Natural Product Synthesis

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Palladium-Catalyzed Decarboxylative Vinylation of Potassium Nitrophenyl Acetate: Application to the Total Synthesis of (±)-Goniomitine**

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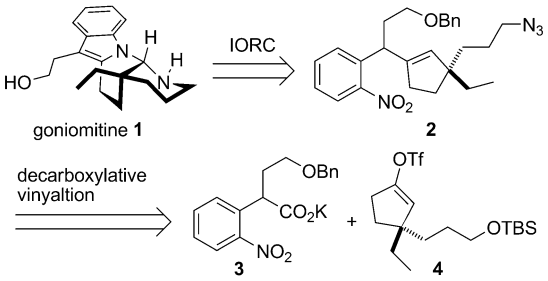
The class of monoterpene indole alkaloids, which is currently comprised of more than 2000 members with broad structural diversity and important bioactivities, has fascinated scientists for over a century.[1] Goniomitine (**1**), a unique member of the aspidosperma alkaloid family, was isolated from the root bark of *Gonioma malagasy* by Husson and co-workers in 1987.[2] The unprecedented octahydroindolo[1,2-*a*][1,8]naphthyridine skeleton, together with a tryptophol moiety, rather than the normal tryptamine fragment, resulted from the oxidative skeletal rearrangement of vincadifformine. The interesting molecular architecture and anti-proliferative activity of this natural product have made it a popular synthetic target.[3] To date, five total syntheses have been reported from the groups of Takano,[4] Pagenkopf,[5] Waser,[6] Mukai,[7] and Bach[8] Although building 2,3-difunctionalized indole followed by the stepwise formation of rings C and D is a common feature of these syntheses, the synthetic routes have been significantly shortened since the inaugural 28 step synthesis of Takano in 1991, thanks to the development of new reactions and strategies for the construction of the key 2,3-disubstituted indoles.

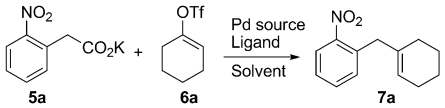
In connection with our continuous interest in the total synthesis of indole alkaloids by late-stage construction of the indole nucleus,[9,10] we thought to build the whole tetracyclic scaffold of goniomitine from functionalized cyclopentene **2** by a one-pot integrated oxidation/reduction/cyclization (IORC) sequence (Scheme 1).[11] Although different multi-step syntheses of **2** could be envisaged,[9d] the as-yet unknown direct decarboxylative coupling of two readily accessible building blocks (the substituted potassium salt of *o*-nitrophenyl acetate **3** and vinyl triflate **4**) was deemed to be the method of choice. This strategy, if realized, would allow us to accomplish the total synthesis of goniomitine in only two operations from the simple building blocks **3** and **4**.

The transition-metal-catalyzed decarboxylative coupling of carboxylic acids (especially aryl, alkenyl, and alkynyl carboxylic acids) has attracted much attention in recent years.[12] Although the intramolecular decarboxylative allylation/benzylation of nitrophenyl acetates[13] and the intermolecular arylation of nitrophenyl acetates are known,[14] we noticed that vinyl triflates have never been employed as coupling partners in decarboxylative couplings with aliphatic carboxylic acids.[15] We began our studies by examining the decarboxylative coupling of potassium 2-nitrophenylacetate (**5a**) with cyclohex-1-en-1-yl trifluoromethanesulfonate (**6a**). As shown in Table 1, only the protiodecarboxylation product



Scheme 1. Retrosynthesis of goniomitine.

Table 1: Survey of reaction conditions for the decarboxylative coupling reaction.[a]



Entry	Pd source	Ligand	Solvent	Yield [%][b]
1[c]	[{PdCl(allyl)}$_2$]	X-Phos	mesitylene	–
2	[{PdCl(allyl)}$_2$]	X-Phos	mesitylene	–
3	[{PdCl(allyl)}$_2$]	X-Phos	diglyme	63
4	**[{PdCl(allyl)}$_2$]**	**X-Phos**	**DMF**	**77(90)**[d]
5[e]	[{PdCl(allyl)}$_2$]	X-Phos	DMF	45
6	[{PdCl(allyl)}$_2$]	S-Phos	DMF	71
7	[{PdCl(allyl)}$_2$]	*t*Bu$_3$P·HBF$_4$	DMF	43
8	[{PdCl(allyl)}$_2$]	Cy$_3$P·HBF$_4$	DMF	58
9	[{PdCl(allyl)}$_2$]	Cy-JohnPhos	DMF	60
10	[{PdCl(allyl)}$_2$]	XantPhos[f]	DMF	51
11	[PdCl$_2$(dppf)]$_2$[g]	–	DMF	54
12	[Pd(Ph$_3$P)$_4$][g]	–	DMF	66

[a] Reaction conditions: **5a** (0.12 mmol), **6a** (0.1 mmol), Pd source (2.0 mol%), ligand (6.0 mol%), in the given solvent (*c* 0.2 M) at 100°C for 2 h. [b] Yield of isolated product. [c] Run at 150°C. [d] Using **6a** (1.5 equiv). [e] Run at 40°C for 16 h. [f] 3.0 mol%. [g] 4.0 mol%. Cy-JohnPhos = (2-biphenyl)dicyclohexylphosphine, diglyme = diethylene glycol dimethyl ether, dppf = 1,1′-bis(diphenylphosphino)ferrocene, S-Phos = 2-dicyclohexylphosphino-2′,6′-dimethyoxylbiphenyl, XantPhos = 4,5-bis(diphenylphophino)-9,9-dimethylxanthene, X-Phos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.

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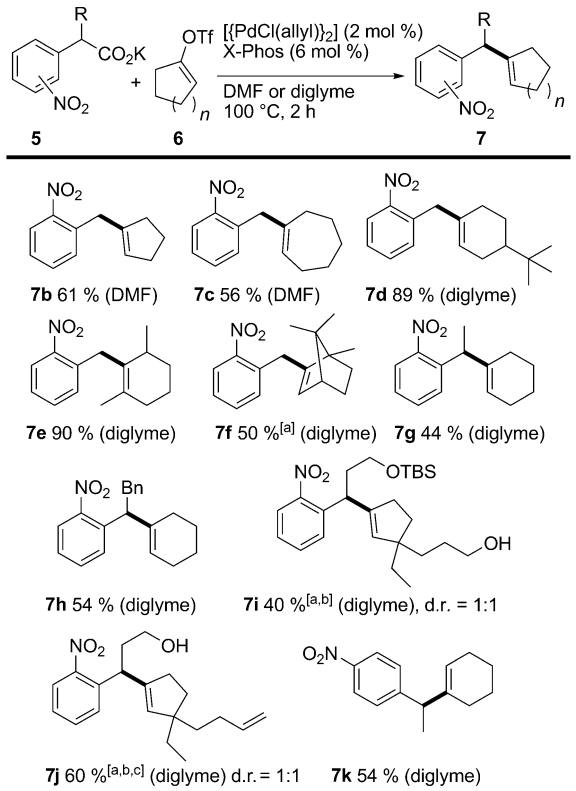
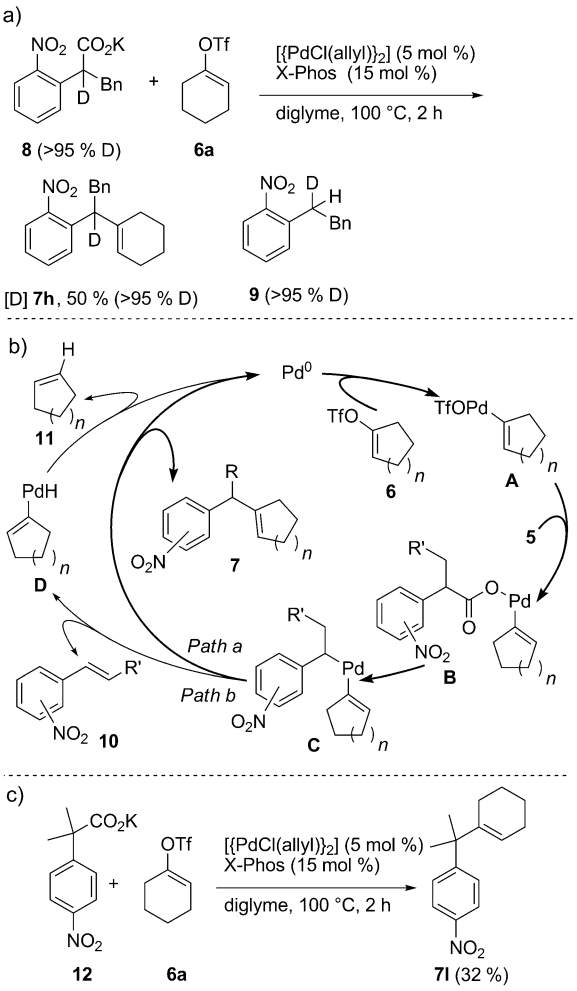
was obtained when the reaction was performed in mesitylene at 150 °C in the presence of [{PdCl(allyl)}$_2$] and X-Phos (entry 1).[14] Lowering the reaction temperature to 100 °C did reduce the rate of the protiodecarboxylation process, but failed to produce the desired cross-coupling product. It was subsequently found that solvent played an important role in this coupling reaction. By simply switching the solvent to diglyme (entry 3) or DMF (entry 4), the cross-coupling product **7a** was isolated in yields of 63% and 77%, respectively. The yield of **7a** was further increased to 90% by using an excess of vinyl triflate (1.5 equiv, entry 4). Even at 40 °C, the reaction proceeded in DMF to provide **7a** in 45% yield, although a longer reaction time (16 h) was needed (entry 5). Both monodentate and bidentate phosphine ligands were effective in the coupling reaction (entries 6–12). Nevertheless, X-Phos stood out as the ligand of choice for the present coupling reaction.

The scope of this reaction was then explored by varying the carboxylates and vinyl triflates used under the optimized conditions: [{PdCl(allyl)}$_2$] (2.0 mol%), X-Phos (6.0 mol%), DMF or diglyme, $c = 0.2$ M, 100 °C, 2 h (Scheme 2). The reaction worked well with cyclopentenyl, cyclohexenyl, and cycloheptenyl triflates, whereas only a trace amount of the coupling product was detected with cyclooctenyl triflate. When sterically congested vinyl triflates were used as coupling partners, diglyme proved to be a better solvent than DMF (**7e** and **7f**). The α-alkylated nitrophenyl acetates participated in the reaction to provide the cross-coupling products (**7g**–**7k**) in good yields. Functional groups such as free hydroxy groups, *tert*-butyldimethylsilyl (TBS) ethers, and double bonds, were tolerated. No diastereoselectivity was observed in the coupling of α-alkylated nitrophenyl acetates with chiral vinyl triflates, which could have important mechanistic implications. The *para*-nitrophenyl acetate can also be used as a coupling partner to produce the vinylated product **7k** in 54% yield.

Mechanistically, decarboxylation could occur either before[16] or after the formation of the C_{sp^3}–C_{sp^2} bond. To gain insight into the reaction pathway, a deuterium labeling experiment was performed. The reaction of vinyl triflate **6a** with potassium 2-deuterium-2-(2-nitrophenyl)-3-phenylpropanoate (**8**; >95% D) under standard conditions afforded the coupling product [D]**7h** in 50% yield (>95% D) together with the protiodecarboxylated product **9** (>95% D, Scheme 3a). The full preservation of deuterium in both [D]**7h** and **9** indicated that the α-vinylation of **8** through its



Scheme 2. Reaction scope of the decarboxylative coupling. General conditions: **5** (0.30 mmol), **6** (0.45 mmol), [{PdCl(allyl)}$_2$] (2.0 mol%), X-Phos (6.0 mol%), 100 °C, 2 h, under argon, in the indicated solvent (1.5 mL, 0.2 M). Yields shown are of product after flash column chromatography. [a] **5** (0.36 mmol), **6** (0.30 mmol) were used. [b] [{PdCl(allyl)}$_2$] (5.0 mol%) and X-Phos (15.0 mol%) were used. [c] Yield obtained after in situ deprotection of the TBS ether by TBAF (2.0 equiv) at room temperature for 4 h. TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonate.



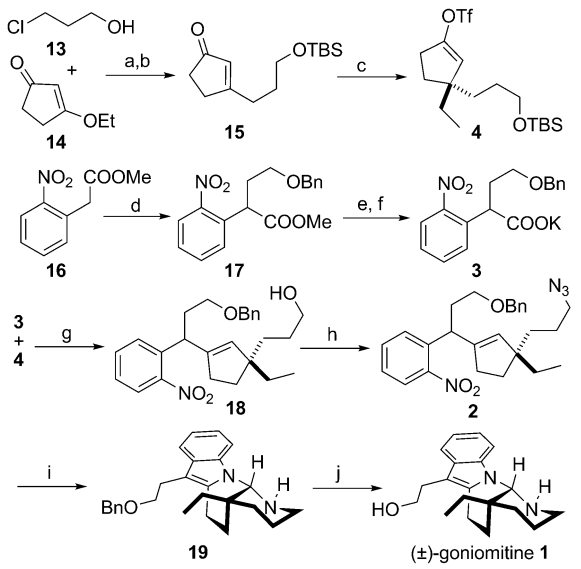
Scheme 3. Proposed mechanism and supportive evidence.

enolate form[17] followed by decarboxylation was not involved in the present catalytic process.

Based on these experimental observations, a possible reaction mechanism is depicted in Scheme 3b. Oxidative addition of vinyl triflate to the Pd^0 generated in situ affords vinyl palladium(II) **A** which, upon ligand exchange with the potassium salt, affords the carboxylic-acid-ligated intermediate **B**. Reductive elimination from intermediate **C** (Path a), which is generated after extruding CO_2 from **B**, then furnishes the desired coupling product **7**.

The following experimental results provided further support to the proposed mechanism. First, a small amount (ca. 6%) of reduction products **10** and **11**, which result from β-hydride elimination from intermediate **C** (Path b) were isolated. That reductive elimination from **C** leading to **7** prevailed over β-hydride elimination under our reaction conditions is remarkable considering that there were no obvious structural constraints in **C** to retard the latter process. Second, the reaction of potassium 2-methyl-2-(4-nitophenyl)-propanoate (**12**) with vinyl triflate **6a** afforded the cross-coupling product **7l** (32% yield, Scheme 3c), thus indicating that the C–C bond formation occurred after the extrusion of CO_2.

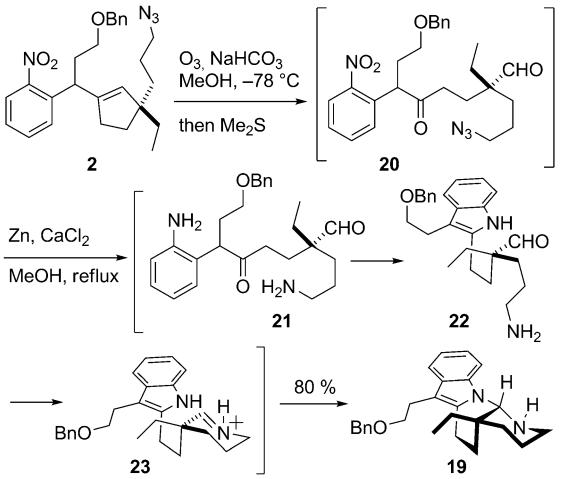
Having a reliable coupling method in hand, the total synthesis of goniomitine was accomplished as shown in Scheme 4. The reaction of the Normant Grignard reagent,[18] prepared in situ from 3-chloropropan-1-ol (**13**), with 3-ethoxy-cyclopent-2-enone (**14**) afforded, after protection of the primary hydroxy group, the 3-substituted cyclopent-2-enone **15**.[19] Conjugate addition of ethyl cuprate to **15** followed by trapping of the resulting enolate with the Comins reagent[20] afforded vinyl triflate **4** in 82% yield. On the other hand, potassium 4-(benzyloxy)-2-(2-nitrophenyl)-butanoate (**3**) was synthesized from **16** by a three-step sequence involving alkylation, hydrolysis, and salt formation. The key decarboxylative coupling of **3** with vinyl triflate **4** proceeded smoothly to provide the desired product in 70% yield. We subsequently found that, after completion of the coupling reaction, adding tetrabutylammonium fluoride (TBAF) to the reaction mixture directly afforded alcohol **18** in 70% yield as a mixture of two diastereomers in a 1:1 ratio. Although the two diastereomers were separable, it was more convenient to proceed with the synthesis using the mixture, as the stereocenter at the benzylic position will disappear at the end of the synthesis. Transformation of the hydroxy group into an azido group under Mitsunobu conditions[21] set the stage for the planned one-step conversion of **2** into the tetracyclic skeleton of goniomitine. After an extensive survey of reaction conditions, the one-pot integrated oxidation/double reduction/triple cyclization (IORC) process was realized as follows: Ozonolysis of **2** in methanol at −78 °C in the presence of $NaHCO_3$,[22] followed by the addition of dimethyl sulfide (−78 °C, then at RT for 24 h) afforded the ketoaldehyde. The addition of activated zinc and $CaCl_2$ followed by heating the reaction mixture to reflux furnished **19** in 80% yield as the only diastereomer.[23] Deprotection of the benzyl ether in the presence of the sensitive aminal group was best realized with sodium naphthalenide to give (±)-goniomitine (**1**) in 65% yield.[24] The spectroscopic data of the synthetic goniomitine were identical to those reported in the literature.[2,4–8]



Scheme 4. Total synthesis of (±)-goniomitine. a) **13**, CH_3MgCl, THF, −78 °C to RT; Mg, reflux; **14**, reflux; 2 N HCl. b) TBSCl, imidazole, DMF, RT, 60% over 2 steps. c) EtMgBr, CuBr·Me_2S, THF, −78 °C to −40 °C; Comins reagent, −40 °C to RT, 24 h, 80%. d) Cs_2CO_3, ICH_2CH_2OBn, DMF, 60 °C, 93%. e) 10% KOH, MeOH/THF (5:1). f) *t*BuOK, EtOH, 91%. g) **3** (1.2 equiv), [{PdCl(allyl)}$_2$] (5 mol%), X-Phos (15 mol%), diglyme, 100 °C, 2 h; TBAF, RT, 4 h, 70%. h) DPPA, DIAD, Ph_3P, THF, 0 °C to RT, 3 h, 72%. i) O_3, $NaHCO_3$, MeOH, −78 °C; Me_2S, −78 °C to RT; Zn, $CaCl_2$, reflux, 2 h, 80%. j) Sodium naphthalenide, THF, −20 °C, 15 min, 65%. Comins reagent = *N*-(5-chloro-2-pyridyl)bis(trifluoromethanesulfonimide), DIAD = diisopropyl azodicarboxylate, DPPA = diphenyl phosphoryl azide.

The remarkable synthetic efficiency and selectivity in the present one-pot multiple-bond-forming IORC process is worthy of additional comment. First, the use of $NaHCO_3$ as an additive for ozonolysis is of the utmost importance to get a high yield of **20**. The ketoaldehyde **20** can be isolated in 60% yield and is fully characterized. However, partial decomposition was observed during flash chromatographic purification. Secondly, all issues of chemo-, regio- and stereoselectivity were addressed in the one-pot reductive triple-cyclization process. The optimal conditions should allow us not only to chemoselectively reduce both the nitro and the azido groups without touching the ketone, the aldehyde, the iminium intermediate, and the final aminal functions, but also to promote the desired regio- and diastereoselective cyclizations. After many unsuccessful trials using different hydrogenolysis conditions and metal/additive combinations, it was found that refluxing a methanol solution of **20** in the presence of zinc dust and calcium chloride ($CaCl_2$) afforded **19** directly and in excellent yield. The presence of $CaCl_2$ was crucial for the success of the reaction, otherwise only the starting ketoaldehyde **20** was recovered. On the other hand, attempts to reduce the ozonide directly after ozonolysis under the same conditions (Zn/$CaCl_2$) resulted in complete decomposition. The cyclization proceeded rapidly in a highly ordered fashion after reduction as no intermediates or side products could be detected from

the reaction mixture at different time intervals. Furthermore, the domino reductive triple cyclization was found to be compatible with the ozonolysis conditions, and the one-pot IORC process of **2** afforded **19** in 80% yield, which is much higher than the overall yield of the stepwise process. In Scheme 5 the reaction pathway of the IORC sequence is



Scheme 5. The one-pot integrated oxidation/reduction/cyclization (IORC) process.

summarized. Concomitant reduction of nitro and azido groups followed by chemo- and regioselective indolization and iminium formation would afford **23** through intermediates **21** and **22**. Intramolecular attack of the indole nitrogen on iminium from the face opposite to the ethyl substituent would diastereoselectively produce the *cis*-fused aminal ring, thus completing the construction of the tetracycle **19**.

In summary, a seven step total synthesis of (±)-goniomitine has been achieved through two key steps: 1) A novel palladium-catalyzed decarboxylative coupling reaction between potassium nitrophenyl acetates and vinyl triflates for the rapid production of a functionalized cyclopentene that incorporates all of the atoms required for the desired natural product. Although this coupling reaction was developed for the synthesis of monoterpene indole alkaloids, we believe that it will also find application in the synthesis of other families of natural products and medicinally relevant compounds. 2) A one-pot multiple-bond-forming IORC process for converting the substituted cyclopentene into the tetracyclic skeleton of goniomitine. In this process, the oxidative scission of a double bond, the chemoselective reduction of an azido and a nitro group, and the concurrent formation of three C–N bonds and three rings took place with high regio-, chemo-, and diastereoselectivity. The sequence completely reorganized the skeleton of the starting material, thus allowing the conversion of an easily accessible cyclopentene derivative into the tetracyclic structure of goniomitine.

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