Intramolecular Palladium-Catalyzed Alkane C-H Arylation from Aryl Chlorides

ARTICLE *in* JOURNAL OF THE AMERICAN CHEMICAL SOCIETY · AUGUST 2010

Impact Factor: 12.11 · DOI: 10.1021/ja1048847 · Source: PubMed

J|A|C|S ARTICLES

Published on Web 07/21/2010

Intramolecular Palladium-Catalyzed Alkane C−H Arylation from Aryl Chlorides

Sophie Rousseaux,*,† Michaël Davi,‡ Julien Sofack-Kreutzer,‡ Cathleen Pierre,‡ Christos E. Kefalidis,§ Eric Clot,*,§ Keith Fagnou,†,# and Olivier Baudoin*,‡

Centre for Catalysis Research and Innovation, Department of Chemistry, University of Ottawa, 10 Marie Curie, Ottawa, Ontario K1N 6N5, Canada, CNRS UMR5246—Institut de Chimie et Biochimie Moléculaires et Supramoléculaires, Université Claude Bernard Lyon 1, CPE Lyon, 43 Boulevard du 11 Novembre 1918, 69622 Villeurbanne, France, and Institut Charles Gerhardt, Université Montpellier 2, CNRS UMR5253, case courrier 1501, Place Eugène Bataillon, 34095 Montpellier, France

Received June 15, 2010; E-mail: srous100@uottawa.ca; clot@univ-montp2.fr; olivier.baudoin@univ-lyon1.fr

Abstract: The first examples of efficient and general palladium-catalyzed intramolecular C(sp^3)−H arylation of (hetero)aryl chlorides, giving rise to a variety of valuable cyclobutarenes, indanes, indolines, dihydrobenzofurans, and indanones, are described. The use of aryl and heteroaryl chlorides significantly improves the scope of C(sp^3)−H arylation by facilitating the preparation of reaction substrates. Careful optimization studies have shown that the palladium ligand and the base/solvent combination are crucial to obtaining the desired class of product in high yields. Overall, three sets of reaction conditions employing P^tBu_3, $PCyp_3$, or PCy_3 as the palladium ligand and K_2CO_3/DMF or Cs_2CO_3/pivalic acid/mesitylene as the base/solvent combination allowed five different classes of products to be accessed using this methodology. In total, more than 40 examples of C−H arylation have been performed successfully. When several types of C(sp^3)−H bond were present in the substrate, the arylation was found to occur regioselectively at primary C−H bonds vs secondary or tertiary positions. In addition, in the presence of several primary C−H bonds, selectivity trends correlate with the size of the palladacyclic intermediate, with five-membered rings being favored over six- and seven-membered rings. Regio- and diastereoselectivity issues were studied computationally in the prototypal case of indane formation. DFT(B3PW91) calculations demonstrated that C−H activation is the rate-determining step and that the creation of a C−H agostic interaction, increasing the acidity of a geminal C−H bond, is a critical factor for the regiochemistry control.

Introduction

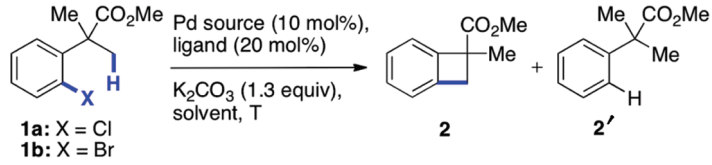
In recent years, transition-metal-catalyzed C−H functionalization has emerged as a powerful tool to transform otherwise unreactive C−H bonds into carbon−carbon or carbon−heteroatom bonds.[1,2] In particular, C−H arylation has become an attractive alternative to traditional C−C cross-coupling reactions due to the minimization of stoichiometric metallic waste and the costs associated with the preparation of starting materials.[3] In regard to the wealth of methods recently developed for the arylation of arene and heteroarene C(sp^2)−H bonds by aryl halides or other aryl electrophiles, relatively little work has focused on the arylation of unreactive C(sp^3)−H bonds of alkyl groups.[4] Efforts by our groups[5,6] and others[7] in the context of alkane arylation under palladium(0) catalysis have led to greater scope for intramolecular reactions, generating various motifs of synthetically useful fused carbocycles and heterocycles.[8] Despite these significant advances in C(sp^3)−H arylation, the aryl halide

† University of Ottawa.
‡ Université Claude Bernard Lyon 1.
§ Université Montpellier 2.
# Deceased November 11, 2009.

(1) *Handbook of C−H Transformations*; Dyker, G., Ed.; Wiley-VCH: Weinheim, 2005.
(2) Selected general reviews: (a) Arndtsen, B. A.; Bergman, R. G.; Mobley, T. A.; Peterson, T. H. *Acc. Chem. Res.* **1995**, *28*, 154. (b) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879. (c) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698. (d) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507. (e) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (f) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439. (g) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (h) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417.
(3) Selected recent reviews: (a) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (b) Goj, L. A.; Gunnoe, T. B. *Curr. Org. Chem.* **2005**, *9*, 671. (c) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2006**, 1253. (d) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (e) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (f) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (g) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447. (h) Bellina, F.; Rossi, R. *Tetrahedron* **2009**, *65*, 10269. (i) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792.
(4) Review on catalytic C(sp^3)−H activation: Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.—Eur. J.* **2010**, *16*, 2654.
(5) (a) Baudoin, O.; Herrbach, A.; Guéritte, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 5736. (b) Hitce, J.; Retailleau, P.; Baudoin, O. *Chem.—Eur. J.* **2007**, *13*, 792. (c) Hitce, J.; Baudoin, O. *Adv. Synth. Catal.* **2007**, *349*, 2054. (d) Chaumontet, M.; Piccardi, R.; Audic, N.; Hitce, J.; Peglion, J.-L.; Clot, E.; Baudoin, O. *J. Am. Chem. Soc.* **2008**, *130*, 15157. (e) Chaumontet, M.; Piccardi, R.; Baudoin, O. *Angew. Chem., Int. Ed.* **2009**, *48*, 179.
(6) Lafrance, M.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 14570.

 10.1021/ja1048847

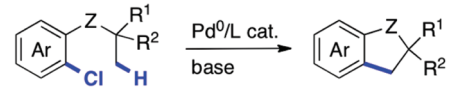
Table 1. Synthesis of Cyclobutarenes: Study of C(sp³)−H Arylation Parameters



entry	halide	Pd source	ligand	solvent	T (°C)	time (h)	conversion (%)[a]	ratio **2**:**2′**[a]	GC yield in **2** (%)[a,b]
1	**1b**	$Pd(OAc)_2$	P^tBu_3[c]	DMF	100	1	>98	>40:1	>98
2	**1a**	$Pd(OAc)_2$	P^tBu_3[c]	DMF	100	16	35	>40:1	29
3	**1a**	$Pd(OAc)_2$	P^tBu_3[c]	DMF	140	3	>98	>40:1	89 (83)
4	**1a**	$Pd(OAc)_2$	PCy_3[c]	DMF	140	16	60	4.3:1	49
5	**1a**	$Pd(OAc)_2$	MeP^tBu_2[c]	DMF	140	16	32	3.1:1	16
6	**1a**	$Pd(OAc)_2$	^{n}BuPAd$_2$[d]	DMF	140	16	95	13.1:1	52
7	**1a**	$Pd(OAc)_2$	JohnPhos	DMF	140	3	29	9.4:1	7
8	**1a**	$Pd(OAc)_2$	Q-Phos	DMF	140	3	60	25:1	33
9	**1a**	$Pd(OAc)_2$	P(*o*-tol)$_3$	DMF	140	16	<2	−	−
10	**1a**	$Pd(TFA)_2$	P^tBu_3[c]	DMF	140	3	94	2.7:1	41
11	**1a**	Pd_2dba_3[e]	P^tBu_3[c]	DMF	140	3	9	1:1.3	4
12	**1a**	$Pd(OAc)_2$	P^tBu_3[c]	DMA	140	3	>98	41:1	92 (77)
13	**1a**	$Pd(OAc)_2$	P^tBu_3[c]	NMP	140	4	94	43:1	82
14	**1a**	$Pd(OAc)_2$	P^tBu_3[c]	mesitylene[f]	140	5	92	7.3:1	45

[a] Calculated using tetradecane as internal standard. [b] Yield of the isolated product in parentheses. [c] Introduced as HBF_4 salt. [d] Introduced as HI salt. [e] 5 mol % Pd_2dba_3/10 mol % P^tBu_3. [f] With 30 mol % pivalic acid as an additive. JohnPhos = 2-(di-*tert*-butylphosphino)biphenyl; Q-Phos = 1,2,3,4,5-pentaphenyl-1′-(di-*tert*-butylphosphino)ferrocene.

coupling partners remain almost exclusively aryl iodides or bromides. The limited use of (hetero)aryl chlorides in these reactions is surprising, considering the advances that have been made in C(sp²)−H arylations as well as in other cross-couplings.[9] This may be attributed in part to the greater strength of the C−Cl bond rendering oxidative addition less facile,[10] in addition to the well-established lack of reactivity of nonacidic C(sp³)−H bonds.[4] However, using aryl and heteroaryl chlorides as substrates for intramolecular C(sp³)−H arylations would have two important advantages over the use of bromides and iodides: (1) lower cost and greater number of commercially available starting materials and (2) improved synthesis of the C−H arylation substrates due to reduced steric hindrance.[11] Herein, we describe our joint efforts to expand the scope of intramolecular C(sp³)−H arylations to include aryl and heteroaryl chlorides for the synthesis of a wide range of polycyclic molecules, including cyclobutarenes, indanes, indolines, dihydrobenzofurans, and indanones, some of which have not been described previously and are hard to access from other aryl halides (eq 1). We also disclose new theoretical studies which greatly improve our understanding of C(sp³)−H activation with regard to regio- and stereoselectivity issues through the use of DFT calculations.



(1)

Z = no atom, CR_2, N–R, O, C=O

Results and Discussion

1. Synthesis of Cyclobutarenes. Cyclobutarenes are both important structural elements in active pharmaceutical ingredients and valuable reactive intermediates for organic synthesis.[12] Despite their high synthetic value, very few general and chemoselective methods exist for the preparation of functionalized cyclobutarenes, limiting their availability and their use as synthetic intermediates. On the basis of previous results from one of our groups on the synthesis of benzocyclobutenes (BCBs) from aryl bromides by intramolecular C(sp³)−H arylation,[5d] we examined the use of aryl chlorides as substrates for this reaction which, if successful, would significantly improve synthetic access to this important class of molecules. The conditions previously described for the reaction of aryl bromide **1b** giving BCB **2** (Table 1) employed $Pd(OAc)_2/P^tBu_3$ as the catalytic system and K_2CO_3 as the base in *N*,*N*-dimethylformamide (DMF) at 140 °C. More recently, we found that the reaction could be run at 100 °C without affecting the reaction efficiency (entry 1). Under the same conditions, only low conversion of aryl chloride **1a** was observed, even after prolonged heating (entry 2). Gratifyingly, by increasing the temperature to 140

(7) (a) Dong, C.-G.; Hu, Q.-S. *Angew. Chem., Int. Ed.* **2006**, *45*, 2289. (b) Ren, H.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3462. (c) Ren, H.; Zi, L.; Knochel, P. *Chem. Asian J.* **2007**, *2*, 416. (d) Liron, F.; Knochel, P. *Tetrahedron Lett.* **2007**, *48*, 4943. (e) Dong, C.-G.; Hu, Q.-S. *Tetrahedron* **2008**, *64*, 2537. (f) Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2008**, *10*, 1759. (g) Salcedo, A.; Neuville, L.; Zhu, J. *J. Org. Chem.* **2008**, *73*, 3600. (h) Kim, H. S.; Gowrisankar, S.; Kim, S. H.; Kim, J. N. *Tetrahedron Lett.* **2008**, *49*, 3858. (i) Huang, Q.; Larock, R. C. *Tetrahedron Lett.* **2009**, *50*, 7235. (j) Kim, K. H.; Lee, H. S.; Kim, S. H.; Kim, S. H.; Kim, J. N. *Chem.−Eur. J.* **2010**, *16*, 2375.

(8) Intermolecular C(sp³)−H arylation under Pd^0/phosphine catalysis: (a) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685. (b) Niwa, T.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2007**, *9*, 2373. (c) Campeau, L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266. (d) Mousseau, J. J.; Larivée, A.; Charette, A. B. *Org. Lett.* **2008**, *10*, 1641. (e) Niwa, T.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2008**, *10*, 4689. (f) Schipper, D. J.; Campeau, L.-C.; Fagnou, K. *Tetrahedron* **2009**, *65*, 3155. (g) Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 9886.

(9) Review on the use of aryl chlorides in palladium-catalyzed coupling reactions: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.

(10) Bond dissociation energies for Ph−X: Cl, 95.5 kcal mol^{-1}; Br, 80.4 kcal mol^{-1}; I, 65.0 kcal mol^{-1}. Luo, Y. R. *Handbook of Bond Dissociation Energies in Organic Compounds*; CRC Press: Boca Raton, FL, 2003; Chapter 5.

(11) Van der Waals radii: Cl, 1.75 Å; Br, 1.85 Å; I, 1.98 Å. *Handbook of Chemistry and Physics*; CRC Press: Boca Raton, FL, 2008.

(12) (a) Mehta, G.; Kotha, S. *Tetrahedron* **2001**, *57*, 625. (b) Sadana, A. K.; Saini, R. K.; Billups, W. E. *Chem. Rev.* **2003**, *103*, 1539.

°C (entry 3), complete conversion of **1a** was reached, and BCB **2** was obtained in 89% GC yield (83% isolated yield). No trace of the protodehalogenated product **2′**, the usual side product in these reactions, was observed. Other catalysts and solvents provided different outcomes for the reactions of **1a** and **1b**. In particular, tri-*tert*-butylphosphine was by far the most efficient ligand with **1a** among a panel of monophosphine ligands (entries 3−9), whereas bulkier monophosphine ligands such as JohnPhos, Q-Phos, and P(*o*-tol)$_3$ gave good results with **1b**.[5d] Thus, P^{t}Bu$_3$ appears to have the optimal electronic and steric properties (Tolman cone angle = 182°) for the intramolecular C−H arylation of chloride **1a**.[13,14] Palladium acetate (entry 3) was also the most active palladium precatalyst (see entries 10 and 11 for examples of other Pd sources). Finally, solvents other than DMF could be employed for the arylation of **1a**, including *N*,*N*-dimethylacetamide (DMA) and *N*-methylpyrrolidone (NMP) (entries 12 and 13), but DMF gave the highest yield of isolated BCB. Interestingly, using mesitylene as the solvent with 30 mol % of pivalic acid as an additive, a combination that gave good results in other intramolecular C(sp^3)−H arylations (*vide infra*),[6] led to irreproducible yields of **2** (entry 14).

The optimal set of conditions was applied to the C(sp^3)−H arylation of a wide range of aryl and heteroaryl chlorides (Table 2). As anticipated, the presence of the chlorine atom greatly facilitated the synthesis of most arylation substrates due to the better availability of starting materials and to the reduced influence of steric hindrance.[15] For instance, dichloride **15** was prepared in one step from a commercially available material using a stoichiometric amount of reagents, whereas four steps and an excess in reagents were required for the corresponding bromide.[5d] Moreover, in some cases, for example chlorides **13**, **27**, and **29**, the corresponding aryl bromide would be almost inaccessible by typical synthetic routes.

The standard arylation conditions were found to be compatible with a wide range of substituents on the benzylic carbon (entries 1−6) and the aromatic ring (entries 7−12), giving rise to the corresponding BCBs in 65−87% yield. In the case of substrates with mutiple arylation sites (entries 4 and 5), the reaction showed complete regioselectivity for arylation at the methyl group. In the case of dichloride **15** (entry 8), careful monitoring of the reaction conversion allowed BCB **16** to be obtained in good yield after 30 min, whereas with prolonged heating a mixture of **16** and the corresponding dechlorinated product was obtained. Arylation of chloride **19** gave rise to a 3.6:1 mixture of BCB isomers **20a**,**b** (entry 10). The formation of isomer **20b**, which was also observed from the corresponding aryl bromide,[5d] presumably arises from a palladium migration within the catalytic cycle.[16] Indeed, DFT calculations have demonstrated that reductive elimination to form the strained BCB four-membered ring is highly energetic and thus is in competition with palladium migration.[5d] The reaction conditions were also effective for heteroaryl chlorides. Indeed, chloropyridine **25** (entry 13), chloroquinoline **27** (entry 14), and chloroindole **29** (entry 15) yielded valuable heterocycles that are typically unaccessible through more traditional synthetic methods. For quinoline **27** (entry 14), the reaction was conducted at a lower temperature (110 °C) to avoid the formation of a side product arising from cyclobutene ring-opening.[17] From indole **29** (entry 15), a 2:5 separable mixture of isomers **30a** and **30b**, arising from cyclization at the C-5 and C-3 position of the indole nucleus, respectively, was obtained. To the best of our knowledge, compound **30b** is surprisingly the first isolated molecule with the 3,4-dihydro-1*H*-cyclopenta[*c*,*d*]indole scaffold, which is structurally related to the orchid alkaloid dendrobine.[18] This isomer most likely arises from palladium migration, similar to that observed with aryl chloride **19** (entry 10). Research is ongoing to further study this rearrangement in detail.

2. Synthesis of Indanes. In a previous report, some of us described the synthesis of indanes from aryl bromides by intramolecular C(sp^3)−H arylation at the terminal carbon of an isopropyl group.[5b] For instance, the reaction of bromide **31b** using 5 mol % Pd(OAc)$_2$ and 20 mol % F-TOTP as catalyst in DMF at 100 °C furnished a 4:1 mixture of indane **32a** (as a single diastereoisomer) and the dehydrogenation product **33** (Table 3, entry 1). This catalyst was found to be ineffective in the reaction of the corresponding aryl chloride **31a**, even at 140 °C (entry 2). A rapid ligand screen (entries 3−9) revealed that trialkylphosphines with cone angles between 160 and 170° have optimal steric properties for this reaction,[14] with PCy$_3$, PCyp$_3$, and P^{i}Pr$_3$ giving rise to an inseparable diastereoisomeric mixture of **32a**:**32b** (dr = 4:1 in favor of the *cis* diastereoisomer **32a**)[19] in high yield and with no trace of olefin **33** (entries 5−7). Interestingly, lower selectivity of indane vs olefin product with concomitant higher diastereoselectivity was obtained with P^{t}Bu$_3$, compared to less bulky trialkylphosphines (entry 3). Tricyclopentylphosphine, which gave the highest isolated yield of diastereoisomers **32a**,**b** (92%, entry 6), was retained for further scope studies (*vide infra*). Decreasing the temperature to 120 °C led to incomplete conversion (entry 9). Finally, replacing DMF by other solvents such as DMA or mesitylene (with 30 mol % of pivalic acid as an additive)[6] gave lower yields of indane products.

The optimal conditions were applied to a range of other aryl and heteroaryl chlorides (Table 4). Again, the ease of synthesis of most arylation substrates was significantly improved compared to that of the corresponding aryl bromides. The presence of electron-withdrawing (entries 2 and 3) or -donating (entry 4) substituents on the aromatic ring did not affect the efficiency of the reaction, and the corresponding indanes were obtained in very good yields as 3.3:1 to 4:1 diastereoisomeric mixtures, always in favor of the *cis* diastereoisomer.[19] Interestingly, no isomerized product arising from palladium migration was observed in the reaction of aryl chloride **34** (entry 2), in contrast to BCB formation from the analogous substrate **19** (Table 2, entry 10). This observation indicates that reductive elimination to form the indane five-membered ring is faster than palladium migration. Remarkably, the intramolecular arylation of homochiral *trans*-dimethylcyclopentane compounds **40** and **42** furnished tricyclic products **41** and **43**, respectively, in very good yield and as a single stereoisomer (entries 5 and 6). The reaction

(13) (a) Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313. (b) Brown, T. L.; Lee, K. J. *Coord. Chem. Rev.* **1993**, *128*, 89. (c) Clavier, H.; Nolan, S. P. *Chem. Commun.* **2010**, *46*, 841.

(14) Tolman cone angles θ:[13] JohnPhos, 246°; CyJohnPhos, 226°; P(*o*-tol)$_3$, 194°; P^{t}Bu$_3$, 182°; PCy$_3$, 170°; MeP^{t}Bu$_2$, 161°; P^{i}Pr$_3$, 160°; P^{n}Bu$_3$, 132°.

(15) See the Supporting Information for detailed experimental procedures.

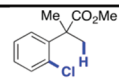
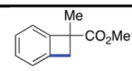
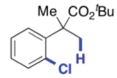
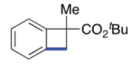
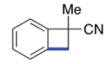
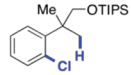
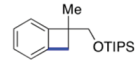
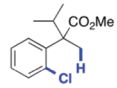
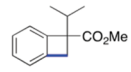
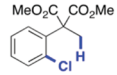
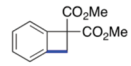
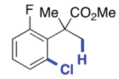
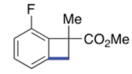
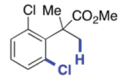
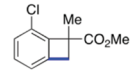
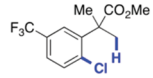
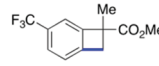
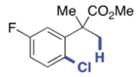
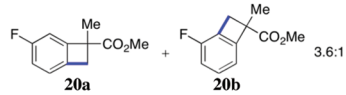
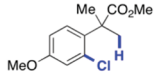
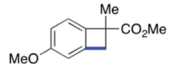
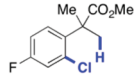
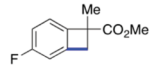
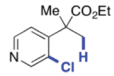
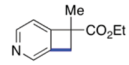
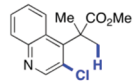
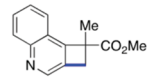
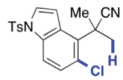
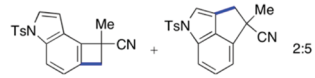
(16) Reviews on palladium migrations: (a) Ma, S.; Gu, Z. *Angew. Chem., Int. Ed.* **2005**, *44*, 7512. (b) Shi, F.; Larock, R. C. *Top. Curr. Chem.* **2010**, *292*, 123.

(17) Jefford, C. W.; Bernardinelli, G.; Wang, Y.; Spellmeyer, D. C.; Buda, A.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 1157.

(18) (a) Yamamura, S.; Hirata, Y. *Tetrahedron Lett.* **1964**, *5*, 79. (b) Inubushi, Y.; Sasaki, Y.; Tsuda, Y.; Yasui, B.; Konita, T.; Matsumoto, J.; Katarao, E.; Nakano, J. *Tetrahedron* **1964**, *20*, 2007. (c) Onaka, R.; Kamata, S.; Maeda, T.; Kawazoe, Y.; Natsume, M.; Okamoto, T.; Uchimaru, F.; Shimizu, M. *Chem. Pharm. Bull.* **1964**, *12*, 506.

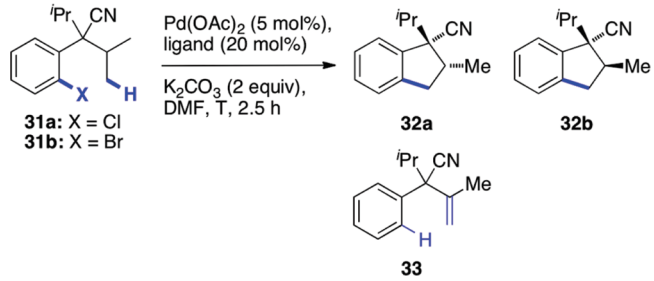
(19) Relative configurations were ascribed by NOESY experiments.

Table 2. Scope of Cyclobutarenes Synthesized by Intramolecular C(sp³)−H Arylation[a]

entry	aryl/heteroaryl chloride	cyclobutarene product(s)[b]	time (h)	yield (%)[c]
1	 **1a**	 **2**	3	83
2	 **3**	 **4**	2	71
3	 **5**	 **6**	2	65
4	 **7**	 **8**	4	66
5	 **9**	 **10**	3	70
6	 **11**	 **12**	2	74
7	 **13**	 **14**	3	85
8[d]	 **15**	 **16**	0.5	72
9	 **17**	 **18**	2	87
10[d]	 **19**	 **20a** + **20b** 3.6:1	6	75
11	 **21**	 **22**	5	66
12	 **23**	 **24**	2	76
13	 **25**	 **26**	5	60
14[e]	 **27**	 **28**	24	63
15	 **29**	 **30a** + **30b** 2:5	2.5	69

[a] Reaction conditions: $Pd(OAc)_2$, 10 mol %; ($^tBu_3PH)BF_4$, 20 mol %; K_2CO_3, 1.3 equiv; DMF; 140 °C. [b] The ratio of isomers (when applicable) was measured by ^1H NMR of the crude mixture. [c] Yields of isolated products. [d] DMA was used instead of DMF. [e] Reaction performed at 110 °C. TIPS = triisopropylsilyl.

Table 3. Synthesis of Indanes: Study of C(sp^3)−H Arylation Parameters



entry	halide	ligand	T (°C)	conversion (%)[a]	selectivity (**32a** + **32b**):**33**[b]	GC yield **32a** + **32b** (%)[a,c]	dr **32a**:**32b**[b]
1	**31b**	F-TOTP	100	>98	4:1	66 (50)	>40:1
2	**31a**	F-TOTP	140	20	−	0	−
3	**31a**	P^{t}Bu$_3$[d]	140	>98	1:1	53	20:1
4	**31a**	CyJohnPhos	140	54	>40:1	18	4:1
5	**31a**	PCy$_3$[d]	140	>98	>40:1	88 (83)	4:1
6	**31a**	PCyp$_3$[d]	140	>98	>40:1	94 (92)	4:1
7	**31a**	P^{i}Pr$_3$[d]	140	>98	>40:1	93 (87)	4:1
8	**31a**	P^{n}Bu$_3$[d]	140	29	>40:1	27	−
9	**31a**	PCy$_3$[d]	120	52	>40:1	49	4:1

[a] Calculated using tetradecane as internal standard. [b] Determined by ^{1}H NMR of the crude mixture. [c] Yield of the isolated product in parentheses. [d] Introduced as HBF_4 salt. F-TOTP = tris(5-fluoro-2-methylphenyl)phosphine; CyJohnPhos = 2-(dicyclohexylphosphino)biphenyl; PCyp$_3$ = tricyclopentylphosphine.

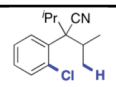
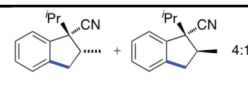
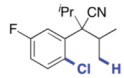
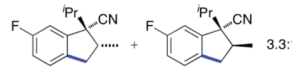
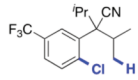
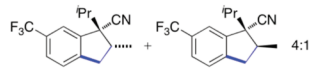
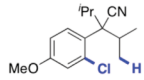
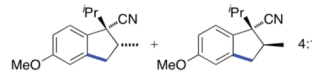
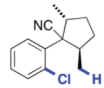
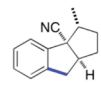
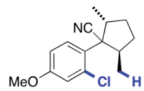
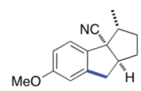
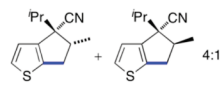
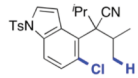
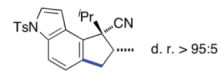
was also effective from heteroaryl chlorides **44** and **46** (entries 7 and 8), giving rise to original fused thiophenes **45a**,**b** and indole **47**, respectively, in good yield. Interestingly, higher diastereoselectivity was attained in the latter case, with only one diastereoisomer being observed due to additional substitution on the aromatic ring at the positon *ortho* to the activated alkyl group. In this study, it is interesting to note that C−H arylation occurs exclusively on the terminal methyl group of aryl chloride substrates, giving rise to five-membered rings (entries 1−8). No trace of arylation at the methyne C−H bond yielding a cyclobutarene was detected.

The mechanism of formation of **32a** and **32b** from **31a** has been studied computationally at the B3PW91 level (see Computational Details). Only the C−H activation and C−C coupling steps have been considered. We have already shown that, for the formation of BCBs from aryl bromides, C−H activation is the rate-determining step through a concerted metalation−deprotonation (CMD) mechanism[6,20,21] with the base coordinated *cis* to the aryl group.[5d] Kinetic studies by Hartwig[22] and Baird[23] of C−X oxidative addition have shown that, for C−Br, reaction at both the bisphosphine and monophosphine Pd^0 complexes is possible, whereas for C−Cl, formation of the monophosphine Pd^0 complex is mandatory to achieve any oxidative addition. The C−X oxidative addition of **31a** (X = Cl) and **31b** (X = Br) to Pd(PCyp$_3$) has been computed; as expected, the activation barrier for X = Cl is higher than for X = Br (12.3 vs 4.7 kcal mol^{-1}), but the values are very low compared to the activation barriers for C−H activation (*vide infra*). Therefore, we can assume that the C−Cl oxidative addition occurs on a monophosphine Pd^0 complex and is not rate-limiting. Substitution of the halide by the base affords an ML$_3$ complex that is the reactant for further functionalization. The transformation studied in the present work is shown in Scheme 1. The calculations make explicit use of the experimental phosphine PCyp$_3$ and bicarbonate (HCO_3^-) as the base. Formation of the experimentally nonobserved BCB **32c** was also characterized computationally to better highlight the factors at the origin of the regioselectivity in the C−H activation.

The starting reactant features a vacant site prone to the establishment of an agostic interaction with a C−H bond of one of the isopropyl groups. Three different agostic complexes (**Agos-a**, **Agos-b**, and **Agos-c**) have been located on the potential energy surface (PES), and they constitute the starting point for the formation of **32a**, **32b**, and **32c**, respectively (Figure 1). **Agos-a** is the most stable structure, with **Agos-b** and **Agos-c** lying ΔG = 4.1 and 6.8 kcal mol^{-1} higher in energy, respectively. In the three complexes, the agostic C−H bond is elongated and has a similar length (1.146 Å, **Agos-a**; 1.144 Å, **Agos-b**; 1.144 Å, **Agos-c**). The H···Pd distance does not mirror the relative stability of the agostic complexes, with the shortest value (1.802 Å) obtained with **Agos-b** and the longest (1.858 Å) with **Agos-c** (H···Pd = 1.814 Å in **Agos-a**). The critical geometrical parameter that explains the relative stability of the agostic complexes is the value of the incipient Pd···C bond distance, with a smaller value for **Agos-a** (2.408 Å) than for the two less stable complexes (2.430 Å, **Agos-b**; 2.819 Å, **Agos-c**).

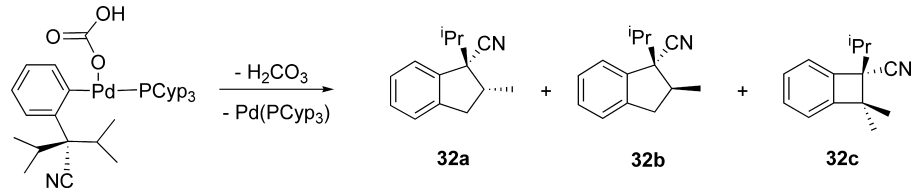
(20) Computational studies on the CMD pathway in C(sp^2)−H activation: (a) Biswas, B.; Sugimoto, M.; Sakaki, S. *Organometallics* **2000**, *19*, 3895. (b) Davies, D. L.; Donald, S. M. A.; Macgregor, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 13754. (c) García-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066. (d) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754. (e) Alonso, I.; Alcamí, M.; Mauleón, P.; Carretero, J. C. *Chem.−Eur. J.* **2006**, *12*, 4576. (f) García-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880. (g) Özdemir, I.; Demir, S.; Çetinkaya, B.; Gourlaouen, C.; Maseras, F.; Bruneau, C.; Dixneuf, P. H. *J. Am. Chem. Soc.* **2008**, *130*, 1156. (h) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848. (i) Pascual, S.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *Tetrahedron* **2008**, *64*, 6021.
(21) Reviews: (a) Boutadla, Y.; Davies, D. L.; Macgregor, S. A.; Poblador-Bahamonde, A. I. *Dalton Trans.* **2009**, 5820. (b) Balcells, D.; Clot, E.; Eisenstein, O. *Chem. Rev.* **2010**, *110*, 749.
(22) Barrios-Landeros, F.; Carrow, B. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 8141.
(23) Mitchell, E. A.; Jessop, P. G.; Baird, M. C. *Organometallics* **2009**, *28*, 6732.

Table 4. Scope of Indanes Synthesized by Intramolecular C(sp³)−H Arylation[a]

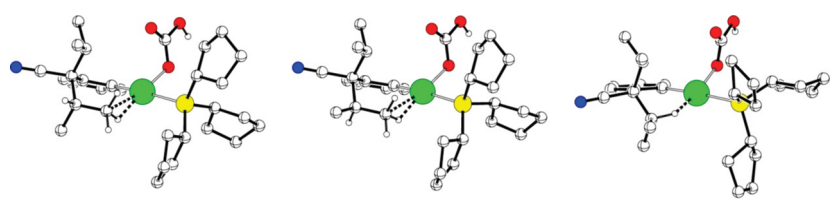
entry	aryl/heteroaryl chloride	product(s)[b]	time (h)	yield (%)[c]
1	 **31a**	 4:1 **32a** **32b**	2.5	92
2	 **34**	 3.3:1 **35a** **35b**	12	84
3	 **36**	 4:1 **37a** **37b**	6	82
4	 **38**	 4:1 **39a** **39b**	12	88
5	 **40**	 **41**	4	79
6	 **42**	 **43**	14	94
7	 **44**	 4:1 **45a** **45b**	2.5	73
8	 **46**	 d. r. > 95:5 **47**	14	62

[a] Reaction conditions: $Pd(OAc)_2$, 5 mol %; $(Cyp_3PH)BF_4$, 20 mol %; K_2CO_3, 2 equiv; DMF; 140 °C. [b] All products are racemic mixtures except for entries 5 and 6. The ratio of diastereoisomers was measured by ^1H NMR of the crude mixture. [c] Yields of isolated products.

Scheme 1. Transformation of ML_3 Intermediate to Potential Alkane C−H Arylation Products Evaluated in the Computational Study



It is interesting to note that, in **Agos-a** and **Agos-b**, the agostic C−H bond is *trans* to the coordinated base. In the classical picture where creation of an agostic interaction weakens the C−H bond to be cleaved, this *trans* geometry constitutes a hurdle to overcome. However, Macgregor has recently demonstrated that an agostic interaction can promote the deprotonation of a geminal C−H bond.[24] The geometry in **Agos-a** and **Agos-b** is particularly adapted to deprotonation of a geminal



Agos-a **Agos-b** **Agos-c**

Figure 1. Optimized geometries for agostic complexes **Agos-a**, **Agos-b**, and **Agos-c**. Most H atoms have been omitted for clarity.

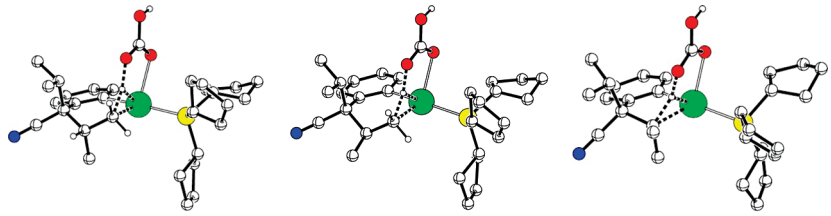


Figure 2. Optimized geometries for the CMD transition states for C−H bond cleavage, **TSCH-a**, **TSCH-b**, and **TSCH-c**. Most H atoms have been omitted for clarity.

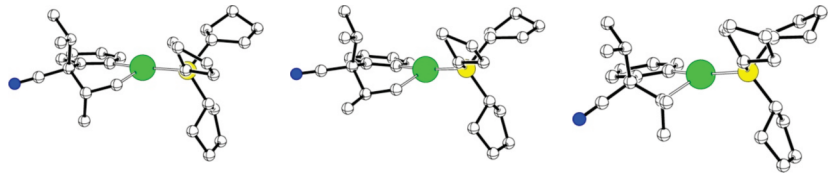


Figure 3. Optimized geometries for palladacycles **Cyc-a**, **Cyc-b**, and **Cyc-c** produced by C−H activation. All H atoms have been omitted for clarity.

C−H bond by the coordinated base, as illustrated by the optimized structure of the transition states **TSCH-a** and **TSCH-b** (Figure 2). In the case of **Agos-c**, the agostic interaction must be cleaved prior to actual C−H bond cleavage, as illustrated by the geometry of **TSCH-c** in Figure 2. The geometries of the transition states for C−H bond cleavage are typical of CMD processes with concerted cleavage of the C−H bond (1.404 Å, **TSCH-a**; 1.407 Å, **TSCH-b**; 1.539 Å, **TSCH-c**) and formation of O−H (1.495 Å, **TSCH-a**; 1.486 Å, **TSCH-b**; 1.421 Å, **TSCH-c**) and Pd−C bonds (2.232 Å, **TSCH-a**; 2.221 Å, **TSCH-b**; 2.344 Å, **TSCH-c**). The activation barrier, $\Delta G_{1,x}^{\#}$, estimated as the Gibbs free energy difference between **TSCH-x** and the agostic complex **Agos-x** (**x** = **a**, **b**, or **c**) from which it originates, varies as follows: $\Delta G_{1,a}^{\#} = 26.2$ kcal mol^{-1}, $\Delta G_{1,b}^{\#} = 27.5$ kcal mol^{-1}, and $\Delta G_{1,c}^{\#} = 33.8$ kcal mol^{-1}. There is thus a clear energetic preference to activate the primary C−H isopropyl bond with respect to the tertiary one. For activation at the primary carbon, the pathway leading to **32a** is preferred over that leading to **32b** by 1.3 kcal mol^{-1}. It is interesting to note that the experimental ratio of 4:1 between **32a** and **32b** at 140 °C corresponds to a difference in activation energy between the two pathways of ca. 1.1 kcal mol^{-1}. The more facile activation in **TSCH-a** can be traced back to the stronger Pd···C interaction in **Agos-a** leading to more acidic character on the geminal hydrogen atom to be transferred. This is illustrated by the shorter C···H and longer O···H bonds in **TSCH-a**. The Pd···C bond is ca. 0.1 Å longer in **TSCH-c** than in **TSCH-b**, as a result of the intrinsic weaker bond energy for a Pd−C bond at a tertiary carbon with respect to a Pd−C bond at a primary carbon.

Following proton transfer to the base, the latter dissociates, and six- or five-membered palladacycles **Cyc-a**, **Cyc-b**, and **Cyc-c** are formed (Figure 3). **Cyc-a** is the most stable palladacycle, with **Cyc-b** and **Cyc-c** lying 1.3 and 5.3 kcal mol^{-1} higher, respectively. With respect to the agostic complex **Agos-x**, the C−H activation is exoergic on the Gibbs free energy surface ($\Delta G_a = -16.9$ kcal mol^{-1}, $\Delta G_b = -19.7$ kcal mol^{-1}, $\Delta G_c = -18.3$ kcal mol^{-1}) due to the dissociation of the protonated base.

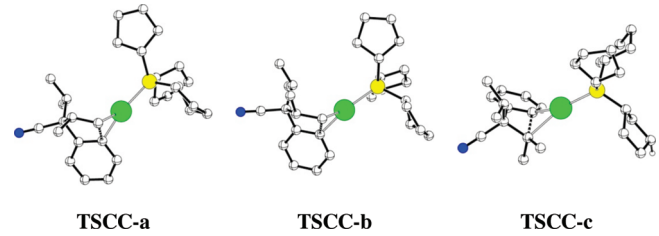


Figure 4. Optimized geometries for the transition states for C−C coupling, **TSCC-a**, **TSCC-b**, and **TSCC-c**. All H atoms have been omitted for clarity.

As expected, C−C reductive elimination through **TSCC-x** (**x** = **a**, **b**, or **c**, Figure 4) is easier from six-membered palladacycles **Cyc-a** and **Cyc-b**, with activation barriers $\Delta G_{2,a}^{\#} = 10.4$ kcal mol^{-1} and $\Delta G_{2,b}^{\#} = 12.6$ kcal mol^{-1}. In contrast, the formation of BCB **32c** through **TSCC-c** is more difficult, with $\Delta G_{2,c}^{\#} = 24.7$ kcal mol^{-1}. This result clearly shows that reductive elimination to form strained BCBs is much less favored than that giving rise to indanes, explaining why palladium migration is operative in the former reaction (Table 2, entries 10 and 15), whereas it is not observed in the latter (Table 4, entry 2). The activation barrier for C−C coupling results essentially from the necessary loss of Pd−C bonding in order to reach a geometry adapted to C−C bond formation (Figure 4). In the case of **TSCC-a**, the Pd−C_{sp^2} bond length increases from 1.994 Å in **Cyc-a** to 2.010 Å in **TSCC-a**, while the Pd−C_{sp^3} bond increases from 2.030 to 2.143 Å. As a consequence, the forming C_{sp^2}···C_{sp^3} bond is 2.069 Å in **TSCC-a**. For **TSCC-b**, the variations are similar, with an increase of Pd−C_{sp^2} from 1.996 Å in **Cyc-b** to 2.005 Å in the transition state, while Pd−C_{sp^3} increases from 2.025 to 2.146 Å. This results in a C_{sp^2}···C_{sp^3} bond of 2.111 Å at the transition state. For the five-membered ring in **Cyc-c**, the situation is drastically different. While the Pd−C_{sp^2} bond is again only slightly elongated in the TS (1.994 Å, **Cyc-c**; 2.030 Å, **TSCC-c**), a significant elongation of the Pd−C_{sp^3} bond from 2.076 to 2.397 Å is observed. This decrease in Pd−C bonding explains the

(24) Häller, L. J. L.; Page, M. J.; Macgregor, S. A.; Mahon, M. F.; Whittlesey, M. K. *J. Am. Chem. Soc.* **2009**, *131*, 4604.

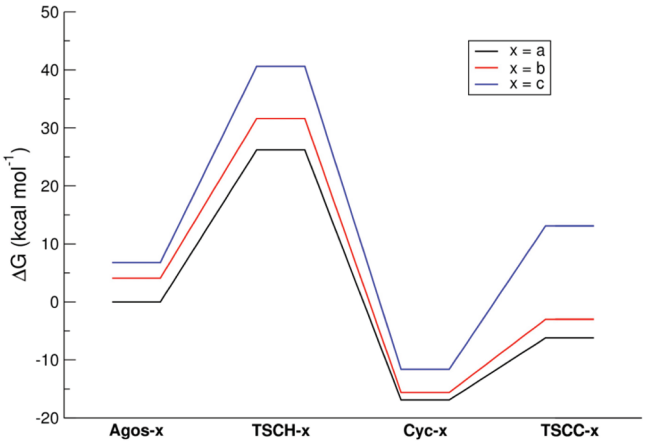


Figure 5. Gibbs free energy (kcal mol^{-1}) profiles for the formation of **32a**, **32b**, and **32c** from the corresponding agostic complexes.

higher value of the activation energy for **TSCC-c**. To compensate for this loss and to accommodate the strain in the forming four-membered ring, the $C_{sp^2}\cdots C_{sp^3}$ bond is shorter in **TSCC-c** (1.933 Å) than in the other transition states.

A comparison of the Gibbs free energy profiles at 298 K for the formation of the three different isomers **32a**, **32b**, and **32c** from the respective agostic complexes **Agos-a**, **Agos-b**, and **Agos-c** is given in Figure 5. In the three cases, C−H activation is the rate-determining step, and activation at the primary position of the isopropyl group is clearly preferred over activation at the tertiary position. If activation barriers are estimated from the most stable agostic complex, **Agos-a**, then the difference between pathways a and b ($\Delta\Delta G^{\#}$ = 5.4 kcal mol^{-1}) would preclude any observation of **32b**. However, the Gibbs free energy in the present work is estimated as a combination of solvent-corrected energy (PCM model) and gas-phase Gibbs free energy corrections (see Computational Details). The latter is obtained within the harmonic approximation for the vibrational component, and this may introduce errors. As a matter of fact, whereas the relative energy of **Agos-a** and **Agos-b** is the same when PCM energies or Gibbs free energies are considered (4.2 vs 4.1 kcal mol^{-1}), the situation is different for the relative energy of the two transition states (3.2 kcal mol^{-1}, PCM; 5.4 kcal mol^{-1} PCM + gas-phase correction). In the transition state for C−H bond cleavage, the incipient six-membered palladacycle presents 1,2-diaxial alkyl groups in **TSCH-a**, while these groups are axial−equatorial in **TSCH-b**. This introduces extra stabilization in the latter and may contribute to reducing the energy difference between the two activation barriers, leading finally to the observation of two diastereoisomers. Nevertheless, according to the calculations, **32a** is the major product of the reaction, and no BCB is likely to be formed.

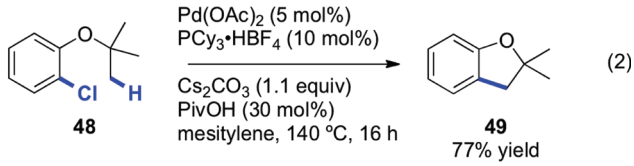
This result is to be compared to the outcome of the reaction of aryl chloride **9** (Table 2, entry 5), where BCB formation is preferred over indane formation. In the case of **9**, the methyl group can create a stabilizing agostic interaction with a C−H bond, while preserving an acidic geminal C−H bond to be deprotonated by the coordinated base. The situation is different in aryl chloride **31a**, where this dual behavior is possible only at the terminal position of the isopropyl group, leading to indane formation. To test the validity of our model for the regiochemistry of C−H activation, calculations were carried out on a model system (**9′**) related to **9**, where the ester group has been substituted with CN in order to keep a system as close as possible to **31a**. Reaction with Pd(PCyp$_3$) and bicarbonate has been considered. In addition to pathways a, b, and c, there is now a new pathway (d) corresponding to C−H activation at the methyl group and formation of a BCB similar to **10**. The geometries of the agostic complexes, the transition states for C−H activation, the palladacycles, and the transition states for C−C coupling are shown in Figure S1 of the Supporting Information, and a comparison of the Gibbs free energy profiles at 298 K is given in Figure S2. The most stable agostic complex is **Agos-d′**, with **Agos-a′** lying only 0.5 kcal mol^{-1} above. There is thus no particular difference in stability between the agostic complexes leading to five- and six-membered palladacycles, provided two hydrogen atoms are present on the agostic carbon (**Agos-c′** is 4.4 kcal mol^{-1} above **Agos-d′**). The lowest transition state is **TSCH-d′**, corresponding to C−H activation at the methyl group, and the activation barrier from **Agos-d′** is 25.6 kcal mol^{-1}. The transition state for C−H activation at the terminal position of the isopropyl group, **TSCH-a′**, leading to an indane diastereoisomer similar to **32a**, lies 2.0 kcal mol^{-1} above **TSCH-d′**, while that corresponding to the other terminal C−H activation, **TSCH-b′**, is 2.6 kcal mol^{-1} above **TSCH-d′**. As expected, the transition state for C−H activation at the tertiary position of the isopropyl group, **TSCH-c′**, lies at significantly higher energy than **TSCH-d′** (13.4 kcal mol^{-1}). Here again, the C−H activation is the rate-determining step, even though the C−C coupling process is more difficult for formation of the four-membered ring with respect to the five-membered ring (Figure S2). Qualitatively, there is thus a significant preference for C−H activation at the methyl group in **9′**, leading to formation of the BCB product. The $\Delta\Delta G^{\#}$ value of 2.0 kcal mol^{-1} between **TSCH-d′** and **TSCH-a′** is in agreement with the exclusive formation of the BCB observed experimentally in the case of **9**. However, experimentally **9** is converted to **10** with P^{t}Bu$_3$ as the phosphine ligand, and the present calculations were carried out with PCyp$_3$. The actual nature of the phosphine ligand could have an important role in the quantitative description of the regiochemistry of the C−H functionalization. More calculations are needed to test the influence of the nature of the phosphine ligand and of the base to orient the regiochemistry toward a desired target; computations are presently being carried out to study this aspect.

3. Synthesis of Dihydrobenzofurans and Indolines. Some of us recently developed conditions for the formation of 2,2-dialkyldihydrobenzofurans from aryl bromides by intramolecular C(sp^3)−H arylation.[6] Given the relevance of this motif in biological[25] and medicinal compounds,[26] the use of aryl chlorides for their formation was investigated. When aryl chloride **48**, possessing an *ortho tert*-butoxy substituent, was subjected to Pd(OAc)$_2$ (5 mol %), (Cy$_3$PH)BF$_4$ (10 mol %), Cs$_2$CO$_3$ (1.1 equiv), and PivOH (30 mol %) in mesitylene at 140 °C for 16 h, the desired product **49** was generated in 77%

(25) (a) Gerwick, W. H.; Fenical, W. *J. Org. Chem.* **1981**, *46*, 22. (b) Torres, R.; Villarroel, L.; Urzua, A.; Delle Monache, F.; Delle Monache, G.; Gacs-Baitz, E. *Phytochemistry* **1994**, *36*, 249.

(26) (a) Cohen, M. L.; Bloomquist, W.; Gidda, J. S.; Lacefield, W. *J. Pharmacol. Exp. Ther.* **1990**, *254*, 350. (b) Ohkawa, S.; Fukatsu, K.; Miki, S.; Hashimoto, T.; Sakamoto, J.; Doi, T.; Nagai, Y.; Aono, T. *J. Med. Chem.* **1997**, *40*, 559. (c) Tamura, K.; Kato, Y.; Ishikawa, A.; Kato, Y.; Himori, M.; Yoshida, M.; Takashima, Y.; Suzuki, T.; Kawabe, Y.; Cynshi, O.; Kodama, T.; Niki, E.; Shimizu, M. *J. Med. Chem.* **2003**, *46*, 3083. (d) Shi, G. Q.; Dropinski, J. F.; Zhang, Y.; Santini, C.; Sahoo, S. P.; Berger, J. P.; MacNaul, K. L.; Zhou, G.; Agrawal, A.; Alvaro, R.; Cai, T.-q.; Hernandez, M.; Wright, S. D.; Moller, D. E.; Heck, J. V.; Meinke, P. T. *J. Med. Chem.* **2005**, *48*, 5589.

yield (eq 2).[6] Curiously, application of the conditions optimized above for the formation of indanes (Table 4) to compound **48** gave an incomplete conversion, even after prolonged heating.

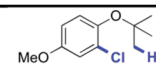
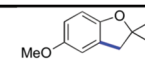
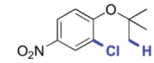
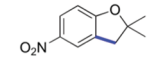
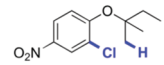
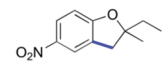
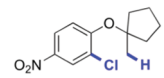
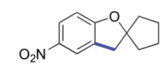
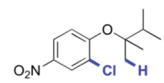
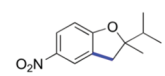
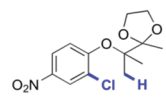
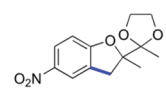
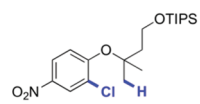
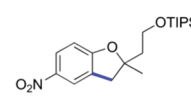
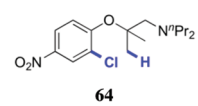
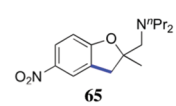
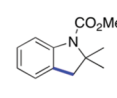
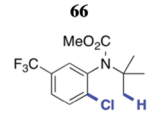
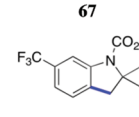
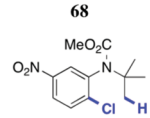
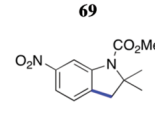
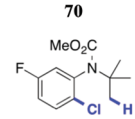
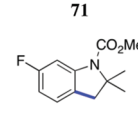
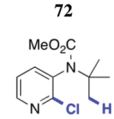
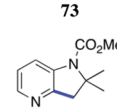


(2)

The scope of this intramolecular C(sp^3)−H arylation from aryl chlorides is outlined in Table 5. Electron-donating (entry 1) and -withdrawing (entry 2) groups on the aromatic ring were well tolerated and generated the corresponding dimethyldihydrobenzofurans in high yields. The reactions were highly regioselective, affording exclusively the products of ring closure at methyl C−H bonds over analogous methylene or methyne positions (entries 3−5). Additionally, five-membered ring closure occurred preferentially over six-membered ring formation in substrates containing multiple methyl substituents (entries 3 and 5). The compatibility of this method with various functional groups was also investigated with aryl chlorides **60**, **62**, and **64**. The reaction of protected ketone **60** led to product **61** in excellent yield (entry 6). Silyl-protected alcohols also reacted nicely, as exemplified by aryl chloride **62** (entry 7). Finally, a Lewis-basic tertiary amine was tolerated under the reaction conditions, albeit leading to the dihydrobenzofuran product in lower yield (entry 8). Of note is the absence of product resulting from arylation at the more "activated" methylene C−H bond adjacent to the nitrogen heteroatom.[27] Finally, the intramolecular arylation of 2-chloroaniline-derived substrates, giving rise to indolines and azaindolines, was also examined (entries 9−13).[7f,28] Gratifyingly, chlorobenzenes **66**, **68**, **70**, and **72** and chloropyridine **74** furnished the expected fused nitrogen heterocycles in high yields under the same reaction conditions. Again, applying the conditions optimized above for the synthesis of indanes, requiring a base/solvent combination of K_2CO_3/DMF instead of Cs_2CO_3/PivOH/mesitylene, gave incomplete substrate conversions. These results indicate that, while the first set of conditions is better adapted to the construction of carbocycles, the second is better suited to the construction of heterocycles, reflecting the necessity to fine-tune the catalytic system depending on the variations of conformation and coordinating ability of the substrate.

4. Synthesis of Indanones. The C(sp^3)−H arylation methodology was also extended to new substrate classes containing other challenging functional groups. Accordingly, (*o*-chloro)ketophenones were chosen due to the potential problematic coordination of the carbonyl oxygen to the Pd^{II} intermediate resulting from oxidative addition of the aryl halide. Gratifyingly, when these substrates were submitted to the conditions previously developed (eq 2), the desired indanones were obtained in good to excellent yields (Table 6). These substrates also appear to be slightly more reactive, since the catalyst loading could be decreased to 2 mol % without affecting the product yield (Table 6, entry 1). This may be due to the activation of the C−Cl bond toward oxidative addition by the presence of an *ortho* electron-withdrawing group. Aryl bromides may react under these conditions, as demonstrated by the formation of **77** from **76b** in 98% yield (entry 2). The reaction of chloride **78**, bearing a *n*-propyl substituent, also furnished indanone **79** selectively but in moderate yield (entry 3). In the presence of an acidic

Table 5. Scope of Dihydrobenzofurans and (Aza)Indolines Synthesized by Intramolecular C(sp^3)−H Arylation[a]

entry	aryl chloride	product	yield (%)[b]
1	 **50**	 **51**	96
2	 **52**	 **53**	88
3	 **54**	 **55**	84
4	 **56**	 **57**	64
5	 **58**	 **59**	77
6	 **60**	 **61**	95
7	 **62**	 **63**	87
8	 **64**	 **65**	55
9	 **66**	 **67**	83
10	 **68**	 **69**	84
11	 **70**	 **71**	62
12	 **72**	 **73**	83
13	 **74**	 **75**	88

[a] Reaction conditions: $Pd(OAc)_2$, 5 mol %; $(Cy_3PH)BF_4$, 10 mol %; Cs_2CO_3, 1.1 equiv; PivOH, 30 mol %; mesitylene; 140 °C; 16 h. [b] Yields of isolated products.

(27) Campos, K. *Chem. Soc. Rev.* **2007**, *36*, 1069.
(28) Alternative synthesis of indolines via C(sp^3)−H activation: Neumann, J. J.; Rakshit, S.; Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2009**, *48*, 6892.

Table 6. Scope of Indanones Synthesized by Intramolecular C(sp³)−H Arylation[a]

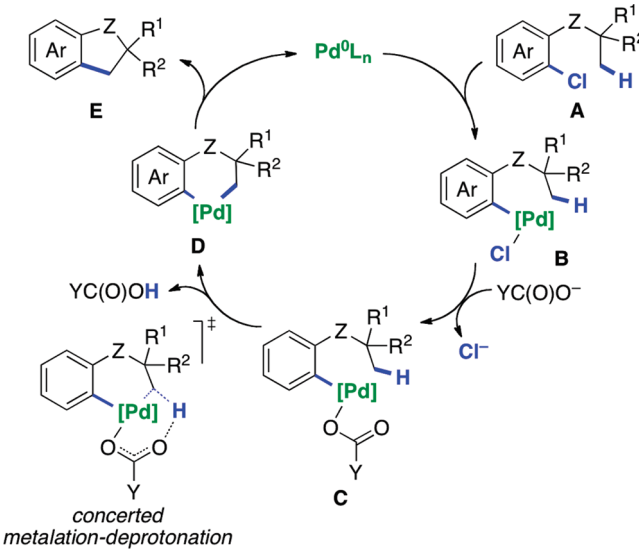
entry	aryl chloride	product(s)	yield (%)[b]
1	**76a:** X = Cl **76b:** X = Br	**77**	93[c] 98
3	**78**	**79**	50
4	**80**	**81**	77
5	**82**	**83**	89
6	**84**	**85**	47
7	**86**	**87a** + **87b**	65 / 32

[a] Reaction conditions: $Pd(OAc)_2$, 5 mol %; $(Cy_3PH)BF_4$, 10 mol %; Cs_2CO_3, 1.1 equiv; PivOH, 30 mol %; mesitylene; 140 °C; 16 h. [b] Yields of isolated products. [c] 2 mol % $Pd(OAc)_2$/4 mol % $(Cy_3PH)BF_4$.

C(sp³)−H bond known to readily react under palladium(0) catalysis to afford the product of α-arylation,[29] this catalytic system favors reactivity at the less activated but more sterically accessible methyl C−H bond (entry 4). Substrate **82**, containing a trifluoromethyl functional group, reacted smoothly and regioselectively to afford **83** in high yield (entry 5). The arylation of **84**, containing a fluorine atom α to the keto group, successfully produced fluorinated indanone **85**, albeit in moderate yield (entry 6). Aryl chloride **86** demonstrates the preference for arylation at a methyl C−H bond over arylation at typically more reactive benzylic C(sp³)−H and aryl C(sp²)−H bonds (entry 7).[3,4] Indeed, indanone **87a** was isolated as the major product in 65% yield, together with the direct arylation product **87b** in 32% yield, while no product resulting from arylation at the benzylic C(sp³)−H bond was detected. These results (Table 6, entries 4, 5, and 7), combined with those for amine **64** (Table 5, entry 8) as well as with previous data,[5d] appear to indicate that steric interactions contribute significantly to reaction site selectivity, overriding electronic influences at the methylene C(sp³)−H bond known to promote reactivity, such as the α heteroatom effect[30] in **64** and acidity in **80**, **82**, and **86**.

5. General Mechanistic Considerations. A simplified general catalytic cycle for intramolecular C(sp³)−H arylation from various aryl and heteroaryl chlorides is proposed (Scheme 2), based on these and previous computational studies.[5d,6] Oxidative addition of the aryl chloride **A** to Pd^0/PR_3 followed by exchange of the chlorine ligand for carbonate (Y = O^-) or pivalate (Y = ^{t}Bu) gives rise to palladium(II) complex **C**. From complex **C**, the base-induced CMD mechanism effects the intramolecular C−H bond cleavage to furnish five- or six-membered palladacycle **D**, which, by reductive elimination, gives rise to the C−C coupling product **E**. All experimental data in this and previous studies from our groups concur with the preferential activation of methyl C−H bonds over methylene and methyne C−H bonds for the formation of a palladacycle (**D**) of a given size, even when an activating group is present on the last two bond types. In cases where several methyl groups are present on the arylation substrate, the selectivity trend inversely correlates with the size of palladacycle **D**: five-membered > six-membered > seven-membered. For instance, the exclusive formation of BCB **10** from aryl chloride **9** (Table 2, entry 5) illustrates selectivities both of methyl vs methyne C−H bond activation and of five- vs six-membered palladacycle formation. Similarly, the exclusive formation of dihydrobenzofuran **59** from aryl chloride **58** (Table 5, entry 5) illustrates selectivities both of methyl vs methyne C−H bond activation and of six- vs seven-membered palladacycle formation.

Scheme 2. General Intramolecular C(sp³)−H Arylation Mechanism[a]



[a] [Pd] = Pd−PR_3 complex; Y = ^{t}Bu or O^-; Z = no atom, CR_2, N−R, O, or C═O.

Conclusion

The first efficient and general palladium-catalyzed intramolecular C(sp³)−H arylation of aryl and heteroaryl chlorides has been performed. This method enables the synthesis of a variety of valuable cyclobutarenes, indanes, indolines, dihydrobenzofurans, and indanones. The use of aryl and heteroaryl chlorides significantly improves the scope of C−H arylation compared to the use of the corresponding bromides by facilitating access to reaction substrates. Careful optimization studies have shown that the palladium ligand and the base/solvent combination must be fine-tuned according to the class of product. Overall, three sets of reaction conditions employing P^tBu_3, $PCyp_3$, or PCy_3 as the palladium ligand and K_2CO_3/DMF or Cs_2CO_3/pivalic acid/mesitylene as the base/solvent combination gave access to the five different classes of products described in this work. In total,

(29) (a) Johansson, C. C. C.; Colacot, T. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 676. (b) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082.

(30) For selected reviews: (a) Murahashi, S.-I.; Takaya, H. *Acc. Chem. Res.* **2000**, *33*, 225. (b) Murahashi, S.-I. In *Handbook of C−H Transformations*; Dyker, G.; Wiley-VCH: Weinheim, 2005; Vol. 2, pp 319−326.

more than 40 examples of C−H arylation have been performed successfully. Selectivity issues in the C−H activation step have been analyzed. When several C(sp^3)−H bond types were present in the chloro(hetero)arene substrate, the arylation was found to occur regioselectively on primary C−H bonds vs secondary or tertiary C−H bonds. In addition, when several primary C−H bonds were present, selectivity trends correlated with the size of the palladacyclic intermediate, with five-membered rings being favored over six- and seven-membered rings. Regio- and diastereoselectivity issues were studied computationally in the prototypal case of indane formation. DFT calculations showed that C−H activation is the rate-determining step and that the creation of a Pd···C−H agostic interaction, inducing increased acidity of a geminal C−H bond, is a critical factor for the control of regiochemistry.

Computational Details

The calculations were performed with the Gaussian 03 package[31] at the B3PW91 level.[32] Palladium was represented by the relativistic effective core potential (RECP) from the Stuttgart group and the associated basis set,[33] augmented by a f polarization function.[34] Phosphorus was represented by the RECP from the Stuttgart group and the associated basis set,[35] augmented by a d polarization function.[36] A 6-31G(d,p) basis set was used for all the other atoms (C, H, O, N).[37] The geometry optimizations were performed without any symmetry constraint, followed by analytical frequency calculations to confirm that a minimum or a transition state had been reached. The nature of the species connected by a given transition-state structure was checked by optimization as minima of slightly altered TS geometries along both directions of the transition-state vector. Single-point PCM calculations[38] in DMF of all the gas-phase optimized structures yielded the solvent-corrected energy, E_{solv}. The united atom topological model with UAKS radii was used, and for DMF the parameters proposed by Stassen were used.[39] For the PCM calculations, the basis set for Pd was the same as in the gas-phase calculations, but for all the other atoms a 6-31+G(d,p) basis set was considered. Gas-phase Gibbs free energy corrections G_{corr} ($P = 1$ atm, $T = 298$ K) were considered for each species, and the total Gibbs free energy G of each optimized structure was taken as $G = E_{solv} + G_{corr}$. Throughout the text, only G values as defined above are given.

Acknowledgment. This work was financially supported by NSERC (CGS-D postgraduate fellowship to S.R.), the University of Ottawa, ANR (programme blanc "AlCaCHA"), Région Rhône-Alpes (Cluster 5), MESR (grant to C.P.), and CNRS (ATIP grant). We also thank Johnson Matthey PLC (loan of palladium acetate), Eli Lilly, Amgen, and Astra Zeneca Montreal for unrestricted financial support. Christopher Whipp is kindly acknowledged for the loan of certain (*o*-chloro)ketophenone starting materials.

Supporting Information Available: Full characterization of all new compounds, detailed experimental procedures, NMR spectra for target molecules, complete ref 31, Cartesian coordinates, and electronic and Gibbs free energies for the systems computed. This material is available free of charge via the Internet at http://pubs.acs.org.

JA1048847

(31) Frisch, M. J.; et al. *Gaussian 03*, Revision E.01; Gaussian, Inc.: Wallingford, CT, 2004.
(32) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Perdew, J. P.; Wang, Y. *Phys. Rev. B* **1992**, *45*, 13244.
(33) Andrae, D.; Haussermann, U.; Dolg, M.; Stoll, H.; Preuss, H. *Theor. Chim. Acta* **1990**, *77*, 123.
(34) Ehlers, A. W.; Bohme, M.; Dapprich, S.; Gobbi, A.; Hollwarth, A.; Jonas, V.; Kohler, K. F.; Stegmann, R.; Veldkamp, A.; Frenking, G. *Chem. Phys. Lett.* **1993**, *208*, 111.
(35) Bergner, A.; Dolg, M.; Kuchle, W.; Stoll, H.; Preuss, H. *Mol. Phys.* **1993**, *80*, 1431.
(36) Hollwarth, A.; Bohme, M.; Dapprich, S.; Ehlers, A. W.; Gobbi, A.; Jonas, V.; Kohler, K. F.; Stegmann, R.; Veldkamp, A.; Frenking, G. *Chem. Phys. Lett.* **1993**, *208*, 237.
(37) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213.
(38) Tomasi, J.; Mennucci, B.; Cammi, R. *Chem. Rev.* **2005**, *105*, 2999.
(39) Böes, E. S.; Livotto, P. R.; Stassen, H. *Chem. Phys.* **2006**, *331*, 142.