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Diversification Reactions of γ -Silyl Allenyl Esters: Selective Conversion to All-Carbon Quaternary Centers and γ -Allene Dicarbinols

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Abstract

The unique reactivity of γ -silyl allenyl esters is described. Taking advantage of the silyl group as a fluoride acceptor, these allenates readily underwent addition to a variety of electrophiles to selectively produce products with all-carbon quaternary centers or allenate dicarbinols. These dicarbinols were subsequently converted to novel highly substituted 6-hydroxy-2-pyrones.

Graphical Abstract

Taking advantage of an organosilicon auxiliary, allenes are selectively converted under mild conditions to either all-carbon quaternary centers (including via S_NAr) or allene dicarbinols depending on the electrophile.

While γ -silyl allenyl esters have appeared in the literature as early as 1979,¹ their potential as diversifiable building blocks² has only been recently exploited. For example, Maruoka demonstrated that a γ -silyl allenolate could be benzylated to give propargyl ester **1** bearing an all-carbon quaternary center.³ Importantly, this asymmetric conversion was accomplished under mild phase-transfer conditions due to facile γ -deprotonation of a γ -silylallenolate resulting from stabilization of the conjugate base by the silyl group (Scheme 1). We also have taken advantage of the unique properties of γ -silyl allenates in developing a highly selective γ -aldol addition⁴ and α -additions leading to azaprolines.⁵ Specifically, silyl allenes **A**, easily accessible from ketoesters,⁶ when treated with an anionic nucleophilic catalyst (e.g. LiOⁱPr), produced γ -allenyl carbinol **F** via dienolate intermediate **B** following a Morita-Baylis-Hillman (MBH) mechanism (Scheme 1). We have previously argued that the observed exclusive γ -selectivity was the result of a favorable second step involving a 1,2-Brooke rearrangement to form a strong Si-O bond.⁴ In an attempt to divert the reaction mechanism to afford α -addition products, we considered that stoichiometric fluoride would

lead to a hypervalent silicon⁷ intermediate such as **C**. We expected this dianion intermediate would bear more partial negative charge on the α -carbon than the γ -carbon. Our hypothesis was that, if intermediate **C** formed, a subsequent addition of an electrophile would lead to **D** followed by a collapse of the silicon anion to afford alkyne **E**, bearing an all-carbon quaternary center.

The main goal of the present work was to further explore the potential of the γ -silyl group of this system as an auxiliary to control regioselectivity and reactivity as outlined above.

However, our reaction design was also aimed at providing a synthetically useful method to complement the work of Hammond and coworkers in this area. Hammond demonstrated that allenyl esters add to electron-deficient olefins under the action of catalytic TBAF to afford propargyl esters.⁸ Using stoichiometric quantities of TBAF (2.0 eq), these same substrates also add aldehydes at the γ -position.⁹ These allenyl esters also add to an impressive variety of alkyl halides and acid chlorides to yield propargyl esters in the presence of LDA (1.5 eq).¹⁰ One of the few limitations of Hammond's work is the apparent need for allenolate substrates to be substituted at the γ -position with an alkyl or aryl group. In addition to removing this substrate limitation, we also sought to develop a reaction that would undergo alkylation and nucleophilic arylation (via S_NAr) under conditions that would allow for the future development of phase transfer catalysis. As we detail in this communication, these goals were accomplished the help of the γ -silyl auxiliary.

We initially examined our hypervalent silicon hypothesis by attempting to alkylate substrate **2** in the presence of lithium isopropoxide in catalytic quantities. This initial reaction did not furnish ethynyl product **4a** but rather γ -alkylation product **3** in a yield equivalent to that of the catalyst used (30%) (Table 1, entry 1). We note that unlike the reaction of Maruoka (Scheme 1), product **3** has lost the silyl group. We next introduced a fluoride source and noticed a substantial increase in the reaction rate. Importantly, the added fluoride altered the regioselectivity of the reaction to give alkyne **4a** as the only product. Further optimization revealed that LiOⁱPr (30 mol%) and TBAF (1.0 eq) at 0 °C in THF led to product in 1.5 h (entry 3). This reaction is compatible with other fluoride sources as well. For example, KF in THF in the presence of a crown ether (18-C-6) led to product **4a** in 3.5 h at 0 °C (entry 8). Perhaps most gratifyingly, alkyne product was also achieved using potassium fluoride and cyclohexanol in the presence of a phase transfer agent (entry 9). Presumably, the fluoride in this reaction generates an alkoxide from cyclohexanol while also serving as the stoichiometric fluoride source.

After establishing optimal conditions using TBAF, we next explored the reaction scope with respect to electrophiles (Table 2). In general, a wide range of electrophiles add to substrate **2** to afford α -adducts **4** exclusively. Not surprisingly, other activated alkylating agents besides allyl bromide led to propargyl products **4** in relatively good isolated yields (60 – 85%); methylation to give **4c** was also successful. Under the same conditions, electron-deficient olefins also react efficiently with substrate **2** leading to products **4g** – **4j** respectively in good yields. We note that all of the products in this phase of our study possess terminal alkynes and thus complement the methods developed by Hammond.^{8,10}

Our generality studies also revealed that this method encompasses nucleophilic additions to aryl fluorides, which has not been previously disclosed. Using the same optimized conditions just described, silyl allene ester **2** reacts with 1-fluoro-4-nitrobenzene to produce **4k** in 77% isolated yield (Table 2). Notably, this product contains an all-carbon quaternary center bearing an ethynyl and an aryl unit.¹¹ The addition also works with an aryl fluoride bearing other electron withdrawing groups. As mentioned, we have previously developed an aldol addition reaction involving γ -silyl allenoates that adds aldehydes exclusively at the γ -position most likely via an MBH mechanism.⁴ However, using an adaptation of Hammond's method,⁹ we discovered that a wide range of aldehydes can be added in a second step in the presence of stoichiometric TBAF (Table 3) to produce allene γ -dicarbinols **5** as a mixture of diastereomers. Optimal yields of diols **5** were realized with stoichiometric aldehyde (1.0 eq) in both steps 1 and 2 as well as excess TBAF in step 2 (3.5 eq). Surprisingly, aliphatic aldehydes do not add in the second step.

γ -Dicarbinol allenoates have not been previously reported,¹² which prompted us to explore their reactivity. One of our initial experiments was inspired by Ma who demonstrated that allene carbinols could be converted to halo-dienes.¹³ Following his protocol, allene dicarbinols **5a** and **5k** were treated with LiI in the presence of hydroquinone (HQ) in AcOH (as solvent) at 50°C. This reaction afforded 6-hydro-2-pyrones **7a** and **7k** bearing an exocyclic double bond (Scheme 2).

These products can be rationalized as resulting from initial 1,3-diene intermediates **6**, which then underwent lactonization under reaction conditions to afford products **7** in good yields. Significantly, this new route to highly substituted pyrones gives 6-aryl (**7a**) and 6-alkyl (**7b**) substitution with equal facility, producing each as a single diastereomer. While reactions to access 2-pyrones abound,¹⁴ methods to produce the 6-hydro analog¹⁵ are virtually unknown.¹⁶ Our route now provides access to a heterocyclic motif that we believe will prove useful, given that the 2-pyrone moiety is found in many bioactive compounds, both natural¹⁷ and designed.¹⁸

In conclusion, we began with a mechanistic hypothesis that a γ -silyl group on allenoates could serve as a fluoride receptor to increase regioselectivity and overall nucleophilicity leading to products bearing an all-carbon quaternary center. This successful strategy has resulted in several synthesis innovations. It makes possible α -arylation with aryl fluoride reagents to produce carbon quaternary centers containing aryl and ethyne. This same γ -silyl-allenoate building block efficiently adds to aldehydes to produce the corresponding γ -dicarbinols for the first time. Finally, these dicarbinols converted to 6-hydro-2-pyrones, a novel hydrogenation state of a medicinally important pyrone system.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Maruoka and coworkers - silyl group to facilitate deprotonation

This work - silyl group as fluoride receptor

Scheme 1. A new strategy for α -selective additions

Scheme 2. Diastereoselective synthesis of 6-hydroxy-2-pyrones

Optimization study

Table 1

entry	Cat (30 mol %)	Fluoride source (1.0 eq)	solvent	Temp (°C)	Time (h)	% conv 4a ^a
1	LiO ⁱ Pr	-	THF	0 and rt	12	0 ^b
2 ^c	LiO ⁱ Pr	TBAF	THF	0	2.5	100
3	LiO ⁱ Pr	TBAF	THF	0	1.5	100
4	LiO ⁱ Pr	TBAF	Et ₂ O	0	5.0	80
5	LiO ⁱ Pr	TBAF	DCM	0	12.0	trace
6	LiO ⁱ Pr	TBAF	THF	-10	4.0	100
7	LiO ⁱ Pr	TBAF	THF	-20	6.0	100
8	LiO ⁱ Pr	18-C-6/KF	THF	0	3.5	100
9 ^d	TBAB/C ₆ H ₁₁ OH	KF	toluene	rt	24	90

^aThe percent conversions were determined based on ¹H-NMR spectroscopy.

^bOnly product **3** was formed in 30% yield.

^c20 mol% LiOⁱPr. ^dTBAB (1 eq) and cyclohexanol (1 eq) were used here.

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Table 2
Reaction scope leading to quaternary products 4^{a,b}

^aReaction conditions: **2** (1.0), electrophile (1.2 eq), TBAF (2.0 eq), LiOiPr (0.3 eq), THF (0.1 M). TBAF was added after 15 min to a mixture of silyl allene, LiOiPr and alkyl halide.

^bYields for products **4** given as isolated yields.

Table 3
Substrate scope leading to allenolate γ -dicarbinols^a

	R^1	X	%yield
5a	Ph	H	74
5b	Ph	Me	60
5c	Ph	OMe	63
5d	Ph	Br	65
5e	Ph	NO_2	73
5f	PhCHMe	$t\text{Bu}$	64
5g	PhCH=CH	H	77
5h	$t\text{Bu}$	$t\text{Bu}$	64

^aYields for products **5** given as isolates yields.