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Direct, Mild, and General *n*-Bu₄NBr-Catalyzed Aldehyde Allylsilylation with Allyl Chlorides

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Abstract

A direct, mild, and general method for the enantioselective allylsilylation of aldehydes with allyl chlorides is reported. The reactions are effectively catalyzed by 5 mol% of *n*-Bu₄NBr, and this rate acceleration allows the use of complex allyl donors in fragment-coupling reactions and of electron-deficient allyl donors. The results are 1) significant progress toward a “universal” asymmetric aldehyde allylation reaction that can reliably and highly stereoselectively couple any allyl chloride-aldehyde combination, and 2) the discovery of a novel mode of nucleophilic catalysis for aldehyde allylsilylation reactions.

Graphical abstract

Despite major progress on effective methods for highly stereoselective aldehyde allylation^{1,2} and crotylation³ reactions, including the Krische approach which heretofore uniquely obviates preformation and isolation of the active allylmethyl species,⁴ the full potential of this reaction type remains unfulfilled. For example, direct fragment coupling allylation reactions with complex and high MW allyl donors (*e.g.* the hypothetical synthesis of the EF half of spongistatin 1 by way of a direct coupling of (*E*)-4-chloropenta-2,4-dienal (1) and complex allyl chloride 2 (Figure 1a) are essentially unknown.⁵ More generally, the development of a “universal” Type 1⁶ aldehyde allylation reaction that can directly and efficiently couple *any* allyl-X donor in a practical and sustainable way and with reliably high levels of both efficiency and stereoselectivity would greatly expand the utility of this reaction type in the synthesis of a broad array of structurally diverse targets (Figure 1b). Our second-generation allylsilylation methodology⁷ is characterized by many of the attributes

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Supporting Information. Experimental procedures and compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Notes

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listed in Figure 1b, but the scope with respect to the allyl donor is limited to simple low MW and alkyl-substituted (*i.e.* electron-rich) allyl fragments by the requirement for preformation (by way of the Benkeser-Furuya reaction^{8,9}) and isolation of the allyl trichlorosilanes and by limited allylsilane reactivity, respectively (Figure 1c). To more fully realize a “universal” and direct allylation reaction, we set out to address these serious limitations and report herein that the critical enabling discovery was that these allylsilylation reactions are effectively catalyzed by tetrabutylammonium bromide.

At the outset, we were optimistic that the Benkeser-Furuya reaction could be effectively telescoped¹⁰ with the allylation reaction given that its only byproduct is Et₃N•HCl. This turned out not to be the case, however, as the fully telescoped reaction with dihydrocinnamaldehyde led to the isolation of the product in only 34% yield (Table 1, entry 1), a result that may be attributed to silylchlorohydrin formation (see Figure S1 and structure F in Figure 4b, below) in direct analogy to the observations of Denmark in Lewis base-catalyzed reactions of allyl- and enoltrichlorosilanes with unhindered aliphatic aldehydes.¹¹ In the course of our attempts to overcome this problem, we found that whereas CuBr performed no better than CuCl (entry 2), use of the crotyl bromide starting material led to improved results (entry 3). While this was encouraging, the considerable practical advantages that would accrue from the use of allyl chlorides led us to wonder whether the bromide ion generated in this reaction may be catalyzing the reaction, and in turn that the reaction with crotyl chloride might be rendered efficient by adding a bromide ion source. Indeed, it was found that 5 mol % of *n*-Bu₄NBr had a dramatic impact on the efficiency of the reaction with crotyl chloride (entry 4), and we note that the *n*-Bu₄NBr has no impact on the Benkeser-Furuya reaction and that there is no Finkelstein reaction under these conditions (see Figure S2). A survey of other salts revealed that *n*-Bu₄NI is equally effective (entry 5) while *n*-Bu₄NOTf, *n*-Bu₄NBF₄, and *n*-Bu₄NPF₆ were found to be competent but less efficient catalysts (entries 6–8).

With optimized conditions identified, we set out to explore the scope of the reaction with respect to the allyl chloride (Table 2). Methallyl chloride (entry 1), and functionalized methallyl chlorides (entries 2 and 3) work well in the reaction, as do *trans*-crotyl chloride (entries 4 and 5), a substituted *trans*-crotyl chloride (entry 6), and *trans*-cinnamyl chloride (entry 7). Entry 6 is particularly noteworthy as the product of that reaction was an intermediate in our synthesis of a “methyl-extended” linker-equipped analog of dictyostatin¹² that was previously prepared by an only moderately diastereoselective and inefficient process. 3,3-Disubstituted allyl chlorides also work well and allow the establishment of all-carbon quaternary centers (entries 8 and 9).¹³ Halogens are well tolerated at the 2-position of the allyl chloride leading to usefully functionalized alkene products (entries 10 and 11),¹⁴ while heteroatom (Cl,¹⁵ BPin¹⁶) substitution is also well tolerated at the 3-position (entries 12–15). Control reactions with no *n*-Bu₄NBr established that the catalysis is in most cases critical for synthetically useful results (entries 4a, 5, 6, 9, 12, and 13), and whereas the reactions with simple alkyl-substituted (*i.e.* electron-rich) allyl donors are efficient when run with isolated allyltrichlorosilanes (*cf.* Figure 1c), reactions with electronically deactivated allyl donors (entries 10–15) are not. Thus, in addition to enabling the significant practical advance of the fully telescoped procedure that obviates the

technically difficult and tedious isolation of the allyltrichlorosilanes, the *n*-Bu₄NBr catalysis also enables a substantial expansion in scope with respect to the allyl donor.

To demonstrate that the *n*-Bu₄NBr catalysis can enable direct complex fragment coupling reactions, we used diallyl chloride 5 to allylate aldehyde 6 to give 7 in 89% yield and 95% ee (Figure 2). Alcohol acetylation produced 8, which, like allyl chloride 2 comprises stereochemical complexity near the allyl chloride as well as an acid-sensitive ketal. Initial attempts to allylate aldehyde 1 with 8 were unsuccessful due to ketal degradation presumably caused by adventitious HCl generated in the Benkeser-Furuya reaction. While simply using excess Et₃N could in principle be a simple solution to this problem, in practice excess Et₃N negatively impacts the ligand complexation. Fortunately, we found that 2,6-di-*t*-Bu-pyridine is an effective and otherwise innocent base, and these modified conditions led to the isolation of 9 in 77% yield and 20:1 dr. In addition to serving as a meaningful model for the spongistatin 1 EF fragment synthesis (*cf.* Figure 1a), this 3-step sequence also demonstrates the direct use of 5 as a linchpin reagent, allowing the rapid buildup of complexity from simple starting materials.

We have measured the rate of conversion of the *trans*-crotylation of benzaldehyde starting from *trans*-crotyltrichlorosilane with 5 mol % *n*-Bu₄NBr and with no additive (Figure 3). As chloride ion is present in these reactions and may also be catalyzing the reaction, we also endeavored to prepare a sample of chloride-free crotylsilane 10 in an attempt to measure the true coordinating anion-free background reaction. Though complete removal of the DBU•HCl salts by trituration is difficult, we were able to isolate a sample of 10 contaminated only with ~8% DBU•HCl, and treated it with 12 mol % AgBAR^F₄ (Ar^F = 3,5-(CF₃)₂C₆H₃)¹⁷ prior to using it in these experiments. As shown, the data establish that chloride and bromide greatly accelerate the reaction relative to the coordinating anion-free background reaction, strongly implying a direct role for the anion component of the tetrabutylammonium salts in the catalysis.

In considering the mechanism of the catalysis, we were cognizant of Berrisford's report that tetra-alkylammonium salts accelerate the DMF-promoted allylation of benzaldehyde with allyltrichlorosilane,¹⁸ and Denmark's demonstration that *n*-Bu₄NI or *n*-Bu₄NOTf led in a few cases to a modest increase in the efficiency of Lewis base-catalyzed reactions with aliphatic aldehydes that suffered from silylchlorohydrin formation.^{11,19} These effects were attributed to an increase in the ionic strength of the medium that would be expected to favor formation of the active ionic species 11 and to disfavor the formally neutral silylchlorohydrin 12 (Figure 4a). The data in Figure 3 strongly imply a direct role for the anion in our system, however, and our allylsilane (A, Figure 4b) has no ionizable substituent, rendering this mechanism highly implausible in our reactions. We propose instead that the catalyst X⁻ activates the allylsilane by forming allylsilicate B, which binds (C) and allylates (D) the aldehyde by way of a 6-coordinate silicate at a greatly accelerated rate (*k*_{X⁻}) over the coordinating anion-free background reaction (*k*₀) before releasing the catalyst and generating the product E (Figure 4b). A propensity to form dianion G would be expected to inhibit the reaction and this may provide an explanation for the poorer performance of certain anions. Indeed, treatment of crotylsilane 10 with excess *n*-Bu₄NBr led to ²⁹Si NMR resonances consistent with 5- and 6-coordinate silicates, thus providing direct spectroscopic

evidence for the formation of both B and G (Figure 4c). Though it has been shown that strong nucleophiles (*e.g.* fluoride, catecholate) may be used to pre-form 5-coordinate allylsilicates that are activated for aldehyde allylsilylation reactions,²⁰ the effective use of more weakly coordinating anions as catalysts reported here is without precedent. We suggest that the key to accessing this mode of nucleophilic catalysis is the pre-activation of the silane by ligand 3, which induces Lewis acidity⁷ sufficient for the reversible binding of less strongly nucleophilic anions.

We have discovered that tetrabutylammonium salts catalyze aldehyde allylsilylation reactions with our diaminophenol-ligated allylsilanes. This catalysis allows both for a significant expansion in scope with respect to the allyl donor and for the direct use of allyl chlorides without preformation and isolation of the allyltrichlorosilanes, which in turn allows, uniquely, for the direct use of stereochemically and/or functionally complex allyl donors in fragment coupling allylation reactions. The result is the most significant progress yet reported toward the realization of a “universal” direct aldehyde allylation reaction possessed of the attributes outlined in Figure 1b. Mechanistically, we have secured evidence that the catalyst plays a direct role in accelerating the carbon-carbon bond-forming event by accessing the more reactive 5-coordinate allylsilicate, and this may have implications for the design of catalytic enantioselective variants of this reaction as well as for the catalysis of a range of otherwise difficult transformations. Efforts along these lines and to further elucidate the mechanistic details of the catalysis are underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

(a) A hypothetical direct complex fragment coupling allylation of aldehyde 1 with stereochemically and functionally complex allyl chloride 2. (b) Desirable attributes of a “universal” and direct aldehyde allylation reaction. (c) Our allylsilylation method entails preformation and isolation of the allyl trichlorosilanes, and has a limited scope with respect to the allyl donor.

Figure 2.

Model fragment coupling allylation reaction for the synthesis of the EF-half of spongistatin 1.

Figure 3.

Rate measurements of the crotylation of PhCHO. Each data point is the average of 3 runs (2 in the case of chloride-free silane **10**), measuring the disappearance of PhCHO (measuring the appearance of product gives similar results) against a quantitative internal standard by ¹H NMR spectroscopy

Figure 4.

(a) Mechanistic scheme for Denmark's LB-catalyzed allylation and aldol reactions. (b) Proposed mechanism of the anion-catalyzed allylation reaction. (c) Spectroscopic evidence for the formation of B and G.

Table 1

Reaction optimization

entry	X	CuY	additive	yield (%)
1	Cl	CuCl	–	34
2	Cl	CuBr	–	27
3	Br	CuBr	–	76
4	Cl	CuBr	<i>n</i>-Bu₄NBr	86
5	Cl	CuBr	<i>n</i> -Bu ₄ NI	86
6	Cl	CuBr	<i>n</i> -Bu ₄ NOTf	76
7	Cl	CuBr	<i>n</i> -Bu ₄ NBF ₄	77
8	Cl	CuBr	<i>n</i> -Bu ₄ NPF ₆	54

Table 2

Exploration of scope for the allyl chloride

entry	allyl chloride	product	yield (%) ^a	ee (%)
1			90	97
2			72	94
3			88	95
4a			86 (27)	97
5 ^b			90 (84)	91
6 ^c			83 (13)	94
7			96	97
8			93	92
9			83 (61)	95
10			74	98
11			71	99
12			78 (24)	95

entry	allyl chloride	product	yield (%) ^a	ee (%)
13 ^b			74 (16)	93
14			72	96
15			95	94

^aThe values in parentheses are the yields of the reactions with no added *n*-Bu₄NBr under otherwise identical conditions.

^bThese reactions were conducted with benzaldehyde.

^cThis reaction was conducted with aldehyde 4, and treated with 1 M HCl prior to workup and product isolation to hydrolyze the ketal.