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Palladium-Catalyzed Intramolecular C(sp^3)−H Functionalization: Catalyst Development and Synthetic Applications

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Dedicated to K. C. Nicolaou on the occasion of his 60th birthday

Abstract: A novel catalytic system, based on a mixture of palladium acetate and tris(5-fluoro-2-methylphenyl)phosphane (F-TOTP), has been designed for the intramolecular C−H functionalization of alkane segments. Among other analogues of tris(2-methylphenyl)phosphane (P(*o*-tol)$_3$), F-TOTP was shown to have the optimal metal-bonding properties for this reaction. This catalytic system operated under milder reaction conditions that allowed the regioselective production of various olefins adjacent to a quaternary benzylic carbon atom, as well as novel bi- and tricyclic molecules. A general mechanism was proposed, with the preferential formation of a six-membered palladium(II) palladacycle after oxidative addition and cyclopalladation. The regioselective C−H functionalization of alkyl groups into olefins was illustrated in the synthesis of the antihypertensive drug verapamil (**14**) and an analogue (**19**). A particularly mild ruthenium-catalyzed direct hydroamidation of the intermediate olefin in this synthesis is also reported.

Keywords: C−H activation · catalysis · dehydrogenation · hydroamidation · palladium

Introduction

The activation and functionalization of unactivated alkane and arene C−H bonds directed toward organic synthesis is currently of great interest.[1] A number of transition-metal-mediated C−H functionalization processes have been described in the literature in the past decade; these processes provide chemists with atom- and step-economical alternatives to standard methods, allow access to novel molecular scaffolds, and offer new bond disconnections for target-oriented synthesis. Compared to those for arenes,[1,2] there are far fewer reports on the C−H functionalization of *alkane* segments of organic molecules. Within this field, C−H insertions of metal carbenes and metal nitrenes have proven to be particularly efficient, both in nonstereoselective and stereoselective forms, and have been successfully applied to natural product synthesis.[3] Other milestones in C−H functionalization have recently been accomplished in the absence[4] or presence[5] of a metal-directing group. In the latter case, the metal is precoordinated by at least one heteroatom of the substrate molecule, which triggers the cleavage of a particular C−H bond through cyclometalation. This approach was utilized by the Sames group in the total syntheses of rhazinilam and the core of teleocidin B4, with a stoichiometric amount of transition metal (Pt^{II} or Pd^{II}).[6]

In 2003, we reported a palladium(0)-catalyzed C−H functionalization of benzylic alkyl groups that gives rise to ole-

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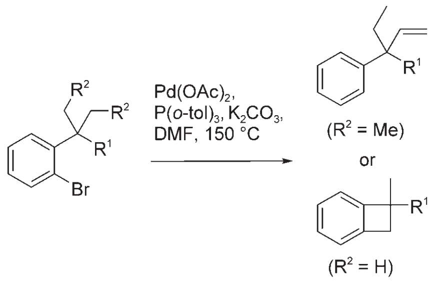
[#] X-ray crystal structure analysis.

Supporting information for this article (full characterization of all new compounds, detailed experimental procedures, and copies of NMR spectra for the target compounds) is available on the WWW under http://www.chemeurj.org/ or from the author.



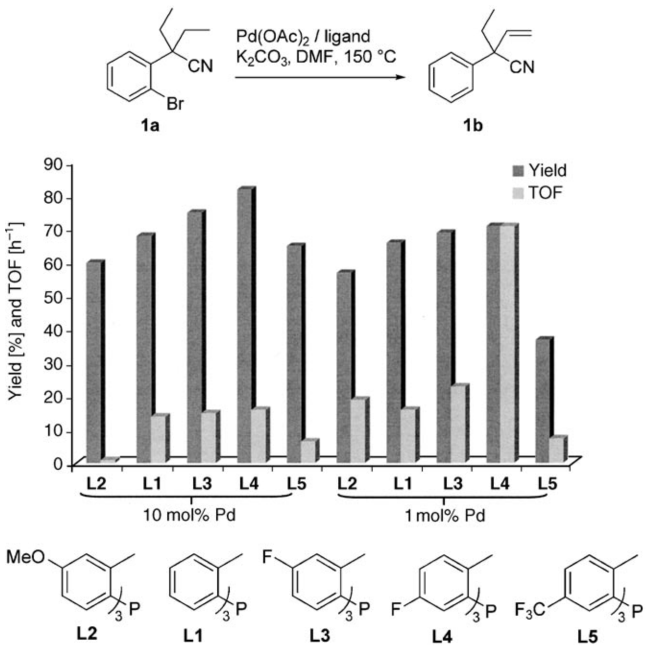
Scheme 1. Palladium(0)-catalyzed C−H functionalization of benzylic alkyl groups. P(*o*-tol)$_3$ = tris(2-methylphenyl)phosphane.

fins (alkane dehydrogenation) or benzocyclobutenes (Scheme 1).[7] In contrast to other reports featuring direct precoordination of Pd^{II} by heteroatoms of the substrate,[5] the Pd^{II} intermediate in our case was generated by oxidative addition of an aryl halide to Pd^0. This initiated an intramolecular C−H bond cleavage, followed by β-H elimination and reductive elimination to give an olefin or by direct reductive elimination to give a benzocyclobutene. In contrast to the seminal work of Dyker[8] and the recent report by Buchwald and co-workers,[9] our process is purely intramolecular and is not accompanied by intermolecular C−C bond formation, but instead by intramolecular C−H or C−C bond formation.[10] Therefore this reaction can best be termed *intramolecular C(sp^3)−H functionalization*. In view of the relatively harsh conditions that we first reported (150 °C, 10 mol % Pd), we decided to reoptimize the catalytic system in order to come up with milder conditions, better suited to applications in target-oriented synthesis. In this article, we report the design of a more efficient catalyst, the extension of the reaction scope (for the formation of olefins and bi- or tricyclic molecules), and the application of the method to the synthesis of the antihypertensive drug verapamil.

Results and Discussion

Design of a new catalytic system: Aside from C−H insertions,[3] we are not aware of previous specific ligand design in the context of C(sp^3)−H functionalization. Our initial ligand screening revealed P(*o*-tol)$_3$ (**L1**) to be the most active ligand among a variety of aryl and alkyl phosphanes for the dehydrogenation of alkyl groups.[7] Optimal conditions were found with DMF as the solvent and K_2CO_3 as the base, with both ingredients having a strong impact on the reaction yield. We concentrated our reoptimization efforts on the reaction of compound **1a** to give olefin **1b** at 150 °C (Scheme 2).

Abstract in French: *Un nouveau système catalytique, formé à partir de l'acétate de palladium et de la tris(5-fluoro-2-methylphenyl)phosphine (F-TOTP), a été conçu pour la fonctionnalisation C−H intramoléculaire de groupements alkyles. Parmi d'autres analogues de P(*o*-tol)$_3$, il a été montré que F-TOTP possède les propriétés de coordination du métal optimales pour cette réaction. Le nouveau système catalytique opère dans des conditions réactionnelles plus douces qui permettent d'obtenir de façon régiosélective différentes oléfines adjacentes à un carbone quaternaire benzylique ainsi que de nouvelles molécules bi- et tricycliques. Un mécanisme général est proposé, mettant en jeu un palladacycle de palladium(II) à six chaînons qui est formé intermédiairement après addition oxydante et cyclopalladation. La fonctionnalisation C−H régiosélective de groupements alkyles en oléfines a été illustrée par la synthèse du vérapamil (**14**), médicament anti-hypertenseur, et d'un analogue (**19**). Au cours de cette synthèse, une hydroamidation directe catalysée par le ruthénium, qui s'effectue dans des conditions particulièrement douces, est également décrite.*



Scheme 2. Effect of ligand basicity on the intramolecular C−H functionalization of **1a**. Reaction conditions: **1a** (0.4 mmol), $Pd(OAc)_2$ (1 mol % or 10 mol %), ligand (2 mol % or 20 mol %), K_2CO_3 (2 equiv), DMF ([**1a**] = 0.2 M), 150 °C.

First, different sources of palladium(II) or palladium(0) were screened, including $PdCl_2$, $PdBr_2$, $Pd(OAc)_2$, [Pd(acac)$_2$] (acac = acetylacetone), and [Pd$_2$(dba)$_3$] (10 mol % Pd; dba = *trans*,*trans*-dibenzylideneacetone), in combination with P(*o*-tol)$_3$ (2 equiv for Pd^{II}, 1 equiv for Pd^0); among these sources, $Pd(OAc)_2$ gave the highest yield (68 %) and reaction rate (0.5 h, turnover frequency (TOF) = 14 h^{-1}). In this case, analysis of the reaction mixture run in [D$_7$]DMF by ^{31}P NMR spectroscopy revealed the presence of the Herrmann–Beller palladacycle (δ = 34.7 ppm),[11] which had been generated in situ, together with the free phosphane (δ = −30.4 ppm) and the phosphane oxide (δ = 35.6 ppm). When run directly with the Herrmann–Beller palladacycle (5 mol %), the reaction gave the same yield as the mixture of $Pd(OAc)_2$ and P(*o*-tol)$_3$, but with much slower kinetics (even when free phosphane was added to the palladacycle). This indicates that the active palladium(0) species is generated faster from the mixture of $Pd(OAc)_2$ and P(*o*-tol)$_3$ than from the palladacycle.

We then decided to study the influence of the phosphane basicity, and to this purpose, we synthesized P(*o*-tol)$_3$ analogues **L2**–**L5** bearing electron-donating or -withdrawing groups at the 4- or 5-positions (Scheme 2). They were obtained in one step and high yield from the corresponding aryl bromides, through formation of the Grignard reagent

Table 1. Comparison of the basicity of $P(o\text{-tol})_3$ analogues.

	Ligand				
	L2	**L1**	**L3**	**L4**	**L5**
ν_{CO} [cm^{-1}][a]	1965	1970	1974	1979	1983
^1J(P,Se) [Hz][b]	689	705	716	726	740

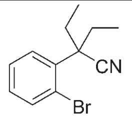
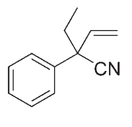
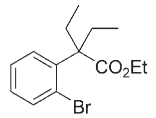
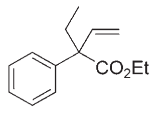
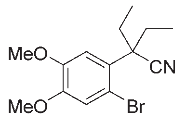
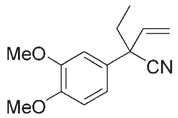
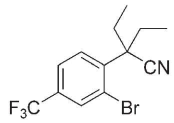
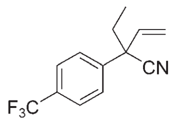
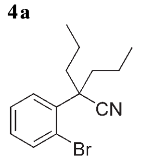
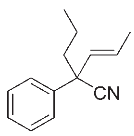
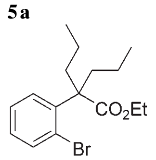
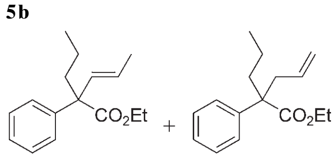
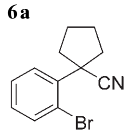
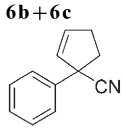
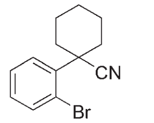
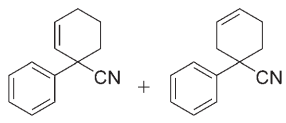
[a] CO absorption band of the *trans*-$[(R_3P)_2Rh(CO)Cl]$ complex, as measured from the FTIR spectrum. [b] $^{31}P-^{77}Se$ coupling constant measured from the ^{31}P NMR spectrum (121.5 MHz, $CDCl_3$) of the R_3P-Se complex.

and reaction with PCl_3.[12] Among them, the *meta*-fluoro analogue **L4** (tris(5-fluoro-2-methylphenyl)phosphane, F-TOTP), which has not been reported previously, was obtained in 82% yield from 2-bromo-4-fluorotoluene.

The classification of phosphanes **L1**–**L5** by decreasing basicity, **L2** > **L1** > **L3** > **L4** > **L5**, was established by two different spectroscopic methods: 1) the measurement of ν_{CO} in the IR spectrum of the *trans*-$(R_3P)_2Rh(CO)Cl$ complexes[13] and 2) the measurement of the ^1J(P,Se) coupling constants of the phosphane selenides (Table 1).[14] The screening of phosphanes **L1**–**L5** in the reaction of compound **1a** with $Pd(OAc)_2$ (10 mol%)/ligand (20 mol%; Scheme 2) revealed F-TOTP (**L4**) to be the most active ligand in terms of yield (82%, turnover number (TON) = 8.2) and rate (TOF ≈ 16 h^{-1}). F-TOTP thus seems to have the optimal basicity for this reaction. A decrease in the amount of palladium to 1 mol% slowed down the reaction, which differentiated further the different ligands and showed again a higher activity for F-TOTP (TON = 71, TOF = 71 h^{-1}). The reaction yield decreased markedly when less than 1 mol% Pd was employed. With these results in hand, we attempted to decrease the reaction temperature. Gratifyingly, the same reaction could be run at 100 °C with 5 mol% $Pd(OAc)_2$ and 10 mol% F-TOTP, to give olefin **1b** in 77% yield in 1 h (see Table 2, entry 1). The Herrmann-type palladacyclic complex **I** was generated thermally from a mixture of $Pd(OAc)_2$ and F-TOTP in toluene (Figure 1). As before with the Herrmann–Beller palladacycle, complex **I** was considerably less reactive than the mixture of $Pd(OAc)_2$ and F-TOTP, giving approximately 10% conversion of **1a** in 10 h at 100 °C (with 2.5 mol% **I**). This shows that the active catalytic species was again generated faster from the Pd/ligand mixture than from the isolated palladacycle.

Extension of the reaction scope: Next, we studied the scope of the new catalytic system at 100 °C (Table 2). The reaction, which was before limited to substrates bearing a bulky ben-

Table 2. Synthesis of olefins.[a]

Entry	Starting material	Product(s)	Yield [%][b] (ratio)
1	 **1a**	 **1b**	77
2	 **2a**	 **2b**	67[c]
3	 **3a**	 **3b**	82[c]
4	 **4a**	 **4b**	68
5	 **5a**	 **5b**	70
6	 **6a**	 **6b** + **6c**	68 (93:7)
7	 **7a**	 **7b**	63
8	 **8a**	 **8b** + **8c**	85 (55:45)

[a] $Pd(OAc)_2$ (5 mol%), F-TOTP (**L4**, 10 mol%), K_2CO_3 (2 equiv), DMF, 100 °C. [b] Yield after isolation by flash chromatography. [c] With 20 mol% of F-TOTP.

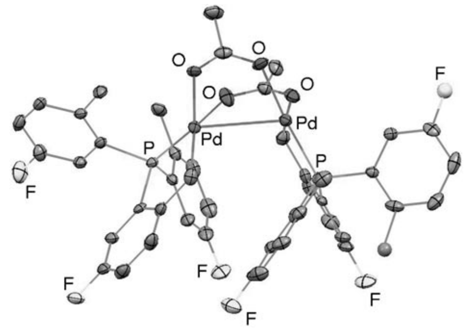


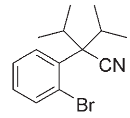
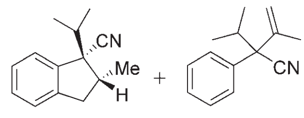
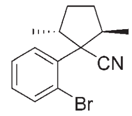
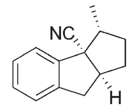
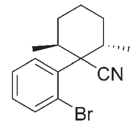
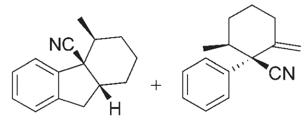
Figure 1. X-ray crystal structure of complex **I** (30% thermal ellipsoids plot, hydrogen atoms were omitted for clarity).[15]

zylic substituent,[7] now works ideally with a benzylic nitrile. This is a clear improvement as a greater variety of alkyl groups (in particular, bulkier groups), undergoing the intramolecular C–H functionalization, can be introduced α to the nitrile group by standard alkylation.

Nevertheless, groups other than nitrile, for instance, ester groups, could be employed successfully (Table 2, entries 2 and 6). Dialkyl substitution was required as before, as the monoethyl analogue of **1a** did not furnish the corresponding olefin. Electron-rich (Table 2, entry 3) or electron-poor (Table 2, entry 4) substituents on the aromatic ring were well tolerated, with a decreased reaction rate for the CF_3 substituent. Di-*n*-propyl substrate **5a** furnished olefin **5b** with complete regioselectivity and *E* stereoselectivity (Table 2, entry 5). It is noteworthy that the corresponding ethyl ester derivative **6a** gave a 93:7 mixture of the substituted and terminal olefins (Table 2, entry 6). The reaction of cycloalkanes **7a** and **8a** (Table 2, entries 7 and 8) gave interesting results: in the first case olefin **7b** was produced regioselectively, whereas in the second case an approximately 1:1 mixture of inseparable regioisomers **8b** and **8c** was obtained.

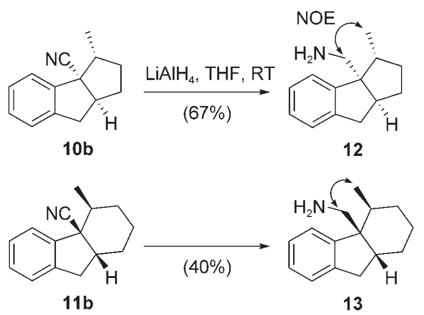
The reaction of substrates bearing a tertiary α-benzylic carbon atom also gave interesting results (Table 3). First, diisopropyl substrate **9a** gave a separable 4:1 mixture of indane **9b** and olefin **9c** (Table 3, entry 1). Compound **9b** was isolated as a single diastereoisomer in 50% yield, and its relative stereochemistry was deduced from NOESY experiments. The synthesis of **9b** via intramolecular C–C bond formation was exploited further with the intramolecular functionalization of (2*R*,5*R*)-dimethylcyclopentane **10a** (Table 3, entry 2), obtained in two steps from commercially available (2*S*,5*S*)-hexanediol. Gratifyingly, the major product was tricyclic molecule **10b**, isolated as a single diastereoisomer, together with a small amount of olefin. To determine the relative, and by extension absolute, configuration of **10b**, the nitrile group was reduced with $LiAlH_4$ to the primary amine **12** (Scheme 3), from which the *cis* ring fusion was deduced. (2*S*,6*S*)-Dimethylcyclohexane **11a** was obtained in a similar fashion from commercially available (2*R*,6*R*)-heptanediol. The intramolecular functionalization of **11a** gave a 7:3 mixture of tricycle **11b** and olefin **11c**

Table 3. Synthesis of bi- and tricyclic molecules.[a]

Entry	Starting material	Product(s)	Yield [%][b] (ratio)
1	 **9a**	 **9b** (±)+**9c**	62 (4:1)
2	 **10a**	 **10b**	62
3	 **11a**	 **11b**+**11c**	70 (7:3)

[a] $Pd(OAc)_2$ (5 mol%), F-TOTP (**L4**, 20 mol%), K_2CO_3 (2 equiv), DMF, 100°C. [b] Yield after isolation by flash chromatography.

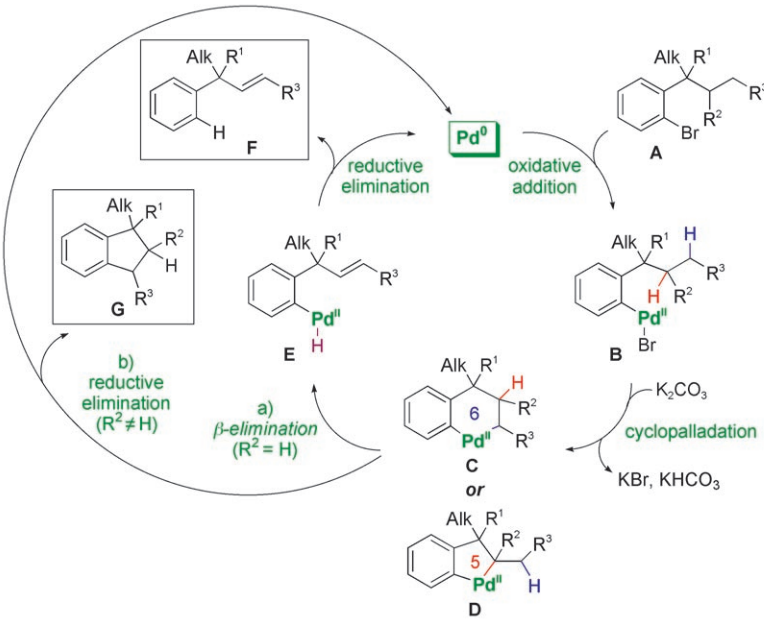
(Table 3, entry 3) in 70% combined yield. Compounds **11b** and **11c** were isolated from this mixture in 50 and 20% yield, respectively, as single diastereoisomers (as determined at the precision of ^1H NMR spectroscopy). The reduction of the nitrile group in **11b** provided primary amine **13** (Scheme 3), which again revealed a *cis* ring fusion by



Scheme 3. Reduction of nitrile groups to primary amines to determine the relative configuration of **10b**.

NOESY experiments. The relative configuration of **11c** was also ascribed from NOESY experiments. The formation mechanism of **11b** and **11c** will be commented on in the next section. Compound **11b** can be seen as a *nor*-abietane-type diterpenoid analogue (benzene–cyclopentane–cyclohexane fused ring system),[16] therefore C–H functionalization could provide an original and stereoselective entry into this series of natural products.

In conclusion, it appears that the C–H functionalization is a useful, versatile, and selective method for the synthesis of olefins adjacent to quaternary benzylic carbon atoms (Table 2).[17] In addition, when the α-benzylic carbon atom is tertiary (Table 3), interesting functionalized polycyclic molecules are obtained at the expense of olefin formation.



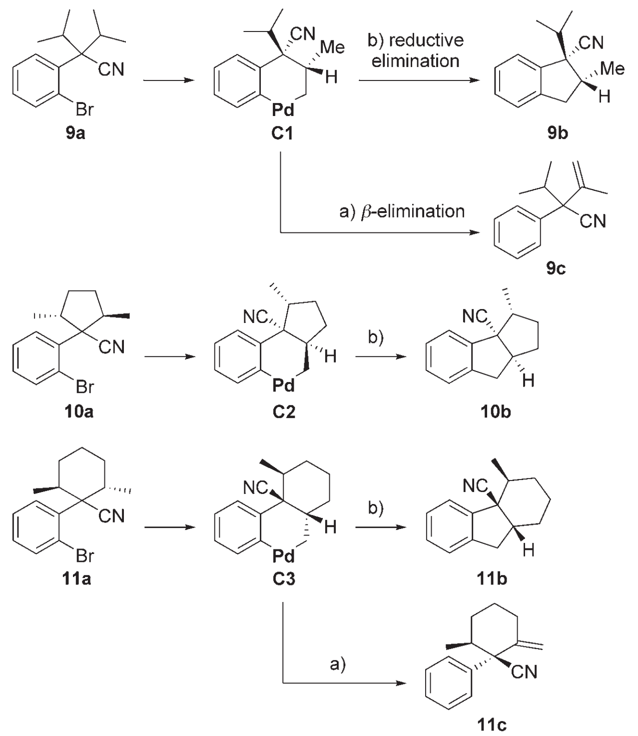
Scheme 4. Proposed general mechanism for the intramolecular C–H functionalization.

mechanism, as the smaller nitrile group leads to an increased proportion of substituted olefin (100 % **5b**) as compared to the ethyl ester (**6b**/**6c** 93:7). By contrast, the formation of olefins **5**–**8b** might be interpreted either as the formation of palladacycle **C** followed by endocyclic β-H elimination or as the formation of palladacycle **D** with exocyclic β-H elimination. However, we suggest that in these cases six-membered palladacycle **C** is also formed preferably. This proposal is supported by the deuterium-labeling experiments that were reported in our initial communication and that were confirmed under the new reaction conditions.[7] Further experiments and theoretical calculations are underway to determine whether concurrent mechanistic pathways may also operate.

Mechanistic proposal: Based on the distribution of products observed in this study (Tables 2 and 3), we propose the following general mechanism for the intramolecular C–H functionalization (Scheme 4).

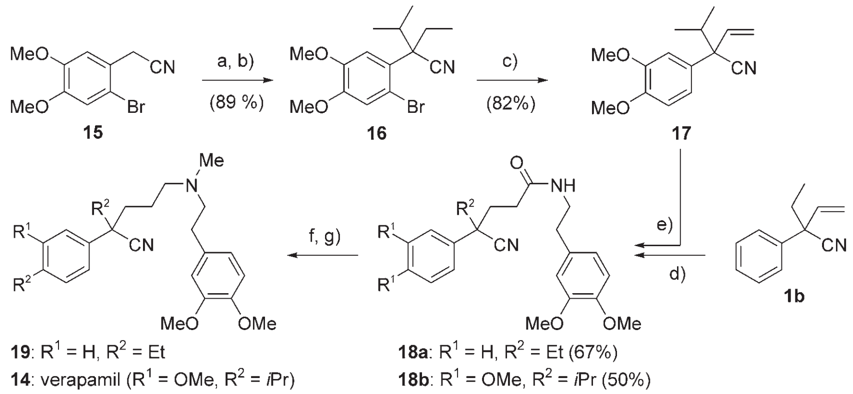
Oxidative addition of substrate **A** to Pd^0 would generate Pd^{II} complex **B**, which would undergo cyclopalladation with concomitant C–H bond cleavage to furnish six-membered palladacycle **C** or five-membered palladacycle **D**, complexes corresponding to cleavage of a β- or α-benzylic C–H bond, respectively (Scheme 4). Recent theoretical studies support a base-induced proton-abstraction mechanism for the cyclopalladation step, rather than a second oxidative addition leading to an energetically disfavored H–Pd^{IV}–Br palladacycle.[18] A β-H elimination step from **C** or **D** (Scheme 4, path a), R^2=H) would then produce palladium hydride **E**, which by reductive elimination would give the olefin product **F**. In complex **D**, the exocyclic position of the CH_2R^3 residue would enable a classical *syn*-β-hydride elimination, whereas in palladacycle **C**, β elimination could occur either from a distorted *syn* Pd–C/C–H conformation or through *anti* elimination.[19] Alternatively, a direct reductive elimination from palladacycle **C** (Scheme 4, path b), $R^2 \neq$H) would furnish indane-type product **G**. While the latter route is unambiguous for the production of indane **9b** and tricyclic molecules **10b** and **11b** (Table 3), the formation of olefins (Table 2) could arise from either palladacycle **C** or **D** (or a mixture of both).

A closer examination of the structure of these olefins (Table 2) suggests that six-membered palladacycle **C** is also preferred in this case. Indeed the intervention of palladacycle **C**, undergoing exocyclic β-H elimination, seems the most probable explanation for the production of terminal olefin **6c** and cyclic olefin **8c**.[20] As shown with **5a** and **6a**, the size of the benzylic R^1 group has a significant influence on the



Scheme 5. Probable intermediate palladacycles **C1**–**C3** in the reactions of **9**–**11a**.

In the proposed catalytic cycle, paths a) and b) seem to coexist, as illustrated by the reaction of bromide **9a** to give the mixture of indane **9b** and olefin **9c** (Table 3, Scheme 5). Intermediately, palladacycle **C1**, in which the CN and Me groups lie *cis* to each other, is probably produced in a diastereoselective fashion and then evolves by reductive elimination (path b)) to give indane **9b** and by β-H elimination (path a)) to give olefin **9c**. An alternative explanation would be that olefin **9c** is produced from the *trans* diastereoisomer of **C1**. Similarly, the formation of palladacycle **C2** explains the formation of tricycle **10b** from bromide **10a** (Scheme 5). Finally, the production of tricycle **11b** and olefin **11c** from bromide **11a** can be explained by the formation of the same palladacyclic intermediate, **C3**. Indeed, the CN and Me groups of **11c** have the same *cis* relationship as those of **11b**, whereas a *trans* stereochemistry would have been observed if **11c** was generated from the **C3** diastereoisomer. It can be noted that the relative stereochemistry of bicyclic compound **9b** is the opposite to that of tricyclic compounds **10b** and **11b**. This probably originates from the fact that different factors—axial versus equatorial position of substituents in the first case, ring strain in the second case—govern the formation of each type of molecule.



Scheme 6. Synthesis of verapamil (**14**) and analogue **19**: a) LiHMDS (1.0 equiv), DMPU (1.0 equiv), EtI (1.0 equiv), THF, 20 °C, 1 h; b) LiHMDS (5 equiv), DMPU (5 equiv), *i*PrI (5 equiv), THF, 20 °C, 1 h; c) Pd(OAc)$_2$ (5 mol %), F-TOTP (20 mol %), K_2CO_3 (2 equiv), DMF, 100 °C, 2 h; d) see Table 4, entry 4; e) see Table 4, entry 8; f) NaHMDS (1.5 equiv), MeI (2.0 equiv), THF, 0 °C, 1 h; g) BH_3·SMe_2 (1.85 equiv), THF, 0→20 °C, 18 h, then 1 M HCl, 100 °C, 4 h (37 % for **19** and 46 % for **14** for two steps). HMDS = 1,1,1,3,3,3-hexamethyldisilazane, DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1*H*)-pyrimidinone.

In conclusion, the analysis of product distribution shows that six-membered palladacycle **C** is a very likely intermediate in this reaction, at least with certain substrates. At this point, there seems to be no evidence of a five-membered palladacycle intermediate **D** in the formation of olefins. However, this intermediate is unambiguously involved in the regioselective formation of benzocyclobutenes from substrates bearing at least one benzylic methyl substituent.[7] Hence the preference for a five- or six-membered palladacycle in these reactions seems to be related to the substitution of the α-benzylic carbon atom bound to the palladium: palladacycle **D** is formed with a primary α-benzylic carbon atom (Me group), while palladacycle **C** is probably formed with more substituted α-benzylic carbon atoms (Et, *n*Pr, *i*Pr, etc.).

Synthesis of verapamil: To demonstrate further the utility of the current method for the functionalization of quaternary centers, we applied it to the synthesis of verapamil (**14**), a well-known calcium-channel blocker (Scheme 6).[21,22] Compound **16**, obtained from commercially available bromide **15** by sequential alkylations with EtI and *i*PrI, underwent regioselective intramolecular C–H functionalization catalyzed by Pd(OAc)$_2$/F-TOTP to give olefin **17**. Traces of reaction on the more bulky *i*Pr group could be observed. The one-carbon homologation of the bulky olefin **17** proved troublesome, so olefin **1b** was chosen for model studies. We decided to examine the *direct* hydroamidation of **1b** with homoveratrylamine (2-(3,4-dimethoxyphenyl)ethylamine) under a CO atmosphere and ruthenium catalysis (Table 4). In the seminal work, primary amines were treated at 120–180 °C

Table 4. Hydroamidation of olefins **1b** and **17** with homoveratrylamine.[a]

Entry	Olefin	Equiv of amine	[$Ru_3(CO)_{12}$] mol %	Gas	Yield [%][b]
1	**1b**	2	33	Ar	47
2	**1b**	4	33	Ar	67
3	**1b**	4	5	CO	34
4	**1b**	4	10	CO	67
5	**1b**	4	20	CO	69
6	**17**	4	33	Ar	36
7	**17**	4	10	CO	32
8	**17**	4	20	CO	50

[a] Olefin (1 equiv), homoveratrylamine, [$Ru_3(CO)_{12}$], DMF, gas atmosphere (balloon), 120 °C, 17 h. [b] Yield after isolation by chromatography.

with an *excess* of simple olefins under CO pressure (39 atm) and with 0.2 mol % [$Ru_3(CO)_{12}$],[23,24] conditions which would not be reasonable for the homologation of the more elaborate olefin **17**. We were pleased to discover that **1b** underwent mild hydroamidation with excess homoveratrylamine by using a stoichiometric amount of Ru under an argon atmosphere (Table 4, entry 1). Optimal reaction conditions were found with DMF as the solvent, at 120 °C, and with 4 equivalents of amine (Table 4, entry 2), to furnish amide **18a** in 67 % yield. The optimal 1:4 ratio of olefin/amine is reversed compared to literature precedents[23,24] and is better adapted to the homologation of elaborate olefins, such as **17**, with commercially available amines. Gratifyingly, catalytic amounts of Ru could be employed by running the reaction under a CO atmosphere, with an optimal quantity of 10 mol % [$Ru_3(CO)_{12}$] (entries 3–5). In all cases the conversion was complete, and the identifiable byproducts included homoveratrylformamide and the reduced olefin. Based on these byproducts and on literature proposals,[24b] we believe that the active catalytic species in this reaction is a triruthenium cluster hydride. Transposition of these conditions to the more bulky olefin **17** gave a 32–36% yield of amide **18b** (Table 4, entries 6 and 7). Finally, an increase in the amount of $[Ru_3(CO)_{12}]$ to 20 mol% (60 mol% Ru) under a CO atmosphere furnished an optimal 50% yield of amide **18b** (Table 4, entry 8). Further investigation of this particularly mild hydroamidation process is underway. The synthesis was completed with methylation of amides **18a** and **18b**, followed by chemoselective reduction of the amide group as previously described,[25] to give verapamil (**14**) and analogue **19** in 46 and 37% yield, respectively (overall yields: 17% for **14** and 18% for **19**).

Conclusion

We have reported a ligand design specifically adapted to the Pd^0-catalyzed intramolecular C–H functionalization of alkane segments. Bulky electron-poor F-TOTP (**L4**) was revealed to be the optimal palladium ligand. The novel catalytic system allowed milder reaction conditions and proved efficient on a range of interesting substrates, with the production of olefins adjacent to a quaternary benzylic carbon atom (dehydrogenation) or of bi- and tricyclic molecules of potential synthetic use. A general mechanism was suggested for this reaction based on the structure of products and literature data. Furthermore, the utility of the method was illustrated by the synthesis of the drug verapamil (**14**) and an analogue, **19**. During this synthesis, a particularly mild Ru-catalyzed hydroamidation step was also reported. We believe that this work might have implications in other catalytic processes and will help extend the use of nontraditional bond disconnections in multistep synthesis.

Experimental Section

General: Reagents were commercially available and were used without further purification unless otherwise stated. All solvents were distilled from the appropriate drying agents immediately before use. Yields refer to chromatographically and spectroscopically homogeneous materials. Merck silica gel 60 (particle size 40–63 mm) was used for flash column chromatography; 1 and 2 mm SDS silica-gel-coated glass plates (60F254) were used for preparative TLC with UV light as the visualizing agent. NMR spectra were recorded on Bruker AC-250, AMX-300, AMX-400, or AMX-500 instruments at 295 K with tetramethylsilane or residual protiated solvent used as an internal reference for ^1H and ^{13}C spectra. ^{31}P and ^{19}F NMR spectra were calibrated with H_3PO_4 and CCl_3F as external references. Attributions were made on the basis of 2D experiments. Products that had been reported previously were isolated in greater than 95% purity, as determined by ^1H NMR spectroscopy and capillary GC. GC analyses were performed with a Shimadzu QP2010 GCMS apparatus, with simultaneous double injection on a DB-5ms column lined with a mass (EI) or an FID detection system.

Tris(5-fluoro-2-methylphenyl)phosphane (F-TOTP, L4): 2-Bromo-4-fluorotoluene (2.25 mL, 18.1 mmol) was added dropwise to a stirred suspension of crushed Mg turnings (0.48 g, 19.7 mmol) in THF (10 mL) under argon at 20°C (water bath). The mixture was heated to 75°C for 2 h then cooled to 25°C. A solution of PCl_3 (500 µL, 5.72 mmol) in THF (5 mL) was added with a syringe pump over 30 min, then the mixture was refluxed for 1 h. Once cooled to 0°C, the reaction was quenched with a saturated solution of NH_4Cl and extracted with diethyl ether. After evaporation, a small volume of ethanol was added to the residue and the mixture was filtered to give F-TOTP as a white powder (1.67 g, 82%). M.p. 162°C; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.34$ (s, 3H), 6.39 (ddd, $J = 9.0$, 3.3, 3.3 Hz, 1H), 6.98 (ddd, $J = 8.5$, 8.5, 3.0 Hz, 1H), 7.21 ppm (ddd, $J = 8.4$, 4.8, 4.8 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 20.2$ (d, $J = 21.6$ Hz), 116.1 (d, $J = 20.6$ Hz), 119.1 (d, $J = 23.2$ Hz), 131.7 (dd, $J = 5.8$, 5.8 Hz), 135.7 (dd, $J = 13.2$, 3.8 Hz), 138.2 (d, $J = 26.0$ Hz), 161.4 ppm (d, $J = 246.3$ Hz); ^{31}P NMR (121.5 MHz, $CDCl_3$); $\delta = -27.1$ ppm; ^{19}F NMR (282.4 MHz, $CDCl_3$): $\delta = -116.5$ ppm; elemental analysis: calcd for $C_{21}H_{18}F_3P$: C 70.39, H 5.06; found: C 70.22, H 5.06; HRMS (ESI, MeOH): m/z: calcd for $C_{21}H_{19}F_3P$: 359.1176 $[M+H]^+$; found: 359.1197.

Palladacycle I: A mixture of palladium acetate (20 mg, 0.09 mmol) and phosphane **L4** (42 mg, 0.12 mmol) in toluene (2 mL) was heated to 100°C for 5 min. After evaporation of the toluene, a mixture of dichloromethane (1 mL) and heptanes (1 mL) was added to the residue and the suspension was filtered through celite. The solution was evaporated and the solid residue was crystallized from chloroform/heptanes, to give pale yellow crystals (31 mg, 67%). A monocrystal was analyzed by X-ray diffraction at low temperature;[15] ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.95$ (s, 3H), 2.0–3.3 (br m, 8H), 6.4–7.3 ppm (br m, 9H); ^{13}P NMR (121.5 MHz, $CDCl_3$): $\delta = 32.3$ ppm; ^{19}F NMR (282.4 MHz, $CDCl_3$): $\delta = -117.1$, -116.2, -115.1 ppm.

Representative procedure for the preparation of brominated substrates (1a): Lithium bis(trimethylsilyl)amide (18.3 mL of a 1 M solution in THF, 18.3 mmol) was added dropwise to a solution of 2-bromophenylacetonitrile (1.2 g, 6.1 mmol) and DMPU (2.2 mL, 18.3 mmol) in THF (40 mL) under argon. After the reaction mixture had been stirred for 30 min at room temperature, iodoethane (1.47 mL, 18.3 mmol) was added with a syringe and the reaction mixture was stirred for 1 h. The reaction was quenched with a saturated NH_4Cl solution (40 mL) and the aqueous layer was extracted with diethyl ether (40 mL×3). The combined organic layers were washed with a 1 M HCl solution (40 mL) and with a saturated solution of $NaHCO_3$ (40 mL). The extracts were then dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography (silica gel, heptanes/ethyl acetate 95:5) to afford **1a** as a colorless oil (1.42 g, 92%).[26] ^1H NMR (250 MHz, $CDCl_3$): $\delta = 0.72$ (t, $J = 7.5$ Hz, 6H), 2.06 (m, 2H), 2.65 (m, 2H), 7.17 (dt, $J = 7.5$, 1.3 Hz, 1H), 7.30 (dt, $J = 8.0$, 1.8 Hz, 1H), 7.62 (dd, $J = 7.8$, 1.8 Hz, 1H), 7.69 ppm (dd, $J = 8.0$, 1.8 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 10.4$, 28.6, 52.4, 118.7, 122.6, 127.7, 129.4, 131.2, 131.9, 136.1 ppm.

Representative procedure for the intramolecular C–H functionalization (Table 2, entry 1): A dry resealable Schlenk tube containing a magnetic rod was charged with bromide **1a** (150 mg, 0.59 mmol), palladium acetate (6.7 mg, 0.030 mmol), F-TOTP (21.3 mg, 0.059 mmol), and potassium carbonate (164 mg, 1.19 mmol). The Schlenk tube was twice evacuated and backfilled with argon, before it was capped with a rubber septum. Dry DMF (3 mL) was injected under argon, then the septum was replaced by a screwcap and the mixture was stirred at 100°C (preheated oil bath) for 45 min. After cooling, the mixture was diluted with diethyl ether and filtered through celite. The organic solution was washed with water (6 mL) and the aqueous layer was extracted with diethyl ether (6 mL×3). The combined organic layers were then dried over magnesium sulfate and evaporated. The residue was purified by flash chromatography (silica gel, heptanes/ethyl acetate 95:5) to afford **1b** as an oil (78 mg, 77%).[7,17] ^1H NMR (250 MHz, $CDCl_3$); $\delta = 1.70$ (t, $J = 7.5$ Hz, 3H), 2.10 (m, 2H), 5.36 (d, $J = 10.5$ Hz, 1H), 5.57 (d, $J = 17.4$ Hz, 1H), 5.97 (dd, $J = 17.5$, 10.5 Hz, 1H), 7.35–7.49 ppm (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 9.7$, 33.1, 51.2, 116.5, 120.6, 126.2, 129.0, 130.1, 137.4, 138.6 ppm.

Representative hydroamidation procedure (Table 4, entry 4): A dry Schlenk tube containing a magnetic rod was charged with olefin **1b** (50 mg, 0.29 mmol) and triruthenium dodecacarbonyl (18.7 mg, 0.096 mmol). The schlenk tube was twice evacuated and backfilled with argon, before it was capped with a rubber septum. Dry DMF (0.6 mL) and homoveratrylamine (197 µL, 1.17 mmol) were injected under argon. The Schlenk tube was then purged with carbon monoxide and the mixture was stirred under carbon monoxide at 120°C (preheated oil bath) for 17 h. After cooling, the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (silica gel, heptanes/ethyl acetate 1:4) to afford **18a** as a colorless oil (74 mg, 67%). ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.90 (t, J=7.4 Hz, 3H), 1.87–2.08 (m, 3H), 2.22–2.37 (m, 3H), 2.69 (t, J=7.4 Hz, 2H), 3.34–3.49 (m, 2H), 3.84 (s, 3H), 3,85 (s, 3H), 5.42 (brs, 1H), 6.67 (s, 1H), 6.68 (d, J=8.4 Hz, 1H), 6.79 (d, J=8.4 Hz, 1H), 7.26–7.29 (m, 1H), 7.30–7.32 ppm (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=9.6, 32.4, 34.5, 35.7, 35.1, 40.7, 48.6, 55.8, 55.9, 111.4, 111.8, 120.6, 121.9, 126.0, 127.9, 129.0, 131.2, 137.3, 147.7, 149.1, 171.2 ppm; HRMS (ESI): m/z: calcd for $C_{23}H_{28}N_2O_3Na$: 403.1998 [M+Na$^+$]; found: 403.2002; IR (film): ν=3302, 2232, 1645, 1513 cm^{-1}.

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