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COMMUNICATION

Intramolecular *N*-Me and *N*-H Aminoetherification for the Synthesis of *N*-Unprotected 3-Amino-*O*-Heterocycles

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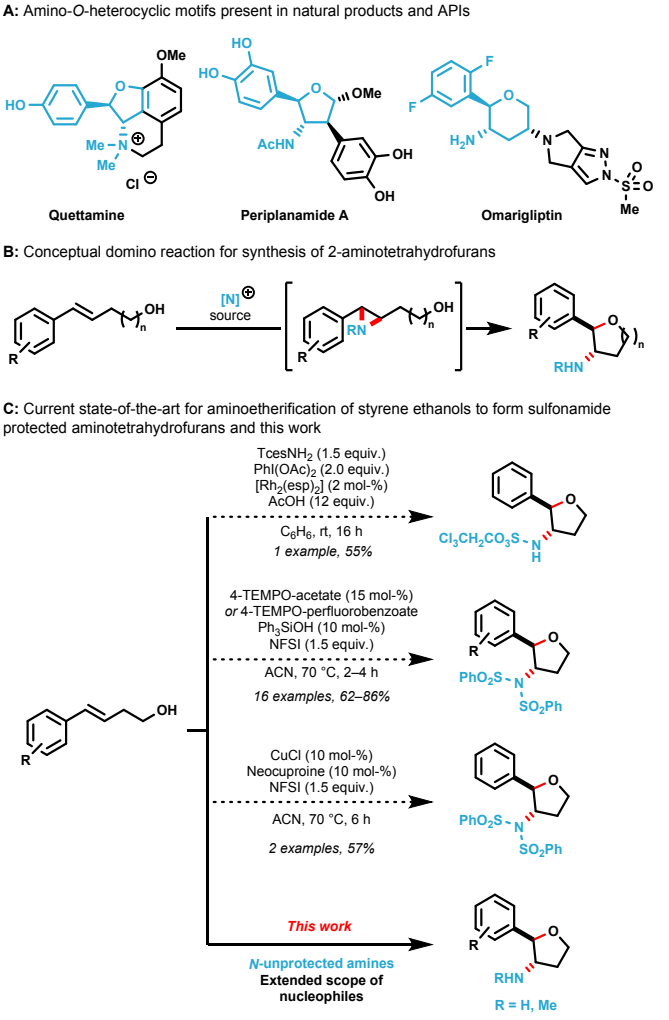
A mild Rh-catalyzed method for synthesis of cyclic unprotected *N*-Me and *N*-H 2,3-aminoethers using an olefin aziridination-aziridine ring-opening domino reaction has been developed. The method is readily applicable to the stereocontrolled synthesis of a variety of 2,3-disubstituted aminoether *O*-heterocyclic scaffolds, including tetrahydrofurans, tetrahydropyrans and chromanes.

The 2-aryl-3-amino-*O*-heterocyclic motif is present in several alkaloids as well as active pharmaceutical ingredients (Scheme 1A).[1] Conceptually, the intramolecular ring-opening of aziridines with *O*-nucleophiles is a very direct synthetic approach for the construction of these 2-aryl-3-amino-*O*-heterocycles (Scheme 1B). This type of an approach has been studied by the Zhang, Weng and Dauban groups (Scheme 1C).[2] However, these previous synthetic approaches result in sulfonamide-protected amines which either require harsh deprotection conditions or suitable deprotection conditions have not yet been developed.[3] We envisioned that our recently developed Rh-catalyzed *N*–H and *N*–Me olefin aziridination reaction could be used in combination with styryl alcohols. This would allow us to circumvent the issues pertaining to the heavily protected amines and gain direct access to readily functionalizable *N*-H heterocyclic scaffolds (Scheme 1C).[4] Furthermore, we were interested in expanding to alternative *O*-nucleophilic partners such as phenols and extended styryl alcohols to access structurally more complex *O*-heterocycles.

The main challenge was to find a suitable aminating reagent for the Rh-catalyzed aziridination: (1) the aminating reagent must be sufficiently active to generate the Rh-nitrenoid and (2) the leaving group of the aminating reagent has to be essentially non-nucleophilic. The low nucleophilicity of the leaving group would ensure that it will not compete with the desired intramolecular aziridine ring-opening.[5]



Scheme 1: A: 2-Aryl-3-amino-*O*-heterocyclic motifs present in alkaloids and pharmaceuticals. **B:** Conceptual approach to preparing 2-aryl-3-amino-O-heterocyclic systems. **C:** Literature precedent for aminoetherification of styrylethanols resulting in sulfonamide protected compounds. Proposed approach to prepare *N*-H and *N*-Me aminoether products.

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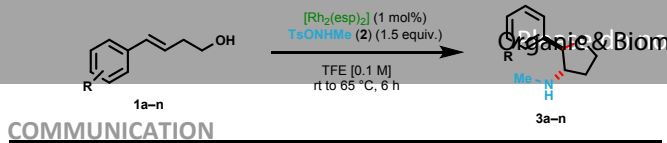
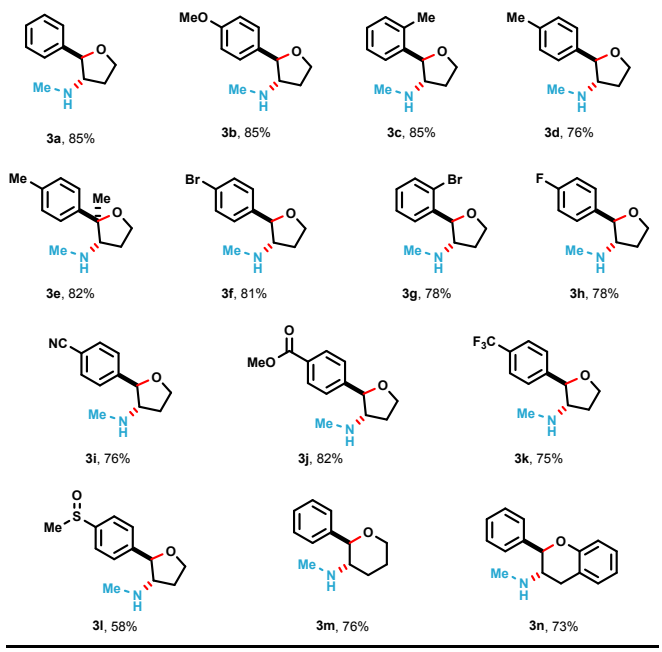
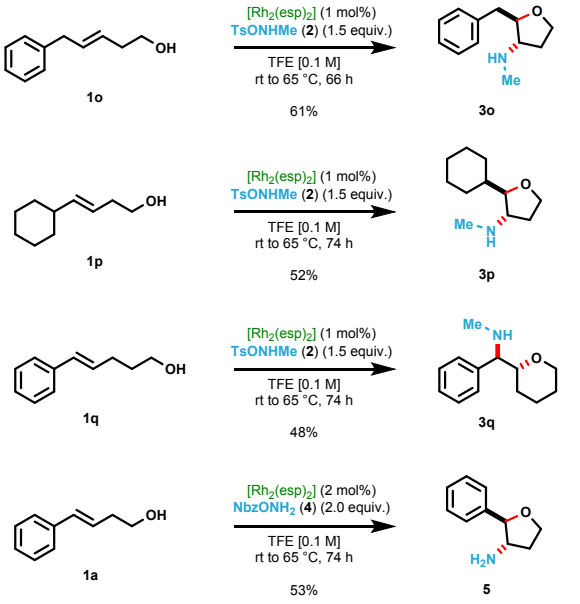




Scheme 2: Substrate scope for aminoetherification protocol to furnish tetrahydrofurans and tetrahydropyrans. Reaction conditions: Substrate (**1**) (1.0 mmol), TsONHMe (**2**) (1.5 mmol), $[Rh_2(esp)_2]$ (1 mol-%) in 2,2,2-trifluoroethanol (TFE).

Scheme 3: Extended scope of the aminoetherification reaction.

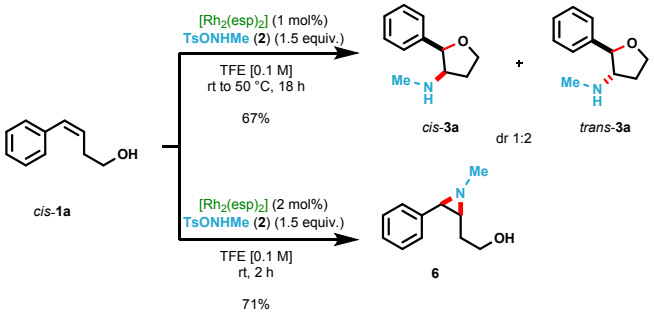
With these two criteria in mind, we initiated the studies with *O*-tosyl hydroxylamines ($TsOHN_2$ and TsONHMe) as electrophilic aminating reagents. After an optimization study with *trans*-styryl ethanol (**1a**) as the model substrate (see SI), the highest-yielding conditions were found to use TsONHMe (**2**) as the nitrogen source with a 1 mol% loading of $[Rh_2(esp)_2]$ in 2,2,2-trifluoroethanol (CF_3CH_2OH, TFE) at 65 °C. This reaction afforded the desired *N*-Me-2,3-*trans*-tetrahydrofuran **3a** in 85% isolated yield as a single *trans*-diastereomer.



With the established optimized conditions in hand, we screened the scope of substrates for the *N*-Me aminoetherification-cyclization reaction using TsONHMe (**2**) as the nitrogen source (Scheme 2). The reaction showed great tolerance toward electronically very different styrenes (compare *p*-OMe **3b** 85%, *p*-F **3h** 78%) as well as a variety of functional groups (*p*-CN **3i** 76%, *p*-CO_2Me **3j** 82%, *p*-S(=O)Me **3l** 58%). The cyclization was also amenable for the synthesis of uncommon *O*-heterocyclic scaffolds. For example, tetrahydropyran **3m** could be obtained in 76% isolated yield when *trans*-styryl-propanol (**1m**) was used as the starting material.[6] The reaction could also be carried out with a phenol as the internal nucleophile, furnishing the corresponding aminochromane **3n**.[7] Notably, aliphatic olefins **1o, 1p** and **1q** proved to be viable substrates in this *N*-Me aminoetherification, yielding tetrahydrofurans **3o** and **3p** and tetrahydropyran **3q** (Scheme 3).[8,9] However, with these aliphatic olefin substrates, extended reaction times were required (74 h for **3p** *vs.* 6 h for **3a**). No other ring-size products apart from those shown in Scheme 3 were isolated from these reactions.

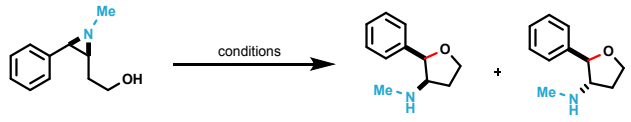
With these results for *N*-Me aminoetherification in hand, next we explored the corresponding *N*-H variant. In the initial screening $TsONH_2$ was found to be too unstable as a practical nitrogen source for the *in-situ* *N*-H aziridination with **1a**. Further screening revealed that *O*-(4-nitrobenzoyl)-hydroxylamine (**4**) ($NbzONH_2$) was a suitable alternative to $TsONH_2$. When styryl-ethanol **1a** was reacted with $NbzONH_2$ (**4**) and $[Rh_2(esp)_2]$ (2 equivalents and 2 mol% respectively), introduced to the reaction mixture in two equal portions, the corresponding primary aminotetrahydrofuran **5** was isolated in 53% yield (Scheme 3). For the most reproducible results, the $[Rh_2(esp)_2]$ catalyst is added directly to a vigorously (1400 rpm) stirred solution of the styryl-alcohol substrate and $NbzONH_2$ (**4**) in TFE as the solvent.

We expected that using *Z*-styryl alcohols as the starting materials would allow us to directly prepare *cis*-2,3-aminotetrahydrofurans. However, the aziridination-cyclization reaction using *Z*-styrylethanol (*Z*-**1a**) as the starting material yielded a 2:1 *trans*/*cis* mixture in a 67% combined isolated yield (Scheme 4). As the aziridination step is stereospecific, the observed scrambling to favour *trans*-**3a** over *cis*-**3a** must take place either before or during the intramolecular cyclization step. To gain further insight into this scrambling process, *cis*-aziridine **6** was prepared separately and exposed to a range of additives to probe the cyclization reaction.



Scheme 4: Unexpected scrambling and experimental proof of the stereospesificity of the aziridination.

Table 1: Effect of different additives on the stereoselectivity of aziridine opening.



6 *cis*-**3a** *trans*-**3b**

Entry	Additive(s)	Solvent	Temp/time	dr	Yield (%)
1	CSA (1.2 equiv.)	ACN	50 °C/5 d	0:1	69
2	CSA (1.2 equiv.)	DCM/hexane (1:1)	50 °C/3 d	0:1	78
3	CSA (1.2 equiv.)	TFE	50 °C/5 d	1:5	-
4	CSA (1.2 equiv.), $[Rh_2(esp_2)]$ (2 mol-%)	TFE	50 °C/5 d	1:5	-
5	$ZnCl_2$ (1.1 equiv.)	TFE	50 °C/3 d	0:1	84
6	$La(OTf)_3$ (1.2 equiv.)	TFE	50 °C/5 d	5:1	-
7	$La(OTf)_3$ (1.2 equiv.)	DCM	50 °C/5 d	1:2	-
8	$La(OTf)_3$ (1.2 equiv.)	PhMe	50 °C/5 d	1:2	-
9	$Yb(OTf)_3$ (1.2 equiv.)	TFE	50 °C/5 d	7:1	66

Treating *cis*-aziridine **6** under Brønsted acidic conditions (Table 1, entries 1–4) or with zinc chloride (Table 1, entry 5) led to either exclusive or highly favoured (dr 1:5) formation of the scrambled *trans*-**3a** product. This type of stereochemical scrambling at benzylic stereogenic centers has also been previously reported.[10] The undesired stereochemical scrambling could be supressed by activating the *cis*-aziridine **6** with rare-earth triflates. Especially $Yb(OTf)_3$ (1.2 equiv.) in TFE supressed the unwanted scrambling to a significant degree, giving *cis*-**3a** 2,3-aminotetrahydrofuran as the major diastereomer (66% yield, dr 7:1) (Table 1, 9).[11] These results seem to indicate that some solvent and activating agent combinations, such as $La(OTf)_3$ in TFE, invoke a more S_N2-type stereospecific ring-opening reaction on a Lewis acid coordinated aziridine, whereas Brønsted-acidic activators (e.g., CSA) cannot be interpreted as simple S_N2 reactions. Instead, development of substantial carbocationic character on the benzylic carbon *via* an S_N1 type pathway would explain the observed stereochemical scrambling.[12]

In conclusion, we have developed a mild one-pot Rh-catalyzed domino reaction for the stereocontrolled synthesis of 2-aryl (or alkyl)-3-amino-substituted tetrahydrofurans, tetrahydropyrans as well as chromanes. The method affords *N*-unprotected products which may be directly taken into further transformations without the need of any protecting group manipulations.

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Conflicts of interest

There are no conflicts to declare

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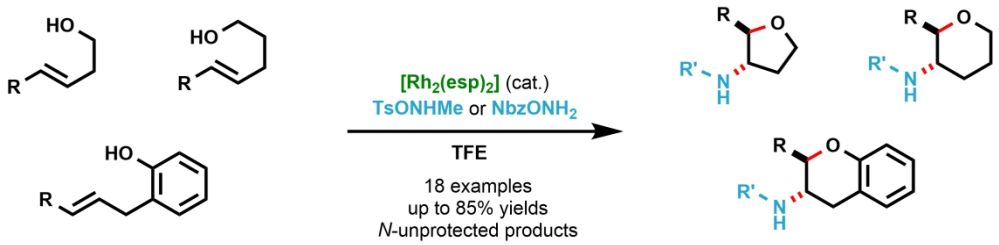
12 See SI for tentative mechanistic proposals for the scrambling process.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