

Asymmetric Formal Carbonyl-Ene Reactions of Formaldehyde *tert*-Butyl Hydrazone with α -Keto Esters: Dual Activation by Bis-urea Catalysts

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S Supporting Information

ABSTRACT: The dual activation of α -keto esters and formaldehyde *tert*-butyl hydrazone by BINAM-derived bisureas is the key to achieve high reactivity and excellent enantioselectivities in nucleophilic addition (formal carbonyl-ene reaction) to functionalized tertiary carbinols. Ensuing high-yielding diazene-to-aldehyde tranformations and subsequent derivatizations provides a direct entry to a variety of densely functionalized products.

T he asymmetric 1,2-addition of acyl anion equivalents to carbonyl compounds is a powerful synthetic tool that provides direct access to functionalized carbinols.¹ Most organocatalyzed nucleophilic acylations are mediated by N-heterocyclic carbene catalysts,² but this strategy fails in the formaldehyde case due to self-condensations (the formose reaction).³ On the other hand, the marked aza-enamine (nucleophilic) character of formaldehyde N,N-dialkyl hydrazones I has been exploited for the functionalization of diverse electrophiles,⁴ including carbonyl compounds such as aldehydes,⁵ trifluoromethyl ketones,⁶ and α -keto esters⁷ (Scheme 1, eq 1). The development of catalytic asymmetric approaches based on chiral Lewis acids is problematic because of the tendency of these reagents I to bind acidic metals and undergo

Scheme 1. Hydrazone-Based Formyl Anion Equivalents



side reactions, decomposition, dimerization, or catalyst deactivation.⁸ The mild nature of the organocatalytic activation of electrophilic compounds, however, appears to be more appropriate for these reactions, and applications have been developed for the addition to imines⁹ and Michael acceptors.¹⁰ Despite intensive efforts, however, we failed to develop asymmetric organocatalytic additions to carbonyl compounds. Baldwin et al. had previously reported on the use of azo anions from bulky monoalkyl hydrazones 2 as acyl anion equivalents (eq 2).¹¹ Additionally, neutral monoalkyl hydrazones have shown reactivity in thermal ene reactions with methyl acrylate and acrylonitrile,¹² but, to the best of our knowledge, these reagents have never been used in nucleophilic additions (formally carbonyl-ene reactions) to carbonyl compounds (eq 3). Considering that the presence of the NH group offers additional opportunities for interaction with an organocatalyst, we decided to explore the reactivity of formaldehyde tert-butyl hydrazone 3 in this context. In this paper we wish to disclose our findings on the reaction with α -keto esters 4.



Preliminary experiments were performed with commercially available ethyl phenylglyoxylate **4a** (Scheme 2). At room temperature, this substrate smoothly reacted with **3** under thermal conditions to afford the α -hydroxy ester **5a** at a reasonable rate (43% conversion after 3 h in toluene; 78% after 24 h, Table 1, entry 1), while addition of 10 mol% of *N*,*N'*-bis[3,5-bis(trifluoromethyl)phenyl] thiourea I slightly accelerated the reaction (reaction finished in 9 h, entry 2), showing that the background reaction could interfere with the catalytic version. Fortunately, cooling to -15 °C practically inhibited the uncatalyzed reaction (<5% conversion after 24 h, entry 3), while a significant acceleration by the catalyst I was observed at this temperature (reaction complete in 10 h, entry 4), thereby

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Table 1. Thermal and Catalytic Reaction of 3 with Keto Ester $4a^{a}$

entry	cat.	<i>t</i> (h)	T (°C)	yield (%) ^b	ee (%) ^c
1	-	24	rt	78	-
2	Ι	9	rt	90	-
3	-	24	-15	<5	-
4	Ι	10	-15	95	-
5	II	72	-15	99	78^d
6	III	72	-15	55 ^e	24 ^f
7	IV	72	-15	99	74^d
8	v	72	-15	51 ^e	22^{f}
9	II	78	-30	96	90^d
10	II	42	-30	97	91 ^{<i>d</i>,g}

^{*a*}Reactions performed at 0.5 mmol scale using 10 mol% catalyst loading unless otherwise stated. ^{*b*}Isolated yield after column chromatography. ^{*c*}Determined by HPLC. ^{*d*}Major enantiomer eluted first. ^{*c*}Yield estimated by ¹H NMR of the crude reaction mixture. ^{*f*}Major enantiomer eluted second. ^{*g*}Reaction performed at 4 mmol scale.



Figure 1. BINAM-derived bis-ureas and bis-thioureas.

opening opportunities for the development of an asymmetric catalytic version. After a screening of available organocatalysts, (R)-BINAM-derived bis-urea II (BINAM = 2,2'-diamino-1,1'binaphthalene, Figure 1) emerged as the most promising catalyst.¹³ Thus, addition of II (10 mol%) to the model reaction in toluene at -15 °C led to the isolation of enantioenriched 5a in a nearly quantitative yield and 78% ee (entry 5). It is noteworthy that the bis-thiourea analogue (R)-III, although reported to be a superior catalyst in related reactions,^{13a,14} proved to be a less efficient one in this case [55% versus 100% conversion after 72 h, respectively (entry 6)], leading to the product 5a with a moderate 24% ee and with the opposite sense of enantioselection. This anomalous behavior was also observed for the partially hydrogenated bis-urea and bis-thiourea analogues IV and V (entries 7 and 8), confirming that the observed phenomenon cannot be taken as an isolated case.¹⁵ Using the best catalysts II, the enantioselectivity was further improved to 90% ee by performing the reaction at -30 °C (entry 9). Moreover, the reaction carried out at 4 mmol scale proved to be even faster, reaching completion in 42 h and affording the product 5a in 97% yield with essentially the same ee (entry 10).¹⁶

The scope of the reaction was then explored with a range of α -keto esters 4 (Table 2). Ethyl pyruvate 4b was used as a representative of aliphatic substrates. Though the observed reactivity is similar to that observed for 4a, a poorer 49% ee was reached, using in this case bis-urea IV as the best catalyst (entry 1). Therefore, we focused on aromatic and heteroaromatic substrates 4c-q with several substitution patterns. The collected data show that the expected products 5c-q (Chart 1) were obtained in nearly quantitative yields and high enantioselectivities in most cases, either using catalyst II (5a,c,f,p) or IV (5d,e,g-o,q) as the best option. As expected, the reaction rates correlate with the electronic properties of the

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Table 2. Catalytic Additions of 3 to α -Keto Esters 4a-q^a

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0 R ³ کار 4a-q	DEt <mark>3</mark> , To	Cat. Iuene HO R	tBu N OEt O	R = Me 4b	X 4a,c-n	40	^{۶۶} 4p	4q
entry	4	Х	cat.	$^{t}_{(h)}$	Т (°С)	yield (%) ^b	5	ee (%) ^c
1	4b	-	IV	72	-15	89 ^d	5b	49
2	4c	4-Me	II	72	-15	96	5c	82
3	4c	4-Me	II	96	-30	91	5c	84
4	4d	4-OMe	IV	144	-15	67	5d	72
								(>99)
5	4e	2-OMe	IV	144	-15	81	5e	91
6	4f	4-CN	II	7	-45	99	5f	92
7	4f	4-CN	II	10	-45	95	5f	94 ^e
8	4f	4-CN	II	12	-45	95	5f	86 ^f
9	4g	2-Br	IV	15	-45	96	5g	91
								(>99)
10	4h	2-Cl	IV	15	-45	94	5h	91
								(>99)
11	4i	2-F	IV	8	-45	99	5i	>99
12	4i	2-F	IV	16	-45	97	5i	96 ^e
13	4i	2-F	IV	19	-45	94	5i	94 ^f
14	4j	2,4-F ₂	IV	4	-45	92	5j	98
15	4j	2,4-F ₂	IV	10	-45	93	5j	98 ^e
16	4j	2,4-F ₂	IV	14	-45	94	5j	90 ^f
17	4k	2,5-F ₂	IV	3	-45	95	5k	97
18	41	4-Br,2-F	IV	5	-45	99	51	>99
19	4m	5-Br,2-F	IV	3	-45	98	5m	97
20	4n	3,4-Cl ₂	IV	9	-45	99	5n	89
21	4o	-	IV	72	-30	99	50	90
								(>99)
22	4p	-	II	72	-30	91	5p	88
23	4q	-	IV	96	-30	93	5q	93
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^{*a*}Reactions performed at 0.5 mmol scale using 10 mol% catalyst loading. ^{*b*}Isolated yield after column chromatography. ^{*c*}Determined by HPLC on chiral stationary phases. In parentheses, ee after a single crystallization. ^{*d*}GC yield. ^{*e*}Catalyst loading 5 mol%. ^{*f*}Catalyst loading 2 mol%.

aryl group: electron-rich derivatives 4c-e required long reaction times for completion (entries 2-5). On the other hand, substrates 4f-n carrying electron-withdrawing groups reacted much faster, reaching completion in shorter times, even at -45 °C (entries 6-20). The high reactivity shown in these cases made it possible to reduce the catalyst loading to 5 mol% without compromising the selectivity nor the chemical yield, as shown for representative cases 4f, 4i, and 4j (entries 7, 13, and 15). Further reduction of the catalyst loading to 2 mol% still gave good results for 4i (entry 13), but the enantioselectivity dropped slightly for 4f and 4j (entries 8 and 16). It is noteworthy that nearly perfect enantioselectivities were observed for ortho-fluorinated substrates 4i-m, giving practically enantiopure derivatives 5i-m (98 to >99% ee). Finally, 2naphthyl, 2-thienyl, and 8-isoquinolyl glyoxylates 40-q were used as representatives of bicyclic and heteroaromatic substrates, affording also the expected products 50-q in good yields and high enantioselectivities for reactions carried out at -30 °C (entries 21-23).

Some of the products **5** proved to be fairly crystalline, and this circumstance was exploited to obtain essentially pure





enantiomers of the *p*-anisyl (5d), *o*-bromo (5g), *o*-chloro (5h), and 2-naphthyl (5o) derivatives after a single crystallization (entries 4, 9, 10, and 21). In the case of (R)-**5h**, the available Xray-quality crystals were used to determine the absolute configuration of the newly created stereogenic center (see Supporting Information).

The divergent stereochemical results obtained with bisthiourea catalysts III/V and bis-urea analogues II/IV suggest that different activation modes are involved in both cases. Considering the close structural similarity between both types of catalysts, the higher hydrogen donor-acceptor capability of the oxygen in the carbonyl group of catalysts II/IV appears as one of the fundamental (and obvious) differences.¹⁷ Consequently, it was suggested that one of the urea carbonyl groups in these catalysts might serve as a H-bond acceptor for the hydrazone NH group, providing an additional interaction that could hardly be effected by bis-thiourea derivatives III/V.¹⁸ This hypothesis led to the proposal of a stereochemical model where the second urea moiety activates the carbonyl substrate 4 in a ternary complex A, which is preorganized for the attack of the azomethine carbon to the Re face of the ketone carbonyl, leading to a zwitterionic intermediate B that releases the product 5a and the catalyst II or IV (Scheme 3).

The proposed formation of an NH···O hydrogen bond is expected to increase the electron density in the conjugated hydrazone system, so the nucleophilicity of the azomethine carbon should be enhanced. This bifunctional mode of activation would therefore explain the better catalytic activity and selectivity of II and IV as the result of the cooperative interactions shown and the highly ordered reactive complex resulting from the dual activation. Additional experimental support for this model was collected from NMR experiments. Thus, ¹H NMR spectra recorded for 3 in the presence of increasing amounts of catalyst II show the azomethine protons shifted upfield ($\Delta\delta$ up to -0.07 ppm at a 1:1 ratio, see Supporting Information for details), as expected from a higher electron density at the azomethine carbon. Additionally, the

Scheme 3. Proposed Catalytic Cycle and Stereochemical Model



Figure 2. Hybrid thiourea-urea bifunctional catalyst VI.

depicted model A suggests the participation of one of the acidic ortho CH bonds of the bis- $(CF_3)C_6H_3$ groups in a H-bond network that places the bulkier aromatic group of the substrate away from the more hindered inner region of the catalyst. In agreement with this hypothesis, the chemical shifts of these protons in the ¹H NMR spectrum of II are affected by the addition of increasing amounts of 4a.¹⁹ Thus, after an initial upfield shift observed upon addition of 0.25 equiv of 4a,²⁰ the chemical shifts of these protons were progressively shifted downfield upon further addition of 4a ($\Delta\delta$ up to 0.1 ppm at a 1:4 II/4a ratio).

Further support for the proposed dual mode of activation was collected from hybrid thiourea-urea catalyst VI (Figure 2). Assuming that just one good H-bond acceptor moiety is required to activate the hydrazone 3, this hybrid catalyst VI should behave as II/IV, not as III/V. In fact, the enantioselectivity reached with this catalyst matched that obtained with the bis-urea II, affording the product with similar enantiomeric excess (88% ee at -30 °C) and in a slightly shorter reaction time of 64 h, which accounts for the slightly better H-bond donor properties of the thiourea moiety.

To demonstrate the announced formyl anion equivalence of reagent 3, representative products 5a,d,i,o,p were transformed into the corresponding aldehydes 6a,d,i,o,p via a tautomerization/hydrolysis sequence efficiently accomplished by simple treatment with HCl in a biphasic H₂O/Et₂O medium (Scheme 4).

Crude aldehydes **6** did not resist chromatographic purification but were isolated with a high degree of purity (estimated by ¹H NMR). Moreover, treatment of these crude products with Bu_4NBH_4 afforded diols **7a,d,i,o,p** in good overall yields, and the structure of crystalline derivative (*R*)-**7p** supported a uniform stereochemical pathway. Additionally,

Scheme 4. Functional Group Transformations from 5



crude 6a was also used in Wittig reactions with stabilized ylides to afford enone 8 or a mixture of unsaturated ester 9 and lactone 10, with good overall yields in both cases. Finally, the acid-catalyzed tautomerization of 5a afforded *tert*-butyl hydrazone 11 in 81% yield.

In summary, the use of 1,1'-binaphthyl-derived bis-ureas as the catalysts enabled the highly enantioselective addition of *tert*butyl hydrazone to aromatic α -keto esters for the synthesis of densely functionalized tertiary carbinols. It is worth noting that, despite the apparent simplicity, products **6** are virtually unknown. This is particularly surprising in light of the presence of this type of functionalized tertiary carbinols as the core structures of pharmacologically relevant compounds such as Anisodine, and marketed antifungal drugs such as Voriconazole (VFEND) and Posaconazole (NOXAFIL). Experimental evidence suggests that the bifunctional H-bond donor/Hbond acceptor character of the catalysts appears to be key for the dual activation of the reactants, leading to enantioenriched products via a highly ordered complex that explains the observed stereochemistry.

ASSOCIATED CONTENT

S Supporting Information

Experimental details and characterization data; CIF data for (R)-**5h** and (R)-**7p**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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