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2-Hydroxybenzophenone as Chemical Auxiliary for the Activation of Ketiminoesters in the Highly Enantioselective Addition to Nitroalkenes under Bifunctional Catalysis†‡

Andrea Guerrero-Corella,[+] Francisco Esteban,[+] Manuel Iniesta, Ana Martín-Somer, Mario Parra, Sergio Díaz-Tendero, Alberto Fraile* and Jose Alemán*

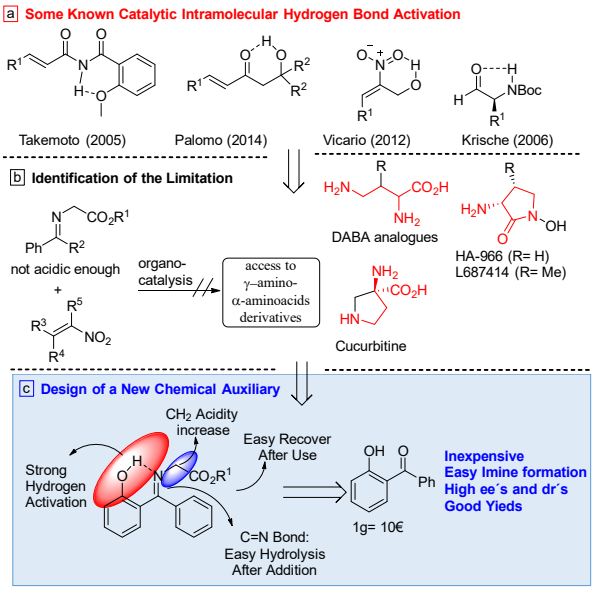
Abstract: *An organocatalytic system for the Michael addition of mono-activated glycine ketimine ylide using a bifunctional catalyst is presented. The ketimine bears an ortho hydroxy group, which increases the acidity of the methylenic protons and enhances the reactivity, allowing the synthesis of a large variety of α,γ-diamino acid derivatives with excellent stereocontrol.*

α-Amino acids are essential molecules in many fields. They are used in the synthesis of peptides and proteins, as chiral catalysts, as a source of chirality in the design of ligands and in total synthesis.[1] Such is the application and demand for enantiomerically enriched α-amino acids that synthetic organic chemists continue to develop new methods of synthesis.[2] Especially important and relevant are α,γ-diamino acid derivatives, which are present in a large number of natural and pharmaceutical products.[3] For example, DABA analogues are used as drugs e.g. anticonvulsants, sedatives, and anxiolytics.[3a] HA-966 and L687414 are used as NMDA antagonists,[3b-c] and cucurbitine, a natural product found in pumpkins, is used against the parasite *Schistosoma japonicum*[3d] (middle-right, Scheme 1).

In recent years, ketiminoesters derived from glycine have become increasingly important because they provide a starting material for the synthesis of optically pure α-amino acid derivatives.[4] The alkylation of glycine ketimines with different alkylating reagents under PTC conditions has been well developed by the excellent works of O´Donnell,[5] Maruoka,[6] and others.[7] However, the number of examples related to their addition to nitroalkenes, that would give access to α, γ-diamino acid derivatives, is scarce (middle, Scheme 1).[8,9] There are no highly asymmetric examples of the organocatalytic approach to these additions in the literature, where the corresponding adducts in the addition of mono-activated ketimines to nitroalkenes can be obtained.[9b] The reason for this absence of reactivity, especially in the field of the bifunctional thiourea catalysis,[9a-b] is related to the lack of acidity of the protons of the α-methylene ester. In fact, for this class of ylides, two EWGs are needed to increase the acidity to promote the organocatalytic addition.

In our investigations with bifunctional catalysis,[10] we speculated that it might be possible to overcome this organocatalytic limitation in the synthesis of α,γ-diamino acid derivatives. Recently, different authors such as Takemoto,[11] Vicario,[12] Palomo,[13] and Krische[14] among others[15] (top, Scheme 1), have published excellent examples showing how different chemical auxiliaries using hydrogen bond activation can increase the electrophilicity of amides or ketones, or be used in the control of the stereochemistry and reactivity (nitroalkenes and aldehydes). However, only a few studies have been reported regarding the increase in nucleophilicity.

The low reactivity in the azomethine ylides in the organocatalytic area is due to the low acidity of the CH_2 protons. Therefore, we wondered if an intramolecular hydrogen bond activation would help in the addition to nitroalkenes and provide good reactivity and enantioselectivity. However, in order to find an appropriate scaffold, the chemical auxiliary must fulfill the following requirements: *i*) be recyclable; *ii*) inexpensive; and *iii*) easily removable. Taking these factors into consideration, we hypothesized that 2-hydroxybenzophenone may be a suitable candidate due to the easy intramolecular six membered-ring via hydrogen bond formation, and the easy ketimine hydrolysis (bottom, Scheme 1). As part of our work to extend the use of the hydrogen bond activation, we describe here a new direct process for the synthesis of γ,α-diamino acid derivatives, using a new chemical auxiliary that is easily recovered, activates the glycine



Scheme 1. Background and strategy for the synthesis of a novel chemical auxiliary in the organocatalytic synthesis of α,γ-diamino acid derivatives.

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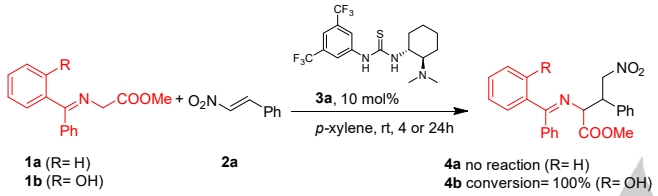
ketimine and provides excellent yields, diastereo- and enantio-selectivities.

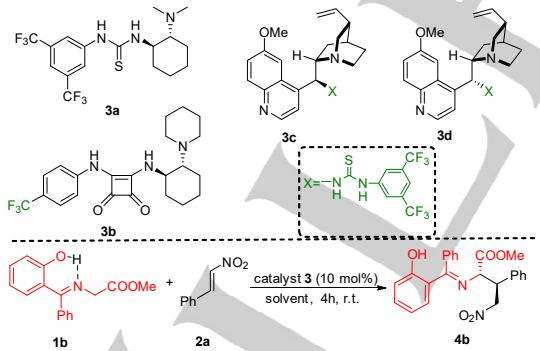
Initially, we synthesized the ketimines **1a** and **1b** (see. S.I.) in good yields from commercially available starting materials (Scheme 2). The stability of ketimine **1b** is very high, and it could be stored at room temperature for months. As a proof of concept, we performed the reaction with the ketimine **1a**, without a hydroxy group. No reaction took place using the ketimine **1a** and after 24 hours no trace of the corresponding product **4a** was detected. However, when the ketimine **1b** was used with Takemoto's catalyst **3a**, a complete conversion to **4b** occurred in only 4 hours. These preliminary results prompted us to screen the reaction and determine the best catalytic conditions in terms of enantioselectivity, diastereoselectivity and yield (Table 1).



Scheme 2. Proof of concept for the intramolecular H-bond activation.

Different thiourea and squaramide catalysts (**3a-3b**), and cinchona thioureas (**3c** and **3d**) were tested (entries 1-4, Table 1). Similar results were found with all the thiourea catalysts (ee>95%, entries 1 and 3-4), but the reaction resulted in a very low conversion with the squaramide catalyst **3b** (entry 2). We then followed the optimization with the commercially available Takemoto catalyst **3a**. Different apolar solvents such as DCE or *p*-xylene produced similar results (entries 5 and 6), whereas the polar solvents such as CH_3CN and MeOH produced worse results (entries 9 and 10). Interestingly, ethereal solvents provided good results, especially in the case of THF which resulted in the product **4b** as a single diastereoisomer with a 98% ee (entry 7 and 8). The conversion with the THF solvent was 83% after 4 hours and this was increased to a full conversion after 15 hours (result between brackets, entry 8). With these conditions defined, the scope of the reaction was studied using different substituted nitroalkenes (Table 2), and ketimines (Scheme 3).

Table 1. Screening of reaction conditions for the synthesis of **4b**.[a]



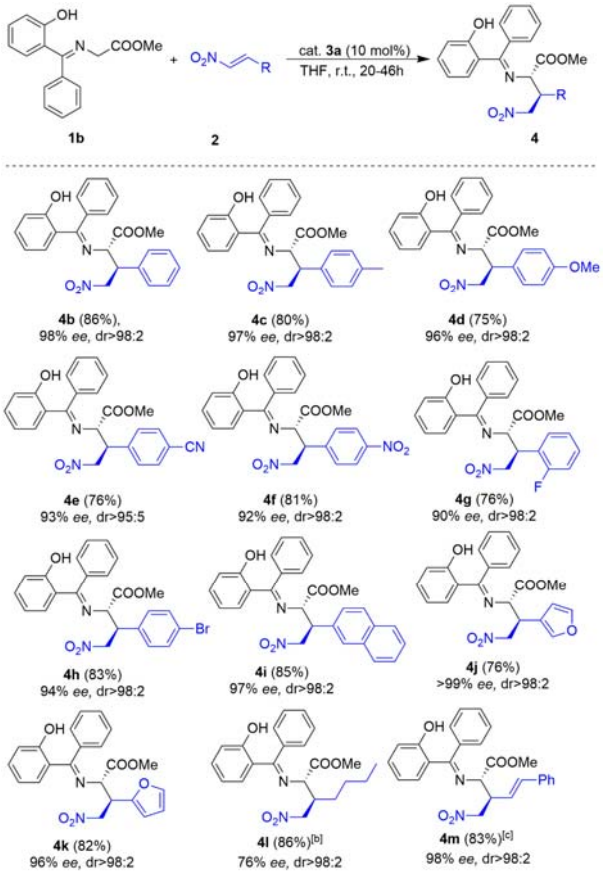
Entry	Cat.	Solvent	Conversion[b]	d.r.[b]	Ee [%][c]
1	**3a**	CH_2Cl_2	100	90:10	97
2	**3b**	CH_2Cl_2	10	80:20	n.d.[d]
3	**3c**	CH_2Cl_2	89	92:8	95
4	**3d**	CH_2Cl_2	100	95:5	97
5	**3a**	*p*-Xylene	92	92:8	95
6	**3a**	DCE	100	88:12	96
7	**3a**	Et_2O	84	85:15	96
8	**3a**	**THF**	**83 (100)[e]**	**>98:2**	**98**
9	**3a**	CH_3CN	94	90:10	96
10	**3a**	MeOH	52	91:9	74

[a] Conditions: 0.2 mmol of **1b**, 0.24 mmol of **2a**, 10 mol% of catalyst **3** in 0.4 mL of the indicated solvent. [b] Determined by ^{1}H NMR analysis. [c] Determined by SFC. [d] Not determined. [e] Determined after 15 h reaction.

The reaction worked with EDGs and EWGs (**4c-4f**) with high enantiomeric excess (92-97% ee) and good yields (74-81%). The addition reaction was also performed with aromatic groups containing halogens in the *ortho* (**4g**) and *para* position (**4h**), bulkier groups such as naphthyl (**4i**) and heterocycles in different positions (**4j** and **4k**) from good to excellent ee (90-99% ee). Interestingly, alkyl groups at the nitroalkene, which are difficult to obtain by other methods, were also tolerated, yielding the amino acid derivative **4l**, but longer reaction times of 4 days were needed. A double bond substitution at the nitroalkene led to the final product **4m** in a good yield (83%) and excellent ee (98% ee).

We analyzed other groups at the azomethine ylides in place of the carboxylate group (Scheme 3). This catalytic system with the hydroxy group allowed the addition of nitrile ylide **1n** and yielded the product **4n** in moderate enantiomeric excess. However, the use of derivatives **1o** and **1p,** with a ketone and amide, respectively, resulted in better enantiomeric excesses (both with 93% ee). The use of CF_3 or an aryl group did not enable

Table 2. Reaction of glycine ketimine **1b** with different nitroalkenes **2**.[a]



[a] All the reactions were performed at 0.2 mmol scale in 0.4 mL THF. Ee (enantiomeric excess) of **4** were determined by SFC. D.r. (diastereomeric ratio) was determined by ^{1}H NMR: Yield isolated after flash chromatography. [b] Reaction time: 4 days. [c] Reaction time: 5 days.

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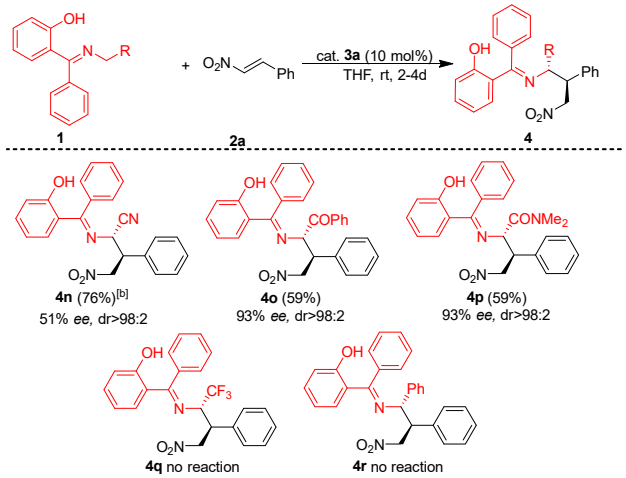
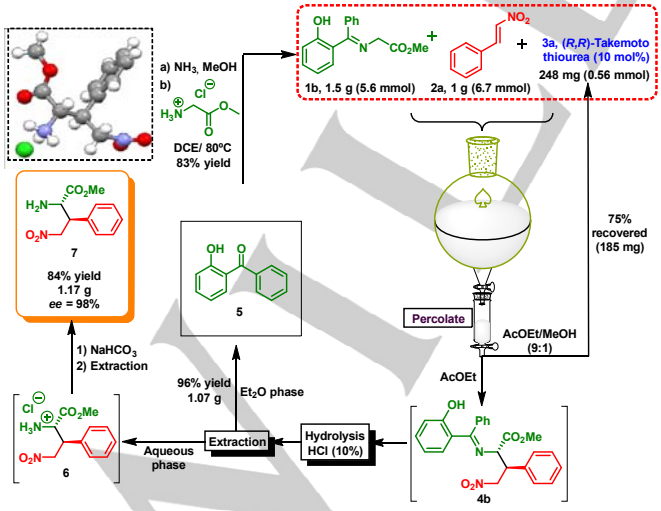
the corresponding products **4q** and **4r**, and we only observed the unaltered starting materials in the crude mixture.



Scheme 3. Use of different glycine ketimines [a] 0.2 mmol (**1**), 0.24 mmol (**2**), 10 mol% of **3a** in 0.4 mL of THF. [b] Yield based on recovered material.

In addition, the reaction was scaled up and the hydroxyketone and catalyst **3a** were easily recovered (Scheme 4). The reaction at this scale (5.6 mmol) took 22 h to complete and using a fast percolate of the crude mixture the compound **4b** (98% ee) was obtained, and catalyst **3a** was recovered with a 75% yield (right, Scheme 4). Compound **4b** was treated with HCl (10%) in smooth conditions, and after a simple extraction, the hydroxyketone **5** was recovered with a 96% yield. The amino acid salt derivative **6** was washed with $NaHCO_3$, and the free amino acid **7** (left, Scheme 4) obtained. The absolute configuration of the asymmetric centres of **6** was unequivocally assigned as 2*S*, 3*S* (left, top-Scheme 4) by X-ray crystallographic analysis and it was assumed to have the same stereochemical outcome as the other compounds **4**.



Scheme 4. Scale up and catalyst and chemical auxiliary recovery.

The reaction mechanism of the nitroalkene **2a** with the glycine ketimine **1b** in presence of catalyst **3a** was studied using DFT calculations (see S.I. for details).[17] Initially, we investigated the reasons for the lack of reactivity of the three nucleophiles **1a**, **1q** and **1r** in comparison with **1b** and **1n-p** (Figure 1). We considered the acid-base equilibrium in which the proton is transferred from the ketimine **1** to the catalyst **3a** and a molecular hydrogen bonded **4A-complex** is formed.[18] The relative Gibbs free energy (ΔG) in the proton transfer equilibrium is presented in Figure 1. We then evaluated the effect of the different substituents in the acidity of the ketimine **1** towards the formation of the ylide **4A-complex**. The ΔG in **1b** (with an OH group) is 5.9 kcal/mol lower than in **1a** (without an OH group), which demonstrates the importance of the intramolecular H bond in increasing the acidity. Electron-withdrawing substituents such as COPh (**1o**), CN (**1n**), $CONMe_2$ (**1p**), CO_2Me (**1b**) present both inductive (–I) and mesomeric (–M) effects; however, **1q** (CF_3) possesses only –I and **1r** (Ph) exclusively –M effect. As was predicted, the reactants that present groups with both effects showed a lower ΔG (higher acidity). For groups at the ketimine **1** showing only one of the effects, the ΔG was increased, (lower acidity). Consequently, these latter cases (**1q** and **1r**) did not react. Therefore, a combination of these factors is needed to increase the acidity: the intramolecular hydrogen bond (C=N---HO-Ar), and the appropriated substituents at the ketimine **1** (R groups with both –I and –M effects).

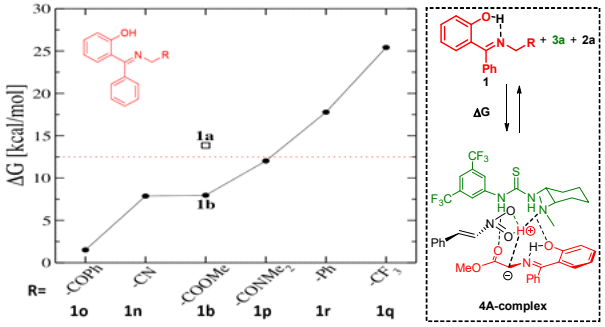


Figure 1. ΔG of proton transfer reactions with different nucleophiles **1**.

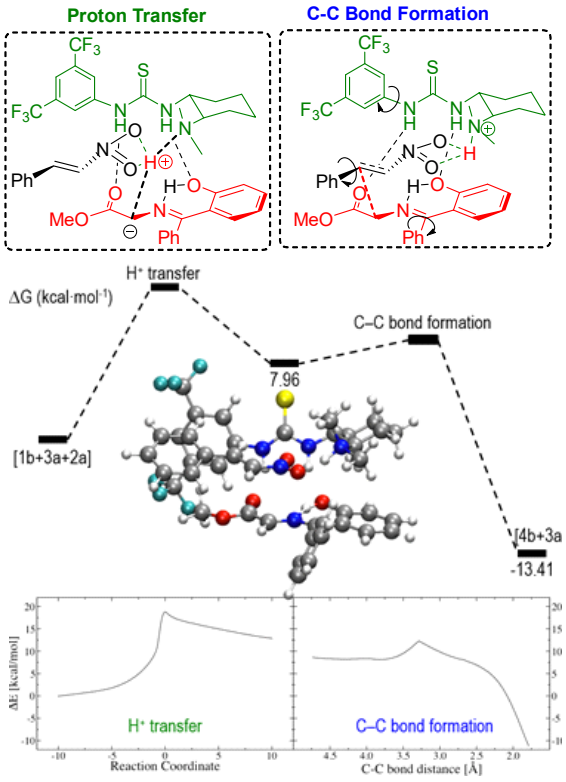


Figure 2. ΔG and energy profile of the two step mechanism.

We then considered the complete picture of the mechanism for the reaction between **1b** and **2a** catalyzed by **3a**. Two steps are involved in this process: a proton transfer leading to the ylide,

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followed by the C–C bond formation (top, Figure 2). The energetic profile of both steps is presented in Figure 2. In the first stage, a transition state consists of the direct migration of the proton from the ketimine **1b** to the catalyst **3a**. The relative position of the nitroalkene **2a** depends on the relative position of the proton, because the intrinsic dipole of the nitro group points towards the positive charge on the proton and assists the proton-migration. Figure 2 also shows how the coordination by means of hydrogen bonds is fundamental to the appropriate orientation of the ketimine **1b** with the catalyst **3a**, enabling the proton transfer to be carried out. The second stage due to the subtle movements involved in the geometric reorganization has a very complex energy profile and therefore only a scan of the C–C bond distance is presented (see details of the complete exploration of the potential energy surface in the S.I.). It implies a reorientation of all the three benzene rings located in the catalyst, in the electrophile, and in the nucleophile, for the new conformation that involves the coordinated rotations of the different dihedral angles. The intramolecular attack of the nitronate intermediate generated on the ketimine is hindered because the orientation of the phenyl ring of the ketimine is blocking this addition, without the formation of the pyrrolidine core by a formal 1,3-dipolar-cycloaddition. In this step, the coordination of the nucleophile **1b** to the catalyst **3a** is also a crucial point in the stereochemistry of the products.[19] Overall, the rate limiting step is the proton transfer with a larger energy barrier than the C-C bond formation (see Figure 2).

In summary, an organocatalytic strategy for the synthesis of α,γ-diamino acid derivatives in high enantiomeric excess is presented. The key to the success is the intramolecular activation *via* hydrogen bonding through an *ortho* hydroxy group, which allows the Michael addition to take place in the presence of glycine ylides bearing only one activating group.

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Keywords: α-amino acids • bifunctional catalysis • hydrogen bond activation • chemical auxiliary

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[19] The opposite prochiral face of the electrophile would be attacked but a strong steric interaction between the aryl group of the catalyst **3a** and the phenyl group of the nitroalkene **2a** could take place. This could be the reason for the lower enantiomeric excess observed for an alkyl substituent **4l** (see Table 2).

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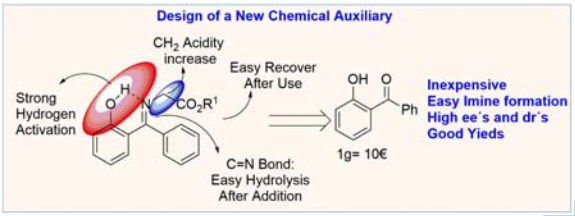

In this communication, a new organocatalytic system for Michael addition of mono-activated azomethine ylides using a bifunctional catalyst is presented.