

[4 + 2] Cycloaddition

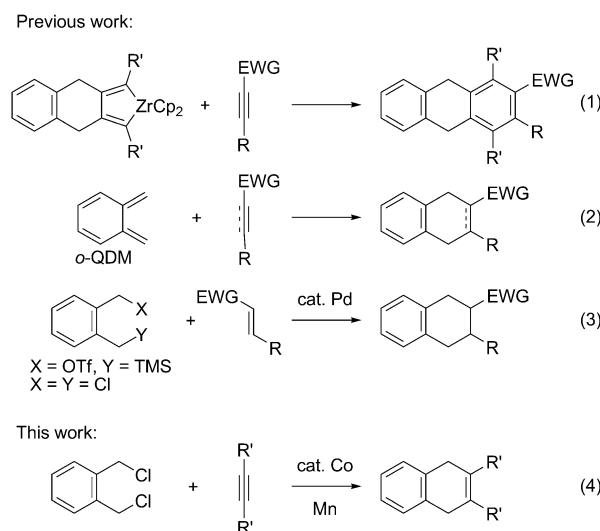
Cobalt-Catalyzed Formal [4+2] Cycloaddition of α,α' -Dichloro-*ortho*-Xylenes with Alkynes**

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Abstract: A formal [4+2] cycloaddition of α,α' -dichloro-*ortho*-xylenes with various alkynes has been developed using a low-valent cobalt catalyst. The transformation has a wide substrate scope and high functional-group tolerance and led to 1,4-dihydronaphthalenes. The formed cycloadducts were easily aromatized with MnO_2 under air. A mechanistic investigation suggests that the transformation proceeds through a benzyl cobaltation of alkyne, not the classical Diels–Alder reaction of *ortho*-quinodimethanes. This methodology provides a straightforward and streamlined access to linearly expanded π -conjugated aromatics.

Organic semiconductors based on linear acenes, such as anthracenes,^[1] tetracenes,^[2] pentacenes,^[3] hexacenes,^[4] and others,^[5] are important materials for organic field-effect transistors (OFETs), often possessing high charge mobilities as a result of their fused planar structure. Despite the prominent role of linear acenes in material chemistry, their synthetic methods have remained unchanged over the past decade. Among them, one of the most attractive protocols for the direct synthesis of acenes is the cycloaddition of zircona-cyclopentadienes, generated from Negishi reagent ($[\text{Cp}_2\text{Zr}]$, Cp = cyclopentadienyl) and α,α' -dialkynyl-*o*-xylenes, with alkynes, affording linear tricycles [Scheme 1, Eq. (1); EWG = electron-withdrawing group, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl].^[6] Although the method enables a straightforward approach to linear acenes from readily available starting materials, the high reactivity of the zirconium reagent limits the functional-group tolerance. In addition, it requires activated alkynes and the stoichiometric organozirconium reagent, which is expensive and sensitive to oxygen and moisture.

On the other hand, the Diels–Alder reaction of *ortho*-quinodimethanes (*o*-QDMs) with alkenes or alkynes is also a powerful and versatile method for the construction of benzene fused with six-membered carbocyclic frameworks, such as tetralines or 1,4-dihydronaphthalenes [Eq. (2)].^[7] In particular, the latter cycloadducts are easily aromatized with



Scheme 1. Comparison of various [4+2] cycloaddition-type reactions of substrates containing carbon–carbon multiple bonds.

a suitable oxidant to construct naphthalenes.^[8] The continuous process would result in a linear expansion of the π -conjugated system.^[9] However, the cycloaddition is often utilized with electronically biased alkenes, and examples with unactivated alkynes have not been reported so far. In contrast, palladium-catalyzed Diels–Alder type reactions of *ortho*-[(trimethylsilyl)methyl]benzyl carbonates^[10] and α,α' -dichloro-*ortho*-xylenes^[11] with activated alkenes were demonstrated by Kuwano and Shige, and Renaud, Bruneau, and Liégault, respectively [Eq. (3)]. However, their protocols need harsh reaction conditions, and are limited to activated alkenes, similar to the reaction with *o*-QDM.

Our group recently developed an efficient cobalt-catalyzed annulation of aryl iodides with alkynes to give multi-substituted naphthalenes. This transformation involves a sequential insertion of two unactivated alkynes to a cobalt–aryl bond generated in situ, followed by a displacement of the aryl C–H bond.^[12] These results obviously indicate a high alkynophilicity of the arylated cobalt species as well as in the Pauson–Khand reaction,^[13] Alder–ene reaction,^[14] and alkyne cyclotrimerization.^[15] The encouraging reactivity of the cobalt species led us to apply the cobalt-catalyzed reaction to more challenging substrates, such as α,α' -halo-*o*-xylenes, to achieve the versatile [4+2] cycloaddition with unactivated alkynes [Eq. (4)].

When α,α' -dichloro-*ortho*-xylene (**1a**) was treated with 1.2 equivalents of 1,4-dimethoxybut-2-yne (**2a**) in the pres-

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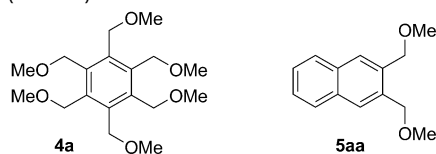
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Table 1: Optimization of reaction conditions.^[a]

Entry	Ligand	Yield [%] ^[b]	3 aa	4 a ^[c]
1	—	66	66	16
2 ^[d]	—	69	69	20
3	PPh ₃	19	19	32
4	P(2-MeC ₆ H ₄) ₃	53	53	22
5	P(2,4,6-Me ₃ C ₆ H ₂) ₃	48	48	25
6	Johnphos ^[e]	38	38	23
7	P(C ₆ F ₅) ₃	64	64	40
8	P[O(2,6- <i>t</i> Bu ₂ C ₆ H ₃)] ₃	54	54	21
9	P(4-CF ₃ C ₆ H ₄) ₃	46	46	6
10 ^[f]	P[3,5-(CF ₃) ₂ C ₆ H ₃] ₃	67	67	7
11 ^[d,f]	P[3,5-(CF ₃) ₂ C ₆ H ₃] ₃	82	82	4

[a] **1a** (1.0 equiv, 0.25 mmol), **2a** (1.2 equiv, 0.30 mmol). [b] Yield determined by GC using *n*-tridecane as an internal standard. [c] Based on **2a**. [d] **2a** (1.5 equiv). [e] 2-(Di-*tert*-butylphosphino)biphenyl. [f] Ligand (5 mol %).



ence of CoBr₂ (10 mol %) and Mn powder (3.0 equiv) in acetonitrile, 2,3-bis(methoxymethyl)-1,4-dihydronaphthalene (**3aa**) was formed in 66 % yield along with the cyclotrimerization product hexa(methoxymethyl)benzene (**4a**) in 16 % yield (Table 1, entry 1).^[16] Use of an excess of the alkyne (1.5 equiv) resulted in an increased yield of **4a** under the conditions (Table 1, entry 2). In the reaction, acetonitrile was a crucial solvent, whereas other solvents, such as toluene, tetrahydrofuran (THF), *N,N*-dimethylformamide (DMF), and *N,N*-dimethylacetamide (DMAc), did not provide the desired product; **1a** was completely consumed while most of alkyne **2a** remained unchanged. No reaction took place in the absence of either the cobalt catalyst or Mn powder. Ligand effects were evaluated next (Table 1, entries 3–10). PPh₃ enhanced the trimerization instead of the cycloaddition (Table 1, entry 3). Bulky phosphine ligands did not improve the yield (Table 1, entries 4–6). Meanwhile, electron-deficient phosphines led to improved yield. Particularly, triarylphosphines possessing trifluoromethyl group(s) depressed the cyclotrimerization (Table 1, entries 7–9). Furthermore, reducing the ligand loading to 5 mol % significantly affected the improvement of the product yield (Table 1, entry 9). Finally, the best result (82 % yield) was obtained by employing a slight excess of **2a** (Table 1, entry 10). A small amount of 2,3-di(methoxymethyl)naphthalene (**5aa**, the aromatized product of **3aa**) was detected by gas chromatography analysis. In a control experiment, exposure of the isolated **3aa** with air or oxygen in acetonitrile did not produce **5aa**. Perhaps, Mn contained traces of MnO₂, which may cause the aromatization

Table 2: Scope of dichlorides **1** in the Co-catalyzed [4+2] cycloaddition with **2a**.^[a]

Entry	Dichloride 1	Products and Yield [%]	3 + 5 ^[b]	ratio (3:5) ^[c]
1		1a	80	51:49
2		1b	73	100:0
3		1c	57	96:4
4		1d	64	0:100
5		1e	64	0:100
6		1f	43	0:100
7		1g	54	0:100
8		1h	29	62:38
9		1i	46	0:100

[a] **1** (1.0 equiv, 0.25 mmol), **2a** (1.5 equiv, 0.38 mmol). [b] Yields of isolated products. [c] Determined by ¹H NMR spectroscopy.

during workup.^[17] Indeed, we confirmed that MnO₂ (5 mol %) induced the aromatization of **3aa** under air at ambient temperature, thus providing **5aa**.

With optimal conditions in hand (Table 1, entry 10), model alkyne (**2a**) was reacted with various substituted dichlorides **1** in order to determine the scope of the cycloaddition (Table 2).^[18] These results were slightly different from Table 1, that is, the aromatized product **5aa** was obtained in 39 % yield along with **3aa** (41 % yield) after standard workup and purification by flash chromatography on silica gel (Table 2, entry 1). The degree of aromatization of **3** strongly depended on the skeleton of the formed 1,4-dihydronaphthalene. For examples, dichlorides bearing methyl and fluoro functions at the *ortho* position, such as **1b** and **1c**, underwent facile cycloaddition to mainly give the corresponding 1,4-dihydronaphthalenes **3ba** and **3ca**, respectively (Table 2, entries 2 and 3). In contrast, *meta* substituents tended to accelerate the aromatization except for the significantly electron-deficient dichloride **1h** (Table 2, entries 4–8). Interestingly, alkynes conjugated to an aryl

Table 3: Scope of alkynes **2** in the Co-catalyzed [4+2] cycloaddition of **1a**.^[a]

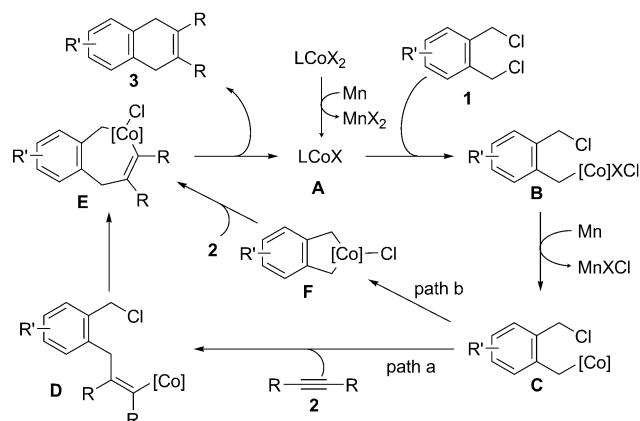
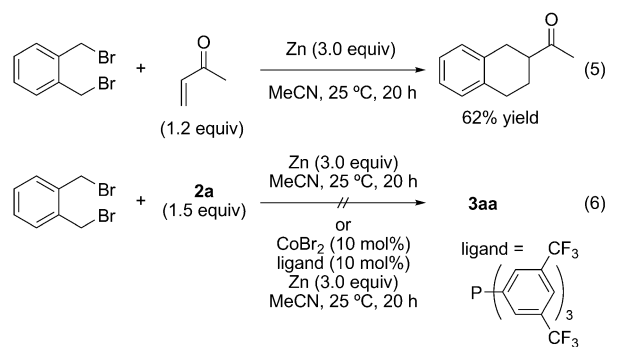
Entry	Alkyne 2		Products and Yield [%] 3 + 5 ^[b]	ratio (3:5) ^[c]
1		2b	88	100:0
2		2c	73	0:100
3		2d	95	97:3
4 ^[d]		2e	39	50:50
5 ^[d]		2f	44	67:33
6		2g	72	96:4

[a] Reaction conditions: **1a** (0.25 mmol), alkyne **2** (0.38 mmol). [b] Yields of isolated products. [c] Determined by ¹H NMR analysis of the crude product. [d] PPh₃ (5 mol %) was used instead of P[3,5-(F₃C)₂C₆H₃]₃.

ring, such as diphenylacetylene and 1-phenylprop-1-yne, did not participate in the cycloaddition. The interesting reactivity of alkynes inspired us to carry out the reaction of **1i** with **2a**. Gratifyingly, the alkyne-selective cycloaddition occurred, yielding **5ai** in 46 % yield (Table 2, entry 9).

Next, we examined the scope of alkynes (Table 3). Similar to **2a**, 1,4-dibenzyloxybut-2-yne (**2b**) participated in the cycloaddition and provided the corresponding dihydronaphthalene **3ab** in high yield (Table 3, entry 1). In the reaction, a propargylic oxygen function was important to drastically enhance the reaction.^[19] Thus, propargyl ethers, even with a phenyl (**2c**) and cyclopropyl group (**2d**) were tolerated, giving rise to the corresponding adducts in good yields (Table 3, entries 2 and 3). In contrast, simple alkynes, such as **2e** and **2f** showed lower reactivity (Table 3, entries 4 and 5).^[20] Additionally, the electron-deficient alkyne **2g** could also be transformed in the reaction (Table 3, entry 6).

To gain an insight into the reaction mechanism, we inspected the possibility of the Diels–Alder reaction with *o*-QDMs. It is known that *o*-QDMs, generated from the reaction of α,α' -dibromo-*ortho*-xylenes with zinc, react with activated olefins to produce tetralin derivatives.^[7b] In fact, the reaction of the dibromide with methyl vinyl ketone (1.2 equiv) in the presence of zinc powder (3.0 equiv) gave the corresponding tetralin in 62 % yield [Eq. (5)]. In contrast, a replacement of the activated olefin with alkyne **2a** did not provide **3aa** in either the presence or absence of the cobalt catalyst [Eq. (6)]. In addition, Mn alone was not sufficient to convert the dichloride **1a** and dibromide to *o*-QDM. These results clearly

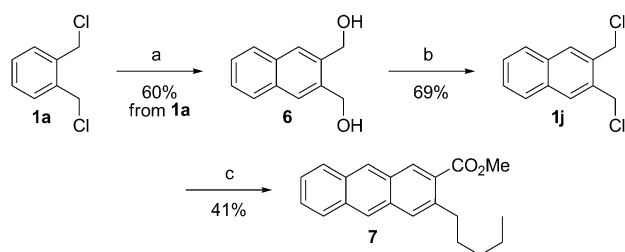


Scheme 2. Plausible reaction mechanism.

indicate that the cobalt-catalyzed reaction did not employ the cycloaddition of *o*-QDM with alkyne.

On the basis of these findings, a proposed mechanism for the cobalt-catalyzed [4+2] cycloaddition is illustrated in Scheme 2. First, active Co^I species **A**, generated from the cobalt salt and Mn powder, adds oxidatively to the benzyl chloride moiety to give a benzyl cobalt intermediate **B**.^[21] Existing Mn would quickly reduce this species to form **C**,^[22] which is a common intermediate for two plausible pathways, paths a and b. Thus, an insertion of the alkyne to **C** gives an alkenyl cobalt species **D**, followed by intramolecular oxidative addition, leading to seven-membered cobaltacycle **E** (path a). In contrast, an intramolecular oxidative addition of **C** provides 2-cobaltaindane **F**, which carries out the insertion of the alkyne to afford the same metallacycle **E** (path b). Finally, reductive elimination of **E** leads to 1,4-dihydronaphthalene and the cobalt catalyst **A**.

Last, the cobalt-catalyzed formal [4+2] cycloaddition was applied as a novel method for a linear expansion of the π -conjugated system (Scheme 3). Treatment of **1a** with 1,4-bis(dimethyl-*tert*-butylsilyloxy)but-2-yne under the present catalytic system afforded the corresponding cycloadducts (**3/5** = 81:19) as a mixture, which were aromatized with MnO₂ and desilylated with TBAF, leading to naphthalene **6** in 60 % yield. Then, a chlorination of **6** with mesyl chloride gave the dichloride **1j** in 69 % yield. Under similar reaction conditions, the dichloride **1j** was reacted with alkyne, and aromatized to give anthracene **7** in 41 % yield.



Scheme 3. Method for linearly expanding π -conjugated aromatics.

a) 1. CoBr_2 (10 mol %), $\text{P}[3,5-(\text{F}_3\text{C})_2\text{C}_6\text{H}_3]_3$ (5 mol %), $\text{TBSOCH}_2\text{CCCH}_2\text{OTBS}$ (1.5 equiv), Mn (3.0 equiv), MeCN , 50°C , 20 h; 2. MnO_2 (2 equiv), benzene, air, 25°C , 3 h; 3. TBAF (3.0 equiv), THF, 2 h. b) MsCl , NEt_3 , CH_2Cl_2 , 25°C , overnight; c) reaction conditions of (a) 1. with $\text{MeO}_2\text{CCCH}_2\text{CCCH}_2\text{OTBS}$ instead of $\text{TBSOCH}_2\text{CCCH}_2\text{OTBS}$; then MnO_2 , benzene, air, 25°C , 4 h. TBS = *tert*-butyldimethylsilyl, TBAF = *t*-trabutylammonium fluoride, Ms = mesyl.

In conclusion, an efficient cobalt-catalyzed formal [4+2] cycloaddition of α,α' -dichloro-*o*-xylenes with unactivated alkynes was described. This methodology provided a streamlined access to benzene-fused bicyclic systems from readily available substrates. The classic [4+2] cycloaddition of *o*-QDM is limited to activated olefins. In contrast, the present cobalt-catalyzed reaction is a more versatile protocol for the synthesis of various benzenes fused with six-membered carbocycles. This reaction may be applied to the synthesis of linear polyaromatic compounds. Further studies concerning other cobalt-catalyzed functionalization of alkynes and synthetic applications of this methodology are in progress and will be reported in due course.

Experimental Section

General procedure for the cobalt-catalyzed formal [4+2] cycloaddition of α,α' -dichloro-*o*-xylenes with alkynes: Anhydrous CoBr_2 (25 μmol) and Mn (0.75 mmol) were placed in a dried, argon-charged 20 mL Schlenk-tube and, after applying a vacuum, heated with a heat-gun (400°C) for 15–30 min, during which the color of cobalt species gradually changed from pale to brilliant green. After cooling the mixture to room temperature, ligand (13 μmol) and acetonitrile (0.5 mL) were sequentially added under argon atmosphere. Alkyne (0.38 mmol) and dichloride (0.25 mmol) was successively added to the mixture. After stirring at 50°C for 20 h, the reaction mixture was cooled and poured into ether and a saturated aqueous solution of NH_4Cl . The aqueous phase was extracted with ether, and the combined ether phases were dried over anhydrous MgSO_4 , filtered, and concentrated to afford the crude product. Purification by column chromatography on silica gel provided the corresponding cycloadduct.

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[1] For A. N. Aleshin, J. Y. Lee, S. W. Chu, J. S. Kim, W. Y. Park, *Appl. Phys. Lett.* **2004**, *84*, 5383.

- [2] R. W. I. De Boer, T. M. Klapwijk, A. F. Morpurgo, *Appl. Phys. Lett.* **2003**, *83*, 4345.
- [3] H. Klauk, M. Halik, U. Zschieschang, G. Schmid, W. Radlik, W. Weber, *J. Appl. Phys.* **2002**, *92*, 5259.
- [4] M. Watanabe, Y. J. Chang, S.-W. Liu, T.-H. Chao, K. Goto, M. M. Islam, C.-H. Yuan, Y.-T. Tao, T. Shinmyozu, T. J. Chow, *Nat. Chem.* **2012**, *4*, 574.
- [5] a) M. M. Payne, S. R. Parkin, J. E. Anthony, *J. Am. Chem. Soc.* **2005**, *127*, 8028; b) D. Chun, Y. Cheng, F. Wudl, *Angew. Chem. Int. Ed.* **2008**, *47*, 8380; *Angew. Chem.* **2008**, *120*, 8508; c) S. S. Zade, M. Bendikov, *Angew. Chem. Int. Ed.* **2010**, *49*, 4012; *Angew. Chem.* **2010**, *122*, 4104; d) J. Xiao, H. M. Duong, Y. Liu, W. Shi, L. Ji, G. Li, S. Li, X.-W. Liu, J. Ma, F. Wudl, Q. Zhang, *Angew. Chem. Int. Ed.* **2012**, *51*, 6094; *Angew. Chem.* **2012**, *124*, 6198.
- [6] a) T. Takahashi, S. Li, W. Huang, F. Kong, K. Nakajima, B. Shen, T. Ohe, K.-I. Kanno, *J. Org. Chem.* **2006**, *71*, 7967; b) T. Takahashi, K. Kashima, S. Li, K. Nakajima, K. Kanno, *J. Am. Chem. Soc.* **2007**, *129*, 125752.
- [7] a) W. Oppolzer, *Synthesis* **1978**, 793; b) J. L. Charlton, M. M. Alauddin, *Tetrahedron* **1987**, *43*, 2873; c) H. Sato, N. Isono, I. Miyoshi, M. Mori, *Tetrahedron* **1996**, *52*, 8143; d) J. L. Segura, N. Martin, *Chem. Rev.* **1999**, *99*, 3199; e) H. Yoshida, M. Mukae, J. Ohshita, *Chem. Commun.* **2010**, *46*, 5253–5255.
- [8] a) E. A. Braude, A. G. Brook, R. P. Linstead, *J. Chem. Soc.* **1954**, 3569; b) E. A. Braude, A. G. Brook, R. P. Linstead, *J. Chem. Soc.* **1954**, 3574; c) P. P. Fu, R. G. Harvey, *Chem. Rev.* **1978**, *78*, 317; d) P. Müller, D. Joly, *Tetrahedron Lett.* **1980**, *21*, 3033; e) G. Georg, H. Albert, *Chem. Ber.* **1991**, *124*, 2623.
- [9] J. L. Morris, C. L. Becker, F. R. Fronczek, W. H. Daly, M. L. McLaughlin, *J. Org. Chem.* **1994**, *59*, 6484.
- [10] R. Kuwano, T. Shige, *J. Am. Chem. Soc.* **2007**, *129*, 3802.
- [11] B. Liégault, J.-L. Renaud, C. Bruneau, *Adv. Synth. Catal.* **2007**, *349*, 841.
- [12] K. Komeyama, T. Kashiwa, K. Takaki, *Tetrahedron Lett.* **2013**, *54*, 5659.
- [13] a) J. Blanco-Urgoiti, L. Añorbe, L. Pérez-Serrano, G. Domínguez, J. Pérez-Castells, *Chem. Soc. Rev.* **2004**, *33*, 32; b) H.-W. Lee, F. Y. Kwong, *Eur. J. Org. Chem.* **2010**, 789.
- [14] a) G. Hilt, *Eur. J. Org. Chem.* **2012**, 4441; b) L. Fiebig, J. Kuttner, G. Hilt, M. C. Schwarzer, G. Frenking, H.-G. Schmalz, M. Schäfer, *J. Org. Chem.* **2013**, *78*, 10485.
- [15] a) G. Hilt, T. Vogler, W. Hess, F. Galbiati, *Chem. Commun.* **2005**, 1474; b) N. Saino, F. Amemiya, E. Tanabe, K. Kase, S. Okamoto, *Org. Lett.* **2006**, *8*, 1439; c) G. Hilt, C. Hengst, W. Hess, *Eur. J. Org. Chem.* **2008**, 2293.
- [16] The reaction mixture was quenched with saturated ammonium chloride solution under air for the GC analysis.
- [17] M. A. Kienzler, S. Suneno, D. Trauner, *J. Am. Chem. Soc.* **2008**, *130*, 8604.
- [18] In all reactions, a small amount of trimer **4a** was detected by GC analysis with complete consumption of the dichlorides.
- [19] T. Sakurada, Y.-K. Sugiyama, S. Okamoto, *J. Org. Chem.* **2013**, *78*, 3583.
- [20] The reaction of **2e** and **2f** with $\text{P}[3,5-(\text{CF}_3)_2\text{C}_6\text{H}_3]_3$ as ligand afforded **3e** + **5e** (34 %, **3e**:**5e** = 55:45) and **3f** + **5f** (18 %, **3f**:**5f** = 65:35).
- [21] a) D. Zhu, P. H. M. Budzelaar, *Organometallics* **2010**, *29*, 5759; b) D. Zhu, I. Thapa, I. Korobkov, S. Gambarotta, P. H. M. Budzelaar, *Inorg. Chem.* **2011**, *50*, 9879; c) D. Zhu, I. Korobkov, P. H. Budzelaar, *Organometallics* **2012**, *31*, 3958.
- [22] a) M. Amatore, C. Gosmini, *Angew. Chem. Int. Ed.* **2008**, *47*, 2089; *Angew. Chem.* **2008**, *120*, 2119; b) A. Moncomble, P. Le Floch, C. Gosmini, *Chem. Eur. J.* **2009**, *15*, 4770; c) A. Moncomble, P. Le Floch, A. Lledos, C. Gosmini, *J. Org. Chem.* **2012**, *77*, 5056.