Catalyst Controlled Regiodivergent C–H Alkynylation of Thiophenes

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Dedicated to Professor Bart Jan Ravoo on the occasion of his 50th birthday

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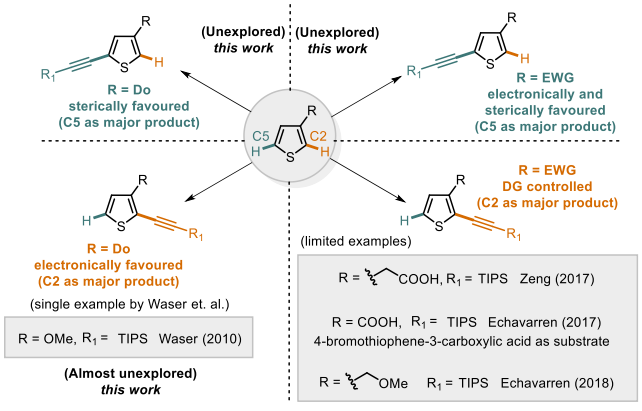
Abstract: Alkynes are highly attractive motifs in organic synthesis due to their presence in natural products and bioactive molecules as well as their versatility in a plethora of subsequent transformations. A common procedure to insert alkynes into hetero(arenes), such as the thiophenes studied herein, consists of a halogenation followed by a Sonogashira cross-coupling. The regioselectivity of this approach depends entirely on the halogenation step. Similarly, direct alkynylations of thiophenes have been described that follow the same regioselectivity patterns. Herein we report the development of a palladium catalyzed C–H activation/alkynylation of thiophenes. The method is applicable to a broad range of thiophene substrates. For 3-substituted substrates where controlling the regioselectivity between the C2 and C5 position is particularly challenging, two sets of reaction conditions enable a regiodivergent reaction, giving access to each regioisomer selectively. Both protocols use the thiophene as limiting reagent and show a broad scope, rendering our method suitable for late-stage modification.

The direct functionalization of thiophenes, to access their valuable derivatives, is an important target in organic chemistry due to the broad use of thiophenes in material sciences and medicinal chemistry.[1] Alkynes are one of the key motifs for organic chemists and the most commonly used method for insertion of it into (hetero)arenes is Sonogashira cross-coupling,[2] where the regioselectivity of the product formation depends on (pseudo)halogenation step. Considering the importance of alkynylated thiophenes in pharmaceuticals and organic materials,[3] an alternative direct access to these products is highly desirable since this would not only make the method more atom- and step-economic, but could also deliver complementary products in cases where there is a challenge in regioselectivity. In 2010, Waser and co-workers reported a gold and Brønsted acid-catalyzed C5-alkynylation of 2-substituted thiophenes.[4] In this study, they also reported one example of an electron-rich 3-substituted thiophene, which was selectively alkynylated in the C2-position (Scheme 1). Furthermore, Su and co-workers reported a Pd-catalyzed oxidative cross-coupling of 2-substituted thiophenes and phenyl acetylenes, the later one being used as limiting reagent.[5] However, to the best of our knowledge no general method, which enables the alkynylation of thiophenes irrespective of the substitution pattern, has been reported to date. Especially for 3-substituted thiophenes, the control over the regioselectivity between C5 and C2 position remains unaddressed.

For such 3-substituted thiophenes, the regioselectivity of the C–H activation is mainly governed by the steric and electronic properties of the substituents as well as the sensitivity of the catalyst system towards these effects.[6-8] For substrates bearing electron-donating substituents in the 3-position, the C2 product is electronically favored and hence an electrophilic reagent or catalyst is expected to induce the functionalization in this position. In contrast, a catalyst that is more sensitive to steric hindrance is expected to lead to C5-substitution through a pathway in which the steric clash between the catalyst and the substituent in the 3-position is avoided. For electron-withdrawing groups in the 3-position another effect comes into play. Since many of these substituents are also Lewis-basic, they can act as directing groups (DGs) thereby favoring the functionalization in the neighboring C2-position (and in principle also the often less reactive C4-position) through chelation control. In 2017, Zeng and co-workers reported a directed Ir-catalyzed ortho-alkynylation of arenes which included one example of such a carboxylate-directed, C2-selective alkynylation of a 3-subsbtituted thiophene (Scheme 1).[9]



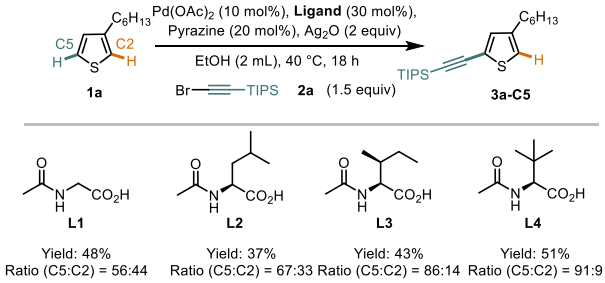
Scheme1. Explored and Unexplored Areas of Regioselective C–H Alkynylation of 3-Substituted Thiophenes.

Also in 2017, Echavarren and co-workers reported a Ru-catalyzed ortho-alkynylation of arenes. As part of this study they demonstrated the carboxylic acid-directed alkynylation of 3-substituted thiophenes to get di-alkynylation at the C2- and C4-position.[10] One example of a C2-selective mono-alkynylation employing 4-bromothiophene-3-carboxylic acid as substrate was

also reported (Scheme 1). In 2018, the same group reported a Rh-catalyzed ortho-alkynylation of arenes, which included one example of a 3-substituted thiophene with benzyl ether as weak DG to deliver the C2 product (Scheme 1).[11] As highlighted above, the direct C–H alkynylation of thiophenes remains a highly challenging yet attractive goal. For C2-substituted substrates substantial limitations still exist with respect to the scope of substrates that can be addressed. The more challenging 3-substituted substrates have to date only been addressed in isolated cases leading to C2-selective functionalization.

Based on these observations and our recent experience in controlling the regioselectivity of C–H activations on heteroarenes,[6m] we hypothesized that through the design of suitable catalysts a regiodivergent reactivity enabling both a C2- and a C5-selective alkynylation of thiophenes could be developed.[12] Additionally, we expected that one of these catalyst systems would likely display a broad scope with respect to thiophenes with simpler substitution patterns as well, thereby allowing us to develop a general method for the alkynylation of thiophenes.

We thus began our studies with 3-hexyl thiophene **1a** as model compound. We expected that by applying our dual ligand enabled catalyst design,[13] which is known to deliver products under steric control, we would be able to induce an alkynylation in the C5-position. Although our initial experiments delivered poor regioselectivities, we observed a highly promising ligand control of the regioselectivity when increasing the steric demand of the substituent on the amino acid-derived ligand (**L1**-**L4**, Scheme 2).



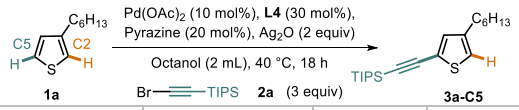
Scheme 2. Effect of Ligands on yield and regioselectivity. All reactions were conducted on a 0.1 mmol scale. Yields and ratios were determined by GC-FID analysis using 1,3,5-trimethoxybenzene as an internal standard.

Using **L4**, we proceeded to optimize the reaction conditions and identified the protocol shown in Entry 1 of Table 1. Under these conditions the target compound **3a-C5** was obtained in good yield (71%) and regioselectivity (94:6). Importantly, our control experiments revealed that the reaction is indeed dual ligand-enabled, since in the absence of either ligand, substantially worse reaction outcomes were observed (Entries 2-4).

With the optimized reaction conditions in hand, we proceed to explore the scope of the reaction (Scheme 3).

The sterically controlled nature of the catalyst system is visible if one compares the selectivity of the entries **3a-C5**–**3c-C5**, where a decrease in the steric bulk of the alkyl substituent somewhat decreases the C5 selectivity, albeit still remaining good even for

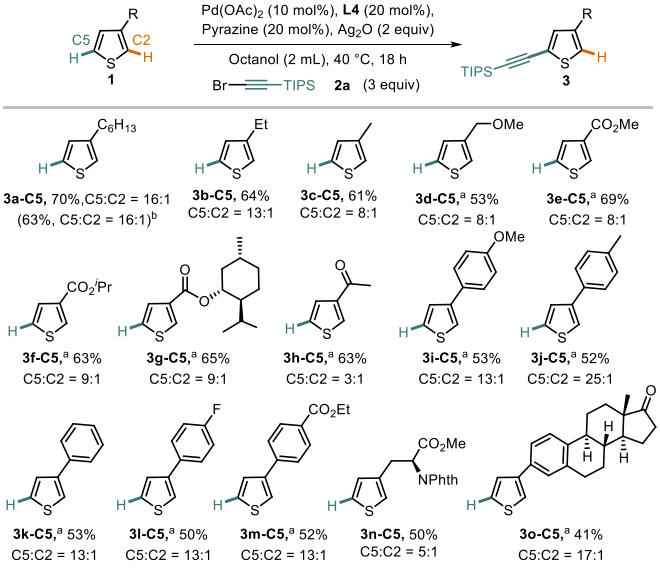
Table 1. Control Experiments (C5 selectivity).



Conditions[a]	Conversion (%)[b]	Yield (%)[b]	Ratio (C5:C2)[b]
As above	97	71	94:6
No Pd, **L4**, pyrazine	5	0	-
No **L4**	26	19	47:53
No pyrazine	22	9	67:33

[a] All reactions were conducted on a 0.1 mmol scale. [b] Conversions, yields, and ratios were determined by GC-FID analysis using 1,3,5-trimethoxybenzene as an internal standard.

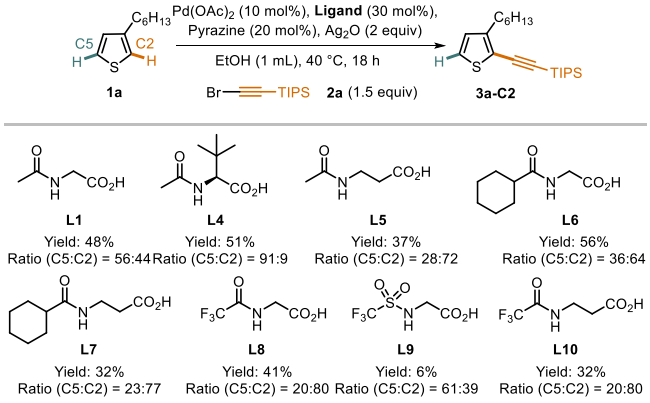
the small methyl group. Electron-withdrawing ester and ketone substituents are also tolerated and give products with good C5 selectivity under both electronic and steric control (Scheme 3, **3e-C5**–**3h-C5**). Our protocol works well for a series of 3-aryl substituted thiophenes (Scheme 3, **3i-C5**–**3m-C5**), which as well



Scheme 3. Scope of the C5-selective alkynylation of thiophenes. All reactions were conducted on a 0.2 mmol scale. a. For these reactions ^{t}Amyl-OH was used as solvent. b. Reaction conducted on a 5 mmol scale.

shows that a number of common functional groups are well tolerated under our reaction conditions, such as ethers, halides, and esters. Finally, our method can be applied to alkynylate a thiophene-containing unnatural amino acid-derivative (**3n-C5**) and an estrone derivative (**3o-C5**) with good C5 selectivity.

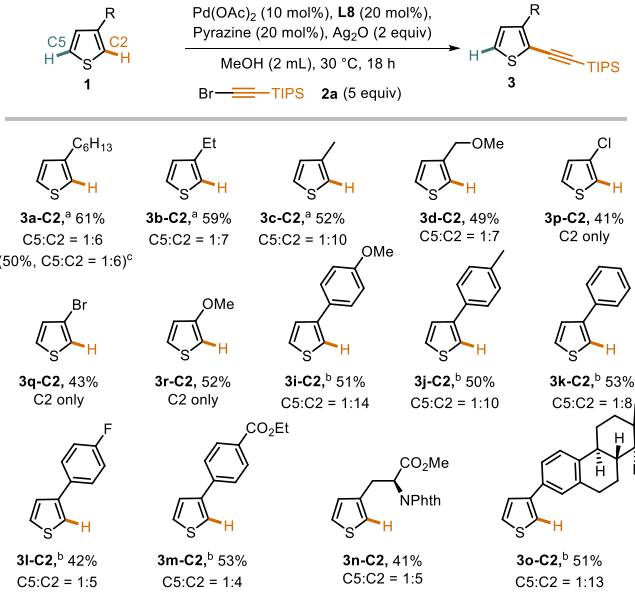
After realizing a broad scope in Scheme 3, we proceeded to attempt the development of a complementary, C2-selective catalyst system. Although in our previous studies, dual ligand-based catalysts always showed a preference for steric over electronic control, we reasoned that by increasing the electrophilicity of the catalyst, an electronically controlled reaction might be enabled. In our previous optimization studies, we noted that *N*-acetyl-β-alanine (**L5**) and a COC_6H_{11}-substituent on nitrogen of glycine as ligand (**L6**) both led to increased amounts of the C2-alkynylated product **3a-C2** (Scheme 4).



Scheme 4. Ligand Development for C2 Selectivity. All reactions were conducted on a 0.1 mmol scale. Yields and ratios were determined using GC-FID analysis using 1,3,5-trimethoxybenzene as an internal standard.

Unfortunately, combining these effects in **L7** did not deliver satisfactory results. We thus proceeded to test stronger electron-withdrawing substituents on the ligand. We installed a $COCF_3$-substituent (**L8**) and a SO_2CF_3-substituent (**L9**) on the nitrogen of glycine and gratifyingly, **L8** was able to deliver a 4:1 selectivity in favor of the C2 product. Lastly, we tested ligand **L10**, which constitutes a permutation of the positive effects seen in **L5** and **L8**. However, this ligand gave a reduced yield and no improvement in the regioselectivity compared to **L8**, which was therefore chosen for further optimization studies. We proceed to screen various other parameters which led us to identify reaction conditions under which a good yield and regioselectivity are obtained (for details, see the Supporting Information).

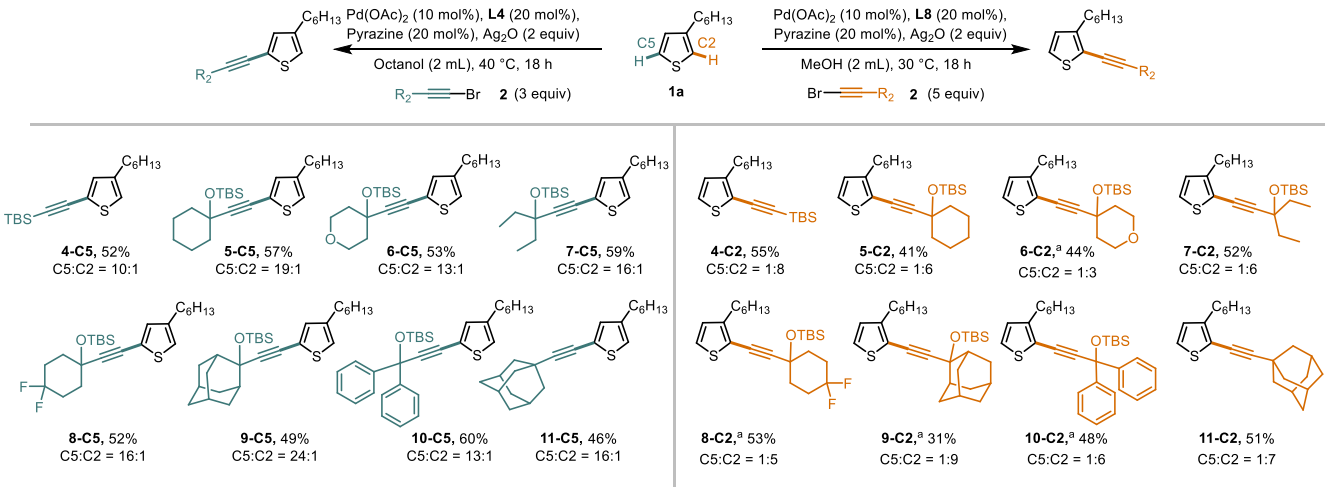
These conditions were then used to explore the scope of the C2-selective alkynylation (Scheme 5). The trend in C2 selectivity observed from hexyl to methyl substituent (Scheme 5, **3a-C2–3c-C2**) shows that this catalyst system, while predominantly controlled by electronics, is sensitive to sterics as well, since the C2-selectivity is best when steric hindrance at this position is low. Halide substituents (**3p-C2** and **3q-C2**) as well as a strong electron-donating methoxy (**3r-C2**) group give the C2 product exclusively. We also tested various aryl-substituted thiophenes (Scheme 5, entries **3i-C2–3m-C2**). In contrast to the C5-selective protocol and as expected for an electronically controlled reaction,



Scheme 5. Reaction scope (C2 selectivity). All reactions were conducted on a 0.2 mmol scale. a. Reaction conducted at 35 °C with 2 equivalents of reagent. b. Reaction conducted at 50 °C. c. Reaction conducted on a 1 mmol scale.

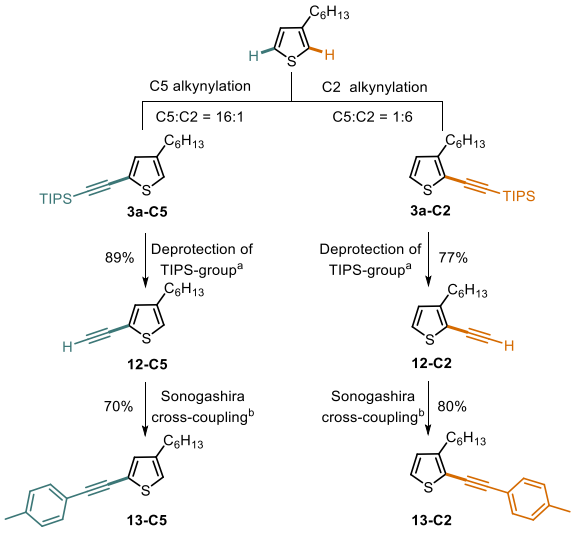
we observed a much stronger dependence of the reaction outcome on the electronic nature of the substituent. An electron-donating methoxy substituent (**3i-C2**) on the phenyl ring gives substantially higher C2-selectivity than an electron-poor ester substituent (**3m-C2**). Irrespective of these effects on the regioselectivity, the functional group compatibility was found to be good for the C2-selective protocol as well. Finally, this catalyst system can also be used to deliver alkynylation product from an amino acid-derived thiophene derivative (**3n-C2**) and an estrone derivative (**3o-C2**) with good C2 selectivity.

Having established the thiophene scope for our regiodivergent protocols, we were interested to evaluate the use of other bromoalkynes with both protocols (Scheme 6).[14] We found that a considerable range of bromoalkynes could be used in both directions with good yield and selectivity.



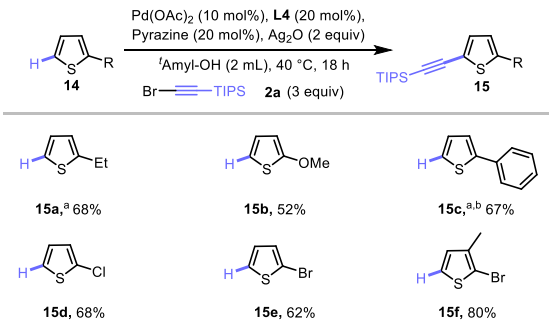
Scheme 6. Alkyne scope. All reactions were conducted on a 0.2 mmol scale. a. Reaction conducted at 35 °C with 2 equivalents of alkyne reagent.

A TBS-group was well tolerated (**4-C5** and **4-C2**), as well as various alkyl-substituted bromoalkynes as reagent (**5-C5–11-C5** and **5-C2–11-C2**).
Unfortunately, phenylacetylene-derived bromoalkynes gave unsatisfactory results under our reaction conditions. However, the regiodivergent reactivity developed herein can nevertheless be harnessed for such target compounds. To demonstrate this, we performed the deprotection of the TIPS-group followed by Sonogashira cross-coupling with 4-iodotoluene in both directions using our standard substrate and isolated the desired products **13-C5** and **13-C2** in synthetically useful yield (Scheme 7).



Scheme 7. Deprotection of TIPS-group and Sonogashira coupling. a. **3a-C5**/**3a-C2** (0.45 mmol), TBAF (1M in THF, 1.1 equiv), THF (5 mL), 0 °C, 1 h. b. **12-C5**/**12-C2** (0.2 mmol), 4-iodotoluene (0.23 mmol), CuI (0.082 mmol), $Pd(PPh_3)_2Cl_2$ (0.041 mmol), PPh_3 (0.041 mmol), NEt_3 (1.1 mL), THF (1.4 mL), 60 °C, 1 h.

As mentioned earlier, we expected that once the challenging regioselective alkynylation of 3-substituted thiophenes would be addressed, the respective catalyst systems would likely also be able to functionalized regioselectivity-wise less challenging thiophenes and thereby provide a general method for the alkynylation of all types of thiophenes. We tried the conditions developed for the C5 and C2-selective alkynylations on 2-ethyl thiophene (**15a**, Scheme 8) as model substrate and found that



Scheme 8. Scope of C2-substituted thiophenes. All reactions were conducted on a 0.2 mmol scale. a. $Pd(OAc)_2$ (10 mol%), **L8** (20 mol%), pyrazine (20 mol%), Ag_2O (2 equiv), MeOH (2 mL), **2a** (5 equiv), 30 °C, 18 h. b. Reaction conducted at 50 °C instead of 30 °C.

the later delivered satisfactory results. An electron donating methoxy substituent (**15b**) is well tolerated. Likewise, an aryl-substituent in the 2-position led to a good reaction outcome (**15c**). Finally, halide substituents (**15d**-**e**) and 2,3-di-substitution (**15f**) were found to be well tolerated.
In summary, we have developed a pair of general catalysts systems for the Pd-catalyzed non-directed C–H activation/ alkynylation of thiophenes that are suitable for all kinds of substitution patterns on the thiophene. For regioselectivity-wise challenging 3-substituted substrates the protocols are complementary, giving a regiodivergent access to the C5- and C2-alkynylated products respectively. Overall, a broad scope with respect to the thiophene and alkyne reaction partner can be addressed, including structurally complex examples. In all cases the thiophene substrate is used as the limiting reagent, which renders this protocol attractive in the context of late-stage modification.

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Keywords: C–H Activation • Alkynylation • Regioselectivity • Regiodivergent • Thiophenes

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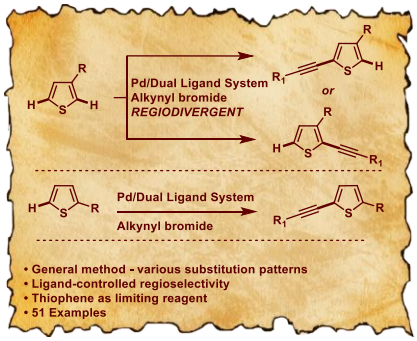

A method for the direct C–H alkynylation of thiophenes has been developed. Complementary sets of reaction conditions enable a regiodivergence for 3-substituted substrates, giving selective access to either the C2 or the C5 alkynylation products. The method works for various substitution patterns on the thiophene, features a broad scope, and uses the thiophene as the limiting reagent, rendering it suitable for late-stage modification

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