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Air-tolerant C–C bond formation via organometallic ruthenium catalysis: diverse catalytic pathways involving (C_5Me_5)Ru or (C_5H_5)Ru are robust to molecular oxygen

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ABSTRACT

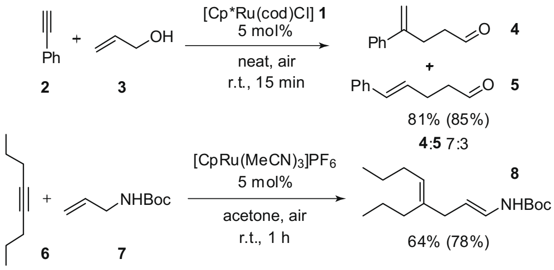
Ruthenium-catalyzed substitutions of carbon pronucleophiles, various [2+2+2] cycloadditions, and addition of a diazo compound to an alkyne are shown to proceed in the presence of air. Notably diverse catalytic manifolds remain supported under conditions generally regarded as prohibitive. Building on rare reports from the literature we show that a range of organometallic transformations based on reaction intermediates derived from (C_5Me_5)Ru or (C_5H_5)Ru moieties are air-compatible.

Ruthenium organometallic catalysis has emerged as an important method for forming various types of bonds in organic synthesis.[1] The majority of these reactions, and indeed the majority of all reactions involving organometallic catalysis, are described under the strict exclusion of air. In this context, the search for oxygen-tolerant reactions catalyzed by organometallics has emerged as a new challenge at the forefront of synthetic chemistry.[2] Although, air-tolerant ruthenium-catalyzed carbon-heteroatom bond formations are known,[3] C-C bond formation catalyzed by molecular ruthenium complexes in the presence of dioxygen has, until very recently, remained generally unrecognized.[4]

Trost's ruthenium-catalyzed alkene-alkyne coupling was one of the first examples of an air-tolerant C–C bond formation via ruthenium organometallic catalysis.[4a] In spite of the fact that the authors point to the oxygen tolerance of their benchmark Alder-ene-type transformations, such reactions are invariably run under an inert atmosphere.[1e,5] As there was no yield reported for the open-flask set-up, we decided to test the efficiency of this simplified procedure. Interestingly, the yields of two representative alkene-alkyne couplings performed in the presence of air with no effort taken to exclude moisture compared very well with the results obtained using traditional air-free conditions (Scheme 1).[5c,5e]

Based on this initial study we speculated that other reactions proceeding via ruthenacyclic intermediates might be air tolerant. Furthermore, catalytic manifolds involving ruthenacyclic intermediates[1e,7] offer a varied set of known C–C bond forming reactions as a testing ground for our investigation of air-compatibility.

Recently, Fokin and co-workers reported that ruthenium-catalyzed azide-alkyne cycloaddition (RuAAC)[3b] is considerably air tolerant. Although RuAAC[8] is not a C–C bond forming process, a putative mechanistic analogy[3b,8a] between RuAAC and ruthenium-catalyzed [2+2+2] cycloadditions[9] led us to investigate the feasibility of a model [2+2+2] cycloaddition[10] under aerobic conditions.



Scheme 1. Alkene–alkyne couplings in air.[6] The yields in parentheses are literature yields[5c,e] for reactions run with exclusion of air. Cp* = pentamethylcyclopentadienyl, Cp = cyclopentadienyl, cod = 1,5-cyclooctadiene.

Initially, we attempted a [2+2+2] intermolecular cycloaddition of dimethyl acetylenedicarboxylate (**9**) using catalyst **1** (1 mol%) in reagent grade 1,2-dichloroethane (DCE) under an atmosphere of air (Scheme 2). The starting material was consumed within 1 h and hexamethylmellitate (**10**) was isolated in 85% yield (cf. 88% yield of **10** under anhydrous conditions and an atmosphere of argon[9a]).

A series of [2+2+2] cycloadditions leading to benzene derivatives **12**,[9a] **15**,[9a] **17**,[9a] **18**[9c] and **20**,[9d] (Schemes 2 and 3) and pyridines **22**[9e] and **23**[9e] (Scheme 4), also exhibited excellent tolerance to air as was evident by comparison with results previously obtained with exclusion of air.[9] This is in line with the working

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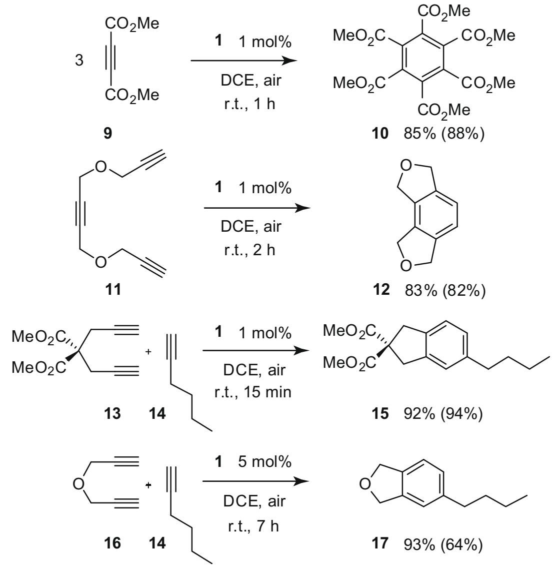
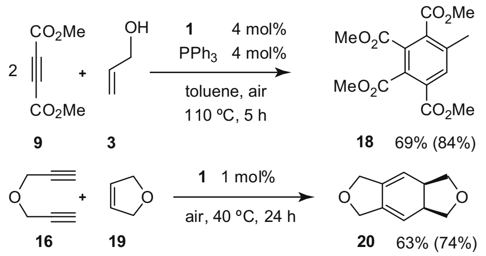
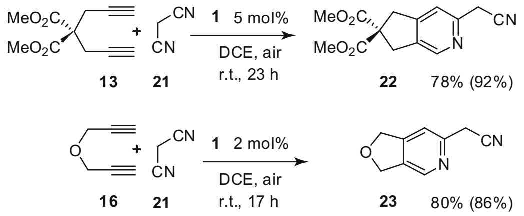


Scheme 2. [2+2+2] Cycloadditions of alkynes in air.[6] The yields in parentheses are literature yields[9a] for reactions run in anhydrous solvents with exclusion of air.



Scheme 3. [2+2+2] Alkene–alkyne cycloadditions in air.[6] The yields in parentheses are literature yields[9c,d] for reactions run with exclusion of air.

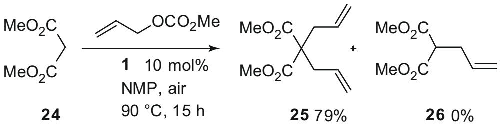


Scheme 4. [2+2+2] Diyne-nitrile cycloadditions in air.[6] The yields in parentheses are literature yields[9e] for reactions run in anhydrous solvents with exclusion of air.

hypothesis that ruthenacyclic intermediates derived from a Cp*Ru fragment are endowed with significant air-stability throughout the reaction pathway.[11]

Recently, Streu and Meggers reported that the catalyst [Cp*Ru(cod)Cl] (**1**) displayed excellent catalytic properties in the deprotection of amines from the corresponding allylcarbamates leading to *S*-allylation under open-flask conditions, and notably, even in living mammalian cells.[3a]

Our previous results indicated that it might be possible to extend this process to a straightforward open-flask C–C bond forming allylation protocol.[12] To this end, we investigated a known C-allylation reaction based on catalyst **1** developed by Yamamoto et al.[13]

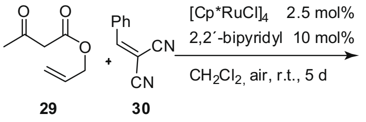


(1)

Indeed, when no precaution was taken to exclude air, the reaction of dimethyl malonate **24** with allyl methyl carbonate (3 equiv) catalyzed by **1** (10 mol %) in reagent grade *N*-methylpiperidine (NMP) at 90 °C was found to proceed smoothly (Eq. 1).[6] Thus, after 15 h, the starting material was consumed and diallylated malonate **25** was isolated as a single product in 79% yield (cf. 83% yield under anhydrous conditions and an argon atmosphere[13]).

We next decided to examine the catalytic activity of several ruthenium complexes in the reaction of malonate **27** with allyl methyl carbonate in the presence of air (Table 1). Among the catalysts investigated, Ru(II) and Ru(III) catalysts with the ligands Cp* or Cp generally performed well (68–98% yields, entries 1–7). Conversely, [$(PPh_3)_4RuH_2$] and [Ru(cod)(η^6-C_8H_{10})] which are reported to catalyze the allylation of pronucleophiles with allyl carbonates in basic media,[12c,d] failed to effect the desired reaction in the presence of air (entries 9 and 10).

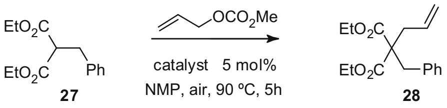
Recently, Wang and Tunge developed a regioselective base-free decarboxylative insertion of electrophiles catalyzed by [Cp*Ru(bipyridyl)Cl] generated in situ from [$Cp^*RuCl]_4$ and 2,2′-bipyridyl.[14] We found that this transformation (Eq. 2) also tolerates air, giving the insertion product **31** in a respectable 65% yield, albeit after a prolonged five-day reaction time[6] (cf. 84% yield of **31** after 2 h under anhydrous conditions with exclusion of air[14]).



(2)

Next we turned to a reaction believed to take place via a carbene mechanism, as originally described by Dixneuf and co-workers.[15] We aimed to test an additional and considerably distinct group of Cp*Ru catalytic species for oxygen-tolerance. It was found, that the synthesis of diene derivative **34** by reaction of but-2-yn-1-ol (**32**) and (trimethylsilyl)diazomethane (**33**) catalyzed by **1** (Eq. 3), proceeded well under aerobic conditions[6] (82% yield of **34**, cf. 95% yield of **34** under anhydrous conditions with exclusion of air[15]).

Table 1
Air-tolerant allylation of carbon pronucleophile **27**[a]



Entry	Catalyst	Yield (%)[b]
1	**1**	72
2	[$Cp^*RuCl(PPh_3)_2$]	98[c]
3	[$CpRuCl(PPh_3)_2$]	96
4	[$Cp^*Ru(MeCN)_3]PF_6$	96[c]
5	[$CpRu(MeCN)_3]PF_6$	89
6	[$Cp^*RuCl]_4$	82
7	[$Cp^*RuCl_2]_n$	68
8	[$(C_9H_7)RuCl(PPh_3)_2$]	13[d,e]
9	[$(PPh_3)_4RuH_2$]	0[f,g]
10	[Ru(cod)(η^6-C_8H_{10})]	0[h,i]

[a] Reaction conditions: **27** (0.3 mmol), allyl methyl carbonate (0.6 mmol), catalyst (0.015 mmol), NMP (1 mL), sealed tube, 90 °C, 5 h.

[b] Yield of isolated product (average of two runs).

[c] Isolated yield after 1 h.

[d] 24 h.

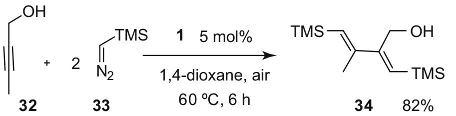
[e] 27% yield of **28** under argon, 24 h.

[f] 8 h.

[g] 25% yield of **28** under argon, 8 h.

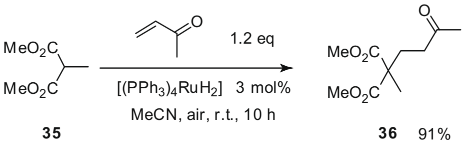
[h] 24 h.

[i] 26% yield of **28** under argon, 24 h. C_9H_7 = indenyl, C_8H_{10} = 1,3,5-cyclooctatriene.



(3)

We then focused on C–C bond forming air-tolerant ruthenium catalysis devoid of Cp* and Cp ligands. It has been shown by the groups of Murahashi et al.[16a] and Echavarren and co-workers[16b] that carbon pronucleophiles can be activated at room temperature by [$(PPh_3)_4RuH_2$] in MeCN. We observed that the Michael-type addition leading to substituted malonate **36** was compatible with the straightforward set-up of an open-flask experiment[6] (Eq. 4, 91% yield of **36**, cf. 96% yield of **36** under anhydrous conditions with exclusion of air[16b]). This transformation is postulated to proceed via a Ru(0) species,[16] and therefore the air-compatibility came rather unexpectedly as both [$(PPh_3)_4RuH_2$] and the Ru(0) catalyst [Ru(cod)(η^6-C_8H_{10})] failed in our allylation study (Table 1, entries 9 and 10).



(4)

In summary, drawing inspiration from mechanistic analogies we found that air tolerance of transformations catalyzed by ruthenium organometallics is not restricted to the rare appearances in the literature. Notably diverse catalytic manifolds, mainly those involving Cp*Ru and CpRu fragments, remain supported under conditions generally regarded as prohibitive. Indeed, we recently took advantage of this air tolerance for the synthesis of the novel helicene-viologen hybrid (helquat).[17] Our study indicates that catalytic pathways based on Cp*Ru-derived species are potentially good candidates for the unveiling of robust, air-tolerant processes which will be of practical interest for organic chemistry.

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Supplementary data

Supplementary data (detailed experimental procedures and characterization data for all products) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.05.079.

References and notes

1. (a) Hoveyda, A. H.; Zhugralin, A. R. *Nature* **2007**, *450*, 243; (b) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, 2003; (c) *Topics in Organometallic Chemistry*; Fürstner, A., Ed.; Springer: Berlin, Heidelberg, 1998; Vol. 1, (d) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490; (e) Trost, B. M.; Frederiksen, M. U.; Rudd, M. T. *Angew. Chem., Int. Ed.* **2005**, *44*, 6630; (f) *Ruthenium Catalysts and Fine Chemistry*; Bruneau, C., Dixneuf, P. H., Eds.; Springer: Berlin, 2004; (g) *Ruthenium in Organic Synthesis*; Murahashi, S.-I., Ed.; Wiley-VCH: Weinheim, 2004.
2. Although there is no detailed review focused on air-tolerant organometallic transformations, examples can be found in: (a) Li, C.-J. *Acc. Chem. Res.* **2002**, *35*, 533; (b) Sherry, B. D.; Toste, F. D. *ChemTracts Org. Chem.* **2005**, *18*, 14; (c) Li, C.-J. In *Organic Reactions in Water*; Lindström, U. M., Ed.; Blackwell Publishing, 2007; (d) *Aqueous-Phase Organometallic Catalysis: Concepts and Applications*; Cornils, B., Herrmann, W. A., Eds., 2nd ed.; Wiley-VCH: Weinheim, 2004; (e) Li, C.-J.; Chan, T.-H. *Comprehensive Organic Reactions in Aqueous Media*; Wiley: Hoboken, 2007; (f) Li, C.-J. *Chem. Rev.* **2005**, *102*, 3095; (g) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596; (h) Link, A. J.; Tirrell, D. A. *J. Am. Chem. Soc.* **2003**, *125*, 11164; (i) Lipshutz, B. H.; Ghorai, S. *Aldrichimica Acta* **2008**, *41*, 59; (j) Villalobos, J. M.; Srogl, J.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2007**, *129*, 15734.
3. (a) Streu, C.; Meggers, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 5645; (b) Boren, B. C.; Narayan, S.; Rasmussen, L. K.; Zhang, L.; Zhao, H.; Lin, Z.; Jia, G.; Fokin, V. V. *J. Am. Chem. Soc.* **2008**, *130*, 8923; (c) Li, C.-J.; Wand, D.; Chen, D. *J. Am. Chem. Soc.* **1995**, *117*, 12867; (d) Li, C.-J. In *Ruthenium Catalysts and Fine Chemistry*; Bruneau, C., Dixneuf, P. H., Eds.; Topics in Organometallic Chemistry; Springer: Berlin, 2004; Vol. 11, p 321; e see also 1g.
4. For a note on oxygen-tolerance of ruthenium-catalyzed alkene-alkyne coupling, see: (a) Trost, B. M.; Pinkerton, A. B.; Toste, F. D.; Sperrle, M. *J. Am. Chem. Soc.* **2001**, *123*, 12504; For accounts on air-tolerant alkene metathesis, see: (b) Lin, Y. A.; Chalker, J. M.; Floyd, N.; Bernardes, G. J.; Davis, B. G. *J. Am. Chem. Soc.* **2008**, *130*, 9642; (c) Binder, J. B.; Blank, J. J.; Raines, R. T. *Org. Lett.* **2007**, *9*, 4885; (d) Lipshutz, B. H.; Ghorai, S.; Aguinaldo, G. T. *Adv. Synth. Catal.* **2008**, *350*, 953; (e) Foltynowicz, Z.; Pietraszuk, C.; Marciniec, B. *Appl. Organomet. Chem.* **1993**, *7*, 539. For ruthenium-catalyzed oxidative coupling of alkenes with arenes, see:; (f) Weissman, H.; Song, X.; Milstein, D. *J. Am. Chem. Soc.* **2001**, *123*, 337; For ruthenium-catalyzed oxidative coupling of phenols leading to biaryls in the presence of molecular oxygen, see: (g) Irie, R.; Masutani, K.; Katsuki, T. *Synlett* **2000**, 1433; (h) Yadav, J. S.; Reddy, B. V. S.; Gayathri, K. U.; Prasad, A. R. *New J. Chem.* **2003**, *27*, 1684; (i) Matsushita, M.; Kamata, K.; Yamaguchi, K.; Mizuno, N. *J. Am. Chem. Soc.* **2005**, *127*, 6632.
5. (a) Trost, B. M.; Indolese, A. F.; Müller, T. J. J.; Treptow, B. *J. Am. Chem. Soc.* **1995**, *117*, 615; (b) Trost, B. M.; Indolese, A. F. *J. Am. Chem. Soc.* **1993**, *115*, 4361; (c) Dérien, S.; Jan, D.; Dixneuf, P. H. *Tetrahedron* **1996**, *52*, 5511; (d) Trost, B. M.; Toste, F. D. *Tetrahedron Lett.* **1999**, *40*, 7739; (e) Trost, B. M.; Surivet, J. P. *Angew. Chem., Int. Ed.* **2001**, *40*, 1468.
6. See Supplementary data for experimental details.
7. For reviews, see: (a) Yamamoto, Y.; Itoh, K. In *Ruthenium in Organic Synthesis*; Murahashi, S.-I., Ed.; Wiley-VCH: Weinheim, 2004; p 95; (b) Dérien, S.; Monnier, F.; Dixneuf, P. H. Ruthenium Catalysts and Fine Chemistry. In *Topics in Organometallic Chemistry*; Bruneau, C., Dixneuf, P. H., Eds.; Springer: Berlin, 2004; Vol. 11, p 1; For an overview of the versatility of the [Cp*Ru(cod)Cl] catalyst, see: (c) Dérien, S.; Dixneuf, P. H. *J. Organomet. Chem.* **2004**, *689*, 1382.
8. (a) Zhang, L.; Chen, X. G.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005**, *127*, 15998; (b) Rasmussen, L. K.; Boren, B. C.; Fokin, V. V. *Org. Lett.* **2007**, *9*, 5337; (c) Majireck, M. M.; Weinreb, S. M. *J. Org. Chem.* **2006**, *71*, 8680.
9. (a) Yamamoto, Y.; Arakawa, T.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2003**, *125*, 12143; (b) Yamamoto, Y.; Ogawa, R.; Itoh, K. *Chem. Commun.* **2000**, 549; (c) Kondo, T.; Kaneko, Y.; Tsunawaki, F.; Okada, T.; Shiotsuki, M.; Morisaki, Y.; Mitsudo, T. *Organometallics* **2002**, *21*, 4564; (d) Yamamoto, Y.; Kitahara, H.; Ogawa, R.; Kawaguchi, H.; Tatsumi, K.; Itoh, K. *J. Am. Chem. Soc.* **2000**, *122*, 4310; (e) Yamamoto, Y.; Kinpara, K.; Ogawa, R.; Nishiyama, H.; Itoh, K. *Chem. Eur. J.* **2006**, *12*, 5618.
10. For leading references on metal-catalyzed [2+2+2] cycloadditions, see: (a) Vollhardt, K. P. C. *Acc. Chem. Res.* **1977**, *10*, 1; (b) Schore, N. E.. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1992; Vol. 5, p 1129; (c) Kotha, S.; Brahmachary, E.; Lahiri, K. *Eur. J. Org. Chem.* **2005**, 4741. and references cited therein; For rare examples of [2+2+2] cycloaddition in the presence of O_2, see: (d) Yokota, T.; Sakurai, Y.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **1997**, *38*, 3923; (e) Ardizzoia, G. A.; Brenna, S.; LaMonica, G.; Maspero, A.; Masciocchi, N. *J. Organomet. Chem.* **2002**, *649*, 173.
11. We note that processes **16**+**14**→**17** and **16**+**21**→**23** in DCE are not stopped in the presence of strongly acidic or basic environments (i.e., 34 mM TFA, and 17 mM DBU, respectively).
12. For C–C bond formation via π-allylruthenium intermediates, see: (a) Kondo, T.; Mitsudo, T. In *Ruthenium in Organic Synthesis*; Murahashi, S.-I., Ed.; Wiley-VCH: Weinheim, 2004; p 129; (b) Bruneau, C.; Renaud, J. L.; Demerseman, B. *Chem. Eur. J.* **2006**, *12*, 5178; For seminal work on ruthenium-catalyzed allylations, see: (c) Minami, I.; Shimizu, I.; Tsuji, J. *J. Organomet. Chem.* **1985**, *296*, 269; (d) Zhang, S.-W.; Mitsudo, T.; Kondo, T.; Watanabe, Y. *J. Organomet. Chem.* **1993**, *450*, 197; (e) Trost, B. M.; Fraisse, P. L.; Ball, Z. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1059; For recent examples of air-stable CpRu catalysts for Carroll rearrangements, see: (f) Constant, S.; Tortoioli, S.; Müller, J.; Lindner, D.; Buron, F.; Lacour, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 8979.
13. Yamamoto, Y.; Nakagai, Y.; Itoh, K. *Chem. Eur. J.* **2004**, *10*, 231.
14. Wang, C.; Tunge, J. A. *Org. Lett.* **2005**, *7*, 2137.
15. (a) Le Paih, J.; Dérien, S.; Özdemir, I.; Dixneuf, P. H. *J. Am. Chem. Soc.* **2000**, *122*, 7400; For a related process in the presence of water under an inert atmosphere, see: (b) Monnier, F.; Vovard-Le Bray, C.; Castillo, D.; Aubert, V.; Dérien, S.; Dixneuf, P. H.; Toupet, L.; Lenco, A.; Mealli, C. *J. Am. Chem. Soc.* **2007**, *129*, 6037.
16. (a) Murahashi, S.-I.; Naota, T.; Taki, H.; Mizuno, M.; Takaya, H.; Komiya, S.; Mizuho, Y.; Oyasato, N.; Hiraoka, M.; Hirano, M.; Fukuoka, A. *J. Am. Chem. Soc.* **1995**, *117*, 12436; (b) Gómez-Bengoa, E.; Cuerva, J. M.; Mateo, C.; Echavarren, A. M. *J. Am. Chem. Soc.* **1996**, *118*, 8553; c of note is the discussion of air stability relating to isolated ruthenium complexes in 16a.
17. Adriaenssens, L.; Severa, L.; Šálová, T.; Císařová, I.; Pohl, R.; Šaman, D.; Rocha, S. V.; Finney, N. S.; Pospíšil, L.; Slavíček, P.; Teplý, F. *Chem. Eur. J.* **2009**, *15*, 1072.