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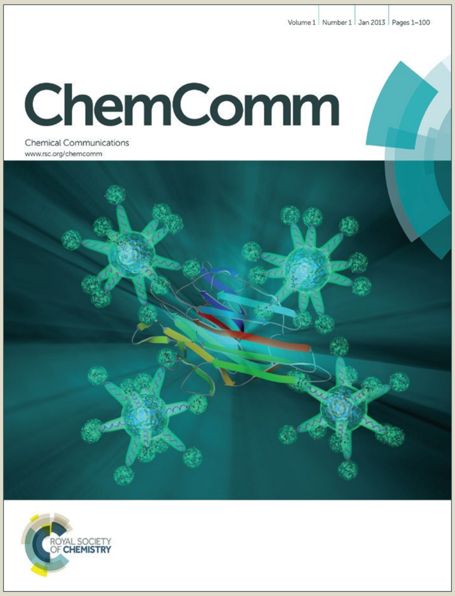

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Maleimides-assisted *Anti*-Markovnikov Wacker-type Oxidation of Vinylarenes Using Molecular Oxygen as a Terminal Oxidant

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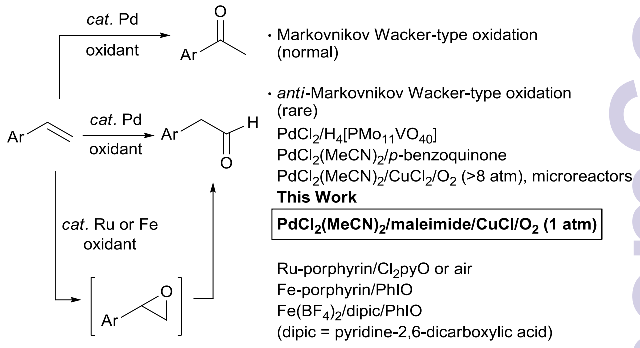
Arylacetaldehydes were successfully synthesized by the *anti*-Markovnikov Wacker-type oxidation of vinylarenes using 1 atm O_2 as a terminal oxidant under mild conditions. Electron-deficient alkenes, such as maleic anhydride and maleimides, were effective additives and would operate as ligands to stabilize the Pd(0) species during the reaction.

Arylacetaldehydes are frequently used as synthetic building blocks for natural products, such as alkaloids[1] and bisabolane sesquiterpenes,[2] and biologically active compounds.[3] Oxidation of vinylarenes using molecular oxygen is a simple and atom-efficient method to synthesize the arylacetaldehydes. Palladium-catalyzed Wacker-type oxidation is a candidate for achieving such a transformation. However, the Wacker-type oxidation of terminal alkenes generally follows Markovnikov's rule to afford methyl ketones, while alkenes with a directing group favor aldehyde formation.[4] Recently, the *anti*-Markovnikov Wacker-type oxidation of unactivated, aliphatic terminal alkenes using a nitrite co-catalyst was also reported.[5] In the case of vinylarenes, although Markovnikov products, *i.e.* acetophenone derivatives, are generally obtained, *anti*-Markovnikov oxidations proceed to afford arylacetaldehydes in some cases.[4a, 6] In the latter reactions, a stoichiometric amount of heteropolyacid[7] or *p*-benzoquinone[8] is required as an oxidant (Scheme 1). One-pot formal *anti*-Markovnikov hydration[9] and hydroamination[10] of vinylarenes were also accomplished by combining the *anti*-Markovnikov oxidation with either transfer hydrogenation or condensation with an amine and subsequent transfer hydrogenation, respectively. With respect to hydroamination, *anti*-Markovnikov oxidative amination was also achieved.[11] An aerobic *anti*-Markovnikov oxidation for the flow-synthesis of arylacetaldehydes was also reported recently. This reaction requires appropriate microreactors and a high oxygen pressure (>8 atm).[12]

On the other hand, ruthenium[13] and iron[14] can also catalyze the oxidation of vinylarenes to arylacetaldehydes. In this case, epoxides are proposed as intermediates (a tandem epoxidation-isomerization pathway), and thus the reaction mechanism is different from that of the Wacker-type oxidation (Scheme 1). These ruthenium and iron-catalyzed oxidations proceed efficiently at room temperature; however, elaborate catalysts such as metal porphyrins,[13, 14b] and/or stoichiometric amounts of the oxidants, 2,6-dichloropyridine *N*-oxide[13b] and iodosylbenzene,[14] are required. Therefore, the development of a simple and efficient catalytic system for the oxidation of vinylarenes, using molecular oxygen, remains challenging.

Recently, we have reported a palladium-catalyzed synthesis of terminal acetals from vinylarenes. This reaction proceeds via a selective *anti*-Markovnikov nucleophilic attack of a bulky diol, *i.e.* pinacol, to the coordinated vinylarenes.[15] In our continuous investigation on the Wacker-type oxidation and related reactions, we discovered the *anti*-Markovnikov oxidation of vinylarenes to arylacetaldehydes. This proceeds using a simple $PdCl_2(MeCN)_2$/maleimide/CuCl catalyst system and molecular oxygen (1 atm) as a terminal oxidant under mild reaction conditions (Scheme 1). Maleimides were found to be key additives in stabilizing the palladium complex during the reaction.



Scheme 1 Transition metal-catalyzed Markovnikov and *anti*-Markovnikov oxidation of vinylarenes to acetophenone derivatives and arylacetaldehydes

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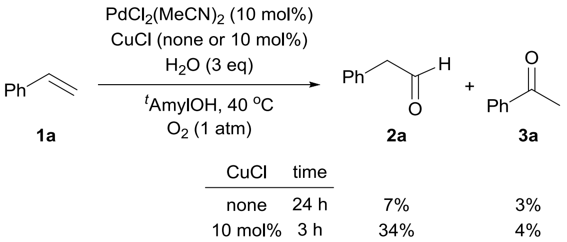
Since bulky alcohols are known to be effective to control the regioselectivity in an *anti*-Markovnikov manner,[8, 15-16] we first attempted the oxidation of styrene (**1a**) using a *t*-AmylOH solvent, which is easier to handle than *t*-BuOH (mp 26 °C) at near room temperature, with a catalytic amount (10 mol%) of PdCl$_2$(MeCN)$_2$ and H$_2$O (3 eq) under 1 atm of O$_2$ at 40 °C (Scheme 2). The reaction proceeded slowly to give phenylacetaldehyde (**2a**) and acetophenone (**3a**) with yields of only 7% and 3%, respectively, after 24 h. The addition of a catalytic amount (10 mol%) of CuCl significantly accelerated the reaction, giving 34% of **2a** after 3 h (Scheme 2). In these reactions, benzaldehyde was also obtained in 10% and 26%, as another by-product. This can be produced by the further oxidation of the formed **2a**. Such aerobic oxidations from **2a** to benzaldehyde, catalyzed by palladium and/or copper complexes, were reported previously.[12, 17]

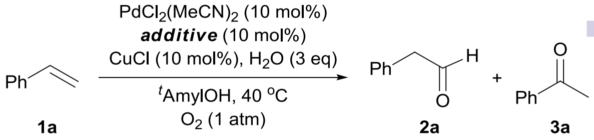


Scheme 2 Effect of CuCl on the *anti*-Markovnikov Wacker-type oxidation of styrene using O$_2$.

In order to further optimize the reaction conditions for the *anti*-Markovnikov Wacker-type oxidation of styrene, effects of a catalytic amount of additives were then examined (Table 1). Initially, *p*-benzoquinone derivatives, which have been used not only as oxidants but also as π-acidic η^2 or η^4 ligands for zerovalent palladium complexes,[18] were tested. Although *p*-benzoquinone was ineffective (entry 2), substituted *p*-benzoquinones gave **2a** in better yields (≤53%) (entries 3–7). Maleic anhydride and maleimides, which are also electron-deficient cyclic alkenes and able to operate as ligands for zerovalent[19] and divalent[20] palladium species, afforded higher yields of **2a** (entries 8–12). Among them, maleimide gave the best results (entry 9). Dimethyl fumarate was also slightly effective (entry 13). Although 2,6-xylylisonitrile was tested as an electron-withdrawing η^1 ligand, the reaction was sluggish and both the yield and aldehyde selectivity were low (entry 14). Several phosphorus and nitrogen ligands were also examined; however, the yields of **2a** were ≤46%, and the aldehyde selectivities were generally low with the exception of P(OPh)$_3$ (entries 15–20). When NEt$_3$ was used, **3a** was obtained as a major product (entry 18). The reversal of regioselectivity by NEt$_3$ has been observed in the aerobic oxidative amination of styrenes reported by Stahl et al.[11]

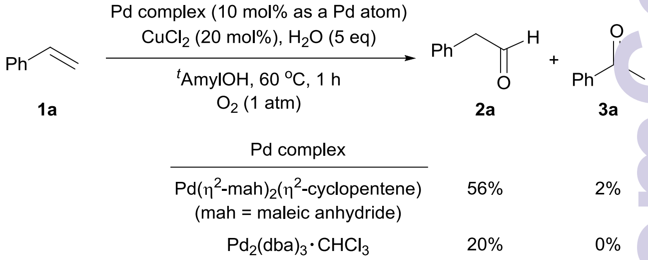
To further examine the effect of additives such as maleic anhydride and maleimides, a Pd(0) complex, Pd(η^2-mah)$_2$(η^2-cyclopentene) (mah = maleic anhydride),[19a] was prepared and used as a catalyst for the *anti*-Markovnikov Wacker-type oxidation (Scheme 3). CuCl$_2$ was employed instead of CuCl as a co-catalyst to oxidize the Pd(0) complex at the beginning of th reaction. As a result, the oxidation proceeded moderately give **2a** and **3a** in 56% and 2% yields after 1 h, respectively. In comparison, another Pd(0) complex, Pd$_2$(dba)$_3$ (dba = dibenzylideneacetone), which is a synthetic precursor of Pd(η -

Table 1 Effects of additives on the *anti*-Markovnikov Wacker-type oxidation of styren using O$_2$[a]



Entry	Additive	Time (h)	Yield (%)[b]	
			2a	3a
1	none	3	34	4
2	BQ[c]	2	29	3
3	2,5-Me$_2$BQ	4	42	3
4	Me$_4$BQ	2	47	14
5	2,5-Ph$_2$BQ	4	53	5
6	2,5-(MeO)$_2$BQ	2	42	8
7	2,6-(MeO)$_2$BQ	2	50	10
8	maleic anhydride	2	56	4
9	maleimide	3	65	12
10	*N*-methylmaleimide	2	58	8
11	*N*-*t*-butylmaleimide	2	55	6
12	*N*-phenylmaleimide	3	60	10
13	dimethyl fumarate	2	45	9
14	2,6-xylylNC	48	13	24
15	P(OMe)$_3$	4	45	17
16	P(OPh)$_3$	4	41	4
17	PPh$_3$	24	0	0
18	NEt$_3$	48	7	46
19	pyridine	3	46	17
20	DMAP[d]	5	34	25

[a] Reaction conditions: **1a** (0.50 mmol), PdCl$_2$(MeCN)$_2$ (0.05 mmol), additiv (0.05 mmol), CuCl (0.05 mmol), H$_2$O (1.5 mmol), *t*-AmylOH (2.0 mL), 40 °C O$_2$ (1 atm), 1–48 h. [b] GC yields. [c] BQ = *p*-benzoquinone. [d] DMAP = -dimethylaminopyridine.



Scheme 3 *Anti*-Markovnikov Wacker-type oxidation of styrene using Pd(0) complexes as catalysts.

mah)$_2$(η^2-cyclopentene) and does not have mah ligands, was also examined as a catalyst. In this case, only 20% yield of **2a** was given, indicating that the mah ligand enhances the catalytic activity.

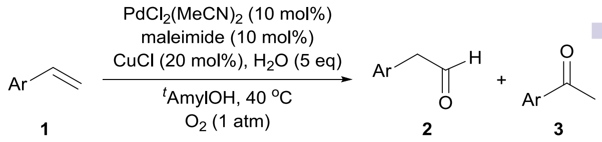
The reaction conditions using maleimide as an additive were further finely optimized (see Table S1), and the optimal conditions were applied to various vinylarenes (Table 2). High aldehyde selectivities were achieved in most cases. *t*-AmylOH appeared to be more appropriate than *t*-BuOH, which is also a popular tertiary alcohol, as a solvent for the present oxidation (entries 1 and 2). Styrenes with methyl, halogen, or strong electron-withdrawing groups gave the corresponding arylacetaldehydes **2** in good to high NMR yields (entries 3–6 and 8–16). Notably, 2-substituted styrenes tended to give higher yields of **2** along with the formation of smaller amounts of benzaldehyde derivatives (entries 3, 6, 10, and 12). Presumably, this occurred because the overoxidations from **2** to the benzaldehyde derivatives were sterically suppressed by the substituents at the 2-positions in these substrates. When highly electron-deficient pentafluorostyrene (**1h**) was used as a substrate, the formation of **3h** and overoxidation from **2h** were both suppressed, although the yield of **2h** was moderate (entry 9). On the other hand, styrene with an electron-donating acetoxy group (**1f**) gave **2f** in a moderate yield (entry 7). In this case the conversion of **1f** was low (80%), whereas in other cases, the conversions of **1** were almost a 100%. Prolonged reaction times, however, did not increase the yield of **2f** because of its competitive overoxidation.

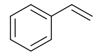
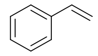
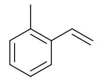
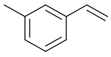
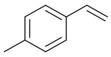
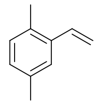
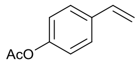
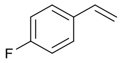
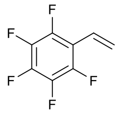
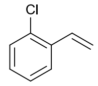
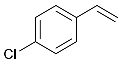
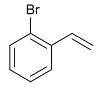
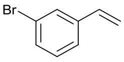
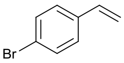
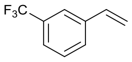
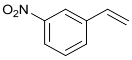
A proposed reaction mechanism for the maleimide-assisted *anti*-Markovnikov oxidation is shown in Scheme 4. Initially, styrene coordinates to palladium in an η^4-manner,[7] and is attacked by *t*-AmylOH at the terminal carbon (*anti*-Markovnikov nucleophilic attack) to give a relatively stable π-benzyl intermediate. The combination of vinylarenes and bulky nucleophiles may lead to *anti*-Markovnikov selectivity.[8-10, 15] After isomerization to a σ-benzyl intermediate, β-hydrogen elimination gives alkenyl ethers and a Pd(0) species along with the release of a proton. The alkenyl ethers are hydrolyzed to **2a**, which is further oxidized to benzaldehyde catalyzed by palladium and/or copper complexes under O_2.[12, 17] The formed Pd(0) species is oxidized by $CuCl_2$ to reproduce L_nPdCl_2. CuCl is then reoxidized to $CuCl_2$ by O_2 and HCl.

According to the results shown in Scheme 3, the role of maleic anhydride and maleimides can be rationalized to operate as a ligand to stabilize the in-situ formed Pd(0) species and prevent the aggregation to Pd black. The fact that, in the present reaction, the catalyst was immediately deactivated at temperatures higher than 60 °C supports the weak coordination of maleic anhydride or maleimides to palladium. Although they are easier to dissociate from Pd(II) than Pd(0) due to weak π-back donation, they possibly keep staying on palladium during the whole catalytic cycle. There are a few examples in which maleic anhydride coordinates to even Pd(II) species.[20]

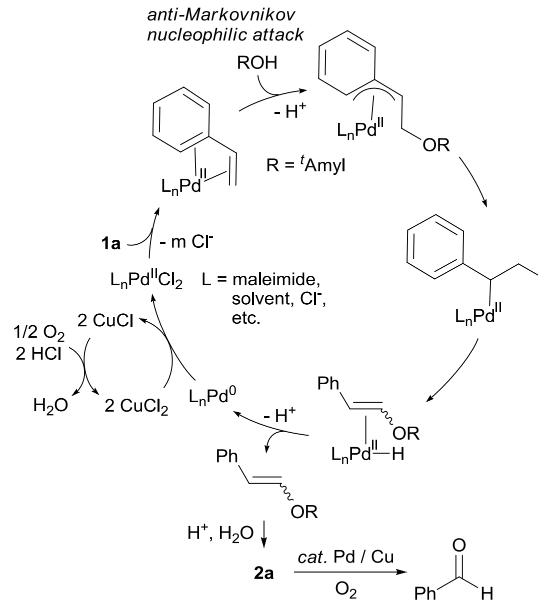
In conclusion, we have developed a palladium-catalyzed *anti*-Markovnikov Wacker-type oxidation of vinylarenes to arylacetaldehydes using 1 atm of O_2. The procedure is simple and the reaction proceeds under mild conditions. The use o maleimide, which would operate as a ligand to stabilize th palladium complex during the reaction, was critical. Furth investigations to increase the catalytic activity and aldehyd selectivity, as well as to suppress the overoxidation are progress.

Table 2 Scope of substrates for the *anti*-Markovnikov Wacker-type oxidation of vinylarenes using O_2[a]



Entry	Vinylarene 1		Time (h)	Yield (%)[b] 2	Yield (%)[b] 3
1		**1a**	3	74 (62)[c]	10
2[d]		**1a**	2	65	11
3		**1b**	2	84 (69)[c]	3
4		**1c**	3	71 (49)[e]	9 (4)[e]
5		**1d**	4	72 (61)[e]	3 (3)[e]
6		**1e**	3	78 (67)	2
7		**1f**	2	57 (56)[f]	3
8		**1g**	2	71 (39)	3
9		**1h**	3	56 (42)	0
10		**1i**	3	84 (77)	2
11		**1j**	2	74 (53)	2
12		**1k**	3	75 (51)	2
13		**1l**	2	70 (45)	4
14		**1m**	2	80 (53)	3
15		**1n**	1	73 (35)	2
16		**1o**	0.8	61 (56)	2

[a] Reaction conditions: **1** (0.50 mmol), $PdCl_2(MeCN)_2$ (0.05 mmol), maleimi (0.05 mmol), CuCl (0.10 mmol), H_2O (2.5 mmol), *t*-AmylOH (5.0 mL), 40 °, O_2 (1 atm), 0.8–4 h. [b] NMR yields. Isolated yields are shown in parenthese. [c] Isolated as 2,4-dinitrophenylhydrazone derivatives. [d] *t*-BuOH was used as a solvent. [e] Isolated as a mixture of **2** and **3** by HPLC. [f] *N*-methylmaleimide used as an additive for isolation.



Scheme 4 Proposed mechanism.

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Notes and references

1 (a) A. Ruiz-Olalla, M. A. Würdemann, M. J. Wanner, S. Ingemann, J. H. van Maarseveen and H. Hiemstra, *J. Org. Chem.*, 2015, **80**, 5125; (b) N. Z. Burns and P. S. Baran, *Angew. Chem., Int. Ed.*, 2008, **47**, 205; (c) C. P. Forbes and G. L. Wenteler, *J. Chem. Soc., Perkin Trans. 1*, 1981, 29.

2 A. Gualandi, P. Canestrari, E. Emer and P. G. Cozzi, *Adv. Synth. Catal.*, 2014, **356**, 528.

3 (a) S. K. Lee and J. K. Park, *J. Org. Chem.*, 2015, **80**, 3723; (b) R. Yan, X. Kang, X. Zhou, X. Li, X. Liu, L. Xiang, Y. Li and G. Huang, *J. Org. Chem.*, 2014, **79**, 465; (c) G. Dagousset, W. Erb, J. Zhu and G. Masson, *Org. Lett.*, 2014, **16**, 2554; (d) C. Zhang, L. Zhang and N. Jiao, *Adv. Synth. Catal.*, 2012, **354**, 1293; (e) J. Pataki, P. Di Raddo and R. G. Harvey, *J. Org. Chem.*, 1989, **54**, 840; (f) E. M. Beccalli, E. Erba, M. L. Gelmi and D. Pocar, *J. Chem. Soc., Perkin Trans. 1*, 1996, 1359.

4 (a) J. Muzart, *Tetrahedron*, 2007, **63**, 7505; (b) J. M. Takacs and X.-t. Jiang, *Curr. Org. Chem.*, 2003, **7**, 369; (c) J. J. Dong, M. Fañanás-Mastral, P. L. Alsters, W. R. Browne and B. L. Feringa, *Angew. Chem., Int. Ed.*, 2013, **52**, 5561; (d) B. W. Michel, L. D. Steffens and M. S. Sigman, in *Organic Reactions*, John Wiley & Sons, Hoboken, 2014, vol. 84, pp. 75; (e) R. Jira, in *Applied Homogeneous Catalysis with Organometallic Compounds*, eds. B. Cornils and W. A. Herrmann, Wiley-VCH, Weinheim, 2nd edn., 2002, vol. 1, pp. 386; (f) S. E. Mann, L. Benhamou and T. D. Sheppard, *Synthesis*, 2015, **47**, 3079.

5 Z. K. Wickens, B. Morandi and R. H. Grubbs, *Angew. Chem., Int. Ed.*, 2013, **52**, 11257.

6 (a) J. Guo and P. Teo, *Dalton Trans.*, 2014, **43**, 6952; (b) J. J. Dong, W. R. Browne and B. L. Feringa, *Angew. Chem., Int. Ed.*, 2015, **54**, 734.

7 J. A. Wright, M. J. Gaunt and J. B. Spencer, *Chem. Eur. J.*, 2006, **12**, 949.

8 P. Teo, Z. K. Wickens, G. Dong and R. H. Grubbs, *Org. Lett.*, 2012, **14**, 3237.

9 G. Dong, P. Teo, Z. K. Wickens and R. H. Grubbs, *Science*, 2011, **333**, 1609.

10 S. M. Bronner and R. H. Grubbs, *Chem. Sci.*, 2014, **5**, 101.

11 (a) V. I. Timokhin, N. R. Anastasi and S. S. Stahl, *J. Am. Chem. Soc.*, 2003, **125**, 12996; (b) V. I. Timokhin and S. S. Stahl, *J. Am. Chem. Soc.*, 2005, **127**, 17888.

12 S. L. Bourne and S. V. Ley, *Adv. Synth. Catal.*, 2013, **355**, 1905.

13 (a) G. Jiang, J. Chen, H.-Y. Thu, J.-S. Huang, N. Zhu and C.-M. Che, *Angew. Chem., Int. Ed.*, 2008, **47**, 6638; (b) J. Chen and C.-M. Che, *Angew. Chem., Int. Ed.*, 2004, **43**, 4950.

14 (a) A. D. Chowdhury, R. Ray and G. K. Lahiri, *Chem. Commun.*, 2012, **48**, 5497; (b) G.-Q. Chen, Z.-J. Xu, C.-Y. Zhou and C.-M. Che, *Chem. Commun.*, 2011, **47**, 10963.

15 M. Yamamoto, S. Nakaoka, Y. Ura and Y. Kataoka, *Chem. Commun.*, 2012, **48**, 1165.

16 (a) B. L. Feringa, *J. Chem. Soc., Chem. Commun.*, 1986, 909; (b) T. Ogura, R. Kamimura, A. Shiga and T. Hosokawa, *Bull. Chem. Soc. Jpn.*, 2005, **78**, 1555.

17 S. J. Jin, P. K. Arora and L. M. Sayre, *J. Org. Chem.*, 1990, **55**, 3011.

18 (a) R. A. Klein, P. Witte, R. van Belzen, J. Fraanje, K. Goubitz, M. Numan, H. Schenk, J. M. Ernsting and C. J. Elsevier, *Eur. J. Inorg. Chem.*, 1998, 319; (b) K. Selvakumar, A. Zapf, A. Spannenberg and M. Beller, *Chem. Eur. J.*, 2002, **8**, 3901; (c) Y. Yamamoto, T. Ohno and K. Itoh, *Organometallics*, 2003, **2**, 2267; (d) L. Canovese, F. Visentin, C. Santo and V. Bertolasi, *J. Organomet. Chem.*, 2014, **749**, 379.

19 (a) K. Itoh, F. Ueda, K. Hirai and Y. Ishii, *Chem. Lett.*, 1977, 877; (b) F. Gómez-de la Torre, F. A. Jalón, A. López-Agenjo, F. R. Manzano, A. Rodríguez, T. Sturm, W. Weissensteiner and M. Martínez-Ripoll, *Organometallics*, 1998, **17**, 4634; (c) K. Selvakumar, M. Valentini, P. S. Pregosin and A. Albinati, *Organometallics*, 1999, **18**, 4591; (d) A. M. Kluwer, C. J. Elsevier, M. Bühl, M. Lutz and A. L. Spek, *Angew. Chem., Int. Ed.*, 2003, **42**, 3501; (e) T. Iwasawa, T. Komano, A. Tajima, M. Tokunaga, Y. Obora, T. Fujihara and Y. Tsuji, *Organometallics*, 2006, **25**, 4665; (f) C. Foltz, M. Enders, S. Bellemin-Laponnaz, H. Wadepohl and L. H. Gade, *Chem. Eur. J.*, 2007, **13**, 599; (g) R. Zalubovskis, A. Bouet, E. Fjellander, S. Constant, D. Linder, A. Fischer, J. Lacour, T. Privalov and C. Moberg, *J. Am. Chem. Soc.*, 2008, **130**, 1845; (h) J.-Y. Lee, P.-Y. Cheng, Y.-H. Tsai, G.-R. Lin, S.-P. Liu, M.-H. Sie and H. M. Lee, *Organometallics*, 2010, **29**, 3901; (i) S. Warsink, I. H. Chang, J. J. Weigand, P. Hauwert, J.-T. Chen and C. J. Elsevier, *Organometallics*, 2010, **29**, 4555; (j) R. Malacea, N. Saffon, M. Gomez and D. Bourissou, *Chem. Commun.*, 2011, **47**, 8163; (k) D. M. Roundhill, *Inorg. Chem.*, 1970, **9**, 254.

20 (a) V. G. Albano, C. Castellari, M. E. Cucciolito, A. Panunzi and A. Vitagliano, *Organometallics*, 1990, **9**, 1269; (b) C. Fernández-Rivas, D. J. Cárdenas, B. Martín-Matute, Á. Monge, E. Gutiérrez-Puebla and A. M. Echavarren, *Organometallics*, 2001, **20**, 2998.