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Cyclization of η^3-Benzylpalladium Intermediates Derived from Carbene Insertion

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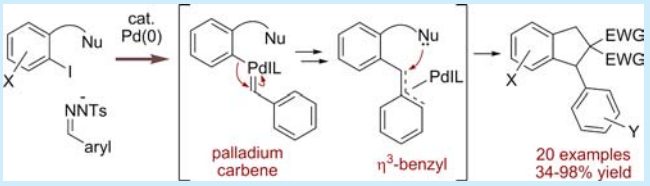
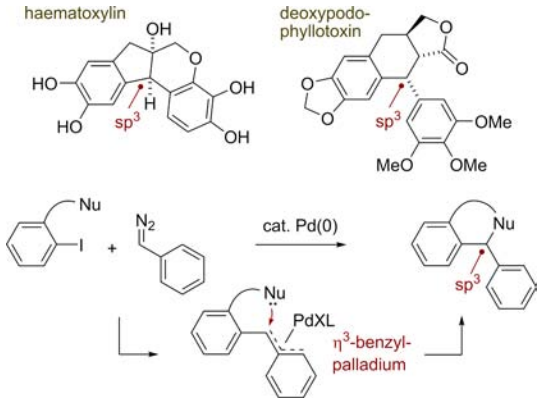
Supporting Information

ABSTRACT: Migratory insertion of benzylidene carbene ligands into arylpalladium(II) species generates η^3-benzylpalladium intermediates that can cyclize to generate five- and six-membered rings with new sp^3 centers. The reaction tolerates a range of arene functional groups and stabilized enolates. The products generated through this reaction are 1-arylindanes and 1-aryltetralins that are common to a range of natural products.



1-Arylindanes and 1-aryltetralins are an important structural feature in many bioactive molecules and natural products (Scheme 1).[1] In early work, Negishi and co-workers synthesized indanones and tetralones through carbonylative cyclization of 2-iodoaryl malonates.[2] We rationalized that an analogous carbenylative[3] cyclization would provide the central sp^3 carbon of 1-arylindanes and 1-aryltetralins through η^1-benzylpalladium that could isomerize to η^3-benzylpalladium intermediates. There is growing interest in η^3-benzylpalladium complexes as intermediates in catalytic reactions.[4]

Scheme 1. Access to Bicyclic Compounds with sp^3 Centers



Traditionally, η^3-benzylpalladium intermediates have been accessed through oxidative addition of palladium to benzyl carbonates, benzyl acetates, or benzyl halides.[5] Migratory insertion of carbenes has been used to access η^1-benzylpalladium intermediates that undergo nucleophilic attack on palladium.[6] For example, Wang and co-workers have intercepted η^1-benzylpalladium intermediates through carbene insertion with acetylide and hydride nucleophiles that attack palladium and then form bonds after reductive elimination.[7] Alternatively, migratory insertion of carbenes has been used to access η^3-allyl- and η^3-oxaallylpalladium intermediates that are trapped by nucleophilic attack on the ligand.[8] For example, Liang and co-workers have intercepted η^3-allylpalladium intermediates derived from carbene insertion with stabilized enolates that attack the π-allyl ligand to form five- and six-membered rings.[9] We envisioned that η^1-benzylpalladium intermediates derived from benzylidene insertion could isomerize to η^3-benzylpalladium intermediates that would then be attacked by pendant stabilized enolates at the benzylic position to generate highly desirable 1-arylindanes and 1-aryltetralins.

Initially, we explored the carbenylative cyclization of dimethyl (2-iodobenzyl) malonate **1a** using the *N*-tosylhydrazone **2a** derived from benzaldehyde as a precursor to phenyldiazomethane.[10] Based on conditions for carbenylative reactions of stabilized enolates involving η^3-allylpalladium intermediates[8a,9] (Table 1), we were able to obtain a promising 54% yield of the 1-phenylindane **3aa** using potassium *tert*-butoxide (entry 5). Most of the *N*-tosylhydrazone anion is insoluble during the reaction. The solubility of the *N*-tosylhydrazone anion and the reaction temperature are important factors that determine the rate at which phenyldiazomethane is generated in the reaction mixture. Better results were obtained at lower temperatures with lower amounts of hydrazone and base (entries 5, 6). The best results were obtained at 60 °C rather than at refluxing THF (entry 8). A brief survey of monodentate phosphine ligands favored phosphines with less donor ability (entries 8−11). Tris(4-fluorophenyl)phosphine proved to be slightly better than triphenylphosphine in terms of reaction time and yield. Other solvents, such as DMF and *tert*-butanol were less effective than THF (see Supporting Information).

The yield was further increased by preforming the sodium enolate and sodium *N*-tosylhydrazone salt with sodium hydride and switching to a palladium(II) precatalyst. Under the optimized conditions using 3.6 equiv of NaH and 2 equiv of *N*-tosylhydrazone **2a**, indane **3aa** was formed in 86% yield in

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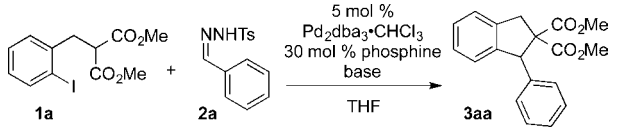
Table 1. Initial Optimization of Carbenylative Insertion



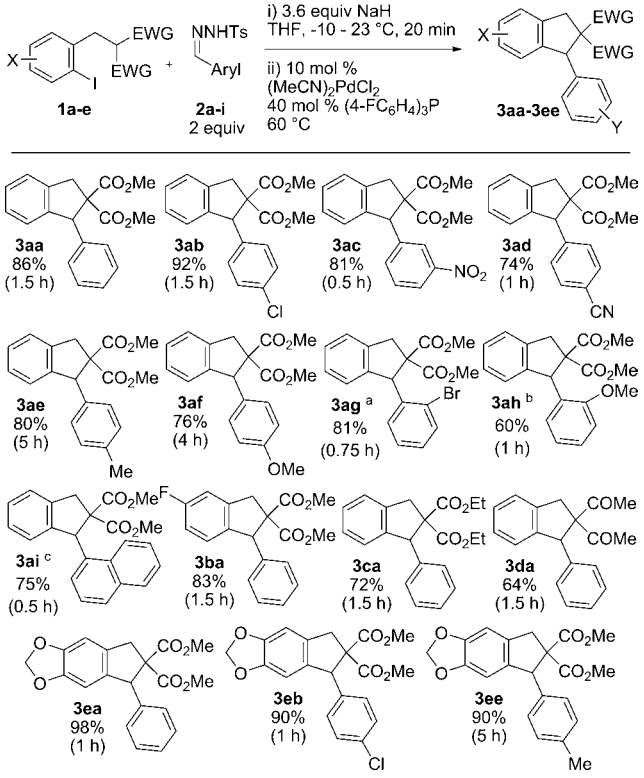
entry	ligand	equiv 2a	base (equiv)	temp (°C)	time (h)	yield 3aa[a]
1	Ph_3P	4	K_2CO_3 (5.2)	66	6	trace
2	Ph_3P	4	NEt_3 (5.2)	66	24	trace
3	Ph_3P	4	K_3PO_4 (5.2)	66	7	trace
4	Ph_3P	4	*t*-BuOLi (5.2)	66	5	45%
5	Ph_3P	4	*t*-BuOK (5.2)	66	5	54%[b]
6	Ph_3P	2	*t*-BuOK (3.2)	50	20	68%
7	Ph_3P	1.5	*t*-BuOK (2.7)	50	22	60%
8	Ph_3P	2	*t*-BuOK (3.2)	60	6	73%
9	$(4\text{-}FC_6H_4)_3P$	2	*t*-BuOK (3.2)	60	4	75%
10	$(4\text{-}F_3CC_6H_4)_3P$	2	*t*-BuOK (3.2)	60	5	70%
11	Ph_3As	2	*t*-BuOK (3.2)	60	7	20%

[a]NMR yields versus dimethoxybenzene as an internal standard. [b]Isolated yield.

1.5 h (Scheme 2); a slightly lower yield (79%) was obtained using 5 mol % of the palladium catalyst. Tris(4-trifluoromethylphenyl)phosphine and tris(2-furyl)phosphine gave comparable yields (see Supporting Information). Using the optimized conditions, we set out to explore the scope of this powerful cyclization reaction. We first examined *N*-tosylhydrazones to evaluate the functional group compatibility of the reaction. Aryl bromides and chlorides were tolerated without competing oxidative addition (**3ab**, **3ag**). Electron-withdrawing groups were also tolerated (**3ac**, **3ad**). If formation of an η^3-benzylpalladium intermediate is a limiting factor in the reaction, then one would expect better results for insertion of 1-naphthylmethylidene over phenylmethylidene (**3aa** versus **3ai**), but the yield was slightly lower when the hydrazone derived from 1-naphthaldehyde was used. However, the partial solubility of the *N*-tosylhydrazone anion is a critical factor for the success of the reaction and may lead to some of the observed differences in yields and rates. *N*-Tosylhydrazones generate aryldiazomethanes at a slower rate when the arene group is electron-rich[11] as evidenced by the longer reaction time for formation of indane **3af**. We then looked to varying the (2-iodobenzyl)malonate. Both oxygen and fluorine substituents are tolerated on the aryl halide (**3ba**, **3ea**). In fact, the methylenedioxyphenyl iodide **1e** gave almost quantitative yield (**3ea**). Other types of stabilized enolates were also effective in the reaction (**3ca**, **3da**).

Rapid decomposition of ortho-substituted *N*-tosylhydrazones necessitates additional equivalents of hydrazone and base to achieve full conversion of aryl iodide (**3ag**, **3ah**, **3ai**). Generally, ortho groups seem to accelerate the rate of the reaction. The sterically demanding, electron-rich *N*-tosylhydrazone **2j** afforded none of the desired product under the optimized conditions in Scheme 2, but when we returned to potassium

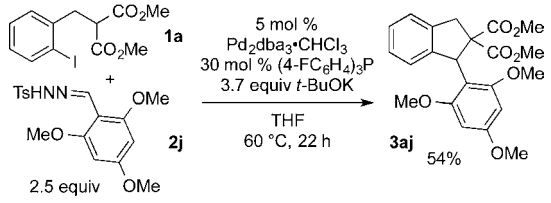
Scheme 2. Scope of Carbene Insertion for Formation of 1-Arylindanes



[a]Isolated as a chromatographically inseparable 9:1 mixture of indane **3ag** and aryl iodide **1a**. [b] 3.0 equiv of *N*-tosylhydrazone, 4.6 equiv of NaH. [c] 4.0 equiv of *N*-tosylhydrazone, 5.6 equiv of NaH. NMR yield versus dimethoxybenzene as an internal standard.

enolate conditions the hindered product **3aj** was formed in 54% yield (Scheme 3).

Scheme 3. Insertion of a Highly Hindered Benzylidene Group



Buoyed by the success of carbenylative insertion for making indanes, we next turned to the formation of six-membered rings (Table 2). The yields and reaction times for six-membered ring formation are comparable to the yields and reaction times for five-membered ring formation, suggesting that the benzylic alkylation step is not limiting the yield. The 3-nitroaryltetralin derivative **4c** (entry 3) appeared to work well by TLC analysis (complete conversion of aryl iodide) but proved difficult to separate from impurities[12] using chromatography and was purified by recrystallization, reducing the isolated yield.

Our mechanistic rationale for the reaction involves addition of the diazo compound to arylpalladium iodide *a* to form an arylpalladium carbene intermediate *b* (Scheme 4). Migratory insertion would generate η^1-benzylpalladium iodide intermediate *c*. Direct cross-coupling of the enolate with the η^1-

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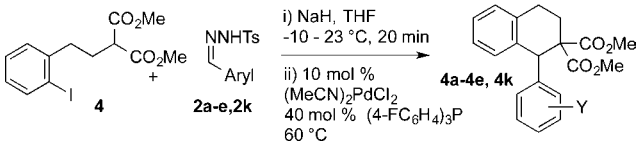
Table 2. Carbenylative Insertion To Access 1-Aryltetralins

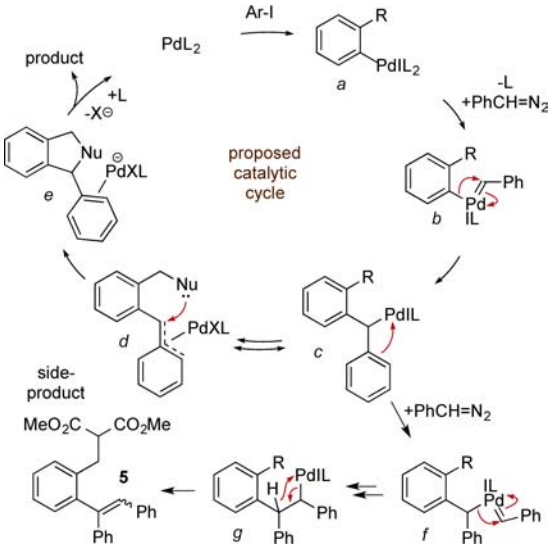


entry	*N*-tosyl hydrazone	aryl	time (h)	product	yield[a]
1	**2a**	Ph	1.5	**4a**	83%
2	**2b**	4-ClC_6H_4	1.5	**4b**	78%
3	**2c**	3-$O_2NC_6H_4$	0.5	**4c**	11%[b]
4	**2d**	4-NCC_6H_4	0.5	**4d**	84%
5	**2e**	4-MeC_6H_4	6.0	**4e**	61%
6[c]	**2k**	2,4-$(MeO)_2C_6H_3$	1.0	**4k**	34%

[a]Isolated yields. [b]Yield after recrystallization. [c]4.0 equiv of *N*-tosylhydrazone, 5.6 equiv of NaH.

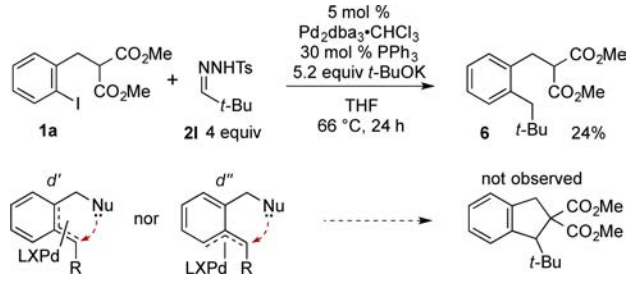
benzylpalladium moiety in intermediate *c* would require a highly unfavorable reductive elimination that is not likely to be facile under our reactions conditions.[13] The η^1-benzylpalladium iodide *c* has two choices. Kuwano has shown that benzhydrylpalladium intermediates couple with malonates through an outer-sphere attack on the η^3-benzyl ligand,[5b] so it is expected that the structurally analogous η^3-benzhydrylpalladium intermediate *d* can undergo 5-exo-trig cyclization through an outer-sphere mechanism to generate product. Other types of η^3-benzylpalladium complexes are possible, but 5-endo-trig ring closures onto analogous η^3-allylpalladium intermediates are strongly disfavored.[14] Alternatively, η^1-benzylpalladium intermediate *c* can insert another carbene[15] followed by rapid β-hydride elimination[16] to afford a stilbene side product **5**. We do not observe any tetralin from the η^3-benzylpalladium complex derived from the cyclization of *g*. In some cases, we observed over 10% of stilbene **5**, but through optimization we reduced the formation of stilbene to just a few percent, implying that the desired pathway was at least an order of magnitude faster than the second insertion of the diazo compound (see Supporting Information).

Scheme 4. Proposed Mechanism for Carbenylative Cyclization and Formation of Side Products



To probe the intermediacy of η^3-benzylpalladium intermediates other than *d* we attempted to carry out the reaction with the *N*-tosylhydrazone **2l**, derived from pivalaldehyde (Scheme 5). Insertion product **6** was isolated in low yield, but

Scheme 5. Evidence against Alternative η^3-Benzylpalladium Intermediates



none of the desired indane was observed, suggesting that η^3-benzylpalladium intermediates *d′* and *d″* are not viable intermediates.

In summary, we have developed a palladium-catalyzed carbenylative cyclization reaction that generates 1-arylindanes and 1-aryltetralins in good yields. The reaction generates sp^3 centers through a mechanism involving the alkylation of an η^3-benzylpalladium complex. This transformation offers a powerful approach to complex natural products with interesting biological activity.

■ 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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Notes

The authors declare no competing financial interest.

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