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Enantioselective Transfer Aminoallylation: Synthesis of Optically Active Homoallylic Primary Amines

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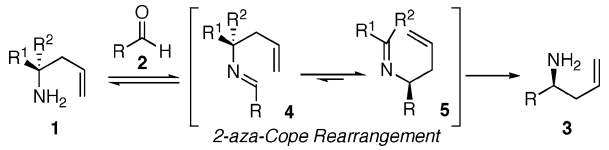
Homoallylic *primary* amines are of great value in organic synthesis because the carbon−carbon double bonds of the allyl groups are readily converted to a variety of functional groups and desired substituents or protective groups can be introduced on the free amine moieties. Addition of allylic nucleophiles to C═N electrophiles is one of the most effective methods for construction of homoallylic amines, and efficient enantioselective methods including asymmetric catalysis have been reported.[1] However, most of those methods require deprotection of substituents on the nitrogen to obtain *primary* amines, and direct routes to those compounds, especially as optically active forms, have been limited. Istuno et al.[2] and Brown et al.[3] reported allylboration of *N*-silylimines with chiral allyboron reagents as a route to those compounds, and although high enantioselectivities were obtained in these cases, only non-enolizable imines were applicable.

We have recently reported α-aminoallylation of aldehydes with ammonia and allylboronates for synthesis of homoallylic *primary* amines[4] and demonstrated an enantioselective version utilizing a chiral allylboronate, although the selectivity was unsatisfactory. In the course of our study into the allylation of hydroxyglycine,[5] we have found that *β*-branched allylglycines isomerized to the corresponding linear isomers via imine formation with glyoxylic acid, followed by 2-aza (or azonia)-Cope rearrangement. This type of sigmatropic rearrangement was first reported in 1950,[6] but has been little utilized in organic synthesis due to the inherent problem of the reversibility of the process. Overman and Kakimoto devised a 2-azonia-Cope rearrangement/Mannich reaction sequence to overcome this problem.[7] Although related transformations of homoallylic alcohols via 2-oxonia-Cope rearrangement have been reported and successfully utilized for the synthesis of optically active homoallylic alcohols,[8] an aza-analogue of this enantioselective transformation has not yet been described. Herein we report, for the first time, the highly enantioselective synthesis of homoallylic *primary* amines via 2-azonia-Cope rearrangement.

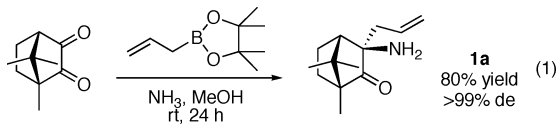
Scheme 1 depicts the general concept. Under this resume, optically active amine **1** reacts with aldehyde **2** to form imine **4**, which could then undergo 2-aza (or azonia, if the nitrogen is protonated)-Cope rearrangement to **5**. Finally, enantio-enriched homoallylic primary amine **3** would be obtained after cleavage of the C═N bond of **5**. We term this sequence "transfer aminoallylation" because both the amino and the allyl groups of **1** are incorporated in product **3**. In addition, optically active amine **1** could be prepared via aminoallylation of chiral carbonyl compounds with ammonia, which we have reported previously.[4]

To examine the feasibility of this concept, we turned our attention to ketone-derived homoallylic amines **1** (R^1, $R^2 \neq H$) because those were expected to sterically bias the rearrangement from **4** to **5**. Considering accessibility by aminoallylation, an activated ketone, (1*R*)-camphorquinone, was selected as a starting chiral ketone. We were pleased to find that its aminoallylation with ammonia and

Scheme 1. Transfer Aminoallylation

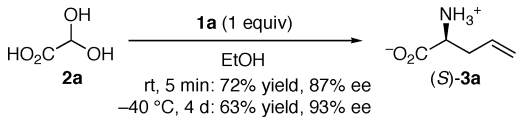


allylboronic acid pinacol ester[4] proceeded smoothly to give α-aminoketone **1a** in good yield with perfect diastereoselectivity (eq 1).



With **1a** in hand, we then examined transfer aminoallylation of glyoxylic acid monohydrate (**2a**) under several conditions, varying solvents (CH_2Cl_2, CH_3CN, EtOH, MeOH, and water) and temperature (−40 °C to room temperature). It was found that high enantioselectivities were obtained regardless of solvents. Of particular note is that the reaction in ethanol at −40 °C provided (*S*)-allylglycine with 93% ee after acidic work-up (Scheme 2). The reaction proceeded much faster at room temperature albeit with slightly lower selectivity.

Scheme 2. Transfer Aminoallylation of Glyoxylic Acid (**2a**) with **1a**



An initial attempt to adapt **1a** to the reaction with benzaldehyde (**2b**) did not result in the formation of the desired product but, instead, the corresponding imine **4b** was obtained (Table 1, entry 1). Considering the superiority of glyoxylic acid as a substrate, acid catalysts were anticipated to accelerate the rearrangement of **4b** via formation of the corresponding iminium ion. In fact, the reaction proceeded well in the presence of a catalytic or stoichiometric amount of an acid. Moreover, it was noted that excellent enantioselectivities (up to 97% ee) were obtained even at 20−50 °C (entries 2−5). Among the acids tested, a catalytic amount of camphorsulfonic acid (CSA) was the best in terms of the yield and the enantioselectivity (entries 4 and 5). In addition, use of hydroxylamine was found to be important to release amine **3b** in high yield from the rearranged product.[9]

Transfer aminoallylation of various aldehydes was then investigated using CSA as a catalyst in DCE (Table 2). In all cases, homoallylic primary amines were obtained with high enantiomeric excesses over 95%. Electron-withdrawing aromatic aldehydes tend to show higher reactivity than electron-donating ones (entries 1−6 and see also entry 5 of Table 1). In comparison with aromatic aldehydes, reactions of aliphatic aldehydes, even though they are

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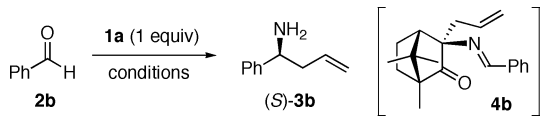
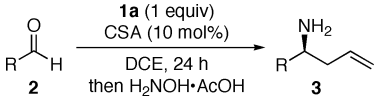
Table 1. Transfer Aminoallylation of Benzaldehyde with **1a**[a]



entry	conditions	% yield[b]	% ee[c]
1	CH_2Cl_2, 20 °C, 1 d	0[d]	
2	AcOH (1.0 equiv), CH_2Cl_2, 20 °C, 3 d	27	97
3	TFA (0.1 equiv), CH_2Cl_2, 20 °C, 3 d	50	95
4	CSA (0.1 equiv), CH_2Cl_2, 20 °C, 3 d	59	97
5	CSA (0.1 equiv), DCE, 50 °C, 1 d	81	97
6	TfOH (0.1 equiv), CH_2Cl_2, 20 °C, 2 d	72	87

[a] All reactions were quenched by treatment with $HONH_2$·AcOH (2.0 equiv) in MeOH at 50 °C for 3 h. [b] Isolated yield. [c] Determined by HPLC analysis (CHIRALCEL OD-H). [d] Compound **4b** was obtained.

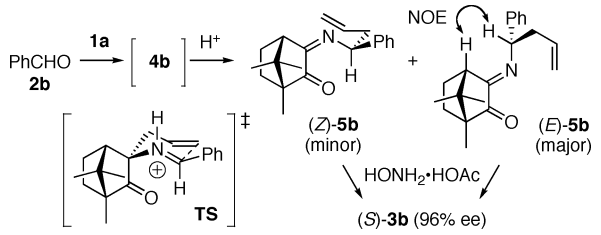
Table 2. Transfer Aminoallylation of Various Aldehydes[a]



entry	R in **2**	temp. (°C)	% yield[b]	% ee[c]
1	*p*-$NO_2C_6H_4$ (**2c**)	50	92	98
2	*p*-BrC_6H_4 (**2d**)	50	88	98
3	*p*-$MeOC_6H_4$ (**2e**)	50	72	97
4	2-thienyl (**2f**)	50	57	98
5	2-furanyl (**2g**)	50	60	97
6	3-pyridyl (**2h**)	50	91	98
7	$PhCH_2CH_2$ (**2i**)	0	88	95
8	$PhCH_2$ (**2j**)	0	77	96
9	*n*-C_7H_{15} (**2k**)	0	81	97[d]
10	(*S*)-$Me_2C{=}CHC_2H_4CH(Me)CH_2$ (**2l**)[e,f]	0	88	93 (98)[g]
11[h]	**2l**[e,f]	0	85	92 (97)[g]
12	cyclohexyl (**2m**)	0	73	95[d]
13	$BnOCH_2CH_2$ (**2n**)	0	87	96
14	$BnOCH_2$ (**2o**)	0	87	95

[a] All reactions were quenched by treatment with $HONH_2$·AcOH (2.0 equiv) in MeOH at 50 °C for 3 h. [b] Isolated yield. [c] Determined by HPLC analysis. [d] Determined by HPLC analysis after benzoylation. [e] The enantiomeric excess of **2l** (purchased from Aldrich) was determined after its transformation to the corresponding *N*′-benzoylhydrozone. [f] 95% ee (*S*). [g] The values represent diastereomeric excesses (determined by ^{13}C NMR analysis). The converted values on the basis of % ee of **2l** are in parentheses. [h] The enantiomer of **1a** was used.

Scheme 3. Isolation of the Rearranged Product **5b**



enolizable, were found to proceed smoothly at 0 °C (entries 7−14). It is significant that the reaction tolerates various functional groups including nitro, bromo, hetereocyclic, benzyloxy, and carboxyl groups (entries 1−6, 13, 14, and see also Scheme 2) and that the stereogenic carbon can be constructed independent of the chiral aldehyde's original configuration (entries 10 and 11).

To gain mechanistic insights, we attempted to isolate the rearranged product **5b** (Scheme 3). It was found that **5b** was isolable by silica gel chromatography and that two stereoisomers of **5b** were obtained in an 83:17 ratio. Both isomers were converted to (*S*)-**3b** with 96% ee by treatment with hydroxylamine, indicating that the two starting isomers were simply geometrical isomers of the C=N double bond. The geometries were assigned by NOESY experiments.[10] Only the major isomer of **5b** showed a strong NOE correlation between the bridgehead proton and the proton adjacent to the nitrogen atom, proving the (*E*)-geometry of the C=N bond. Formation of (*S*)-**3b** with high enantiomeric excess from both isomers of **5b** strongly supports that the rearrangement of **4b** proceeds via chair-like transition state **TS** to give (*Z*)-**5b** (Scheme 3) and that (*E*)-**5b** is generated through isomerization of (*Z*)-**5b** under the acidic conditions.

In addition, the whole reaction process before quenching was found to be reversible. When a geometrical mixture of **5b** (*E*/*Z* = 89:11) was subjected to CSA (10 mol %) in $CDCl_3$ at 50 °C, formation of imine **4b** was observed by ^1H NMR analysis.[10] The reaction was allowed to equilibrate within 48 h with a ratio of **2b**/**4b**/(*Z*)-**5b**/(*E*)-**5b** = 1:5:18:76, and almost the same ratio was obtained starting from isolated imine **4b**. As expected, the equilibrium position is dependent on the aldehyde structure. For example, the reaction of 2-thiophenecarboxaldehyde (**2f**) with **1a** in $CDCl_3$ resulted in a ratio of **2f**/**4f**/(*Z*)-**5f**/(*E*)-**5f** = 4:35:18:43 at 50 °C after 48 h.[10] The product ratio was much smaller than that of the reaction with benzaldehyde.

In summary, we have demonstrated a direct, enantioselective route to homoallylic primary amines based on asymmetric 2-azonia-Cope rearrangement. Due to the high functional group tolerance and practical level of enantioselectivity, application of this new protocol to the synthesis of complex molecules would be possible. Further studies including development of a catalytic, enantioselective method are now in progress.

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Supporting Information Available: Experimental details and physical data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org

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(10) For details, see Supporting Information.

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