Enantioselective Allylation and Crotylation of in situ Generated β,γ-Unsaturated Aldehydes

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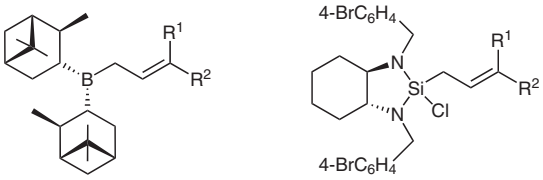
Abstract: β,γ-Unsaturated aldehydes generated in situ by treatment of 2-vinyloxiranes with a catalytic amount of $Sc(OTf)_3$ are effectively trapped by ring-strained allyl- and crotylsilane reagents to afford bishomoallylic alcohols as single diastereomers in high enantiomeric excess.

Key words: vinyloxiranes, enantioselective crotylation, silanes, Lewis acid catalysis, rearrangement reaction

The in situ generation of unstable intermediates and their subsequent conversion to diversified products has been a useful strategy for the preparation of compounds that are difficult to prepare by other means. For example, β,γ-unsaturated aldehydes have rarely been used[1] as building blocks in synthetic organic chemistry due to their very low stability with respect to olefin isomerization.[2] They can, however, be generated in solution by treatment with an appropriate Lewis acid (LA).[3,4] In recent years we have been interested in exploiting this rearrangement by the application of a variety of nucleophilic traps.[5] We were particularly pleased to observe that use of allylB(Ipc)$_2$[6] (**1**, Figure 1) gave enantiomerically enriched bishomoallylic alcohols in high yield with exceptional selectivity and good substrate scope.[5b]

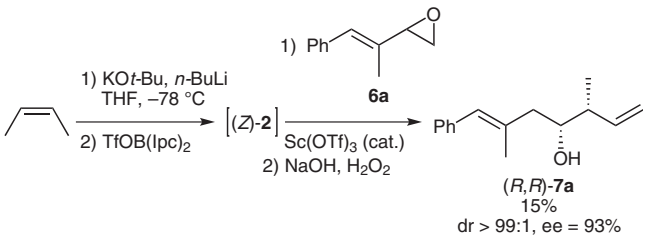


1: $R^1 = R^2 = H$
(*E*)-**2**: $R^1 = H$, $R^2 = Me$
(*Z*)-**2**: $R^1 = Me$, $R^2 = H$

3: $R^1 = R^2 = H$
(*E*)-**4**: $R^1 = H$, $R^2 = Me$
(*Z*)-**4**: $R^1 = Me$, $R^2 = H$

Figure 1 Reagents for asymmetric allylation and crotylation

With this result in hand, it seemed that effecting asymmetric crotylation would be a relatively simple extension, since the corresponding (*E*)- and (*Z*)-crotylB(Ipc)$_2$ [(*E*)-**2** and (*Z*)-**2**, respectively] derivatives are well known.[7] Unfortunately, this was not the case and the difficulty lay in the required protocol for their preparation.[7c] The addition of metalated (*E*)- or (*Z*)-2-butene[8] to *B*-methoxydiisopinocampheylborane[9] does not directly afford the reactive nucleophile but rather results in the formation of an 'ate' complex which must be subsequently decomposed with 1.33 equivalents of $BF_3{\cdot}OEt_2$.[10] The resulting crotyldialkylborane is then immediately used in reaction with various electrophiles. Although (*E*)-**2** [and (*Z*)-**2**] are configurationally stable below –45 °C,[7d] borotropic rearrangement occurs at higher temperatures precluding isolation of these compounds. The additional additives imparted from the metalation of 2-butene (K^+ and Li^+ ions) and necessary decomposition of the intervening 'ate' complex proved to be incompatible with the sensitive rearrangement sequence required of the 2-vinyloxiranes. Control experiments with allylB(Ipc)$_2$ demonstrated that the large excess of $BF_3{\cdot}OEt_2$ was not the culprit,[11] and it is likely that the large amount of methoxide present is the principle cause. We speculated that a less Lewis basic counterion than methoxide might avoid the formation of that 'ate' complex and negate the necessity of adding $BF_3{\cdot}OEt_2$. To this end we prepared TfOB(Ipc)$_2$[12] and tested its ability to act as a substitute for MeOB(Ipc)$_2$ (Scheme 1). With the model vinyl oxirane **6a** we were pleased to observe the formation of a single diastereomer of the desired bishomoallylic alcohol **7a** in high enantiomeric excess. Unfortunately, the yield was low, and most probably is due to over-addition of the highly nucleophilic anion of metalated 2-butene to the boron center forming an unreactive ate complex [(crotyl)$_2$B(Ipc)$_2$]$^-$.[13] We were unable to improve the yield by modification of the order of addition of reagents or by changing the nature of the leaving group. Consequently, we were forced to consider the application of other nucleophilic species.



Scheme 1 Enantioselective crotylation

Since the seminal report by Hoffmann[14] over two decades ago, many classes of allylic organometallic reagents[15] have been developed to prepare nonracemic homoallylic alcohols. Of these we selected the recently developed allyl- (**3**) and crotylsilane reagents [(*E*)-**4** and (*Z*)-**4**] as they

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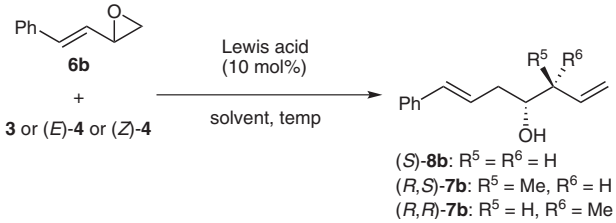
most closely satisfied our perceived requirements (Figure 1).[15c–h] Namely, the reagent must be isolable, prepared as either antipode, nonbasic, nonnucleophilic in the absence of a carbonyl species, compatible with Lewis acids, and afford products in predictable high diastereoselectivity and enantioselectivity.

Conditions for the rearrangement–allylation sequence with Leighton's allylating reagent **3** were briefly surveyed (Table 1). Combining the conditions established for the racemic[5a] and enantioselective[5b] allylation of in situ generated β,γ-unsaturated aldehydes with those used for Leighton allylation of conventional aldehydes,[15f] imposed significant limitations on the conditions (LA, solvent, and temperature) that could be used for our purposes with a reasonable chance of success. With some experimentation, we found that slow addition of a solution of the vinyl oxirane **6b** (over 3 h) to a cooled solution of the LA and **3** was the best method to limit byproduct formation.

Table 1 Optimization of Reaction Conditions



Entry	Conditions	Product	Yield (%)[a]	ee (%)[b]
1	**3**, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C	(*S*)-**8b**	0[c]	–
2	**3**, $Sc(OTf)_3$, CH_2Cl_2, 0 °C	(*S*)-**8b**	45	85
3	**3**, $Sc(OTf)_3$, Et_2O, 0 °C	(*S*)-**8b**	72	96
4	**3**, $Sc(OTf)_3$, Et_2O, –10 °C	(*S*)-**8b**	67	86
5	**3**, $Sc(OTf)_3$, THF, 0 °C	(*S*)-**8b**	62	64
6	**3**, $Sc(OTf)_3$, PhMe, 0 °C	(*S*)-**8b**	21	81
7	(*E*)-**4**, CH_2Cl_2, 0 °C	(*R*,*S*)-**7b**	51	92
8	(*E*)-**4**, Et_2O, 0 °C	(*R*,*S*)-**7b**	12	62
9	(*E*)-**4**, PhMe, 0 °C	(*R*,*S*)-**7b**	51	89
10	(*Z*)-**4**, CH_2Cl_2, 0 °C	(*R*,*R*)-**7b**	39	82
11	(*Z*)-**4**, Et_2O, 0 °C	(*R*,*R*)-**7b**	19	82
12	(*Z*)-**4**, PhMe, 0 °C	(*R*,*R*)-**7b**	58	86

[a] Isolated yields.
[b] The ee were determined by CSP-HPLC.
[c] Complete decomposition of starting materials.

In an early experiment, we found the reagent **3** to be incompatible with $BF_3{\cdot}OEt_2$ (Table 1, entry 1), however, the use of $Sc(OTf)_3$, another optimal LA for the rearrangement reaction,[5] gave more promising results (Table 1, entry 2).[16] The best results, in terms of both yield and ee were obtained with Et_2O as the solvent (Table 1, entry 3). Attempts to lower the reaction temperature resulted in significantly decreased enantioselectivity (Table 1, entry 4), an effect that was observed previously with **3**.[15f] Using either THF or toluene as the solvent resulted in decreased yield and enantioselectivity of the reaction.

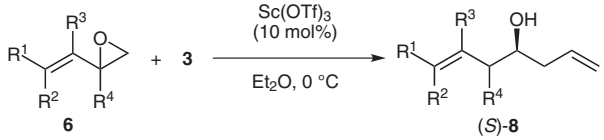
Optimization of the crotylation reaction using **6b** was limited to solvent effects, and the mode of addition was the same as for allylation. The use of CH_2Cl_2 afforded the products (*R*,*S*)- and (*R*,*R*)-**7b** in moderate yield and good ee, employing (*E*)- and (*Z*)-**13**, respectively (Table 1, entries 7 and 10). Surprisingly, when the conditions used for allylation were applied to the crotylation reaction (Table 1, entries 8 and 11), a large decrease in both yield and enantioselectivity was observed. However, we were pleased to find that by using toluene as the solvent (Table 1, entries 9 and 12), both the enantioselectivity and yields of the products (*R*,*S*)- and (*R*,*R*)-**7b** were improved.

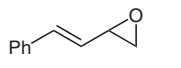
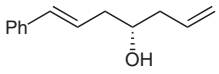
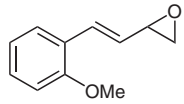
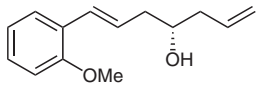
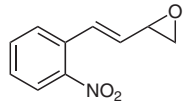
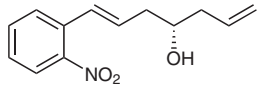
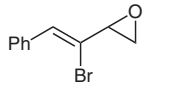
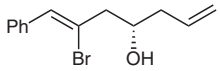
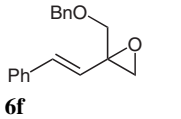
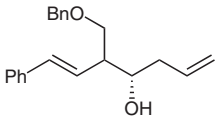
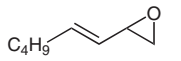
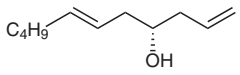
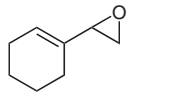
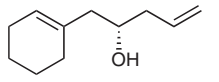
With optimal conditions in hand, we began studies on the scope of the allylation reaction (Table 2). Better results, in terms of both enantioselectivity and yield, were obtained for electron-neutral substrates (e.g., **6b**) than for electron-rich (**6c**) or electron-poor (**6d**) ones (Table 2, cf. entry 1 and entries 2 and 3). Sterically hindered substrates **6e** and **6f** (Table 2, entries 4 and 5) also performed well under these conditions. Allylation of aliphatic vinyloxiranes **6g** and **6h** afforded products (*S*)-**8g** and (*S*)-**8h**, respectively, in high ee, but with slightly decreased yields as compared to the aromatic substrates. In most cases, the yields and enantioselectivites obtained with vinyloxiranes **6** are comparable to those observed in the allylation of conventional aldehydes with **3**.[15f] As compared to the previously reported Brown allylation of vinyloxiranes **6**,[5b] the enantioselectivities observed for the Leighton allylation are in some cases slightly diminished and the yields are somewhat lower for most examples. A notable exception to these trends is the result for **6e** (Table 2, entry 4), a substrate that failed completely using the Brown protocol.[5b] Significantly, this demonstrates the complimentarity of these methods, and we have shown that the product (*S*)-**8e** of this reaction has high synthetic utility in the preparation of complex structures.[17]

Using the protocol developed for the enantioselective crotylation of **6b** (Table 1), we began expanding the scope of the reaction (Table 3). There did not appear to be a significant difference in yield or enantioselectivity obtained with (*E*)- and (*Z*)-**4**, and in all cases diastereoselectivity was in excess of 19:1. The yields in all cases were modest, but the enantioselectivities ranged from good to excellent. In contrast to the allylation reaction, aromatic substrates bearing electron-withdrawing substituents (**6d** and **6e**) afforded the products in somewhat higher ee (Table 3, entries 5–8) than those with electron-donating or electron-neutral substituents (Table 3, entries 1–4), but with slightly decreased yields.

Sterically hindered substrates (e.g., **6f**) faired relatively well in both of these aspects (Table 3, entries 9 and 10), although the diastereoselectivities (with respect to the

Table 2 Allylation Scope[18]



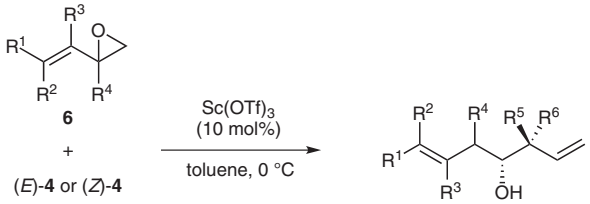
Entry	6	8	Yield (%)	ee (%)
1	 **6b**	 (*S*)-**8b**	73	96
2	 **6c**	 (*S*)-**8c**	61	90
3	 **6d**	 (*S*)-**8d**	57	93
4	 **6e**	 (*S*)-**8e**	67	94
5	 **6f**	 (*S*)-**8f**	68	97[a]
6	 **6g**	 (*S*)-**8g**	53	95[b]
7	 **6h**	 (*S*)-**8h**	61	93[b]

[a] The product was a 1:1 mixture of diastereomers.
[b] The ee were determined by CSP-HPLC analysis of the 4-nitrobenzoate derivatives [(*S*)-**9g** and (*S*)-**9h**] for (*S*)-**8g** and (*S*)-**8h**, respectively.

CH_2OBn group) for these cases were somewhat lower than for the racemic ones.[20] As compared to the crotylation of conventional aldehydes,[15g] enantioselectivities are comparable, whereas product yields are somewhat lower. The sensitive rearrangement process coupled with the lower reactivity of the crotylation reagents may be responsible for the decreased yields. Despite this minor drawback, the consistently high diastereoselectivites observed and the potential utility of the uniquely substituted products makes this method a synthetically useful one.

In summary, we have developed an alternative and complimentary method to the previously reported Brown allylation of in situ generated β,γ-unsaturated aldehydes. Difficulties with the enantioselective crotylation of these substrates using crotylB(Ipc)$_2$ reagents have been overcome with the use of Leighton's crotylating reagents in complete diasteroselectivity, good to excellent enantioselectivity, and moderate to good yield in most cases. The products resulting from the crotylation reaction afford useful products with substitution patterns that would be difficult to achieve by other means.

Table 3 Crotylation Scope[19]



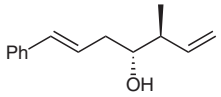
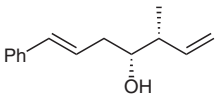
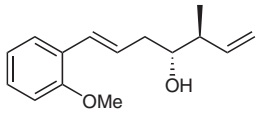
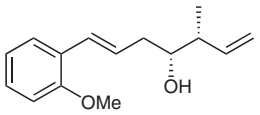
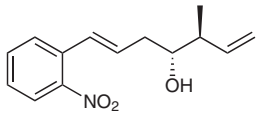
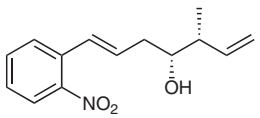
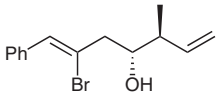
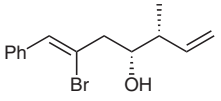
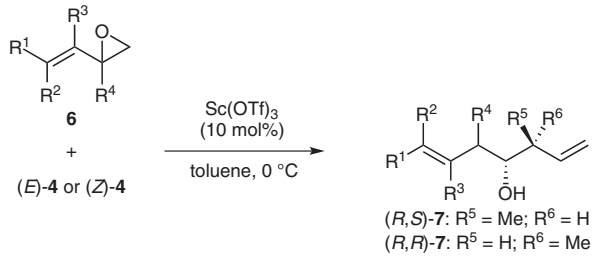
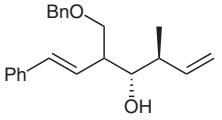
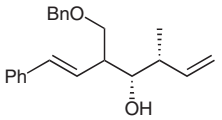
Entry	6	4	7	Yield (%)	ee (%)
1	**6b**	(*E*)	 (*R*,*S*)-**7b**	51	89
2	**6b**	(*Z*)	 (*R*,*R*)-**7b**	58	86
3	**6c**	(*E*)	 (*R*,*S*)-**7c**	50	94
4	**6c**	(*Z*)	 (*R*,*R*)-**7c**	16	92
5	**6d**	(*E*)	 (*R*,*S*)-**7d**	46	95
6	**6d**	(*Z*)	 (*R*,*R*)-**7d**	38	97
7	**6e**	(*E*)	 (*R*,*S*)-**7e**	36	96
8	**6e**	(*Z*)	 (*R*,*R*)-**7e**	31	97

Table 3 Crotylation Scope[19] (continued)



Entry	6	4	7	Yield (%)	ee (%)
9	**6f**	(*E*)	 (*R*,*S*)-**7f**	53[a]	99[b], 95[c]
10	**6f**	(*Z*)	 (*R*,*R*)-**7f**	55[d]	94[b], 88[c]

[a] dr = 2.2:1.
[b] Major isomer.
[c] Minor isomer.
[d] dr = 1.2:1.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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References and Notes

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(18) The following procedure is representative for the allylation reaction. See Supporting Information for full characterization data of all products.
Synthesis of (*S*)-8b
A 25 mL round-bottom flask was flame dried under a stream of nitrogen and allowed to cool to r.t. To this was added **3** (250 mg, 0.45 mmol) and Et_2O (3.0 mL). The mixture was cooled to 0 °C, and $Sc(OTf)_3$ (14.8 mg, 0.03 mmol) was added followed by the slow addition of **6b** (44 mg, 0.3

mmol) over 3 h as a solution in Et_2O (2.0 mL). After the addition was complete the reaction was stirred for 2 h at 0 °C, and then an equal volume of aq HCl (1 N) was added, and the mixture stirred for 10 min at r.t. The reaction mixture was diluted with H_2O and transferred to a separatory funnel with Et_2O. The organic layer was isolated, and the aqueous layer was extracted with Et_2O (2×). The combined organic layers were dried with $MgSO_4$, filtered, concentrated in vacuo, and the crude residue was purified by flash chromatography (5–10% EtOAc–hexane) to afford the desired product (*S*)-**8b** as a colorless oil (yield 73%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.35 (m, 2 H), 7.33–7.28 (m, 2 H), 7.24–7.19 (m, 1 H), 6.48 (d, *J* = 15.9 Hz, 1 H), 6.24 (ddd, *J* = 15.9, 7.4, 7.4 Hz, 1 H), 5.92–5.81 (m, 1 H), 5.19–5.13 (m, 2 H), 3.84–3.74 (m, 1 H), 2.50–2.21 (m, 4 H), 1.81 (d, *J* = 3.6 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.5, 134.8, 133.3, 128.7, 127.5 126.3, 126.3, 118.4 70.4, 41.6, 40.7. HPLC [CHIRALCEL OD, 1 mL/min, hexane–2-PrOH (95:5), 30 °C, 1 μL injection]: t_{R1} = 14.4 min (minor), t_{R2} = 17.7 min (major);96% ee.

(19) The following procedure is representative for the crotylation reaction. See Supporting Information for full characterization data of all products.

Synthesis of (*R*,*S*)-7b

To a 25 mL round-bottom flask was added Leightons' reagent [(*E*)-**4**, 256 mg, 0.45 mmol] and toluene (3.0 mL). The mixture was cooled to 0 °C, and $Sc(OTf)_3$ (14.8 mg, 0.03 mmol) was added followed by the slow addition of **6b** (44 mg, 0.3 mmol) over 3 h as a solution in toluene (2.0 mL). After 2 h at 0 °C, an equal volume of aq HCl (1 N) was added, and the mixture was stirred for 10 min at r.t. The reaction mixture was diluted with H_2O and transferred to a separatory funnel with Et_2O. The organic layer was isolated, and the aqueous layer was extracted with Et_2O (2×), the combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (10% EtOAc–hexane) to afford the desired product (*R*,*S*)-**7b** as a colorless oil (yield 51%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.35 (m, 2 H), 7.32–7.27 (m, 2 H), 7.23–7.18 (tt, *J* = 4.3, 1.8 Hz, 1 H), 6.51–6.45 (d, *J* = 15.9 Hz, 1 H), 6.31–6.23 (ddd, *J* = 15.8, 7.8, 6.7 Hz, 1 H), 5.86–5.76 (ddd, *J* = 16.6, 11.0, 8.2 Hz, 1 H), 5.16–5.15 (s, 1 H), 5.14–5.10 (ddd, *J* = 8.2, 1.9, 0.9 Hz, 1 H), 3.59–3.48 (ddt, *J* = 7.8, 5.9, 3.7 Hz, 1 H), 2.52–2.45 (dddd, *J* = 14.2, 6.6, 3.9, 1.5 Hz, 1 H), 1.74–1.71 (d, *J* = 3.4 Hz, 1 H), 1.10–1.07 (d, *J* = 6.9 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.0, 137.3, 132.7, 128.5, 127.1, 126.5, 126.0, 116.3, 74.2, 43.5, 38.0, 16.2. FTIR (neat): ν = 3392, 2971, 2930, 1640, 1598, 1495, 1450, 1418, 1028, 999, 966, 915, 745, 693 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{14}H_{18}O$ [M$^+$] 202.1358; found: 202.1363. HPLC [CHIRACEL OD, 1 mL/min, hexane–2-PrOH (95:5), 30 °C, 1 μL injection]: t_{R1} = 13.1 min, t_{R2} = 14.3 min (major); 92% ee; $[\alpha]_D^{20}$ +29.7 (*c* 0.024, $CHCl_3$).

(20) See Supporting Information.