Organocalcium Chemistry

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Insertion of Pyridine into the Calcium Allyl Bond: Regioselective 1,4-Dihydropyridine Formation and C–H Bond Activation**

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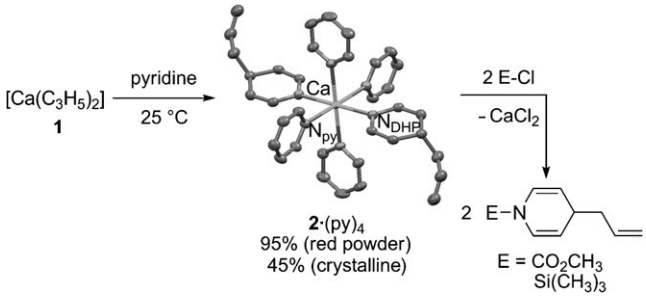
Selective functionalization of pyridine is currently of interest for the synthesis of pharmacologically important nitrogen heterocycles, such as dihydropyridines (DHPs).[1,2] Whereas nucleophilic *ortho* substitution of pyridine with retention of aromaticity is facile, synthesis of DHPs by nucleophilic addition is complicated owing to loss of aromaticity. Besides Hantzsch-type multicomponent reactions,[3] approaches to 1,2- and 1,4-DHPs require the use of *N*-acylpyridinium ions.[2a,4] Grignard[5] or organotin[6] reagents mainly add to give 2-substituted DHPs. 1,4-DHPs with substituents in the 4-position can be obtained with ill-defined organotitanium reagents,[7] lithium dialkylcuprates,[8] and mixtures of Grignard reagents or zinc organyls with cuprous salts.[8b,9] Organometallic reagents of the early transition and f-block metals, on the other hand, typically metalate the *ortho* C–H bond of pyridine to give η^2-(C,N)-pyridyl complexes.[10] Herein we show that the recently introduced organocalcium complex bis(allyl)calcium (**1**)[11] selectively transfers its allyl groups to pyridine (py) to give 4-allyl-1,4-DHP, whereas the C–H bond of *ortho*- and *para*-methyl groups in picolines and lutidines are metalated only under thermodynamic control.

Stoichiometric amounts of **1** reacted with pyridine in THF upon mixing to give $[Ca(NC_5H_5\text{-}4\text{-}C_3H_5)_2(L)_n]$ (**2**; L = THF, py) quantitatively. In the presence of excess pyridine, the new calcium amide **2**·$(py)_4$ could be isolated as a red powder in almost quantitative yield and be fully characterized (Scheme 1). Variable-temperature NMR spectroscopy in $[D_8]$THF showed that for **2**·$(py)_4$, an equilibrium exists, presumably between the *cis* and *trans* octahedral isomers. The reaction of electrophiles E–Cl (E = CO_2CH_3, $Si(CH_3)_3$) with **2**·$(py)_4$ gave the corresponding N-protected 1,4-DHP with concomitant precipitation of $CaCl_2$ (Scheme 1).



Scheme 1. Formation of the insertion product **2**·$(py)_4$ and subsequent reaction to form N-protected 1,4-DHP. py = pyridine.

The solid-state structure of **2**·$(py)_4$ features a symmetric octahedral coordination geometry with *trans*-arranged anionic $NC_5H_5\text{-}4\text{-}C_3H_5$ ligands.[12] The presence of four pyridine and two dearomatized $NC_5H_5\text{-}4\text{-}C_3H_5$ (1,4-DHP) rings is apparent from their equal and alternating C–C bond lengths, respectively. This structure could be reproduced by computational methods. The only significant difference between the observed and calculated structure is a twist of the *trans*-arranged six-membered rings, which is attributed to π-packing effects.

A solution of **1** in a 1:1 mixture of py and $[D_5]$py led to a product that has proton signals with half the intensity expected for the ring CH groups in **2**. This observation indicates the absence of a significant kinetic deuterium effect and an insertion reaction without a rate-determining C–H bond-cleavage step. Compound **2** undergoes slow decomposition with first-order kinetics ($k = 0.12\ d^{-1}$, 0.65 M solution in $[D_5]$py) to give an intermediate that, upon heating for several hours, was converted into propene and an unidentified metalation product.[13]

The overall mechanism for the reaction of **1** with pyridine was deduced by NMR spectroscopy (Scheme 2). The reaction is initiated by coordination of pyridine at the calcium center to give complex **3**.[14] Attack at the *ortho* position by the nucleophilic allyl group results in the rapid formation of the *ortho*-allylated product **4** via a six-membered, metalacyclic transition state **TS1**. Intermediate **4** has a half-life of $t_{1/2} =$ 10 min at 25 °C. The final 1,4-insertion product **2** is formed by a rate-determining Cope rearrangement (Scheme 2). In this second, six-membered transition state **TS2**, a lack of conformational flexibility of both the allyl and the pyridine ring fragment disfavors the 1,3-rearrangement. This sequence of allylic rearrangements is analogous to Claisen and subsequent

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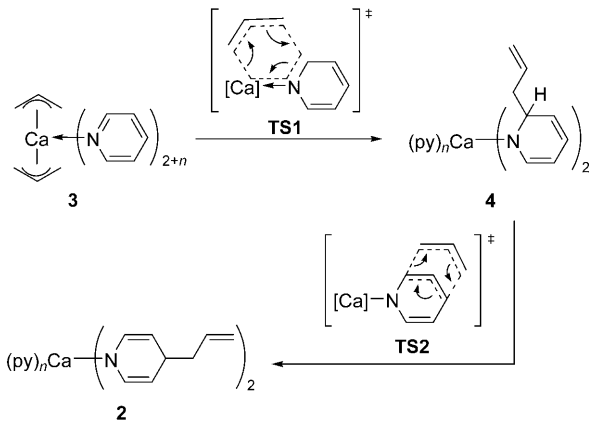


Scheme 2. Proposed mechanism for the reaction of **1** with pyridine ($n = 3, 4$). **TS** = transition state.

Cope rearrangement observed for *ortho*-disubstituted allyloxybenzenes to give 4-allylcyclohexa-2,5-dienones.[15]

The reaction energy profile for the proposed mechanism was studied by means of computational methods (Figure 1). With $[Ca(\eta^3\text{-}C_3H_5)_2(py)_3]$ as reference, the overall reaction leading to $\mathbf{2}\cdot(py)_4$ is exothermic ($\Delta_r H^\circ = -27.4$ kcal mol^{-1}). The initial 1,2-insertion of two pyridine molecules (**TS1**) to give $[Ca(NC_5H_5\text{-}2\text{-}C_3H_5)_2(py)_3]$ ($\mathbf{4}\cdot(py)_3$) proceeds in two steps with an activation enthalpy of $\Delta_r H^{\neq} = 14.3$ (**TS1a**) and 3.4 kcal mol^{-1} (**TS1b**) ($\Delta_r H^\circ = -7.2$ and -8.6 kcal mol^{-1}), for each allyl ligand. Coordination of two additional pyridine molecules leads to the six-coordinate complex $\mathbf{4}\cdot(py)_4$ ($\Delta_r H^\circ = -18.9$ kcal mol^{-1}). In agreement with experimental results, the subsequent 1,3-rearrangement is the rate-determining step of the overall reaction. This rearrangement has activation barriers of $\Delta_r H^{\neq} = 8.5$ kcal mol^{-1} (27.4 kcal mol^{-1} relative to $\mathbf{4}\cdot(py)_4$) for **TS2a** and $\Delta_r H^{\neq} = 5.1$ kcal mol^{-1} for **TS2b**. Direct 1,4-insertion and *ortho* metalation are found to be unfavorable.

The proposed mechanism is in agreement with results of NMR-scale reactions of **1** with two equiv of the methylated pyridine derivatives 2-, 3-, and 4-methylpyridine (**5**, **7**, **8**) and also 2,6- and 3,5-dimethylpyridine (**6**, **9**; Scheme 3). The importance of vacant *ortho* and *para* positions for the insertion to occur is reflected by the metalation of C–H bond activation products along with propene evolution, as observed with 2-picoline (**5**), 2,6-lutidine (**6**), and 4-picoline (**7**). Reaction with **5** led to a 2:1 mixture of the C–H bond activation product bis(2-pyridylmethyl)calcium (**5act**) and the 1,4-insertion product calcium 4-allyl-2-methyl-4*H*-pyridin-1-ide (**5ins**). Over a period of three weeks at room temperature, **5ins** was quantitatively transformed into **5act**. Reaction with **6** gave **6act** quantitatively within one day.

Consistent with the fact that the Cope rearrangement is rate-determining, 3-picoline (**7**) showed only 66% conversion within one hour to give **7ins**. After four weeks at room temperature, **7ins** was completely converted into **7act** and propene. The transformation of insertion products **5ins** and **7ins** to the corresponding metalated products **5act** and **7act** was found to follow first-order kinetics with half-lifes of $t_{1/2} = 11$ d (**5ins**) and $t_{1/2} = 10$ d (**7ins**). In agreement with the mechanism proposed, methyl groups at 3- and 5-positions have no effect on the 1,4-insertion. The formation of the products **8ins** and **9ins** was therefore observed quantitatively within one day, and no change was noted over a period of

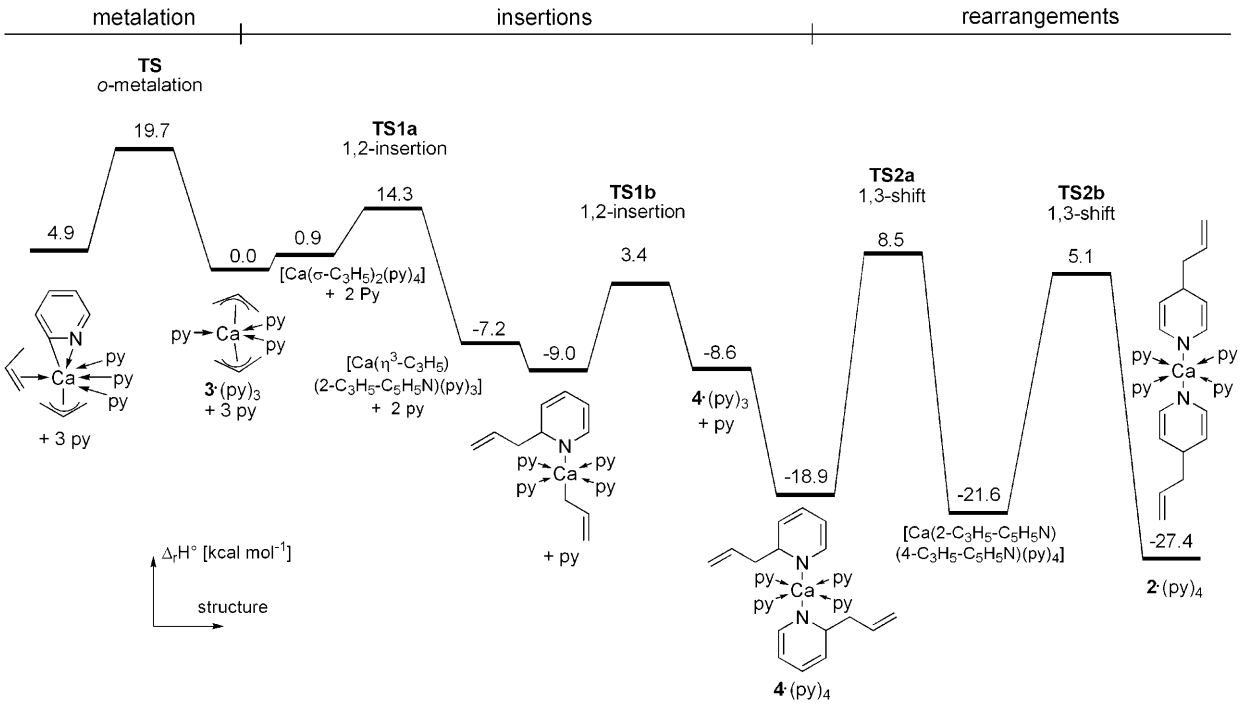
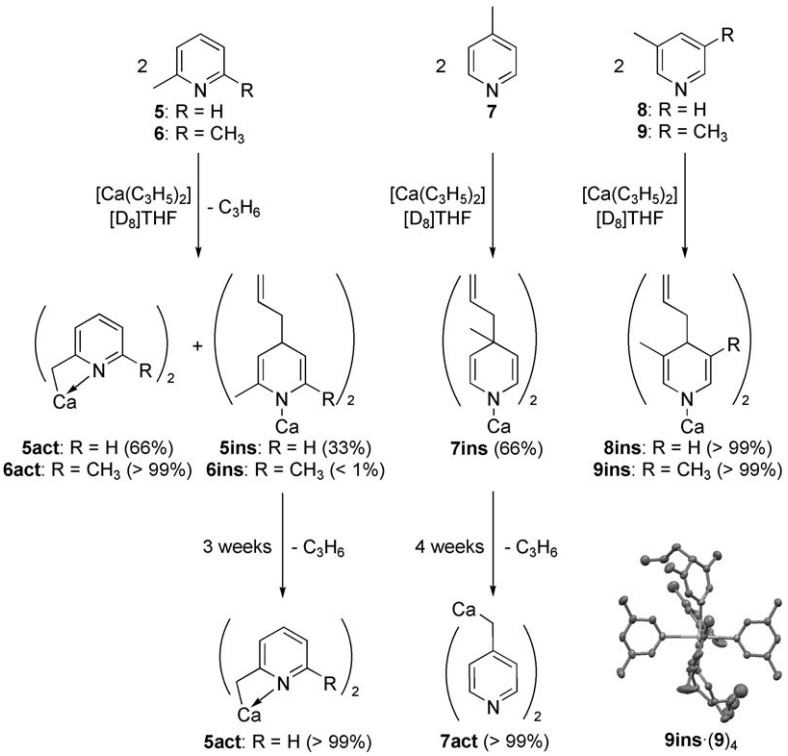


Figure 1. Enthalpy profile for the reaction of bis(allyl)calcium with pyridine: 1,2-insertion, subsequent 1,3-rearrangement, and alternative *o*-metalation. For details of the DFT calculations, see the Supporting Information.



Scheme 3. Reactions of **1** with methylated pyridine derivatives.

several days. **9ins** was crystallized as an octahedrally coordinated 3,5-lutidine adduct **9ins**·(**9**)$_4$.[12]

When 4-*tert*-butylpyridine (**10**) was reacted with **1** in [D$_8$]THF, the *ortho*-metalation product bis(4-*tert*-butylpyridin-2-yl)calcium (**10act**) was formed quantitatively within four days. This observation is ascribed to steric shielding of the 4-position, thus blocking the 1,3-rearrangement. These findings indicate an equilibrium between the reactants, the allylated products, and also the metalated complex **10act**. Whereas the insertion products are formed under kinetic control, the 4-*tert*-butyl substituent shifts the equilibrium toward the thermodynamically favored *ortho*-metalation product.

In conclusion, insertion of pyridine into the polar allyl calcium bond gave 1,4-dihydropyridine derivatives regioselectively. The presence of methyl groups on the pyridine ring resulted in 1,4-addition under kinetic control, followed by C–H bond activation of the methyl group. Organocalcium reagents[16] evidently display an unprecedented reactivity pattern with respect to the balance between nucleophilicity and basicity.

Experimental Section

2·(py)$_4$: a) Bis(allyl)calcium (**1**, 63 mg, 0.52 mmol) was dissolved in pyridine (1.0 mL). Upon cooling, red crystals suitable for X-ray diffraction were formed (138 mg, 0.23 mmol, 45 %).[12] b) **1** (40 mg, 0.33 mmol) was dissolved in THF (0.8 mL), and a solution of pyridine (155 mg, 196 mmol) in THF (0.2 mL) was added and stirred for 30 min. Removal of all volatiles resulted in a dark-red powder **2**·(py)$_4$ (188 mg, 32 mmol, 95 %). Further drying in vacuo resulted in the loss of pyridine ligands, a viscous product **2**·(py)$_n$ (n = 1–1.5), and an increase of impurities. ^{1}H NMR (400 MHz, [D$_5$]py, 25 °C): δ = 8.71 (m, 8H, *o*-CH^{py}), 7.55 (m, 4H, *p*-CH^{py}), 7.19 (m, 8H, *m*-CH^{py}), 6.50 (d, ^3J(H,H) = 6.5 Hz, 4H, *o*-CH^{DHP}), 6.22 (m, 2H, CH^{allyl}), 5.18 (d, ^3J(H,H) = 17.5 Hz, 2H, =CH$_2^{trans,allyl}$), 5.13 (d, ^3J(H,H) = 10.3 Hz, 2H, =CH$_2^{cis,allyl}$), 4.34 (dd, ^3J(H,H) = 2.3, 6.5 Hz, 4H, *m*-CH^{DHP}), 4.02 (br, 2H, *p*-CH), 2.48 ppm (t, ^3J(H,H) = 6.5 Hz, 4H, -CH$_2$-^{allyl}). ^{13}C{^{1}H} NMR (100 MHz, [D$_5$]py, 25 °C): δ = 149.9 (*o*-CH^{py}), 141.7 (*o*-CH^{DHP}), 138.6 (CH^{allyl}), 135.5 (*p*-CH^{py}), 123.5 (*m*-CH^{py}), 112.3–110.8 (=CH$_2^{allyl}$), 90.1–95.1 (*m*-CH^{DHP}), 55.8 (-CH$_2$-^{allyl}), 42–36 ppm (*p*-CH^{DHP}). ^{1}H NMR (400 MHz, [D$_8$]THF, 25 °C): δ = 8.56 (m, 8H, *o*-CH^{py}), 7.66 (tt, ^3J(H,H) = 7.7 Hz, ^4J(H,H) = 1.8 Hz, 4H, *p*-CH^{py}), 7.26 (m, 8H, *m*-CH^{py}), 6.09–6.17 (br, 4H, *o*-CH^{DHP}), 5.84 (br, 2H, CH^{allyl}), 4.89 (d, ^3J(H,H) = 10.1 Hz, 2H, =CH$_2^{trans,allyl}$), 4.87 (d, ^3J(H,H) = 7.0 Hz, 2H, =CH$_2^{cis,allyl}$), 3.82–3.97 (br, 4H, *m*-CH^{DHP}), 3.39 (br, 2H, *p*-CH^{DHP}), 2.04 ppm (br, 4H, -CH$_2$-^{allyl}). ^{13}C{^{1}H} NMR (100 MHz, [D$_8$]THF, 25 °C): δ = 150.8 (*o*-CH^{py}), 136.2 (*p*-CH^{py}), 124.3 (*m*-CH^{py}), 140.2 (*o*-CH^{DHP}), 138.7 (CH^{allyl}), 114.4/113.5 (=CH$_2^{allyl}$), 98.4/94.8 (*m*-CH^{DHP}), 50.7/49.7 (-CH$_2$-^{allyl}), 36.9/36.1 ppm (*p*-CH^{DHP}).

9ins·(**9**)$_4$: a) **1** (63 mg, 0.52 mmol) was dissolved in 3,5-dimethylpyridine (1.0 mL). Upon cooling, red crystals suitable for X-ray diffraction were formed (185 mg, 0.24 mmol, 47 %).[12] ^{1}H NMR (400 MHz, [D$_8$]THF, 25 °C): δ = 8.18 (m, 8H, *o*-CH^{9}), 7.30 (m, 4, *p*-CH^{9}), 6.10 (s, 4H, *o*-CH^{DHP}), 5.99 (m, 2H, CH^{allyl}), 4.73–4.97 (m, 4H, =CH$_2^{allyl}$), 3.33 (t, ^3J(H,H) = 3.8 Hz, 2H, *p*-CH^{DHP}), 2.24 (br, 28H, CH$_3^{9}$, -CH$_2$-^{allyl}), 1.50 ppm (br, 12H, CH$_3^{DHP}$). ^{13}C{^{1}H} NMR (100 MHz, [D$_8$]THF, 25 °C): δ = 148.32 (*o*-CH^{9}), 140.44 (CH^{allyl}), 137.36 (*p*-CH^{9}), 136.06 (*o*-CH^{DHP}), 133.01 (*m*-C^{9}), 113.64 (=CH$_2^{allyl}$), 100.28 (*m*-C^{DHP}), 46.32 (-CH$_2$-^{allyl}), 37.90 (*p*-CH^{DHP}), 20.64 (CH$_3^{DHP}$), 18.19 ppm (CH$_3^{9}$).

For further experimental details, NMR data of compounds **5ins**, **7ins**, **8ins**, **10ins**, **5act**–**7act**, **10act**, kinetic data, and computational details, see the Supporting Information.

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[1] a) S. Goldmann, J. Stoltefuß, *Angew. Chem.* **1991**, *103*, 1587–1605; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1559–1578; b) L. Prokai, K. Prokai-Tatrai, N. Bodor, *Med. Res. Rev.* **2000**, *20*, 367–416; c) M. Schlosser, F. Mongin, *Chem. Soc. Rev.* **2007**, *36*, 1161–1172; d) Y.-G. Zhou, *Acc. Chem. Res.* **2007**, *40*, 1357–1366.

[2] a) R. Lavilla, *J. Chem. Soc. Perkin Trans. 1* **2002**, 1141–1156; b) S. Visentin, B. Rolando, A. D. Di Stilo, R. Fruttero, M. Novara, E. Carbone, C. Roussel, N. Vanthuyne, A. Gasco, *J. Med. Chem.* **2004**, *47*, 2688–2693; c) M. Litvic, I. Cepanec, M. Filipan, K. Kos, A. Bartolincic, V. Druskovic, M. M. Tibi, V. Vinkovic, *Heterocycles* **2005**, *65*, 23–35.

[3] a) B. Das, K. Suneel, K. Venkateswarlu, B. Ravikanth, *Chem. Pharm. Bull.* **2008**, *56*, 366–368; b) J. Jiang, J. Yu, X.-X. Sun, Q.-Q. Rao, L.-Z. Gong, *Angew. Chem.* **2008**, *120*, 2492–2496; *Angew. Chem. Int. Ed.* **2008**, *47*, 2458–2462; c) V. Sivamurugan, A. Vinu, M. Palanichamy, V. Murugesan, *Heteroat. Chem.* **2006**, *17*, 267–271.

[4] J. Bräckow, K. T. Wanner, *Tetrahedron* **2006**, *62*, 2395–2404.

[5] a) R. Yamaguchi, Y. Nakazono, M. Kawanisi, *Tetrahedron Lett.* **1983**, *24*, 1801–1804; b) H. Gilman, J. Eisch, T. Soddy, *J. Am.*

Chem. Soc. **1957**, *79*, 1245 – 1249; c) W. L. C. Veer, S. Goldschmidt, *Recl. Trav. Chim. Pays-Bas* **1946**, *65*, 796 – 798.
[6] R. Yamaguchi, M. Moriyasu, M. Yoshioka, M. Kawanisi, *J. Org. Chem.* **1988**, *53*, 3507 – 3512.
[7] D. L. Comins, J. D. Brown, *Tetrahedron Lett.* **1984**, *25*, 3297 – 3300.
[8] a) E. Piers, M. Soucy, *Can. J. Chem.* **1974**, *52*, 3563 – 3564; b) P. Mangeney, R. Gosmini, S. Raussou, M. Commercon, A. Alexakis, *J. Org. Chem.* **1994**, *59*, 1877 – 1888.
[9] a) D. L. Comins, A. H. Abdullah, *J. Org. Chem.* **1982**, *47*, 4315 – 4319; b) K. Akiba, Y. Iseki, M. Wada, *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1994 – 1999; c) X. Wang, A. M. Kauppi, R. Olsson, F. Almqvist, *Eur. J. Org. Chem.* **2003**, 4586 – 4592; d) M. J. Shiao, K. H. Liu, L. G. Lin, *Synlett* **1992**, 655 – 656.
[10] a) M. E. Thompson, S. M. Baxter, A. R. Bulls, B. J. Burger, M. C. Nolan, B. D. Santarsiero, W. P. Schaefer, J. E. Bercaw, *J. Am. Chem. Soc.* **1987**, *109*, 203 – 219; b) B.-H. Deelman, W. M. Stevels, J. H. Teuben, M. T. Lakin, A. L. Spek, *Organometallics* **1994**, *13*, 3881 – 3891; c) P. L. Diaconescu, *Curr. Org. Chem.* **2008**, *12*, 1388 – 1405; d) S. Arndt, B. R. Elvidge, P. M. Zeimentz, T. P. Spaniol, J. Okuda, *Organometallics* **2006**, *25*, 793 – 795; e) J. D. Scollard, D. H. McConville, J. J. Vittal, *Organometallics* **1997**, *16*, 4415 – 4420; f) H. Sugiyama, G. Aharonian, S. Gambarotta, G. P. A. Yap, P. H. M. Budzelaar, *J. Am. Chem. Soc.* **2002**, *124*, 12268 – 12274.
[11] P. Jochmann, T. S. Dols, T. P. Spaniol, L. Perrin, L. Maron, J. Okuda, *Angew. Chem.* **2009**, *121*, 5825 – 5829; *Angew. Chem. Int. Ed.* **2009**, *48*, 5715 – 5719.
[12] CCDC 780948 (**2**·$(py)_4$) and CCDC 780949 (**9ins**·$(\mathbf{9})_4$) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[13] The ^{1}H NMR spectrum showed broad signals for all of the species. Together with an increase of the aromatic/olefinic integration ratio from initial 2:1 to 11:1 (9 h at 70 °C), these observations indicate an H/D exchange similar to that in Ref. [10b].
[14] Although the presence of [Ca(σ-$C_3H_5)_2$] cannot be excluded (the calculated interaction between the allyl ligand at the calcium center and the 2-position of a *cis* coordinated pyridine molecule may indicate incipient 1,2-insertion), the ^{1}H NMR spectrum of the σ-allyl complex (**4f** reported in Ref. [11]) is due to **2**·([D_5]py). The ^{13}C NMR spectrum of **2**·([D_5]py) in [D_5]py shows three triplets at $\delta = 140.84$ (^1J(C,D) = 21 Hz), 94.70 (^1J(C,D) = 23 Hz), and 35.97 ppm (^1J(C,D) = 19 Hz) for the ring carbon atoms.
[15] a) H. Conroy, R. Firestone, *J. Am. Chem. Soc.* **1956**, *78*, 2290 – 2297; b) S. Blechert, *Synthesis* **1989**, 71 – 82; c) N. S. Barta, G. R. Cook, M. S. Landis, J. R. Stille, *J. Org. Chem.* **1992**, *57*, 7188 – 7194.
[16] a) S. Harder, *Chem. Rev.* **2010**, 110, 3852 – 3876; b) A. G. M. Barrett, M. R. Crimmin, M. S. Hill, P. A. Procopiou, *Proc. R. Soc. A* **2010**, *466*, 927 – 963.

