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# Murai Reaction on Furfural Derivatives Enabled by Removable N,N'-Bidentate Directing Groups

Cristofer Pezzetta,[a] Luis F. Veiros,[b] Julie Oble,*[a] Giovanni Poli*[a]

*Dedicated to Dr. Carlo Mealli on the occasion of his 70th birthday*

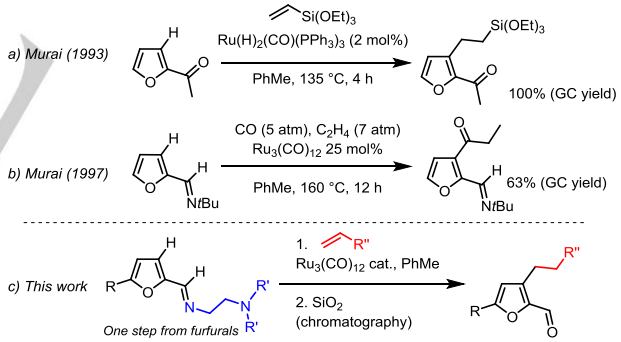
**Abstract:** Furfural and related compounds are industrially relevant building-blocks obtained from lignocellulosic biomass. To enhance the added value of these renewable resources, a Ru-catalyzed hydrofurylation of alkenes, involving a directed C-H activation at C3 of the furan ring, was developed. A thorough experimental study revealed that a bidentate amino-imine directing group enables the desired coupling. Removal of the directing group takes place during the purification step, directly releasing the C3-functionalized furfurals. Development of the reaction, as well as optimization and scope of the method are described. A mechanism is proposed on the basis of Density Functional Theory (DFT) calculations.

The main source of functionalized carbon compounds for the chemical industry still arises from the fossil-fuel reservoir. However, the irreversible depletion of this finite resource, along with the increase in demand, prices as well as environmental concerns, pushes our society to progressively focus on renewable sources. In this regard, lignocellulosic biomass,[1] constitutes a cheap alternative. In particular, furan-containing heterocycles like furfural **1**[2] and 5-(hydroxymethyl)furfural (HMF) **2**,[3] [Eq. 1] deriving from hemicelluloses materials, are two prototypical industrially relevant building blocks, amenable for fine chemistry purposes.


(1)

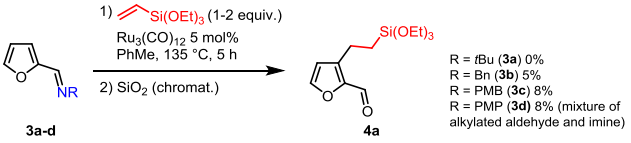
Although some simple industrial transformations of these heterocycles have been already reported,[4,5] the development of more advanced and modern protocols is still unachieved. Such an endeavor automatically calls for the discovery of straightforward methods for new C-C bond formation from furfurals.[6] In this perspective, the use of direct catalytic C-H functionalization processes[7] is an extremely attractive eco-compatible strategy that can be easily applied to furfurals. Although some transition metal (TM)-catalyzed direct functionalizations have been reported, these studies have mainly addressed furan arylation,[8,9] other transformations such as alkylation,[10] alkenylation[11] and alkynylation[12] having only been very marginally touched. In particular, no example of TM-catalyzed C3-selective alkylation of the furan ring has been reported.

Following our interests in atom- and step-economic syntheses, we focused on the direct implementation of the Murai reaction[13] on furfurals. This reaction, in which an olefin inserts into an aromatic C-H bond,[14] represents an ideal atom economical transformation, offering a waste-free alternative to conventional aromatic Friedel-Crafts type functionalizations. Despite its advantages, this transformation has not been much exploited in organic chemistry due to restrictions such as the limited number of effective directing groups. Ketones can be efficiently used, as described by Murai and Chatani for the functionalization of 2-acetylfuran (Scheme 1, eq. a).[13a, 15] Conversely, aldehydes are inefficient directing groups, generating decarbonylated products.[16] To circumvent this drawback, some examples have been reported using the corresponding aldimines.[17] However, to the best of our knowledge, the C3-selective propionylation of furfural *t*-butylimine (eq. b) [18] is the only example reported so far on a furfural imine. Herein, we disclose the first Murai reaction on furfural derivatives, through the corresponding N,N'-bidentate imines, which act as removable directing groups[19] (eq. c).




**Scheme 1.** Murai reaction on furan derivatives.

At the outset of our investigation, a series of furfural-imines **3a-d** (readily prepared in one step from furfural **1**) was considered (Scheme 2).[20] Typical catalyst and conditions for Murai reactions with aldimines were investigated, namely $Ru_3(CO)_{12}$ (5 mol%) as pre-catalyst,[17a] vinylsilanes as olefin partners, in toluene at high temperatures.




**Scheme 2.** Murai reaction on monodentate imines **3a-d**.

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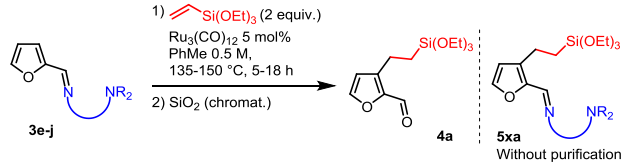
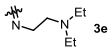
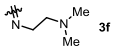
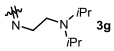
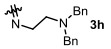
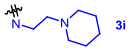
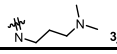
Furfuryl *t*-butylimine (**3a**) afforded no reactivity, whereas the corresponding benzyl-, *p*-methoxybenzyl-, and *p*-methoxyphenyl-imines **3b**, **3c** and **3d** only displayed a very modest reactivity (Scheme 2). It should be noted that the imine hydrolysis occurs smoothly during the purification.

With the aim of strengthening, via chelation, the template effect toward the metal and possibly stabilize the subsequent intermediates along the catalytic cycle,[21,22] we next considered furyl amino-imines bearing an additional coordinating unit (Table 1).

**Table 1.** Murai reaction on bidentate imines **3e-j**.[a]

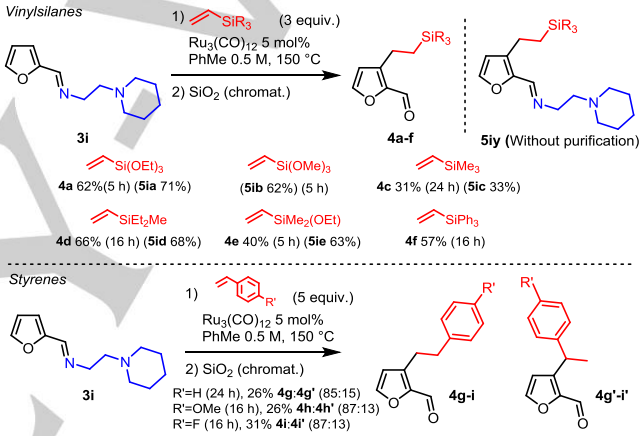



| Entry | Substrate | T (°C), t (h) | Yield[b] |
|---|---|---|---|
| 1 |  **3e** | 135 °C, 18 h | 47% (50% **5ea**) |
| 2 | | 150 °C, 5 h | (51% **5ea**) |
| 3 |  **3f** | 135 °C, 18 h | (9% **5fa**) |
| 4 |  **3g** | 135 °C, 18 h | 5% |
| 5 |  **3h** | 135 °C, 18 h | 0 |
| 6 |  **3i** | 135 °C, 18 h | 49% (55% **5ia**) |
| 7 | | 150 °C, 5 h | (70% **5ia**) |
| **8**[c] | | **150 °C, 5 h** | **62% (71% 5ia)** |
| 9 |  **3j** | 135 °C, 5 h | 0 |

[a] Reaction conditions: **3e-j** (0.5 mmol), triethoxyvinylsilane (1 mmol), $Ru_3(CO)_{12}$ (0.025 mmol), PhMe (1 mL). [b] Isolated yield of **4a** (in parentheses $^1$H-NMR yield of corresponding alkylated imines **5xa**[23], determined using *p*-dinitrobenzene as internal standard). [c] 3 equiv. of vinylsilane used.

We first examined the reaction on imine **3e**. Whether at 135 or at 150 °C, the expected alkylated products - aldehyde **4a** (isolated yield) or imine **5ea** (NMR yield prior to purification) - were obtained in ~50% yields (entries 1-2).[24] Variations of the steric hindrance of the N,N-dialkyl moiety on the directing group were next considered. While a decrease ($NMe_2$, **3f**) or an increase ($NPr^i_2$ **3g**, $NBn_2$ **3h**) of the steric hindrance led to a diminution or a stop of reactivity (entries 3-5), the cyclohexylamino substrate **3i**) displayed a much more satisfactory reactivity. While at 135 °C, results were only slightly better than those obtained with **3e** (compare entries 1 and 6), the reaction carried out at 150 °C showed a spectroscopic yield of 70% (entry 7). Furthermore, using 3 equivalents of vinylsilane, the alkylated aldehyde **4a** was isolated in 62% yield (entry 8).[25] Finally, no conversion was obtained with the amino-imine **3j** bearing an homologated three-carbon tether between the two nitrogen atoms (entry 9).

With optimal conditions in hand, we reacted imine **3i** with a variety of trialkoxy-, trialkyl- and triaryl vinylsilanes (3 equiv.) (Scheme 3, top), obtaining moderate to good yields of coupled/hydrolyzed products **4a-f** (31-66% isolated yields after chromatography or 33-72% NMR yields of the corresponding alkylated imines **5ix**). With trimethoxyvinylsilane, only alkylated imine **5ib** was characterized, due to the formation of siloxanes during chromatography, which prevented the isolation of **4b**. The moderate yield for aldehyde **4c** (or imine **5ic**) is likely due to the low boiling point of the trimethylvinylsilane (55 °C) in comparison with the reaction temperature. In the case of ethoxydimethylvinylsilane, aldehyde **4e** could be isolated in only 40% yield (vs 63% NMR yield of **5ie**) due to formation of a dimeric siloxane during storage. Then, the use of styrene derivatives was investigated (Scheme 3, bottom). While the coupling did take place, only moderate yields were obtained, even employing 5 equivalents of alkenes. Furthermore, as described by Murai,[13b] products were isolated as a mixture of linear **4g-i** and branched products **4g'-l'**, whether in presence of electron-withdrawing or -donating groups in *para* position.[26]

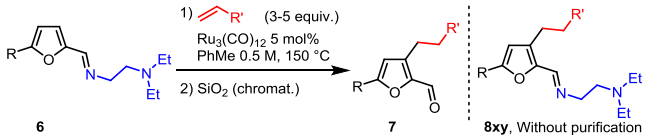



**Scheme 3.** Scope of olefins in the Murai reaction with imine **3i**.

The scope was next extended with the study of C5 substituted furfurals. Accordingly, the desired imines were prepared from various O-protected hydroxymethyl furfural (HMF) derivatives (**2a-e**), as well as 5-methyl and 5-phenyl furfurals. A preliminary screening on the TBDMS protected HMF derivatives revealed that an N,N-diethylaminoethyl group is more effective than a 2-(piperidin-1-yl)ethyl group on the imine function (Table 2, entries 1 and 2, see also SI). Thereafter, only the former amino-imines **6a-g** were considered (Table 2). The O-TBDMS-protected HMF imine **6a** showed a good reactivity with different vinylsilanes (entries 1, 3 and 4). The corresponding alkylated aldehydes (**7aa** and **7af**) could be isolated after purification, except when using trimethoxyvinylsilane, which required characterization at the stage of the alkylated imine **8ab**. With O-acetyl- and O-THP-protected HMF derivatives **6b** and **6d**, no conversion was observed (entries 5, 7), while the O-benzyl and O-trityl-protected derivatives **6c** and **6e** gave only modest yields (entries 6 and 8). We speculated that the scarce or null reactivity of HMF derivatives could be due to the formation of a catalytically inactive $N_{amine}/OCH_2$ chelated ruthenium complex, a notable exception being the case of the poorly basic silyl ether oxygen of **6a**.

As a matter of fact, the 5-methyl furfural derivative **6f**, lacking the oxygen atom at C6, provided moderate yields of the coupled products with vinylsilanes (**7fa** and **7fe**) as well as with styrene (**7fg-7fg'**) (entries 9-11). Finally, the 5-phenyl derivative **6g** proved less efficient, affording only a moderate 20% yield of the product **7ga** with triethoxyvinylsilane.

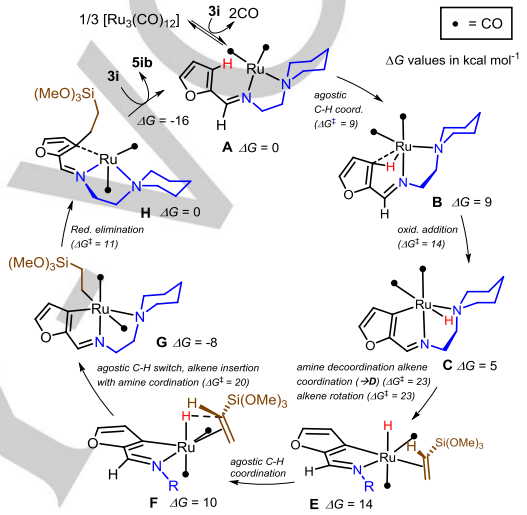
**Table 2.** Scope of C5-substitued furfural imines **6a-g** in the Murai reaction.




| Entry | R | R'[a] | t (h) | Yields[b] |
|---|---|---|---|---|
| 1 | TBDMSOCH$_2$ (**6a**) | Si(OEt)$_3$ | 5 h | 57% **7aa** |
| 2 | TBDMSOCH$_2$ (**6a'**)[c] | Si(OEt)$_3$ | 5 h | (44% **8a'a**) |
| 3 | TBDMSOCH$_2$ (**6a**) | Si(OMe)$_3$ | 16 h | (59% **8ab**) |
| 4 | TBDMSOCH$_2$ (**6a**) | SiPh$_3$ | 17 h | 62% **7af** (66% **8af**) |
| 5 | AcOCH$_2$ (**6b**) | Si(OEt)$_3$ | 5 h | NR |
| 6 | BnOCH$_2$ (**6c**) | Si(OEt)$_3$ | 5 h | 20% **7ca** |
| 7 | THPOCH$_2$ (**6d**) | Si(OEt)$_3$ | 5 h | NR |
| 8 | TrOCH$_2$ (**6e**) | Si(OEt)$_3$ | 17 h | 17% **7ea** |
| 9 | CH$_3$ (**6f**) | Si(OEt)$_3$ | 5 h | 56% **7fa** (64% **8fa**) |
| 10 | CH$_3$ (**6f**) | SiMe$_2$(OEt) | 5 h | 40% **7fe** (65% **8fe**) |
| 11 | CH$_3$ (**6f**) | Ph | 17 h | 38% **7fg:7fg'**[d] |
| 12 | Ph (**6g**) | Si(OEt)$_3$ | 16 h | 20% **7ga** |

[a] 3 equiv. for vinylsilanes, 5 equiv. for styrenes. [b] Isolated yield of **7** (in parentheses $^1$H-NMR yield of corresponding alkylated imines **8xy**, determined using *p*-dinitrobenzene as internal standard). [c] Imine **6a'** bears the 2-(piperidin-1-yl)ethyl group on the directing group. [d] Linear:branched = 88:12.

The mechanism of this transformation was studied via DFT calculations.[27] The generally accepted mechanism for Murai reaction involves a mononuclear Ru(0) complex as first active species.[28] We thus anticipated the conversion of the $Ru_3(CO)_{12}$ pre-catalyst into a mononuclear ruthenium carbonyl by Ru-Ru breaking and CO releasing.[29] Accordingly, two free energy profiles have been calculated, one involving $Ru(CO)_3$ and the other $Ru(CO)_2$. While the former path was ruled out, as it presents a barrier above 50 kcal/mol (see SI for details), the latter appears more realistic and underlines the crucial role of the bidentate amino-imine group throughout the catalytic cycle. Accordingly, the following catalytic cycle is proposed (Scheme 4). Generation of the catalytically active mononuclear $\kappa^2$ N,N-coordinated intermediate **A** from the pre-catalyst takes first place. Then, after agostic coordination of the furyl C3-H bond to Ru(0) (9 kcal/mol above **A**) to give **B**, oxidative addition leading to the Ru(II) hydride **C** is completed via an energetic barrier of 14 kcal/mol. Decoordination of the amine followed by $\eta^2$ olefin coordination and successive alkene rotation yields **E** ($\Delta G$ = 14 kcal/mol, relative to **A**). This globally endergonic sequence involves two high energy transitions states (23 kcal/mol above **A**). The subsequent olefin insertion into the Ru-H bond results first in an agostic interaction involving the newly formed C-H bond, in intermediate **F** ($\Delta G$ = 10 kcal/mol). From **F**, and after the switch of the agostic C-H bond (to give **F'**, see SI), formation of a $\kappa^2$ N,N-coordinated σ-alkylruthenium complex **G** ($\Delta G$ = -8 kcal/mol), takes place through a highly exergonic insertion. The central role of the amine side arm in assisting this latter step is noteworthy, filling one coordination position and pushing forward the formation of the alkyl ligand.[30] The subsequent reductive elimination to give the 3-alkylated furane **H** is thermodynamically disfavored ($\Delta G$ = 8 kcal/mol), and requires a high activation energy ($\Delta G^{\ddagger}$ = 19 kcal/mol). Finally, trans-imination between **H** and a new molecule of furylimine **3i** releases product **5ib** and regenerates **A** through an exergonic process that efficiently closes the catalytic cycle.




**Scheme 4.** Proposed mechanism of the catalytic cycle

In summary, the directed alkylation of furfurals with olefins (Murai reaction) was successfully developed under Ru-catalysis. The use of a removable N,N'-bidentate directing group is the key to provide satisfactory yields of the desired C3-alkylated furfurals With the help of DFT calculations, a plausible catalytic cycle was put forward. To the best of our knowledge, this method represents the first example of directed olefin insertion to C3 of furfurals. These results offer significant breakthroughs in the valorization of lignocellulosic biomass substrates as well as in the Murai reaction.

## Experimental Section

In a sealed tube, a solution of $Ru_3(CO)_{12}$ (16 mg, 285 mg), imine **3i** (103 mg, 0.5 mmol) and triethoxyvinysilane (317 µL, 1.5 mmol) in toluene (1 mL) was stirred for 5 h at 150 °C. The reaction mixture was let cool to room temperature, diluted with $CH_2Cl_2$ and filtered through Celite. The solvent was removed and the crude product was purified by silica gel chromatography (cyclohexane:ethyl acetate 8:2 as eluent) to afford 89 mg of **4a** as a yellow oil (yield 62%).

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**Keywords:** aldimines • alkenes • C-H activation • furfural • ruthenium

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[23] In compounds **5, 7, 8 xy**, **x** refers to the starting material and **y** refers to the olefin introduced.

[24] Further variations of the reaction conditions on **3e** were screened, but no significant impact was observed (see SI for more details).

[25] The reaction was investigated with substoichiometric amounts of diamine. Using 50 mol% of diamine, only a 15% NMR yield of the alkylated imine could be obtained.

[26] Other unsaturated substrates were tested, and showed little or no reactivity. See SI for more details.

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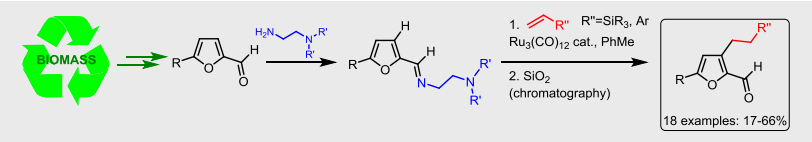


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**Murai Reaction on Furfural Derivatives Enabled by Removable N,N'-Bidentate Directing Groups**

**Furfural Activated:** a ruthenium(0)-catalyzed Murai reaction of furfural derivatives, enabled by N,N'-bidentate directing groups, has been developed. This C-H activation process provides a straightforward valorization pathway of a major class of lignocellulosic-derived biomass substrates. The importance of the directing group design has been evaluated and the reaction mechanism has been elucidated using DFT calculations.