Palladium-Catalyzed Alkylation–Alkenylation Reactions: Rapid Access to Tricyclic Mescaline Analogues

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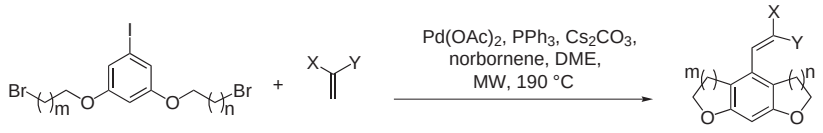
Abstract: A norbornene-mediated palladium-catalyzed sequence is described in which two alkyl–aryl bonds and one alkenyl–aryl bond are formed in one pot. A variety of symmetrical and unsymmetrical tricyclic heterocycles were synthesized in good yields from a Heck acceptor and an aryl iodide containing two tethered alkyl bromides. This methodology was applied to the synthesis of a tricyclic mescaline analogue.

Key words: palladium, annulations, Heck reaction, mescaline, microwave irradiation

Multicomponent carbon–carbon bond-forming reactions continue to evolve as a powerful method for the synthesis of complex molecules from simple building blocks.[1] In particular, great attention has been given to the development of sequential reactions involving metal-catalyzed processes.[2] Previously, we reported a palladium-catalyzed reaction, based upon modified Catellani conditions,[3] for the synthesis of fused aromatic carbocycles and heterocycles from aryl iodides and functionalized alkyl bromides.[4] We also described a three-component reaction employing an iodoarene containing a tethered alkyl halide, an external alkyl halide, and a Heck acceptor.[5] We now report a new approach to tricyclic heterocycles from an aryl iodide containing two tethered alkyl bromides and an external Heck acceptor (Table 1). Using this approach, both symmetrical and unsymmetrical substituted tricyclic heterocycles can be easily prepared from readily accessible starting materials and three C–C bonds are formed in one pot. Compounds with these motifs are widely found in natural products exhibiting notable biological and pharmaceutical properties.[6,7]

Table 1 Norbornene-Mediated Palladium-Catalyzed Alkylation–Alkenylation[a]



1, **7**, **9**, **11** **2–6**, **8**, **10**, **12**

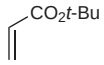
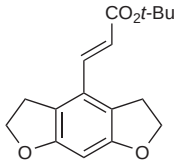
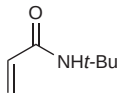
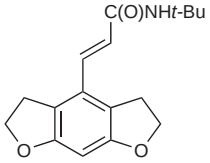
Entry	Substrate	Heck acceptor H_2C=CXY	Product	Yield (%)[b]
1	**1** m = 1 n = 1		 **2**	85
2	**1** m = 1 n = 1		 **3**	61

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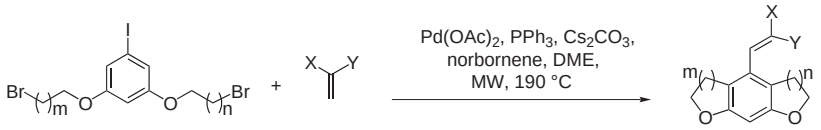
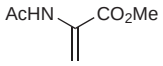
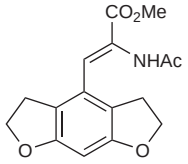
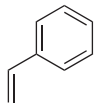
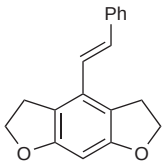
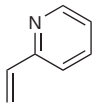
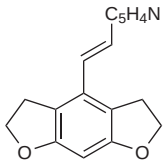
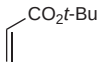
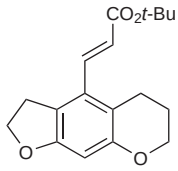
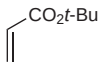
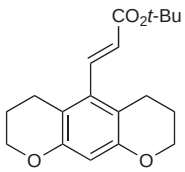
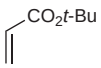
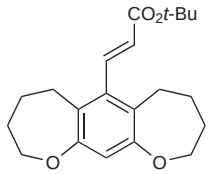
Table 1 Norbornene-Mediated Palladium-Catalyzed Alkylation–Alkenylation[a] (continued)



1, **7**, **9**, **11** **2**–**6**, **8**, **10**, **12**

Entry	Substrate	Heck acceptor H_2C=CXY	Product	Yield (%)[b]
3	**1** m = 1 n = 1		 **4**	42
4	**1** m = 1 n = 1		 **5**	77
5	**1** m = 1 n = 1		 **6**	57
6	**7** m = 1 n = 2		 **8**	80[c]
7	**9** m = 2 n = 2		 **10**	70[c]
8	**11** m = 3 n = 3		 **12**	68[d]

[a] All reactions were run under the following conditions unless otherwise specified: iodoarene (0.20 mmol, 1 equiv), $Pd(OAc)_2$ (10 mol%), PPh_3 (22 mol%), Cs_2CO_3 (5 equiv), norbornene (3 equiv), and Heck acceptor (5 equiv) in DME (4 mL) were exposed to microwave irradiation for 5 min at 190 °C.
[b] Isolated yield.
[c] The reaction was carried out for 10 min.
[d] The reaction was carried out for 20 min.

We initially explored the synthesis of 5,6,5-ring systems from **1** and various Heck acceptors using iodoarene (1 equiv), $Pd(OAc)_2$ (10 mol%), triphenylphosphine (22 mol%), Cs_2CO_3 (5 equiv), norbornene (3 equiv), and Heck acceptor (5 equiv) in dimethoxyethane (0.05 M) under microwave irradiation[8] for 5 minutes at 190 °C (entries 1–5, Table 1). While use of an acrylate afforded the corresponding product in a good yield (entry 1), acrylamides

and acetamidoacrylates bearing a free NH gave only modest yields (entries 2 and 3). We note that **4** is of particular interest as subsequent asymmetric hydrogenation and allows access to a variety of phenylalanine analogues.[9] Vinyl aromatic Heck acceptors were also compatible under the reaction conditions (entries 4 and 5).

The successful preparation of compounds containing the 5,6,5-ring system prompted us to extend the reaction scope to include other ring sizes. Reaction of **7** with *tert*-butyl acrylate resulted in a good yield of an unsymmetrical compound having a 5,6,6-ring system (entry 6). Compounds with 6,6,6-ring systems (entry 7) and 7,6,7-ring systems (entry 8) were also isolated in good yields. The primary difference as the ring size was varied was an increase in the reaction time.

To demonstrate the synthetic potential of this reaction, we carried out a synthesis of tricyclic mescaline analogue **14** (Figure 1); first synthesized by Nichols,[6] and later by Bergman and Ellman.[10] Mescaline (**13**), which is the active component in the hallucinogenic plant Peyote,[11] has served as a prototype for structure–activity relationship (SAR) studies linking molecular structure to hallucinogenic activity.[12] The behavioral effects produced by mescaline have been used as a standard against which other hallucinogenic compounds are measured. Its behavioral effects primarily occur through interactions with 5-hydroxytryptamine$_2$ (5-HT$_2$) receptors.[13] The mescaline analogue **14**, containing tetrahydrobenzodifuran functionalities as rotationally restricted bioisosteres of the aromatic methoxy groups in mescaline, showed an enhanced affinity for 5-HT$_2$ receptors with decreased hallucinogenic activity. Hence, the mescaline analogue **14** and other rotationally restricted analogues may be valuable in SAR studies of hallucinogenic agents.

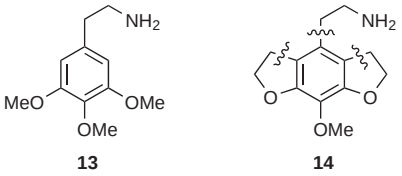


Figure 1 Mescaline and tricyclic mescaline analogue

The proposed disconnection is illustrated in Figure 2. The key step is the bis-alkylation–Heck reaction sequence involving aryl iodide **15** and a Heck acceptor.

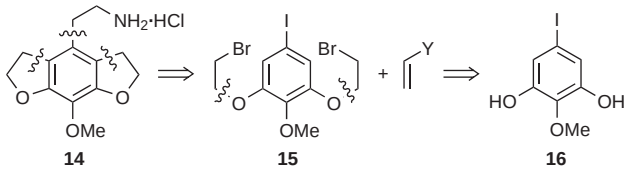
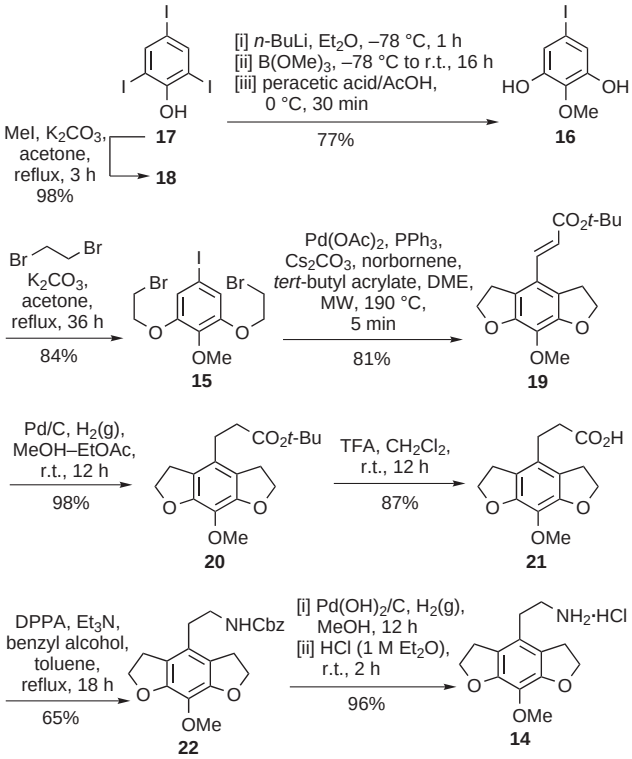


Figure 2 Retrosynthetic analysis

Our synthesis began with the methylation of commercially available 2,4,6-triiodophenol (**17**) in 98% yield (Scheme 1). Selective halogen–lithium exchange followed by quenching with trimethyl borate and subsequent oxidation with peracetic acid solution resulted in 77% yield of diol **16**.[14] Alkylation of **16** with 1,2-dibromoethane provided **15** in 84% yield. The one-pot palladium-catalyzed bis-intramolecular *ortho*-alkylation of **15** and subsequent Heck reaction with *tert*-butyl acrylate afforded the tricyclic heterocycle **19** in 81% yield. Catalytic hydrogenation of **19** afforded the aryl propionate **20** in 98% yield, which was converted to the desired carboxylic acid **21** in 87% yield by treatment with trifluoroacetic acid. Conversion of **21** to the mescaline analogue **14**·HCl was the achieved by a Curtius rearrangement[15] followed by hydrogenolysis and treatment with HCl (1 M in Et$_2$O) in 62% yield over two steps.



Scheme 1 Synthesis of Tricyclic Mescaline Analogue

In summary, we have shown that tricyclic symmetrical and unsymmetrical heterocycles can be easily prepared from a Heck acceptor and an aryl iodide containing two tethered alkyl bromides via a palladium-catalyzed intramolecular bis-alkylation–intermolecular alkenylation reaction. In addition, application of this methodology to the synthesis of mescaline analogue **14** was obtained in 27% yield over eight steps with an average yield per step of 85%. The value of this approach is that a variety of rotationally restricted mescaline analogues with varying ring sizes can be easily prepared. We are currently exploring the application of this methodology to the synthesis other tricyclic hetero- and carbocycles.

General Procedure for the Alkylation–Alkenylation Reaction 3-(2,3,5,6-Tetrahydrobenzo[1,2-*b*;5,4-*b*′]difuran-4-yl)acrylic Acid *tert*-Butyl Ester (2)

Microwave-assisted reactions were preformed in a Emrys Liberator model from Biotage (formerly Personal Chemistry) using Biotage Microwave Vials (2–5 mL). Microwave irradiation time was conducted using ramp time and hold time at the final temperature.

To a microwave reaction vessel were added Cs_2CO_3 (323 mg, 1.00 mmol, 5 equiv), norbornene (56.0 mg, 0.600 mmol, 3 equiv), $Pd(OAc)_2$ (4.50 mg, 0.0200 mmol, 10 mol%), PPh_3 (11.5 mg, 0.0440 mmol, 22 mol%), aryl iodide **1** (90.0 mg, 0.200 mmol, 1 equiv) and *tert*-butyl acrylate (146 μL, 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 Et_2O (4 mL) and quenched with H_2O (4 mL). The aqueous layer was extracted with Et_2O (3×) and the combined organic layers were washed with brine, dried with anhyd $MgSO_4$ and filtered. Removal of the solvent and purification by flash chromatography using 10% EtOAc–hexanes as eluant resulted in **2** (49.1 mg, 85%) as a pale yellow solid; mp 108–109 °C. R_f = 0.35 (silica gel, 10% EtOAc–hexanes). IR (neat). ν = 1707, 1593, 1440, 1293, 1154 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 16.3 Hz, 1 H), 6.32 (s, 1 H), 6.17 (d, *J* = 16.4 Hz, 1 H), 4.61 (t, *J* = 8.6 Hz, 4 H), 3.25 (t, *J* = 8.6 Hz, 4 H), 1.53 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.6, 160.9, 140.4, 127.3, 123.2, 118.4, 94.3, 81.0, 72.2, 29.6, 28.4. HRMS: *m/z* calcd for $C_{17}H_{20}O_4$ $[M]^+$: 288.1363; found: 288.1361.

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