OL | Organic Letters

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

Letter

pubs.acs.org/OrgLett

Chemoselective Cobalt(I)-Catalyzed Cyclotrimerization of (Un)Symmetrical 1,3-Butadiynes for the Synthesis of 1,2,4-Regioisomers

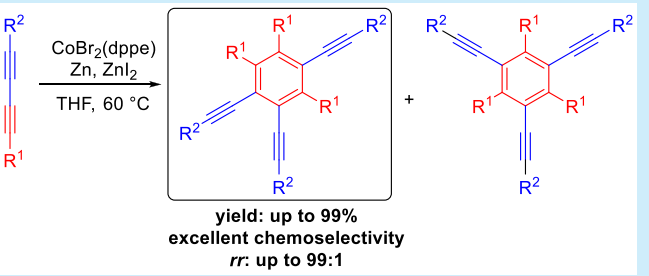
Sebastian M. Weber[†,‡] and Gerhard Hilt*[,†,‡]

[†]Fachbereich Chemie Philipps Universität Marburg, Hans-Meerwein Strasse 4, D-35032 Marburg, Germany

[‡]Institut für Chemie, Universität Oldenburg, Carl-von-Ossietzky-Strasse 9-11, D-26111 Oldenburg, Germany

Supporting Information

ABSTRACT: The cobalt(I)-catalyzed cyclotrimerization of (un)symmetrical 1,4-disubstituted 1,3-butadiynes is presented. In the case of unsymmetrical 1,3-butadiynes, this reaction can generate eight 1,2,4-substituted and four 1,3,5-substituted isomers. A single 1,2,4-substituted isomer was formed in excellent yields (up to 99%) and exclusive regioselectivities (>99:1) when symmetrical or a 1,3-butadiyne with an aryl or alkyl substituent and a trimethylsilyl group were applied. A large number of products accepting a wide variety of functional groups were synthesized.



The transition-metal-catalyzed cyclotrimerization of terminal and internal alkynes is a well-known method in organic synthesis for the formation of aromatic compounds. Since its discovery by Berthelot and Reppe, many transition metals (e.g., Fe, Ru, Co, Rh, Ir, Ni, Pd, Au) could be identified as suitable catalysts for this transformation.[1] A large number of different cobalt-based catalysts could be identified for this reaction and in addition to mechanistic investigations performed by Vollhardt, Malacria, Aubert, Gandon, Dahy, Koga, and many others,[2] this method was also successfully applied in several natural product syntheses (e.g., vitamin B_6 or (±)-allocolchicine).[3] For the cyclotrimerization of alkynes, most often, cyclopentadienyl-cobalt-based catalysts have been used while the number of in situ generated cobalt(I) catalysts with phosphine- and imine-type ligands has been reported in increasing numbers over the last few years.[4]

Interestingly, bench-stable cyclopentadienylcobalt catalysts **1**−**3** (selected examples, Figure 1) also have been reported by

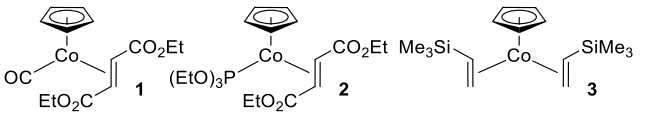


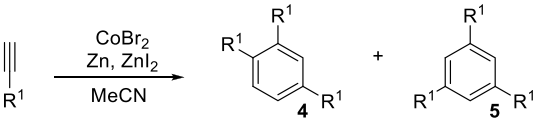
Figure 1. Air-stable cyclopentadienylcobalt(I) catalysts.

Gandon and Hapke, who were able to catalyze the cocyclotrimerization reaction of alkynes and nitriles for the synthesis of pyridine derivatives under relatively mild conditions with good to excellent yields and regioselectivities.[5]

Our group has reported a "low-budget" cobalt catalyst system, composed of cobalt(II) bromide, zinc, and zinc iodide, which generated the catalytically active cobalt(I) species in situ in acetonitrile as solvent.

This catalyst system gave very good yields and an excellent regioselectivity where the unsymmetrical product **4** was formed in a regioisomeric ratio of >95:5 (Scheme 1).[6]

Scheme 1. Regioselective Cobalt(I)-Catalyzed Cyclotrimerization of Alkynes



Besides this, we were able to alter the regioselectivity by using disulfide-based ligands (e.g., 1,2-bis(phenylthio)ethane) in THF as solvent to favor the symmetrical cyclotrimerization product **5**.[6b]

In a recent study toward the regioselective Alder−ene reaction of unsymmetrical 1,4-substituted 1,3-butadiynes, the cyclotrimerization of the diynes was observed as a side reaction.[7] Interestingly, up to 12 regioisomers, eight unsymmetrical and four symmetrical regioisomers (see Supporting Information) are possible when starting from unsymmetrical disubstituted 1,3-butadiynes.

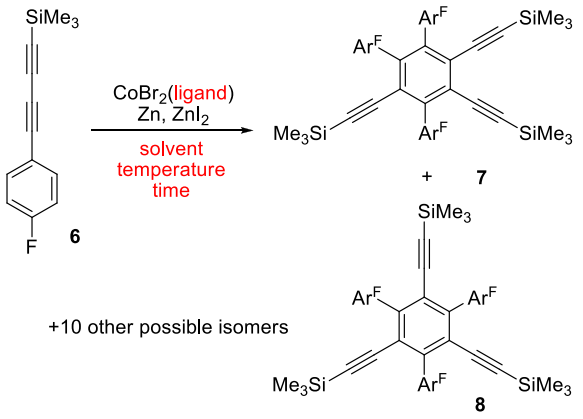
Based on these results, our approach for this study was the (a) identification of the formed regioisomers, (b) optimization of the reaction conditions, and if possible, (c) regioselective

Received: April 12, 2019

DOI: 10.1021/acs.orglett.9b01281
Org. Lett. XXXX, XXX, XXX−XXX

formation of only one regioisomer by altering the ligands and solvents. Our initial optimization started with 1,3-butadiyne **6** as the test substrate, and fortunately, out of the 12 possible isomers, only two isomers, **7** and **8**, were formed, luckily because the cyclotrimerization took place exclusively at the triple bond adjacent to the arene moiety and not at the triple bond next to the trimethylsilyl group. The results of the optimization process are summarized in Table 1, and the

Table 1. Optimization of the Reaction Conditions



no.	ligand	solvent, temp., time	conversion[a] (%) (ratio 7/**8**)
1	none	CH_3CN, 25 °C 18 h	99 (69:31)
2	Cy_2(diimine)	CH_3CN, 25 °C 18 h	90 (63:37)
3	py-imine	CH_3CN, 25 °C 18 h	86 (65:35)
4	dppe	CH_3CN, 25 °C 18 h	0, –
5	dppm	CH_3CN, 60 °C 18 h	69 (74:26)
6	dppe	CH_2Cl_2, 40 °C 72 h	30 (nd)
7	dppe	CH_3CN, 60 °C 18 h	99 (97:3)
8	dppe	THF, 60 °C 18 h	99 (99:1) **isolated: 99%**
9	Cy_2(diimine)	THF, 60 °C 72 h	99 (64:36)
10	disulfide	THF, 60 °C 72 h	0, –

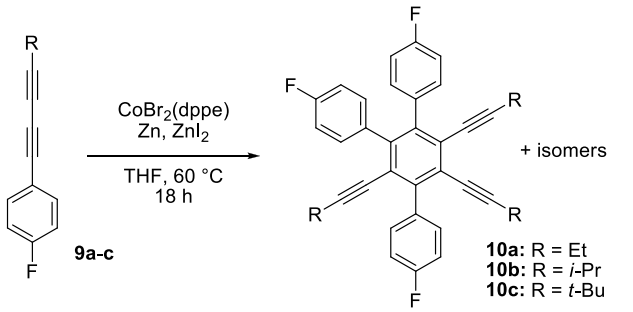
[a]Reaction conditions: cobalt catalyst (5 mol %), Zn, ZnI_2 (10 mol % each), 1,3-butadiyne (0.30 mmol, 1.0 equiv), solvent (0.3 mL). Conversion and ratio were determined by ^{19}F NMR spectroscopy. For a detailed table of optimization, see the SI. Cy_2(diimin) = dicyclohexylethane-1,2-diimine; py-imine = *N*-mesityl-1-(pyridin-2-yl)methanimine, dppe = 1,2-bis(diphenylphosphino)ethane, dppm = 1,1-bis(diphenylphosphino)methane, disulfide = 1,2-bis(4-methoxyphenyl)thio)ethane.

choice for a 4-fluorophenyl substituent in **6** proved to be of high value as the ratios of starting material to products as well as the ratios of the products (**7**/**8**) could be easily evaluated by ^{19}F NMR on the crude reaction mixture as well as for the purified compounds.

Based on the previous study for the cyclotrimerization of alkynes, we tested a number of solvents to investigate if the solvent effect (see Tables S1 and S2) to alter the regioselectivity could also be seen in the present reactions. In the ligand-free reaction in acetonitrile, already complete conversion could be observed, although the regioselectivity was only moderate in favor of **7**. The use of imine-type ligands (entries 2 and 3) improved neither the yield nor the regioselectivity. Surprisingly, the standard conditions for the Alder–ene reaction with dppe as ligand gave no conversion in acetonitrile (entry 3), while in dichloromethane as solvent only 30% conversion could be observed (entry 6). However, increasing the reaction temperature to 60 °C resulted in complete conversion of the starting material combined with a very good regioselectivity of *rr* (**7**/**8**) = 97:3 (entry 7). The ligand dppm was also tested but gave inferior results (entry 5). Eventually, we identified THF as the solvent of choice because complete conversion and an exclusive regioselectivity were observed (entry 8), which led to the product **7** in 97–99% isolated yield, the latter on a 2.0 g scale. Unfortunately, the solvent effect obtained for simple alkynes could not be reproduced with unsymmetrical 1,3-diynes when diamine or disulfide ligands were applied in THF (entries 9 and 10) and remains an unsolved problem for the future to generate one of the symmetrical isomers as the main product (for further information, see the SI).

With the optimized reaction conditions in hand, the steric effects of the trimethylsilyl residue on the starting material **6** were investigated next. The trimethylsilyl residue was altered to contain simple alkyl substituents (**9a–c**) with increasing steric hindrance (Table 2).

Table 2. Sterical Effects of the Alkyne Residue toward the Chemo- and Regioselectivity of the Cyclotrimerization



no.	1,3-diyne	R	conv (%)	yield[a] (%)	detectable isomers
1	**9a**	Et	>99	99	7[b]
2	**9b**	*i*-Pr	>99	98	7[b]
3	**9c**	*t*-Bu	>99	99	1

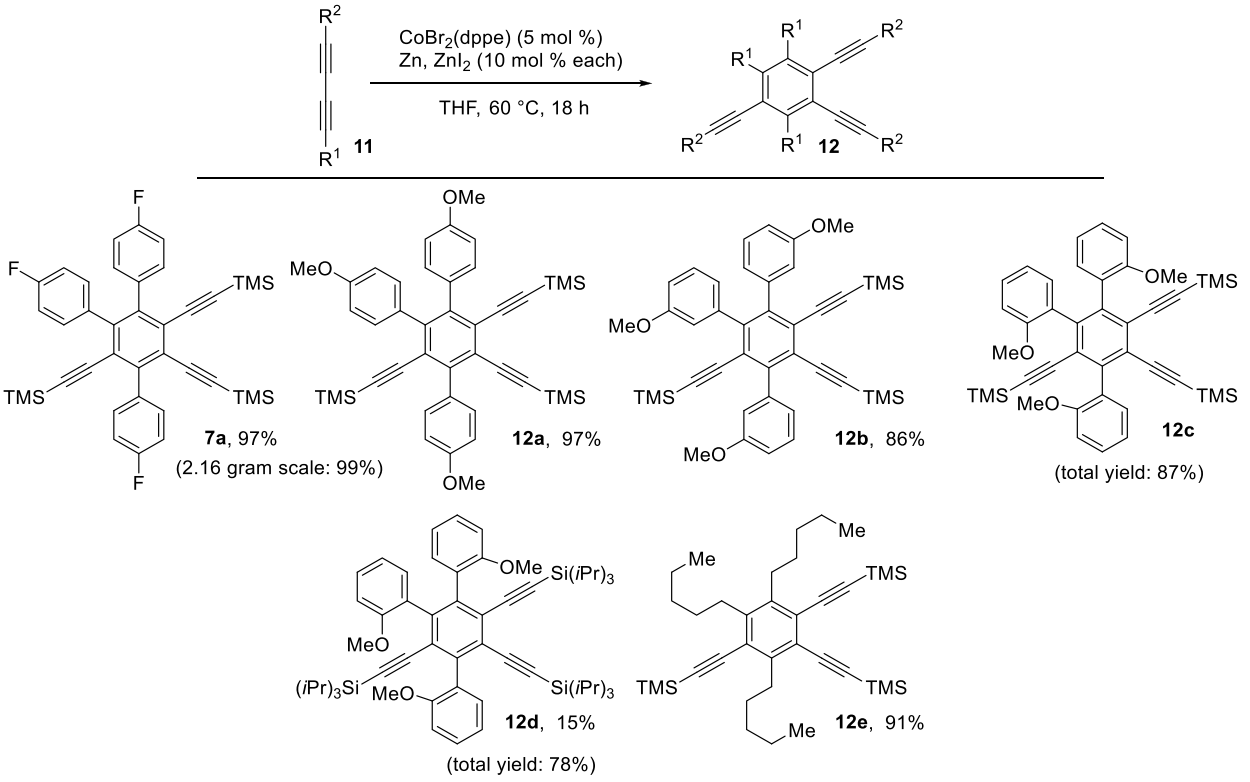
[a]Reaction conditions: $CoBr_2$(dppe) (5 mol %), Zn, ZnI_2 (10 mol % each), 1,3-diyne **9a–c** (3.0 mmol), THF (3.0 mL).The conversion was detected by ^{19}F NMR spectroscopy. [b]The number of isomers were detected by ^{19}F NMR spectroscopy. The products were obtained as an inseparable mixture of regioisomers.

For all starting materials, complete conversions could be observed, and the isolated yields were excellent as well. However, the ethyl and isopropyl residues in **9a** and **9b** gave a complex mixture of regioisomers, consisting of up to seven isomers which could be detected by ^{19}F NMR spectroscopy (see the SI) (entries 1 and 2). Nevertheless, when a *tert*-butyl residue was used (**9c**), again, only a single regioisomer was observed and the unsymmetrical product **10c** could be isolated in an excellent yield of 99% (entry 3). Accordingly, we rationalized that only steric interactions of the substituents on the 1,3-butadiyne are responsible for the chemoselectivity (reaction on the less hindered triple bond) as well as for the regioselectivity, which prohibits the formation of a cobaltacycle intermediate with a steric bulky substituent bonded directly to the cobaltacycle.

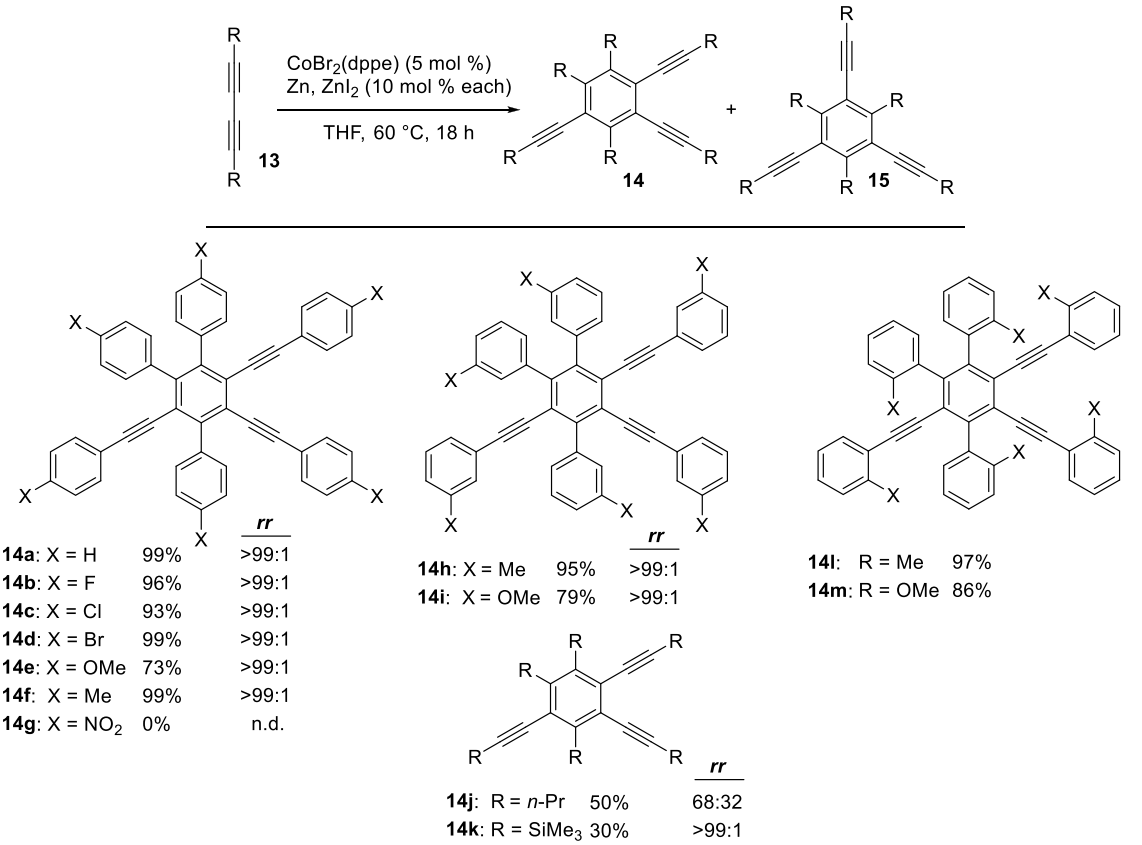
After these preliminary investigations concerning the most efficient catalyst and the steric hindrance effect, we investigated several unsymmetrical 1,3-butadiynes as reactants, and the results are summarized in Scheme 2.

DOI: 10.1021/acs.orglett.9b01281
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 2. Unsymmetrical 1,3-Butadiynes Applied in the Cobalt-Catalyzed Cyctotrimerization



Scheme 3. Symmetrical 1,3-Butadiynes in the Cobalt-Catalyzed [2 + 2 + 2] Cyclotrimerization Reaction



DOI: 10.1021/acs.orglett.9b01281
Org. Lett. XXXX, XXX, XXX−XXX

First, the cobalt-catalyzed cyclotrimerization reaction was performed on a larger scale to illustrate that this method can be applied for the synthesis of gram amounts of the product **7a**, which was isolated in an undiminished yield of 99%. Thereafter, as an alteration of the previous study, the 4-fluorobenzene substituent in the 1,3-butadiyne **6a** was varied toward the three possible methoxybenzene-substituted diynes to generate the products **12a−c**. All of these reactions proceeded well and gave yields between 86 and 97%. If the 4- and 3-methoxybenzene residues were used, an excellent yield of 97% and a somewhat lower yield of 87% were obtained, respectively. In case of the 2-methoxybenzene derivative **12c**, a product mixture consisting of different isomers was observed (87% yield of all isomers). For once, due to its increased steric hindrance at the 2-position, the alkyne subunit next to the trimethylsilyl-substituted alkyne could be involved in the [2 + 2 + 2] cycloaddition process leading to other chemoisomers. On the other hand, the free rotation of the 2-methoxybenzene substituent is hindered, leading to a number of diastereomers (see the SI). Unfortunately, it was neither possible to separate the chemo- or regioisomers via column chromatography nor to obtain a significantly reduced number of NMR signals for the methoxy protons at elevated temperatures. Because of this observation, the 1,3-butadiyne with a triisopropylsilane group was reacted under the optimized reaction conditions. In addition, in this reaction, the chemo- and/or regioselectivity could not be forced toward the formation of a single isomer. Nevertheless, in this case, a separation of the desired isomer was possible so that the product **12d** could be isolated in 15% yield (total yield of all isomers: 78%).

Accordingly, we rationalize that the product mixture of **12c** most likely consisted of chemoisomers where both double bonds are incorporated in the [2 + 2 + 2] cycloaddition reaction. Thereafter, an alkyl-substituted 1,3-butadiyne was reacted to generate the product **12e** as a single chemo- and regioisomer in 91% yield, which also indicates that the steric hindrance is of high importance in these reactions.

Finally, we investigated symmetric substituted 1,3-diynes in the cobalt-catalyzed cyclotrimerization reaction. As far as we know, mostly symmetrical 1,4-diaryl-substituted 1,3-butadiyne derivatives have been applied in cobalt-catalyzed [2 + 2 + 2] cycloaddition reactions utilizing CpCo-type catalysts reported in a small number of publications over the last decades.[8] In the present [2 + 2 + 2] cycloaddition reaction with diyne **13**, only two isomers (**14** and **15**) are possible (Scheme 3). At first, the optimized reaction conditions were confirmed with 1,3-diyne **13b** as test substrate. It could be shown by ^{19}F NMR spectroscopy that the optimized reaction conditions for unsymmetrical diynes of type **3** also work well with symmetrical substituted 1,3-diynes of type **13** (for a detailed optimization, see the SI). Next, we examined different 1,3-butadiynes in the cycloaddition reaction (Scheme 3).

A variety of unsymmetrical products of type **14** could be obtained in good to excellent yields (73−99%) and excellent regioselectivity (>99:1), outperforming the results obtained with $Co_2(CO)_8$- or CpCo-type catalysts.[8] While a large number of functional groups on the aryl substituents in the 3- and 4-positions were well tolerated, it should be noted that the nitro group inhibited the cyclotrimerization completely (**14g**, 0%). One reason could be the very low solubility of the starting material in organic solvents.[9] The only drawback was encountered when the substrates deca-4,6-diyne (**13j**) and 1,4-bis(trimethylsilyl)-1,3-butadiyne (**13k**) were used. The corresponding products **14j** and **14k** were isolated in only 50 and 30% yield, respectively, but while **14k** was generated as a single regioisomer in a very slow reaction (after 72 h still incomplete), the alkyl-substituted derivative **14j** gave a 2:1 mixture of the two regioisomers. When substituents in the 2-position of the aryl subunit were applied, the cyclotrimerization products **14l** and **14m** were also obtained in good to excellent yields. However, the ^{1}H and ^{13}C NMR data show a large number of isomers which are most likely attributed to diastereomers, as mentioned above. High-temperature NMR spectra (up to 100 °C, see SI) were inconclusive because the number of signals were reduced but still too high for all arene subunits rotating unhindered (six signals for the methyl groups in ^{1}H NMR for **14l** and six signals for the methoxy groups in **14m** as was found for **14h** and **14i**). The formation of the corresponding symmetrical 1,3,5-regioisomer **15l**/**15m** is possible but unlikely based on all other results obtained in this study. In addition, the symmetrical isomers **15l** and **15m** cannot account for the number of signals observed for the methyl (**14l**) and the methoxy protons (**14m**).[10]

In conclusion, we were able to react symmetrical and unsymmetrical 1,3-butadiynes toward the unsymmetrical cyclotrimerization product as soon as the steric difference of the substituents at position 1 and 4 of the 1,3-butadiyne were significant toward the unsymmetrical chemo- and regioisomers of type **12** and **14** in good to excellent yields. Fortunately, the cobalt-catalyzed cyclotrimerization reaction of unsymmetrical butadiynes generated a single isomer out of 12 possible isomers; however, the alteration of the chemo- and regioselectivity toward a 1,3,5-regioisomer could not be accomplished.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01281.

Experimental procedures, analytical data, NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: gerhard.hilt@uni-oldenburg.de.

ORCID

Gerhard Hilt: 0000-0002-5279-3378

Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) For a review concerning transition-metal-catalyzed cyclotrimerization of alkynes, see: (a) Hapke, M.; Weding, N.; Kral, K. In *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B., Herrmann, W. A., Beller, M., Paciello, R., Eds.; Wiley, 2018; Vol. *1*, pp 375−409. (b) Kotha, S.; Lahiri, K.; Sreevani, G. *Synlett* **2018**, *29*, 2342−2361. (c) Loxq, P.; Manoury, E.; Poli, R.; Deydier, E.; Labande, A. *Coord. Chem. Rev.* **2016**, *308*, 131−190. (d) Okamoto, S.; Sugiyama, Y. *Synlett* **2013**, *24*, 1044−1060. (e) Gandon, V. In *Transition-Metal Mediated Aromatic Ring Construction*; Tanaka, K., Ed.; Wiley, 2013; pp 3−35. (f) Shibata, Y.; Tanaka, K. *Synthesis* **2012**, *44*, 323−350. (g) Broere, D. L. J.;

DOI: 10.1021/acs.orglett.9b01281
Org. Lett. XXXX, XXX, XXX−XXX

Ruijter, E. *Synthesis* **2012**, *44*, 2639−2672. (h) Tanaka, K. *Heterocycles* **2012**, *85*, 1017−1043. (i) Domínguez, G.; Pérez-Castells, J. *Chem. Soc. Rev.* **2011**, *40*, 3430−3444. (j) Hua, R.; Abrenica, M. V. A.; Wang, P. *Curr. Org. Chem.* **2011**, *15*, 712−729. (k) Weding, N.; Hapke, M. *Chem. Soc. Rev.* **2011**, *40*, 4525−4538. (l) Zhou, L.; Li, S.; Kanno, K.; Takahashi, T. *Heterocycles* **2010**, *80*, 725−738. (m) Pla-Quintana; Roglans, A. *Molecules* **2010**, *15*, 9230−9251.

(2) (a) Agenet, N.; Gandon, V.; Vollhardt, K. P. C.; Malacria, M.; Aubert, C. *J. Am. Chem. Soc.* **2007**, *129*, 8860−8871. (b) Gandon, V.; Agenet, N.; Vollhardt, K. P. C.; Malacria, M.; Aubert, C. *J. Am. Chem. Soc.* **2006**, *128*, 8509−8520. (c) Dahy, A. A.; Suresh, C. H.; Koga, N. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 792−803. (d) Dahy, A. A.; Koga, N. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 781−791. For recent investigations, see: (e) Yamamoto, K.; Nagae, H.; Tsurugi, H.; Mashima, K. *Dalton Trans* **2016**, *45*, 17072−17081. (f) Lomont, J. P.; Nguyen, S. C.; Harris, C. B. *Acc. Chem. Res.* **2014**, *47*, 1634−1642. (g) Baldridge, K. K.; Bunker, K. D.; Vélez, C. L.; Holland, R. L.; Rheingold, A. L.; Moore, C. E.; O'Connor, J. M. *Organometallics* **2013**, *32*, 5473−5480. (h) Lomont, J. P.; Nguyen, S. C.; Schlegel, J. P.; Zoerb, M. C.; Hill, A. D.; Harris, C. B. *J. Am. Chem. Soc.* **2012**, *134*, 3120−3126. (i) Lomont, J. P.; Nguyen, S. C.; Zoerb, M. C.; Hill, A. D.; Schlegel, J. P.; Harris, C. B. *Organometallics* **2012**, *31*, 3582−3587.

(3) For the synthesis of vitamin B_6, see: (a) Parnell, C. A.; Peter, K.; Vollhardt, K. P. C. *Tetrahedron* **1985**, *41*, 5791−5796. For the synthesis of (±)-allocolchicine, see: (b) Paymode, D. J.; Ramana, C. V. *ACS Omega* **2017**, *2*, 5591−5600.

(4) (a) Kumon, T.; Yamada, S.; Agou, T.; Kubota, T.; Konno, T. *J. Fluorine Chem.* **2018**, *213*, 11−17. (b) Jungk, P.; Fischer, F.; Thiel, I.; Hapke, M. *J. Org. Chem.* **2015**, *80*, 9781−9793. (c) Sugiyama, Y.-k.; Kariwa, T.; Sakurada, T.; Okamoto, S. *Synlett* **2012**, *23*, 2549−2553.

(5) (a) Thiel, I.; Jiao, H.; Spannenberg, A.; Hapke, M. *Chem. - Eur. J.* **2013**, *19*, 2548−2554. (b) Thiel, I.; Spannenberg, A.; Hapke, M. *ChemCatChem* **2013**, *5*, 2865−2868. (c) Hapke, M.; Weding, N.; Spannenberg, A. *Organometallics* **2010**, *29*, 4298−4304. (d) Geny, A.; Agenet, N.; Iannazzo, L.; Malacria, M.; Aubert, C.; Gandon, V. *Angew. Chem., Int. Ed.* **2009**, *48*, 1810−1813.

(6) (a) Hilt, G.; Vogler, T.; Hess, W.; Galbiati, F. *Chem. Commun.* **2005**, 1474−1475. (b) Hilt, G.; Hengst, C.; Hess, W. *Eur. J. Org. Chem.* **2008**, *2008*, 2293−2297.

(7) Weber, S. M.; Hilt, G. *Org. Lett.* **2017**, *19*, 564−567.

(8) (a) García-Lacuna, J.; Domínguez, G.; Blanco-Urgoiti, J.; Pérez-Castells, J. *Org. Lett.* **2018**, *20*, 5219−5223. (b) Steffen, A.; Ward, R. M.; Tay, M. G.; Edkins, R. M.; Seeler, F.; van Leeuwen, M.; Pålsson, L.-O.; Beeby, A.; Batsanov, A. S.; Howard, J. A. K.; Marder, T. B. *Chem. - Eur. J.* **2014**, *20*, 3652−3666. (c) Chalk, A. J.; Jerussi, R. A. *Tetrahedron Lett.* **1972**, *13*, 61−62. (d) Hübel, W.; Merényi, R. *Chem. Ber.* **1963**, *96*, 930−943.

(9) Hilt, G.; Hengst, C.; Arndt, M. *Synthesis* **2009**, 395−398.

(10) Comparable NMR data were obtained for hexaphenylbenzene-type molecules with substituents in the 2-position; see: Shukla, R. S.; Lindeman, S. V.; Rathore, R. *Org. Lett.* **2007**, *9*, 1291−1294.

DOI: 10.1021/acs.orglett.9b01281
Org. Lett. XXXX, XXX, XXX−XXX