Pd-Catalyzed C(sp^3)-H Functionalization/Carbenoid Insertion: All-Carbon Quaternary Centers via Multiple C–C Bond-Formation

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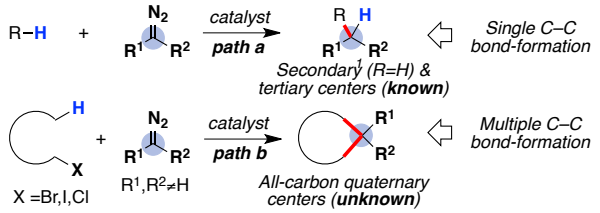
Supporting Information Placeholder

ABSTRACT: A Pd-catalyzed C(sp^3)-H functionalization/carbenoid insertion is described. The method allows for the rapid synthesis of bicyclic frameworks, generating all-carbon quaternary centers via multiple C–C bond-formations in a straightforward manner.

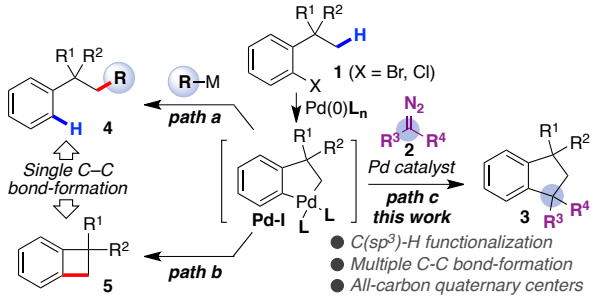
Over the last few years, there has been a growing consensus that C–H functionalization has profoundly changed the landscape of organic synthesis while establishing new paradigms in retrosynthetic analysis.[1] While spectacular advances have been realized, this area of expertise primarily relies on the utilization of directing groups, particularly via C(sp^2)–H functionalization. Indeed, a close inspection into the literature data reveals that the preparation of all-carbon quaternary centers[2] via C(sp^3)–H functionalization in the absence of directing groups still remains rather elusive.[3,4]

Scheme 1. C(sp^3)–H Functionalization/Carbenoid Insertion.



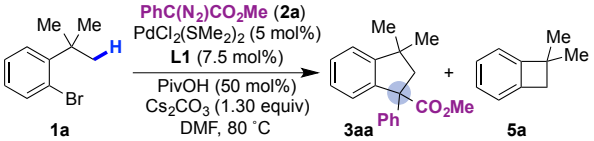
While originally designed for cyclopropanation events, carbenoid species have shown to be superb synthons in a myriad of relevant transformations.[5] Indeed, these reagents have successfully been employed in C–H functionalization without the need for directing groups, allowing for installing *secondary or tertiary carbon centers via single C–C bond-formation* (Scheme 1, *path a*).[6] To the best of our knowledge, all-carbon quaternary stereocenters derived from the corresponding carbenoid species are beyond reach in C–H functionalization.[7,8] Undoubtedly, the ability to promote *multiple C–C bond-formations* initiated by C(sp^3)–H functionalization while installing all-carbon quaternary centers would be of particular interest (Scheme 1, *path b*).[9] If successful, such a protocol would not only represent an unconventional, yet powerful, technique for our synthetic arsenal, but also a unique opportunity to improve our ever-growing knowledge in C–H functionalization. However, the difficulty for effecting C(sp^3)–H functionalization in the absence of directing groups[3] and the inherent propensity of carbenoids towards competitive dimerization[5,6] constitute serious drawbacks to be overcome. To such end, we hypothesized that the intermediacy of *in situ* generated **Pd-I**[10] via C(sp^3)–H functionalization would be critical for success (Scheme 2). At the outset of our investigations, it was unclear whether such scenario could ever be conducted given the known proclivity of **Pd-I** towards C–C reductive elimination (*path b*)[11,12] or competitive [1,4]-shifts en route to **4** (*path a*).[13] Herein, we report a mild catalytic C(sp^3)–H functionalization/carbenoid insertion en route to indanes **3** bearing all-carbon quaternary centers (*path c*). This protocol is distinguished by a wide scope and excellent chemoselectivity profile, thus constituting a unique tool to rapidly build up molecular complexity.

Scheme 2. Intermediacy of Pd-I in C-H Functionalization.

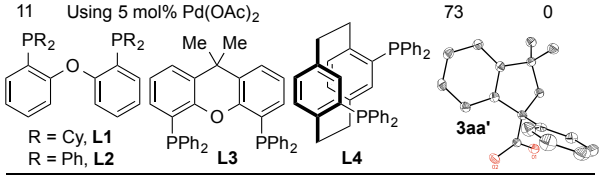


We initiated our study by investigating the reaction of **1a** with **2a** (Table 1). After considerable experimentation,[14] a protocol based on $PdCl_2(SMe_2)_2$, **L1**, PivOH and Cs_2CO_3 in DMF at 80 ºC provided the best results (entry 1). Although the structure of **3aa** was evident by NMR spectroscopy, we univocally assigned its structure by comparison with **3aa'** derived from the hydrolysis of **3aa** by X-ray crystallography.[14] Not surprisingly, the ligand backbone had a critical impact on both reactivity and selectivity (entries 2-6). While the significant lower reactivity of **L2** and **L3** might suggest an intimate interplay of steric and electronic effects, care must be taken when generalizing this since we found that **L4** was equally effective. The use of monodentate phosphines (entries 5 and 6) had a deleterious effect; strikingly, the utilization of P*t*Bu$_3$ resulted in a selectivity switch, obtaining exclusively **5a**.[11c] Similarly, the base and the solvent exerted a profound influence on reactivity (entries 7-10), with toluene favoring the formation of **5a** (entry 9). Interestingly, inferior results were found for protocols based on $Pd(OAc)_2$ (entry 11). The higher reactivity of $PdCl_2(SMe)_2$ is tentatively attributed to its high solubility; at present, we cannot rule out that Me_2S facilitates the reduction to Pd(0) while forming DMSO. Additionally, otherwise related aryl chlorides, iodides and triflate congeners failed to deliver **3aa**. As anticipated, control experiments univocally revealed that all parameters were essential for the reaction to occur.[14,15]

Table 1. Optimization of the Reaction Conditions.[a]



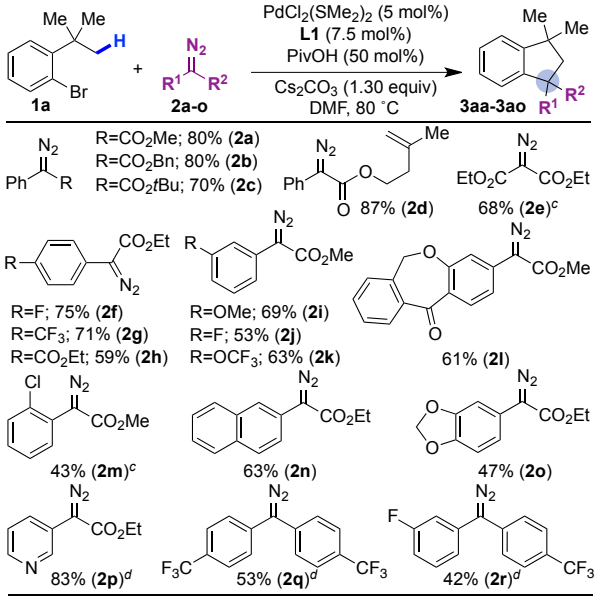
Entry	Deviation from the standard conditions	**3aa** (%)[b]	**5a** (%)[b]
1	none	93 (80)[c]	0
2	using **L2** as the ligand	36	0
3	using **L3** as the ligand	0	0
4	Using **L4** as the ligand	83	0
5	Using P*t*Bu$_3$·HBF$_4$ (15 mol%) as the ligand	0	58
6	Using PCy_3 (15 mol%) as the ligand	0	0
7	Using CsOPiv (1.30 equiv) as the base[d]	43	0
8	Using CsOAc as the base	38	0
9	Using PhMe instead of DMF	15	73
10	Using DMA instead of DMF	49	0
11	Using 5 mol% $Pd(OAc)_2$	73	0



[a] **1a** (0.10 mmol), **2a** (0.18 mmol), $PdCl_2(SMe_2)_2$ (5 mol%), **L1** (7.50 mol%), PivOH (50 mol%), Cs_2CO_3 (0.13 mmol), DMF (0.25 M) at 80 ºC. [b] GC yields using *o*-xylene as standard. [c] Isolated yield. [d] No PivOH was added.

Prompted by these results, we sought to examine the influence of the carbenoid species (Table 2). As shown, the scope was insensitive to electronic changes at the para and meta positions on the aromatic ring (**2f-2l**). Likewise, the substitution pattern on the ester motif was inconsequential to the reactivity profile (**2a-2c**), invariably leading to the targeted products in high yields. The chemoselectivity profile of our protocol is nicely illustrated by the fact that a wide variety of diazoester derivatives bearing aryl halides (**2f**, **2j** and **2m**), esters (**2e** and **2h**), ketones (**2l**) or acetals (**2o**) were all well accommodated. Notably, nitrogen-containing heterocycles posed no problems (**2p**). Particularly interesting was the observation that the presence of alkene on the side chain did not interfere, affording **3ad** in high yields without traces of intramolecular cyclopropanation being observed in the crude mixtures. Gratifyingly, the diazo compound derived from Isoxepac (**2l**),[16] a nonstereoidal anti-inflammatory drug (NSID), could be employed with equal ease. Notably, this transformation was not limited to diazoester derivatives, as diaryldiazomethanes could also be coupled, albeit in lower yields (**2q-r**). Unfortunately, donor/donor diazocompounds and monosubstituted carbene precursors could not participate in the targeted reaction, recovering starting material unaltered.

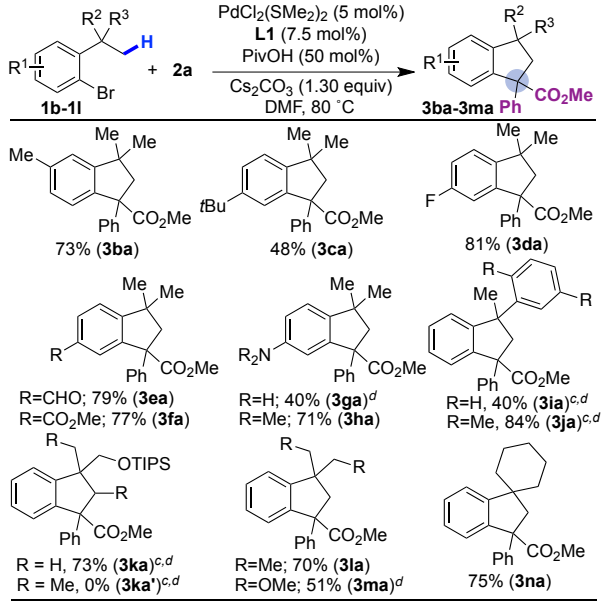
Table 2. Scope of Diazo Compounds.[a,b]



[a] As Table 1 (entry 1), 0.50 mmol scale. [b] Isolated yields, average of at least two independent runs. [c] $PdCl_2(SMe)_2$ (10 mol%) at 100 ºC. [d] $PdCl_2(SMe)_2$ (10 mol%).

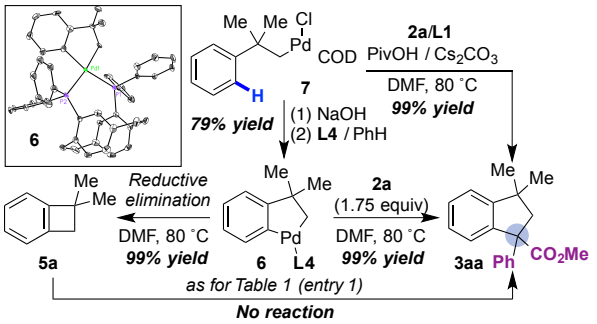
Next, we turned our attention to study the substitution pattern on the aryl halide backbone (Table 3). As shown, the preparative scope was rather general regardless of whether electron-donating or electron-withdrawing groups were present or not. Notably, a variety of aryl fluorides (**3da**), aldehydes (**3ea**), esters (**3fa**), amines (**3ga** and **3ha**) or silyl ethers (**3ka**) could perfectly be tolerated. Importantly, even free amines could be employed as substrates, albeit in lower yields (**3ga**). Although the presence of an *ortho t*-butyl group statistically accelerates the key C(sp^3)–H functionalization,[17] we found that a variety of *ortho* substituents other than *t*-butyl groups could be equally accommodated (**3ia-3na**). In all cases analyzed, the targeted C(sp^3)–H functionalization occurred exclusively at the primary C(sp^3)–H bonds of methyl groups, leaving the corresponding methylene positions intact. In line with this notion, no reaction occurred when employing **3ka'**. Unfortunately, no diastereoselection was observed in the presence of *gem*-dimethyl groups (**3ia-3ka**), even in the presence of bulky silyl or aromatic motifs (**3ja-3ka**).[18] Likewise, tertiary benzylic carbons (R^2=H) resulted in β-hydride elimination, even with bulkier mesityl groups. Taken together, the results in Tables 2 and 3 show the prospective impact of our protocol for rapidly preparing indane skeletons bearing all-carbon quaternary centers.

Table 3. Scope of Aryl Bromides.[a,b]



[a] As for Table 1 (entry 1), but at 0.50 mmol scale. [b] Isolated yields, average of at least two independent runs. [c] 1:1 diastereomeric ratio. [d] $PdCl_2(SMe)_2$ (10 mol%) at 100 ºC.

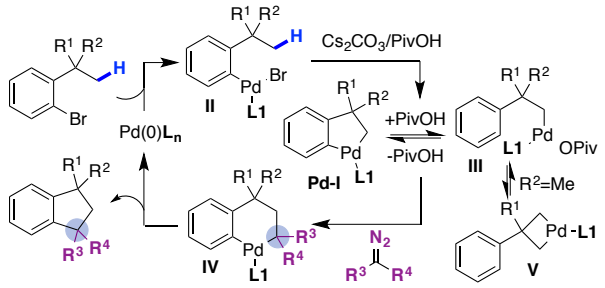
Scheme 3. **Mechanistic Experiments.**



Next, we decided to gather indirect evidence on the mechanism by examining the reactivity of **1a** with PivOD. Interestingly, a non-negligible deuteration at *ortho* position of **3aa** was observed, suggesting that **Pd-I** (Scheme 2) might coexist in equilibrium with homobenzylic Pd(II) intermediates generated upon protonolysis with PivOD via [1,4]-shift.[10c,11c,13,14] Next, we studied the reactivity of the putative metallacycle **Pd-I**. Following the methodology described by Cámpora,[10b] we prepared **6** from **7** in high yield (Scheme 3, bottom), which was fully characterized by X-ray structure analysis.[14] Interestingly, while **6** rapidly underwent reductive elimination en route to **5a** in the absence of **2a**,[11] **3aa** was exclusively obtained with **2a** (Scheme 3, bottom).[19,20] Notably, **3aa** was not obtained from **5a**, thus ruling out the possibility of a C–C cleavage event. We believe these results reinforce a scenario consisting of **Pd-I** via concerted metallation-deprotonation from **II** (Scheme 4).[11,21] While **Pd-I** might coexist in equilibrium with **III** upon protonolysis with PivOH, a 1,2-insertion of a diazo

compound[10a,22,23] might generate **IV** that ultimately delivers the targeted product via reductive elimination. At present, we cannot rule out the intermediacy of **V** via rapid equilibration with **III** and **Pd-I**,[24] as traces of cyclopropane derivatives via reductive elimination from **V** were detected in reactions of aryl bromides possessing bulky groups at the geminal position.[25]

Scheme 4. **Mechanistic Hypothesis.**



In conclusion, we have developed a mild and robust Pd-catalyzed C(sp^3)-H functionalization/carbenoid insertion event. This technique represents a unique synthetic tool in the C(sp^3)–H functionalization arena for building up bicyclic frameworks in which the all-carbon quaternary center is derived from carbenoid species.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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No competing financial interests have been declared.

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REFERENCES

(1) (a) Gutekunst, W. R.; Baran, P. L. *Chem. Soc. Rev.* **2011**, *40*, 1976. (b) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (c) Chen, X.; Engle, K. M.; Wang, D. H.; Yu, J. –Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094.

(2) All-carbon quaternary centers are defined as carbon atoms to which *four distinct carbon substituents* are attached. (a) Quasdorf, K. W.; Overman, L. E. *Nature*, **2014**, *516*, 181. (b) Das, J. P.; Marek, I. *Chem. Commun*, **2011**, *47*, 4593.

(3) (a) Li, H.; Li, B.-J.; Shi, Z.-J. *Catal. Sci. Technol*, **2011**, *1*, 191. (b) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem. Eur. J.* **2010**, *16*, 2654. (c) Herrmann, P.; Bach, T. *Chem. Soc. Rev.* **2011**, *40*, 2022.

(4) (a) Pedroni, J.; Saget, T.; Donets, P. A.; Cramer, N. *Chem. Sci.* **2015**, *6*, 5164. (b) Davies, H. M. L.; Hansen, T.; Churchill, M. R. *J. Am. Chem. Soc.* **2000**, *122,* 3063. (c) Janody, S.; Jazzar, R.; Comte, A.; Holstein, P. M.; Vors, J. –P.; Ford, M. J.; Baudoin, O. *Chem. Eur. J.* **2014**, *20*, 11084. (d) Saget, T.; Cramer, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 12842. (e) Martin, N.; Pierre, C.; Davi, M.; Jazzar, R.; Baudoin, O. *Chem. Eur. J.* **2012**, *18*, 4480. (f) Holstein, P. M.; Vogler, M.; Karini, P.; Pilet, G.; Clot, E.; Baudoin, O. *ACS Catal.* **2015**, *5*, 4300. (g) Yu, S.; Liu, S.; Lan, Y.; Wan, B.; Li, X. *J. Am. Chem. Soc.* **2015**, *137*, 1623.

(5) (a) Ford, A.; Miel, H.; Ring, A.; Slattery, C. N.; Maguire, A: R.; McKervey, A. *Chem. Rev.* **2015**, *115*, 9981. For selected carbenoid insertions into organopalladium intermediates: (b) Kudirka, R.; Devine, S. K. J.; Adams, C. S.; VanVranken, D. L. *Angew. Chem. Int. Ed.* **2009**, *48*, 3677. (c) Premachandra, I. D.; Nguyen, T. A.: Shen, C.; Gutman, E. S.; VanVranken, D. L. *Org. Lett.* **2015,** *17*, 5464. (d) Zhou, L.; Ye, F.; Zhang, Y.; Wang, J. *Org. Lett.* **2012**, *14*, 922. (e) Barluenga, J.; Escribano, M.; Aznar, F.; Valdes, C. *Angew. Chem. Int. Ed.* **2010**, *49*, 6856.

(6) For selected reviews of C–H functionalization dealing with diazoderivatives: (a) Caballero, A.; Pérez, P. J. *Chem. Soc. Rev*., **2013**, *42*, 8809. (b) Davies, H. M. L.; Morton, D. *Chem. Soc. Rev.* **2011**, *40*, 1857.

(7) For selected syntheses of quaternary center *not derived from carbenoids* via C–H activation: (a) Fuentes, M. A.; Muñoz, B. K.; Jacob, K.; Vendier, L.; Caballero, A.; Etienne, M.; Pérez, P. J. *Chem. Eur. J.* **2013**, *19*, 1327. (b) ref. 4c.

(8) While this paper was under preparation, a functionalization of *activated* C(sp^3)–H bonds using expensive *Rh catalysts* followed by carbenoid insertion was reported: Zhou, B.; Chen, Z.; Yang, Y.; Ai, W.; Tang, H.; Wu, Y.; Zhu, W.; Li, Y. *Angew. Chem. Int. Ed.* **2015**, *54*, 12121.

(9) For syntheses of not *all-carbon* quaternary centers via C(sp^2)–H/carbenoid insertion: (a) Ye, B.; Cramer, N. *Angew. Chem. Int. Ed.* **2014**, *53*, 7896. (b) Hyster, T. K.; Ruhl, K. E.; Rovis, T. *J. Am. Chem. Soc.* **2013**, *135*, 5364.

(10) For selected stoichiometric transformations of these Pd(II) metallacycles: (a) Cámpora, J.; Palma, P.; del Río, D.; López, J. A.; Valerga, P. *Chem. Commun.* **2004**, 1490. (b) Cámpora, J.; López, J. A.; Palma, P.; del Río, D.; Carmona, E. *Inorg. Chem.* **2001**, *40*, 4116. (c) Cámpora, J.; López, J. A.; Palma, P.; Valerga, P.; Spillner, E.; Carmona, E. *Angew. Chem. Int. Ed.* **1999**, *38*, 147.

(11) (a) Kefalidis, C. E.; Davi, M.; Holstein, P. M.; Clot, E.; Baudoin, O. *J. Org. Chem.* **2014**, *79*, 11903. (b) Rousseaux, S.; Davi, M.; Sofack-Kreutzer, J.; Pierre, C.; Kefalidis, C. E.; Clot, E.; Fagnou, K.; Baudoin, O. *J. Am. Chem. Soc.* **2010**, *132*, 10706. (c) Chaumontet, M.; Piccardi, R.; Audic, N.; Hitce, J.; Peglion, J. –L.; Clot, E.; Baudoin, O. *J. Am. Chem. Soc.* **2008**, *130*, 15157.

(12) For preparing otherwise related benzocyclobutenones: (a) Flores-Gaspar, A.; Gutiérrez-Bonet, A.; Martin, R. *Org. Lett.* **2012**, *14*, 5234. (b) Álvarez-Bercedo, P.; Flores-Gaspar, A.; Correa, A.; Martin, R. *J. Am. Chem. Soc.* **2010**, *132*, 466.

(13) (a) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. *J. Am. Chem. Soc.*, **2005**, *127*, 4685. (b) Hoshi, T.; Honma, T.; Mori, A.; Konishi, M.; Sato, T.; Hagiwara, H.; Suzuki, T. *J. Org. Chem.*, **2013**, *78*, 11513.

(14) See Supporting information for details.

(15) The use of tosyl hydrazones as carbenoid species resulted in dehalogenation while not observing even traces of **3aa**.

(16) Scott, J.; Huskinsson, E. C. *Rheumatology*, **1982**, *21*, 48
(17) For selected C(sp^3)-H functionalization of *ortho t*-butyl groups: (a) Yan, J.-X.; Li, H.; Liu, X.-W.; Shi, J.-L.; Wang, X.; Shi, Z.-J. *Angew. Chem. Int. Ed.* **2014**, *53*, 4945. (b) Lafrance, M.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 14570. (d) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542.
(18) DFT calculations (B3LYP & M06) showed that the energy difference of the transition states leading to the two possible diastereoisomers (**IV**, Scheme 4) is negligible (0.3-2.3 kcal·mol^{-1}). Additionally, the overall energy barrier for [1,2]-insertion was found to be 1.7-3.3 kcal·mol^{-1} (ref.14).
(19) Although **6-L1** could be isolated and characterized by X-ray crystallography (see ref. 14), its insolubility prevented its characterization by NMR spectroscopy. Still, **6-L1** could be converted into either **5a** or **3aa** in quantitative yields.
(20) **6** and **7** were found to be catalytically competent on the conversion of **1a** into **3aa**. See ref. 14.
(21) (a) Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1118. (b) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848. (c) ref. 20c. (d) Garcia-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc*. **2007**, *129*, 6880.
(22) We propose the intermediacy of Pd carbenoid species from **Pd-I** prior 1,2-insertion at the C(sp^3)–C bond en route to **IV**. Preliminar DFT calculations (B3LYP & M06) revealed that 1,2-insertion at C(sp^2)–C was less favorable by 12-15 kcal·mol^{-1} (ref.14).
(23) (a) Hu, F.; Xia, Y.; Ma, C.; Zhang, Y.; Wang, J. *Chem. Commun.* **2015**, *51*, 7986. (b) Xia, Y.; Zhang, Y.; Wang, J. *ACS Catal.* **2013**, *3*, 2586.
(24) (a) Miyashita, A.; Ohyoshi, M.; Shitara, H.; Nohira, H. *J. Organomet. Chem.* **1988***, 338,* 103. (b) Jennings P. W.; Johnson L. L. *Chem. Rev.* **1994**, *94*, 2241.
(25) 0% *ee* was observed by reacting diethyl 2-diazomalonate with aryl halides containing *gem*-dimethyl groups. See Supporting information for a mechanistic rationale.