Oxidative Trifluoromethylation and other Functionalization Reactions of Alkenes and Alkynes

Pär Janson
What is most important is invisible to the eye.

The Little Prince -
Antoine de Saint Exupéry
Abstract

This thesis concerns the use of various potent oxidants in organic synthesis. The main focus is directed at selectively introducing trifluoromethyl groups into compounds containing double or triple bonds. All reactions proceed under mild conditions and can in most cases be performed on the bench-top.

We have developed three different procedures for transformations of activated alkenes and alkynes as well as quinones. In paper I the selective introduction of a trifluoromethyl group together with an oxygen functionality to double and triple bonds is demonstrated. Paper II is focused on the related chemoselective cyanotrifluoromethylation in which a cyano group is added instead of the oxygen functionality.

Paper III describes a new procedure for C–H trifluoromethylation of quinones. Our studies on the mechanistic aspects of the above reactions are described in Paper IV. In these studies we investigated the ligand and substituent effects in Cu-catalyzed reactions.

Paper V is focused on a conceptually new palladium-catalyzed allylic C–H acyloxylation of olefins under oxidative conditions. The procedure uses an inexpensive, safe and environmentally benign oxidant, sodium perborate, which is activated with acetic anhydride.
List of Publications

This thesis is based on the following papers, which will be referred to by Roman numerals. Reprints were made with kind permission from the publishers.

I. Electrophilic Trifluoromethylation by Copper-Catalyzed Addition of CF\textsubscript{3}-Transfer Reagents to Alkenes and Alkynes

II. Copper-Mediated Cyanotrifluoromethylation of Styrenes Using the Togni Reagent

III. Copper-mediated C–H trifluoromethylation of quinones

IV. Effects of B\textsubscript{2}pin\textsubscript{2} and PC\textsubscript{y}\textsubscript{3} on Copper-catalyzed Trifluoromethylation of Substituted Alkenes and Alkynes with the Togni Reagent
    Pär G. Janson, Nadia O. Ilchenko, Alberto Diez-Varga, Kálmán J. Szabó, *Submitted*

V. Palladium-Catalyzed Selective Acyloxylation Using Sodium Perborate as Oxidant
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Abbreviations

The abbreviations are used in agreement with standards of the subject. Only non-standard and unconventional ones that appear in the thesis are listed here.

- B$_2$Pin$_2$: bis(pinacolato)diboron
- BQ: 1,4-benzoquinone
- CuTc: copper(I) thiophenecarboxylate
- DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene
- DMAc: N,N-dimethylacetamide
- mCPBA: meta-chloroperbenzoic acid
- L: ligand, neutral
- MTBE: methyl tert-butyl ether
- ND: not determined
- NR: no reaction
- NSAID: non-steroidal anti-inflammatory drug
- PIDA: (Diacetoxyiodo)benzene
- PIFA: [Bis(trifluoroacetoxy)iodo]benzene
- RT: room temperature
- TEMPO: (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl

1. Introduction

1.1 Catalysis

Any substance that enhances the rate of a chemical reaction without itself being consumed is referred to as a catalyst. A catalyst can be considered as both a reactant and a product of the reaction. Since the catalyst is not consumed it can be employed in sub-stoichiometric amounts. A catalyst does not change the overall heat of reaction but lowers the activation barrier or opens new mechanistic pathways (Figure 1). Thus a catalytic reaction is allowed to proceed at a lower temperature and under milder conditions than the corresponding uncatalyzed process.¹

![Figure 1. Principle of catalysis](image)

The nature of a catalyst can be remarkably different depending on the reaction. A reaction can be catalyzed by a single proton, so-called Brønsted acid catalysis, or a multitude of proteins catalyzing reactions in our cells throughout our lives. This thesis is focused on the application of late transition metal catalysis, which uses metals like copper and palladium. These transition metals are commonly used as catalysts, mainly because of their ability to easily undergo fundamental organometallic reaction steps, such as oxidative addition, reductive elimination and migratory insertion.²
1.2 Copper-catalyzed trifluoromethylation

The trifluoromethyl group (–CF₃) is an electron withdrawing and, at the same time, a lipophilic group. This makes it a very attractive functional group for pharmaceutical chemists because it can be used to tune both the electronic and pharmacokinetic properties of a drug. About 30 – 40 percent of all new pharmaceutical and agrochemical compounds contain fluorine, most commonly as single fluoride and trifluoromethyl groups. Several examples currently on the list of top-selling pharmaceuticals are displayed in Figure 2.

Figure 2. Examples of pharmaceuticals containing trifluoromethyl groups.

Early synthetic examples of molecules containing CF₃-groups, such as the Swarts reaction⁴, used harsh reaction conditions. This has a severe impact on the functional group tolerance, and therefore these methods need to be used early in a multi-step synthesis. Trifluoromethyl groups are important because they can help tune that it allows fine tuning of the polarity and electronic properties of organic molecules. This often requires a late stage introduction, usually at a point where many sensitive functional groups are already installed in a compound. Therefore, research on mild selective methods for the introduction of trifluoromethyl groups has become a highly active field.⁵

1.2.1 Brief overview of modern trifluoromethylation reactions

Research efforts towards mild and selective trifluoromethylation reactions started with the introduction and application of stable and easily handled sources of the CF₃ group. Pioneering work by Togni,⁶
Umemoto,\textsuperscript{7} Langlois,\textsuperscript{8} Grushin,\textsuperscript{9} and Hartwig\textsuperscript{10} has resulted in a variety of reagents for selective delivery of either the electrophilic CF\textsubscript{3}\textsuperscript{+}, the radical CF\textsubscript{3}\textsuperscript{•} or the nucleophilic CF\textsubscript{3}\textsuperscript{−} species (Figure 3). Most of these reagents have been synthesized using the so called Ruppert-Prakash reagent, TMS–CF\textsubscript{3}. Most work in modern trifluoromethylation has been focused on aryl functionalization, mainly because of the large demand from medicinal chemistry (where the –CF\textsubscript{3} group is used as a more metabolically stable isostere for –CH\textsubscript{3}). Most procedures are either catalyzed or mediated by copper.

![Figure 3. Stable, easily handled trifluoromethylating agents.](image)

**Figure 3.** Stable, easily handled trifluoromethylating agents.

**Scheme 1.** Most common strategies for aryl trifluoromethylation. (DG = directing group)

The most common route for CF\textsubscript{3} introduction is substitution reactions, mainly from halides\textsuperscript{10-11} or boronic acid derivatives\textsuperscript{12} (Scheme 1). Recently, methods based on C–H functionalization\textsuperscript{13} and one-pot procedures from simple, readily available starting materials such as anilines\textsuperscript{10b,14} have been developed.
Trifluoromethylation of alkenes has received less attention than aryl substrates. A handful of methods have been published on trifluoromethylation of vinyl boronic acid derivatives using copper catalysts. Transformation of vinyl halides or pseudohalides usually requires harsh conditions or toxic reagents. However, recently the groups of Bräse and Buchwald demonstrated that trifluoromethylation of vinyl halides can be performed using benign reagents under mild conditions. Similar halogen to CF₃ exchange methods can also be applied for allylic trifluoromethylation. Some of the more synthetically useful reactions are displayed in Scheme 2 below. Using CF₃Cu(PPh₃)₃ 1d or catalytic amounts of copper, the groups of Nishibayashi, Szabó, and Altman have developed synthetically useful trifluoromethylations by substitution of allyl halides or allylic alcohol derivatives.

Scheme 2. Copper-catalyzed (Nishibayashi, left) and -mediated (Szabó, right) allylic trifluoromethylation.

The groups of Sodeoka and Gouverneur independently developed efficient procedures for the trifluoromethylation of allyl silanes. Both groups used the electrophilic hypervalent iodine reagent 1a (Togni’s reagent). The Gouverneur group also applied a visible light driven process using Ru(bpy)₃Cl₂ as photosensitizer for trifluoromethylation.

The trifluoromethylation of alkynes is even less studied than trifluoromethylation of aryl and alkene substrates. Most examples of this reaction are focused on transformation of terminal C–H or C–B(OH)₂ derivatives. This field was pioneered by the Qing group who generated (Phen)CuCF₃ reagent 1e in situ from Ruppert’s reagent and catalytic or stoichiometric amounts of simple copper salts (Scheme 3, right). Huang and Weng also developed methods for performing electrophilic copper-catalyzed trifluoromethylations using an analogue to 1a (Scheme 3, left).
Scheme 3. Copper-catalyzed and -mediated methods for alkyne trifluoromethylation

1.2.2 Allylic and vinylic C–H trifluoromethylation

Alkenes with trifluoromethyl groups in the allylic position are useful substrates in oxidations, metathesis reactions and Heck reactions. The area of allylic C–H trifluoromethylation has recently received considerable attention. The groups of Buchwald, Liu, and Wang independently reported copper-catalyzed C–H trifluoromethylation of allylic systems in 2011. All of these procedures are based on the use of electrophilic trifluoromethyl sources (such as 1a or 1b). In addition, a useful procedure with hypervalent oxidant PIDA and TMSCF₃ as the CF₃ source has also been reported by the Qing group.

Scheme 4. Example of an allylic C–H trifluoromethylation reaction using 1a.

Vinylic C–H trifluoromethylation has received much interest because CF₃-bearing double bonds are metabolically stable isosteres for the amide bonds. Sodeoka and co-workers reported one of the first reactions for copper-catalyzed vinylic C–H trifluoromethylation of alkenes (Scheme 5).
Scheme 5. Example for vinylic C–H trifluoromethylation.\textsuperscript{28}

Since this example, many additional copper-catalyzed trifluoromethylation reactions have been reported. Most of the substrates in these reactions are activated by directing groups\textsuperscript{29} or by electron donor substituents on the double bonds.\textsuperscript{30} This activation leads to excellent regioselectivity. Using a different approach, Cho and co-workers demonstrated vinylic C–H trifluoromethylation of non-activated alkenes using photoredox catalysis and CF\textsubscript{3}I as the trifluoromethyl source (Scheme 6).\textsuperscript{31} Despite the presence of allylic protons the reaction proceeded with excellent selectivity for vinylic products.


1.2.3 Oxytrifluoromethylation of double and triple bonds

Oxytrifluoromethylation is the simultaneous introduction of both a trifluoromethyl and an oxygen-based functional group. This reaction was first reported when Sodeoka and Gouverneur independently detected formation of oxytrifluoromethylated products in trifluoromethylation reactions of allyl silanes. Oxytrifluoromethylated products were formed as side products (Scheme 7a) in reaction of allyl silanes (such as 16) with 1a but also from alkenes, such as 14b (Scheme 7b). Many of the early examples of metal-catalyzed oxytrifluoromethylations were intramolecular reactions with an external electrophilic trifluoromethyl source.\textsuperscript{32}
Scheme 7. First reported copper-catalyzed oxytrifluoromethylation reactions.

Buchwald reported selective procedures for three- to six-membered ring formation using unsaturated alcohols or acids as precursors.\textsuperscript{33} This methodology was later extended to the synthesis of enantiomerically enriched lactones using chiral bidentate ligands (Scheme 8).\textsuperscript{34}

Scheme 8. Intramolecular enantioselective oxytrifluoromethylation.

Other oxytrifluoromethylation methods without copper-catalysis\textsuperscript{32a,35} and/or electrophilic trifluoromethylating reagents\textsuperscript{36} have also been published. In these methods CF\textsubscript{3} radicals are usually generated, either by photoredox catalysis or by using the sulfinate salt 1\textsuperscript{c} in combination with a radical source like \textsuperscript{\textit{t}}BuOOH. The latter method is particularly attractive as it uses easily handled, inexpensive reagents under environmentally friendly conditions.\textsuperscript{13c,37}

Synthetic procedures have been developed involving simultaneous formation of C–CF\textsubscript{3} and C–C or C–N bonds. These reactions are
mainly copper-catalyzed cyclizations (Figure 4)\textsuperscript{37-38}, but a few reports on intermolecular processes have also been published.\textsuperscript{39}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{Examples of CF\textsubscript{3}-containing products synthesized by simultaneous trifluoromethylation/C–C or C–N bond formations. The bonds formed in these processes are marked in bold.}
\end{figure}

Our aim was to develop selective trifluoromethylation reactions because trifluoromethylated compounds are important in synthetic organic chemistry (Chapters 2 – 4). Given the special interest of vinylic and allylic functionalization in our group the efforts have been focused on alkene systems.

1.3 Allylic C–H Acyloxylation

Allylic alcohol derivatives (in particular allylic esters) are common precursors for the synthesis of more complicated allylic systems. For example, this can be done through the Tsuji-Trost reaction (Scheme 9).\textsuperscript{40} For this reason allylic esters are widely used intermediates in organic synthesis.\textsuperscript{41} Allylic esters are mainly synthesized via two pathways. These are: i) Acylation of allylic alcohols with carboxylic acids, anhydrides or acid chlorides (requires prefunctionalization) and ii) Replacement of the allylic C–H bond by a carboxylate via transition metal catalysis.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme9.png}
\caption{General example for the Tsuji-Trost reaction.}
\end{figure}
Scheme 10. Palladium-catalyzed allylic C–H acetoxylation reported by Tsuji.

The first example of allylic C–H acetoxylation was published by Tsuji in 1981. However, the reaction scope was rather limited, possibly because of the strongly oxidizing and/or acidic conditions. Later work by McMurry/Kocovsky and the Åkermark group resulted in milder, synthetically useful reactions (Scheme 11a). In these reactions acetic acid is used as both the solvent and the source of acetate. Similar reaction conditions have been applied by White and co-workers to perform enantioselective reactions and acetoxylations in the late stages of natural product syntheses.

Mechanistic investigations by Bäckvall and co-workers showed that the reaction proceeds through an η3-allyl palladium complex. It was suggested that the strongly electron-withdrawing 1,4-benzoquinone (BQ) is coordinated to the metal center (Scheme 11b). Thus, BQ is a π-acidic ligand that facilitates the product forming reductive elimination and also, in the later stage, oxidizes Pd0 to PdII. To overcome the difficulty of the reductive elimination the Szabó group has utilized hypervalent iodine reagents as oxidants and sources of carboxylates (Scheme 12). The reaction was suggested to proceed through PdIV intermediates.

Scheme 11. Allylic C–H acetoxylation developed by Åkermark and co-workers.
**Scheme 12.** High oxidation state palladium-catalyzed acyloxylation.

Considering the large synthetic utility of allyl acetate substrates, we decided to develop a novel methodology for inexpensive and environmentally benign C–H bond functionalization of these species (Chapter 5).
2. Difunctionalization-based trifluoromethylation reactions (Papers I & II)

As mentioned above (Section 1.2) introduction of trifluoromethyl groups into organic compounds is a highly desirable transformation. Addition reactions, or difunctionalizations, of alkenes and alkynes are well-studied and can be used for building up complexity in organic compounds. This chapter shows two examples of difunctionalization based incorporation of a trifluoromethyl group to alkenes and alkynes.

2.1. Oxytrifluoromethylation of alkenes and alkynes (Paper I)

In our attempts to develop copper-catalyzed allylic C–H trifluoromethylation reactions of 13d (Scheme 13), we observed formation of a saturated product (28a). The $^1$H and $^{19}$F NMR spectra of 28a indicated that an addition of both a trifluoromethyl group at the terminal carbon and another functionality at the neighboring carbon had occurred. We hypothesized that if the reaction was performed with a substrate without an allylic C–H group, a synthetically useful difunctionalization could be achieved.

![Scheme 13. Allylic C–H trifluoromethylation product and the unexpected addition product.](image-url)
2.1.1 Reaction optimization

As a model system for the desired transformation para-methoxy styrene 14a as the substrate and 1a as the trifluoromethyl source were chosen (scheme 14) in the presence of stoichiometric amounts of CuI.

Scheme 14. Reaction of 14a with reagent 1a in the presence of CuI.

The reaction (Scheme 14) afforded an addition product but instead of 28b we obtained 18b containing an iodobenzoate group. The structure of 18b was easily determined on the basis of its $^1$H and $^{19}$F NMR spectra. Some important results for the optimization of the oxytrifluoromethylation reaction are given in Table 1. The best results were obtained by CuI in CDCl$_3$ at 60 °C. CuOAc and Cu(MeCN)$_4$PF$_6$ gave lower yields (entries 3 – 4) and in the latter case we observed substantial rearrangement of 1a to 29. Similarly, using CD$_3$OD as the solvent led to extensive formation of 29. Formation of 29 is undesired as it cannot be used as a CF$_3$ transfer reagent in oxytrifluoromethylation reactions. The rearrangement of 1a to 29 is a thermal process (Scheme 15), which can be accelerated by solvents and additives.\textsuperscript{49}
Table 1. Optimization of oxytrifluoromethylation.

\[
\begin{array}{cccc}
\text{Entry} & [\text{Cu}] & \text{Solvent} & 18b:29 \text{ ratio} & \text{Isolated yield (18b)} \\
1 & \text{CuI} & \text{CDCl}_3 & 50:1 & 86\% \\
2 & - & \text{CDCl}_3 & \text{29 only} & \text{nd} \\
3 & \text{CuOAc} & \text{CDCl}_3 & 20:1 & 61\% \\
4 & \text{Cu(MeCN)}_2\text{PF}_6 & \text{CDCl}_3 & 64:36 & \text{nd} \\
5 & \text{Cu} & \text{CD}_3\text{OD} & 6:1 & \text{nd} \\
6 & \text{Cu(MeCN)}_2\text{PF}_6 & \text{CD}_3\text{OD} & 45:55 & \text{nd} \\
\end{array}
\]

Scheme 15. Undesired thermal decomposition of trifluoromethylating agent 1a.

2.1.2 Scope of the oxytrifluoromethylation reaction

We tested other alkenes (analogous to 14a) using the best conditions (Table 1, entry 1). The reaction is highly selective, as only a single regioisomer was formed (Table 2). In the products (18) the CF₃ group appeared exclusively at the terminal position. Para- and ortho-methoxy styrenes (entries 1 and 2) reacted readily and in good yields. However, meta-substituted styrene 14c could not be oxytrifluoromethylated under the above conditions (entry 3). Not only styrenes but also phenyl-vinyl sulfide 14f gave the expected product 18f.
Table 2. Representative substrates for the oxytrifluoromethylation of alkenes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Conditions (°C / h)</th>
<th>Product</th>
<th>Isolated Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeO</td>
<td>60 / 16</td>
<td>18b</td>
<td>86</td>
</tr>
<tr>
<td>2a</td>
<td>MeO</td>
<td>120 / 1</td>
<td>18c</td>
<td>58</td>
</tr>
<tr>
<td>3</td>
<td>MeO</td>
<td>60 / 18</td>
<td>18d</td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td>OMe</td>
<td>60 / 18</td>
<td>18e</td>
<td>77</td>
</tr>
<tr>
<td>5</td>
<td>PhS</td>
<td>60 / 18</td>
<td>18f</td>
<td>51</td>
</tr>
<tr>
<td>6a</td>
<td>Ph</td>
<td>120 / 0.5</td>
<td>18g</td>
<td>71</td>
</tr>
</tbody>
</table>

* a) Microwave irradiation was used for heating

The sterically hindered substrate 14g also reacted readily indicating that the introduction of the iodobenzoate group is not particularly sensitive to steric effects (entry 6). In the case of 14g we could also observe minor formation of the vinyl product 15c (Scheme 16), which apparently arose from elimination of iodobenzoic acid from 18g. As mentioned above the Sodeoka group reported the formation of similar vinyl–CF₃ derivatives from trifluoromethylation reactions with 1a.
Scheme 16. Formation of vinyl–CF$_3$ product 15c in oxytrifluoromethylation of 14g.

Interestingly iodotrifluoromethylation occurred when vinyl silane 14g was subjected to the above reaction conditions (with a stoichiometric amount of CuI). Using CuBr or CuCl also provided the corresponding halotrifluoromethylation products 28d–e (Scheme 17). We attempted to extend the halotrifluoromethylation to other substrates. However, under the above reaction conditions only vinyl silane 14h underwent halotrifluoromethylation.

Scheme 17. Halotrifluoromethylation of vinylsilanes.

Hydrolysis of the iodobenzoate ester can easily be performed by K$_2$CO$_3$ in MeOH affording the benzyl alcohol derivative 30 (Scheme 18). We have found that the hydrolysis can be performed without isolation of 18b from the crude reaction mixture.

Scheme 18. One-pot synthesis of substituted 3,3,3-trifluoropropanols.

Inspired by the successful oxytrifluoromethylation of alkenes (Table 2) we investigated the possibility of extending the process to analo-
gous alkynes. Indeed, aryl acetylenes 11a – d undergo regio- and stereoselective oxytrifluoromethylation (Table 3) using 1a and CuI. The reaction requires higher reaction temperatures than oxytrifluoromethylation of styrenes. Similar to styrenes, para-methoxy substituted substrate 11a reacted fastest (entries 1 – 2). However, for alkynes the parent phenyl acetylene (11c) and p-nitro derivative 11d could also be oxytrifluoromethylated at elevated temperatures (entries 4 – 5). Silyl acetylene 11e also underwent oxytrifluoromethylation but microwave conditions are necessary to get acceptable yields (entry 6).

Table 3. Scope of the alkyne oxytrifluoromethylation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Conditions (°C / h)</th>
<th>Product</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>MeO-&lt;sup&gt;-&lt;/sup&gt;</td>
<td></td>
<td>&lt;sup&gt;-&lt;/sup&gt;</td>
<td>120 / 1</td>
</tr>
<tr>
<td>2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>11a</td>
<td>60 / 18</td>
<td>31a</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>MeO-&lt;sup&gt;-&lt;/sup&gt;</td>
<td></td>
<td>&lt;sup&gt;-&lt;/sup&gt;</td>
<td>60 / 18</td>
</tr>
<tr>
<td>4</td>
<td>11c</td>
<td>100 / 18</td>
<td>31c</td>
<td>55</td>
</tr>
<tr>
<td>5</td>
<td>O&lt;sub&gt;2&lt;/sub&gt;N-&lt;sup&gt;-&lt;/sup&gt;</td>
<td>100 / 18</td>
<td>31d</td>
<td>41</td>
</tr>
<tr>
<td>6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>PhMe&lt;sub&gt;2&lt;/sub&gt;Si-&lt;sup&gt;-&lt;/sup&gt;</td>
<td>120 / 0.5</td>
<td>31e</td>
<td>53</td>
</tr>
</tbody>
</table>

<sup>a</sup> Microwave irradiation used for heating
<sup>b</sup> 1 equiv. of Cul used
As mentioned above (Table 3) the oxytrifluoromethylation of alkynes resulted in a single stereoisomer. As the products 31 are trisubstituted alkenes, it was difficult to determine if the $E$ or $Z$ isomers were formed. The $Z$-isomer (31f – g) would give a NOE effect between the alkenyl and the aromatic protons (Scheme 19), however we could not observe such an effect. A missing NOE effect does not support the $Z$-isomer but cannot be used as evidence for the $E$ geometry (such as 31a) of the oxytrifluoromethylation products either. Therefore we performed an alternative synthesis of the oxytrifluoromethylated product. First we synthetized 12, which was subjected to Ru-catalyzed stereoselective addition of iodobenzoic acid according to literature procedures. The product formed in this reaction (31a) was identical to the product of the oxytrifluoromethylation reactions (Table 3, entries 1 – 2). Thus, we conclude that the oxytrifluoromethylation proceeds with anti-selectivity. Independently from our studies the anti-selectivity of the reaction was also confirmed by Sodeoka by chemical derivatization of the products formed and comparison to compounds of known geometry.

The fact that the reaction is anti-selective has a very important mechanistic implication. This stereochemistry requires that the CF$_3$ and the iodobenzoate groups are added to the triple bond in two consecutive steps and not in a concerted migratory insertion. This latter process would proceed via a cis mechanism and form $Z$-products, such as 31f – g.

Scheme 19. a) Lack of NOE indicating products being formed in $E$-configuration. (b) Synthetic procedure for $E$-selective synthesis of 31a.
Some previous studies suggested that radical CF$_3$ intermediates are involved in the Cu-mediated trifluoromethylation reactions with 1a.$^{5e,25c,32b,51}$ When the oxytrifluoromethylation reaction was performed in the presence of TEMPO 32 (Scheme 20) the reaction was completely inhibited. TEMPO can act as a radical trap, which indicates that radical intermediates can be involved in the oxytrifluoromethylation reaction.

Scheme 20. Reaction inhibition by TEMPO

<table>
<thead>
<tr>
<th>Substrate 1</th>
<th>Substrate 2</th>
<th>1a, 0.9 equiv.</th>
<th>Product 1</th>
<th>Product 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 eq.</td>
<td>1 eq.</td>
<td>Cul, 1 equiv.</td>
<td>CDCl$_3$, 60 °C, 18h</td>
<td></td>
</tr>
<tr>
<td>a) 11c</td>
<td>11a</td>
<td>31c 1 : 2</td>
<td>31a</td>
<td></td>
</tr>
<tr>
<td>b) 14a</td>
<td>14c</td>
<td>18b 3 : 1</td>
<td>18c</td>
<td></td>
</tr>
<tr>
<td>c) 14a</td>
<td>11a</td>
<td>18b 4 : 1</td>
<td>31a</td>
<td></td>
</tr>
</tbody>
</table>

Figure 5. Competitive experiments for oxytrifluoromethylation.

To obtain some mechanistic information on the substituent and π-effects of the CC bonds in the substrate, we performed competitive oxytrifluoromethylation reactions (Figure 5). These experiments indicated that i) the para-methoxy group has an accelerating effect (Figure 5a); ii) the reaction is faster with a para-methoxy group than an ortho-
methoxy group (Figure 5b) and iii) the process is faster for alkene than alkyne substrates (Figure 5c). This indicates that electron-donating groups have an accelerating effect on the oxytrifluoromethylation, in particular in the para-position of the aromatic ring. We also monitored (by NMR) the reaction of various alkynes and alkenes in the Cu-catalyzed oxytrifluoromethylation reaction. These results are presented in Chapter 4 and also compared to the studies of the trifluoromethylation of quinones (discussed in Chapter 3).

2.2 Copper-mediated alkene cyanotrifluoromethylation (Paper II)

Halotrifluoromethylation of vinylsilanes (Section 2.1.2, Scheme 17) demonstrated that under the above conditions not only oxytrifluoromethylation (Section 2.1) but also other trifluoromethylation based difunctionalization reactions can be performed. Screening different Cu-salts, we found that in the presence of B2pin2 or PCy3 additives a cyanotrifluoromethylation reaction can also be performed. Independently from our studies similar carbotrifluoromethylation reactions have been performed by Sodeoka, Nevado and others.38c,38f,52 However, these reactions are usually based on intramolecular C–C bond formation (Scheme 21).

Scheme 21. Copper-catalyzed carbotrifluoromethylation.

2.2.1 Development of the cyanotrifluoromethylation reactions

As mentioned above, the oxytrifluoromethylation reaction is accelerated in the presence of electron-donating substituents in the aromatic ring of the substrates (Figure 5). However, in the presence of electron-withdrawing substituents, such as in 14i, trifluoromethylation was not
observed. Earlier attempts to develop trifluoromethylation based borylation reactions indicated that in the presence of B_2pin\_2 the trifluoromethylation reactions were accelerated. In these reactions we did not observe C–B bond formation, which indicated that the acceleration effect did not arise from formation of organoboron intermediates. Indeed, catalytic amounts of diboronates efficiently accelerated the cyanotrifluoromethylation allowing the isolation of 34a with promising yields (Table 4, entries 2 – 4). Xu and co-workers\textsuperscript{53} have shown that PCy\textsubscript{3} accelerates trifluoromethylation reactions, particularly when CuCN is used as a catalyst. We have found that cyanotrifluoromethylation is also accelerated by phosphines (entries 5 – 7). In fact PCy\textsubscript{3} (entry 6) was more efficient than B_2pin\_2 (entry 2), and therefore we used PCy\textsubscript{3} as additive for further studies. The reaction could be performed in catalytic amounts of CuCN using 1 equivalent of external cyanide source (entries 9 and 10) but no reaction was detected in the absence of CuCN (entry 11). These findings indicate that the

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive/solvent</th>
<th>Isolated Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>B_2pin_2 (5 mol%)</td>
<td>52 %</td>
</tr>
<tr>
<td>3</td>
<td>B_2gly_2 (5 mol%)</td>
<td>56 %</td>
</tr>
<tr>
<td>4</td>
<td>Bis(diethyltartrate)diboron (5 mol%)</td>
<td>31 %</td>
</tr>
<tr>
<td>5</td>
<td>PPh\textsubscript{3} (5 mol%)</td>
<td>56%</td>
</tr>
<tr>
<td>6</td>
<td>PCy\textsubscript{3} (10 mol%)</td>
<td>73 %</td>
</tr>
<tr>
<td>7</td>
<td>PtBu_3 (10 mol%)</td>
<td>28 %</td>
</tr>
<tr>
<td>8</td>
<td>PCy\textsubscript{3} (10 mol%) and B_2pin_2 (5 mol%)</td>
<td>49 %</td>
</tr>
<tr>
<td>9</td>
<td>CuCN (10 mol%), PCy\textsubscript{3} (10 mol%) and Bu\textsubscript{4}NCN (1 equiv.)</td>
<td>54 %</td>
</tr>
<tr>
<td>10</td>
<td>CuCN (10 mol%), PCy\textsubscript{3} (10 mol%) and KCN (1 equiv.)</td>
<td>32 %</td>
</tr>
<tr>
<td>11</td>
<td>PCy\textsubscript{3} (10 mol%), Bu\textsubscript{4}NCN (1 equiv.), no CuCN</td>
<td>NR</td>
</tr>
<tr>
<td>12</td>
<td>THF</td>
<td>4 %</td>
</tr>
<tr>
<td>13</td>
<td>DMF</td>
<td>12 %</td>
</tr>
<tr>
<td>14</td>
<td>DMSO</td>
<td>7 %</td>
</tr>
<tr>
<td>15</td>
<td>MeOH</td>
<td>22 %</td>
</tr>
</tbody>
</table>

Table 4. Conditions screening for the cyanotrifluoromethylation
reaction requires only catalytic amounts of Cu. However, considering that CuCN is inexpensive and gave higher yields, we employed stoichiometric amounts of CuCN in the subsequent reactions. A brief screening of solvents (entries 12 – 15) showed that CDCl₃ resulted in the highest yield.

2.2.2 Scope for the alkene cyanotrifluoromethylation

We studied the scope for the reaction using the optimized conditions. As it appears from Table 5 styrene derivatives with electron-withdrawing (entries 1 – 7) substituents in the para- or ortho-positions undergo efficient cyanotrifluoromethylation. Even in the presence of moderately electron-donating substituents (entries 8 and 9) or with a methoxy substituent in the meta-position of the aromatic group (entry 11) the cyanotrifluoromethylation reaction provides satisfactory yields. However, para-methoxy styrene 14a did not give any cyanotrifluoromethylation product 34j (entry 10). Instead, oxytrifluoromethylation product 18b was isolated in high yield (Scheme 22).

Scheme 22. Selective oxytrifluoromethylation over cyanotrifluoromethylation.
Table 5. Scope for the alkene cyanotrifluoromethylation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>X = F, 14i</td>
<td>34a</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>X = Cl, 14j</td>
<td>34b</td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td>X = Br, 14k</td>
<td>34c</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>X = CF₃, 14l</td>
<td>34d</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>X = Br, 14m</td>
<td>34e</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>X = CF₃, 14n</td>
<td>34f</td>
<td>68</td>
</tr>
</tbody>
</table>
| 7     | Ph⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋


In the above studies 1a was used both as the oxidant and the CF$_3$ source. We wanted to separate these functions and employ an alternative oxidant, such as BQ 35a. However, BQ is also an alkene, such as the above styrene derivatives (14). Therefore, we first tested if it reacted under the usual conditions of the oxidative trifluoromethylation. Indeed, we found that 1a reacts with BQ in the presence of Cu-salts. However, this reaction does not afford oxytrifluoromethylated or cyano trifluoromethylated products, but monotrifluoromethylated product 36a. Thus, we concluded that BQ cannot be used as an oxidant for oxidative trifluoromethylation reactions. However, considering the biological activity of quinones, and to some extent trifluoromethylated quinones (such as 36b), we decided to explore the synthetic utility of the Cu-mediated oxidative trifluoromethylation with 1a for the synthesis of CF$_3$-functionalized quinones.

**Scheme 23.** Initial observations of trifluoromethylated benzoquinone.

### 3.1 Importance of quinones

Quinone motifs often occur in the electron transport chain and in the blood coagulation cascade. This is explained by the ability of quinones to easily undergo reduction to the aromatic hydroquinone structure. One of the most important quinone containing co-factors is the vitamin K family, which is essential for e.g. photosynthetic processes (Figure 6). Davioud-Charvet$^{54}$ and co-workers studied the anti-malaria
activity of \( \textbf{36b} \) and its analogs (Scheme 24). These authors published a four step synthesis of \( \textbf{36b} \) from naphthoquinone \( \textbf{35b} \). It would be useful to shorten this synthesis sequence with a single step process using oxidative trifluoromethylation (see below).

Figure 6. Important quinones in nature and organic synthesis.

Scheme 24. Synthesis of anti-malaria substance \( \textbf{36b} \) from naphthoquinone by Davioud-Charvet
The fact that quinones can undergo redox reactions quite readily has also made its use possible both as terminal oxidants in organic synthesis or as redox catalysts.\(^{55}\) For example, BQ is used as an oxidant in allylic C–H acetoxylation reactions (Section 1.3).

### 3.2 Reaction optimization

When 35a was reacted with 1a in the presence of CuCN in CDCl\(_3\), we obtained 36a in low yield. There were also issues with reproducibility. As mentioned above (Table 4, entry 2) B\(_2\)pin\(_2\) accelerated the trifluoromethylation reactions with 1a. The same accelerating effect was also observed for trifluoromethylation of BQ (Table 6, entry 2) and the reproducibility of the reaction was also substantially improved.

Various Cu-salts were tested but CuCN was the best mediator for the reaction (entries 3 – 5). A brief solvent screening indicated that CDCl\(_3\) was the best solvent (entries 6 – 8). The yields were decreased when catalytic amounts of CuCN were used (entries 9 – 13). In the presence of Bu\(_4\)NCN and KCN we were able to isolate 36a in 37 – 45% yield.

**Table 6. Optimization of quinone C–H trifluoromethylation**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuCN (1 equiv.)</td>
<td>Unreproducible reaction</td>
</tr>
<tr>
<td>2</td>
<td><strong>CuCN (1 equiv.), B(_2)pin(_2) (5 mol%)</strong></td>
<td>89 %</td>
</tr>
<tr>
<td>3</td>
<td>CuCl (1 equiv.), B(_2)pin(_2) (5 mol%)</td>
<td>17 %</td>
</tr>
<tr>
<td>4</td>
<td>CuI (1 equiv.), B(_2)pin(_2) (5 mol%)</td>
<td>36 %</td>
</tr>
<tr>
<td>5</td>
<td>CuOAc (1 equiv.), B(_2)pin(_2) (5 mol%)</td>
<td>53 %</td>
</tr>
<tr>
<td>6</td>
<td>CuCN (1 equiv.), B(_2)pin(_2) (5 mol%) in THF, benzene or MeOH</td>
<td>NR</td>
</tr>
<tr>
<td>7</td>
<td>CuCN (1 equiv.), B(_2)pin(_2) (5 mol%) in MeCN</td>
<td>38 %</td>
</tr>
<tr>
<td>8</td>
<td>CuCN (1 equiv.), B(_2)pin(_2) (5 mol%) in DMF</td>
<td>22 %</td>
</tr>
<tr>
<td>9</td>
<td>CuCN (10 mol%), B(_2)pin(_2) (20 mol%)</td>
<td>NR</td>
</tr>
<tr>
<td>10</td>
<td>CuCN (10 mol%), B(_2)pin(_2) (5 mol%), Bu(_4)NCN (1 equiv.)</td>
<td>37 %</td>
</tr>
<tr>
<td>11</td>
<td>CuCN (10 mol%), B(_2)pin(_2) (5 mol%), KCN (1 equiv.)</td>
<td>45 %</td>
</tr>
<tr>
<td>12</td>
<td>CuCN (10 mol%), B(_2)pin(_2) (5 mol%), Bu(_4)NCl (1 equiv.)</td>
<td>NR</td>
</tr>
<tr>
<td>13</td>
<td>CuCN (10 mol%), B(_2)pin(_2) (5 mol%), NaHCO(_3), Na(_2)CO(_3), NEt(_3) or Bu(_4)NHCO(_3) (1 equiv.)</td>
<td>NR</td>
</tr>
</tbody>
</table>
(entries 10 and 11). This suggested that the cyanide ion acts as a base in a deprotonation step. However, addition of other bases proved to be inefficient (entries 12 and 13). Based on the above studies we concluded that the best conditions involve using CuCN and B$_2$Pin$_2$ in stoichiometric and catalytic amounts, respectively, (entry 2) for the trifluoromethylation of quinones with 1a.

### 3.3 Synthetic scope of C–H trifluoromethylation of quinones

Using the above optimized reaction conditions (Table 6 entry 3) we could trifluoromethylate several quinone derivatives (35a – h) with high selectivity and with fair to good yields (Table 7). The trifluoromethylation of BQ could be scaled up without a significant decrease in yield (entry 1). As mentioned above (Scheme 24), trifluoromethylated naphthoquinones are promising anti-malaria agents. Synthesis of 36b could be carried out in a single step from naphthoquinone, instead of the four step classical synthesis given in Scheme 4 (entry 2). Chloro-quinone 35e reacted fast and with high yield and selectivity (entry 5). However, methoxy-substituted quinones, such as 35f reacted relatively slowly and with lower yield than the above substrates. Interestingly, the substituent effect for quinone trifluoromethylation seems to be the opposite than for oxytrifluoromethylation (section 2.1). For quinones the presence of electron-donating (e.g. –OMe) substituents slows the reaction. A similar effect was observed for dimethoxy-substrate 35g, which required microwave conditions to give 36g in acceptable yields. Compound 36i is the trifluoromethyl analog of apoptosis initiator 35j, which has been used in cancer research. Importantly, 35h itself could be trifluoromethylated to give coenzyme Q analog 36h.

For some BQ derivatives, such as 35i – k the above optimized reaction conditions (Table 6 entry 3) gave mixtures of mono- and bisfunctionalized products. The selectivity could be increased by changing the ratio of the quinone substrate to 1a (Table 8). For example, when 35i and 1a were used in a 2:1 ratio monofunctionalization product 36i could be isolated in 58% yield (entry 1). When 1a was used in excess, bisfunctionalized product 36j was afforded with 77% yield (entry 2).
Table 7. Representative examples for C–H trifluoromethylation of quinones.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Substrate 35a" /></td>
<td><img src="image" alt="Product 36a" /></td>
<td>89 % (73 %)\textsuperscript{a}</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Substrate 35b" /></td>
<td><img src="image" alt="Product 36b-d" /></td>
<td>76 %</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Substrate 35c" /></td>
<td><img src="image" alt="Product 36b-d" /></td>
<td>71 %</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Substrate 35d" /></td>
<td><img src="image" alt="Product 36b-d" /></td>
<td>67 %</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Substrate 35e" /></td>
<td><img src="image" alt="Product 36e" /></td>
<td>63 %</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="Substrate 35f" /></td>
<td><img src="image" alt="Product 36f" /></td>
<td>51 %</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="Substrate 35g" /></td>
<td><img src="image" alt="Product 36g" /></td>
<td>51 %</td>
</tr>
<tr>
<td>8</td>
<td><img src="image" alt="Substrate 35h" /></td>
<td><img src="image" alt="Product 36h" /></td>
<td>64 %</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Yield in parenthesis was isolated after a 10 times scale-up  
\textsuperscript{b} Reaction was performed by microwave irradiation at 100 °C for 1h using 20 mol% B\textsubscript{2}pin\textsubscript{2}

Using a similar change of the standard conditions we selectively obtained mono- (36k, 36m) and bisfunctionalized (36l – n) products from dimethyl quinones 35j – m.
Table 8. Mono- and bisfunctionalization of disubstituted quinones.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Ratio 35 : 1a</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Image" /></td>
<td>2 : 1</td>
<td><img src="image2.png" alt="Image" /></td>
<td>36i</td>
</tr>
<tr>
<td>2</td>
<td>35i</td>
<td>1 : 3</td>
<td><img src="image3.png" alt="Image" /></td>
<td>36j</td>
</tr>
<tr>
<td>3</td>
<td>35j</td>
<td>2 : 1</td>
<td><img src="image4.png" alt="Image" /></td>
<td>36k</td>
</tr>
<tr>
<td>4</td>
<td>35j</td>
<td>1 : 3</td>
<td><img src="image5.png" alt="Image" /></td>
<td>36l</td>
</tr>
<tr>
<td>5</td>
<td>35k</td>
<td>2 : 1</td>
<td><img src="image6.png" alt="Image" /></td>
<td>36m</td>
</tr>
<tr>
<td>6</td>
<td>35k</td>
<td>1 : 3</td>
<td><img src="image7.png" alt="Image" /></td>
<td>36n</td>
</tr>
</tbody>
</table>

Trifluoromethylation of non-quinone type α,β-unsaturated compounds was unsuccessful. For example, maleic anhydride or maleic imide 39, coumarin 40 and partially saturated quinone analog 41 (Scheme 25) did not undergo C–H trifluoromethylation under the optimized standard conditions. We also attempted to trifluoromethylate quinone derivative 42. This reaction gave a complex mixture in which trifluoromethylated compounds could be detected by $^{19}$F NMR.
Figure 7. Unsuccessful substrates in the C–H trifluoromethylation.

Similar to the oxytrifluoromethylation (Scheme 20) trifluoromethylation of quinones was also inhibited by TEMPO (Scheme 25). In the crude reaction mixture of this process we could detect formation of trifluoromethylated TEMPO 43. This indicates that this latter process can proceed via a CF₃ radical intermediate.

Scheme 25. Inhibition of C–H trifluoromethylation by TEMPO addition.
4. Effects of substituents and additives on the trifluoromethylation of alkynes and quinones (paper IV)

Despite the large number of method development papers on Cu-catalyzed trifluoromethylation of alkenes, relatively few mechanistic studies have appeared\(^2\) to rationalize the effect of substituents and additives. As mentioned in Chapters 2 and 3, the trifluoromethylations show interesting substituent effects; electron-donating substituents accelerate the oxytrifluoromethylation of alkenes and alkynes, whereas electron-withdrawing substituents accelerate the trifluoromethylation of quinones. Certain additives, such as B\(_2\)pin\(_2\) and PCy\(_3\) accelerate the trifluoromethylation reactions. Furthermore, both the oxytrifluoromethylation and the C–H functionalization of quinones are inhibited by the presence of radical traps, such as TEMPO. This indicates that CF\(_3\) radicals may be involved in these processes. This chapter presents our results on the effect of substituents and additives on the rate of trifluoromethylation reactions described in Chapter 2 – 3 of this thesis. This chapter also suggests mechanisms for these reactions.

4.1 Study of the oxytrifluoromethylation rates by NMR

The substituent and additive effects were studied by monitoring the formation of the trifluoromethylated products in the oxytrifluoromethylation of alkynes 11a – d and styrene 14a (Figures 8 – 10). We chose to monitor the progress of the reactions with \(^1\)H NMR using a deuterated solvent (CDCl\(_3\)). This requires that the reactions are homogeneous. Therefore, we did not use the reaction conditions optimized to achieve the best yields (Chapter 2 and 3) but reaction conditions adapted to the \(^1\)H NMR monitoring of the trifluoromethylation reactions. Thus, we used catalytic amounts of CuTC (copper(I) thiophene-carboxylate), which was readily soluble in CDCl\(_3\). We also conducted the experiments on 0.025 mmol scale to avoid precipitations in the reaction mixture. The reaction was conducted at 40 °C to obtain easily
measurable rates for the formation of the products. We used the appropriate $^1$H or $^{19}$F internal standards to calculate the NMR yield of the products. In case of the trifluoromethylation of alkynes (11) product 31 underwent partial hydrolysis to 44 (Scheme 26) probably because of the presence of residual water. The NMR yield of the reaction was calculated from the sum of the amounts of 31 and 44.

Scheme 26. Reaction followed by NMR.

As it appears from Figures 8 to 10, the oxytrifluoromethylation of alkynes is fastest for the methoxy substituted substrate 11a and slowest for the nitro derivative 11d (Figure 10a). The initial rate of reaction for the oxytrifluoromethylation of $p$-methoxyphenylacetylene 11a is higher than for the styrene analog 14a. This is interesting considering the fact (Figure 5c in section 2.13) that in the competitive experiments using stoichiometric amounts of CuI, we observed a higher rate for formation of 18b (formed from styrene 14a) than for 31a (formed from 11a).

Addition of B$_2$pin$_2$ substantially accelerates the oxytrifluoromethylation of the nitro derivative 11d (Figure 8a) and the methoxy derivative 11a. Surprisingly, PCy$_3$ inhibits the reaction of 11a. Conversely, after an induction period the oxytrifluoromethylation of styrene 14a is accelerated by both PCy$_3$ and B$_2$pin$_2$.

These results confirm our previous observations that the oxytrifluoromethylation is faster for substrates with electron-donating than with electron-withdrawing groups. In addition, both PCy$_3$ and B$_2$pin$_2$ can accelerate the reaction but the acceleration is substrate dependent and the extent is different for the two different additives. PCy$_3$ and B$_2$pin$_2$ probably accelerate different steps of the catalytic cycle.
Figure 8. Oxytrifluoromethylation of alkynes with or without additives (10 mol%). Legends: (•) no additive, (○) B₂pin₂, (♦) PCy₃.
Figure 9. Oxytrifluoromethylation of 4-methoxystyrene with or without additives (10 mol%). Legends: (●) no additive, (▲) B$_2$pin$_2$, (▲) PCy$_3$. 
4.2 Hammett studies of the oxytrifluoromethylation reaction

To gain information about the nature of the para-substituent effect in phenyl acetylene derivatives the relative rates were compared in a Hammett plot (Figure 11) using $\sigma^+_p$ values. The reaction without additives gave a $\rho$ value of -0.76. The negative slope indicates that positive charge is building up in the rate determining step of the reaction. However, this value is much lower than in a process in which formation of a free carbocation (benzyl cation) is the rate determining step. For example, the $\rho$ value is about -5 for a typical $S_N1$ reaction. When $B_2\text{pin}_2$ was used as an additive, the $\rho$ value decreased to -0.54 indicating a decreasing substituent effect on the oxytrifluoromethylation rate. However, it should be noted that the linear correlation between the rates and $\sigma^+_p$ values is rather poor for the Hammett plot of the oxytrifluoromethylation performed in the presence of $B_2\text{pin}_2$. 

Figure 10. Comparisons of substrates per additive: a) no additive, (b) $B_2\text{pin}_2$, (c) $\text{PCy}_3$. Legends: (•) $p$-methoxystyrene, (♦) $p$-methoxyphenylacetylene, (●) phenylacetylene, (♦) $p$-nitrophenylacetylene.
Figure 11. Hammett plots for the oxytrifluoromethylation of alkynes. Legends (–) no additive: -0.76σ_p^+ +0.14 \quad r^2 = 0.902, (–) 10 mol% B_2pin_2: 0.54σ_p^+ +0.28 \quad r^2 = 0.777.

4.3 NMR studies of C–H trifluoromethylation reaction rates

The progress of the trifluoromethylation of quinones was also monitored by NMR spectroscopy (Figures 12 – 13). In these reactions we employed the same reaction conditions (Scheme 27) as for the oxytrifluoromethylation reactions (section 4.2.1). The reaction rates without additives (Figure 13a) were low and similar for BQ (35a) and its derivatives (35b, h and k). Similar to the oxytrifluoromethylation the reaction was accelerated by catalytic amounts of B_2pin_2 and PCy_3 (Figure 12a – c). However, for the trifluoromethylation of quinones PCy_3 is superior to B_2pin_2 and leads to faster rates of reaction.

Scheme 27. Catalytic C–H trifluoromethylation followed by NMR.
Figure 12. Copper-catalyzed C–H trifluoromethylation of quinones with or without additives (10 mol%). Legends: (●) no additive, (▲) B$_2$pin$_2$, (♦) PCy$_3$. 
Figure 13. a) Quinones without additive. (b) Quinones with PCy3. (c) Reaction of different quinones using 10 mol% B$_2$pin$_2$ as additive. Legends: (•) Benzoquinone, (•) 2,6-Dichloro-benzoquinone, (•) 2,6-Dimethoxybenzoquinone, (•) Naphthoquinone

The rate of formation of substituted quinones (in the presence of additives) confirms our previous observation (section 3.3): the process is faster for substrates with electron-withdrawing substituents (e.g. 35i) than with electron-donating ones (e.g. 35f). This effect is the opposite of that observed in the oxytrifluoromethylation. This is probably due to mechanistic differences between the oxytrifluoromethylation and the C–H trifluoromethylation. An obvious difference is that the latter process involves C–H bond cleavage as well. Therefore, we studied the deuterium isotope effect in the C–H trifluoromethylation of quinones.

4.4 Studies of the deuterium isotope effect in the C–H trifluoromethylation of quinones

Using literature procedures, we synthesized per-deuterated BQ 35a-d$_4$ and monodeuterated naphthoquinone 35b. We performed two types of experiments. We studied the C–H vs. C–D trifluoromethylation in a competitive study (Scheme 28) under reaction conditions similar to those optimized for the preparative studies (section 3.2).
Scheme 28. a) Intermolecular competitive trifluoromethylation experiment. (b) Intramolecular competitive trifluoromethylation experiment.

In addition, we monitored the formation of the trifluoromethylated product separately from $35a$ and $35a-d_4$ (Figure 14) under the reaction conditions that we employed for the above NMR studies (section 4.1). Both experiments clearly indicated there is no significant primary deuterium isotope effect in the trifluoromethylation of quinones. This

![Figure 14](image-url)

**Figure 14.** Reaction curves for KIE experiments under catalytic conditions. Legends: (•) $35a$, (•) $35a-d_4$. 

39
suggests that C–H bond cleavage is not involved in the rate determin- ing step. Thus, the different substituent effects for the oxytrifluoro- methylation and the trifluoromethylation of quinones cannot be ex- plained on the basis of electronic requirements of the C–H cleavage in the latter process.

4.5 Suggested reaction mechanisms for the above trifluoromethylation reactions

The mechanistic studies in Chapters 2 – 4 together with the results of the synthetic studies provide sufficient data to propose catalytic cycles for the reactions. Given the breadth of the field, the final mechanistic characterization of the processes will require substantial kinetic and modeling studies in the future.

There should be some similarities in the catalytic cycles of the oxytri- fluoromethylation of alkenes/alkynes and the trifluoromethylation of quinones. First, both reactions proceed under very similar conditions, using 1a as the CF₃ source and Cu-catalysis. Second, both reactions are inhibited by TEMPO, suggesting that a CF₃ radical intermediate is formed. Finally both reactions are accelerated by B₂pin₂ and PCy₃ for most of the studied substrates. Despite these similarities, the electronic requirements of the rate determining steps are different. The oxytri- fluoromethylation is accelerated, whereas the C–H trifluoromethyla- tion is decelerated in the presence of electron-donating substituents in the substrates.

4.5.1 Oxytrifluoromethylation

The suggested catalytic cycle for oxytrifluoromethylation is initiated with transmetalation of the Cu¹ catalyst with B₂pin₂ (Figure 15). This creates an electron-rich Cu-Bpin precursor, which readily undergoes oxidative addition with 1a to give Cu³ complex 46a. PCy₃ or other σ- donor ligands coordinated to Cu may have the same type of activating effect as Bpin. The Cu–CF₃ bond in 46a is proposed to undergo a ho- molytic cleavage followed by capture of the CF₃ radical by the corre- sponding phenylacetylene derivative 11. Transfer of a CF₃ radical from 46a to 11 would explain the inhibition of the reaction in the
presence of TEMPO. The CF$_3$ radical is easily captured by TEMPO, if it is present in the reaction mixture. However, in the absence of TEMPO CF$_3$ transfers from 46a to 11, resulting in benzyl-vinyl radical 48 and Cu$^{II}$ complex 47a.

**Figure 15.** Proposed catalytic cycle of the copper-catalyzed oxytrifluoromethylation.

Radical 48 and Cu$^{II}$ complex 47a can easily recombine to form complex 46b, in which the Cu formally has an oxidation state of +3. Reductive elimination from 46b gives product 31 and regenerates the Cu$^I$ catalyst. The substituent effects and the Hammett studies suggest that the reductive elimination of 31 from 46b could be the rate determining step of the reaction. Reduction of Cu$^{III}$ to Cu$^I$ is probably faster when the carbon atom (of the substrate) attached to Cu is electron rich. This is typically the case in the presence of electron donating (e.g. para-OMe) substituent on the aromatic ring. A syn migratory insertion of the Cu–CF$_3$ complex to the triple bond (Figure 16) can be discontinued on the basis of the stereochemistry of the oxytrifluoromethylation. In case of a migratory insertion the Cu–C and C–CF$_3$ bonds are expected to be syn (46d) resulting in a cis oxy trifluoromethylated prod-
uct Z-31 after reductive elimination from 46d. However, our results show (Section 2.1.3, Scheme 19) that the CF₃ and the OCOAr groups are trans in the final oxytrifluoromethylated products 31. This requires a two-step reaction, such as 46 → (47a, 48) → 46b, instead of a concerted (one step) migratory insertion.

**Figure 16.** Reaction via syn migratory insertion of 46c to 11, which would give the Z-product Z-31.

4.5.2 Cyanotrifluoromethylation

The cyanotrifluoromethylation is suggested to follow a similar mechanism as the oxytrifluoromethylation (Figure 16). The catalytic cycle is constructed involving PCy₃ as the additive, but as mentioned above (Table 4), B₂pin₂ also has an accelerating effect. Formation of 46f from 46e and 14i is probably also a two-step process (involving transfer of a CF₃ radical), as for the above oxytrifluoromethylation (Figure 15). In complex 46f the cyano group preferentially undergoes reductive elimination to give cyanotrifluoromethylated product 34a. The methoxy styrene 14a does not undergo cyanotrifluoromethylation (section 2.2.2, Scheme 22), possibly because the PCy₃ group and the electron-rich methoxy benzyl moieties try to avoid a trans relationship.
which is known as “trans-phobia”. Instead the electron-deficient CN group and the methoxy benzyl moieties are trans to each other and the corresponding cyanotrifluoromethylated product cannot be formed.

![Catalytic Cycle Diagram]

**Figure 16.** Proposed catalytic cycle of the copper-mediated cyanotrifluoromethylation.

4.5.3 Quinone C–H trifluoromethylation

Studies of the deuterium isotope effect suggested that deprotonation is not the rate determining step in the trifluoromethylation of quinones. Therefore, there must be another important mechanistic difference between the oxytrifluoromethylation (Figure 14) and the trifluoromethylation of quinones that accounts for the different electronic demands of the two processes. We suggest that the initial step of the trifluoromethylation of quinones involves oxidative addition of 1a to the catalyst. However, the next step could be a rate determining coordination of the quinone substrate to the CuIII complex to give 46g. The double bond of quinones is electron deficient, which could explain why (prior to CF3 transfer) the coordination is slow. Previous *ab initio*
studies in the group have shown that the coordination of transition metals to the double bond (of quinones) is easier for quinones containing electron-withdrawing substituents. This may explain why quinones with electron-withdrawing substituents, such as dichloro-quinone 35i, react faster than those bearing electron-donating groups (such as 35f).

**Figure 17.** Proposed catalytic cycle for the quinone C–H trifluoro-methylation.

After formation of 46g a homolytic cleavage of the Cu–CF₃ bond followed by transfer of the CF₃ radical may result in a semiquinone type intermediate 50 and Cu⁡II complex 47c. In 50 the unpaired electron can
be stabilized by delocalization, which could be the driving force for CF₃ transfer. Two important resonance structures of 50 are given in Figure 17. The left, in which the radical is localized on the oxygen probably has the largest contribution. Semiquinone 50 may undergo SET with Cu⁺ complex 47c to give a cation, which can be deprotonated by an external base to give product 36. However, this is probably a high energy pathway involving a quinone cation. We suggest an alternative process by recombination of 47c and 50 to give 46h. Complex 46h may undergo an internal deprotonation. The carbonyl group of the coordinated 2-iodobenzoate may remove the proton triggering the reduction of Cu³⁺ to Cu¹ and formation of the trifluoromethylated product.

4.6 Conclusions and outlook for trifluoromethylation

Alkenes and alkynes easily undergo oxidative trifluoromethylation reactions using reagent 1a in the presence of Cu-salts. The reactions can be used for regio- and stereoselective oxytrifluoromethylation of styrenes, phenylacetylenes, and their analogs. Using stoichiometric amounts of CuCN cyanotrifluoromethylation can be achieved. Quinone substrates undergo C–H trifluoromethylation under similar conditions. The reactions are accelerated by B₂pin₂, PCy₃ and other di-boronates and phosphines. The degree of acceleration is substrate dependent. All reactions are inhibited by TEMPO, and therefore a radical mechanism involving a CF₃ radical intermediate was postulated.

The oxytrifluoromethylation is accelerated in the presence of electron-donating substituents. Hammett studies of the oxytrifluoromethylation of phenylacetylenes gave a ρ value of -0.76. This indicates that in the rate determining step a positive charge is accumulated. We suggest that the rate determining step could be the reductive elimination of the benzoate ion in the last step of the process.

The C–H trifluoromethylation of quinones is accelerated in the presence of electron withdrawing substituents. According to our studies the C–H cleavage is not rate determining, since a deuterium isotope effect cannot be observed.
Oxidative trifluoromethylation of organic substrates has attracted much interest and it has become a very competitive field in organic synthesis. This can be demonstrated by the fact that several independent studies appeared at the same time, or just shortly after, we published our results on oxytrifluoromethylation, cyanotri fluoromethylation and trifluoromethylation of quinones. In the future hopefully more experimental mechanistic and modeling studies will appear to improve the understanding of the underlying principles of this reaction.
5. Palladium-catalyzed allylic C–H acyloxylation (paper V)

As mentioned in section 1.3 allylic acetates and their analogs are valuable precursors for the synthesis of organic molecules. An efficient and inexpensive way to obtain these synthetic precursors is allylic C–H acyloxylation of alkenes. The Szabó group has previously published new methods for C–H acyloxylation of alkenes using hypervalent iodine compounds, such as PIDA and PIFA as oxidant and acyloxy sources. A potential drawback of this reaction is the poor atom economy (as iodobenzene is wasted in the reaction) and the relatively high price of the hypervalent iodine reagents. Obviously, a similar reaction avoiding pre-synthesized oxidants and generating less waste would be desirable.

5.1 Attempts for acyloxylation via in situ regeneration of hypervalent iodine reagents

Ochiai and Kita have independently developed methods using catalytic amounts of PIDA as the oxidant in chemical syntheses. The phenyl iodide formed in these reactions was re-oxidized in situ to PIDA using a stoichiometric amount of a terminal oxidant (mCPBA). Inspired by these reports, we envisioned the use of catalytic amount of phenyl iodide or PIDA along with an external oxidant for allylic C–H acyloxylation.

Several oxidants are capable of forming PIDA from PhI. Sodium perborate (SPB, 51) was more efficient that other oxidants such as H2O2, mCPBA and peracetic acid. Previously published conditions are shown in Scheme 29. The inorganic oxidant SPB is a mild environmentally friendly crystalline solid, commonly used in washing detergents. It is inexpensive and produced industrially on a very large scale. The structure of SPB is different from other peroxy species like peracetic acid or tBuOOH. SPB has a dimeric chair-form structure, which typically co-crystallizes with water (51 in Scheme 29).
Scheme 29. Synthesis of PIDA from SPB (left) and structure of “monohydrous” SPB 51.

An attractive feature of SPB is the possibility of acylating the OH groups. Tao showed that peroxybis-(diacetoxy)borane 52 can be isolated from reaction mixtures of SPB and acetic acid and is a strong oxidant.\(^{67}\) The envisioned concept of a Pd\(^{II}/\)PhI co-catalyzed reaction is illustrated in Scheme 30 below.

Scheme 30. Dual catalysis by palladium and phenyl iodide.

It is interesting to note that the application of SPB in organic synthesis is still largely unexplored. It is known that the solubility of SPB is very low in organic solvents unless it reacts with the solvent (e.g. AcOH) or forms a more soluble adduct (e.g. with Ac\(_2\)O).\(^{66a}\)

5.2 Optimization of reaction conditions

To test the overall feasibility of the above concept (Scheme 30), methyl ester 13e was allowed to react with 1 equiv. of PhI, 4 equiv. of SPB and 5 mol% Pd(OAc)\(_2\) in AcOH. Pleasingly, the reaction gave full conversion of the starting alkene (Table 11, entry 1). To further explore the concept of a reaction co-catalyzed by PhI the same reac-
tion was performed using a 25 mol% loading (entry 2). The reaction still proceeded to full conversion and the product was isolated in 53% yield. A control experiment was also performed in the absence of the aryl iodide. To our surprise, the reaction still went to completion (entry 3), demonstrating that SPB alone (or another species formed in situ) can act as the oxidant in the reaction. It would be desirable to use another solvent than acetic acid. Therefore we performed the reaction in MeCN using acetic anhydride as both the acylating agent for SPB and as a source of acetate for the acyloxylation process. After optimization it was found that 16 equiv. of Ac₂O resulted in full conversion of 13f to 25d (entries 4 – 7).

Table 11. Optimization of allylic C–H acetoxylation with SPB.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Equiv. PhI</th>
<th>Equiv. SPB</th>
<th>Equiv. Ac₂O</th>
<th>13:25&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Isolated yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Me</td>
<td>1</td>
<td>4</td>
<td>-</td>
<td>full conv.</td>
<td></td>
</tr>
<tr>
<td>2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Me</td>
<td>0.25</td>
<td>4</td>
<td>-</td>
<td>full conv.</td>
<td>53%</td>
</tr>
<tr>
<td>3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Me</td>
<td>-</td>
<td>4</td>
<td>-</td>
<td>full conv.</td>
<td>46%</td>
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<tr>
<td>4</td>
<td>Bn</td>
<td>-</td>
<td>4</td>
<td>4</td>
<td>90:10</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Bn</td>
<td>-</td>
<td>4</td>
<td>8</td>
<td>20:80</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Bn</td>
<td>-</td>
<td>4</td>
<td>12</td>
<td>64:36</td>
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</tr>
<tr>
<td>7</td>
<td>Bn</td>
<td>-</td>
<td>4</td>
<td>16</td>
<td>full conv.</td>
<td>40%</td>
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<tr>
<td>8</td>
<td>Bn</td>
<td>-</td>
<td>3</td>
<td>12</td>
<td>19:81</td>
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</tr>
<tr>
<td>9</td>
<td>Bn</td>
<td>-</td>
<td>2</td>
<td>8</td>
<td>30:70</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Bn</td>
<td>-</td>
<td>1</td>
<td>4</td>
<td>63:37</td>
<td></td>
</tr>
<tr>
<td>11&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Bn</td>
<td>-</td>
<td>4</td>
<td>16</td>
<td>Only 13</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Bn</td>
<td>-</td>
<td>4</td>
<td>16</td>
<td>full conv.</td>
<td>74%</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined by <sup>1</sup>H-NMR
<sup>b</sup> Reaction performed in AcOH
<sup>c</sup> Reaction performed in absence of palladium catalyst

While maintaining the ratio of SPB and Ac₂O at 1 : 4 we tested the reaction at lower oxidant loadings (entries 8 – 10). It was found that the optimal conditions were indeed a 1 : 4 : 16 ratio of 13 : SPB :
Ac₂O. A control experiment without Pd-catalyst confirmed that palladium is crucial for the reaction to proceed (entry 11). With our optimized reaction conditions in hand and with an improved work-up and purification protocol we were able to isolate 25d in a synthetically useful 74 % yield (entry 12). The isolated yield is somewhat lowered due to hydrolysis.

The acyloxylation reaction under optimized conditions (entry 12) is not sensitive to moisture or air. The preparations with these optimized conditions (see section 5.3 below) are performed on the benchtop without attempts to exclude oxygen or water. In fact, commercially available SPB used in these reactions is the tetrahydrate form, which means at least 12 equiv. of water are present in the reaction.

Since PhI can be oxidized to PIDA by different oxidants, several other common oxidants were also screened. However, potassium persulfate, oxone and 1 atm. O₂ were all unsuccessful in our reaction. The only reagent capable of performing the desired oxidation was H₂O₂•urea, although conversion was not complete and the product was only isolated in 20% yield.

5.3 Scope of the allylic C–H acyloxylation

The scope of the allylic C–H acyloxylation was investigated using the optimized conditions established above (Table 11, entry 12). The most important results are summarized in Table 12. The scope for terminal alkenes is broad with respect to functional groups. Many carbonyl functional groups, aside from the optimized benzyl and methyl esters, are tolerated. For instance, sulfones (entries 4 – 6) were functionalized in good to excellent yields. Ketones and amides were tolerated (entries 7 and 8). Additionally, less polar substances lacking coordinating functional groups, like allyl benzene, reacted with a synthetically useful isolated yield (entry 9). The more challenging internal olefins, such as 13k and 13l, also reacted to give the secondary alcohol derivatives 25m – o (entries 10 – 12).

Using the hypervalent iodine reagent PIDA and similar conditions as for the allylic C–H acetoxylation by Szabó, the Sanford group functionalized a variety of C–H bonds using directing groups.⁶⁸ To test the compatibility with these reactions, 8-methylquinoline 13m was selected. In this case formation of a five-membered palladacycle would be expected to stabilize the intermediate. When applying the previously
Table 12. Scope for the allylic C–H acyloxylation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Temp (°C)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
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<td>13m</td>
<td>Me, 25p</td>
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a) For acetic anhydride 16 equivs. were used. For benzoic and pivalic anhydrides 4 equivs. were used. (b) The reaction was run at 100 °C for 22 h in AcOH.
reported conditions benzylic acetate 25p was indeed isolated in 52% yield (entry 13).

We envisioned that other carboxylic anhydrides could be used instead of acetic anhydride. We found that the reaction is also efficient using pivalic and benzoic anhydrides. Indeed, as can be seen in Table 12, several of the substrates that were acetoxylated (by Ac₂O) could be pivaloxylated (entries 2, 6 and 11) and benzoyloxylated (entries 3 and 5). In the case of these anhydrides the amount could be lowered to 4 equiv. The use of these anhydrides is illustrating an additional attractive feature of this reaction, namely the potentially wider nucleophile scope compared to previous techniques. There are only a handful of commercially available PhI(OCOR)₂ reagents compared to a multitude of carboxylic anhydrides.

The reaction is remarkably stereo- and regioselective. In all cases (Table 12, entries 1 – 11) E-products were exclusively obtained. No traces of the Z-isomers were detected when analyzing the crude reaction mixtures by ¹H-NMR. All products were formed with high level of regioselectivity as the γ-isomer. No traces of the α-isomers were detected, likely because of the formation of conjugated systems.

For internal olefins (such as 13k) we observed a side-reaction, which decreased the yield (Scheme 31). The side product 53 was formed by epoxidation of the double bond. This epoxidation proceeded without Pd-catalysis. Formation of epoxides using SPB under similar conditions was published by Tao.⁶⁷

![Scheme 31. Non-catalyzed side-reaction observed for internal alkenes.](image-url)
reactions is probably the migration of the double bond to various positions relative to the acetoxy group. Several 1,1-disubstituted alkenes, such as 13o – q were unreactive. This can be due to the steric influence at the 2-position.

**Figure 18.** Examples of substrates that did not undergo C–H acyloxylation.

### 5.4 Mechanistic discussion

Based on several findings in this work and in previous studies, we suggest that the reaction proceeds through a PdII/PdIV catalytic cycle. It has previously been shown by NMR experiments that PIDA can oxidize the NCN–PdII–Br pincer complex 26c to the octahedral PdIV complex 54a (Scheme 32). Since SPB is capable of oxidizing PhI to PIDA it is reasonable to suggest that it has the oxidation potential to oxidize a PdII salt to a PdIV complex.

**Scheme 32.** NMR experiment showing the potential of PIDA driving a PdII/PdIV catalytic cycle.

It is widely accepted that the Pd-catalyzed allylic C–H acetoxylations published by McMurry and Åkermark proceeds via a Pd0/PdII catalytic cycle. The rate-determining step is the reductive elimination of the allyl fragment and the acetate from the PdII-complex 26b. This step is facilitated by the
coordination of the strongly electron withdrawing ligand BQ.\textsuperscript{47}

Several findings confirm that formation of Pd\textsuperscript{0} is unlikely in the presented Pd-catalyzed SPB/Ac\textsubscript{2}O mediated process.

1) The reductive elimination from a Pd\textsuperscript{II}-complex would be unlikely because no BQ or other strongly electron withdrawing ligand was present in our reaction.

2) If Pd\textsuperscript{0} was indeed formed in the reaction, this would likely form colloidal palladium metal (“Pd black”) due to the absence of stabilizing ligands. However no such formation of Pd black was observed.

3) Another important indication is that the initial optimization reactions were run with up to one equivalent of PhI present. If any Pd\textsuperscript{0} was formed during our reactions an oxidative addition of PhI to the Pd\textsuperscript{0} metal center would trap the catalyst and inhibit the reaction.

Although we cannot unambiguously disprove a Pd\textsuperscript{0}/Pd\textsuperscript{II} cycle, findings 1–3 above suggest a Pd\textsuperscript{II}/Pd\textsuperscript{IV}-cycle for the above process (Figure 19). The catalytic cycle is probably initiated by oxidation of Pd(OAc)\textsubscript{2} to Pd\textsuperscript{IV} complex 54b. After ligand exchange (54c) alkene substrate 13 coordinates to give 54d. Complex 54d undergoes deprotonation, most probably by a coordinated acetate forming (\eta\textsuperscript{3}-allyl)Pd\textsuperscript{IV} complex 54e. Complex 54e may undergo a rapid reductive elimination to the product 25 and regenerate the Pd\textsuperscript{II} catalyst. This last step does not require \pi-electron acceptor ligands which are required for reductive elimination from (\eta\textsuperscript{3}-allyl)Pd\textsuperscript{II} complexes, as the +4 oxidation state itself is favorable for the reductive elimination process.

5.5 Conclusions and outlook for the Pd-catalyzed C–H acyloxylation

A new, environmentally benign method for allylic C–H acyloxylation has been developed. The reaction proceeds under mild conditions and is not sensitive to oxygen or moisture. The products are exclusively formed in the E-configuration and with the carboxylate installed at the \gamma-position for the linear products.
Figure 19. Proposed catalytic cycle for the allylic C–H acetoxylation.

The reaction uses commercially available carboxylic acid anhydrides as activators and for the nucleophile source. This opens new synthetic routes for installation of various allylic acetoxy functionalities.

Based on experimental findings and results from previous studies, we suggest that the reaction proceeds via a Pd$^{II}$/Pd$^{IV}$ catalytic cycle. In this cycle the product forming reductive elimination is easy and therefore the reaction can be carried out without application of π-acceptor activator ligands.
6. Closing remarks

In this thesis it has been shown that the hypervalent iodine reagent 1a (Togni’s reagent) is a versatile reagent for both trifluoromethylation-based difunctionalizations of alkenes and alkynes and C–H trifluoromethylation of quinones. The difunctionalizations (oxytrifluoromethylation and cyanotrifluoromethylation) are performed under mild conditions using commercially available reagents and catalysts. Both difunctionalizations proceed with excellent regioselectivity and an excellent, albeit substrate dependent, chemoselectivity.

A separate mechanistic study has revealed that the reactions can be accelerated by diboronate and phosphine additives. The oxytrifluoromethylation and C–H trifluoromethylation of quinones have opposite electronic demands. The suggested catalytic cycles are based on formation of CF$_3$ radical intermediates for all studied reactions.

Furthermore a novel method for environmentally friendly palladium-catalyzed allylic C–H acyloxylation has been demonstrated. The reaction proceeds under mild conditions and is suggested to proceed via Pd$^{IV}$ intermediates. This reaction can potentially be further developed into a green reaction.
I owe a great deal of gratitude to many people for aiding me towards this thesis:

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8. References


