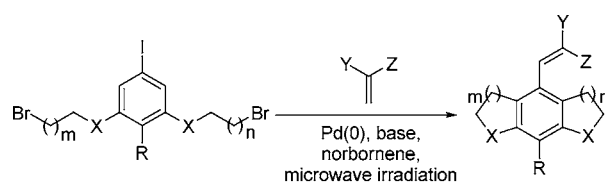# JOC Article

Synthesis of Tricyclic Heterocycles via a Tandem Aryl Alkylation/Heck Coupling Sequence

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X = O, S, NTs, -CH₂O-, -OCH₂SiMe₂-
R = H, OMe
m, n = 1, 2, 3
Y, Z = H, alkyl, ester, nitrile, aryl, amide, sulfone, sulfoxide

A norbornene-mediated palladium-catalyzed sequence is described in which two alkyl−aryl bonds and one alkenyl−aryl bond are formed in one pot with use of microwave irradiation. A variety of symmetrical and unsymmetrical oxygen-, nitrogen-, silicon-, and sulfur-containing tricyclic heterocycles were synthesized from a Heck acceptor and an aryl iodide containing two tethered alkyl halides. This approach was further applied to the synthesis of a tricyclic mescaline analogue.

Introduction

The formation of multiple carbon−carbon bonds in a tandem process is a powerful method for generating complex molecules from simple substrates.[1] Unlike stepwise carbon−carbon bond formation, tandem processes allow for rapid access of target molecules in fewer steps and with reduced waste. Those involving carbon−carbon bond formation via the direct functionalization of aromatic C−H bonds[2] have an added advantage, as they avoid the need for activating groups. We have been

developing annulation and cyclization reactions[3] based on a process first reported by Catellani[4] involving a palladium-catalyzed norbornene-mediated tandem process, wherein the alkylation of an *ortho* C−H bond is followed by a Heck reaction at the *ipso* carbon of the aryl iodide. This process relies on the high reactivity of norbornene to mediate the relative rates of several competing processes. Using this method, we were able to generate a number of highly functionalized bi- and tricyclic carbocycles and oxygen-containing heterocycles (Figure 1).[3]

Herein, we describe an extension of these studies whereby tricyclic oxygen-, nitrogen-, silicon-, and sulfur-containing

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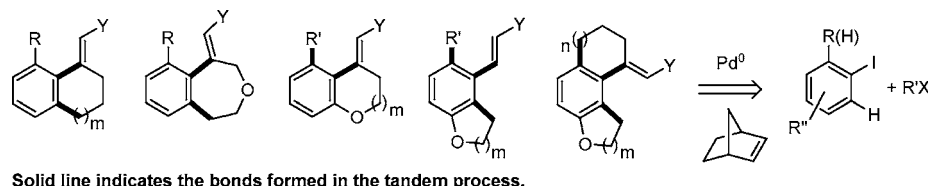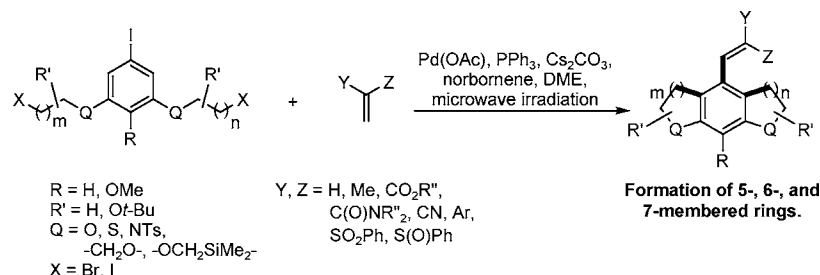
Solid line indicates the bonds formed in the tandem process.

FIGURE 1. Bi- and tricyclic carbocyclic and oxygen-containing heterocyclic scaffolds.

SCHEME 1. Norbornene-Mediated Palladium-Catalyzed Synthesis of Tricyclic Heterocycles

R = H, OMe
R' = H, O*t*-Bu
Q = O, S, NTs,
   $-CH_2O-$, $-OCH_2SiMe_2-$
X = Br, I

Y, Z = H, Me, CO_2R'',
   $C(O)NR''_2$, CN, Ar,
   SO_2Ph, S(O)Ph

Formation of 5-, 6-, and
7-membered rings.

heterocycles are generated in a tandem process involving two intramolecular *ortho* alkylations of aromatic C−H bonds followed by an intermolecular Heck reaction (Scheme 1).[5]

Tricyclic compounds of this type are found in natural products exhibiting notable biological and pharmaceutical properties.[6] Tricyclic analogue **2** and other rotationally restricted analogues of mescaline **1** (Figure 2) are of particular interest since they may be valuable in SAR studies of hallucinogenic agents.[6] To demonstrate the synthetic potential of our methodology, we report a synthesis of **2**, first synthesized by Nichols,[6a] and later by Bergman and Ellman.[7] The disconnections for a synthesis of **2** utilizing the new methodology are illustrated in Figure 3. The key step is the bis-alkylation/Heck reaction sequence involving aryl iodide **3** and a Heck acceptor. This step would introduce two rings and form three new C−C bonds in one pot.
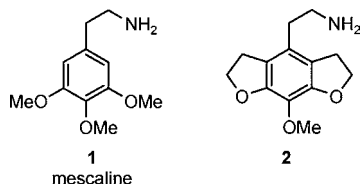

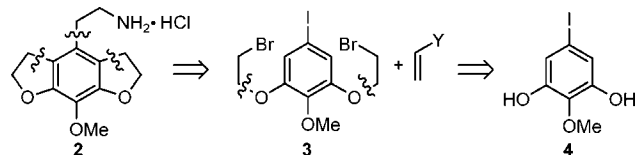**FIGURE 2.** Mescaline and tricyclic mescaline analogue.

FIGURE 3. Retrosynthesis of mescaline analogue **2**.

Results and Discussion

Synthesis of Annulated Phenyl Ethers. Starting materials for the synthesis of annulated phenyl ethers were prepared by converting commercially available 5-bromo-1,3-dimethoxybenzene to the iodide via lithium−halogen exchange and quenching with iodine. Demethylation with aqueous HI, followed by alkylation of the bisphenol with the corresponding dibromoalkane furnished the desired aryl iodides. We initially explored

the synthesis of 5,6,5-ring systems containing phenolic oxygens (Table 1) from various Heck acceptors using iodoarene **5** (1 equiv), Pd(OAc)$_2$ (10 mol %), triphenylphosphine (22 mol %), Cs$_2$CO$_3$ (5 equiv), norbornene (3 equiv),[8] and Heck acceptor (5 equiv) in degassed dimethoxyethane (0.05 M) under microwave irradiation[9] for 5 min at 190 °C (Table 1). While the use of unsubstituted acrylates afforded the corresponding products in good yields (entries 1−3), *tert*-butyl methacrylate gave a modest yield of **9** as a 1:1 mixture of internal (**9a**) and terminal (**9b**) alkenes (entry 4). *N-tert*-Butyl acrylamide gave only a modest yield (entry 5), while acrylonitrile gave **11** in 71% yield (entry 6). Product **11** was observed to be light-sensitive, undergoing partial isomerization to the *cis*-alkene upon standing in solution. When phenyl vinyl sulfone and phenyl vinyl sulfoxide were reacted with **5**, low yields of the desired tricyclic products were obtained (entries 7 and 8). Vinyl pyridine Heck acceptors were also compatible under the reaction conditions (entries 9 and 10), giving modest yields of the tricyclic products.

We also investigated the feasibility of employing a mixed acetal with this methodology since it allows for further functionalization of the product. Acetal **16** is available in one step from the corresponding bisphenol via an alkoxy-bromination with *tert*-butyl vinyl ether in the presence of *N*-bromosuccinimide.[10] Subjecting **16** to the standard reaction conditions with *tert*-butyl acrylate afforded the desired product **17** in 52% yield as a 1:1 mixture of diastereomers (Scheme 2).

(6) (a) Monte, A. P.; Waldman, S. R.; Marona-Lewicka, D.; Wainscott, D. B.; Nelson, D. L.; Sanders-Bush, E.; Nichols, D. E. *J. Med. Chem.* **1997**, *40*, 2997. (b) Huang, K.-S.; Lin, M.; Yu, L.-N.; Kong, M. *Tetrahedron* **2000**, *56*, 1321. (c) Chambers, J. J.; Kurrasch-Orbaugh, D. M.; Nichols, D. E. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1997.

(7) (a) Ahrendt, K. A. A.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2003**, *5*, 1301. (b) Thalji, R. K.; Ahrendt, K. A. A.; Bergman, R. G.; Ellman, J. A. *J. Org. Chem.* **2005**, *70*, 6775.
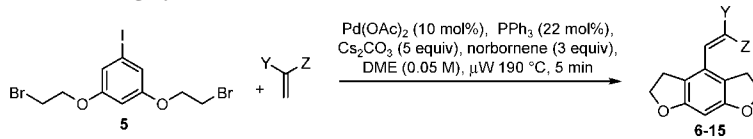
(8) While norbornene is theoretically only required in a catalytic amount, an excess is used to suppress the competing Heck reaction. This excess, however, often results in the formation of various norbornane-containing aromatic compounds. For examples see ref 4d and the following: Motti, E.; Ippomei, C. P.; Deledda, S.; Catellani, M. *Synthesis* **2003**, 2671.

(9) (a) Lindstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225. (b) Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717. (c) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250. (d) Hayes, B. L. *Aldrichim. Acta* **2004**, *37*, 66.

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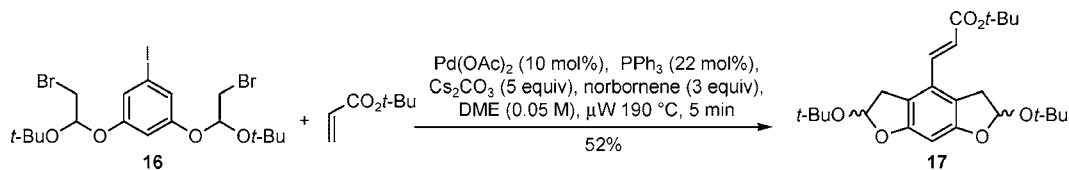
(5) For a preliminary communication, see ref 3h.

TABLE 1. Formation of Phenyl Ether 5,6,5-Ring Systems

entry	Heck acceptor $CH_2=CYZ$	product	isolated yield (%)
1		CO_2R **6**, R= Me	80
2	CO_2R	**7**, R= *t*-Bu	85[3h]
3		**8**, R= Bn	77
4	*t*-BuO$_2$C	**9a** **9b** (CO_2*t*-Bu)	57 (1:1)
5	NH*t*-Bu	C(O)NH*t*-Bu **10**	61[3h]
6	CN	CN **11**	71
7	S Ph (O, O)	SO_2Ph **12**	38
8	S Ph (O)	$S(O)Ph$ **13**	37
9	(pyridin-2-yl vinyl)	**14**	57[3h]
10	(pyridin-4-yl vinyl)	**15**	43

SCHEME 2. Formation of a 5,6,5-Mixed Acetal Ring System

The successful preparation of compounds containing a 5,6,5-ring system prompted us to determine the efficiency with other ring sizes. Reaction of **18** with *tert*-butyl acrylate (Table 2, entry 1) resulted in a good yield of an unsymmetrical tricycle having a 5,6,6-ring system. Products with 6,6,6-ring systems (entries 2 and 3) and 7,6,7-ring systems (entry 4) were also isolated in

good yields. Under the optimized reaction conditions, longer heating times were required as the ring size being formed increased.

Synthesis of Annulated Benzyl Ethers. Having successfully generated products with phenolic oxygens, we next investigated the effect of having oxygen at other positions within the

TABLE 2. Formation of Phenyl Ether 5,6,6-, 6,6,6-, and 7,6,7-Ring Systems

entry	Y	aryl iodide	product	isolated yield (%)
1	CO$_2$t-Bu	**18** (m=1, n=2)	**19**	80[3h]
2	CO$_2$Me	**20** (m=2, n=2)	**21**	67
3	CO$_2$t-Bu	**20** (m=2, n=2)	**22**	70[3h]
4[a]	CO$_2$t-Bu	**23** (m=3, n=3)	**24**	68[3h]

[a] Reaction run for 20 min.

TABLE 3. Formation of Benzyl Ether 6,6,6-Ring Systems

entry	Y	product	isolated yield (%)
1[a]	CO$_2$t-Bu	**26**	45
2	CO$_2$t-Bu	**26**	65
3	C(O)NMe$_2$	**27**	58
4	CN	**28**	40

[a] With 3 equiv of norbornene.

bromoalkyl tether. For example, substrate **25** was prepared with oxygen at the benzylic positions and subjected to the optimized reaction conditions with *tert*-butyl acrylate as the Heck acceptor (Table 3). The 6,6,6-ring product **26** was obtained in 45% yield (entry 1). Extending the reaction time did not have an effect on the isolated yield; however, increasing the amount of norbornene to 5 equiv improved the yield of **26** to 65% (entry 2). While *tert*-butyl acrylate and *N,N*-dimethylacrylamide afforded the corresponding products in moderate yields (entries 2 and 3), acrylonitrile (entry 4) gave a reduced yield of annulated product. As observed in our previous studies, the decreased reactivity of the benzyl ether analogues compared to the phenol ethers might be explained by a complexation between the oxygen atom and the palladium center, which inhibits subsequent steps in the catalytic cycle.[3b]

Synthesis of Annuated Phenyl Thioethers. We next prepared a series of compounds wherein the phenolic oxygen was

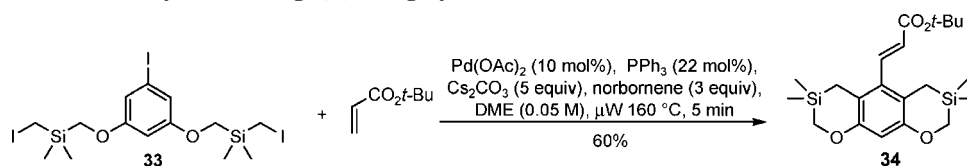**TABLE 4. Formation of Phenyl Thioether-Containing 5,6,5-Ring Systems**

entry	Y	product	isolated yield (%)
1[a]	CO$_2$t-Bu	**30**	27
2		**30**	43
3[b]			52
4	C(O)NMe$_2$	**31**	26
5	CN	**32**	19

[a] Reaction run for 5 min. [b] Reaction run with 20 mol % of Pd(OAc)$_2$.

replaced with a sulfur atom (Table 4). Starting with *tert*-butyl acrylate as the Heck acceptor, **30** was isolated in 27% yield under the optimized conditions (entry 1). Extending the reaction time to 10 min increased the yield to 43% (entry 2), while decreasing the reaction temperature to 160 °C for 10 min showed no improvement. In addition, increasing the catalyst loading to 20 mol % gave a modest increase in yield (entry 3). Various other ligands were examined including tris(*p*-fluorophenyl)-phosphine, tris(*p*-trifluoromethylphenyl)phosphine, tris(*p*-methoxyphenyl)phosphine, and tri-*n*-butylphosphine; however, triphenylphosphine proved to be the best. We also conducted an analogous alkylation/alkenylation reaction in a sealed tube with heating in an oil bath at 190 °C for 10 min, and a comparable yield of 43% for **30** was obtained. Under our previously reported conditions,[3d] which employed conventional heating at 80 °C for 16 h, the reaction of **29** with *tert*-butyl acrylate only gave trace amounts of **30**. Finally, reactions with *N,N*-dimethylacrylamide (entry 4) and acrylonitrile (entry 5) also afforded the desired products, albeit in lower yields.

Synthesis of an Annulated Silaoxacycle. We envisioned adding a silyl group to the alkyl halide tether, as in **33**, which would allow for the formation of a benzylic silane as part of the newly formed fused six-membered ring (Scheme 3). Under our standard conditions, **33** resulted in the desired product **34** in 47% yield. However, when the reaction temperature was lowered to 160 °C for 5 min, the yield improved to 60%. The preparation of tricycle **34** represents the first example in norbornene-mediated *ortho*-alkylation chemistry that utilizes a primary alkyl halide containing a heteroatom in the α-position. Previous attempts at incorporating other heteroatoms, such as oxygen and nitrogen, at the α-position to the alkyl halide have failed. Since silyl groups can be selectively manipulated in a variety of ways,[11] incorporation of the SiMe$_2$ moiety offers a route to products that have not otherwise been accessible by this methodology. For example, protodesilation would give
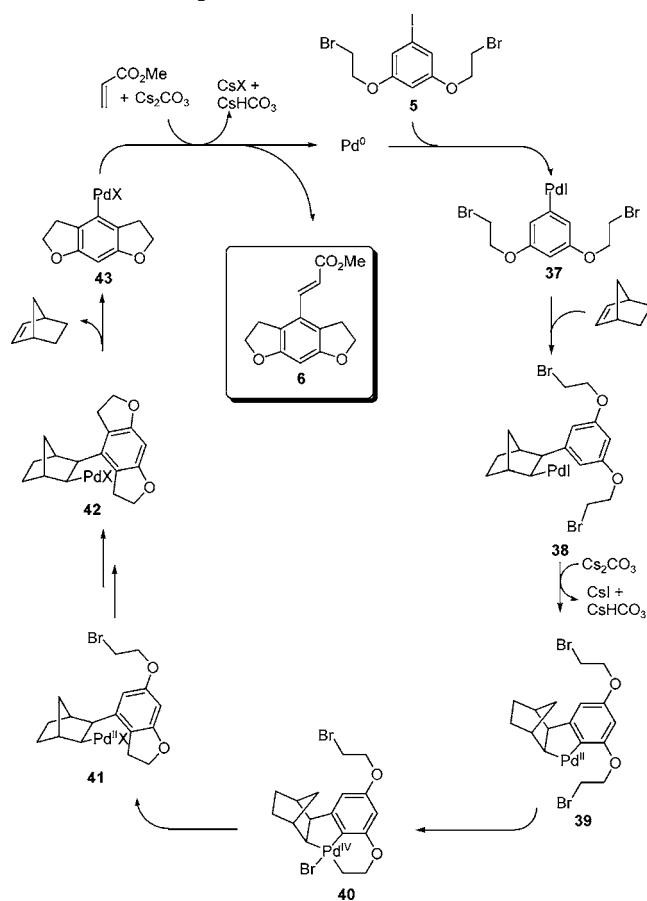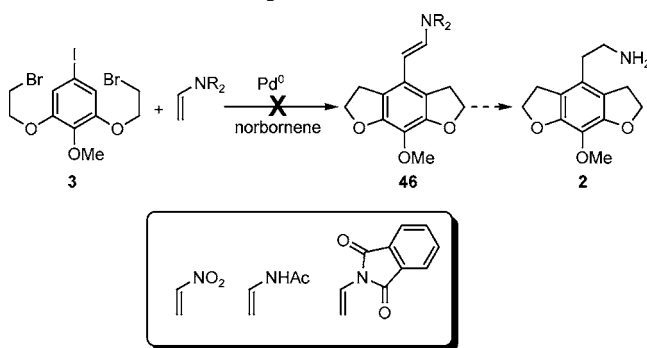
SCHEME 3. Formation of a Silyl-Containing 6,6,6-Ring System

Pd(OAc)$_2$ (10 mol%), PPh$_3$ (22 mol%), Cs$_2$CO$_3$ (5 equiv), norbornene (3 equiv), DME (0.05 M), μW 160 °C, 5 min

60%

SCHEME 4. Formation of a Nitrogen-Containing 5,6,5-Ring System

Pd(OAc)$_2$ (10 mol%), PPh$_3$ (22 mol%), Cs$_2$CO$_3$ (5 equiv), norbornene (5 equiv), DME (0.05 M), μW 160 °C, 5 min

39%

SCHEME 5. Proposed Mechanism

SCHEME 6. Preparation of Mescaline Analogue Precursor 3

[i] *n*-BuLi, ether, -78 °C
[ii] B(OMe)$_3$, -78 °C to rt
[iii] peracetic acid, 0 °C
77%

Br⌒Br, K$_2$CO$_3$, acetone, reflux
84%

R=H; **44**
R=Me; **45** — MeI, K$_2$CO$_3$, acetone, reflux 98%

products arising from the use of methyl iodide as the alkylation agent, a reaction that fails under all conditions that we have tried.

(11) Brook, M. A. *Silicon in Organic, Organometallic and Polymer Chemistry*; John Wiley and Sons, Inc.: Toronto, Canada, 2000; Chapter 16.
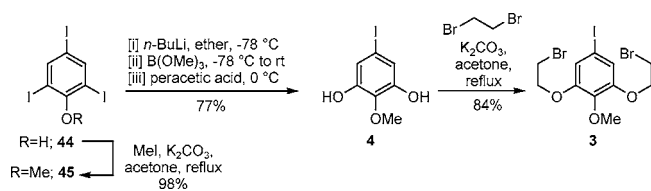
SCHEME 7. Initial Proposed Route toward 2

Synthesis of a Bisindoline. We also tested the feasibility of using a substrate containing a tosyl protected nitrogen in the tether (Scheme 4). With use of the optimized reaction conditions employed in the synthesis of annulated phenyl ethers, **36** was isolated in 17% yield from **35**. When the reaction temperature was decreased to 160 °C and the amount of norbornene was increased to 5 equiv, the yield improved to 39%. It should be noted that unlike other annulated products containing an acrylate, **36** readily isomerizes completely to the *cis*-alkene in solution when exposed to light.

Mechanism. The proposed mechanism (Scheme 5) for these reactions is based upon the findings of Catellani[4] and begins with the oxidative addition of Pd(0) to **5**, forming arylpalladium iodide **37**. *Syn* insertion of norbornene into **37** affords the *cis*,*exo*-complex **38**. Due to the rigidity of the alkene, and the absence of a *syn* β-hydrogen, **38** forms palladacycle **39** rather than undergo a disfavored *anti* β-hydride elimination. Intermediate **39** then undergoes oxidative addition with the tethered alkylbromide forming Pd(IV) complex **40**. Reductive elimination of **40** results in the formation of the C(sp^3)−C(sp^2) bond and generates the first ring in **41**. The same sequence of steps, namely the oxidative addition of the alkyl halide followed by reductive elimination, is repeated generating the second ring in **42**. Finally, extrusion of norbornene generates **43**, which then undergoes an intermolecular Heck coupling to afford **6**.

Application to the Synthesis of a Tricyclic Mescaline Analogue. We applied the bisannulation methodology to the synthesis of tricyclic mescaline analogue **2**. To access bisphenol precursor **4**, we began by methylation of commercially available 2,4,6-triiodophenol **44** to give **45** in 98% yield (Scheme 6). Subjecting **45** to regioselective lithium−halogen exchange, followed by addition of trimethyl borate and oxidation with

SCHEME 8. Alkylation/Alkenylation Approach Employing *tert*-Butyl Acrylate
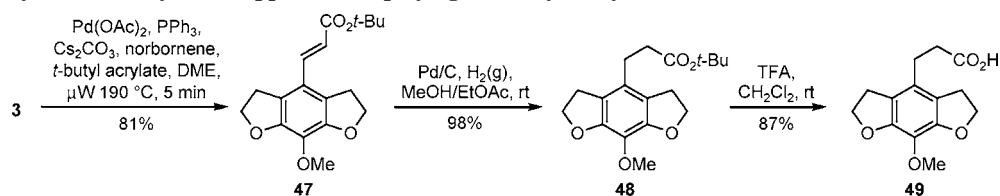
SCHEME 9. Alternate Approach Employing Benzyl Acrylate in the Alkylation/Alkenylation Reaction
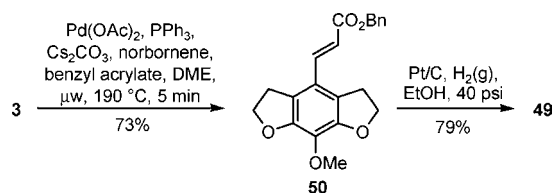
SCHEME 10. Completion of Mescaline Analogue Synthesis
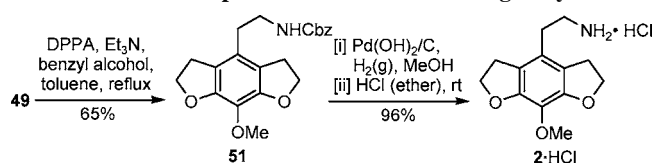
DPPA: diphenyl phosphoryl azide

peracetic acid (32 wt % in acetic acid) afforded **4** in 77% yield.[12] Alkylation of **4** with 1,2-dibromoethane (15 equiv) provided bisannulation precursor **3** in 84% yield.

The next step was to form the tricyclic core of **2** by using the alkylation/alkenylation sequence. We envisaged the final coupling using a vinyl nitrogen compound as the Heck acceptor to give **46**, which places the nitrogen atom in the desired position (Scheme 7). Initial attempts with nitroethylene[13] did not produce the desired product and afforded a messy reaction mixture. When *N*-vinylacetamide or *N*-vinylphthalimide were used, starting material was recovered, which is surprising since the Heck reaction of *N*-vinylphthalimide has been previously reported.[14]

The next approach involved a Heck reaction with an acrylate, followed by functional group interconversions to introduce the amine moiety. Two pathways were examined. We first examined the alkylation/alkenylation reaction of **3** with *tert*-butyl acrylate, which afforded the desired product **47** in 81% yield (Scheme 8). Having successfully assembled the tricyclic core, we next reduced the alkenyl double bond by catalytic hydrogenation to afford the aryl propionate **48** in 98% yield. Hydrolysis of **48** with trifluoroacetic acid[15] gave the desired carboxylic acid **49** in 87% yield.

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(14) (a) Ziegler, C. B., Jr.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2949. (b) Hutchison, A. J.; Williams, M.; de Jesus, R.; Yokoyama, R.; Oei, H. H.; Ghai, G. R.; Webb, R. L.; Zoganas, H. C.; Stone, G. A.; Jarvis, M. F. *J. Med. Chem.* **1990**, *33*, 1919. (c) Furstner, A.; Mamane, V. *Chem. Commun.* **2003**, 2112.

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The second approach used benzyl acrylate as the Heck acceptor, and resulted in the desired tricyclic product **50** in 73% yield (Scheme 9). The one-pot olefin reduction/benzyl cleavage[16] to afford **49** was achieved in 79% yield via hydrogenation with Pt/C. The use of Pd/C as the catalyst for this hydrogenation resulted in olefin reduction without benzyl cleavage whereas the use of Pd(OH)$_2$/C resulted in recovered starting material. Although this route required fewer steps, the *tert*-butyl acrylate approach is more attractive with regard to yield as it gives a 69% yield over three steps, rather than 58% over two steps.

Final conversion to the mescaline analogue was readily achieved via a Curtius rearrangement[17] of **49** to give **51**, followed by hydrogenolysis and salt formation with HCl (1 M in ether) to afford **2·HCl** in a combined yield of 62% over the two steps (Scheme 10). Our most efficient route toward mescaline analogue **2·HCl** was achieved in 8 steps with an overall yield of 27%.

Conclusions

We have developed a route to tricyclic heterocycles using a palladium-catalyzed norbornene-mediated tandem process involving two intramolecular *ortho* alkylations of aromatic C−H bonds followed by an intermolecular Heck reaction. The reaction tolerates alkyl halide tethers of various lengths containing oxygen, sulfur, nitrogen, or silicon moieties. A number of functionalized, mono- or disubstituted alkenes are compatible as Heck acceptors and the products are rapidly accessed within minutes with use of microwave irradiation. Furthermore, the synthetic utility of this reaction was demonstrated by the synthesis of tricyclic mescaline analogue **2**.

Experimental Section

The following is a representative experimental procedure toward the synthesis of products **6−15**, **17**, **19**, **21**, **22**, **24**, **26−28**, **30−32**, **34**, **36**, **47**, and **50**. Specific experimental details and characterization data for the aforementioned compounds and other new compounds can be found in the Supporting Information.

General Procedure for the Alkylation/Alkenylation Reaction. To a microwave reaction vessel were added Cs$_2$CO$_3$ (1.00 mmol, 5 equiv), norbornene (0.600 mmol, 3 equiv), Pd(OAc)$_2$ (10 mol %), triphenylphosphine (22 mol %), aryl iodide (0.200 mmol, 1 equiv), and the Heck acceptor (1.00 mmol, 5 equiv). The vessel was sealed and flushed with N$_2$. Through the septa was added degassed dry DME (4 mL). The reaction vessel was subjected to microwave irradiation at 190 °C for 5 min. The mixture was diluted with ether (4 mL) and quenched with water (4 mL). The aqueous layer was extracted with ether (3×) and the combined organic layers were washed with brine, dried with anhydrous MgSO$_4$, and filtered. Removal of the solvent gave a crude product that was purified by flash chromatography.

Supporting Information Available: Experimental details and characterization data for compounds **2**−**5**, **16**, **18**, **20**, **23**, **25**, **29**, **33**, **35**, **45**−**51**, and their precursors. This material is available free of charge via the Internet at http://pubs.acs.org.

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