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Modular and Stereoselective Synthesis of Tetrasubstituted Helical Alkenes via a Palladium-Catalyzed Domino Reaction

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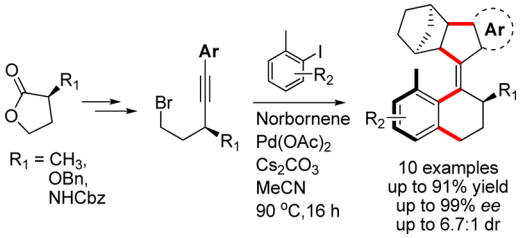
ABSTRACT



A highly modular and stereoselective synthesis of tetrasubstituted helical alkenes is accomplished by a Pd-catalyzed norbornene-mediated domino reaction. This protocol features the rapid assembly of four C−C bonds via sequential C−H activations and carbopalladations along with efficient access to enantiopure bromoalkyl aryl alkyne precursors using homologative alkynylation as the key transformation. Three distinct elements of stereoselectivity were observed in the preparation of the chiral helical alkenes: retention of stereochemistry of the substrates, induced helical diastereoselectivity in the alkene formation, and the exclusive *exo*-facial selectivity of the norbornene incorporation.

With the rapid development of nanotechnology, the design and efficient construction of molecular motors that power future nanomachines are highly desirable.[1] Among various types of motors, the light-driven chiral tetrasubstituted helical alkenes developed by Feringa and coworkers[2] have attracted attention (Figure 1). In particular, alkene (**1**) can undergo unidirectional 360° rotation around the olefin axis upon light irradiation. Many versatile designs based on these molecules have been realized, such as a molecular switch[3] (**2**), showing potential in the application of binary data storage, and a light-driven asymmetric catalyst[4] (**3**) with the capacity to form either enantiomer of the product upon modulating the catalyst form by irradiation. Interestingly, the direction of rotation of these molecules upon irradiation with light is dictated by the absolute configuration of stereogenic center(s) next to the central double bond.[2] In order to understand and harness the unidirectional rotation, efficient access to these enantiomerically pure helical alkenes has recently intensified research activity in this area.[2c,3,5] Herein, we report a highly modular and stereoselective approach to synthesize sterically crowded tetrasubstituted helical alkenes via a domino reaction from simple starting materials.

On the basis of our previous synthesis of tetrasubstituted helical alkenes,[6a] chiral alkenes (**4**) should be accessible from the commercially available *ortho*-subsubstituted aryl iodides (**5**) and enantiomerically pure bromoalkyl aryl alkynes (**6**) via a palladium-catalyzed, norbornene-mediated

(1) (a) Balzani, V., Credi, A., Venturi, M. *Molecular Devices and Machines-Concepts and Perspectives for the Nanoworld*, 2nd ed.; Wiley-VCH: Weinheim, 2008. (b) Sauvage, J.-P., Ed. *Molecular Machines and Motors*; Springer: New York, 2001.

(2) (a) Feringa, B. L. *J. Org. Chem.* **2007**, *72*, 6635–6652 and references therein. (b) Feringa, B. L.; van Delden, R. A.; Koumura, N.; Geertsema, E. M. *Chem. Rev.* **2000**, *100*, 1789–1816 and references therein. (c) Ruangsupapichat, N.; Pollard, M. M.; Harutyunyan, S. R.; Feringa, B. L. *Nat. Chem.* **2011**, *3*, 53–60.

(3) Tietze, L. F.; Düfert, M. A.; Lotz, F.; Sçlter, L.; Oum, K.; Lenzer, T.; Beck, T.; Herbst-Irmer, R. *J. Am. Chem. Soc.* **2009**, *131*, 17879–17884.

(4) Wang, J.; Feringa, B. L. *Science* **2011**, *331*, 1429–1432.

(5) (a) Tietze, L. F.; Düfert, M. A.; Hungerland, T.; Oum, K.; Lenzer, T. *Chem.—Eur. J.* **2011**, *17*, 8452–8461. (b) Tietze, L. F.; Hungerland, T.; Dufert, A.; Objartel, I.; Stalke, D. *Chem.—Eur. J.* **2012**, *18*, 3286–3291. (c) Hojo, D.; Noguchi, K.; Tanaka, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 8129–8132. (d) Pijper, T. C; Pijper, D.; Pollard, M. M.; Dumur, F.; Davey, S. G.; Meetsma, A.; Feringa, B. L. *J. Org. Chem.* **2010**, *75*, 825–838.

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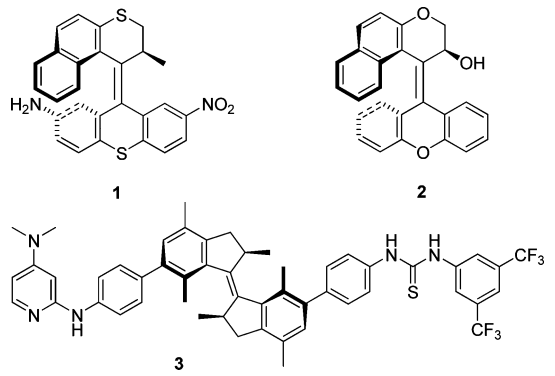
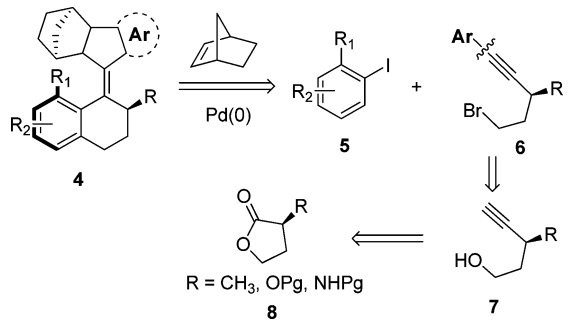


Figure 1. Representative examples of a light-driven molecular motor (**1**), molecular switch (**2**), and motor-based asymmetric catalyst (**3**).

domino reaction[6b] (Scheme 1). This process forms four carbon−carbon bonds in one synthetic sequence. We

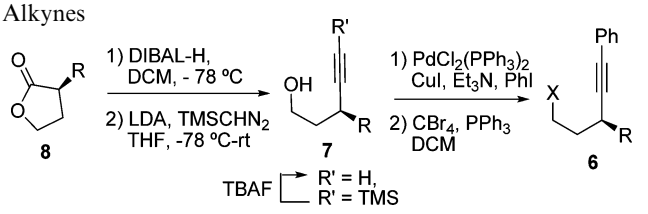


Scheme 1. Proposed synthesis of Chiral Tetrasubstituted Helical Alkenes

anticipate that the stereochemistry of the bromide-containing precursor remains intact during the reaction sequence. The bromides can be retrosynthetically derived from chiral alkynes (**7**), which are made from chiral α-substituted lactones (**8**). Notably, the ease of access to chiral α-lactones offers structural diversity of the helical alkene, as a variety of substituted groups, based on carbon, oxygen, and nitrogen, can be introduced at the stereogenic center.

Our synthesis begins with the preparation of optically pure alkynes **7**. During the course of the investigation, we compared several synthetic pathways, and the most modular and high yielding method is shown in Table 1. Alkynes with various α-substituents (OBn, CH_3, NHCbz) were efficiently synthesized from corresponding lactones **8**[7] via a homologative alkynylation sequence.[8] Reduction of the lactones to lactols with diisobutylaluminum hydride (DIBAL) followed by a homologative rearrangement with $TMSCHN_2$ and LDA provided the corresponding alkynes in good yields. Interestingly, the formation of C-silated alkynes **7a′** was observed during the rearrangement to **7a**, which was readily converted to the desired products through TBAF desilation.[9] The required chiral bromoalkyl aryl alkyne **6** was readily obtained in high yield with excellent enantioselectivity (up to 99% ee) through a modular two-step sequence, including installation of an aryl group via a Sonogashira coupling and conversion of

Table 1. Synthesis of Enantiomerically Pure Bromoalkyl Aryl Alkynes



entry	**8** (R)	**7**,[a] yield (%)	**6**,[a] yield (%) (ee,[b] %)
1	(3*S*)-**8a** (OBn)	(3*S*)-**7a** R′ = H, 30 (3*S*)-**7a′** R′ = TMS, 25	(3*S*)-**6a** X = OH, 80 (3*S*)-**6aa** X = Br, 89 (>99)
2	(3*R*)-**8b** (OBn)	(3*R*)-**7b** R′ = H, 55	(3*R*)-**6b** X = OH, 83 (3*R*)-**6ba** X = Br, 86 (>99)
3	(3*S*)-**8c** (NHCbz)	(3*S*)-**7c** R′ = H, 38	(3*S*)-**6c** X = OH, 82 (3*S*)-**6ca** X = Br, 93 (98.5)
4	(3*R*)-**8d** (NHCbz)	(3*R*)-**7d** R′ = H, 41	(3*R*)-**6d** X = OH, 82 (3*R*)-**6da** X = Br, 92 (98.5)
5	(3*R*)-**8e** (CH_3)	(3*R*)-**7e** R′ = H, 51	(3*R*)-**6e** X = OH, 80 (3*R*)-**6ea** X = Br, 80 (>99)

[a] Yield of isolated products. [b] The ee values were determined by chiral HPLC.

the alcohol to a bromide via an Appel reaction.[10] The corresponding enantiomers of the bromide precursors were prepared from the enantiomers of the chiral lactones through an identical synthetic sequence. The formation of both enantiomers allows for an investigation of the stereochemical outcome of the helical alkene formation, along with the capacity to study their respective rotational path upon irradiation with light.

With the enantiopure substrates in hand, we examined the domino process between bromide (3*S*)-**6aa** and

(6) (a) Gericke, K. M.; Chai, D. I.; Bieler, N.; Lautens, M. *Angew. Chem.* **2009**, *121*, 1475–1479. *Angew. Chem., Int. Ed.* **2009**, *48*, 1447–1451. (b) Catellani, M.; Frignani, F.; Rangoni, A. *Angew. Chem., Int. Ed.* **1997**, *36*, 119–122. For a review on norbornene mediated *ortho* C−H functionalization, see: *Topics in Current Chemistry: C−H Activation*; Yu, J.-Q., Shi, Z., Eds.; Springer: Berlin, 2010; Vol. 292, pp 1−33.

(7) The enantiomerically pure α-lactones were prepared according to literature procedures. See the Supporting Information for details.

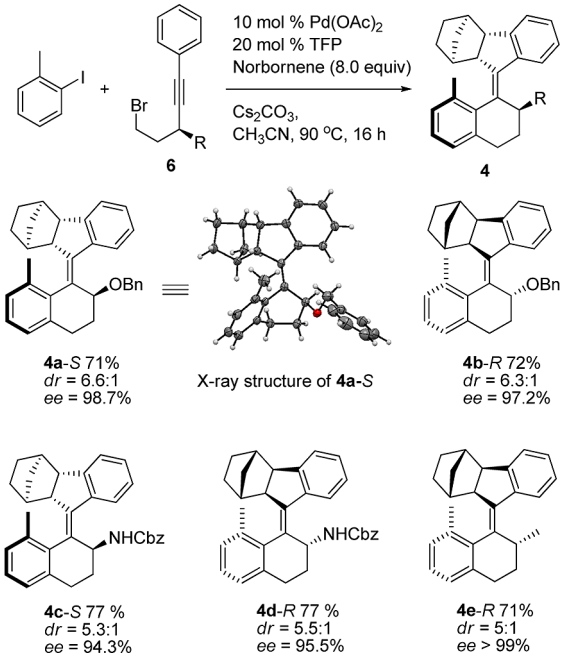
(8) (a) Myers, A. G.; Goldberg, S. D. *Angew. Chem., Int. Ed.* **2000**, *29*, 2732. (b) Smith, A. B.; Fox, R. J.; Vanecko, J. A. *Org. Lett.* **2005**, *7*, 3099.

(9) The side product formation was also observed by others. See: Fürstner, A.; Wuchrer, M. *Chem.−Eur. J.* **2006**, *12*, 76–89.

(10) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467–4470. (b) Appel, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 801–811. (c) Gericke, K. M.; Chai, D. I.; Lautens, M. *Tetrahedron* **2008**, *64*, 6002–6014.

2-iodotoluene using the standard condition used in our previous work.[6a] The desired tetrasubstituted alkene **4a-*S*** was formed in 71% yield (Scheme 2). Its helical structure and connectivity as well as the absolute stereochemistry were confirmed by X-ray crystal analysis. No significant improvement in yield was observed upon reaction optimization (see the Supporting Information). In the same manner as **4a-*S***, the corresponding enantiomer **4b-*R*** was prepared from bromide (3*R*)-**6ba** in good yield. The tetrasubstituted alkenes bearing nitrogen (**4c-*S*** and **4d-*R***) and carbon **4e-*R*** substituents at the stereogenic center were also obtained in good yield. It is noteworthy that the

Scheme 2. Synthesis of Tetrasubstituted Alkenes with Various Substitutents at the Stereogenic Center[a−d]



[a] Reaction was conducted on a 0.2 mmol scale (**4a**-*S* in 0.4 mmol scale). [b] Yield of isolated products. [c] The dr values were determined by ^{1}H NMR of the crude. [d] The ee values were determined by chiral HPLC.

installation of a nitrogen-substituted group at the stereogenic center has not been demonstrated in previous helical alkene synthesis.[2,3,5]

The stereochemical outcome of the domino reaction was analyzed using ^{1}H NMR spectroscopy, HPLC along with X-ray crystallography. The chiral helical alkenes were obtained in excellent enantioselectivity (up to 99% ee) in all cases, suggesting the retention of stereochemistry of the bromide precursors throughout the various bond formation process. We observed moderate diastereoselectivity (5:1−6.6:1), yet the formation of single diastereomer was observed in our previous synthesis of tetrasubstituted alkenes, such as **4g**[6a] (Figure 2). This indicates that the observed moderate diastereoselectivity is attributed to the presence of the substituent at the propargyl position of the bromide precursors. It appears that incorporation of norbornene in this domino reaction can be a highly stereoselective process with exclusive *exo*-facial selectivity as shown by the two X-ray crystal structures, **4f** and **4g**.

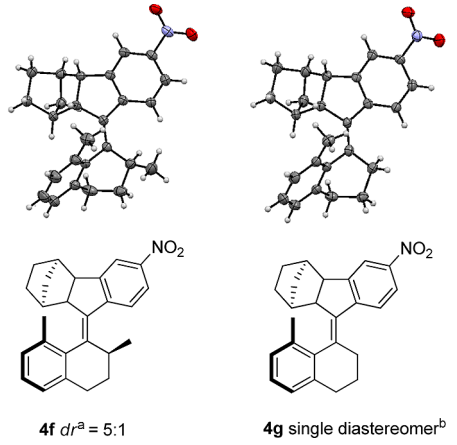


Figure 2. X-ray crystal structures of **4f** and **4g**. (a) **4f** was synthesized in racemic form, and the dr value was determined by ^{1}H NMR of crude product. (b) **4g** was taken from ref 6a.

The origin of the observed diastereoselectivity possibly results from the induced helical chirality upon carbopalladation onto the tethered alkyne (**A** to **B**), as shown in the proposed reaction mechanism (Scheme 3). Interestingly, the induced helical chirality is irrelevant to the nature of the substitutent (OBn vs CH_3) as shown in the crystal structure of **4a-*S*** and **4f**. We postulate that the helical chirality in the alkene formation is the result of a conformational preference of the ring containing the exocyclic double bond (**B** to **C**).[11] Presumably, this induction of helical chirality is driven by the unfavorable 1,3 allylic strain in **B** between the pseudoequatorial R group and the phenyl substitutent,[12] which leads to the favorable comformation in **C** with R being in the pseudoaxial position. Notably, the induced helical chirality is controlled by the stereogenic center in the bromide starting materials, given that the (S)-enantiomer predominantly affords (*P*)-helicity and the (*R*)-enantiomer (*M*)-helicity.[13] It is noteworthy that these tetrasubstituted alkenes are configurationally stable and *E*/*Z* isomerization was not observed.

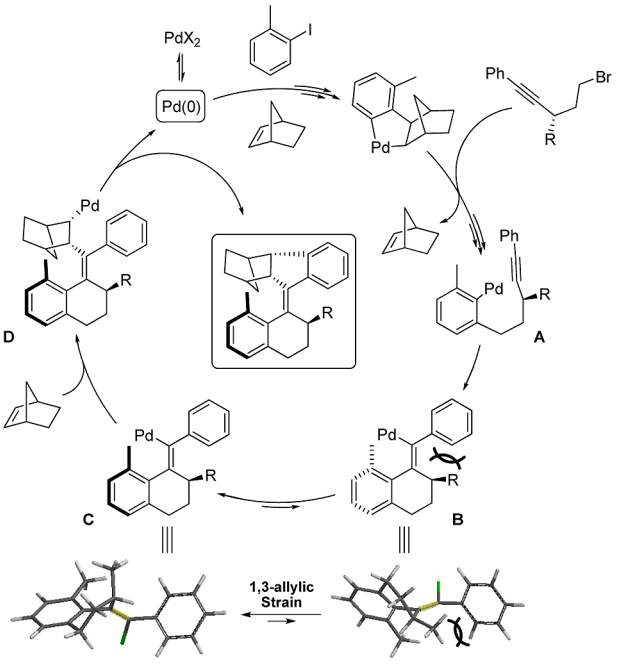
The ease of introducing aryl groups on chiral alkynes through Sonogashira coupling offers a high degree of modularity for the synthesis of chiral helical alkenes (Table 2). The bromide precursors bearing an electron-withdrawing group (NO_2, **6ha**) and an electron-donating group (OMe, **6ia**) on the aryl moieties afforded **4h** and **4i** in

(11) A chelation model between the palladium and hydroxyl substituent during carbopalladation onto the alkyne was proposed to explain the complete diastereoselectivity in the tetrasubstituted alkene formation via a domino reaction. See ref 3 and Machotta, A. B.; Straub, B. F.; Oestreich, M. *J. Am. Chem. Soc.* **2007**, *129*, 13455–13463.

(12) For 1,3 allylic strain as a controlling factor in stereoselective transformations, see: (a) Johnson, F. *Chem. Rev.* **1968**, *68*, 375–411. (b) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841–1860.

(13) These stereochemical control results are consistent with Tietze's work in the synthesis of helical alkenes via an intramolecular domino reaction; see ref 3 for details.

Scheme 3. Proposed Reaction Mechanism Explaining the Stereoselectivity in the Domino Reaction[a,b]



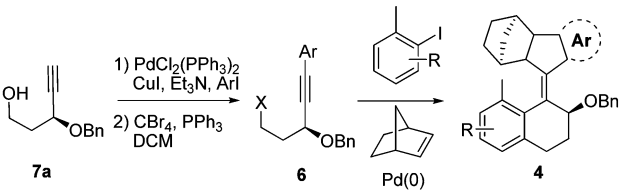
[a] Ligand and solvent molecules omitted for clarity. Only key intermediates are shown; for the detailed mechansim, see ref 6a. [b] Modeling on the substrate (3*R*)-**6ea** bearing a methyl substituent was performed.

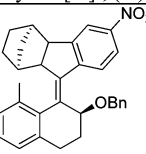
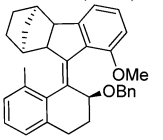
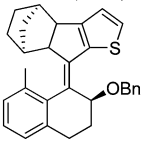
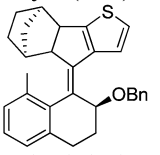
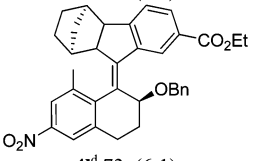
good yield, respectively. Heterocyles can also be introduced onto the alkyne to give the corresponding bromide precursors (**6ja** and **6ka**), which delivered the tetrasubstituted alkene products (**4j** and **4k**) in good to excellent yield. Interestingly, a single isomer **4k** was observed for the 3-thiophene-yl-substituted precursor **6ka**. This protocol also allows for the synthesis of alkene product **4l** bearing a carboxylate group on one aryl ring and nitro group on the other, which can be used as handles for further manipulation and incorporation into a larger system.[14]

In conclusion, we have developed a rapid and highly modular approach to accessing chiral tetra-substituted helical alkenes by employing a palladium-catalyzed norbornene-mediated domino reaction as the key step. The high structural diversity and excellent stereoselectivity is owed to a very efficient synthesis of a diverse class of enantiopure bromide precursors stemming from chiral lactones. Three characteristic elements of stereoselectivity during the multiple bond formation were observed, and the capacity to form both isomers gives rise to further studies on their photochemical properties as light-driven rotary molecular motors.

(14) (a) van Delden, R. A.; ter Wiel, M. K. J.; Pollard, M. M.; Vicario, J.; Koumura, N.; Feringa, B. L. *Nature* **2005**, *437*, 1337. (b) Eelkema, R.; Pollard, M. M.; Vicario, J.; Katsonis, N.; Ramon, B. S.; Bastiaansen, C. W. M.; Broer, D. J.; Feringa, B. L. *Nature* **2006**, *440*, 163.

Table 2. Scope of Tetrasubstituted Alkenes with Various Aromatic Substitutents[a]



entry	**6** yield [%][b]	**4** yield [%][b], (dr)[c]
1	Ar = 4-$NO_2C_6H_4$, **6h** X = OH, 81 **6ha** X = Br, 89	 **4h** 60, (5:5:1)
2	Ar = 2-$MeOC_6H_4$, **6i** X = OH, 83 **6ia** X = Br, 99	 **4i** 76, (5.3:1)
3	Ar = 2-thiophene, **6j** X = OH, 84 **6ja** X = Br, 99	 **4j**91, (6.7:1)
4	Ar = 3-thiophene, **6k** X = OH, 94 **6ka** X = Br, 99	 **4k** 73, (5:1)
5	Ar = 3-$CO_2EtC_6H_4$, **6l** X = OH, 80 **6la** X = Br, 91	 **4l**[d] 73, (6:1)

[a] The domino reaction was conducted in 0.2 mmol scale using the same reaction conditions as in Scheme 2. [b] Yield of isolated products. [c] The dr values were determined by ^{1}H NMR of the crude. [d] Performed on 1.0 mmol scale.

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Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.