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SHORT COMMUNICATION

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ortho-Olefination of Arylaldehyde *O*-Methyloximes through Palladium-Catalyzed C–H Activation

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Keywords: Palladium / C–H activation / Olefination / Aldehydes / Isotope effects

Palladium(II)-catalyzed *ortho*-olefination of arylaldehyde *O*-methyloximes by using *O*-methyloxime as a directing group gave 2-alkenylarylaldehyde *O*-methyloximes in moderate to good yields. After various reaction parameters (catalyst, oxidant, solvent, and reaction temperature) were examined, the optimal conditions for the reaction were identified. 2-Alkenylarylaldehydes could be obtained conveniently by hydrolysis of the coupling products. The kinetic isotope effect (k_H/k_D) for the C–H bond activation was provided, and the possible mechanism of the reaction was proposed.

Introduction

Because alkenylarene structures play an important role in the synthesis of various fine chemicals,[1] the development of more efficient methods to construct these building blocks has attracted much attention. In addition, the aldehyde group is considered to be one of the most easily transformable functional groups.[2] Considering the importance of compounds with these two structural units, an efficient approach for the synthesis of 2-alkenylarylaldehyde derivatives is therefore desirable. However, to synthesize these derivatives through conventional methods such as aldol condensation or a Wittig-type reaction from phthalaldehydes is generally difficult, because it is challenging to control the regioselectivity between the two aldehyde groups at different sites. Another method is the Mizoroki–Heck reaction. Still, 2-iodo- or 2-bromobenzaldehydes are needed, and also, some side reactions may take place on the aldehyde group under the basic reaction condition.

In the last decade, C–H bond activation catalyzed by transition metals has become one of the most modern and well-recognized tactics for the synthesis of many kinds of functional compounds because of its atom- and step-economic nature.[3] As a powerful tool for the olefination of arenes, the palladium-catalyzed intermolecular dehydrogenative Heck reaction, which is also called the oxidative Heck reaction, has been developed in recent years.[4] *ortho*-Olefinations with the assistance of a directing group such as carboxyl,[5] acetamido,[6] *N*,*N*-dimethylaminomethyl,[7] *N*-methoxyacylamino,[8] or pyridylsulfinyl[9] have been reported. However, no palladium-catalyzed *ortho*-olefination to form 2-alkenylarylaldehydes has been reported, as the aldehyde group is not an effective directing group in Pd-catalyzed C–H functionalization,[10] despite the fact that Ru and Rh complexes have been used in this transformation.[11] Arylaldehyde *O*-methyloxime, which can be easily prepared by the condensation of the corresponding aldehyde and *O*-methylhydroxylamine, is part of a class of protected aldehydes or precursors of aldehydes. Recently, palladium-catalyzed *ortho*-acetoxylation,[12] etherification,[12] arylation,[13] acylation,[14] and bromination[15] of arylaldehyde *O*-methyloximes have been developed. In these pioneer works, the oxime group was proven to have effective directing action to *ortho* C–H functionalization. Herein, we present a facile palladium-catalyzed *ortho*-olefination reaction of arylaldehyde *O*-methyloximes by using *O*-methyloxime as a directing group to form 2-alkenylarylaldehyde *O*-methyloximes. 2-Alkenylarylaldehydes could be obtained conveniently from the hydrolysis of the coupling products.

Results and Discussion

As an initial experiment, treatment of benzaldehyde *O*-methyloxime (**1a**) with methyl acrylate (**2a**) in the presence of $Pd(OAc)_2$ afforded desired product **3a** (Table 1). The reaction could proceed in air without protection. The effects of different palladium sources, solvents, oxidants, and temperature were systematically examined. Without palladium, the starting materials were recovered entirely (Table 1, Entry 1). $Pd(OAc)_2$ showed evident catalytic activity to the reaction and 2 mol-% of the catalyst could catalyze the reaction effectively, whereas other palladium species such as $PdCl_2$, $Pd(PPh_3)_4$, and Pd nanoparticles were substantially less effective (Table 1, Entries 2–5). A weakly acidic medium

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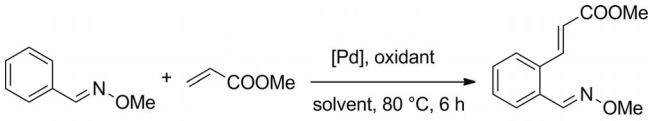
was favorable to the reaction. AcOH proved to be a suitable solvent for this transformation, whereas the addition of a strong acid (TFA, *p*TsOH) decreased the yield substantially, because a stronger acid might lead to the decomposition of the oxime group (Table 1, Entries 6 & 7). Neutral solvents such as CH_3CN, toluene, DMF, DMSO, dioxane, and DCE were disadvantageous to the reaction (Table 1, Entries 8–13). As a general oxidant and ligand, *p*-benzoquinone (BQ) also played an important role. Without BQ, only a trace quantity of the corresponding product was detected (Table 1, Entry 14). Other oxidants such as $Cu(OAc)_2$, Cu_2O, Ag_2O, Ag_2CO_3, and $Na_2S_2O_8$ were less effective for this reaction (Table 1, Entries 15–19). Under an Ar atmosphere, the reaction gave almost the same yield as that in air (Table 1, Entry 20). At 80 °C, the reaction was complete in 6 h with a yield of 74%. A decrease in the reaction temperature led to a lower conversion. However, an increase in the reaction temperature above 100 °C might induce the decomposition of the substrate and therefore reduce the yield (Table 1, Entry 2). Taking the above into consideration, the reaction efficiently proceeded when 2 mol-% of $Pd(OAc)_2$ was used in combination with BQ (1.0 equiv.) in acetic acid at 80 °C.

Table 1. Optimization of the reaction conditions.[a]



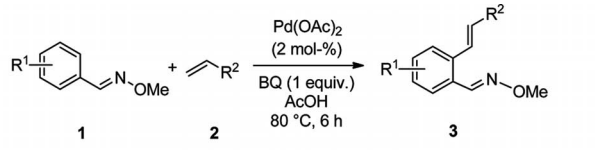
1a 2a 3a

Entry	Catalyst	Oxidant	Solvent	Yield [%][b]
1	–	BQ	AcOH	NR
2	$Pd(OAc)_2$	BQ	AcOH	**74** (41, 69, 53)[c]
3	$PdCl_2$	BQ	AcOH	trace
4	$Pd(PPh_3)_4$	BQ	AcOH	trace
5	nano-Pd	BQ	AcOH	trace
6	$Pd(OAc)_2$	BQ	AcOH	57[d]
7	$Pd(OAc)_2$	BQ	AcOH	43[e]
8	$Pd(OAc)_2$	BQ	CH_3CN	NR
9	$Pd(OAc)_2$	BQ	toluene	NR
10	$Pd(OAc)_2$	BQ	DMF	NR
11	$Pd(OAc)_2$	BQ	DMSO	NR
12	$Pd(OAc)_2$	BQ	dioxane	NR
13	$Pd(OAc)_2$	BQ	DCE	NR
14	$Pd(OAc)_2$	–	AcOH	trace
15	$Pd(OAc)_2$	$Cu(OAc)_2$	AcOH	15
16	$Pd(OAc)_2$	Cu_2O	AcOH	21
17	$Pd(OAc)_2$	Ag_2O	AcOH	12
18	$Pd(OAc)_2$	Ag_2CO_3	AcOH	trace
19	$Pd(OAc)_2$	$Na_2S_2O_8$	AcOH	NR
20	$Pd(OAc)_2$	BQ	AcOH	72[f]

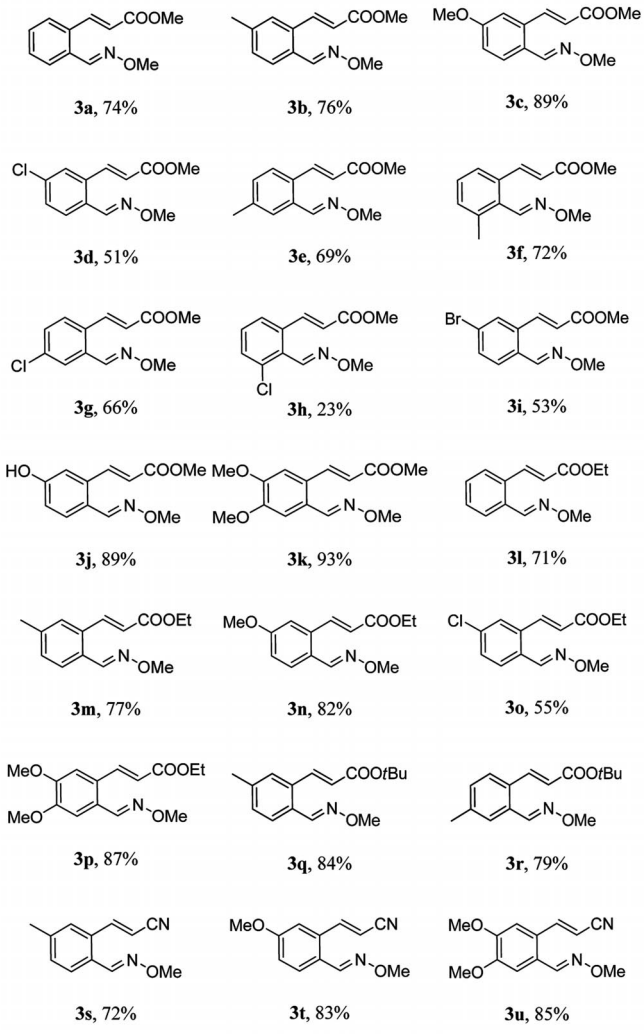
[a] Reaction conditions: benzaldehyde *O*-methyloxime (**1a**, 0.5 mmol), methyl acrylate (**2a**, 1.0 mmol), catalyst (0.01 mmol), solvent (2 mL), and oxidant (1 equiv.) in air at 80 °C for 6 h. [b] Isolated yield; NR = no reaction. [c] Reaction proceeded at 60, 100, and 120 °C, respectively. [d] TFA (1.0 equiv.) was added. [e] *p*TsOH (1.0 equiv.) was added. [f] Under an Ar atmosphere.

With the optimized reaction conditions established, we examined the reactions between various substituted arylaldehyde *O*-methyloximes and acrylates or acrylonitrile (Table 2). All products we obtained were confirmed to be *E*-isomers by ^1H NMR spectroscopy. It seems that the reaction of arylaldehyde *O*-methyloximes with electron-donating groups gave higher yields than those with electron-withdrawing groups. For example, methyl acrylate reacted smoothly with 4-methoxybenzaldehyde *O*-methyloxime and 3,4-dimethoxybenzaldehyde *O*-methyloxime to give the *ortho*-olefinated product in 89 and 93% isolated yield, respectively (i.e., **3c** and **3n**), whereas it reacted with 4-chlorobenzaldehyde *O*-methyloxime and 4-bromobenzaldehyde *O*-methyloxime to provide a moderate yield of 51 and 53%,

Table 2. Alkenylation of arylaldehyde *O*-methyloximes with alkenes. Reaction conditions: arylaldehyde *O*-methyloxime **1** (0.5 mmol), alkene **2** (1.0 mmol), $Pd(OAc)_2$ (0.01 mmol), acetic acid (2 mL), and BQ (1 equiv.) in air at 80 °C for 6 h. Isolated yield (for **3a**–**u**) is reported (reaction times for each substrate were not optimized).



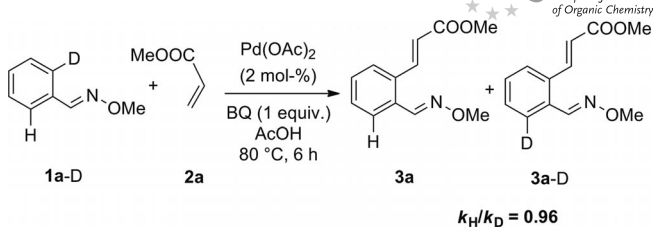
1 2 3



respectively (i.e., **3d** and **3i**). Unfortunately, the reaction of a substrate containing a strong electron-withdrawing substituent such as NO_2 only gave a trace amount of the product. These results may be attributed to the fact that an electron-withdrawing group substituted on the aromatic ring of the substrate disfavors the formation of a cyclopalladated intermediate. Regarding the reaction of *meta*-substituted arylaldehyde *O*-methyloximes, which might have two C–H bond activation sites (C2 and C6), only *ortho*-olefinated products at C6 were isolated (i.e., **3e**, **3g**, **3p**, **3r**, and **3u**). This regioselectivity was generally attributed to the steric effect of the substituent at the C3 position instead of the electronic nature of the substrate.[16] Furthermore, it is worthy to note that chloride and bromide groups on the aromatic ring were tolerated, and the surviving C–Cl or C–Br bond could be further transformed into different useful functional groups (i.e., **3d**, **3g**, **3h**, **3i**, and **3o**). The reaction of the phenol substrate also gave a good yield (i.e., **3j**), which accounted for an excellent functional group tolerance of this reaction even under the oxidizing reaction conditions. With methyl, ethyl, and *tert*-butyl acrylate, as well as acrylonitrile, the corresponding coupling products were obtained in moderate to good yields. Unfortunately, almost no desired product was obtained when styrene was employed under the reaction conditions, because the acetoxylation of styrene occurred under the acidic conditions.[17]

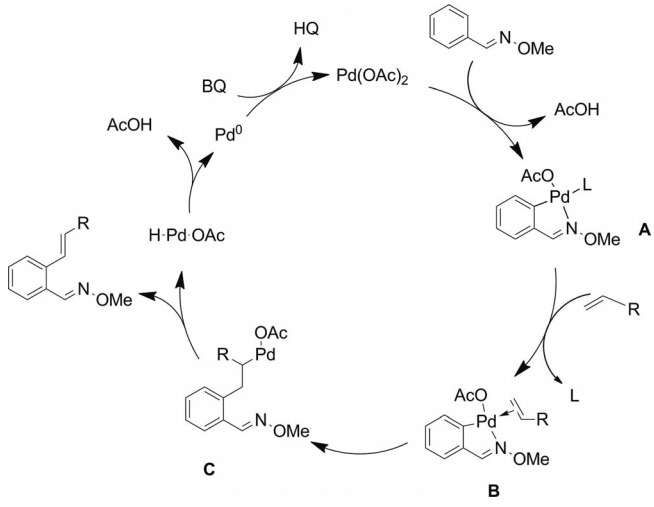
To understand the catalytic process of this reaction, a kinetic isotope effect was investigated by using 2-deuteriobenzaldehyde *O*-methyloxime (**1a**-D) to react with **2a** to form **3a** and **3a**-D (Scheme 1). The k_H/k_D ratio was determined to be 0.96,[18] which indicated that the palladium(II)-catalyzed C–H bond cleavage of benzaldehyde *O*-methyloxime (**1a**) does not occur in the rate-determining step. We presume that the C–H activation might proceed via an agostic intermediate[19] or a concerted metalation deprotonation.[20]

A possible mechanism for this palladium(II)-catalyzed olefination reaction is proposed in Scheme 2, although details await further investigation. The reaction is probably initiated by oxime-coordinated *ortho*-selective cyclometalation on the aromatic ring with $Pd(OAc)_2$, in which acetate presumably participates in aromatic proton abstraction



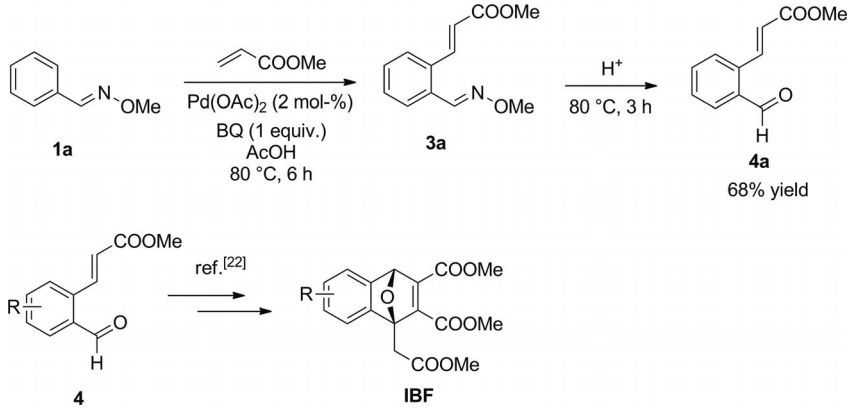
Scheme 1. Isotope effect.

to form aryl palladium intermediate **A**.[21] Acetate or BQ might act as a ligand coordinating to palladium. Afterward, the ligand in intermediate **A** interchanges with an olefin to form **B**, which is followed by insertion of the C=C bond into the Ar–Pd bond. Subsequent β-hydroelimination and reductive elimination results in the generation of the product and liberation of acetic acid and a palladium(0) species. Finally, the released palladium(0) can be reoxidized by BQ to regenerate palladium(II), which can continue the catalytic cycle.



Scheme 2. Proposed reaction mechanism.

One of the applications of this olefination reaction is to synthesize 2-alkenylarylaldehydes by hydrolysis of the coupling products. As an example, (*E*)-methyl 3-{2-[(*E*)-(meth-



Scheme 3. Synthesis of (–)-podophyllotoxin (**6**) from arylaldehyde *O*-methyloxime.

oxyimino)methyl]phenyl}acrylate (**3a**) was further hydrolyzed conveniently by treatment with HCl (2 M) to give methyl 2-formylcinnamate (**4a**, Scheme 3). Multisubstituted methyl 2-formylcinnamates are precursors to synthesize versatile isobenzofurans (IBFs), which have been employed in the synthesis of aromatic and hydroaromatic natural products.[22] For example, IBF could be used as a material to synthesize the natural product (–)-podophyllotoxin,[23] which is an aryl tetralin lignan isolated from the American May apple tree[24] and which may be used in the treatment of venereal warts, a chemotherapeutic for cancer, and as anti-HIV agent.[25]

Conclusions

In conclusion, we developed the *ortho*-olefination of arylaldehyde *O*-methyloximes through Pd-catalyzed oxidative coupling with olefins to form 2-alkenylarylaldehyde *O*-methyloximes. This protocol, when followed by simple deprotection to the coupling products, could afford 2-alkenylarylaldehydes, which are important precursors for the synthesis of natural products. Therefore, the present work also provided a simple method for the synthesis of 2-alkenylarylaldehydes. The mild reaction conditions provide future opportunities to apply this methodology in the synthesis of natural products and medicines.

Experimental Section

General Experimental Procedures for the Palladium-Catalyzed *ortho*-Olefination of Arylaldehyde *O*-Methyloxime: Arylaldehyde *O*-methyloxime (0.5 mmol), alkene (1.0 mmol), BQ (0.5 mmol), $Pd(OAc)_2$ (2.24 mg, 0.01 mmol, 2 mol-%), and acetic acid (2 mL) were added in a 25-mL sealed tube with a Teflon lined cap. The mixture was heated at 80 °C (oil bath temperature) for 6 h. After cooling to room temperature, the solvent was removed under reduced pressure, and the residue was purified by a flash column chromatography on silica gel (hexane/ethyl acetate) to give the corresponding product.

Supporting Information (see footnote on the first page of this article): Experimental procedures and full characterization for all compounds; copies of the ^1H NMR and ^{13}C NMR spectra for all compounds.

Acknowledgments

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[1] a) A. C. Grimsdale, K. L. Chan, R. E. Martin, P. G. Jokisz, A. B. Holmes, *Chem. Rev.* **2009**, *109*, 897–1091; b) Y. Kong, Y. J. Fu, Y. G. Zu, W. Liu, W. Wang, X. Hua, M. Yang, *Food Chem.* **2009**, *117*, 152–159; c) X. Hua, Y. J. Fu, Y. G. Zu, N. Wu, Y. Kong, J. Li, X. Peng, T. Efferth, *J. Pharm. Biomed. Anal.* **2010**, *52*, 273–279; d) S. R. Marder, B. Kippelen, A. K. Y. Jen, N. Peyghambarian, *Nature* **1997**, *388*, 845–851.

[2] R. C. Larock, *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, Wiley-VCH, New York, **1999**.

[3] a) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174–238; b) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem.* **2009**, *121*, 5196; *Angew. Chem. Int. Ed.* **2009**, *48*, 5094–5115; c) B. M. Rosen, K. W. Quasdorf, D. A. Wilson, N. Zhang, A.-M. Resmerita, N. K. Garg, V. Percec, *Chem. Rev.* **2011**, *111*, 1346–1416; d) C.-L. Sun, B.-J. Li, Z.-J. Shi, *Chem. Rev.* **2011**, *111*, 1293–1314; e) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer, O. Baudoin, *Chem. Eur. J.* **2010**, *16*, 2654–2672; f) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215–1292; g) W. Shi, C. Liu, A. Lei, *Chem. Soc. Rev.* **2011**, *40*, 2761–2776; h) C. Liu, H. Zhang, W. Shi, A. Lei, *Chem. Rev.* **2011**, *111*, 1780–1824; i) R. Jana, T. P. Pathak, M. S. Sigman, *Chem. Rev.* **2011**, *111*, 1417–1492; j) I. P. Beletskaya, V. P. Ananikov, *Chem. Rev.* **2011**, *111*, 1596–1636.

[4] a) E. M. Beck, N. P. Grimster, R. Hatley, M. J. Gaunt, *J. Am. Chem. Soc.* **2006**, *128*, 2528–2529; b) M. Dams, D. E. De Vos, S. Celen, P. A. Jacobs, *Angew. Chem.* **2003**, *115*, 3636; *Angew. Chem. Int. Ed.* **2003**, *42*, 3512–3515; c) Y. Fujiwara, I. Moritani, M. Matsuda, S. Teranishi, *Tetrahedron Lett.* **1968**, *9*, 633–636; d) Y. Fujiwara, I. Noritani, S. Danno, R. Asano, S. Teranishi, *J. Am. Chem. Soc.* **1969**, *91*, 7166–7169; e) J. Le Bras, J. Muzart, *Chem. Rev.* **2011**, *111*, 1170–1214; f) I. Moritanl, Y. Fujiwara, *Tetrahedron Lett.* **1967**, *8*, 1119–1122; g) A. García-Rubia, B. Urones, R. Gómez Arrayás, J. C. Carretero, *Angew. Chem. Int. Ed.* **2011**, *50*, 10927–10931; h) Y. Yang, K. Cheng, Y. Zhang, *Org. Lett.* **2009**, *11*, 5606–5609.

[5] a) M. Miura, T. Tsuda, T. Satoh, S. Pivsa-Art, M. Nomura, *J. Org. Chem.* **1998**, *63*, 5211–5215; b) D.-H. Wang, K. M. Engle, B.-F. Shi, J.-Q. Yu, *Science* **2010**, *327*, 315–319; c) B.-F. Shi, Y.-H. Zhang, J. K. Lam, D.-H. Wang, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 460–461; d) K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2010**, *49*, 6169–6173.

[6] a) M. D. K. Boele, G. P. F. van Strijdonck, A. H. M. de Vries, P. C. J. Kamer, J. G. de Vries, P. W. N. M. van Leeuwen, *J. Am. Chem. Soc.* **2002**, *124*, 1586–1587; b) T. Nishikata, B. H. Lipshutz, *Org. Lett.* **2010**, *12*, 1972–1975.

[7] G. Cai, Y. Fu, Y. Li, X. Wan, Z. Shi, *J. Am. Chem. Soc.* **2007**, *129*, 7666–7673.

[8] a) D.-D. Li, T.-T. Yuan, G.-W. Wang, *Chem. Commun.* **2011**, *47*, 12789–12791; b) J. W. Wrigglesworth, B. Cox, G. C. Lloyd-Jones, K. I. Booker-Milburn, *Org. Lett.* **2011**, *13*, 5326–5329.

[9] M. Yu, Z. Liang, Y. Wang, Y. Zhang, *J. Org. Chem.* **2011**, *76*, 4987–4994.

[10] a) N. Gürbüz, I. Özdemir, B. Çetinkaya, *Tetrahedron Lett.* **2005**, *46*, 2273–2277; b) D. Kalyani, A. R. Dick, W. Q. Anani, M. S. Sanford, *Tetrahedron* **2006**, *62*, 11483–11498; c) Y. Terao, Y. Kametani, H. Wakui, T. Satoh, M. Miura, M. Nomura, *Tetrahedron* **2001**, *57*, 5967–5974.

[11] a) K. Padala, M. Jeganmohan, *Org. Lett.* **2012**, *14*, 1134–1137; b) S. H. Park, J. Y. Kim, S. Chang, *Org. Lett.* **2011**, *13*, 2372–2375.

[12] L. V. Desai, H. A. Malik, M. S. Sanford, *Org. Lett.* **2006**, *8*, 1141–1144.

[13] a) C.-L. Sun, N. Liu, B.-J. Li, D.-G. Yu, Y. Wang, Z.-J. Shi, *Org. Lett.* **2010**, *12*, 184–187; b) V. S. Thirunavukkarasu, K. Parthasarathy, C.-H. Cheng, *Angew. Chem.* **2008**, *120*, 9604; *Angew. Chem. Int. Ed.* **2008**, *47*, 9462–9465.

[14] C.-W. Chan, Z. Zhou, A. S. C. Chan, W.-Y. Yu, *Org. Lett.* **2010**, *12*, 3926–3929.

[15] E. Dubost, C. Fossey, T. Cailly, S. Rault, F. Fabis, *J. Org. Chem.* **2011**, *76*, 6414–6420.

[16] a) R. E. Maleczka, F. Shi, D. Holmes, M. R. Smith, *J. Am. Chem. Soc.* **2003**, *125*, 7792–7793; b) K. Orito, A. Horibata, T. Nakamura, H. Ushito, H. Nagasaki, M. Yuguchi, S. Yamashita, M. Tokuda, *J. Am. Chem. Soc.* **2004**, *126*, 14342–14343.

[17] T. Yamane, K. Kikukawa, M. Takagi, T. Matsuda, *Tetrahedron* **1973**, *29*, 955–962.

[18] The ratio was obtained by ^{1}H NMR spectroscopy; see the Supporting Information.
[19] D. L. Davies, S. M. A. Donald, S. A. Macgregor, *J. Am. Chem. Soc.* **2005**, *127*, 13754–13755.
[20] a) S. I. Gorelsky, D. Lapointe, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 10848–10849; b) M. Lafrance, C. N. Rowley, T. K. Woo, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 8754–8756; c) H.-Y. Sun, S. I. Gorelsky, D. R. Stuart, L.-C. Campeau, K. Fagnou, *J. Org. Chem.* **2010**, *75*, 8180–8189.
[21] K. M. Engle, D.-H. Wang, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 14137–14151.
[22] S. K. Meegalla, R. Rodrigo, *J. Org. Chem.* **1991**, *56*, 1882–1888.
[23] D. B. Berkowitz, S. Choi, J.-H. Maeng, *J. Org. Chem.* **2000**, *65*, 847–860.
[24] M. L. S. King, M. M. Sullivan, *Science* **1946**, *104*, 244–245.
[25] a) U. Claesson, A. Lassus, H. Happonen, L. Hogstrom, A. Siboulet, *Int. J. STD AIDS* **1996**, *7*, 429–434; b) Y. Damayanthi, J. W. Lown, *Curr. Med. Chem.* **1998**, *5*, 205–252; c) C. T. L. Lee, V. C. K. Lin, S. X. Zhang, X. K. Zhu, D. VanVliet, H. Hu, S. A. Beers, Z. Q. Wang, L. M. Cosentino, S. L. Morris-Natschke, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2897–2902.

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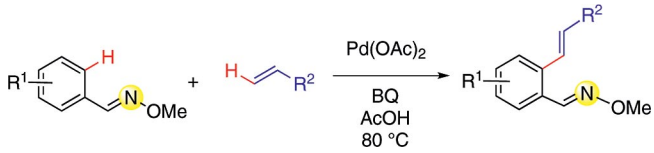
C–H Activation



2-Alkenylarylaldehyde *O*-methyloximes were obtained through palladium(II)-catalyzed *ortho*-olefination of arylaldehyde *O*-methyloximes by using *O*-methyloxime as a directing group in moderate to good yields. Hydrolysis of the coupling products conveniently gave 2-alkenylarylaldehydes.

Keywords: Palladium / C–H activation / Olefination / Aldehydes / Isotope effects

