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Catalytic C−H and C−S Bond Activation of Thiophenes

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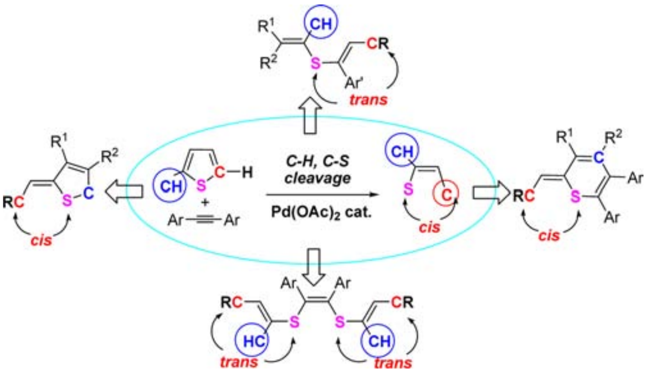
ABSTRACT



A new Pd-catalyzed reaction of thiophenes with alkynes via C−H and C−S bond activation has been developed. This provides a new approach to prepare sulfur-containing compounds. An interesting salt effect was observed, and the reaction's efficiency and selectivity depend not only on the type but also on the amount of the salt used.

Carbon−sulfur bond activation of thiophene is an important reaction in the modern petroleum industry. Considerable attention has been paid to this area, and the representative examples are the insertion of a transition metal into the C−S bond of thiophene-forming related complexes, which provided deeper understanding of the key step in hydrodesulfurization (HDS).[1]

Very recently, we have reported a catalytic method to prepare sulfur-containing heterocycles via C−S bond activation and formation from bromothiophenes.[2] This reaction proceeds with high efficiency and regioselectivity, but the presence of a reactive C−Br bond at the α position is required. An alternative reaction via catalytic C−H activation[3] would provide an atom-economical approach for this reaction. Herein, we report a palladium-catalyzed activation of C−H and C−S bonds of thiophene and their application in the preparation of sulfur-containing compounds.

Inspired by the related α-C−H activation of thiophene,[4] we investigated the palladium-catalyzed reaction between thiophene **1a** and alkyne **2a** through C−H activation and the brief screening of reaction conditions (summarized

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(1) (a) Wang, L. D.; He, W.; Yu, Z. K. *Chem. Soc. Rev.* **2013**, *42*, 599. (b) Chen, J. B.; Angelici, R. J. *Coord. Chem. Rev.* **2000**, *206*, 63. (c) Angelici, R. J. *Organometallics* **2001**, *7*, 1259. (d) Bianchini, C.; Meli, A. *Acc. Chem. Res.* **1998**, *31*, 109. (e) Bianchini, C.; Meli, A. *J. Chem. Soc., Dalton Trans.* **1996**, 801.

(2) Huang, H. N.; Li, J.; Lescop, C.; Duan, Z. *Org. Lett.* **2011**, *13*, 5252.

(3) (a) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788. (b) Schnuerch, M.; Dastbaravardeh, N.; Ghobrial, M.; Mrozek, B.; Mihovilovic, M. D. *Curr. Org. Chem.* **2011**, *15*, 2694. (c) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (d) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (e) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147.

(4) (a) Mitsuda, S.; Fujiwara, T.; Kimigafukuro, K.; Monguchi, D.; Mori, A. *Tetrahedron* **2012**, *68*, 3585. (b) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Org. Chem.* **2012**, *77*, 658. (c) Bugaut, X.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 7479. (d) Tanaka, S.; Tamba, S.; Tanaka, D.; Sugie, A.; Mori, A. *J. Am. Chem. Soc.* **2011**, *133*, 16734. (e) Tamba, S.; Okubo, Y.; Tanaka, S.; Monguchi, D.; Mori, A. *J. Org. Chem.* **2010**, *75*, 6998. (f) Xi, P.; Yang, F.; Qin, S.; Zhao, D.; Lan, J.; Gao, G.; Hu, C.; You, J. *J. Am. Chem. Soc.* **2010**, *132*, 1822. (g) He, C.-Y.; Fan, S.-L.; Zhang, X. *J. Am. Chem. Soc.* **2010**, *132*, 12850. (h) Masuda, N.; Tanba, S.; Sugie, A.; Monguchi, D.; Koumura, N.; Hara, K.; Mori, A. *Org. Lett.* **2009**, *11*, 2297. (i) Mori, A.; Sugie, A. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 548. (j) Takahashi, M.; Masui, K.; Sekiguchi, H.; Kobayashi, N.; Mori, A.; Funahashi, M.; Tamaoki, N. *J. Am. Chem. Soc.* **2006**, *128*, 10930. (k) Kobayashi, K.; Sugie, A.; Takahashi, M.; Masui, K.; Mori, A. *Org. Lett.* **2005**, *7*, 5083. (l) Masui, K.; Ikegami, H.; Mori, A. *J. Am. Chem. Soc.* **2004**, *126*, 5074.

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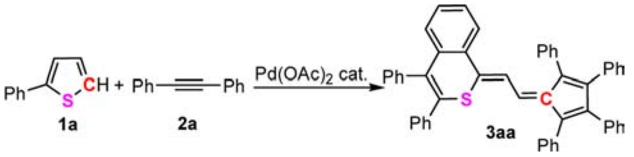
in Table 1). The presence of organic oxidant did not provide any desired product (Table 1, entries 1–2). Similar results were observed with $Mn(OAc)_2$, $CuCl_2$ or $CuBr_2$ (entries 3–5). To our delight, in the presence of $K_2S_2O_8$ (entry 6), **3aa** was isolated in 32% yield. A better result was obtained with $Cu(OAc)_2$ (entry 7, 36%). $Cu(OAc)_2$ was chosen as the oxidant for further optimizations. Solvent is crucial to this reaction. In the presence of $Pd(OAc)_2$ (10 mol %) and $Cu(OAc)_2$ (75 mol %), **3aa** was isolated in ~30% yield when toluene (entry 7), DMF (entry 8) or dioxane (entry 10) was the solvent, while no reaction occurred in DMSO (entry 9). A better result was obtained when the reaction was performed in the mixture of toluene–DMF (64%, entry 12). The yield could be improved to 72% at elevated temperature (entry 14), and the reaction conditions of entry 14 were chosen as optimized conditions for further investigations. Various 2-arylthiophenes **1** and alkynes **2** were investigated, and the results are shown in Table 2. This reaction is compatible with both electron rich (entries 6, 7, 11, 12) and electron deficient (entries 8, 9, 10, 13) arylthiophenes and proceeded smoothly with alkynes through two C–H bonds and one C–S bond activation. The structure of **3ad** was confirmed by X-ray crystal analysis (see SI). The crystal structure shows that one C–S bond of thiophene was cleaved. The carbon fragment was captured by two alkynes and formed the fulvene moiety. The sulfur part was trapped by one alkyne and a neighboring sp^2-carbon through C_{sp^2}–H activation (see SI for proposed mechanism). The carbon and sulfur moieties are cis to each other, which is inconsistent with our previous results.[2] Noticeably, reactions of 2-(*ortho*-substituted aryl)-thiophenes **1h**, **1i** and **1j** with alkyne **2a** also proceeded efficiently to give the corresponding products in good yields (entries 11–13). Interestingly, although

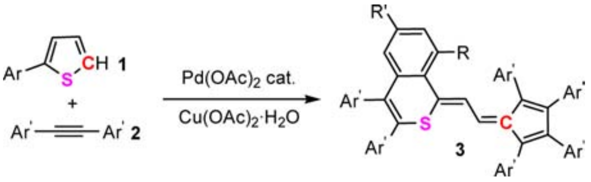
Table 1. Optimization of Reaction Conditions[a]



entry	solvent	oxidant	yield (%)
1	Toluene	$PhI(OAc)_2$	N.R.
2	Toluene	BQ	trace
3	Toluene	$Mn(OAc)_2 \cdot 4H_2O$	trace
4	Toluene	$CuBr_2$	N.R.
5	Toluene	$CuCl_2$	N.R.
6	Toluene	$K_2S_2O_8$	32
7	Toluene	$Cu(OAc)_2 \cdot H_2O$	36
8	DMF	$Cu(OAc)_2 \cdot H_2O$	28
9	DMSO	$Cu(OAc)_2 \cdot H_2O$	N.R.
10	1,4-Dioxane	$Cu(OAc)_2 \cdot H_2O$	30
11	Toluene–DMF(20:1)	$Cu(OAc)_2 \cdot H_2O$	63
12	Toluene–DMF(9:1)	$Cu(OAc)_2 \cdot H_2O$	64
13	Toluene–DMF(5:1)	$Cu(OAc)_2 \cdot H_2O$	48
14[b]	Toluene–DMF(9:1)	$Cu(OAc)_2 \cdot H_2O$	72

[a] Reaction conditions (unless otherwise specified): **1a** (0.5 mmol), **2a** (1.5 mmol), $Pd(OAc)_2$ (10 mol %), $Cu(OAc)_2 \cdot H_2O$ (75 mol %), solvent (5 mL), 120 °C, under air, 24 h. [b] 140 °C

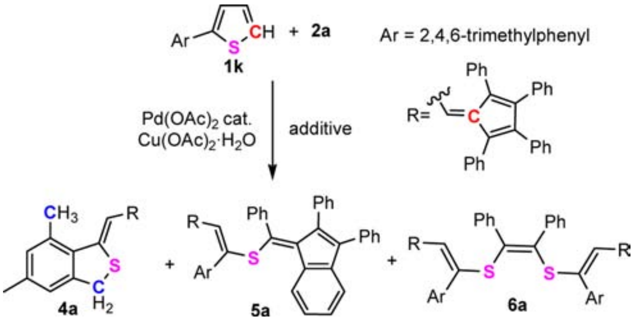
Table 2. Reactions of 2-Arylthiophenes with Alkynes[a]



entry	arylthiophene	alkyne	yield (%)[e]
1	**1a** (Ar = Ph)	**2a** (Ar′ = Ph)	**3aa** (72)
2[b]	**1a**	**2b** (Ar′ = *p*-Me–Ph)	**3ab** (56)
3	**1a**	**2c** (Ar′ = *p*-OMe–Ph)	**3ac** (52)
4	**1a**	**2d** (Ar′ = *p*-F–Ph)	**3ad** (46)
5[c]	**1b** (Ar = 1-Naphthyl)	**2a**	**3ba** (63)
6	**1c** (Ar = *p*-Me–Ph)	**2a**	**3ca** (R′ = Me, 62)
7	**1d** (Ar = *p*-OMe–Ph)	**2a**	**3da** (R′ = OMe, 48)
8	**1e** (Ar = *p*-F–Ph)	**2a**	**3ea** (R′ = F, 69)
9[d]	**1f** (Ar = *p*-CN–Ph)	**2a**	**3fa** (R′ = CN, 30)
10	**1g** (Ar = *p*-Acetyl–Ph)	**2a**	**3ga** (R′ = Acetyl, 45)
11	**1h** (Ar = *o*-Me–Ph)	**2a**	**3ha** (R = Me, 60)
12[c]	**1i** (Ar = *o*-OMe–Ph)	**2a**	**3ia** (R = OMe, 50)
13	**1j** (Ar = *o*-F–Ph)	**2a**	**3ja** (R = F, 61)

[a] Reaction conditions (unless otherwise specified): **1** (0.5 mmol), **2** (1.5 mmol), $Pd(OAc)_2$ (10 mol %), $Cu(OAc)_2 \cdot H_2O$ (75 mol %), Toluene–DMF (5 mL, 9:1), air, 140 °C, 24 h. [b] Toluene–DMF(5 mL,1:1). [c] 1,4-Dioxane–DMF (5 mL, 9:1). [d] Benzoic acid (0.5 mmol) was added. [e] R = R′ = H (unless otherwise specified).

Table 3. Reactions of **1k** with **2a** in the Presence of Additives[a]



entry	additive	product	yield[b]
1	None	**4a**+**5a**	29%(**4a**/**5a** = 3:1)[c]
2	**4a**+**5a** (28 mg)	**4a**+**5a**	24 mg
3	**4a**+**5a** (56 mg)	**4a**+**5a**	48 mg
4	LiCl (25 mol %)	**4a**+**6a**	12%(**4a**) + 5%(**6a**)
5	LiCl (50 mol %)	**4a**+**6a**	21%(**4a**) + 10%(**6a**)
6	LiCl (75 mol %)	**4a**+**6a**	trace (**4a**) + 15%(**6a**)
7	LiCl (100 mol %)	**6a**	trace
8	LiCl (125 mol %)	none	N.R.
9	$NiCl_2$ (25 mol %)	**4a**+**5a**	29%(**4a**/**5a** = 7:1)[b]
10	$NiCl_2$ (50 mol %)	**4a**+**5a**+**6a**	28%(**4a**/**5a** = 20:1)[b] + trace (**6a**)
11	$NiCl_2$ (75 mol %)	**4a**+**6a**	trace

[a] Recation conditions: **1k** (0.5 mmol), **2a** (1.5 mmol), $Pd(OAc)_2$ (10 mol %), $Cu(OAc)_2 \cdot H_2O$ (75 mol %), Toluene-1.4-dioxane(5 mL, v:v = 1:1), 100 °C, 24 h, under air. [b] Isolated yield. [c] Ratio was determined by ^1H NMR.

thiophene **1h** has two types of C−H bonds at ortho positions of the aryl group, only the *ortho*-C_{sp^2}−H bond was activated and product from *ortho*-C_{sp^3}−H activation was not observed. Next, we started to investigate the possibility of forming a C−S bond with a sp^3-carbon through more stable C_{sp^3}−H bond activation.[5]

Our initial studies focused on the use of thiophene **1k**. Under modified conditions (100 °C, toluene-dioxane = 1:1, see SI for the optimizations of reaction conditions), thiophene **1k** reacted smoothly with **2a** and a mixture of two products was isolated (Table 3, entry 1). After careful separations and recrystallizations, the two composites, **4a** and **5a**, were isolated partially from this mixture. The ratio of these two compounds was determined by the ^1H NMR of the crude reaction mixture. As expected, one *ortho*-C_{sp^3}-H bond was activated and provided the desired **4a**. The structure of **5a** was confirmed by X-ray crystal analysis (Figure 1). The formation of **5a** is quite surprising. Until now, only *cis*-carbothiolations of alkynes were observed with our Pd-catalyzed C−S bond activation of thiophenes and the captured fragments are *cis*-fused in the final product,[2] but the crystal structure of **5a** clearly indicated a *trans*-carbothiolation, and the fulvene moiety is located trans to sulfur. Promoted by these expected and unexpected results, we decided to investigate this palladium catalyzed reaction of **1k** with **2a** in depth. After many efforts, the yield of this reaction could not be improved. In order to check the effect of the products on the catalyst, controlled reactions were carried out. When the reaction was carried out in the presence of 28 or 56 mg of the mixture of **4a** and **5a**, 24 or 48 mg of the mixed **4a** and **5a** was isolated (entries 2, 3), respectively. These results indicated that our catalytic system could be deactivated by the formation of products. The research on the relationship between catalyst, **4a** and **5a** is underway in our group. Our attempts to maintain the activity of catalyst by adding different ligands was also unsuccessful (see SI). Then our attentions were shifted to salt effects, which might change the reactivity and/or selectivity of this thiophene activation process. LiCl was chosen as the additive first.[6] In the presence of 25 mol % of LiCl (Table 3, entry 4), besides the major product **4a**, a new product **6a** was isolated, and the formation of **5a** was not observed. The structure of **6a** was determined by X-ray crystal analysis (Figure 2).

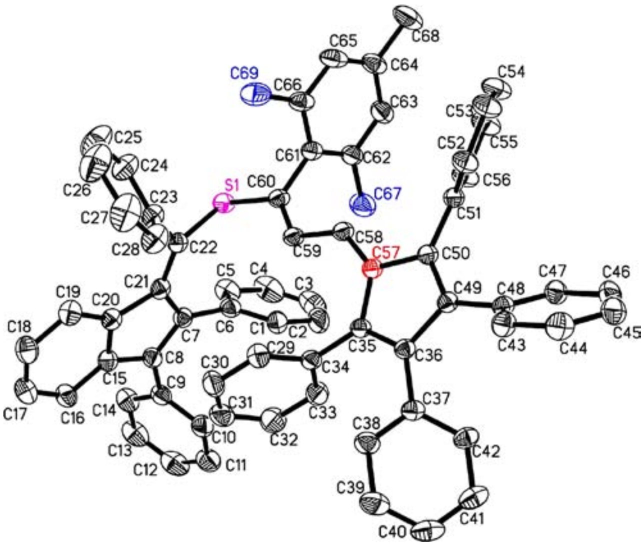


Figure 1. Molecular structure of **5a**.

To our surprise, this 1, 2-diorganothio-substitued alkene **6a** was formed with high stereoselectivity and only *cis*-thiolation product was obtained. It should be mentioned that the fulvene moiety is located trans to sulfur also (Figure 2). When 50 mol % of LiCl was added (Table 3, entry 5), higher yields of **4a** and **6a** were obtained in almost same chemoselectivity as entry 4 and **4a** was the major product. When the amount of LiCl was increased to 75 mol %, the reaction proceeded with higher chemoselectivity, **6a** was obtained as major product, and only trace amount of **4a** was observed (entry 6). However, the activity of catalyst

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(5) (a) Ramirez, T. A.; Zhao, B.; Shi, Y. *Chem. Soc. Rev.* **2012**, *41*, 931. (b) Li, H.; Li, B.-J.; Shi, Z.-J. *Catal. Sci. Technol.* **2011**, *1*, 191. (c) Zhang, S.-Y.; Zhang, F.-M.; Tu, Y.-Q. *Chem. Soc. Rev.* **2011**, *40*, 1937. (d) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082. (e) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242. (f) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094.

(6) Hevia, E.; Mulvey, R. E. *Angew. Chem., Int. Ed.* **2011**, *50*, 6448.

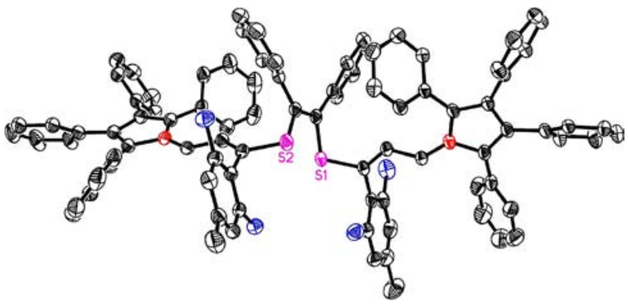
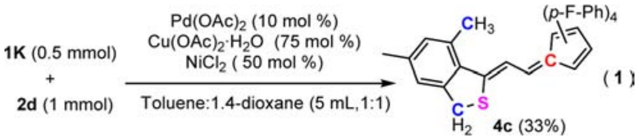


Figure 2. Molecular structure of **6a**.

was suppressed with overloaded LiCl (entries 7, 8). Since there are several reports on the formations *cis*-1,2-diorganothio-substitued alkenes with Ni catalyzed reactions between sulfur containing compounds and alkynes,[7] $NiCl_2$ was examined as additive. It was observed that the presence of 25 or 50 mol % of $NiCl_2$ was not useful for the formation of **6a**. To our delight, without altering the efficiency, the presence of $NiCl_2$ can improve the chemoselective formation of **4a** dramatically and the ratio of **4a**:**5a** was increased from 3:1 (entry 1) to 7:1 (entry 9) and 20:1 (entry 10), respectively.

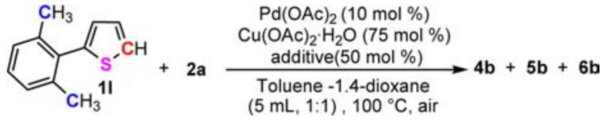
Similarly, when thiophene **1l** was used, a mixture of **4b** and **5b**, in a molar ratio of 4:1 was isolated in a total 31% yield (Table 4, entry 1). In the presence of 50 mol % of LiCl, **4b** and **6b** were isolated in 15 and 20% yields, respectively, while the formation of **5b** was not observed (entry 2). When $NiCl_2$ was added (entry 3), **4b** was isolated in 28% yield, with trace amount of **6b**.

In the presence of $NiCl_2$ (50 mol %), only **4c** was formed in 33% yield from the reaction of thiophene **1k** with alkyne **2d** (eq 1). The structure of **4c** was examined via X-ray crystallography. As expected, a new *ortho*-C_{sp^3}−S bond was formed (Figure 3).



From these results, it can be seen that: (a) the chemoselective formation of C_{sp^3}−S type product **4** can be achieved with the presence of right amount of $NiCl_2$ through C−S and C_{sp^3}−H bond activation; (b) the presence of suitable amount of LiCl will favor the formation of *cis*-diorganothio-substitued alkene **6**, and an unexpected cis-to-trans isomerization of the cleaved carbon and sulfur fragment was observed also; (c) overloaded additive will reduce the reaction's efficiency; (d) the selective formation of **5** is still a challenge. The reaction mechanism is proposed in the Supporting Information.

Table 4. Reactions of **1l** with **2a**[a]



entry	additive	product	isolated yield (%)
1	None	**4b**+**5b**	**4b**/**5b** (31, 4:1[b])
2	LiCl	**4b**+**6b**	**4b**(15) + **6b**(20)
3	$NiCl_2$	**4b**+**6b**	**4b**(28) + **6b**(trace)

[a] Reaction conditions: **1l** (0.5 mmol), **2a** (1.5 mmol). [b] Ratio was determined by ^{1}H NMR.

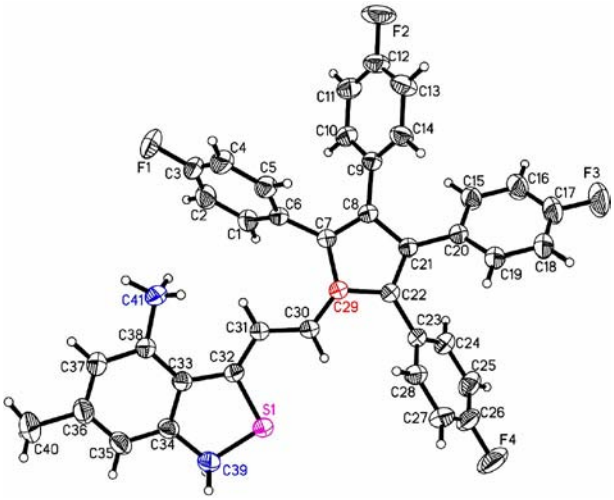


Figure 3. Molecular structure of **4c**.

In summary, we have found a new palladium catalyzed reaction of simple thiophenes with alkynes through a domino type C−H and C−S bond activation. Compared with our previous results, no reactive α-C−Br bond is needed. During the research with C_{sp^3}−H bond activation, an interesting salt effect was observed. The reaction's efficiency and selectivity depend not only on the type but also the amount of the salt used. Further investigation on the scope and the mechanism of this reaction is in progress.

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Supporting Information Available. Experimental procedures, characterization data of compounds, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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[7] (a) Inami, T.; Baba, Y.; Kurahashi, T.; Matsubara, S. *Org. Lett.* **2011**, *13*, 1912. (b) Ananikov, V. P.; Gayduk, K. A.; Orlov, N. V.; Beletskaya, I. P.; Khrustalev, V. N.; Antipin, M. Y. *Chem.—Eur. J.* **2010**, *16*, 2063. (c) Ananikov, V. P.; Gayduk, K. A.; Starikova, Z. A.; Beletskaya, I. P. *Organometallics* **2010**, *29*, 5098.

The authors declare no competing financial interest.