REVIEW

From negative results to a highly stereoselective organocatalyst

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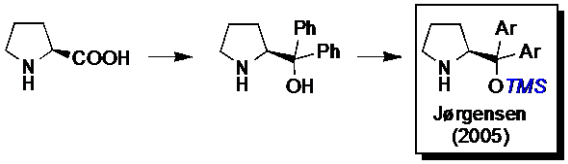
From negative results to a highly stereoselective organocatalyst

Pablo Bernal*[,a] and David Monge*[,b]

a) Instituto de Investigaciones Químicas (CSIC-US), Isla de la Cartuja, Americo Vespucio 49, E-41092 Seville, Spain. E-mail: pablo.bernal@iiq.csic.es. *b) Center for Catalysis, Department of Chemistry, Aarhus University, DK-8000 Aarhus C, Denmark. E-mail:* davmonfer@alum.us.es.

Graphical Abstract



Abstract: Organocatalysis has become a well-established and powerful synthetic tool. The aim of this minireview is to describe one of the essential discoveries for the progress of the field in the "gold rush" era of aminocatalysis: Jørgensen catalyst. Our discussion makes emphasis on how negative results may change the outcome of a discipline providing new impetus and inspiring exciting new scenarios.

Keywords: organocatalysis; proline analogous; diarylprolinol ethers; enamine/iminium catalysis;

1. Introduction

In the last decades, the stereocontrolled synthesis of chiral molecules has become one of the main challenges of organic chemistry as many bioactive natural and synthetic compounds contain at least one stereogenic center. Among the different ways to synthesize chiral molecules, asymmetric catalysis represents the most efficient strategy.[1, 2]

The term "organic catalysts" was introduced by Ostwald (1900), in order to distinguish small organic molecules as catalytic principles from enzymes or inorganic catalysts.[3] Nowadays, MacMillan's neologism "organocatalysis" has become the catchword for this field of research.[4, 5]

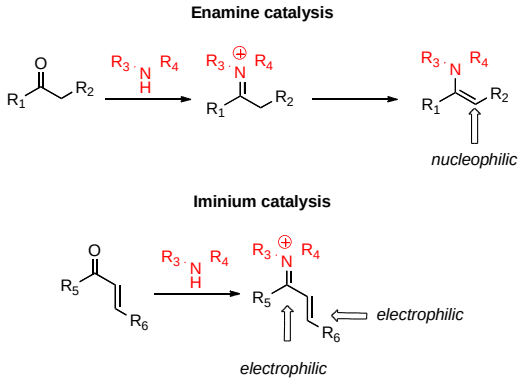
Organocatalysis is "The catalysis with small organic molecules, where an inorganic element is not part of the active principle".[6]

Generally, some of the remarkable practical advantages of the Organocatalysis are:

- There is not necessary the use of inert atmosphere or anhydrous solvents.
- The organocatalysts are less expensive than the metallic analogs and more stable than bioorganic enzymes and other catalysts.
- These organic molecules can be easily immobilized on a solid support.
- The molecular structures of the organocatalyst are easily modifiable.

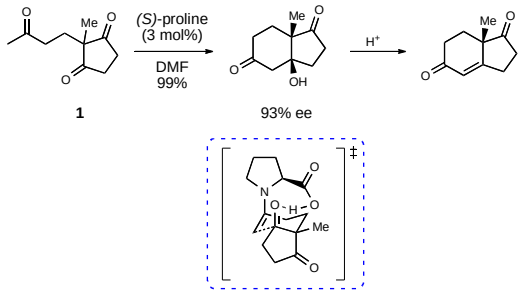
The progress of organocatalysis over the last ten years has been breathtaking from a small collection of exotic and underdeveloped transformations that were mechanistically poorly understood. The origins of aminocatalysis,[7] which comprises reactions catalyzed by secondary and primary amines via enamine and iminium ion intermediates (Scheme

1) go back to the pioneering and insightful contributions of Emil Knoevenagel over 100 years ago.



Scheme 1: Enamine and Iminium catalysis

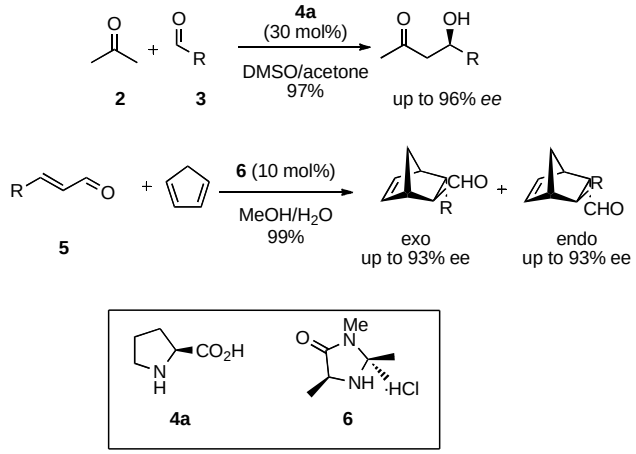
The first asymmetric amine-catalyzed aldolization appeared in 1971, Hajos and Parrish at Hoffmann-La Roche[8, 9] and Eder, Sauer and Wiechert at Schering[10, 11] independently reported a proline-catalyzed intramolecular aldol reaction of a triketone **1** (Scheme 2).



Scheme 2: Synthesis of Hajos-Parrish ketone.

However, the real potential of proline as organocatalyt for enantioselective aldol,[12-24] Mannich,[25-33] amination[34-38] and α-aminoxylation reactions[39-42] was not re-discovered until beginnings of the 21st century.

Two publications on metal-free catalysis in 2000 showed the way again. List, Lerner and Barbas reported that the simple amino acid proline **4a** catalyzed enantioselective cross-aldol reactions between acetone **2** and different aldehydes **3** (Scheme 3),[12] while MacMillan, Ahrendt and Borths demonstrated that chiral imidazolidinium salts **6** were able to activate α,β-unsaturated aldehydes **5** for asymmetric Diels–Alder reactions (Scheme 3).[43]



Scheme 3: Key reactions for the renaissance of organocatalysis.

These two examples reflect a connection between enamine and iminium catalysis, the two fundamental principles ("Yin and Yang") of asymmetric aminocatalysis.[44]

2. General mechanisms

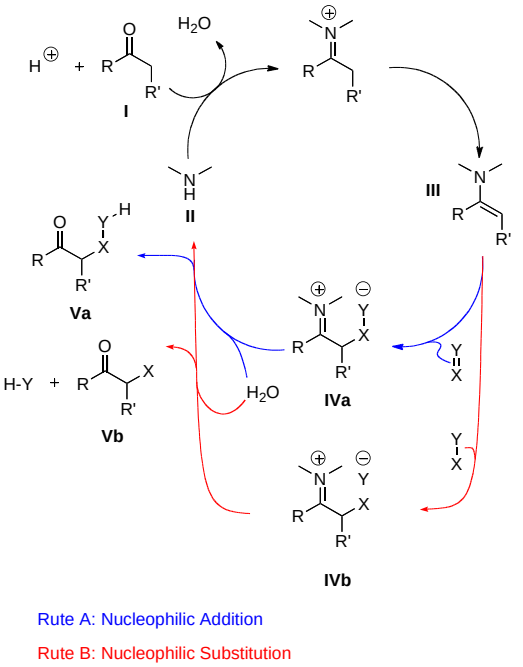
2.1. *Enamine Catalysis*

The catalysis by primary and secondary amines of electrophilic substitution reactions in the α-position of carbonyl compounds and related reactions via enamine intermediates is called enamine catalysis (Scheme 1).[45, 46]

This chemistry can be considered the catalytic variant of the classical performed enamine chemistry pioneered by Stork.[47-50]

As outline in Scheme 4, the enamine **III** is generated by reacting to a carbonyl compound **I** with an amine **II** under dehydration conditions. Reaction of the enamine **III** can proceed via an addition (route A) or substitution (route B) depending on the nature of the reaction partner (electrophile). In either case, iminium ions **IV** are usually formed, which are then hydrolyzed to afford the products **V**.[51]

Key to enamine formation is the LUMO lowering effect and the resulting dramatic increase in C-H acidity upon initial conversion of the carbonyl compound into an iminium ion.



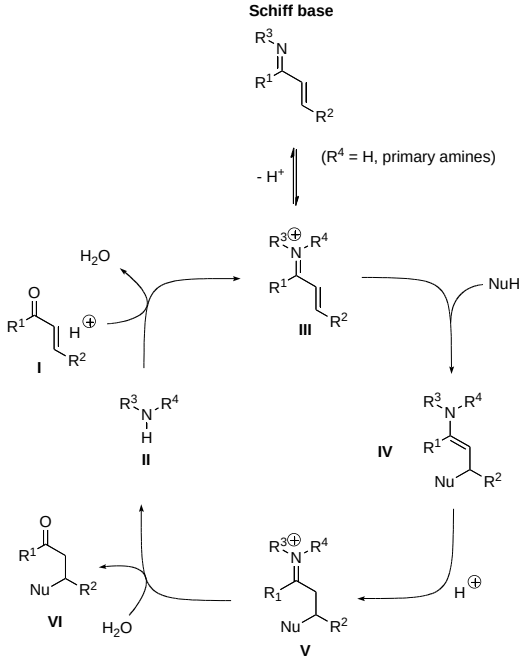
Scheme 4: Enamine catalysis mechanism.

2.2 *Iminium Catalysis*

The condensation of aldehydes or ketones with primary amines typically results in equilibrium where a considerable amount of the imine is present (Scheme 5).[52] This reaction was discovered in 1864 by Schiff,[53] and the resulting imines are also called Schiff bases. For iminium catalysis, both primary and secondary amines may be used. Although the secondary amines have dominated the field for activation of α,β-unsaturated aldehydes, primary amines have proven to be more suited for α,β-unsaturated ketones.[54] This activation mode exploits the reversible formation of iminium ion intermediate **III** (Scheme 5), in which the lower energetic LUMO π-system is susceptible toward nucleophilic attack. Subsequent hydrolysis of intermediate **IV** affords the corresponding β-functionalized product **VI** and amine **II**.

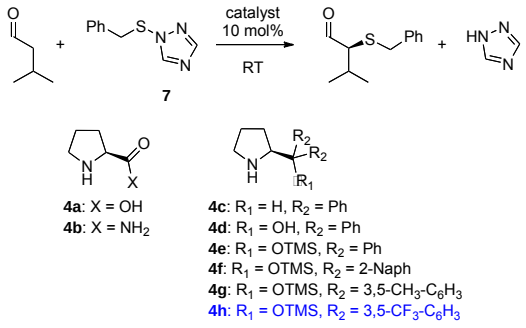
3. Design of trimethylsilyl (TMS) O-protected diarylprolinols from negative results

Years from 2004 to now are quoted to be the ”Golden age of Organocatalysis”[54-56] and a large number of new and exciting developments have been created in this field. Organocatalytic methods have reached the standards of modern well-established asymmetric reactions in terms of chemical efficiency and selectivity. In retrospect, the experiments shown in Scheme 2 opened our eyes to the enormous possibilities of aminocatalysis. However, here will try to describe one significant contribution which made the field to reach its maturity over 2005, when Jørgensen and co-workers reported on the synthesis of a new class of general organocatalysts: trimethylsilyl (TMS) *O*-protected diarylprolinols.



Scheme 5: Iminium catalysis mechanism.

Interestingly the design of these catalysts came from careful observation and analysis of negative results. In the context of enamine activation, excellent results obtained in the halogenation reactions revealed the tremendous potential of the organocatalytic approach, opening up unexplored possibilities for many asymmetric nucleophilic substitutions.



Scheme 6: Preliminary results: enantioselective sulfenylation of aldehydes.

When the chlorination reaction first appeared in the literature, a new organocatalytic electrophilic α-sulfenylation reaction of aldehydes was already being studied. In early 2005, Jørgensen’s group published the first highly enantioselective version of this elusive yet important transformation, which was not possible with other classical asymmetric methodologies.[57] As outline in Scheme 6, a novel sulfenylating agent **7** represented the best compromise

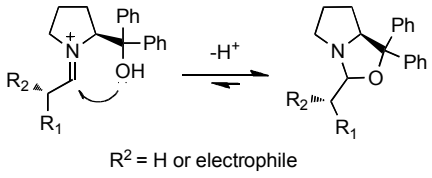
in terms of stability, reactivity, easy preparation, and synthetic utility for this reaction.

Table 1: Organocatalyzed enantioselective α-sulfenylation of isovaleraldehyde.

Entry	4	Solvent	Yield (%)	*ee* (%)
1	**a**	toluene	16	0
2	**b**	DMSO	-	-
3	**b**	Et_2O	5	18
4	**b**	CH_2Cl_2	7	22
5	**b**	toluene	30	25
6	**c**	toluene	56	52
7	**d**	toluene	-	-
8	**e**	toluene	90	77
9	**f**	toluene	75	84
10	**g**	toluene	73	90
11	**h**	toluene	90	98

However, preliminary results (entries 1-7, Table 1) were not very promising as proline **4a** and proline derivative **4b** shown low reactivities and enantioselectivities (entries 1-3, Table 1). Catalyst **4c** afforded moderate reactivity and enantioselectivity up to 52% (entry 6, Table 1). Diphenyl prolinol **4d** (entry 7, Table 1), an amino alcohol developed by Corey and co-workers, was used as a ligand in Lewis acid reactions. This compound showed, in general, negative results as enamine activator, although in some other transformations it could induce high stereocontrol.[58] For early observations on the high stereocontrol but low catalyst turnover inherent to diphenyl prolinol, see references[47, 58, 59] The extended reaction times and poor yields obtained with this catalyst were explained by the larger size of the substituents relative to catalyst **4c**, which, in contrast, often showed good activity and low level of stereocontrol.

Carefully analysis of these results and ^{1}H-NMR spectroscopy observations, led Jørgensen and co-workers to suggest that the reason for the disappointing behaviour of **4d** in enamine catalyzed reactions relied on the formation of unreactive oxazolidinone species as a resting state for the catalyst (Scheme 7).



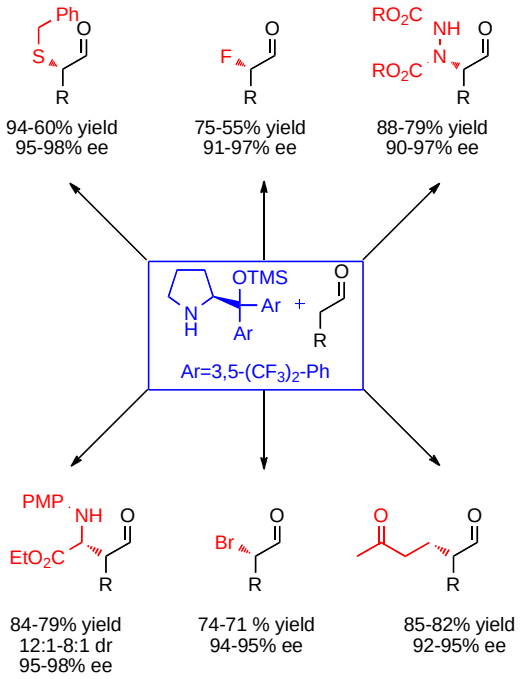
Scheme 7: Hemiaminal equilibrium.

It was not the size but the chemical reactivity of the free hydroxyl group that needed to be addressed. Consequently, a simple trimethylsilyl *O*-protection of this functionality restored the high activity (Entry 8-11, Table 1). Therefore catalyst **4f** directs the incoming electrophile through steric interactions, while avoiding the formation of oxazolidinones (90% Conv., 77% ee). From this groundbreaking result, a small structure optimization of the aromatic moieties of the catalyst led to the (*S*)-α,α-Bis[3,5-bis(trifluoromethyl)phenyl]-2 pyrrolidinemethanol trimethylsilyl ether **4h** (Jørgensen catalyst), which catalyzes the formation of sulfenylated products in high yield with ee consistently over 95%.

The family of *O*-TMS protected diarylprolinols has found wide applicability in organocatalysis and nowadays, commercially available, contribute to the fast-growing research field with a scope that goes beyond aminocatalyzed reactions.

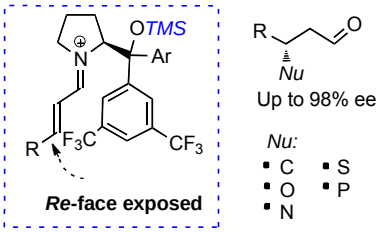
4. Diarylprolinol ethers-expanding the scope of aminocatalysis

Proceeding by this report on α-sulfenylation of aldehydes, the ability of diarylprolinol ethers to promote both asymmetric nucleophilic additions and substitution reactions was exploited[60] (Scheme 8) in various conjugated additions,[61] Mannich, α-amination, α-bromination,[62] α-fluorination and so on.



Scheme 8: Expanded α-functionalization of aldehydes.

Interestingly, a catalyst designed for enamine-catalyzed reactions, turned out to be effective in iniminium catalysis. The addition of C nucleophiles in Michael[63-67] and cycloaddition reactions,[68, 69] the addition of N,[70-73] O,[74, 75] S[76] and P,[77-79] based nucleophiles to α,β-unsaturated aldehydes were reported to be highly enantioselective in the presence of Jørgensen catalyst or its derivatives (Scheme 9)



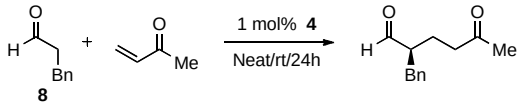
Scheme 9: Expanded iminium ion activation.

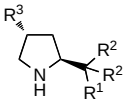
5. Comparative of selected examples on aminocatalyzed reactions.

The design of diarylprolinol ethers in the context of negative results in α-functionalizations of aldehydes via enamine activation (Section 3) affords a precious tool in the hands of synthetic chemist. However, in other context this design could have been different.

5.1. *1,4-Conjugated Additions*

For example, diphenylprolinol methyl ether **4i**, instead of silyl protected **4h**, catalyzes the intermolecular Michael addition of simple aldehydes to relatively non-activated enones (Scheme 10) with the highest enantioselectivities reported to date (95-99% ee) and significantly lower catalyst loadings than have been typical in this area.[80]





4c: R_1 = H, R_2 = Ph, R_3 = H
4d: R_1 = OH, R_2 = Ph, R_3 = H
4h: R_1 = OTMS, R_2 = 3,5-CF_3-C_6H_3, R_3 = H
4i: R_1 = OMe, R_2 = Ph, R_3 = H
4j: R_1 = OMe. R_2 = Ph, R_3 = COOH
4k: R_1 = OMe. R_2 = Ph, R_3 = OH
4l: R_1 = OMe. R_2 = Me, R_3 = H

Scheme 10: Michael Addition of Hydro-cinnamaldehyde to Methyl Vinyl Ketone

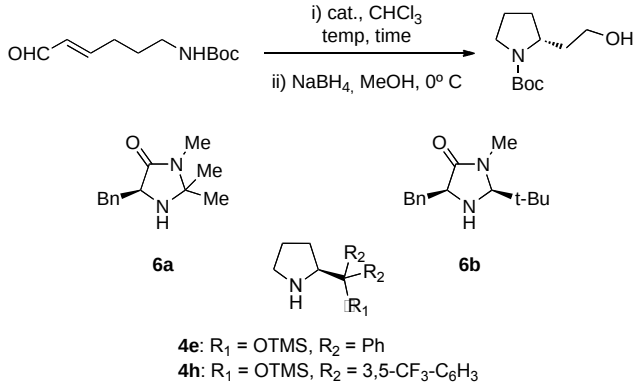
Pyrrolidine **4c** was the first catalyst evaluated in the seminal study by Melchiorre and Jørgensen,[58] and the reactivity was low (Entry 1,Table 2). The oxygen atom in **4d** must be etherified, as diphenylprolinol was shown to be completely inactive (Entry 2, Table 2). As we highlighted in Scheme 7, this catalyst is believed to form a stable cyclic hemiaminal trapping the iminium species. **4j** and **4k** gave excellent enantioselectivities but lower conversions than **4i** (Entry 3 and 6, Table 2). The substituents in the ring (carboxyl or hydroxyl) may diminish the nucleophilic reactivity of the nitrogen atom.

Table 2: Michael Addtition of Hydrocinnamaldehyde to Methyl Vinyl Ketone.

Entry	4	Yields (%)	*ee* (%)
1	**c**	28	80
2	**d**	<1	nd
3	**k**	27	96
4	**h**[a]	20	97
5	**i**	60	97
6	**j**	33	99
7	**l**	15	77

[a] Hayashi report[81] a single Michael addition, hydrocinnamaldehyde to methyl vinyl ketone, with 30 mol % **4h**, giving 52% yield and 97% ee; reaction time and temperature were not given.

The *O*-TMS diarylprolinol **4h** provided enantioselectivities comparable to that obtained with **4i** (Entry 5, Table 2), but less efficiently (only 20% conversion).



Scheme 11: Organocatalytic Intramolecular Aza-Michael Reaction.

Fustero *et al.* have developed a highly enantioselective intramolecular aza-Michael addition reaction of carbamates containing a pendent conjugated aldehyde (Scheme 11).

Imidazolidinone **6a** catalyzed the reaction with prolonged reaction time, poor yield and less than 5% ee (Entry 1, Table 3). Catalyst **6b** proved to be more reactive, the product was isolated in 73% yield and with only 23% ee (Entry 2, Table 3). In the same conditions, **4e** afforded the desired product in 78% yield but 40% ee (Entry 3, Table 3).

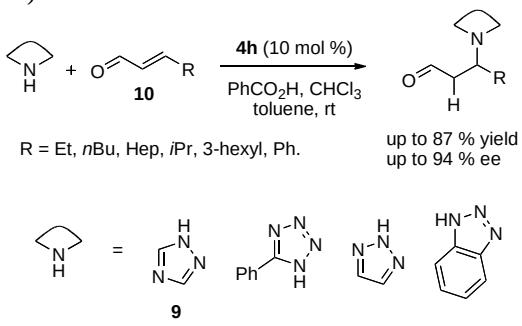
Fortunately, **4h** (20 mol %) in combination with PhCOOH as cocatalyst at -50ºC afforded the corresponding pyrrolidine in 71% yield and 93% ee (Entry 6, Table 3).

Table 3: Intramolecular Aza-Michael Reaction.

Entry	Cat.	Additive	T (° C)	Time (h)	Yield (%)	*ee* (%)
1	**6a**	HCl	–20	120	60	<5
2	**6b**	TFA	–20	7	73	27
3	**4e**	$PhCO_2H$	–20	7	78	40
4	**4e**	$PhCO_2H$	–30	22	Nd	75
5	**4h**	$PhCO_2H$	–40	22	74	79
6	**4h**	$PhCO_2H$	–50	22	71	93
7	**4h**	$PhCO_2H$	–60	45	67	93

In a similar strategy than that developed by Fustero, Carter has reported the intramolecular heteroatom Michael addition, which gives rise to homoproline, pelletierine and homopipecolic acid.[82]

In 2007, Jørgensen reported the 1,4-conjugate addition of nitrogen heterocycle to α,β-unsaturated aldehydes using the same prolinol derivate **4h** (Scheme 12).[70] This reaction also had firsts negative results and a strong solvent influence in enantioselectivity induction (entries 1-3, Table 4).



Scheme 12: Jørgensen's conjugate addition of *N*-heterocycles.

The model reaction of 1,2,4-triazole **9** with 2-pentenal **10** in presence of 10 mol % of catalysts **4h** and benzoic acid in pentane, only gave low yield (Entry 2, Table 4), whereas in CH_2Cl_2, MeCN, toluene and benzene is complete (Entry 1, 3-7, Table 4). However the enantioselectivity decreased significantly in CH_2Cl_2 and MeCN (Entry 1 and 3, Table 4). The best result concerning reactivity and selectivity were obtained in toluene [0.1 M] (Entry 7, Table 4).

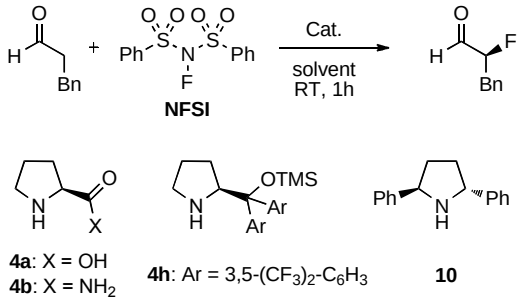
Table 4: 1,4 -conjugate addition of 1,2,4-triazole 9 to 2-pentanal

Entry	Solvent	$PhCO_2H$ [mol %]	Time (h)	Yield (%)	*ee* (%)
1	CH_2Cl_2	10[a]	2	100	3
2	pentane	10[a]	4	24	-
3	MeCN	10[a]	4	100	7
4	benzene	10[a]	2	96	89
5	toluene	-[a]	4.5	100	88
6	toluene	10[b]	1	100	68
7	toluene	10[c]	2	100	92

[a] [1,2,4-triazole] = 0.5 M. [b] [1,2,4-triazole] = 2.5 M. [c] [1,2,4-triazole] = 0.1 M

5.2. *α-Fluorination*

The catalytic methods for the asymmetric construction of C-F bonds are rare,[83] the majority involving α-substituted β-keto ester substrates that are structurally precluded from product epimerization. Recently, the amino-catalyzed enantioselective α-fluorination of aldehydes was independently reported by the groups of Macmillan,[84] Barbas,[85] Ender[86] and Jørgensen.[87]



Scheme 13: α-fluorination of 3-phenylpropanal with NFSI as F^+ ion source.

As show in Scheme 13 using catalyst **4a-b** or the C_2-symmetric pyrrolidine **10** for the α-fluorination of 3-phenylpropanal with NFSI as F^+ ion source afforded low yields and moderate enantioselectivities (Entry 1-3,table 5)

The chemical and physical properties of fluorine amplify some of the problem encountered in the related chlorination reaction, because of the high electronegativity of fluorine. Catalysts easily generate enamine species from both the starting aldehyde and the fluorinated product. The enhanced acidity of the α proton in the fluorinated aldehyde even favours its enamine formation and moreover, the small fluorine atom does not contribute to an added steric shielding that would disfavour the enamine equilibrium.

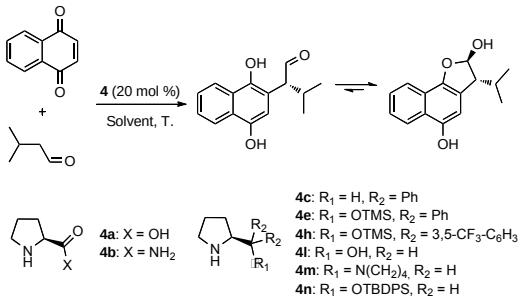
Table 5: Screening of catalysts and solvents: α-fluorination of 3-phenylpropanal with NFSI.

Entry	Cat. [mol%]	Solvent	Yield (%)	*ee* (%)
1	**4a (20)**	CH_2Cl_2	< 10	30
2	**4b (20)**	CH_2Cl_2	24	40
3	**10 (20)**	CH_2Cl_2	17	48
4	**4h (20)**	CH_2Cl_2	40	87
5	**4h (20)**	MeCN	61	93
6	**4h (20)**	MTBE	53	93
7	**4h (5)**	MTBE	74	93
8	**4h (0.25)**	MTBE	90	93

Once again, using silylated prolinol derivative **4h** improved conversions and enantioselectivities (Entry 4-6, Table 5). ^{1}H-NMR spectroscopy studies revealed that the catalyst is slowly desilylated upon mixing with NFSI leading to inactivation of the catalyst. Interestingly, lowering the catalyst loading (as low as 0.25 mol%) diminished this problem (Entry 8 Table 5).

α-arylation of aldehydes

Another important α-functionalization of aldehydes is shown in Scheme 14, the α-arylation.[88]



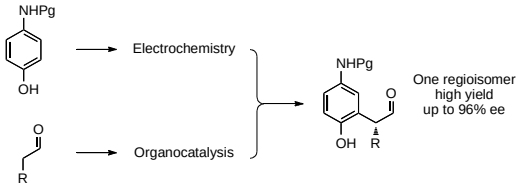
Scheme 14: α-arylation of aldehydes.

Table 6: α-arylation of aldehydes

Entry	4	Solvent	Yield (%)	*ee* (%)
1	**a**	CH_2Cl_2	nr	-
2	**a**	MeCN	66	33
3	**a**	DMF	71	30
4	**a**	DMSO/7% H_2O	100	20
5	**b**	DMSO/7% H_2O	100	74
6	**l**	DMSO/7% H_2O	90	49
7	**n**	DMSO/7% H_2O	93	94
8	**m**	DMSO/7% H_2O	100	65
9	**c**	DMSO/7% H_2O	96	88
10	**h**	DMSO/7% H_2O	nr	-
11	**e**	DMSO/7% H_2O	100	>99
12	**e**	H_2O	100	93
13	**e**	EtOH/7% H_2O	100	97
14	**e**	DMSO (dried)	nr	-

It appears from the results given in entries 1-4 (Table 6) that the proline **4a** is an effective catalyst for the reaction in term of the extent of conversion. However, only low enantioselectivity is obtained. Interestingly, the lack of reactivity in CH_2Cl_2 (entry 1, Table 6) is in sharp contrast while comparing with other polar solvents, especially wet DMSO. Proline amide **4b** is an effective catalyst for the reaction and led to an improvement of the enantioselectivity (Entry 5, Table 6). The screening of different solvent showed that the reaction in presence of water is essential for success in this reactions (Entry 4-13, Table 6). Surprinsingly, the catalyst **4h** was not active in the present reaction (entry 10, Table 6) while **4e** afforded effectively the α-arylated aldehydes in enantioselectivities of over 99% with a loading down to 5 mol %.

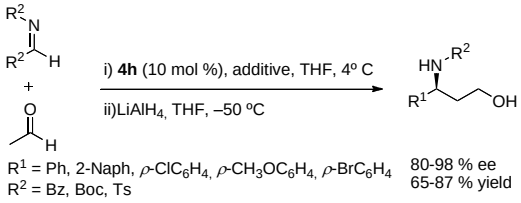
The α-arylation of aldehydes has been used as a platform for developing a new concept: the combination of electrochemistry and asymmetric organocatalysis, giving access to *meta*-substituted anilines (Scheme 15).[89]



Scheme 15: Regio- and stereoselective anodic oxidation/organocatalytic α-arylation of aldehydes and formal meta-addition to anilines.

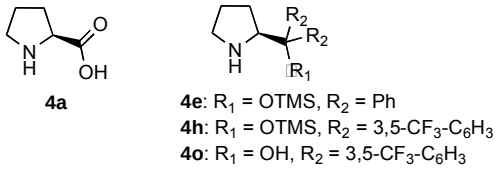
5.4. *Mannich Reaction*

The direct Mannich reaction using acetaldehyde has been reported by Hayashi (Scheme 16).[90]



Scheme 16: Hayashi's Mannich mediated amino alcohol synthesis.

Treatment of a range of protected imines (Bz, Boc or Ts) with acetaldehyde and the proline-derived catalyst **4h** followed by reduction with lithium aluminium hydride affords arrange of amino alcohols with excellent levels of enantiomeric excess and moderate to good yields.



Scheme 17: Organocatalysts examined in the Mannich Reaction.

Table 7: The effect of catalyst and solvent in the Mannich reaction.

Entry	4	Additive	Yield (%)	*ee* (%)
1	**a**	-	51	92
2	**h**	-	< 5	-
3	**o**	-	< 5	-
4	**e**	-	< 5	-
5	**h**	$PhCO_2H$	60	98
6	**h**	*p*-NO_2PhCO_2H	83	98
7	**h**	*p*-TsOH	< 5	-
8	**e**	$PhCO_2H$	63	98
9	**e**	*p*-NO_2PhCO_2H	< 5	-
10	**o**	*p*-NO_2PhCO_2H	< 5	-

Scarcely any reaction occurred in the presence of trifluoromethylsubstituted diaryl prolinol **4o** (Entry 3, Table 7), which was a suitable catalyst in a cross-aldol reaction. Diaryl prolinol silyl ethers **4h** and **4e** were not effective unless an additive was used (Entry 2 and 4, Table 7). The acidity of the additive dramatically affected the yield. The reaction with catalyst **4h** achieved better yields and excellent enantioselectivities when *p*-nitrobenzoic acid was added

(Entry 6, Table 7). Only decomposition of the imine occurred, without formation of the Mannich adduct, in the presence of a stronger acid such as ρ-TsOH (Entry 7, Table 7). Diphenylprolinol silyl ether **4e** is a suitable catalyst with benzoic acid as the additive (Entry 8, Table 7). The silyl ether functional group proved to be essential, as diaryl prolinol **4o** with ρ-nitrobenzoic acid did not promote the reaction (Entry 10, Table 7).

6. Conclusions

In the broad field of asymmetric catalysis, the number of experiments to be made during the optimization of a given process is quite high, and the analysis of the results concerning reactivity and enantioselectivity is highly time-demanding. More than 70% of the experiments fail, mainly from stereoselectivity point of view, after a hard reactivity optimization process. In this minireview we have highlighted the importance of analyzing negative results for the development of new improved catalysts, using the example of *O*-TMS protected diarylprolinols.

7. References

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