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Communication

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Stereodivergent Intramolecular C(sp^3)–H Functionalization of Azavinyl Carbenes: Synthesis of Saturated Heterocycles and Fused *N*-Heterotricycles

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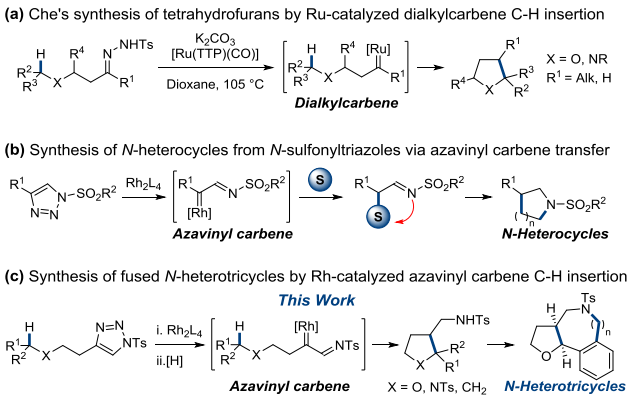
Supporting Information Placeholder

ABSTRACT: A general approach for the formation of five-membered saturated heterocycles by intramolecular C(sp^3)-H functionalization is reported. Using *N*-sulfonyltriazoles as Rh(II) azavinyl carbene equivalents, a wide variety of stereodefined *cis*-2,3-disubstituted tetrahydrofurans were obtained in good to excellent diastereoselectivity from acyclic, readily available precursors. The reaction is shown to be amenable to gram-scale, and judicious choice of reaction conditions allowed for stereodivergence, providing selective access to the *trans* diastereomer, in good yield. The resulting products were shown to be valuable intermediates for the direct preparation of fused *N*-heterotricycles in one step by intramolecular C–H amination or Pictet-Spengler cyclization.

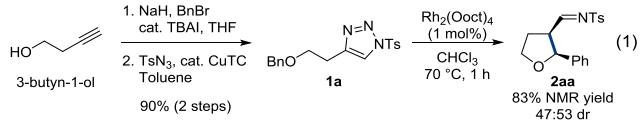
Saturated five-membered heterocycles such as tetrahydrofurans are ubiquitous structural motifs found in an array of natural products and other biologically relevant molecules.[1] For the synthesis of polysubstituted and ring-fused analogues of these compounds, efficient access to stereodefined products remains a formidable challenge.[2] The preparation of substituted tetrahydrofurans often proceeds by C–O bond formation, *via* cyclization of linear substrates with predefined stereochemistry. A strategically powerful alternative to this approach involves intramolecular C–C bond formation from an acyclic aliphatic ether, where both the cyclization and the generation of stereocenters occur in the same step, ideally from an unactivated substrate. In recent years, metal-catalyzed carbenoid C–H insertion reactions have been shown to be robust processes for stereoselective C–C bond formation from ethereal C–H bonds.[3] While such a stategy has been widely utilized for the intramolecular formation of stereodefined dihydrobenzofurans from aryl ethers,[4] only scarce and specific examples have been reported for the analogous formation of polysubstituted tetrahydrofurans.[4b,5] A common challenge in these reactions, typically using Rh(II) carbenoids derived from α-diazocarbonyl compounds, lies in the diastereocontrol of the intramolecular C–H insertion step when flexible aliphatic ethers are employed as substrates. Very recently, Che *et al.* demonstrated that Ru-porphyrin catalysts are particularly efficient in such a process with dialkyldiazomethanes formed in situ from *N*-sulfonylhydrazones, leading to a variety of stereodefined saturated heterocycles *via* a Ru dialkylcarbene (Scheme 1a).[5g]

Scheme 1. Synthesis of tetrahydrofurans and *N*-heterocycles via metal-catalyzed C–H insertion



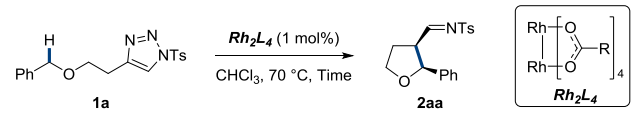
In the last few years, 1-sulfonyl-1,2,3-triazoles have proven to be extremely versatile Rh(II) azavinyl carbene equivalents in numerous carbene transfer processes.[6] In contrast with α-diazocarbonyl compounds or dialkyldiazomethanes, the use of *N*-sulfonyltriazoles as carbenoid precursors can lead to the rapid elaboration of substituted *N*-heterocycles, by cyclization of the resulting imino group after the carbene transfer has occurred (Scheme 1b).[6a] When these transformations are applied in an intramolecular sense, ring-fused *N*-heterocycles are directly obtained from acyclic precursors in a particularly efficient manner.[7] In our continuing efforts to utilize such intramolecular azavinyl carbene transfer reactions for the expedient synthesis of fused *N*-heterocycles,[7c-d] we envisioned that the corresponding intramolecular C–H insertion into an ethereal C–H bond would lead to a stereodefined 3-imino tetrahydrofuran, which could be elaborated into fused *N*-heterocycles by engaging the resulting *N*-sulfonylamino moiety of the product (Scheme 1c).[8] In this work, we report a general approach to the synthesis of saturated heterocycles using a stereodivergent intramolecular Rh-catalyzed azavinyl carbenoid C(sp^3)–H insertion reaction. Moreover, the resulting products were directly utilized for the synthesis of ring-fused *N*-heterotricycles such as a tetrahydroquinoline and a tetrahydrobenzazepine, through the use of an intramolecular C–H amination or Pictet-Spengler cyclization, respectively. Considering the ubiquity of polysubstituted and ring-fused tetrahydrofurans and the lack of a unified route for their stereoselective formation, this work should find broad applicability in the elaboration of complex molecules.

In order to evaluate the viability of our approach, we first synthesized *N*-sulfonyltriazole **1a** in two simple steps from commercially available 3-butyn-1-ol, and subjected it to standard conditions for Rh(II)-catalyzed azavinyl carbene transfer reactions (eq 1).[6a] While the desired 3-iminotetrahydrofuran **2aa** was cleanly formed in good NMR yield (83%), only very poor diastereoselectivity was obtained (47:53). Interestingly, no 1,2-hydride shift side-product was observed, a common problem with alkyl-substituted carbenoid precursors.[7e,9]



A survey of various Rh(II) catalysts revealed that the nature of the carboxylate ligands had an enormous impact on the diastereoselectivity of the reaction, with the most hindered complexes affording the highest *cis*:*trans* ratio of **2aa** (Table 1, entries 1-8). Commercially available catalyst $Rh_2(tpa)_4$ gave optimal diastereoselectivity, though it proved to be significantly less reactive and the reaction time had to be increased to 4 h in order to achieve complete conversion (entries 8-9). Most non-coordinating solvents were tolerated, however the use of CH_2Cl_2 led to an increase in both the yield and the diastereoselectivity (entry 10).[10]

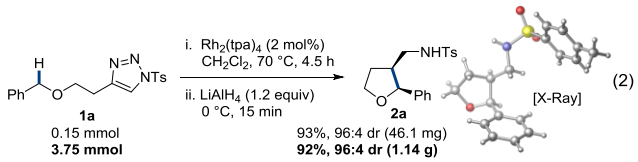
Table 1. Optimization of the intramolecular Rh(II)-catalyzed azavinyl carbene C–H insertion



entry	Rh_2L_4	R	time (h)	yield (%)[a,b]	dr (*c*:*t*)[a]
1	$Rh_2(O_2CH)_4$	H	1	23 (77)	38:62
2	$Rh_2(OAc)_4$	Me	1	72 (13)	33:67
3	$Rh_2(Oct)_4$	*n*-C_7H_{15}	1	83 (<5)	47:53
4	$Rh_2(tfa)_4$	CF_3	1	<5 (83)	-
5	$Rh_2(Adc)_4$	1-Ad	1	83 (<5)	69:31
6	$Rh_2(OPiv)_4$	CMe_3	1	80 (<5)	72:28
7	$Rh_2(esp)_2$	[c]	1	79 (<5)	82:18
8	$Rh_2(tpa)_4$	CPh_3	1	17 (71)	**95:5**
9	$Rh_2(tpa)_4$	CPh_3	4	72 (5)	93:7
10[d]	$Rh_2(tpa)_4$	CPh_3	4	81 (18)	96:4
11[d,e]	$Rh_2(tpa)_4$	CPh_3	4.5	**96 (<5)**	**96:4**

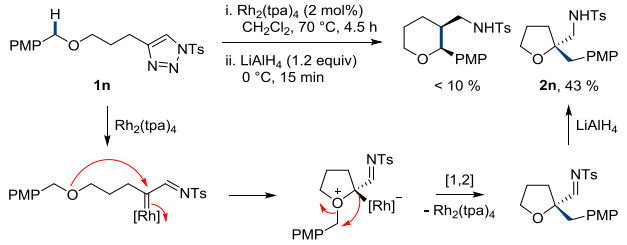
[a]Determined by NMR analysis of the crude mixture using 1,3,5-trimethoxybenzene as internal standard. [b]Yield of remaining **1a** in parentheses. [c]$Rh_2(esp)_2$: Bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)]. [d]Using CH_2Cl_2 as solvent. [e]2 mol% catalyst was used.

In view of developing a general method, the catalyst loading was increased to 2 mol%, insuring complete conversion in a timely fashion for most substrates (entry 11). It was found that prolonged reaction times (>5 h) or higher reaction temperatures led to partial decomposition of the product and were therefore avoided.[11] While the resulting imine product is somewhat unstable to silica gel chromatography, isolation of the product was readily achieved after reduction with $LiAlH_4$, directly added at 0 °C to the crude mixture (eq 2).[8a] Under the optimized conditions, the resulting *N*-sulfonyl amide **2a** was isolated in 93% yield and 96:4 dr, and the procedure could be conducted on gram-scale with similar efficiency.



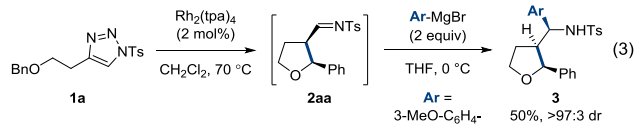
With these conditions in hand, a variety of stereodefined saturated five-membered heterocycles were efficiently prepared (Table 2). Various substituted benzyl ethers were well tolerated as substrates, as well as an electron rich heterocyclic variant (entries 1-7). C(sp^3)–H insertion into an allylic ethereal position is also possible, with a minimal amount of competitive cyclopropanation observed on the proximal double bond (entry 8). Gratifyingly, substrates bearing an aliphatic R group, though less activated towards C–H insertion, afford a high yield of the corresponding tetrahydrofuran (entry 9). Insertion into methine C–H bonds, leading to highly substituted analogues **2j** and **2k**, was found to also proceed, in good yields (entries 10-11). In addition to tetrahydrofurans, the formation of products such as **2l** and **2m** demonstrate that pyrrolidines and cyclopentanes can be accessed by this method in excellent diastereoselectivity (entries 12-13). The use of a homologated substrate such as **1n** afforded tetrahydrofuran **2n** instead of the expected tetrahydropyran, presumably by a Rh(II)-catalyzed oxonium ylide formation / [1,2]-alkyl shift sequence (Scheme 2).[12]

Scheme 2. Rh(II)-catalyzed oxonium ylide formation / [1,2]-alkyl shift with extended tethers



[a]PMP: 4-MeO-C_6H_4

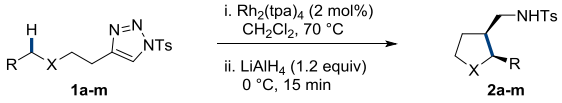
The crude imine intermediate obtained following C–H insertion can be directly used as an electrophile in a 1,2-addition reaction, as exemplified by Grignard addition to imine **2aa**, affording tetrahydrofuran **3** possessing three contiguous stereocenters (eq 3).[12b,13-14]

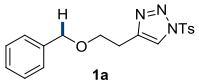
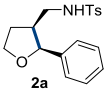
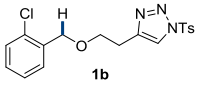
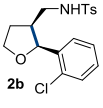
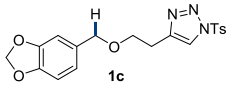
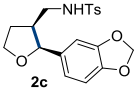
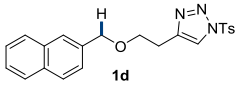
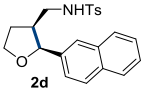
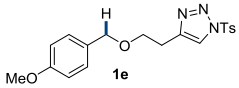
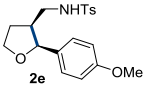
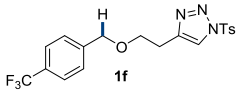
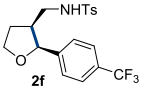
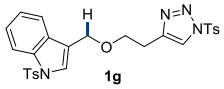
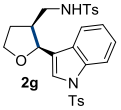
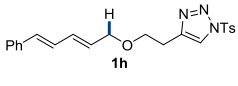
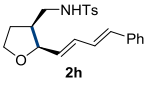
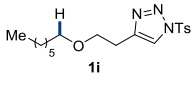
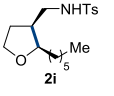
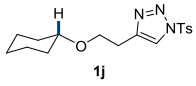
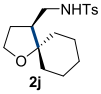
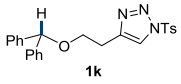
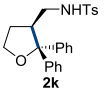
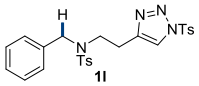
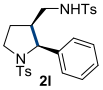
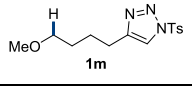
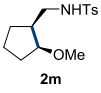


While sterically hindered $Rh_2(tpa)_4$ affords the *cis* product in high diastereoselectivity, our initial investigations had revealed that the use of other catalysts such as $Rh_2(OAc)_4$ can provide a *trans*-selective reaction, allowing the development of a stereodivergent approach (see Table 1, entry 2). Such an effect on the diastereoselectivity might be due to a difference in the degrees of freedom of the substituents around the C–C bond being formed, where small carboxylates such as OAc allow these groups (here, Ph and C=NTs) to be placed in a more stable *trans* configuration in the transition state. After further optimization,[10] performing the $Rh_2(OAc)_4$-catalyzed reaction with substrate **1a** in toluene in the presence of 2-picoline as an additive (5 mol%)[15]

allowed access to the *trans* diastereomer, in good yield (Scheme 3).

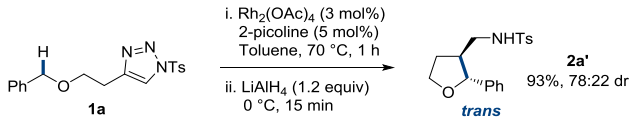
Table 2. Substrate scope of the intramolecular Rh(II)-catalyzed azavinyl carbene C–H insertion



entry	substrate	product	yield (%)[a]	dr (*c*:*t*)[b]
1	 1a	 2a	93	96:4
2	 1b	 2b	89	93:7
3	 1c	 2c	89	90:10
4	 1d	 2d	80	98:2
5	 1e	 2e	77	95:5
6	 1f	 2f	78	89:11
7	 1g	 2g	81	97:3
8[c]	 1h	 2h	71	82:18
9	 1i	 2i	88	87:13
10	 1j	 2j	82	-
11[d]	 1k	 2k	97	-
12[e]	 1l	 2l	58	>98:2
13	 1m	 2m	67	>98:2

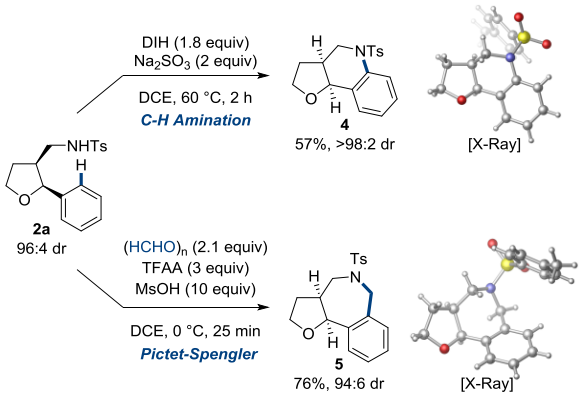
[a]Isolated yield. [b]Determined by NMR analysis of the crude mixture. [c]Rh_2(*S*-PTAD)$_4$ (2 mol%) was used as catalyst. [d]Rh_2(Adc)$_4$ (3 mol%) was used as catalyst. [e]Using 3 mol% of Rh_2(tpa)$_4$.

Scheme 3. Stereodivergence of the C(sp^3)–H insertion: access to the *trans* diastereomer



Finally, the 3-methylamino moiety of the products obtained following imine reduction can be further utilized for the rapid construction of *N*-heterotricycles by intramolecular C–N bond formation events (Scheme 4). As exemplified with *N*-sulfonyl amide **2a**, the use of commercially available 1,3-diiodo-5,5-dimethylhydantoin (DIH) allowed the direct formation of 5-6-6 fused tetrahydroquinoline **4** by a metal-free C–H amination process.[16] Furthermore, modified Pictet-Spengler conditions using paraformaldehyde, TFAA and MsOH in DCE provided fused tetrahydrobenzazepine **5** in good yield, without the need for an electron-donating aromatic ring.[17] In both cases, X-ray crystal structures were obtained to unambiguously confirm the structure of the *N*-heterotricyclic products.

Scheme 4. Synthesis of *N*-Heterotricycles via intramolecular C–H amination and Pictet-Spengler[a]



In summary, a general and stereodivergent intramolecular Rh(II)-catalyzed azavinyl carbene C(sp^3)–H insertion reaction was developed, providing access to an array of stereodefined *cis*-2,3-disubstituted saturated heterocycles. The reaction proceeds on gram-scale with similar efficiency, and the use of an alternative set of conditions is shown to provide access to the *trans* diastereomer of these compounds, in good yield. The resulting products were utilized for the rapid formation of fused *N*-heterotricycles through different intramolecular C–N bond forming processes. Cognizant of the ubiquity of polysubstituted and ring-fused tetrahydrofurans, this work should find broad applicability in the synthesis of biologically relevant molecules. Future studies in the field of intramolecular azavinyl carbene insertion reactions will seek to render these transformations enantioselective.[11]

ASSOCIATED CONTENT

Supporting Information

Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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