C–H Activation

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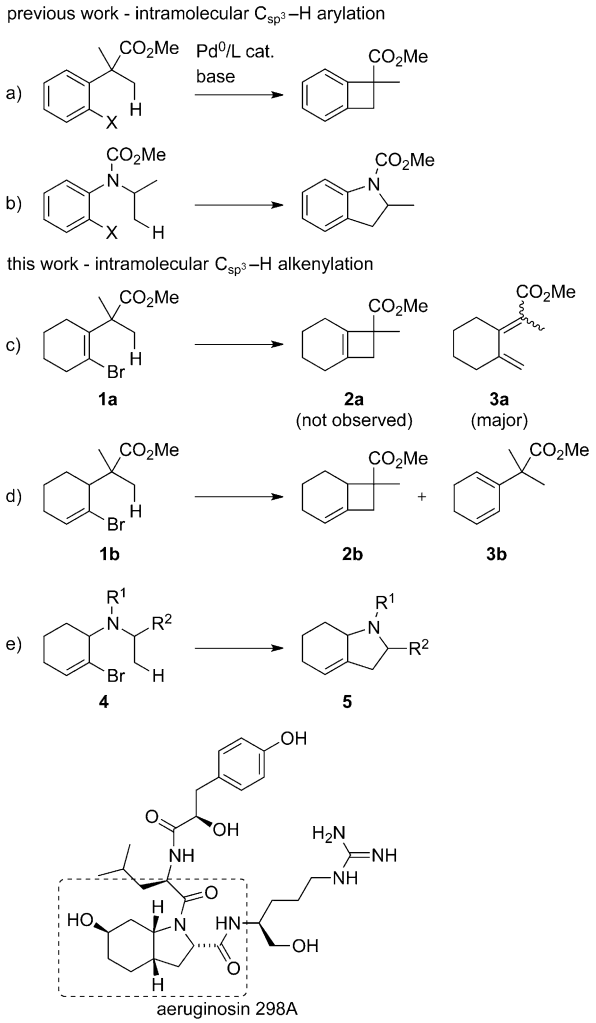
Synthesis of Hexahydroindoles by Intramolecular C_{sp^3}–H Alkenylation: Application to the Synthesis of the Core of Aeruginosins**

*Julien Sofack-Kreutzer, Nicolas Martin, Alice Renaudat, Rodolphe Jazzar, and Olivier Baudoin**

The functionalization of C–H bonds has recently emerged as an atom- and step-economical alternative to more traditional synthetic methods based on functional group transformation, which often require multistep sequences.[1] In particular, transition metal catalysis has been shown to be a powerful tool to functionalize otherwise unreactive C_{sp^2}–H and C_{sp^3}–H bonds. These advances have enabled the construction of a variety of carbon–carbon and carbon–heteroatom bonds with great efficiency and selectivity, even in structurally complex organic molecules.[2] In this context, our recent research has focused on the intramolecular arylation of unactivated C_{sp^3}–H bonds with aryl halides under palladium(0) catalysis,[3] to give synthetically useful polycylic molecules such as benzocyclobutenes (Scheme 1 a).[4] Unlike C_{sp^3}–H arylations with aryl halides, C_{sp^3}–H alkenylations with alkenyl halides are very scarce.[5,6] In such reactions, the replacement of a benzene by a cyclohexene ring is actually more challenging than it first appears. Indeed, when cyclohexenyl bromide **1a** was subjected to Pd-catalyzed C–H activation under similar reaction conditions as the corresponding aryl bromide (Scheme 1 c), a complex mixture was obtained, in which diene **3a** (as a mixture of *E* and *Z* isomers) was identified and not the desired fused cyclobutene **2a**. Diene **3a** arises from the electrocyclic ring opening of **2a**, a transformation that occurs easily under thermal conditions.[7] The reaction of isomeric cyclohexenyl bromide **1b**, which was designed to avoid cyclobutene ring opening, resulted in an inseparable mixture of the desired cyclobutane **2b** and diene **3b** in low yield (Scheme 1 d). Diene **3b** presumably arises from opening of the five-membered palladacycle intermediate leading to **2b**, followed by C–H activation on the cyclohexene ring, in a similar way to 1,4-palladium migrations observed with benzocyclobutenes.[4c] Therefore, C–H activation occurred in both cases, but it did not give rise to the desired fused four-membered rings because of the instability of the desired products and because of the high activation energy for the final C–C coupling step. In light of these initial findings, we turned our attention to the formation of five-membered rings, the synthesis of which was deemed more facile due to a much more kinetically favorable C–C reductive elimination step.[8] Inspired by the related C–H arylation of nitrogen-containing substrates to give indolines (Scheme 1 b),[9,4e] we turned our attention toward the alkenylation of cyclohexenyl bromides **4** that should give hexahydroindoles **5** (Scheme 1 e). The latter are interesting nitrogen heterocycles that should be easily converted into bicyclic analogues of proline ($R^2 = CO_2H$),[10] which are of interest for asymmetric organocatalysis[11] and natural product synthesis. In particular, octahydroindoles are found as the



Scheme 1. Palladium(0)-catalyzed C_{sp^3}–H arylations and alkenylations from aryl and alkenyl halides.

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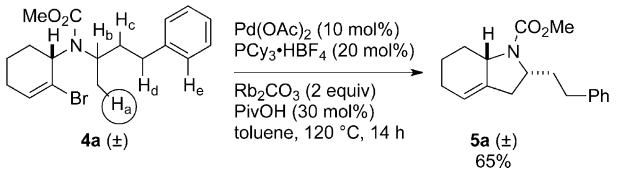

Scheme 2. Optimized C_{sp^3}–H alkenylation conditions.

core of the aeruginosin family of marine natural products (see Scheme 1 for the structure of aeruginosin 298A), which show interesting biological properties as inhibitors of serine proteases.[12]

We first examined the reactivity of bromoalkene **4a** (Scheme 2), which was synthesized as a racemic single diastereoisomer in four steps from cyclopentene.[13] Compound **4a** is a particularly challenging substrate because the nitrogen substituent contains several types of C–H bonds that could potentially be activated: primary C_{sp^3}–H_a bonds, a tertiary C_{sp^3}–H_b bond adjacent to a nitrogen atom, two types of secondary C_{sp^3}–$H_{c,d}$ bonds including more-acidic benzylic protons (H_d), and arylic C_{sp^2}–H_e bonds.

Different palladium sources, phosphine ligands, bases, solvents, and acid additives were screened.[14] Optimal conditions were $Pd(OAc)_2/PCy_3$ as the catalyst, rubidium carbonate as the base,[15] and pivalic acid (PivOH) as the additive[16] in toluene at 120 °C, and gave product **5a** in 65 % yield upon isolation. The regioselectivity of the C–H activation step involved in this reaction is remarkable. Indeed, compound **4a** underwent selective C–H bond cleavage at the most favorable primary C_{sp^3}–H_a bond, in the presence of C_{sp^3}–H_{b-d} bonds as well as C_{sp^2}–H_e bonds; this result is consistent with previous mechanistic studies.[4e]

We next examined the reactivity of other bromoalkene substrates (Table 1). A first set of bromoalkenes, bearing at least two methyl substituents at the carbon atom α to the nitrogen atom (C_α), was subjected to the optimized C–H alkenylation conditions (entries 1–8). Entries 1–6 highlight the effect of the nitrogen substituent (R^1). A trifluoroacetyl substituent was found to be optimal for compounds bearing diastereotopic methyl groups at C_α (**4b–e**, entries 1–4) to effect the desired cyclization efficiently (entry 2). The lower yield in the case of **5b** (entry 1) is attributable to the formation of substantial amounts of olefin **6b**, which likely arises from competitive β-H elimination after the C–H activation step.[4b,17] Interestingly, hexahydroindoles **5b–c** were isolated as single *cis* diastereoisomers. For compound **4d**, having an *N*-acetyl substituent, C–H activation occurred at the most acidic position to give the corresponding fused γ-lactam in good yield (entry 3). In addition, the presence of a nonacidic electron-withdrawing R^1 group (CO_2Me or $COCF_3$) was essential, as shown by the complete lack of reactivity of *N*-methyl-substituted **4e** (entry 4). Interestingly, compounds **4f** and **4g** bearing a quaternary C_α center (entries 5 and 6) showed a reversal of reactivity as compared to **4b** and **4c** (entries 1 and 2), and the reaction of the compound having an *N*-CO_2Me substituent (**4f**) had a slightly higher yield (entry 5). This result shows that subtle electronic effects affect the reaction selectivity (entries 1 and 2) and efficiency (entries 5 and 6). The use of more sterically hindered bromocyclohexenes **4h** and **4i**, which have diastereotopic methyl groups on the quaternary C_α center, provided the corresponding products **5h** and **5i** with moderate yields and diastereoselectivities (entries 7 and 8). We next studied the reactivity of diastereomerically pure substrates **4j–p** bearing two different substituents on the C_α atom (entries 9–15). For compounds **4j**, **4k**, and **4m–o**, which have the same relative configuration, intramolecular C–H alkenylation occurred efficiently and with a high regioselectivity in favor of activation at the primary β C–H bond (entries 9, 10, and 12–14). However, different diastereoisomers of the same substrate showed a markedly different reactivity, as illustrated with **4k** and **4l** (entries 10 and 11). Indeed, **4k** gave the expected *cis*-configured cyclization product **5k**, whereas **4l** gave a complex mixture containing mainly olefin isomers. This diastereodivergent behavior mirrors the *cis* diastereoselectivity obtained for compounds **4b** and **4c** (entries 1 and 2) and shows that the product selectivity, that is, the formation of a five-membered ring versus an olefin, is strongly affected by steric or conformational effects.[18] The reaction of cyclohexenyl bromide **4p**, bearing a phenyl group at C_α, was also examined (entry 15). Intramolecular alkenylation occurred at the phenyl instead of the methyl group to give tricyclic product **7p** in good yield; this result is consistent with previous observations that C_{sp^2}–H activation is usually favored over C_{sp^3}–H activation for the formation of small (five to seven-membered) rings.[3] Next, the reaction of other cycloalkenyl bromides was studied (entries 16–18). Methyl-substituted cyclohexene **4q** underwent intramolecular C–H alkenylation successfully (entry 16), whereas the reaction of analogous cyclopentene **4r** (entry 17) and cycloheptene **4s** (entry 18) only led to degradation products. This finding illustrates the impact of conformational effects and shows that cyclohexenyl bromides, which are the closest analogues of aryl halides, are also the optimal C_{sp^3}–H alkenylation substrates.

The above C_{sp^3}–H alkenylation reaction seemed to work well for the synthesis of hexahydroindoles with the *cis* configuration (entries 9–14). We hypothesized that reduction of the C=C bond should provide a unique route to octahydroindoles related to aeruginosins (Scheme 1e), with the correct relative configuration.[19–20] To demonstrate this, enantiopure benzyl-protected bromide **4t** was synthesized in four steps and 31 % yield, from dibromocyclopropane **6** and L-alaninol (Scheme 3). 2,3-Dibromocyclohexene **7** was obtained by thermal rearrangement of **6**, which is synthesized from the cyclopropanation of cyclopentene with dibromocarbene.[13] The nucleophilic substitution of allylic bromide **7** with L-alaninol gave a 1:1 mixture of diastereoisomers, which were separated after the benzylation step. Protected compound **4t** was then subjected to the above optimized C–H alkenylation conditions, to give *cis*-hexahydroindole **5t** in 75 % yield. Next, concomitant diastereoselective alkene hydrogenation and debenzylation were achieved by using Pearlman's catalyst, to afford octahydroindole **8** with the desired *cis*, *cis* configuration.

Derivatization of the latter as *p*-nitrobenzoyl ester **9** gave single crystals suitable for X-ray analysis (Scheme 3),[21] thereby confirming that the structure and absolute config-

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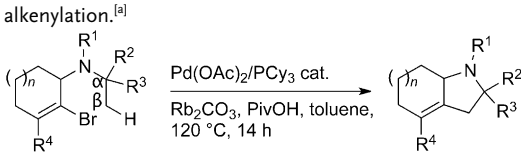
Table 1: Scope of the intramolecular C_{sp^3}–H alkenylation.[a]



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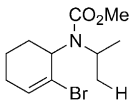
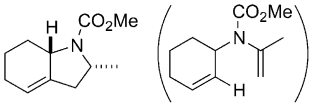
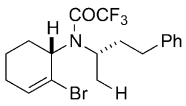
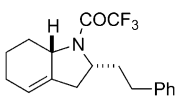
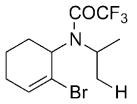
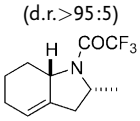
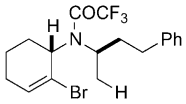
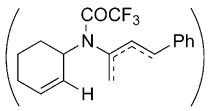
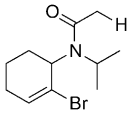
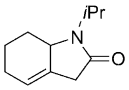
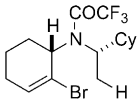
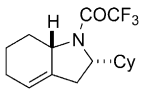
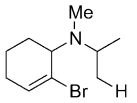
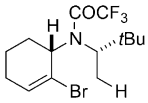
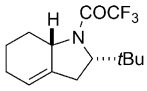
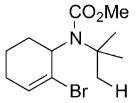
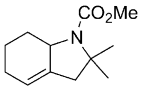
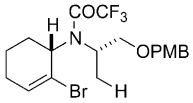
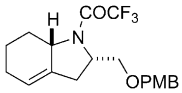
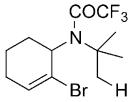
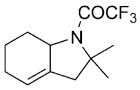
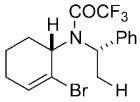
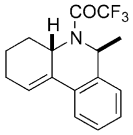
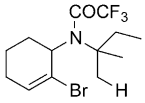
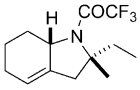
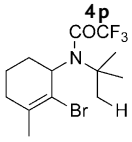
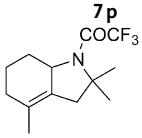
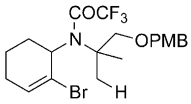
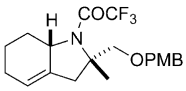
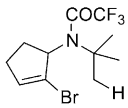
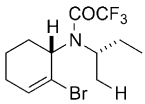
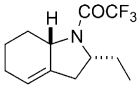
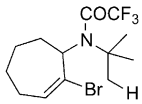
1	 **4b**	 **5b** (d.r.>95:5) **6b**	40	10	 **4k**	 **5k**	71
2	 **4c**	 **5c** (d.r.>95:5)	73	11	 **4l**		–
3	 **4d**	 **5d**	83	12	 **4m**	 **5m**	68
4	 **4e**	–	0	13	 **4n**	 **5n**	71
5	 **4f**	 **5f**	86	14	 **4o**	 **5o**	84
6	 **4g**	 **5g**	78	15	 **4p**	 **7p**	78
7	 **4h**	 **5h** (d.r.=2:1)[c]	67	16	 **4q**	 **5q**	77
8	 **4i**	 **5i** (d.r.=3:1)[c]	53	17	 **4r**	–	–
9	 **4j**	 **5j**	73	18	 **4s**	–	–

[a] Reaction conditions: see Scheme 2. All compounds in this Table are racemic mixtures. [b] Yield of the isolated product or of the isolated mixture of diastereoisomers (d.r. determined by ^{1}H NMR analysis). Relative configurations of products were assigned by NOESY experiments. [c] Only the major diastereoisomer is shown. Cy = cyclohexyl, PMB = *p*-methoxybenzyl.

uration was the same as that of the octahydroindole core of the aeruginosins.

In conclusion, we have shown that the intramolecular C_{sp^3}–H alkenylation from a cycloalkenyl bromide is a non-trivial extension of the previously developed C_{sp^3}–H arylation reaction which shows impressive regioselectivity and interesting diastereodivergent behavior. This method provides a unique route to hexahydroindoles that are relevant to

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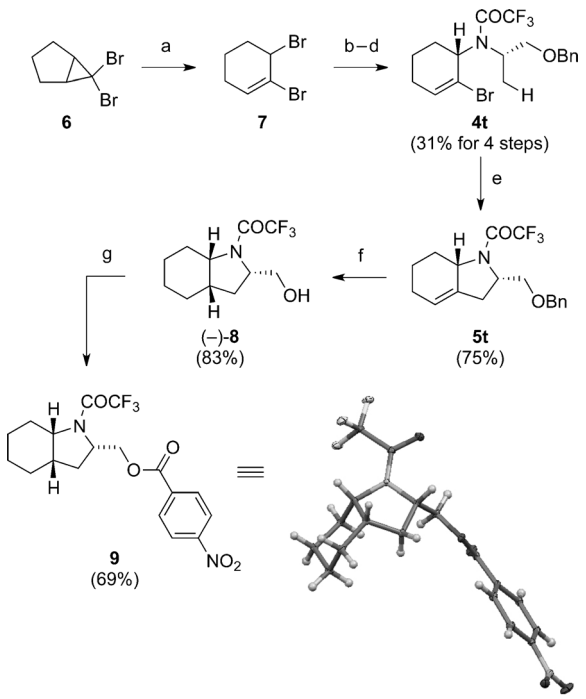

Scheme 3. Synthesis of the octahydroindole core of the aeruginosins. The X-ray structure of compound **9** is shown with the thermal ellipsoids set at 30% probability. Reagents and conditions: a) neat, 130 °C; b) L-alaninol, K_2CO_3, DMF, 50 °C (1:1 mixture of diastereoisomers); c) NaH, benzyl bromide, DMF, 20 °C; d) trifluoroacetic anhydride, pyridine, CH_2Cl_2, 0→20 °C (31 % for 4 steps); e) $Pd(OAc)_2$ (10 mol %), $PCy_3{\cdot}HBF_4$ (20 mol %), Rb_2CO_3, PivOH (30 mol %), toluene, 120 °C (75 %); f) H_2, $Pd(OH)_2/C$ (10 mol %), THF, 20 °C (83 %); g) p-$NO_2C_6H_4COCl$, Et_3N, CH_2Cl_2, 0→20 °C (69 %). Bn = benzyl, DMF = *N*,*N*-dimethylformamide, Piv = trimethylacetyl.

natural product synthesis, as demonstrated with the synthesis of the octahydroindole core of aeruginosins.

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[21] CCDC 884456 (**9**) contains 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.

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