Domino Reactions

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Expeditious Synthesis of Tetrasubstituted Helical Alkenes by a Cascade of Palladium-Catalyzed C–H Activations**

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The design and construction of molecular analogues of mechanical machines has attracted increasing attention over the past decade.[1–4] In particular, artificial molecular devices based on chiral tetrasubstituted helical alkenes, which were developed by Feringa and co-workers,[5] have received growing interest. Synthetic rotary molecular motors such as **1** are capable of performing perpetual unidirectional 360° rotation around the center of the olefin upon light irradiation (Figure 1).[6] The direction of rotary motion is governed by

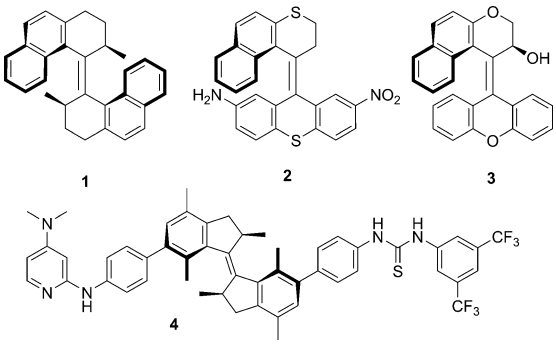
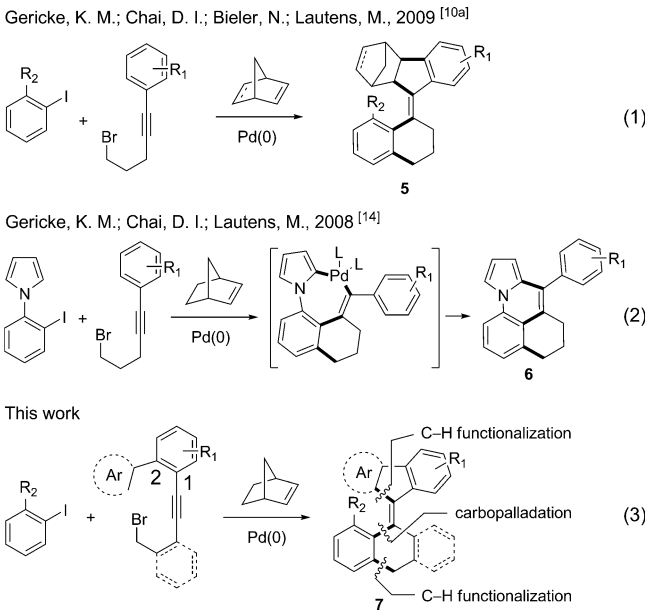


Figure 1. Representative examples of a light-driven molecular motor (**1**), a switch (**2**,**3**) and a motor-based asymmetric catalyst (**4**).

the chirality of the stereogenic center(s) in the helical molecule. Furthermore, molecules with different applications have been designed and studied in recent years, such as molecular switches[7] (for example, **2** and **3**) with the potential for optical data storage. Moreover, asymmetric organocatalyst **4**[8] can be modulated by light in situ to generate either enantiomer of the product. Subtle and distinct structural modifications are generally required for fine-tuning of the rotary motion of such artificial molecular devices.[9] To attain this goal, methods for the rapid and modular synthesis of tetrasubstituted helical alkenes are highly desirable.[7,10] In particular, domino reactions[11] involving sequential C–H activations have become more attractive, as they significantly shorten the number of synthetic steps, thus avoiding the necessity to prefunctionalize one or both of the coupling partners.[12]

We have previously demonstrated the feasibility of forming tetrasubstituted alkene **5** by a Pd-catalyzed norbornene mediated domino reaction involving multiple C–H functionalizations [Scheme 1, Eq. (1)].[10a] In this reaction, norbornene not only acts as a promoter,[13] but is incorporated into the product. To increase the molecular diversity of these products and to allow for the fine-tuning of their photochemical properties, we disclose herein a novel domino reaction to access sterically crowded helical alkenes **7** without norbornene incorporation, whilst using norbornene to facilitate the C–H activations.



Scheme 1. Work preceding this report and a proposed retrosynthetic disconnection of **7**.

Our design was inspired by our previous synthesis of fused tetracyclic pyrroles **6** using a Pd-catalyzed domino reaction[14] [Scheme 1, Eq. (2)], wherein a norbornene mediated *ortho*-alkylation of an aryl iodide followed by carbopalladation of a tethered alkyne resulted in a vinylpalladium species. This intermediate subsequently underwent an intramolecular C–H functionalization on the pendant pyrrole to afford the desired product. We envisioned that, if the bromoalkyl aryl alkyne

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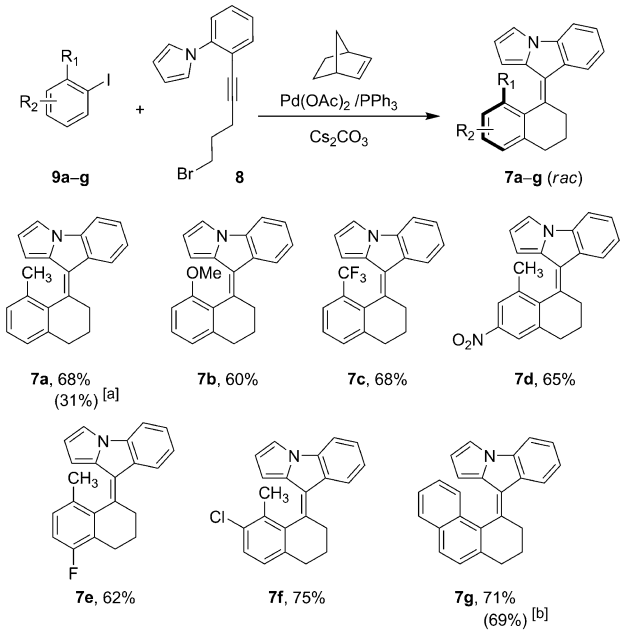
precursor was appended with a 2-substituted aryl/heterocyclic group on the aromatic ring [Scheme 1, Eq. (3)], then carbon–carbon bond formation should occur between the vinylpalladium species and the pendant aryl/heterocyclic group by C–H functionalization, thereby providing tetrasubstituted alkenes lacking the norbornene moiety.

To test this approach, we chose a pyrrole moiety as the pendant heterocycle in the bromoalkyl aryl alkyne precursor. The 2-pyrrolyl substituted bromoalkyl aryl alkyne **8** can be easily obtained from *o*-iodoanilines in a three step synthesis.[15] With substrate **8** in hand, we examined this domino process using the standard reaction conditions previously used in our earlier work. To our delight, the desired tetrasubstituted alkene **7a** was obtained in 31% yield (Scheme 2). Interestingly, the product was isolated as a mixture of *E*/*Z* isomers.[16] Presumably, the isomerization could be acid-catalyzed and/or light-driven.[17] Indeed, under acid-free conditions and with protection from light, the desired product was obtained as a single isomer. In the optimization study we found that upon switching the ligand from tri(2-furyl)phosphine (TFP) to triphenylphosphine (PPh_3), **7a** can be isolated in 68% yield.



Scheme 2. Scope of the reaction with *ortho*-substituted aryl iodides. Reagents and reaction conditions: 2-pyrrolyl substituted aryl alkyne **8** (ca. 0.2 mmol; 1 equiv), aryl iodide **9a–g** (2.0 equiv), norbornene (2.0 equiv), $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), Cs_2CO_3 (3.0 equiv), acetonitrile (2.0 mL), 90°C, 24 h, sealed tube. Yields given are of isolated products. [a] Reaction conducted under earlier conditions: as described, but using TFP in place of PPh_3 and with norbornene (3 equiv). [b] Reaction conducted on 1.0 mmol of **8**.

We then investigated the scope of the reaction using various *ortho*-substituted aryl iodides (Scheme 2). Both aryl iodides bearing electron-donating (OMe, **9b**) and electron-withdrawing (CF_3, **9c**) substitution in the *ortho*-position afforded the corresponding products (**7b** and **7c**, respectively) in good yields. Aryl iodides containing both an *ortho*-methyl group and either a *para*-nitro (**9d**), *meta*-chloro (**9e**), or *meta*-fluoro (**9f**) substituent gave the corresponding products (**7d–f**) in good yields. More importantly, the tolerance of nitro or chloro substitutents in the final product allows for further manipulation and is suitable for incorporation into a larger system.[18,19] Notably, the helical alkene **7g**, which bears a naphthalene substitutent, can be prepared in good yield from 1-iodonaphthalene (**9g**). The X-ray crystal structures of **7d** and **7g** confirm the connectivity and relative configuration of the tetrasubstituted alkenes (Figure 2). The

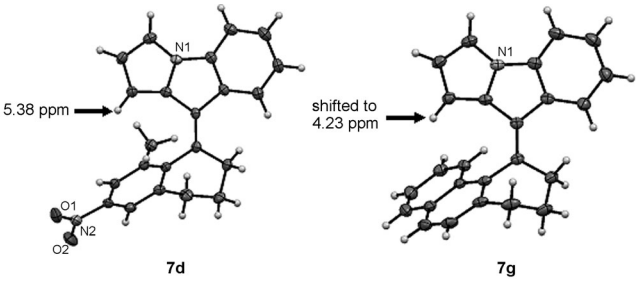
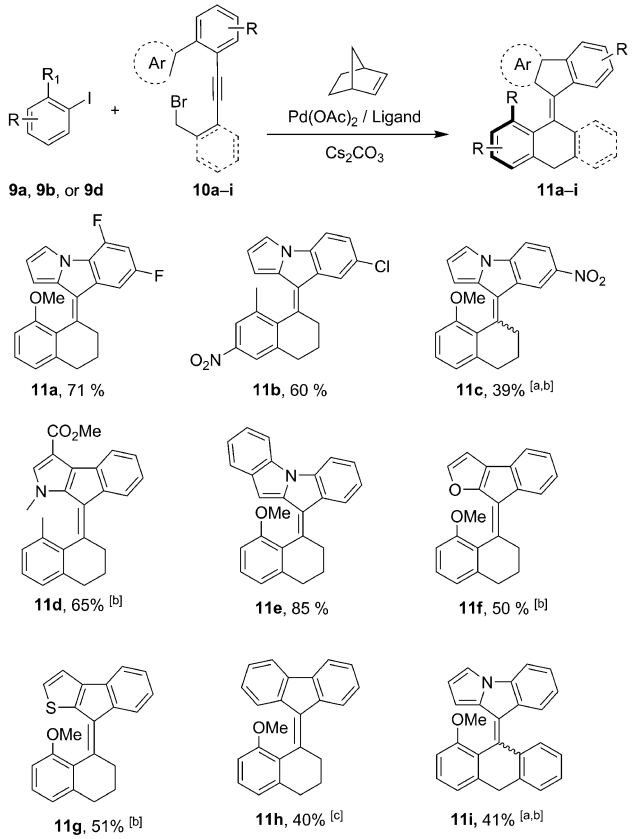


Figure 2. X-ray crystal structures of **7d** and **7g**.

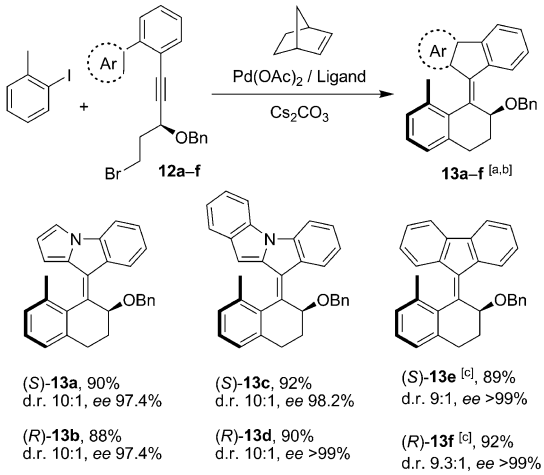
helical structure of **7g** was also unambiguously confirmed by proton NMR spectroscopy. The chemical shift of one of the protons in the pyrrole ring is shifted significantly upfield compared to the corresponding proton in **7d** (4.23 ppm vs. 5.38 ppm). Presumably, this is due to a shielding effect by the ring current of the aromatic naphthalene moiety, as suggested by the crystal structure of **7g**. The reaction can also be performed on a preparatively useful scale (1 mmol), resulting in a similar yield and affording more than 200 mg of material.

The reaction scope was further investigated using bromoalkyl aryl alkynes **10a–i**[15] (Scheme 3), which were easily accessible in a similar manner to **7**. A variety of substituents (F, Cl, NO_2) at different positions on the aryl ring of the alkyne system were tolerated, producing the corresponding products **11a–c** in moderate to good yields. **11c** was isolated as a mixture of *E*/*Z* isomers (1:1) despite all efforts to prevent the acid catalyzed isomerization. Presumably, this compound undergoes fast isomerization upon exposure to visible light. Substrate **10d**, which bears a differently substituted 2-pyrrolyl moiety, afforded product **11d** in good yield. This reaction also tolerated pendant heterocycles other than pyrrole; C–H activation was successful on indole, furan, and thiophene systems to form products **11e–g**, respectively, in moderate to good yields. Interestingly, single isomers were observed for furyl and thienyl substituted compounds (**11f** and **11g**, respectively); unlike their pyrrole based counterparts, these compounds were not sensitive to acid. We also observed that nonheterocyclic nucleophile **10h** can be used to give **11h** in moderate yield. The reaction scope can be further extended to form crowded helical alkene **11i** with four aromatic substitutents, which was found to be very sensitive to light when in solution.[20]

This method also provides quick access to chiral and enantiomerically enriched tetrasubstituted helical alkenes,



Scheme 3. Scope of the reaction with bromoalkyl aryl alkynes. Reagents and reaction conditions: bromoalkyl aryl alkynes **10a–i** (ca. 0.2 mmol, 1 equiv), aryl iodide **9a**, **9b**, or **9d** (2.0 equiv), norbornene (2.0 equiv), $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), Cs_2CO_3 (3.0 equiv), acetonitrile (2.0 mL), 90°C, 24 h, sealed tube. Yields given are of isolated products. [a] Product was isolated as an *E*/*Z* mixture (1:1). [b] Reaction conducted with TFP as the ligand. [c] Reaction conducted at 120°C with TFP as the ligand.

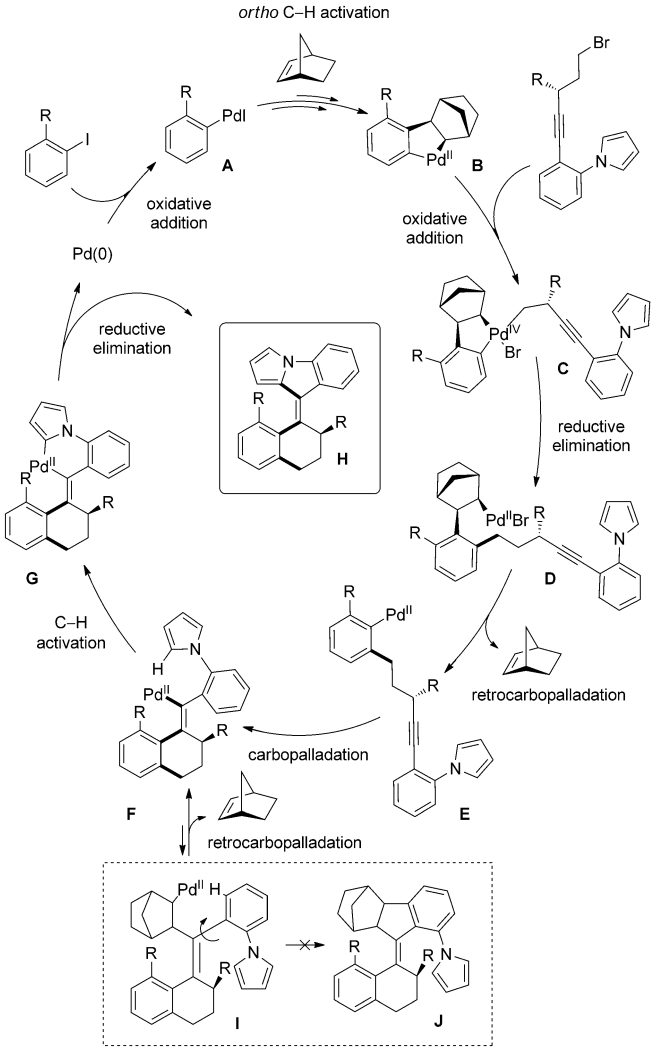


Scheme 4. Stereoselective synthesis of tetrasubsituted alkenes **13a–f**. Reagents and reaction conditions: bromoalkyl aryl alkynes **12a–f** (ca. 0.2 mmol, 1 equiv), aryl iodide (2.0 equiv), norbornene (2.0 equiv), $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), Cs_2CO_3 (3.0 equiv), acetonitrile (2.0 mL), 90°C, 24 h, sealed tube. Yields given are of isolated products. [a] d.r. determined by ^1H NMR analysis of the crude product. [b] *ee* determined by HPLC analysis on a chiral stationary phase. [c] Reaction conducted at 120°C with TFP as the ligand.

(**13a–f**) which possess a stereogenic center next to the olefin (Scheme 4). It is noteworthy that, as shown by Feringa, the absolute stereochemistry in these alkenes can dictate the direction of molecular rotation upon irradiation.[7a] Utilizing the optically pure bromoalkyl aryl akynes **12a–f**,[15] the domino reaction with 2-iodotoluene afforded the corresponding chiral helical alkenes in excellent yield and good stereoselectivity. Both enantiomers can be accessed from the corresponding enantiomerically pure precursors, which allows for the study of their distinct rotational behavior upon irradiation. These reactions proceed with retention of stereochemistry of the bromide precursors in excellent enantioselectivity (up to 99% *ee*). The induction of helical chirality in this multiple bond forming process was observed, as was suggested by the moderate diastereoselectivity of the reaction. We reported a stereoselective synthesis of tetrasubstituted alkenes bearing norbornene, which also bear the observed helical chirality, in accordance with these findings.[22]

The proposed mechanism of the domino reaction is outlined in Scheme 5. Similar to the other norbornene mediated C–H functionalization processes,[13] a series of reactions involving oxidative addition of the aryl iodide, carbopalladation of norbornene, and electronic metalation followed by deprotonation gives palladacycle **B**. Oxidative addition of a bromoalkyl aryl alkyne leads to **C**, and rapid reductive elimination delivers *ortho*-alkylated intermediate **D**. Because of increased steric demand, a retrocarbopalladation of norbornene then occurs, leading to arylpalladium species **E**. Next, intramolecular carbopalladation on the tethered alkyne generates the vinylpalladium species **F**. At this point the intermediate can directly induce C–H functionalization on the adjacent pyrrole ring to form **G**, and subsequent reductive elimination generates the desired product **H**. Because of the high reactivity associated with norbornene (strain energy = 21.6 kcal mol^{-1})[23] and its presence in large excess, the vinyl palladium species **F** could undergo intermolecular carbopalladation of norbornene, thus leading to complex **I**, to which another C–H functionalization on the adjacent aromatic ring could occur to liberate tetrasubstituted alkene **J**. However, this reaction pathway is not followed, as revealed by the formation of product **H**. Presumably, the C–H functionalization of **F** to provide **G** is much faster than the carbopalladation of norbornene, thereby preventing the formation of **I**. Another potential explanation could be the increased steric congestion in complex **I**, which would result from the bulky 2-substituted aryl/heterocyclic group. If formed, this species, particularly for **12a–f** containing a pendant stereogenic center, would favor the retrocarbopalladation of norbornene to produce **F**, despite the use of a large excess of norbornene.[24]

In conclusion, we have developed an effective and highly modular synthesis of sterically crowded tetrasubstituted helical alkenes possessing high structural diversity through a palladium-catalyzed norbornene mediated cascade of C–H activations. The molecules synthesized can act as lead



Scheme 5. Proposed reaction mechanism for the domino process. Ligand and solvent molecules omitted for clarity.

structures for the design of light-driven molecular devices. Investigations into their photochemical behavior upon light irradiation are currently underway.

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[20] **11i** was isolated as a mixture of *E*/*Z* isomers because of a rapid isomerization process under visible light. The CD_2Cl_2 solution of **11i** changed color and decomposed at room temperature after

one day under visible light, as confirmed by ^{1}H NMR analysis of the solution.

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[24] It was found that even with a large excess of norbornene (8.0 equiv), **7a** was still formed in 55% yield, based on NMR analysis. This suggests that the norbornene incorporation pathway is less favorable than the directed C–H functionalization. Perhaps this is due to the presence of the pyrrole, which disfavors species **I**.

