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A Double Activation Method for the Conversion of Vinyl Epoxides into *vic*-Amino Alcohols and Chiral Benzoxazine/Quinoxaline Derivatives

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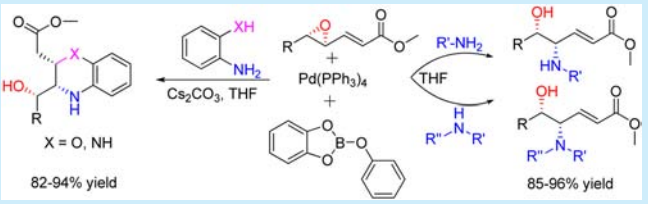
Supporting Information

ABSTRACT: A new method for the synthesis of 1,2-*syn*-*vic* amino alcohols (with double inversion of configuration) from vinyl epoxides, by the amination of a π-allyl palladium−borate complex generated by using Pd(0) and phenyl-*o*-phenylene borate (a double activation technique), is reported. Further, this new method with broad functional group compatibility was extended to a one-pot/two-step synthesis of chiral benzoxazine and quinoxaline derivatives.



Development of strategies for efficient C−N bond formation is highly fascinating, as the chiral amines, *vic*-aminols, and other related products are very useful in organic synthesis.[1] Since the 1,2-aminols are part structures of a wide variety of biologically active compounds and useful chiral synthons for the synthesis of complex natural products,[2] much interest has been focused on the advancement of their stereoselective syntheses. A variety of methods have evolved for the synthesis of *vic*-aminols by adopting diverse protocols.[3−9] Likewise, methods such as Sharpless aminohydroxylation,[10a,b] hydroxyamination through catalytic aminoboration[10c−f] of olefins, and ring opening reactions with appropriate nucleophiles[11−13] have been reported for the synthesis of *vic*-aminols, without alteration of the carbon skeleton.

Trost et al.[14] reported opening of vinyl epoxides in the presence of Pd(0) and trialkyl phosphites by tethering the nucleophile, while the same group developed the concept of a two-component catalyst system for the allylic alkylation of vinyl epoxides using palladium and boron reagents.[15] Saeguse et al.[16] reported opening of vinyl epoxides in the presence of Pd(0) with amide nucleophiles, having a highly acidic proton, while Lautens et al.[17] reported a Rh mediated method for forming 1,2-*anti* addition products with alcohols and aryl amines. Miyashita et al.[11e] reported a tethered boronic acid method to give the 1,2-azido alcohols from epoxy alcohols. A further report by Miyashita et al.[18] used a Pd(0)-triphenyl borate mediated method of opening vinyl epoxides to give the *vic*-*syn*-diols, via a tethered borate system, restricted to alcohols as nucleophiles, while a Pd(0) mediated ring opening was adopted with a tethered azide reagent to give the 1,2-*syn*-azido alcohols with double inversion.[19]

Thus, opening of an epoxide ring with nucleophiles by a stereo- and regioselective manner to deliver the 1,2-addition products gains prominence, though reports on stereospecific opening with retention of configuration are very limited. Further, reaction of nucleophiles and π-allyl palladium complexes bearing two functional groups at both ends of the allylic carbons nonetheless is useful for the synthesis of complex organic molecules. However, such reports are limited in literature. The nucleophilic opening of π-allyl palladium complexes of vinyl epoxides preferentially gives 1,4-addition products.[20] The regioselectivity in such systems is controlled by the hydroxyalkyl and alkoxycarbonyl groups. However, tethering of the reagent helps in the regioselective delivery of the nucleophile to give 1,2-addition products in an intramolecular fashion. Although the method by Lautens et al.[17] is found to be an attractive alternative to Bronsted and Lewis acid mediated routes,[21] it is restricted to the use of only aromatic amines as nucleophiles.

From the above discussion it is evident that the introduction of an amine nucleophile by the opening of an α,β-unsaturated γ,δ-epoxy ester (vinyl epoxide) is scarce. A general and efficient method for the stereo- and regioselective introduction of the N-nucleophile to obtain *vic*-*syn*-amino alcohols is thus warranted. Herein, we report the synthesis of *vic*-*syn*-aminols from vinyl epoxides by a double activation method, using the amination of a π-allyl palladium−borate complex system, and extend the protocol for a one-pot/two-step synthesis of very useful chiral benzoxazine/quinoxaline derivatives, by epoxide ring opening and subsequent oxo-/aza-Michael addition reactions (Scheme 1).

In the present study, it was anticipated that the palladium catalyzed stereoselective opening of *trans*- and *cis*-vinyl epoxides with an amine nucleophile might occur in the presence of an appropriate boron reagent (for tethering), to give 1,2-*syn* and 1,2-*anti*-amino alcohols respectively, with a double inversion of configuration. Accordingly, triphenyl borate was chosen as a

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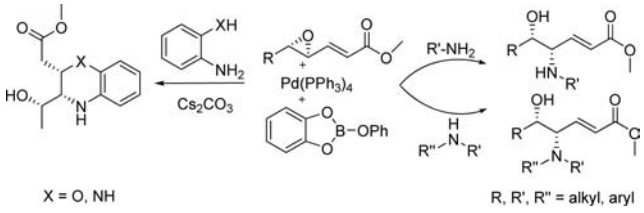
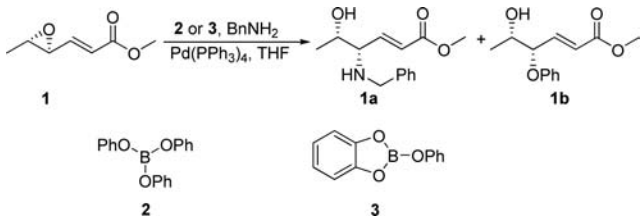
Scheme 1. Synthesis of *syn-vic*-Amino Alcohols and Heterocyclic Derivatives



tethering reagent, since it was found to be inactive as a nucleophile in the earlier studies.[18] In addition, unlike the trialkyl borates, the triaryl borates, based on the electronic factors of the two systems, were anticipated to form stable adducts with aromatic/aliphatic amines, transferring the amine component in an intramolecular fashion.

Accordingly, the reaction of **1**[22] with triphenyl borate **2** (1 equiv), benzylamine (1 equiv), and 10 mol % of $Pd(PPh_3)_4$ in THF at room temperature for 30 min unexpectedly gave **1b** (80%) (entry 1, Table 1), a phenoxy substitution product exclusively, with no trace of the desired 1,2-aminol **1a**.

Table 1. Pd(0) Catalyzed Opening of *α,β*-Unsaturated *γ,δ*-Epoxy Esters with Benzyl Amine, in the Presence of Aryl Borate 2 or 3 in THF



entry	borate (1.0 equiv)	$BnNH_2$ (equiv)	Pd(0) (mol %)	ratio[a] **1a:1b**	time (h)/ yield (%)
1	**2**	1.0	10	0:100	0.5/80
2	**2**	2.0	10	36:64	0.5/–
3	**2**	3.0	10	48:52	0.5/–
4	**3**	1.0	10	–	6[b]
5	**3**	2.0	10	100:0	0.5/84
6	**3**	2.0	5	100:0	6/64
7	**3**[c]	2.2	10	100:0	0.17/94

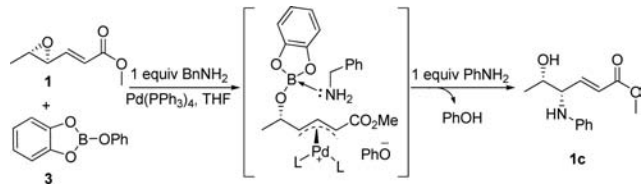
[a]Ratio was determined by ^1H NMR. [b]Starting material was absent with the formation of traces of **1a**. [c]1.1 equiv.

Further, the attempted opening of **1** with increased concentration of the amine (2–3 equiv) though resulted in **1a** with increased yields, albeit along with **1b** (entries 2 and 3, Table 1).

To circumvent the problems associated with borate **2**, phenyl *o*-phenylene borate **3**,[23] a cyclic catechol derivative, was chosen, since it is more stable and capable of coordinating with amines. Thus, the reaction of **1** with benzylamine (1 equiv), in the presence of $Pd(PPh_3)_4$ (10 mol %) and **3** (1 equiv) in THF at 0 °C, even after 6 h (entry 4, Table 1), gave **1a** in traces. However, the reaction of **1** with 2 equiv of benzylamine, under the above reaction conditions, furnished the 1,2-*syn* amino alcohol **1a** in 84% yield exclusively (entry 5, Table 1). However, the reaction of **1** with 1.1 equiv of **3**, 2.2 equiv of benzylamine, and 10 mol % $Pd(PPh_3)_4$ was found to be very efficient, and in 10 min, it gave **1a** with improved yield (94%) (entry 7, Table 1), after purification by column chromatography. A low catalyst (5 mol %) loading led to a prolonged reaction time and reduced yield (entry 6, Table 1).

To understand the nature of epoxide opening with an amine in an intra- or intermolecular way and the role of the amine as a nucleophile and as a base, a stepwise experiment was carried out. Accordingly, 1 equiv of benzylamine was added to the reaction mixture containing epoxide **1** and borate **3** in THF at 0 °C, followed by the addition of 1 equiv of aniline after 2 min and 10 mol % $Pd(PPh_3)_4$.[24] The reaction was complete in 25 min, and it gave **1c** in 85% yield (Scheme 2).

Scheme 2. Plausible Mechanism of Pd(0) Catalyzed Amine Substitution Reaction of *α,β*-Unsaturated *γ,δ*-Epoxy Ester



The above discussions clearly show that borates **2** and **3** form 1:1 adducts with 1 equiv of benzylamine. In the case of borate **2**, the attack of a second phenoxide ion as a nucleophile will lead to the exclusive formation of **1b** (Table 1). However, in the case of borate **3**, the second equivalent of benzylamine acted as a nucleophile onto π-allyl palladium species at the γ-position to give γ-amino substituted *syn*-aminol **1a** (Table 1) as an exclusive product, with double inversion (two consecutive S_N2 reactions) of configuration.

Further, the formation of **1c** (Scheme 2) demonstrates that the first amine ($BnNH_2$) acts as a base, while the second amine (aniline) participates in nucleophilic substitution in an intermolecular fashion.[24] Borate **3** thus plays an important role in the irreversible formation of a cationic η^3-allyl complex and finally gives the 1,2-*syn* amino alcohol as shown in Scheme 2. Thus, this study follows a double activation protocol, wherein borate and Pd(0) activate the epoxide and the olefin, respectively.

From the successful preliminary results on the opening of vinyl epoxide **1** with amines in the presence of Pd(0)-borate to give *vic*-aminols **1a** and **1c**, in a stereo- and regioselective way, the scope of the new methodology was extended to diverse vinyl epoxides **4**–**9**, and aliphatic, aromatic, and primary/secondary amines. The requisite vinyl epoxides **4**–**9** (Figure 1) were prepared from the corresponding epoxy alcohols,[25] in a two-step sequence, viz. oxidation and Horner–Wittig–Emmons reactions.

The *trans*-epoxy ester **4** with a benzylic carbon underwent facile ring opening to give the aminols **4a** (92%), **4b** (96%), **4c** (88%), and **4d** (92%) with cyclopropylamine, morpholine, (*R*)-

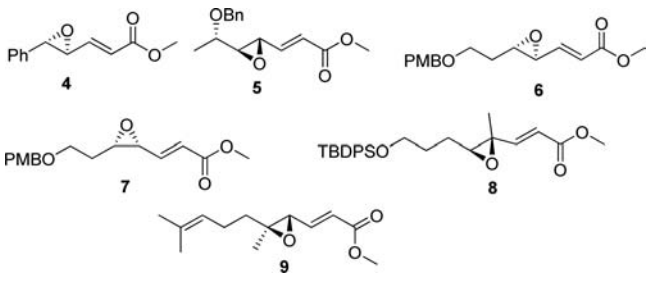


Figure 1. Structures of *α,β*-unsaturated *γ*, *δ*-epoxy esters.

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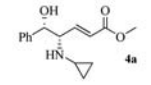
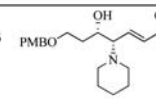
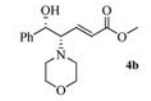
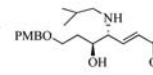
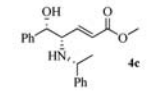
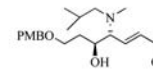
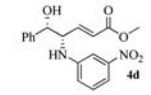
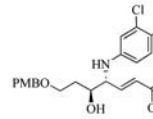
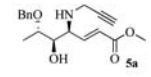
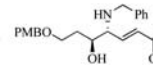
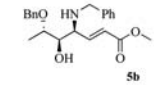
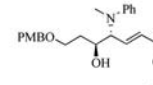
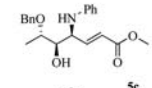
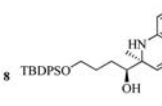
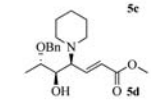
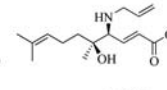
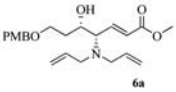
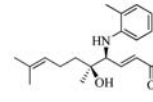
phenethylamine, and 3-nitroaniline respectively (entries 1−4, Table 2).

Table 2. $Pd(PPh_3)_4$-Catalyzed Stereoselective Amine Substitution of α,β-Unsaturated γ,δ-Epoxy Esters with Various Amines in the Presence of Borate[a,b]

entry	substrate	product	syn:anti time (h) yield (%)	entry	substrate	product	syn:anti time (h) yield (%)
[1]	4	 4a	>99:1 0.17 92	[10]	6	 6b	>99:1 0.17 94
[2]	4	 4b	>99:1 0.17 96	[11]	7	 7a	>1:99 0.17 86
[3]	4	 4c	>99:1 0.5 88	[12]	7	 7b	>1:99 0.17 88
[4]	4	 4d	>99:1 4 92	[13]	7	 7c	4:96 1.5 93
[5]	5	 5a	97:3 0.17 89	[14]	7	 7d	>1:99 0.17 90
[6]	5	 5b	>99:1 0.5 92	[15]	7	 7e	>1:99 1 94
[7]	5	 5c	>99:1 3 94	[16]	8	 8a	>99:1 1 90
[8]	5	 5d	>99:1 0.5 96	[17]	9	 9a	>99:1 30 85%[c]
[9]	6	 6a	>99:1 0.17 92	[18]	9	 9b	98:2 1 88[c]

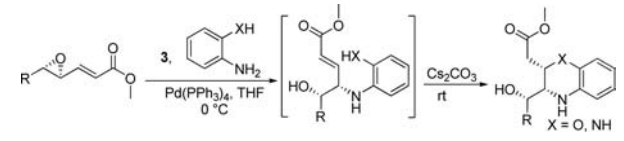
[a]Ratio was determined by ^1H NMR analysis. [b]Yield of the isolated product. [c]15 mol % catalyst was used.

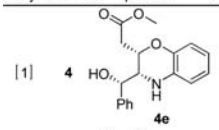
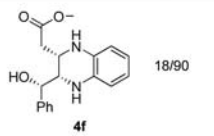
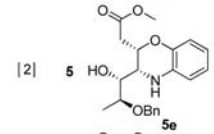
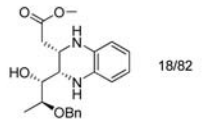
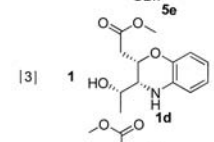
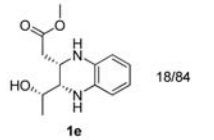
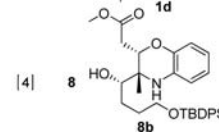
The opening reaction of epoxy ester **5** with proargylamine, benzylamine, aniline, and piperidine under the same reaction conditions stereoselectively furnished the *syn*-substituted aminols **5a** (89%),[24] **5b** (92%),[24] **5c** (94%), and **5d** (96%) respectively (entries 5−8, Table 2). Similar results were gleaned from the *trans*-epoxy ester **6**, which afforded the *syn*-amino alcohols **6a** (92%) and **6b** (94%) (entries 9 and 10, Table 2) with high stereoselectivity.[26] Similarly, the reaction of *cis*-epoxy ester **7**, having an oxygen on the side chain, with isobutylamine, isobutylmethylamine, 3-Cl-4-F-aniline, benzylamine, and *N*-methylaniline, proceeded stereoselectively to furnish the 1,2-*anti*-amino alcohols **7a** (86%), **7b** (88%), **7c** (93%), **7d** (90%), and **7e** (94%) respectively (entries 11−15, Table 2). Likewise, epoxides **8** and **9** gave the *syn*-aminols **8a** (90%) (entry 16, Table 2) and **9a** (85%)/**9b** (88%) (entries 17 and 18, Table 2) respectively. Although both epoxides **8** and **9** gave stereoselective aminols with allylic and aromatic amines, they resisted undergoing reactions with secondary amines.

Having successfully established reaction conditions for the preparation of *vic*-aminols from α,β-unsaturated γ,δ-epoxy esters **1** and **4**−**9**, the attention then was focused on the use of both functionalities to effect the opening of epoxide followed by oxo-/aza-Michael addition, by the addition of a base in a one-pot/two-step sequence. The resultant chiral 3,4-dihydro-2*H*-1,4-benzoxazine and 1,2,3,4-tetrahydroquinoxaline derivatives are of considerable importance due to their wide range of biological and therapeutic properties.[27] These are ubiquitous structural moieties in biologically interesting natural alkaloids and chiral pharmaceuticals and, in addition, serve as synthetic building blocks.[28]

Accordingly, **4** was subjected to a reaction with *o*-amino-phenol, borate **3**, and $Pd(PPh_3)_4$ under the above-mentioned reaction conditions. After reaction completion, addition of 2 equiv of Cs_2CO_3 in the same reaction pot smoothly effected the oxo-Michael addition[29] to furnish 1, 4-benzoxazine derivative **4e** as a single stereoisomer[26] in 94% yield (entry 1, Table 3).

Table 3. 3,4-Dihydro-1,4-benzoxazine-1,2,3,4-tetrahydroquinoxaline Derivatives



entry	substrate	product	time (h)/yield (%)	entry	substrate	product	time (h)/yield (%)
[1]	4	 4e	4/94	[5]	4	 4f	18/90
[2]	5	 5e	5/92	[6]	5	 5f	18/82
[3]	1	 1d	4/92	[7]	1	 1e	18/84
[4]	8	 8b	5/84				

The one-pot/two-step sequence was extended to substrates **5**, **1**, and **8** with *o*-amino phenol to give **5e** (92%), **1d** (92%), and **8b** (84%) (entries 2−4, Table 3), while use of 1,2-diaminobenzene as a coupling partner with **4**, **5**, and **1** afforded the chiral 1,2,3,4-tetrahydroquinoxaline derivatives **4f** (90%), **5f** (82%), and **1e** (84%), as single stereoisomers (entries 5−7, Table 3) respectively.

In summary, a double activation protocol using palladium(0) and borate is developed for the stereo- and regioselective opening of α,β-unsaturated-γ,δ-epoxyesters with amines as nucleophiles to afford the *vic*-aminols. The reaction conditions of the present protocol, unlike the earlier ones, are facile and compatible to diverse aliphatic and aromatic amines. For the first time, the present method is amenable to affording 1,2-*syn*-aminols with high selectivity. Further, the reaction conditions are effectively utilized for the one-pot/two-step sequence of epoxide opening and Michael addition, to give highly functionalized chiral 3,4-dihydro-1,4-benzoxazine and 1,2,3,4-tetrhydro-quinoxaline derivatives in high yields. Since the preparation of diverse vinyl epoxides is well-known, the reaction conditions of the present study gain importance for the synthesis of a wide

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variety of *vic*-aminols and heterocyclic derivatives. In addition, it thus provides an opportunity for the synthesis of a wide variety of chiral compounds that are otherwise easily inaccessible by other methods that serve as versatile intermediates and useful scaffolds for the target and diversity oriented syntheses.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02304.

Experimental procedures and spectroscopic data for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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