Use of (NHC)Pd(η³-allyl)Cl (NHC = *N*-Heterocyclic Carbene) in a Palladium-mediated Approach to *Cryptocarya* Alkaloids

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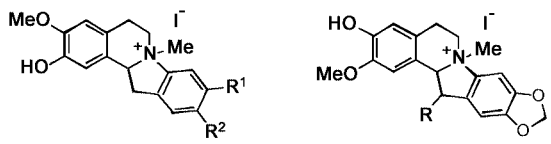
Abstract: The palladium-mediated intramolecular aryl amination of 7-benzyloxy-1-(2-bromo-4,5-dimethoxy-benzyl)-1,2,3,4-tetrahydro-6-methoxy-isoquinoline catalyzed by a recently discovered, air and moisture stable (NHC)Pd(η³-allyl)Cl (NHC = *N*-heterocyclic carbene) complex provides 2-benzyloxy-5,6,12,12a-tetrahydro-3,9,10-trime-thoxydibenz-[*b*,*g*]-indolizine in high yield. Effects of the solvent, the catalyst loading and the nature of the NHC-ancilliary ligand on the efficacy of the reaction were examined. Using identical conditions 7-benzyloxy-1-(2-chloro-4,5-methylendioxybenzyl)-1,2,3,4-tetrahydro-6-methoxyisoquinoline leads to 2-benzyloxy-5,6-12,12a-tetrahydro-3-methoxy-9,10-methylendioxydibenz-[*b*,*g*]-indolizine, also in high yield. Use of the catalytic intramolecular aryl amination step allows for the straightforward synthesis of the alkaloids *rac*-cryptaustoline and *rac*-cryptowoline.

Keywords: Pd-mediated aryl amination, *N*-heterocyclic carbene, dibenzopyrrocoline-alkaloids

The dibenzopyrrocoline-alkaloids cryptaustoline **1** and cryptowoline **2** (Figure 1) were isolated from the bark of *cryptocarya bowiei*.[1a] The plant, found in northern New South Wales and southern Queensland, varies in size from a small shrub to a tree of about 9 m high.[1a] Whereas the northern plant contains only cryptaustoline, the southern species contains cryptowoline as the main alkaloid.[1a] Historically these alkaloids appeared to be the only dibenzopyrrocoline-alkaloids in existence, until 1988, when Moskowitz[1b] isolated two additional alkaloids of this class. Cryptowolinol **4**, was isolated from *Cryptocarya Phyllostemon* and *Cryptocarya Oubatchensis*, two related plants from New Caledonia and the New Hebrides. Cryptowolidine **3** was reported to occur only in *Cryptocarya Phyllostemon.* In addition to a curare-like paralytic action,[1a] the alkaloids are reported to have antileukemic and antitumor properties.[2,3]



1: cryptaustoline $R^1 = R^2 = OMe$ **3**: cryptowolidine R = H
2: cryptowoline $R^1 = R^2 = OCH_2O$ **4**: cryptowolinol R = OH

Figure 1 Cryptacarya alkaloids

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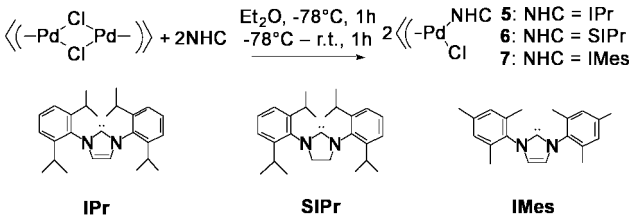
The ammonium salts of these compounds are known to enhance therapeutic activity.[2,3] Several methods for the total synthesis of these alkaloids have been developed since their isolation. The first total synthesis of Kametani[1] was an excellent general approach but suffered from a low yield. Application of an enamine photocycization,[2] a silicon-mediated approach,[3] and a radical cyclization[4] are known. An intramolecular cyclization of a formamidine by *s*-BuLi lead to the first asymmetric route to the dibenzopyrrocoline alkaloids.[5] An intramolecular cyclization of 1-(2′-bromobenzyl)-3,4-dihydroisoquinoline in the presence of K_2CO_3 in boiling THF was reported recently.[6] A transition metal-mediated approach has not been reported to date. In the course of studies dealing with transition metal *N*-heterocyclic carbene (NHC) complexes and their applications to organic synthesis, we have recently synthesized a number of air- and moisture-stable palladium-NHC catalysts[7–9] easily prepared from $[(\eta^3\text{-allyl})PdCl]_2$ and an NHC in Et_2O[11] most of these (NHC)Pd(η³-allyl)Cl complexes are obtained in high yield[11] and prove to have high catalytic activity in a number of coupling reactions. One such successful use of these catalysts is in the aryl amination[10a,b] reaction (Buchwald–Hartwig reaction).

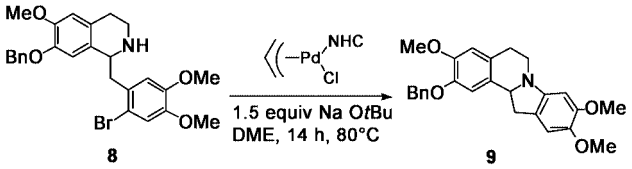


Scheme 1 (NHC)Pd(η³-allyl)Cl complexes

The aryl amination reaction catalyzed by the (NHC)Pd(η³-allyl)Cl complexes tolerates a wide variety of functional groups and most aryl halides are usually converted to the corresponding anilines in high yield.[12] (SIPr)Pd(η³-allyl)Cl **6** (Scheme 1) proved to be the best catalyst for the intermolecular aryl amination[12] being capable of catalyzing some reactions at room temperature with a reasonable rate. In order to test our catalysts for this transformation, we chose **8** as a precursor for an alkaloid from the *Cryptocarya Bowiei* family.

Previous results with these Pd-NHC catalysts encouraged us to test a palladium-mediated intramolecular aryl-amination of **8** to **9** expecting no interference with functional

groups on **8**. The 7-benzyloxy-1-(2-bromo-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-6-methoxyisoquinoline[4] (**8**) was prepared according the procedure of Moskowitz.[1b] We then applied the (NHC)Pd(η³-allyl)Cl catalysts to the palladium-mediated intramolecular aryl-amination of **8** to **9**. (Scheme 2).



Scheme 2 Intramolecular aryl-amination leading to **9**

We first examined the effects of the catalyst loading and the nature of the NHC ancillary ligand on the reaction. Heating a solution of 0.23 mmol of the bromotetrahydroisoquinoline **8** in 2 mL of DME with 1.5 equivalents of *t*-BuONa and 0.02 equivalent of (IPr)Pd(η³-allyl)Cl **5** to 80 °C for 14 hours produced the indolizine **9** in a yield of 48%. Increasing the catalyst loading under the same reaction conditions to 0.04 equivalent resulted in a yield of 70%. A catalyst loading of 0.06 equivalent resulted in essentially no change. The use of (SIPr)Pd(η³-allyl)Cl **6** as catalyst gave only 57% at a catalyst loading of 0.02 equivalent and 0.04 equivalent. Using 0.06 equivalent of **6**, 64% of the indolizine **9** was obtained. The (IMes)Pd(η³-allyl)Cl **7** gave the best results of 88% of **9** at a catalyst loading of 0.06 equivalent. Whereas **6** proved to be the best catalyst in the intermolecular aryl-amination,[11,12] **7** was found to be best catalyst for the intramolecular aryl-amination of **8** to **9**. This can possibly be explained by the smaller steric hindrance of the aryl substituents of **7** resulting in the smaller repulsive interaction with the bulky substituents attached to the reaction center compared to a more sterically encumbered situation in **6**.

We then examined the effect of the solvent on the reaction. Heating 0.23 mmol of the bromotetrahydroisoquinoline **8** with 1.5 equivalents of *t*-BuONa and 0.06 equivalent of **7** in 2 mL of DME to 80 °C for 14 hours produced indolizine **9** in a yield of 88%. When the reaction is performed in toluene under the same conditions, the product is obtained in quantitative yield. To confirm the identity of **9**, single crystals were obtained by slow cooling a hot saturated solution of **9** in degassed EtOH. Results of the X-ray diffraction study are presented in Figure 2 where the ORTEP confirms the identity and structure of **9**.

Having succeeded with the intramolecular aryl-amination of 7-benzyl-1-(2-bromo-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-6-methoxyisoquinoline (**8**), we attempted to perform an intramolecular arylamination of 7-benzyloxy-1-(2-chloro-4,5-methylen-dioxybenzyl)- 1,2,3,4-tetrahydro-6-methoxyisoquinoline (**10**) (Scheme 3) in order to achieve a palladium-mediated approach to cryptowoline **2**. (Figure 1)

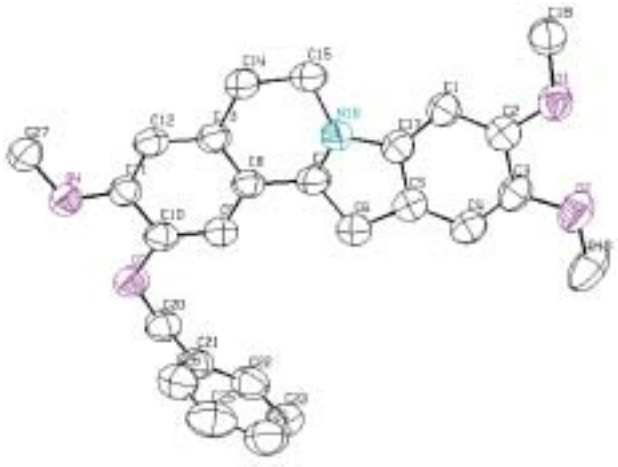
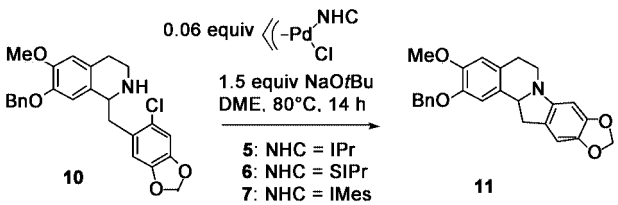


Figure 2 ORTEP of **9**. Hydrogens have been removed for clarity

The chlorotetrahydroisoquinoline **10** was prepared according to the procedure of. Moskowitz.[1b] First, we examined the effect of the nature of the NHC-ancilliary ligand on the reaction. (Table 1)

Heating 0.23 mmol of the chlorotetrahydroisoquinoline **10** with 1.5 equivalents of NaO*t*-Bu and 0.06 equivalent of **5** in 2 mL DME to 80 °C for 14 hours produced the indolizine **11** in a 60% yield. The use of 0.06 equivalent of **6** resulted in a yield of only 56%. Compound **7** was found to be the best catalyst, producing **11** in 83%yield. This result was shown to be consistent with the aryl amination of **8** to **9**, **7** seems to be the best catalyst for the intramolecular aryl-amination resulting in the formation of a sterically demanding five-membered ring heterocyclic structure. Using toluene as a solvent increased the yield to 99%. The solvent effect of this reaction, almost in agreement with the intramolecular ring-closing aryl-amination of **8** to **9**,



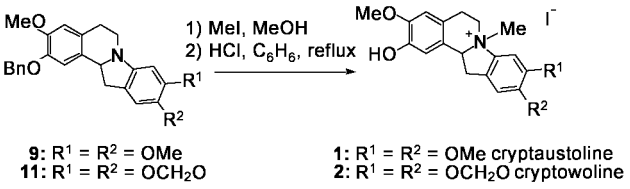
Scheme 3 Intramolecular aryl amination of **10**

Table 1 Effect of the Carbene and the Solvent in the Pd-mediated Arylamination of **10**

Catalyst	Solvent	mMol calatyst 9 mmol (mmol)(equiv)	Yield(%)
5	DME	0.06	60
6	DME	0.06	56
7	DME	0.06	83
7	Toluene	0.06	99

might lead one to assume that a less polar transition state is involved in the rate-determining step of the catalytic cycle. Attempts to lower the catalyst loading, the reaction temperature or the reaction time did lead to product formation but in lower yields.

Conversion of the two indolizines **9** and **11** to the corresponding alkaloids according to the procedure of Kametani[4] results in the first formal synthesis of *rac*-cryptaustoline[4] **1** and *rac*-cryptowoline[4] **2** involving a critical palladium-mediated step (Scheme 4).



Scheme 4 Conversion of **9** and **11** to the alkaloids **1** and **2**

The application of a (NHC)Pd(η^3-allyl)Cl complex to the palladium-mediated intramolecular ring-closing arylamination of 7-benzyloxy-1-(2-bromo-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-6-methoxyisoquinoline (**8**) and 7-benzyloxy-1-(2-chloro-4,5-methy-len-dioxybenzyl)-1,2,3,4-tetrahydro-6-methoxyisoquinoline (**10**) resulting in the formation of 2-benzyloxy-5,6,12,12a-tetrahydro-3,9,10-trimethoxydibenz-[*b*,*g*]-indolizine (**9**) and 2-benzyloxy-5,6,12,12a-tetrahydro-3-methoxy-9,10-methylendioxydibenz-[*b*,*g*]-indolizine (**11**)**,** respectively demonstrates the usefulness of such catalyst in alkaloid total synthesis. Whereas **6** was proven recently to be the best catalyst for intermolecular aryl-amination, **7** proved to be the superior catalyst in the two intramolecular arylamination reactions presented here. One possible explanation for these results can be the lower steric hindrance of the NHC-ancilliary ligand (IMes vs. IPr and SIPr) of the catalyst, resulting in the less sterically crowded reactive center. This hypothesis is presently being tested on even less sterically demanding NHC in the (NHC)Pd(η^3-allyl)Cl system. Toluene was shown to be the best solvent for the reaction resulting in quantitative yields. The solvent effect suggests a possible involvement of a low polarity transition state in the rate-determining step of the catalytic cycle. Transformation of the two indolizine-structures by straightforward methods leads to the formal synthesis of two alkaloids from *Cryptocarya Bowiei*, *rac*-cryptaustoline and *rac*-cryptowoline.

Acknowledgment

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References

(1) (a) Ewing, J.; Hughes, G. K.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1953**, *6*, 78. (b) Moskowitz, H.; Leboeuf, M.; Care, A.; Ranaivo, A. *Can. J. Chem.* **1989**, *67*, 947.
(2) Ambros, A.; von Angerer, A.; Wiegrebe, W. *Arch. Pharm. (Weinheim, Ger.)* **1988**, *321*, 481.
(3) Ambros, A.; von Angerer, A.; Wiegrebe, W. *Arch. Pharm. (Weinheim, Ger.)* **1988**, *321*, 743.
(4) Kametani, T.; Ogasawara, K. J. *J. Chem. Soc.* **1967**, *21*, 2208.
(5) Ninomiya, I.; Yasui, J.; Kiguchi, T. *Heterocycles* **1977**, *6*, 1855.
(6) Takano, S.; Satoh, S.; Ogasawara, K. *Heterocycles* **1987**, *26*, 1483.
(7) Yasuda, S.; Hirasawa, T.; Yoshida, S.; Hanaoka, M. *Chem. Pharm. Bull.* **1989**, *37*, 1682.
(8) Sielecki Thais, M.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 3673.
(9) Orito, K.; Harada, R.; Uchiiti, S.; Tokuda, M. *Org. Lett.* **2000**, *2*, 1799.
(10) (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J. F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (b) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852. (c) Viciu, M. S.; Kissling, R. M.; Stevens, E. D.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 2229.
(11) Viciu, M. S.; Germaneau, R. F.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 4053.
(12) Viciu, M. S.; Germaneau, R. F.; Navarro-Fernandez, O.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2002**, *21*, 5470.