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Anion Catalyzed Addition of γ -Silylallenyl Esters to Aldehydes: A New Entry into [3.2.1] Bicyclic Natural Products

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Abstract

A significant improvement in generality and reactivity of MBH-type reactions made possible by anion-catalysis and a 1,3-Brook rearrangement. In this new reaction, both aliphatic and aromatic aldehydes are rapidly added to silylallenes leading to γ -carbinol allenates at cold temperatures. The utility of these reaction products is demonstrated by a fast-tracked synthesis of a [3.2.1] bisoxabicycle which makes up the framework of many biologically active natural products including vitisinol D, an anti-thrombotic agent.

Catalytic reactions that lead to functionally dense intermediates are of great value in target-oriented synthesis. We are particularly interested in allenyl carbonyls and their synthetic utilization owing to the unique juxtaposition of functional groups including the reactively distinct cumulated double bonds. As part of our ongoing efforts in the total synthesis of vitisinol D, an anti-thrombotic natural product,¹ we required a general and robust method for the preparation of γ -carbinol allenates as a multifunctional coupling partner for maximal convergency. A review of existing methods including those developed in our lab² revealed no efficient catalytic approach to the synthesis of these allenates save Mukaiyama aldol-type reactions.³ Seeking a Lewis basic approach, we were intrigued by a report demonstrating an amine-catalyzed Morita-Baylis-Hillman (MBH) coupling of an allenyl ketone to aldehydes.⁴ However, this reaction only appears to work with electron-deficient aromatic aldehydes and requires forcing conditions (DMSO, 80 °C).

From a mechanistic perspective, two possible rate limiting steps have been attributed to MBH reactions.⁵ In the context of allene synthesis, these would be the nucleophilic addition to form **C** and a proton transfer and catalyst elimination to regenerate the original unsaturation giving product **D** (Scheme 1).⁶ Neutral nucleophiles, especially tertiary amines, have been used exclusively as catalysts in this reaction leading to zwitterionic intermediates **B** (where Nuc is positively charged). Probably due to their overall neutral charge, intermediates such as **B** have poor nucleophilicities leading to slow addition.

Though unprecedented, a logical remedy might be to use anionic catalysts leading to intermediate **B** with a net negative charge possessing enolate-like reactivity. However, others have demonstrated with acrylates that an anionic nucleophile (PhSLi) only allows for the formation of adducts such as **C** without catalyst regeneration.⁷ Thus while a negatively charged Nuc may improve the reactivity of intermediate **B**, the catalytic cycle would likely be arrested due to the diminished acidity of the γ -proton in intermediate **C** (Scheme 1, X = H). We hypothesized that the unique combination of an anionic catalyst and a 1,3-Brook rearrangement would address reactivity problems associated with these two slow steps. By analogy with other systems,⁸ we reasoned that silyl-substituted allenates would lead to intermediates **C** in which the Nuc would eliminate to form allenic unsaturation with greater facility due to the enhanced propensity of the silyl group to undergo a 1,3-shift relative to the proton of the classic MBH reaction (X = R₃Si vs H).

To test our hypothesis, we first prepared γ -TMS allenylester **1** from 2-benzyl-2,3-butadienoic ethyl ester.⁹ Our initial optimization involved the addition of **1** to *p*-anisaldehyde while varying nucleophilic catalysts and reaction parameters (table 1). We were gratified to discover that LiOPr^t led to regiospecific γ -carbinol products **3** in most cases within several hours. Thus with 20 mol% LiOPr^t, the addition of *p*-anisaldehyde to **1** to give **3c** was complete within 1 h at 0 °C (entry 2). By contrast, we observed that allenyl esters lacking silyl substitution at the γ -position afforded no addition products under these same conditions. Products **3** were prone to dehydration at 0 °C; however, an improvement in yield was achieved at –20 °C and especially at –78 °C (entries 3 and 4). As expected, the colder temperature slowed the reaction considerably but we found that reasonable reaction times (4 – 5 h) could be realized by simply increasing the catalyst amount to 70 mol%. Importantly, the lower temperature did appear to depress the formation of dehydration side-products leading to a 20% increase in yields (entries 5 and 6). There is also a strong preference in this reaction for lithium salts which gave considerably better yields than sodium and potassium salts otherwise a variety of alkoxides and even thiophenoxide led to good yields. The ideal reaction solvent is THF. As anticipated, trialkyl and triaryl phosphines¹⁰ and neutral amines such as DABCO and DMAP did not lead to the desired allene substitution products.

We recently reported a convenient one-pot procedure for the preparation of allenyl esters starting from inexpensive and readily available β -ketoesters.^{2e} However, in the case of silyl allenes, this method usually gives inseparable mixtures of silyl allenes and deconjugated alkynyl esters such as **1** and **2** (scheme of table 1). We reasoned that **2** could be equilibrated to **1** by the action of the anion catalyst of the allene/aldehyde addition reaction. Furthermore, the equilibrium should be shifted in favor of **1** as it is consumed through irreversible addition to aldehyde. Indeed, mixtures of allene **1** and alkyne **2** gave the same product yield as with pure **1** albeit with slightly longer reaction times (compare entries 5 and 6). The reaction gives good yields with a variety of α -substituents in allene **4** which is a significant advantage over previous related methods (table 2).⁴ Aryl aldehydes with both electron withdrawing and donating groups have virtually no effect on the formation of carbinol **3** giving in each case moderate to high yields. The ester group in allenes **4** are also compatible with the alkoxide catalyst in that no trans-esterification is observed including with phenoxide esters (entries 3 and 4). Significantly, aliphatic and alkynyl aldehydes are also suitable for this transformation. Overall, this reaction is both scaleable and robust leading to allenyl carbinols **3** under operationally simple conditions starting from easily obtained γ -silyl allenyl esters.

As part of our strategy for the synthesis of vitisinol D we required an hydroxyl-protected carbinol allenate. Thus we performed an alkoxide catalyzed reaction with γ -triethylsilyl allenate phenyl ester in order to obtain TES protected alcohol **3d**. The reaction gave good yields and was completed in 1 h at –10 °C (table 2, entry 4). In addition to economizing on synthetic steps, the TES transfer leading to **3d** turned out to be a significant benefit. Situated

in many cases between two unsaturated moieties, the hydroxyl group of products **3** proved difficult to protect with silyl or other groups.

Despite their rich functional group density, allenyl esters have been underutilized in total syntheses with a few recent exceptions.¹¹ We had previously disclosed our findings demonstrating the utility of allenyl carbonyls in Michael-Stork enamine additions although this method had only limited application to the synthesis of bicycles.^{2d} However, in our current studies towards the total synthesis of vitisinol D, we recently discovered that stabilized enolates are highly effective in double addition reactions to allenates. Thus cyclic β -ketoester **5** was successfully added to allenate **3d** to give enol lactone **6** with dehydration of the TES alcohol (scheme 2). This one step involving the formation of three bonds efficiently exploits the multiple functional groups of an allenyl ester carbinol. The required [3.2.1] bicycle was then brought about by a reduction of lactone **6** presumably to give the lactolate which then underwent an intramolecular aldol reaction to give the bicycle. Subsequent DMP oxidation led to **7** in an unoptimized 2-step yield of 32%. Importantly, this “reductive aldol” strategy, enabled by our convenient preparation of allenate γ -carbinols, appears to be a general solution for the synthesis of [3.n.1] oxa-bicycle systems which have proven challenging to construct in other natural product targets.¹²

In conclusion, we have demonstrated that anionic catalysts coupled with a 1,3-Brook rearrangement largely overcomes lack of generality in nucleophile catalyzed coupling of allenates and aldehydes. We anticipate that our anionic catalyst approach will be useful with other silyl-containing Michael acceptors. Finally, to highlight the utility of allenate carbinols conveniently obtained using the present method, we demonstrated a three-step convergent synthesis which provided the carbon framework and most of the functionality of the natural product vitisinol D. Our full total synthesis along with additional studies will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.
Anion-catalyzed versus traditional MBH reactions

Scheme 2.
Model synthesis of vitisinol D.

Table 1

Role of catalyst and reaction conditions on yield of **3c**.

entry	catalyst	mol%	1:2	T (°C)	time, h	%yield 3c ^a
1	LiOPr ⁱ	10	100:0	-20	6	25 ^b
2	LiOPr ⁱ	20	100:0	0	1	52
3	LiOPr ⁱ	20	100:0	-20	2	64
4	LiOPr ⁱ	20	100:0	-78	8	35 ^c
5	LiOPr ⁱ	70	100:0	-78	1.5	74
6	LiOPr ⁱ	70	60:40	-78	4	78
7	LiOEt	20	60:40	-20	2	76
8	LiOMe	20	60:40	-78	2	69
9	LiSPh	20	60:40	-10	2	55
10	KOBu ^t	70	60:40	-78	1	10
11	LiOPr ⁱ	70	30:70	0	5	67 ^d
12	LiOPr ⁱ	70	60:40	rt	6	NR ^e
13	LiOPr ⁱ	70	60:40	rt	6	NR ^f

^a Isolated yields.

^b 60% SM recovered.

^c 50% SM recovered.

$d_{\text{Solvent Et}_2\text{O}}$
 $\epsilon_{\text{Solvent toluene}}$
 $f_{\text{Solvent CH}_2\text{Cl}_2}$

Table 2

Substrate generality for anion catalyzed addition reaction

entry	R ¹	R ²	X or R ³	product	time, h	%yield 3 ^d
1	Et	ⁱ Pr	OMe	3a	1	64
2	Et	Bn	OMe	3b	1	66
3	Ph	Me	OMe	3c	1	71
4	Ph	Me	OMe	3d	2	68 ^b
5	Et	Bn	H	3e	1	71
6	Et	Bn	Me	3f	2	79
7	Et	Bn	^t Bu	3g	2	76
8	Et	Me	^t Bu	3h	1.5	78
9	Et	Me	Cl	3i	1	77
10	Et	Me	NO ₂	3j	1	59
11	Et	Me	F	3k	1.5	81
12	Et	Bn	C≡CC ₆ H ₁₃	3l	1	86
13	Et	Bn	^t Bu	3m	1.5	93
14	Et	Bn	Cyclohexyl	3n	1	91
15	Et	Bn	4-pyridyl	3o	1	76

^a Isolated yields.

^b The TES-analog of allene **4** was used here, reaction temp -10 °C, leading to TES-protected allenolate carbinol **3d**