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Organoyttrium-Catalyzed Sequential Cyclization/Silylation Reactions of Nitrogen-Heteroaromatic Dienes Demonstrating "Aryl-Directed" Regioselectivity

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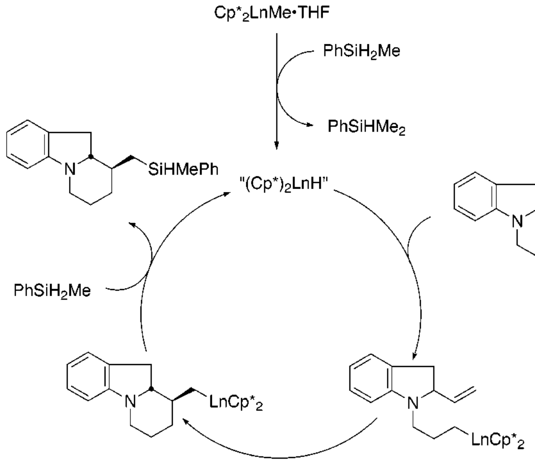
The reaction of 1-allyl-2-vinyl-1*H*-pyrroles and 1-allyl-2-vinyl-1*H*-indoles with arylsilanes in the presence of catalytic $[\mathrm{Cp^{TMS}}_2\mathrm{Y}(\mu\text{-Me})]_2$ leads to highly selective cyclization/silylation events. In this process the active catalyst for the reaction, "$\mathrm{Cp^{TMS}}_2\mathrm{YH}$", undergoes initial olefin insertion at the vinyl group. Even isopropenyl substituents on the heteroaromatics react in preference to less sterically encumbered allyl groups. Furthermore, the observed regioselectivity reflects an "aryl-directed" process, whereby the more highly substituted secondary or tertiary organometallic is initially generated. This intermediate undergoes cyclization onto the remaining alkene and subsequent silylation by a σ-bond metathesis reaction, affording the observed products.

The use of group 3 and lanthanide metallocenes as catalysts for stereoselective cyclization/silylation reactions of substituted 1,5- and 1,6-dienes to functionalized carbocycles is by now well established.[1] Previous investigations have demonstrated that, despite their recognized Lewis acidity and the propensity to complex with Lewis bases, these metallocenes can also be utilized for the synthesis of nitrogen heterocycles either via cyclization/silylation[1d,h] or hydroamination protocols.[2] Because this class of catalysts is highly sensitive to steric encumbrance about the alkene, and because steric factors predominate in the insertion process,[3] nearly all of the research in this area has focused on monosubstituted olefins. Disubstituted alkene systems cannot be accommodated by sterically crowded catalysts such as $\mathrm{Cp^*}_2\mathrm{YMe{\cdot}THF}$. This allows exquisite selectivity in complicated, polyunsaturated substrates wherein less sterically encumbered alkenes react in preference to their more sterically shielded counterparts.[1c]

Scheme 1



More open ligand arrays about the metal have been enlisted to allow incorporation of 1,1-disubstituted alkenes.[1b] In the current contribution we report the use of one of this new generation of complexes, $[\mathrm{Cp^{TMS}}_2\mathrm{Y}(\mu\text{-Me})]_2$,[1c,4] in cyclization/silylation reactions of heteroaromatic dienes. This catalyst allows the extension of this chemistry to 1,1-disubstituted olefins with "aryl-directed" regioselectivity.

In previous studies on *saturated* nitrogen heterocycles, the catalytic cycle depicted in Scheme 1 was established.[1d,h,5] The precatalyst reacts with the silane via a σ-bond metathesis reaction[6] to generate an organolanthanide hydride, the active catalyst for the process. The hydride catalyst "$(\mathrm{Cp^{TMS}})_2\mathrm{YH}$"[7] preferentially inserts the least hindered olefin with the same regioselectivity as hydroboration reactions,[8] placing the bulky metal and associated ligands at the terminus of the carbon chain.

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(1) (a) Molander, G. A. *Chemtracts* **1998**, *11*, 237 and references therein. (b) Molander, G. A.; Dowdy, E. D.; Schumann, H. *J. Org. Chem.* **1998**, *63*, 3386. (c) Molander, G. A.; Nichols, P. J.; Noll, B. C. *J. Org. Chem.* **1998**, *63*, 2292. (d) Molander, G. A.; Nichols, P. J. *J. Org. Chem.* **1996**, *61*, 6040. (e) Molander, G. A.; Nichols, P. J. *J. Am. Chem. Soc.* **1995**, *117*, 4415. (f) Onozawa, S.; Sakakura, T.; Tanaka, M. *Tetrahedron Lett.* **1994**, *35*, 8177. (g) Molander, G. A.; Dowdy, E. D. In *Topics In Organometallic Chemistry*; Kobayashi, S., Ed.; Springer-Verlag: New York, 1999; Vol. 2, pp 120−154. (h) Molander, G. A.; Corrette, C. P. *J. Org. Chem.* **1999**, *64*, 9697.

(2) (a) Gagné, M. R.; Marks, T. J. *J. Am. Chem. Soc.* **1989**, *111*, 4108. (b) Gagné, M. R.; Nolan, S. P.; Marks, T. J. *Organometallics* **1990**, *9*, 1716. (c) Gagné, M. R.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 275. (d) Gagné, M. R.; Brard, L.; Conticello, V. P.; Giardello, M. A.; Stern, C. L.; Marks, T. J. *Organometallics* **1992**, *11*, 2003. (e) Li, Y.; Fu, P.-F.; Marks, T. J. *Organometallics* **1994**, *13*, 439. (f) Li, Y.; Marks, T. J. *J. Am. Chem. Soc.* **1996**, *118*, 707. (g) Li, Y.; Marks, T. J. *Organometallics* **1996**, *15*, 3770. (h) Li, Y.; Marks, T. J. *J. Am. Chem. Soc.* **1996**, *118*, 9295. (i) Giardello, M. A.; Conticello, V. P.; Brard, L.; Gagné, M. R.; Marks, T. J. *J. Am. Chem. Soc.* **1994**, *116*, 10241. (j) Arredondo, V. M.; Tian, S.; McDonald, F. E.; Marks, T. J. *J. Am. Chem. Soc.* **1999**, *121*, 3633. (k) Molander, G. A.; Dowdy, E. D. *J. Org. Chem.* **1999**, *64*, 6515. (l) Molander, G. A.; Dowdy, E. D. *J. Org. Chem.* **1998**, *63*, 8983.

(3) Molander, G. A.; Knight, E. E. *J. Org. Chem.* **1998**, *63*, 7009.

(4) Schumann, H.; Keitsch, M. R.; Demtschuk, J.; Molander, G. A. *J. Organomet. Chem.* **1999**, *582*, 70.

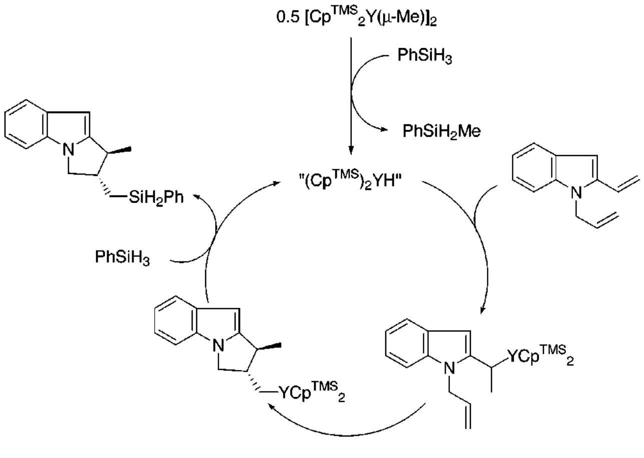
(5) Nichols, P. J. Ph.D. Thesis, University of Colorado at Boulder, 1997.

10.1021/jo0000527 CCC: $19.00

The hydrocarbyl formed undergoes intramolecular olefin insertion through a chairlike transition structure before reacting with the silane via σ-bond metathesis to generate the desired product. All of the individual steps of this transformation are well documented.[1,2b,9]

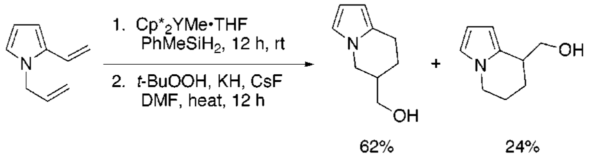
During the early stages of the present work on substituted vinylpyrrole and -indole systems, relative rate studies were being carried out on organoyttrium-catalyzed hydrosilylation reactions.[3] Somewhat surprisingly, these investigations revealed that the hydrosilylation of *N*-methyl-2-vinylpyrrole was at least 10 times faster than that of 1-decene. 1-Decene was determined to be the most reactive of the nonconjugated alkenes investigated. Furthermore, Marks had previously noted that the hydrosilylation of styrene derivatives led to benzylically substituted silanes.[10] This reaction presumably transpired through a benzylic organometallic via a regioinverted insertion process on the olefin. The combination of these prior investigations led us to propose the cycle pictured in Scheme 2 for heteroaromatic dienes.

Scheme 2

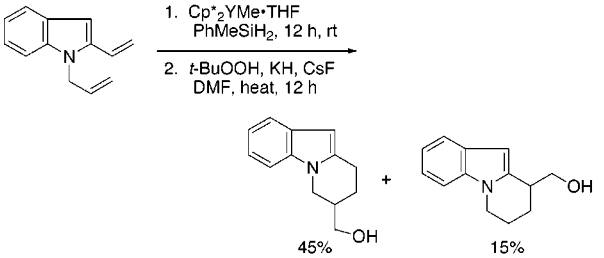


Thus according to the relative rate studies, the hydride catalyst was anticipated to react preferentially with the vinyl substituent.[3] In analogy to the Marks hydrosilylation chemistry of styrene derivatives,[10] the regioselectivity of this process was expected to create a secondary organometallic intermediate. Subsequent cyclization via a chairlike transition structure and σ-bond metathesis to the organosilane would lead to the desired product.

Initial cyclization reactions on the heteroaromatic dienes were conducted with 1-allyl-2-vinyl-1*H*-pyrrole and 1-allyl-2-vinyl-1*H*-indole using Cp*$_2$YMe·THF as a precatalyst.[11] Somewhat unexpectedly, the material isolated after oxidation of the reaction contained none of the desired products (eqs 1 and 2). Thus, although the major product of these reactions had resulted from initial insertion at the conjugated alkene as expected on the basis of the relative rate studies, in contrast to the Marks chemistry the insertion had proceeded predominantly with the same characteristic regiochemistry of nonconjugated, terminal alkenes.

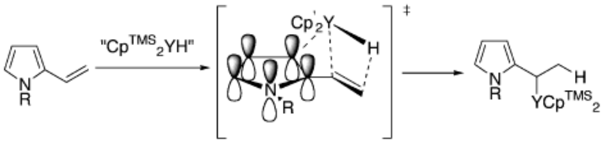


(1)



(2)

The "aryl-directed" process proposed by Marks[10] infers that the aromatic moiety serves as a Lewis base, interacting with the Lewis acidic metal center. Least motion insertion of the alkene leads to the benzylic organometallic. Rationalizing that this interaction (as well as the insertion at the more highly substituted terminus of the alkene) could be facilitated by a more sterically open organometallic complex (eq 3), we turned to the use of [Cp^{TMS}$_2$Y(μ-Me)]$_2$ as a catalyst for the remainder of our study. This catalyst had previously proven effective for cyclization/silylation reactions of a variety of 1,1-disubstituted dienes,[1b] a class of molecules that had previously proved resistant to this process.



(3)

The initial cyclizations employing this catalyst were explored with 1-allyl-2-vinyl-1*H*-pyrrole (**1**) as a substrate (Table 1). In a typical reaction using this protocol, heterocyclic diene **1** (0.5 M in cyclohexane) and 1.1 equiv of phenylsilane were reacted in the presence of 8−10 mol % of [Cp^{TMS}$_2$Y(μ-Me)]$_2$ for 6 h at room temperature.[12] This provided an essentially quantitative yield of (1*R**,2*R**)-

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(6) (a) Zinnen, H. A.; Pluth, J. J.; Evans, W. J. *J. Chem. Soc., Chem. Commun.* **1980**, 810. (b) Brothers, P. J. *Prog. Inorg. Chem.* **1981**, *28*, 1. (c) Evans, W. J.; Meadow, J. H.; Wayda, A.; Hunter, W. E.; Atwood, J. L. *J. Am. Chem. Soc.* **1982**, *104*, 2008. (d) Schumann, H.; Genthe, W. *J. Organomet. Chem.* **1981**, *213*, C7. (e) Marks, T. J. *Inorg. Chim. Acta* **1987**, 140. (f) Thompsen, M. E.; Baxter, S. M.; Bulls, A. R.; Burger, B. J.; Nolan, M. C.; Santarrisiero, B. D.; Schaefer, W. P.; Bercaw, J. E. *J. Am. Chem. Soc.* **1987**, *109*, 203.

(7) Schumann, H.; Keitsch, M.; Demtschuk, J.; Molander, G. A. *J. Organomet. Chem.* **1999**, *582*, 70. Although the methyl precatalyst is a dimer, the active hydride catalyst is most likely a monomer and is capable of a rapid olefin insertion of most 1,1-disubstituted alkenes. Another interesting feature of the catalyst is its unusual stability. Members of this class of precatalyst have been weighed in the air and utilized in hydrosilylation reactions employing normal procedures for the benchtop handling of air-sensitive materials.

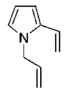
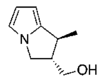
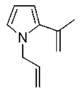
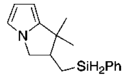
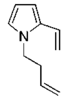
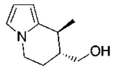
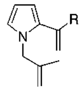
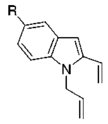
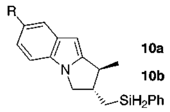
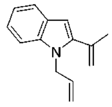
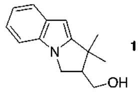
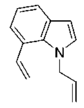
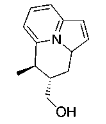
(8) Brown, H. C. *Hydroboration*; W. A. Benjamin, Inc.: New York, 1962.

(9) (a) Molander, G. A.; Hoberg, J. O. *J. Am. Chem. Soc.* **1992**, *114*, 3123. (b) Piers, W. E.; Bercaw, J. E. *J. Am. Chem. Soc.* **1990**, *112*, 9406. (c) Piers, W. E.; Shapiro, P. J.; Bunel, E. E.; Bercaw, J. E. *Synlett* **1990**, 74. (e) Heeres, H. J.; Teuben, J. H. *Organometallics* **1990**, *9*, 1508. (f) Gagné, M. R.; Marks, T. J. *J. Am. Chem. Soc.* **1989**, *111*, 4108. (g) den Haan, K. H.; Wielstra, Y.; Teuben, J. H. *Organometallics* **1987**, *6*, 2053.

(10) Fu, P.-F.; Brard, L.; Li, Y.; Marks, T. J. *J. Am. Chem. Soc.* **1995**, *117*, 7157.

(11) Prepared by a modification of the procedure found in: Baskoboynikow, A. Z.; Parshina, I. N.; Shestakova, A. K.; Butin, K. P.; Beletskaya, I. P.; Kuz'mina, L. G.; Howard, J. A. K. *Organometallics* **1997**, *16*, 4041. KCp^{TMS} (6 mmol) and YCl$_3$ (3 mmol) were heated at reflux in THF for 4 h. The solvent was removed in vacuo and replaced with Et$_2$O. MeLi (2.15 mL of a 1.5 M solution in Et$_2$O, 3.2 mmol) was added at −78 °C, and the reaction was warmed to room temperature. After the solution was stirred for 4 h, the solvent was removed and the solids were extracted with hexanes to provide the desired organometallics.

Table 1. $[Cp^{TMS}{}_2Y(\mu\text{-}Me)]_2$-Catalyzed Cyclization/Silylation Reactions of Substituted Heteroaromatic Dienes[a]

substrate[b]		product		(isoltd yield, ds)[c]	reaction time (h)[d]
	**1**		**3**	(90%, 98:2)[e]	6
	**4**		**5**	(94%)	12
	**6**		**7**	(60%, 98:2)[e,f]	12-18
	**8a** R = H **8b** R = Me	complex mixture			
	**9a** R = H **9b** R = OMe		**10a** **10b**	(85%, 98:2) (80%, 98:2)	12 4
	**11**		**12**	(68%)[e,f]	18
	**13**		**14**	(58%, 9:1)[e,f]	18

[a] Some phenylsilanes were immediately converted to the corresponding alcohols by known transformations for structural characterization. [b] All reactions were performed with 8−10 mol % of catalyst and $PhSiH_3$ unless otherwise noted. [c] Isolated by flash chromatography. The diastereoselectivity was determined on isolated material by spectroscopic data. All of these compounds have been fully characterized spectroscopically (^1H NMR, ^{13}C NMR, IR), and elemental composition has been established by high-resolution mass spectrometry and/or combustion analysis. The products were >98% pure by GC analysis and none of the cis isomer could be observed by NMR. [d] The reaction time indicated is for the cyclization/silylation reaction. [e] Isolated yield for the two-step process (cyclization/silylation and oxidation). [f] The reaction was performed with $PhMeSiH_2$ instead of $PhSiH_3$.

1-methyl-2-[(1-phenylsilyl)methyl]-2,3-dihydro-1*H*-pyrrolizine (**2**).[13] Because structural characterization of the newly generated phenylsilane **2** proved difficult, this intermediate was converted to the corresponding alcohol **3** by facile oxidation using excess KH and *t*-BuOOH in the presence of DMF according to the method developed by Woerpel and Smitrovich.[14] Analysis of the resulting alcohol[15] revealed that all of the steps proceeded in excellent yields and with high selectivities. None of the products derived from the regioisomeric organometallic intermediate could be detected in the crude reaction mixtures.

Remarkably, we observed that this process works extremely well for conjugated 1,1-disubstituted alkenes, even though the competitive rate studies had indicated that 1-decene and 1-methyl-2−isopropenylpyrrole had nearly the same reaction rate in the hydrosilylation reaction.[3] Thus the cyclization/silylation reaction of the heteroaromatic diene **4** provided product **5** in excellent yield. This reaction required 12 h to proceed to completion (Table 1). Presumably, the increased reaction time was necessary because the sterically more congested 1,1-disubstituted alkene makes it much less reactive than monosubstituted alkenes, and the creation of a tertiary organometallic should also be extraordinarily difficult, further retarding the reaction. Importantly, although there are examples for the same sense of regioselection in enantioselective catalytic hydrogenation and hydrosilylation reactions of styrene derivatives,[2i,10] this appears to be the first such selectivity observed in polyunsaturated systems where chemoselectivity is an issue. Furthermore, it is the first example of which we are aware in which olefin insertion takes place into a tertiary metal−carbon bond.

As evidenced by the remainder of the results depicted in Table 1, a variety of substrates could be efficiently converted to cyclized organosilanes in high yield and with excellent diastereoselectivities using this protocol. For 1,5-diene **6**, the product can again be attributable to “aryl-directed” olefin insertion of the organoyttrium hydride catalyst at the conjugated alkene, followed by cyclization to provide 1,2-disubstituted bicyclic product **7**. To avoid the formation of cyclized, dialkylated silanes in the slower cyclization of 1,6-dienes, phenylmethylsilane can be employed as a chain terminator.[1c,e] Utilizing this more hindered silane slows the intermolecular σ-bond metathesis of the intermediate organometallic with the silane sufficiently to allow the cyclization to take place.

The cyclization/silylation process does not work well for substrates **8a**,**b**. Apparently, the intermediate tertiary organometallic is not able to effectively cyclize onto the more highly hindered 1,1-disubstituted alkene center, and a complex mixture of products is generated.

Indole derivatives were examined, and as expected, they worked as well as the analogous pyrroles. The strongly Lewis acidic catalyst tolerates the Lewis basic ether as illustrated with substrate **9b**. Interestingly, this electron-releasing group significantly accelerates the process (compare the reaction time for **9a** to that of **9b**). As in the pyrrole series, 1,1-disubstituted alkenes were tolerated as well, and thus, **11** can be converted to **12** in reasonable overall yield. Finally, a juxtaposition of reacting substituents is possible in the indole platform, with substrate **13** leading to **14** in good yields through initial olefin insertion of the vinyl group on the carbocycle.

In summary, $[Cp^{TMS}{}_2Y(\mu\text{-}Me)]_2$ has been shown to be an efficient precatalyst for the cyclization and subsequent silylation of substituted heteroaromatic dienes. This process has been extended to 1,1-disubstituted olefins and provided excellent selectivities and yields in many cases. The relatively easy preparation of the organometallic catalyst and the facile oxidation of the resulting phenylsilanes to the synthetically more versatile alcohols provide an attractive synthetic method for the construction of functionalized five- and six-membered nitrogen

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(12) One problem with the catalyst is that it apparently becomes deactivated over time because of hydride dimer formation. Ideal conditions involve the addition of smaller portions of the catalyst at fixed intervals to maintain an active concentration of the catalyst.

(13) The general workup procedure involved filtration of the crude mixture through a small plug of Florisil prior to concentration by rotary evaporation and purification by flash chromatography. Many of these reactions are so clean, in fact, that pouring the reaction mixture through a short bed of Florisil to remove the catalyst, followed by evaporation of the solvent and bulb-to-bulb distillation, leads to essentially quantitative yields of analytically pure products.

(14) Smitrovich, J. H.; Woerpel, K. H. *J. Org. Chem.* **1996**, *61*, 6044.

(15) The relative stereochemistry of the major isomer of **2** was assigned on the basis of NOE difference experiments using alcohol **3**.

heterocycles. Many of these structural motifs are present in diverse natural products. Most remarkable is the fact that heteroaromatic dienes react cleanly at the conjugated alkene with “inverted” regioselectivity. The “aryl-directed” insertion process allows the normal (sterically and electronically driven) regioselectivity patterns to be overcome even with 1,1-disubstituted alkenes, and thus, structures complementary to those observed in nonaromatic systems can be accessed.

Supporting Information Available: Text providing full experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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