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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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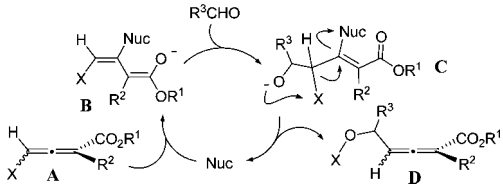
Catalytic reactions that lead to functionally dense intermediates are of great value in target-oriented synthesis. We are particularly interested in allenyl carbonyls and their synthetic utilization, given their unique juxtaposition of functional groups, including the reactively distinct cumulated double bonds. As part of our ongoing efforts on the total synthesis of vitisinol D, an antithrombotic natural product,[1] we required a general and robust method for the preparation of γ-carbinol allenoates as a multifunctional coupling partner for maximal convergency. A review of existing methods, including those developed in our laboratory,[2] revealed no efficient catalytic approach to the synthesis of these allenoates 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 appears to work only 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 proton transfer followed by catalyst elimination to regenerate the orginal 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 because of their overall neutral charge, intermediates such as **B** have poor nucleophilicities, leading to slow addition.

Scheme 1. Anion-Catalyzed versus Traditional MBH Reactions



Though unprecedented, a logical remedy might be to use anionic catalysts, leading to intermediate **B** having a net negative charge and possessing enolate-like reactivity. However, others have demonstrated with acrylates that an anionic nucleophile (PhSLi) allows only 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 because of 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 allenoates would lead to intermediates **C** in which Nuc would eliminate to form allenic unsaturation with greater facility as a result of the enhanced propensity of the silyl group to undergo a 1,3-shift relative to the proton of the classic MBH reaction (X = R_3Si vs H).

To test our hypothesis, we first prepared γ-TMS allenyl ester **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 $LiOPr^i$ led to regiospecific γ-carbinol products **3**, in most cases within several hours. Thus, with 20 mol % $LiOPr^i$, the addition of *p*-anisaldehyde to **1** to give **3c** was complete within 1 h at 0 °C (entry 2). In 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 lower temperature slowed the reaction considerably, but we found that reasonable reaction times (4−5 h) could be realized simply by increasing the amount of catalyst to 70 mol %. Importantly, the lower temperature did appear to depress the formation of dehydration side products, leading to a 20% increase in yield (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 phosphines[10] 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-keto esters.[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** (see the scheme in 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 gave good yields with a variety of α-substituents in allene **4**, which is a significant advantage over previous related methods (Table 2).[4] Use of either electron-withdrawing or electron-donating groups on the aryl aldehyde had virtually no effect on the formation of carbinol **3**, giving in either case moderate to high yields. The ester groups in allenes **4** are also compatible with the alkoxide catalyst in that no transesterification was observed, including with phenoxide esters (entries 3 and 4). Significantly, aliphatic and alkynyl aldehydes were 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 a hydroxyl-protected carbinol allenoate. We thus performed an alkoxide-catalyzed reaction with γ-triethylsilyl allenoate phenyl ester in order to obtain TES-protected alcohol **3d**. The reaction gave good yields and was complete in 1 h at −10 °C (Table 2, entry 4). In addition

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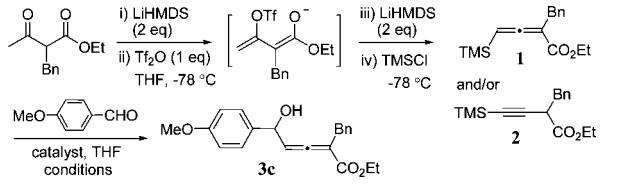
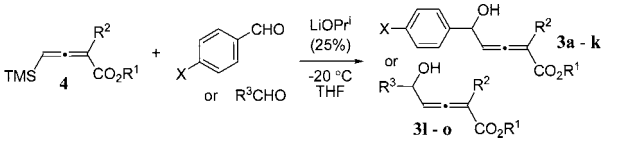
Table 1. Role of Catalyst and Reaction Conditions in Yield of **3c**



entry	catalyst	mol %	1/2	*T* (°C)	time (h)	yield of **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] Recovered 60% of the starting material. [c] Recovered 50% of the starting material. [d] Et_2O solvent. [e] Toluene solvent. [f] CH_2Cl_2 solvent.

Table 2. Substrate Generality in the Anion-Catalyzed Addition Reaction



entry	R^1	R^2	X or R^3	product	time (h)	yield of **3** (%)[a]
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_6H_{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

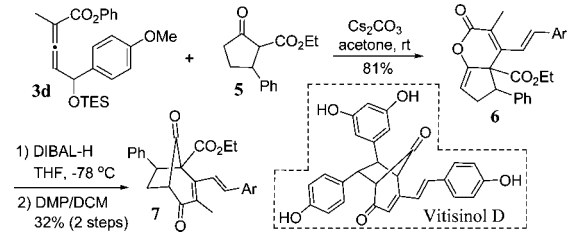
[a] Isolated yields. [b] The TES analogue of allene **4** was used here, at a reaction temperature of −10 °C, leading to the TES-protected allenoate carbinol **3d**.

to the economization of 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 aimed toward the total synthesis of vitisinol D, we recently discovered that stabilized enolates are highly effective in double-addition reactions to allenoates. Thus, cyclic β-keto ester **5** was successfully added to allenoate **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 formed by 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 two-step yield of 32%. Importantly, this "reductive aldol" strategy, enabled by our convenient preparation of allenoate γ-carbinols, appears to be a general solution for the synthesis of [3.*n*.1] oxabicycle systems, which have proven challenging to construct in other natural product targets.[12]

In conclusion, we have demonstrated that the use of anionic catalysts coupled with a 1,3-Brook rearrangement largely overcomes the lack of generality in nucleophile-catalyzed coupling of allenoates and aldehydes. We anticipate that our anionic-catalyst approach will be useful with other silyl-containing Michael acceptors. Finally, to highlight the utility of the allenoate carbinols conveniently obtained using the present method, we demonstrated a three-step convergent synthesis that 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.

Scheme 2. Model Synthesis of Vitisinol D



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Supporting Information Available: Experimental procedures and spectral data for all of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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