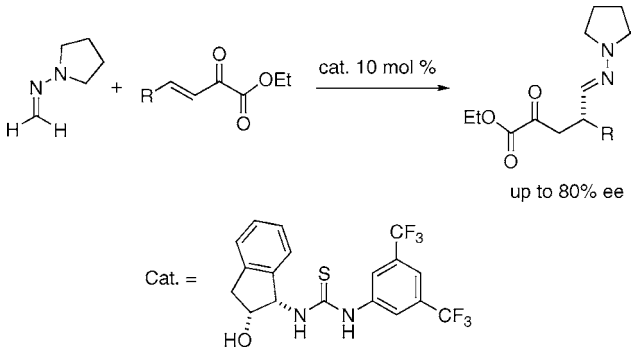
ABSTRACT



(1*S*,2*R*)-1-Aminoindan-2-ol-derived thioureas behave as efficient H-bonding organocatalysts for the nucleophilic conjugate addition of formaldehyde hydrazones to β,γ-unsaturated α-keto esters as enoate surrogates, affording the corresponding adducts in good yields and enantioselectivities.

The asymmetric conjugate addition of umpoled acyl anion equivalents to α,β-unsaturated carbonyl compounds is a powerful synthetic tool that provides a direct access to 1,4-dicarbonyl compounds.[1] Though a number of chiral, auxiliary-based acyl anion equivalents have been used in aldol and related reactions, only metalated α-amino nitriles[2] and mandelic acid derived metalated 1,3-dioxolan-4-ones[3] have been successfully used in conjugate additions. More recently, catalytic, enantioselective Stetter additions by chiral *N*-heterocyclic carbene catalysts have emerged as an elegant solution that avoids the use of chiral auxiliaries,[4] and metallophosphite-catalyzed conjugate addition of acyl silanes to unsaturated amides[5] provides an interesting alternative for intermolecular reactions.

The asymmetric conjugate addition of formyl anion equivalents, however, appears to be a more restricted reaction. In fact, there are only three formyl anion equivalents reported for the diastereoselective addition to α,β-unsaturated carbonyl compounds: lithiated *S*,*S*-acetal *S*-oxide **1**,[6] lithiated (*S*)-4-isopropyl-3-[(methylthio)-methyl]-5,5-diphenyl-oxazolidin-

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(2) Review: Enders, D.; Shilvock, J. P. *Chem. Soc. Rev.* **2000**, *29*, 359−373.

(3) Blay, G.; Fernández, I.; Monje, B.; Muñoz, M. C.; Pedro, J. R.; Vila, C. *Tetrahedron* **2006**, *62*, 9174−9180.

(4) (a) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534−541. (b) Christmann, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 2632−2634. (c) Johnson, J. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1326−1328.

(5) (a) Nahm, M. R.; Linghu, X.; Potnick, J. R.; Yates, C. M.; White, P. S.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 2377−2379. (b) Nahm, M. R.; Potnick, J. R.: White, P. S.; Johnson, J. S. *J. Am. Chem. Soc.* **2006**, *128*, 2751−2756.

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2-one **2**,[7] and neutral formaldehyde *N*,*N*-dialkyl-hydrazones **3**[8] (Figure 1).

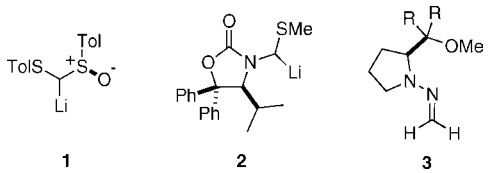


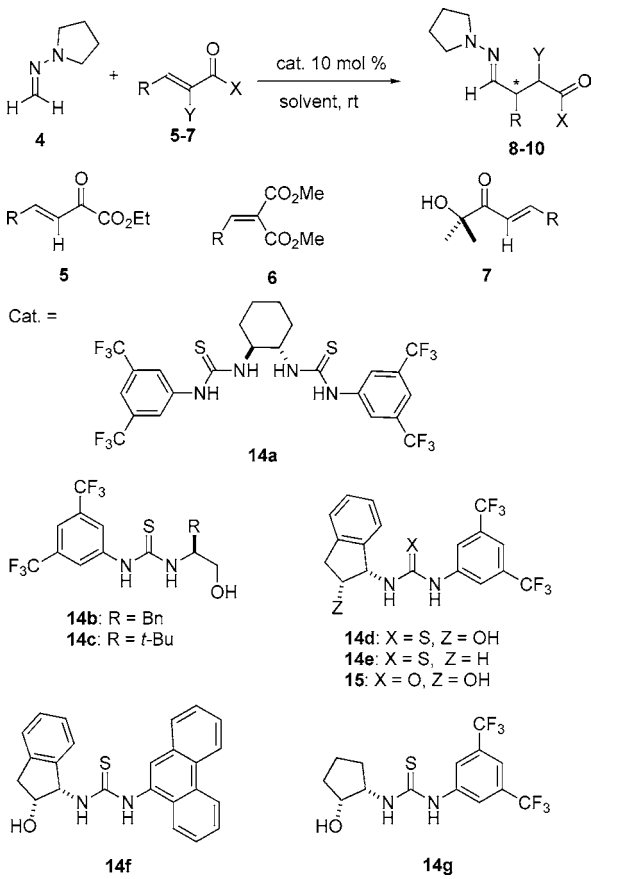
Figure 1. Reagents used as formyl anion equivalents in the asymmetric conjugate addition to α,β-unsaturated carbonyl compounds.

Unfortunately, the umpolung strategies used in the catalytic Stetter reaction fail in the formaldehyde case due to oligomerizations (the formose reaction).[9] Thus, the lack of catalytic approaches for this reaction encouraged studies directed to develop catalytic conjugate additions of achiral *N*,*N*-dialkylhydrazones to enoate surrogates.

Besides the use of chiral Lewis acids as catalysts,[10] often troublesome due to the concurrence of side reactions,[8a,11] the use of milder species as H-bonding organocatalysts[12] was found to be effective in the activation of imines[13] and appears a priori to be particularly appropriated to this reaction. We wish to report here on the thiourea-catalyzed enantioselective addition of 1-methyleneaminopyrrolidine **4** to β,γ-unsaturated α-keto esters **5**.

Initially, alkylidene malonates **6** and α-hydroxy enones **7**[14] were also considered as potential enoate surrogates. During the preliminary reactivity tests, however, no addition reactions were observed with these substrates under a variety of conditions and catalysts.

Scheme 1. Nucleophilic Addition of 1-Methyleneaminopyrrolidine **4** to Enoate Surrogates



Therefore, further experiments were conducted with glyoxylate **5a** and 1-methyleneaminopyrrolidine **4** as model reactants. Other considered *N*,*N*-dialkylamino groups such as *N*,*N*-dimethyl, *N*,*N*-diisopropyl, *N*-*tert*-butyl-*N*-methyl, and piperidin-1-yl had a detrimental effect on the reactivities and selectivities of their corresponding formaldehyde hydrazones. BINOL (**11**), BINOL-phosphate (**12**), mandelic acid (**13**), and a series of (thio)ureas **14a**−**g** and **15**[15] were used as potential catalysts. BINOL **11** showed a moderate catalytic activity in toluene but afforded **8a** in racemic form, whereas stronger Brønsted acids **12** and **13** were inefficient, probably because of deactivation by the basic reagent **4**. Thioureas

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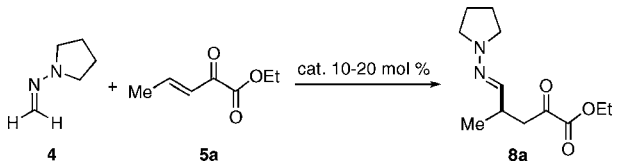
14a−**g** and urea **15**, however, efficiently accelerated the reaction with respect to the noncatalyzed background reaction (Table 1, entry 1), leading to the desired product **8a** in high

Table 1. Thiourea- or Urea-Catalyzed Addition of **4** to **5a**[a]



4 **5a** **8a**

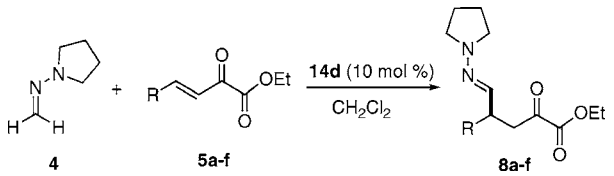
entry	catalyst[b]	solvent	temp (°C)	time (h)	conversion (%)[c]	ee (%)[d]
1		toluene	20	18	50	
2	**14a**	toluene	20	18	>90	0
3	**14b**	toluene	20	18	>90	8
4	**14c**	toluene	20	18	>90	14
5	**14d**	toluene	20	18	>90	30
6	**14e**	toluene	20	18	>90	14
7	**14f**	toluene	20	18	>90	28
8	**15**	toluene	20	18	>90	32
9	**14g**	toluene	20	18	>90	17
10	**14d**	THF	20	18	>90	14
11	**14d**	CH_3CN	20	18	>90	14
12	**14d**	CH_2Cl_2	20	18	>90	33
13	**14d**	CH_2Cl_2	−45	48	68[e]	64
14	**14d**[f]	CH_2Cl_2	−45	72	74[e]	72
15	**14d**[fg]	CH_2Cl_2	−45	72	70[e]	76
16	**14d**[fg]	CH_2Cl_2	−60	72	60[e]	80

[a] Reactions performed at 0.1 mmol scale. [b] 20 mol %. [c] Determined by ^{1}H NMR of the crude reaction mixtures. [d] Determined by HPLC. [e] Isolated yield. [f] 10 mol %. [g] Reactions performed at 0.25 mmol scale.

conversions (entries 2−9). On the other hand, only (1*S*,2*R*)-1-aminoindan-2-ol derived catalysts **14d**, **14f**, and **15** afforded a moderate yet promising asymmetric induction, leading to product **4a** in 30%, 28%, and 32% ee, respectively (entries 5, 7, and 8). Catalyst **14d** proved finally to be slightly better than **14f** or **15** by analyzing the effect of the solvent, reaction temperature, catalyst loading, and scaling up in the enantioselectivity. Thus, ee dropped for **14d** in THF or CH_3CN (entries 10 and 11), but the use of CH_2Cl_2 resulted in a slight improvement (33% ee, entry 12). Cooling to −45 °C in CH_2Cl_2 had a remarkable effect on the enantioselectivity, leading to product **4a** in 64% ee with good yield (entry 13). Moreover, decreasing the catalyst loading to 10% improved the enantioselectivity up to 72% while maintaining a good conversion (entry 14). Finally, scaling up the reaction from 0.1 to 0.25 mmol resulted in a further increase of ee to 76% at −45 °C and to 80% at −60 °C (entries 15 and 16).

We finally explored the scope of the reaction by adding hydrazone **4** to β,γ-unsaturated α-keto esters **5 b**−**f** bearing different aliphatic side chains. Under the optimized reaction conditions, the corresponding derivatives **8a**−**f** were obtained in good yields and ee's (Table 2). Unfortunately, less reactive aromatic substrates (R = Ph, 2-thienyl, etc.) required higher reaction temperatures, and the corresponding adducts were obtained with low ee's.

Table 2. Addition of Reagent **4** to β,γ-Unsaturated α-Keto Esters **5**[a]



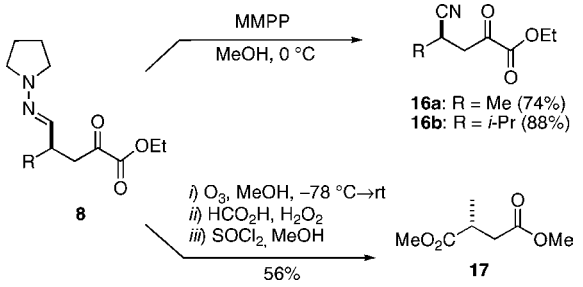
4 **5a-f** **8a-f**

R	product	temp (°C)	yield (%)[b]	ee (%)[c]
Me	**8a**	−60	60	80
i-Pr	**8b**	−45	80	78
i-Bu	**8c**	−45	75	78
n-C_5H_{11}[d]	**8d**	−60	61	70
$(CH_3)_3CH_2$	**8e**	−45	64	58
Cy	**8f**	−45	82	72

[a] Reactions at 0.25 mmol scale with 10 mol % of **14d** as the catalyst. [b] Isolated yield after 72 h. [c] Determined by HPLC. [d] 20 mol % of **14d** used.

Compounds **8** are versatile 1,4-dicarbonyl compounds that can be transformed into nitriles **16** by applying a simple, racemization-free oxidative cleavage of the hydrazone moiety by magnesium monoperoxyphtalate hexahydrate (MMPP·$6H_2O$)[16] (Scheme 2). Additionally, ozonolytic cleavage of

Scheme 2. Synthesis of 1,4-Dicarbonyl Derivatives **16** and **17**



8 **17**

8a afforded an unstable intermediate that was further oxidized by a HCO_2H/H_2O_2 mixture and treated with $SOCl_2$/MeOH to obtain the succinate derivative **17** resulting from deoxidative decarboxylation.[17] Comparison of its optical rotation with literature data[18] was used for the assignment of its absolute configuration and that of the parent adduct **8a**. The absolute configuration of other adducts **8** was assigned by analogy.

The role played by the hydroxy group in the catalysts **14d**, **14f**, or **15** and the absolute configuration observed are consistent with a bifunctional mode of action by the

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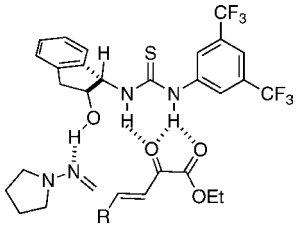

Figure 2. Stereochemical model.

catalyst.[19] According to this assumption a stereochemical model is proposed, where the approach of the azomethine carbon of **4** to the target γ-carbon of the activated substrate **5** is driven by a OH-N(2) hydrogen bond, resulting in the addition of the reagent to the *re* face as depicted in Figure 2.

In summary, the H-bonding activation by chiral thioureas appears as a suitable approach for the enantioselective nucleophilic addition of *N*,*N*-dialkylhydrazones as umpoled d^1 reagents to β,γ-unsaturated α-keto esters as enoate surrogates. This reaction represents a first example of the organocatalytic addition of neutral, electron-rich π-nucleophiles to α,β-unsaturated carbonyl compounds.

Acknowledgment. We thank the MEC (grants CTQ2004-00290 and CTQ2004-0241, predoctoral fellowship to D.M., postdoctoral fellowship to R.P.H.) and the Junta de Andalucía (grant FQM-658) for financial support.

Supporting Information Available: Experimetal procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) The bifunctional catalysis by thiourea **14d** has been also proposed in the addition of indoles to nitroalkenes (ref 14d), and the aza-Michael addition of *O*-benzylhydroxylamines to pyrazole enoates: Sibi, M. P.; Itoh, K. *J. Am. Chem. Soc.* **2007**, *129*, 8064−8065. For a review of bifunctional thiourea catalysts, see ref. 12f.