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Palladium-Catalyzed Suzuki Carbonylative Reaction of α-Halomethyl Oxime Ethers: A Regioselective Route to Unsymmetrical 1,3-Oxyiminoketones

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Abstract: The three-component reaction of α-halomethyl oxime ethers, boronic acids and carbon monoxide at atmospheric pressure catalyzed by tetrakis-(triphenylphosphine)palladium(0) gives efficiently unsymmetrical β-alkoxyimino carbonyl compounds with total control of the regioselectivity, in high yield and atomic economy. Simple commercially available starting materials are used in this synthetic procedure. The three components assembly takes place preferentially *versus* the competing direct coupling or other possible side reactions. The mechanism of the transformation was investigated by NMR and intermediate palladium(II) complexes were detected.

Keywords: carbonylation; cross-coupling; palladium; reaction mechanisms; synthetic methods

Introduction

Transition metal-catalyzed cross-coupling reactions are nowadays among the most simple and successful C–C bond forming reactions with wide functional group tolerance on both the electrophilic and nucleophilic reactive partners.[1] The three components carbonylative version of these reactions using CO, an organohalide and an organometallic derivative has been widely applied to the synthesis of ketones, compounds that occupy a central role in synthetic organic chemistry.[2] The palladium-catalyzed carbonylative Suzuki reaction is the most popular over other versions since boronic acids are commercially available compounds inert to oxygen and moisture, thermally stable and generally non-toxic.[3] Kojima et al. first reported the synthesis of unsymmetrical ketones by this methodology from aryl iodides or benzyl chlorides using $Zn(acac)_2$ to promote the formation of an intermediate RCOPd(II)(acac) species which undergoes transmetallation.[4] This reaction later was extended by others to the preparation of unsymmetrical ketones containing a wide variety of substituents.[5–9] This approach to the synthesis of ketones is very attractive since the efficient assembly of three simple starting materials occurs in just one step with high atom economy. The success of the transformation requires high selectivity in the three components assembly *versus* the competing direct coupling, the main competing alternative reaction. The main advances in this area have been focused to the search of new catalytic systems[10] for the purpose of (i) avoiding the use of additives, (ii) avoiding or diminishing the formation of secondary products such as those derived from homocoupling or direct cross-coupling reactions thus expanding the range of suitable electrophiles[11] and (iii) conducting the catalysis in a heterogeneous phase.[12] Alkyl aryl ketones have also been synthesized by Pd/light induced carbonylative cross-coupling of alkyl iodides and arylboronic acids circumventing the β-elimination reaction.[13]

Recently we reported that (*Z*)-α-halomethyl oxime ethers (**1**) are suitable substrates for palladium-catalyzed Suzuki cross-coupling reactions with a wide variety of aryl-, heteroaryl- and vinylboronic acids to afford the corresponding α-substituted oxime ethers with good yields.[14] Compounds **1** can be considered as synthetic equivalents of ketones in palladium-catalyzed Suzuki reactions. This finding prompted us to explore the palladium-catalyzed carbonylative Suzuki version of this reaction which would provide the challenging regioselective preparation of *N,O*-1,3-difunctional compounds within a non-symmetrical backbone. Compounds with this connectivity cannot be prepared from direct precursors such as 1,3-dicarbonyl compounds[15] and hydroxylamine *O*-ether due to

the formation of mixtures of regioisomers.[16] This type of compounds can be obtained by reaction of an aldehyde and methyl aryl or methyl alkyl oxime ether in the presence of BuLi followed by oxidation of the alcohol. Another approach to these compounds is the condensation of hydroxylamine *O*-ether with 1,3-hydroxy ketones and subsequent oxidation.[17] This route provides a mixture of stereoisomers of the *E*-/*Z*-oxime ether.

Now we report the easy synthesis of 1,3-oxyimino ketones **3** with complete regiocontrol within a non-symmetrical carbon skeleton by the three components carbonylative Suzuki–Miyaura reaction of α-halomethyl oxime ethers **1**. Compounds **3** constitute a facile entry to β-oxyimino alcohols[18] and γ-amino alcohols[19] upon stereo- or enantioselective reduction, two classes of compounds with remarkable interest from the biological point of view and also as metal ligands. Furthermore, oxyimino carbonyl compounds (**3**) have found a recent application for the synthesis of pyrroles.[17]

Results and Discussion

α-Halomethyl oxime ethers **1** (Figure 1) were submitted to reaction with boronic acids **2** (Figure 2) under CO contained in a balloon at atmospheric pressure in the presence of a Pd(0) catalyst and cesium fluoride

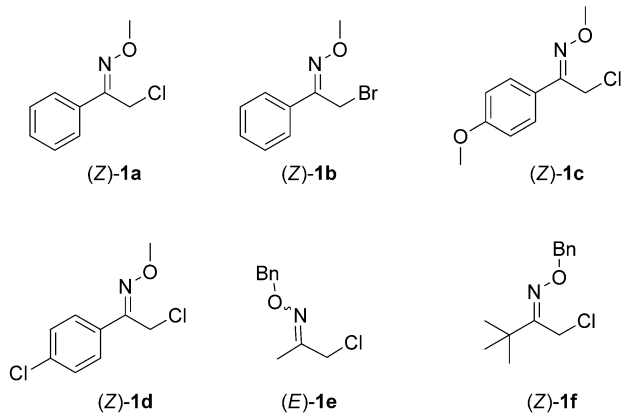


Figure 1. Halomethyl oxime ethers **1**.

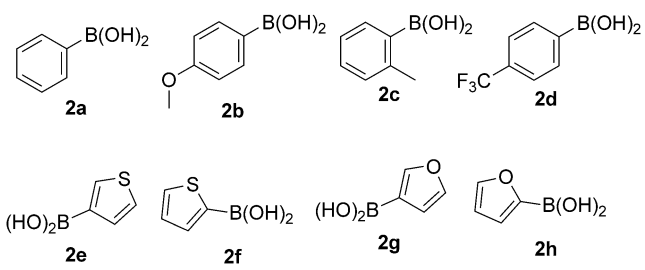


Figure 2. Boronic acids **2**.

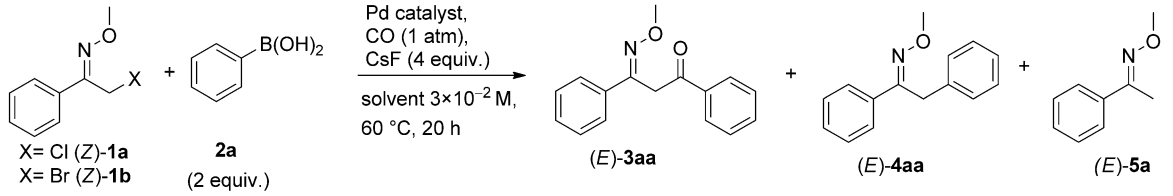
to afford the corresponding oxyimino ketones **3** with good yields.

First, to optimize the experimental conditions, α-halomethyl oxime ethers (*Z*)-**1a** or (*Z*)-**1b** and the parent boronic acid **2a** were selected as model substrates and a number of Pd(0) catalytic systems with different ligands were essayed in several solvents (see Table 1). Reaction of (*Z*)-**1a** and **2a** catalyzed with $Pd(PPh_3)_4$ (run 3, Table 1) in THF gave high conversion and selectivity but formation of polymers made extraction of the product difficult thus lowering the isolated yield in this case (see the Supporting Information). Other ether solvents like 1,4-dioxane facilitate the formation of cross-coupled or dehalogenated products (*E*)-**4aa** and (*E*)-**5a** (run 4, Table 1). Reactions were also assayed in toluene solution (runs 5 and 6, Table 1). Different results were obtained in this solvent depending on the nature of the halide present in the starting halomethyl oxime ether **1**. The oxidative addition reaction was easier with (*Z*)-**1b** than in the case of (*Z*)-**1a** but (*E*)-**5a** was the major product besides the expected oxyimino ketone (*E*)-**3aa** in 23% yield (run 6, Table 1). However, chloromethyl oxime ether (*Z*)-**1a** gave as the major product in this solvent the alkoxycarbonylation derivative (*E*)-**7a** from phenol produced in the *in situ* decomposition of **2a** (run 5, Table 1). Best yields and selectivities towards the carbonylative Suzuki–Miyaura coupling were obtained in chloroform as the solvent (runs 7 and 8, Table 1).

Regarding the influence of the ligand in the catalytic system (runs 3, 7 and 9–17, Table 1), $Pd(PPh_3)_4$ was revealed as the most effective of the tested catalysts (runs 3 and 7, Table 1). The electron-rich monodentate phosphine $P(o\text{-tolyl})_3$ provided the desired product (*E*)-**3aa** with very low yield (run 9, Table 1). The electron-poor phosphine $P(p\text{-}FC_6H_4)_3$ did not promote the oxidative addition reaction and most of the starting material (*Z*)-**1a** was recovered unchanged after 20 h (run 10, Table 1). The results obtained with other more sophisticated monodentate phosphines were not satisfactory in this case (runs 11 and 12, Table 1). Bidentate phosphines commonly used in other carbonylative reactions (runs 13–17, Table 1) were assayed in THF (run 13, Table 1 and Table S1 in the Supporting Information) or chloroform solution but gave in general a poor conversion with formation of hydroxy- or alkoxycarbonylation products. Cesium fluoride was very effective in promoting the transmetallation of boronic acids in the carbonylative oxime ether coupling process. Use of KF or Cs_2CO_3 to promote the reaction gave the desired product (*E*)-**3aa** with relatively good conversion (runs 18 and 19, Table 1). By contrast, CsOAc was less effective giving (*E*)-**5a** and alkoxycarbonylation products (run 20, Table 1)

With the optimized conditions in hand, carbonylative cross-coupling reactions of representative α-halo-

Table 1. Development of the catalytic system[a] for the Pd-catalyzed carbonylative cross-coupling reaction of α-halomethyl oxime ethers with phenylboronic acid.[b]



Run	1	Pd catalyst	Solvent[c]	Base	(*Z*)-**1** [%]	(*E*)-**3aa** [%]	(*E*)-**4aa** [%]	(*E*)-**5a** [%]
1	**b**	$Pd(PPh_3)_4$	THF	CsF	0	47	27	11
2[d]	**b**	$Pd(PPh_3)_4$	THF	NEt_3	0	10	12	30
3	**a**	$Pd(PPh_3)_4$	THF[e]	CsF	0	43	3	5
4	**a**	$Pd(PPh_3)_4$	1,4-dioxane	CsF	55	6	24	15
5[f]	**a**	$Pd(PPh_3)_4$	toluene	CsF	39	8	0	0
6	**b**	$Pd(PPh_3)_4$	toluene	CsF	0	23	0	60
7	**a**	$Pd(PPh_3)_4$	$CHCl_3$	CsF	9	87	4	0
8	**b**	$Pd(PPh_3)_4$	$CHCl_3$	CsF	0	84	4	12
9	**a**	$Pd(dba)_2$/P(*o*-tolyl)$_3$ 20 mol%	THF	CsF	97	2	1	0
10	**a**	$Pd(dba)_2$/P(*p*-FC_6H_4)$_3$ 20 mol%	THF	CsF	97	0	1	2
11	**a**	$Pd(dba)_2$/DavePhos 20 mol%	THF	CsF	72	0	1	27
12	**a**	$Pd(dba)_2$/*t*-BuXphos 20 mol%	THF	CsF	99	0	1	0
13[g]	**a**	$Pd(dba)_2$/Xantphos 7 mol%	THF	CsF	92	0	1	1
14[h]	**a**	$Pd(OAc)_2$/Xantphos 7 mol%	$CHCl_3$	CsF	10	0	0	5
15	**a**	$Pd(OAc)_2$/binap 10 mol%	$CHCl_3$	CsF	98	1	1	0
16[h]	**a**	$Pd(OAc)_2$/dppb 10 mol%	$CHCl_3$	CsF	49	1	2	1
17	**a**	$Pd(OAc)_2$/dppe 10 mol%	$CHCl_3$	CsF	94	2	1	3
18	**a**	$Pd(PPh_3)_4$	$CHCl_3$	KF	26	64	0	10
19[h]	**a**	$Pd(PPh_3)_4$	$CHCl_3$	Cs_2CO_3	0	72	5	9
20[h]	**a**	$Pd(PPh_3)_4$	$CHCl_3$	CsOAc	3	16	0	29

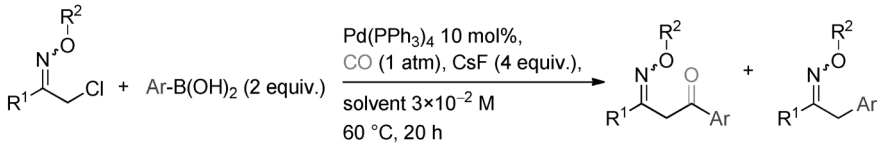
[a] *Reaction conditions:* 0.3 mmol **1a** or **1b**, 0.6 mmol **2a**,10 mol% Pd source, phosphine ligand, 1.2 mmol base, 10 mL solvent, 60 °C, 20 h. Yields were determined by ^{1}H NMR analysis with acetophenone as internal standard.
[b] Less than 15% of 1,1′-biphenyl was obtained.
[c] All solvents were dried and distilled prior to use.
[d] (1*E*,4*E*)-1,4-Diphenylbutane-1,4-dione *O,O*-dimethyl dioxime [(*E,E*)-**6a**] was obtained in 24% yield.
[e] A polymer formed in these reaction conditions hampers the extraction of the product.
[f] (*E*)-Phenyl 3-(methoxyimino)-3-phenylpropanoate [(*E*)-**7a**] was obtained in 53% yield.
[g] (*E*)-**7a** was obtained in 6% yield.
[h] Alkoxy- and hydroxycarbonylation side products were also detected.

methyl oxime ethers **1a–1f** and boronic acids **2a–2h** with different electronic properties and substitution patterns were assayed. High selectivity was observed in all the cases in the carbonylative Suzuki coupling with regard to the undesired competing direct coupling. Parent boronic acid **2a** and *para*-substituted electron-rich arylboronic acid **2b** reacted very efficiently leading to the corresponding three components product with high yields (runs 1 and 2, Table 2).

The position of the electron-donating group in the aromatic ring did not induce noticeable differences in the selectivity of the carbonylative reaction. The overall conversion was only 55% with the relatively hindered *ortho*-methyl substituted boronic acid **2c** (run 3, Table 2). The influence of electron-withdrawing groups in the aromatic ring was tested in the carbonylative arylation of (*Z*)-**1a** with *para*-trifluoromethylphenylboronic acid (**2d**) giving the expected product with slightly lower yield than the parent boronic acid (run 4, Table 2). The reaction was general regarding the nucleophilic partner and satisfactory results were also obtained with heteroarylboronic acids **2e–h** (runs 5–8, Table 2). Butylboronic acid was also tested in carbonylative Suzuki cross-coupling reactions in THF and $CHCl_3$ as solvents but formation of the expected carbonylated product was not observed in any case.

Several modifications were introduced in the reacting α-halomethyl oxime ethers **1** as well (runs 9–14, Table 2). Oxime (*Z*)-**1c** led to the carbonylation products (*E*)-**3ca** and (*E*)-**3ch** with excellent selectivity over the competitive direct coupling products (*E*)-**4ca** and (*E*)-**4ch** (runs 9 and 10, Table 2) despite the electron-releasing character of the substituent attached to the aryl group that could make sluggish the oxidative

Table 2. Regioselective Pd-catalyzed three-component Suzuki–Miyaura cross-coupling reaction of α-halomethyl oxime ether **1** with boronic acids **2** in THF or $CHCl_3$.[a]



1 **2a-h** **3** **4** <5%

Run	2	Conv.[%]	(*E*)-3	Yield [%][b]	Run	2	Conv. [%]	(*E*)-3	Yield [%][b]
1	**a**	90	(*E*)-**3aa**	85	8	**h**	90	(*E*)-**3ah**	70
2	**b**	91	(*E*)-**3ab**	80	9	**a**	85	(*E*)-**3ca**	70
3	**c**	55	(*E*)-**3ac**	50	10	**h**	80	(*E*)-**3ch**	75
4	**d**	85	(*E*)-**3ad**	75	11	**a**	66	(*E*)-**3da**	29[c]
5	**e**	100	(*E*)-**3ae**	90	12	**g**	100	(*E*)-**3dg**	86
6	**f**	85	(*E*)-**3af**	75	13	**g**	100	(*E/Z*)-**3eg** *E/Z* 63/37	82
7	**g**	100	(*E*)-**3ag**	91	14	**g**	74	(*E*)-**3fg**	70

[a] *Reaction conditions:* 0.3 mmol **1**, 0.6 mmol **2a–h**, 0.03 mmol $Pd(PPh_3)_4$, 1.2 mmol CsF, 10 mL dry THF for heteroarylboronic acids or $CHCl_3$ for arylboronic acids, 60 °C, 20 h.
[b] Isolated yields. Side products (*E*)-**5** and (*E,E*)-**6** were obtained in less than 7%.
[c] In this case (*E*)-**4da** was also obtained with 37% yield.

addition step. The effect on the reactivity of an electron-withdrawing group attached to the aryl oxime moiety depends on the type of boronic acid considered. So, the direct cross-coupling is the main process in the reaction of compound (*Z*)-**1d** with the parent boronic acid **2a** affording (*E*)-**4da** as the major product with a moderate conversion (run 11, Table 2).[20] Conversely, the carbonylative coupling occurs nicely in the reaction of (*Z*)-**1d** with 3-furylboronic acid (**2g**) affording with total conversion the desired product (*E*)-**3dg** (run 12, Table 2). Alkyl oxime ethers (*E*)-**1e** and (*Z*)-**1f** gave excellent results in the carbonylative cross-coupling reaction yielding compounds (*E*)-**3eg** and (*E*)-**3fg** with total selectivity (runs 13 and 14,

Table 2). Complete conversion could not be achieved after 20 h with the hindered oxime (*Z*)-**1f**.

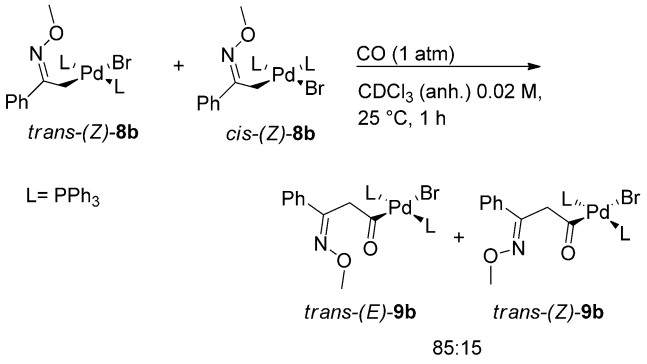
Mechanism

The usual reaction sequence in Suzuki carbonylative reactions between aryl halides and boronic acids, namely, oxidative addition, CO coordination followed by aryl migration and then transmetallation of the resulting acylpalladium(II) complex, hardly explains our previous findings in the palladium-catalyzed carbonylative Suzuki reaction of bromomethyl sulfoxides. With these compounds as electrophiles the insertion of carbon monoxide takes place after the transmetallation step.[21] Halomethyl oxime ethers also contain an electron-withdrawing substituent in the α-position relative to the halide. Then, to ascertain the CO insertion sequence in this latter case, the migratory ability of the oxime ether fragment in (*Z*)-**1b** was investigated. The complexes *trans*- and *cis*-(*Z*)-**8b** were treated under CO at atmospheric pressure. The reaction mixture (see the Supporting Information) was transferred to a sealed NMR tube and the ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded. Complete conversion of complexes (*Z*)-**8b** took place affording a mixture of CO insertion complexes *trans*-**9b** containing the *E*- and *Z*-stereoisomers of the oxime ether ligand (Scheme 1). The most characteristic feature displayed by the ^{1}H NMR spectrum of the mixture was the appearance of two sets of two pairs of signals in an 85/15 ratio assigned to the methylene ($\delta = 3.64$ and 3.67 ppm) and methoxy ($\delta = 3.81$ and 3.88 ppm) protons of the *E/Z* diastereoisomers.[22] A small deshielded signal in the ^{13}C NMR spectrum at $\delta = 226.8$ ppm revealed the presence of CO in the major component of the mixture. Characteristic signals at $\delta = 19.2$ and 19.4 ppm were detected in the ^{31}P NMR spectrum corresponding to square planar complexes *trans*-(*Z*)-**9b** and *trans*-(*E*)-**9b** respectively. The presence of PPh_3 ($\delta = -5.2$ ppm), $OPPh_3$ ($\delta = 29.1$ ppm) and $PdBr_2(PPh_3)_2$ ($\delta = 22.0$ ppm) was also detected. These observations are in good agreement with data reported by Beller and Beck et al.[23] for other acyl palladium complexes. The equilibrating complex *cis*-**9b** could not be detected under our experimental conditions. Minor ligand *E/Z* isomerization observed in complex *trans*-**9b** contrasts with the configurational stability shown by oxime ether ligands in oxidative addition complexes obtained in the absence of CO.[14] In the same sense, complexes *trans*-(*E*)- and *trans*-(*Z*)-**9b** were static species with sharp NMR signals at room temperature while the corresponding oxidative addition complexes (*Z*)-**8b** show a dynamic NMR behavior.[14]

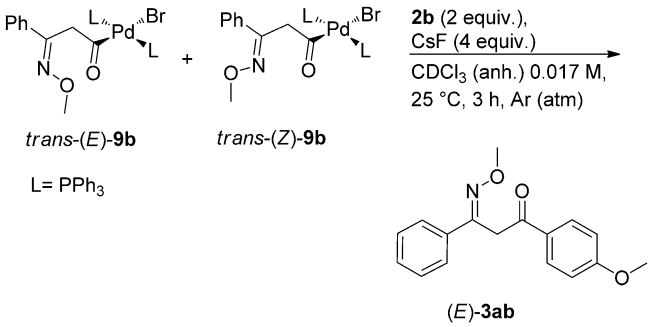
Acylpalladium complex *trans*-**9b** was quite stable and it could be stored in the NMR tube for a time. Small signals corresponding to dehalogenation and reductive homocoupling products (*E*)-**5a** and (*E,E*)-**6a** appeared after 5 h under an argon atmosphere. Simultaneous formation of complex $Pd_2(\mu\text{-}CO)Br_2(PPh_3)_3$ was detected by ^{31}P NMR.[24] Equimolecular amounts of compounds *trans*-(*Z*)-**9b**, *trans*-(*E*)-**9b** and (*E*)-**5a** were formed by decomposition of the 85/15 *trans*-(*E/Z*)-**9b** mixture after 72 h. It is to be noted that only *trans*-(*E*)-**9b** decomposed, while the minor stereoisomer *trans*-(*Z*)-**9b** remained unchanged (see the Supporting Information). Formation of direct oxidative addition complex (*Z*)-**8b** was never observed along the decomposition process revealing the irreversibility of the insertion–migration step.[25]

The transmetallation step was also monitored by ^{1}H, ^{13}C and ^{31}P NMR in $CDCl_3$ solution. Upon treatment of the mixture of complexes *trans*-(*E*)- and t*rans-(Z)*-**9b** with **2b** and CsF only the carbonylative cross-coupled product (*E*)-**3ab** was observed after 3 h (Scheme 2). Extrusion of CO could not be even detected (see the Supporting Information). These experiments allow ascertaining that the carbonylative cross-coupling catalytic cycle in halomethyl oxime ethers follows the usual reaction sequence of regular carbonylative Suzuki reactions, that is, the CO insertion precedes the transmetallation step.

The electron-withdrawing character of chlorine in the 4-chloro-substituted oxime ether (*Z*)-**1d** appears



Scheme 1. Carbonylation reaction of complexes (*Z*)-**8b**.



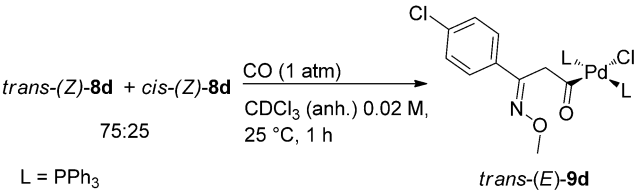
Scheme 2. Stoichiometric reaction between *trans*-(*E/Z*)-**9b** and **2b**.

to diminish the electron density at the methylene oxime fragment decelerating the migration step. In this case, the carbonylated product (*E*)-**3da** was obtained with lower yield in the coupling of (*Z*)-**1d** with **2a**. Formation of the direct cross-coupling product (*E*)-**4da** was favored instead. However, the same effect was not observed in the coupling of (*Z*)-**1d** with the electron-rich 3-furylboronic acid (**2g**) whose transmetallation reactions[26] are known to proceed more readily.

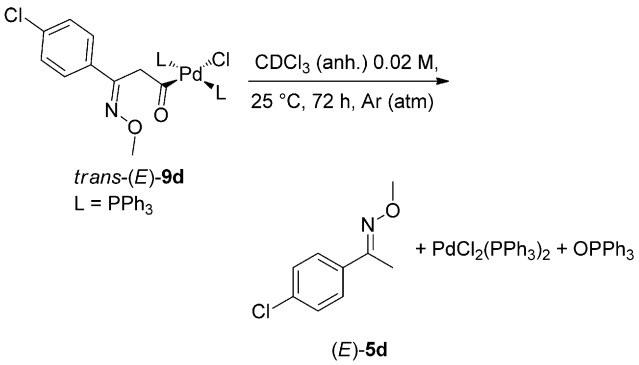
To clarify further the different behavior of **2a** and **2g** the carbonylative cross-coupling of (*Z*)-**1d** was studied in detail. First, oxime ether (*Z*)-**1d** was treated in an NMR tube with $Pd(PPh_3)_4$ in $CDCl_3$ as solvent. ^1H and ^{31}P NMR spectra were recorded at room temperature in order to detect the oxidative addition complex (*Z*)-**8d** (Scheme 3). Signals at $\delta = 2.41$ (dd, $J = 10.3$, 3.9 Hz, CH_2) and 3.82 (br s, CH_3) ppm in the ^1H NMR (400 MHz) spectrum and $\delta = 19.0$ (d, $J =$ 38.0 Hz, 1P) and 39.8 (d, $J = 38.0$ Hz, 1P) ppm in the proton decoupled ^{31}P (162 MHz) spectrum revealed the presence in solution of the square-planar complex *cis*-(*Z*)-**8d** in low concentration.[27] In addition, broad proton NMR bands centered at $\delta = 2.17$ and 3.53 ppm and a phosphorus NMR signal at $\delta = 14.1$ ppm accounted respectively for the oxime ether methylene and methyl protons and the phosphorus in the oxidative addition complex *trans*-(*Z*)-**8d**. The broad bands suggest a fast ligand coordination–decoordination process at room temperature in this latter complex. The equilibrium between phosphorus-containing species and free PPh_3 was slow when the temperature decreased to −20 °C. It could finally be frozen at −60 °C giving rise to two sharp phosphorus signals at $\delta = 26.2$ and −7.3 ppm assigned to the square-planar complex *trans*-(*Z*)-**8d** and free PPh_3 respectively besides small signals corresponding to *cis*-(*Z*)-**8d**.

The above mixture containing complexes (*Z*)-**8d** was submitted to react with CO, contained in a balloon at atmospheric pressure, for 1 h at room temperature to afford with total conversion a new acylpalladium(II) complex *trans*-(*E*)-**9d** which exhibited an NMR pattern similar to that of *trans*-(*E*)-**9b** (Scheme 4). By contrast, *E/Z* isomerization could not be detected in transformations involving oxime ether (*Z*)-**1d**. Decomposition of *trans*-(*E*)-**9d** was monitored by NMR as above described, affording an equimolecular mixture of $PdCl_2(PPh_3)_2$ and (*E*)-**5d** after 72 h (Scheme 5).

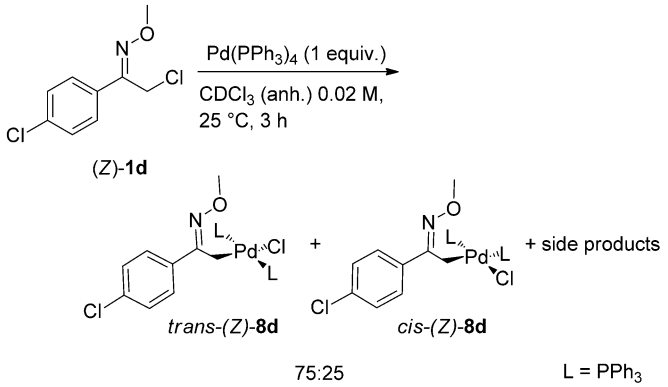
The cross-coupling reaction of *trans*-(*E*)-**9d** with boronic acids was tested in the presence of CsF (Scheme 6 and Scheme 7). Complex *trans*-(*E*)-**9d** reacted with **2g** yielding the expected product (*E*)-**3dg** almost quantitatively in 10 h. The same product was obtained when complexes *trans*- and *cis*-(*Z*)-**8d** were submitted to reaction with **2g** and CsF under a CO atmosphere at 60 °C after an hour, while 18 h were necessary in the reaction at room temperature



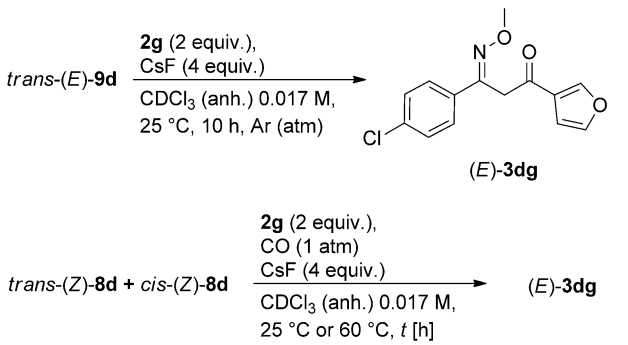
Scheme 4. Carbonylation reaction of complexes (*Z*)-**8d**.



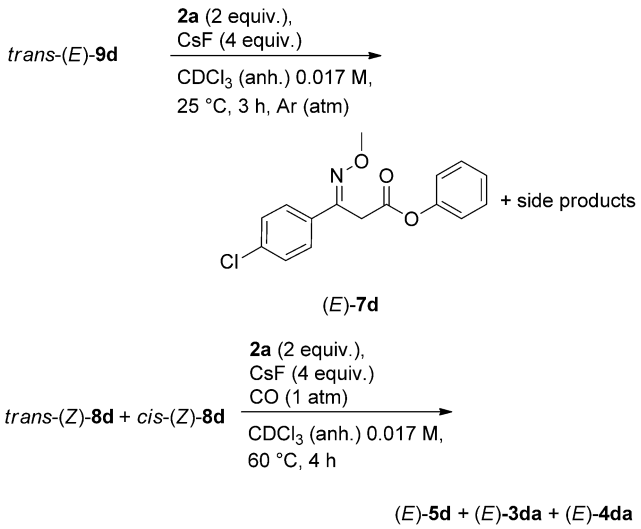
Scheme 5. Decomposition reaction of complex *trans*-(*E*)-**9d**.



Scheme 3. Oxidative addition reaction of (*Z*)-**1d**.



Scheme 6. Stoichiometric reactions of *trans*-(*E*)-**9d** and complexes (*Z*)-**8d** with **2g**.



Scheme 7. Stoichiometric reactions of *trans*-(*E*)-**9d** and complexes (*Z*)-**8d** with **2a**.

(Scheme 6). In the last experiment, the quantitative formation of *trans*-(*E*)-**9d** from *trans*- and *cis*-(*Z*)-**8d** can be observed at the initial stage of the reaction. These results strongly suggest that the CO insertion reaction precedes the transmetallation step. Conversely, (*E*)-**7d** was the major product when *trans*-(*E*)-**9d** reacted with phenylboronic acid (**2a**) due to alkoxylation of the acylpalladium(II) complex with phenol generated by decomposition of **2a**. Small amounts of (*E*)-**4da** were also obtained by direct cross-coupling reaction but product (*E*)-**3da** could not be even detected under these reaction conditions (see the Supporting Information). Alkoxycarbonylation was also the main reaction when *trans*- and *cis*-(*Z*)-**8d** were reacted at room temperature with **2a** in the presence of CsF under CO at atmospheric pressure giving (*E*)-**7d** as the major compound besides the carbonylated product (*E*)-**3da**. The Suzuki carbonylative reaction took place more efficiently when the reaction was performed under heating. In fact, at 60 °C the reaction led to (*E*)-**3da** and (*E*)-**5d** in nearly equimolecular amounts together with less than 15% of (*E*)-**4da**, the direct cross-coupled product. It should be noted that the low value of the ratio phenylboronic acid (**2a**):palladium complex in the stoichiometric reaction does not favor the transmetallation over other side reactions of **2a**.[28]

Our experiments clearly demonstrate the migrating ability of the methylene oxime ether fragment, however, when it carries an electron-withdrawing substituent the success of the carbonylative Suzuki cross-coupling requires using a boronic acid with increased transmetallating ability to avoid undesired decomposition side processes.

Conclusions

The new palladium-catalyzed carbonylative cross-coupling reaction of α-halomethyl oxime ethers described herein allows the selective preparation of unsymmetrical β-alkoxyimino carbonyl derivatives bearing the oxime ether function at a prefixed position with high yield and atomic economy. Simple commercially available starting materials are used in our methodology. Each heteroatom derives from a different component and, consequently, the regiocontrol regarding the products is guaranteed by the unequivocal assembly in the multicomponent reaction. Unsymmetrical oxyimino carbonyl compounds **3** are synthesized in good to moderate yields in pure stereoisomeric form.

The migrating ability of the methylene oxime ether fragment in Suzuki carbonylative reactions of halomethyl oxime ethers is general and it has been clearly established. Extrusion of CO does not occur in the intermediate Pd(II) complexes. Use of a boronic acid with increased transmetallating ability may be required to avoid undesired decomposition side processes in the carbonylative Suzuki cross-coupling when the starting halomethyl oxime ether carries an electron-withdrawing substituent.

These experiments allow ascertaining that the carbonylative cross-coupling catalytic cycle with halomethyl oxime ethers follows the reaction sequence of regular carbonylative Suzuki reactions, that is, the CO insertion precedes the transmetallation step.

Experimental Section

General Methods

Reactions were carried out in Schlenk tubes under a CO atmosphere. All reagents were used as received from the commercial supplier. THF was distilled from sodium/benzophenone. $CHCl_3$ was distilled from P_2O_5. Carbonylation reactions were monitored by analytical thin layer chromatography using commercial aluminium sheets pre-coated (0.2 mm layer thickness) with silica gel 60 F_{254} (E. Merck) or by gas chromatography. GC analyses were performed with Finnigan Focus GC systems equipped with a glass capillary column SGE PBX5 (30 m length, 0.25 mm inner diameter, 0.25 μm film thickness) and flame ionization detection under a constant flow 1 mL min^{-1} helium carrier gas. GC-MS analyses were performed with a GC Agilent 6890N system equipped with a glass capillary column HP-5 MS UI (30 m length, 0.25 mm inner diameter, 0.25 μm film thickness) and a low resolution quadrupole analyzer detector with a constant velocity of 1 mL min^{-1} helium carrier gas. Product purification by flash chromatography was performed using E. Merck Silica Gel (230–400 mesh). Visualization was carried out with UV light. Proton, phosphorus and carbon magnetic nuclear resonance were recorded at 300, 122 and 75 MHz, respectively, with a Bruker DPX-300, at 400, 162 and 101 MHz with a Bruker AV-400 or at 500,

203 and 126 MHz with a Bruker DRX-500. Chemical shifts are reported in ppm relative to TMS peak at 0.000 ppm (^{1}H), H_3PO_4 at 0.000 (^{31}P) and $CDCl_3$ peak at 77.00 ppm (^{13}C). Coupling constants (*J*) are given in Hertz (Hz). The letters m, s, d, t and q stand for multiplet, singlet, doublet, triplet and quartet respectively. The letters br indicate broad signal. High resolution mass spectra were determined on a TRIPLETOFT5600 (ABSciex, USA) spectrometer or on a Fisons VG Autospec instrument. All melting points are uncorrected and were recorded on a Cambridge Instruments apparatus.

Palladium-Catalyzed Three Component Suzuki–Miyaura Reaction with α-Halomethyl oxime Ether (1); General Procedure

To an oven-dried 20-mL flask previously evacuated and flushed with argon for three times, the appropriate boronic acid **2a–h** (0.6 mmol), CsF (1.2 mmol), $Pd(PPh_3)_4$ (0.03 mmol), α-halomethyl oxime ether **1** (0.3 mmol) and dry THF or dry $CHCl_3$ (10 mL) were added. Then, a reflux condenser and a carbon monoxide balloon were fitted under an argon atmosphere. The system was evacuated and flushed with carbon monoxide for three times. The mixture was stirred at 60 °C in a carbon monoxide at atmospheric pressure for 20 h, and then cooled at room temperature, filtered through a celite pad and washed with CH_2Cl_2 (20 mL). Solvents were removed under reduced pressure and the residue purified by column chromatography yielding the corresponding product **3**.

Characterization of compounds 3

(*E*)-3-(Methoxyimino)-1,3-diphenylpropan-1-one[17] (3aa) [CAS: 1361387-64-5]: $CHCl_3$ was used as solvent; yield: 85%; white solid; mp 87–90 °C; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.93 (dm, *J* = 6.9 Hz, 2H), 7.54–7.57 (m, 3H), 7.38–7.51 (m, 2H), 7.26–7.29 (m, 3H), 4.34 (s, 2H), 3.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.6, 152.6, 136.5, 135.5, 133.3, 129.3, 128.7, 128.5, 128.3, 126.3, 62.1, 37.8; HR-MS (EI): *m*/*z* (M^+) = 253.1095, calcd. for $C_{16}H_{15}NO_2$: 253.1103.

(*E*)-3-(Methoxyimino)-1-(4-methoxyphenyl)-3-phenylpropan-1-one[29] (3ab) [CAS: 1361387-65-6]: $CHCl_3$ was used as solvent; yield: 80%; white solid; mp 58–60 °C; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 7,92 (dm, *J* = 9 Hz, 2H), 7.54–7,57 (m, 2H), 7.26–7.28 (m, 3H), 6.87 (dm, *J* = 9 Hz, 2H), 4.31 (s, 2H), 3.90 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.1, 163.7, 152.8, 135.6, 130.6, 129.5, 129.2, 128.5, 126.3, 113.8, 62.1, 55.5, 37.5; HR-MS (EI): *m*/*z* (M^+) = 283.1200, calcd. for $C_{17}H_{17}NO_3$: 283.1208.

(*E*)-3-(Methoxyimino)-3-phenyl-1-*ortho*-tolylpropan-1-one (3ac): $CHCl_3$ was used as solvent; yield: 50%; colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.63 (d, *J* = 7.8 Hz, 1H), 7.52–7.55 (m, 2H), 7.27–7.30 (m, 4H), 7.15–7.20 (m, 2H), 4.24 (s, 2H), 3.88 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.4, 152.8, 138.4, 137.3, 135.6, 131.9, 131.5, 129.3, 128.5, 128.4, 126.3, 125.5, 62.1, 40.7, 21.0; HR-MS (EI): *m*/*z* (M^+) = 267.1251, calcd. for $C_{17}H_{17}NO_2$: 267.1259.

(*E*)-3-(Methoxyimino)-3-phenyl-1-[4-(trifluoromethyl)-phenyl]propan-1-one (3ad): $CHCl_3$ was used as solvent; yield: 75%; colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 8.03 (dm, *J* = 8.1 Hz, 2H), 7.67 (dm, *J* = 8.1 Hz, 2H), 7.54–7.57 (m, 2H), 7.29–7.31 (m, 3H), 4.33 (s, 2H), 3.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.9, 152.1, 135.2, 129.5, 128.6, 128.3 (q, *J* = 257 Hz), 126.3, 125.8, 125.7 (q, *J* = 3.7 Hz), 121.9, 62.2, 38.1; HR-MS (EI): *m*/*z* (M^+) = 321.0976, calcd. for $C_{17}H_{14}F_3NO_2$: 321.09766.

(*E*)-3-(Methoxyimino)-3-phenyl-1-(thiophen-3-yl)propan-1-one (3ae): THF was used as solvent; yield: 90%; pale yellow solid; mp 46–49 °C; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 8.09 (dd, *J* = 3 Hz, 1H), 7.55–7.58 (m, 2H), 7.49 (dd, *J* = 1.2 Hz, 1H), 7.26–7.28 (m, 3H), 7.23 (dd, *J* = 3 Hz, 1H), 4.26 (s, 2H), 3.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 188.8, 152.2, 141.4, 135.3, 132.5, 129.3, 128.5, 127.0, 126.4, 126.3, 62.2, 38.8; HR-MS (EI): *m*/*z* (M^+) = 259.0658, calcd. for $C_{14}H_{13}NO_2S$: 259.0667.

(*E*)-3-(Methoxyimino)-3-phenyl-1-(thiophen-2-yl)propan-1-one (3af): THF was used as solvent; yield: 75%; pale yellow solid; mp 54–58 °C; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.76 (dd, *J* = 1.2 Hz, 1H), 7.57–7.60 (m, 3H), 7.28–7.30 (m, 3H), 7.07 (dd, *J* = 3.9 Hz, 1H), 4.30 (s, 2H), 3.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.3, 152.0, 143.4, 135.3, 134.0, 132.4, 129.3, 128.5, 128.1, 126.3, 62.2, 38.3; HR-MS (EI): *m*/*z* (M^+) = 259.0659, calcd. for $C_{14}H_{13}NO_2S$: 259.0667.

(*E*)-1-(Furan-3-yl)-3-(methoxyimino)-3-phenylpropan-1-one (3ag): THF was used as solvent; yield: 91%; pale yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 8.06 (s, 1H), 7.56–7.59 (m, 2H), 7,35 (t, *J* = 1.5 Hz, 1H), 7.26–7.28 (m, 3H), 6.70 (d, *J* = 1.8 Hz, 1H), 4.12 (s, 2H), 3.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 189.1, 151.9, 147.6, 146.8, 144.1, 135.2, 129.4, 128.5, 126.3, 108.8, 62.2, 39.3; HR-MS (EI): *m*/*z* (M^+) = 243.0888, calcd. for $C_{14}H_{13}NO_3$: 243.0895.

(*E*)-1-(Furan-2-yl)-3-(methoxyimino)-3-phenylpropan-1-one[17] (3ah) [CAS: 1361387-66-7]: THF was used as solvent; yield: 70%; pale yellow solid; mp 73–75 °C; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.60–7.54 (m, 2H), 7.52 (dd, *J* = 1.6, 0.7 Hz, 1H), 7.36–7.21 (m, 3H), 7.23–7.10 (m, 1H), 6.47 (dd, *J* = 3.6, 1.7 Hz, 1H), 4.21 (s, 2H), 3.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 183.3, 152.1, 151.9, 146.4, 135.4, 129.3, 128.5, 126.3, 117.4, 112.4, 62.2, 37.6; HR-MS (EI): *m*/*z* (M^+) = 243.0885, calcd. for $C_{14}H_{13}NO_3$: 243.0895.

(*E*)-3-(Methoxyimino)-3-(4-methoxyphenyl)-1-phenylpropan-1-one (3ca): $CHCl_3$ was used as solvent; yield: 70%; white solid; mp 76–78 °C; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 8.01–7.82 (m, 2H), 7.54–7.47 (m, 3H), 7.43–7.37 (m, 2H), 6.82–6.77 (m, 2H), 4.32 (s, 2H), 3.87 (s, 3H), 3.73 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.8, 160.5, 152.2, 136.4, 133.3, 128.6, 128.3, 127.7, 113.9, 62.0, 55.3, 37.7; HR-MS (EI): *m*/*z* ($M+H^+$) = 284.1279, calcd. for $C_{17}H_{18}NO_3$: 284.1281.

(*E*)-1-(Furan-2-yl)-3-(methoxyimino)-3-(4-methoxyphenyl)propan-1-one (3ch): THF was used as solvent; yield: 75%; pale yellow solid; mp 71–73 °C; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.57–7.45 (m, 3H), 7.20 (dd, *J* = 3.6, 0.7 Hz, 1H), 6.80 (d, *J* = 9.0 Hz, 2H), 6.47 (dd, *J* = 3.6, 1.7 Hz, 1H), 4.18 (s, 2H), 3.88 (s, 3H), 3.73 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 183.5, 160.5, 152.0, 151.4, 146.5, 127.7, 117.6, 113.9, 112.3, 62.0, 55.3, 37.5; HR-MS (EI): *m*/*z* ($M+H^+$) = 274.1071, calcd. for $C_{15}H_{16}NO_4$: 274.1074.

(*E*)-3-(4-Chlorophenyl)-3-(methoxyimino)-1-phenylpropan-1-one (3da): THF was used as solvent; yield: 29%; white solid; mp 68–70 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.97–7.90 (m, 2H), 7.54–7.47 (m, 3H), 7.44–7.38 (m, 2H), 7.27–7.22 (m, 2H), 4.33 (s, 2H), 3.89 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 194.5, 151.6, 136.3, 135.3, 134.0, 133.5, 128.7, 128.7, 128.3, 127.6, 62.3, 37.5; HR-MS (EI): *m*/*z* ($M+H^+$) = 288.0789, calcd. for $C_{16}H_{15}ClNO_2$: 288.0786.

(*E*)-3-(4-Chlorophenyl)-1-(furan-3-yl)-3-(methoxyimino)-propan-1-one (3dg): THF was used as solvent; yield: 86%; pale yellow oil; ^{1}H NMR 400 MHz, $CDCl_3$, TMS): δ = 8.10–8.01 (m, 1H), 7.56–7.45 (m, 2H), 7.38–7.29 (m, 1H), 7.27–7.18 (m, 2H), 6.68 (dd, *J* = 1.9, 0.7 Hz, 1H), 4.09 (s, 2H), 3.91 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 188.8, 150.8, 147.7, 144.2, 135.4, 133.6, 128.7, 127.6, 126.9, 108.7, 62.3, 38.9; HR-MS (EI): *m*/*z* ($M+H^+$) = 278.0577, calcd. for $C_{14}H_{13}ClNO_3$: 278.0578.

(*E,Z*)-3-[(Benzyloxy)imino]-1-(furan-3-yl)butan-1-one (3eg): THF was used as solvent; after flash chromatography the product was obtained with (63:37) isomeric ratio; yield: 82%; pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 8.01–7.89 (m, 100/100 × 1H), 7.36–7.30 (m, 100/100 × 1H), 7.30–7.20 (m, 100/100 × 5H), 6.72–6.61 (m, 100/100 × 1H), 5.04 (s, 63/100 × 2H), 5.02 (s, 37/100 × 2H), 3.73 (s, 37/100 × 2H), 3.52 (s, 63/100 × 2H), 1.87 (s, 37/100 × 3H), 1.86 (s, 63/100 × 3H); ^{13}C NMR (75 MHz, $CDCl_3$, isomer *E*): δ = 190.5, 153.0, 148.3, 144.0, 138.1, 128.3, 127.9, 127.7, 126.8, 108.6, 75.6, 48.1, 14.7; ^{13}C NMR (75 MHz, $CDCl_3$, isomer *Z*): δ = 189.3, 151.5, 148.3, 144.2, 137.4, 128.4, 128.1, 127.9, 127.1, 108.6, 75.7, 41.7, 20.5; HR-MS (EI): *m*/*z* ($M+H^+$) = 258.1125, calcd. for $C_{15}H_{16}NO_3$ 258.1125.

(*E*)-3-[(Benzyloxy)imino]-1-(furan-3-yl)-4,4-dimethylpentan-1-one (3fg): THF was used as solvent; yield: 70%; white solid; mp 64–66 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.90 (dd, *J* = 1.4, 0.8 Hz, 1H), 7.30 (dd, *J* = 1.9, 1.4 Hz, 1H), 7.18–7.09 (m, 5H), 6.66 (dd, *J* = 1.9, 0.8 Hz, 1H), 4.93 (s, 2H), 3.60 (s, 2H), 1.09 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 189.5, 161.0, 147.1, 143.9, 137.6, 128.1, 128.1, 127.5, 108.8, 75.6, 37.7, 37.0, 27.6; HR-MS (EI): *m*/*z* ($M+H^+$) = 300.1594, calcd. for $C_{18}H_{22}NO_3$: 300.1594.

Data for compounds *trans*- and *cis*-(*Z*)-**8b**, *trans*-(*E/Z*)-**9b**, *trans*- and *cis*-(*Z*)-**8d**, *trans*-(*E*)-**9d** and their decomposition reaction are collected in the Supporting Information

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