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A More Comprehensive and Highly Practical Solution to Enantioselective Aldehyde Crotylation

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Supporting Information

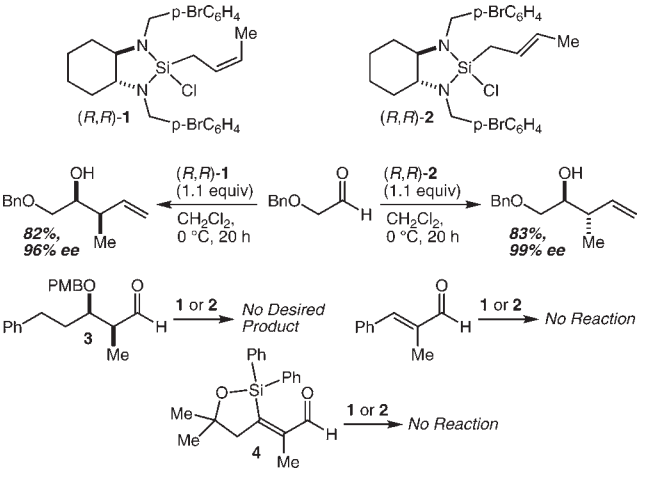
ABSTRACT: The enantioselective crotylation of aldehydes with 1,2-diaminochlorocrotylsilane reagents is effectively catalyzed by $Sc(OTf)_3$. The one significant limitation on the utility of these reagents — substrate scope — has thus been addressed. The net result is the most comprehensive and highly practical method for enantioselective aldehyde crotylation yet advanced.

Due to the direct relevance of the products to important classes of natural products, the development of diastereo- and enantioselective aldehyde crotylation reactions has been the subject of an enormous amount of effort over the past three decades. The first generally highly diastereo- and enantioselective and practicable solution was advanced by Brown in 1986,[1] and remarkably, this chiral crotylborane methodology remains the most widely employed to the present day.[2] Despite what might be assumed based on its near-total dominance of the market, the Brown method does suffer both from an inability to fully or even partly overcome the inherent diastereofacial bias of certain chiral aldehydes[3] and from significant practical liabilities.[4] Because of this, efforts to supplant it as the method of choice have continued,[5] with only limited success.

Our previously reported crotylsilanes **1** and **2** are crystalline solids that may be prepared in bulk and stored, and that react with aldehydes at 0 °C over the course of ~20 h to consistently provide enantioselectivities (93−99% ee) among the highest ever recorded for aldehyde crotylation reactions (Scheme 1).[6] While these characteristics go a long way toward realization of a more practical and user-friendly system, the reagents suffer from one highly significant limitation: the substrate scope is exceedingly narrow with aromatic, unsaturated, and sterically hindered aliphatic aldehydes all giving moderate to low yields, or even, in many cases, no product at all. For example, reagents **1** and **2** completely fail to react productively or at all with **3**, α-methylcinnamaldehyde, and **4**.

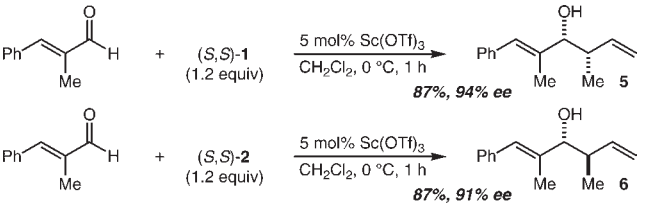
Because the successful crotylation of aldehydes such as **4** is relevant to several current synthetic projects in our group, we recently decided to revisit this methodology and attempt to solve the reactivity problem. We had two relevant pieces of information at the outset: (1) protonation of our aminochlorosilane Lewis acids (by way of reaction with protic nucleophiles, which displace the chloride and generate an equivalent of HCl) leads to a significant boost in their reactivity,[7] and (2) Lewis acids[8] ($Sc(OTf)_3$ is particularly effective) and Brønsted acids[9] may be used to catalyze the reactions of allylboronates with aldehydes by

Scheme 1



binding or protonating one of the boronate oxygen atoms. Initial experiments quickly revealed that whereas both Brønsted and Lewis acids could effectively catalyze the reactions of **1** and **2** with aldehydes, the Brønsted acid catalyzed reactions were generally less highly enantioselective. A broad screen of Lewis acids revealed that $Sc(OTf)_3$ provided the best combination of high enantioselectivity and effective catalysis.[10] Thus, treatment of α-methylcinnamaldehyde with reagents (*S*,*S*)-**1** and (*S*,*S*)-**2** and 5 mol % $Sc(OTf)_3$ in CH_2Cl_2 at 0 °C for 1 h led to the isolation of products **5** and **6** as single diastereomers (≥40:1 dr) in 87% yield and 94% and 91% ee, respectively (Scheme 2).

Scheme 2



The results of a survey of the crotylation reactions of three standard aldehydes using silanes (*S*,*S*)-**1** and (*S*,*S*)-**2** are compiled in Table 1. As shown, the yields and enantioselectivities are

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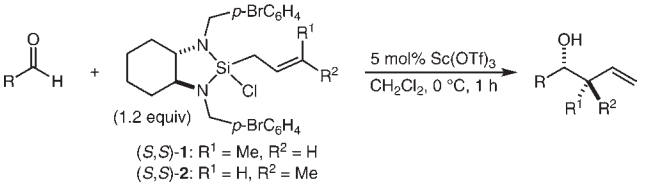
Table 1. $Sc(OTf)_3$-Catalyzed Aldehdye Crotylation Reactions



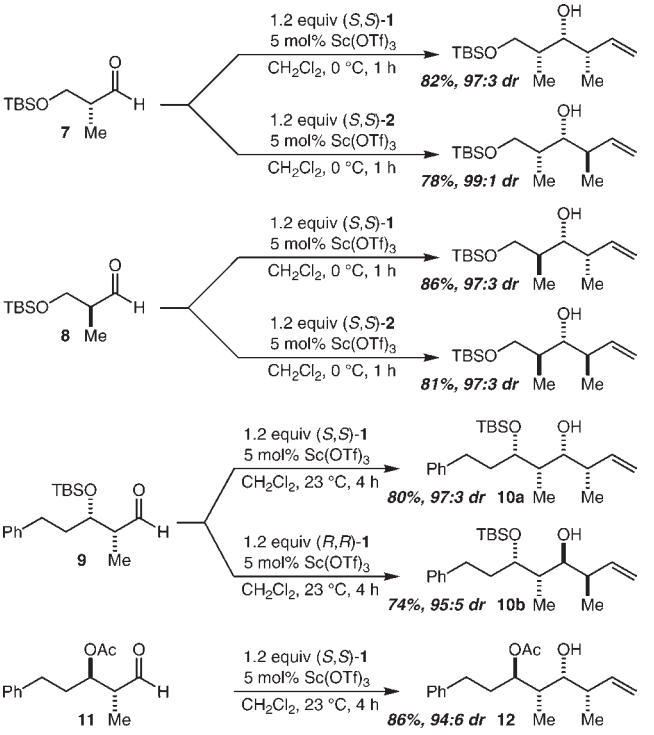
entry	R	silane	yield (%)	ee (%)
1	$PhCH_2CH_2$	(*S*,*S*)-**1**	96	96
2	$PhCH_2CH_2$	(*S*,*S*)-**2**	96	97
3	Ph	(*S*,*S*)-**1**	94	93
4	Ph	(*S*,*S*)-**2**	96	91
5	(*E*)-PhCH=CH	(*S*,*S*)-**1**	96	95
6	(*E*)-PhCH=CH	(*S*,*S*)-**2**	93	91

excellent across the board (in all cases the diastereoselectivity was ≥40:1), whereas the corresponding reactions without $Sc(OTf)_3$ required significantly longer reaction times (~20 h) and provided yields that were in the range 52−83%.[6]

Complex chiral aldehydes such as **3** represent one of the more important classes of aldehydes for crotylation reactions, and any method that would lay claim to being a comprehensive solution should be able to provide for high levels of reagent control for all possible stereochemical permutations. Commonly employed Roche ester-derived aldehydes **7** and **8**[11] were treated with (*S*,*S*)-**1** and (*S*,*S*)-**2** using the standard conditions outlined above, and in every case the reactions proceeded with excellent diastereoselectivity (≥97:3 dr, major diastereomer:sum of all minor diastereomers) corresponding to reagent control (Scheme 3). While these results were encouraging, it is also the case that aldehydes with a chiral center at the β-position (e.g., **3**) can be more challenging, and indeed most of the cases where the Brown reagents cannot override the diastereofacial bias of a chiral aldehyde fall into this category.[3b−e] We therefore prepared aldehyde **9** and subjected it to reaction with (*S*,*S*)-**1** and (*R*,*R*)-**1** using the same reaction conditions as above. Although the reactions were slower, requiring ~4 h at ambient temperature to proceed to completion, they delivered the products of reagent control (**10a** and **10b**, respectively) in good yields and with excellent levels of diastereoselectivity. Product **10b** is of particular interest because the Brown method cannot deliver this stereochemical permutation at all with a β-TBS protecting group on the aldehyde[3d] and with better than 2:1 diastereoselectivity with a β-PMB protecting group.[3c] Aldehyde **11** was also subjected to crotylation with (*S*,*S*)-**1** leading to the isolation of **12** in 86% yield and with 94:6 diastereoselectivity. The stereochemical array in **12** is another that may not be accessed highly selectively with the Brown method,[12] further supporting the claim that the present method is possessed of greater scope and an ability to override the diastereofacial biases of some of the most difficult chiral aldehydes.

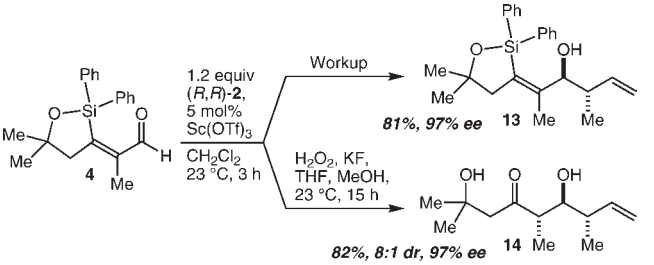
Finally, we examined the crotylation of aldehyde **4**, one of the more sterically and electronically deactivated aldehydes relevant to polyketide natural product synthesis imaginable. Reaction with (*R*,*R*)-**2** and 5 mol % $Sc(OTf)_3$ (CH_2Cl_2, 23 °C, 3 h) led to the isolation of **13** in 81% yield and 97% ee (Scheme 4).

Scheme 3



Alternatively, the unpurified reaction mixture may be submitted to a Tamao oxidation/diastereoselective tautomerization reaction[13] to provide **14** in 82% yield (with 8:1 diastereoselectivity for the stereocenter α to the ketone) and 97% ee. This one pot conversion of **4** to **14** explicates our interest in aldehydes like **4** and highlights the power of the methodology rapidly to deliver stereochemically complex polyketide fragments.

Scheme 4



Although the main focus of this study is crotylation reactions, we have confirmed that, as expected, $Sc(OTf)_3$ is an effective catalyst for the corresponding reactions of the parent allylsilane reagent **15**.[14] Thus, reaction of aldehydes **7** and **8** with (*S*,*S*)-**15** and 5 mol % $Sc(OTf)_3$ (CH_2Cl_2, 0 °C, 1 h) gave the illustrated products in 77 and 83% yields respectively and with >99:1 diastereoselectivity in both cases (Scheme 5).

In order fully to leverage the fact that the silane reagents are crystalline solids and render the experimental procedures as straightforward as possible, we have prepared mixtures of the crotylsilanes **1** and **2** and the allylsilanes **15** with $Sc(OTf)_3$ in a 25:1 molar ratio for which we propose the general names

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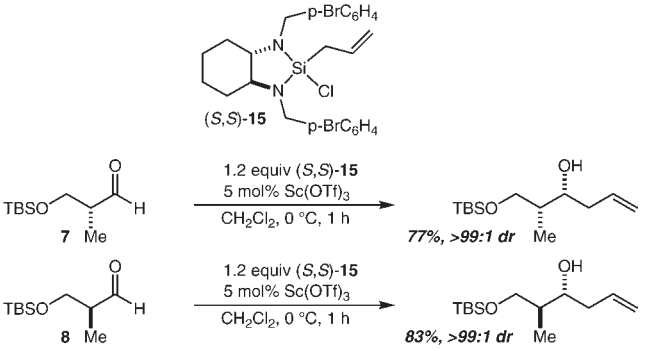
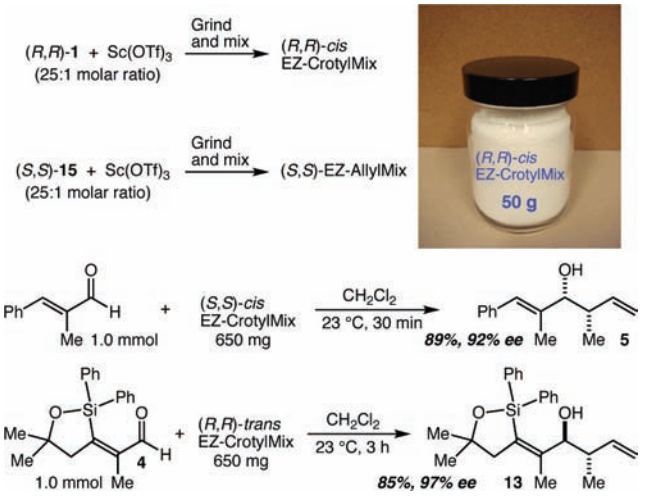
Scheme 5



EZ-CrotylMix and EZ-AllylMix (Scheme 6). The use of 650 mg of an EZ-CrotylMix (or 635 mg of an EZ-AllylMix) per 1.0 mmol of aldehyde corresponds to 1.1 equiv of the silane and 4.4 mol % of $Sc(OTf)_3$. Thus, treatment of 1.0 mmol of α-methylcinnamaldehyde with 650 mg of (*S,S*)-*cis* EZ-CrotylMix (in CH_2Cl_2 at ambient temperature for 30 min) resulted in the isolation of **5** in 89% yield and 92% ee.[15] The EZ-CrotylMix stoichiometry (in the form of (*R,R*)-*trans* EZ-CrotylMix) also sufficed for less reactive aldehdye **4**, giving **13** in 85% yield and 97% ee. Of course, additional $Sc(OTf)_3$ or EZ-CrotylMix may be added to the reactions of particularly unreactive aldehydes, but this EZ-CrotylMix/EZ-AllylMix formulation appears to be effective for most aldehydes.

Scheme 6



$Sc(OTf)_3$ is an effective catalyst for the enantioselective crotylation of aldehydes using crotylsilanes **1** and **2**, and this has resulted in a dramatic increase in the scope of aldehydes that may be effectively crotylated using this methodology. Indeed, based primarily on the reactions of aldehydes **4**, **7**, **8**, **9**, and **11**, we may conclude that our method has a broader scope than any other asymmetric crotylation methodology. That the silanes and $Sc(OTf)_3$ are crystalline solids has further facilitated the EZ-CrotylMix formulation,[16] rendering this methodology the most comprehensive and highly practical solution to the enduring problem of enantioselective aldehyde crotylation yet advanced.

■ ASSOCIATED CONTENT

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

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(2) By performing a citation analysis on the two papers in ref 1, we have identified 32 distinct uses of the Brown crotylation method published in original research papers just in the period of 2009−2010.

(3) For example, see: (a) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1989**, *54*, 1570. (b) Ogawa, A. K.; Armstrong, R. W. *J. Am. Chem. Soc.* **1998**, *120*, 12435. (c) Kobayashi, Y.; Lee, J.; Tezuka, K.; Kishi, Y. *Org. Lett.* **1999**, *1*, 2177. (d) Nicolaou, K. C.; Fylaktakidou, K. C.; Monenschein, H.; Li, Y.; Weyershausen, B.; Mitchell, H. J.; Wei, H.-X.; Guntupalli, P.; Hepworth, D.; Sugita, K. *J. Am. Chem. Soc.* **2003**, *125*, 15433. (e) Zampella, A.; Sepe, V.; D'Orsi, R.; Bifulco, G.; Bassarello, C.; Valeria D'Auria, M. *Tetrahedron: Asymmetry* **2003**, *14*, 1787.

(4) The preparation of the requisite *cis*- or *trans*-crotylborane reagent entails the carefully (low and variable) temperature-controlled metalation of either *cis*- or *trans*-2-butene with *n*-BuLi and KO*t*-Bu, addition of the resulting crotylpotassium species to either (+)- or (−)-(*ipc*)$_2$BOMe, and then addition of BF_3•OEt_2 and the aldehyde. In addition, the workup procedure entails the oxidative cleavage of the borane from the product alcohol, which has the side effect of generating 2 equiv of isopinocampheol that can, and often does, render product isolation significantly more laborious.

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(10) Details of the results of our screen of Lewis acids are provided in the Supporting Information.

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(12) The analogous Brown crotylation of the β-OPMB aldehyde corresponding to **11** proceeded with 2:1 diastereoselectivity favoring the product analogous to **12** (see ref 3c). Although there is no evidence in the literature that β-OPMB and β-acyloxy groups have dramatically different impacts on the diastereoselectivities of these reactions, we nevertheless note the caveat that we cannot in this case make a direct comparison.

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(15) The experimental procedure is as follows: To a solution of 650 mg of (*S*,*S*)-*cis* EZ-CrotylMix in 10 mL of CH_2Cl_2 was added 1.0 mmol of α-methylcinnamaldehyde. The mixture was stirred vigorously for 30 min ($Sc(OTf)_3$ is only sparingly soluble in CH_2Cl_2, the stirring promotes its faster and more complete dissolution) and then concentrated. The residue was treated with Et_2O and 1 M HCl, and the resulting mixture was stirred vigorously for 1 h. The mixture was filtered (with Et_2O washes) to recover the diamine as its bis HCl salt (in 95% yield), and the layers of the biphasic filtrate were separated. The aqueous phase was extracted with Et_2O, and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated. The homoallylic alcohol **5** thus obtained was >95% pure (see the Supporting Information for a ^1H NMR spectrum of this material) but, for the purposes of obtaining an accurate isolated yield, was purified by flash chromatography. In most cases the entire procedure can be executed in ∼2−6 h.

(16) The allyl- and crotylsilanes and the EZ-CrotylMixes are commercially available from Sigma-Aldrich and Strem. The EZ-Allylmixes are in the late stages of development and will be available soon.