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N-Heterocyclic Carbene-Catalyzed Annulation of α-Cyano-1,4-diketones with Ynals

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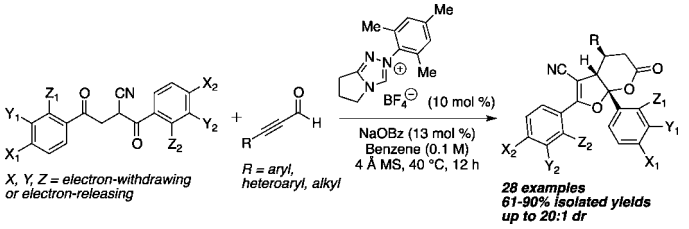
ABSTRACT



In this paper, the first stereoselective annulation reaction between α-cyano-1,4-diketones and ynals, mediated by catalytic amounts of a triazolium salt precatalyst and cocatalytic amounts of a weak carboxylate base, is disclosed. The title transformation proceeds smoothly under mild reaction conditions and generates three contiguous stereogenic centers, one of which is a quaternary acetal carbon. This reaction tolerates a wide variety of electronically distinct substituents on both reaction partners and affords privileged bicyclic scaffolds in 61−90% isolated yields and with up to 20:1 diastereomeric preference.

A thiamine diphosphate (vitamin B_1) derived α,β-unsaturated acylazolium ion was recently shown to be an intermediate in the biosynthesis of clavulanic acid, a potent β-lactamase inhibitor.[1] The use of transiently formed α,β-unsaturated acylazolium species to conduct modern organocatalytic transformations has gained wide popularity in the course of the past decade. The most commonly used method to access these key intermediates relies on internal redox activation of α-oxidizable aldehydes with *N*-heterocyclic carbenes.[2] Stemming from the seminal works of Lupton et al.[3] and Bode et al.,[4] many enolizable compounds were used as nucleophiles to trap catalytically formed α,β-unsaturated acylazoliums. Among which, 1,2-dicarbonyl,[4] 1,3-dicarbonyl,[5] vinylogous amides,[6] and oxindoles[7] are of particular importance. All of the title NHC-catalyzed reactions afforded (spiro)annulated products based on the dihydropyranone skeleton. Moreover, very recent mechanistic and theoretical studies further emphasize the utility of NHC-derived α,β-unsaturated acylazolium ions as reactive intermediates in organic synthesis.[8]

Acetals, molecular substructures that contain two oxygen atoms bound to the same sp^3-hybridized carbon atom, represent a ubiquitous motif widely found in natural

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products of insecticidal,[9] bacterial,[10] and marine[11] origins. The acetal subunit is equally important in pharmacologically relevant compounds.[12] Most importantly, *ring-junction* acetals are widely present in the ginkgolide class of spongiane terpenoids, namely, paeonilide,[13] bilobalide,[14] gracilins B and C,[15] specionin,[16] and udoteatrial hydrate.[17] To the best of our knowledge, a NHC-catalyzed process leading to the formation of ring-junction acetals has not been reported so far.

Inspired by these facts and as part of our ongoing program to explore multistep (domino) chemical transformations mediated by NHCs as organocatalysts, we envisioned that the combination of a catalytically generated α,β-unsaturated acylazolium ion **1** with an α-cyano-1,4-diketone **3** would lead to the formation of a 4,5-dihydro 3*H*-(furo)pyran-6-one of the type **5**, with three contiguous stereogenic centers (see Scheme 1). This idea was based on the assumption that **3** could react with **1** through the intermediacy of its bis-enol form. The behavior of these species vis-à-vis **1** was based on the premise that related bis-enolates prefer to react with electrophiles through their least conjugated terminus.[18] If proven successful, this strategy offered a facile access to highly functionalized 5,6-fused ring acetals that may furnish promising candidates for drug discovery. Herein, we wish to report our preliminary results in this field.

Scheme 1. NHC-Catalyzed Annulation of Ynals with α-Cyano-1,4-dicarbonyl Compounds **3**

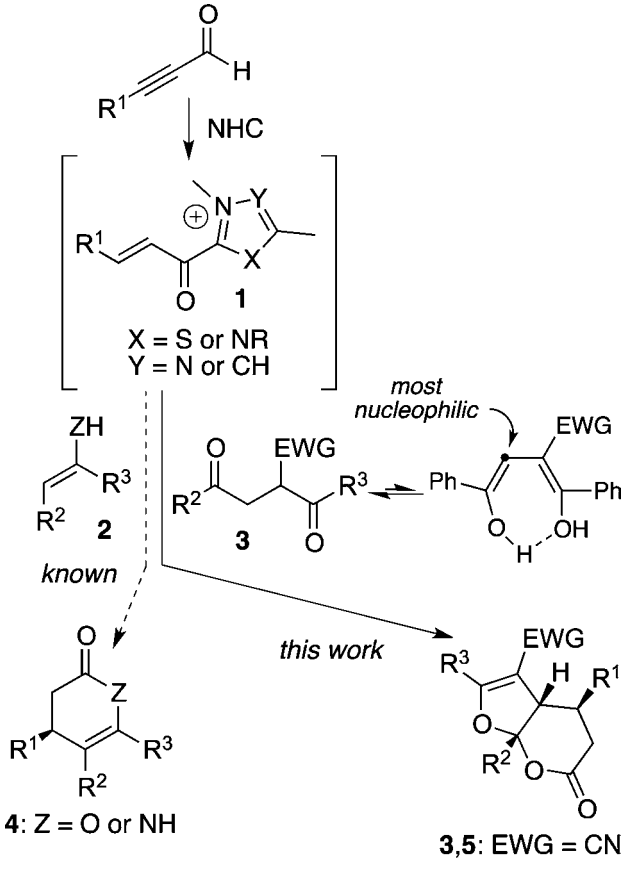
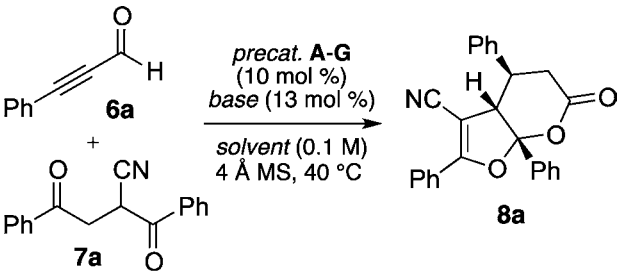
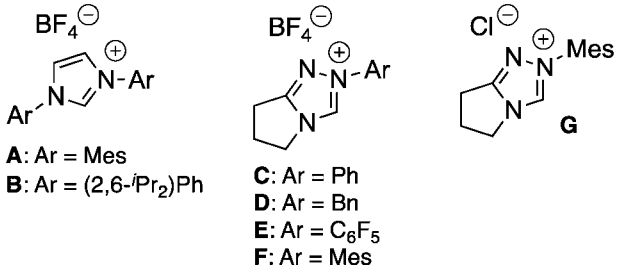


Table 1. Selected Optimization Studies[19]





entry	precat.	solvent	base	*dr*[b]	yield[c] (%)	yield *mjr.*[d] (%)
1[a]	**A**	toluene	Cs_2CO_3	5:9	33	–
2	**B**	toluene	Cs_2CO_3	–	0	0
3	**C**	toluene	Cs_2CO_3	7:2	56	29
4	**D**	toluene	Cs_2CO_3	2:1	29	–
5	**E**	toluene	Cs_2CO_3	9:5	40	12
6	**F**	toluene	Cs_2CO_3	9:1	80	56
7	**G**	toluene	none	9:1	79	59
8	**F**	toluene	$^iPr_2NEt$	9:1	73	52
9	**F**	toluene	NaOAc	>9:1	88	66
10	**F**	toluene	NaOBz	7:1	84	65
11	**F**	THF	NaOBz	10:1	80	63
12	**F**	dioxan	NaOBz	16:1	53	38
13	**F**	DCE	NaOBz	8:3	83	57
14	**F**	MeCN	NaOBz	3:2	57	24
15	*F*	C_6H_6	*NaOBz*	*12:1*	*86*	*67*
16	**F**	C_6H_5F	NaOBz	10:1	70	46

[a] Reaction conditions: 1,4-diketone **7a** (0.30 mmol, 1.0 equiv), ynal **6a** (0.36 mmol, 1.2 equiv), azolium salt **A-G** (0.03 mmol, 10 mol %), base (0.04 mmol, 13 mol %), 4 Å molecular sieves (300 mg), and solvent (3.0 mL, 0.1 M) were stirred at 40 °C for 12 h. [b] Determined by ^1H NMR analysis of unpurified reaction mixtures. [c] Isolated yields after flash chromatography on silica gel. [d] Isolated yields of the major diastereomer after recrystallization from methanol.

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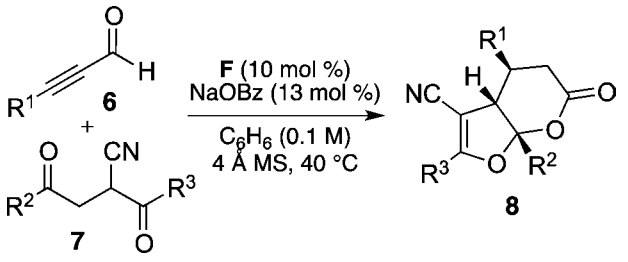
Table 2. Scope of the Reaction between Ynals **6** and α-Cyano-1,4-diketones **7**



entry	R^1, **6**	R^2, R^3, **7**	**8**	*dr*[b]	yield (%)[c]	yield *mjr.* (%)
1[a]	Ph, **a**	Ph, Ph, **a**	**a**	12:1	86	67[d]
2	Ph, **a**	(4-F)Ph, (4-F)Ph, **b**	**b**	13:1	77	57[d]
3	Ph, **a**	(4-Cl)Ph, (4-Cl)Ph, **c**	**c**	12:1	77	54[d]
4	Ph, **a**	(4-Br)Ph, (4-Br)Ph, **d**	**d**	12:1	84	62[e]
5	Ph, **a**	(4-Me)Ph, (4-Me)Ph, **e**	**e**	17:1	80	63[e]
6	Ph, **a**	(4-CF_3)Ph, (4- CF_3)Ph, **f**	**f**	20:1	65	–
7	Ph, **a**	(3-Cl)Ph, (3-Cl)Ph, **g**	**g**	9:1	75	47[e]
8	Ph, **a**	(3-Br)Ph, (3-Br)Ph, **h**	**h**	9:1	70	50[e]
9	Ph, **a**	Ph, (4-F)Ph, **i**	**i**	12:1	80	59[d]
10	Ph, **a**	Ph, (4-Me)Ph, **j**	**j**	9:1	78	57[d]
11	Ph, **a**	Ph, (4-OMe)Ph, **k**	**k**	13:1	77	60[d]
12	Ph, **a**	(4-F)Ph, Ph, **l**	**l**	11:1	73	52[d]
13	Ph, **a**	(4-Me)Ph, Ph, **m**	**m**	10:1	80	57[d]
14	Ph, **a**	(4-OMe)Ph, Ph, **n**	**n**	20:1	69	54[d]
15	(4-F)Ph, **b**	Ph, Ph, **a**	**o**	11:1	61	54[e]
16	(4-Cl)Ph, **c**	Ph, Ph, **a**	**p**	9:1	77	58[e]
17	(4-Me)Ph, **d**	Ph, Ph, **a**	**q**	10:1	86	67[e]
18	(4-OMe)Ph, **e**	Ph, Ph, **a**	**r**	13:1	87	71[e]
19	(2-OMe)Ph, **f**	Ph, Ph, **a**	**s**	7:1	88	70[d]
20	(3-Cl)Ph, **g**	Ph, Ph, **a**	**t**	10:1	59	48[e]
21	2-furyl, **h**	Ph, Ph, **a**	**u**	12:1	77	47[e]
22	piperyl, **i**	Ph, Ph, **a**	**v**	8:1	82	63[d]
23	*c*-Pr, **j**	Ph, Ph, **a**	**w**	8:1	76	–
24	(4-OMe)Ph, **e**	Ph, (4-F)Ph, **i**	**x**	12:1	90	60[e]
25	(4-OMe)Ph, **e**	Me, Me, **o**	**y**	3:1	43	22[e]
26	Ph, **a**	(2-F)Ph, (2-F)Ph, **p**	**z**	<3:1	63	–
27	Ph, **a**	(2-Cl)Ph, Ph, **q**	*δ*	<5:2	47	–
28	*n*-Pent, **k**	Ph, Ph, **a**	*π*	7:1	47	–

[a] Reaction conditions: 1,4-diketone **7** (0.30 mmol, 1.0 equiv), ynal **6** (0.36 mmol, 1.2 equiv), azolium salt **F** (0.03 mmol, 10 mol %), NaOBz (0.04 mmol, 13 mol %), 4 Å molecular sieves (300 mg), and benzene (3.0 mL, 0.1 M) were stirred at 40 °C for 12 h. [b] Determined by ^{1}H NMR analysis of unpurified reaction mixtures. [c] Isolated yields after flash chromatography on silica gel. [d] Isolated yields of the major diastereomer after recrystallization. [e] The major diastereomer was isolated by silica gel chromatography. Piperyl = 1,3-benzodioxyl.

At the beginning of our studies, an optimized set of reaction conditions was established. To this end, we examined a model reaction between 3-phenylpropiolaldehyde **6a** (1.2 equiv) and α-cyano-1,4-diketone **7a** (1.0 equiv) in the presence of catalytic amounts of azolium salt precatalysts **A**−**G** (see Table 1). NHCs derived from imidazolium precursors **A** and **B** proved unsuitable for the title transformation, leading to either zero or poor conversion with concomitantly low diastereoselectivity (entries 1 and 2). Among the bicyclic triazolium precursors **C**−**F**, solely the mesityl-substituted salt **F** afforded the desired 4,5-dihydro-3*H*-(furo)pyran-6-one **8a** in good isolated yield (80%) and high diastereoselectivity (9:1 *dr*, entry 6). Further screening of various bases suggested NaOBz as the optimal one. Moreover, examination of several organic solvents such as THF; 1,4-dioxane; 1,2-dichloroethane; and acetonitrile did not improve the outcome of the reaction. Nevertheless, a slightly better result in terms of isolated yield and diastereoselectivity was obatained when using benzene as solvent (entry 15).

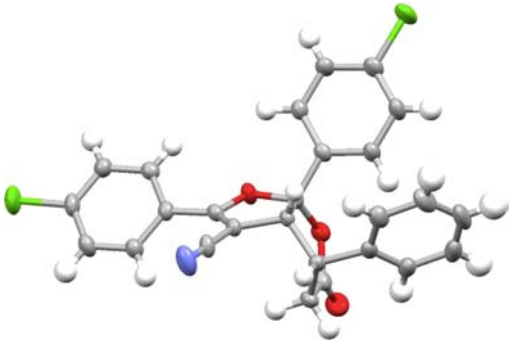
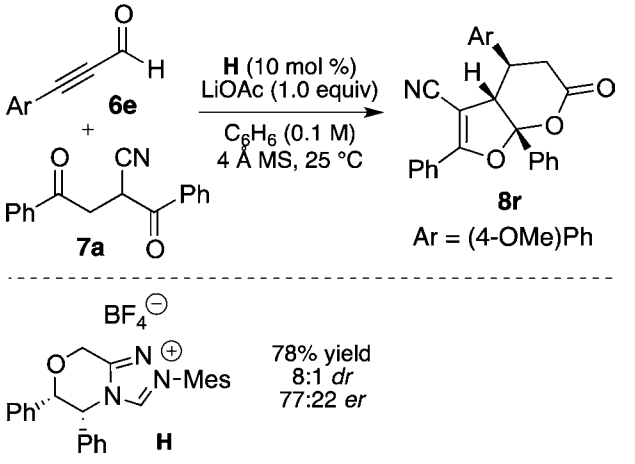


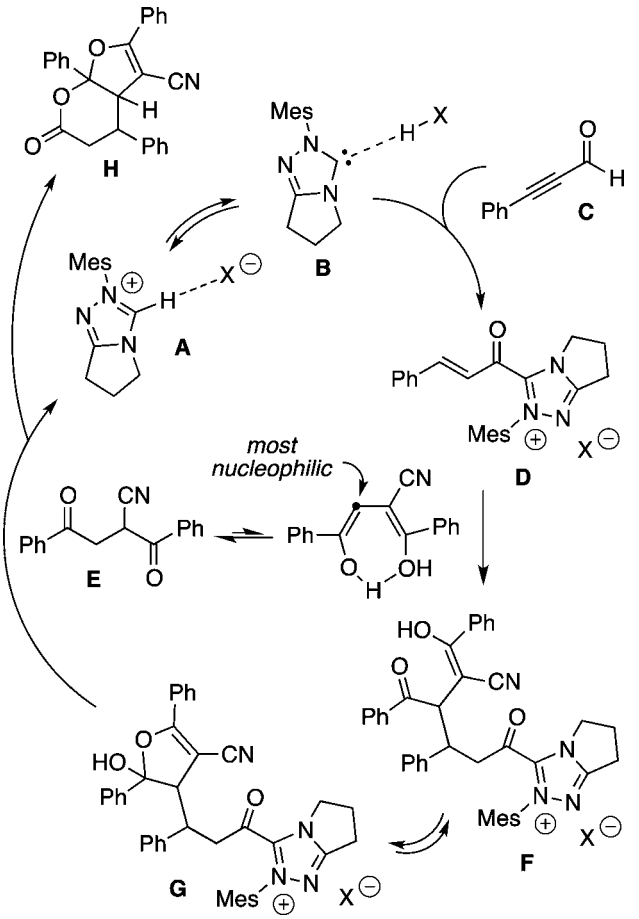
Figure 1. X-ray crystal structure of **8c**. Thermal ellipsoids are shown at the 50% probability level.

Scheme 2. Attempt at an Enantioselective Variant[a]



[a] Enantiomer ratio (*er*) was determined by chiral SFC analysis.

Scheme 3. Proposed Mechanism for NHC-Catalyzed Annulation of α-Cyano-1,4-diketones with Ynals



Interestingly, when triazolium *chloride* **G** was used as the carbene precursor the reaction took place in the absence of an added base, furnishing **8a** in comparably high yield and diastereoselectivity (entry 7). This observation is in accordance with recent literature precedence.[4] Finally, a single diastereomer of acetal **8a** could be recovered following a simple trituration/recrystallization from hot methanol.

With the optimal experimental conditions in hand, the scope of the reaction was studied next (see Table 2). We found that the reaction could accommodate a broad range of symmetrical and unsymmetrical, *para*- and *meta*-substituted α-cyano-1,4-diketones **7**, while maintaining high isolated yields (61−90%) and diastereoselectivities (up to 20:1 *dr*). Aromatic (**6a**−**g**), heteroaromatic (**6h**), and alkyl (**6j**) ynals proved to be suitable reaction partners, with no significant impact on the yields and diastereoselectivities. Unfortunately, in the case of *ortho*-substituted aromatic 1,4-diketones **7p** and **7q**, and the alkyl-substituted 1,4-diketone **7o**, a drop in yields and diastereoselectivities was observed.

The structure and the relative configuration of the annulation products were established by spectroscopy. Further confirmation came from X-ray crystallographic analysis of **8c** (see Figure 1).[19]

Of great importance, the title transformation proved to be amenable to asymmetric catalysis. Numerous preliminary attempts were made, and the best result thus far was obtained with the commercially available carbene precursor **H** and stoichiometric LiOAc as base (see Scheme 2).

A mechanistic rationalization for the NHC-catalyzed annulation of α-cyano-1,4-diketones with ynals is presented in Scheme 3. Initially, the free carbene **B**, generated by equilibrium deprotonation of the precursor salt **A**, condenses with a molecule of ynal **C** to form the key α,*β*-unsaturated acylazolium intermediate **D**. The direct conjugate addition of 1,4-diketone **E** to **D** presumably takes place at the most nucleophilic terminus of the bis-enol derived from **E**. Subsequent intramolecular H-migration gives adduct **F**, which probably exists in a reversible equilibrium with hemiacetal **G**. Finally, an irreversible lactonization furnishes the observed bicyclic product **H** and liberates **A** for the next catalytic cycle.

In conclusion, we have developed the first NHC-catalyzed domino reaction of α-cyano-1,4-diketones with ynals. The title transformation offers a high-yielding and stereoselective strategy for the synthesis of densely functionalized 4,5-dihydro-3*H*-(furo)pyran-6-ones, with three contiguous stereogenic centers. These privileged ring-junction acetal skeletons may be attractive drug candidates. Efforts on improving the enantioselectivity of this protocol are currently underway in our laboratory.

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Supporting Information Available. Detailed experimental procedures, complete optimization studies, spectroscopic characterization of newly synthesized compounds, and chiral SFC chromatograms for compound **8r**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) See Supporting Information for details.

The authors declare no competing financial interest.