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Synthesis of Polysubstituted Iodobenzene Derivatives from Alkynylsilanes and 1,3-Dienes via Diels–Alder/Oxidation/Iodination Reaction Sequence

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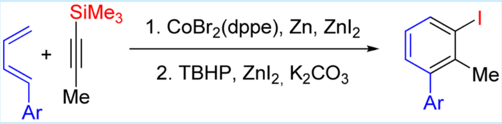
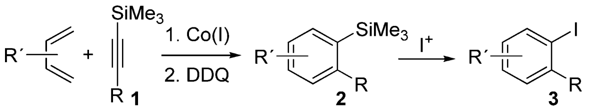
Supporting Information



ABSTRACT: The cobalt-catalyzed Diels–Alder reaction of trimethylsilyl-substituted alkynes with 1,3-dienes led to dihydroaromatic intermediates which were transformed into iodobenzene derivatives. For this transformation, the dihydroaromatic intermediates had to be oxidized and the trimethylsilyl-substituted arene had to undergo a silicon–iodine exchange reaction. For this purpose, a number of oxidizing agents and iodonium sources were tested in order to realize the desired two transformations in a single step. Eventually, the combination of *tert*-butyl hydroperoxide (TBHP), zinc iodide, and potassium carbonate led to the desired oxidation/iodination in good to excellent yields in a short reaction time at ambient temperatures.

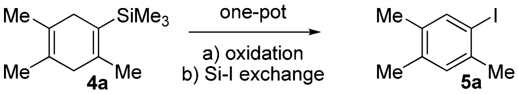
Iodobenzene derivatives are excellent starting materials for transition-metal-catalyzed cross-coupling under mild conditions based on the high reactivity of the carbon iodine bond in the oxidative addition process.[1] A drawback of the iodobenzene derivatives is the high price for commercially available materials. Nevertheless, the further need for simple synthesis of polysubstituted iodobenzene derivatives with a predictable incorporation of the iodine substituent at a precisely predictable position is undisputable. In this respect, we envisaged the use of alkynyl iodides as starting material in a cobalt-catalyzed Diels–Alder reaction.[2] However, under the reaction conditions of the cobalt-catalyzed Diels–Alder reaction, the use of alkynyl iodides led into oxidative insertions either of the metallic zinc or the low-valent cobalt catalyst, which eventually resulted in a number of undesired side reactions. Therefore, we alternatively envisaged the use of alkynylsilanes (**1**) as building blocks for the synthesis of more complex iodobenzene derivatives (Scheme 1).[3] The use of alkynylsilanes (**1**) as dienophiles in a cobalt-catalyzed Diels–Alder reaction for the synthesis of silyl-functionalized arenes (**2**) has been disclosed before with simple 1,3-dienes.[4] These cobalt-catalyzed reactions were conducted under reductive conditions utilizing zinc powder for the in situ reduction of the cobalt(II) catalyst precursor to the reactive cobalt(I) complex. Under these reaction conditions, the alkynyltrimethylsilanes were stable and led to the desired dihydroaromatic intermediates in good yields (compare **4** in Scheme 2).

Scheme 1. Outline of the Synthesis of Iodobenzene Derivatives



Moreover, the alkynyltrimethylsilanes have a number of advantages. First, the syntheses of the alkynylsilane derivatives are easy and the products are stable over a long period of time. Second, the trimethylsilyl group is an excellent directing group for the regioselective cobalt-catalyzed Diels–Alder reactions when unsymmetrical starting materials are used.

Scheme 2. Desired Oxidation/Silicon–Iodine Exchange Reaction



Third, the silyl group can be substituted under relatively mild conditions in an *ipso*-substitution by various iodonium sources resulting in products of type **3**.

In order to guarantee a high flexibility of substitution patterns, we addressed the synthesis of different commercially unavailable 1,3-dienes via two methods. Either a Wittig reaction of an aldehyde with allyltriphenylphosphonium bromide and a base was used for the synthesis of 1-substituted 1,3-dienes[5] or a ruthenium-catalyzed enyne-metathesis reaction an of internal alkyne with ethene was utilized to generate 2,3-disubstituted 1,3-diene.[6] However, at the early stage of the investigation the main focus was set on commercially available 1,3-dienes, such as 2,3-dimethyl-1,3-butadiene or isoprene.

In previous work, the silyl-substituted arenes (**2**) were isolated after DDQ oxidation, which proved that the trimethylsilyl substituent tolerates these reaction conditions.[4] For this investigation, oxidation of the primarily produced dihydroaromatic Diels–Alder product (**4**) to the aromatic compound and, furthermore, silyl–iodine exchange should be realized in a single transformation to yield **5** (Scheme 2). To achieve this goal, either the iodonium source should be capable of oxidizing the dihydroaromatic intermediate **4** or the oxidizing agent should

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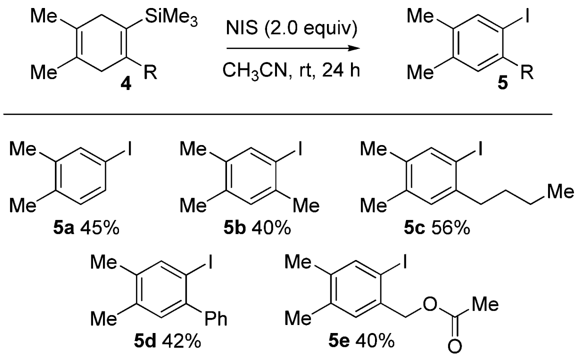
also be able to generate iodonium ions from simple iodine sources in situ.

The first attempt to realize the desired transformation was the conversion of **4** with ICl (2.0 equiv) in dichloromethane.[7] Surprisingly, after 15 min reaction time at room temperature only 17% of the desired product **5** could be isolated. In addition to **5**, also several HCl-addition products could be detected by GCMS analysis and were isolated as a mixture of isomers (>50%). Accordingly, these conditions were not useful for a clean conversion of **4** to **5**. Next, we investigated the use of NIS (*N*-iodosuccinimide) as iodonium source and oxidizing agent (Scheme 3).[8] Although NIS has not been described as the oxidizing agent for the synthesis of arenes from intermediates such as **4**, the first results were promising.

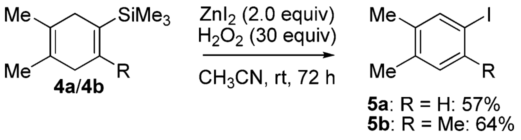
Scheme 3. NIS-Induced Oxidation/Iodination Reaction



The NIS-induced protocol for the synthesis of products **5** led to the desired iodobenzene derivatives in moderate yields. The high conversion of material into unidentified side products, the long reaction time, and the tendency of the products to decompose, most likely by the unidentified side products which were not separable from the products by simple column chromatography, were unsatisfying. Nevertheless, the yield of **5a** could be increased to 67% when the reaction was performed in dichloromethane instead of acetonitrile utilizing 3.0 equiv of NIS after 72 h, but still these conditions were not particularly practical.

In a small set of experiments, we then investigated the use of a combination of hydrogen peroxide as an inexpensive and readily available oxidizing agent for dihydroaromatic intermediates of type **4** in combination with zinc iodide as an easy to handle iodine source (Scheme 4).[9]

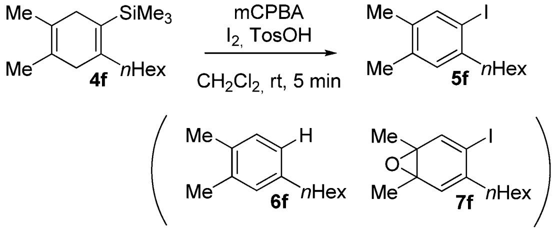
Scheme 4. ZnI_2/H_2O_2-Induced Oxidation/Iodination Reaction



While the yields of products **5a** and **5b** were increased, the reaction time was quite long to obtain the desired products and either DDQ or NIS had to be added at the end to achieve either complete oxidation of dihydroaromatic intermediates or to complete the silicon−iodine exchange.

Considerably better results were obtained when a combination of *m*-CPBA (*m*-chloroperbenzoic acid) and iodine under acidic conditions (TosOH) was applied for the formation of **5** (Scheme 5).[10]

Scheme 5. *m*-CPBA/I_2-Induced Oxidation/Iodination Reaction



In this set of experiments, **4f** was used as easily accessible intermediate of type **4** and the corresponding iodobenzene **5f** was generated in only 5 min reaction time at ambient temperatures. We then investigated different ratios of oxidizing agent, acid, and iodonium source. The results of the *m*-CPBA/I_2-induced oxidation/iodination reaction sequence are summarized in Table 1.

Table 1. Results of the *m*-CPBA/I_2 Reaction

no.	*m*-CPBA/TosOH/I_2 (equiv)	**6g/7g**[a] (%)	**5g**[a] (%)
1	2.0/0.6/1.0	7/14	54
2	2.0/0.6/3.0	7/31	53
3	2.0/2.0/3.0	6/4	76
4	2.0/2.0/2.0	8/4	77
5	2.0/2.0/4.0	7/5	83
6	2.0/3.0/4.0	7/2	89
7	**3.0/3.0/3.0**	**6/2**	**92**

[a] Yields were obtained from GC analysis using decane as the internal standard.

Under optimized reaction conditions, up to 92% of **5f** was obtained using an excess of each *m*-CPBA, TosOH, and iodine. Nevertheless, under all tested conditions, the desired product was accompanied by a small amount of proto-desilylated **6f** and varying amounts of epoxidized side product, whose structure was tentatively assigned to **7f**. The separation of the desired product from the side products is very tedious which disfavors these reaction protocols.

Although the overall results of the *m*-CPBA/TosOH/I_2 process were already quite promising, we were not satisfied with the encountered proto-desilylation side product. Therefore, basic conditions were tested for the oxidation/iodination using *tert*-butyl hydroperoxide (TBHP) as oxidant,[11] and iodine or zinc iodide were applied as iodonium source (Scheme 6).

The results of the TBHP-induced oxidation/iodination reaction sequence are summarized in Table 2.

While in the absence of base 80% of **5f** was obtained using 2.0 equiv of I_2, the addition of further amounts of I_2 resulted in decreased yields (entries 1−3). Organic bases such as NEt_3,

Scheme 6. TBHP/I_2- or TBHP/ZnI_2-Induced Oxidation/Iodination Reaction

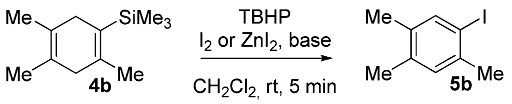
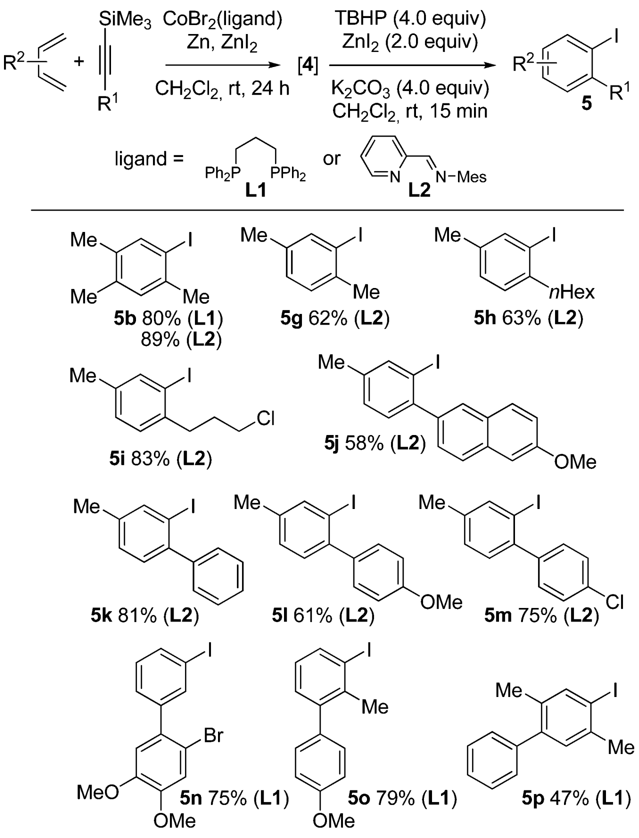


Table 2. Results of the TBHP/I_2 and TBHP/ZnI_2 Reaction

no.	TBHP/I_2	base	$5g^a$ (%)
1	4.0/1.0		62
2	4.0/2.0		80
3	4.0/3.0		56
4	4.0/2.0	NEt_3 (4.0 equiv)	0
5	4.0/2.0	pyridine (4.0 equiv)	50
6	4.0/2.0	lutidine (4.0 equiv)	64
7	4.0/2.0	KOH (4.0 equiv)	43
8	4.0/2.0	KOAc (4.0 equiv)	77
9	4.0/2.0	Na_3PO_4 (4.0 equiv)	87
10	4.0/2.0	KOtBu (4.0 equiv)	58
11	4.0/2.0	K_2CO_3 (4.0 equiv)	89
no.	TBHP/ZnI_2	base	5g (%)
12	4.0/2.0		86
13	4.0/2.0	K_2CO_3 (1.0 equiv)	76
14	4.0/2.0	K_2CO_3 (2.0 equiv)	91
15	**4.0/2.0**	**K_2CO_3 (4.0 equiv)**	**98**

[a]Yields were obtained from GC analysis using decane as internal standard.

Scheme 7. Two-Step Synthesis of Iodobenzene Derivatives[a]



[a]Reaction conditions: $CoBr_2$(ligand) (10 mol %), zinc powder (20 mol %), zinc iodide (20 mol %), alkyne (1.0 equiv) and diene (1.0 equiv), CH_2Cl_2, 24 h, rt, filtration through silica gel, then K_2CO_3 (4.0 equiv), TBHP (4.0 equiv), ZnI_2 (2.0 equiv), CH_2Cl_2, rt, 24–48 h.

pyridine, and lutidine gave only moderate yields, but considerably better results were obtained with inorganic bases, such as sodium phosphate or potassium carbonate (entries 9 and 11). When the iodonium source ws changed to zinc iodide, the yields could be further increased so that eventually the combination of TBHP/ZnI_2/K_2CO_3 in a ratio of 4:2:4 equiv gave excellent results (entry 15) without any trace of protodesilylation or epoxidation side products.

Finally, the combination of the cobalt-catalyzed Diels–Alder reaction and TBHP/ZnI_2/K_2CO_3-oxidation/iodination were tested without purification of the dihydroaromatic intermediates of type **4** (Scheme 7). After complete conversion of the starting materials in the cobalt-catalyzed Diels–Alder reaction, the dihydroaromatic intermediates were filtered over a small plug of silica gel and used in the oxidation/iodination reactions as obtained. The use of symmetrical as well as unsymmetrical 1,3-dienes could be achieved. The regioselectivity of the cobalt-catalyzed Diels–Alder reaction was controlled by the ligand (bidentate phosphine versus pyridine–imine ligand) as we described in the past.[12] The excellent control of the regiochemistry of functionalized alkynes with unsymmetrical 1,3-dienes was only recently demonstrated with alkynylboronates as functionalized building blocks for the synthesis of complex monomers for the palladium-catalyzed Suzuki polymerization reaction.[13] The desired iodobenzene derivatives were obtained in moderate to good yields, and several functional groups were tolerated in both reactions.

The commercially available symmetrical 2,3-dimethyl-1,3-butadiene could be utilized for the synthesis of the trimethyliodobenzene derivative **5b** in a good overall yield of 80%. As a prototype of an unsymmetrical 1,3-diene, isoprene was converted to the corresponding iodobenzene derivatives **5g–m** with the Co(pyridine-imine)-type catalyst to generate products with the methyl group of the isoprene and the iodine substituent in a 1,3-relation. These iodine-containing products were isolated in 58–83% yields for the Diels–Alder/oxidation/iodination reaction sequence. Moreover, two different 1-aryl-substituted 1,3-dienes were converted to the desired products **5n** and **5o** in very good yields of 75% and 79%, respectively. Finally, the Co(dppe)-type catalyst led to the regioselective formation of **5p** with the iodine substituent and the phenyl substituent of the diene component in a 1,4-relation in moderate 47% yield.

In conclusion, we were able to generate the trimethylsilyl-functionalized dihydroaromatic compounds in a regioselective fashion and tested a number of oxidizing/iodination conditions. Eventually, we were able to realize a mild and benign protocol for the synthesis of multiple-substituted iodobenzenes from dihydroaromatic intermediates in a single synthetic step. In particular, we were able to generate interesting materials such as the bromoiodo-substituted biaryl derivative (**5n**) as well as 2,3-disubstituted iodobenzene derivative (**5o**). In addition, 2,5-disubstituted products, such as the chloroiodobiphenyl **5m**, and also 2,4,5-trisubstituted iodobenzenes (**5p**) were synthesized. Based on these results we are confident that we will be able to generate highly interesting iodobenzene building blocks for palladium-catalyzed cross-coupling reactions utilizing the regiodiverse and powerful cobalt-catalyzed Diels–Alder reaction of alkynyltrimethylsilanes with substituted 1,3-dienes in the future.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Synthesis, analytical data, NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

REFERENCES

(1) For recent selected reviews concerning the application of aryl halides, see: (a) Skulski, L. *Molecules* **2000**, *5*, 1331. (b) Knappke, C. E. I.; Grupe, S.; Gärtner, D.; Corpet, M.; Gosmini, C.; Jacobi von Wangelin, A. *Chem.—Eur. J.* **2014**, *20*, 6828. (c) Moragas, T.; Correa, A.; Martin, R. *Chem.—Eur. J.* **2014**, *20*, 8242. (d) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082. (e) Stavber, S.; Jereb, M.; Zupan, M. *Synthesis* **2008**, 1487. (f) Merkushev, E. B. *Synthesis* **1988**, 923.

(2) (a) Hilt, G. *Chem. Rec.* **2014**, *14*, 386. (b) Hess, W.; Treutwein, J.; Hilt, G. *Synthesis* **2008**, 3537.

(3) (a) Welker, M. E. *Tetrahedron* **2008**, *64*, 11529. (b) Nikolai, J.; Schlegel, J.; Regitz, M.; Maas, G. *Synthesis* **2002**, 497.

(4) Hilt, G.; Janikowski. *J. Org. Lett.* **2009**, *11*, 773.

(5) (a) Hilt, G.; Danz, M. *Synthesis* **2008**, 2257. (b) Hilt, G.; Danz, M.; Treutwein, J. *Org. Lett.* **2009**, *11*, 3322.

(6) (a) Danz, M.; Hilt, G. *Adv. Synth. Catal.* **2011**, *353*, 303. (b) Tonogaki, K.; Mori, M. *Tetrahedron Lett.* **2002**, *43*, 2235. (c) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317.

(7) (a) Waldo, J. P.; Mehta, S.; Larock, R. C. *J. Org. Chem.* **2008**, *73*, 6666. (b) Jacob, L. A.; Chen, B.-L.; Stec, D. *Synthesis* **1993**, 611.

(8) (a) Carreño, M. C.; García Ruano, J.; Sanz, G.; Toledo, M. A.; Urbano, A. *Tetrahedron Lett.* **1996**, *37*, 4081. (b) Zhou, L.; Zhou, J.; Tan, C. K.; Chen, J.; Yeung, Y.-Y. *Org. Lett.* **2011**, *13*, 2448. (c) Sidera, M.; Costa, A. M.; Vilarrasa, J. *Org. Lett.* **2011**, *13*, 4934. (d) Pawluć, P.; Franczyk, A.; Walkowiak, J.; Hreczycho, G.; Kubicki, M.; Marciniec, B. *Org. Lett.* **2011**, *13*, 1976.

(9) (a) Maleki, B.; Veisi, H. *Bull. Korean Chem. Soc.* **2011**, *32*, 4366. (b) Shahabi, D.; Amrollahi, M. A.; Jafari, A. A. *J. Iran. Chem. Soc.* **2011**, *8*, 1052. (c) Uyanik, M.; Ishihara, K. *ChemCatChem* **2012**, *4*, 177.

(10) (a) Sha, C.-K.; Young, J.-J.; Jean, T.-S. *J. Org. Chem.* **1987**, *52*, 3919. (b) Uyanik, M.; Ishihara, K. *ChemCatChem* **2011**, *4*, 177.

(11) (a) Ilangovan, A.; Satish, G. *J. Org. Chem.* **2014**, *79*, 4984. (b) Zhang, X.; Wang, L. *Green Chem.* **2012**, *14*, 2141. (c) Montoro, R.; Wirth, T. *Org. Lett.* **2003**, *5*, 4729. (d) Tanner, D. D.; Gidley, G. C.; Das, N.; Rowe, J. E.; Potter, A. *J. Am. Chem. Soc.* **1984**, *106*, 5261. (e) Reddy, K. R.; Maheswari, C. U.; Venkateshwar, M.; Kantam, M. L. *Adv. Synth. Catal.* **2009**, *351*, 93.

(12) (a) Hilt, G.; Janikowski, J.; Hess, W. *Angew. Chem., Int. Ed.* **2006**, *45*, 5204. (b) Mörschel, P.; Janikowski, J.; Hilt, G.; Frenking, G. *J. Am. Chem. Soc.* **2008**, *130*, 8952. (c) Hilt, G.; Janikowski, J.; Schwarzer, M.; Burghaus, O.; Sakow, D.; Bröring, M.; Drüschler, M.; Huber, B.; Roling, B.; Harms, K.; Frenking, G. *J. Organomet. Chem.* **2014**, *749*, 219. (d) Fiebig, L.; Kuttner, J.; Hilt, G.; Schwarzer, M. C.; Frenking, G.; Schmalz, H.-G.; Schäfer, M. *J. Org. Chem.* **2013**, *78*, 10485.

(13) Kuttner, J. R.; Hilt, G. *Macromolecules* **2014**, *47*, 5532.

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