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Calcium-Mediated Dearomatization, C–H Bond Activation, and Allylation of Alkylated and Benzannulated Pyridine Derivatives

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Abstract: A facile and general synthetic pathway for the production of dearomatized, allylated, and C–H bond activated pyridine derivatives is presented. Reaction of the corresponding derivative with the previously reported reagent bis(allyl)calcium, $[Ca(C_3H_5)_2]$ (**1**), cleanly affords the product in high yield. The range of N-heterocyclic compounds studied comprised 2-picoline (**2**), 4-picoline (**3**), 2,6-lutidine (**4**), 4-*tert*-butylpyridine (**5**), 2,2′-bipyridine (**6**), acridine (**7**), quinoline (**8**), and isoquinoline (**9**). Depending on the substitution pattern of the pyridine derivative, either carbometalation or C–H bond activation products are obtained. In the absence of methyl groups *ortho* or *para* to the nitrogen atom, carbometalation leads to dearomatized products. $C(sp^3)$–H bond activation occurs at *ortho* and *para* situated methyl groups. Steric shielding of the 4-position in pyridine yields the ring-metalated product through $C(sp^2)$–H bond activation instead. The isolated compounds $[Ca(2\text{-}CH_2\text{-}C_5H_4N)_2(THF)]$ (**2b**·(THF)), $[Ca(4\text{-}CH_2\text{-}C_5H_4N)_2(THF)_2]$ (**3b**·$(THF)_2$), $[Ca(2\text{-}CH_2\text{-}C_5H_3N\text{-}6\text{-}CH_3)_2(THF)_n]$ (**4b**·$(THF)_n$; $n=0$, 0.75), $[Ca\{2\text{-}C_5H_3N\text{-}4\text{-}C(CH_3)_3\}_2(THF)_2]$ (**5c**·$(THF)_2$), $[Ca\{4,4'\text{-}(C_3H_5)_2(C_{10}H_8N_2)\}(THF)]$ (**6a**·(THF)), $[Ca(NC_{13}H_9\text{-}9\text{-}C_3H_5)_2(THF)]$ (**7a**·(THF)), $[Ca(4\text{-}C_3H_5\text{-}C_9H_7N)_2(THF)]$ (**8b**·(THF)), and $[Ca(1\text{-}C_3H_5\text{-}C_9H_7N)_2(THF)_3]$ (**9a**·$(THF)_3$) have been characterized by NMR spectroscopy and metal analysis. **9a**·$(THF)_4$ and **4b**·$(THF)_3$ were additionally characterized in the solid state by X-ray diffraction experiments. **4b**·$(THF)_3$ shows an aza-allyl coordination mode in the solid state. Based on the results, mechanistic aspects are discussed in the context of previous findings.

Keywords: allyl ligands · allylation · calcium · nitrogen heterocycles · reaction mechanisms

Introduction

A vast range of bioactive molecules contain pyridine (Py) and quinoline units as essential building blocks for biological function. Thus, the development of new strategies for the preparation of this class of compounds has become an important endeavor in synthetic chemistry.[1] Apart from reactions for the construction of substituted N-heterocycles,[2,3] C–H bond activation and substituent modification reactions of inexpensive and readily available pyridine and quinoline derivatives play a major role in their functionalization. In the latter case, attaching activating substituents is crucial for further transformations. The introduction of olefinic functionalities such as vinyl or allyl substituents results in valuable starting materials for ring-closing metathesis,[4] epoxidation/dihydroxylation,[5] cyclopropanation,[5b] and polymerization[6] reactions. Cross-coupling reactions, including Hiyama,[7] Kumada,[8] Negishi,[9] Stille,[10] and Suzuki–Miyaura[11] reactions, have broadened the scope of applications of substituent modification reactions.

Numerous reports have demonstrated that simple transformations of pyridine often rely on its π-deficient character. Additional activating and/or directing groups open access to a variety of pyridine derivatives when metal catalysis is employed.[1a,12] Metalation is an important tool for the introduction of (hetero)organic substituents on the pyridine ring, as well as for the introduction of a pyridyl nucleophile itself. In this context, lithiated or magnesiated pyridyls are the commonly used starting materials. Alkyl lithium reagents usually show a preference for addition over deprotonation and often undergo unwanted coupling reactions. *ortho*-Lithiated or magnesiated pyridyls can easily be obtained by halogen–metal exchange.[13] Direct *ortho*-metalation is observed in the reactions of pyridine with many organometallic compounds of early transition and f-block metals.[14] Common methods for the introduction of late transition and p-block metals often utilize the abovementioned lithiated or magnesiated derivatives in metal-exchange reactions.[13,15,16] Notably, there have been various reports on the allylation of (iso)quinolines with allylic reagents of boron,[17] tin,[17d,18] silicon,[12d,17d,18a,19] indium,[18e,20] and magnesium.[21] As was found for the activation of pyridine itself, these transformations mostly require N-acylation prior to functionalization, and, with some exceptions, give the desired allylated derivatives in yields lower than 80%. Pyridine insertion of an in situ generated magnesium hydride complex has also been observed.[22] The importance of

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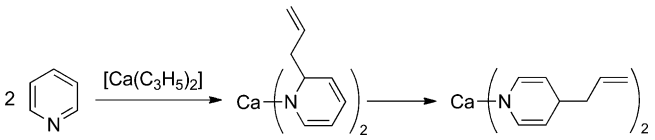
dearomatization reactions for the synthesis of complex natural products has recently been reported.[23]

The previously reported compound bis(allyl)calcium (**1**)[24] undergoes rapid 1,2-insertion of pyridine and subsequent rearrangement to give the 1,4-carbometalated product (Scheme 1).[25] By this procedure, an allyl moiety can easily



Scheme 1. General reaction scheme for the reaction of $[Ca(C_3H_5)_2]$ (**1**) with pyridine involving 1,2-insertion and subsequent rearrangement.

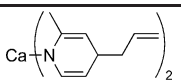
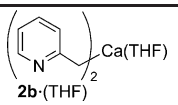
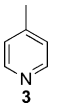
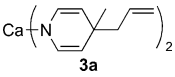
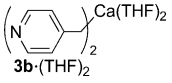
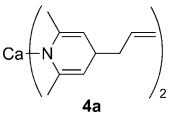
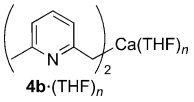
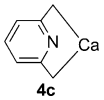
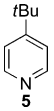
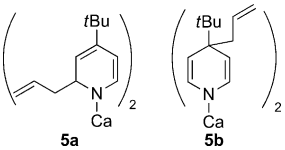
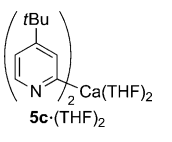
be attached to the C_5H_5N ring, without the need for an activating or protecting group. The polar calcium–nitrogen bond of the carbometalation product can be utilized for further functionalization, for example, N-protection as carbamate or silylamide.[25] Instead of insertion and formation of allylated dihydropyridines, in situ studies have indicated C–H bond activation when *ortho*- and *para*-methylated pyridines (i.e., picolines or lutidines) are reacted with **1**. This reaction pathway results in aromatic calcium pyridylmethanide complexes and concomitant release of propene. We describe herein the calcium-mediated functionalization of alkylated and benzannulated pyridine derivatives through carbometalation and C–H bond activation reactions. These competing reactions can be exploited to isolate dearomatized dihydropyridyl derivatives or carbanionic pyridyl derivatives with intact aromaticity. To study the substituent control of insertion versus C–H bond activation, reactions of bis(allyl)calcium (**1**) with 2-picoline (**2**), 4-picoline (**3**), 2,6-lutidine (**4**), 4-*tert*-butylpyridine (**5**), 2,2′-bipyridine (**6**), acridine (**7**), quinoline (**8**), and isoquinoline (**9**) have been investigated.

Results and Discussion

2-Picoline (2): The reaction of bis(allyl)calcium (**1**) with two equivalents of 2-picoline in refluxing THF for 3 h led to the formation of bis(pyridin-2-ylmethyl)calcium (**2b**) as a mono-(THF) adduct in 96% yield (Table 1, entry 1). Attempted removal of all THF molecules under vacuum resulted in a material that was insoluble in THF. The formation of **2b** was previously observed on the NMR scale when the carbometalation product **2a** was stored for several weeks at ambient temperature.[25] A shorter reaction time of 3 h and heating to 70 °C led to the isolation of the thermodynamically favored aromatic product **2b**.

4-Picoline (3): Similar to the reaction with 2-picoline, the reaction of **1** with two equivalents of 4-picoline (**3**) gave the carbometalated intermediate **3a**, which underwent subsequent C–H bond activation (Table 1, entry 2).[25] On the NMR scale, the formation of bis(pyridin-4-ylmethyl)calcium (**3b**) was detected, but at higher concentrations an insoluble precipitate was formed. Precipitation was also observed in laboratory-scale reactions carried out in refluxing THF. The dark precipitate was shown to consist of **3b**·$(THF)_2$. This product was isolated in 59% yield after 18 h at 70 °C, removal of all volatiles, and washing with pentane and THF. The crude, dried powder was rinsed with THF until the filtrate was colorless. Evaporation of the THF from the filtrate and drying of the insoluble fraction afforded 12 wt% and 88 wt%, respectively. The former was found to consist of a minor amount of **3b** together with **3** and THF. Portions of the insoluble fraction were taken-up in $[D_8]$THF and D_2O to probe its composition. ^{1}H NMR spectra recorded in $[D_8]$THF revealed small amounts of pure **3b** with non-stoichiometric amounts of THF, whereas spectra recorded in D_2O displayed the signals of pure monodeuterated 4-picoline[26] together with 1 equivalent of THF. The exclusive formation of NC_5H_4-CH_2D as the product from quenching with D_2O suggests that the brown precipitate was **3b**·$(THF)_2$.

Table 1. C–H bond activation products and observed intermediates from reactions of pyridine derivatives **2**–**5** with 0.5 equiv **1** in THF.

Entry	Substrate	Time, Temp.	Intermediate	Product	Yield [%]
1	 **2**	3 h, 70 °C	 **2a**	 **2b**·(THF)	96
2	 **3**	18 h, 70 °C	 **3a**	 **3b**·$(THF)_2$	59
3	 **4**	24 h, 25 °C	 **4a**	 **4b**·$(THF)_n$	95, 23 (n = 0.75, 0)
4[a]	**4**	18 d, 25 °C	**4a**	 **4c**	62[b]
5[a]	**4**	24 h, 60 °C	**4a**	**4c**	67[b]
6	 **5**	7 days, 25 °C	 **5a** **5b**	 **5c**·$(THF)_2$	>99

[a] ^{1}H NMR experiment in $[D_8]$THF solution with 1 equiv **1** with respect to **4**. [b] Determined by ^{1}H NMR spectroscopy.

Apparently, once precipitated or dried under vacuum, **3b** becomes sparingly soluble.

Reduced reaction times resulted in incomplete conversion of **3a** to **3b** (1:0.7 and 1:1.4 after 3 and 6 h at 70 °C, respectively; note that **1** had already been consumed at these early stages).

A tentative explanation for the solubility properties of **3b** may be the distance between the metalation site and the nitrogen donor. In contrast to **2b** and **4b**, **3b** may form a coordination polymer in the solid state, which would preclude any intramolecular coordination of the calcium center to the nitrogen atom. Instead, intermolecular coordination leads to a tightly connected framework of units of **3b**, which is virtually insoluble in THF.

2,6-Lutidine (4): Reaction of bis(allyl)calcium with two equivalents of **4** led to bis[(6-methylpyridin-2-yl)methyl]calcium (**4b**), which was obtained in 95% yield after 24 h at 25 °C (Table 1, entry 3). In contrast to the other reported products, **4b** was isolated with a substoichiometric amount of THF (0.75 molecules per **4b**). When precipitated from the reaction mixture by the addition of a large excess of pentane, **4b** was obtained free from any donor molecules in 23% yield (Table 1, entry 3). Cooling a solution of **4b** in THF/pentane to −30 °C resulted in the formation of single crystals of **4b**·$(THF)_3$ suitable for X-ray structure determination (Figure 1).[27] When single crystals of **4b**·$(THF)_3$ were

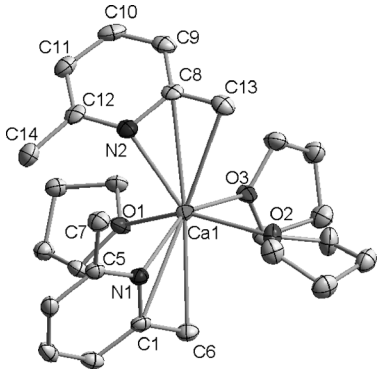


Figure 1. ORTEP drawing of the molecular structure of **4b**·$(THF)_3$. Thermal ellipsoids are shown at the 50% probability level. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and angles [°]: Ca1−N2 2.4331(19), Ca1−C8 2.858(2), Ca1−C13 2.813(3), C8−C13 1.373(4), C12−C14 1.501(3), Ca1−O1 2.4001(16); N2-C8-C13 117.5(2), N1-Ca1-N2 97.69(6), O1-Ca1-O2 149.70(6).

dried under argon at ambient pressure, rapid loss of one THF molecule per formula unit resulted in a powder of **4b**·$(THF)_2$. The observation that **4b**·$(THF)_n$ were isolated with $n = 0$, 0.75, 2, and 3 reflects a facile release of THF from the coordination sphere of **4b**. This process might be accompanied by a change of the coordination mode towards the η^3-aza-allyl lutidyl ligand.

In THF solution, a benzyl-type calcium complex with a metal-bound CH_2 group showing ^1H and ^{13}C NMR shifts at $\delta = 2.32$ and 55.79 ppm, respectively, is suggested. In the solid state, the molecular structure of **4b**·$(THF)_3$ shows an aza-allyl η^3-coordination mode of the N1-C1-C6 and N2-C8-C13 fragments of the 2,6-lutidine anionic ligands (Figure 1). The mesomerism of picolyl anions has been described previously and aza-allyl coordination by a doubly-activated β-diketiminato ligand to calcium has been discussed.[28,29] Figure 1 depicts a formally seven-coordinate calcium center. The bond lengths of 2.846(3) (Ca1–C6) and 2.813(3) Å (Ca1–C13) lie in the range of calcium–carbon bonds observed for the triglyme adduct of bis(η^3-allyl)calcium and exclude σ-bound carbanionic ligands.[24] The Ca1–N1 and Ca1–N2 bond lengths of 2.407(2) and 2.4331(19) Å are somewhat longer than those in **9a**·$(THF)_4$ (see below, Figure 2), but compare well with those observed for the amide bonds in the parent compounds $[Ca(NC_5H_5\text{-}4\text{-}C_3H_5)_2(py)_4]$ and $[Ca\{NC_5H_2\text{-}3,5\text{-}(CH_3)_2\text{-}4\text{-}C_3H_5\}_2(3,5\text{-lu})_4]$ (3,5-lu = 3,5-lutidine).[25] These observations indicate an aza-allyl coordination mode in the solid state rather than an anionic or enamide bonding of the anionic ligand. The C1-C6 (1.376(3) Å) and C8-C13 (1.373(4) Å) bond distances are indicative of significant double-bond character, as expected for a delocalized fragment. This is in contrast to the bond lengths observed for the non-activated methyl groups (C5–C7 1.499(3) Å, C12–C14 1.501(3) Å). Unlike in solution, the aromaticity of the pyridine ring is strongly perturbed in the solid state. For free 2,6-lutidine, $C(sp^2)$–$C(sp^2)$ bond lengths of 1.397(3) and 1.381(4) Å have been reported.[30] In contrast, alternating carbon–carbon bond lengths are observed for the C_5N ring in **4b**·$(THF)_3$ (C8-C9 1.438(3) Å, C9–C10 1.354(4) Å, C10–C11 1.413(4) Å, C11–C12 1.366(3) Å). This is consistent with the aza-allyl coordination mode, as depicted in Scheme 2. The calcium–oxygen bond lengths are

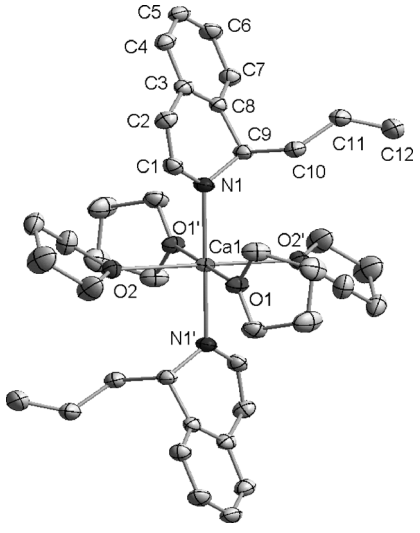
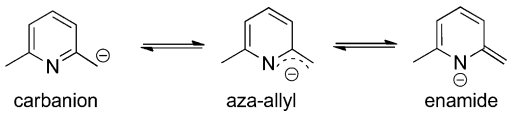


Figure 2. ORTEP drawing of the molecular structure of **9a**·$(THF)_4$. Thermal ellipsoids are shown at the 50% probability level. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and angles [°]: Ca1−N1 2.3777(12), Ca1−O1 2.3916(11), C10−C11 1.491(2), C11−C12 1.303(2); N1-Ca1-N1′ 180.0, O1-Ca1-O1′ 180.0, O1-Ca1-O2 87.54(4), C8-C9-C10 110.70(12), N1-C9-C10 108.37(12).

2.3957(16) Å (Ca1–O3), 2.4358(16) Å (Ca1–O2), and 2.4001(16) Å (Ca1–O1) and compare well with the Ca–O distances in **9a**·$(THF)_4$ (see Figure 2) and similar compounds.[31] The calcium center is drawn out of the O1-O2-O3 plane by 0.5928(4) Å. The related magnesium complex $[Mg(2\text{-}CH\{Si(CH_3)_3\}C_5H_4N)_2(HMPT)_2]$ (HMPT = hexamethyl phosphoric triamide), bearing a trimethylsilyl group at the benzylic position of 2-picoline, shows a clear enamide coordination mode. Disregarding the presence of neutral donor molecules, the observation of an aza-allyl fragment for **4b**·$(THF)_3$ is most likely the result of the much larger metal size and the preference of calcium to bind to delocalized anions.



Scheme 2. Mesomerism in the 2,6-lutidine anion.

The reaction of 2,6-lutidine (**4**) with **1** proceeds in distinct steps: while the monoactivated product **4b** is formed quantitatively, small amounts of the carbometalated intermediate **4a** can be observed in the ^1H NMR spectrum. Total depletion of **4** and **4a** then allows for the second C–H bond activation. Of course, residual $(C_3H_5)^-$ ligands are required for activation of the CH_3 group in **4b**. This was achieved by applying the corresponding stoichiometry of **1**/**4** = 1:1 (Table 1, entries 4 and 5). When **4b** was obtained by applying a stoichiometry of **1**/**4** = 1:2 at elevated temperatures, contamination with **4c** resulted from activation of the second C–H bond as a side reaction. The formation of **4c** was studied on the NMR scale by adjusting the stoichiometry (**4**/**1** = 1:1) in $[D_8]$THF (Table 1, entries 4 and 5). The reaction at 25 °C revealed the initial formation of monoactivated **4b** and the carbometalated intermediate **4a**, but not of **4c** (see the Supporting Information for a time–conversion plot). After **4** had been almost entirely consumed and **4b** had reached its peak concentration, the formation of **4c** was observed. Complete conversion of **4b** to **4c** could not be achieved, neither by extending the reaction time (18 days, Table 1, entry 4) nor by heating (60 °C, Table 1, entry 5). The yields from the former and latter reactions were 62 and 67%, respectively.

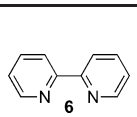
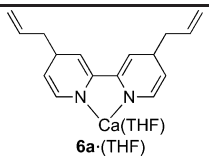
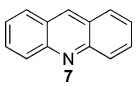
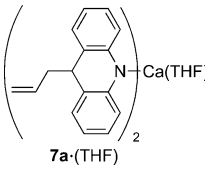
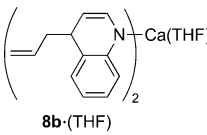
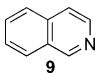
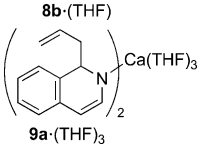
In contrast to the reaction of **1** with 2-picoline (**2**), the formation of the C–H bond activation product **4b** did not require heating. This difference in reactivity can be explained in terms of the unsubstituted *ortho* position in **2**. The insertion–rearrangement reaction (Scheme 1) to give **2a** proceeded smoothly, whereas for **4** the carbometalated intermediate **4a** could only be observed in trace amounts. Instead, the thermodynamically favored C–H bond activation and concomitant propene elimination easily occurred for **4** (to give **4b**) at ambient temperature. Long reaction times or heating are required for the isolation of **2b**. Evidently, **2a** is kinetically more favored than **4a**.

4-*tert*-Butylpyridine (5): The reaction of **1** with **5** was studied to evaluate the steric influence of a bulky *tert*-butyl group at the *para* position of the pyridine ring. As shown by in situ NMR experiments, the 2- and 4-carbometalated intermediates **5a** and **5b** were formed in the presence of the starting compounds. This equilibrium mixture resulted in the quantitative formation of the thermodynamically favored *ortho*-metalation product bis(4-*tert*-butylpyridin-2-yl)calcium (**5c**),[25] which was isolated as the dark purple bis(THF) adduct in quantitative yield (Table 1, entry 6). The reaction was carried out at 25 °C for 7 days to ensure complete conversion of all intermediates.

2,2′-Bipyridine (6): The reaction of **1** with one equivalent of 2,2′-bipyridine (**6**) afforded the doubly allylated, dearomatized product calcium 4,4′-diallyl-4*H*,4′*H*-(2,2′-bipyridine)-1,1′-diide (**6a**) in 98% yield (Table 2, entry 1). Similarly to the reaction of **1** with pyridine, a short reaction time of 30 min was sufficient for quantitative formation of the dark-red product. Since **6** has vacant 6,6′- but arylated 2,2′-positions, the proposed insertion–rearrangement sequence can easily proceed via the vacant sites. This results in rapid and clean formation of **6a**.

When the stoichiometry was changed to **6**/**1** = 2:1, a completely different product distribution of unknown composition was obtained. This contained propene as the product of

Table 2. Allylated insertion products from reactions of pyridine derivatives **6–9** with 0.5 equiv **1** in THF.

Entry	Substrate	Time, Temperature	Product	Yield [%]
1[a]	 **6**	0.5 h, 25 °C	 **6a**·(THF)	98
2	 **7**	0.5 h, 25 °C	 **7a**·(THF)	94
3[b]	 **8**	5 days, 25 °C	 **8b**·(THF)	>99
4	 **9**	0.5 h, 25 °C	 **9a**·$(THF)_3$	99

[a] 1 equiv **1** with respect to **6**. [b] The 2-allylated intermediate **8a** was identified during monitoring of this reaction by ^1H NMR spectroscopy.

C–H bond activation, and multiple σ-bound allyl fragments, as was evident from a ^{1}H NMR spectrum recorded in [D$_8$]THF. However, the number and shape of the signals did not allow for detailed analysis of the products formed in the reaction.

Acridine (7): The reaction of **1** with two equivalents of **7** in THF resulted in the clean formation of calcium 9-allyl-9*H*-acridin-10-ide (**7a**) in 94% yield after a reaction time of 30 min at 25°C (Table 2, entry 2). This product was isolated from the red reaction solution as a beige mono(THF) adduct by removing all volatiles under reduced pressure.

This reaction provides mechanistic information as both *ortho* positions are involved in an extended π-system. The previously proposed insertion/rearrangement sequence appears to be disfavored for acridine. Attack of the allyl nucleophile at a carbon atom attached to nitrogen would result in a strong disruption of the aromatic system. Direct transfer of the $(C_3H_5)^-$ ligand to the 9-position of acridine seems more plausible for the formation of **7a**.

Quinoline (8): Stirring combined solutions of **1** and **8** in THF for 5 days at 25°C afforded the expected insertion product calcium 4-allyl-4*H*-quinolin-1-ide (**8b**) as the mono(THF) adduct in quantitative yield (Table 2, entry 3). A long reaction time was applied after ^{1}H NMR studies revealed slow formation of **8b** from the 2-allylated intermediate **8a**. Apparently, **8a** displays a long lifetime in the reaction mixture. This might be explained in terms of a similar electron-deficient character of the 2- and 4-positions in **8**.[32] No indication of any migration of the allyl moiety to other positions, such as the annulated ring system, was observed.

Isoquinoline (9): The tris(THF) adduct of calcium 1-allyl-1*H*-isoquinolin-2-ide (**9a**) was obtained as an orange powder in 99% yield from the reaction of **1** with two equivalents of **9** after 30 min at 25°C (Table 2, entry 4). Again, the reaction proceeded with complete regioselectivity to afford the 1-allylated isoquinoline derivative. Single crystals of **9a**·(THF)$_4$ suitable for X-ray diffraction experiments were obtained from a cooled solution of **9a**·(THF)$_3$ in THF containing triglyme as an additive. To the best of our knowledge, **9a**·(THF)$_4$ is the first example of a structurally characterized 1-substituted and dearomatized isoquinoline derivative.

The molecular structure of **9a**·(THF)$_4$ in the solid state is shown in Figure 2. It features an octahedral coordination geometry around the calcium center.[27] Four THF donor ligands occupy the equatorial plane, whereas the apical positions are occupied by the anionic 1-allyl-1*H*-isoquinol-2-ide ligands. Due to crystallographic C_i symmetry, all *trans* angles are 180.0°. The bond lengths of Ca1–O1 (2.3916(11) Å) and Ca1–O2 (2.4148(10) Å) are similar and correspond well to those in other tetrakis(THF) adducts of organocalcium compounds.[31] The Ca1–N1 distance of 2.3777(12) Å is similar to the corresponding bond length in the related compound [Ca(NC$_5$H$_5$-4-C$_3$H$_5$)$_2$(py)$_4$].[25] The allylated positions exhibit distinct sp^3 character, as is evident from the angles about C9 (C8-C9-C10 110.70(12)°, N1-C9-C10 108.37(12)°, N1-C9-C8 112.39(12)°). One single (C10–C11 1.491(2) Å) and one double (C11–C12 1.303(2) Å) carbon–carbon bond can be observed in the allyl fragment. For the dearomatized N-heterocycle, the shortest carbon–carbon bond length of 1.373(2) Å can be observed for C1–C2, indicating a double bond at this position. The bond lengths within the annulated ring system range from 1.410(2) Å (C3–C8) to 1.380(2) Å (C4–C5) and lie in the typical range for aromatic carbon–carbon bonds. The ^{13}C NMR spectrum of **9a** in [D$_8$]THF solution displays two sets of signals for certain carbon atoms. This is attributed to the presence of two diastereomers. The non-stereoselective allylation of isoquinoline produces both enantiomers of the 1-allyl-1*H*-isoquinoline ligand. Therefore, homo- and heterochiral complexes of **9a** are formed, which undergo ligand exchange reactions in THF solution. However, the solid-state structure (Figure 2) shows only the centrosymmetric heterochiral (*meso*) complex. The other diastereomer (*rac*) was not found in the crystal structure.

For all of the products except **4b** and **9a**, attempted crystallizations from neat THF or THF/pentane mixtures were unsuccessful, presumably due to large amounts of loosely coordinated THF at the metal center. For **6a** in particular, a higher number than one THF was expected, as the bidentate 4,4′-diallyl-4*H*,4′*H*-(2,2′-bipyridine)-1,1′-diide ligand should leave the calcium center coordinatively unsaturated. The varying number of THF molecules at the metal center may suggest aggregation in the solid state. Depending on the method of isolation (crystallization or drying), these easily disrupted aggregates may be formed by long-range intermolecular interactions. This would increase the effective coordination number. In addition, a color change was observed depending on the presence or absence of an excess of donor solvent. While all of the reaction mixtures were orange to purple in color, isolated **7a**·(THF), **8b**·(THF), and **9a**·(THF)$_3$ were lighter colored.

In general, reactions of aromatic N-heterocycles with **1** give two classes of products: i) carbometalated and therefore dearomatized, and ii) C–H bond activated products with retained aromaticity. The reaction course is critically determined by the substitution pattern of the pyridine skeleton. The allyl ligand is smoothly transferred to electron-deficient carbon atoms in the α or γ position with respect to the nitrogen atom, as observed for pyridine, 3,5-lutidine,[25] 2,2′-bipyridine (**6**), acridine (**7**), quinoline (**8**), and isoquinoline (**9**). In this case, aromaticity is sacrificed for the formation of new C–C and Ca–N bonds. When somewhat more acidic CH$_3$ groups are present at the α or γ position, the allyl ligand acts as a base, generating propene and forming new Ca–C bonds. This was observed for 2-picoline (**2**), 4-picoline (**3**), and 2,6-lutidine (**4**). As carbometalated intermediates were frequently observed, the intramolecular C(sp^3)–H bond activation is accompanied by rearomatization. A C(sp^2)–H bond activation can be achieved by steric shielding of the γ position, as was demonstrated by the reaction of 4-*tert*-butylpyridine (**5**). This leads to ring-metalation with concomitant

release of propene. High thermodynamic stability of the carbometalated products or high activation barriers for C–H bond activation are demonstrated by a long reaction time for **5** and the persistence of intermediates **5a** and **5b** in the reaction mixture. This also holds for **2**–**4**, but to a much lesser extent. The transformations of carbometalated products giving C–H bond activated products may hint at reversibility of the initial insertion step. An indication of reversible pyridine functionalization by organoruthenium catalysts has recently been reported.[12e,33] Interestingly, allylic rearrangements at pyridine rings were described long ago for allylmagnesium halides, and were suggested to proceed via (intramolecular) Cope- and Claisen-like rearrangements.[21a–d,34] These reports are consistent with the reactivity patterns described in this contribution and our earlier work.[25]

Conclusion

A general procedure for the regioselective production of allylated and calciated pyridines and quinolines using bis(allyl)calcium (**1**) has been achieved. The simple protocol involves stirring a stoichiometric amount of **1** with the corresponding N-heterocycle in THF, removal of all volatiles, and washing of the air- and moisture-sensitive products. Due to essentially quantitative yields, side product formation or contamination of the products is minimal. Methyl groups at *ortho*- or *para*-positions on the N-heterocycle are easily metalated by **1** with concomitant release of propene, but dearomatized carbometalation products are formed exclusively in their absence.

Experimental Section

General considerations: All operations were performed under an inert atmosphere of argon using standard Schlenk-line or glove-box techniques. [D_8]THF was distilled under argon from sodium/benzophenone ketyl prior to use. D_2O was used as purchased. 2-Picoline (**2**), 4-picoline (**3**), 2,6-lutidine (**4**), 4-*tert*-butylpyridine (**5**), quinoline (**8**), and isoquinoline (**9**) were dried over CaH_2 and distilled under argon prior to use. 2,2′-Bipyridine (**6**) and acridine (**7**) were purified by vacuum sublimation. THF and pentane were purified using an MB SPS-800 solvent purification system. NMR spectra were recorded on a Bruker DRX400 spectrometer (^{1}H, 400.1 MHz; ^{13}C{^{1}H}, 100.6 MHz) at 25 °C unless otherwise stated. Chemical shifts in ^{1}H and ^{13}C{^{1}H} NMR spectra were referenced internally using the residual solvent resonances and are reported relative to tetramethylsilane. Due to extreme sensitivity, no elemental analyses could be performed. Instead, metal titration by the following procedure was applied. A portion of the product (10–30 mg) was dissolved in THF (0.5–1 mL) and hydrolyzed by slow addition of water. After the addition of 25% aqueous ammonia solution (1–2 mL), the total volume was increased to 20–30 mL by the addition of water. An indicator buffer tablet was dissolved and the solution was titrated with a 0.01 M solution of EDTA disodium salt until the transition point from red to green was observed.

[Ca(2-CH_2-C_5H_4N)$_2$(THF)] (2b·(THF)): A solution of 2-picoline (152 mg, 1.63 mmol) in THF (5 mL) was added to a stirred solution of [$Ca(C_3H_5)_2$] (**1**) (100 mg, 0.82 mmol) in THF (10 mL). Heating under reflux conditions for 3 h at 70 °C resulted in a color change from orange to dark red. After removal of all volatiles, washing with pentane, and drying under reduced pressure, the product was obtained as a dark red-brown, glossy powder (232 mg, 0.78 mmol, 96%). ^{1}H NMR (400 MHz, [D_8]THF, 25 °C): δ = 1.77 (m, 4H; THF), 2.37 (s, 4H; CH_2-Ca), 3.62 (m, 4H; THF), 5.08 (t, ^3J(H,H) = 5.9 Hz, 2H; CH-5), 5.83 (d, ^3J(H,H) = 9.0 Hz, 2H; CH-3), 6.23 (t, ^3J(H,H) = 7.6 Hz, 2H; CH-4), 7.11 ppm (d, ^3J(H,H) = 5.8 Hz, 2H; CH-6); ^{13}C{^{1}H} NMR (100 MHz, [D_8]THF, 25 °C): δ = 26.35 (THF), 55.32 (CH_2-Ca), 68.22 (THF), 98.76 (CH-5), 116.36 (CH-3), 132.73 (CH-4), 148.21 (C-2), 148.23 ppm (CH-6); metal analysis calcd (%) for $C_{20}H_{28}CaN_2O_2$ (368.53): Ca 8.68; found: Ca 8.84.

[Ca(4-CH_2-C_5H_4N)$_2$(THF)$_2$] (3b·(THF)$_2$): A solution of **3** (152 mg, 1.63 mmol) in THF (2 mL) was added to a stirred solution of **1** (100 mg, 0.82 mmol) in THF (8 mL). The reaction mixture was heated under reflux conditions for 18 h at 70 °C. A color change to black and the formation of a dark precipitate was observed. After removal of all volatiles, the product was washed first with pentane and then with THF (ca. 20 mL). Drying of the remaining solid under reduced pressure afforded the product as a light-brown powder (178 mg, 0.48 mmol, 59%). ^{1}H NMR (400 MHz, [D_8]THF, 25 °C): δ = 1.77 (m, 8H; THF), 2.84 (s, 4H; CH_2-Ca), 3.62 (m, 8H; THF), 5.26 (d, ^3J(H,H) = 6.2 Hz, 4H; CH-3,5), 6.32 ppm (br, 4H; CH-2,6); ^{13}C{^{1}H} NMR (100 MHz, [D_8]THF, 25 °C): δ = 26.55 (THF), 68.39 (THF), 71.79 (CH_2-Ca), 110.21 (CH-3,5), 141.69 (CH-2,6), 150.69 ppm (C-4); metal analysis calcd (%) for $C_{20}H_{28}CaN_2O_2$ (368.53): Ca 10.88; found: Ca 10.98.

[Ca(2-CH_2-C_5H_3N-6-CH_3)$_2$(THF)$_n$] (4b·(THF)$_n$; n = 0–1): Method a: A solution of **4** (263 mg, 2.45 mmol) in THF (3 mL) was added to a stirred solution of **1** (150 mg, 1.23 mmol) in THF (12 mL). The reaction mixture was stirred for 24 h at 25 °C, whereupon a color change from orange to red was observed. After removal of all volatiles, washing with pentane, and drying under reduced pressure, the product was obtained as a dark orange powder (n = 0.75, 356 mg, 1.16 mmol, 95%). ^{1}H NMR (400 MHz, [D_8]THF, 25 °C): δ = 1.78 (m, 3H; THF), 1.88 (s, 6H; CH_3), 2.32 (s, 4H; CH_2-Ca), 3.64 (m, 3H; THF), 5.11 (d, ^3J(H,H) = 6.3 Hz, 2H; CH-5), 5.76 (d, ^3J(H,H) = 8.5 Hz, 2H; CH-3), 6.28 ppm (dd, ^3J(H,H) = 6.5, 8.8 Hz, 2H; CH-4); ^{13}C{^{1}H} NMR (100 MHz, [D_8]THF, 25 °C): δ = 24.26 (CH_3), 26.22 (THF), 55.79 (CH_2-Ca), 68.20 (THF), 99.33 (CH-5), 112.66 (CH-3), 133.27 (CH-4), 156.19 (C-6), 165.18 (C-2); metal analysis calcd (%) for $C_{17}H_{22}CaN_2O_{0.75}$ (306.45): Ca 13.08; found: Ca 13.36.

Method b: A solution of **1** (50 mg, 0.41 mmol) in THF (4 mL) was added to a solution of **4** (88 mg, 0.82 mmol) in THF (1 mL). The reaction mixture was stirred at 25 °C for 24 h, which resulted in a darkening of the orange color. Pentane (50 mL) was added, whereupon a slight clouding was observed. Reducing the volume of this mixture to < 5 mL resulted in the precipitation of a yellow solid, which was isolated by filtration. After washing with pentane and drying under reduced pressure, the base-free product **4b** was obtained as a yellow powder (n = 0, 24 mg, 0.10 mmol, 23%). Single crystals of **4b**·(THF)$_3$ were obtained by cooling the combined filtrate and washings to −30 °C. The yield (47 mg, 0.12 mmol, 29%) is given for the bis(THF) adduct, **4b**·(THF)$_2$, as drying under argon at ambient pressure resulted in the rapid loss of one THF molecule per formula unit to give a powder instead of orange crystals. Metal analysis calcd (%) for $C_{14}H_{16}CaN_2$ (252.37): Ca 15.88; found: Ca 15.44.

During the course of the reaction, the insertion product **4a** and the double-activation product **4c** were observed in the NMR spectra. Spectroscopic data have been reported for **4a**.[25] Data for **4c** are given for in situ formed compound. **[Ca(2,6-CH_2-C_5H_3N)] (4c)**: ^{1}H NMR (400 MHz, [D_8]THF, 25 °C): δ = 2.04 (br, 4H; CH_2), 4.89 (br d, ^3J(H,H) = 8.3 Hz, 2H; CH-3,5), 6.10 ppm (t, ^3J(H,H) = 7.8 Hz, 1H; CH-4); ^{13}C{^{1}H} NMR (100 MHz, [D_8]THF, 25 °C): δ = 47.59 (br; CH_2), 93.92 (br; CH-3,5), 135.32 (CH-4), 168.10 ppm (C-2,6).

[Ca{2-C_5H_3N-4-C(CH_3)$_3$}$_2$(THF)$_2$] (5c·(THF)$_2$): A solution of 4-*tert*-butylpyridine (221 mg, 1.63 mmol) in THF (5 mL) was added to a solution of **1** (100 mg, 0.82 mmol) in THF (15 mL). The dark reaction mixture was stirred for 7 days at 25 °C. After removal of all volatiles, washing with pentane, and drying under reduced pressure, the product was obtained as a dark powder (373 mg, 0.82 mmol, > 99%). ^{1}H NMR (400 MHz, [D_8]THF, 25 °C): δ = 0.90 (s, 18H; CH_3), 1.77 (m, 8H; THF), 3.62 (m, 8H; THF), 4.09 (dd, ^3J(H,H) = 6.8 Hz, ^4J(H,H) = 1.8 Hz, 2H; CH-5), 5.29 (d, ^4J(H,H) = 1.3 Hz, 2H; CH-3), 6.55 ppm (d, ^3J(H,H) = 6.8 Hz, 2H; CH-

6); $^{13}C\{^1H\}$ NMR (100 MHz, [D$_8$]THF, 25 °C): δ = 26.37 (THF), 29.46 (CH_3), 33.99 (C), 68.20 (THF), 93.26 (CH-5), 110.31 (CH-3), 120.30 (C-2), 141.31 (C-4), 150.44 ppm (CH-6); metal analysis calcd (%) for $C_{26}H_{40}CaN_2O_2$ (452.69): Ca 8.85; found: Ca 8.61.

[Ca{4,4′-(C_3H_5)$_2$-($C_{10}H_8N_2$)}(THF)] (6a·(THF)): A solution of 2,2′-bipyridine (128 mg, 0.82 mmol) in THF (2 mL) was added to a solution of **1** (100 mg, 0.82 mmol) in THF (2 mL). After stirring for 30 min, all volatiles were removed under reduced pressure. After washing with pentane and drying under vacuum, the product was obtained as a dark red powder (281 mg, 0.80 mmol, 98 %). ^1H NMR (400 MHz, [D$_8$]THF, 25 °C): δ = 1.76 (m, 4H; THF), 1.98 (br t, ^3J(H,H) = 6.0 Hz, 4H; CH_2^{allyl}), 3.32 (br, 2H; CH-4,4′), 3.62 (m, 4H; THF), 3.89 (br d, ^3J(H,H) = 6.9 Hz, 2H; CH-5,5′), 4.34 (br, 2H; CH-3,3′), 4.85 (br m, 4H; =CH_2^{allyl}), 5.79 (m, 2H; CH^{allyl}), 6.30 ppm (br d, ^3J(H,H) = 7.0 Hz, 2H; CH-6,6′); $^{13}C\{^1H\}$ NMR (100 MHz, [D$_8$]THF, 25 °C): δ = 26.38 (THF), 37.56 (CH-4,4′), 50.04 (CH_2^{allyl}), 68.22 (THF), 92.42 (CH-3,3′), 96.52 (CH-5,5′), 114.11 (=CH_2), 138.99 (CH^{allyl}), 139.39 (CH-6,6′), 150.07 ppm (C-2,2′); metal analysis calcd (%) for $C_{20}H_{26}CaN_2O$ (350.51): Ca 11.43; found: Ca 10.93.

[Ca(9-C_3H_5-$C_{13}H_9N$)$_2$(THF)] (7a·(THF)): A solution of acridine (293 mg, 1.64 mmol) in THF (1 mL) was added to a stirred solution of **1** (100 mg, 0.82 mmol) in THF (1 mL). The resulting dark red reaction mixture was stirred for 30 min at 25 °C. After removal of all volatiles, washing with pentane, and drying under reduced pressure, the product was obtained as a beige powder (422 mg, 0.76 mmol, 94 %). ^1H NMR (400 MHz, [D$_8$]THF, 25 °C): δ = 1.77 (m, 4H; THF), 2.21 (t, ^3J(H,H) = 7.1 Hz, 4H; CH_2^{allyl}), 3.62 (m, 4H; THF), 3.87 (t, ^3J(H,H) = 6.7 Hz, 2H; CH-9), 4.80 (m, 4H; =CH_2^{allyl}), 5.76 (m, 2H; CH^{allyl}), 6.41 (t, ^3J(H,H) = 7.3 Hz, 4H; CH-2,7), 6.61 (d, ^3J(H,H) = 7.3 Hz, 4H; CH-1,8), 6.78 (t, ^3J(H,H) = 7.4 Hz, 4H; CH-3,6), 6.86 ppm (d, ^3J(H,H) = 7.4 Hz, 4H; CH-4,5); $^{13}C\{^1H\}$ NMR (100 MHz, [D$_8$]THF, 25 °C): δ = 26.37 (THF), 45.90 (CH-9), 46.39 (CH_2^{allyl}), 68.21 (THF), 115.62 (=CH_2^{allyl}), 116.07 (CH-2,7), 116.65 (CH-1,8), 125.69 (CH-3,6), 127.10 (CH-4,5), 129.73 (C-8a,9a), 138.69 (CH^{allyl}), 151.99 ppm (C-4a,10a); metal analysis calcd (%) for $C_{36}H_{36}CaN_2O$ (552.76): Ca 7.25; found: Ca 7.30.

[Ca(4-C_3H_5-C_9H_7N)$_2$(THF)] (8b·(THF)): A solution of quinoline (212 mg, 1.64 mmol) in THF (1 mL) was added to a stirred solution of **1** (100 mg, 0.82 mmol) in THF (2 mL). The dark orange mixture was stirred for 5 days at 25 °C. After removal of all volatiles, washing with pentane, and drying under reduced pressure, the product was obtained as an orange powder (370 mg, 0.82 mmol, >99 %). ^1H NMR (400 MHz, [D$_8$]THF, 25 °C): δ = 1.77 (m, 4H; THF), 2.12 (m, 4H; CH_2^{allyl}), 3.62 (m, 4H; THF), 3.64 (m, 2H; CH-4), 4.02 (dd, ^3J(H,H) = 4.3, 7.4 Hz, 2H; CH-3), 4.82 (m, 4H; =CH_2^{allyl}), 5.82 (m, 2H; CH^{allyl}), 6.26 (td, ^3J(H,H) = 7.3 Hz, ^4J(H,H) = 1.2 Hz, 2H; CH-6 or 7), 6.28 (d, ^3J(H,H) = 7.0 Hz, 2H; CH-5 or 8), 6.36 (d, ^3J(H,H) = 7.5 Hz, 2H; CH-2), 6.62 (dd, ^3J(H,H) = 7.0 Hz, ^4J(H,H) = 1.6 Hz, 2H; CH-8 or 5), 6.65 ppm (td, ^3J(H,H) = 7.5 Hz, ^4J(H,H) = 1.5 Hz, 2H; CH-7 or 6); $^{13}C\{^1H\}$ NMR (100 MHz, [D$_8$]THF, 25 °C): δ = 26.41 (THF), 40.00 (CH-4), 49.02 (CH_2^{allyl}), 68.37 (THF), 92.46 (CH-3), 114.39 (=CH_2^{allyl}), 115.49 (CH-6 or 7), 118.48 (CH-2), 124.77 (C-4a), 125.48 (CH-5 or 8), 129.45 (CH-7 or 6), 138.95 (CH^{allyl}), 139.23 (CH-8 or 5), 152.71 ppm (C-8a); metal analysis calcd (%) for $C_{29}H_{32}CaN_2O$ (452.64): Ca 8.85; found: Ca 8.02.

[Ca(1-C_3H_5-C_9H_7N)$_2$(THF)$_3$] (9a·(THF)$_3$): A solution of isoquinoline (212 mg, 1.64 mmol) in THF (1 mL) was added to a stirred solution of **1** (100 mg, 0.82 mmol) in THF (2 mL). The dark red mixture was stirred for 30 min. After removal of the solvent under reduced pressure, washing with pentane, and drying in vacuum, the product was obtained as an orange powder (484 mg, 0.81 mmol, 99 %). Single crystals of **9a**·(THF)$_4$ were obtained in low yield from a cooled 0.13 M solution of **9a**·(THF)$_3$ in THF to which 1 equiv of triglyme had been added. The ^{13}C NMR spectrum displayed two distinct resonances for certain carbon atoms (marked with *). These were attributed to the presence of two diastereomers of the product complex. ^1H NMR (400 MHz, [D$_8$]THF, 25 °C): δ = 1.77 (m, 12H; THF), 1.83 (m, 2H; CH_2^{allyl}), 2.80 (m, 2H; CH_2^{allyl}), 3.62 (m, 12H; THF), 4.26 (m, 2H; CH-1), 4.74 (m, 4H; =CH_2^{allyl}), 4.80 (d, ^3J(H,H) = 6.1 Hz, 2H; CH-4), 5.64 (m, 2H; CH^{allyl}), 6.46 (d, ^3J(H,H) = 7.5 Hz, 2H; CH-5 or 8), 6.48 (td, ^3J(H,H) = 7.3 Hz, ^4J(H,H) = 1.0 Hz, 2H; CH-6 or 7), 6.56 (d, ^3J(H,H) = 6.6 Hz, 2H; CH-3), 6.72 ppm (m, 4H; CH-8 or 5 and 7 or 6); $^{13}C\{^1H\}$ NMR (100 MHz, [D$_8$]THF, 25 °C): δ = 26.54 (THF), 39.54 (CH_2^{allyl}), 39.59 (CH_2^{allyl*}), 63.02 (CH-1), 63.05 (CH-1*), 68.39 (THF), 88.99 (CH-4), 113.98 (=CH_2^{allyl}), 118.82 (CH-5–8), 119.28 (CH-5–8), 125.98 (CH-5–8), 126.38 (CH-3), 126.41 (CH-3*), 126.47 (C-4a or 8a), 126.52 (C-4a* or 8a*), 139.06 (C-8a or 4a), 139.07 (C-8a* or 4a*), 140.06 (CH-10), 140.10 (CH-10*), 149.17 (CH-5–8), 149.20 ppm (CH-5*–8*); metal analysis calcd (%) for $C_{36}H_{48}CaN_2O_3$ (596.86): Ca 6.71; found: Ca 6.68.

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