Ion-pairing catalysis in the enantioselective addition of hydrazones to *N*-acyldihydropyrrole derivatives

Nagore Zabaleta, Uxue Uria, Efraim Reyes, Luisa Carrillo and Jose L. Vicario

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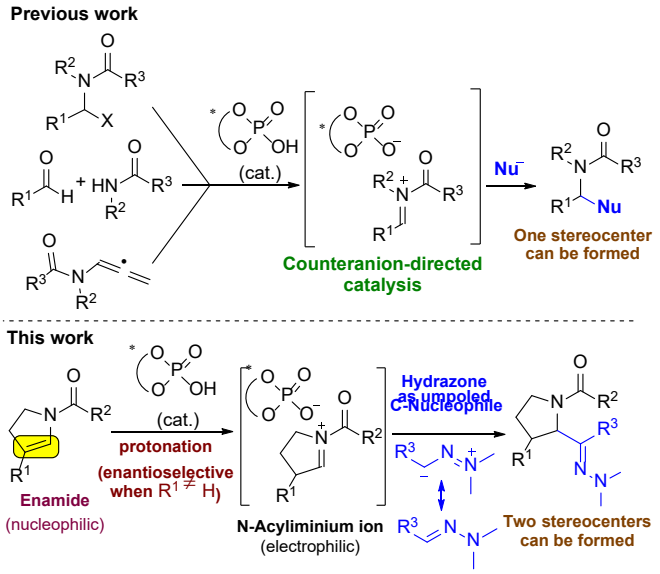
Nagore Zabaleta, [a] Uxue Uria,*[a] Efraim Reyes, [a] Luisa Carrillo [a] and Jose L. Vicario *[a]

We have demonstrated that tertiary enamides can act as efficient precursors of chiral quaternary *N*-acyliminium salts under Brønsted acid catalysis that undergo reaction with hydrazones, the latter participating as masked nucleophilic carbonyl group equivalents. The optimized methodology provides a variety of enantiopure α-substituted proline derivatives in excellent yields, being even compatible with disubstituted β-enamides that generate two contiguous stereocentres.

Asymmetric counteranion-directed catalysis has emerged as a new strategy to achieve stereocontrol in organic reactions.[1] This approach relies on the generation of a cationic reactive intermediate that remains closely bounded to the enantiomerically pure anionic catalyst through contact ion-pair, that allows transfer of stereochemical information to the new stereogenic centres. In this context, BINOL-based chiral phosphoric acids and related derivatives have demonstrated their proficiency as a privileged family of catalysts.[2] These strong Brønsted acids are able to promote the formation of an activated cationic intermediate from the starting material through protonation/elimination and, in this sense, a variety of reactions have been reported under this type of catalytic activation, being *N*-acyliminium ion chemistry particularly suited for the application of this concept.[3] In fact, several reports exist in which enantioselective 1,2-addition reactions to *N*-acyliminium ions have been carried out catalysed by a chiral phosphoric acid or derivative as catalyst, in all cases relying on the use of hemiaminals or related substrates as starting materials.[4] Alternatively, quaternary N-acyliminium ions have been generated under chiral Bronsted acid-catalysis *via* the in situ generation of the starting enamide through condensation from the corresponding precursors[5] or using allenamides as starting materials[6] (Scheme 1).



Scheme 1 Methods for the generation of quaternary *N*-acyliminium ions in reactions under counterion-directed catalysis and the enantioselective addition of hydrazones to enamides reported in this work.

In this report we wish to present the use of simple tertiary enamides as precursors of quaternary *N*-acyliminium ion electrophiles through activation with a BINOL-based chiral phosphoric acid catalyst and their subsequent reaction with donor-acceptor hydrazones as umpoled nucleophiles.[7] This implies the reversal of the natural nucleophilic reactivity of the starting enamide substrate in the presence of the Brønsted acid catalyst[8] and also involves inversion of the natural polarity of the hydrazone moiety from its natural electrophilic behavior to the less conventional character as an acyl anion equivalent (Scheme 1). In addition, there are only two examples where hydrazones have been employed as umpoled reagents undergoing addition to an imine under chiral phosphoric acid catalysis but in both cases the reaction involves activation of the azomethine electrophile via H-bonding (or protonation).[9]

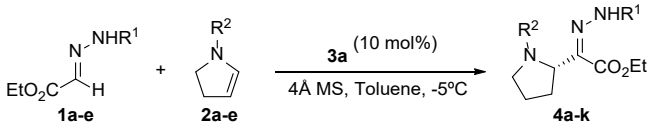
We started using hydrazone **1a** as a model system due to its proven ability to act as glyoxyl anion equivalent in previous research.[7c] In a series of preliminary experiments, this hydrazone was reacted with *N*-Boc dihydropyrrole **2a**, which serves as aliphatic *N*-acyliminium ion precursor, in the presence of a catalytic amount of different chiral phosphoric acids (see

[a] *Department of Organic Chemistry II, University of the Basque Country (UPV/EHU). P. O. Box 644, 48080 Bilbao (Spain). E-mail: joseluis.vicario@ehu.es; uxue.uria@ehu.es*

Electronic Supplementary Information (ESI) available: Survey of the performance of a variety of chiral phosphoric acids **3** in the model reaction and effect of solvent and temperature using catalyst **3a**. Characterization of all new compounds and copies of ^{1}H and ^{13}C NMR spectra. HPLC traces of all adducts prepared (PDF). See DOI: 10.1039/x0xx00000x

Supporting Information for details). In all cases, the formation of product **4a** in moderate to good yields and with a variable e.e. was observed. From all these preliminary experiments, TRIP phosphoric acid **3a** was identified as the best catalyst in terms of enantiocontrol, working in toluene at -5°C and in the presence of 4Å MS as water scavenger (entry 1 in Table 1). The enantioselectivity could be improved by modifying the *N*-substituent of the hydrazone to the more donating 4-$MeSC_6H_4$ at the expense of a lower yield (entry 2 vs 1) while the simpler *N*-phenyl hydrazone **1c** performed efficiently (entry 4). Remarkably, when hydrazone **1d** containing an electron-withdrawing substituent at this position was tested, the starting material was recovered (entry 5). This is pointing towards the necessity of an electron-donating substituent at this position of the hydrazone to become reactive as C-nucleophile. In this sense, *N*-*tert*-butyl substituted hydrazone **1e** was also found to be reactive, although providing a lower e.e. (entry 6).

Table 1 Role of the *N*-substituents at the hydrazone and enamide reagents.[a]



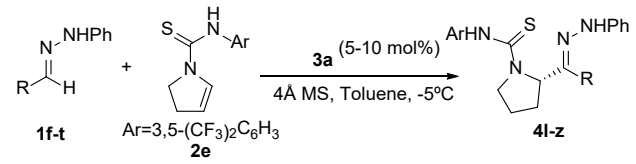
Entry	Prod.	R^1	R^2	Yield (%)[c]	e.e. (%)[d]
1[a]	**4a**	4-$MeOC_6H_4$ (**1a**)	Boc (**2a**)	60	86
2[a]	**4b**	4-$MeSC_6H_4$ (**1b**)	Boc (**2a**)	53	92
3[a]	**4c**	Ph (**1c**)	Boc (**2a**)	63	90
4[b]	**4c**	Ph (**1c**)	Boc (**2a**)	96	93
5[a]	**4d**	4-$NO_2C_6H_4$ (**1d**)	Boc (**2a**)	<5	<5
6[a]	**4e**	^{t}Bu (**1e**)	Boc (**2a**)	87	72
7[b,e]	**4f**	Ph (**1c**)	Fmoc (**2b**)	93	92
8[b]	**4g**	Ph (**1c**)	Ph (**2c**)	<5	<5
9[b]	**4h**	Ph (**1c**)	C(S)NHBn (**2d**)	95	92
10[b]	**4i**	Ph (**1c**)	C(S)NHAr[f] (**2e**)	98	>99
11[b]	**4j**	4-$MeOC_6H_4$ (**1a**)	C(S)NHAr[f] (**2e**)	85	98
12[b]	**4k**	^{t}Bu (**1e**)	C(S)NHAr[f] (**2e**)	80	91

[a] Reaction carried out in a 0.13 mmol scale of **2**, 1.2 eq. of **1**. [b] Reaction carried out in a 0.09 mmol scale of **1**, 1.5 eq. of **2** and 10 mol% of **3a** in 0.18 mL of toluene. [c] Yield of pure product after flash column chromatography. Hydrazones **4h-j** were isolated as thermodynamic mixtures of *Z*/*E* diastereoisomers in ratios varying from 5:1 to 6.7:1. [d] Determined by HPLC analysis on a chiral stationary phase (see Supporting Information). [e] The reaction was carried out at 10ºC. [f] Ar: 3,5-$(CF_3)_2C_6H_3$.

We next evaluated the role played by the *N*-protecting group at the enamide reagent, observing that other carbamate substituents like Fmoc could be successfully used in combination with hydrazone **1c** (entry 7). However, the use of *N*-phenyldihydropyrrole **2c** led to the formation of a complex mixture of unknown products (entry 8). Remarkably, dihydropyrroles **2d** and **2e** reacted efficiently in terms of both yield and enantiocontrol (entries 9 and 10). These results were interpreted in terms of the beneficial effect of this acidic NH moiety which can engage in additional H-bonding interactions with the phosphoryl moiety of the phosphate counteranion, In fact, dihydropyrrole **2e** with a more acidic NH group performs better than **2d** with respect to enantiocontrol, being possible to reduce the catalyst loading to 1 mol%[10] or to carry out the reaction at higher scale.[11] Moreover, **2e** also performed well in the reaction with hydrazones **1a** and **1e**, in both cases affording the desired products with excellent e.e. (entries 11 and 12).

Subsequently, the scope of the reaction towards the use of hydrazones with different substituents at the azomethine position was evaluated (Table 2). In general, the reaction performed excellently when strongly electron-withdrawing substituents such as alkoxycarbonyl, acetyl or CF_3 were incorporated (entries 1-3). Remarkably, the simple benzaldehyde-derived hydrazone **1i**, which had been found to be unreactive as C-nucleophile in other literature examples, was also found to undergo smooth reaction with **2e**, furnishing adduct **4o** in high yield and enantioselectivity (entry 4).

Table 2 Scope of the reaction.[a]



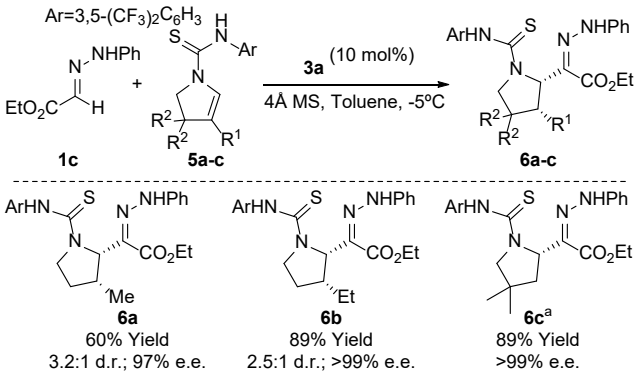
Entry	R	Prod.	Yield (%)[b]	e.e. (%)[c]
1[d]	$CO_2{}^i$Pr (**1f**)	**4l**	87	>99
2[d]	Ac (**1g**)	**4m**	87	98
3[d]	CF_3 (**1h**)	**4n**	73	99
4	Ph (**1i**)	**4o**	94	90
5	C_6F_5 (**1j**)	**4p**	78	97
6	4-CNC_6H_4 (**1k**)	**4q**	90	88
7	4-$CF_3C_6H_4$ (**1l**)	**4r**	90	86
8	4-$(MeO_2C)C_6H_4$ (**1m**)	**4s**	65	83
9	4-BrC_6H_4 (**1n**)	**4t**	79	92
10	4-ClC_6H_4 (**1o**)	**4u**	82	90
11	4-FC_6H_4 (**1p**)	**4v**	95	94
12	3-FC_6H_4 (**1q**)	**4w**	80	84
13	2-FC_6H_4 (**1r**)	**4x**	94	82
14	4-MeC_6H_4 (**1s**)	**4y**	83	91
15	4-$MeOC_6H_4$ (**1t**)	**4z**	60	83

[a] Reaction carried out in a 0.09 mmol scale of **1**, 1.5 eq. of **2e** and 10 mol% of **3a** in 0.18 mL of toluene. [b] Yield of pure product after flash column chromatography. Hydrazones **4l-z** were isolated as thermodynamic mixtures of *Z*/*E* diastereoisomers (see Supporting Information). [c] Determined by HPLC analysis on a chiral stationary phase (see Supporting Information). [d] 5 mol% of **3a** was employed.

Other hydrazones with aryl substituents that incorporate electron-withdrawing groups performed excellently (entries 5-11), regardless the position of this substituent at the aryl moiety (entries 11-13). More interestingly, the less reactive hydrazones **1s** and **1t** provided the corresponding adducts in high yields and e.e. The absolute stereostructure of the cycloadducts obtained by this protocol was established by single-crystal X-ray analysis of enantiopure samples of compound **4m**.[12]

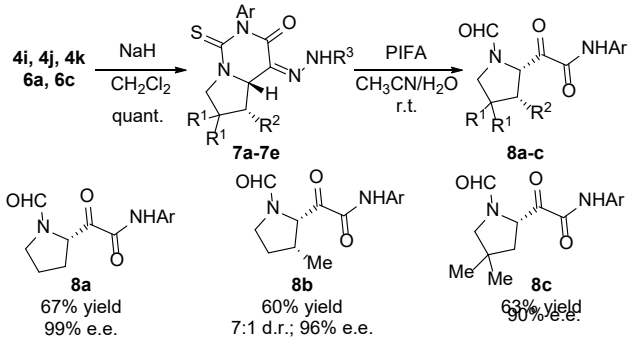
In addition, we also evaluated the possibility of using 3-substituted dihydropyrroles as potential *N*-acyliminium ion precursors that would result in the formation of two contiguous stereocentres (Scheme 2). Remarkably, enamides **5a** and **5b** provided adducts **6a** and **6b** respectively in good yields and moderate d.r., being the cis-diastereoisomers the major one. This is indicating that phosphoric acid catalyst **3a** is promoting a highly enantioselective β-protonation of the enamide moiety, which is followed by the addition of the hydrazone to the

formed acyliminium cation, presumably under catalyst control, in view of the cis relative arrangement that implies the reaction of the hydrazone through the most hindered face of the acyl iminium intermediate. We also verified the excellent performance of the more sterically hindered substrate **5c**.



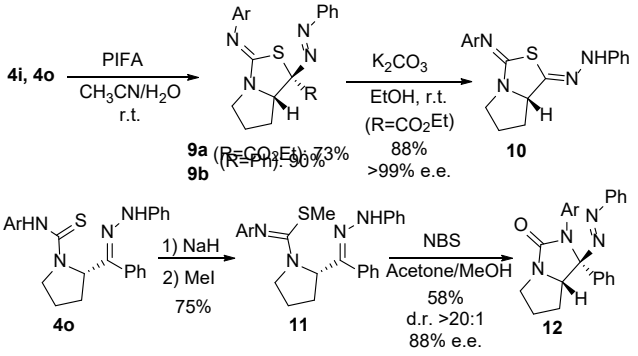
Scheme 2 Reaction using substituted dihydropyrroles.

Having succeeded in the development of a general method for the addition of hydrazones to enamides, its synthetic potential as a tool in synthesis was demonstrated by preparing the scaffold of anti-amnesic pyrrolidine derivatives which inhibit or decrease the enzymatic activity of prolyl endopeptidase.[13] For this propose, we set up an effective procedure to transform the hydrazone moiety of glyoxylate hydrazones (**1a**, **1c** and **1e**) derived adducts to the corresponding ketones (Scheme 3). Firstly bicyclic intermediate **7** was quantitatively formed under basic conditions and next, PIFA-mediated oxidative hydrolysis provided the desired α-ketoamide **8**.[14] These conditions were successfully employed on a set of representative compounds.[15]



Scheme 3 Synthesis of PEP inhibitor analogues.

Finally, we surveyed different chemical manipulations of the thiourea moiety present in adducts **4** in order to illustrate the synthetic applicability of the reaction (Scheme 4). For example, the oxidation of the hydrazone moiety together with the intramolecular *N*-addition of the thiourea could be carried out by the use of PIFA providing bicyclic adducts 9a-b in good yields, as a single diastereoisomer and without erosion of the enantiopurity of the starting material. Moreover, compound 9a could be easily decarboxylated under mild basic conditions leading to the formation of **10** in very good yield. Furthermore, closely related enantioenriched bicyclic compound **12** could be obtained in good yields if compound **4o** is methylated prior to the oxidative process employing NBS.



Scheme 4 Chemical manipulation of adducts **4**.

In conclusion, we have demonstrated that previously prepared enamides are efficient substrates to generate chiral cuaternary *N*-acyliminium salt intermediates in the presence of a strong chiral Brønsted acid catalyst. Their reaction with *N*-monosubstituted hydrazones **1a-t** provide a wide range of enantiopure α-hydrazono proline derivatives in excellent yields, being even possible to generate two contiguous stereocentres starting from β-disubstituted enamides. Moreover, an efficient protocol to cleavage the glyoxylate derived hydrazone has been developed proving the potential synthetic applicability of the present methodology.

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Conflicts of interest

There are no conflicts to declare.

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11 When the reaction was carried out with 0.4 mmol of hydrazone **1c**, adduct **4i** was isolated in 93% yield and >99% ee (see the Supporting Information for details).

12 CCDC 1841491-1841492 contains the supplementary crystallographic data for this paper.

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