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A Short Covalent Synthesis of an All-Carbon-Ring [2]Rotaxane

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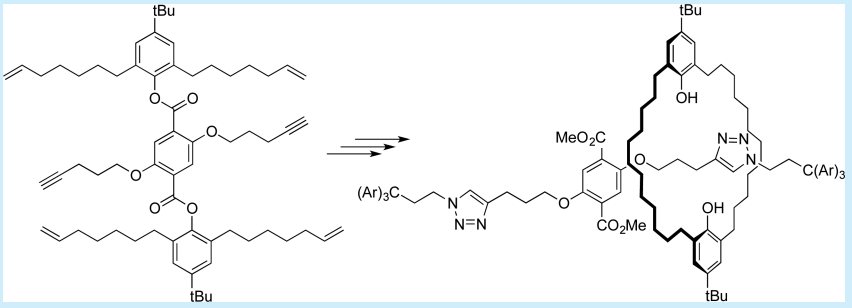
Supporting Information



ABSTRACT: While the current supramolecular syntheses of [2]rotaxanes are generally efficient, the final product always retains the functional groups required for non-covalent preorganization. A short and high-yielding covalent-template-assisted approach is reported for the synthesis of a [2]rotaxane. A terephthalic acid template core preorganizes the covalently connected ring precursor fragments to induce a clipping-type cyclization over the thread moiety. Cleavage of the temporary ester bonds that connect the ring and thread fragments liberates the [2]rotaxane.

Both the synthesis of rotaxanes and their applications in especially materials research have become increasingly important over the last 25 years, as indicated by the award of the 2016 Nobel Prize in Chemistry. In contrast to the vast number of publications on rotaxanes, the available synthetic strategies are somewhat limited. For the preparation of threaded molecules, in general three main strategies exist.[1] The first is clipping-type cyclization of the ring precursor over the thread fragment. The second is capping of the ends of a thread that is non-covalently bound within a macrocycle. Finally, approaches have been reported in which two thread fragment precursors are connected by a reaction that is promoted by an active metal that is bound within the macrocycle. In essence, all of these synthetic methods rely on non-covalent interactions such as H-bonding,[2] crown ether−ammonium,[3] $\pi-\pi$,[4] and metal ion interactions.[5] In all of these methods, the motif used for preorganization is retained in the final product. Usually this is of no consequence, and it can be even desirable for the formation of functional spots (stations) on the thread. Nevertheless, the structural diversity of rotaxanes is somewhat restricted because of the specific functional groups that are required as supramolecular handles for these synthetic strategies. To make such "impossible" rotaxanes, alternative strategies are required, such as late-stage modifications or a strategy obviating non-covalent recognition elements.[6] Interestingly, the first rotaxane and catenane syntheses were reported back in the 1960s by Schill and Lüttringhaus and relied on covalent-template-directed macrocyclizations followed by liberation of the free [2]rotaxanes or catenanes after cleavage of temporary bonds as the last step.[7] Consequently, no non-covalent interactions are present between ring and thread fragments in the final mechanically interlocked molecules. In the same period a statistical approach to a [2]rotaxane was reported starting from an all-carbon-ring fragment.[8] Although low-yielding, this strategy led to an "impossible" rotaxane lacking interactions between the ring and thread fragments. Since those early pioneers, covalent approaches have remained a niche, and over the last two decades only a few successful covalent approaches toward "impossible" rotaxanes and catenanes have been reported.[9] Most recently, the Höger group reported the use of a terephthalic acid template as a temporary covalent template for the synthesis of a [2]rotaxane.[9g] On the basis of an earlier unsuccessful approach toward [2]rotaxanes by Morin, a huge 50-membered-ring pre-rotaxane was constructed after clipping by two consecutive Glaser couplings of two fragments that were both covalently attached as phenol esters over the templating terephthalic acid core.[10,11] Next, the bulky stopper elements were installed at the terephthalate core 2- and 5-positions, followed by ester cleavage via aminolysis using *n*-propylamine to liberate the [2]rotaxane.

Inspired by these reports, we set out to synthesize a [2]rotaxane, **1**, using a terephthalic acid template toward a relatively small ring system in the range of most commonly described rotaxanes (Scheme 1). For the macrocyclization reaction, the proven Ru-catalyzed ring-closing metathesis

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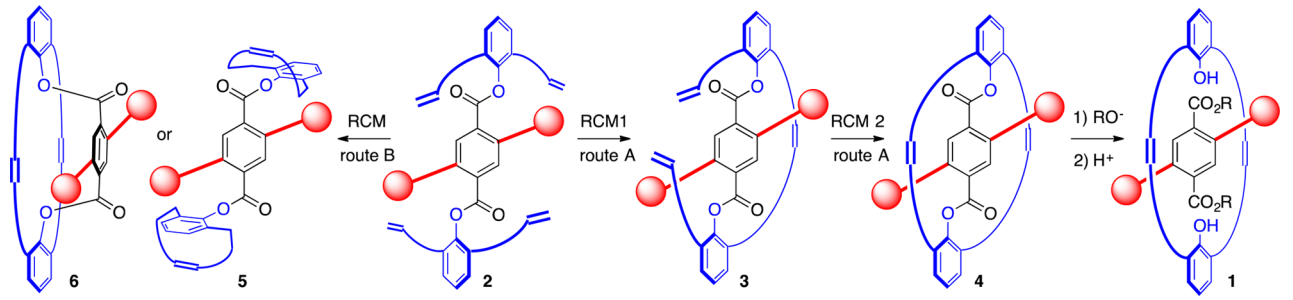
Scheme 1. Outline of the Synthetic Strategy to [2]Rotaxanes 1 via a Terephthalic Acid Template



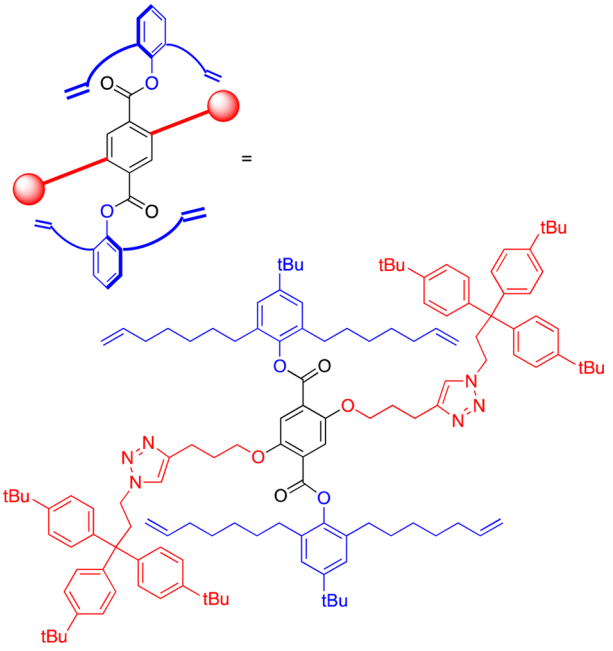
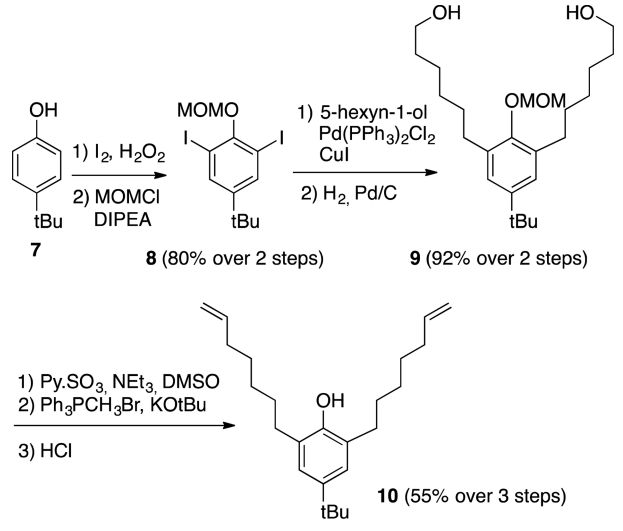


Figure 1. Design of the covalent [2]rotaxane precursor **2**.

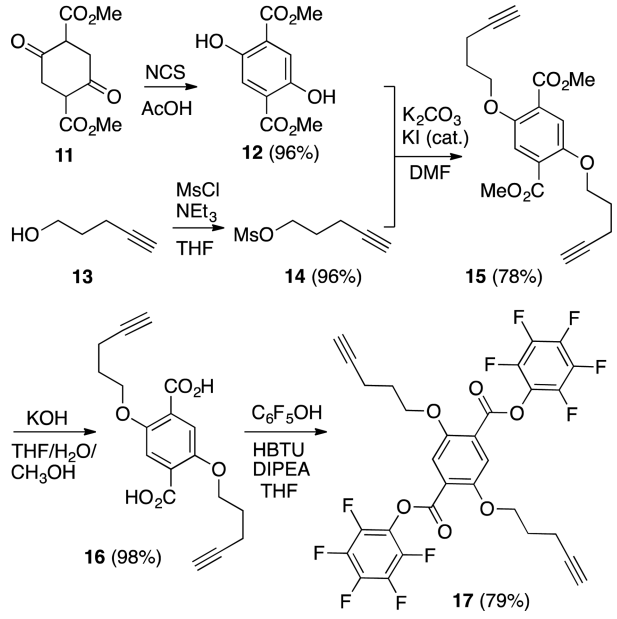
Scheme 2. Synthesis of Macrocycle Precursor 10



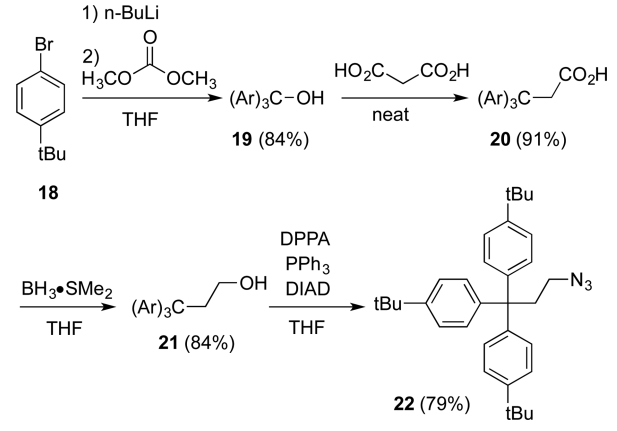
(RCM) reaction appeared most suitable. Besides its robustness, RCM obviates the need for protecting groups.[12]

In our modification of the approaches of Höger and Morin, both using short tethers, the 2,6-di-ω-alkenyl ring fragment phenols were directly esterified to form the terephthalic acid

Scheme 3. Synthesis of Terephthalic Acid Template 17



Scheme 4. Synthesis of Azide-Functionalized Stopper 22



thread fragment bearing the stopper elements, giving bisester **2** (see Figure 1). Semiempirical models at the PM6 level showed that after the first RCM reaction both phenol rings are locked in a perpendicular arrangement with respect to the terephthalic core (Scheme 1, route A, compound **3**). As a result, in the second RCM reaction the two remaining alkenyl chains are well-positioned to cyclize in a clipping fashion over the ring fragment to give pre-rotaxane **4**. Cleavage of the terephthalate esters by transesterification liberates the mechanically locked [2]rotaxane **1**. Besides the usual intermolecular oligomerization reaction, two

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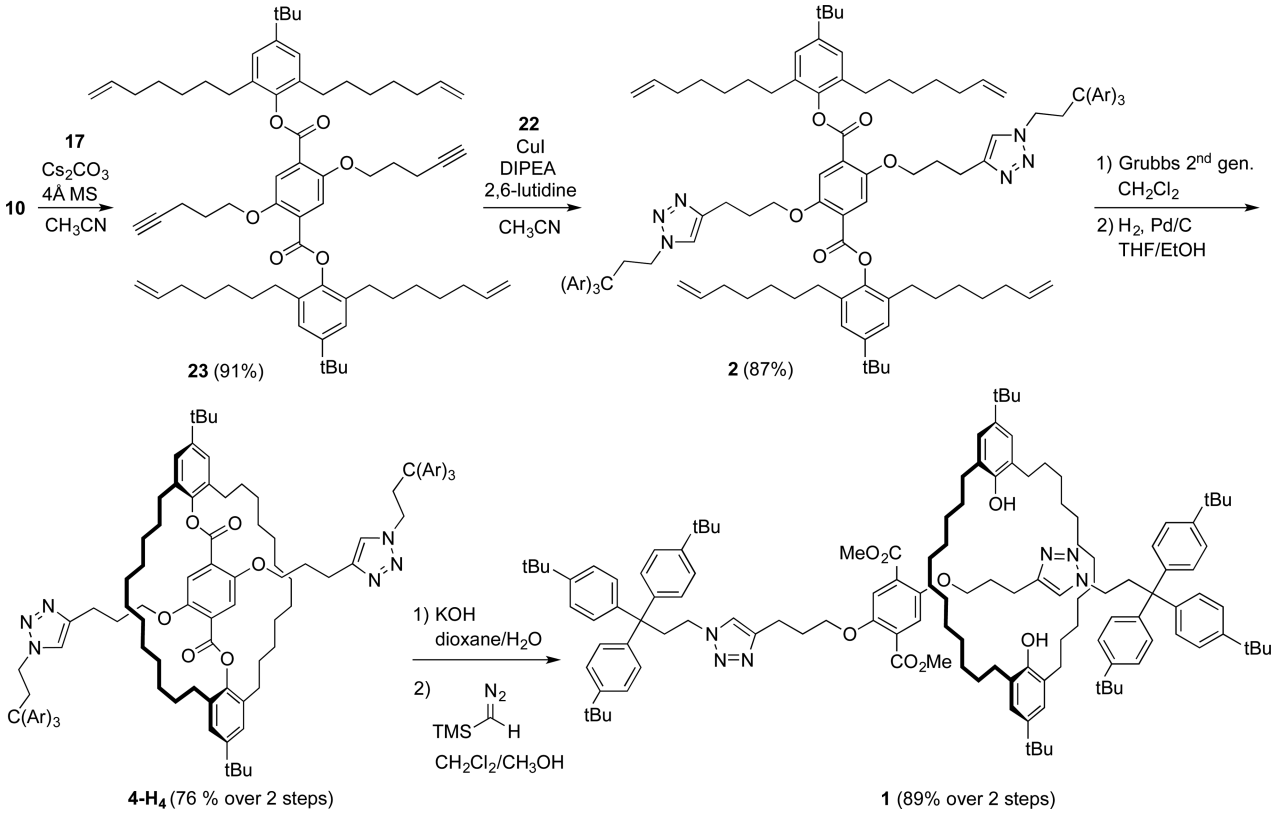
Scheme 5. Assembly of [2]Rotaxane 1



potential side reactions (Scheme 1, route B) may take place during macrocyclizations despite the terephthalate-moiety-driven preorganization. First, as a competitive ring closure, the alkenyl chains attached at the same phenol may cyclize to give two isolated cycloalkenes as in **5**. Second, the desired macrocycle may cyclize in a noninterlocked manner to give **6**. In the unsuccessful approach by the Morin group, this latter undesired pathway had indeed occurred because of a too-flexible linker between the phenol and the ester.[10]

In the current synthetic route, the phenols are directly esterified to the terephthalic acid (see Figure 1) to introduce more conformational constraints, hampering these potential side reactions. DFT calculations at the PM6//wB97XD/6-31G(d) level of theory showed conformers **5** and **6** to actually be higher in energy than **4** by 18.1 and 31.4 kcal/mol, respectively (see the Supporting Information). This suggests that the dynamics of succeeding ring-opening/ring-closing metathesis steps may favor the thermodynamically most stable product **4**.

For the synthesis of the 2,6-difunctionalized phenol (see Scheme 2), 4-*tert*-butylphenol (**7**) was chosen as the starting material to block the 4-position during iodination and ensure the solubility of intermediates. Iodination of **7** followed by MOM protection gave **8** in 80% yield over the two steps.[13] Subsequent Sonogashira reaction with 5-hexyn-1-ol and catalytic hydrogenation yielded **9** in 92% overall yield. Parikh–Doering oxidation of the alcohols followed by Wittig reaction completed the synthesis of the 6-heptenyl arms. A final MOM removal with concentrated aqueous HCl in THF gave the desired phenol-based macrocycle precursor **10** in quantitative yield.

The synthesis of the terephthalic acid template (see Scheme 3) started from **11**, NCS-mediated oxidation of which gave **12**. Subsequent alkylation with **14** (obtained via mesylation of 4-pentyn-1-ol (**13**)) provided compound **15** in 78% yield.[14] The terminal alkynes allowed installation of the bulky stopper groups via Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC).

It is worth mentioning that the very bright blue fluorescence of the terephthalate moiety under UV light at both 254 and 355 nm allows for easy identification of products on TLC. Product **15** was smoothly saponified with KOH, and the resulting carboxylic acid groups of **16** were activated as pentafluorophenol esters using HBTU as the coupling reagent, giving **17** in 79% yield. As the stopper unit, the tris(4-*tert*-butyl)trityl group was chosen, attached to a flexible azidoethane linker.[15] The stopper synthesis (see Scheme 4) started by lithiation of 4-*tert*-butylbromobenzene (**18**) followed by quenching with dimethyl carbonate to give trityl alcohol **19** in 84% yield.[15a] Subsequent reaction with malonic acid at elevated temperature yielded propionic acid derivative **20**, which was subsequently reduced by borane–dimethyl sulfide complex in 76% overall yield.[15b] Transformation of the resulting alcohol **21** into the desired azide **22** via the Mitsunobu reaction proceeded in 79% yield.

With all of the building blocks in hand, the convergent assembly of the rotaxane skeleton commenced with coupling of the activated terephthalic template **17** via transesterification with the sterically congested phenol **10** using Cs_2CO_3 as the base (see Scheme 5). Gratifyingly, clean and full conversion was observed to give terephthalate **23** in 91% isolated yield. To avoid hydrolysis of the activated pentafluorophenyl esters, 4 Å molecular sieves were added. Installation of the stopper groups had to be done at this stage because subsequent Ru-catalyzed olefin metathesis would lead to competing ene–yne metathesis reactions.[16] CuAAC coupling between **23** and **22** (2 equiv) using CuI, DIPEA, and 2,6-lutidine as the catalytic system in acetonitrile gave the rotaxane precursor **2** cleanly in 87% yield. The sequential clipping RCM reactions of the alkenyl chains over the thread fragment were performed using 20 mol % Grubbs

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second-generation catalyst at high dilution (1 mM) to prevent competing intermolecular reactions and solely gave the anticipated pre-rotaxane **4** in 80% yield as an *E*/*Z* mixture of isomers. Catalytic hydrogenation to remove this mixture was performed at 60 °C to ensure full conversion and gave pre-rotaxane **4-H$_4$** in almost quantitative yield.

Despite the absence of the olefinic *E*/*Z* mixture, the ^{1}H NMR spectrum remained complex with broad signals (see the Supporting Information), indicating a nonsymmetric arrangement of the ring fragment. A first sign that indeed the rotaxane architecture had been obtained was the fact that the final cleavage steps to liberate the mechanically interlocked [2]rotaxane skeleton required harsh conditions to overcome the steric hindrance around the endocyclic ester bonds. Unexpectedly, reaction with excess methylamine at 50 °C, used in a similar case by Höger (with *n*-propylamine), did not give any aminolysis product. Even transesterification with excess sodium methoxide failed to give any conversion. Nevertheless, saponification proceeded well using aqueous KOH in a sealed tube in 1,4-dioxane at 130 °C, giving complete conversion in 2 h to a single, fairly polar product. To facilitate chromatographic purification, the carboxylic acids were transformed into methyl esters using TMS-diazomethane, providing pure [2]rotaxane **1** after chromatographic purification in 89% yield over two steps. High-resolution field-desorption mass spectrometry of **1** showed the expected molecular weight of 1953.3888 Da corresponding to the bruto formula of $C_{130}H_{180}N_6O_8$, ultimately proving that indeed the [2]rotaxane skeleton was obtained. The ^{1}H NMR spectrum of [2]rotaxane **1** shows sharp and symmetric signals, probably indicating a weak hydrogen bond between the phenolic hydroxyl groups and the ester carbonyls. In contrast to Höger's case, no dethreading was observed despite the fact that a temperature of 130 °C was required for the final ester cleavage step.

In conclusion, we have developed a convergent and robust synthetic route toward [2]rotaxanes using a temporary covalent template to correctly position the ring precursors for the clipping-type cyclization over the thread fragment. Saponification disconnects the template-containing thread from the ring fragment in the last step. This strategy gives facile access to [2]rotaxanes with an all-carbon ring fragment that lacks the currently common functional groups that are required for the supramolecular preorganization during the synthesis. Further work on all-carbon rotaxanes and catenanes and further functionalization for various applications in materials and pharmaceutical research fields is in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00877.

Full experimental and characterization data for all compounds and the coordinates and structures from the theoretical calculations (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) *The Nature of the Mechanical Bond: From Molecules to Machines*; Bruns, C. J., Stoddart, J. F., Eds.; Wiley: Hoboken, NJ, 2016.

(2) (a) Vögtle, F.; Händel, M.; Meier, S.; Ottens-Hildebrandt, S.; Ott, F.; Schmidt, T. *Liebigs Ann. Chem.* **1995**, *1995*, 739. (b) Johnston, A. G.; Leigh, D. A.; Murphy, A.; Smart, J. P.; Deegan, M. D. *J. Am. Chem. Soc.* **1996**, *118*, 10662.

(3) (a) Ashton, P. R.; Glink, P. T.; Stoddart, J. F.; Tasker, P. A.; White, A. J. P.; Williams, D. J. *Chem. - Eur. J.* **1996**, *2*, 729. (b) Thibeault, D.; Morin, J.-F. *Molecules* **2010**, *15*, 3709.

(4) Ashton, P. R.; Grognuz, M.; Slawin, A. M. Z.; Stoddart, J. F.; Williams, D. J. *Tetrahedron Lett.* **1991**, *32*, 6235.

(5) Dietrich-Buchecker, C. O.; Sauvage, J.-P.; Kern, J. M. *J. Am. Chem. Soc.* **1984**, *106*, 3043.

(6) (a) Hannam, J. S.; Lacy, S. M.; Leigh, D. A.; Saiz, C. G.; Slawin, A. M. Z.; Stitchell, S. G. *Angew. Chem., Int. Ed.* **2004**, *43*, 3260. (b) Chao, S.; Romuald, C.; Fournel-Marotte, K.; Clavel, C.; Coutrot, F. *Angew. Chem., Int. Ed.* **2014**, *53*, 6914. (c) Steemers, L.; Wanner, M. J.; Lutz, M.; Hiemstra, H.; van Maarseveen, J. H. *Nat. Commun.* **2017**, *8*, 15392.

(7) (a) Schill, G.; Lüttringhaus, A. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 546. (b) Schill, G.; Zollenkopf, H. *Liebigs Ann. Chem.* **1969**, *721*, 53.

(8) Harrison, I. T.; Harrison, S. *J. Am. Chem. Soc.* **1967**, *89*, 5723.

(9) (a) Ünsal, Ö.; Godt, A. *Chem. - Eur. J.* **1999**, *5*, 1728. (b) Hiratani, K.; Suga, J.-I.; Nagawa, Y.; Houjou, H.; Tokuhisa, H.; Numata, M.; Watanabe, K. *Tetrahedron Lett.* **2002**, *43*, 5747. (c) Hiratani, K.; Kaneyama, M.; Nagawa, Y.; Koyama, Y.; Kanesato, M. *J. Am. Chem. Soc.* **2004**, *126*, 13568. (d) Kameta, N.; Hiratani, K.; Nagawa, Y. *Chem. Commun.* **2004**, 466. (e) Hirose, K.; Nishihara, K.; Harada, N.; Nakamura, Y.; Masuda, D.; Araki, M.; Tobe, Y. *Org. Lett.* **2007**, *9*, 2969. (f) Kawai, H.; Umehara, T.; Fujiwara, K.; Tsuji, T.; Suzuki, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4281. (g) Schweez, C.; Shushkov, P.; Grimme, S.; Höger, S. *Angew. Chem., Int. Ed.* **2016**, *55*, 3328.

(10) Cantin, K.; Lafleur-Lambert, A.; Dufour, P.; Morin, J.-F. *Eur. J. Org. Chem.* **2012**, *2012*, 5335.

(11) Becker, K.; Lagoudakis, P. G.; Gaefke, G.; Höger, S.; Lupton, J. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 3450.

(12) Gradillas, A.; Pérez-Castells, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6086.

(13) Boughton, B. A.; Hor, L.; Gerrard, J. A.; Hutton, C. A. *Bioorg. Med. Chem.* **2012**, *20*, 2419.

(14) Masuo, R.; Ohmori, K.; Hintermann, L.; Yoshida, S.; Suzuki, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 3462.

(15) (a) Gibson, H. W.; Lee, S.-H.; Engen, P. T.; Lecavalier, P.; Sze, J.; Shen, Y. X.; Bheda, M. *J. Org. Chem.* **1993**, *58*, 3748. (b) Barlan, A. U.; Basak, A.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 5849.

(16) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317.

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