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Direct Stereospecific Synthesis of Unprotected N-H and N-Me Aziridines from Olefins

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Science **343**, 61 (2014);
DOI: 10.1126/science.1245727

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to achieve a 4-mm RMS error under identical imaging conditions.

Reflectivity measurements with a test pattern showed that our method provided at least 4 bits of information; that is, 16 linear gray-scale levels could be distinguished (figs. S6 to S9). We also tested the repeatability of our method by collecting 500 independent first-photon data trials for the mannequin. We found our first-photon imager to consistently demonstrate qualitative and quantitative improvement over pointwise processing (movie S2). Its performance was also reproducible with other real-world scenes composed of multiple distinct objects at different ranges (figs. S10 to S12).

For completeness, we compared our imager with image-denoising techniques. One such method median filters the pointwise estimates (Fig. 2, A to C). Its reduction of noise resulting from anomalous detections comes at the expense of image oversmoothing, which leads to loss of perceptual information contained in edges, reflectivity, and structural variations. State-of-the-art denoising algorithms, like BM3D (*21*), exploit spatial correlations to mitigate high levels of noise, but they fail to match the performance of our imager because first-photon detection statistics differ from the conventional noise models that such algorithms presume (figs. S13 and S14).

Our computational first-photon imaging technique achieves its high-quality performance by using spatial correlations to suppress Poisson noise in reflectivity images and censor range anomalies from arrival-time data. It extracts more information from the collection of single detections than state-of-the-art active imagers would. Thus, it allows laser power to be reduced without sacrificing image quality, something that can be crucial for biological applications, such as fluorescence-lifetime imaging (*22*, *23*). It also enables remote sensing at longer standoff distances with power-limited transmitters and could be combined with techniques for detecting multiple depths per pixel (*24*). The system we have demonstrated can be improved with better background-light suppression (*25*), range gating (*26*), and advances in single-photon detector technology (*27*, *28*).

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Acknowledgments: This work was supported by the Defense Advanced Research Projects Agency InPho program through U.S. Army Research Office award W911NF-10-1-0404, the U.S. NSF under grant number 1161413, a Qualcomm Innovation Fellowship, a Samsung Scholarship, and a Microsoft Ph.D. Fellowship. The authors thank H. S. Yang for assistance with figure preparation and the Research Laboratory of Electronics for hosting external database S1 (www.rle.mit.edu/first-photon-imaging), which contains the experiment's data and computer codes for Figs. 2 to 4, movie S2, and the parts of movie S1 that contain the mannequin data set.

Supplementary Materials

www.sciencemag.org/content/343/6166/58/suppl/DC1
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3 October 2013; accepted 20 November 2013
Published online 28 November 2013;
10.1126/science.1246775

Direct Stereospecific Synthesis of Unprotected N-H and N-Me Aziridines from Olefins

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Despite the prevalence of the N-H aziridine motif in bioactive natural products and the clear advantages of this unprotected parent structure over N-protected derivatives as a synthetic building block, no practical methods have emerged for direct synthesis of this compound class from unfunctionalized olefins. Here, we present a mild, versatile method for the direct stereospecific conversion of structurally diverse mono-, di-, tri-, and tetrasubstituted olefins to N-H aziridines using *O*-(2,4-dinitrophenyl)hydroxylamine (DPH) via homogeneous rhodium catalysis with no external oxidants. This method is operationally simple (i.e., one-pot), scalable, and fast at ambient temperature, furnishing N-H aziridines in good-to-excellent yields. Likewise, N-alkyl aziridines are prepared from N-alkylated DPH derivatives. Quantum-mechanical calculations suggest a plausible Rh-nitrene pathway.

Aziridines, the triangular, comparably highly strained nitrogen analogs of epoxides, are important synthetic intermediates (i.e., building blocks) en route to structurally complex molecules because of their versatility in myriad regio- and stereoselective transformations (ring openings and expansions, as well as rearrangements) (*1*–*6*). The aziridine structural motif, predominantly N-H and to a lesser extent N-alkyl, also appears in biologically active natural products (e.g., azinomycins and mitomycins) (*7*–*9*). As a result, the synthesis and chemistry of aziridines have been the subject of intense research during the past 25 years, resulting in multiple aziridination methods (*10*–*23*). Most of these methods rely either on the transfer of substituted nitrenes, which are generated by using strong external oxidants, to the C=C bond of olefins or the transfer of substituted carbenes to the C=N bond of imines. Normally, the result is an aziridine bearing a strongly electron-withdrawing N-protecting group (e.g., Ts: *para*-toluenesulfonyl; Ns: *para*-nitrophenylsulfonyl); removal of these *N*-sulfonyl protecting groups is problematic as it often results in the undesired

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opening of the aziridine ring. In addition, the high reactivity of N-protected nitrenes might give rise to nonproductive allylic C-H amination products, as well as the loss of stereospecificity. Clearly, the direct synthesis of N-H (i.e., N-unprotected) and N-alkyl aziridines would alleviate the above problems. However, a practical, functional group-tolerant and environmentally benign direct preparation of N-H aziridines from structurally diverse olefins has so far eluded synthetic chemists (*24*–*31*). Here, we report an operationally simple, inherently safe, chemoselective and stereospecific conversion of a wide range of olefins to the corresponding N-H or N-Me aziridines via a rhodium-catalyzed pathway free of external oxidants.

Recently, we developed a metal-free protocol for primary amination of arylboronic acids using only *O*-(2,4-dinitrophenyl)hydroxylamine (DPH, **1a,** Fig. 1) as the stoichiometric aminating agent (*32*). The transformation proceeds under neutral or basic conditions and can be conducted on a multigram scale to provide structurally diverse primary arylamines. The versatility and robustness of **1a** prompted us to explore other uses of this aminating agent, specifically for the direct functionalization of readily available and inexpensive olefins. Our investigations began by subjecting 1:1.5 mixtures of *cis*-methyl oleate (**7**)/**1a,** as well as styrenes (**3a** and **3b**)/**1a,** to a vigorous screening with various transition metal complexes (tables S1 and S2). This initial screen identified $Rh_2(OAc)_4$ as a promising catalyst for *vic*-amino-oxyarylation of olefins. Further evaluation of dimeric rhodium dicarboxylate complexes (table S3) revealed that just 1 mol % loading of Du Bois' catalyst (*33*–*36*) (**2**, Fig. 1) in acetonitrile (MeCN) leads to amino-oxyarylated styrenes **4a** and **4b** at room temperature in 56% and 75% isolated yields, respectively. These promising results prompted us to conduct a thorough solvent screen.

In methanol, we observed the incorporation of the MeO group at the benzylic position (**5**) in addition to the amino-oxyarylated product **4b**; these compounds were isolated in a combined yield of 78%. At this juncture, we reasoned that a highly polar, hydroxylic, and nonnucleophilic solvent such as 2,2,2-trifluoroethanol (CF_3CH_2OH, TFE) would completely avoid the incorporation of solvent into the products. Indeed, **3b** was cleanly amino-oxyarylated in TFE, and **4b** was isolated in 66% yield. It was unclear whether the transformation **3b**→**4b** involved the opening of a highly reactive aziridine (**6**) or an alternative process. Surprisingly, when **7** was reacted in trifluoroethanol as solvent, *cis*-N-H aziridine **8** was isolated in excellent yield (83%) instead of the expected amino-oxyarylated product. The transformation proceeded with complete stereospecificity as no traces of the *trans*-N-H aziridine were detected by ^{1}H- and ^{13}C–nuclear magnetic resonance (^{13}C-NMR) analysis (≤2% sensitivity).

Encouraged by this unexpected result, we initiated a systematic study using representative aliphatic olefins with a wide range of substitution patterns and functionalities (Fig. 2). Terminal aliphatic olefin substrates (entries 1 to 3, Fig. 2) either did not react or reacted sluggishly (i.e., days) when 1 mol % of catalyst **2** was used; however, increasing the catalyst loading to 5 mol % led to rapid conversion at room temperature to the corresponding N-H aziridines (**10a** to **10c**). We empirically found that in some of the reactions (i.e., entries 4, 5, 7, 9, 11, 14, and 20), addition of the catalyst in several 1 mol % portions minimized decomposition of both the catalyst and aminating agent and invariably led to higher isolated yield of product. Notably, the N-H aziridination took place efficiently in the presence of a labile terminal epoxide (**10c**), as well as an unprotected primary alcohol (**10a**); these functionalities typically interfere with currently used aziridination protocols. In case of the transformation **9c**→**10c**, only the product was detected in the crude reaction mixture by NMR analysis. In the presence of 1 mol % of catalyst **2**, both *cis*- and *trans*-1,2-disubstituted aliphatic olefins (entries 4 to 10, Fig. 2) underwent smooth and stereospecific N-H aziridination at room temperature as established by ^{13}C-NMR analysis (≤2% sensitivity). The presence of an unprotected secondary alcohol in substrate **9i** (entry 9) did not influence the stereochemical outcome of the N-H aziridination and **10i** was isolated as a 1:1 mixture of diastereomers.

Benzoyloxy and acetyloxy *cis*-olefins **9k** and **9m** (entries 11 and 14), when exposed to 1 mol % of catalyst **2** and 1.2 equivalents of aminating agent **1a** at 50°C, were smoothly aziridinated followed by an in situ aziridine ring-opening (via transacylation) to yield the corresponding *trans*-2,3- disubstituted furans **10kk** and **10mm** in 84% and 61% yields, respectively. By contrast, when olefin **9k** was exposed to 5 mol % loading of catalyst **2** and 1.2 equivalents of **1a** at 25°C, the expected N-H aziridine **10k** (entry 12) was formed in just 2 hours and isolated in 69% yield. As anticipated, when the rate of N-H aziridination is slow and elevated temperatures are used, secondary processes (i.e., intramolecular annulation) that consume the initially formed N-H aziridines can dominate. Apparently, a fivefold increase in catalyst loading increased the rate of N-H aziridination sufficiently that it could take place rapidly at ambient temperature.

Cyclohexene **9n** (entry 15) was aziridinated at room temperature to afford cyclic N-H aziridine **10n**; no traces of allylic C-H amination (i.e., 1-amino-2-cyclohexene) could be detected by ^{1}H-NMR analysis (≤2% sensitivity), in sharp contrast with other metal nitrene-based aziridination methods (*37*). Geraniol (**9o**, entry 16) and geranyl acetate (**9q**, entry 18), which incorporate two trisubstituted C=C double bonds, were N-H aziridinated regioselectively, favoring the double bond at the $\Delta^{6,7}$-position over the $\Delta^{2,3}$-position in both cases.

The shift of the regioisomeric ratio from 1:5 in **10o** to 1:14 in **10q** suggests a subtle directing effect of the free allylic alcohol and/or an inductive deactivation by the acetate; perhaps the extent of H-bonding in the solvent also plays a role. Entry 17 stands as a testament to the extraordinarily mild reaction conditions as trisubstituted olefin **9p**, which possesses a highly sensitive epoxy

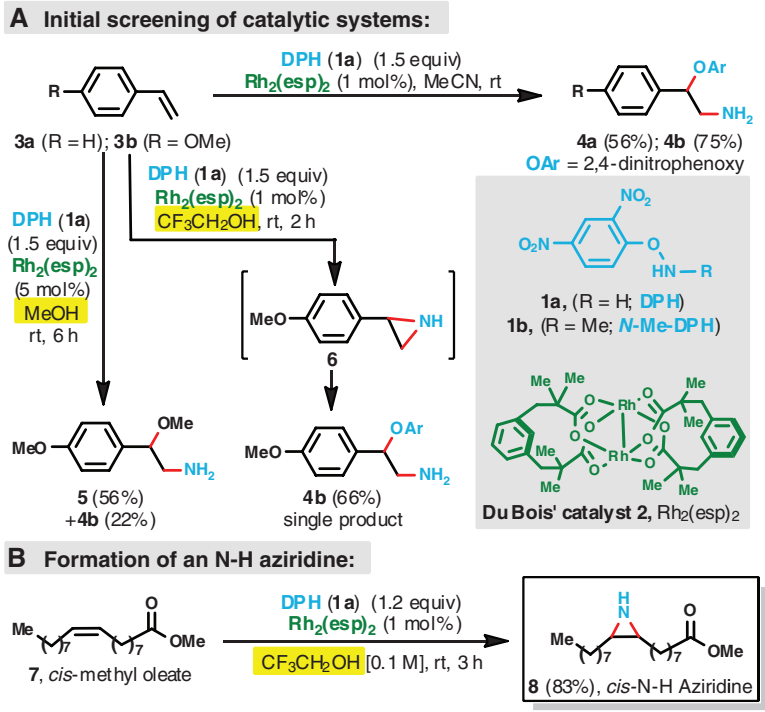

Fig. 1. Exploration of DPH (1a) as a versatile aminating agent. (**A**) $Rh_2(esp)_2$ is an effective catalyst for olefin difunctionalization. (**B**) In 2,2,2-trifluoroethanol (TFE or CF_3CH_2OH), **7** undergoes direct aziridination to N-H aziridine **8** in excellent isolated yield.

alcohol, was aziridinated rapidly and efficiently to epoxy N-H aziridine **10p** in excellent yield. The transformation **9q**→**10q** (entry 18) could be readily scaled up (6 mmol) with minimal erosion of the isolated yield to provide gram quantities of **10q**. N-H aziridination of limonene **9r** (entry 19) favored the trisubstituted ring double bond with 9:1 regioselectivity; however, the chiral center had no evident influence on the diastereoselectivity (1:1 drdr, diastereomeric ratio). In contrast with the lack of stereoselectivity in **9i**, cholesterol **9s** (entry 20) exclusively yielded the β-N-H aziridine **10s** in 71% yield; this unexpected stereochemical outcome, confirmed by single-crystal x-ray analysis of **10ss** (a crystalline derivative of **10s**), suggests a directing effect by the adjacent C(3)-β-alcohol not observed in conformationally more mobile acyclic molecules such as **9i**. The success with cholesterol and other natural products (**7**, **9h**, **9i**, **9o** and **9r**; Figs. 1 and 2) highlights the prospective utility of this method in the straightforward elaboration of molecules of biomedical interest (e.g., for ^{15}N-labeling studies).

Next, we turned our attention to the direct N-H aziridination of di-, tri- and tetrasubstituted styrenes and stilbene (entries 21 to 28, Fig. 3A). In general, styrenes were more reactive than aliphatic olefins, and often lower temperatures (–10° to 25°C) were adequate. Conspicuously, *cis*-β-methyl styrene **11d** furnished the corresponding *cis*-2-Ph-3-Me *N*-H aziridine (**12d**, entry 24) without isomerization. Similarly, *trans*-β-methyl styrene **11c** readily furnished *trans*-2-Ph-3-Me N-H aziridine (**12c**, entry 23) even on a 1- to 8-mmol scale. The N-H aziridine derived from 2-Me indene (**12h**, entry 28) was not isolated owing to its high reactivity, but instead reduced in situ to amine **12hh**. Evaluation of the effect of catalyst loading on the reaction **11f**→**12f** (entry 26) revealed that the

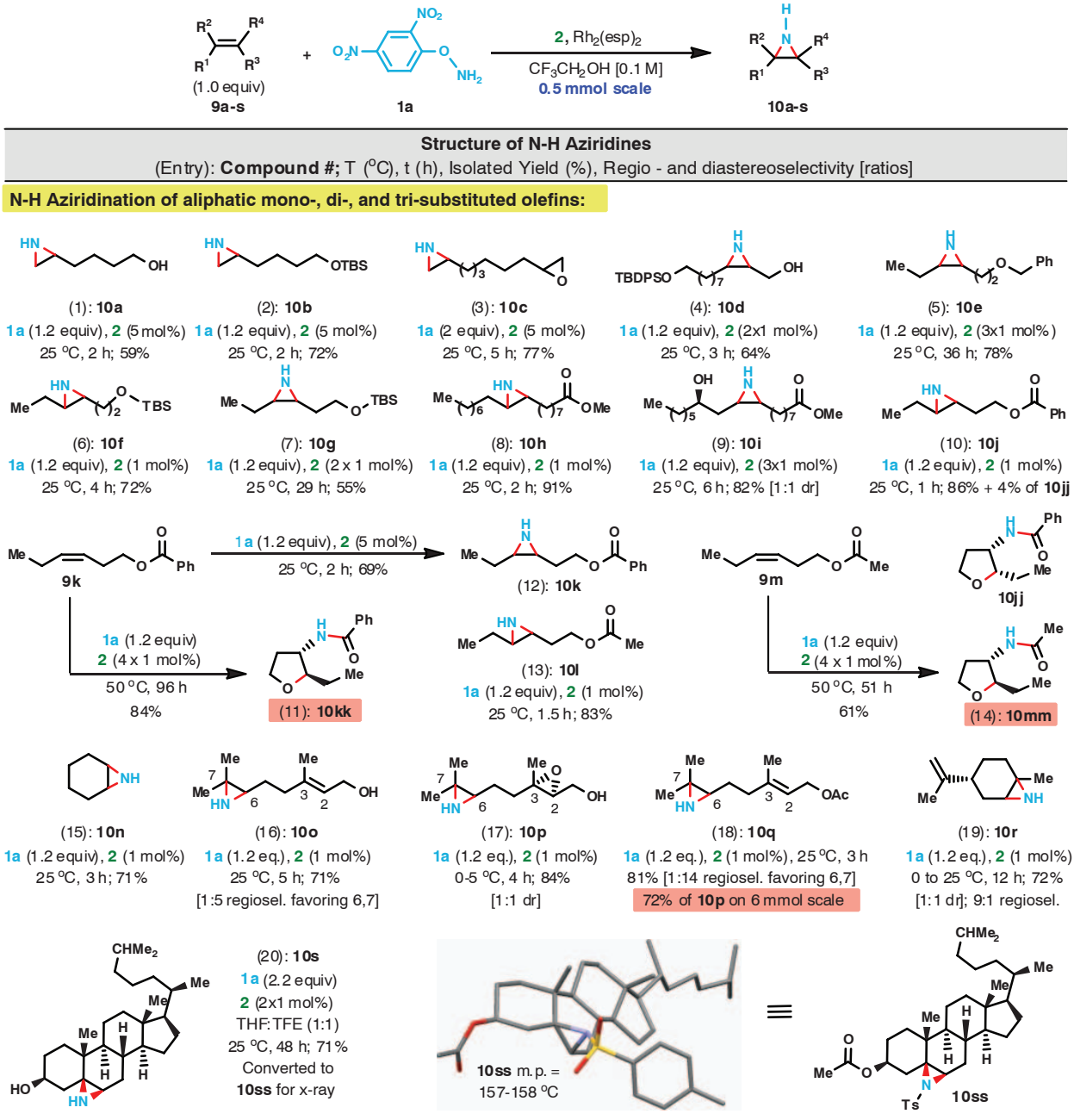

Fig. 2. Direct and stereospecific N-H aziridination of olefins. Reactions were conducted at 0.1 M using 2,2,2-trifluoroethanol as solvent and at 0.5-mmol scale unless otherwise indicated. To obtain crystalline material, **10s** was *O*-acetylated and *N*-tosylated (Ts, *para*-toluenesulfonyl) to afford derivative **10ss**. (TBS, *tert*-butyl-dimethylsilyl; TBDPS, *tert*-butyl-diphenylsilyl)

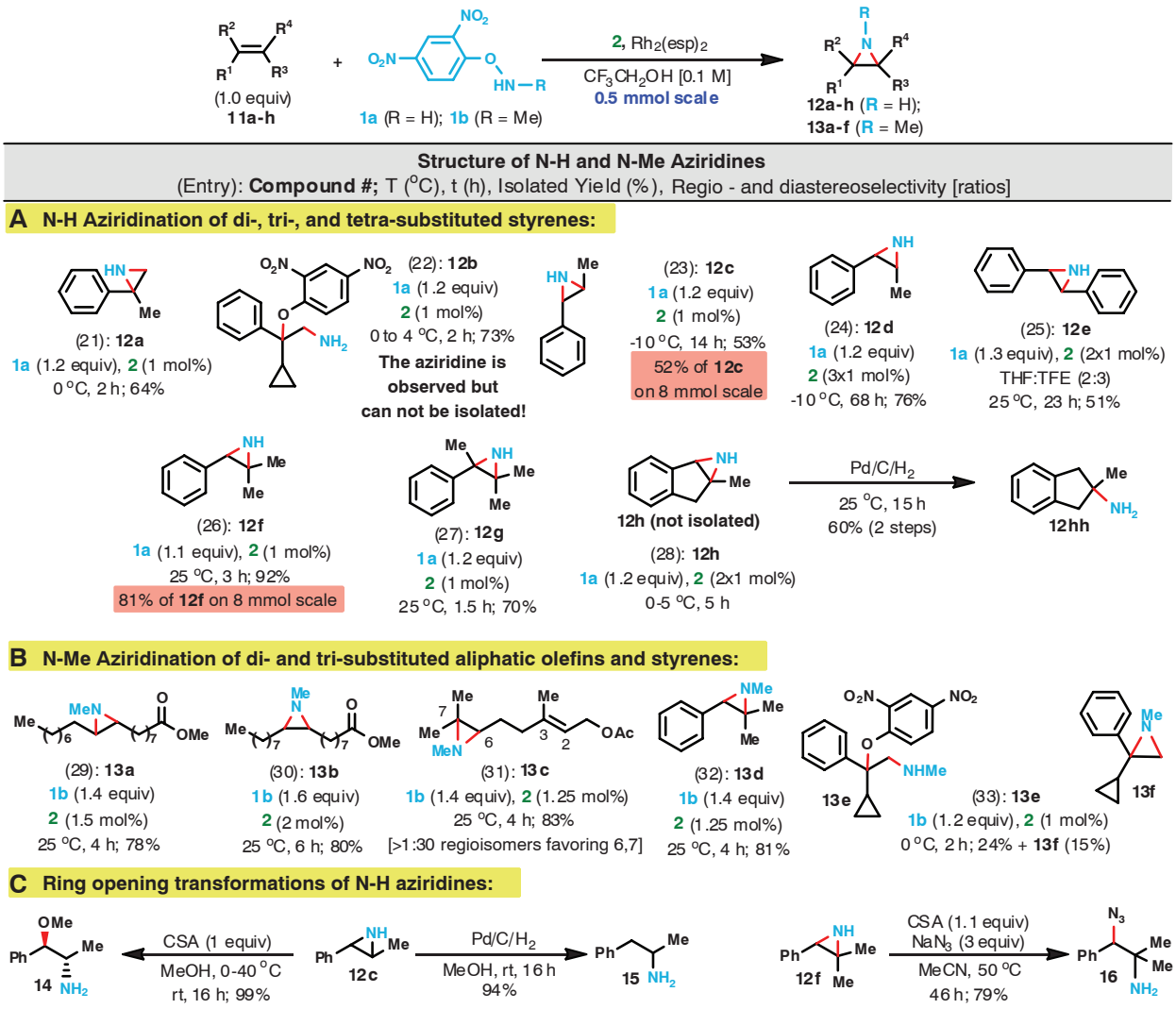

Fig. 3. Direct and stereospecific N-H and N-Me aziridination of olefins. Reactions were conducted at 0.1 M using 2,2,2-trifluoroethanol as solvent and at 0.5-mmol scale unless otherwise indicated. CSA, camphorsulfonic acid.

lowest practical loading of catalyst **2**, without decreasing the isolated yield or drastically increasing the reaction time, was 0.5 mol %. This low catalyst loading renders the process economical and environmentally friendly. A further fivefold reduction in catalyst loading (from 0.5 to 0.1 mol %) resulted in a 25-fold increase in reaction time and a 30% drop in the isolated yield of **12f**. Tetrasubstituted olefin **11g** (entry 27) was easily N-H aziridinated at room temperature; **12g** was isolated in 70% yield. The attempted direct N-H aziridination of 1-Ph-1-cyclopropylethene (**11b**) yielded only amino-oxyarylated product **12b**; the complete lack of cyclopropane ring-opening products corroborate an aziridination pathway that does not involve long-lived radical or carbocation intermediates (see more detailed discussion of the mechanism in the computation section and in Fig. 4).

The practicality and broad scope of the preceding direct and stereospecific N-H aziridination of olefins (Fig. 2 and Fig. 3A) prompted an investigation of direct N-Me aziridination. Toward this end, several di- and trisubstituted aliphatic olefin and styrene substrates (entries 29 to 33, Fig. 3B) were examined in the presence of **1b** as the stoichiometric aminating agent and 1 to 2 mol % of catalyst **2**. The N-Me aziridination of olefins also proceeded stereospecifically (entries 29 and 30) and, in the case of geraniol acetate **9q**, the regioselectivity increased from 1:14 (in **10q**) to >1:30 (in **13c**), favoring the $\Delta^{6,7}$-olefin in both cases.

Two of the N-H aziridine products (**12c** and **12f**) were subjected to ring-opening transformations (Fig. 3C). Upon catalytic hydrogenation, aziridine **12c** afforded a 94% yield of amphetamine **15**, the active pharmaceutical ingredient in Adderall, an approved medication for attention deficit hyperactivity disorder, as well as narcolepsy, that is marketed as a mixture of enantiomers. Under acidic conditions, at slightly elevated temperature (40°C) in MeOH, **12c** was converted to *O*-Me-norephedrine **14** with complete regioselectivity and in nearly quantitative yield. Likewise, the ring-opening of trisubstituted *N*-H aziridine **12f** with sodium azide furnished azidoamine **16** in 79% yield. These transformations by example illustrate how readily a nitrogen atom can be introduced into molecules.

We also examined prospective reaction mechanisms using quantum mechanical density-functional theory calculations (Fig. 4). Our (U)M06 calculations were carried out in Gaussian 09 (*38*) using a polarizable conductor continuum solvent model for trifluoroethanol. Details of calculated transition states and intermediates are given in the supplementary materials.

We first examined plausible rhodium nitrene pathways. Generation of a rhodium nitrene intermediate is possible if the amino group of **1a** coordinates to $Rh_2(esp)_2$ followed by loss of dinitrophenol (pathway A, Fig. 4). Calculations suggest that the triplet-spin state of the nitrene (^{3}**17**) is more than 8 kcal/mol lower in energy than the open-shell singlet, and reaction pathways identified on the triplet-spin energy surface were

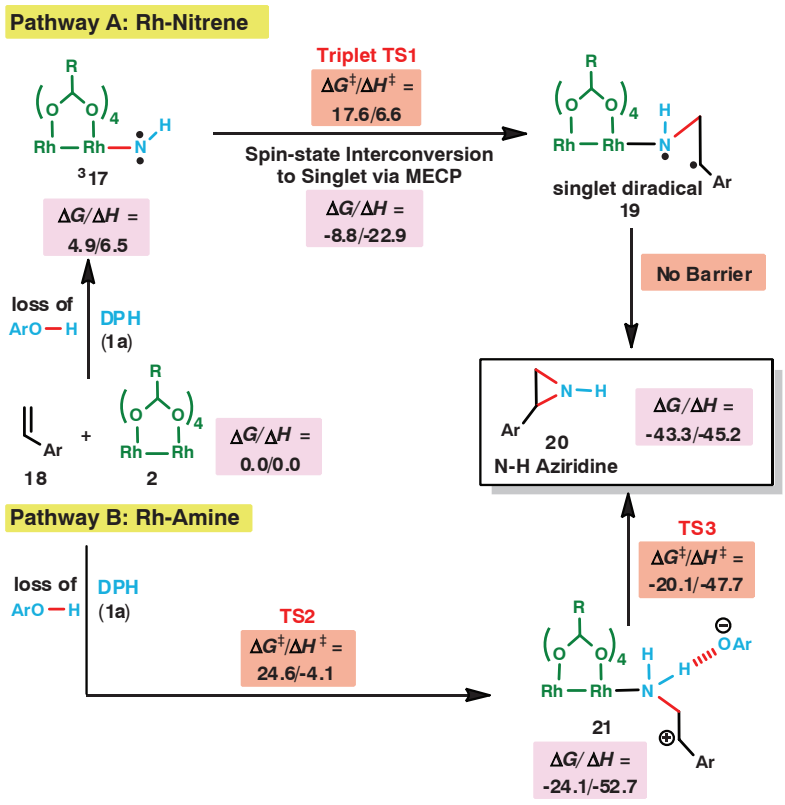

Fig. 4. Selected DFT-examined pathways for N-H aziridination of styrene in 2,2,2-trifluoroethanol solvent. R, esp ligands. Energies in kcal/mol. MECP, minimum energy crossing point.

found to be lower in energy than reaction pathways on the singlet-spin energy surface (*39*, *40*). Because the $Rh_2(esp)_2$ catalyst and aziridine product have singlet-spin ground states, the reaction pathway must involve spin interconversion. The mechanism outlined in Fig. 4 provides a route for stereospecific aziridination if ^{3}**17** reacts with alkenes by forming the first C–N bond via triplet transition state **TS1** followed by spin interconversion along the pathway to diradical intermediate **19** or fast spin interconversion at the diradical intermediate (*41*). After spin interconversion, the second C–N bond is formed by the coupling of singlet-paired electrons without a barrier and leads directly to aziridine **20**.

As alternatives to nitrene pathways, we also explored polar mechanisms involving Rh-amine and Rh-alkene coordination modes (see supplementary materials). One of several possible polar mechanisms is outlined as pathway B in Fig. 4. This pathway is akin to the mechanism proposed for amination of aryl boronic acids with **1a** (*32*). Although this mechanism may account for aminooxyarylated products (e.g., **4a** and **4b**) observed under some experimental conditions, the calculated barrier for this mechanism, as well as alternative polar mechanisms, is higher in energy than the nitrene mechanism presented in pathway A.

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Acknowledgments: J.R.F. thanks NIH (GM31278, DK38226) and the Robert A. Welch Foundation (grant GL625910) for funding. L.K. gratefully acknowledges the generous financial support of the UT Southwestern Endowed Scholars in Biomedical Research Program (W.W. Caruth Jr. Endowed Scholarship in Biomedical Research), the Robert A. Welch Foundation (grant I-1764), the American Chemical Society–Petroleum Research Fund (grant 51707-DNI1), and the American Cancer Society and Simmons Cancer Center Institutional Research Grant (New Investigator Award in Cancer Research, ACS-IRG 02-196). D.H.E. thanks Brigham Young University and the Fulton Supercomputing Lab. M.Y. acknowledges a grant from UT Arlington to support the upgrade of the x-ray facility. We also thank K. Schug, M. Kukula, and the Shimadzu Center for Advanced Analytical Chemistry (SCAAC, UT Arlington) for assistance in the full characterization of new compounds. The generous donation of 100 g of aminating agent **1a** and 5 g of aminating agent **1b** by Corvinus Chemicals, LLC (Dallas, TX), as well as 20 kg of 2,2,2-trifluoroethanol (TFE) by Joyant Pharmaceuticals, Inc. (Dallas, TX), is also gratefully acknowledged. We thank P. S. Baran, J. Du Bois, E. M. Carreira, A. J. Catino, M. P. Doyle, M. Krische, and R. Sarpong for helpful commentary. Metrical parameters for the structure of compound **10ss** are available free of charge from the Cambridge Crystallographic Data Centre under reference no. CCDC-959664.

Supplementary Materials

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Materials and Methods
Figs. S1 to S5
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9 September 2013; accepted 19 November 2013
10.1126/science.1245727