ARTICLE

Formaldehyde tert-butyl hydrazone as a formyl anion equivalent: Asymmetric addition to carbonyl compounds

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The asymmetric 1,2-addition of formyl anion equivalents to carbonyl compounds is a powerful synthetic tool that ideally provide access to highly functionalizable α-hydroxy aldehydes in an enantioselective fashion. In this context, the nucleophilic character of formaldehyde hydrazones, together with their remarkable stability as monomeric species, has been exploited for the functionalization of diverse carbonyl compounds, using initially auxiliary-based methodologies and, more recently, catalytic enantioselective versions. This feature article highlights our research progress employing formaldehyde tert-butyl hydrazone as a versatile formyl anion equivalent, in combination with bifunctional H-bonding organocatalysis. The design and optimization of different catalytic systems, focusing on a dual activation of both reagents, is reviewed, as well as the racemization free unmasking of the formyl group and representative product transformations for the construction of valuable, densely functionalyzed chiral building blocks.

1. Introduction

Umpolung strategies for inverting the natural reactivity of functional groups are powerful synthetic tools for generation of molecular complexity in organic synthesis.1 In particular, the asymmetric 1,2-addition of acyl anion equivalents (d1 reagents) to carbonyl compounds provides direct access to valuable functionlalyzed alcohols.2 Most direct nucleophilic acylations are catalyzed by N-heterocyclic carbenes (Scheme 1, a),3 but this strategy fails in the case of formaldehyde due to oligomerizations (the formose reaction).4 Therefore, several masked formyl anion reagents (anionic or neutral) have been developed to circumvent such limitation (Scheme 1, b).5 These strategies are based on two key steps: i) asymmetric C-C bond formation, and ii) subsequent unmasking to reveal the formyl group.

Approaches based on anionic reagents require in general harsh, strongly basic conditions and catalytic asymmetric variants have not been developed. Whereas this feature article will focus on the use of the more versatile neutral formyl anion equivalents in asymmetric catalysis, a selection of chiral auxiliary-based reagents is also shown, with the aim to provide a clear background of the topic. It should be noted that, for some reagents, the catalytic systems are highly reminiscent of the corresponding stoichiometric methods that inspired them and for others, the catalytic enantioselective reactions remain elusive. Key aspects which have allowed us to develop efficient reactions employing formaldehyde tert-butyl hydrazone (FTBH) as masked d1 reagent in combination with bifunctional organocatalysts are highlighted.

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2. Background: From chiral auxiliary-based reagents to enantioselective reactions

2.1. Anion-stabilized reagents

A number of studies have been focused on diastereoselective additions to aldehydes accomplished by using sulfur-stabilized carbanions carrying various chiral auxiliaries such as dithioacetals mono-3,4-5 or N-Boc-thiazoline/benzothiazoline 61-8 in the presence of stoichiometric amounts of enantipure catalysts and functional groups, that underwent undesired side reactions. Moreover, unmasking of the formyl group from the primary adducts is still a major difficulty, requiring toxic mercury salts, iodine reagents or multistep sequences.

Alternatively, cyanohydrin derivatives 17 can also be easily obtained after oxidative N–N bond cleavage (aza-Cope type elimination) promoted by magnesium monoperoxyphthalate hexahydrate (MMPP).18

2.2. Neutral reagents: N,N-dialkyl hydrazones

Over the years, we have exploited the enhanced aza-enamine (nucleophilic) character of formaldehyde N,N-dialkyl hydrazones for the stereoselective introduction of single-carbon functional groups into more complex molecular scaffolds.12 In particular, the enhanced reactivity provided by the pyrrolidine ring was exploited to perform diastereoselective additions to diverse electrophiles, including carbonyl compounds. Thus, the simplest achiral derivative 11, along with chiral proline derivatives such as SAMP [(S)-1-amino-2(methoxyethyl) pyrrolidine] hydrazone 1213 or analogue 13 have been successfully employed in reactions with chiral α-alkoxy- and α-amino aldehydes14 (substrate-controlled stereoselectivity) and simple aldehydes15 or trifluoromethyl ketones16 (reagent-controlled stereoselectivity) to afford densely functionalized α-hydroxy hydrazones 14 (Scheme 4). These procedures, based in a soft and neutral reagent, not only benefit of milder reaction conditions, but also provides a remarkable versatility associated to efficient transformations of the hydrazone moiety. The primary targets, aldehydes 15, can be readily synthesized by C=N bond cleavage using acid hydrolysis or ozonolysis,17 and eventually reduced to diols 16. Alternatively, cyanohydrin derivatives 17 can also be easily obtained after oxidative N–N bond cleavage (aza-Cope type elimination) promoted by magnesium monoperoxyphthalate hexahydrate (MMPP).18
The development of catalytic enantioselective versions of these reactions proved to be a difficult task due to the sensitivity of hydrazones toward most Lewis acidic metal complexes, usually employed for the activation of weakly electrophilic substrates. The milder nature of organocatalytic activation strategies, however, appeared to solve these compatibility issues. Thus, $H$-bonding activation by thioureas was identified as a suitable strategy for the conjugate addition of achiral pyrrolidine hydrazones to carbonyl compounds. These limitations prompted us to explore a dual activation mode as an alternative strategy for the development of the targeted enantioselective formylation of these types of substrates.

### 3. Asymmetric organocatalytic 1,2-additions of formaldehyde tert-butyl hydrazone to carbonyl compounds

#### 3.1. Hypothesis and design of the catalytic system

Due to the $N,N$-disubstitution in hydrazones such as 11, the attack of the nitrogen atom to neutral electrophilic reagents results in the formation of zwitterionic compounds in a non-productive, reversible process. In monosubstituted analogues, however, the attack of the more nucleophilic nitrogen atom must be avoided to prevent undesired side reactions. In this context, Baldwin and co-workers had reported on the use of azo-anions from 1-nitro-1-t-butyl hydrazones as acyl anion equivalents using the steric protection provided by the bulky tert-butyl group to avoid reaction at the N atom (Scheme 6, a), although the reaction with the formaldehyde derivative was not reported. Later, the same group also reported on the reactivity of neutral $N$-monosubstituted hydrazones in thermal ene reactions with highly reactive Michael acceptors such as methyl acrylate and acrylonitrile (Scheme 6, b). Inspired by these pioneering reports, we envisioned that reactions of neutral formaldehyde $N,N$-dialkyl hydrazones (FTBH) 22 with carbonyl compounds should take place at the azomethine carbon for steric reasons, while the presence of the alkylamino NH group could eventually offer additional opportunities for interactions with bifunctional organocatalysts (Scheme 6, c). This strategy proved to be successful for 1,2-additions to carbonyl compounds (formally hetero-carbonyl-ene reactions) as disclosed below.

### Scheme 5 Seminal enantioselective organocatalytic reactions employing formaldehyde $N,N$-dialkyl hydrazones.
3.2. Addition of FTBH to activated carbonyl compounds

The first asymmetric organocatalytic reactions were planned considering a series of carbonyl substrates containing additional activating functionalities such as a second carbonyl group in α-keto esters and isatins (1,2-dicarbonyl systems) or a phosphonyl group in α-keto phosphonates. In this way, well-defined three-dimensional environments are expected to be created upon engagement with H-bond donor catalysts by multiple-point interactions.

α-Keto esters

Ethyl phenylglyoxylate 23a was initially chosen as a model α-keto ester substrate (Scheme 7). The preliminary screenings served to identify BINAM-bis urea I as the best catalyst, which afforded, in toluene at −15 °C, the expected azomethyl alcohol 24a in 98% yield and 78% ee. Remarkably, bis-thiourea analogue II performed better to show a moderate enantioselectivity (up to 64% ee) and isatins (1,2-dicarbonyl systems) showed significantly enhanced enantioselectivities in most cases (94–99% ee). Additionally, essentially pure enantiomers [(R)-24] were also obtained for ortho-fluorinated derivatives. Alkyl-substituted α-keto esters proved to be more challenging substrates for which enantioselectivities were highly dependent on the alkyl chains. For most of these substrates, multifunctional D-glucosamine-derived thiourea III showed slightly superior catalytic activity than (R)-BINAM bis-urea I, reaching full conversions in cleaner reactions, albeit with moderate enantioselectivities (up to 64% ee).

Considering the close structural similarity between bis-urea I (I′) and bis-thiourea II (II′) catalysts, the higher hydrogen bond acceptor capability of the oxygen in the carbonyl group of the urea was suggested as the distinct factor. Accordingly, the mechanism and stereochemical model depicted in Scheme 8 was proposed. Hence, a bifunctional behaviour of the catalyst results in the activation of both the hydrazine, by means of a NH⋯O=C hydrogen bond, and the α-keto ester, through a multiple hydrogen bond network provided by a second urea unit. In this way, a ternary complex is generated, in which the orientation of the bidentate electrophile avoids the aromatic ring being placed in the inner, more crowded region of the catalyst. After nucleophilic attack of the azomethine carbon to the activated carbonyl group and release of the product, the model predicts the formation of the product with the observed (R) absolute configuration at the newly created stereogenic center.
Scheme 8 Proposed catalytic cycle and stereochemical model.

Additional support was obtained from NMR experiments. Thus, $^1$H NMR spectra recorded for 22 in the presence of increasing amounts of catalyst I showed the signals of the azomethine protons shifted upfield (∆δ up to −0.1 ppm at a 1:1 ratio, Figure 1), as expected from a higher electron density at the azomethine carbon resulting from the polarization of the N–H bond. Moreover, $^1$H NMR spectra recorded for I in the presence of increasing amounts of keto ester 23a showed an additional perturbation of the ortho-protons of the catalyst (Figure 2), suggesting their participation as H-bond donors in a cooperative network.\(^{28}\) Initially, an upfield shift of the signals of these protons was observed upon addition of 0.25 equiv. of keto ester, presumably due to the disruption of inter- and/or intra-molecular self-aggregation of bis-urea catalyst. Progressively, a downfield shift was then observed upon further addition of 23a (∆δ up to 0.1 ppm at a 1:4 ratio), consistent with the establishment of a catalyst-substrate intermolecular H-bonding network.

Figure 1 $^1$H NMR titration experiment of 22 with catalyst I.

Figure 2 $^1$H NMR titration experiment of I with α-keto ester 23a.

Further support for the proposed bifunctional working model was collected from experiments performed with hybrid thiourea-urea catalyst IV (Figure 3). According to the proposed mechanism, a single urea moiety is required to activate the reagent 22 and, therefore, IV was expected to imitate the behaviour of I, and not that of II. In fact, this hybrid catalyst afforded azomethyl alcohols with similar enantiomeric excess as I and slightly shorter reaction times, which accounts for the better activation of α-keto esters by the thiourea moiety. However, there is a limitation on the catalyst design: incorporation of a better H-bond acceptor urea, as in pyrrolidine derivative V, results in a lower catalytic activity and the obtention of racemic products. These facts can be explained by the deactivation of the catalyst due to a strong intramolecular H-bonding interaction between the amide carbonyl group, with enhanced H-bond acceptor ability, and the thiourea moiety as a double H-bond donor.\(^{29}\)

Diazones 24 are densely functionalized tertiary alcohols which...
contain the core structures of pharmacologically relevant compounds such as Anisodine, Voriconazole (VFEND®), Posaconazole (NOXAFIL®), and isoserines (2-substituted α-hydroxy-β-amino acids) which are present in several taxoid-based anticancer agents, among others.

To demonstrate that FTBH 22 can indeed be designated as a formyl anion equivalent, representative diazenes 24 were transformed into aldehydes 26 through a tautomerization (→ 25)/hydrolysis sequence efficiently performed by simple treatment with HCl in a biphasic H2O/Et2O medium (Scheme 9). Crude aldehydes were sensitive products that could not be purified by chromatographic techniques but were isolated with a high degree of purity and could be used directly in subsequent transformations. For example, reductions or reductive aminations afforded diols 27 or α-hydroxy-β-amino esters 28 in good overall yields.

Isatins

Aiming to expand the scope of this dual activation strategy, we reported later the enantioselective reaction of 22 with isatins 29, a different family of dicarbonyl substrates. The particular motivation in this case was the construction of the important 3-hydroxy-2-oxindol core, found in a lot of natural products and plenty of bioactive molecules. The influence of the substitution at the amide nitrogen atom was investigated using bis-urea catalyst I in toluene at ~78 °C. N-Benzyl derivative 29(Bn) afforded the desired adduct 30 in high yield and the highest enantioselectivity (90% ee). Unfortunately, such high enantioselectivities were observed only in isolated experiments, and, on the other hand, it was found out that enantioselectically enriched samples slowly racemized in solution, even at low temperatures. The uncatalyzed racemization is believed to proceed by a thermal retro-hetero-carbonyl ene reaction, through a 6-membered ring transition state involving an intramolecular OH·N bond (Scheme 10). Fortunately, however, in situ O-alkylation of 30 regularly afforded O-methyl and O-propargyl derivatives 31 in excellent yields and enantioselectivities (96-98% ee). Alternatively, rapid oxidation of the fresh crude diazenes was performed with magnesium monoperoxypthalate hexahydrate (MMPP·6H2O) to afford azoxy compounds 32 in high yields, complete regioselectivities and excellent enantioselectivities (up to 99% ee). As anticipated, O-alkylated products and azoxy compounds were configurationally stable, as the hypothesized racemization mechanism is avoided in both cases. The diazene-to-aldehyde transformation from products 31 was easily performed under acidic hydrolysis and the crude aldehydes 33 were subsequently used in Wittig olefination to give enones 34 in good overall yields.

α-Keto phosphonates

Considering the possibility of incorporating other substrates into the dual activation model by bis-urea catalyst I, we next decided to explore the behavior of α-keto phosphonates 35 as activated electrophiles, aiming to obtain functionalized α-aryl α-hydroxy phosphonates, precursors of biologically active...
phosphoalysines.\textsuperscript{35} The phosphonate is a strong electron-withdrawing group which, unlike planar carbonyl derivatives, is featured by a tetrahedral phosphorous centre next to the reactive carbonyl group. These substrates showed high reactivities in absence of catalysts, making necessary to control the undesired background reaction. Moreover, diazene 36 were relatively unstable and a ‘one-pot’ oxidation into azoxy compounds 37 was required to analyze the reaction by chromatographic techniques (Scheme 11). To our delight, employing again BINAM bis-urea in toluene at \textasciitilde78 °C, this procedure afforded azoxy compounds 37 in good overall yields and excellent enantioselectivities (up to 97% ee).

Transformation of the \textit{N}-tert-butyldiazeyl methyl group of crude products 36 into the formyl group in aldehydes 39 was also performed by treatment with HCl in a biphasic \textit{H}_2\text{O}/\textit{Et}_2\text{O} medium via hydrazone intermediates 38. Aldehydes 39 were not isolable by chromatographic techniques but were directly subjected to reductive amination to afford quaternary \textit{β}-amino-\textit{α}-hydroxyphosphonates 40 in satisfactory overall yields (3 reactions, 1 chromatographic purification) and high enantioselectivities (Scheme 12).

3.3. Addition of FTBH to monocarbonyl compounds

In the next stage, we investigated enantioselective reactions of FTBH with single carbonyl compounds (simple aldehydes\textsuperscript{36} and fluoromethyl ketones\textsuperscript{37}). These are \textit{a priori} more challenging substrates for two main reasons: First, the intrinsic electrophilicity of the carbonyl group in these substrates, highly dependent on the substitution patterns, is expected to translate into a significant uncatalyzed, racemic background reaction. Second, the geometry of the catalyst-substrate complexes should be fixed using weak H-bonding interactions with a single acceptor site, in contrast with the above-mentioned precedents.

\textbf{Simple aldehydes}

\textit{p}-Chlorobenzaldehyde 41a, a relative reactive aromatic aldehyde, was chosen as model substrate for preliminary experiments. The thermal reaction between 22 and 41a, in toluene at room temperature, proved to be reversible. Therefore, diazene 42a was transformed \textit{in situ} into its azoxy compound 43a which could be isolated and analyzed by chromatographic techniques. BINAM bis-(thio)urea catalysts I or II failed in this particular case, affording products in racemic way. Preliminary screenings employing many bifunctional thioureas with different architectures evidenced the need of more active (acidic) catalysts. Thus, an additional screening was performed, leading to the identification of bifunctional squaramides derived from L-tert-leucine as the most promising

\textbf{Scheme 11} Asymmetric addition of FTBH to \textit{α}-keto phosphonates.

\textbf{Scheme 12} Synthetic sequence to \textit{β}-amino-\textit{α}-hydroxyphosphonates.

\textbf{Scheme 13} Asymmetric addition of FTBH to simple aldehydes.
structures. Initially, moderate levels of asymmetric induction (up to 50% ee) were reached employing VI, in toluene at 5 °C (Scheme 13). The solubility of VI in toluene (<3 mg/mL at room temperature) was considered as a possible explanation. This circumstance is frequently associated to the formation of self-aggregates through hydrogen bonds into head-to-tail ladder networks, a fact that could be confirmed by X-ray diffraction analysis as shown in Figure 4, and that frequently limits further implementation of squaramides in asymmetric organocatalysis. To our delight, though, the higher solubility of VI in α,α,α-trifluorotoluene (∼16 mg/mL at room temperature) resulted in homogeneous reaction media in which higher conversions (95%) and enantioselectivities (up to 76% ee) were obtained with reliable reproducibility. Interestingly, comparison of the catalytic performance of VI with those of related squaramides bearing different H-bond donor groups, such as pentafluoroaniline (VII) and [3,5-bis(trifluoromethyl)benzyl]amine (VIII) derivatives allows to establish a direct correlation between the H-bond donor ability of the most acidic NH moiety of the catalysts [VI > VII > VIII (inferred from chemical shift of NH protons in 1H NMR)] and the observed enantioselectivities, which drop to 55% and 23% ee for less acidic VII and VIII, respectively (Figure 5). Temperature and concentration were further optimized: performing the reaction with catalyst VI at −10 °C (0.5 M), followed by in situ N-oxidation, afforded 43a in 90% yield and 90% ee. The scope of the reaction was explored employing different aromatic and heteroaromatic aldehydes; the corresponding azoxy compounds 43 were isolated in excellent yields and high enantioselectivities (up to 96% ee). Remarkably, aliphatic aldehydes with representative types of alkyl chains (cyclopropyl, benzyloxymethyl, benzyl, isopropyl, and n-heptyl) were also tolerated.
However, the observed effect was relatively low as reactions
of nonlinear effect suggested a more complex scenario involving
repulsions during the C–C bond formation. A slightly negative
activation of both reagents was proposed, accounting for the
observed high enantioselectivities and absolute configuration
activation and the positioning of both carbonyl group behaves as an efficient H-bond acceptor for the
hydrazone NH donor. The activation and the positioning of both reagents drive the preferential approach of azomethine carbon
(Figure 6). The aldehyde is believed to be activated by the
observed high enantioselectivities and absolute configuration
activation of both reagents was proposed, accounting for the
enantioenriched, densely functionalized fluorinated alcohols
Consequently, a stereochemical model based on a dual
enantiocontrol [Raney Ni, H2, MeOH]
irreversible N–N bond
transformation involves three consecutive steps [hydrogenolytic N–
and without significant erosion of enantioselectivity (Scheme 15).
Despite all efforts, the inherent instability of diazenes 42 made it
impossible to obtain α-hydroxy aldehydes in this particular case.
Alternatively, azoxy compounds 44 were transformed into free
amino alcohols 44 by applying standard hydrogenation conditions
[Toluene, 5 °C, BTC, DIPEA, 2013, 00, 1-3].

Di/tri-fluoromethylketones

Aiming to further expand the scope of this catalytic system, we
next focused on the asymmetric functionalization of di- and tri-
fluoromethylketones 46 and 47 for the synthesis of enantioenriched, densely functionalized fluorinated alcohols 48

![Figure 6](image-url)

**Figure 6** Off-cycle catalyst homochiral self-aggregates and stereochemical model.

**Scheme 15** Synthesis of amino alcohols 44 and oxazolidinones 45.

**Scheme 16** Asymmetric addition of FTBH to fluorinated methylketones.
Conclusions

The combination of formaldehyde tert-butyl hydrazone, as a neutral formyl anion equivalent, with bifunctional H-bond donor/acceptor organocatalysts has emerged as a versatile tool for the asymmetric formylation of carbonyl compounds. The design of a dual activation strategy has been key to successfully perform highly enantioselective nucleophilic additions, formally aza-carbonyl-ene reactions, with a broad scope of substrates including α-keto esters, isatines, α-keto phosphonates, simple aldehydes and fluorinated ketones, efficiently yielding tert-butyl azomethine carbinols as the primary reaction products. In these reactions, ternary catalyst-reagent-substrate complexes are generated, in which the carbonyl compound of the substrate is activated by multiple H-bond interactions (with a urea/thiourea/squaramide moiety), while the nucleophilicity of the hydrazone reagent is enhanced by an additional H-bonding interaction with the basic oxygen atom of an urea or amide group. In most cases, the formylation procedure is efficiently completed after a simple 'one-pot' transformation of the obtained diazines into the targeted aldehydes via tautomerization followed by hydrolytic cleavage of the hydrazone intermediates. Moreover, a variety of other densely functionalized chiral building blocks can be also obtained after simple functional group transformations. Despite the high reactivity observed for some substrates, none of the catalysts used allowed to expand the reactivity to N-tertbutoxyhydrazones from higher aldehydes.43 Future investigations based in alternative catalysts and/or activation strategies, therefore, will be needed to overcome this limitation and develop a more general method for the asymmetric acylation of carbonyl compounds. Moreover, the implementation of some of these approaches in target-oriented synthesis might be also explored for accessing on-demand biologically active targets.

Conflicts of interest

There are no conflicts to declare.

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