Note

Palladium-Catalyzed *β*-Arylation of Cyclic *α*,*β*-Unsaturated *O*-Methyl Oximes with Aryl Iodides

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We report a Pd-catalyzed *β*-arylation of cyclic *α*,*β*-unsaturated *O*-methyl oximes with aryl iodides. This reaction shows complete regioselectivity and excellent functional group tolerance. *β*-Arylation of 2-cyclohexen-1-one *O*-methyl oxime (existing as 2 : 1 *E*/*Z* mixture) with certain aryl iodides such as 4-iodoanisole affords only *β*-arylated (*E*)-*O*-methyl oximes.

Key words *O*-methyl oxime; *β*-arylation; palladium; aryl iodide; Fujiwara–Moritani reaction

Introduction

Carbonyl compounds are very important in organic and organometallic chemistry. Functionalization of carbonyl compounds using metal catalysts has been widely and energetically researched.[1–5] Recently, numerous reports on the direct *β*-functionalization of carbonyl compounds have been published, using simple saturated and *α*,*β*-unsaturated carbonyl compounds[6–15] (Chart 1A). Similarly, acyclic oxime species have also been investigated.[16–23] Oxime species are easily prepared from carbonyl compounds, and play an important and versatile role in organic synthesis.[16–30] In metal-promoted direct *β*-functionalization of acyclic oxime species, the oxime group usually behaves as a directing *N*-coordinating functionality[16–23] (Chart 1B). On the other hand, metal-promoted direct *β*-functionalization of cyclic oxime species such as 2-cyclohexen-1-one oxime, whose oxime group is not effective as a directing *N*-coordinating functionality, has not been reported yet (Chart 1C). Thus, we focused on the *β*-functionalization of cyclic *α*,*β*-unsaturated oxime species. This paper describes the Pd-catalyzed *β*-arylation of cyclic *α*,*β*-unsaturated *O*-methyl oximes with aryl iodides.

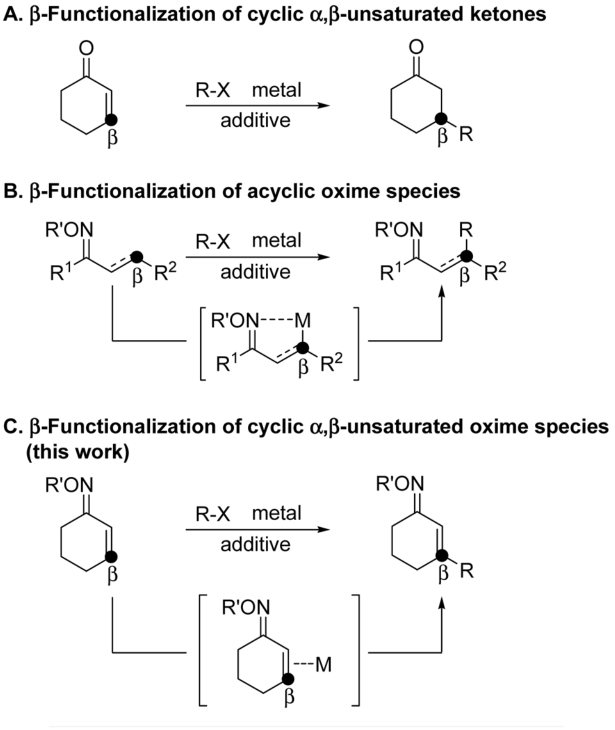
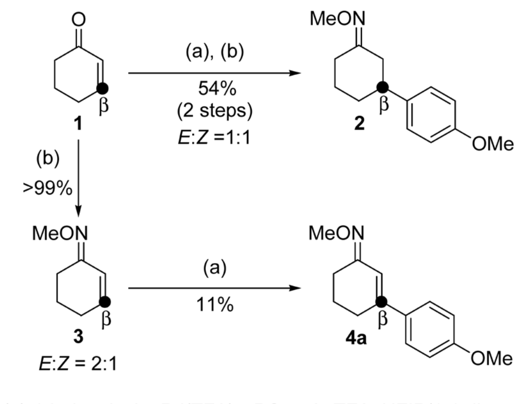


Chart 1. *β*-Functionalization of Ketones and Oxime Species

Results and Discussion

As a model study, we first examined the *β*-arylation of 2-cyclohexen-1-one (**1**) with aryl iodide according to the procedures described by Huang and Dong.[10] This was followed by oximation of the resulting *β*-arylated ketone to yield the desired *β*-arylated oxime species (Chart 2). Pd-catalyzed *β*-arylation of 2-cyclohexen-1-one (**1**) with 4-iodoanisole afforded 3-(4-methoxyphenyl)cyclohexanone. Subsequent oximation of the resulting ketone gave the desired 3-(4-methoxyphenyl)cyclohexanone *O*-methyl oxime (**2**) in 54% yield (2 steps). The obtained product (**2**) was a 1 : 1 mixture of *E*- and *Z*-isomers.

Next, we attempted the *β*-arylation of *O*-methyl oxime (**3**)[31] (existing as a 2 : 1 *E*/*Z* mixture), prepared from 2-cyclohexen-1-one (**1**), with 4-iodoanisole. This reaction proceeded to afford 3-(4-methoxyphenyl)-2-cyclohexen-1-one *O*-methyl oxime (**4a**) instead of 3-(4-methoxyphenyl)cyclohexanone *O*-methyl



(a) 4-Iodoanisole, Pd(TFA)$_2$, PCy$_3$, AgTFA, HFIP/1,4-dioxane
(b) H$_2$NOMe·HCl, pyridine

Chart 2. Synthesis of *O*-Methyl Oximes (**2**) and (**4a**)

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oxime (**2**). Conjugate addition to the *α*,*β*-unsaturated ketone and subsequent protonation of the resulting Pd(II) enolate typically occurs.10,14,15) However, in the *O*-methyl oxime, it is thought that *β*-hydrogen elimination occurred (Chart 3). The reaction yield was low (11% yield), but this series of reactions, oximation of ketone (**1**) followed by *β*-arylation of *O*-methyl oxime (**3**), had the synthetic advantage of giving *α*,*β*-unsaturated *O*-methyl oxime (**4a**) which could not be obtained by *β*-arylation of the ketone (**1**) and subsequent oximation.

To improve the yield of the resulting *O*-methyl oxime (**4a**), we examined the reaction conditions (Table 1). Using Pd(OAc)$_2$ and AgOAc, the yield was twice as much as that using the trifluoroacetate counterion (entry 2). Cu(OAc)$_2$, AgTFA, Cs$_2$CO$_3$ and NaO^{t}Bu were less effective as additives (entries 3–6). It was thought that the less electron-rich PPh$_3$ would be more suitable as the phosphine ligand (entries 8 and 9), but the presence or absence of PPh$_3$ was not crucial in this reaction (entry 9 *vs.* entry 10). In contrast to the phosphine ligands, AgOAc was essential (entry 11). Solvent effects were also surveyed. Only 1,4-dioxane without 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) resulted in a decreased yield (entry 7), thus HFIP was important. Toluene also proved to be efficient (entries 12 and 13). However, toluene afforded not only the desired 3-(4-methoxyphenyl)-2-cyclohexen-1-one *O*-methyl oxime (**4a**) but also a mixture of undesired *β*-arylated *O*-methyl oximes, 3-tolyl-2-cyclohexen-1-one *O*-methyl oximes (**4e**–**g**),32) resulting from starting *O*-methyl oxime (**3**) and toluene instead of 4-iodoanisole. Finally, Pd catalysts were investigated (entries 14 and 15). As a result, replacing Pd(OAc)$_2$ with Pd(PPh$_3$)$_2$Cl$_2$ afforded the desired product (**4a**) in 48% yield (entry 15). The resulting product (**4a**) was only the *E*-isomer, which was determined by a 2D nuclear Overhauser effect spectroscopy (NOESY) NMR experiment. Along with the product (**4a**), only the starting *O*-methyl oxime (**3**) was recovered (46% recovery). *O*-Methyl oxime (**2**) was not observed. From the ratio of *E*- and *Z*-isomers of recovered starting *O*-methyl oxime (**3**) (existing as approx. 2 : 3 *E*/*Z* mixture), it was considered that there was no possibility of isomerization of the *O*-methyl oxime under this reaction conditions.33)

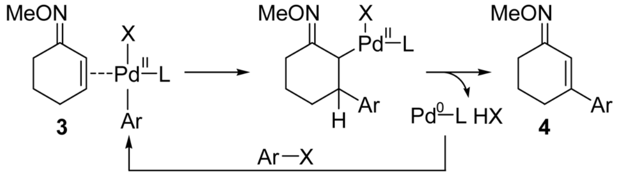
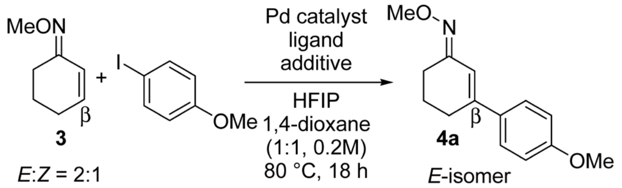


Chart 3. Proposed Mechanism for *β*-Arylation of *O*-Methyl Oxime (**3**)

Table 1. Optimization of Reaction Conditionsa)

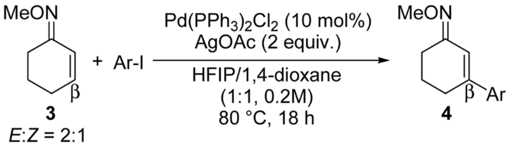


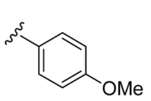
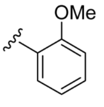
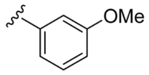
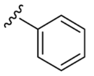
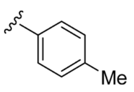
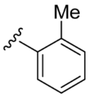
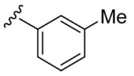
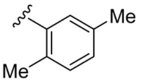
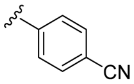
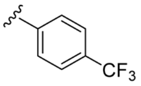
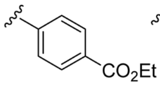
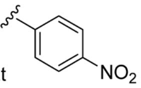
Entry	Pd catalyst (10 mol%)	Ligand (20 mol%)	Additive (2 equiv.)	Yield (%)
1	Pd(TFA)$_2$	PCy$_3$	AgTFA	11
2	Pd(OAc)$_2$	PCy$_3$	AgOAc	22
3	Pd(OAc)$_2$	PCy$_3$	Cu(OAc)$_2$	6
4	Pd(OAc)$_2$	PCy$_3$	AgTFA	2
5b)	Pd(OAc)$_2$	PCy$_3$	Cs$_2$CO$_3$	8
6b)	Pd(OAc)$_2$	PCy$_3$	NaO^{t}Bu	7
7b)	Pd(OAc)$_2$	PCy$_3$	AgOAc	9
8	Pd(OAc)$_2$	P(^{i}Pr)$_3$	AgOAc	28
9	Pd(OAc)$_2$	PPh$_3$	AgOAc	34
10	Pd(OAc)$_2$	None	AgOAc	30
11	Pd(OAc)$_2$	PPh$_3$	None	0
12c)	Pd(OAc)$_2$	PPh$_3$	AgOAc	37
13c)	Pd(OAc)$_2$	None	AgOAc	32
14	Pd(dppf)Cl$_2$	None	AgOAc	36
15	Pd(PPh$_3$)$_2$Cl$_2$	None	AgOAc	48

a) All the reactions were run with **3** (0.2 mmol) and 4-iodoanisole (0.2 mmol) in 1.0 mL solvent for 18 h. *b*) HFIP was not added. *c*) Toluene was used instead of 1,4-dioxane.

With the optimized conditions in hand, the substrate scope of the aryl iodides was investigated (Table 2). Substitutions on the aryl group at the *ortho*, *meta*, or *para* positions were all tolerated (**4a**–**c**, **4e**–**h**). Aryl iodides with both electron-donating and electron-withdrawing groups participated to give the corresponding *β*-arylated *O*-methyl oximes (**4i**–**l**). Under this reaction conditions, a variety of functional groups were tolerated, including nitriles (**4i**), esters (**4k**), and nitro groups (**4l**). In all cases, *E*-isomers were obtained preferentially over *Z*-isomers.34) The *E*- and *Z*-isomers were easily separable by silica gel column chromatography. The exact reason for the different ratios of resulting *E*- and *Z*-isomers based on the

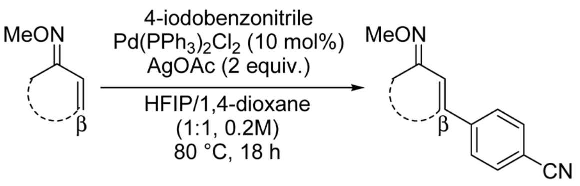
Table 2. Substrate Scope of Aryl Iodidesa)

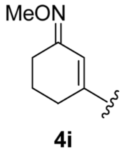
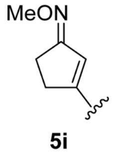
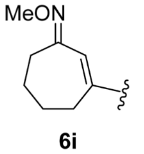


				
	4a	**4b**	**4c**	**4d**
(*E*)	48%	43%	53%	59%
(*Z*)	0%	10%	11%	25%
				
	4e	**4f**	**4g**	**4h**
(*E*)	38%	54%	47%	68%
(*Z*)	9%	14%	10%	17%
				
	4i	**4j**	**4k**	**4l**
(*E*)	37%	40%	36%	34%
(*Z*)	0%	0%	0%	7%

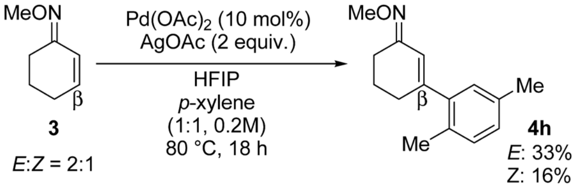
a) All the reactions were run with **3** (0.2 mmol) and aryl iodide (0.2 mmol) in 1.0 mL solvent for 18 h.

Table 3. Substrate Scope of *O*-Methyl Oximes[a)]



	 **4i**	 **5i**	 **6i**
(*E*)	37%	45%	33%
(*Z*)	0%	0%	14%

a) All the reactions were run with *O*-methyl oxime (0.2 mmol) and 4-iodobenzonitrile (0.2 mmol) in 1.0 mL solvent for 18 h.



3
E:*Z* = 2:1

4h
E: 33%
Z: 16%

Chart 4. Synthesis of *O*-Methyl Oxime (**4h**) Using *p*-Xylene

starting aryl iodides is unclear.

The scope of the *O*-methyl oxime component with different ring sizes was also examined (Table 3). The 5- and 7-membered ring *O*-methyl oximes such as 2-cyclopenten-1-one *O*-methyl oxime[35,36)] and 2-cyclohepten-1-one *O*-methyl oxime[37)] afforded the desired products (**5i**, **6i**).[34,38)]

Inspired by the side reaction of *O*-methyl oxime (**3**) and toluene in Table 1 (entries 12 and 13), we also examined Fujiwara-Moritani-type arylation.[39–42)] Using *p*-xylene as both the aryl source and solvent resulted in the β-arylated product (**4h**) in 49% total yield[43)] (Chart 4).

Conclusion

In summary, we have developed a novel method for the Pd-catalyzed β-arylation of *O*-methyl oximes, which can be prepared from cyclic α,β-unsaturated ketones such as 2-cyclohexen-1-one. This reaction can stand further improvement with respect to the yield, but it shows complete site-selectivity and extensive functional group tolerance. Using certain aryl iodides, only the *E*-isomer was obtained from the starting *O*-methyl oxime which existed as a mixture of *E*- and *Z*-isomers. In addition, not only aryl iodides but also arenes (*e.g.*, *p*-xylene and toluene) can be used as the aryl sources. Efforts on direct β-arylation of cyclic saturated *O*-methyl oximes with aryl halides and arenes are ongoing.

Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials.

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32) See Table 2. A mixture of 3-tolyl-2-cyclohexen-1-one *O*-methyl oximes (**4e**–**g**) were not separable by silica-gel column chromatography.
33) From the results of Table 2 [especially (**4d**)], isomerization of the *O*-methyl oxime under this reaction conditions was unlikely.
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37) 2-Cyclohepten-1-one *O*-methyl oxime was a 1 : 1 mixture of *E*- and *Z*-isomers, see supplementary materials.

38) See supplementary materials for details on the results of β-arylation of 5- and 7-membered ring *O*-methyl oximes with other aryl iodides.

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43) See supplementary materials for details on the studies of β-arylation of *O*-methyl oxime (**3**) with *p*-xylene.