Organocatalysis

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Enantioselective Organocatalytic Conjugate Addition of N Heterocycles to α,β-Unsaturated Aldehydes**

*Peter Dinér, Martin Nielsen, Mauro Marigo, and Karl Anker Jørgensen**

Organocatalysis[1] has expanded widely within the last few years, since the rediscovery of the proline-catalyzed aldol reaction.[2] Since then, several different methods, such as fluorination,[3] chlorination,[4] bromination,[5] sulfenylation,[6] amination,[7] and Mannich reactions,[8] have been developed for the α-functionalization of aldehydes and ketones with high stereoselectivity. The catalysts for these reactions are mainly chiral secondary amines and imidazolidinones, which activate the carbonyl compounds by an enamine mechanism.[9]

Chiral secondary amines are also effective catalysts for enantioselective β addition to α,β-unsaturated carbonyl compounds. In the case of these α,β-unsaturated systems, the catalyst activates the substrate through the iminium-ion mechanism, thereby facilitating the addition of the nucleophile to the β-carbon atom. This reaction protocol has been developed organocatalytically for a number of different reactions such as cycloaddition reactions,[10] reductions,[11] and Michael additions.[12]

Recently, several organocatalyzed nucleophilic nitrogen addition reactions to α,β-unsaturated carbonyl compounds have been presented. For example, Miller and co-workers[13] accomplished the addition of azide to unsaturated imides with moderate to good enantioselectivity, and MacMillan and co-workers[14] demonstrated the enantioselective formation of β-amino aldehydes by addition of O-*tert*-butyldimethylsilyl-protected carbamates to α,β-unsaturated aldehydes. Furthermore, Jacobsen and Gandelman[15] succeeded with the addition of a range of different aromatic N-heterocyclic compounds to unsaturated ketones and imides with high enantioselectivities using a chiral Al-salen catalyst.

The products of the addition of N-heterocyclic compounds to α,β-unsaturated aldehydes have shown important biological activities.[16] Several compounds containing N-heterocyclic groups such as 1,2,4-triazoles and tetrazoles are, for example, included in drugs such as Voriconazole (antifungal), Fluconazole (antifungal), and Losartan (high blood pressure).

[*] Dr. P. Dinér, M. Nielsen, Dr. M. Marigo, Prof. Dr. K. A. Jørgensen
Danish National Research Foundation: Center for Catalysis
Department of Chemistry, Aarhus University
DK-8000 Aarhus C (Denmark)
Fax: (+45) 8919-6199
E-mail: kaj@chem.au.dk

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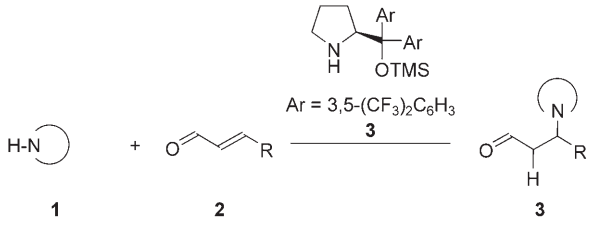
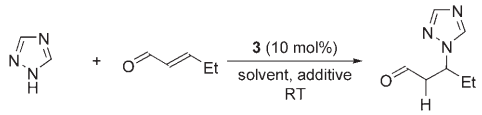
Here we present the first organocatalytic conjugate addition of aromatic N heterocycles to α,β-unsaturated aldehydes using the catalyst 2-[bis(3,5-bis-trifluoromethyl-phenyl)trimethylsilanyloxymethyl]pyrrolidine (Scheme 1).[17] Furthermore, we also include DFT calculations in an attempt to better understand the catalytic cycle and the stereochemical outcome of the reaction.



Scheme 1. TMS = trimethylsilyl.

We started out with the reaction of 1,2,4-triazole (**1**) with 2-pentenal (**2a**) in the presence of catalyst **3**. A screening of solvents, concentration, and additives was performed to optimize the reaction conditions, some representative results of which are given in Table 1. The results therein show that full conversion was achieved in 2–4 h in the presence of 10 mol% benzoic acid in solvents such as CH_2Cl_2, MeCN, toluene, and [D_6]benzene, whereas pentane only gave a low conversion. The reaction performed in [D_6]benzene and toluene gave high enantioselectivity, 89 and 88% *ee*, respec-

Table 1: Screening of various reaction conditions for the addition of 1,2,4-triazole **1** to 2-pentenal **2a** using catalyst **3**.[a]



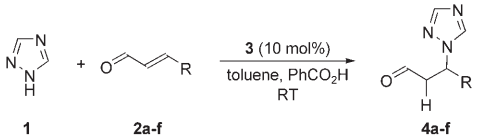
Entry	Solvent	[1] [M]	$PhCO_2H$ [mol%]	*t* [h]	conv. [%][b]	*ee* [%][c]
1	CH_2Cl_2	0.5	10	2	100	33
2	pentane	0.5	10	4	24	–
3	MeCN	0.5	10	4	100	7
4	benzene	0.5	10	2	96	89
5	toluene	0.5	–	4.5	100	88
6	toluene	2.5	10	1	100	68
7	toluene	0.1	10	2	100	92

[a] Performed with **1** (0.25 mmol), **2** (0.375 mmol), and **3** (0.025 mmol). Additive: $PhCO_2H$. [b] Determined by ^1H NMR spectroscopy. [c] Determined by chiral GC.

tively (entries 4 and 5, Table 1), whereas the enantioselectivity decreased significantly in CH_2Cl_2 and MeCN (entries 1, 3). An increase in the enantioselectivity (from 88 to 92% *ee*) was observed upon decreasing the concentration of the reaction (entry 5 vs 7, Table 1), and the enantioselectivity decreased at higher concentrations (entry 6).

With the optimized conditions in hand, the scope of the reaction for different α,β-unsaturated aldehydes was investigated. Table 2 shows the results of the variation of substituents in the α,β-unsaturated aldehydes **2a–f** in reaction with 1,2,4-triazole (**1**). As seen from the results, all aliphatic α,β-unsaturated aldehydes gave the 1,2,4-triazole addition products **4a–d** in high yields and with high enantioselectivities (entries 1–4, Table 2). The reaction times increased with the bulkier isopropyl group in the side chain, however, it also led to a small increase of the enantioselectivity to 94% *ee* compared to the linear aliphatic chains. The introduction of an extra double bond in the side chain (entry 5, Table 2) gave also the Michael addition product **4e** in high yield and with high enantioselectivity. It is notable that aromatic α,β-unsaturated aldehydes such as cinnamic aldehyde (**2f**) only gave low conversions in this reaction (entry 6, Table 2).

Table 2: Scope of the organocatalytic addition of 1,2,4-triazole (**1**) to α,β-unsaturated aldehydes **2a–f**.[a]

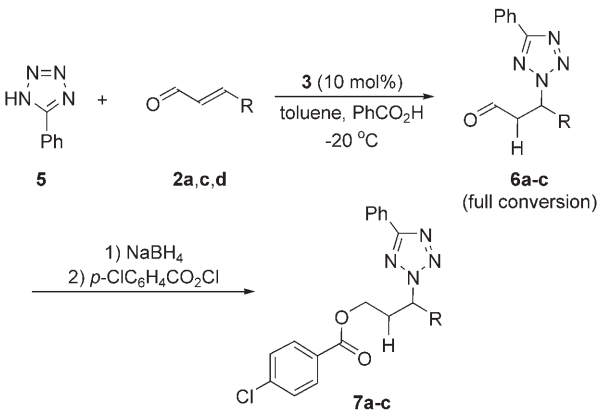


Entry	R	*t* [h]	Yield [%][b]	*ee* [%][c]
1	Et	2	78 (**4a**)	92
2	*n*Bu	3	87 (**4b**)	92
3	Hep	4	76 (**4c**)	93
4	*i*Pr	19	76 (**4d**)	94
5	3-hexenyl	4	87 (**4e**)	92
6	Ph	20	<20 (**4f**)	–

[a] Performed with **1** (0.25 mmol), **2** (0.375 mmol), **3** (0.025 mmol), and $PhCO_2H$ (0.025 mmol) in toluene. [b] Purified by flash chromatography. [c] Determined by chiral GC.

To expand the scope of the reaction, the addition of aromatic N heterocycles using other nucleophiles than 1,2,4-triazole (**1**) was investigated. The reaction of 5-phenyltetrazole (**5**) with α,β-unsaturated aldehydes **2a**,**c**,**d** catalyzed by **3** at room temperature gave the addition products **6a–c** with full conversion (Scheme 2). These products were reduced with $NaBH_4$, and the resulting alcohols were subsequently functionalized to the corresponding esters using *p*-chlorobenzoyl chloride. However, the observed enantioselectivity was merely 50% *ee*, indicating that the product may racemize. Therefore, the reaction was carried out at −20 °C, followed by subsequent reduction and functionalization of the alcohol to an ester. By the use of these reaction conditions, the reaction now proceeded with excellent enantioselectivity and acceptable yields for a three-step reaction (Table 3, entries 1–4).

Additional nucleophiles that were investigated in this addition reaction to α,β-unsaturated aldehydes were 1,2,3-benzotriazole (**8**) and 1,2,3-triazole (**9**). Both nucleophiles were treated with the aldehydes, and the resulting products were subsequently reduced and esterified (Scheme 3, Table 4). The addition of 1,2,3-benzotriazole (**8**) and 1,2,3-triazole (**9**) gave a mixture of two regioisomers (2:1), **10** and **11**, respectively, which were separated by flash chromatography. The results in Table 4 show that **10** and **11** were formed with similar enantioselectivities in acceptable yields after three reaction steps.



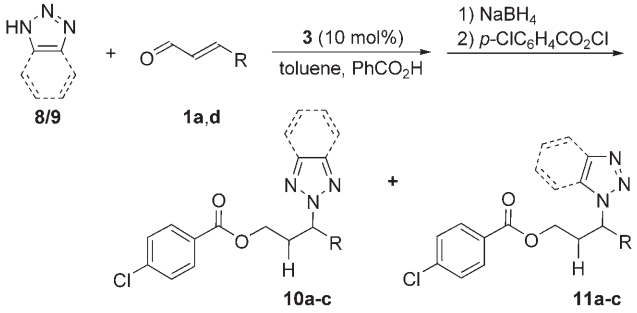
Scheme 2.

Table 3: Scope of the organocatalytic addition of 5-phenyl-*1H*-tetrazole (**5**) to α,β-unsaturated aldehydes **2a**,**c**,**d** (see Scheme 2).[a]

Entry	R	[**5**] [M]	*t* [h]	Yield [%][b]	*ee* [%][c]
1	Et	0.1	22	45 (**7a**)	90
2	Hept	0.1	23	52 (**7b**)	92
3	*i*Pr	0.1	51	66 (**7c**)	91
4	*i*Pr	0.5	19	55 (**7c**)	85

[a] Performed with **1** (0.25 mmol), **2** (0.375 mmol), **3** (0.025 mmol), and $PhCO_2H$ (0.025 mmmol) in toluene at −20 °C. [b] Purified by flash chromatography after reduction with $NaBH_4$ and functionalization with *p*-chlorobenzoyl chloride. [c] Determined by chiral HPLC.

The absolute configuration of the optically active products formed was determined by X-ray analysis.[18] The product **7c** obtained from the addition of 5-phenyltetrazole (**5**) to the α,β-unsaturated aldehyde **2d**, followed by reduction and esterification, revealed the absolute configuration to be *S* (Figure 1).



Scheme 3.

Table 4: Scope of the organocatalytic addition of benzotriazole **8** and 1,2,3-triazole (**9**) to α,β-unsaturated aldehydes **1a**,**d** (see Scheme 3).[a]

Entry	R	**8**/**9** [M]	*T* [°C]	*t* [h]	**10**/**11** Yield [%][b]	*ee* [%][c]
1	Et	**8** (0.1)	−20	27	44:19	80:91
2	*i*Pr	**8** (0.5)	−20	19	47:30	88:89
3	Et	**9** (0.5)	RT	19	30:20	81:80

[a] Performed with **8** or **9** (0.25 mmol), **2** (0.375 mmol), **3** (0.025 mmol), and $PhCO_2H$ (0.025 mmol) in toluene. [b] Isolated yield for each regioisomer purified by flash chromatography after reduction with $NaBH_4$ and functionalization with *p*-chlorobenzoyl chloride. [c] Determined by chiral HPLC.

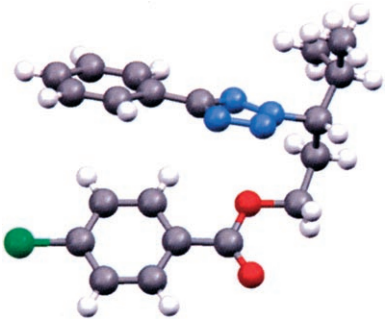
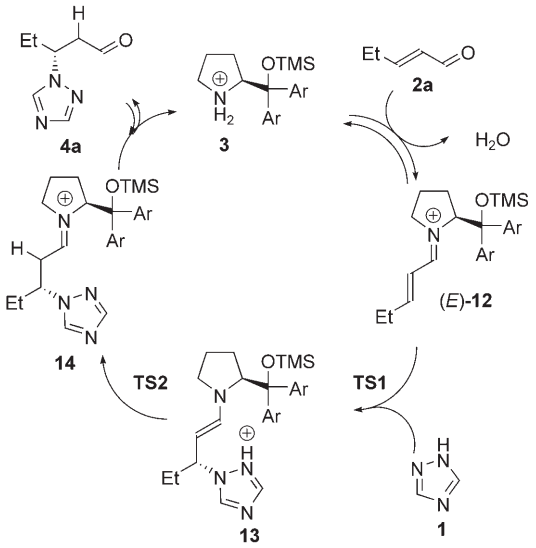


Figure 1. X-ray crystal structure of (*S*)-4-methyl-3-(5-phenyl-2*H*-tetrazol-2-yl)pentyl 4-chlorobenzoate ((*S*)-**7c**). Cl green, N blue, O red, C gray, H white.

The results for the organocatalytic Michael addition reactions given in Tables 2–4 show that these reactions proceed well for different aliphatic α,β-unsaturated aldehydes reacting with various N-heterocyclic compounds. To better understand the mechanism of the chiral amine catalyzed β-addition of N-heterocyclic compounds by the iminium mechanism using catalyst **3**, the intermediates and transition states involved in the catalytic cycle were investigated computationally with DFT calculations.[19] The proposed catalytic cycle is outlined in Scheme 4.

The α,β-unsaturated aldehyde **2a** reacts with the protonated catalyst **3** and forms an iminium ion with loss of water. Owing to the chirality of the catalyst, two different iminium ions that have *E* and *Z* configurations can be formed. The structures of these isomers, (*E*)-**12** and (*Z*)-**12**, were optimized at the B3LYP/6-31G(d) level of theory and are shown in Figure 2.[20] The calculations show that the formation of (*E*)-**12** is favored ($\Delta G = -0.17$ kcal mol^{-1}) over the formation of (*Z*)-**12** ($\Delta G = 1.39$ kcal mol^{-1}) relative to the protonated catalyst and 2-pentenal (**2a**). These results show that (*E*)-**12** is expected to be the major intermediate present in which the *Si* face is shielded by the chiral group in the catalyst, leaving the *Re* face available for the approach of the N-heterocyclic compounds.

To understand the enantioselectivity of the addition of 1,2,4-triazole, transition states (**TS1a** and **TS1c**) for the addition from the unshielded face of (*E*)-**12** and (*Z*)-**12**, leading to *R* and *S* configurations of the product, respectively, were optimized.[21] Additionally, the transition state for the addition from the top side of the iminium ion (*E*)-**12**, leading to the *S* configuration, was also considered (**TS1b**). The transition states were initially optimized at the B3LYP/6-31G(d) level of theory and further optimized at the B3LYP/6-311G(d,p)[22] level of theory and are shown in Figure 3.



Scheme 4. Proposed catalytic cycle with intermediates and transition states studied computationally.

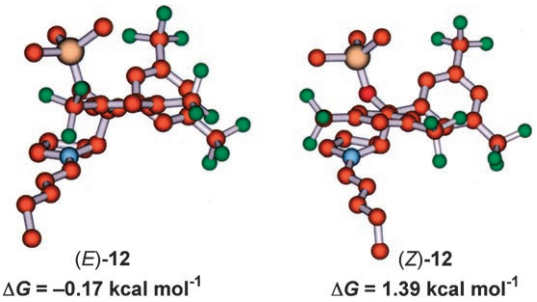


Figure 2. Optimized structure of the iminium ions (*E*)-**12** and (*Z*)-**12**. Si beige, N blue, O red, C orange, H green.

The difference in relative Gibbs free energies of the transition states shows that **TS1a** (0.0 kcal mol^{-1}) is favored compared to **TS1b** (2.0 kcal mol^{-1}) and **TS1c** (3.0 kcal mol^{-1}). This shows that the reaction most likely proceeds via transition state **TS1a**, corresponding to an addition from below the *Re* face to (*E*)-**12**. The difference in Gibbs free energy corresponds to an enantioselectivity of 94% *ee*. The influence of the solvent was included in the calculations of the transition states by a single-point calculation of the solvation energy at the B3LYP/6-311G(d,p) level of theory using the CPCM model.[22] The difference in energy between **TS1a** and **TS1b** is 1.8 kcal mol^{-1}, which corresponds to an enantioselectivity of 90% *ee*. Thus, these calculated results are in good agreement with the experimentally obtained enantioselectivity (92% *ee*).

A comparison of the calculated C–N distances (1.913–1.923 Å) in the transition states **TS1a**, **TS1b**, and **TS1c**

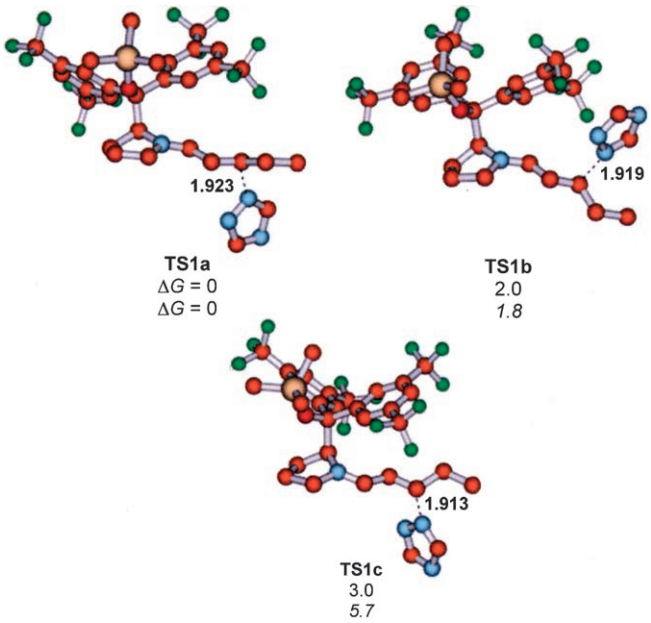


Figure 3. Optimized structures and relative energies [kcal mol^{-1}] of the transition states **TS1a**, **TS1b**, and **TS1c** for the addition of 1,2,4-triazole. The upper numbers are results in the gas phase and the lower numbers are results in a solvent. Calculated C–N distances [Å] are shown.

depicted in Figure 3 shows that these are very similar and independent of the approach of the 1,2,4-triazole.

The addition of 1,2,4-triazole to the iminium ion (*E*)-**12** gives the enamine intermediate **13**, which bears a positive charge on the protonated triazole ring. We considered that this proton is then transferred from the nitrogen atom in the triazole ring to the enamine carbon atom to form the iminium intermediate **14** (see Scheme 4). Two transition states were investigated for the proton transfer: 1) a direct transfer of the proton from the 1,2,4-triazole nitrogen atom to the α-carbon atom (**TS2a**), and 2) transfer involving one molecule of water that works as a relay in the transfer of the proton from the 1,2,4-triazole nitrogen atom to the α-carbon atom (**TS2b**). These two transition-state structures are outlined in Figure 4.

The calculated Gibbs free energies for the transition states **TS2a** and **TS2b** show that the water-assisted proton transfer between enamine intermediate **13** leading to the iminium ion **14** (**TS2b**) has a lower barrier of activation compared to the direct transfer of a proton (**TS2a**). The energy diagram in Figure 5 also shows that **TS2b** is lower in free energy than the transition state for 1,2,4-triazole addition (**TS1a**), thus the triazole addition is the rate-limiting step of the reaction.

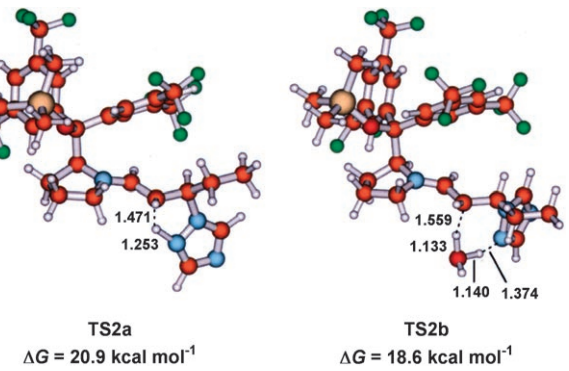


Figure 4. Optimized structures of different transition states (**TS2a** and **TS2b**) for the proton transfer, without water and with water assistance, respectively, from the nitrogen atom in the 1,2,4-triazole ring to the α-carbon atom. Calculated C–N distances [Å] are shown.

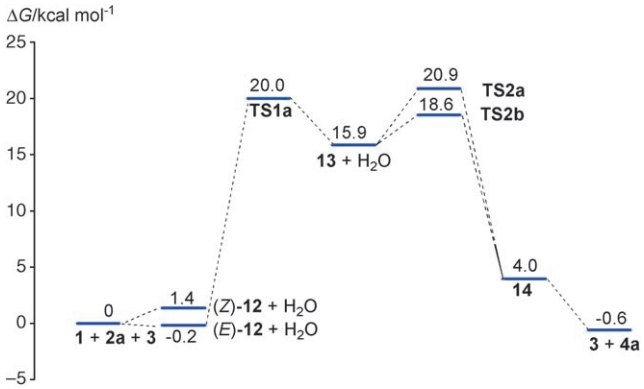


Figure 5. Gibbs free energy diagram of the catalytic cycle.

Hydrolysis of the iminium ion **14** leads to regeneration of the catalyst **3** and product **4a**. The reaction energy of −0.6 kcal mol^{-1} on going from aldehyde **2a** to the 1,2,4-triazole adduct **4** shows that the reaction is energetically favored. The calculated energy profile for the catalytic cycle is presented in Figure 5.

In summary, we have presented the first organocatalytic conjugate addition of N heterocycles to α,β-unsaturated aldehydes which proceeds in moderate to high yields and with high enantioselectivity. Computational studies show that N heterocycles add to the unshielded *Re* face of the *E*-configured iminium ion intermediate, thereby predicting the high enantioselectivity observed in the reaction.

Experimental Section

Catalyst **3** (10 mol%, 0.025 mmol, 15 mg), **2a** (37 μL, 0.375 mmol), toluene (0.5 mL), and benzoic acid (3 mg, 0.025 mmol) were introduced into a sample vial equipped with a magnetic stirring bar. The mixture was stirred for a short time at ambient temperature, and **1** (0.0173 g, 0.25 mmol) was added. After about 2 h (monitored by ^{1}H NMR spectroscopy), the reaction was complete. The reaction mixture was loaded onto SiO_2, and the product **4a** (29.9 mg, 0.195 mmol, 78% yield) was obtained by flash chromatography eluting with CH_2Cl_2/*i*PrOH (90:10).

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