Advanced Synthesis & Catalysis

DOI: 10.1002/adsc.201500573

Platinum(IV)-Catalyzed Synthesis of Unsymmetrical Polysubstituted Benzenes *via* Intramolecular Cycloaromatization Reaction

Shuyan Zheng,[+a] Jinghua Zhang,[+a] and Zhengwu Shen[b,*]

[a] School of Pharmacy, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, People's Republic of China
[b] School of Medicine, Shanghai Jiao Tong University, Shanghai 200025, People's Republic of China
E-mail: Jeff_shen_1999@yahoo.com
[+] These authors contributed equally.

Received: June 14, 2015; Published online: September 11, 2015

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201500573.

Abstract: A one-pot synthesis of polysubstituted benzene derivatives was achieved *via* a platinum(IV)-catalyzed intramolecular cycloaromatization reaction. The reaction proceeds *via* a tandem skeletal rearrangment, dehydration and double bond isomerization, which proved to be very useful for the syntheses of a range of interesting polyalkyl-substituted benzenes.

Keywords: cycloaromatization; double bond isomerization; platinum(IV); polysubstituted benzenes; rearrangement

Polysubstituted aromatics are an important class of organic compounds with wide reaching and significant applications in industry and research laboratories.[1]

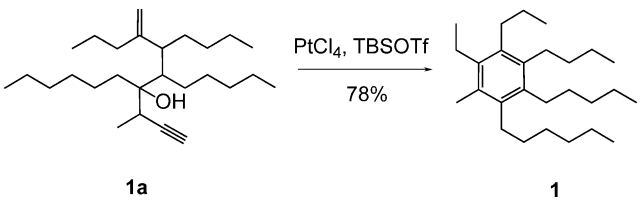
A number of methods has been developed for the synthesis of polysubstituted benzene over the years. For example, traditional approaches often include the Friedel–Crafts reaction,[2] transition metal-catalyzed [2+2+2]cyclotrimerization,[3] [4+2]cycloaddition reactions[4] and dehydrogenation reactions of cyclohexenones.[5] Whilst each method has its own merit, there is still great interest in developing new and efficient strategies for the synthesis of polysubstituted benzenes.

Recently, the metal-mediated cycloisomerization of 1,n-enynes has emerged as an extremely attractive approach for the synthesis of various cyclic compounds, including substituted benzenes.[6,7] However, the formation of six-membered rings from 1,7-enynes by metathesis is not always easy and can sometimes be challenging. In addition, application of ring closure metathesis–aromatization to the synthesis of benzene derivatives often requires additional steps that involve dehydration, oxidation, and tautomerization of the metathesis products.[6c,d]

Herein, we report a novel strategy employing a platinum(IV)-catalyzed 1,7-enyne skeletal rearrangement–aromatization, for the synthesis of polyalkyl-substituted benzenes (Scheme 1). This reaction is actually a one-pot combination of skeletal rearrangement, elimination and double bond isomerization. Hence, we believe it offers a convenient and complementary approach towards the synthesis of polysubstituted benzenes that may otherwise be difficult to obtain *via* existing methods.

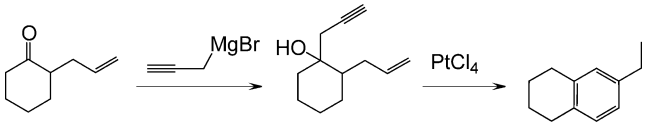
To optimize the reaction conditions and identify essential additives for the platinum(IV)-catalyzed process, compound **2a** was selected as a suitable model substrate. A number of Lewis acids, solvents and noble metal catalysts was screened, and selected results are presented in Table 1. Gratifyingly, although the reaction yield was rather low, the target benzannulated **2** was formed under the $PtCl_4$ reaction conditions (entry 1, Table 1).

Next, to assist with the elimination of the tertiary OH group, a selection of Lewis acids was added as co-catalyst (entries 2, 3, 4 and 5, Table 1). Interestingly, each Lewis acid tested improved the reaction performance, with TBSOTf performing best and leading to a 72% yield of **2**. In addition to $PtCl_4$, other noble metal catalysts were also investigated. $PtCl_2$ (entry 6,



Scheme 1. Platinum (IV)-catalyzed cycloaromatization.

Table 1. Optimization of the reaction conditions[a]



2b **2a** **2**

Entry	Solvent	Catalyst	Additive	*t* [°C]	Yield [%][b]
1	toluene	$PtCl_4$	No	80	16
2	toluene	$PtCl_4$	$Sc(OTf)_3$	80	23
3	toluene	$PtCl_4$	$BF_3{\cdot}OEt_2$	80	47
4	toluene	$PtCl_4$	TBSOTf	80	72
5	toluene	$PtCl_4$	$LiClO_4$	80	12
6	toluene	$PtCl_2$	TBSOTf	80	0
7	CH_2Cl_2	$PtCl_4$	TBSOTf	40	0
8	CH_2Cl_2	$PtCl_4$	No	40	0
9	toluene	$Au(PPh_3)Cl$	TBSOTf	80	11
10	toluene	$PtCl_4$	TBSOTf	100	66
11	toluene	$PtCl_4$ (0.1 equiv.)	TBSOTf	80	68
12[c]	toluene	$PtCl_4$	TBSOTf	80	70

[a] *Typical reaction conditions:* substrate (1.0 mmol); $PtCl_4$, 0.05 equiv.; Lewis acid, 0.06 equiv., stirred at 80 °C for 12 h.
[b] Isolated yield.
[c] Under an air atmosphere.

Table 1) did not yield the desired aromatic product under otherwise equivalent reaction conditions. The Grubbs II catalyst was also tried but the reaction gives very complicate products. However, $Au(PPh_3)Cl$ could form the compound **2**, although the yield was quite low. Toluene was identified as the most suitable solvent, with an optimal reaction temperature of 80 °C. In addition, increasing the amount of the catalyst (entry 11, Table 1) and the presence of air (entry 12, Table 1) in the system seemed to have no impact on the yield of the reaction. Hence, the optimal reaction conditions were concluded to be as follows: substrate (1.0 mmol); $PtCl_4$, 0.05 equiv.; Lewis acid, 0.06 equiv., stirred at 80 °C for 12 h.

In order to explore the scope of the reaction, a selection of tri-, tetra-, penta- and hexa-substituted benzene derivatives was synthesized. In general, as depicted in Table 2, the standard reaction conditions gave pleasingly good yields. Multi-substituted biphenyl derivatives (entries 6, 7, 8, 11, 12 and 13, Table 2) could be obtained readily in high yields. Compared with other well established methods for biphenyl synthesis, such as Suzuki[8] and Kumada couplings,[9] the present method provides a useful alternative for the synthesis of biphenyl derivatives. Benzo-fused cycloalkanes, including benzocyclohexane and benzocyclopentane derivatives, can also be obtained *via* the cycloaromatization reaction.

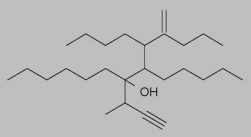
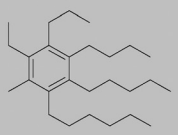
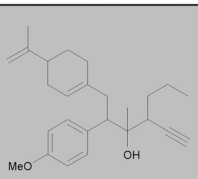
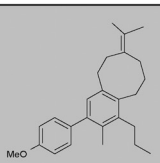
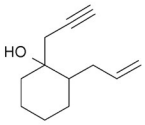
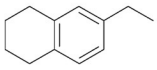
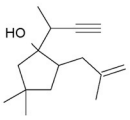
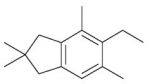
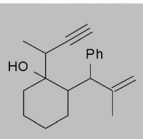
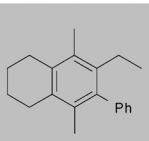
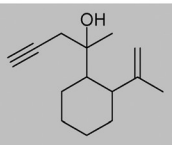
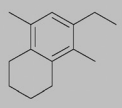
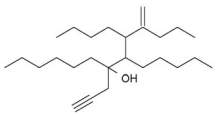
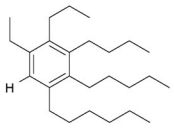
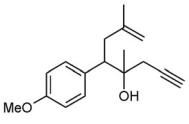
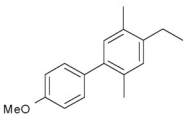
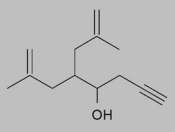
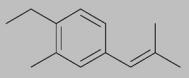
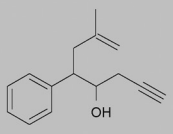
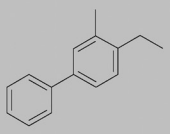
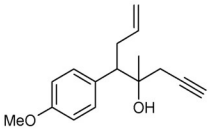
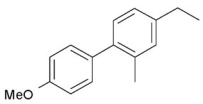
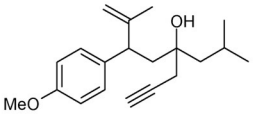
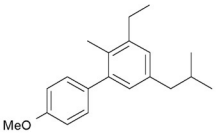
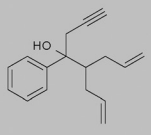
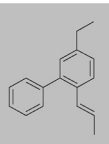
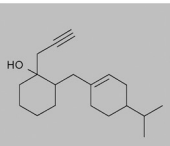
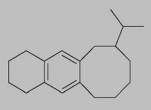
Both cyclopentane and cyclohexane were used as tethers in the 1,7-enyne, which yielded benzocyclopentane and benzocyclohexane in good yields, respectively (entries 2, 3, 9 and 10, Table 2). This represents a convenient strategy for the syntheses of such benzocycloalkanes. However, it was found that when the double bond of the 1,7-enyne is located within a ring system, ring expansion took place during the reaction leading to the formation of a benzocycloalkane. The ring size of benzo-fused cycloalkane depends on the size of the cycloalkene in the precursors (entry 8, Table 2). For example, when the cyclohexene moiety participated in the cycloaromatization reaction, the final product was the corresponding benzocyclooctene derivative. The combination of both strategies could be useful for the synthesis of a poly-membered ring system (entry 14, Table 2). In order to confirm this hypothesis, compound **27** was synthesized to examine whether this strategy could be applied for thee formation of other ring systems instead of an 8-membered ring. Indeed, as expected, the benzo-fused cycloheptane **28** was formed in 74% yields (Scheme 2). This finding provides an alternative strategy for the synthesis of benzo-fused cycloalkanes.

In the course of the synthesis of the compound **12** (entry 12, Table 2), three compounds were isolated in the absence of the co-catalyst TBSOTf (Scheme 3).

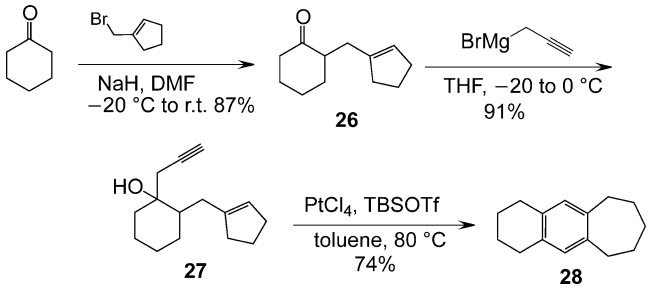
The compound **15** (35%) corresponds to the first intermediate formed in the 1,7-enyne metathesis. The compound **15** simultaneously underwent elimination of the hydroxy group and isomerization of conjugated diene to form the compound **12**. The isolation of the compound **16** (24%), indicated that dehydrogenation of **15** may take place rather than the elimination of the hydroxy group if the TBSOTf is absent. The identification of the compounds **15** and **16** provided supporting evidence for the mechanism of this cycloaromatization reaction. The compound **15** could be completely converted into **12** when TBSOTf was added to the reaction system. Thus, we speculate that TBSOTf enhances the acidity of the $PtCl_4$, thereby promoting the elimination of the hydroxy group. Because the $PtCl_4$/TBSOTf mixture efficiently converted **15** into **12**, we were interested to examine whether the system could be used to catalyze the isomerization of double bonds.

Two compounds, namely 4-phenyl-1-butene (**17**) and L-carvone (**19**) were selected to explore whether the exocyclic double bonds of these two compounds underwent the isomerization reaction under the $PtCl_4$/TBSOTf conditions. As illustrated in Scheme 4, the compounds **17** and L-carvone (**19**) were converted into 1-phenyl-1-butene (**18**) and 2-methyl-5-isopropylphenol (**20**), respectively, and with very good yields. Although a Pt(II) complex was recently reported to promote the isomerization of allylbenzenes,[10] the formation of compound **20** is the first example of a Pt(IV)-catalyzed aromatization reaction *via* isomerization of the terminal alkene.

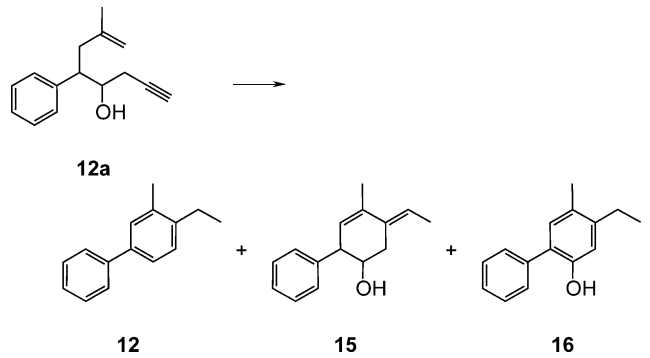
Table 2. Synthesis of polysubstituted benzene derivatives

Entry	Substrate	Product / Yield(%)	Entry	Substrate	Product / Yield(%)
1			8		
	1a	**1** (78%)		**8a**	**8** (61%)
2			9		
	2a	**2** (80%)		**9a**	**9** (64%)
3			10		
	3a	**3** (75%)		**10a**	**10** (78%)
4			11		
	4a	**4** (73%)		**11a**	**11** (63%)
5			12		
	5a	**5** (80%)		**12a**	**12** (89%)
6			13		
	6a	**6** (89%)		**13a**	**13** (73%)
7			14		
	7a	**7** (79%)		**14a**	**14** (71%)

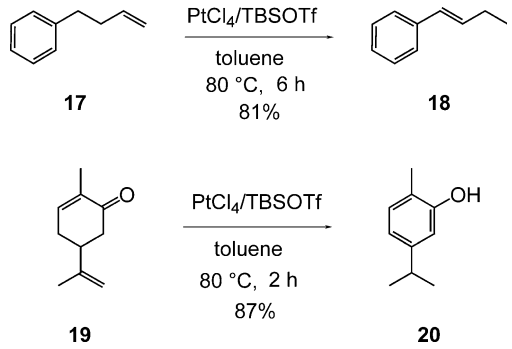
To further evaluate the scope of this reaction, a topologically interesting molecule: 1-ethyl-2-propyl-3-butyl-4-pentyl-5-hexyl-toluene (**1**) (entry 1, Table 2), was chosen to be the target molecule for the synthesis. This compound has six different linear alkyl substituents, arranged on the benzene ring clockwise according to size. Thus, it would be very challenging for such compounds to be synthesized by the other currently available methods.



Scheme 2. The synthesis of compound **28**.



Scheme 3. Identification of two important by-products.



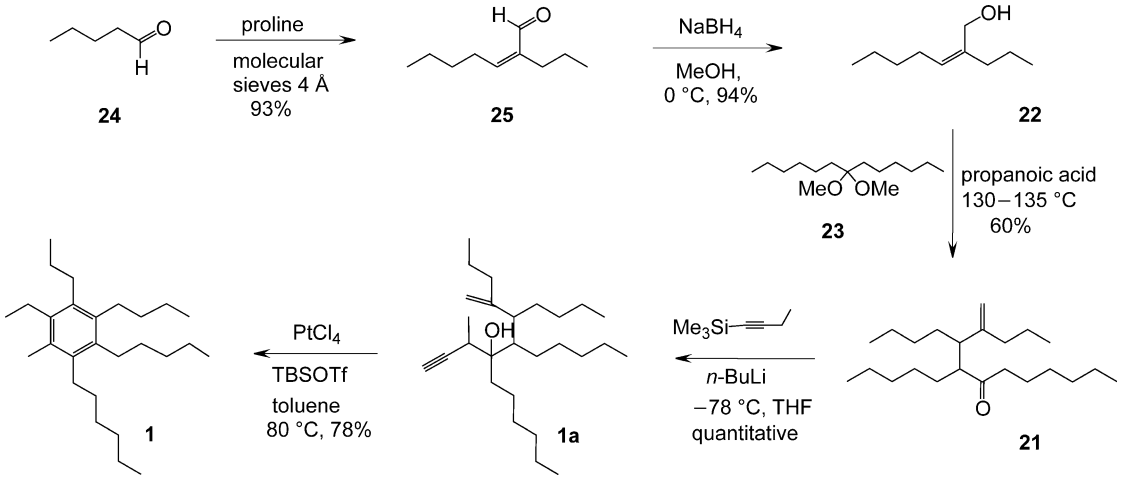
Scheme 4. The double bond migration catalyzed by $PtCl_4$/TBSOTf.

As shown in Scheme 5, the synthesis began from propyl butyl acrolein (**25**), which was readily obtained from the pentanal (**24**) through an aldol condensation reaction. The aldehyde group of compound **25** was reduced to an alcohol by $NaBH_4$ in quantitative yield. The obtained compound **22** condensed with 7-tridecanone dimethyl ketal **23** to form the key intermediate **21**.[11] Compound **21** underwent a nucleophilic addition reaction with trimethylsilylbutyne to afford compound **1a**, the precursor for the cycloaromatization.

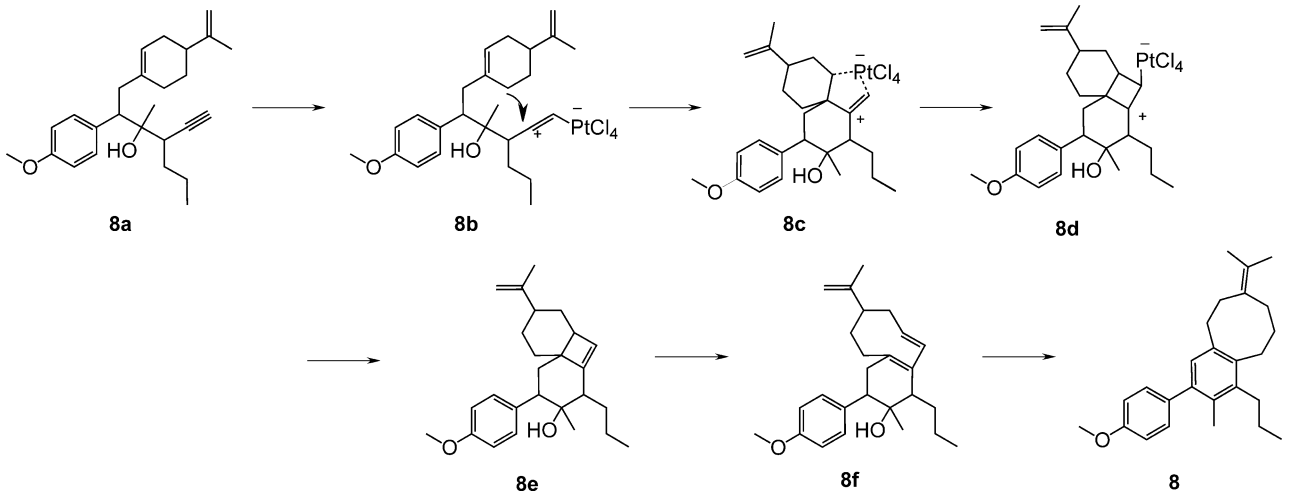
Finally, the compound **1** was prepared under the standard reaction conditions described above in 78% yield. The synthesis of the key intermediate **1a** from pentanal required only four steps, demonstrating the efficiency of this cycloaromatization reaction. A similar molecule, compound **4** was obtained in 73% yield using the same strategy (entry 4, Table 2).

Based on the above results and analyses of the by-products from the reaction, a preliminary mechanism was proposed,[12,13] as shown in Scheme 6.

To the best of our knowledge, reports on the formation of an aromatic ring by enyne cyclization are very rare.[3,6a,14,15] In some cases, it needs an aromatic ring in the tether part[6] to form a naphthalene core. The cycloaromatization method described here is the first example of a Pt(IV)-mediated cycloaromatization. This method has the following advantages: (i) The unsaturated tether unit is not needed for the skeletal rearrangement step, and thus the precursors for this reaction are relatively straightforward to synthesize. (ii) The aromatic ring was produced *via* a tandem process of elimination and double bond isomerization; hence no additional treatment was needed such as oxidation or dehydrogenation. $PtCl_4$ exhibits triple roles in the reaction. (i) As a typical transition metal catalyst, $PtCl_4$ catalyzes the skeletal rearrangement to produce the six-membered 1,3-dienes (**8f**). (ii) As a Lewis acidic catalyst, $PtCl_4$ assists the elimination of tertiary OH group. (iii) More importantly, it plays a role as



Scheme 5. The synthesis of compound **1**.



Scheme 6. A proposed reaction mechanism.

a double bond isomerization catalyst to promote the isomerization of double bonds toward the aromatic products. The addition of a Lewis acid, such as TBSOTf, into the system, actually increases the acidity of the catalyst, which accelerates the elimination of the hydroxy group and improves the yield of the reaction. In conclusion, the Pt(IV)/TBSOTf proved not only to be able to catalyze the cycloaromatization reaction but was also efficient in promoting the alkene isomerization. The present procedure provides a new regiospecific and synthetically useful route to polysubstituted benzenes, which complements and offers additional benefits to other existing methods.

Experimental Section

General Procedure for cycloaromatization Reaction (Entry 6, Table 2)

$PtCl_4$ (4.5 mg, 1.25 mmol%) and TBSOTf (trifluoromethanesulfonic acid *tert*-butyldimethylsilyl ester, 4.0 mg, 1.5 mmol%) were added into a solution of alcohol **6a** (enyne substrate) (45 mg, 0.25 mmol) in toluene (5 mL). The resulting mixture was stirred for 12 h at 80 °C. The reaction mixture was cooled to room temperature and washed with saturated aqueous $NaHCO_3$ solution (5 mL) and brine (5 mL), dried over (Na_2SO_4) and concentrated under vacuum. Flash column chromatography (silica gel, PE: EtOAc 50:1) afforded **6** as a colorless oil; yield: 29 mg (71%).

Acknowledgements

We would like to thank the Science & Technology Commission of Shanghai municipality (grant number: 14401900600) and Basilea Pharmaceutica China Ltd. for their generous financial support

References

[1] a) D. S. Tarbell, A. T. Tarbell, *Essays on the History of Organic Chemistry in the United States, 1875–1955*. Folio, Nashville, TN, **1986**, p 139–151; b) D. Astruc, *Modern Arene Chemistry*, Wiley-VCH, Weinheim, **2002**.

[2] a) G. Olah, *Friedel–Crafts and Related Reactions*, Wiley Interscience, New York, **1963**, Vols. I–IV; b) R. Taylor, *Electrophilic Aromatic Substitution*, Wiley, New York, **1990**; c) J. A. Zoltewicz, *Top. Curr. Chem.* **1975**, *59*, 33.

[3] a) S. Saito, Y. Yamamoto, *Chem. Rev.* **2000**, *100*, 2901. and references cited therein; b) M. Shanmugasundaram, M. S. Wu, C. H. Cheng, *Org. Lett.* **2001**, *3*, 4233; c) S. Sato, H. Isobe, T. Tanaka, T. Ushijima, E. Nakamura, *Tetrahedron* **2005**, *61*, 11449; d) D. Y. Park, S. Gowrisankar, J. N. Kim, *Tetrahedron Lett.* **2006**, *47*, 6641; e) C. G. Yan, X. K. Song, Q. F. Wang, J. Sun, U. Siemeling, C. Bruhn, *Chem. Commun.* **2008**, 1440.

[4] a) J. A. Marshall, *Chem. Rev.* **1996**, *96*, 31; b) Y. Yamamoto, U. Radhakrishnan, *Chem. Soc. Rev.* **1999**, *28*, 199; c) R. Zimmer, C. U. Dinesh, E. Nandanan, F. A. Khan, *Chem. Rev.* **2000**, *100*, 3067; d) A. S. K. Hashmi, *Angew. Chem.* **2000**, *112*, 3737; *Angew. Chem. Int. Ed.* **2000**, *39*, 3590; e) S. Saito, M. M. Salter, V. Gevorgyan, N. Tsuboya, K. Tando, Y. Yamamoto, *J. Am. Chem. Soc.* **1996**, *118*, 3970.

[5] a) Y. Izawa, D. Pun, S. S. Stahl, *Science.* **2011**, *333*, 209; b) T. Diao, S. S. Stahl, *J. Am. Chem. Soc.* **2011**, *133*, 14566; c) T. Diao, T. J. Wadzinski, S. S. Stahl, *Chem. Sci.* **2012**, *3*, 887; d) Y. Izawa, C. W. Zheng, S. S. Stahl, *Angew. Chem.* **2013**, *125*, 3760; *Angew. Chem. Int. Ed.* **2013**, *52*, 3672; e) K. Manna, T. Zhang, W. B. Lin, *J. Am. Chem. Soc.* **2014**, *136*, 6566.

[6] a) W. A. L. Otterlo, C. B. Koning, *Chem. Rev.* **2009**, *109*, 3743 and references cited therein; b) S. Monfette, D. E. Fogg, *Chem. Rev.* **2009**, *109*, 3783; c) K. Yoshida, T. Toyoshima, T. Imamoto, *Chem. Commun.* **2007**, 3774; d) H. Takahashi, K. Yoshida, A. Yanagisawa, *J. Org. Chem.* **2009**, *74*, 3632; e) K. Yoshida, Y. Shishikura, H. Takahashi, T. Imamoto, *Org. Lett.* **2008**, *10*,

2777; f) M. J. Geier, M. R. Gagné, *J. Am. Chem. Soc.* **2014**, *136*, 3032; g) J. A. Feducia, A. N. Campbell, M. Q. Doherty, M. R. Gagné, *J. Am. Chem. Soc.* **2006**, *128*, 13290.

[7] a) B. M. Trost, *Acc. Chem. Res.* **1990**, *23*, 34; b) B. M. Trost, *Angew. Chem.* **1995**, *107*, 285; *Angew. Chem. Int. Ed.* **1995**, *34*, 259; c) B. Schmidt, *Angew. Chem.* **2003**, *115*, 5146; *Angew. Chem. Int. Ed.* **2003**, *42*, 4996; d) I. J. S. Fairlamb, *Angew. Chem.* **2004**, *116*, 1066; *Angew. Chem. Int. Ed.* **2004**, *43*, 1048; e) I. Nakamura, Y. Yamamoto, *Chem. Rev.* **2004**, *104*, 2127; f) L. Zhang, J. Sun, S. A. Kozmin, *Adv. Synth. Catal.* **2006**, *348*, 2271.

[8] a) N. Miyauar, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457; b) A. J. Suzuki, *Organomet. Chem.* **1999**, *576*, 147; c) O. Navarro, R. A. Kelly, S. P. Nolan, *J. Am. Chem. Soc.* **2003**, *125*, 16194.

[9] a) A. Krasovskiy, P. Knochel, *Angew. Chem.* **2004**, *116*, 3396; *Angew. Chem. Int. Ed.* **2004**, *43*, 3333; b) R. Martin, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, *129*, 3844.

[10] a) A. Scarso, M. Colladon, P. Sgarbossa, C. Santo, R. A. Michelin, G. Strukul, *Organometallics* **2010**, *29*, 1487.

[11] a) G. W. Daub, D. A. Griffith, *Tetrahedron Lett.* **1986**, *27*, 6311; b) J. Poulin, C. M. Grisé-Bard, L. Barriault, *Angew. Chem.* **2012**, *124*, 2153; *Angew. Chem. Int. Ed.* **2012**, *51*, 2111.

[12] a) M. Méndez, M. P. Muñoz, C. Nevado, D. J. Cérdenas, A. M. Echavarren, *J. Am. Chem. Soc.* **2001**, *123*, 10511.

[13] a) S. Oi, I. Tsukamoto, S. Miyano, Y. Inoue, *Organometallics* **2001**, *20*, 3704; b) E. Mainetti, V. Mouriès, L. Fensterbank, M. Malacria, J. Marco-Contelles, *Angew. Chem.* **2002**, *114*, 2236; *Angew. Chem. Int. Ed.* **2002**, *41*, 2132; c) N. Chatani, H. Inoue, T. Kotsuma, S. Murai, *J. Am. Chem. Soc.* **2002**, *124*, 10294.

[14] a) T. Miura, N. Iwasawa, *J. Am. Chem. Soc.* **2002**, *124*, 518; b) H. C. Shen, S. Pal, J. J. Lian, R. S. Liu, *J. Am. Chem. Soc.* **2003**, *125*, 15762; c) K. Imamura, E. Yoshikawa, V. Gevorgyan, Y. Yamamoto, *Tetrahedron Lett.* **1999**, *40*, 4081.

[15] a) J. W. Dankwardt, *Tetrahedron Lett.* **2001**, *42*, 5809; b) A. Fürstner, V. Mamane, *J. Org. Chem.* **2002**, *67*, 6264; c) B. Martín-Matute, C. Nevado, D. J. Cárdenas, A. M. Echavarren, *J. Am. Chem. Soc.* **2003**, *125*, 5757.

