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

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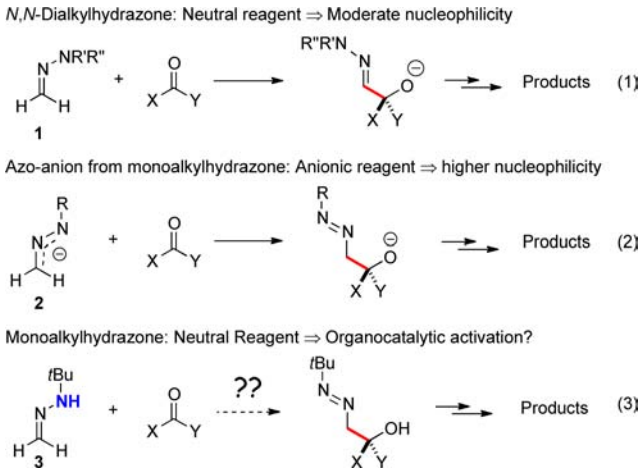
Supporting Information

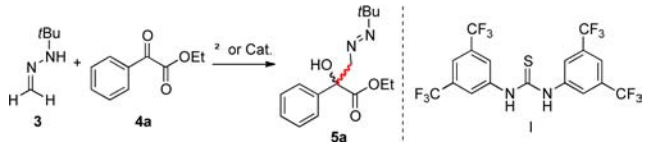
ABSTRACT: The dual activation of α-keto esters and formaldehyde *tert*-butyl hydrazone by BINAM-derived bis-ureas is the key to achieve high reactivity and excellent enantioselectivities in nucleophilic addition (formal carbonyl-ene reaction) to functionalized tertiary carbinols. Ensuing high-yielding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

The 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 **1** has been exploited for the functionalization of diverse electrophiles,[4] including carbonyl compounds such as aldehydes,[5] trifluoromethyl ketones,[6] and α-keto esters[7] (Scheme 1, eq 1). The development of catalytic asymmetric approaches based on chiral Lewis acids is problematic because of the tendency of these reagents **1** to bind acidic metals and undergo 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 imines[9] 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**.

Scheme 1. Hydrazone-Based Formyl Anion Equivalents



Scheme 2



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

Received: May 29, 2012
Published: July 23, 2012

   dx.doi.org/10.1021/ja305209w | J. Am. Chem. Soc. 2012, 134, 12912−12915

Table 1. Thermal and Catalytic Reaction of 3 with Keto Ester 4a[a]

entry	cat.	t (h)	T (°C)	yield (%)[b]	ee (%)[c]
1	-	24	rt	78	-
2	**I**	9	rt	90	-
3	-	24	-15	<5	-
4	**I**	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[d,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. [e]Yield estimated by ^{1}H NMR of the crude reaction mixture. [f]Major enantiomer eluted second. [g]Reaction performed at 4 mmol scale.

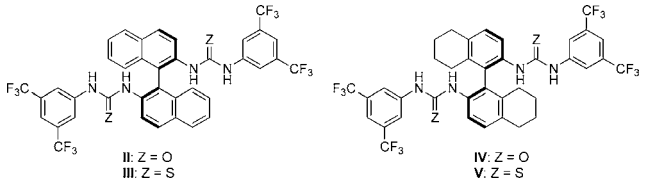
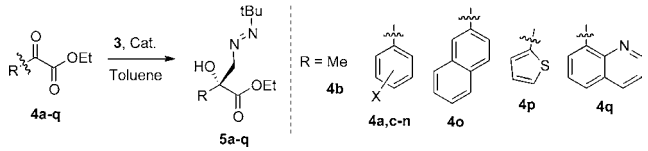


Figure 1. BINAM-derived bis-ureas and bis-thioureas.

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

Table 2. Catalytic Additions of 3 to α-Keto Esters 4a−q[a]



entry	**4**	X	cat.	t (h)	T (°C)	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	**4l**	4-Br,2-F	**IV**	5	-45	99	**5l**	>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	**5o**	90 (>99)
22	**4p**	-	**II**	72	-30	91	**5p**	88
23	**4q**	-	**IV**	96	-30	93	**5q**	93

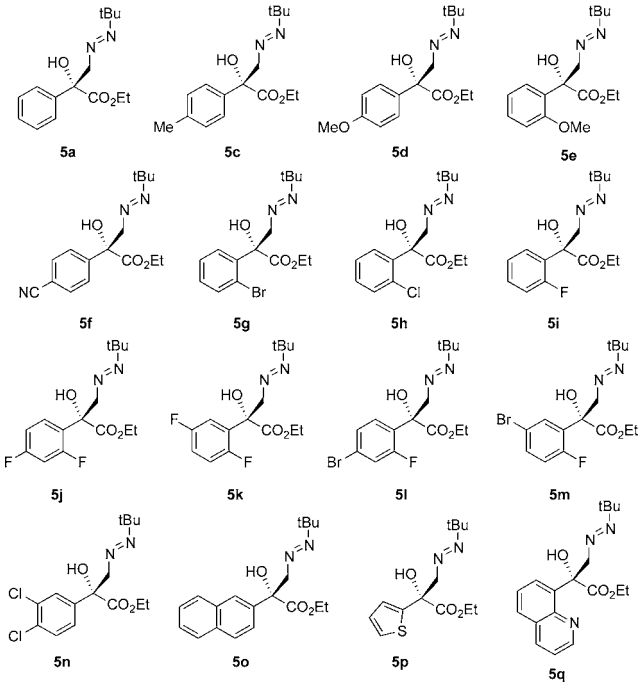
[a]Reactions performed at 0.5 mmol scale using 10 mol% catalyst loading. [b]Isolated yield after column chromatography. [c]Determined by HPLC on chiral stationary phases. In parentheses, ee after a single crystallization. [d]GC yield. [e]Catalyst loading 5 mol%. [f]Catalyst loading 2 mol%.

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, 2-naphthyl, 2-thienyl, and 8-isoquinolyl glyoxylates **4o−q** were used as representatives of bicyclic and heteroaromatic substrates, affording also the expected products **5o−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

dx.doi.org/10.1021/ja305209w | J. Am. Chem. Soc. 2012, 134, 12912−12915

Chart 1. Structures of Products 5a,c−q

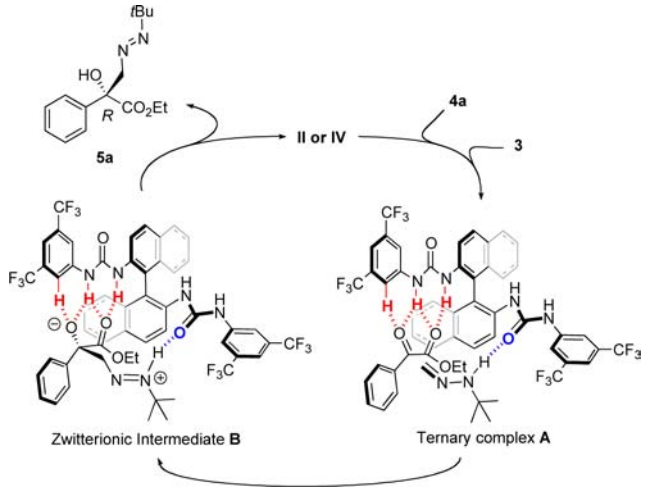


enantiomers of the *p*-anisyl (**5d**), *o*-bromo (**5g**), *o*-chloro (**5h**), and 2-naphthyl (**5o**) derivatives after a single crystallization (entries 4, 9, 10, and 21). In the case of (*R*)-**5h**, the available X-ray-quality crystals were used to determine the absolute configuration of the newly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

The divergent stereochemical results obtained with bis-thiourea 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, ^{1}H 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



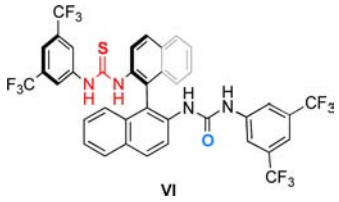


Figure 2. Hybrid thiourea−urea bifunctional catalyst **VI**.

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 ^{1}H 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 shitfs 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).

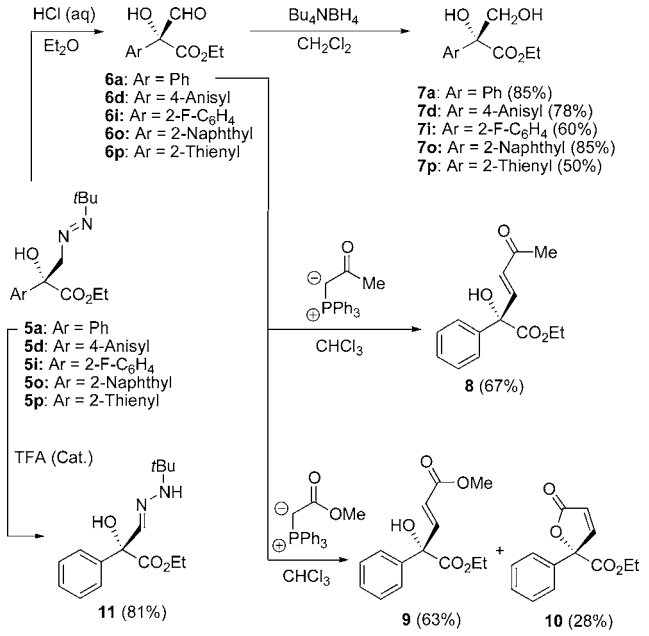
Further support for the proposed dual mode of activation was collected from hybrid thiourea−urea catalyst **VI** (Figure 2). Assuming that just one good H-bond acceptor moiety is required to activate the hydrazone **3**, this hybrid catalyst **VI** should behave as **II**/**IV**, not as **III**/**V**. 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 slighty 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 H_2O/Et_2O medium (Scheme 4).

Crude aldehydes **6** did not resist chromatographic purification but were isolated with a high degree of purity (estimated by ^{1}H 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,

dx.doi.org/10.1021/ja305209w | J. Am. Chem. Soc. 2012, 134, 12912−12915

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/H-bond 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

Ⓢ 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.

■ ACKNOWLEDGMENTS

Dedicated to Prof. Miguel Angel Miranda on the occasion of his 60th birthday. We thank the Spanish "Ministerio de Ciencia e Innovación" (grants CTQ2010-15297 and CTQ2010-14974), the European FEDER funds, and the Junta de Andalucía (grants 2008/FQM-3833 and 2009/FQM-4537) for financial support. A.C.-P. thanks CSIC for a JAE predoctoral fellowship. D.M. acknowledges a "Juan de la Cierva" contract.

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