Kinetic Resolution of Secondary Allyl Boronates and Their Application in the Synthesis of Homoallylic Amines

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Kinetic resolution of secondary allylboronates and their application in the synthesis of homoallylic amines

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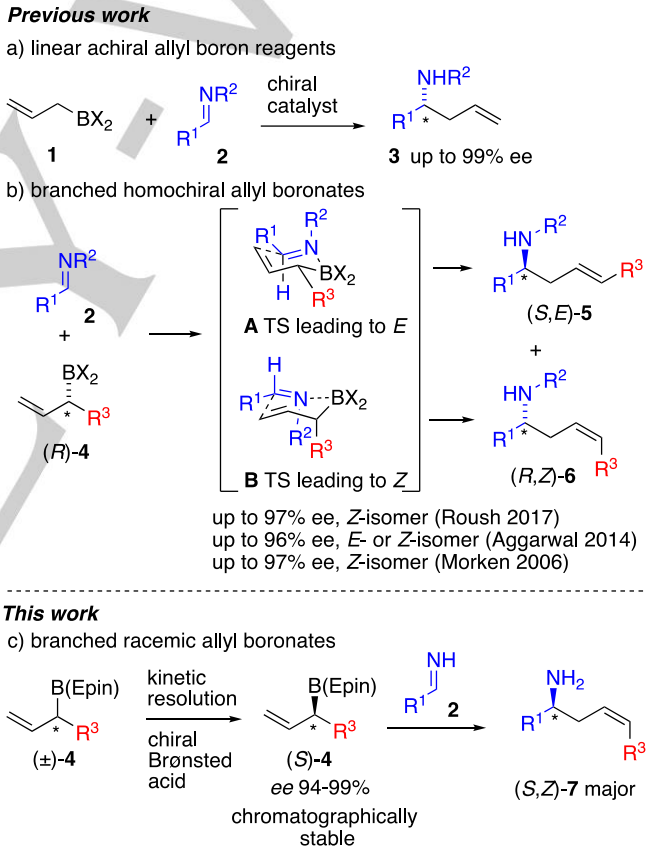
Dedication ((optional))

Abstract: Highly enantioenriched, chromatographically-stable secondary allylboronates featuring 1,1,2,2-tetraethyl-1,2-ethanediol fragment were obtained by kinetic resolution of their racemic mixtures. The resolved reagents were applied in stereoselective synthesis of homoallylic amines with an internal double bond employing unprotected imines formed *in situ* from aldehydes and ammonia. The reactions proceeded with an excellent transfer of chirality.

Chiral amines are powerful pharmacophore groups due to their favourable physico-chemical properties. Homochiral amines and their derivatives belong to the class of strategic building blocks for pharmaceutical, agrochemical and fine chemical development.[1] In this context, chiral homoallylic amines that feature two conveniently placed functional groups, amine and a double bond, occupy an important niche. Allylation of imines can be performed with high enantioselectivity leading to enantioenriched chiral homoallylic amines,[2] where allyl boronates emerged as highly versatile nucleophilic reagents. However, the vast majority of the existing methods are focused on the use of primary achiral reagents **1** that in the presence of a chiral catalyst produce terminal alkenes (Scheme 1a, **1** + **2** → **3**).[3] Synthesis of homologues *E*-**5** and *Z*-**6** is less straightforward. The shortest approach requires the use of chiral reagents **4**, which competently relay their chirality onto the products (Scheme 1b). However, the geometry of the resulting alkenes relies on the interplay of steric and electronic factors in the TS **A** and **B**[4,5] leading to the *E* and *Z* isomers of the opposite enantiomeric series, thus making control of the geometry a very important factor. The existing synthetic approaches[6] to homochiral boronates **4** can be divided into three main groups: use of chiral auxiliary on boron,[7] use of stoichiometric chiral reagents,[8] and catalytic asymmetric synthesis.[9] It is worth noting that in many instances, boron reagents of type **4**, due to their limited stability, have to be used *in situ*, without isolation.

Herein, we present an alternative practical approach to highly enantioenriched, bench-stable boronates **4** through kinetic resolution of their readily available racemates. Importantly, the Epin fragment (1,1,2,2-tetraethyl-1,2-ethanediol) developed by us plays a dual role: (i) it improves the hydrolytic stability of the boronates and (ii) the increased steric radius of this fragment favors TS **B** with the α-alkyl substituent placed in the pseudo-axial position, which enables stereoselective formation of *Z*-homoallylic amines **6,7** (Schemes 1b and 1c).



Scheme 1. Asymmetric synthesis of homoallylic amines (Epin = 1,1,2,2-tetraethyl-1,2-ethanediol).

Earlier,[10a] we reported on the asymmetric allylation of aldehydes with racemic boronates **4** catalyzed by chiral phosphoric acid TRIP (**9**) that proceeded under the conditions of kinetic resolution furnishing stereoselectively *Z*-alcohols **10** (Scheme 2). The original method was aiming at the allylation products **10** using excess boronates (±)-**4**, while the fate of the unreacted boronates was ignored, partly because they generally tend to decompose under the standard basic work up conditions.[10b] However, the Epin-derived boronates turned out

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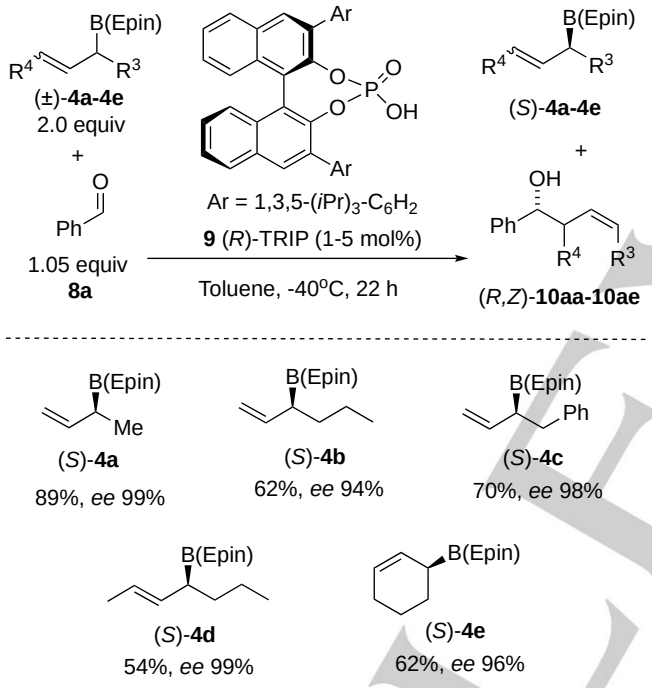
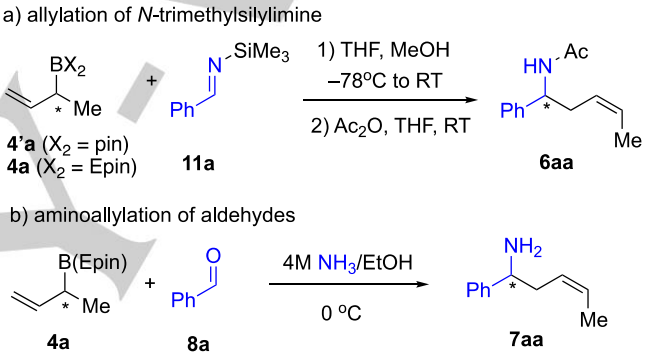
to remain intact and could be readily separated from **10** by chromatography on silica. Therefore, we reasoned that the method could be recast into obtaining highly enantioenriched boronates **4** by resolving their racemic mixtures. The initial trials produced encouraging results. With a 2:1 ratio of boronate (±)-**4a** to benzaldehyde **8a** using 5 mol% of *(R)*-TRIP at -40ºC, allylboronate (*S*)-**4a** was obtained in 45% yield (or 91% with respect to the maximum expected amount) and in 97% ee; the alcohol (*Z*)-**10aa** formed in the same process was isolated in 47% yield and 75% ee (*Z*/*E* 5:1). In the absence of a direct procedure, the enantiopurity of the isolated boronate was established by reacting it with benzaldehyde and measuring ee of the resulting alcohols (*S*)-**10aa**.[7b] We were able to further boost the enantiomeric purity of the boronate to 99% ee by slightly increasing the amount of benzaldehyde to 1.05 equiv. These conditions were set as optimal. Furthermore, for the resolution of **4a**, the catalysts loading can be reduced to 1 mol% without affecting the efficiency of the reaction (89% yield, 99% ee).



Scheme 2. Kinetic resolution of racemic secondary allylboronates. The yields of boronates **4** are given with respect to the maximum expected amount in the resolution protocol.

Next, we examined kinetic resolution of a range of secondary boronates **4b**-**4e**, where **4b** and **4c** are higher homologues of **4a**, whereas substrates **4d** and **4e** feature *E* and *Z* internal double bond, respectively. All the substrates were readily synthesized in a 1- or 2-step sequence by known methods.[11] The additional steric bias brought by the substituents affected the reactivity of these boronates compared to the parent **4a**, therefore the catalyst loading of 5 mol% had to be employed. In all cases, the kinetic resolution proceeded efficiently to furnish highly enantioenriched boronates **4b**-**4e** (Scheme 2). It is worth mentioning the respectable enantiopurity of the alcohols (*R*)-**10** formed during the resolution of the boronates: (*R*)-**10ab** – 84% ee), (*R*)-**10ac** – 70% ee, (*R*)-**10ae** – 84% ee.

With the set of enantioenriched boronates in hand, we embarked on their application in the synthesis of chiral amines. In contrast to the well-understood asymmetric allylation of aldehydes, proceeding via highly organised chair-like transition state, the related allylation of imines is more multifaceted and hence more challenging.[2b] Substitution on the imine nitrogen provides an excellent opportunity to tune electrophilicity of the C=N bond, however it also brings additional elements of complexity. These, among others, include *E*/*Z* isomerism about the C=N bond and a possible imine-enamine tautomerism in the case of enolisable imines. Furthermore, the steric constraints imposed by the R^2 substituent on the nitrogen in **2** and forcing it into a pseudo-axial position in the cyclic transition state (see TS **A** and **B**, Scheme 1b) often lead to different stereochemical outcome to what would be normally observed with aldehydes.[12] Taking into consideration that the steric arrangement of the transition state of NH imines should resemble that of aldehydes, they would represent an ideal choice. However, due to their poor stability, the NH aldimines are usually synthesized and used in situ. In this work, two approaches were explored (Scheme 3).



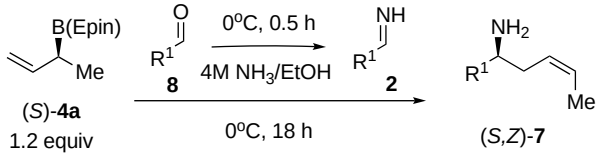
Scheme 3. Optimization of crotylation of imines with **4**.

First, the *N*-trimethylsilylimine **11a** was assessed (Scheme 3a). The TMS protection is removed during the reaction to expose the NH group.[4b,8a,13] In preliminary trials that were conducted using racemic **4'a** and **4a**, the Bpin boronate **4'a** afforded *Z*-**6aa** in 70% and 5:1 dr. The selectivity towards *Z* isomer improved to 10:1 when **4a** was employed (82% yield). With the enantioenriched (*S*)-**4a** (98% ee), a complete transfer of chirality was observed, in agreement with previous reports on the addition of homochiral secondary allylboronates.[4b,4d,8a] However, synthesis of pure *N*-TMS imines requires purification by distillation, which narrows the substrate scope.[13] Alternatively, they can be made and used in situ at low temperature, which adds complexity to the synthetic protocol.

Therefore, our attention turned to the aminoallylation of aldehydes in a solution of ammonia in ethanol (Scheme 3b, **4a** → **7aa**). The racemic variant of the method was reported by Kobayashi,[14] who employed primary pinacol-derived allyl- and crotylboronates. It is noteworthy that primary boronates decorated with a chiral auxiliary in the diol moiety failed to induce practical enantioselectivity.[14a] Later, the use of chiral boron reagents was reported by Morken.[4b] In our initial trial, imine **2a** was formed by stirring benzaldehyde in 4M ammonia in ethanol (1 mL, *ca.* 8 equiv) for 0.5 h at -10°C, followed by addition of racemic boronate **4a** (1.2 equiv). After 18 h, the amine **7aa** was isolated in 83% yield (*Z*/*E* 8:1). A similar result

was obtained at 0ºC (yield 78%, *Z/E* 8:1). Other solvents, such as MeOH, *i*PrOH *t*BuOH and THF proved inferior. The conditions shown in Scheme 3 were taken as optimal for investigating the reaction scope using resolved (*S*)-**4a** (Table 1).

Table 1. Scope in the allylation of imines with enantioenriched (*S*)-**4a**.[a]

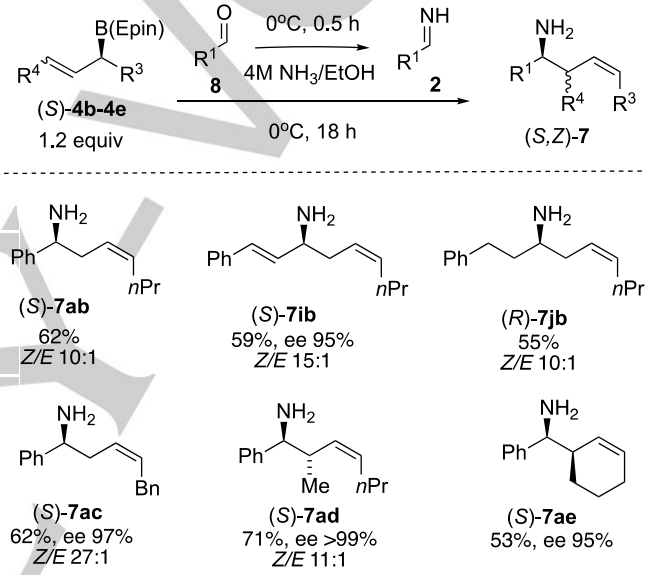


	8, R^1	**7**	Yield [%]	**7**, *Z/E*	**7**, ee [%]
1	**8a**, Ph	**7aa**	76	8:1	97
2[b]	**8a**, Ph	**7aa**	29	24:1	n.d.
3	**8b**, 4-MeC_6H_4	**7ba**	72	10:1	99
4	**8c**, 4-BrC_6H_4	**7ca**	65	8:1	98
5	**8d**, 4-ClC_6H_4	**7da**	75	9:1	99
6[c]	**8d**, 4-ClC_6H_4	**7da**	57	10:1	99
7[d]	**8e**, 4-FC_6H_4	**7ea**	53	7:1	99
8	**8f**, 4-$MeOC_6H_4$	**7fa**	63	9:1	98
9	**8g**, 3-$MeOC_6H_4$	**7ga**	78	9:1	98
10[e]	**8h**, 2-$MeOC_6H_4$	**7ha**	61	10:1	85
11	**8i**, PhCH=CH	**7ia**	72	10:1	94
12	**8j**, $PhCH_2CH_2$	**7ja**	59	8:1	93[f]
13	**8k**, *n*-C_7H_{15}	**7ka**	76	8:1	96[f]
14[e]	**8l**, *c*-C_6H_{11}	**7la**	34	8:1	91
15[e]	**8m**, 2-Furyl	**7ma**	<10	n.d.	n.d.

[a] The reactions were carried out at 0.1-0.2 mmol scale at 0ºC unless stated otherwise; yields of the isolated compounds are given; the *Z/E* ratios were determined by ^{1}H NMR of a crude reaction mixture; n.d. – not determined. [b] At -40ºC, reaction time 96 h. [c] At -10ºC. [d] The absolute configuration was confirmed by X-ray analysis of the corresponding acetamide (see Supporting Information for details). [e] At RT. [f] The product was (*R*)-configured due to the change in the preference of the substituents in the Cahn-Ingold-Prelog system.

Allylation of **2a** with (*S*)-**4a** gave (*S*)-**7aa** in 97% ee and with the *Z/E* ratio (8:1), analogous to the racemic reaction (entry 1). A higher *Z*-selectivity was observed at -40ºC (24:1), though at the expense of lower product yield, even after 4 days (entry 2). With aromatic aldehydes **8b**-**8g** (entries 3-9), the reaction followed the same trend with a highly efficient chirality transfer. Note a slight improvement in the *Z*/*E* ratio for **7da** at–10ºC (cf. entries 5 and 6). For a more sterically hindered *ortho*-substituted aldehyde **8h**, the reaction had to be carried out at RT, which also affected the stereoselectivity of the process (entry 10). A slight erosion of enantioselectivity was observed for cinnamaldehyde **8i** and aliphatic aldehydes **8j**-**8l**, though enantiopurity of the products still remained high (entries 11-14). No product was formed with 2-furylaldehyde **8**m, which was probably due to a very slow formation of the respective imine under the reaction conditions (entry 15).

Next, other resolved allylboronates **4b**-**4e** were examined in the aminoallylation reaction (Scheme 4). Boronates (*S*)-**4b** and (*S*)-**4c** with an extended alkyl chain exhibited somewhat slower reaction rates, possibly due to the increased steric size of the substituent at the chiral center. However, this had a positive influence on the *Z/E* ratio. Boronates (*S*)-**4d** and (*S*)-**4e** with *E* and *Z* internal double bond produced, respectively, *anti*-**7ad** and *syn*-**7ae**, which suggests that the reaction proceeded through the chair-like transition states resembling those of the aldehydes. Enantiopurity of the products closely matches the enantiopurity of the starting boronates reflecting an efficient transfer of chirality in the process.



Scheme 4. Allylation of imines with enantioenriched boronates (*S*)-**4b**-**4e**.

In conclusion, we have developed an expedient practical method for obtaining highly enantioenriched secondary allylboronates by kinetic resolution of their racemic mixtures. The resolved boronates were employed for the efficient stereoselective synthesis of chiral homoallylic amines with *Z*-configured internal double bond. The work is currently underway in our laboratories on other synthetic applications of the resolved enantioenriched allylboronates.

Acknowledgements

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Keywords: asymmetric synthesis • allylation • amines • kinetic resolution • stereoselectivity

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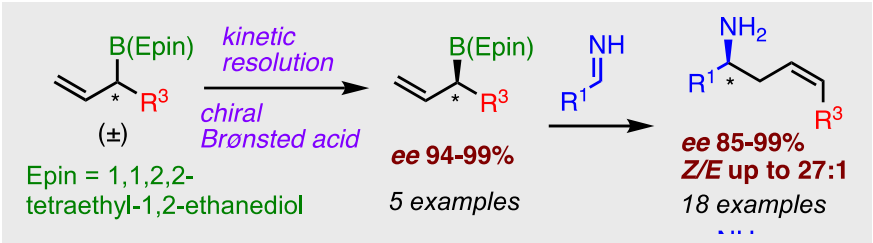

Size matters: increased hydrolytic stability of allylboronates with Epin fragment enabled facile kinetic resolution of their racemic mixture followed by stereoselective allylation of unprotected imines

Laura Villar, Nikolai V. Orlov, Nikolay S. Kondratyev, Uxue Uria, Jose L. Vicario, and Andrei V. Malkov**

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