Communication

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Matthew R. Porter, Rami M. Shaker, Cristian Calcanas, and Joseph J. Topczewski

J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.7b11299 • Publication Date (Web): 05 Jan 2018

Stereoselective Dynamic Cyclization of Allylic Azides: Synthesis of Tetralins, Chromanes, and Tetrahydroquinolines

Matthew R. Porter, Rami M. Shaker, Cristian Calcanas, and Joseph J. Topczewski*

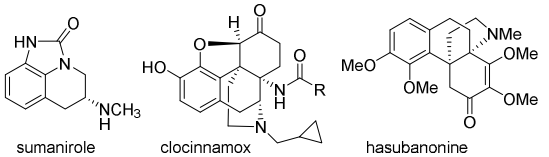
Department of Chemistry, University of Minnesota Twin Cities, Minneapolis, Minnesota, 55455, United States

Supporting Information Placeholder

ABSTRACT: This report describes the stereoselective synthesis of 3-azido-tetralins, -chromanes, and -tetrahydroquinolines via a tandem allylic azide rearrangement/Friedel-Crafts alkylation. Exposure of allylic azides with a pendant trichloroacetimidate to catalytic quantities of $AgSbF_6$ proved optimal for this transformation. This cascade successfully differentiates the equilibrating azide isomers, providing products in excellent yield and selectivity (>25 examples, up to 94% yield and >25:1 dr). In many cases, the reactive isomer is only a trace fraction of the equilibrium mixture, keenly illustrating the dynamic nature of these systems. We demonstrate the utility of this process via a synthesis of hasubanan.

Tetralins, chromanes, and tetrahydroquinolines represent privileged structural motifs present in pharmaceuticals, agrochemicals, and natural products. Many feature an amino substituent at the C-3 position (Figure 1). These molecules display a wide range of activity including treatments or potential treatments for cancer, pain, depression, thrombosis, Parkinson's disease, and malaria.[1–9] Due to this rich history, numerous synthetic methods can generate these systems including cyclization,[10–15] annulation,[16,17] cycloaddition,[18,19] partial reduction,[20,21] and others.[6,22–24] Presented herein is a distinctive carbon-carbon bond forming reaction that generates these privileged motifs with the required 3-amino-functionality by manipulating the allylic azide rearrangement.

Figure 1. Representative Biologically Active Compounds

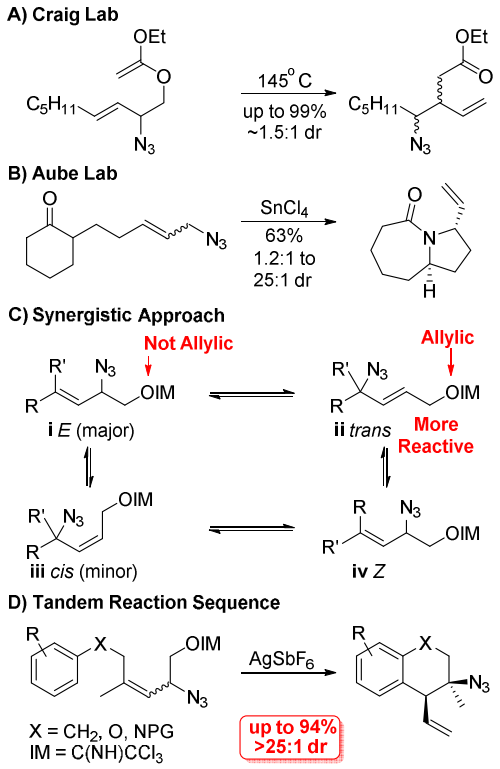


Allylic azides exist as an equilibrating mixture of isomers. This was first noted by Winstein, who documented the rate of isomerization for prenyl and crotyl azides.[25] Since then, chemists have struggled to exploit this rearrangement synthetically because of difficulty differentiating the azide isomers.[26–33] Only a few reports accomplish selective elaboration. The Craig lab reported a tandem Claisen rearrangement (Figure 2a).[34] Selectivity was achieved by orchestrating a second irreversible sigmatropic process. The Aubé lab reported a tandem Schmidt reaction that attained selectivity through cyclization and achieved diastereocontrol via chair-like intermediates (Figure 2b).[35] Recently, we initiated a program to explore the allylic azide rearrangement's potential.[36] We reported the first example of enantioselective resolution of symmetric systems.[37] Herein, we report a synergistic approach that combines the use of proximal functionality with a complexity generating cyclization. By merging these tactics (Figure 2c), we obtain selectivity on un-symmetric systems and accomplished a tandem Friedel-Crafts alkylation (Figure 2d). This reaction results in the highest combined yield and diastereoselectivity reported to date for a dynamic allylic azide functionalization. We demonstrate the utility of this chemistry through a succinct synthesis of hasubanan.

Our strategy incorporated a second proximal allylic functional group. When the azide is proximal (Figure 2c, OIM group, isomers **i** *E* and **iv** *Z*), the second group would be primary. However, when the azide is distal (Figure 2c, **ii** *trans* isomer), the second group would be allylic and therefore substantially more reactive. We chose a trichloroacteimidate because it could be readily activated under electrophilic conditions, such as those for glycosylation,[38,39] rearrangement,[40–45] or substitution.[46–50] A pendent arene might intercept the putative electrophile in a Friedel-Crafts alkylation. Ring closure could potentially proceed from either allylic terminus and the tether would enforce regioselectivity. Imposing selectivity by these combined approaches could afford a highly chemo-, site-, regio-, and diastereoselective protocol for the synthesis of 3-azido-tetralins, -chromanes, and -tetrahydroquinolines (X = CH_2, O, or N-PG, respectively; Figure 2d).

We began with allylic azide **1a** (Table 1). This allylic azide exists as an equilibrium mixture (1.3:1.0:0.7:trace *E*:*trans*:*Z*:*cis*, representations shown in Figure 2c). The reactive *trans* isomer is only ~30% of the mixture. We exposed azide **1a** to a number of activators, including Lewis acids (entries 1-3), Brønsted acids (entries 4-7), and transition metal complexes (entries 8-10). Most conditions led to decomposition (entry 1), poor selectivity (entries 2,3), or poor reactivity (entries 3-5, 8, and 9). Control experiments, conducted after an initial hit with cationic gold(I) (entry 10), provided encouraging results with silver salts. Silver salts with non-coordinating counter ions were efficacious (entries 12-14) and those with more lipophilic counter ions provided superior results. Conditions with catalytic $AgSbF_6$ are mild, high yielding, and highly stereoselective (entry 14). In a control experiment, 2,6-di-*tert*-buty-4-methyl-pyridine inhibited the reaction (entry 15). The reaction is slow in ethanol stabilized chloroform (entry 16) or in the presence of deliberately added water (entry 17). These observations implicate general acid catalysis.[51] The reaction was tolerant to ambient conditions (entry 18).

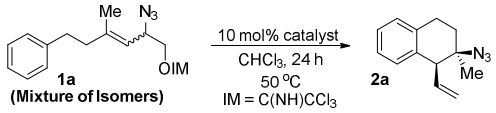
Figure 2. Selectivity for Allylic Azide Functionalization



We explored the scope of this cyclization with a series of allylic azides (Scheme 1). Common substituents on the aryl ring were tolerated (H, OMe, Cl, or Br, **2a**-**2d**). Conveniently, derivative **2d** provided diffraction quality crystals. Analysis unambiguously demonstrated the relative configuration of **2d**. Other compounds were assigned by analogy to compound **2d**. Different tethers were tolerated. The 3-methyl group is not required for diastereoselectivity (**2e**). Azide **2e** maps onto biologically active 3-amino-tetralins (Figure 1). Interestingly, imidate **1f** exists almost exclusively as the unreactive isomers by ^{1}H NMR analysis (>99% *E* and *Z*). The reactive *trans* isomer is destabilized by *syn*-pentane interactions with the geminal methyl groups. However, this does not inhibit reactivity and compound **2f** was isolated in acceptable yield. This observation supports Curtin-Hammett kinetics with rate limiting aromatic substitution. Moving the methyl group to the center of the allylic system eroded the dr (1.7:1 for compound **2g**). We propose a putative stereochemical model based on chair like transition states (Figure 3). The pathways differ in the orientation of the vinyl group. The major diastereomer could arise from the pseudo-equatorial orientation. When the hydrogen atom is replaced with a methyl (**1g**), then the relative energy approaches unity and diastereoselectivity is reduced (**2g**). Lastly, a group larger than methyl was permitted in the backbone (**2h**).

Incorporating a heteroatom into the system would generate valuable heterocycles. A number of ethereal allylic azides were converted into chromanes in high yield and selectivity (Scheme 2, **4a**). Activating groups such as methyl (**4b**) or methoxy (**4c**) were competent as were compounds with a halogen substituent (entries **4d**-**4f**). Poly-substituted aromatics were tolerated (entries **4g**-**4i**). These results are gratifying because the heteroatom is a basic site that could slow catalysis. The proximal oxygen would inductively reduce the stability of a cationic intermediate and could disrupt the azide equilibrium.[52] These substrates also indicate limitations in this method. The formation of **4j** was slow and imidate decomposition occurred. Chromane **4k** was isolated as a mixture of regioisomers (1.4:1).

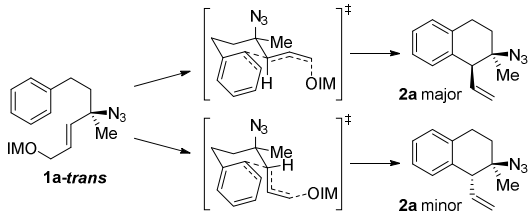
Table 1. Optimization of Tandem Rearrangement Friedel-Crafts Alkylation



entry[a]	catalyst	yield %[b]	dr[c]
1	$BF_3{\cdot}OEt_2$	35	28:1
2	$Cu(OTf)_2$	75	9:1
3	$Zn(OTf)_2$	58	9:1
4	TFA	4	4:1
5	TsOH	4	7:1
6	Tf_2NH	80	13:1
7	TfOH	49	7:1
8	$PdCl_2$	0	nd
9	$[(COP)PdCl]_2$	0	nd
10	JohnPhosAuSbF$_6$	75	21:1
11	AgOTs	0	nd
12	$AgClO_4$	81	7:1
13	AgOTf	80	7:1
14	$AgSbF_6$	92	21:1
15[d]	$AgSbF_6$	3	3:1
16[e]	$AgSbF_6$	55	16:1
17[f]	$AgSbF_6$	71	21:1
18[g]	$AgSbF_6$	77	20:1

[a]0.10 mmol substrate at 0.1 M in $CHCl_3$ for 24 h. [b] Determined by GC-FID analysis using naphthalene as an internal standard. Values are the average of duplicate trials. [c]Determined by GC-FID analysis. [d]20 mol% 2,6-di-*tert*-butyl-4-methylpyridine was added. nd = not determined. [e]The reaction was conducted in $CHCl_3$ stabilized with EtOH. [f]5 equivalents of water were deliberately added. [g]The reaction was conducted under ambient conditions.

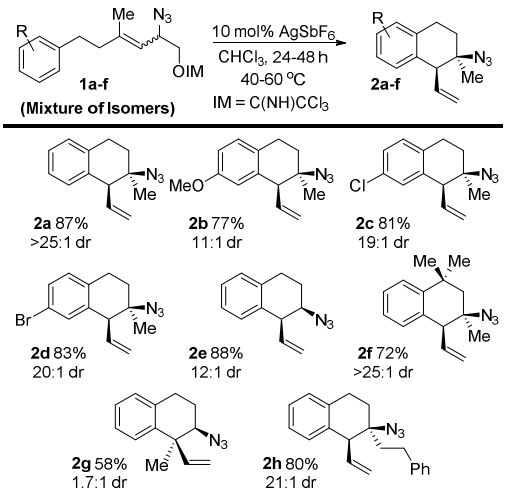
Figure 3. Putative Cyclic Stereochemical Model



We explored aniline derived allylic azides that lead to azido-tetrahydroquinolines (Scheme 3). Several azides were prepared with varying arene substitution and *N*-protecting group. All imidate precursors in this class contained less than 10% of the reactive *trans* isomer at equilibrium. Gratifyingly, these azides readily afforded tetrahydroquinolines in good yield with high dr. A number of aryl-substituents were tolerated (entries **6a**-**6f**).

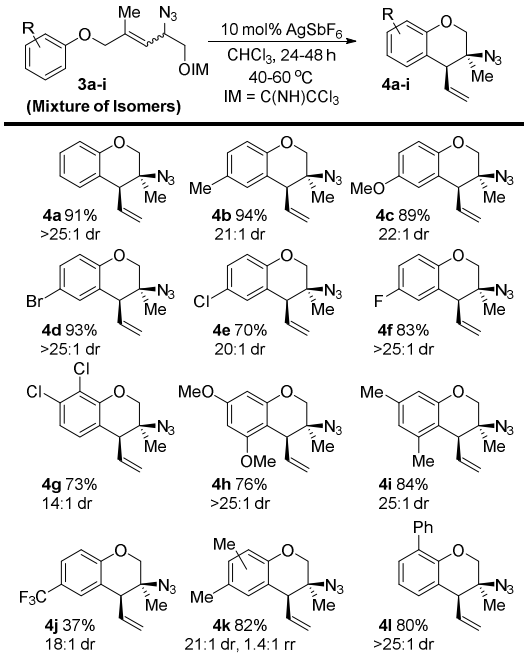
We conducted the reaction on a gram scale (Scheme 4). Using >1 g of imidate **1a** provided tetralin **2a** in 82% yield. The product could be oxidized under the Upjohn protocol[53] to afford diol **7**. Reduction using palladium on carbon provided amine **8**. Selective reduction of the azide with $LiAlH_4$ afforded amine **9**. The protocol of Evans[54] was used to form pyrrolidine **10**. Cycloaddition provided triazole **11**.

Scheme 1. Formation of Tetralins 2a-g by Tandem Process



Yields reported for isolated material as the average of duplicate trials. The dr was determined by ^{1}H NMR.

Scheme 2. Formation of Chromanes 3a-k by Tandem Process

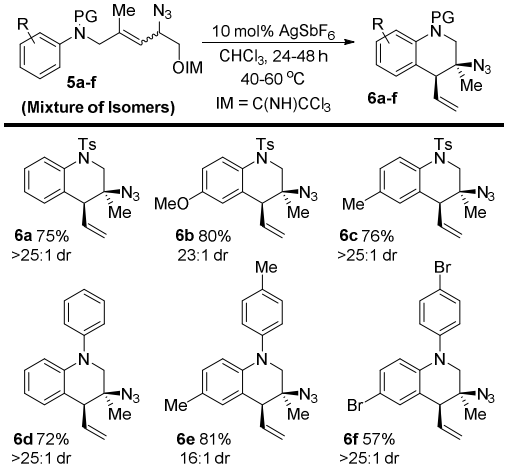


Yields reported for isolated material as the average of duplicate trials. The dr was determined by ^{1}H NMR.

We were emboldened to attempt a synthesis of hasubanan (Scheme 5). Hasubanan is the parent structure of the hasubanan alkaloids, a large family of botanical natural products. Members of this family have been studied synthetically and display diverse biological activities.[55–60] The vicinal tetrasubstituted centers in the core provide a significant synthetic challenge. To the best of our knowledge, there are no prior reported syntheses of the parent molecule hasubanan. We began with ester **12**, which is directly available from commercial material.[61–63] Reduction and partial re-oxidation afforded aldehyde **13**, which was elaborated by Corey-Chaykovsky epoxidation. Epoxide **14** was opened regioselectively with NaN_3 in acetone/water yielding allylic azide **15**. Imidate **16** was isolated after activation with trichloroacetonitrile. The key cyclization proceeded as expected to establish the necessary stereochemical relationship and the quaternary carbon center. The minor diastereomer was not observed. The final functional group manipulation was accomplished through reduction and ring closure with dicyclohexyl borane.[54] This last step clearly illustrates the advantage of using an allylic azide in this synthesis because the final amine functionality was established with concurrent C-N bond formation.

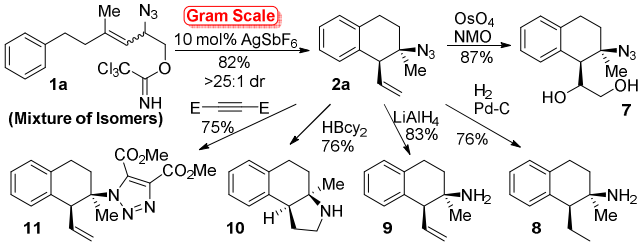
In conclusion, we report a tandem allylic azide rearrangement-Friedel Crafts alkylation. This dynamic cyclization process resolves a mixture of equilibrating allylic azide isomers by exploiting the enhanced reactivity of the allylic electrophile. We demonstrated that this process is general and leads to valuable 3-azido-tetralin, –chromane, and –tetrahydroquinoline heterocycles. Furthermore, the products of this reaction are readily diversifiable.

Scheme 3. Formation of Tetrahydroquinolines 5a-f

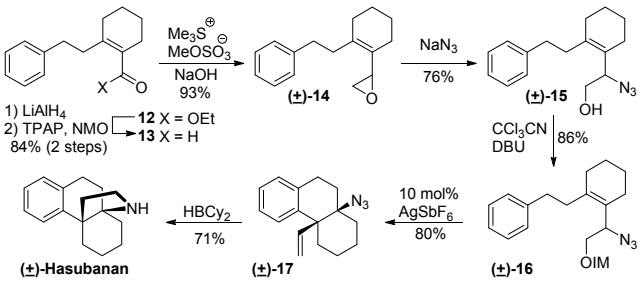


Yields reported for isolated material as the average of duplicate trials. The dr was determined by ^{1}H NMR.

Scheme 4. Gram Scale Reaction and Diversification of Product



Scheme 5. Synthesis of Hasubanan by Tandem Process



ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and characterization data (PDF)
Crystallographic data for compound **2d** (CIF)

AUTHOR INFORMATION

Corresponding Author

*jtopczew@umn.edu

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

We thank Ryan Daley for assistance in the analysis of compound **2d**. Madeline Newcomb for creating the cover art associated with this manuscript. Financial support was provided by the University of Minnesota and The American Chemical Society's Petroleum Research Fund (PRF # 56505-DNI1). This research was supported by the National Institute of General Medical Sciences of the National Institutes of Health under Award Number R35GM124718. We also acknowledge NIH Shared Instrumentation Grant #S10OD011952.

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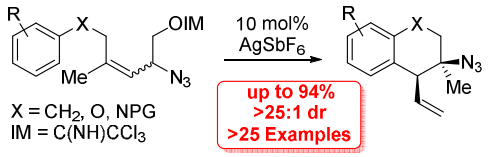
R
X
OIM
Me
N3
10 mol%
AgSbF6
R
X
N3
Me
X = CH2, O, NPG
IM = C(NH)CCl3
up to 94%
>25:1 dr
>25 Examples