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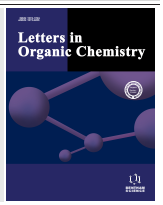
RESEARCH ARTICLE



A Proof of Concept: 2-Pyrazolines (4,5-Dihydro-1*H*-pyrazoles) Can Be Used as Organocatalysts *via* Iminium Activation

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Abstract: ***Background***: In the field of asymmetric aminocatalysis, chiral catalysts derived from azoles (five-membered heterocycles containing exclusively *N* atoms) play an important role. Surprisingly, all the catalysts used for enamine and/or iminium ion activation derive from pyrrole or imidazole. We decided to test if other reduced azole derivatives could be used as organocatalysts and particularly in aminocatalysis *via* iminium ion activation. The azole derivatives that came naturally to mind are the 3,5-disubstituted 2-pyrazolines (also called 4,5-dihydro-1*H*-pyrazoles).

Methods: We synthesized racemic 3,5-diphenyl-2-pyrazoline, separated both enantiomers by chiral-HPLC on a Lux-Cellulose-4 column (heptane/ethanol 70:30 as mobile phase), determined the absolute configuration of their hydrochloride salts (pyrazolinium) by the combined use of experimental rotatory power and B3LYP/6-311++G(d,p) theoretical calculations and use one the enantiomers, the *R*, as the catalyst.

Results: We have demonstrated that the enantiopure (*R*)-3,5-diphenyl-2-pyrazoline is able to catalyze the Michael addition of 1-(4-nitrophenyl)propan-2-one to cinnamaldehyde and crotonaldehyde *via* iminium activation.

Conclusion: This is the first example of activation of both types of enals, aliphatic and aromatic, *via* pyrazolinium salts and opens new possibilities to the design of other type of chiral organocatalysts than the traditional pyrrole and imidazole derivatives.

Eduardo Rodrigo

Keywords: Absolute configuration, DFT calculations, 4,5-dihydro-1*H*-pyrazoles, Michael addition, organocatalysis, Pyrazolines.

1. INTRODUCTION

In the field of asymmetric aminocatalysis [1], chiral catalysts derived from azoles (five-membered heterocycles containing exclusively *N* atoms) [2] play an important role. Surprisingly, all the catalysts used for enamine and/or iminium ion activation derive from pyrrole or imidazole. Fig. (**1**) gathers some of the most employed chiral catalysts in iminium and enamine activation.

Nowadays, the most popular catalysts in iminium and enamine activation are probably the diarylprolinol silyl ethers **2** [4] and **3** [5], which have resulted from proline (**1**) evolution (for general reviews on the use of silyl diarylprolinol ethers as catalysts see [3]). However, at the early times in iminium ion catalysis, the most frequent catalysts were MacMillan's imidazolidinone-based catalysts (**6** [8] and **7** [9]). These catalysts were later also applied in SOMO catalysis and enamine catalysis, yet they had been designed mostly for iminium ion catalysis. Nowadays, these catalysts are still being widely used; see for example [4].

To our knowledge, the use of imidazolines derivatives in aminocatalysis (covalent catalysis involving iminium or enamine activation) has not been described so far. Although **4** has been used as catalyst in a Friedel-Crafts type reaction, it implied a non-covalent catalysis by hydrogen-bond [5].

We decided to test if other reduced azole derivatives could be used as organocatalysts and particularly in aminocatalysis *via* iminium ion activation. For a review of iminium activation, see [12] and for our previous experience in iminium activation see [13].

2. RESULTS AND DISCUSSION

The azole derivatives that came naturally to mind are the 3,5-disubstituted 2-pyrazolines (Fig. **2**). Although several

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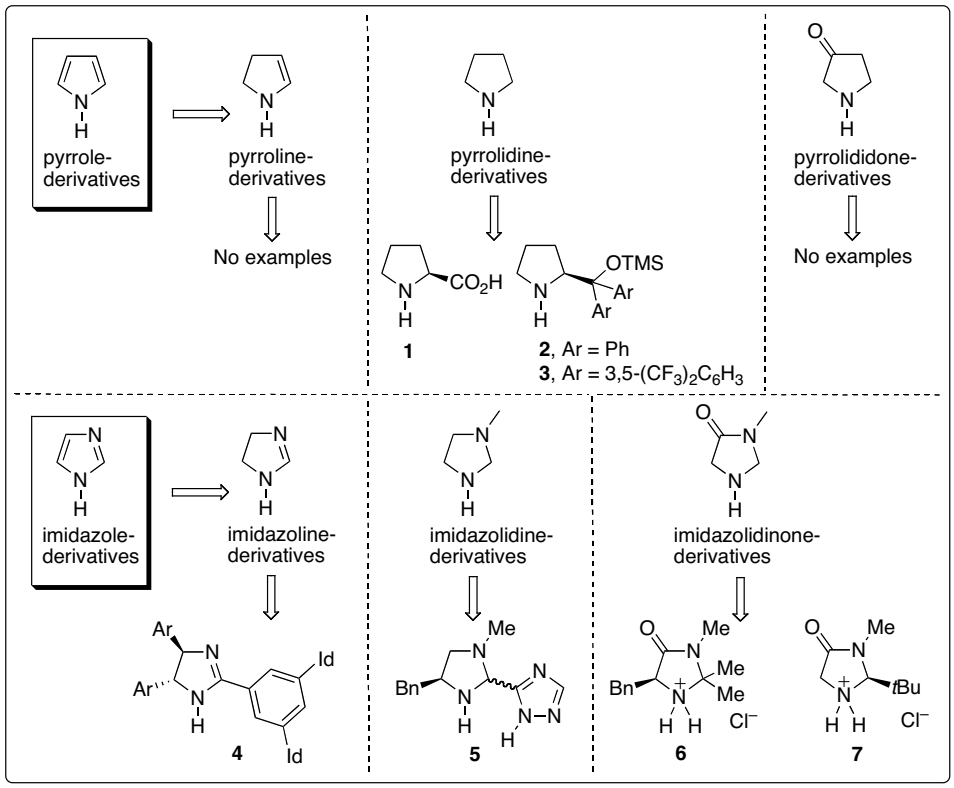


Fig. (1). Examples of chiral organocatalysts derived from pyrrole or imidazole: **1** [6], **2** [7], **3** [8], **4** [5], **5** [9], **6** [10] and **7** [11].

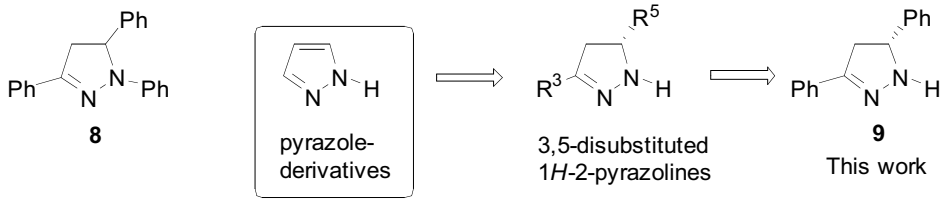


Fig. (2). 3,5-Diphenyl-2-pyrazoline (**9**) proposed as aminocatalyst.

enantioselective syntheses have been reported [14], this kind of compounds is usually prepared as racemates, for instance 1,3,5-triphenyl-2-pyrazoline (**8**) (see later) [15]. Due to simplicity reasons in its synthesis [16], 3,5-diphenyl-2-pyrazoline (**9**) was chosen as tentative catalyst.

Several facts supported the viability of the use of compound **9** in iminium activation processes. Firstly, it is known that 2-pyrazolines protonate on N_1 [17]. Also, **10**, **11** and some other iminium derivatives bearing the pyrazoline moiety have been isolated (**12** and **13** [18]) (Fig. **3**). The X-ray structures of **10**-**12** were reported in the CSD under the code names of PYZOLC, VIDKUO and UPIPUT, respectively [19].

We demonstrated that a *p*-nitrophenyl group converts acetone in an excellent and versatile nucleophile in the Michael addition to α,β-unsaturated aldehydes *via* iminium activation using catalysts **2** and **3** (Scheme **1**) [13c]. The adducts were obtained with good yields and variable enantioselectivities according to the aromatic or aliphatic nature of the substituent. The Michael reaction/aldol reaction/ dehydration sequence provided 5-substituted 6-(4-nitrophenyl)-2-cyclohexen-1-ones **16** in good yields and complete diastereoselectivity.

Therefore, in order to test the catalytic possibilities of **9** *via* iminium activation, we have selected the Michael reaction between 1-(4-nitrophenyl)propan-2-one (**14**) and both cinnamaldehyde (**21**a) and crotonaldehyde (**21**b) as model reactions (Schemes **2** and **3**). Firstly, a preliminary study of reactivity of the racemic catalyst was performed (Scheme **2**). The use of the hydrochloride (*rac*)-**9**.HCl led only to the diethoxyacetal of cinnamaldehyde, and no Michael addition was observed. Nevertheless, when the free base **9** was liberated (by treatment with an aqueous solution of saturated K_2CO_3 followed by extraction with Et_2O) and the reaction was carried out in the presence of benzoic acid, the corresponding Michael adducts **15**a of cinnamaldehyde were obtained, although with low conversions. Under the same conditions, no reaction was observed after 24 h when crotonaldehyde (**21**b) was used.

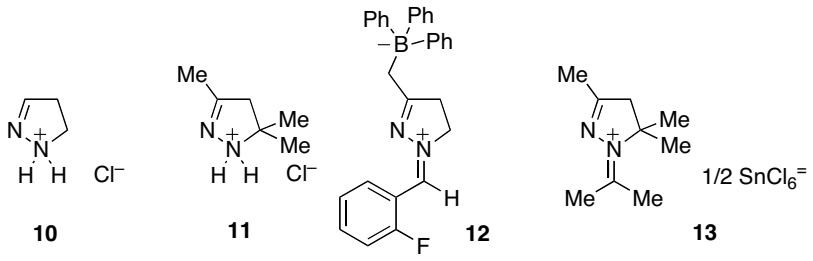
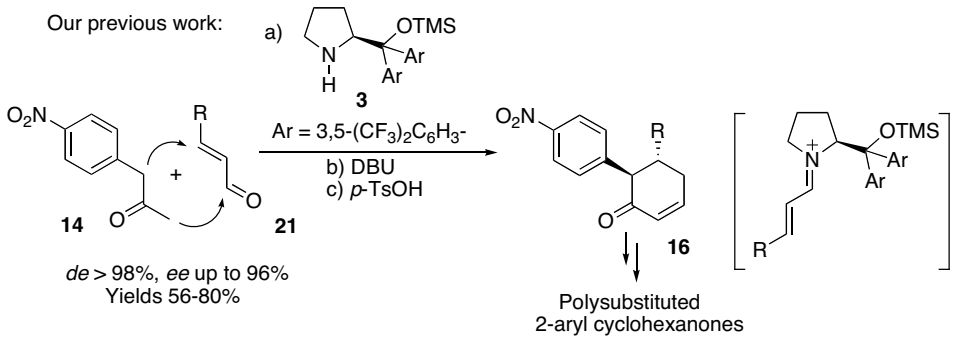
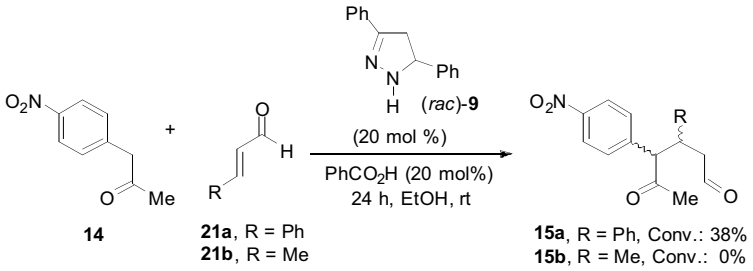


Fig. (3). Different salts derived from 2-pyrazolines.



Scheme (1). Previous work as model reaction [13b].



Scheme (2). Preliminary study of Michael reactivity with catalyst **9**.

We confirmed that the reaction does not occur in the absence of the catalyst after 24 h in the case of cinnamaldehyde (**21a**). Consequently, although the conversion was not very high, the formation of the adduct **15a** (as a mixture of diastereoisomers) demonstrated that pyrazoline **9** was able to activate the enal *via* iminium activation. This result prompted us to prepare **9** in enantiomerically pure form by chromatographic separation of both enantiomers and evaluate its possibilities in enantioselective catalysis.

Compound **9** was analyzed by chiral HPLC on a Lux-Cellulose-4 column (heptane/ethanol 70:30 as mobile phase, UV 220 nm, 1 mL·min^{-1}, 25°C, see Fig. **4**). Compound **9** proved to be not very stable; therefore the separation had to be done on the corresponding hydrochloride. At preparative scale, **9**.HCl was injected on a Lux-Cellulose-4 column (250 x 10 mm), with hexane/ethanol (70/30) with 0.01 % of triethylamine as mobile phase and 5 mL·min^{-1} as flow-rate. Each enantiomer was collected separately, in a flask containing ethanol with aqueous hydrochloric acid to avoid its decomposition, by formation of the hydrochloride. After evaporation of the solvents, each enantiomer of **9**.HCl was obtained as a mixture with triethylamine hydrochloride. In our experiments, we employed the first eluted sample, which had a rotatory power value of $[\alpha]_D$ –109.

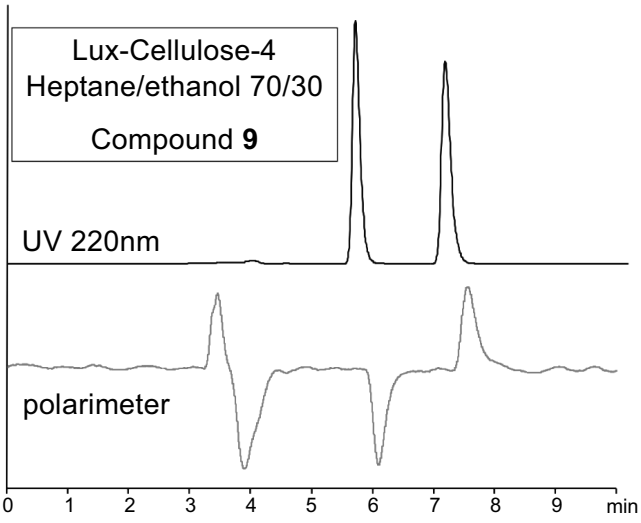
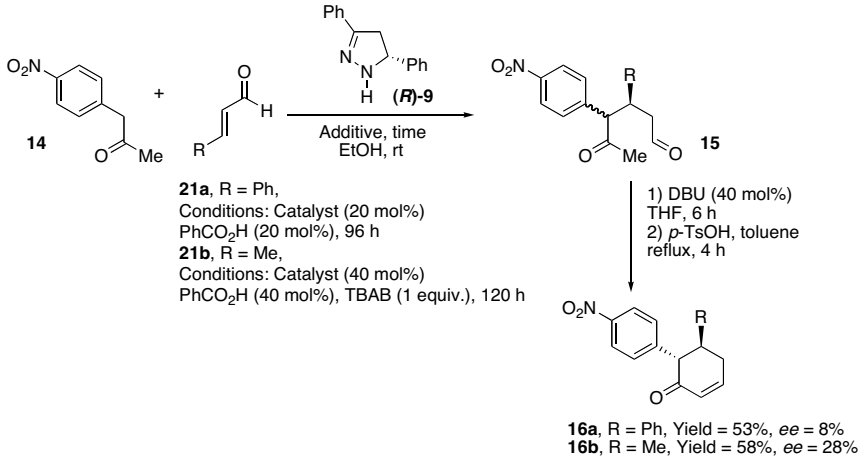


Fig. (4). Analytical chiral HPLC chromatogram of **9**.

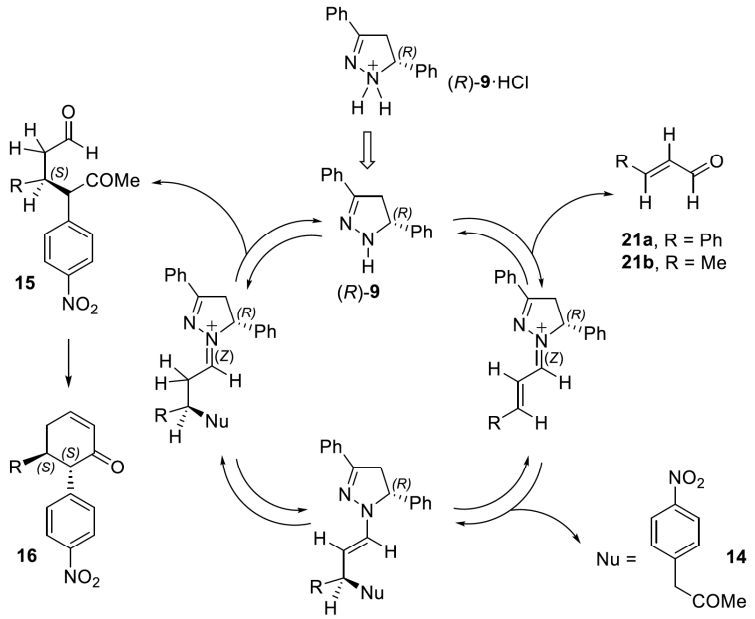
To determine the absolute configuration of **9**, first we calculated, using the Gaussian 09 facilities, at the B3LYP/6-311++G(d,p) level, the static $[\alpha]_D$ of one of the enantiomers of 1,3,5-triphenyl-2-pyrazoline (**8**) in CH_2Cl_2 that is equal to –547, the experimental value being –424 (1.3 times greater). Then, we calculated the (*S*)-enantiomer of **9.HCl** and obtained $[\alpha]_D$ = +260. Thus, the first eluted compound is the **(*R*)-9**. Here the ratio is ~2.4, much larger than 1.3 but the hydrochloride **9.HCl** is a mixture containing about 50 % (determined by ^{1}H NMR) of triethylamine hydrochloride, thus the ratio becomes comparable.

The liberated catalyst **(*R*)-9** was employed in the stereoselective Michael addition. In order to get higher conversions, some small changes were performed compared to the preliminary experiments carried out with the racemic catalyst. In the case of the aromatic aldehyde **21a**, just longer reaction times led to higher conversions. In the case of the aliphatic aldehyde **21b**, an increase of the catalyst loading as well as the use of a combination of additives were mandatory to obtain the corresponding adduct **15b** (Scheme **3**). The transformation of the adducts **15** into the corresponding cyclohexenones **16** was necessary to determine the enantioselectivity of the process by HPLC. After cyclization, epimerization of the benzylic position towards the most stable anti cyclohexanone occurs [13]. Although the enantiomeric excess of **16a** [derived form cinnamaldehyde (**21a**)] was rather low (8 %), the cyclohexenone **16b** derived from the aliphatic enal **21b** could be obtained with a preliminary promising 28 % *ee*.

The (*S,S*) stereochemistry of the final products **16** was determined by comparison with a HPLC sample we had from our previous works, whose configuration was unequivocally determined by X-ray diffraction [13b]. This configuration agreed with a steric controlled mechanism (which seems reasonable in the absence of a stereodirecting substituent) and the formation of the (*Z*)-iminium. The attack of the nucleophile would take place through the less hindered face, opposite to one of the phenyl group. This is in accordance



Scheme (3). (*R*)-3,5-Diphenyl-2-pyrazoline (**9**) as organocatalyst.



Scheme (4). Proposed mechanism of formation of **16**.

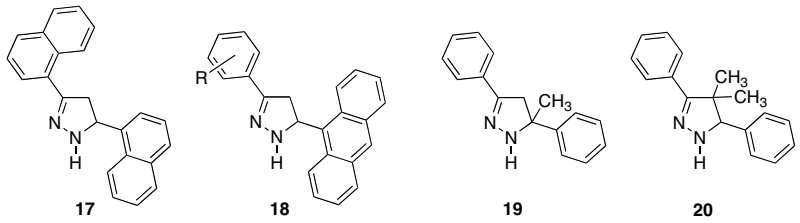


Fig. (4). Formulas of **17-20**.

with the proposed one when using catalysts **2**-**7** [3c] (Scheme **4**).

In conclusion, we have demonstrated that enantiopure (*R*)-4,5-dihydro-3,5-diphenyl-1*H*-pyrazole (**9**) can be used as chiral organocatalyst in Michael addition *via* iminium activation. The replacement of the 5-phenyl group by more electron-withdrawing and bulkier groups should increase the reactivity of the catalyst and the enantioselectivity of the process, for instance, compounds **17** [20] and **18** [21] (Fig. **4**). On the same way, the introduction of a supplementary 5-methyl substituent [5-methyl-3,5-diphenyl-2-pyrazoline (**19**)] [22] or a 4,4-dimethyl one [4,4-dimethyl-3,5-diphenyl-2-pyrazoline (**20**)] could prevent the catalyst from oxidation, increasing its stability. Note that many N-H pyrazolines have been reported as stable compounds, amongst them **17** and **18**.

EXPERIMENTAL

Experimental Procedure for Michael Addition to Cinnamaldehyde (21a, R = Ph) and Crotonaldehyde (21b, R = Me)

Free base **(*R*)-9** (20 mol% for **21a** and 40 mol% for **21b**), the corresponding aldehyde **21** (0.75 mmol) and the additives [20 mol % $PhCO_2H$ for **21a**, and 40 mol % $PhCO_2H$ and 1 equiv of TBAB (tetrabutylammonium bromide) for **21b**] were dissolved in EtOH (1.5 mL) and the mixture was stirred at room temperature for 5 min, whereupon the nucleophile **14** (26.8 mg, 0.15 mmol) was added to the solution. The solution was stirred at room temperature 96 and 120 h for **21a** (R = Ph) and **21b** (R = Me) respectively. Whereupon, the solvent was removed under reduced pressure and the crude purified by flash column chromatography (hexane/ethyl acetate 4:1) to afford the corresponding Michael adducts **15**. The yields for **15a** (13.6 mg, 68 %) and **15b** (12.1 mg, 72 %) were calculated based on the recovered starting material (brsm).

Experimental Procedure to Prepare Cyclohexenones 16

The previously obtained Michael adduct **15** was dissolved in 0.5 mL of THF and DBU (1,8-diazabicyclo [5.4.0]undec-7-ene, 0.4 equiv) was added to the solution. The mixture was stirred at room temperature until completion of the reaction (6 h). Then, it was filtered through a short pad of silica to remove the DBU eluting with EtOAc. The solvent was evaporated under reduced pressure and the crude was redissolved in 1 mL of toluene. *p*-TsOH (0.2 equiv) was added to the solution and the mixture was heated and vigorously stirred at 120 ºC for 4 h. The solvent was removed under reduced pressure and the crude purified by flash column chromatography (hexane/ethyl acetate 4:1) to afford the corresponding cyclohexenones [**16a**, R = Ph (79 %); **16b**, R = Me, (81 %)].

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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SUPPLEMENTARY MATERIAL

More detailed experimental procedure for the chiral HPLC, separation of catalyst **9** and Michael addition, NMR spectra and data of compounds **15** and **16** as well as computational details.

Supplementary material is available on the publisher's web site along with the published article.

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