C–H Functionalization

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The Norbornene Shuttle: Multicomponent Domino Synthesis of Tetrasubstituted Helical Alkenes through Multiple C–H Functionalization**

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In our ongoing interest in the development of highly efficient synthetic procedures towards complex molecules, the concepts of domino synthesis[1] and multicomponent reactions[2] play a fundamental role. Particularly attractive are reaction sequences that involve C–H activation processes, since this strategy precludes the requirement for prefunctionalization of one or both coupling partners and therefore significantly shortens the synthetic route.[3]

Herein we describe the discovery of a powerful method for the efficient synthesis of tetrasubstituted helical alkenes by utilizing a multiple C–H-functionalization domino process. Interest in tetrasubstituted overcrowded alkenes has recently grown, owing to their fascinating switching properties under UV irradiation.[4] In particular, the helical structures **1**–**3**, reported by Feringa and co-workers, have been applied to the development of chiroptical molecular switches and light-driven molecular motors (Figure 1).[5]

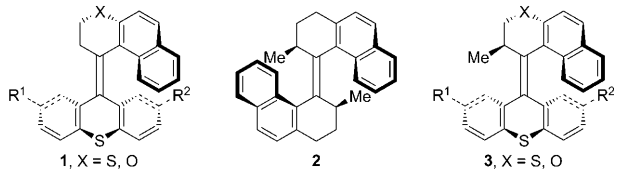


Figure 1. Chiral photochromic molecules synthesized by Feringa and co-workers.

We have been developing annulation and cyclization reactions,[6] based on a method by Catellani and co-workers,[7] involving a palladium-catalyzed norbornene-mediated domino process, wherein the alkylation of an *ortho* C–H bond is followed by a Heck reaction at the *ipso* carbon of the aryl iodide. During our investigation of alkylation reagents containing a tethered alkyne, we discovered that the vinyl-palladium intermediate reacts with norbornene leading to interesting tetrasubstituted alkene derivatives.[8] In this novel reaction sequence, four carbon–carbon bonds are constructed in a single-step operation, two of them by challenging C–H activation processes (Figure 2).

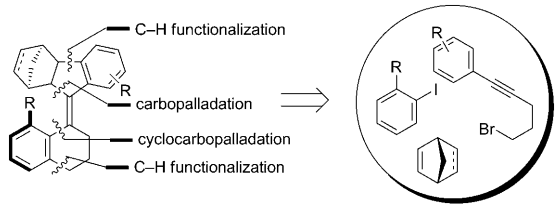
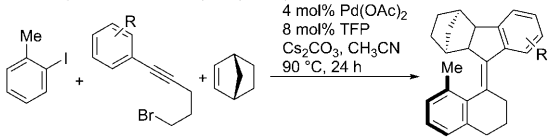


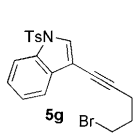
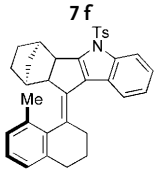
Figure 2. Retrosynthetic analysis of tetrasubstituted alkenes.

To probe the feasibility of this domino process, palladium complexes derived from different ligands were screened with commercially available 2-iodotoluene **4** and easily accessible substituted bromoalkyl aryl alkynes **5a–g** (Table 1).[9] In

Table 1: Scope of bromoalkyl aryl alkynes.[a]



4 **5a–g** **6** **7a–g** (*rac*)

Entry	R	Alkyne	Product	Yield [%][b]
1	H	**5a**	**7a**	75
2	2-F	**5b**	**7b**	80
3	2-OMe	**5c**	**7c**	95
4	4-Me	**5d**	**7d**	95
5	4-NO_2	**5e**	**7e**	90
6	3-CO_2Et	**5f**	**7f**	90
7		**5g**	 **7g**	40

[a] Reaction Conditions: **4** (0.60 mmol), **5a–g** (0.40 mmol), **6** (1.20 mmol), $Pd(OAc)_2$ (4.0 mol%), TFP (8.0 mol%), Cs_2CO_3 (1.2 mmol), acetonitrile (4.0 mL), 90°C, 24 h, sealed tube; [b] yield of isolated products.

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optimization studies, in the presence of an excess of norbornene, cesium carbonate, catalytic amounts of $Pd(OAc)_2$ and tri-(2-furyl)phosphine (TFP), and acetonitrile, the corresponding products **8a–g** were obtained in good-to-excellent yields as racemic mixtures. Both electron-withdrawing (Table 1, entries 2, 5, and 6) and electron-donating groups (Table 1, entries 3 and 4) as well as different positions for the substituent on the aryl ring of the alkyne system were tolerated. The connectivity and the relative configuration of the products were unambiguously determined by X-ray analysis of compound **8e** (Figure 3). It was also possible to carry out the final C–H activation step on an indole system, giving access to a heterocyclic analogue (Table 1, entry 7).

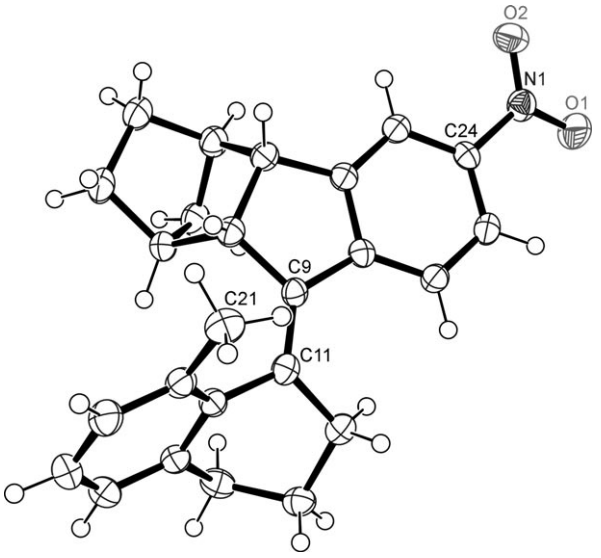
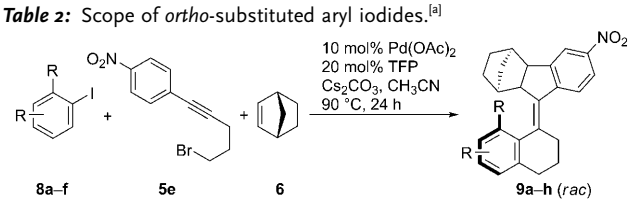
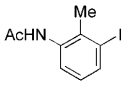
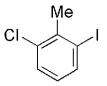
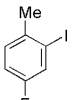
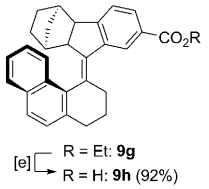


Figure 3. ORTEP representation of compound **7e**. Thermal ellipsoids are set at 50% probability.

With these promising results in hand, we turned our attention to variations of the aryl iodide coupling partner. Since it is known to be crucial to block the *ortho* position of the aryl iodide to avoid additional C–H activation reactions, we investigated different *ortho*-substituted aryl iodides for the domino process (Table 2). As a coupling partner we introduced either the nitro-substituted alkyne **5e** or the ester-substituted derivative **5f**, as both of these groups are suitable for further manipulation.[10] In addition, aryl iodides with both electron-donating (OMe, Table 2, entry 1) and electron-withdrawing substituents (trifluoromethyl, Table 2, entry 2) gave the corresponding products **9a** and **9b** in good yields. In contrast, aryl iodides with fluorine, chlorine, and nitrogen-containing blocking groups furnished complex product mixtures and only minor amounts of the desired products. Blocking the *ortho* position with a methyl group and switching the nitrogen-containing, chlorine, or fluorine substituent to the *meta*, improved the outcome of the reaction significantly and products **9c–9e** could be furnished in good yields (Table 2, entries 3–5). In this context, the tolerance of a chlorine substituent was of special interest, since this functionality offers opportunities for further metal-catalyzed

Table 2: Scope of *ortho*-substituted aryl iodides.[a]



Entry	Aryl Iodide	Product	Yield [%][b]
1	 **8a**	**9a**	77
2	 **8b**	**9b**	87
3	 **8c**	**9c**	60
4	 **8d**	**9d**	62
5	 **8e**	**9e**	85
6	 **8f**	**9f**	68 64[c]
7	 **8f**	 [e] R = Et: **9g**, R = H: **9h** (92%)	65[d]

[a] Reaction conditions: **8a–f** (0.20 mmol), **5e** (0.40 mmol), **6** (0.60 mmol), $Pd(OAc)_2$ (10 mol%), TFP (20 mol%), Cs_2CO_3 (0.60 mmol), acetonitrile (4.0 mL), 90°C, 24 h, sealed tube; [b] yield of isolated products; [c] the reaction was carried out on a 4.0 mmol scale; [d] **5f** was used instead of **5e**; [e] $LiOH \cdot H_2O$ (5.0 equivalents), THF/MeOH/H_2O (5:1:1), room temperature, 2 days.

cross-coupling reactions.[11] Particularly useful products were obtained when 1-iodonaphthalene **8f** was used within the domino process (Table 2, entries 6 and 7). The products **9f** and **9g** were obtained in good yields and their helical structure was clearly confirmed by proton NMR spectroscopic and X-ray crystallographic analysis (Figure 4). Interestingly, one of the methylene protons of the norbornene moiety gave rise to a resonance which was shifted significantly upfield ($\delta \approx 0.25$ ppm). The crystal structure clearly indicates a conformation leading to a shielding effect by the ring current of the aromatic naphthalene moiety. The synthesis of **9f** also proceeded in similar yield on a tenfold higher scale, and product **9g** was easily converted into the corresponding carboxylic acid derivative **9h** by base-promoted ester hydrol-

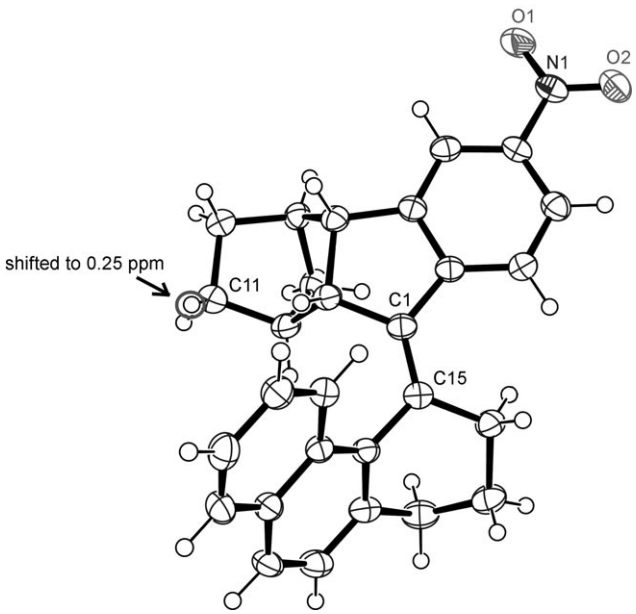
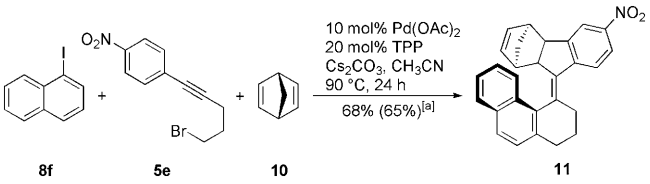


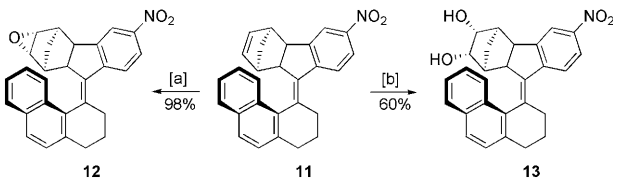
Figure 4. ORTEP representation of compound **9 f**. Thermal ellipsoids are set at 50% probability.

ysis. Our next goal was the replacement of the strained alkene norbornene with norbonadiene to explore further variations of the novel helical products by adding functionality at an otherwise inert position. When we applied our standard method to the reaction of 1-iodonaphthalene **8 f**, alkyne **5 e** and norbornadiene, the desired product **11** was detected in minor amounts. Norbornadiene is not known as an efficient mediator of the Catellani process (Scheme 1), but upon



Scheme 1. Domino reaction with norbornadiene as mediator/substrate; Reaction conditions: **8 f** (0.40 mmol), **5 e** (0.80 mmol), **10** (4.80 mmol), $Pd(OAc)_2$ (10 mol%), triphenylphosphine (TPP, 20 mol%), Cs_2CO_3 (1.20 mmol), acetonitrile (4.0 mL), 90°C, 24 h, sealed tube; yields given are of isolated products; [a] yield based on a 4.00 mmol scale.

switching the phosphine ligand from tri-(2-furyl)phosphine to triphenylphosphine, we could isolate the desired product **11** in 68% yield (65% on a 4.0 mmol scale). Finally, we investigated the ability to selectively derivatize the olefin at the norbornadiene unit of product **11**. Hence, submitting **11** to *meta*-chloroperoxybenzoic acid in dichloromethane resulted in the formation of the corresponding epoxide **12** in nearly quantitative yield (Scheme 2). The connectivity as well as the relative configuration was proven by X-ray analysis (Figure 5). As expected, the attack of the double bond by the electrophilic oxygen occurs from the less hindered side.



Scheme 2. Derivatization of product **11**; Reaction conditions: [a] *meta*-chloroperbenzoic acid, CH_2Cl_2, 0°C to room temperature, 2.5 h; [b] cat. OsO_4, *N*-methylmorpholine *N*-oxide, THF/H_2O (2.5:1), room temperature, 1.5 h.

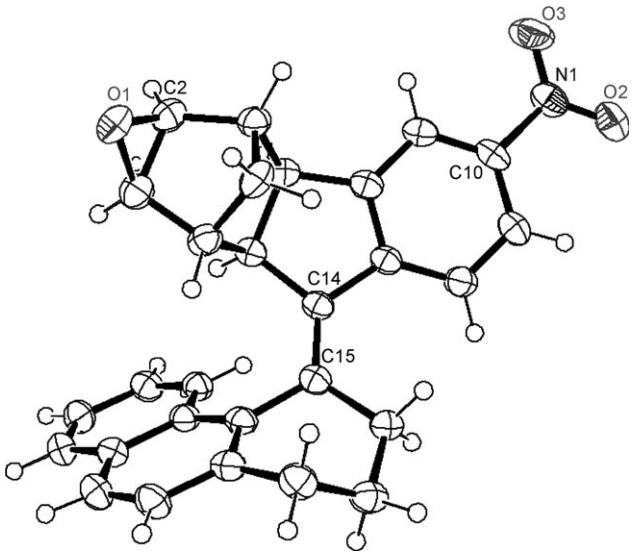
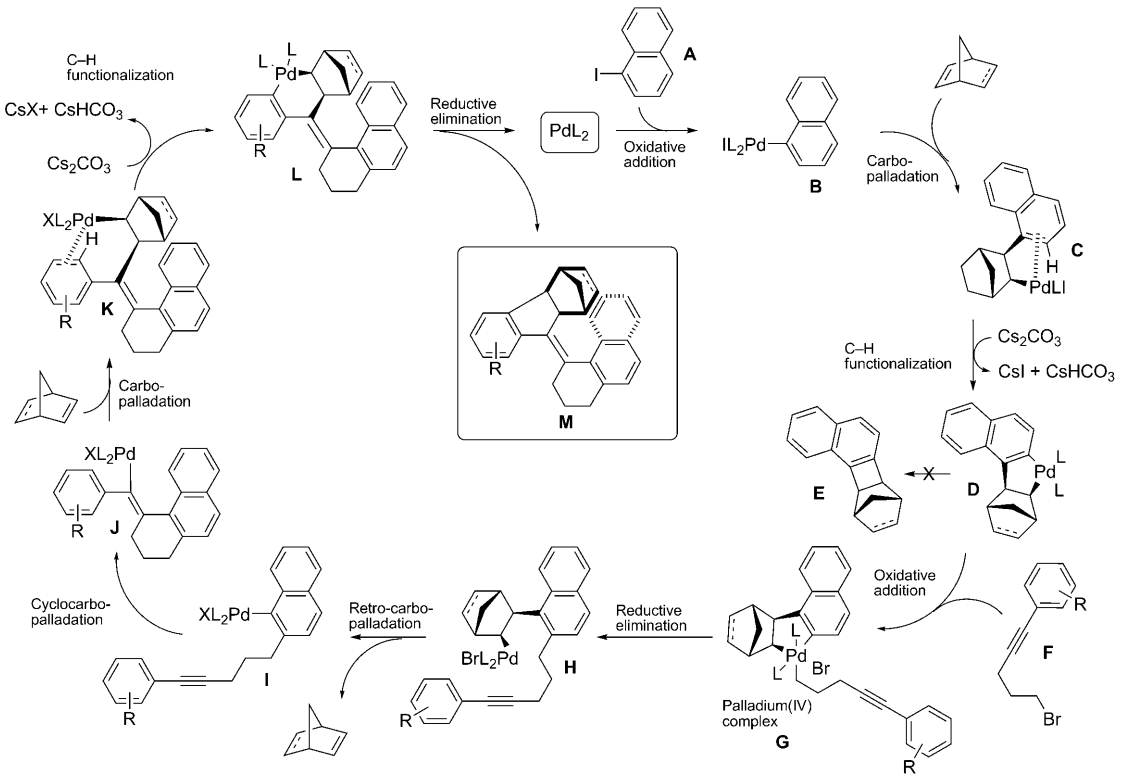


Figure 5. ORTEP representation of compound **12**. Thermal ellipsoids are set at 50% probability.

Osmium tetroxide catalyzed dihydroxylation was also feasible, delivering compound **13** in 60% yield.

The proposed mechanism of the domino reaction is outlined in Scheme 3. Within the proposed reaction mechanism, the strained alkene norbornene (or norbornadiene) enters and exits the catalytic cycle in a remarkable "square dance," eventually becoming permanently incorporated in the product. We hypothesize that the reaction is initiated by an oxidative addition of a preformed Pd^0 complex to aryl iodide **A**, generating the arylpalladium(II) intermediate **B**. Subsequent *syn*-carbopalladation of either the reactive olefin norbornene or norbornadiene in an *exo*-fashion leads to complex **C**. While in the standard Catellani reaction, norbornene could theoretically be used in catalytic quantities, it often requires more than 1 equivalent to become efficient, whereas in this reaction norbornene is incorporated into the final product so at least 1 equivalent is required but usually an excess is used to favor carbopalladation and subsequent C–H activation as the early steps in the process. In our novel process the strained alkene acts as a promoter as well as a coupling partner—the alkene is consumed within the last reaction step—the reaction requires an excess of this reagent. With no possibility for a syn-β-hydride elimination, an electrophilic metalation takes place, followed by deprotonation in the *ortho*-position to the five-membered palladacycle



Scheme 3. The norbornene dance—proposed mechanism of the multicomponent domino synthesis.

D. Instead of undergoing previously described[7e,12] reductive elimination to build the strained cyclobutene **E**, complex **D** undergoes oxidative addition of bromoalkyl aryl alkyne **F**, furnishing octahedral palladium(IV) complex **G**, which then undergoes rapid reductive elimination to deliver the *ortho*-alkylated intermediate **H**. Owing to increased steric demand and no possibility of *syn*-β-H elimination, a retro-carbopalladation of the strained alkene occurs, providing arylpalladium(II) species **I**. Intramolecular carbopalladation of **I** onto the tethered alkyne forms the second carbon–carbon bond. Following the formation of the new 6-membered ring, vinylpalladium(II) intermediate **J** subsequently undergoes an intermolecular carbopalladation of norbornene (or norbornadiene), leading to complex **K** in which the palladium induces another C–H functionalization on the adjacent aromatic ring. This process is believed to proceed rather by a direct C–H insertion than by an electrophilic aromatic substitution by attack of the aryl onto the palladium(II) species, since the functionalization occurs with either electron-rich or electron-deficient systems. Nonetheless, reductive elimination from the previously formed six-membered palladacycle **L** leads finally to the construction of the fourth carbon–carbon bond to deliver the desired helical structure **M**.

In conclusion, we have developed an efficient Pd-catalyzed multicomponent domino process which allows access to highly complex tetrasubstituted helical alkenes. In this novel reaction, four carbon–carbon bonds are constructed in a single operation including two challenging C–H activation processes. The synthesized molecules are variants of a known class of molecular switches and light-driven motors. Further experiments, concerning the behavior of these compounds under light irradiation are currently underway.

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Keywords: C–H activation · domino reactions · multicomponent reactions · palladium · strained molecules

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