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**C–H Activation**

# Sterically Controlled C–H Olefination of Heteroarenes**

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*In memory of Professor Walter Thiel*

***Abstract:*** *The regioselective functionalization of heteroarenes is a highly attractive synthetic target due to the prevalence of multiply substituted heteroarenes in nature and bioactive compounds. Some substitution patterns remain challenging: While highly efficient methods for the C2-selective olefination of 3-substituted five-membered heteroarenes have been reported, analogous methods to access the 5-olefinated products have remained limited by poor regioselectivities and/or the requirement to use an excess of the valuable heteroarene starting material. Herein we report a sterically controlled C–H olefination using heteroarenes as the limiting reagent. The method enables the highly C5-selective olefination of a wide range of heteroarenes and is shown to be useful in the context of late-stage functionalization.*

## Introduction

The transition-metal-catalyzed C–H functionalization of heteroarenes bears the potential to enable the rapid construction of complex bioactive compounds.[1] In order to obtain site-selectivity, prefunctionalized substrates or substrates containing directing groups (DGs) are often required, but the prefunctionalization or the steps required for the introduction/removal of the DGs add steps to the overall synthetic sequence. The potential to avoid such extra steps renders the nondirected C–H activation/functionalization of heteroarenes highly attractive, especially in the context of late-stage modification.[2] However, in the absence of DGs, control of reactivity and selectivity has to be achieved through the identification of suitable catalysts and reaction conditions that enable the differentiation between competing sites on the substrate. This can prove highly challenging, due to inherently small differences in the respective free energies of activation for the key concerted metalation–deprotonation processes.[3]

In the C–H activation/functionalization of 3-substituted five-membered heteroarenes, such as thiophenes, furans, and pyrroles, the differentiation between the C2 and C5 position constitutes a prototypical example of such a selectivity challenge.[4–12] Amongst other transformations,[5,6,8,10,12] the olefination of such substrates has raised significant interest (Scheme 1).[4,7,9,11] The site selectivity of the C–H activation of 3-substituted five-membered heteroarenes is characterized by a competition between effects favoring different positions in these substrates. For substrates bearing electron-donating substituents in the 3-position, the C–H activation in the C2-position is electronically favored, since the employed catalysts are typically electrophilic in nature and thus favor the activation in the most electron-rich position. At the same time, the C5-position in these substrates is favored for steric reasons, given that a potential steric repulsion with the substituent in the 3-position is avoided.[4d,13]

The C–H activation of thiophenes, furans, and pyrroles bearing an electron-withdrawing group in the 3-position is likewise characterized by a competition of several effects. In these substrates, the C5-position is more electron-rich, since the electron-withdrawing effect is more pronounced in the vinylogous C2-position. Steric factors also favor the C5-position.[13] However, since most electron-withdrawing groups are also suited to act as DGs, the C2-position (and sometimes also the C4-position) is favored in a competition between directed and nondirected C–H activation pathways. Since DGs can substantially lower activation barriers through the complexation-induced proximity effect,[14] the C–H activation in the C2-position is thus often observed with catalysts that are susceptible to DGs.

Recently, our group has developed palladium catalysts that, through the combined action of a pyridine-derived ligand and an *N*-acetyl amino acid,[15,16] enable the arene-limited nondirected C–H activation of arenes (Figure 1).[17] The active species in these systems was found to be a palladium catalyst bearing one equivalent of each ligand employed.[17a,b] As expected for nondirected C–H activation, the regioselectivity of these systems is dictated by both steric and electronic effects. Our studies revealed that these catalysts display a comparably low sensitivity towards electronic effects, such that other factors could strongly influence the regioselectivity. Since the active species features a single free coordination site, the directing effect typically exerted by Lewis basic functional groups, which would favor *ortho*-selective product formation, is partially or completely sup-

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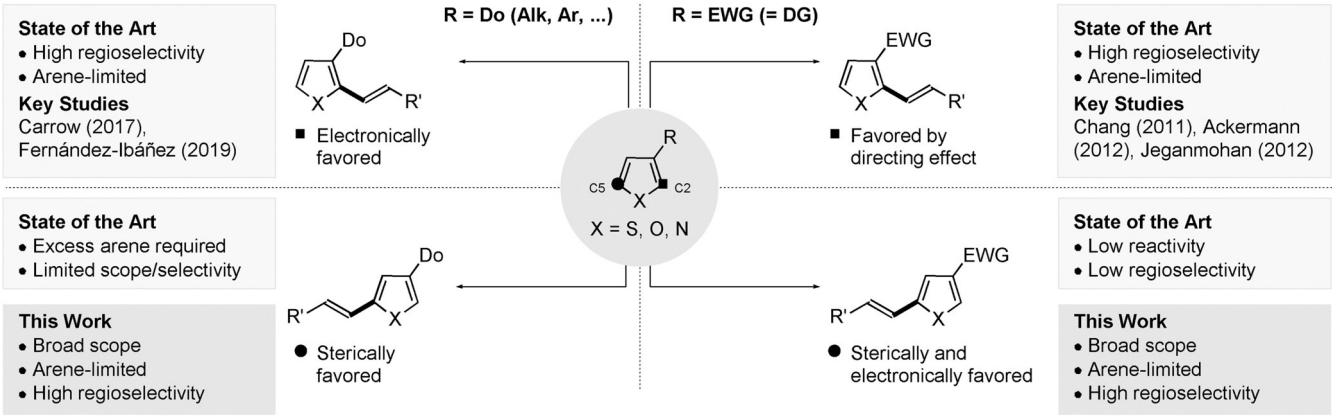



***Scheme 1.*** Overview of the regioselective olefination of 3-substituted heteroarenes.

pressed. Additionally, the steric hindrance around the coordination site on palladium leads to a strong repulsion with substituents on the substrate, thereby suppressing the formation of *ortho* product. For example, the olefination of cumene resulted in a mixture of *meta* and *para* products.

We reasoned that building upon these studies it might be possible to develop a general method allowing for the C5-selective olefination of a broad range of 3-substituted thiophenes, furans, and pyrroles and concluded that such a method would be a both conceptually and synthetically attractive target. Interestingly, although they have not been studied extensively (presumably due to the cumbersome syntheses previously required), some promising bioactivities have been reported for compounds containing the core structures that result from a C5-selective olefination of 3-substituted thiophenes, furans, and pyrroles.[18]

Building upon our previous studies centered on arenes as substrates, 3-substituted five-membered heteroarenes presented several additional challenges. Firstly, the angle between the substituent in 3-position and the C2–H bond is larger than the one between a substituent on a six-membered arene and the *ortho*-C–H bond. This reduces steric clash and thus renders steric control more challenging.[6e] Secondly, the heteroarenes employed as substrates and the respective products are substantially more reactive than typical arenes, leading to challenges such as overreaction and product decomposition, which in many studies have been compensated by using the heteroarene as excess component, but must be controlled to achieve useful yields in a heteroarene-limited reaction. Thirdly, irrespective of the nature of the substituent a competition between steric, electronic, and directing effects was expected in all cases (cf. Scheme 1). Herein we report the development of sets of reaction conditions that enable the olefination of five-membered heteroarenes bearing both electron-donating and electron-withdrawing substituents in the 3-position.

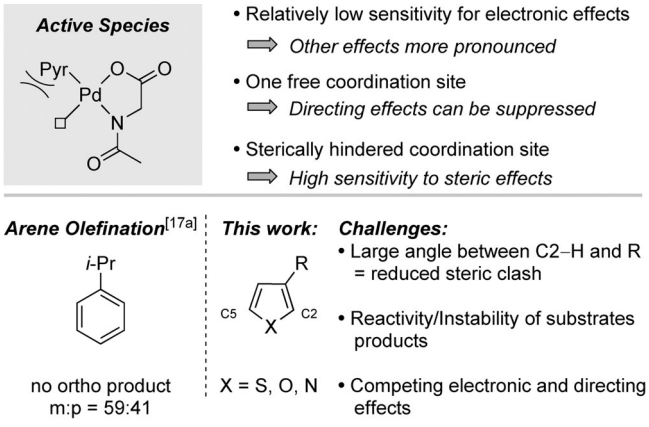



***Figure 1.*** Steric control in dual ligand-enabled nondirected C–H activation with palladium catalysts.

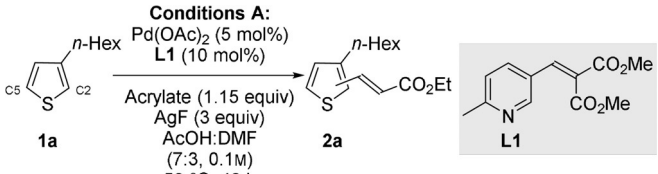
## *Results and Discussion*

We began our studies focusing on donor-substituted thiophenes, for which the competition between C2- and C5-selective olefination is well documented. The olefination of 3-methylthiophene, for example, has been reported to proceed with poor selectivity (C5/C2 = 1.3:1 to 2.5:1).[4a–c] In 2017, the Carrow group developed a Pd catalyst bearing an anionic thioether ligand, which through the generation of a highly electrophilic palladium species enables the olefination of 3-alkylthiophene to occur selectively at the more electron-rich C2-position.[4d] Recently, the group of Fernández-Ibáñez reported that by using a bidentate S,O-ligand thiophene derivatives can be olefinated in the C2-position with the thiophene as the limiting reagent.[4f] Although an interesting effect of pyridine as ligand on the C5/C2-selectivity has been described (64%, C5/C2 = 5:1 with a 5-fold excess of the 3-hexylthiophene),[4d] no synthetic method has been described that would allow for the C5-selective olefination of such substrates with the valuable heteroarene as the limiting reagent.

We began our studies using 3-hexylthiophene (**1a**) as the model substrate, since it is known to undergo the Fujiwara–Moritani reaction, although the transformation had previously been reported with an excess of the heteroarene and a poor selectivity for the C5-position.[4a] After a systematic optimization of the reaction conditions, we identified the Conditions A depicted in Table 1, which build upon the sterically

***Table 1:*** Control experiments for 3-hexylthiophene.



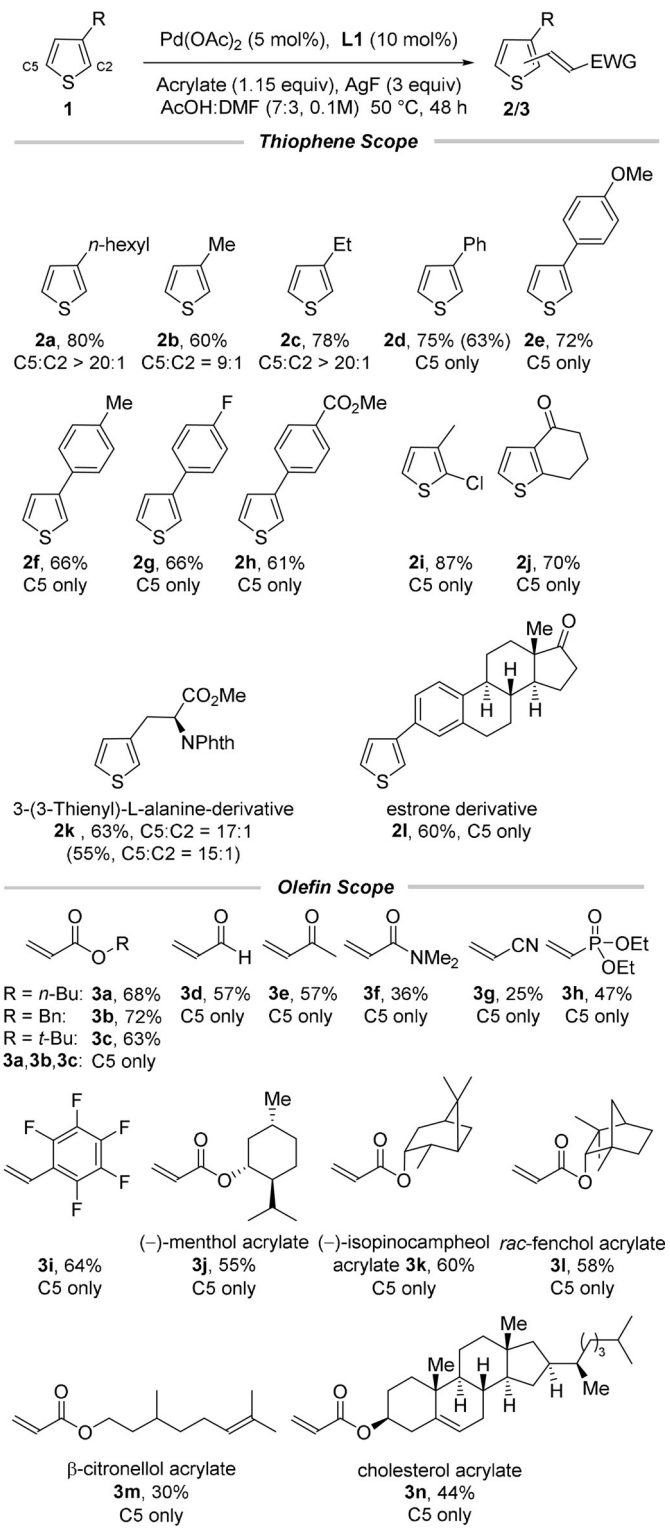

| Entry[a] | Deviation from Conditions A | GC yield [%][b] | C5:C2[b] |
|---|---|---|---|
| 1 | none | 81 | 32:1 |
| 2 | with *N*-acetylglycine[c] | 85 | 32:1 |
| 3 | no **L1** | 60 | 5:1 |
| 4 | pyridine instead of **L1** | 71 | 16:1 |

[a] All reactions were conducted on a 0.1 mmol scale. [b] Yields and ratios were determined by GC-FID using 1,3,5-trimethoxybenzene as an internal standard. [c] 15 mol% *N*-acetylglycine was used.

hindered, electron-poor pyridine ligand **L1** developed in our previous studies.[17a] Under these conditions, the desired C5-isomer was obtained in high yield (81%) and with excellent regioselectivity (entry 1). Our control experiments showed that in contrast to our previous studies, no substantial improvements occurred for this substrate under dual ligand conditions (entry 2) and confirmed both the importance of the pyridine ligand **L1** and its superiority to simple pyridine (entries 3 and 4).

Having established conditions that enable sterically controlled C–H olefination of 3-donor-substituted thiophenes, we were interested in exploring the substrate scope of this method (Scheme 2). Even when the carbon chain on the thiophene was shortened from hexyl to methyl, good yield and regioselectivity were observed. The somewhat reduced yield and selectivity for this substrate can be explained by the lower steric hindrance of the methyl group and an increased formation of di-olefinated product (**2a** vs. **2b**). We were pleased to find that 3-ethylthiophene (**2c**) delivers results very similar to those of our model substrate. Products **2d–h** bearing differently substituted arenes in the 3-position were obtained in good yields and with exclusive functionalization in the C5-position, and 2,3-disubstituted thiophenes were also found to be olefinated smoothly under these conditions (**2i,j**).[4]

One of the key features of our method is the use of the heteroarene as the limiting reagent. Considering that these substrates are often costly or have to be accessed through multistep synthetic routes, this feature renders our method attractive in the context of late-stage modification. To evaluate the suitability of our protocol for this purpose, we first tested a thiophene-based nonnatural amino acid derivative and obtained the desired product **2k** in good yield and high selectivity for the C5-position. Similarly, exclusive selectivity for the C5-position was observed for the estrone-derived product **2l**. We next probed the olefin scope of this transformation with 3-phenylthiophene (**1d**) as a model substrate. We found that the olefination can be performed with different acrylates (**3a–c**), acrolein (**3d**), and methyl vinyl ketone (**3e**), giving good yields of a single regioisomer in all cases. Likewise, *N*,*N*-dimethylacrylamide (**3f**), acryloni-




***Scheme 2.*** Scope of donor-substituted thiophenes. The structures of the respective starting materials are shown for simplicity. All reactions were conducted on a 0.2 mmol scale. Yields given in parentheses were obtained on a 2 mmol scale under otherwise identical conditions. Ethyl acrylate was used as the olefin reaction partner to evaluate the thiophene scope. 3-Phenylthiophene (**1d**) was used as substrate to evaluate the scope of the olefin reaction partners. HFIP = 1,1,1,3,3,3-hexafluoroisopropanol.

trile (**3g**), diehtyl vinylphosphonate (**3h**), and pentafluorostyrene (**3i**) gave the desired products regioselectively in reasonable to good yields. We furthermore tested the use of natural-product-derived acrylates and obtained the products derived from (−)-menthol (**3j**), (−)-isopinocampheol (**3k**), *rac*-fenchol (**3l**), β-citronellol (**3m**), and cholesterol (**3n**), as single regioisomers.

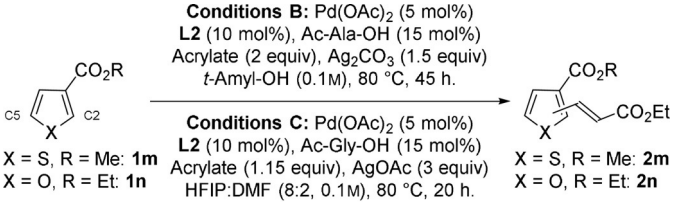
For five-membered heteroarenes bearing electron-withdrawing groups in the 3-position, the regioselectivity is likewise defined by competing effects favoring different positions. In such substrates the C5-position is both sterically more accessible and electronically favored, but the directing effect exerted by the Lewis basic electron-withdrawing group in the 3-position typically outcompetes the C5-selective nondirected pathway.[13,14] This is well reflected in methods for the functionalization of thiophenes with an electron-withdrawing group in the 3-position.[6–8]

Typical reports, especially concerning C–C bond-forming reactions such as arylations,[8] describe the preferential substitution in the C2-position. The functionalization in the C5-position has been achieved through indirect routes,[8c] on multiply substituted substrates,[7e] and in the case of sterically controlled borylations and silylations,[6] where catalysts are known not to be susceptible to directing effects. Furthermore, Sharp and co-workers described a case of the catalyst-controlled switch between C2- and C5-selective arylation, albeit using an excess of the heteroarene substrate.[8b] The olefination of such substrates has been achieved with excellent selectivities for the C2-position by using the electron-withdrawing group as DG,[7] but no general method has been described that would allow the selective olefination of such substrates in the C5-position. However, it should be noted that Fernández-lbáñez and co-workers reported the olefination of methyl thiophene-3-carboxylate, used as the limiting reagent, providing the desired product in 41% isolated yield and with a moderate selectivity for the C5-position (C5/C2 = 3:1).[4f]

As expected based on the literature reports discussed above and the different factors relevant for regioselectivity, the reaction conditions developed for donor-substituted thiophenes could not be used directly for a substrate bearing an electron-withdrawing group such as methyl thiophene-3-carboxylate (**1m**). We hypothesized that in order to overcome directing effects favoring the C2-position, a dual ligand system could be used, since the respective active species offers only one empty coordination site on the catalyst,[17] thereby suppressing a possible interaction between the DG and the catalysts and the resulting directing effect (cf. Figure 1). A separate optimization of the reaction conditions with **1m** as the model substrate revealed that for substrates bearing potential DGs a dual ligand-based catalyst does indeed deliver improved results (Table 2, entry 1). The control experiments confirmed the positive impact of both ligands on the reaction outcome (entries 2–4).

Since the same factors influencing the regioselectivity are also relevant in the case of furans, we wondered whether the dual ligand-based catalyst system could be employed with furans bearing an electron-withdrawing group in the 3-position as well. Again, for such 3-substituted furans the inherent preference for C–H activation in the C2-position by palladium catalysts has been documented, while broadly applicable methods for C5-selective functionalization, for example, borylation or silylation, have been developed using Ir catalysis.

***Table 2:*** Control experiments using Conditions B and C for the olefination of 3-EWG thiophenes and furans.[a]




X = S, R = Me: **1m**
X = O, R = Et: **1n**

X = S, R = Me: **2m**
X = O, R = Et: **2n**

| Entry | Substrate, Conditions | GC yield [%][b] | C5:C2[b] |
|---|---|---|---|
| 1[c] | **1m**, B | 55 | 9:1 |
| 2 | **1m**, B, no **L2** | 43 | 6:1 |
| 3 | **1m**, B, no *N*-acetylalanine | 24 | 2:1 |
| 4 | **1m**, B, no *N*-acetylalanine, no **L2** | 7 | 2:1 |
| 5[d] | **1n**, C | 56 | 6:1 |

[a] All reactions were conducted on a 0.1 mmol scale. **L2** = Methyl 6-methylnicotinate [b] Yields and ratios were determined by GC-FID using 1,3,5-trimethoxybenzene as an internal standard. [c] Using Conditions A: 38%, C5:C2 = 4:1; Using Conditions C: 38%, C5:C2 = 2:1. [d] Using Conditions B: 34%, C5:C2 > 20:1; Control experiments in the absence of either or both ligands confirmed the necessity for all catalyst components; see the Supporting Information for details.

Using ethyl furan-3-carboxylate (**1n**) as a model substrate and starting from Conditions B, we could indeed identify suitable conditions for the palladium-catalyzed C5-selective C–H activation/olefination of such substrates using a dual ligand catalyst system (Conditions C, Table 2, entry 5). Control experiments revealed that these conditions are indeed better suited for furan substrates, while Conditions B give better results for thiophenes.

Having established two sets of reaction conditions that enable sterically controlled C–H olefination of furans and electron-poor thiophenes, we proceeded to explore the scope of these Conditions B and C (Scheme 3). Using Conditions B, we obtained the model product **2m** in good yield and regioselectivity (Scheme 3A). Interestingly, the degree of regioselectivity was found to increase with a sterically more demanding substituent on the carboxylate group (**2o**). Additionally, a menthol-derived thiophene could also be olefinated giving **2p** in 55% yield and with full selectivity for the C5-position.

We next proceeded to evaluate the olefination of furans using Conditions C (Scheme 3B). The model furan **2n** was likewise obtained in good yield. The regioisomeric ratio was improved relative to that observed during the optimization studies, presumably due to a partial separation of the two regioisomers during purification. Good results were also observed for the natural-product-derived menthol ester **2q.** We were pleased to find that Conditions C were also suitable for the olefination of 3-donor-substituted furans, when the temperature was slightly lowered to compensate for the higher reactivity of these compounds (**2r**,**s**). Furan derivatives

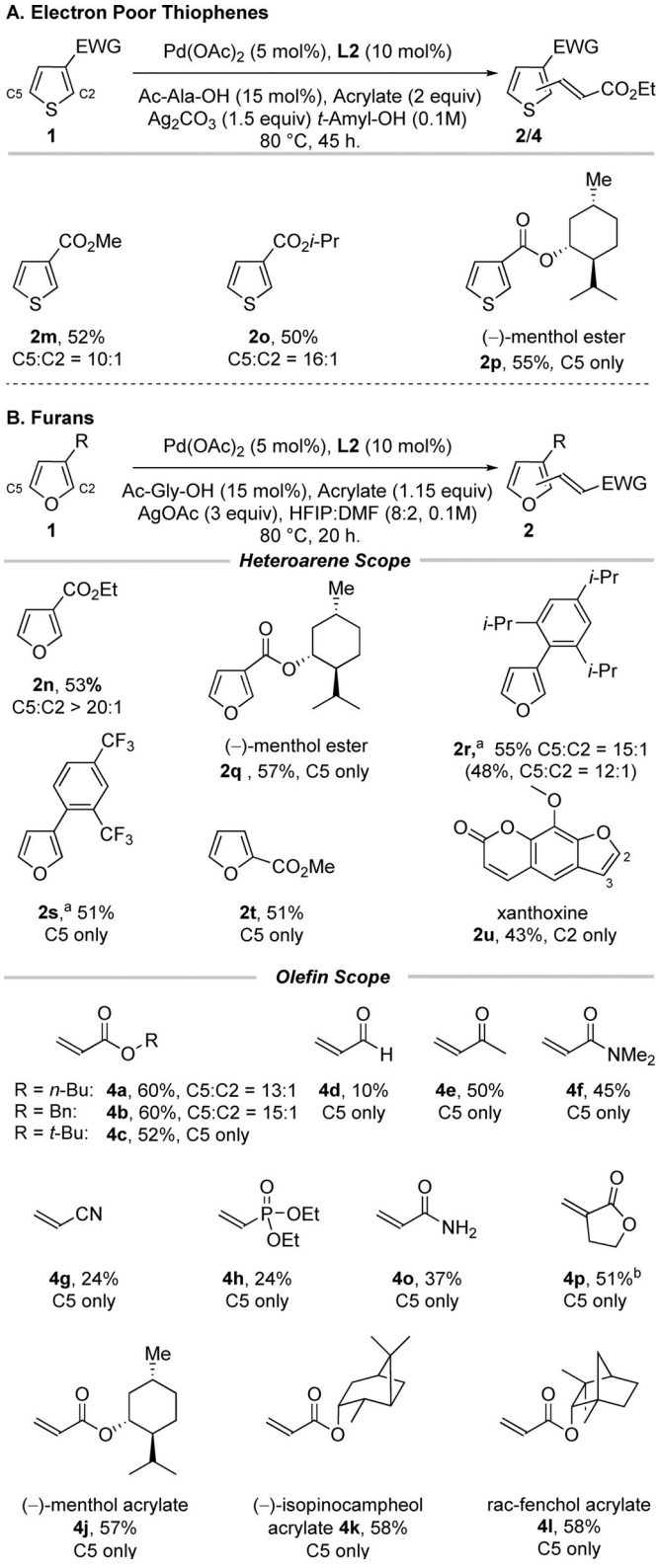
  

with other substitution patterns including xanthoxine were likewise found to be suitable substrates (**2t**,**u**).

We studied the olefin scope for these reaction conditions with furan substrate **1r** and obtained the products derived from different acrylates (**4a**–**c**), methyl vinyl ketone (**4e**), as well as *N*,*N*-dimethylacrylamide (**4f**), acrylonitrile (**4g**), diethyl vinylphosphonate (**4h**), acrylamide (**4o**), and β-methylene butyrolactone (**4p**) in good regioselectivities. Natural-product-derived acrylates could again be used successfully, giving **4j**–**l** as single regioisomers.

Motivated by the olefination of thiophenes and furans, we wondered whether an analogous arene-limited method could be developed for 3-substituted pyrroles as substrates. As for the previous substrate classes, the competition between C2- and C5-functionalization has been well-documented,[11,12] although the control of the selectivity between the C2- and C3-position has been studied more extensively.[19] For pyrroles bearing an electron-withdrawing group in the 3-position, no C5-selective intermolecular method has been reported to date, although it should be noted that in cases where the directing effect of the substituent is suppressed, reactions can occur selectively in the C5-position.[11b,12] Additionally, Lin, Yao, and co-workers have demonstrated a solvent-induced switch between directed and nondirected reactivity in 3,4-disubstituted pyrroles bearing one electron-withdrawing group.[11c,d] Analogously, for 3-donor-substituted pyrroles, Gaunt and co-workers have described a C5-selective reaction in one instance with an excess of the heteroarene substrate, while Carrow and colleagues showed that their highly electrophilic catalysts can direct the reaction to the more electron-rich C2-position. Despite these advances, no generally applicable C5-selective method has been reported to date for the C–H activation of 3-substituted pyrroles with the valuable heteroarene substrate as the limiting reagent.

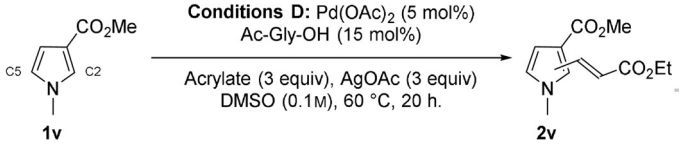
Beginning from the conditions developed for furan substrates and using methyl *N*-methyl pyrrole-3-carboxylate (**1v**) as a model substrate, we could indeed identify Conditions D for the C5-selective olefination (entry 1, Table 3). Our control reactions revealed that in this case, the pyridine ligand exerted no positive effect under the otherwise optimized conditions (entry 2). Thus, the olefination of pyrroles was found to proceed best using a single ligand system. The absence of the amino acid derived ligand had a noticeable detrimental effect (entry 3). Interestingly, even under these "ligand-free" conditions, the C5-product was formed as major component. We reasoned that this could be due to the use of strongly coordinating DMSO as solvent, which is suitable to suppress directing effects.[11c] This interpretation would explain the negligible effect of the pyridine ligand, the coordination of which would be outcompeted by the solvent, and the absence of a directing effect to the C2-position. To probe this hypothesis, we tested the olefination of **1v** under the previously developed conditions in other solvents and as




***Scheme 3.*** Scope of acceptor-substituted thiophenes (A) and furans (B). The structures of the respective starting materials are shown for simplicity. All reactions were conducted on a 0.2 mmol scale. Yields given in parentheses were obtained on a 2 mmol scale under otherwise identical conditions. Ethyl acrylate was used as the olefin reaction partner to evaluate the heteroarene scope. 3-(1,3,5-(*i*-Pr)$_3$C$_6$H$_2$)Furan (**1r**) was used as the substrate to evaluate the scope of the olefin reaction partners at 70 °C. [a] The reaction was conducted at 70 °C. [b] The olefination (21 %) and allylation (30 %) products were isolated separately.

***Table 3:*** Control experiments using Conditions D for the olefination of pyrroles.[a]




| Entry | Deviations from Conditions D | GC yield [%][b] | C5:C2:C4[b] |
|---|---|---|---|
| 1 | none | 59 | 95:3:2 |
| 2 | with **L2** | 56 | 94:4:2 |
| 3 | no *N*-acetylglycine | 30 | 86:10:4 |
| 4 | Conditions C | 68 | 1:62:38 |

[a] All reactions were conducted on a 0.1 mmol scale. **L2** = Methyl 6-methylnicotinate [b] Yields and ratios were determined by GC-FID using 1,3,5-trimethoxybenzene as an internal standard.

expected observed the preferential formation of the C2-olefination product, as well as C4-olefination product, which can likewise form through a directed pathway (entry 4).

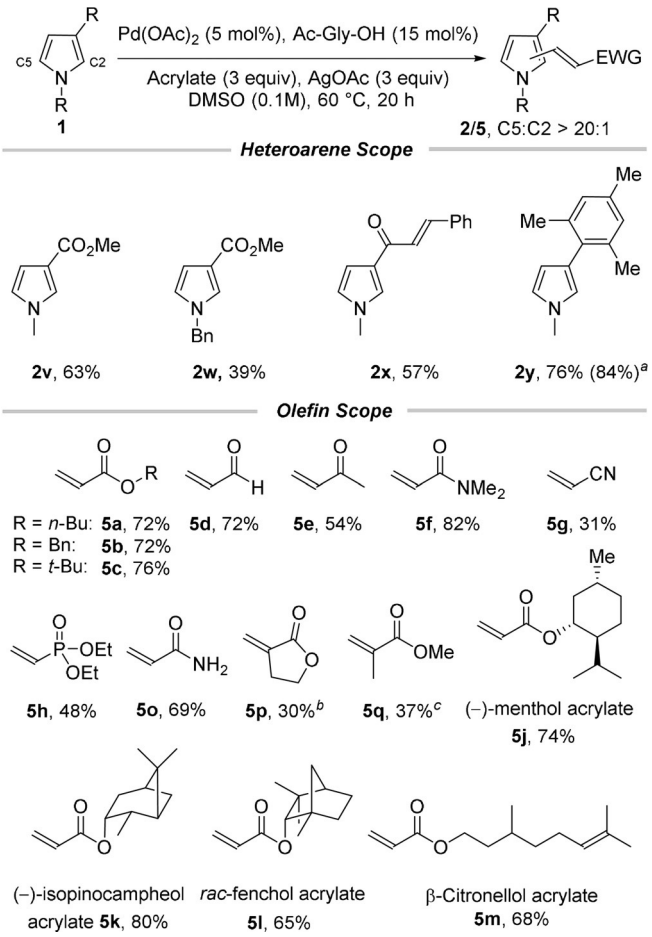
Scheme 4

With suitable conditions for the C5-olefination of **1v** in hand, we proceeded to study the scope of these conditions with respect to the pyrrole substrate and olefin reaction partner. When Conditions D were used, substrates bearing electron-withdrawing groups, as well as aryl substituents in the 3-position could be olefinated with exclusive selectivity for the C5-position (**2v**–**y**).[11] It is worthwhile to highlight that the core structure of histone deacetylase inhibitors can be constructed in an efficient way, the synthesis of **2x** constituting a formal synthesis of the respective compound.[18b,e]

Different olefins were tested with pyrrole substrate **1y**. The products derived from different acrylates could again be obtained as single isomers (**5a**–**c**). Similarly, acrolein, methyl vinyl ketone, and *N*,*N*-dimethylacrylamide gave the desired products **5d**–**f** in good yields and as single regioisomers. Acrylonitrile, diethyl vinylphosphonate, simple acrylamide, β-methylene butyrolactone, and methyl methacrylate gave the desired products (**5g**,**h**,**o**,**p**,**q**) in reasonable yields and complete regioselectivity. As for the previous substrate classes, we proceeded to test natural-product-derived acrylates and obtained the products derived from (−)-menthol (**5j**), (−)-isopinocampheol (**5k**), *rac*-fenchol (**5l**), and β-citronellol (**5m**) in good yields and as single regioisomers.

Finally, we probed the scalability of our protocol by submitting representative compounds to the respective optimized reaction conditions on a 2 mmol scale. The compounds **2d**, **2k**, **2r**, and **2y** were obtained in synthetically useful yields at this scale.

In this study, we have identified conditions that enable the sterically controlled olefination of thiophenes, furans, and pyrroles. All three types of heterocycles can be either donor- or acceptor-substituted in the 3-position. Although our studies were initiated starting from our experience with dual ligand-enabled palladium catalysis (Figure 1),[17] the optimal reaction conditions identified for the different substrate classes vary significantly. The olefination of 3-donor-substituted thiophenes was found to be best catalyzed using palladium and a sterically demanding electron-poor pyridine,




***Scheme 4.*** Scope of pyrroles. The structures of the respective starting materials are shown for simplicity. All reactions were conducted on a 0.2 mmol. Yields given in parentheses were obtained on a 2 mmol scale under otherwise identical conditions. Ethyl acrylate was used as the olefin reaction partner to evaluate the heteroarene scope. 3-mesityl-*N*-methyl-pyrrole (**1y**) was used as the substrate to evaluate the scope of the olefin reaction partners with 1.15 equivalents of the olefin reaction partner. [a] 1.15 equivalents of olefin were used. [b] The product was obtained as a mixture of allylation, *E*-olefination, and *Z*-olefination products (88:11:1). [c] The allylation (29%) and olefination (8%) products were isolated separately.

without requiring the additional activation through an amino acid derived ligand. In contrast, for 3-acceptor-substituted thiophenes, as well as all furans studied, the use of a dual ligand system was found to deliver the best results. For substrates containing potential directing groups, the ability of the catalysts to overcome directing effects was found to be crucial for good yields and regioselectivities. Finally, the olefination of pyrroles was found to require a catalyst with *N*-acetylglycine as ligand in DMSO as solvent. Here, the use of a pyridine-type ligand exhibited neither a positive nor a detrimental effect, presumably because the solvent occupies the respective coordination site. Our findings provide guidance regarding the choice of reaction conditions for each substrate class. In this context it should be noted that we tested each of the model substrates shown in Tables 1–3 under all of the conditions developed in this study (Conditions A–D) and could confirm that indeed each set of reaction

conditions is specific and optimal for the respective substrate class.[20]

## Conclusion

In summary, we have developed four sets of reaction conditions, which enable the olefination of 3-substituted thiophenes, furans, and pyrroles in the challenging C5-position. The method features a broad scope of heteroarenes, including electron-donating and -withdrawing substituents, and can be used in conjunction with a variety of olefin coupling partners. The scalability to a synthetically valuable scale was demonstrated and the core structures of several compounds with known bioactivities were obtained. Importantly, the heterocyclic substrates can be employed as the limiting reagent, which renders this protocol attractive for the late-stage modification of complex heterocyclic substrates, for example in the context of lead diversification for the synthesis of bioactive compounds.

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## Conflict of interest

The authors declare no conflict of interest.

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