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Phosphine-Catalyzed α-Umpolung–Aldol Reaction for the Synthesis of Benzo[*b*]azapin-3-ones

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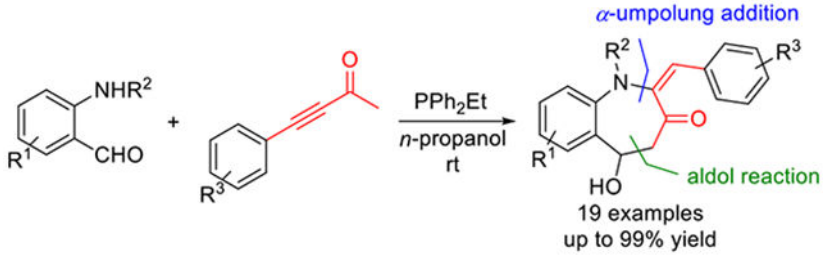
Abstract

A novel phosphine-catalyzed intermolecular cyclization between 2-sulfonamidobenzaldehyes and ynones is reported. This methodology serves as a conduit for the construction of benzo[*b*]azepin-3-ones in good to excellent yields under mild conditions. The resulting 2-benzylidene moieties are formed exclusively in the *E*-configuration. Mechanistically, this unusual annulation occurs through a phosphine-catalyzed α-umpolung addition, followed by an aldol reaction. One of the benzo[*b*]azepin-3-one products was converted to the core structure of 3-amino-[*a*]benzazepin-2-one-1-alkanoic acids, many of which function as angiotensin-converting enzyme inhibitors.

Graphical Abstract



Benzoazepines are structural motifs within a wide variety of biologically and pharmacologically significant compounds.[1] In particular, a benzo[*b*]azepine moiety is a core unit of several marketed tricyclic antidepressant drugs, including tienopramine, anafranil, amezepine, and imipramine (Figure 1).[2] Lotensin, which features a benzoazepine nucleus as the key subunit, is used in the treatment of hypertension, congestive heart failure, and heart attacks, and also to prevent the renal and retinal complications of diabetes.[3] Mozavaptan, which also possesses a benzoazepine skeleton, is an effective vasopressin V-2 receptor antagonist.[4] Despite their promising biological properties, benzo[*b*]azepines have drawn

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ASSOCIATED CONTENT

Supporting Information

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Experimental procedures and characterization data for all new compounds (PDF)

The authors declare no competing financial interest.

relatively little synthetic attention. Nevertheless, several methods have been described for the construction of benzo[*b*]azepines, including approaches through intramolecular Heck coupling,[5] iridium-catalyzed asymmetric allylic amination,[6] cyclizations of suitably substituted Morita–Baylis–Hillman adducts,[7] $FeCl_3^-$ and Au-catalyzed cyclizations of alkynes and alkenes,[8] Pd-catalyzed oxidative annulations of *ortho*-alkenylanilines and allenes,[9] and Pd- and Au-catalyzed ring-expansions of alkylidenecyclopropanes.[10] Despite the great potential of these methods, they require harsh reaction conditions and/or starting materials that are synthesized in several steps. In this regard, we became interested in developing new pathways for the synthesis of benzoazepines from readily available starting materials under benign reaction conditions.

Nucleophilic phosphine-catalyzed cyclizations have expanded chemical space by allowing access to a variety of carbo- and heterocycles.[11] While the use of electron-deficient alkenes, allenes, and alkynoates in those reactions has been explored widely,[12] the application of α,β-ynones in phosphine-catalyzed annulations has drawn scant attention until quite recently. The products of ynone annulations can be synthetically useful and biologically important compounds, including oxazolidines,[13a] thiazolidines,[13a] pyrrolidines,[13a] dihydropyrrolopyridines,[13b] benzimidazoline,[13b] benzomorpholines,[13b] tetrahydroquinolines, 3-oxanones, 3-oxepanones, spirooxazolines, spirooxindoles,[13e] spirocyclopentanones,[13f] spiro-cyclopentanone pyrazolones,[13g] cyclopent[*b*]annulated heteroarenes,[13h] hydropyridazines,[13i] cyclopentanone-fused benzosultams,[13j] and spirobarbiturate-cyclopentanones.[13k] In almost all of these examples, the α,β-ynone provides two- or three-carbon atoms for the formation ofcommon five- or six-membered rings; to the best of our knowledge, there has been only one report of seven-membered ring formation.[14]

Considering these precedents and based on our previously described tandem γ-umpolung addition–Wittig olefination,[15] we envisioned the possibility of synthesizing the dihydroquinoline **3′** through α-umpolung addition–Wittig alkenylation (Scheme 1). We found, however, that a solution of *o*-(*p*-toluenesulfonamido)benzaldehyde (**1a**) and the α,β-ynone **2a** in toluene produced, in the presence of 1 equiv of PPh_3, the benzo[*b*]azepin-3-one **3a** in 38% yield. We identified the *E*-configuration of this benzylidene moiety through NOESY analysis of the product 3a.

As displayed in Scheme 2, we suspect that the mechanism begins with nucleophilic addition of PPh_3 to the ynone **2a** to generate the zwitterion **I**. The intermediate **I** subsequently deprotonates the sulfonamide **1a**, with α-umpolung addition of the resulting amide anion onto the vinylphosphonium species producing the ylide **II**. Proton transfer delivers the enolate **III**, which is ready for the aldol reaction with the aldehydic unit to construct the benzoazapin-3-one ring **IV**. Alkoxide-to-enolate proton transfer and subsequent β-elimination of the catalyst (PPh_3) furnishes the product **3a**. The exclusive formation of the *E*-benzylidene moiety is due, we believe, to steric repulsion between the *p*-toluenesulfonyl group and the phenyl ring when forming the alternative *Z*-isomer. Although there have been reported α-umpolung additions[16] and tandem reactions involving α-umpolung addition,[17] to the best of our knowledge there are no previous reports of phosphine-catalyzed α-umpolung-aldol processes. Herein, we describe our study of this cascade process for the

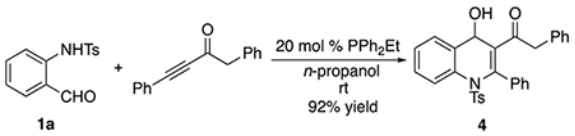
synthesis of benzo[*b*]azapin-3-ones through a phosphine-catalyzed *α*-umpolung-aldol reaction.

Recognizing that the *α*-umpolung–aldol reaction is catalytic in PPh_3, we tested various catalysis conditions for the *α*-umpolung–aldol reaction, engaging ethyl *o*-(*p*-toluenesulfonamido)benzaldehyde (**1a**) and the ynone **2a** as model substrates and employing various tertiary phosphines as catalysts at 20 mol%. We first screened various solvents in the presence of 20 mol % of PPh_3 at room temperature (Table 1). The product benzo[*b*]azepin-3-one **3a** was obtained in 10–42% yields in toluene, CH_2Cl_2, $CHCl_3$, and benzene (entries 1–4), but no product formed in tetrahydrofuran (THF), MeCN, or dioxane (entries 5–7). Noting that $CHCl_3$, with its acidic proton, was a particularly efficacious medium, we tested other protic solvents—alcohols, which could be deprotonated by the zwitterionic phosphonium enolate intermediates to promote the aldol reaction—for this reaction.[18] Interestingly, the Michael addition product **3**" was generated in 83% yield when using MeOH as the solvent (entry 8).[19] In contrast, EtOH and *n*-propanol enhanced the yield of the *α*-umpolung–aldol reaction to 58 and 69%, respectively (entries 9 and 10). *n*-Butanol could be used as the solvent without increasing the yield, but no significant product formed when running the reaction in isopropanol or *tert*-butanol (entries 11 and 13). Furthermore, we examined the effects of other phosphine catalysts (entries 14–17). Performing the reaction in the presence of tributylphosphine, a more nucleophilic catalyst, did not provide any product, but the yield increased to 74% when employing ethyldiphenylphosphine as the catalyst. Attempts to modulate the electronic properties of PPh_3 by using tris(*p*-fluorophenyl)-phosphine or tris(*p*-tolyl)phosphine had no significant benefits, supplying the benzo[*b*]azapin-3-one in yields of 69 and 54%, respectively.

Hereafter, employing ethyldiphenylphosphine as the catalyst in *n*-propanol as the solvent, our focus shifted to applying various other *o*-sulfonamidobenzaldehydes **1** and ynones **2** for the synthesis of a range of benzoazapinones 3 (Table 2). Initially, we studied the effects of varying the substituents on the benzene ring of the *o*-sulfonamidobenzaldehydes in reactions with the ynone **2a**. Electron-donating 5-methoxy and 5-methyl substituents on the benzene ring generated the desired products **3b** and **3c** in yields of 82 and 77%, respectively, while *N*-(3-formylnaphth-2-yl)-4-methylbenzenesulfonamide provided the benzo[*b*]azapin-3-one **3d** in 70% yield (entries 2–4). Electron-withdrawing groups, namely, 5-iodo, 5-bromo, and 5-chloro units, on the benzene ring induced the formation of the desired products **3e–g** in yields of 70–75% (entries 5–7). When we employed the 3-methyl-substituted 2-sulfonamidobenzaldehyde as the pronucleophile, no reaction occurred, presumably because of steric effects (entry 8). Performing the reaction with 4-methyl-2-sulfonamidobenzaldehyde delivered the benzoazapin-3-one **3h** in 72% yield (entry 9). Next, we probed the effects of various protecting groups of the aniline functionality. *N*-(2-Formylphenyl)benzenesulfonamide, *N*-(2-formylphenyl)-4-methoxybenzenesulfonamide, and *N*-(2-formylphenyl)-4-bromobenzenesulfonamide produced their desired products **3i–k**, respectively, in moderate yields (59–63%, entries 10–12).

We examine a range of ynones for the ethyldiphenylphosphine-catalyzed *α*-umpolung–aldol reaction. An electron-donating group on the benzene ring of the ynone **2** seemed crucial for a highly efficient reaction. When 4-(4-methoxyphenyl)but-3-yn-2-one was involved in the

annulation with **1a**, the desired product was obtained in 94% yield (entry 13). When run on 1 mmol scale, the reaction produced the product **3l** in 83% yield. The combination of electron-rich *o*-sulfonamidobenzaldehydes and 4-(4-methoxyphenyl)but-3-yn-2-one produced the desired benzo[*b*]azapin-3-ones **3m** and **3n** in the highest yields of this study: 95 and 99%, respectively (entries 14 and 15). Following this trend, 4-(4-methylphenyl)but-3-yn-2-one, when reacted with *N*-(2-formylphenyl)-4-methylbenzenesulfonamide and *N*-(2-formyl-4-methoxyphenyl)-4-methylbenzenesulfonamide, also provided high yields of the benzoazapin-3-ones **3o** and **3p** (91 and 93%, respectively; entries 16 and 17). Conducting the reactions of 4-(3-methylphenyl)but-3-yn-2-one with *N*-(2-formylphenyl)-4-methylbenzenesulfonamide and *N*-(2-formyl-4-methoxyphenyl)-4-methylbenzenesulfonamide gave the desired products **3q** and **3r** in slightly lower yields (85 and 81%, respectively; entries 18 and 19). When we employed 4-(2-methylphenyl)but-3-yn-2-one, however, no reaction occurred, presumably because the *o*-methyl group on the benzene ring of the alkynone blocked the nucleophilic addition of ethyldiphenylphosphine to the β-carbon atom of the α,β-ynone (entry 20). When an electron-withdrawing chlorine atom was positioned on the phenyl ring of the ynone, the corresponding product **3s** was furnished in 75% yield (entry 21). Interestingly, when 1,4-diphenylbut-3-yn-2-one was subjected to the standard reaction conditions, we obtained the 1,4-dihydroquinoline **4** instead of the benzo[*b*]azapin-3-one (eq 1).[20]



(1)

Applying this α-umpolung–aldol technology, we realized the rapid synthesis of the 3-amino-benzo[*b*]-azepin-2-one skeleton–the core unit of 3-amino-[*a*]benzazepin-2-one-1-alkanoic acids that are known angiotensin-converting enzyme (ACE) inhibitors.[21] Starting from the benzo[*b*]azapin-3-one **3a**, diastereoselective reductive amination generated the *syn*-aminoalcohol **5**, whose benzylidene motif was readily converted to a C=O group through ozonolysis to obtain the 3-amino-[*a*]benzazepin-2-one **6** (Scheme 3).

In conclusion, we have developed a phosphine-catalyzed intermolecular cyclization of *o*-sulfonamidobenzaldehydes and ynones to yield highly functionalized (*E*)-benzo[*b*]azapin-3-ones under mild reaction conditions at room temperature. This α-umpolung–aldol process provides a range of benzo[*b*]azapin-3-ones **3** in synthetically useful yields and with exclusive *E*-selectivity. In the further functionalization of **3a**, we found that compound **6** could be constructed rapidly through reductive amination and ozonolysis, providing an alternative means toward the skeleton of 3-amino-[*a*]benzazepin-2-one-1-alkanoic acids that are useful ACE inhibitors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

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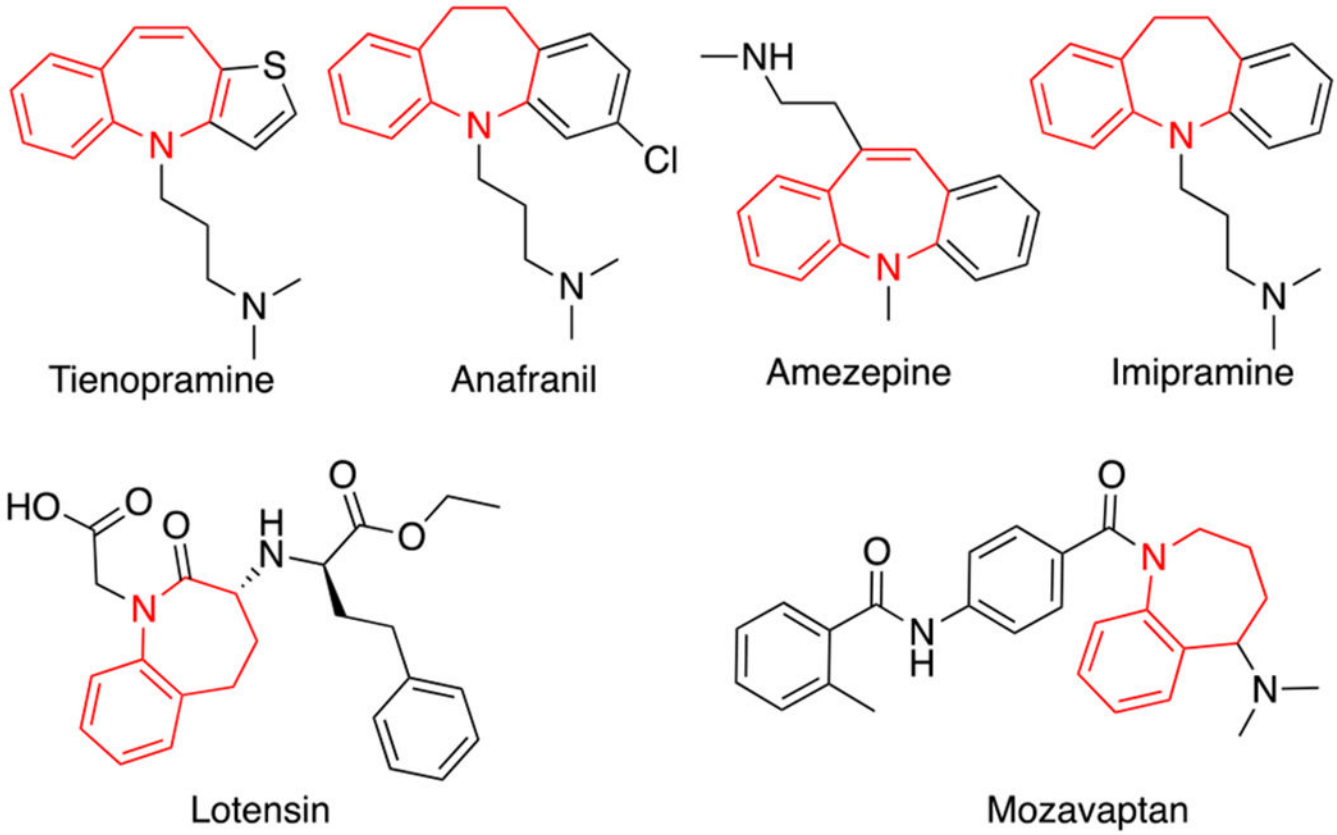
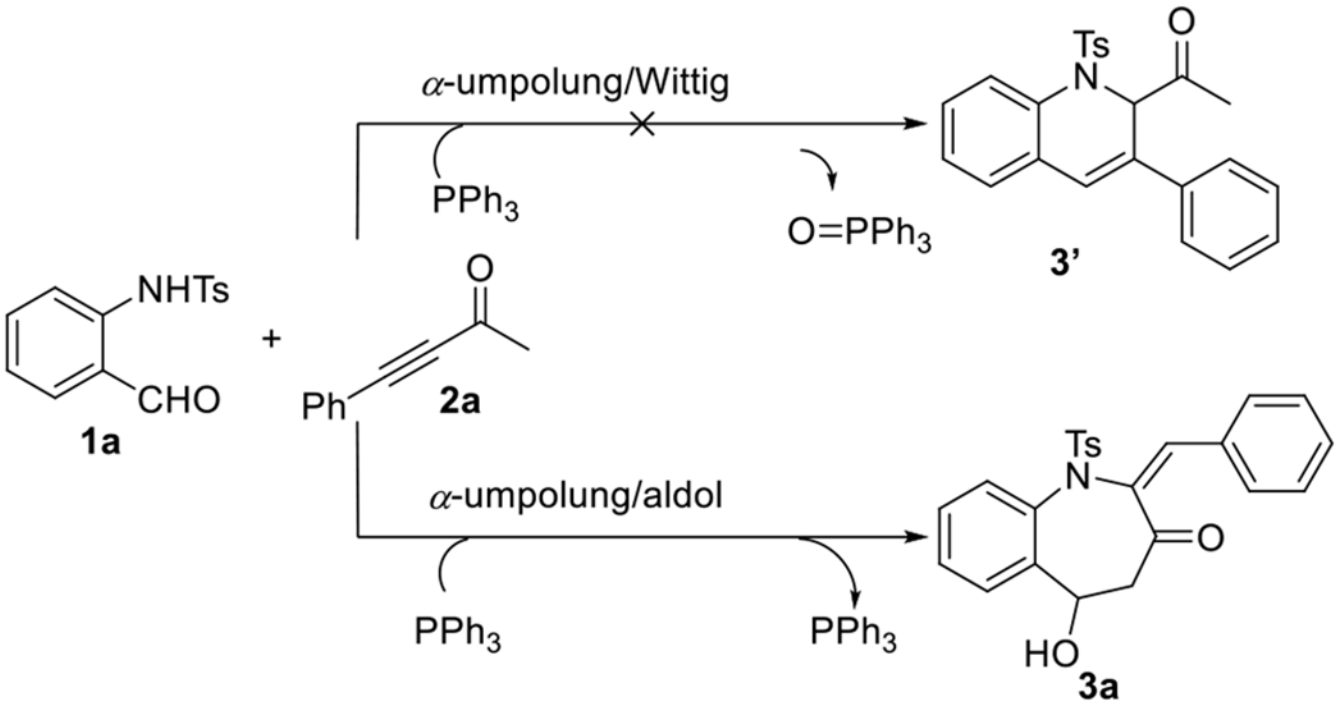
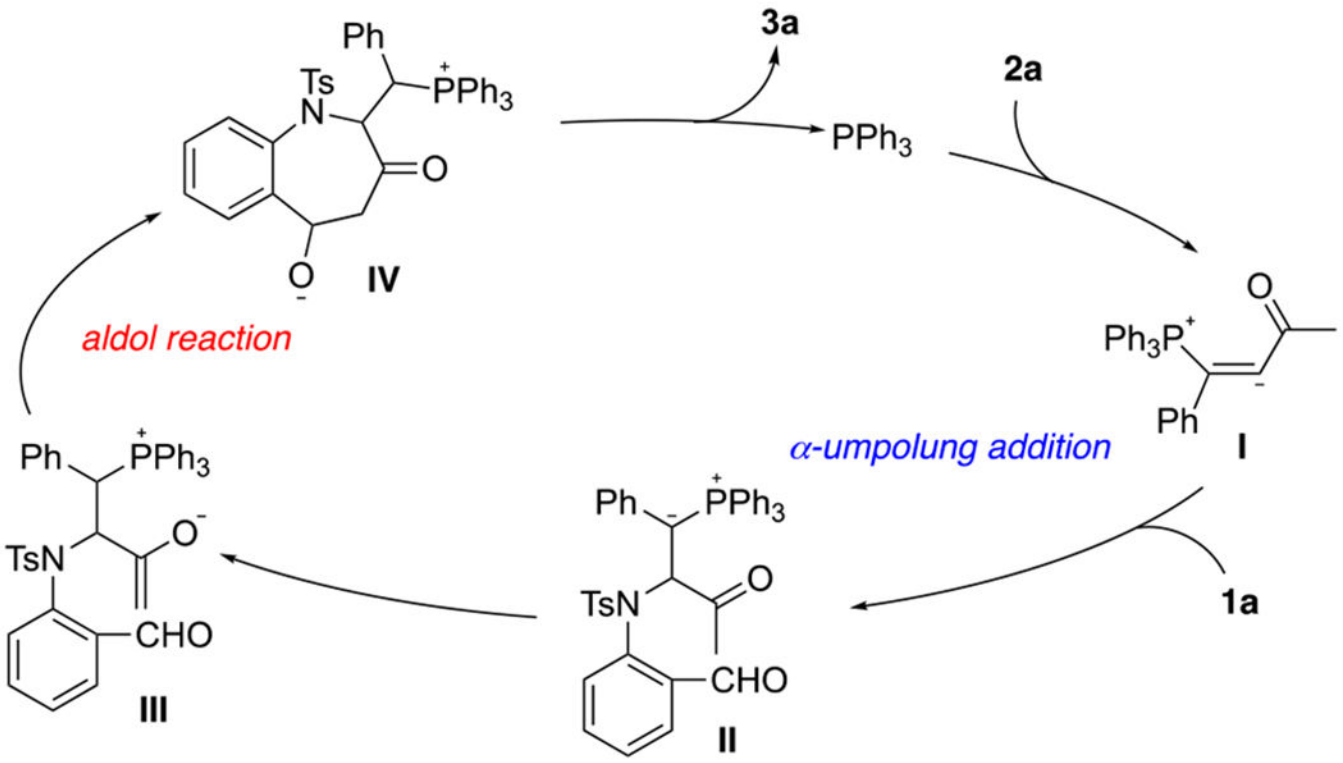


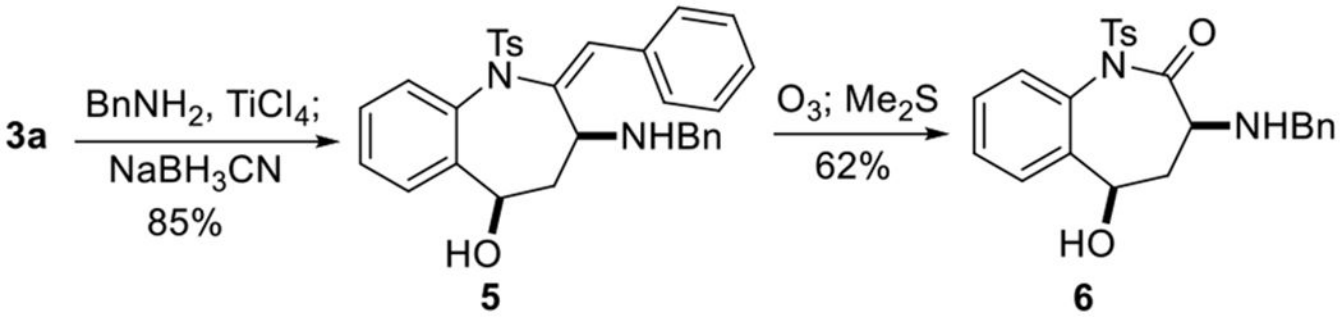
Figure 1.
Representative marketed drugs containing benzo[*b*]azepine core structures.



Scheme 1.
Discovery of ***α***-Umpolung–Aldol Reaction



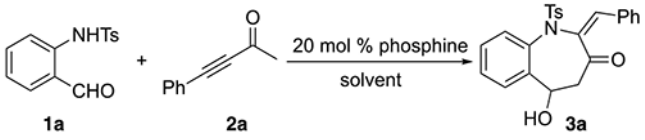
Scheme 2.
Proposed Mechanism for the Formation of the Benzo[*b*]azepin-3-one 3a



Scheme 3.
Synthetic Application of the α-Umpolung–Aldol Reaction

Table 1.

optimization of the Reaction Conditions[a]



entry	phosphine	solvent	temp. (°C)	yield (%)[b]
1	Ph_3P	toluene	rt	36
2	Ph_3P	CH_2Cl_2	rt	10
3	Ph_3P	$CHCl_3$	rt	42
4	Ph_3P	benzene	rt	14
5	Ph_3P	THF	rt	NR
6	Ph_3P	MeCN	rt	NR
7	Ph_3P	dioxane	rt	NR
8	Ph_3P	MeOH	rt	3″(83%)[c]
9	Ph_3P	EtOH	rt	58
10	Ph_3P	*n*-propanol	rt	69
11	Ph_3P	isopropanol	rt	NR
12	Ph_3P	*n*-butanol	rt	40
13	Ph_3P	*tert*-butanol	rt	NR
14	*n*-Bu_3P	*n*-propanol	rt	NR
15	$EtPh_2P$	*n*-propanol	rt	74
16	(*p*-$FC_6H_4)_3P$	*n*-propanol	rt	69
17	(*p*-$MeC_6H_4)_3P$	*n*-propanol	rt	54

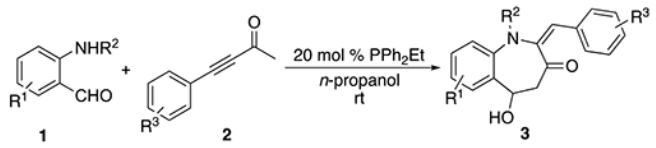
[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), phosphine (0.04 mmol), and solvent (2 mL) at room temperature.

[b]Isolated yield of **3a**.

[c]**3″** = 4-methoxy-4-phenyl-3-buten-2-one.

Table 2.

Synthesis of Benzo[*b*]azapin-3-ones[a]



entry	R^1	R^2	R^3	yield (%)[b]
1	H	Ts	H	**3a**, 74
2	5-MeO	Ts	H	**3b**, 82
3	5-Me	Ts	H	**3c**, 77
4	**1d**[c]	Ts	H	**3d**, 70
5	5-I	Ts	H	**3e**, 75
6	5-Br	Ts	H	**3f**, 73
7	5-Cl	Ts	H	**3g**, 70
8	3-Me	Ts	H	NR
9	4-Me	Ts	H	**3h**, 72
10	H	$PhSO_2$	H	**3i**, 63
11	H	$(4\text{-}MeOC_6H_4)SO_2$	H	**3j**, 65
12	H	$(4\text{-}BrC_6H_4)SO_2$	H	**3k**, 59
13	H	Ts	4-MeO	**3l**, 94 (83)[d]
14	5-MeO	Ts	4-MeO	**3m**, 99
15	5-Me	Ts	4-MeO	**3n**, 95
16	H	Ts	4-Me	**3o**, 91
17	5-MeO	Ts	4-Me	**3p**, 93
18	H	Ts	3-Me	**3q**, 85
19	5-MeO	Ts	3-Me	**3r**, 81
20	H	Ts	2-Me	NR
21	H	Ts	4-Cl	**3s**, 75

[a]Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), phosphine (0.04 mmol), and *n*-propanol (2 mL) at room temperature.

[b]Isolated yields.

[c]**1d** = *N*-(3-formylnaphth-2-yl)-4-methylbenzenesulfbnamide.

[d]Reaction run on 1 mmol scale.