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# Stereoselective geminal difunctionalization of vinyl arenes mediated by the bromonium ion†

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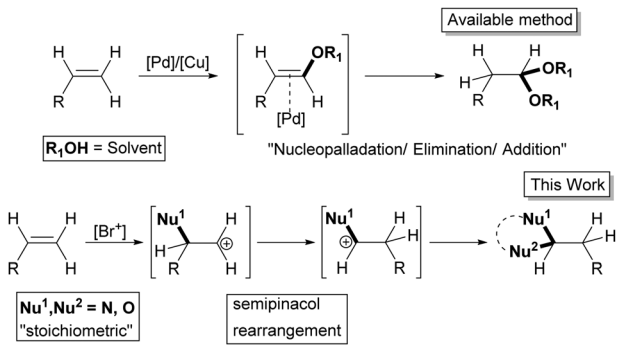
**An anti-Markovnikov geminal oxyamination of styrenyl alkenes in an intermolecular fashion using the umpolung strategy mediated by the bromonium ion is reported. Isotope labeling studies confirm the migration of the phenyl group in the semipinacol rearrangement.**

Difunctionalization of alkenes is a preeminent strategy used in organic synthesis which has been extensively studied and widely utilized as a transformative tool and has profound utiltity in various branches of chemistry.[1] The much studied 1,2-difunctionalization (vicinal) of alkenes involves a simple addition across the double bond.[2–7] Whereas the geminal difunctionalization of alkenes is an intricate process, where the single $sp^2$ carbon of the C=C bond gets difunctionalized. The addition of two nucleophiles to the electron rich alkene moiety, especially in a geminal fashion, still remains challenging. Most of the reported methods utilize the modified Wacker process[8] and are limited to simple oxidation[9,10] and use of tethered nucleophiles to form heterocycles in an intramolecular fashion.[11] No promising reagent system other than the Wacker type is available yet.

The methods that are available for the geminal difunctionalization of alkenes in an intermolecular process using stoichiometric nucleophiles are very scarce. Especially the intermolecular geminal oxyamination of alkenes still remains obscure and to the best of our knowledge it has not yet been reported under non-Wacker conditions.[12] In this context, we report the first non-Wacker method for the intermolecular geminal oxyamination of alkenes using the umpolung strategy mediated by the bromonium ion through a semipinacol rearrangement (Scheme 1).

We originally intended to add 1,2-dinucleophiles (such as 1,2-aminoalcohol or 1,2-diol) across the double bond of alkenes to get 1,4-heterocycles by an annulation process. To examine the feasibility of this addition, we first attempted to add *N*-Ts-phenylalaninol **1a** to styrene **2a** using NBS as the electrophilic bromine source and there was no observable product formed.

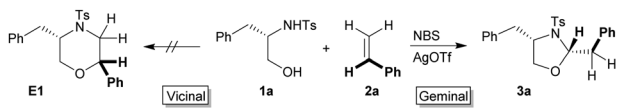



Scheme 1 Geminal difunctionalization of alkenes.

Then we sought to increase the electrophilicity of the bromonium ion to facilitate this addition. After some optimization, we found that in the presence of NBS, which is activated by AgOTf, *N*-Ts-phenylalaninol **1a** and styrene **2a** effectively reacted to provide a single product within 1 h in a very good yield (88%).[13] We were thrilled to find that the product formed was a 5-membered oxazolidine **3a** (Scheme 2) with excellent diastereoselectivity, formed by the addition of the nitrogen and oxygen atoms to the same carbon rather than the expected morpholine derivative **E1** which comes from vicinal addition.

This method allows the straightforward stereoselective umpolung installation of two new heteroatoms into a single carbon of an alkene in a domino process. Attracted by the novelty and the potential of this addition process, further studies were taken up to understand the scope and limitation of this protocol.

First the effect of substituents in the aminoalcohols on the stereoselectivity of addition was studied and the results are summarized in Table 1. The *N*-Ts-aminoalcohol **1b**, the norephedrine derived




Scheme 2 Oxazolidine formation by the addition of *N*-Ts-phenylalaninol **1a** to styrene **2a**.

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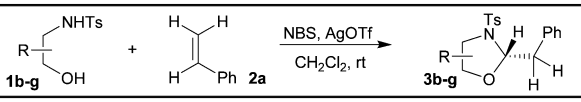
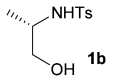
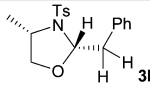
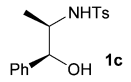
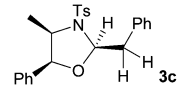
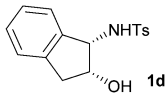
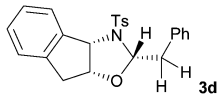
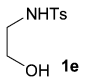
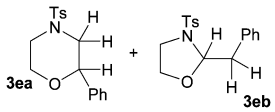
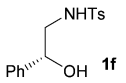
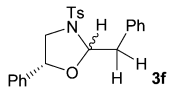
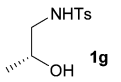
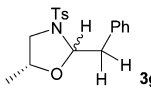
† Electronic supplementary information (ESI) available: Experimental procedures and spectral data of compounds **1a–1t** and **3a–3t**. CCDC 942034 and 942035. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc46003g

Table 1 Effect of substituents in the aminoalcohol on the stereoselectivity of addition[a,b]




| Entry | Amino alcohol | Product | Yield[c] (%) |
|---|---|---|---|
| 1 |  1b |  3b | 75 |
| 2 |  1c |  3c | 72 |
| 3 |  1d |  3d | 79 |
| 4 |  1e |  3ea + 3eb | 65[d] |
| 5 |  1f |  3f | 74[b,e] |
| 6 |  1g |  3g | 65[b,f] |

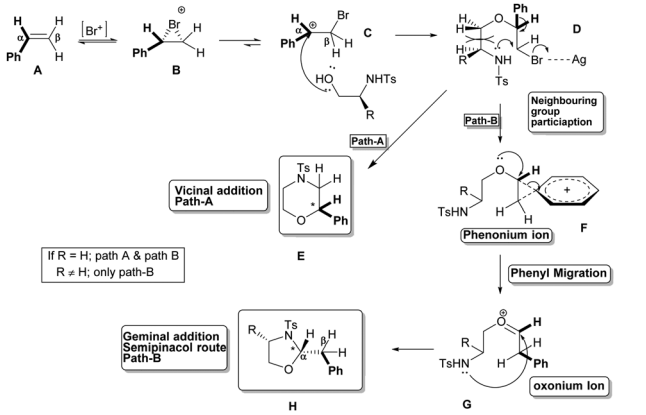
[a] Conditions: 1 equiv. (0.2 mmol) of amino alcohol, 1.2 equiv. of **2a**, 1.2 equiv. of NBS, 1.4 equiv. of AgOTf, $CH_2Cl_2$, rt, 60 min. [b] **1f** and **1g**: rt, 30 min. [c] Isolated yields. [d] Ratio of **3ea**:**3eb** is 2:1. [e] d.r = 1:1.7. [f] d.r = 1:1.5.

**1c** and the bicyclic 2-*N*-Ts-indanol **1d** provided the oxazolidines **3b**, **3c** and a tricyclic, linearly fused oxazolidine **3d**, respectively, as the sole product with excellent diastereoselectivity at the newly formed endocyclic stereogenic center (entries 1–3, Table 1). The X-ray diffraction analysis of the product **3b** provided a robust proof for the oxazolidine structure assigned.[14]

Interestingly, when the simple unsubstituted *N*-Ts-aminoalcohol **1e** was treated with styrene (NBS, AgOTf, $CH_2Cl_2$, rt) [entry 4, Table 1] it yielded a mixture of two different heterocycles, 6-membered morpholine **3ea** and 5-membered oxazolidine **3eb** in a 2:1 ratio, which are formed by the vicinal and geminal addition respectively.

However, when the 1-substituted *N*-Ts-aminoalcohols **1f** and **1g** were reacted with styrene under the reaction conditions the corresponding oxazolidines were obtained in good yields with moderate diastereoselectivity (d.r. = 1:1.7 for **3f**; d.r. = 1:1.5 for **3g**). This decrease in the diastereoselectivity can be attributed to the lack of geminal substituents at the annulating nucleophile.

In light of the above observations, we propose a mechanism as depicted in Scheme 3 for this stereoselective intermolecular geminal difunctionalization of styrenes. Initially the NBS activated by AgOTf delivers an electrophilic bromonium ion, which gets added to the electron rich π-bond of vinyl benzene **A** (styrene) to form a bridged bromonium ion **B**. This gets equilibrated to the more stable open benzylic carbocation **C**. The hydroxyl group of the nucleophile adds intermolecularly to this carbocation **C** in a rate determining step to give a bromobenzylether intermediate **D**. The bromogroup of ether **D** gets activated by Ag; at this stage the intramolecular reaction can take place *via* two kinetically controlled pathways. (i) The tethered




Scheme 3 Proposed mechanism for the addition of 1,2-aminoalcohols to styrene.

nitrogen can undergo a 6-*exo*-tet cyclization (**Path-A**) to give morpholine **E** (vicinal addition) and (ii) the phenyl group can render neighbouring group assistance to facilitate bromide ion departure to form a transient phenonium ion **F**.[15] The species **F** then readily undergoes a semipinacol rearrangement involving the migration of the phenyl group, which is favoured by the formation of the planar oxonium ion **G**, which finally gets cyclized in a 5-*endo*-trig fashion to give oxazolidine **H**. In the reaction of unsubstituted *N*-Ts-aminoalcohol (*e.g.* **1e**) (when R = H) both the pathways become possible, whereas in the case of substituted *N*-Ts-aminoalcohols like **1a–d** (when R ≠ H) **path-B** dominates due to steric interactions (**D**, Scheme 3) and forms only the oxazolidine as the product. The mechanism shown above also explains the greater control over the stereoselectivity offered by the geminal substituent of nitrogen than that of oxygen, since the former heteroatom gets added at the cyclization step.

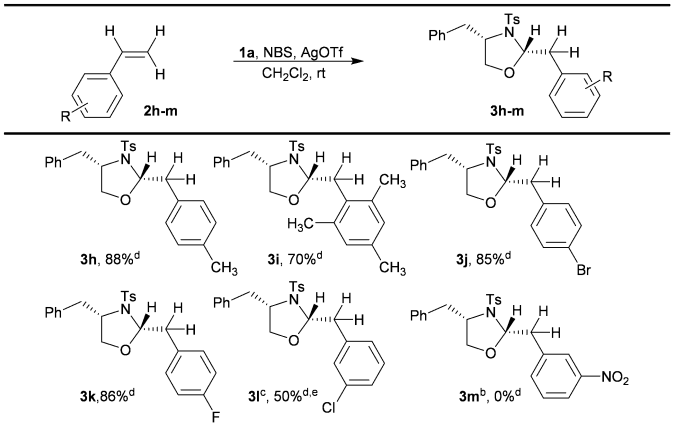
Since we envisaged that this addition process must involve a benzylic carbocationic intermediate (**C**, Scheme 3) and also a semipinacol rearrangement (**F**, Scheme 3) by a Whitmore 1,2 shift of the phenyl group, the effect of the substituent in the migrating phenyl group of styrene on the course of the reaction was studied and the results are shown in Table 2.

The *p*-methyl substituted styrene **2h** and 2,4,6-trimethyl substituted styrene **2i** gave the corresponding oxazolidines **3h** and **3i**, respectively, in good yields and high diastereoselectivity as observed for styrene **2a**. Interestingly, the substrates with electron withdrawing groups *p*-bromo **2j** and the *p*-fluoro **2k** also gave the products **3j** and **3k**, respectively, in high yields. In the case of *m*-Cl-styrene **2l** the oxazolidine **3l** was obtained along with the uncyclized bromoether (intermediate **D**, Scheme 3). The highly electron deficient *m*-$NO_2$ styrene **2m** failed to undergo the addition reaction. This relative decrease/absence of reactivity of electron deficient styrenes to undergo oxidative addition-cum-annulation provides additional support for the intermediacy of the benzylic carbocation and the migration of the nucleophile.

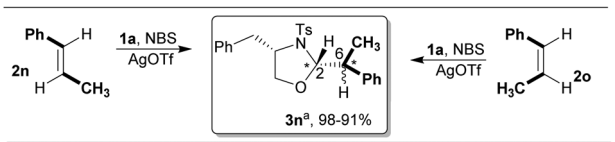
Next, the influence of stereochemistry of olefin on the diastereoselectivity of product formation was examined and the results are depicted in Scheme 4.

Intriguingly, when the diastereomeric alkenes of β-methylstyrene **2n** and **2o** were subjected to this addition (NBS, AgOTf, $CH_2Cl_2$, rt)

Table 2 Effect of substituents in the phenyl group of styrene in the annulation process[a,b,c]




[a] Conditions: the same as Table 1. [b] **3m**: rt, 12 h. [c] **3l**: rt, 4 h. [d] Isolated yields. [e] Uncyclized bromoether = 29%.




[a] $CH_2Cl_2$, rt, 30 min, observed d.r. = 1.6: 1.0 at $C_6$; 91% from **2n**; 98% from **2o**.

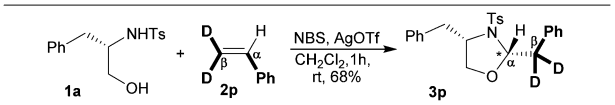
Scheme 4 Stereoconvergence of diastereomeric alkenes.

they were found to furnish oxazolidine **3n** as the sole product with the same stereochemistry at both the newly formed endocyclic and exocyclic stereogenic centers. The observed stereoidentity of the products formed strongly implies the convergence of the diastereomeric intermediates formed from the diastereomeric olefins. It is pertinent to speculate that the rotation of the $C_\alpha$–$C_\beta$ bond (intermediate **C**, Scheme 3) of the open or weakly bound carbocation causes the loss of stereogenicity of the olefin, which eventually causes the loss of stereospecificity through stereoconvergence.

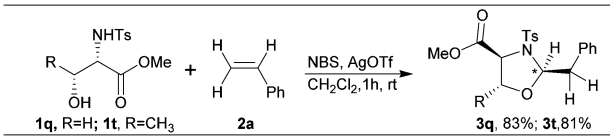
To follow the trajectory of the migration process, the β,β-dideuterated-styrene **2p** was chosen as the olefin for investigation.

This styrene containing two deuteriums and a phenyl group at the vicinal position, under these oxidative addition conditions, got transformed into an oxazolidine **3p** containing the exocyclic methylene group constituting two deuteriums and a phenyl group on the same carbon (Scheme 5). This result unequivocally confirms the migration of the phenyl group from the hydrogen attached carbon ($C_\alpha$, migration origin) to the di-deuterium attached carbon ($C_\beta$, migration terminus) through a semipinacol rearrangement (intermediates **D–G**, Scheme 3).

The potency and the expediency of this geminal oxidative addition were exemplified in the straightforward synthesis of pseudoprolines **3q** and **3t** from styrene **2a** in a single pot with a very high stereoselectivity (Scheme 6).




Scheme 5 Deuterium labeling study.




Scheme 6 Synthesis of pseudoprolines from styrene.

In conclusion, the first report on the non-Wacker intermolecular geminal oxyamination of vinyl arenes (styrenes) through a domino process is described. This highly stereoselective oxidative geminal addition is found to involve a semipinacol rearrangement. The diastereomeric alkenes were found to show stereoconvergence in the product formation. The migration of the phenyl group in the semipinacol rearrangement was confirmed by deuterium labeling studies. The efficacy of this method was exemplified in the synthesis of pseudoprolines from styrene.

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13 When the reaction was performed with the lesser equivalents (catalytic) of NBS (0.2 equiv.) or AgOTf (0.2 equiv.), the yield of the product was found to decrease proportionally. For optimization data refer to ESI†.
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