Alkyne Activation

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Catalytic Synthesis of Nonracemic Azaproline Derivatives by Cyclization of β-Alkynyl Hydrazines under Kinetic Resolution Conditions**

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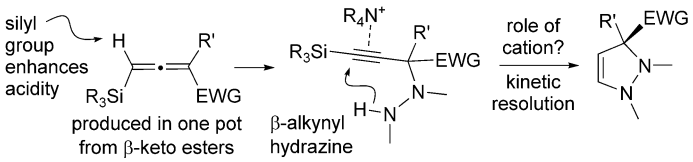
Heteroatom addition reactions to unactivated alkynes are thought to be best mediated by transition-metal catalysts such as palladium[1] and gold.[2] Recent studies by Hammond and co-workers[3] and others[4] demonstrate that cyclizations of alkynes with nitrogen- and oxygen-containing nucleophiles are possible using stoichiometric amounts of tetra-*n*-butylammonium fluoride. However, these examples appear to be limited to aryl or α,α-difluoro alkynes. As described herein, we have discovered by serendipity a nonmetal catalyzed addition of amine to unactivated alkynes to yield azaproline derivatives (Scheme 1). Although the nature of this catalysis reaction is not clear, these reactions proceed in excellent yields and lead to enantioenriched azaprolines under kinetic resolution conditions using ammonium phase-transfer catalysts.



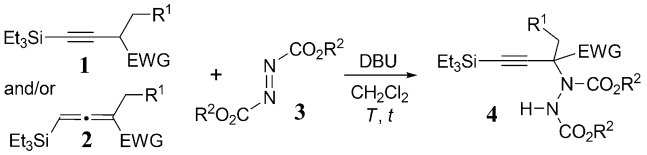
Scheme 1. Catalytic generation of azaprolines by cyclization of β-alkynyl hydrazine compounds. EWG = electron-withdrawing group.

We decided to further investigate this cyclization reaction partly out of mechanistic curiosity but also mindful that azaprolines have taken on an increasingly important role in bioorganic[5] and medicinal chemistry.[6] Indeed, there has been a great deal of interest in the synthesis of azaproline derivatives over the last decade. The earliest approach pioneered by Carreira and co-workers involved diastereoselective [3+2] additions of diazoalkanes with α,β-unsaturated chiral esters.[7] More recently this method has been expanded to include other dipolar diazo reactions[8] including those catalyzed by chiral magnesium bisoxazole[9] as well as titanium BINOL-ate.[10] The pyrazolidine ring of azaprolines has also been prepared by palladium-catalyzed cyclizations of optically active allenylic hydrazines[11] or hydrazine adducts produced from racemic allenyl phosphine oxides.[12] However, herein we report related cyclization reactions catalyzed by nonmetal cations, which have allowed for an exciting class of chiral ammonium phase-transfer catalysts to be brought to bear to produce nonracemic azaproline derivatives (Scheme 1).

Based on our previous experience with γ-silyl allenyl esters,[13] we hypothesized that base-catalyzed addition of dinitrogen-containing electrophiles such as azidodicarboxylates should lead to β-alkynyl hydrazine intermediates. Indeed, with substrates **1** and **2** (EWG = CO_2tBu and CO_2Et) DBU catalyzed this transformation but the reactions were sluggish especially with larger α-substituents (Table 1).

By applying a procedure similar to one we had previously reported,[14] γ-silyl allenyl and propargyl thioesters (EWG = COS*t*Bu) were prepared and, as expected, these substrates underwent rapid addition to azidodicarboxylates with DBU even at −20 °C. Less basic amines failed to give hydrazine products even with these thio-

Table 1: Additions of allenyl esters to azidodicarboxylates catalyzed by DBU.



Entry	EWG	R^1	SiR_3	R^2	*T* [°C]	*t* [h]	Yield [%][a]
1	CO_2tBu	Ph	TES	*i*Pr	RT	12	83
2	CO_2Et	H	TES	*i*Pr	0	4	87
3	CO_2Et	H	TES	Bn	0	4	67
4	COSBu	Ph	TES	*i*Pr	−20	1	69
5	COS*t*Bu	Ph	TMS	*i*Pr	−20	1	67
6	COS*t*Bu	Ph	TIPS	*i*Pr	−20	1	75
7	COS*t*Bu	Ph	TES	*t*Bu	−20	1	78
8	COS*t*Bu	vinyl	TES	*i*Pr	−20	1	71
9	COS*t*Bu	2-naph	TES	*i*Pr	−20	1	76
10	COS*t*Bu	*o*-tol	TES	*i*Pr	−20	1	79
11	COS*t*Bu	*p*-ClC_6H_4	TES	*i*Pr	−20	1	68

[a] Yield of isolated product. With thioester substrates < 5% of γ-addition hydrazine products (allenes) were also observed. Bn = benzyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, naph = naphthyl, TES = triethylsilyl, TIPS = triisopropylsilyl, tol = tolyl, TMS = trimethylsilyl.

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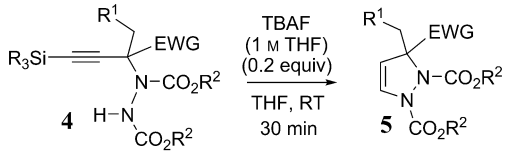
esters except with DMF as the reaction solvent. The DMF solvent gave no enantioselectivity when chiral amine catalysts such as quinine were used to catalyze the addition reaction to give **4**.

For improved characterization, we thought it useful to remove the silyl group from product **4**. However, we were surprised to discover that the desilylation of **4** using tetra-*n*-butylammonium fluoride (TBAF) led to dehydroazaproline **5** in nearly quantitative yields. Our subsequent studies of this system revealed that the ammonium salt acts catalytically to form the heterocycle and that the reaction appears to tolerate a variety of substituents at the quaternary carbon center (Table 2). We note that the TBAF used was a commercially

Table 2: Cyclization of β-alkynyl hydrazines catalyzed by TBAF.



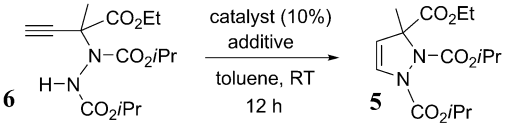
Entry	EWG	R^1	R^2	SiR_3	Yield [%][a]
1	CO_2tBu	Ph	*i*Pr	TES	99
2[b]	COS*t*Bu	Ph	*i*Pr	TES	97
3	COS*t*Bu	Ph	*i*Pr	TMS	98
4	COS*t*Bu	Ph	*i*Pr	TIPS	99
5	COS*t*Bu	Ph	*t*Bu	TES	94
6	CO_2Et	H	*i*Pr	TES	99
7	COS*t*Bu	vinyl	*i*Pr	TES	99
8	COS*t*Bu	*p*-ClC_6H_4	*i*Pr	TES	99
9	COS*t*Bu	*o*-tol	*i*Pr	TES	99
10	COS*t*Bu	2-naph	*i*Pr	TES	99
11	CO_2Et	H	Bn	TES	99
12[c]	$CONR_2$	vinyl	*i*Pr	TES	97

[a] Yield of isolated product. [b] Starting with nonracemic **4** led to product with the same *ee* value. [c] Amide derivative of pyrrolidine. THF = tetrahydrofuran.

available solution in THF containing up to 5% dissolved water, which is likely the stoichiometric agent responsible for removal of the silyl group. Although the present TBAF-catalyzed cyclization step is unprecedented, another study details the cyclization of aryl alkynes with nitrogen- and oxygen-containing nucleophiles mediated by stoichiometric amounts TBAF.[4] In addition, Hammond and co-workers describe a cyclization with a nitrogen-containing nucleophile with an α,α-difluoro methylene that requires two equivalents of TBAF.[3]

To better understand the role of the nonmetal catalyst in the present reaction, several factors were examined. To separate issues of desilylation versus cyclization, we prepared silyl-free substrate **6** using stoichiometric amounts of TBAF in isopropanol (alcohol solvents do not lead to cyclization products). Now, using TBAF as the catalyst (0.1 equiv), the cyclization reaction of **6** gave excellent yields in THF, CH_2Cl_2, and toluene. The use of tetra-*n*-butylammonium bromide (TBAB) as a catalyst gave no cyclization product except with the addition of CsF (Table 3, entry 3). However, the anion

Table 3: Role of cation and anion in catalyzed cyclization of **4**.



Entry	Cat.	Additive (equiv)	Yield [%][a]
1	TBAF	–	99
2	TBAB	–	NR
3	TBAB	CsF (0.5)	97
4	TBPB	–	NR
5	TBPB	CsF (0.5)	98
6	TBAB	K_2CO_3 (0.5)	95
7	TBPB	K_2CO_3 (0.5)	94

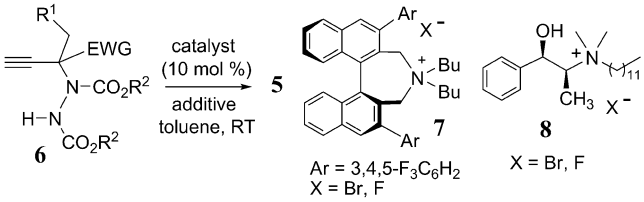
NR = no reaction.

need not be fluoride as added carbonate leads to the same result with TBAB (Table 3, entry 6).

Interestingly, tetra-*n*-butylphosphonium bromide (TBPB) also effectively catalyzed the cyclization[15] with either fluoride or carbonate additives. Clearly, neither ammonium nor fluoride is strictly required to catalyze this cyclization reaction.

The discovery that the present cyclization reaction is mediated by catalytic nonmetal cations suggested that kinetic resolution might be possible. Our initial experiments with α-benzyl ester and chiral ammonium bromides **7** and **8** (Table 4, entries 1 and 2) gave no reaction. However, less steric bulk at the quaternary carbon center led to successful reactions (Table 4, entries 4–7) that proceed fairly rapidly to approximately 50% conversion with catalysts **7** and **8**. Importantly, this reaction led to products (and recovered starting materials) of high enantioselectivity. Catalysts containing the bromide counter ion required added CsF to afford product. This cyclization reaction is particularly sensitive to steric

Table 4: Nonracemic azaproline products by kinetic resolution.



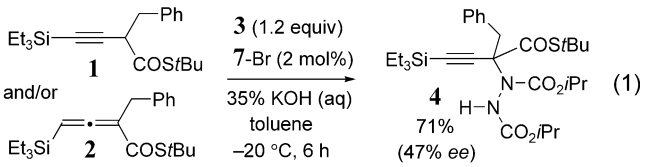
Entry	EWG	R^1	R^2	Cat.	Additive	*t* [h]	Yield [%][a]	*ee* [%][b]
1	CO_2Et	Ph	*i*Pr	**7**-Br	CsF	12	NR	–
2	CO_2Et	Ph	*i*Pr	**8**-Br	CsF	12	NR	–
4	CO_2Et	H	Bn	**7**-Br	CsF	48	47	93[c]
5	CO_2Et	H	Bn	**7**-F	–	48	48	93[c]
6	COS*t*Bu	vinyl	*i*Pr	**8**-Br	CsF	12	54	76
7	COS*t*Bu	vinyl	*i*Pr	**8**-F	–	12	51	81
8	COS*t*Bu	vinyl	*i*Pr	TBAF	–	1	quant.	99[d]
9[e]	$CONR_2$	vinyl	*i*Pr	**8**-F	–	8	73[f]	4

[a] Yield of isolated product. [b] Determined by HPLC on a chiral stationary phase. [c] Based on analysis of remaining starting material by using HPLC on a chiral stationary phase. [d] Recovered starting material from previous reaction (entry 7) was utilized. [e] Amide of pyrrolidine. [f] Recovered 25% starting material.

crowding. Thus with allyl substitution at the α position, catalyst **7** proved ineffective whereas the much smaller **8** led to product with good resolution (Table 4, entries 6 and 7). As expected, recovered starting material from a kinetic resolution reaction (Table 4, entry 7) led to cyclization product **5** in high enantiomeric excess using catalytic amounts of TBAF (Table 4, entry 8).

It appears that a modestly basic counteranion (F^- or CO_3^{2-}) is required for this cyclization reaction—presumably to deprotonate the attacking carbamate nitrogen center. Hiroya, Sakamoto, and co-workers have proposed an ammonium cation activation of alkynes in cycloaddition reactions involving aryl alkynes.[4a] While additional theoretical and physical investigations are needed to substantiate these claims, we remain intrigued by the possibility that the carbamate nitrogen-centered nucleophile in our case attacks the alkyne group similarly activated by an ammonium or phosphonium catalyst. In this manner, the catalyzing ability of a chiral organic cation is expected to be influenced by the configuration of the quaternary center immediately adjacent to the alkyne: thus, perhaps explaining our successful kinetic resolution in this cyclization reaction.

The main thrust of this project was to develop a kinetic resolution technique to take advantage of the unprecedented nonmetal-catalyzed cyclic heteroatom addition mentioned above. Nevertheless we briefly explored asymmetric phase-transfer-catalyzed additions of azidodicarboxylates to our γ-silyl allenyl ester system by using a recent precedent by Maruoka and co-workers involving carbon electrophiles.[16] While aqueous/organic biphasic systems resulted in no reaction with allenyl oxyesters, we observed that $CsOH{\cdot}H_2O$ in toluene led to their successful hydrazination. However, this solid/liquid phase reaction led to entirely racemic product when a variety of commercially available phase-transfer catalysts (PTC) we employed.[17] We returned to the organic/aqueous systems with thioester substrates and observed addition products in good yields and moderate enantioselectivities [Eq. (1)]. For this study we employed several commercially available PTCs including cinchona-based catalysts and Maruoka catalyst **7**. These results suggest that a suitable catalyst can be engineered for higher selectivities.



(1)

In conclusion, a robust α-selective hydrazination of allenyl esters has been developed. This reaction was also expanded to include asymmetric catalysis conditions using chiral phase-transfer catalysts that led to promising results. Importantly, these hydrazino adducts underwent ammonium- and phosphonium-catalyzed cyclization to afford dehydroazaproline derivatives. This amine addition to unactivated alkynes is uniquely mediated by nonmetal cation catalysts. Although the precise mechanism of this cyclization reaction is not yet understood, highly enantioenriched azaproline derivatives have been prepared using readily available chiral ammonium salts as catalysts. Further mechanistic studies and exploration of the reactivity of the dehydroazaproline system are currently underway.

Experimental Section

Neutral base-catalyzed α-amination: Allene/alkyne mixture (1 mmol) was added to a round-bottom flask which was then charged with solvent (5 mL). The mixture was cooled to the required temperature before base (20 mol%) was added. After 5 min of stirring, azidodicarboxylate (1.2 equiv) was slowly added to the mixture and the reaction was stirred. Once the reaction was complete (as evident by TLC), the mixture was quenched with aqueous HCl (1M). The organic layer was removed and the aqueous layer was extracted twice with diethyl ether. All organic layers were combined, concentrated in vacuo, and purified by flash column chromatography on silica gel.

TBAF-catalyzed cyclization: The substrate (0.5 mmol) was dissolved in THF (2 mL) before TBAF (1M THF, 20 mol%) was added. The reaction was stirred for 30 min, quenched with aqueous HCl (1M) and extracted with diethyl ether. The organic layer was removed and the aqueous layer was extracted twice with diethyl ether. All organic layers were combined, concentrated in vacuo, and purified by flash column chromatography on silica gel to give nearly quantitative yield of product.

General procedure for kinetic resolution with ammonium fluoride catalysts: Substrate (0.5 mmol) was added to a round-bottom flask which was then charged with toluene (5 mL). Catalyst (10 mol%) was then added and the mixture was stirred for the required time. The reaction was quenched with aqueous HCl (1M) and extracted with diethyl ether. All organic layers were combined, concentrated in vacuo, and purified by flash column chromatography on silica gel. The enantiomeric excesses of the separated products and starting materials were determined by HPLC on a chiral stationary phase.

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