Chemistry–A European Journal
Research Article
doi.org/10.1002/chem.202200625
Chemistry Europe
European Chemical Societies Publishing
www.chemeurj.org

Nickel-Catalyzed C_{sp2}–OMe Functionalization for Chemoselective Aromatic Homologation En Route to Nanographenes

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Abstract: A Ni-catalyzed C_{sp2}–OMe *ortho*-functionalization methodology to form chemoselectively alkyne monoannulation or aromatic homologation products is reported as a novel protocol towards the valorisation of substrates containing C_{sp2}–OMe units. Double activation of C_{sp2}–OMe and C_{sp2}–F bonds is also demonstrated. Further use of aromatic homologation products towards the synthesis of nanographene-like compounds is described.

Introduction

Activation of C_{sp2}–O bonds of aryl ethers by transition metals is much more difficult than those of aryl halides, thus their use as electrophilic counterparts in cross coupling protocols is much more limited. This is probably due to the reluctance of the C–OMe bond towards oxidative addition and the lower propensity of the methoxy residue to act as a leaving group. However, among all transition metals, Ni^0-catalyzed C_{sp2}–O activation has become the methodology of choice to effect the cleavage of C_{sp2}–OR (R=Me, Ph) bonds.[1] Simple model C_{sp2}–OMe substrates have been used as electrophiles in Kumada,[2] Negishi[3] and Suzuki cross coupling catalysis (Figure 1a).[4] Also, the cleavage of C_{sp2}–OMe to C_{sp2}-H has also been achieved via reductive protocols with silanes[5] or in the presence of H_2.[6] On the other hand, C_{sp2}–OPh bond activation have been recently engaged into Ni-catalyzed C–O/N–H annulation of aromatic amides with alkynes for the production of isoquinolinones, by using C_{sp2}–OPh substrates bearing N-phenyl-benzamide directing groups (Figure 1b).[7] Concerning the mechanism of C_{sp2}–OMe activation, it is generally believed that oxidative addition at nickel(0) species is the key step in the process, although current knowledge is still limited.[8] In addition to the oxidative addition mechanism, non-classical modes of activation should be taken into account depending on the nature of the nucleophile and the ligand used.[1a] For instance, the involvement of in situ formed nickel(I) species has also been proposed in $Ni^0(COD)_2/PCy_3$-catalyzed reductive cleavage of aryl ethers using hydrosilane.[1c,9] A very relevant raw source of C_{sp2}–OR moieties is lignin, which constitutes up to 30 wt% of wood-based biomass and is considered the largest source of renewable aromatics.[10] However, lignin decomposition is hampered by the difficulty in converting it into synthetically useful monomeric units by activation of the uniting C_{sp2}–OR (R=Me, Alkyl, Ar) and C–C bonds.[11] Nevertheless, the inert C_{sp2}–O bonds of aryl ethers contained in lignin remain in the monomers and new methodologies are needed to unlock this bottleneck of the lignin valorisation process.[12]

Recently we reported a nickel-catalyzed C_{sp2}–F functionalization with internal alkynes to form either alkyne monoannulation or aromatic homologation products in a chemodivergent manner, demonstrating the ability of the 8-aminoquinoline[13]

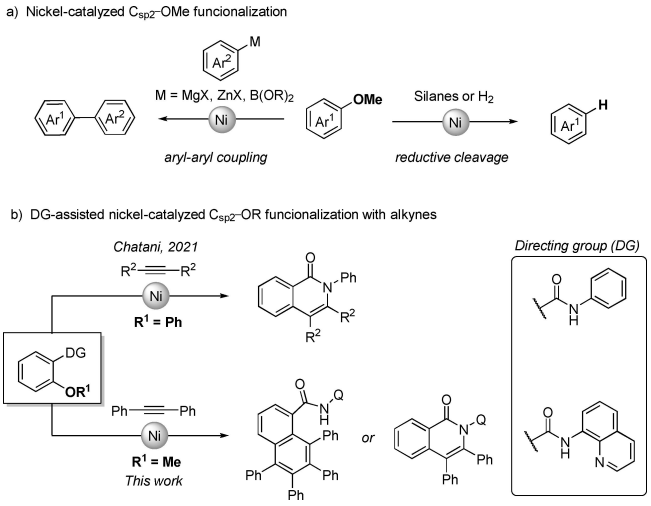

Figure 1. (a) Nickel-catalyzed C_{sp2}–OMe activation reaction using preactivated R–M nucleophiles to form C_{sp2}–C_{sp2} coupling and reductive cleavage. (b) Directing group-assisted nickel-catalyzed C_{sp2}–OR functionalization with alkynes.

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Supporting information for this article is available on the WWW under https://doi.org/10.1002/chem.202200625

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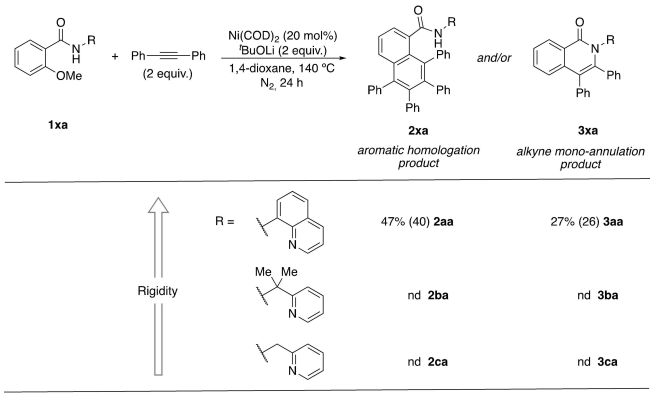
directing group to activate the strong C_{sp2}–F bonds.[14] Here we report an analogous Ni-catalyzed methodology to form alkyne monoannulation or aromatic homologation products via the functionalization of strong C_{sp2}–OMe bonds, as a novel protocol towards the valorization of lignin monomers containing C_{sp2}–OMe units.

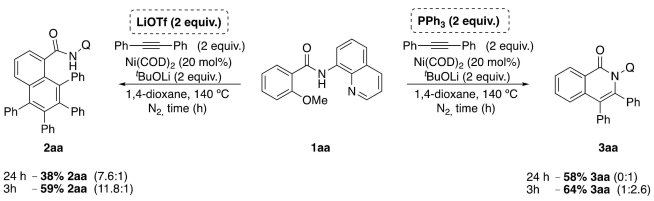
Results and Discussion

We first focused on whether C_{sp2}–OMe could be functionalized with internal alkynes using a similar Ni^0-based methodology as for the C_{sp2}–F substrates recently reported by us. We screened as directing group (DG) the 8-aminoquinoline (8-AQ)[13,15] (**1 aa**), 2-pyridylisopropylamine (PIP)[16] (**1 ba**) and 2-pyridylmethylamine (PM)[17] (**1 ca**) units in *ortho*-position to the C_{sp2}–OMe substrate and diphenylacetylene (Scheme 1). Only positive outcome of the reaction was found for 8-AQ-containing substrate **1 aa**, affording the aromatic homologation product **2 aa** in 47% yield and the alkyne monoannulation product **3 aa** in 27% yield. These results point out to the requirement of a rigid and bidentate DG for the reaction to proceed.

The **2 aa/3 aa** ratio of 1.7 obtained under these conditions was similar to the analogous C_{sp2}–F cleavage to obtain the same products (**2 aa/3 aa** ratio = 3.7),[14a] what suggested a similar mechanism of chemodivergent product formation. At this point, we pursued the optimization of the chemodivergence, and found that the **2 aa/3 aa** ratio could be completely reversed; if, additionally to the standard conditions, LiOTf (2 equiv.) was added, the aromatic homologation product **2 aa** was maximized to a **2 aa/3 aa** ratio of 11.8 in a 59% yield (3 h) (Scheme 2). However, when PPh_3 (2 equiv.) was added in lieu of LiOTf, a switch of chemoselectivity occurred and **3 aa** was obtained in 64% yield within 3 h (**2 aa/3 aa** ratio = 1:2.6). It is worth to note that by increasing the reaction time up to 24 h, the alkyne monoannulation product **3 aa** was obtained in an exclusive manner due to the decomposition of **2 aa** under these conditions.



Scheme 1. Screening of effective DG for the Ni-catalyzed C_{sp2}–OMe functionalization with diphenylacetylene (in parenthesis: isolated yields; nd = non detected).

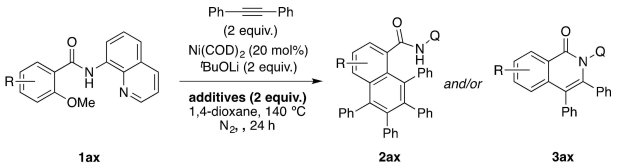


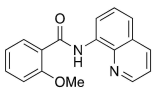
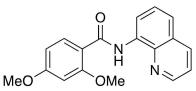
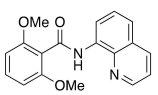
Scheme 2. Chemodivergent behavior towards the aromatic homologation and the alkyne monoannulation product (**2 aa/3 aa** ratio in parenthesis).

Then, we turned our attention to substrates bearing a second –OMe group in *para*- (**1 ab**) and *ortho*- (**1 ac**) to the DG, in order to analyse the electronic and steric effects of the additional methoxy- group to the reaction outcome (Table 1). On the one hand, the yield for **2 ab** (26%) and **3 ab** (22%) decreased and the ratio **2 ab**/**3 ab** was ~1 when using substrate **1 ab**. The same trend as in **1 aa** was observed, and adding LiOTf, the formation of the aromatic homologation **2 ab** was observed in a selective manner (32% in 24 h). Instead, adding PPh_3 the corresponding alkyne monoannulation product was formed in higher yields (70% in 3 h). The higher reactivity observed towards the formation of the alkyne monoannulation product suggested that the aromatic homologation reaction was impeded by the steric effect of the second –OMe group in *meta*. On the other hand, although no reactivity was observed using **1 ac** under the standard conditions (Table 1, entry 7), full chemoselectivity for the aromatic homologation product **2 ac** was regained (48% yield in 24 h, entry 8) when LiOTf was used as the additive.

Strikingly, substrate **1 ac** afforded the double activation of both –OMe groups in *ortho* to the DG when PPh_3 was used, affording product **4** in 25% yield (29% using 50 mol% of

Table 1. C_{sp2}–OMe functionalization using different methoxyarene substrates.



Entry	Substrate **1 ax**	Additives	Yield [%] of **2 ax**[a]	Yield [%] of **3 ax**[a]
1		without	47%	27%
2		LiOTf	38% (59%)	tr (tr)
3		PPh_3	tr (25%)	58% (64%)
	1aa			
4		without	26% (tr)	22% (tr)
5		LiOTf	32% (tr)	tr (tr)
6		PPh_3	tr (tr)	43% (70%)
	1ab			
7		without	tr	tr
8		LiOTf	48% (26%)	tr (tr)
9[b]		PPh_3	–	–
	1ac			

[a] Yield calculated from ^{1}H NMR of crude mixture using 1,3,5-trimethoxybenzene as internal standard (in parenthesis, yield at 3 h); tr = traces. [b] Formation of product **4** in 25% yield.

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$Ni(COD)_2$), featuring the aromatic homologation and the alkyne monoannulation simultaneously (Figure 2a). Gratifyingly, the crystal structure of **4** was obtained by slow evaporation of a $CHCl_3$ solution and consisted of a racemic mixture of the two enantiomeric helical species that arise from the isoquinolinone formation at the monoannulation step (Figure 2b).

We then focused our efforts in comparing the reactivity of the C_{sp2}–F and C_{sp2}–OMe groups. To this end, substrate **1 ad** was synthesized bearing fluoride and methoxy groups in *ortho* to the amide motif (Scheme 3). Using the standard conditions and LiOTf, only the C_{sp2}–F moiety was activated to afford 44% of product **2 ad**, with no traces of C_{sp2}–OMe activation. The intramolecular monoannulation product was not detected. Since we could achieve the simultaneous activation of two C_{sp2}–OMe bonds in *ortho* in **1 ac**, and C_{sp2}–F was more reactive than C_{sp2}–OMe, we hypothesized that **1 ad** could also undergo the simultaneous aromatic homologation and alkyne monoannulation to form **4**. Indeed, after optimization studies, we found that product **4** was formed, when employing both LiOTf and PPh_3.

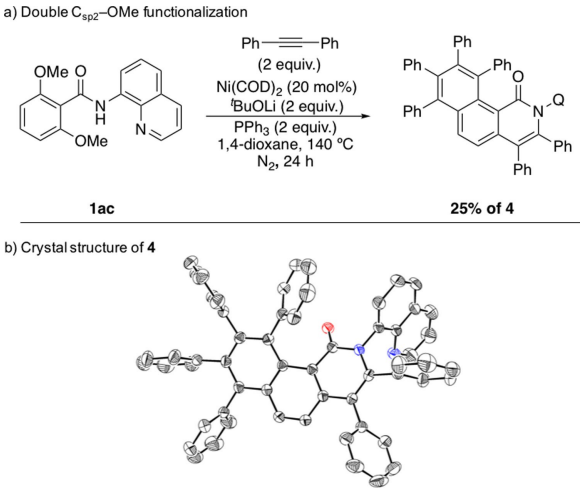
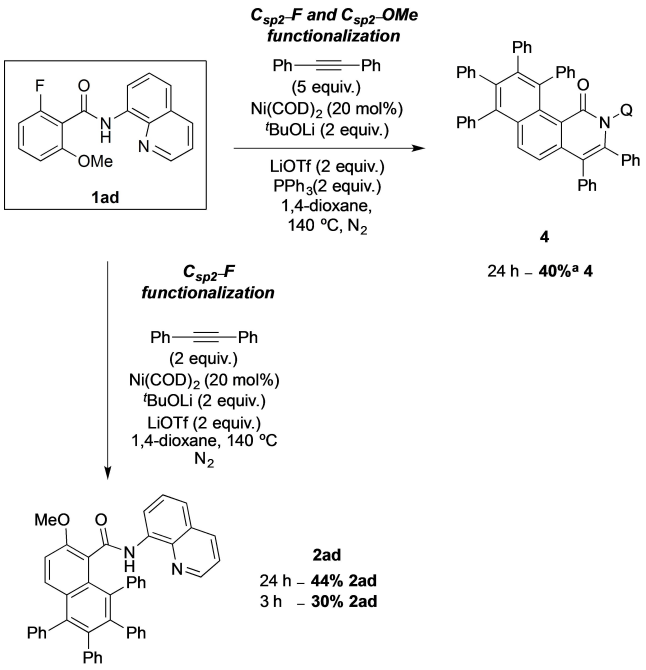


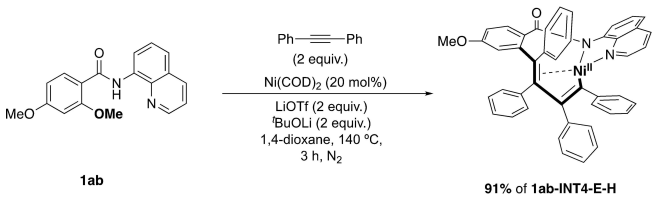
Figure 2. (a) Double C_{sp2}–OMe activation using substrate **1 ac** to afford product **4** (yield based on alkyne). (b) Crystal structure of **4** (only shown one of the helical enantiomers of the racemic mixture).



Scheme 3. Competition experiment between C_{sp2}–OMe vs. C_{sp2}–F *ortho*-functionalization in **1 ad** towards the formation of aromatic homologation and the simultaneous double functionalization. [a] Isolated yield.

At the current stage of this investigation, we envision an analogous mechanism for the C_{sp2}–OMe activation as the one described for C_{sp2}–F in our previous report.[14a] Indeed, when substrate **1 ab** was reacted with diphenylacetylene under the aromatic homologation conditions for 3 h, the square-planar nine-membered nickelacyclic intermediate complex **1 ab-INT4-E-H** was selectively formed in a 91% NMR yield (Scheme 4). 2D NMR structural characterization clearly showed that **1 ab-INT4-E-H** featured two alkynes inserted. The species **1 ab-INT4-E-H** undergoes formation of the corresponding aromatic homologation product **2 ab** in 32% yield after 24 h (Table 1, entry 5). This low yield compared to the almost quantitative accumulation of **1 ab-INT4-E-H** might be related to the steric hindrance imposed by the –OMe group adjacent to the C–H activated in the aromatic homologation process, thus hampering the formation of **2 ab**. As in the case of the C_{sp2}–F functionalization, the presence of lithium ions is crucial to stabilize the LiOMe as leaving group.

Remarkably, the 1,2,3,4-tetraphenylnaphthalene unit in the homologation product **2 aa** was envisioned as suitable to undergo Scholl or DDQ oxidative coupling to synthesize nanographene-like compounds (7-fused aromatic rings, pyrenoid type).[18] We first attempted the $FeCl_3$-mediated Scholl reaction, but inconclusive results were obtained. On the contrary, DDQ-based protocol afforded the oxidative fusion of the two phenyl moieties, along with in situ amide hydrolysis and esterification product **5** in 27% yield (Scheme 5). It is worth mentioning that a 9-fused ring compound was detected in the crude mixture (Figure S9), suggesting that it might also be accessible under modified experimental conditions. This type of transformation opens new opportunities in the use of these multi-ring products as starting scaffolds for bottom-up synthesis of unprecedented nanographene derivatives.[19] We are currently working on widening the scope of diphenylacetylene derivatives in order to expand the size of nanographenes.



Scheme 4. Isolation of the **1 ab-INT4-E-H** intermediate species. Yield calculated using 1,3,5-trimethoxybenzene as internal standard and based on the total Ni content.

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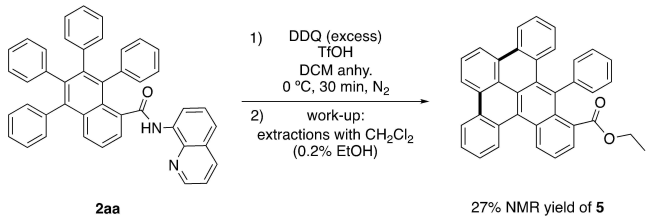

Scheme 5. Adjacent arene fusion reaction of **2aa** via DDQ-mediated oxidative coupling to form nanographene monofunctionalized derivative **5**.

Conclusion

In summary, we have developed a novel Ni^0-catalyzed methodology to achieve the C_{sp2}–OMe functionalization using internal alkynes, forming chemoselectively either aromatic homologation or intramolecular monoannulation products upon fine optimization of the reaction. This methodology stands as a new tool to activate C_{sp2}–OMe bonds showing the potential use of aryl-alkyl ethers as alternative electrophiles to aryl halides. Furthermore, aromatic homologation products are proven as valid precursors towards bottom-up nanographene-like synthesis, as a further diversification of the possible uses of these compounds.

Experimental Section

See Supporting Information for materials, instrumentation, experimental procedures and spectroscopic characterization of all compounds. Deposition Number 2144669 (compound **4**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe http://www.ccdc.cam.ac.uk/structures Access Structures service.

Acknowledgements

This work was financially supported by grants from MINECO-Spain (CTQ2016-77989-P and PID2019-104498GB-I00 to X.R.), the DFG (Gottfried-Wilhelm-Leibniz award to L.A.), and Generalitat de Catalunya (2017SGR264 and ICREA Acadèmia to X.R.).

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: aromatic homologation · C_{sp2}–OMe activation · intramolecular monoannulation · nanographene-like compounds · nickel catalysis

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Manuscript received: February 25, 2022
Accepted manuscript online: March 24, 2022
Version of record online: ■■, ■■■

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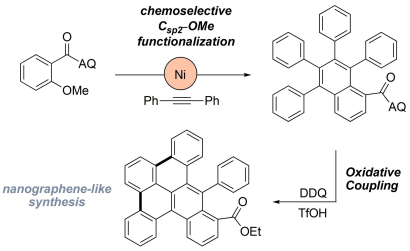
RESEARCH ARTICLE

A Ni(0)-catalyzed methodology efficiently achieves C_{sp2}–OMe functionalization in the presence of internal alkynes, forming chemoselectively either aromatic homologation or intramolecular monoannulation products. Furthermore, aromatic homologation products are proven as valid precursors for further diversification towards nanographene-like synthesis.



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