ENANTIOSELECTIVE, NUCLEOPHILIC CARBENE-CATALYZED REACTIONS OF ACYL ANION EQUIVALENTS

Reported by Michelle M. Adams October 4, 2004

INTRODUCTION

Nontraditional bond disconnections become available by reversing the alternating donor-acceptor reactivity pattern imposed by heteroatoms. This inversion of a normal reactivity pattern is described as "umpolung."[1] Change of polarity is achieved by a temporary heteroatom modification that imparts opposite electronic character on an adjacent carbon. The reversal of the normally electrophilic reactivity of aldehydes is commonly effected though intermediates such as cyanohydrin or dithiane, which function as a nucleophilic acyl anion equivalents after deprotonation at the modified carbonyl carbon.

Asymmetric carbon-carbon bond forming reactions using umpolung chemistry are found in nature. Vitamin B_1 (**1**) functions as a cofactor for thiamin diphosphate-dependent enzymes, including transketolase, pyruvate decarboxylase, and acetolactate synthase, to catalyze the formation of stabilized acyl anion intermediates.[2]

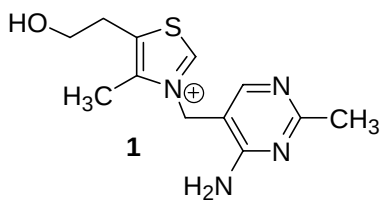

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Figure 1. Thiamin, Vitamin B_1

Umpolung chemistry of the carbonyl carbon is also featured in several familiar organic reactions that create new carbon-carbon bonds.[3,4] One of the oldest known reactions in organic chemistry, the cyanide-catalyzed benzoin condensation, employs this mode of reactivity. Ugai[5] and Breslow[4] have shown that under basic conditions, the benzoin condensation can also be catalyzed by thiazol-2-ylidenes by a mechanism analogous to that of thiamin diphosphate in nature. Unlike classic cyanide catalysis, nucleophilic carbene catalysis can be used with enolizable aldehyde substrates because of the mildly basic reaction conditions. In addition, high enantioselectivities and yields can be obtained using an asymmetric variant. Stetter[6] extended nucleophilic carbene catalysis to the reaction of acyl anion equivalents with activated Michael acceptors. This review covers the recent application of nucleophilic carbene catalysis to the enantioselective benzoin condensation and to the related enantioselective intramolecular Stetter reaction.

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NUCLEOPHILIC CARBENES

Although carbenes have been defined classically as reactive intermediates containing a neutral divalent carbon atom, nucleophilic Wanzlick-type carbenes (Figure 2) can be drawn with zwitterionic resonance forms and often are often referred to as ylides. Electron-donating substituents convert the naturally electrophilic carbene to a nucleophilic species. The mesomeric and inductive effects of these donor heteroatoms in nucleophilic carbenes bestow unique stability to this class of carbenes and dictate singlet ground state multiplicity. In the case of carbenes of types **3**, **4**, and **5**, the dipolar resonance structures also illustrate the aromatic stabilization of the heterocycle.

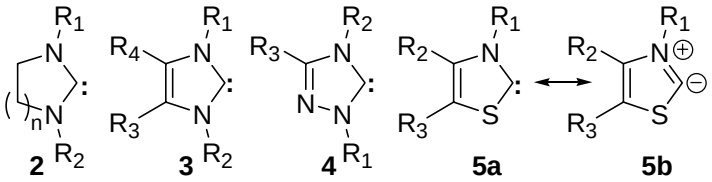
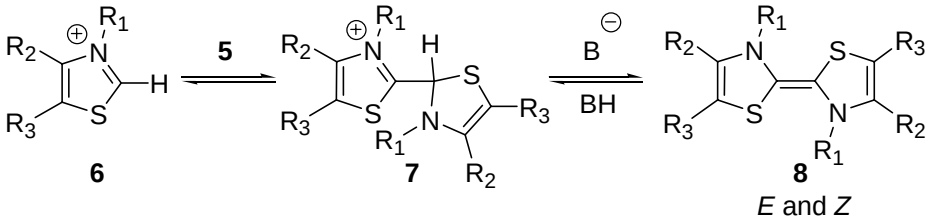


Figure 2. Nucleophilic carbenes: cyclic diaminocarbenes **2**, imidazol-2-ylidenes **3**, 1,2,4-triazol-3-ylidenes **4**, and 1,3-thiazol-2-ylidenes **5**

Known since the 1960's, persistent nucleophilic carbenes are usually generated *in situ* from the deprotonation of the air-stable heterazolium salts with weak bases. In 1991 Arduengo isolated an example of imidazolylidene **3** as a crystalline, thermally stable "carbene in a bottle." Subsequently, many other Wanzlick-type singlet carbenes have been isolated that are stable under anaerobic conditions.[7] Whereas nucleophilic carbenes demonstrate carbene-like character in insertion reactions, the extent of the carbene versus ylide nature of these species is disputed.[7] Under certain conditions, these species exhibit the nucleophilic reactivity of ylides. For example, in the presence of a base and in the absence of other electrophiles, solvated thiazolium salt **6** (Scheme 1) undergoes self-condensation to form bithiazolylidene **8** in nearly equal mixtures of *E*- and *Z*-geometrical isomers. These dimers do not form by direct addition of two carbene molecules, as confirmed by the spectroscopic observation of the unsymmetrical intermediate **7**.[8] Crossover experiments indicate that

Scheme 1.



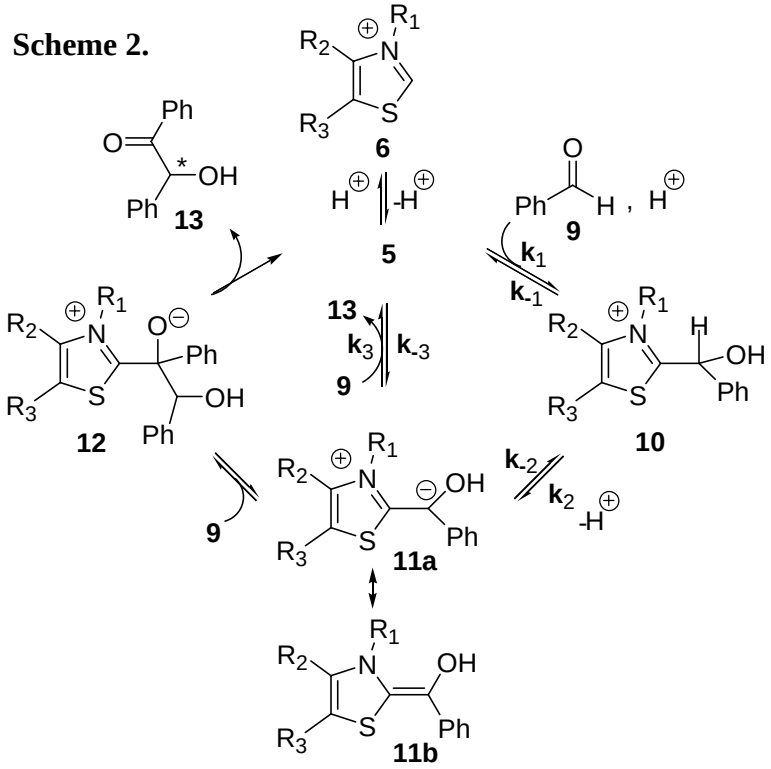
bithiazolylium **7** forms by nucleophilic addition of the ylide **6** to its conjugate acid rather than by carbene insertion of **5** into the C-H bond of **6**.[8]

BENZOIN CONDENSATION

Mechanism

Breslow[2] proposed a model for the thiamin-catalyzed benzoin condensation, which was inspired by the mechanism for the corresponding cyanide-catalyzed transformation.[9] As shown in Scheme 2, deprotonation of the thiazolium salt **6** generates the active catalyst **5**, and nucleophilic addition of ylide **5** to benzaldyde (**9**) provides, after deprotonation, the resonance-stabilized enolamine **11**, which is referred to as the Breslow intermediate. The acyl carbanion equivalent **11** adds to a second equivalent of benzaldehyde to form diphenylhydroxy thiazoium adduct **12**, which collapses to release benzoin **13** and regenerate thiazolylidene **5**.

Scheme 2.



Challenges to Breslow's well-accepted mechanism assert that dimer **8** is the active catalytic species in the benzoin condensation. However, several experimental observations support the original Breslow mechanism. For example, the benzoin reaction can be catalyzed by thiamin **1** bound in the macrocyclic cavity of cyclophanes[10] where thiazolium dimerization is unlikely to occur. Spectroscopic studies by Jordan[15] contradict claims by Castells, López-Calahorra,[11,12,13] and Metzger[14] that the benzoin condensation cannot proceed following complete conversion of the precatalyst **6** to dimer **8** under rigorously anhydrous conditions. When base is added to the precatalyst in the presence of excess benzaldehyde acceptor, Breslow intermediate **11** is formed, but no bis(thiazolin-2-ylidene) **8** is detected by ^{13}C NMR. Finally, kinetic studies of the benzoin condensation by Breslow[16] show first order dependence on the concentration of thiazolium salt and refute literature claims of second order dependence.[17]

KINETIC STUDIES

A more thorough investigation of the kinetic parameters of the thiazolium-catalyzed benzoin condensation was reported by Leeper.[18] Initial-rate studies at low catalyst concentration and varying concentrations of benzaldehyde show that the benzoin reaction displays approximately first order dependence on benzaldehyde. At stoichiometric catalyst concentrations, the rate constants are calculated by monitoring reaction component concentrations using ^{1}H NMR. Under a simplified kinetic model of the benzoin condensation (Scheme 2), each of the three key steps is partially rate determining: the attack of the ylide **5** on the first molecule of benzaldehyde (k_1/k_{-1}), the deprotonation of hydroxybenzyl thiazolium **10** to form enolamine **11** (k_2/k_{-2}), and the attack of this enolamine **11** on the second equivalent of benzaldehyde with subsequent benzoin formation (k_3/k_{-3}).

ENANTIOSELECTIVE BENZOIN CONDENSATION

The search for enantioselective variants of thiazolium-catalyzed reactions is a current area of active research. The first reported asymmetric benzoin condensation employed thiazolium salt **14**[20] as the precatalyst and afforded benzoin in 76:24 e.r. and 6% yield.[19] Other chiral thiazolium salts, including those with conformationally-locked cyclic stereogenic centers, give little improvement in asymmetric induction.[21,22]

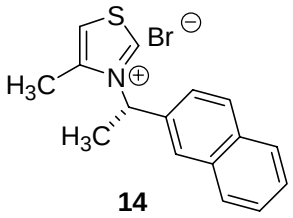


Figure 3. The Sheehan precatalyst **14**[20]

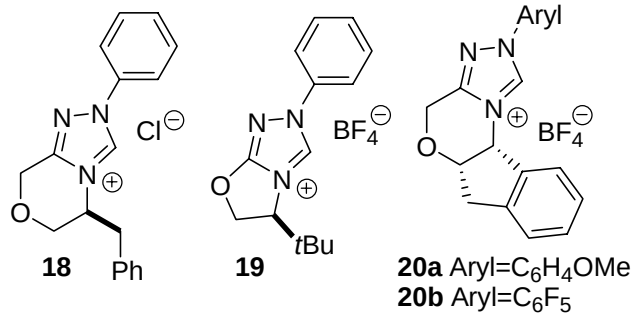


Figure 4. The chiral triazolium salts **18**,[24] **19**,[25] and **20**[29,31]

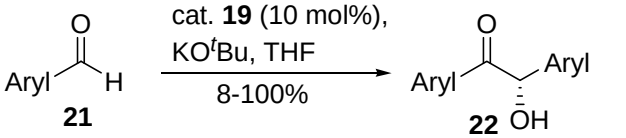
Ender's use of triazolium salts is a breakthrough in the development of chiral, non-metal catalysts for nucleophilic aldehyde activation.[23] The incorporation of an additional nitrogen atom in the heterocyclic ring gives improved catalytic activity and selectivity with decreased catalyst loading. Triazolium catalysis also expands the benzoin condensation scope to include aryl aldehydes other than benzaldehyde.

The conformationally rigid dihydro-oxazinotriazolium salt **18** developed by Leeper gives enantioselectivities up to 91:9 e.r. for the condensation of aryl aldehydes.[24] Dihydro-oxazolotriazolium salt **19** gives enantiomeric ratios as high as 97:3 under Ender's optimized

conditions (Scheme 3).[25] The best enantioselectivities are observed for electron-rich aldehydes, but good asymmetric induction with electron-poor aldehydes can be realized by reducing the reaction temperature to 0 ºC. Condensation of benzaldehydes with electron donating *para*-substituents proceeds in diminished yields.

The enantioselective benzoin condensation has been optimized for *R*- and *S*-configured benzoins. However, unsolved synthetic challenges still remain. The condensation of aliphatic aldehydes proceeds only with poor selectivities.[27] No examples of non-enzymatic asymmetric-cross benzoin reaction and enantioselective benzoin-type condensations of imines have been reported. The synthesis of preanthraquinones[28] through an intramolecular cross-benzoin reaction illustrates that ketones can also serve as electrophiles in benzoin-type condensations and that stereoselective benzoin-type carbonyl couplings are feasible on more complex structural scaffolds.

Scheme 3.[3]



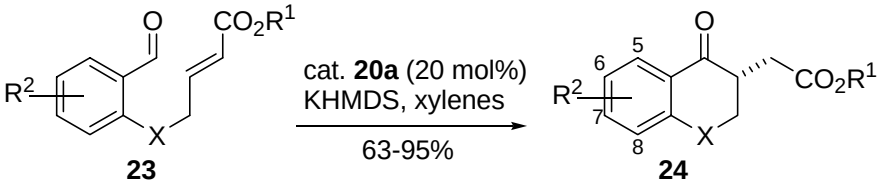
e.r = 90:10 - 95:5

Aryl = 4-Br-Ph, 4-Cl-Ph, 4-F-Ph, 3-Cl-Ph, 3-Me-Ph, 4-Me-Ph, 4-MeO-Ph, 2-Furyl, 2-Naphthyl, Ph

STETTER REACTION

Concurrent with their research on the asymmetric benzoin condensation, Enders provided the first example of a non-enzymatic enantioselective intermolecular Stetter reaction catalyzed by thiazolium.[23] However, this method suffers from the low catalytic activity and selectivity that characterizes the thiazolium-catalyzed benzoin condensation.[3] A highly enantioselective, intermolecular Stetter reaction remains elusive. A problem may be the competitive addition of triazolium carbenes to activated alkenes to form stable adducts.[7]

Scheme 4.[3]



R^1 = Me, Et
R^2 = 6-Me, 8-Me, 8-MeO
X = O, S, NMe

e.r. = 91:9 - 98:2

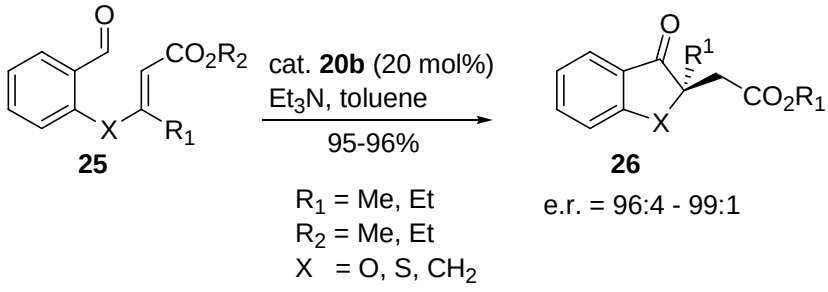
In contrast to the intermolecular reactions, the enantioselective intramolecular Stetter reaction has been quite successful. Enders *et al.* employed triazolium salts with chiral *N*-substituents to effect the first asymmetric intramolecular Stetter reaction in 70:30 – 87:13 e.r. and 22-73% yield.[3] Rovis, *et al*. dramatically improved the yields and

enantioselectivities of the intramolecular Stetter reaction by using the conformationally-locked chiral triazolium precatalysts **20** (Scheme 4).[29]

The enantioselective intramolecular Stetter reaction is sensitive to the nature of the activating group as the electrophilicity of the Michael acceptor greatly affects reactivity and selectivity.[30] The scope of reactivity is limited to *E*-configured Michael acceptors with an appropriate level of activation, i.e., less activated than α,β-unsaturated nitro compounds and more activated than α,β-unsaturated amides. The reaction scope extends to aryl and aliphatic substrates, although rotational freedom of the linker connecting the aldehyde with the Michael acceptor diminishes the magnitude of the enantioselectivity of non-aryl substrates. Formation of 5- and 6-membered rings are possible in good yields and excellent enantioselectivites.

Quaternary stereogenic centers can be created using this catalytic, intramolecular, asymmetric Stetter reaction in the annulation of aldehydes and β,β-disubstituted Michael acceptors (Scheme 5). Whereas electron-rich precatalyst **20a** promotes the formation of benzofuranone products **26** with excellent enantioselectivities, the yields are modest. Interestingly, the electron-poor catalyst **20b** effects this same transformation in 85% yield without loss of selectivity. This change in catalyst electronic preference may be caused by slight mechanistic differences for doubly □-substituted Michael acceptors.[31] Additionally, replacement of KHMDS with triethylamine results in dramatic yield improvements for aromatic substrates with little cost to enantioselectivity. Triazolium salt **20b** also catalyzes the formation of aliphatic cyclopentanones bearing α-quaternary centers in 84-99% ee and 63-90% yield.

Scheme 5.[31]



CONCLUSION

Chiral nucleophilic carbenes catalyze the benzoin condensation and the intramolecular Stetter reaction in good yields and excellent enantioselectivities. This catalytic method holds promise for greater versatility because the precatalyst substituents can be tuned to optimize the yield and asymmetric induction of a specific substrate class. Nucleophilic carbene catalysis may offer new reaction pathways involving acyl anion equivalents beyond the benzoin condensation and the

mechanistically similar Stetter reaction. Indeed, this umpolung reactivity has recently been applied to synthesis of imidazoles[32] and pyrroles,[33] and to transesterification, and acylation.[34]

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