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Cyclocondensation of Amino-propargyl Silanes

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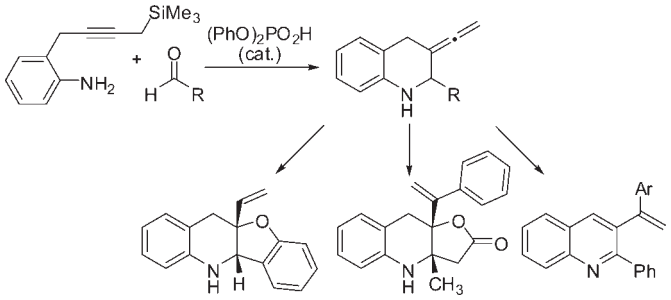
ABSTRACT



Amino-propargyl silanes condense with carbonyl compounds to form imines and subsequently cyclize to form allenylidene tetrahydroquinolines. The cyclocondensations are catalyzed by a variety of Brønsted acids, among which phosphoric acids provide the highest yields. Subsequent intramolecular and intermolecular additions to the allene moiety provide complex polycyclic amines.

The rapid generation of complex molecules from simple precursors remains an important challenge in organic synthesis.[1] Strategies to create molecular diversity are valuable in medicinal chemistry and the synthesis of small molecule libraries. Among many approaches to this problem, we considered reaction sequences that would fulfill two criteria (Scheme 1A). An initial transformation should join two or more fragments to form new rings and/or stereocenters. Second, the initial step should convert one reactive functional group to an alternative functional group that *also displays high reactivity, but under conditions orthogonal to those of the initial reactions*. Thus, in a second step, the new functional group could be used to promote cyclization, fragment coupling, or conversion to stable functionality.

Several known reaction sequences fit these criteria. For instance, Denmark's tandem [4 + 2]/[3 + 2] sequence involves an initial cycloaddition between a nitro olefin and an electron-rich olefin. The cycloadduct, a cyclic nitronate, participates in a second cycloaddition, but with electron-deficient olefins.[2] As another example, cyclopropanation of enol ethers converts one high-energy material, a diazo-carbonyl compound, to a different reactive substance, a donor−acceptor cyclopropane. In this example, the first operation joins two fragments even as it prepares the substrate for subsequent cycloaddition reactions.[3] As a final example, Schreiber and co-workers reported a diversity-generating protocol in which an initial Petasis three-component coupling facilitated formation of functionalized enynes, which were then subject to a variety of cyclization conditions.[4]

In this context, we considered the reactivity of propargyl silanes.[5] Specifically, we wondered if amino-propargyl

(1) Tan, D. S. In *Chemical Biology*; Schreiber, S. L., Kapoor, T. M., Wess, G., Eds.; Wiley-VCH Verlag GmbH: 2008; p 483. (b) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46.

(2) Denmark, S. E.; Moon, Y. C.; Senanayake, C. B. W. *J. Am. Chem. Soc.* **1990**, *112*, 311.

(3) Qi, X.; Ready, J. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 7068.

(4) Kumagai, N.; Muncipinto, G.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 3635.

(5) Reviews:Blumenkopf, T. A.; Overman, L. E. *Chem. Rev.* **1986**, *86*, 857. Schinzer, D. *Synthesis* **1988**, 263. Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293.

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(7) Representative aza-Prins reactions: (a) Kim, C.; Bae, H. J.; Lee, J. H.; Jeong, W.; Kim, H.; Sampath, V.; Rhee, Y. H. *J. Am. Chem. Soc.* **2009**, *131*, 14660. (b) Carballo, R. M.; Valdomir, G.; Purino, M.; Martin, V. S.; Padron, J. I. *Eur. J. Org. Chem.* **2010**, 2304. (c) Reddy, B. V. S.; Borkar, P.; Yadav, J. S.; Sridhar, B.; Gree, R. *J. Org. Chem.* **2011**, *76*, 7677.

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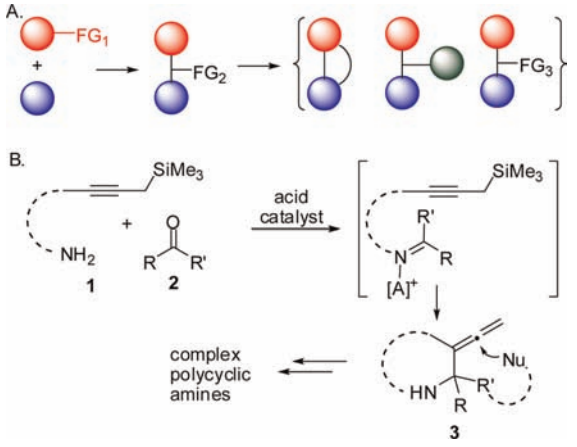
silanes (**1**) would condense with carbonyl compounds and, under acidic conditions, cyclize to generate allenes (**3**, Scheme 1B).[6,7] Allenes are subject to a wide range of transformations, and we postulated that they could react with a variety of nucleophiles to yield complex polycyclic amines. Herein, we report the successful development of a cyclocondensation to form allenylidene tetrahydroquinolines and preliminary exploration of derivatization strategies. Since quinolines and their derivatives appear in a wide range of natural products and pharmaceutical agents,[8] this approach may facilitate the discovery of novel biologically active small molecules.

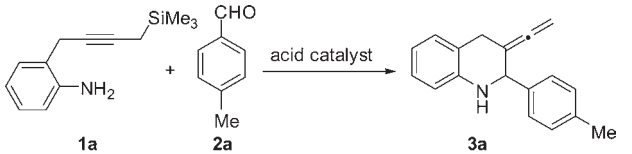
Scheme 1. Reaction Sequences To Rapidly Generate Molecular Diversity



Initial experiments probed the reactivity of propargyl silane **1a** with aldehyde **2a** (Table 1). Several Brønsted acids catalyze the cyclocondensation in good yield. Acetic acid was insufficient to promote cyclization, and imine formation was observed. However, stronger carboxylic acids (entry 2) and sulfonic acids (entries 3−5) formed the cyclized product **3a** in good yield. Diphenyl phosphate emerged as the most efficient catalyst, and catalyst loadings as low as 1 mol % generated **1a** in quantitative yields. Faster reaction times were observed with 2 mol % catalyst, and these conditions were adopted in subsequent experiments. The cyclization required polar solvents, with both acetonitrile (entry 6) and methanol (entry 8) supporting product formation. In contrast, only imine was observed in less polar solvents (entries 9−12). Several Lewis acids promoted cyclization as well.[9] However, since these reactions were inhibited by 2,6-di-*tert*-butylpyridine, we concluded that Brønsted acids arising from hydrolysis of the metal salts were responsible for catalysis.

Under optimized conditions, propargyl silane **1a** was condensed with a variety of aldehydes and ketones (Scheme 2). Complete conversion, high yields, and low catalyst loadings characterized the reactions with substituted benzaldehydes. Thus, electron-rich and -poor aldehydes participated equally well. Protic functionality was tolerated, including phenols (**3f**, **3g**, **3h**) and carboxylic acids (**3m**). Steric hindrance was not problematic as demonstrated by series of 2-substituted and 2,6-disubstituted benzaldehydes. Only the hindered and electron-rich 2,4,6-trimethoxy benzaldehyde reacted in lower yield (**3l**). Thiophene and furan carboxaldehydes were excellent substrates (**3q**, **3r**, **3w**), but no product was obtained from pyrrole carboxyaldehyde (**3s**). Likewise, 3- and 4-pyridine carboxyaldehyde reacted cleanly, but the 2-pyridyl analog was inactive.[10] Both linear and branched aliphatic aldehydes were suitable substrates (**3y**, **3z**, **3aa**), although an enal was unsuccessful (**3ab**). Finally, whereas simple ketones like acetophenone provided no product, certain classes of ketones worked well. Thus, a series of isatins condensed in high yield to form a quaternary carbon.[11] Similarly, a β-keto-ester reacted with high efficiency.

Table 1. Acid-Catalyzed Cyclocondensation[a]



1a (1 equiv) **2a** (1.1 equiv) **3a**

entry	catalyst (mol %)	solvent	yield (%)[b]
1	CH_3CO_2H (15)	MeCN	0
2	CF_3CO_2H (15)	MeCN	84
3	CSA (15)	MeCN	90
4	TsOH (15)	MeCN	96
5	Amberlyst (15)	MeCN	45
6	**$(PhO)_2P(O)OH$ (2)**	**MeCN**	**100**
7[c]	$(PhO)_2P(O)OH$ (1)	MeCN	100
8	$(PhO)_2P(O)OH$ (15)	MeOH	100
9	$(PhO)_2P(O)OH$ (15)	DCM	0
10	$(PhO)_2P(O)OH$ (15)	THF	0
11	$(PhO)_2P(O)OH$ (15)	Et_2O	0
12	$(PhO)_2P(O)OH$ (15)	PhMe	0

[a] Reactions carried out on a 10 mg scale with [**1a**] = 0.045 under an air atmosphere for 16 h unless otherwise noted. [b] NMR yield based on an internal standard. [c] 24 h reaction time.

Several characteristics of the cyclocondensation deserve comment. First, the reactions are relatively insensitive to water and air and could be carried out using unpurified solvents open to the atmosphere. Second, the reaction appears to scale well, as allene **3ai** was prepared with equal efficiency on 0.1 and 1 mmol scales. Finally, we never

(8) (a) Khan, M. T. H. *Top. Heterocycl. Chem.* **2007**, *11*, 213. (b) Kaur, K.; Jain, M.; Reddy, R. P.; Jain, R. *Eur. J. Med. Chem.* **2010**, *45*, 3245. (c) Bongarzone, S.; Bolognesi, M. L. *Expert Opin. Drug Discovery* **2011**, *6*, 1. (d) Solomon, V. R.; Lee, H. *Curr. Med. Chem.* **2011**, *18*, 1488.

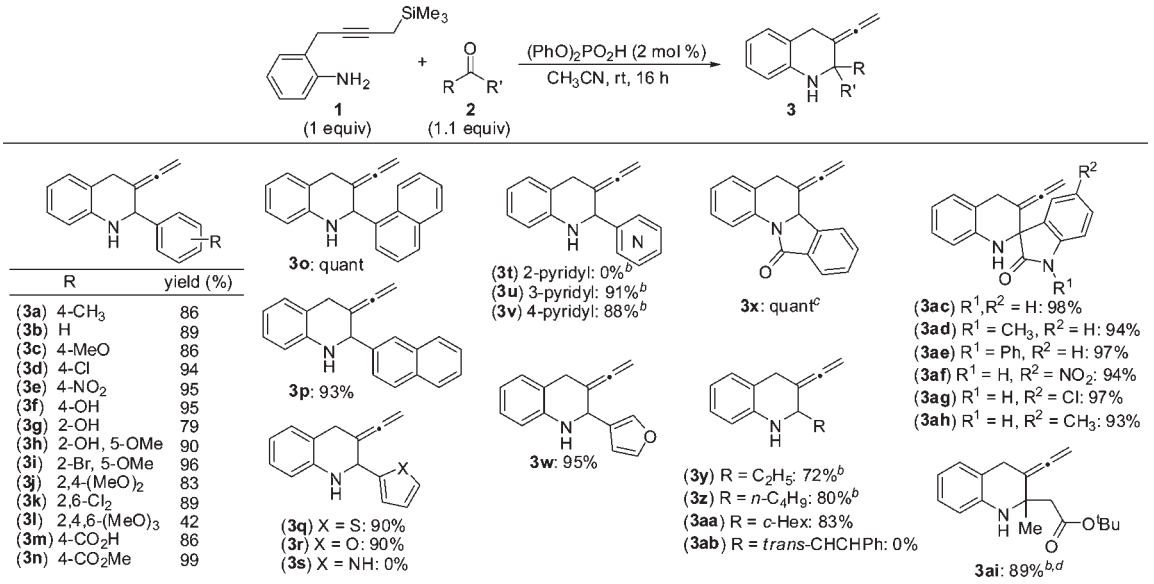
(9) For example, $Sc(OTf)_3$, $FeCl_3$, $Zn(OTf)_2$, $InCl_3$, $Cu(OTf)_2$.

(10) Hydrogen bonding of the protonated pyridine to the imine nitrogen may deactivate this substrate.

(11) (a) Castaldi, M. P.; Troast, D. M.; Porco, J. A. *Org. Lett.* **2009**, *11*, 3362. (b) Zhang, Y.; Panek, J. S. *Org. Lett.* **2009**, *11*, 3366. (c) Wang, J.; Crane, E. A.; Scheidt, K. A. *Org. Lett.* **2011**, *13*, 3086.

(12) Crouch, I. T.; Dreier, T.; Frantz, D. E. *Angew. Chem., Int. Ed.* **2011**, *50*, 6128.

Scheme 2. Catalytic Synthesis of Alleneylidene Tetrahydroquinolines[a]



[a] Reactions carried out on a 0.09 mmol scale with 2 mol % catalyst in **1** mL of CH_3CH under an air atmosphere for 16 h unless otherwise noted. Isolated yields of purified products indicated. [b]10 mol % catalyst. [c]From 2-carboxybenzaldehyde. [d]1.15 mmol scale.

observed isomerization of the allene to the conjugated diene,[12] demonstrating that these products are stable under the acidic reaction conditions.

Substituted anilines participated in the cyclocondensation with variable results (Table 2). Methyl substituted silane **1b** condensed with aromatic and aliphatic aldehydes and with isatin to generate the corresponding allenes in high yield. In contrast, amide- or ester-substituted substrates **1c** and **1d** only provided clean products with certain aldehydes. Aliphatic aldehydes reacted cleanly (entries 4−5), but most aromatic aldehydes were converted into unstable products. Thus, analysis of crude reaction mixtures indicated the formation of the expected heterocycle (**3**), but attempts to isolate pure samples proved unsuccessful because the products decomposed into complex mixtures.

With a high-yielding and general cyclocondensation in hand, we sought conditions under which the allenes might be converted to more complex polycyclic products.[13] Accordingly, we exposed allene **3g** to $Pd(PPh_3)_4$ and observed the formation of the tetracyclic benzofuran **4** in 91% yield (eq 1). Pd(0)-catalyzed cyclization of phenols onto allenes has not been reported previously, although cyclization of phenols and alcohols in the presence of electrophilic metals is known.[14,15] In this case, $Pd(OAc)_2$ and $PdCl_2$ did not catalyze the formation of **4** at all, arguing against an electrophilic activation of the allene. Rather, this transformation may involve the formation of a Pd(II)−H species via protonation of Pd(0) with phenol. Hydrometalation followed by reductive elimination would yield the observed product (Scheme 3).[16] Similarly, carboxylic acid **3ai′** underwent arylation and cyclization to form lactone **5** (eq 3). Here, aryl addition to the allene likely generated a Pd(π-allyl) species that was trapped by the carboxylate.[17] Cyclization of both the phenol and the carboxylic acid occurred with complete control of relative stereochemistry to yield the cis-fused 5,6-ring systems.

Finally, exposure of allene **3b** to $Pd(PPh_3)_4$ and a series of aryl iodides resulted in the formation of a mixture of dihydroquinolines and quinolines (**6**, eq 3). Oxidation of the crude reaction mixture yielded the arylated quinolines (**6**) in uniformly high yield. The tandem

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(15) Intermolecular addition of phenols to allene catalyzed by (a) Pd(0): Grigg, R.; Kongkathip, N.; Kongkathip, B.; Luangkamin, S.; Dondas, H. A. *Tetrahedron* **2001**, *57*, 7965. (b) Phosphine: Meng, X.; Huang, Y.; Chen, R. *Org. Lett.* **2008**, *11*, 137. (c) DBU: Kumar, N. N. B.; Reddy, M. N.; Swamy, K. C. K. *J. Org. Chem.* **2009**, *74*, 5395. (d) Uncatalyzed: Nixon, N. S.; Scheinmann, F.; Suschitzky, J. L. *Tetrahedron Lett.* **1983**, *24*, 597.

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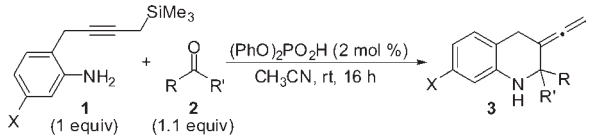
Table 2. Cyclocondensation with Substituted Amino-propargyl Silanes[a]



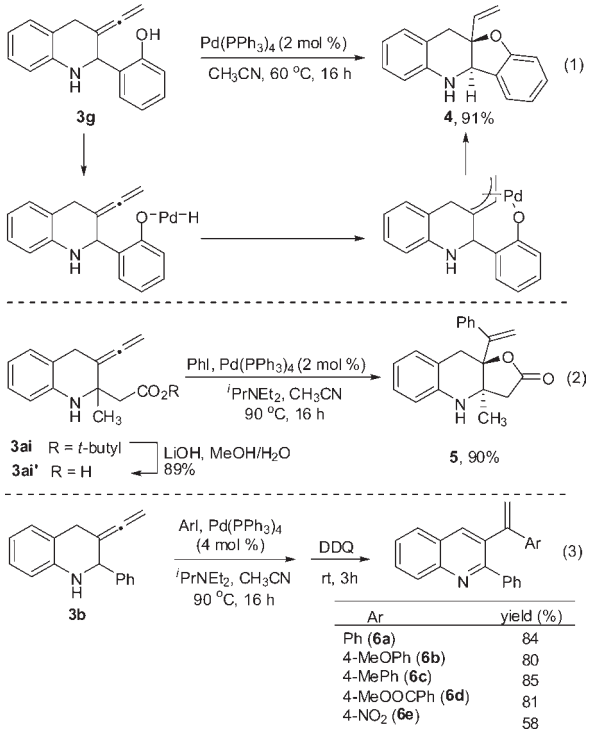
		propargyl silane **1**: X =		
entry	**2**	CH_3 (**1b**)	$C(O)NMe_2$ (**1c**)	CO_2Et (**1d**)
1	PhCHO	90%	[b]	[b]
2	4-OH-C_6H_4-CHO	92%	[b]	[b]
3	4-NO_2-C_6H_4-CHO	96%	[b]	[b]
4	2,4,6-$(MeO)_3$-C_6H_2-CHO	72%[c]	[b]	74%[c]
5	furfural	87%	[b]	[b]
6	propionaldehyde	94%	80%	71%
7	*c*-Hex-CHO	94%	89%	82%
8	isatin	94%	[b]	84%

[a] Reactions carried out on a 0.09 mmol scale in 1 mL of CH_3CN under an air atmosphere for 16 h unless otherwise noted. Isolated yields indicated. [b] Product unstable to silica gel chromatography. [c] 10 mol % catalyst used.

Heck reaction/oxidation tolerated electron-rich, -poor, and -neutral aryl iodides.

Overall, the protocols described here outline an approach to transforming relatively simple starting materials into complex polycyclic products. For instance, the example in eq 2 merges three components, creating two new rings and two adjacent quaternary stereocenters in two operations. The key strategic element involves the conversion of one reactive substructure, propargylic silanes, into an alternative reactive functional group, an allene. We anticipate that this design principle will have numerous applications in organic synthesis.

Scheme 3. Derivatization of Allenes



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Supporting Information Available. Complete characterization data and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.