Ruthenium Pincer Complexes Hot Paper

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Direct Catalytic Olefination of Alcohols with Sulfones**

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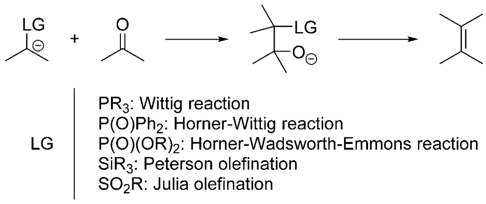
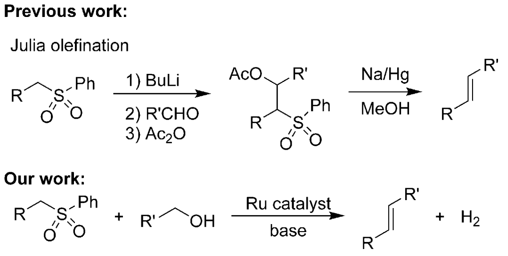
Abstract: *The synthesis of terminal, as well as internal, olefins was achieved by the one-step olefination of alcohols with sulfones catalyzed by a ruthenium pincer complex. Furthermore, performing the reaction with dimethyl sulfone under mild hydrogen pressure provides a direct route for the replacement of alcohol hydroxy groups by methyl groups in one step.*

Olefins are essential building blocks[1] in organic chemistry, and their synthesis is a crucial strategic method for the construction of complex molecules. Among all of the synthetic methods, the most powerful and widely used approach is based on the olefination of carbonyl compounds. The general strategy entails the reaction of carbanions with aldehydes or ketones. The carbanions are usually stabilized by an electron-withdrawing group, which at the same time acts as a good leaving group (LG, Scheme 1).[2] Depending on the leaving group, these transformations form some of the most important reactions[3–7] in organic chemistry (Scheme 1). Carbonyl olefination with metal carbenes is another useful strategy for the synthesis of olefins.[8]



Scheme 1. Olefination of carbonyl compounds.

Olefination of alcohols generally involves sequential stoichiometric one-pot oxidation–olefination procedures.[9] Those procedures are typically restricted to the use of a stoichiometric amount of oxidant and an excess of a phosphorus ylide. Recently, the catalytic olefination of alcohols to form alkenes was developed by a combination of palladium-catalyzed oxidation and rhodium-catalyzed methylenation of carbonyl derivatives in a single vessel using trimethylsilyldiazomethane and an equivalent amount of triphenylphosphine.[10] Direct olefination of alcohols was also achieved by one-pot processes that combined the nickel-, ruthenium-, or copper-catalyzed oxidation of alcohols with a Wittig reaction.[11] However, the highly desirable direct catalytic Julia-type olefination of alcohols using a single catalyst is unknown. Sulfones are commonly utilized in the multi-step classical Julia olefination, which is based on the formation of β-acyloxy alkyl sulfones from aldehydes, followed by elimination induced by strong reductants.[6] Since its discovery, considerable improvements[12] have been made, and this transformation has become a key process in the synthesis of many natural products.[6,12,13] Herein, we present the first one-step strategy for the olefination of alcohols using sulfones (Scheme 2), which is catalyzed by ruthenium pincer complexes. Such a single-step process that replaces traditional multi-step approaches can greatly enhance the efficiency of organic synthesis. It would not only eliminate intermediate recovery steps, but also significantly decrease the amount of generated waste, which is an important concern of the chemical industry. In this regard, our group has developed several environmentally benign reactions that are catalyzed by pincer complexes of ruthenium[14] or iron.[15]



Scheme 2. Catalytic olefination of alcohols.

The reaction of 4-methoxybenzyl alcohol with dimethyl sulfone was chosen as a model system for the study of the direct olefination of alcohols using sulfones. Thus, a dioxane solution containing 4-methoxybenzyl alcohol (1 mmol), dimethyl sulfone (1.06 mmol), KO*t*Bu (1.16 mmol), and the pincer PNN complex **1** (0.025 mmol; see Figure 1) was heated at reflux for five hours. The products were analyzed by GC–MS and NMR spectroscopy and identified by comparison with authentic samples. Only 35 % of the desired 4-methoxystyrene was formed (Table 1, entry 1). Under similar reaction conditions, the PNP complex **2** gave only 27 % yield of the desired styrene (entry 2). When the bipyridyl-based PNN complex **3** was employed, the yield of the desired styrene increased to 50 % (entry 3). Increasing the amount of the base

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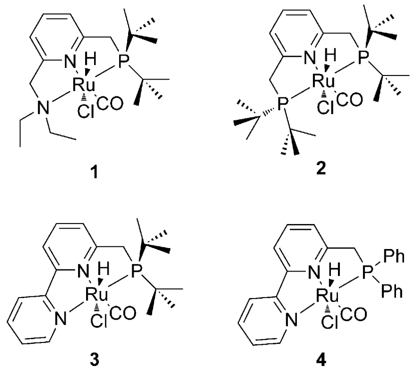
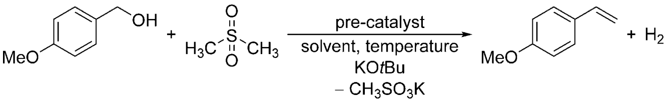


Figure 1. PNN- and PNP-based ruthenium pincer complexes.

Table 1: Optimization of the reaction conditions for alcohol olefination.[a]



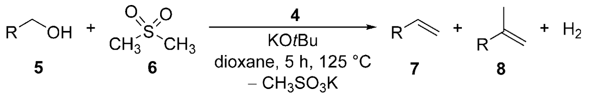
Entry	Solvent	Complex	T [°C]	t [h]	Yield[b] [%]
1	dioxane	**1**	125	5	35
2	dioxane	**2**	125	5	27
3	dioxane	**3**	125	5	50
4[c]	dioxane	**3**	125	5	45
5[d]	dioxane	**3**	125	10	15
6[e]	dioxane	**3**	125	10	–
7	dioxane	**4**	125	5	73
8	THF	**4**	85	10	65
9	toluene	**4**	135	5	68
10	dioxane	[Ru(nbd)Cl_2]	125	5	27
11	dioxane	[{Ru(p-cymene)Cl_2}$_2$]	125	5	24
12	dioxane	[$RuH_2CO(PPh_3)_3$]	125	5	24
13	dioxane	[$RuHClCO(PPh_3)_3$]	125	5	22

[a] Reaction conditions: alcohol (1 mmol), dimethyl sulfone (1.06 mmol), KO*t*Bu (1.16 mmol), and the pre-catalyst (0.025 mmol) were heated at reflux in the indicated solvent (2 mL) in an open system under argon at 125 °C (oil-bath temperature). [b] Yield determined by NMR spectroscopy using acetonitrile as the internal standard. [c] KO*t*Bu (2 equiv) was used. [d] KO*t*Bu (0.5 equiv) was used. [e] Cs_2CO_3 (1.16 equiv) was used. nbd = norbornadiene.

did not improve the yield of the desired styrene, whereas decreasing the amount of base to 0.5 equivalents resulted in a drop in yield to 15% (entries 4 and 5). Using the weaker base Cs_2CO_3 gave mostly the ester 4-methoxybenzyl 4-methoxybenzoate. Utilizing the less sterically hindered complex **4** under similar reaction conditions resulted in the formation of 4-methoxystyrene in 73% yield (entry 7). The solvent dioxane was found to be somewhat better than THF or toluene (entries 8 and 9). Commercially available ruthenium catalysts were also tested, but they gave only poor yields of the desired product (22–27%, entries 10–13). Hydrogen gas formation was detected by GC analysis of the gas phase above the reaction mixture.

With the optimized reaction conditions in hand, we set out to test the reactivity of other benzyl alcohols with dimethyl sulfone. A dioxane solution containing benzyl alcohol, dimethyl sulfone, KO*t*Bu, and pre-catalyst **4** was heated to reflux for five hours and then cooled to room temperature.

Table 2: Ruthenium-catalyzed methenylation reaction of alcohols.[a]



Entry	R	Product	Yield [%][b]
1	Ph	**7a**	63
		8a	8
2	3,4-$(MeO)_2C_6H_3$	**7b**	75 (69)[c]
		8b	10
3	p-$MeOC_6H_4$	**7c**	73 (61)[c]
		8c	7
4	p-MeC_6H_4	**7d**	80
		8d	7
5	p-ClC_6H_4	**7e**	78
		8e	9
6	p-FC_6H_4	**7f**	70
		8f	6
7	p-PhC_6H_4	**7g**	85 (75)[c]
		8g	8
8	1-naphthyl	**7h**	50[c]
		8h	–
9	2-naphthyl	**7i**	83 (76)[c]
		8i	7
10	Ph_2CH	**7j**	42[c]
		8j	–
11	$CH_3(CH_2)_8$	complicated mixture	

[a] Reaction conditions: alcohol (1 mmol), dimethyl sulfone (1.06 mmol), KO*t*Bu (1.16 mmol), and pre-catalyst **4** (2.5 mol%) were heated at reflux in dioxane (2 mL) in an open system under argon for 5 hours at 125 °C (oil-bath temperature). [b] Yield determined by NMR spectroscopy using acetonitrile or pyridine as the internal standard. [c] Yield of isolated product.

The products were analyzed by GC–MS and NMR spectroscopy, which showed the formation of styrene (**7a**) in 63% yield (Table 2, entry 1). Interestingly, prop-1-en-2-ylbenzene (**8a**; 8%) was also formed, together with a trace amount of ethylbenzene. To explore the synthetic utility of this methenylation reaction, various alcohols were studied. Thus, under similar conditions, the use of 3,4-dimethoxybenzyl alcohol led to the formation of 1,2-dimethoxy-4-vinylbenzene (**7b**) in 69% yield (entry 2). Under the same conditions, methenylation of 4-methylbenzyl alcohol, 4-chlorobenzyl alcohol, 4-fluorobenzyl alcohol, 4-biphenylmethanol, and 1- and 2-naphthylmethanol gave the corresponding styrene derivatives 1-methyl-4-vinylbenzene (**7d**; 80%), 1-chloro-4-vinylbenzene (**7e**; 78%), 1-fluoro-4-vinylbenzene (**7f**; 70%), 4-vinylbiphenyl (**7g**; 85%), 1-vinylnaphthalene (**7h**; 50%), and 2-vinylnaphthalene (**7i**; 83%) in good yields (entries 3–9). Interestingly, secondary alcohols also reacted, albeit at a slower rate. Thus, the reaction of diphenylmethanol resulted in the formation of desired 1,1-diphenylethylene (**7j**) in 42% yield after 24 hours, the rest being the starting materials and some benzophenone (entry 10). The reaction of 1-decanol with dimethyl sulfone under similar reaction conditions gave a complicated mixture of products. The initially formed 1-undecene underwent double-bond isomerization to give several isomers.

Next, the scope of the olefination reaction with regard to different sulfones was studied. Thus, the reaction of various benzyl alcohols with benzyl phenyl sulfone under analogous

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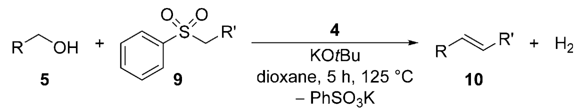
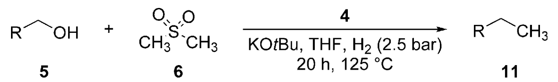
Table 3: Catalytic olefination of alcohols with aryl alkyl sulfones using complex **4**.[a]



Entry	R	R′	Product	Yield[b] [%]
1	*p*-MeOC$_6$H$_4$	Ph	**10a**	71
2	*p*-ClC$_6$H$_4$	Ph	**10b**	70
3	*p*-MeC$_6$H$_4$	Ph	**10c**	72
4	*p*-PhC$_6$H$_4$	Ph	**10d**	69
5	1-naphthyl	Ph	**10e**	76
6	*p*-MeOC$_6$H$_4$	Me	**10f**	71
7	*p*-MeC$_6$H$_4$	Me	**10g**	50
8	2-naphthyl	Me	**10h**	52
9	(*E*)-Ph–CH=CH	Ph	**10i**	55
10	6-methylpyridyl	Ph	**10j**	61
11	benzyl	Ph	**10k**	35

[a] Reaction conditions: alcohol (1 mmol), sulfone (1.06 mmol), KO*t*Bu (1.16 mmol), and pre-catalyst **4** (0.025 mmol) were heated at reflux in dioxane (2 mL) in an open system under argon for 5 hours at 125 °C (oil-bath temperature). [b] Yield of isolated product.

Table 4: Direct conversion of alcohol hydroxy groups into methyl groups.[a]

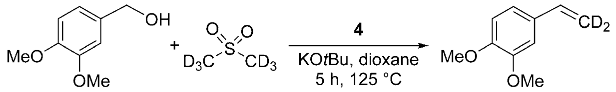


Entry	R	Product	Yield[b] [%]
1	*p*-MeOC$_6$H$_4$	**11a**	61
2	3,4-(MeO)$_2$C$_6$H$_3$	**11b**	75
3	*p*-PhC$_6$H$_4$	**11c**	72
4	2-naphthyl	**11d**	71

[a] Reaction conditions: alcohol (1 mmol), dimethyl sulfone (1.06 mmol), KO*t*Bu (1.16 mmol), and pre-catalyst **4** (2.5 mol%) were heated at 125 °C at 2.5 bar H$_2$ pressure in THF (2 mL) for 20 hours. [b] Yield of isolated product.

reaction conditions gave the corresponding *E*-stilbenes in good yields (69–76%; Table 3, entries 1–5). Similarly, the reaction of ethyl phenyl sulfone with 4-methoxybenzyl alcohol and 4-methylbenzyl alcohol gave **10f** and **10g** in good yields (entries 6–8). Under similar reaction conditions, cinnamyl alcohol also reacted with benzyl phenyl sulfone to give **10i**, which was isolated in 55% yield. Heterocyclic alcohols, such as 6-methyl-2-pyridinemethanol, reacted with benzyl phenyl sulfone under similar reaction conditions, giving 2-methyl-6-styrylpyridine (**10j**) in 61% yield with an *E*/*Z* ratio of 3:1 (entry 10). The reaction of 2-phenylethanol with benzyl phenyl sulfone gave the desired product **10k** in 35% yield.

Significantly, although hydrogen gas was liberated in these reactions, no (or only a trace amount of) hydrogenation to form the corresponding alkanes was observed when the reactions were performed in an open system under reflux. The iridium-catalyzed Wittig olefination with transfer hydrogenation was reported to convert alcohols into alkanes.[16] Encouraged by our results on the Julia olefination, we explored the possibility of obtaining the hydrogenated product by performing the reaction in a sealed vessel. Thus the reaction of 4-methoxybenzyl alcohol and dimethyl sulfone was performed in a closed vessel, which resulted in a mixture of both alkane and alkene (20:80). However, performing the reaction under 2.5 bar H$_2$ pressure gave exclusively the alkane, with no olefin being observed. Thus, when a THF solution containing 4-methoxybenzyl alcohol, dimethyl sulfone, KO*t*Bu, and pre-catalyst **4** was heated in a Fischer–Porter tube under 2.5 bar hydrogen pressure for 20 hours, GC–MS analysis showed the formation of 1-ethyl-4-methoxybenzene. A small amount of 1-isopropyl-4-methoxybenzene was detected as well, and no 4-methoxystyrene was detected. The crude product was purified by flash column chromatography to give 1-ethyl-4-methoxybenzene (**11a**) in 61% yield (Table 4). Similarly, 3,4-dimethoxybenzyl alcohol, 4-biphenylmethanol, and 2-naphthylmethanol gave the corresponding alkanes in good yields (71–75%; entries 2–4). This reaction sequence with only one catalyst enables the unprecedented direct conversion of a hydroxy group into a methyl group. The reaction of 3,4-dimethoxybenzyl alcohol with deuterated dimethyl sulfone, which resulted in deuterium incorporation at the terminal carbon atom of the desired styrene, provided direct evidence that the methylene group originates from dimethyl sulfone (Scheme 3).



Scheme 3. Deuterium-labelling experiments confirm that the carbon source is dimethyl sulfone.

During the reaction of differently substituted benzyl alcohols with benzyl phenyl sulfone, potassium benzenesulfonate was also isolated as an insoluble salt, which precipitated from the organic solvent.

To gain insight about possible intermediates during the reaction course, complex **4** was treated with 1.1 equivalents of KO*t*Bu in THF and was then added to a THF solution containing 10 equivalents of dimethyl sulfone and KO*t*Bu, and the mixture was stirred at room temperature for two hours. Single crystals that were suitable for X-ray diffraction were grown by layering the THF solution with *n*-pentane. The crystal structure shows a polymeric complex, in which each asymmetric unit contains one ruthenium pincer unit, two C–H-activated dimethyl sulfone ligands, three potassium ions, and five THF molecules (see the Supporting Information).[17] For clarity, we show only one unit (Figure 2). The crystal structure shows the coordination of dimethyl sulfone to ruthenium through the C25 carbon atom, the Ru1–C25 distance being 2.209 (4) Å. One of the potassium cations is connected to the oxygen atom (O1) of a carbonyl group and to one of the oxygen atoms (O3) of the coordinated dimethyl sulfone. Each potassium ion is also connected to another dimethyl sulfone unit in the polymeric structure, shown as a dotted line. The C10–C11 bond length is 1.378(8) Å, and there is only one hydrogen atom (H11) in the arm (C11), revealing that the complex is dearomatized. In the ^{1}H NMR

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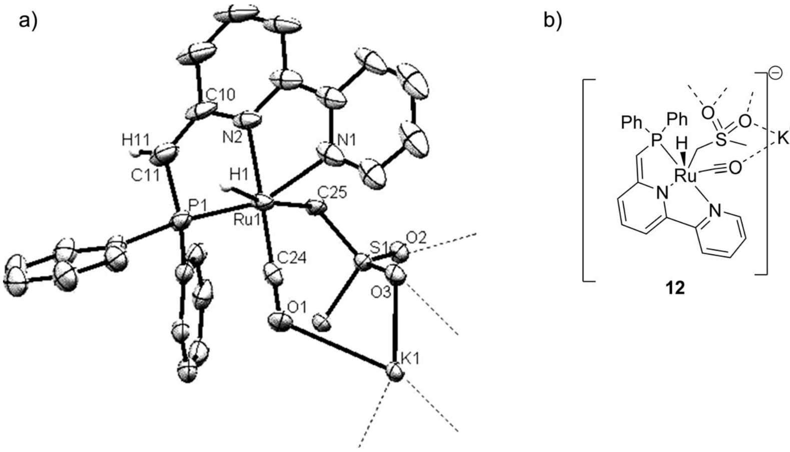

Figure 2. a) Molecular structure of complex **12** with thermal ellipsoids set at 50% probability. Selected bond lengths [Å] and angles [°]: Ru1–C24 1.825(4), Ru1–C25 2.209(4), Ru1–N1 2.130(4), Ru1–N2 2.087(4), Ru1–H1 1.67(5), Ru1–P1 2.2530(15); C24-Ru1-N2 178.39(18), C24-Ru1-N1 104.70(17), C24-Ru1-C25 98.16(15), C25-Ru1-H1 169.0(18). b) Complex **12**.

spectrum, H11 appears as a singlet at $\delta = 3.61$ ppm, and C11 appears as a doublet at $\delta = 167.7$ ppm ($J_{PC} = 21.7$ Hz) in the ^{13}C NMR spectrum. The hydride attached to the ruthenium center appears as a doublet at $\delta = -8.73$ ppm ($^2J_{PH} = 23.6$ Hz).

As complex **12** is dearomatized, it can potentially activate alcohols by metal–ligand cooperation. We have observed that complex **12** catalyzes the olefination of benzyl alcohol to styrene with the same efficiency as pre-catalyst **4**, suggesting that **12** might be a catalytic intermediate in the process.

It is expected that an aldehyde intermediate is initially formed in this reaction. Surprisingly, when a dioxane solution of benzaldehyde (1 mmol) and dimethyl sulfone (1.06 mmol) was heated in the presence of pre-catalyst **4** and KO*t*Bu (1.16 mmol) for five hours, only 10% of styrene was obtained together with a complex mixture of products. Furthermore, under similar reaction conditions, β-hydroxy sulfones, such as 2-(methylsulfonyl)-1-phenylethanol, which is also a possible intermediate, gave only traces of the corresponding styrenes in complex mixtures of unidentified products. These results suggest that the reaction mechanism is more complicated and might not proceed through a Julia-type pathway. It is possible that a metal-coordinated aldehyde, rather than free aldehyde, is involved, followed by formation of a complex β-hydroxy sulfone intermediate, thus suppressing side reactions that might result from the free aldehyde or β-hydroxy sulfone.

In conclusion, an unprecedented one-step olefination of alcohols with sulfones has been achieved. The reaction, which is catalyzed by a ruthenium pincer complex, liberates hydrogen gas and does not involve any added oxidant. Furthermore, performing the reaction under mild hydrogen pressure offers a direct route for the conversion of an alcohol hydroxy group into a methyl group in one step. Mechanistic studies of these unique processes are in progress.

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[1] S. Matar, L. F. Hatch, *Chemistry of Petrochemical Processes*, Gulf Professional Publishing, Houston, Texas, **2001**.

[2] R. Dumeunier, I. E. Markó, *Modern Carbonyl Olefination* (Ed.: T. Takeda), Wiley-VCH, Weinheim, **2004**.

[3] a) G. Wittig, G. Geissler, *Justus Liebigs Ann. Chem.* **1953**, *580*, 44; b) B. E. Maryanoff, A. B. Reitz, *Chem. Rev.* **1989**, *89*, 863.

[4] a) L. Horner, H. Hoffmann, H. C. Wipel, G. Klahre, *Chem. Ber.* **1959**, *92*, 2499; b) J. Clayden, S. Warren, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 241; *Angew. Chem.* **1996**, *108*, 261.

[5] a) W. S. Wadsworth, Jr., W. D. Emmons, *J. Am. Chem. Soc.* **1961**, *83*, 1733; b) J. Boutagy, R. Thomas, *Chem. Rev.* **1974**, *74*, 87.

[6] a) M. Julia, J.-M. Paris, *Tetrahedron Lett.* **1973**, *14*, 4833; Reviews: b) P. R. Blakemore, *J. Chem. Soc. Perkin Trans* **2002**, 2563; c) B. Chatterjee, S. Bera, D. Mondal, *Tetrahedron: Asymmetry* **2014**, *25*, 1.

[7] a) D. J. Peterson, *J. Org. Chem.* **1968**, *33*, 780; b) L. F. van Staden, D. Gravestock, D. J. Ager, *Chem. Soc. Rev.* **2002**, *31*, 195.

[8] N. A. Petasis, E. I. Bzowej, *J. Am. Chem. Soc.* **1990**, *112*, 6392.

[9] a) A. R. Bressette, L. C. Glover, *Synlett* **2004**, 738; b) L. Blackburn, H. Kanno, R. J. K. Taylor, *Tetrahedron Lett.* **2003**, *44*, 115; c) R. N. MacCoss, E. P. Balskus, S. V. Ley, *Tetrahedron Lett.* **2003**, *44*, 7779; d) J. M. Vatèle, *Tetrahedron Lett.* **2006**, *47*, 715; e) R. E. Ireland, D. W. Norbeck, *J. Org. Chem.* **1985**, *50*, 2198; f) A. G. M. Barrett, D. Hamprecht, M. Ohkubo, *J. Org. Chem.* **1997**, *62*, 9376; g) S. Shuto, S. Niizuma, A. Matsuda, *J. Org. Chem.* **1998**, *63*, 4489; h) F. R. Pinacho Crisóstomo, R. Carrillo, T. Martin, F. Garcia-Tellado, V. S. Martin, *J. Org. Chem.* **2005**, *70*, 10099; i) R. J. K. Taylor, M. Reid, J. Foot, S. A. Raw, *Acc. Chem. Res.* **2005**, *38*, 851.

[10] H. Lebel, V. Paquet, *J. Am. Chem. Soc.* **2004**, *126*, 11152.

[11] a) G. Kim, D. G. Lee, S. Chang, *Bull. Korean Chem. Soc.* **2001**, *22*, 943; b) M. Davi, H. Lebel, *Org. Lett.* **2009**, *11*, 41; c) E. Y. Lee, Y. Kim, J. S. Lee, J. Park, *Eur. J. Org. Chem.* **2009**, 2943; d) F. Alonso, P. Riente, M. Yus, *Eur. J. Org. Chem.* **2009**, 6034.

[12] a) J. Pospíšil, I. E. Markó, *Org. Lett.* **2006**, *8*, 5983; b) M. E. Lebrun, P. Le Marquand, C. Berthelette, *J. Org. Chem.* **2006**, *71*, 2009; c) F. Billard, R. Robiette, J. Pospíšil, *J. Org. Chem.* **2012**, *77*, 6358.

[13] E. N. Prilezhaeva, *Russ. Chem. Rev.* **2000**, *69*, 367.

[14] a) C. Gunanathan, D. Milstein, *Science* **2013**, *341*, 1229712, and references therein; b) C. Gunanathan, D. Milstein, *Acc. Chem. Res.* **2011**, *44*, 588.

[15] a) D. Srimani, Y. Diskin-Posner, Y. Ben-David, D. Milstein, *Angew. Chem. Int. Ed.* **2013**, *52*, 14131; *Angew. Chem.* **2013**, *125*, 14381; b) T. Zell, Y. Ben-David, D. Milstein, *Angew. Chem. Int. Ed.* **2014**, *53*, 4685; *Angew. Chem.* **2014**, *126*, 4773.

[16] a) M. G. Edwards, J. M. J. Williams, *Angew. Chem. Int. Ed.* **2002**, *41*, 4740; *Angew. Chem.* **2002**, *114*, 4934; b) P. J. Black, M. G. Edwards, J. M. J. Williams, *Eur. J. Org. Chem.* **2006**, 4367.

[17] CCDC 1013255 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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