



**NANYANG  
TECHNOLOGICAL  
UNIVERSITY**

**DEVELOPMENT OF ORGANO- AND  
METAL- CATALYZED REACTIONS WITH  
WATER AS THE SOLVENT**

**WENDY WEN YI LEONG**

**SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES**

**2013**

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**WENDY WEN YI LEONG**

School of Physical and Mathematical Sciences

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in partial fulfillment of the requirement for the degree of

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*To my beloved family: Dad, Mom, Cherie and Jermyn*

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*“If I have seen further, it is by standing on the shoulders of giants.”*

*- Sir Isaac Newton*

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## ABSTRACT

The work described in this thesis is devoted to the development of environmentally benign organo- and metal-catalyzed reactions through the use of water as the solvent. With the use of a “designer surfactant”, TPGS-750-M, copper-catalyzed conjugate additions in water using organozinc reagents formed *in situ* were successfully achieved. This methodology could be applied to a broad spectrum of substrates, affording the desired 1,4-adducts in good to excellent yields.

NHC-catalyzed reactions involving enals were shown to take place efficiently with water as the only solvent. The simple and mild reaction conditions, often without the need for an inert atmosphere, low catalyst loading and the desirable characteristics of water, make this an attractive methodology for large scale synthesis. Deuterated compounds could also be synthesized easily and inexpensively by using D<sub>2</sub>O as the solvent.

The synthesis and evaluation of TADDOL-based phosphoric acids in organic solvent were carried out. In addition, the PQS-BINAP-Rh catalyst was synthesized and applied to the asymmetric hydrogenation and 1,4-addition of arylboronic acids to fumaric compounds in water. These studies lay the foundation for PQS-bound phosphoric acid catalyzed reactions in water which allow for recycling of the catalyst.

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11. Lin H. S., Leong W. W. Y., Yang J. A., Lee P., Chan S. Y., Ho P. C., Biopharmaceutics of 13-*cis*-Retinoic Acid (Isotretinoin) Formulated with Modified  $\beta$ -Cyclodextrins, *Int. J. Pharm.* **2007**, *341*, 238-245.

## APPENDIX

$\delta$	NMR chemical shift/ppm
$J$	NMR coupling constant/Hz
$\lambda$	Wavelength/nm
Ac	Acetyl
Ar	Arene
Bn	Benzyl
BINOL	1,1'-Bi-2-naphthol
c/conc.	Concentration
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
dr	Diastereomeric ratio
DMAP	4-Dimethylaminopyridine
ee	Enantiomeric excess
EWG	Electron-withdrawing group
HPLC	High Performance Liquid Chromatography
mg	milligram

mL	milliliter
mmol	millimole
NMR	Nuclear magnetic resonance
Ph	Phenyl
PQS	Polyethyleneglycol Ubiquinol Sebacate
ppm	Parts per million
R	arbitrary substituent
rt	room temperature
TADDOL	$\alpha,\alpha,\alpha,\alpha$ -tetraaryl-1,3-dioxolane-4,5-dimethanol
THF	Tetrahydrofuran
TLC	Thin layer chromatography
t <sub>R</sub>	Retention time

## CHAPTER 1:

# Organic Reactions in Aqueous Media

## 1.1 Green Chemistry

As defined by the United States Environmental Protection Agency (EPA),<sup>1</sup> Green Chemistry or Sustainable Chemistry is “the design of chemical products and processes that reduce or eliminate the use or generation of hazardous substances”. Solvents typically make use of more than 80% of the material usage for Active Pharmaceutical Ingredient (API) manufacture,<sup>2</sup> account for 50% of the post treatment green-house gas emissions and consume about 60% of the overall energy.<sup>3</sup> Traditionally, organic reactions have been carried out in organic solvents because they can easily dissolve organic compounds, and their use can be selected based on their physiochemical properties like polarity, boiling point, and viscosity. However, disadvantages of organic solvents include flammability, toxicity, and lack of sustainability. Because of these latter issues, the past few decades have seen the rise of greener and more sustainable chemical processes through the use of environmentally friendly solvents that cause less harm to the health and safety of researchers, and contribute less to environmental pollution. Various solvent selection guides have been reported by academics,<sup>4</sup> GSK,<sup>3</sup> Pfizer,<sup>5</sup> and the Pharmaceutical Roundtable.<sup>6</sup> For example, Pfizer assesses and categorizes solvents based on their impact on health, safety and the environment (Figure 1).

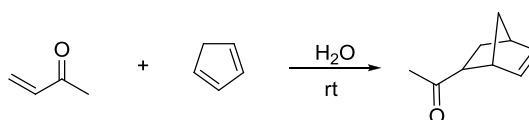
Preferred	Usable	Undesirable
Water	Cyclohexane	Pentane
Acetone	Heptane	Hexane (s)
Ethanol	Toluene	Di-isopropyl ether
2-Propanol	Methylcyclohexane	Diethyl ether
1-Propanol	Methyl <i>t</i> -butyl ether	Dichloromethane
Ethyl Acetate	Isooctane	Dichloroethane
Isopropyl acetate	Acetonitrile	Dimethyl formamide
Methanol	2-MethylTHF	<i>N</i> -Methylpyrrolidinone
Methyl ethyl ketone	Tetrahydrofuran	Pyridine
1-Butanol	Xylenes	Dimethyl acetate
<i>t</i> -Butanol	Dimethyl sulfoxide	Dioxane
	Acetic acid	Benzene
	Ethylene glycol	Carbon tetrachloride

**Figure 1.1** Pfizer solvent selection guide.

Ideally, running a reaction without any solvent would be most desired. However, most of the time, a solvent is necessary as it facilitates heat and mass transfer. Furthermore, solvents play an important part in the reaction rate, selectivity, and the position of the chemical equilibrium.<sup>7</sup> As such, water holds the potential to be an ideal solvent because it is inexpensive, easily available, non-toxic, and non-flammable. Consequently, a lot of efforts have been made towards the development of catalytic reactions that can operate with water as the medium.<sup>8</sup>

At the beginning, water was avoided for common organic reactions because of the low solubility of organic compounds in water. However, the pioneering studies by Breslow demonstrated a rate enhancement of Diels-Alder reactions in aqueous media over those occurring in organic solvents, which changed the perception of water as a solvent (Scheme 1.1).<sup>9</sup>

**Scheme 1.1** Diels-Alder reaction in water.



It was observed that the reaction between butenone and cyclopentadiene proceeded 740 times faster in water than in isooctane, and with a five-fold higher selectivity in water than in cyclopentadiene. It was particularly noteworthy that the use of protic polar solvents (e.g. alcohols) gave similar results to those obtained in hydrocarbon solvents. This was later found to be due to the hydrophobic effect, which arises due to the repulsive interactions between hydrophobic molecules and water, and leads to the formation of hydrophobic aggregates that reduce the contact surface between them.<sup>9a</sup>

Since then, it is well established that the unique physical and chemical properties of water can lead to interactions like hydrogen bonding and the hydrophobic effect that may

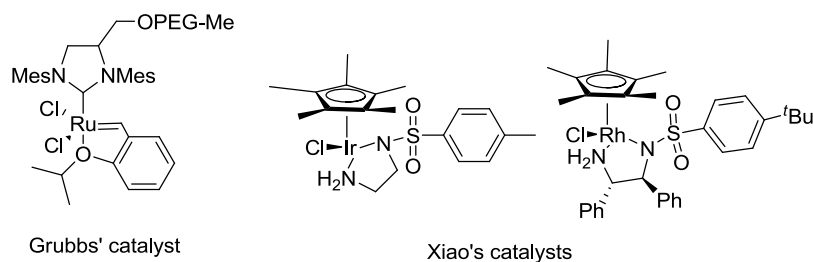
greatly impact the reaction outcome. Due to the hydrophobic effect, reactions carried out in water have been shown to exhibit accelerated reaction rates and enhanced reaction selectivities, even when the reactants used are sparingly soluble or insoluble. Sharpless and co-workers later demonstrated that the addition of sodium azide to nitriles to afford 1*H*-tetrazoles can proceed readily in water.<sup>10</sup> Another seminal work by the same group demonstrated the “on water” phenomenon, in which a rate acceleration was observed when water insoluble reactants were used. It was also found that vigorous stirring was essential, probably due to the increased area of surface contact.<sup>11</sup> At one point of time, there was a debate as to whether reactions in which water is the only solvent should be called “in water”, “on water” or “in the presence of water”.<sup>12</sup> For reactions carried out “in water”, the reactants are completely soluble in water and three effects, namely the hydrophobic, hydrogen bonding, and solvent polarity effects, operate simultaneously.<sup>13</sup> In the case of “on water” reactions, the dominating effect is a *trans*-phase H-bonding catalytic effect which arises from penetration by water OH<sub>free</sub> groups across the water-organic phase boundary.<sup>14</sup> Alternatively, the “on water” phenomenon can be explained by a simple acid-catalysis mechanism that is facilitated by penetration of the phase boundary by a free proton, and consequent strong adsorption of the hydroxide ion by-product.<sup>15</sup> In many cases, the reaction is made up of a complex two or three phase system.<sup>16</sup> The latter three phase system is created due to the use of partially soluble organic liquid and solid reactants, and comprises of: (1) an aqueous solution; (2) undissolved organic liquid; (3) the remaining undissolved solid. In the case of these reaction mixtures, it is unclear as to whether “in water” or “on water” effects are predominant. Following the opinion of Singh et al., in this thesis, when the reaction occurs in an excess of water, without any organic solvent or excess of any reactant, it will be termed as a reaction “in water”, regardless of whether the reaction occurs in the homogeneous or heterogeneous phase.<sup>8b</sup>

Besides Diels–Alder reactions, there is a plethora of useful organic reactions that can be efficiently carried out in a fully aqueous environment, even those involving water-sensitive compounds. In addition, air-sensitive transition-metal catalysis can now be carried out in water due to the low solubility of oxygen gas in the medium.<sup>8a</sup>

## 1.2 Metal-catalyzed reactions in water

Recently, metal-catalyzed reactions in water have been prolifically explored and extensively reviewed.<sup>17</sup> It is conventionally believed that organometallic reagents are incompatible with water due to the extreme basicity and rapid hydrolysis of organolithium and organomagnesium compounds, which most organic chemists are familiar with. However, this is in fact not true, because the hydrolysis of their carbon-metal bond is actually kinetically disfavoured in an aqueous environment.<sup>14b</sup> With their accessible d-orbitals, transition metals can selectively interact with the “soft” nucleophilic ( $\pi$ ) and electrophilic ( $\pi^*$ ) orbitals of alkynes, arenes, and olefins, and pay little attention to “hard” nucleophilic groups that may be present in the aqueous media. This property is responsible for the extensive and expanding development of reactions in aqueous media, which include oxidations, reductions, carbon-carbon and carbon-heteroatom bond forming reactions.<sup>18</sup>

Grubbs and co-workers have actively developed ruthenium catalysts for olefin metathesis in organic solvent as well as in water. By using a modified *N*-heterocyclic carbene type ligand bearing a water-soluble polyethylene glycol chain, they were able to carry out ring closing metathesis (RCM) and ring-opening metathesis polymerization (ROMP) in water (Figure 1.2).<sup>19</sup> Xiao and co-workers have also shown that iridium-catalyzed transfer hydrogenation reaction of aryl aldehydes as well as Rh-catalyzed transfer hydrogenation of quinolines can be carried out in water (Figure 1.2).<sup>20</sup> In addition, Lewis acid catalysts, which have found application in a wide range of reaction types, have been demonstrated to work well in water by Kobayashi and co-workers.<sup>21</sup>



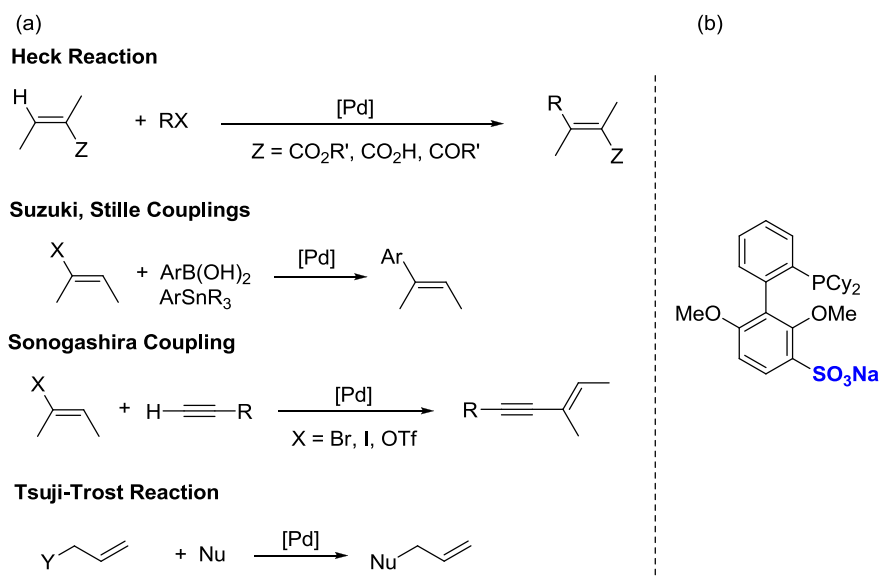
**Figure 1.2** Modified catalysts for metal-catalyzed reactions in water.

Metal-catalyzed cross-coupling reactions have developed into an indispensable component of the synthetic chemist's toolbox.<sup>22</sup> These reactions date back to the early 1900s, when Ullmann and Goldberg demonstrated copper-promoted carbon-carbon and carbon-heteroatom bond formations. Copper was frequently used for mediating carbon-carbon bond formation, until the pioneering work of Heck, Suzuki, Stille, Negishi, and others on palladium-catalyzed cross-coupling reactions (Scheme 1.2a).<sup>23</sup>

Since their discovery, palladium-catalyzed carbon-carbon bond forming reactions have found widespread use in synthetic organic chemistry. This is due to the mild reaction conditions and tolerance to a large range of functional groups. Consequently, they have been frequently used in the fine chemical and pharmaceutical industries. In 2010, Heck, Suzuki and Negishi were awarded the Nobel Prize, which confirmed the importance of Pd-catalyzed cross-coupling reactions.<sup>24</sup> Although these reactions are commonly carried out in organic solvents, various groups have reported such reactions in water or other greener solvents.<sup>14b,18b,25,26</sup>

Alternatively, such reactions are achieved through the modification of the catalyst or ligand. Buchwald and Anderson reported that the Suzuki reaction could be efficiently carried out with a range of highly functionalized aryl chlorides and boronic acids by the use of a ligand bearing a sulfonate group (Scheme 1.2b).<sup>27</sup>

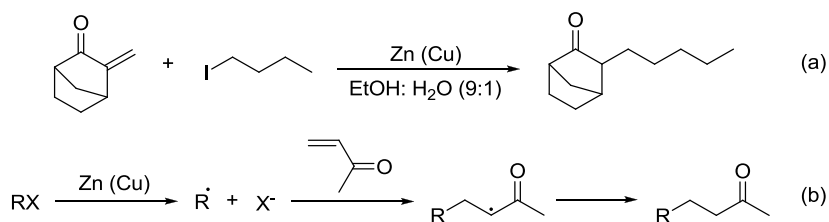
**Scheme 1.2** (a) Pd-catalyzed cross-coupling reactions. (b) Ligand by Buchwald et al.



On the other hand, organocuprates became less popular in this field because non-catalytic amounts of the reagents are usually required. In addition, they require stringent moisture-free conditions.<sup>28</sup> Consequently, great lengths have to be made to ensure that the copper salt precursors and organic, aprotic solvents are dry. In addition, proper handling of the commercially available or freshly prepared organometallic precursors is necessary.<sup>29</sup>

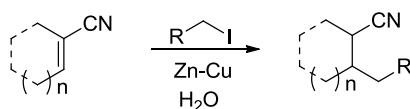
Nevertheless, after Kharasch<sup>30</sup> and Gilman<sup>31</sup> reported the preparation of Grignard- and organolithium-derived organocuprates, respectively, these reagents are frequently seen in basic organic chemistry textbooks due to their ability to facilitate the addition of  $C_{sp^3}$  and  $C_{sp^2}$  groups to substrates in a conjugate addition fashion.<sup>32,33</sup> Despite the importance of these reactions, there are only a few literature reports that enable such conjugate additions in aqueous media. Pioneering works by Luche et al. demonstrated the use of a Zn/Cu couple in aqueous media through a radical pathway (Scheme 1.3). The use of copper or  $NH_4Cl$  was employed to activate zinc,<sup>34</sup> but these works have the limitation of requiring sonication to ensure good yields.

**Scheme 1.3** (a) Luche method involving sonication. (b) Proposed radical mechanism.



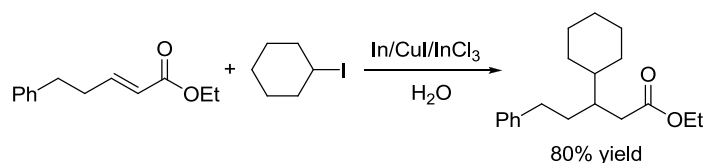
Subsequently, Fleming and co-workers developed a methodology that makes use of a silica-supported zinc-copper matrix reagent that promotes the conjugate addition of alkyl iodides to unsaturated nitriles in water (Scheme 1.4).<sup>35</sup> However, this methodology suffers from a lack of atom economy due to the need for large quantities of alkyl halide (8 equiv) and Zn (6 equiv). In addition, this reaction works best for unsaturated nitriles, which make excellent radical acceptors,<sup>36</sup> but are not good partners for copper-catalyzed conjugate additions.

**Scheme 1.4** Silica-supported Zn-Cu matrix promoted reactions in water.



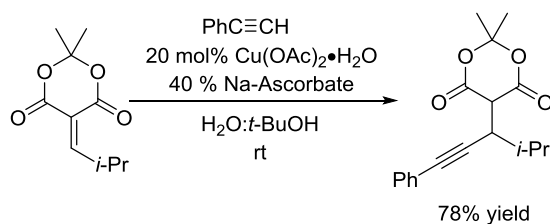
More recently, Loh and co-workers reported the use of an indium/copper catalyst system towards the conjugate addition of unactivated alkyl iodides to  $\alpha,\beta$ -unsaturated compounds in water. It was proposed that this reaction occurred via a radical pathway (Scheme 1.5).<sup>37</sup>

**Scheme 1.5** In/Cu-mediated conjugate addition in water.

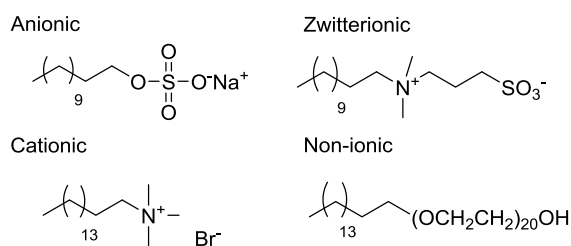


In another study by Carreira et al., copper-catalyzed conjugate addition reactions of terminal alkynes were reported to occur efficiently in a 10:1 H<sub>2</sub>O/*t*-BuOH mixture.<sup>38</sup> Thus, it can be seen that copper-catalyzed conjugate additions of alkyl, alkenyl, or aryl groups to  $\alpha$ ,  $\beta$ -unsaturated ketones in water have not yet been reported (Scheme 1.6).

**Scheme 1.6** Conjugate addition of alkynes in water.



Much emphasis has also been directed towards the development of greener solvents like ionic liquids,<sup>39</sup> supercritical carbon dioxide,<sup>40</sup> to minimize our dependence on organic solvents.<sup>41</sup> However, water is still the preferred solvent. Through the use of micellar catalysis, reactants can be “solubilized” within the aqueous environment with the aid of surfactants. Although this is not a new concept, there exists only a limited number of each kind (ionic, non-ionic and zwitterionic) of commercially available surfactants that can be found in the literature (Figure 1.3).<sup>42</sup> Thus, there is a lot of potential for the development of new surfactants to broaden the scope of organic reactions that can take place in aqueous media.



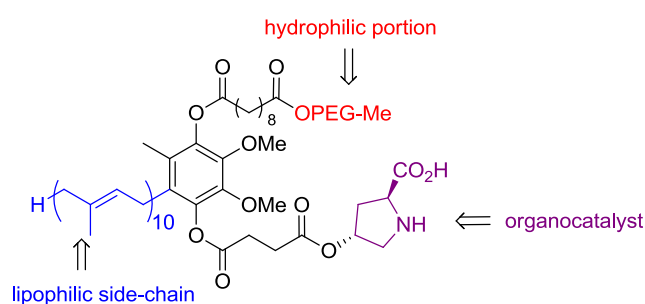
**Figure 1.3** Types of surfactants.

To address this issue, Lipshutz and co-workers have developed “designer” surfactants that are able to facilitate transition metal-catalyzed reactions like Heck, Suzuki-Miyaura, Negishi and Stille cross-couplings in water, thereby successfully replacing organic solvents with a more environmentally benign solvent.<sup>43</sup> In recognition of the group’s efforts, Lipshutz was awarded the 2011 Presidential Green Chemistry Challenge award from the EPA.

### 1.3 Organocatalyzed reactions in water

Organocatalysis, the use of small organic molecules to catalyze organic reactions, has been sporadically reported since the 1900s. However, it was only recently that it was regarded as a fundamental *concept* that could provide catalysts for a broad spectrum of important transformations that neither relied on transition metals nor enzymes.<sup>44</sup> Although metal-catalyzed reactions tend to have a larger substrate scope, such reactions have disadvantages such as high cost of the catalysts and leeching of the toxic metals into the products. On the other hand, organocatalysts are non-toxic, cheaper, more readily available, and environmentally friendly. Furthermore, the reproducibility and operational simplicity of these reactions are enhanced because they are relatively less sensitive to the presence of water or air. As a result, organocatalytic reactions are becoming increasingly popular for the large-scale synthesis of biologically active compounds and active pharmaceutical ingredients.<sup>45</sup>

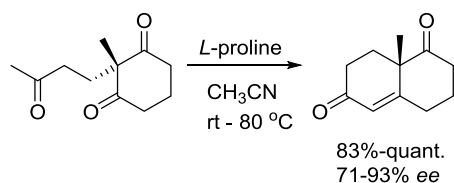
Organocatalysts can also be more readily attached to a solid support, which facilitates recycling and recovery of the catalyst, and simplifies the reaction work up. In 2012, Lipshutz and co-workers developed a “designer surfactant”, polyethyleneglycol ubiquinol sebacate (PQS), which has a free hydroxyl group to which different catalysts can be attached to. By covalently attaching 4-hydroxy proline to the PQS scaffold (Figure 1.4), aldol reactions could be carried out efficiently in water.<sup>46</sup> Recycling of the catalyst was found to be easy because the catalyst remained in the aqueous phase.



**Figure 1.4** PQS attached proline catalyst.

Most organocatalysts activate substrates through covalent bonding, van der Waals forces or hydrogen bonding, which result in an acceleration of the reaction rate. The first asymmetric organocatalytic reaction was reported by Bredig and Fiske, which involved the acceleration of the addition of HCN to benzaldehyde by quinine and quinidine.<sup>47</sup> Later on, Pracejus et al. made use of alkaloids as catalysts to carry out the addition of methanol to phenylmethylketene with 74% ee.<sup>48</sup> A further breakthrough was achieved in the 1970s when Hajos, Parrish, Eder, Sauer and Wiechert demonstrated that intramolecular aldol reaction of triketones with *L*-proline could afford the desired products with up to 93% ee (Scheme 1.7).<sup>49</sup> However, the field of organocatalysis only truly emerged in 2000, when List and Barbas et al. reported the *L*-proline-catalyzed intermolecular aldol reaction.<sup>50</sup> Around the same time, MacMillan et al. reported the enantioselective organocatalytic Diels-Alder reaction.<sup>51</sup>

**Scheme 1.7** The Hajos-Parrish-Eder-Sauer-Wiechert-reaction.

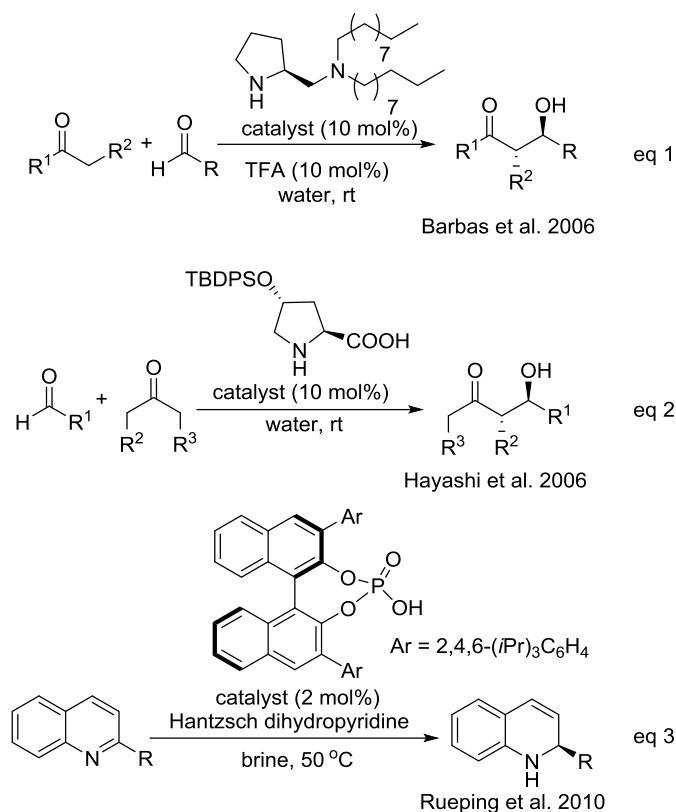


As water is the ideal solvent, efforts have also been made to carry out organocatalytic reactions in water. Initially, water was believed to be an unsuitable solvent for organic reactions because the water molecules may interfere with the transition state formed between the organocatalyst and reactants. Disruption of the hydrogen bonds and other polar interactions may occur, consequently adversely affecting the catalytic activity and stereocontrol.<sup>52</sup>

Since the pioneering studies by Breslow<sup>9b</sup> and Sharpless<sup>10,11</sup> that were mentioned earlier, a variety of carbon-carbon and carbon-heteroatom bond forming reactions catalyzed by organocatalysts in water have been successfully developed.<sup>8b</sup> The seminal work by Janda et al. showed the role of water in a norricotine-catalyzed aldol reaction of acetone with *p*-chloro-benzaldehyde in water,<sup>53</sup> while Pihko et al. observed enhanced chemical yields in an intermolecular aldol reaction catalyzed by *L*-proline.<sup>54</sup> The latter proposed that water played a role in assisting the hydrolysis of oxazolidinone, which is believed to deactivate the catalyst, and consequently accelerates and improves the reaction yield. Later on, Barbas et al. reported a highly enantioselective direct aldol reaction catalyzed by a bifunctional organocatalyst bearing hydrophobic groups to achieve products with moderate to excellent enantioselectivity (Scheme 1.8, eq 1).<sup>55</sup> The same catalyst was also shown to be efficient in the direct Michael reaction of ketones and aldehydes with  $\beta$ -nitrostyrene in brine.<sup>56</sup> In a similar study, Hayashi and coworkers, reported a highly enantioselective and diastereoselective direct aldol reaction in water using a silyloxy

proline catalyst (Scheme 1.8, eq 2).<sup>57</sup> More recently, Rueping et al. achieved the first phosphoric acid-catalyzed reduction of imines in water (Scheme 1.8, eq 3).<sup>58</sup>

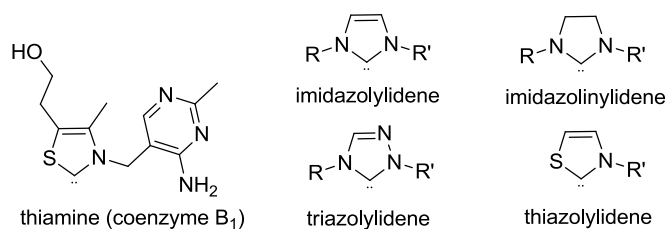
**Scheme 1.8** Seminal organocatalytic reactions in water.



**NHC-catalyzed reactions**

In 1958, Breslow postulated that upon deprotonation, the thiazolium moiety of thiamine, otherwise known as vitamin B<sub>1</sub>, can give rise to a thiazolylidene species that is nucleophilic enough to undergo a reaction with carbonyl groups, leading to a polarity reversal (“umpolung”) of the latter (Figure 1.5).<sup>59,60</sup> Pioneered by Seebach, the “umpolung” concept changed the traditional way of thinking which is associated with a retrosynthetic analysis of target molecules.<sup>61</sup> Following the contributions of the groups of Bertrand and Arduengo,<sup>62,63</sup> which involved the isolation of stable nucleophilic carbenes, there has been a widespread application of *N*-heterocyclic carbenes (NHCs) in organic synthesis (Figure

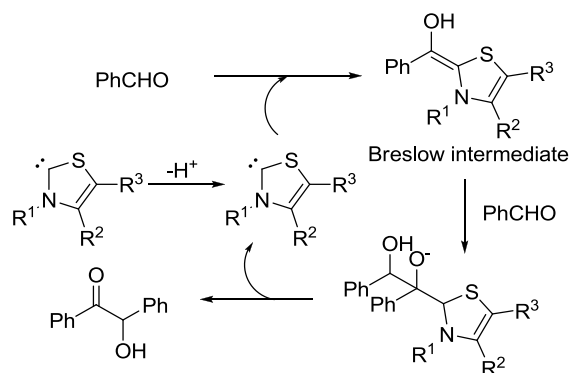
1.5). NHCs have proven to be excellent ligands for metal-based catalysis, and also suitable organocatalysts for various reactions.<sup>64</sup>



**Figure 1.5** Structure of thiamine and major types of *N*-heterocyclic carbenes.

In his seminal study, Breslow proposed a mechanism for the self-benzoin reaction of carbonyl compounds, which has become the basis for the developments observed in NHC-catalyzed reactions, including asymmetric versions (Scheme 1.9).

**Scheme 1.9** Breslow's postulate of the benzoin reaction.

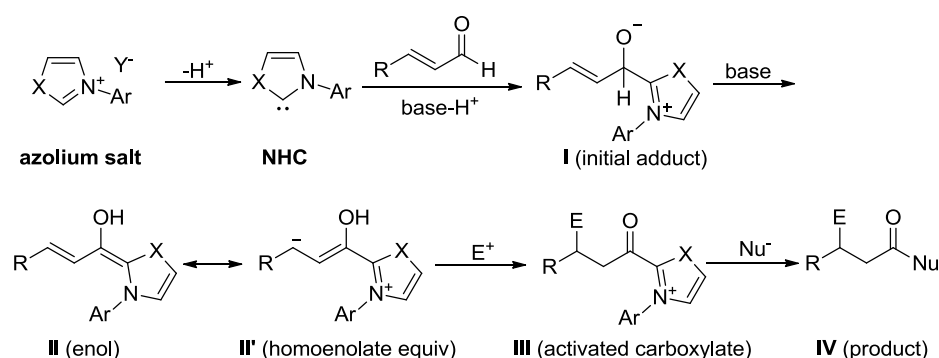


It is assumed that upon deprotonation of the azolium to afford a nucleophilic carbene, an enamine-type intermediate (Breslow intermediate) is formed by addition of an aldehyde to the carbene, followed by a subsequent proton transfer. This consequently leads to the formation of an “umpolung”, in which the originally electrophilic nature of the

aldehyde carbon becomes nucleophilic. It then attacks a second molecule of aldehyde to furnish the benzoin product. The formation of 1,2- or 1,4-functionalized products, instead of 1,3- or 1,5-substituted products which are obtained from normal polarity reactions, arises from the “umpolung” activity.

In 2004, the groups of Glorius and Bode independently reported that ‘extended Breslow intermediates’ can be generated from  $\alpha,\beta$ -unsaturated aldehydes (Scheme 1.10).<sup>65</sup> Due to the extended conjugation, a homoenolate is formed, which exhibits significant nucleophilic reactivity at the  $\beta$ -position. In such cases, the steric bulk of the carbene catalyst plays a vital role in hindering reaction at the  $\alpha$ -carbon. Consequently, a new bond at the  $\beta$ -position is formed with an electrophile to afford an enol, which tautomerises to the activated carboxylate equivalent and reacts with a nucleophile to give the product and regenerates the catalyst. An annulation reaction will result if the electrophile (E) and the nucleophile (Nu) are part of a single molecule.

**Scheme 1.10** Mechanism of NHC-catalyzed reaction with  $\alpha,\beta$ -unsaturated aldehydes.



Since then, many reactions that employ the use of homoenolates with carbon-based electrophiles such as aldehydes, enones and imines have resulted in the formation of a variety of annulated and acyclic products.<sup>64g</sup> In addition, asymmetric versions of these

reactions have been explored, sometimes with the cooperative use of magnesium and titanium based Lewis acids.<sup>64i,66</sup>

Compared to other organocatalysts, there are only a limited number of literature reports that document the employment of water as the solvent in *N*-heterocyclic carbene (NHC)-catalyzed reactions. To our knowledge, the first NHC-catalyzed reaction was disclosed by Bode and co-workers, in which an organic/water co-solvent (10:1, THF:H<sub>2</sub>O mixture) was used for the annulation of enals and aldehydes.<sup>65b</sup> Although this solvent system was not determined to be the ideal, it demonstrated that the presence of a small amount of water was tolerated. Subsequently, the same group demonstrated the use of water as a nucleophile in redox esterifications of chiral formylcyclopropanes to prepare the corresponding acid, and as a co-solvent for the NHC-catalyzed activation of  $\alpha$ -chloroaldehyde bisulfite salts.<sup>67</sup> In 2010, Rovis and co-workers reported the synthesis of  $\alpha$ -chloro and  $\alpha$ -fluoro carboxylic acids using a toluene/water biphasic solvent containing 1.0 equiv of 1M aqueous K<sub>2</sub>CO<sub>3</sub> and 10 mol% of brine/Bu<sub>4</sub>NI as additive.<sup>68</sup> In another study, Hoveyda and co-workers demonstrated the NHC-catalyzed enantioselective silyl conjugate addition to enones in an aqueous medium (3:1, THF:H<sub>2</sub>O mixture).<sup>69</sup> Furthermore, it has also been shown that NHCs are reasonably stable in aqueous media.<sup>70</sup>

Despite the existence of these studies that have demonstrated the compatibility of water with NHC catalysis, the use of water as the sole solvent for NHC-catalyzed reactions of aldehydes remains undisclosed. This is surprising considering that the naturally occurring *N*-heterocyclic carbene precursor, thiamine, catalyzes many biological processes predominantly in an aqueous environment.<sup>59a</sup>

## 1.4 Thesis aim

The use of water as a solvent has many economic and environmental benefits. As a result, since the early works of Breslow and Sharpless,<sup>9b,11</sup> countless reactions that occur in water have mushroomed. The once-held belief that water is an unsuitable reaction media has been proven to be untrue, and in some cases, water has had a beneficial effect. Although many metal- and organo-catalyzed reactions have been successfully explored in water, there is still room for development. As discussed earlier, reactions involving organocuprates require stringent moisture-free conditions. Hence, it is no surprise that copper-catalyzed conjugate additions of alkyl, alkenyl, or aryl groups to  $\alpha,\beta$ -unsaturated aldehydes in water have not yet been reported. Accordingly, chapter 2 describes the development of such conjugate additions using *in-situ* formed organozinc reagents, with the help of micellar catalysis. Furthermore, in the field of organocatalysis, reports that demonstrate the use of water as a reagent or co-solvent in NHC-catalyzed reactions have been sporadic. To date, there is still no study in which water was used as the only solvent for NHC-catalyzed reactions. As such, chapter 3 describes for the first time, organocatalytic NHC-catalyzed reactions involving  $\alpha,\beta$ -unsaturated aldehydes with water as the sole solvent. Chapter 4 describes the synthesis and evaluation of TADDOL-based phosphoric acids in organic solvent, as well as the application of a surfactant platform, PQS, in which a Rh-BINAP species may be bound to. These studies lay the foundation for PQS-bound phosphoric acid catalyzed reactions in water, which consequently allow for recycling of the catalyst.

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## CHAPTER 2:

Metal-catalyzed Reactions in Aqueous Media:

Copper-Catalyzed Conjugate Addition

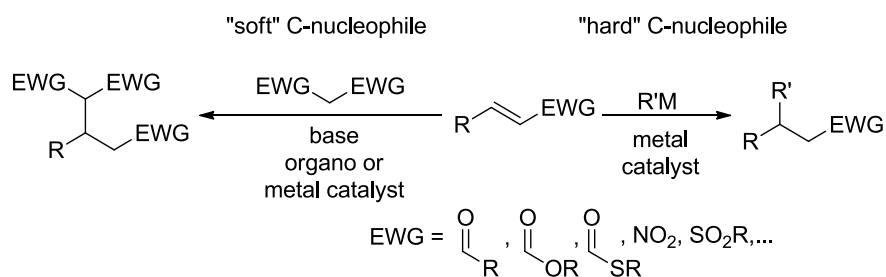
Reactions to Enones in Water

## 2.1 Cross-coupling reactions in water

The use of organometallic nucleophiles to form carbon-carbon bonds are among the most important of organic transformations.<sup>1</sup> Various name reactions with almost every metal in the periodic table have been developed, including organoboron (Suzuki), Grignard reagents (Kumada), organotin (Stille), organozinc (Negishi), organosilicon (Hiyama), and *in situ* generated acetylide anions (Sonogashira). These reactions typically involve an oxidative addition of the organic halide, transmetalation of the nucleophilic carbon, followed by reductive elimination to afford the product.

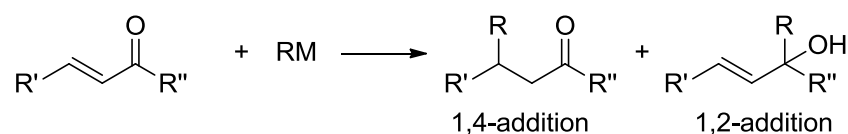
Besides these metals, protocols that make use of copper to form C-C bonds have also been developed.<sup>2</sup> One example is the conjugate addition reaction, which has evolved to become one of the most versatile reaction that has found application in the synthesis of pharmacologically active compounds.<sup>3</sup> This transformation is complementary to the allylic alkylation and the Michael addition, which employs soft carbon nucleophiles (Scheme 2.1). Traditionally, copper has found the broadest application and various organocopper species have been widely used. A significant advantage of these processes is the high compatibility with many functional groups, which consequently enables them to be used as key steps in the synthesis of numerous biologically active compounds. Besides, they show a broad substrate scope because of the large variety of donor and acceptor compounds that can be employed. In addition, this transformation is desirable due to low cost of the copper salts, and the often high regio- and enantioselectivities.

**Scheme 2.1** Conjugate addition reaction vs Michael addition.



The past few decades have seen dramatic breakthroughs in the area of catalytic asymmetric 1,4-addition of alkyl organometallic nucleophiles to enones. Most of these asymmetric versions make use of organozinc reagents, especially  $\text{ZnEt}_2$ , a trend started by Alexakis and Soai.<sup>4</sup> One of the challenges often associated with conjugate addition reactions is the regioselectivity. By fine tuning the electronic and steric properties of the active catalyst, 1,2-addition or 1,4-addition can occur (Scheme 2.2). In order to favour formation of the 1,4-adduct, the use of organometallic reagents (e.g.  $\text{R}_2\text{Zn}$  reagents) by transmetallation and transition metals like copper, to generate a more reactive or softer organometallic reagent, has traditionally been employed.

**Scheme 2.2** Typical competing reaction for conjugation addition reactions.

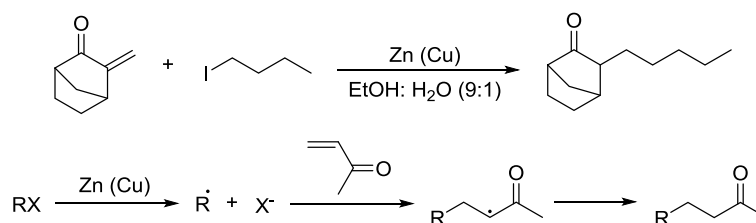


In recent years, a large number of metal-catalyzed reactions have been explored in water and extensively reviewed.<sup>5</sup> However, as mentioned earlier in the Introduction, there is no true precedent for copper-catalyzed reactions in aqueous media. This may be because organocuprate chemistry is much less tolerant to conditions, and requires stringent moisture-free conditions.<sup>2b</sup> Consequently, great efforts have to be made to ensure that the copper salt precursors and organic, aprotic solvents are dry. In addition, proper handling of

the commercially available or freshly prepared organometallic precursors is necessary.<sup>1b</sup> Furthermore, the use of Zn reagents in protic media, which possesses an inherently green characteristic by reducing the use of organic solvents, faces the possibility of undesired side reactions such as hydrolysis, reduction of the enone and Wurtz coupling.

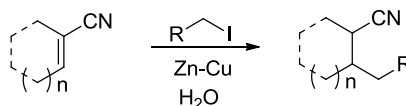
Early studies by Luche and co-workers reported the use of a Zn/Cu couple in aqueous media, which was activated by copper or NH<sub>4</sub>Cl, through a radical pathway (Scheme 2.3).<sup>6</sup> However, these works were not carried out completely in water (EtOH: water = 9:1), and have the limitation of requiring sonication to ensure good yields.

**Scheme 2.3** (a) Luche method involving sonication. (b) Proposed radical mechanism.



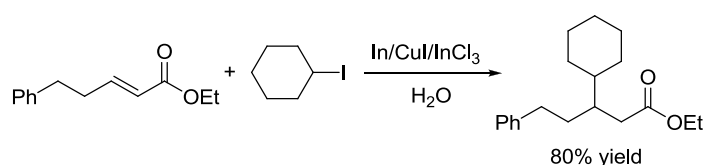
In addition, Fleming and co-workers<sup>7</sup> reported the use of a silica-supported zinc-copper matrix reagent for the conjugate addition of alkyl iodides to unsaturated nitriles in water (Scheme 2.4). This reaction suffers from lack of atom economy due to the need for large amounts of alkyl halide (8 equiv) and Zn (6 equiv). Also, this reaction works best for unsaturated nitriles, which are excellent radical acceptors,<sup>8</sup> but not good partners for copper-catalyzed conjugate additions. This is primarily because the powerful electron withdrawal of the nitrile group polarizes the  $\alpha$ -carbon more than the  $\beta$ -carbon, often redirecting nucleophilic attack to the nitrile group.

**Scheme 2.4** Silica-supported Zn-Cu matrix promoted reactions in water.



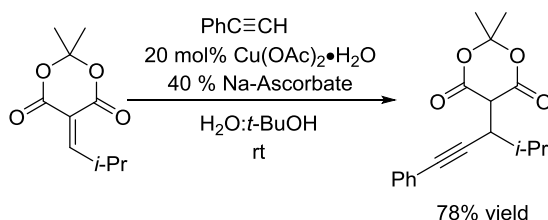
Another study by Loh and co-workers reported the employment of indium/copper towards the conjugate addition of unactivated alkyl iodides to  $\alpha,\beta$ -unsaturated compounds in water. It was proposed that this reaction took place via a radical pathway (Scheme 2.5).<sup>9</sup>

**Scheme 2.5** In/Cu-mediated conjugate addition in water.



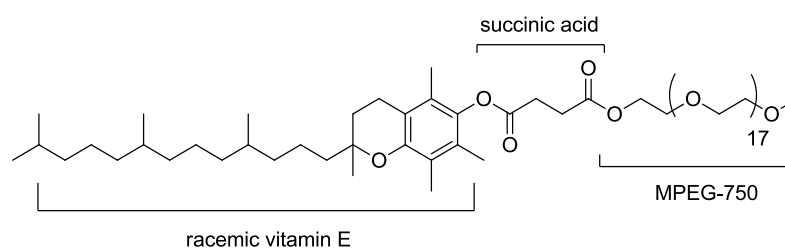
Besides, Carreira et al. carried out copper-catalyzed conjugate addition reactions of terminal alkynes in a 10:1  $\text{H}_2\text{O}/t\text{-BuOH}$  mixture (Scheme 2.6).<sup>10</sup> As such, there is currently no report which enables copper-catalyzed conjugate additions of alkyl, alkenyl, or aryl groups to  $\alpha,\beta$ -unsaturated ketones in water.

**Scheme 2.6** Conjugate addition of alkynes in water.



For the past 5 years, Lipshutz and co-workers have worked towards the development of “designer surfactants” to enable cross-coupling reactions in water by micellar catalysis. In 2011, they reported that the “designer surfactant”, TPGS-750-M (to

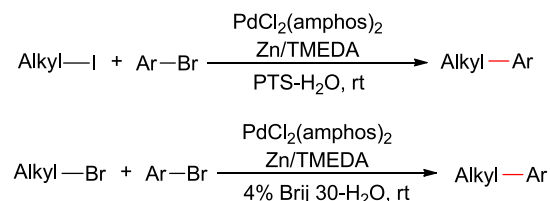
DL- $\alpha$ -tocopherol methoxypolyethylene glycol-750-succinate) is an excellent commercially available surfactant that forms nanomicelles in water, within which various cross-couplings like Stille, Heck, Suzuki-Miyaura and Sonogashira, can efficiently take place in water and at room temperature (Figure 2.1).<sup>11</sup>



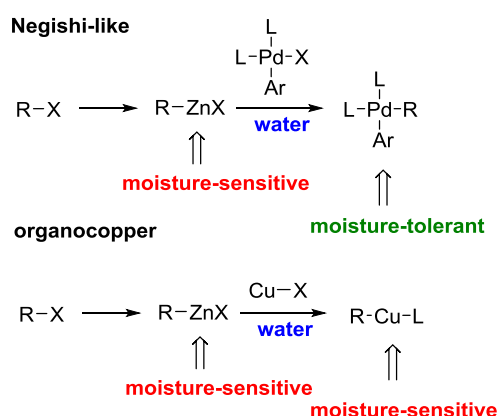
**Figure 2.1** Structure of TPGS-750-M.

By applying micellar catalysis, the same group also successfully developed protocols that make use of moisture-sensitive, zinc-mediated, Pd-catalyzed (Negishi-like) cross-couplings with alkyl iodides and bromides (Scheme 2.7).<sup>12</sup> Normally, preformation of an organozinc halide (e.g., RZnI) is necessary, and once formed, they are usually very reactive and intolerant to traces of water. However, in these studies, carbon-carbon bond formation was achieved with the absence of a stoichiometrically preformed organometallic coupling partner due to the judicious choice of surfactants. It is proposed that within the surfactant nanoparticles, the reactants are densely packed due to the hydrophobic effect. As the nanoparticles collide with the surface of the zinc metal, preferential insertion of Zn into the alkyl halide bond occurs in a likely successive one-electron-transfer sequence. The resulting water-sensitive RZnX is insulated from the aqueous environment and is stabilized by TMEDA, which likely assists in shuttling it into the micelle, where it can react with the Pd catalyst and aryl halide.

**Scheme 2.7** Pd-catalyzed cross-couplings in water.



As such, we decided to develop a methodology for the 1,4-addition of  $\alpha,\beta$ -unsaturated ketones in water. This would be challenging because reactions involving organocuprates are far more demanding than organopalladium species, due to their intolerance towards moisture (Figure 2.2).



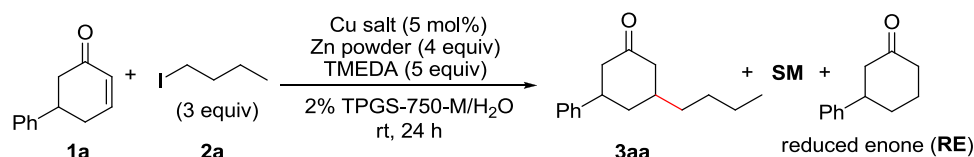
**Figure 2.2** Differences between intermediates formed by organocuprate and organopalladium species.

## 2.2 Results and discussion

At the beginning, the reaction between 5-phenyl-cyclohexenone and iodobutane was studied using the conditions that were previously used for the Pd-couplings.<sup>12</sup> However, this afforded moderate yields of the desired product, a large amount of unreacted starting material (**SM**, 41%) and a small amount (5%) of reduced enone (**RE**) (Table 2.1, entry 1). A survey of various copper salts revealed that  $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ ,  $\text{Cu}(\text{CH}_3\text{CN})_4\text{NTf}_2$  and

(CuOTf)<sub>2</sub>•PhCH<sub>3</sub> gave comparable yields of the desired product, with Cu(OAc)<sub>2</sub>•H<sub>2</sub>O being eventually chosen due to its low cost (Table 2.1, entries 1, 6 and 7).

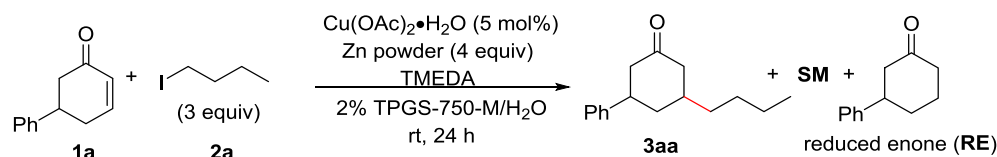
**Table 2.1** Survey of copper salts.<sup>a</sup>



entry	Cu salt	<i>trans</i> - <b>3aa</b> : <i>cis</i> - <b>3aa</b> : SM : RE	yield of <b>3aa</b> (%) <sup>b</sup>
1	Cu(OAc) <sub>2</sub> •H <sub>2</sub> O	46 : 8 : 41 : 5	54
2	CuBr•SMe <sub>2</sub>	2.2 : 0.3 : 97.5 : 0	2.5
3	Cu(NO <sub>3</sub> ) <sub>2</sub> •1/2H <sub>2</sub> O	2 : 0 : 98 : 0	2
4	Cu(TMHD) <sub>2</sub>	40 : 7 : 43 : 10	47
5	Cu(CH <sub>3</sub> CN) <sub>4</sub> PF <sub>6</sub>	18 : 3 : 79 : 0	21
6	Cu(CH <sub>3</sub> CN) <sub>4</sub> NTf <sub>2</sub>	46 : 8 : 38 : 8	54
7	(CuOTf) <sub>2</sub> •PhCH <sub>3</sub>	46 : 8 : 38 : 8	54

<sup>a</sup> Reaction conditions: **1a** (0.25 mmol), **2a** (3 equiv), Zn powder (4 equiv), TMEDA (5 equiv), 5 mol% [Cu], 2%-TPGS-750M/H<sub>2</sub>O (0.5 mL), rt, 24 h. <sup>b</sup> Determined by GC on crude material.

Screening the loading of TMEDA led to the finding that the optimal amount was two equivalents (Table 2.2, entry 2). Although the exact role of TMEDA remains to be elucidated, it is proposed that similar to the study involving zinc-mediated, Pd-catalyzed (Negishi-like) cross-couplings with alkyl iodides and bromides,<sup>12</sup> where TMEDA was found to be the diamine of choice, TMEDA is likely to play a few important roles in this reaction, namely (1) to clean the surface of the Zn metal, thereby promoting electron transfer; (2) chelates and stabilise the RZnX complex; (3) to facilitate the transfer of RZnX into the nanomicellar interior, where the other reactants await.

**Table 2.2** Screening of TMEDA loading.<sup>a</sup>

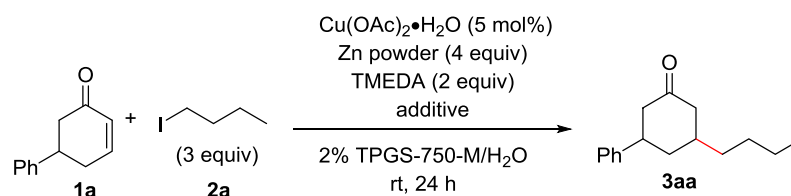
entry	TMEDA (equiv)	<i>trans</i> - <b>3aa</b> : <i>cis</i> - <b>3aa</b> : <b>SM</b> : <b>RE</b>	yield of <b>3aa</b> (%) <sup>b</sup>
1	5	46 : 8 : 41 : 5	54
2	2	57 : 10 : 32 : 1	67
3	0.5	50 : 9 : 40 : 1	59
4	0.05	33 : 6 : 61 : 0	39

<sup>a</sup> Reaction conditions: **1a** (0.25 mmol), **2a** (3 equiv), Zn powder (4 equiv), TMEDA,  $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$  (5 mol%), 2%-TPGS-750M/ $\text{H}_2\text{O}$  (0.5 mL), rt, 24 h. <sup>b</sup> Determined by GC on crude material.

Since the pioneering studies of Yamamoto and co-workers on the use of Lewis acid additives with organocopper compounds to achieve unique reactivities and selectivities, presumably due to the coordination of the Lewis acid with the carbonyl group, Lewis acids have been frequently used in combination with organocopper reagents.<sup>13</sup> Hence, we envisioned that similarly, the use of a small amount of Lewis acid (e.g.  $\text{LiClO}_4$ ) could activate the enone towards nucleophilic attack. Gratifyingly, this dramatically improved the conversion of the reaction, presumably by complexation of the lithium to the carbonyl group (Table 2.3, entry 1). Studies have shown that the addition of NaCl to a micellar solution may lead to a “salting out” effect, which removes water from the PEGylated portions of the micelles as the PEG expands into the water, resulting in an increase in the size of the micelles.<sup>14</sup> The addition of dodecane has been found to affect the size of the micelle due to the increase in hydrophobic interactions. In addition, an increase in reaction temperature has been found to lead to the formation of larger micelles, which would

enhance the migration of the reagents into the micellar reaction chamber, thereby resulting in better conversions.<sup>14</sup> Hence, attempts to increase the reaction conversion by the addition of 2 equivalents of dodecane, 3M NaCl or increasing the reaction temperature to 40 °C were carried out. Unfortunately, all these attempts led to diminished yields of the desired product (2%, 18% and 32% GC yield, respectively). Subsequent screening of various additives such as gold derivatives, which have been shown to effectively facilitate conjugate addition reactions,<sup>15</sup> showed that AuCl<sub>3</sub> was the most effective Lewis acid additive (Table 2.3, entry 19). Furthermore, it was determined that the addition of the alkyl halide and zinc reagents in two portions improved the conversion to 93% (Table 2.3, entry 21). The proposed reasons being: (a) better stirring due to less solids and unsolubilized reagents in the reaction mixture; (b) minimized protioquenching due to the zinc insertion occurring faster than the conjugate addition; (c) smaller amount of enone reduction by zinc.

**Table 2.3** Screening of Lewis acid additive.<sup>a</sup>



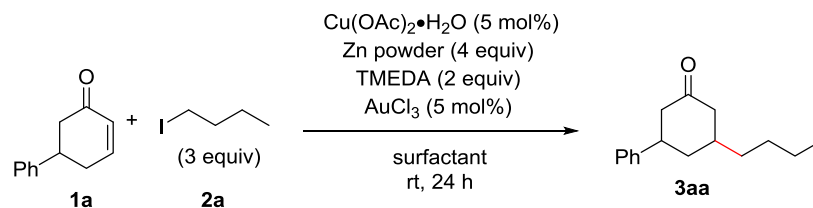
entry	additive (equiv)	yield (%) <sup>b</sup>	entry	additive (equiv)	yield (%) <sup>b</sup>
1	LiClO <sub>4</sub> (0.05)	78	12	Ni(dppf)Cl <sub>2</sub> (0.05)	79
2	LiBr (1)	85	13	Ni(acac) <sub>2</sub> (0.05)	70
3	LiCl (1)	58	14	Sc(OTf) <sub>3</sub> (0.03)	47
4	LiI (1)	48	15	AuBr <sub>3</sub> (0.05)	71
5	LiOTf (1)	87	16	KAuCl <sub>4</sub> (0.05)	31
6	LiOH (1.5)	43	17	IPrAuNTf <sub>2</sub> (0.05)	61

7	LiOH (1.5), TIPSOH (1.5)	83	18	Ph <sub>3</sub> PAuNTf <sub>2</sub> (0.05)	73
8	KOH (1.5), TIPSOH (1.5)	82	19	AuCl <sub>3</sub> (0.05)	87
9	NiCl <sub>2</sub> (0.05)	45	20	AuCl <sub>3</sub> (0.03)	64
10	Ni(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub>	62	21 <sup>c</sup>	AuCl <sub>3</sub> (0.05)	93
11	Ni(dppp)Cl <sub>2</sub>	54	22 <sup>c</sup>	AuCl (0.05)	92

<sup>a</sup> Reaction conditions: **1a** (0.25 mmol), **2a** (3 equiv), Zn powder (4 equiv), TMEDA (2 equiv), 5 mol% Cu(OAc)<sub>2</sub>•H<sub>2</sub>O, 2%-TPGS-750M/H<sub>2</sub>O (0.5 mL), additive, rt, 24 h. <sup>b</sup> Determined by GC on crude material. <sup>c</sup> Iodobutane was added in two portions: t = 0 h, 1.5 equiv; t = 6 h, 1.5 equiv.

A survey with other commonly used commercially available surfactants like Brij 30 and 35, Triton X-100, cremophor EL, and solutol HS, was carried out and TPGS-750-M was determined to be the best surfactant (Table 2.4, entry 1). The differences in reaction outcome arise from the fact that each surfactant has distinct characteristics, like particle size, shape (e.g., spherical, rod-like), functionality (e.g., a cyclic or linear hydrocarbon interior), and hydrophilic-lipophilic balance (i.e., the ratio of its hydrophilic to lipophilic components). These factors correspond to observed variations in their efficacy in various reactions, but a complete understanding of their correlation remains elusive.<sup>11d</sup>

A control reaction carried out in water gave significantly diminished results, thereby demonstrating the importance of TPGS-750-M in facilitating conjugate additions in aqueous media (Table 2.4, entry 7). In addition, absence of the copper salt results in negligible formation (2% GC yield) of the product, thereby showing that both Cu(OAc)<sub>2</sub>•H<sub>2</sub>O and AuCl<sub>3</sub> are essential for this reaction.

**Table 2.4** Screening of the surfactant.<sup>a</sup>

entry	surfactant	yield of <b>3aa</b> (%) <sup>b</sup>
1	TPGS-750-M	93
2	Brij 30	52
3	Brij 35	61
4	Solutol HS	72
5	Triton X-100	68
6	Cremophor EL	58
7	none	50

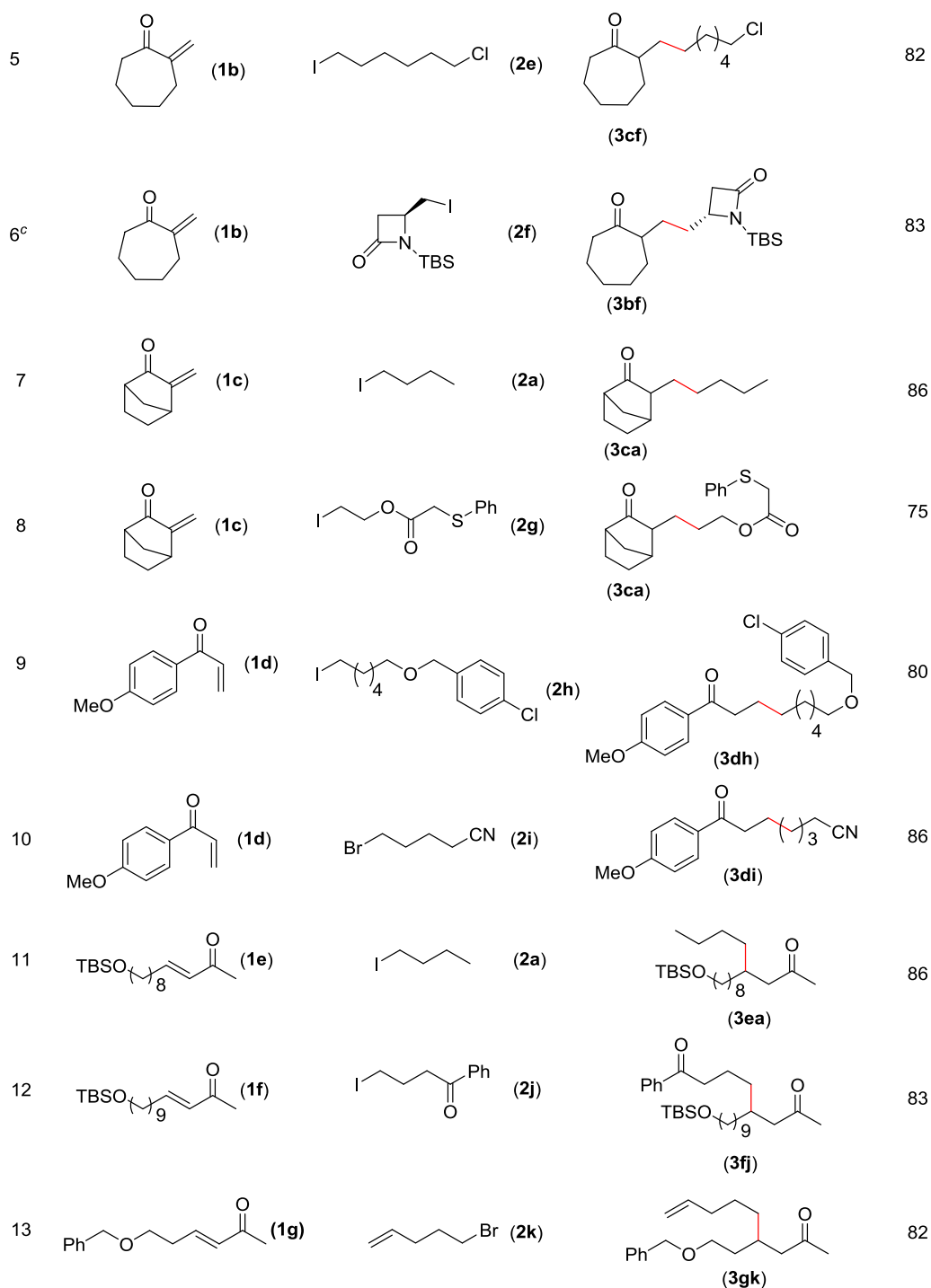
<sup>a</sup> Reaction conditions: **1a** (0.25 mmol), **2a** (3 equiv), Zn powder (4 equiv), TMEDA (2 equiv),  $\text{Cu(OAc)}_2 \cdot \text{H}_2\text{O}$  (5 mol%),  $\text{AuCl}_3$  (5 mol%), surfactant, rt, 24 h. <sup>b</sup> Determined by GC on crude material.

With the optimized reaction conditions in hand, the substrate scope was investigated with various alkyl halides and cyclic enones. As shown in Table 2.5, the reactions proceeded with excellent yields in water, at room temperature. Simple alkyl halides bearing short or long chain lengths (Table 2.5, entries 1 and 2), and alkyl halides bearing ester or ether residues (entries 3-4) afforded the desired products in good yields. This methodology could also be applied efficiently to various acyclic enones and alkyl halides bearing different functional groups. Alkyl halides bearing a chloride or cyanide group (entries 5 and 10), a cyclic amide (entry 6) and sensitive groups like a ketone (entry 12), gave the corresponding addition products in high yields. Furthermore, alkyl halides that bear both an ester functionality and sulfur group were also well tolerated, albeit with a slight drop in

yield (entry 8, obtained by Nicholas Isley). Notably, the desired product was furnished in higher yields than that obtained by the Luche method, in which the product was obtained in 72% (entry 7).<sup>6</sup> In the case of alkyl halides bearing a terminal double bond (entry 13), retention of the double bond was observed, which rules out the possibility of radical formation of the alkyl halide.

**Table 2.5** Conjugate additions of alkyl halides to enones.<sup>a</sup>

entry	enone	RX	product	yield (%) <sup>b</sup>
1				87
2				89
3				87
4				80



Reaction conditions: RX (3 equiv), Zn powder (4 equiv, X = I) or Zn dust (4 equiv, X = Br), TMEDA (2 equiv), Cu(OAc)<sub>2</sub>•H<sub>2</sub>O (5 mol%), AuCl<sub>3</sub> (5 mol%), 2%-TPGS-750M/H<sub>2</sub>O, rt, 24 h. <sup>b</sup> Isolated yield after SiO<sub>2</sub> column chromatography. <sup>c</sup> Zinc dust used.

Secondary iodides and bromides were also found to work well using our optimized conditions (Table 2.6). It is particularly noteworthy that rearrangement of the secondary halide, which may occur due to  $\beta$ -hydride elimination, was not observed.<sup>16</sup>

**Table 2.6** Conjugate addition reactions of secondary alkyl halides to enones.<sup>a</sup>

entry	enone	RX	product	yield (%) <sup>b</sup>
1				85
2 <sup>c</sup>				83
3				90
4				85
5				88
6				89
7				85

<sup>a</sup> Reaction conditions: RX (3 equiv), Zn powder (4 equiv, X = I) or Zn dust (4 equiv, X = Br), TMEDA (2 equiv), Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (5 mol%), AuCl<sub>3</sub> (5 mol%), 2%-TPGS-750M/H<sub>2</sub>O,

rt, 24 h. <sup>b</sup> Isolated yield after SiO<sub>2</sub> column chromatography. <sup>c</sup> Tetraethyl derivative of TMEDA used.

In the case of the conjugate addition of 2-iodobutane (**2m**) to  $\alpha,\beta$ -unsaturated ketone **1e**, the use of a more sterically hindered tetraethylethylenediamine (TEEDA) ligand resulted in a better yield (Table 2.6, entry 2).<sup>4</sup> This may be attributed to the slower rate of zinc insertion, which allows more time for the conjugate addition to occur.

The diastereoselectivity of the products using the optimized conditions were compared to that in organic solvents (Table 2.7).<sup>17</sup> Although the diastereoselectivity obtained was significantly lower than in THF (entry 4), the result was comparable with that in diethyl ether (entry 3). In all these reactions, the *trans* product was predominantly obtained, and their stereochemical outcome has been discussed in the literature.<sup>18a</sup>

**Table 2.7** Diastereoselectivity obtained in aqueous media vs organic solvents.

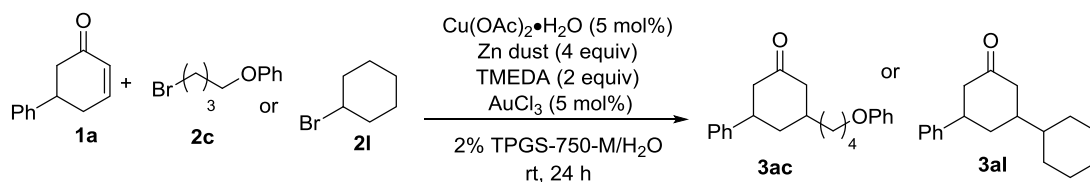
entry	conditions	dr ( <i>trans</i> : <i>cis</i> )
1	our method	85: 15
2	<i>n</i> -Bu <sub>2</sub> CuLi, Et <sub>2</sub> O, -20 °C	92: 8
3	<i>n</i> -Bu <sub>2</sub> CuLi, Et <sub>2</sub> O, rt	87: 13
4	<i>n</i> -Bu <sub>2</sub> CuLi, THF, rt	94: 6

<sup>a</sup> Determined by GC on crude material.

Attempts to investigate the recyclability of the reaction medium showed that it could be recycled up to 4 times (Table 2.8). By using hexanes to extract out the left over alkyl halide and desired product, followed by addition of more TMEDA, enone, and alkyl halide, the reaction media could be reused (Table 2.8, recycle study 1). The addition of fresh

surfactant or AuCl<sub>3</sub> was unnecessary and each cycle showed negligible decrease in reaction rate and minimal reduced enone. Furthermore, changing of the substrate combination after each recycle could be done without affecting the performance of the reaction, thereby increasing the utility of TPGS-750-M/H<sub>2</sub>O (Table 2.8, recycle study 2).

**Table 2.8** Recycling of reaction medium.<sup>a</sup>

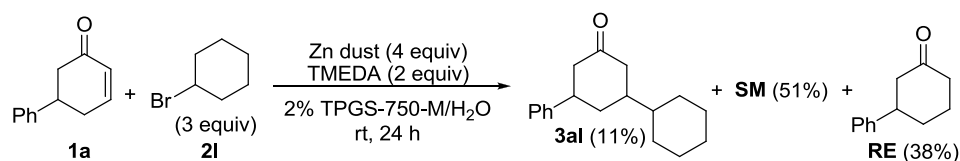


Recycle study 1			Recycle study 2	
cycle	conv. (%) <sup>b</sup>	yield (%) <sup>c</sup>	cycle	yield (%) <sup>c</sup>
1	>99	<b>3al</b> , 89	1	<b>3al</b> , 88
2	>99(2) <sup>d</sup>	<b>3al</b> , 86	2	<b>3ac</b> , 84
3	97(3) <sup>d</sup>	<b>3al</b> , 83	3	<b>3al</b> , 85
4	95 <sup>e</sup> (1.5) <sup>d</sup>	<b>3al</b> , 84		

<sup>a</sup> Reaction conditions: **1a** (0.5 mmol), **2c** or **2l** (3 equiv), Zn dust (4 equiv), TMEDA (2 equiv), Cu(OAc)<sub>2</sub>•H<sub>2</sub>O (5 mol%), AuCl<sub>3</sub> (5 mol%), 2% TPGS-750-M/H<sub>2</sub>O (1 mL), rt, 24 h. <sup>b</sup> Determined by GC on crude material. <sup>c</sup> Isolated yield after SiO<sub>2</sub> column chromatography. <sup>d</sup> Reduced enone. <sup>e</sup> After 48 h.

A control reaction was carried out involving the conjugate addition of 1-bromocyclohexane (**2l**) to 5-phenylcyclohexenone in the absence of Cu(OAc)<sub>2</sub>•H<sub>2</sub>O and AuCl<sub>3</sub> (Scheme 2.8). It was determined that the desired product (**3al**) was obtained in low yields (11%), with the majority of the crude mixture being unreacted starting material (51%) and reduced enone (38%), thereby demonstrating the importance of using the copper and gold catalysts.

**Scheme 2.8** Control reaction.



During the investigation of the substrate scope, attempts were made to vary the substituent on the cyclic enones (Table 2.9, entries 1-4). Good yields were obtained when the phenyl group was replaced by dimethyl groups (entry 1). However, the reaction was adversely affected when 4-Bn-cyclohexenone and 4-*t*Bu-cyclohexenone was used (entries 2 and 3). Generation of a quaternary centre was attempted with the use of 3-phenylcyclohexenone (entry 4) using the optimized conditions. Varying of the conditions showed that an increase of TMEDA to 4 equivalents, led to a higher yield of the desired product. It was also determined that alkyl halides bearing free hydroxyl groups were not well tolerated (entries 5 and 6). In the case of *N*-containing alkyl iodides, zinc dust was necessary in order for the product to be obtained. Once again, this may be attributed to the slower rate of zinc insertion, which allows more time for the conjugate addition to occur.

Table 2.9 Limitations.<sup>a</sup>

entry	enone	RX	product	yield (%) <sup>b</sup>
1				78
2				50
3				21
4				16 (38) <sup>c</sup>
5				25
6				38
7				-(83) <sup>d</sup>
8				-

<sup>a</sup> Reaction conditions: RX (3 equiv), Zn powder (4 equiv, X = I) or Zn dust (4 equiv, X = Br), TMEDA (2 equiv), Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (5 mol%), AuCl<sub>3</sub> (5 mol%), 2%-TPGS-750M/H<sub>2</sub>O, rt, 24 h. <sup>b</sup> Isolated yield after SiO<sub>2</sub> column chromatography. <sup>c</sup> 4 equiv TMEDA used. <sup>d</sup> Zinc dust used.

## 2.3 Conclusion

By making use of the “designer surfactant”, TPGS-750-M, copper-catalyzed conjugate additions in water using organozinc reagents formed *in situ* were successfully achieved. Unlike most conjugate reactions that occur at low temperatures, these reactions proceeded efficiently at room temperature. This methodology is not only environmentally friendly, but it also allows the reaction medium to be recycled up to 4 times without any significant change in the reaction outcome. In addition, it can be applied to a broad substrate scope and shows tolerance to a wide range of functional groups.

## 2.4 Experimental Section

### 2.4.1 General Information

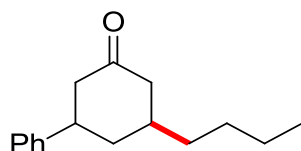
Unless otherwise noted, all reactions were performed under an atmosphere of argon. All commercially available reagents were used without further purification. Zinc dust (LOT#: A019970201), 1-iodobutane, 1-iodooctane, and 4-phenoxybutylbromide (LOT#: A004983601) were purchased from Acros Organics. *N,N,N',N'*-tetramethylethylenediamine and *N,N,N',N'*-tetraethylethylenediamine were purchased from Sigma-Aldrich®. Zinc powder (LOT#: A7637038) and AuCl<sub>3</sub> (LOT#: A2180108) were purchased from Strem Chemicals. (*R*)-1-(tert-butyldimethylsilyl)-4-(iodomethyl)azetid-2-one was purchased from Merck Research Laboratories (LOT#: L-701,997-0008). Ethyl 5-bromovalerate (LOT#: 10121073), bromocyclohexane, and 2-iodobutane were purchased from Alfa Aesar®. 5-bromo-1-pentene was purchased from TCI America (LOT#: WRE4E).  $\alpha,\beta$ -Unsaturated ketones 5-phenyl-2-cyclohexenone;<sup>20</sup> 5,5-dimethylcyclohex-2-enone and 3-methylenebicyclo[2.2.1]heptan-2-one;<sup>21</sup> 1-(4-methoxyphenyl)prop-2-en-1-one, (*E*)-6-(benzyloxy)hex-3-en-2-one and (*E*)-12-((tert-butyldimethylsilyl)oxy)dodec-3-en-2-one;<sup>22</sup> (*E*)-13-((tert-butyldimethylsilyl)oxy)tridec-3-en-2-one;<sup>23</sup> and alkyl halides 1-chloro-6-iodohexane;<sup>24</sup> 5-bromopentanenitrile;<sup>25</sup> and 2-

iodopropane;<sup>26</sup> were prepared according to literature procedures. 4-iodobutylphenone was synthesized via a Finkelstein reaction of 4-chlorobutylphenone which was purchased from Alfa Aesar®. A 2 wt % TPGS-750-M/H<sub>2</sub>O solution was prepared by dissolving 4 g TPGS-750-M in 196 g water (HPLC grade), followed by degassing with argon. TPGS-750-M was made as previously described,<sup>11d</sup> and is available from Sigma-Aldrich (catalog #733857). Analytical thin layer chromatography (TLC) was performed using Silica Gel 60 F254 plates (Merck, 0.25 mm thick). The developed chromatograms were analyzed by UV (lamp, 254 nm). Non-UV active compounds were developed using aqueous potassium permanganate (KMnO<sub>4</sub>) or vanillin stain. Flash chromatography was performed in glass columns using Silica Flash® P60 (SiliCycle, 40-63 μm). GCMS data was recorded on a 5975C Mass Selective Detector S5 coupled with a 7890A Gas Chromatograph (Agilent Technologies). A capillary column (HP-5MS crosslinked 5% phenylmethylpolysiloxanediphenyl, 30 m x 0.250 mm, 0.25 micron, Agilent Technologies) was employed. Helium was used as carrier gas at a constant flow of 1 mL/min. Retention times (t<sub>R</sub>) refer to the following temperature program: 50 °C for 5 min; heating rate 20 °C/min; 300 °C for 20 min; injection temperature 250 °C; detection temperature 280 °C. <sup>1</sup>H and <sup>13</sup>C NMR were recorded at 22 °C on a Varian UNITY INOVA Avance at 400, 500, or 600 MHz. Chemical shifts in <sup>1</sup>H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sep = septet, m = multiplet, br = broad), coupling constant in Hertz (Hz), and integration. Chemical shifts of <sup>13</sup>C NMR spectra are reported in ppm from the central peak of CDCl<sub>3</sub> (77.23 ppm) on the δ scale. Chiral HPLC data were collected using a Shimadzu SPD-m20a Prominence diode array detector. Chiral GC analysis was performed using a Restek RT-*beta*DEXcst column (30 m x 0.250 mm, 0.25 micron). Retention times (t<sub>R</sub>) are from compound dependent temperature programs; split-inlet at 200 °C at 11.60 psi (H<sub>2</sub>,

constant pressure) with 20:1 split, FID 290 °C. High resolution mass analyses were obtained using an APE Sciex QStar Pulsar quadrupole/TOF instrument (API) for ESI, or a GCT Premier TOF MS (Waters Corp) for FI.

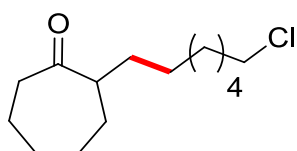
## 2.4.2 Procedure for Cu-Catalyzed conjugate additions in water:

*Note:* Stirring is a very important parameter in this chemistry, as is the nature of the reaction vessel. Common vials, or more frequently, microwave vials, should be used for small-scale reactions.

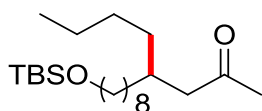


**3-Butyl-5-phenylcyclohexanone:** A 5 mL microwave vial containing a stir bar was charged with zinc powder (66 mg, 1 mmol), Cu(OAc)<sub>2</sub>•H<sub>2</sub>O (1.5 mg, 3 mol %), AuCl<sub>3</sub> (3.8 mg, 5 mol %), 5-phenyl-2-cyclohexenone (42 mg, 0.25 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 75 μL, 0.5 mmol). The vial was capped with a rubber septum and placed under an Argon atmosphere, and 0.5 mL of a 2 wt% TPGS-750-M solution in water was added via syringe followed by the addition of 1-iodobutane (42 μL, 0.375 mmol). The resulting mixture was stirred vigorously at rt for 6 h. Another 42 μL 1-iodobutane was added and the reaction was continued to stir for 18 h. After filtration through a pad of silica gel, the solvent was evaporated *in vacuo* and the crude reaction mixture was analyzed by NMR, GC, and GC/MS. Flash column chromatography provided 3-butyl-5-phenylcyclohexanone (*trans* : *cis* = 85 : 15, 50 mg, 87% yield). The *trans* and *cis* product were isolated by multiple time preparative TLC. *trans*-Product: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.34-7.31 (m, 2H), 7.27-7.21 (m, 3H), 3.33 (m, 1H), 2.60 (m, 2H), 2.55 (dd, *J* = 14.4, 4.8 Hz, 1H), 2.40 (dd, *J* = 14, 6 Hz, 1H), 2.07 (m, 1H), 2.04 (dd, *J* = 13.6, 4 Hz, 1H),

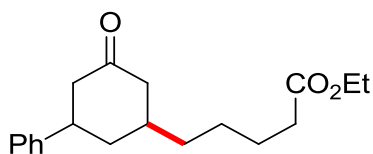
1.94 (dd,  $J = 13.6, 8$  Hz, 1H), 1.34-1.27 (m, 6H), 0.87 (t,  $J = 8$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  211.7, 144.5, 128.7, 127.0, 126.6, 47.6, 46.8, 39.6, 37.4, 34.5, 33.9, 29.3, 22.8, 14.1; HREI-MS (m/z):  $[\text{M}]^+$  calcd. for  $\text{C}_{16}\text{H}_{22}\text{O}$ , 230.1671; found 230.1676. *cis*-Product:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35-7.30 (m, 2H), 7.26-7.20 (m, 3H), 2.95 (tt,  $J = 12.8, 4$  Hz 1H), 2.61-2.45 (m, 2H), 2.13-2.04 (m, 2H), 1.90-1.82 (m, 1H), 1.60-1.43 (m, 2H), 1.41-1.24 (m, 6H), 0.89 (t,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  211.2, 144.6, 128.9, 126.9, 126.7, 49.0, 48.0, 44.0, 40.0, 38.5, 37.0, 29.0, 22.9, 14.2; HREI-MS (m/z):  $[\text{M}]^+$  calcd. for  $\text{C}_{16}\text{H}_{22}\text{O}$ , 230.1671; found 230.1677.



**2-(7-Chloroheptyl)cycloheptanone:** A 5 mL microwave vial containing a stir bar was charged with zinc powder (66 mg, 1 mmol),  $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$  (1.5 mg, 3 mol %),  $\text{AuCl}_3$  (3.8 mg, 5 mol %), 2-methylenecycloheptanone (31 mg, 0.25 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 75  $\mu\text{L}$ , 0.5 mmol). The vial was capped with a rubber septum and placed under an Argon atmosphere, and 0.5 mL of a 2 wt% TPGS-750-M solution in water was added via syringe followed by the addition of 1-chloro-6-iodohexane (55  $\mu\text{L}$ , 0.375 mmol). The resulting mixture was stirred vigorously at rt for 6 h. Another 55  $\mu\text{L}$  1-chloro-6-iodohexane was added and the reaction was continued to stir for 18 h. After filtration through a pad of silica gel, the solvent was evaporated *in vacuo*. Flash column chromatography provided 2-(7-chloroheptyl)cycloheptanone (50 mg, 82% yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.52 (t,  $J = 7.2$  Hz, 2H), 2.53-2.38 (m, 3H), 1.87-1.83 (m, 4H), 1.78-1.71 (m, 2H), 1.68-1.57 (m, 2H), 1.42-1.27 (m, 12H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  216.8, 52.6, 45.4, 42.9, 32.8, 32.5, 31.5, 29.8, 29.7, 28.9, 28.7, 27.3, 27.0, 24.9; HREI-MS (m/z):  $[\text{M}]^+$  calcd. for  $\text{C}_{14}\text{H}_{25}\text{OCl}$ , 244.1594; found 244.1618.

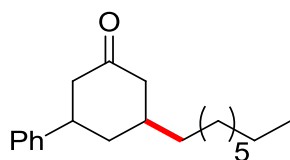


**4-Butyl-12-((*tert*-butyldimethylsilyl)oxy)dodecan-2-one:** A 5 mL microwave vial containing a stir bar was charged with zinc powder (66 mg, 1 mmol), Cu(OAc)<sub>2</sub>•H<sub>2</sub>O (1.5 mg, 3 mol %), AuCl<sub>3</sub> (3.8 mg, 5 mol %), (*E*)-12-((*tert*-butyldimethylsilyl)oxy)dodec-3-en-2-one (78 mg, 0.25 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 75  $\mu$ L, 0.5 mmol). The vial was capped with a rubber septum and placed under an Argon atmosphere, and 0.5 mL of a 2 wt% TPGS-750-M solution in water was added via syringe followed by the addition of 1-iodobutane (42  $\mu$ L, 0.375 mmol). The resulting mixture was stirred vigorously at rt for 6 h. Another 42  $\mu$ L 1-iodobutane was added and the reaction was continued to stir for 18 h. After filtration through a pad of silica gel, the solvent was evaporated *in vacuo*. Flash column chromatography provided 4-butyl-12-((*tert*-butyldimethylsilyl)oxy)dodecan-2-one (79.5 mg, 86% yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  3.59 (t, *J* = 6.8 Hz, 2H), 2.33 (d, *J* = 6.8 Hz, 2H), 2.17 (s, 3H), 1.88 (m, 1H), 1.57-1.47 (m, 2H), 1.27-1.24 (m, 18H), 0.89 (s, 9H), 0.88 (t, *J* = 6.8 Hz, 3H), 0.05 (s, 6H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>)  $\delta$  209.7, 63.5, 49.1, 34.2, 34.1, 33.9, 33.1, 30.6, 30.1, 29.8, 29.6, 29.0, 26.8, 26.2, 26.0, 23.2, 18.6, 14.3, -5.0; HRESI-MS (*m/z*): [M+Na]<sup>+</sup> calcd. for C<sub>22</sub>H<sub>46</sub>O<sub>2</sub>SiNa, 393.3165; found 393.3150.



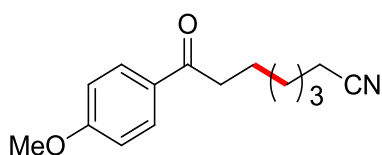
**Ethyl 5-(3-oxo-5-phenylcyclohexyl)pentanoate:** A 5 mL microwave vial containing a stir bar was charged with zinc powder (66 mg, 1 mmol), Cu(OAc)<sub>2</sub>•H<sub>2</sub>O (1.5 mg, 3 mol %), AuCl<sub>3</sub> (3.8 mg, 5 mol %), 5-phenyl-2-cyclohexenone (42 mg, 0.25 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 75  $\mu$ L, 0.5 mmol). The vial was capped with a

rubber septum and placed under an Argon atmosphere, and 0.5 mL of a 2 wt% TPGS-750-M solution in water was added via syringe followed by the addition of ethyl 5-bromopentanoate (59  $\mu$ L, 0.375 mmol). The resulting mixture was stirred vigorously at rt for 6 h. Another 59  $\mu$ L ethyl 5-bromopentanoate was added and the reaction was continued to stir for 18 h. After filtration through a pad of silica gel, the solvent was evaporated *in vacuo* and the crude reaction mixture was analyzed by NMR, GC, and GC/MS. Flash column chromatography provided ethyl 5-(3-oxo-5-phenylcyclohexyl)pentanoate (*trans* : *cis* = 80 : 20, 60.5 mg, 80% yield). *trans*-Product:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.34-7.30 (m, 2H), 7.25-7.20 (m, 3H), 4.11 (q,  $J = 7.2$  Hz, 2H), 3.50-3.29 (m, 1H), 2.63-2.53 (m, 3H), 2.27 (t,  $J = 7.2$  Hz, 2H), 2.22 (dd,  $J = 15, 6$  Hz, 1H), 2.11-2.03 (m, 2H), 1.94-1.90 (m, 1H), 1.63-1.54 (m, 2H), 1.41-1.27 (m, 4H), 1.24 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  211.7, 144.5, 128.7, 127.0, 126.6, 47.6, 46.8, 39.6, 37.4, 34.5, 33.9, 29.3, 22.8, 14.1; HRESI-MS ( $m/z$ ):  $[\text{M}+\text{Na}]^+$  calcd. for  $\text{C}_{19}\text{H}_{26}\text{O}_3\text{Na}$ , 325.1780; found 325.1771.



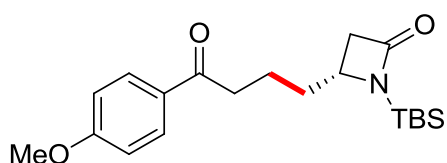
**3-Octyl-5-phenylcyclohexanone:** A 5 mL microwave vial containing a stir bar was charged with zinc powder (66 mg, 1 mmol),  $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$  (1.5 mg, 3 mol %),  $\text{AuCl}_3$  (3.8 mg, 5 mol %), 5-phenyl-2-cyclohexenone (42 mg, 0.25 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 75  $\mu$ L, 0.5 mmol). The vial was capped with a rubber septum and placed under an Argon atmosphere, and 0.5 mL of a 2 wt% TPGS-750-M solution in water was added via syringe followed by the addition of 1-iodooctane (42  $\mu$ L, 0.375 mmol). The resulting mixture was stirred vigorously at rt for 6h. Another 42  $\mu$ L 1-iodooctane was added and the reaction was continued to stir for 18 h. After filtration through a pad of silica gel, the solvent was evaporated *in vacuo* and the crude reaction

mixture was analyzed by NMR, GC, and GC/MS. Flash column chromatography provided 3-octyl-5-phenylcyclohexanone (*trans* : *cis* = 83 : 17, 63.7 mg, 89% yield). The *trans* and *cis* product were isolated by multiple time preparative TLC. *trans*-Product:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.34-7.30 (m, 2H), 7.24-7.20 (m, 3H), 3.33 (m, 1H), 2.61-2.48 (m, 3H), 2.23 (dd,  $J = 14.4, 6$  Hz, 1H), 2.08-2.02 (m, 2H), 2.01-1.91 (m, 1H), 1.30-1.24 (m, 14H), 0.87 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  211.9, 144.6, 128.8, 127.1, 126.7, 47.7, 47.0, 39.7, 37.5, 34.6, 34.3, 32.1, 29.8, 29.7, 29.5, 27.2, 22.9, 14.3; HREI-MS ( $m/z$ ):  $[\text{M}]^+$  calcd. for  $\text{C}_{20}\text{H}_{30}\text{O}$ , 286.2297; found 286.2301. *cis*-Product:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35-7.28 (m, 2H), 7.25-7.21 (m, 3H), 2.95 (tt,  $J = 13.2, 3.6$  Hz 1H), 2.59-2.46 (m, 3H), 2.12-2.05 (m, 3H), 1.89-1.83 (m, 1H), 1.42-1.26 (m, 14H), 0.88 (t,  $J = 7.2$  Hz, 3H); HREI-MS ( $m/z$ ):  $[\text{M}]^+$  calcd.  $\text{C}_{20}\text{H}_{30}\text{O}$ , 286.2297; found 286.2308.

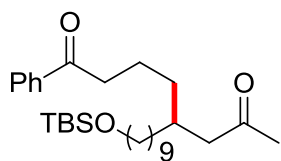


**8-(4-Methoxyphenyl)-8-oxooctanenitrile:** A 5 mL microwave vial containing a stir bar was charged with zinc dust (66 mg, 1 mmol),  $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$  (1.5 mg, 3 mol %),  $\text{AuCl}_3$  (3.8 mg, 5 mol %), 1-(4-methoxyphenyl)prop-2-en-1-one (40 mg, 0.25 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 75  $\mu\text{L}$ , 0.5 mmol). The vial was capped with a rubber septum and placed under an Argon atmosphere, and 0.5 mL of a 2 wt% TPGS-750-M solution in water was added via syringe followed by the addition of 5-bromovaleronitrile (44  $\mu\text{L}$ , 0.375 mmol). The resulting mixture was stirred vigorously at rt for 6 h. Another 44  $\mu\text{L}$  5-bromovaleronitrile was added and the reaction was continued to stir for 18 h. After filtration through a pad of silica gel, the solvent was evaporated *in vacuo*. Flash column chromatography provided 8-(4-methoxyphenyl)-8-oxooctanenitrile (53 mg, 86% yield).  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.94 (d,  $J = 8.4$  Hz, 2H), 6.94 (d,  $J = 8.4$  Hz,

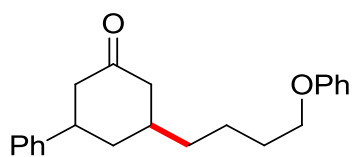
2H), 3.87 (s, 3H), 2.93 (t,  $J = 7.2$  Hz, 2H), 3.35 (t,  $J = 7.2$  Hz, 2H), 1.75 (m, 2H), 1.69 (m, 2H), 1.54-1.49 (m, 2H), 1.43 (m, 2H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  198.9, 163.6, 130.5, 130.3, 120.0, 113.9, 55.7, 38.1, 28.72, 28.66, 25.4, 24.2, 17.3; HRESI-MS ( $m/z$ ):  $[\text{M}+\text{Na}]^+$  calcd. for  $\text{C}_{15}\text{H}_{19}\text{NO}_2\text{Na}$ , 268.1313; found 268.1305.



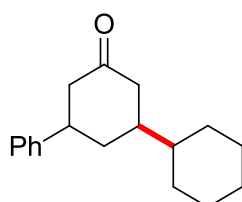
**1-(*tert*-Butyldimethylsilyl)-4-(4-(4-methoxyphenyl)-4-oxobutyl)azetidin-2-one:** A 5 mL microwave vial containing a stir bar was charged with zinc dust (66 mg, 1 mmol),  $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$  (1.5 mg, 3 mol %),  $\text{AuCl}_3$  (3.8 mg, 5 mol %), 1-(4-methoxyphenyl)prop-2-en-1-one (40 mg, 0.25 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 75  $\mu\text{L}$ , 0.5 mmol). The vial was capped with a rubber septum and placed under an Argon atmosphere, and 0.5 mL of a 2 wt% TPGS-750-M solution in water was added via syringe followed by the addition of 1-(*tert*-butyldimethylsilyl)-4-(iodomethyl)azetidin-2-one (122 mg, 0.375 mmol). The resulting mixture was stirred vigorously at rt for 6 h. Another 122 mg 1-(*tert*-butyldimethylsilyl)-4-(iodomethyl)azetidin-2-one was added and the reaction was continued to stir for 18 h. After filtration through a pad of silica gel, the solvent was evaporated *in vacuo*. Flash column chromatography provided 1-(*tert*-butyldimethylsilyl)-4-(4-(4-methoxyphenyl)-4-oxobutyl)azetidin-2-one (50 mg, 87% yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.93 (d,  $J = 8.8$  Hz, 2H), 6.94 (d,  $J = 8.8$  Hz, 2H), 3.83 (s, 3H), 3.57-3.51 (m, 1H), 3.17-3.12 (dd,  $J = 15.2, 5.6$  Hz, 1H), 2.96 (t,  $J = 7.2$  Hz, 2H), 2.67-2.62 (dd,  $J = 15.2, 2.4$  Hz, 1H), 1.98-1.89 (m, 1H), 1.75-1.62 (m, 2H), 1.53-1.42 (m, 1H), 0.95 (s, 9H), 0.23 (s, 3H), 0.21 (s, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  198.2, 172.9, 163.7, 130.5, 130.1, 114.0, 55.7, 49.6, 44.1, 37.9, 36.1, 26.5, 20.6, 18.5, -5.1, -5.5; HRESI-MS ( $m/z$ ):  $[\text{M}+\text{Na}]^+$  calcd. for  $\text{C}_{20}\text{H}_{31}\text{NO}_3\text{SiNa}$ , 384.1971; found 384.1961.



**5-(9-((*tert*-Butyldimethylsilyl)oxy)nonyl)-1-phenyloctane-1,7-dione:** A 5 mL microwave vial containing a stir bar was charged with zinc powder (66 mg, 1 mmol), Cu(OAc)<sub>2</sub>•H<sub>2</sub>O (1.5 mg, 3 mol %), AuCl<sub>3</sub> (3.8 mg, 5 mol %), (*E*)-13-((*tert*-butyldimethylsilyl)oxy)tridec-3-en-2-one (81.6 mg, 0.25 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 75 μL, 0.5 mmol). The vial was capped with a rubber septum and placed under an Argon atmosphere, and 0.5 mL of a 2 wt% TPGS-750-M solution in water was added via syringe followed by the addition of 4-iodo-1-phenylbutan-1-one (102.5 mg, 0.375 mmol). The resulting mixture was stirred vigorously at rt for 6 h. Another 102.5 mg 4-iodo-1-phenylbutan-1-one was added and the reaction was continued to stir for 18 h. After filtration through a pad of silica gel, the solvent was evaporated *in vacuo*. Flash column chromatography provided 5-(9-((*tert*-butyldimethylsilyl)oxy)nonyl)-1-phenyloctane-1,7-dione (98.5 mg, 83% yield). <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.95 (dd, *J* = 7.2, 4.2 Hz, 2H), 7.55 (t, *J* = 7.2 Hz, 1H), 7.46 (t, *J* = 7.2 Hz, 2H), 3.59 (t, *J* = 7.2 Hz, 2H), 2.99-2.94 (m, 2H), 2.38 (d, *J* = 6.6 Hz, 2H), 2.13 (s, 3H), 1.96 (m, 1H), 1.77-1.69 (m, 4H), 1.52-1.44 (m, 4H), 1.39-1.24 (m, 12H), 0.89 (s, 9H), 0.04 (s, 6H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 209.4, 200.5, 137.2, 133.2, 128.8, 128.2, 63.6, 48.7, 38.9, 34.1, 33.9, 33.7, 33.1, 30.7, 30.1, 29.8, 29.7, 29.4, 26.9, 26.2, 26.0, 24.4, 21.4, -5.0; HRESI-MS (*m/z*): [M+Na]<sup>+</sup> calcd. for C<sub>29</sub>H<sub>50</sub>O<sub>3</sub>SiNa, 497.3427; found 497.3405.

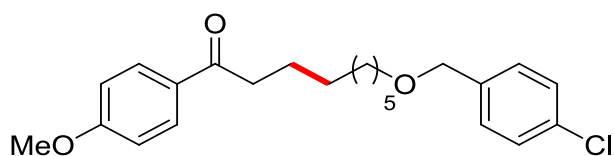


**3-(4-Phenoxybutyl)-5-phenylcyclohexanone:** A 5 mL microwave vial containing a stir bar was charged with zinc dust (33 mg, 0.5 mmol), Cu(OAc)<sub>2</sub>•H<sub>2</sub>O (1.5 mg, 3 mol %), AuCl<sub>3</sub> (3.8 mg, 5 mol %), 5-phenyl-2-cyclohexenone (42 mg, 0.25 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 75 μL, 0.5 mmol). The vial was capped with a rubber septum and placed under an Argon atmosphere, and 0.5 mL of a 2 wt% TPGS-750-M solution in water was added via syringe followed by the addition of 4-bromobutyl phenyl ether (85 mg, 0.375 mmol). The resulting mixture was stirred vigorously at rt for 6 h. Another 85 mg 1-(3-bromopropoxy)benzene and 33 mg zinc dust were added and the reaction was stirred continuously for 18 h. After filtration through a pad of silica gel, the solvent was evaporated *in vacuo* and the crude reaction mixture was analyzed by NMR. Flash column chromatography provided 3-(4-phenoxybutyl)-5-phenylcyclohexanone (70 mg, 87% yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of two isomers: δ 7.28-7.12 (m, 7H), 6.87-6.79 (m, 3H), 3.92-3.84 (m, 2H), 3.28-3.22 (m, 1H), 2.97-2.88 (m, 1H), 2.58-2.30 (m, 3H), 2.17 (dd, *J* = 17.5, 7.5 Hz, 1H), 2.11-1.96 (m, 2H), 1.90-1.62 (m, 2H), 1.48-1.30 (m, 4H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) of two isomers: δ 211.7, 159.2, 144.5, 144.4, 129.6, 128.9, 128.88, 128.81, 127.1, 126.9, 126.88, 126.76, 126.74, 120.8, 114.6, 67.7, 49.1, 48.9, 47.8, 47.6, 46.9, 44.9, 44.0, 41.4, 39.9, 39.7, 38.4, 37.4, 36.9, 34.5, 34.1, 33.0, 29.5, 29.4, 25.7, 23.8, 23.4; HREI-MS (*m/z*): [M]<sup>+</sup> calcd. for C<sub>22</sub>H<sub>26</sub>O<sub>2</sub>, 322.1933; found 322.1939.



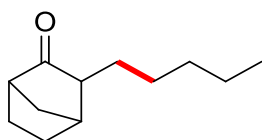
**3-Cyclohexyl-5-phenylcyclohexanone:** A 5 mL microwave vial (oven-dried and under Ar) containing a Teflon<sup>®</sup> stir bar was charged with zinc dust (33 mg, 0.5 mmol), Cu(OAc)<sub>2</sub>•H<sub>2</sub>O (1.5 mg, 3 mol %), AuCl<sub>3</sub> (3.8 mg, 5 mol %), 5-phenyl-2-cyclohexenone (42 mg, 0.25 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 75 μL, 0.5 mmol). The vial

was capped with a rubber septum and placed under an Argon atmosphere, and 0.5 mL of a 2 wt% TPGS-750-M solution in water was added via syringe followed by the addition of bromocyclohexane (46  $\mu$ L, 0.375 mmol). The resulting mixture was stirred vigorously at rt for 6 h. Another 46  $\mu$ L bromocyclohexane and 33 mg zinc dust were added and the reaction was stirred continuously for 18 h. After filtration through a pad of silica gel, the solvent was evaporated *in vacuo* and the crude reaction mixture was analyzed by NMR. Flash column chromatography provided 3-cyclohexyl-5-phenylcyclohexanone (*trans* : *cis* = 85 : 15, 54 mg, 85% yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) of major isomer:  $\delta$  7.24-7.19 (m, 2H), 7.16-7.12 (m, 3H), 3.32-3.26 (m, 1H), 2.62-2.50 (m, 2H), 2.41-2.28 (m, 2H), 2.07-1.89 (m, 2H), 1.73-1.64 (m, 4H), 1.58-1.52 (m, 2H), 1.18-1.00 (m, 4H), 0.86-0.74 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) of major isomer:  $\delta$  212.5, 144.6, 128.8, 127.2, 126.6, 47.0, 44.7, 40.2, 39.7, 39.4, 35.2, 30.5, 30.3, 26.63, 26.60, 26.5; HREI-MS (*m/z*):  $[\text{M}]^+$  calcd. for  $\text{C}_{18}\text{H}_{24}\text{O}$ , 256.1827; found 256.1828.



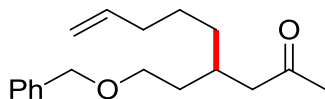
**9-(4-Chlorobenzoyloxy)-1-(4-methoxyphenyl)nonan-1-one:** A 5 mL microwave vial containing a stir bar was charged with zinc powder (33 mg, 0.5 mmol),  $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$  (1.5 mg, 3 mol %),  $\text{AuCl}_3$  (3.8 mg, 5 mol %), 1-(4-methoxyphenyl)prop-2-en-1-one (41 mg, 0.25 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 75  $\mu$ L, 0.5 mmol). The vial was capped with a rubber septum and placed under an Argon atmosphere, and 0.5 mL of a 2 wt% TPGS-750-M solution in water was added via syringe followed by the addition of 1-chloro-4-(6-iodohexyloxymethyl)-benzene (132 mg, 0.375 mmol). The resulting mixture was stirred vigorously at rt for 6 h. Another 132 mg 1-((6-iodohexyloxy)methyl)-4-chlorobenzene and 33 mg zinc powder were added and the reaction was stirred

continuously for 18 h. After filtration through a pad of silica gel, the solvent was evaporated *in vacuo* and the crude reaction mixture was analyzed by NMR. Flash column chromatography provided 9-(4-chlorobenzyloxy)-1-(4-methoxyphenyl)nonan-1-one (78 mg, 80% yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.94 (d, J = 8.9 Hz, 2H), 7.35-7.20 (m, 4H), 6.93 (d, J = 8.9 Hz, 2H), 4.45 (s, 2H), 3.86 (s, 3H), 3.45 (t, J = 6.6 Hz, 2H), 2.90 (t, J = 7.5 Hz, 2H), 1.77- 1.61 (m, 2H), 1.68-1.47 (m, 4H), 1.44-1.16 (m, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 199.4, 163.5, 137.5, 133.4, 130.5, 130.4, 130.4, 129.1, 128.7, 113.9, 72.3, 70.8, 55.7, 38.5, 29.9, 29.6, 29.6, 29.5, 26.3, 24.8; HREI-MS (m/z): [M]<sup>+</sup> calcd. for C<sub>23</sub>H<sub>29</sub>ClO<sub>3</sub>, 388.1805; found 388.1812.

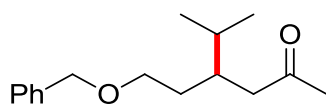


**3-Pentylbicyclo[2.2.1]heptan-2-one:** A 5 mL microwave vial containing a stir bar was charged with zinc powder (66 mg, 1.0 mmol), Cu(OAc)<sub>2</sub>•H<sub>2</sub>O (3.0 mg, 3 mol %), AuCl<sub>3</sub> (7.6 mg, 5 mol %), 3-methylenebicyclo[2.2.1]heptan-2-one (59 μL, 0.50 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 150 μL, 1.0 mmol). The vial was capped with a rubber septum and placed under an Argon atmosphere, and 1.0 mL of a 2 wt% TPGS-750-M solution in water was added via syringe followed by the addition of 1-iodobutane (84 μL, 0.75 mmol). The resulting mixture was stirred vigorously at rt for 6 h. Another 84 μL 1-iodobutane and 66 mg zinc powder were added and the reaction was stirred continuously for 18 h. After filtration through a pad of silica gel, the solvent was evaporated *in vacuo* and the crude reaction mixture was analyzed by NMR. Flash column chromatography provided 3-pentylbicyclo[2.2.1]heptan-2-one (78 mg, 86% yield). The *endo* isomer was exclusively observed by comparison of the <sup>1</sup>H-NMR spectrum to an analogous reaction with 3-alkylsubstituted-2-norbornanones previously reported.<sup>9</sup> <sup>1</sup>H NMR

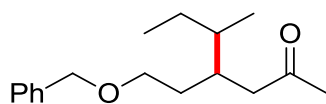
(400 MHz, CDCl<sub>3</sub>) of two isomers:  $\delta$  2.53 (t,  $J$ = 4.5 Hz, 2H), 1.95-1.91 (m, 1H), 1.79-1.72 (m, 1H), 1.66-1.60 (m, 2H), 1.55-1.49 (m, 4H), 1.39-1.07 (m, 7H), 0.88-0.78 (m, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) of two isomers:  $\delta$  220.2, 53.69, 53.67, 50.64, 50.61, 38.28, 38.26, 37.1, 31.8, 27.8, 26.3, 25.4, 22.6, 21.2, 14.1; HREI-MS (m/z): [M]<sup>+</sup> calcd. for C<sub>12</sub>H<sub>20</sub>O, 180.1514; found 180.1504.



**4-(2-(benzyloxy)ethyl)non-8-en-2-one:** A 10 mL round bottom flask containing a stir bar was charged with zinc dust (66 mg, 1.0 mmol), Cu(OAc)<sub>2</sub>•H<sub>2</sub>O (5.0 mg, 5 mol %), AuCl<sub>3</sub> (7.6 mg, 5 mol %), (*E*)-6-(benzyloxy)hex-3-en-2-one (102 mg, 0.5 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 0.15 mL, 1.0 mmol). The vial was capped with a rubber septum and placed under an Argon atmosphere, and 1.0 mL of a 2 wt% TPGS-750-M solution in water was added via syringe followed by the addition of 5-bromopent-1-ene (89  $\mu$ L, 0.75 mmol). The resulting mixture was stirred vigorously at rt for 6 h. Another 89  $\mu$ L 5-bromopent-1-ene and 66 mg zinc dust were added and the reaction was stirred continuously for 18 h. After filtration through a pad of silica gel, the solvent was evaporated *in vacuo* and the crude reaction mixture was analyzed by NMR. Flash column chromatography provided 4-(2-(benzyloxy)ethyl)non-8-en-2-one (225 mg, 82% yield). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  7.29-7.19 (m, 4H), 5.75-5.67 (m, 1H), 4.93-4.86 (m, 2H), 4.39 (s, 2H), 3.41-3.31 (m, 2H), 2.38-2.26 (m, 2H), 2.05- 2.00 (m, 3H), 1.97- 1.93 (m, 2H), 1.63- 1.55 (m, 1H), 1.49- 1.44 (m, 1H), 1.33-1.19 (m, 5H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  209.0, 138.9, 138.7, 128.5, 127.8, 127.7, 114.7, 73.1, 68.6, 48.9, 34.1, 34.0, 33.98, 31.4, 30.5, 26.1; HRESI-MS (m/z): [M+Na]<sup>+</sup> calcd. for C<sub>18</sub>H<sub>26</sub>O<sub>2</sub>Na, 297.1830; found 297.1816.

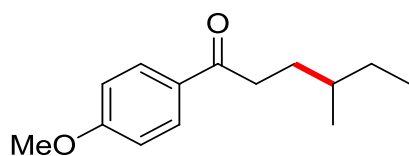


**6-(Benzyloxy)-4-isopropylhexan-2-one:** A 5 mL microwave vial containing a stir bar was charged with zinc powder (33 mg, 0.5 mmol), Cu(OAc)<sub>2</sub>•H<sub>2</sub>O (2.5 mg, 5 mol %), AuCl<sub>3</sub> (3.8 mg, 5 mol %), (*E*)-6-(benzyloxy)hex-3-en-2-one (51 mg, 0.25 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 75 μL, 0.5 mmol). The vial was capped with a rubber septum and placed under an Argon atmosphere, and 0.5 mL of a 2 wt% TPGS-750-M solution in water was added via syringe followed by the addition of 2-iodopropane (38 μL, 0.375 mmol). The resulting mixture was stirred vigorously at rt for 6 h. Another 38 μL 2-iodopropane and 33 mg zinc powder were added and the reaction was stirred continuously for 18 h. After filtration through a pad of silica gel, the solvent was evaporated *in vacuo* and the crude reaction mixture was analyzed by NMR. Flash column chromatography provided 6-(benzyloxy)-4-isopropylhexan-2-one (56 mg, 90% yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.29-7.20 (m, 5H), 4.30 (s, 2H), 3.44-3.36 (m, 2H), 2.29 (ddd, *J* = 22.5, 17.0, 6.0 Hz, 2H), 2.03 (s, 2H), 1.99-1.93 (m, 2H), 1.65-1.57 (m, 2H), 1.43-1.36 (m, 1H), 0.94-0.78 (m, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 209.3, 138.7, 128.5, 127.8, 127.7, 73.1, 69.3, 45.9, 36.8, 31.5, 30.6, 30.4, 19.3, 18.9; HREI-MS (*m/z*): [M]<sup>+</sup> calcd. for C<sub>16</sub>H<sub>24</sub>O<sub>2</sub>, 248.1776; found 248.1778.



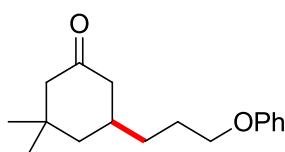
**4-(2-(Benzyloxy)ethyl)-5-methylheptan-2-one:** A 10 mL round bottom flask containing a stir bar was charged with zinc powder (66 mg, 1.0 mmol), Cu(OAc)<sub>2</sub>•H<sub>2</sub>O (5.0 mg, 5 mol %), AuCl<sub>3</sub> (7.6 mg, 5 mol %), (*E*)-6-(benzyloxy)hex-3-en-2-one (102 mg, 0.5 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 0.15 mL, 1.0 mmol). The vial was capped with a rubber septum and placed under an Argon atmosphere, and 1.0 mL of a 2

wt% TPGS-750-M solution in water was added via syringe followed by the addition of 2-iodobutane (86  $\mu\text{L}$ , 0.75 mmol). The resulting mixture was stirred vigorously at rt for 6 h. Another 86  $\mu\text{L}$  2-iodobutane and 66 mg zinc powder were added and the reaction was stirred continuously for 18 h. After filtration through a pad of silica gel, the solvent was evaporated *in vacuo* and the crude reaction mixture was analyzed by NMR. Flash column chromatography provided 4-(2-(benzyloxy)ethyl)-5-methylheptan-2-one (121 mg, 85% yield).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) of both isomers:  $\delta$  7.36-7.26 (m, 4H), 4.46 (s, 2H), 3.50-3.42 (m, 2H), 2.36 (dd,  $J = 13.5, 7.0$  Hz, 2H), 2.27 (dd,  $J = 16.5, 8.5$  Hz, 1H), 2.17-2.11 (m, 3H), 1.71-1.59 (m, 1H), 1.55-1.43 (m, 1H), 1.41-1.24 (m, 3H), 1.16-1.06 (m, 1H), 0.88 (t,  $J = 7.5$  Hz, 3H), 0.81 (q,  $J = 3.5$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) of both isomers:  $\delta$  209.3, 209.28, 138.7, 128.6, 128.5, 127.9, 127.72, 127.7, 73.1, 73.07, 69.4, 69.2, 46.9, 45.2, 37.8, 37.5, 35.5, 35.3, 32.5, 30.5, 30.4, 27.0, 26.6, 15.3, 15.1, 12.5, 12.4; HRESI-MS ( $m/z$ ):  $[\text{M}+\text{Na}]^+$  calcd. for  $\text{C}_{17}\text{H}_{26}\text{O}_2\text{Na}$ , 285.1831; found 285.1813.



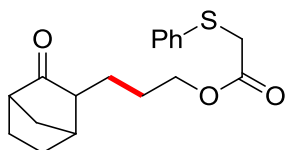
**1-(4-Methoxyphenyl)-4-methylhexan-1-one:** A 5 mL microwave vial containing a stir bar was charged with zinc powder (33 mg, 0.5 mmol),  $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$  (2.5 mg, 5 mol %),  $\text{AuCl}_3$  (3.8 mg, 5 mol %), 1-(4-methoxyphenyl)prop-2-en-1-one (41 mg, 0.25 mmol), and *N,N,N',N'*-tetraethylethylenediamine (TEEDA, 110  $\mu\text{L}$ , 0.5 mmol). The vial was capped with a rubber septum and placed under an Argon atmosphere, and 0.5 mL of a 2 wt% TPGS-750-M solution in water was added via syringe followed by the addition of 2-iodobutane (43  $\mu\text{L}$ , 0.375 mmol). The resulting mixture was stirred vigorously at rt for 6 h. Another 43  $\mu\text{L}$  2-iodobutane and 33 mg zinc powder were added and the reaction was stirred continuously for 18 h. After filtration through a pad of silica gel, the solvent was evaporated

*in vacuo* and the crude reaction mixture was analyzed by NMR. Flash column chromatography provided 1-(4-methoxyphenyl)-4-methylhexan-1-one (46 mg, 83% yield).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.95 (d,  $J = 9.0$  Hz, 2H), 6.93 (d,  $J = 8.9$  Hz, 2H), 3.87 (s, 3H), 2.97-2.85 (m, 2H), 1.79-1.72 (m, 1H), 1.58- 1.49 (m, 1H), 1.46-1.36 (m, 2H), 1.25-1.16 (m, 1H), 0.95- 0.87 (m, 6H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  199.7, 163.5, 130.5, 130.4, 113.9, 55.7, 36.3, 34.5, 31.5, 29.5, 19.3, 11.6; HRESI-MS ( $m/z$ ):  $[\text{M}+\text{Na}]^+$  calcd. for  $\text{C}_{14}\text{H}_{20}\text{O}_2\text{Na}$ , 243.1361; found 243.1351.



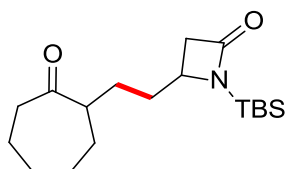
**3,3-Dimethyl-5-(3-phenoxypropyl)cyclohexanone:** A 10 mL round bottom flask containing a stir bar was charged with zinc dust (66 mg, 1 mmol),  $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$  (3.0 mg, 3 mol %),  $\text{AuCl}_3$  (7.6 mg, 5 mol %), 5,5-dimethylcyclohex-2-enone (62 mg, 0.5 mmol), and  $N,N,N',N'$ -tetramethylethylenediamine (TMEDA, 0.15 mL, 1.0 mmol). The vial was capped with a rubber septum and placed under an Argon atmosphere, and a 1.0 mL 2 wt% TPGS-750-M solution in water was added via syringe followed by the addition (3-bromopropoxy)benzene (0.16g, 0.75 mmol). The resulting mixture was stirred vigorously at rt for 6h. Another 0.16g (3-bromopropoxy)benzene and 66 mg of zinc dust were added and the reaction was continued to stir for 18 h. After filtration through a pad of silica gel, the solvent was evaporated *in vacuo*. Flash column chromatography provided 3,3-dimethyl-5-(3-phenoxypropyl)cyclohexanone (105 mg, 81% yield).  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.29-7.26 (m, 2H), 6.94 (t,  $J = 6$  Hz, 1H), 6.88 (d,  $J = 7.2$  Hz, 2H), 3.95 (t,  $J = 6$  Hz, 2H), 2.42 (d,  $J = 12$  Hz, 1H), 2.20 (d,  $J = 13.2$  Hz, 1H), 2.09 (d,  $J = 13.2$  Hz, 1H), 1.97-1.90 (m, 2H), 1.83-1.78 (m, 2H), 1.67 (d,  $J = 13.2$  Hz, 1H), 1.56-1.47 (m, 2H), 1.33 (t,  $J = 13.2$  Hz, 1H), 1.07 (s, 3H), 0.89 (s, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  212.0, 159.1, 129.7, 120.9,

114.7, 67.9, 54.8, 47.6, 45.5, 35.5, 34.7, 34.0, 32.4, 26.8, 26.0; HREI-MS (m/z): [M]<sup>+</sup> calcd. for C<sub>17</sub>H<sub>24</sub>O<sub>2</sub>, 260.1776; found 260.1870.

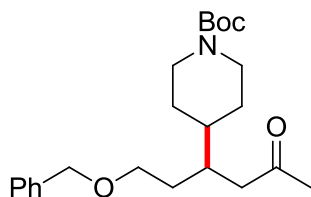


**3-(3-oxobicyclo[2.2.1]heptan-2-yl)propyl 2-(phenylthio)acetate:** A 5 mL microwave vial (oven-dried and under Ar) containing a Teflon<sup>®</sup> stir bar was charged with zinc powder (66 mg, 1 mmol), Cu(OAc)<sub>2</sub>•H<sub>2</sub>O (1.5 mg, 3 mol %), AuCl<sub>3</sub> (3.8 mg, 5 mol %), 3-methylenebicyclo[2.2.1]heptan-2-one (31 μL, 0.25 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 75 μL, 0.5 mmol). The vial was capped with a rubber septum and placed under an Argon atmosphere, and 0.5 mL of a 2 wt% TPGS-750-M solution in water was added via syringe followed by the addition of 2-iodoethyl 2-(phenylthio)acetate (120 mg, 0.375 mmol). The resulting mixture was stirred vigorously at rt for 6 h. Another 120 mg of 2-iodoethyl 2-(phenylthio)acetate was added and the reaction was continued to stir for 18 h. After filtration through a pad of silica gel using EtOAc as the mobile phase, the solvent was evaporated *in vacuo* and the crude reaction mixture was analyzed by NMR, GC, and GC/MS. Flash column chromatography (EtOAc/hexanes) provided 3-(3-oxobicyclo[2.2.1]heptan-2-yl)propyl 2-(phenylthio)acetate (62 mg, 75% yield). The *endo* isomer was exclusively observed by comparison of the <sup>1</sup>H-NMR spectrum to an analogous reaction with 3-alkylsubstituted-2-norbornanones previously reported.<sup>9</sup> Note: Most, but not all coupling constants were identified due to overlap/resolution issues. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.40 (d, *J* = 7.2 Hz, 2H), 7.30 (m, *J* = 7.2 Hz, 2H) 7.22 (m, *J* = 7.2 Hz, 1H), 4.11 (m, *J* = 6.6 Hz, 2H), 3.64 (s, 2H), 2.60 (br d, *J* = 4.8 Hz, 1H), 2.56 (s br, 1H), 1.98-1.95 (m, *J* = 4.8 and 10.2 Hz, 1H), 1.84-1.78 (m, *J* = 4.8 and 12.6 Hz, 1H), 1.73-1.65 (m, 4H), 1.64-1.50 (m, 3H), 1.40-1.36 (m, 1H), 1.26-1.17 (m, *J* = 6.0 and 10.2

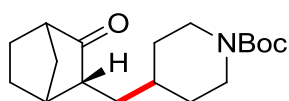
Hz, 1H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  219.5, 169.8, 135.1, 130.0, 129.2, 127.1, 65.4, 53.1, 50.6, 38.4, 37.1, 36.7, 27.2, 25.5, 23.0, 21.2; HRESI-MS  $m/z$ :  $[\text{M}]^+$  calcd. for  $\text{C}_{18}\text{H}_{22}\text{O}_3\text{SNa}$ , 341.1187;  $[\text{M}+\text{Na}]^+$  found 341.1194.



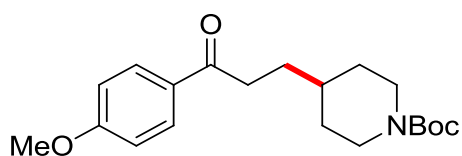
**1-(tert-butyldimethylsilyl)-4-(2-(2-oxocycloheptyl)ethyl)azetidin-2-one:** A 5 mL microwave vial containing a stir bar was charged with zinc dust (66 mg, 1.0 mmol),  $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$  (5.0 mg, 5 mol %),  $\text{AuCl}_3$  (7.6 mg, 5 mol %), 3-methylenebicyclo[2.2.1]heptan-2-one (31  $\mu\text{L}$ , 0.25 mmol), and  $N,N,N',N'$ -tetramethylethylenediamine (TMEDA, 75  $\mu\text{L}$ , 0.5 mmol). The vial was capped with a rubber septum and placed under an Argon atmosphere, and 0.5 mL of a 2 wt% TPGS-750-M solution in water was added via syringe followed by the addition of The resulting mixture was stirred vigorously at rt for 6 h. Another 244 mg of 1-(tert-butyldimethylsilyl)-4-(iodomethyl)azetidin-2-one and 66 mg zinc dust were added and the reaction was stirred continuously for 18 h. After filtration through a pad of silica gel, the solvent was evaporated *in vacuo* and the crude reaction mixture was analyzed by NMR. Flash column chromatography provided 1-(tert-butyldimethylsilyl)-4-(2-(2-oxocycloheptyl)ethyl)azetidin-2-one (134mg, 83% yield).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) of both isomers:  $\delta$  3.46-3.44 (m, 1H), 3.09 (dd,  $J = 15, 5.5$  Hz, 1H), 2.57 (t,  $J = 16.5$  Hz, 1H), 2.49- 2.43 (m, 3H), 1.88- 1.76 (m, 5H), 1.63- 1.56 (m, 2H), 1.42- 1.19 (m, 5H), 0.92 (s, 9H), 0.19 (d,  $J = 8$  Hz, 6H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) of both isomers:  $\delta$  215.7, 215.6, 172.8, 51.9, 51.7, 50.1, 49.5, 49.47, 46.5, 44.0, 43.9, 43.94, 43.2, 43.1, 34.1, 33.8, 31.9, 31.6, 29.5, 28.8, 28.3, 28.2, 26.4, 26.35, 24.5, 24.45, 18.6, 18.5, 9.9, -5.14, -5.15, -5.5; HRESI-MS ( $m/z$ ):  $[\text{M}+\text{Na}]^+$  calcd. for  $\text{C}_{18}\text{H}_{33}\text{NO}_2\text{SiNa}$ , 346.2178; found 346.2179.



**tert-butyl 4-(1-(benzyloxy)-5-oxohexan-3-yl)piperidine-1-carboxylate:** A 10 mL round bottom flask containing a stir bar was charged with zinc powder (66 mg, 1.0 mmol), Cu(OAc)<sub>2</sub>•H<sub>2</sub>O (5.0 mg, 5 mol %), AuCl<sub>3</sub> (7.6 mg, 5 mol %), (*E*)-6-(benzyloxy)hex-3-en-2-one (233 mg, 0.5 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 150  $\mu$ L, 1.0 mmol). The vial was capped with a rubber septum and placed under an Argon atmosphere, and 1.0 mL of a 2 wt% TPGS-750-M solution in water was added via syringe followed by the addition of 1tert-butyl 4-iodopiperidine-1-carboxylate (233 mg, 0.75 mmol). The resulting mixture was stirred vigorously at rt for 6 h. Another 244 mg of tert-butyl 4-iodopiperidine-1-carboxylate and 66 mg zinc powder were added and the reaction was stirred continuously for 18 h. After filtration through a pad of silica gel using EtOAc as the mobile phase, the solvent was evaporated *in vacuo* and the crude reaction mixture was analyzed by NMR. Flash column chromatography provided tert-butyl 4-(1-(benzyloxy)-5-oxohexan-3-yl)piperidine-1-carboxylate (171 mg, 88% yield). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  7.28-7.19 (m, 5H), 4.38 (s, 2H), 4.06-4.02 (m, 2H), 3.41-3.37 (m, 2H), 2.52-2.47 (m, 2H), 2.36-2.27 (m, 2H), 2.03-1.97 (m, 4H), 1.77-1.50 (m, 1H), 1.47-1.34 (m, 13H), 1.13-1.05 (m, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  208.6, 154.9, 138.5, 128.5, 127.8, 127.7, 79.4, 73.0, 68.9, 45.8, 39.6, 35.6, 31.5, 30.4, 28.6; HRFI-MS (*m/z*): [M]<sup>+</sup> calcd. for C<sub>23</sub>H<sub>35</sub>NO<sub>4</sub>, 389.2566; found 389.2598.



***tert*-butyl 4-((3-oxobicyclo[2.2.1]heptan-2-yl)methyl)piperidine-1-carboxylate:** A 5 mL microwave vial (oven-dried and under Ar) containing a Teflon<sup>®</sup> stir bar was charged with zinc dust (65 mg, 1.0 mmol), Cu(OAc)<sub>2</sub>•H<sub>2</sub>O (1.5 mg, 3 mol %), AuCl<sub>3</sub> (3.8 mg, 5 mol %), 3-methylenebicyclo[2.2.1]heptan-2-one (31 μL, 0.25 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 75 μL, 0.5 mmol). The vial was capped with a rubber septum and placed under an Argon atmosphere, and 0.5 mL of a 2 wt% TPGS-750-M solution in water was added via syringe followed by the addition of *tert*-butyl 4-iodopiperidine-1-carboxylate (117 mg, 0.375 mmol). The resulting mixture was stirred vigorously at rt for 6 h. Another 117 mg of *tert*-butyl 4-iodopiperidine-1-carboxylate and the reaction was stirred continuously for 18 h. After filtration through a pad of silica gel using EtOAc as the mobile phase, the solvent was evaporated *in vacuo* and the crude reaction mixture was analyzed by NMR. Flash column chromatography (EtOAc/hexanes) provided the desired product as a colorless oil (65 mg, 85% yield). The *endo* isomer was exclusively observed by comparison of the <sup>1</sup>H-NMR spectrum to an analogous reaction with 3-alkylsubstituted-2-norbornanones previously reported.<sup>9</sup> Most, but not all coupling constants were identified due to overlap/resolution issues. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 4.08 (s br, 2H), 2.69 (m br, 2H), 2.62 (d br, *J* = 4.8 Hz, 1H), 2.59 (s br, 1H), 2.09 (m, *J* = 4.2, 4.8 Hz, 1H), 1.83 (sept, *J* = 5.4 Hz, 1H), 1.70-1.47 (m, 7H), 1.46 (s, 9H), 1.42-1.35 (m, 1H), 1.26 (br m, 1H), 1.22-1.04 (m, 3H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 220.6, 155.2, 79.5, 51.1, 50.6, 38.9, 37.3, 34.5, 33.1, 29.9, 28.6, 28.3, 25.5, 21.5; HRESI-MS (*m/z*): [M+Na]<sup>+</sup> calcd. for C<sub>18</sub>H<sub>29</sub>NO<sub>3</sub>Na, 330.2045; found 330.2037.



***tert*-butyl 4-(3-(4-methoxyphenyl)-3-oxopropyl)piperidine-1-carboxylate:** A 5 mL microwave vial (oven-dried and under Ar) containing a Teflon<sup>®</sup> stir bar was charged with

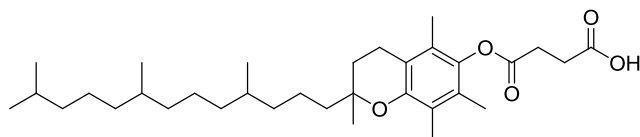
zinc dust (65 mg, 1.0 mmol), Cu(OAc)<sub>2</sub>•H<sub>2</sub>O (1.5 mg, 3 mol %), AuCl<sub>3</sub> (3.8 mg, 5 mol %), 1-(4-methoxyphenyl)prop-2-en-1-one (41 mg, 0.25 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 75 μL, 0.5 mmol). The vial was capped with a rubber septum and placed under an Argon atmosphere, and 0.5 mL of a 2 wt% TPGS-750-M solution in water was added via syringe followed by the addition of *tert*-butyl 4-iodopiperidine-1-carboxylate (117 mg, 0.375 mmol). The resulting mixture was stirred vigorously at rt for 6 h. Another 117 mg of *tert*-butyl 4-iodopiperidine-1-carboxylate and the reaction was stirred continuously for 18 h. After filtration through a pad of silica gel using EtOAc as the mobile phase, the solvent was evaporated *in vacuo* and the crude reaction mixture was analyzed by NMR. Flash column chromatography (EtOAc/hexanes) provided the desired product as a white solid (77 mg, 89% yield). <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 7.94 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 11.4 Hz, 2H), 4.10 (s br, 2H), 3.87 (s, 3H), 2.95 (t, *J* = 7.2 Hz, 2H), 2.68 (s br, 2H), 1.82 (m, 1H), 1.69 (m, 3H), 1.54-1.48 (m, 2H), 1.56 (s, 9H), 1.26-1.11 (m, 3H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 199.0, 163.6, 155.0, 130.5, 130.2, 113.9, 79.4, 55.6, 35.8, 35.4, 31.1, 28.6; HRESI-MS (*m/z*): [M+Na]<sup>+</sup> calcd. for C<sub>20</sub>H<sub>29</sub>NO<sub>4</sub>Na, 370.1994; found 370.1981.

#### 2.4.3 Procedure for recycling reaction media for 1,4-Addition reactions:

A 5 mL round-bottom flask (oven-dried and under Ar) containing a Teflon<sup>®</sup> stir bar was charged with zinc dust (135 mg, 2 mmol), Cu(OAc)<sub>2</sub>•H<sub>2</sub>O (6.0 mg, 6 mol %), AuCl<sub>3</sub> (7.6 mg, 5 mol %), 5-phenyl-2-cyclohexenone (86 mg, 0.50 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 150 μL, 1.0 mmol). The vial was capped with a rubber septum and placed under an Argon atmosphere, and 1.0 mL of a 2 wt% TPGS-750-M solution in water was added via syringe followed by the addition of bromocyclohexane (92 μL, 0.75 mmol). The resulting mixture was stirred vigorously at rt for 6h. Another 92 μL bromocyclohexane was added and the reaction was stirred continuously for 18 h. Next the stir plate was turned off. The product was extracted using hexanes (3 x 2 mL). To ensure

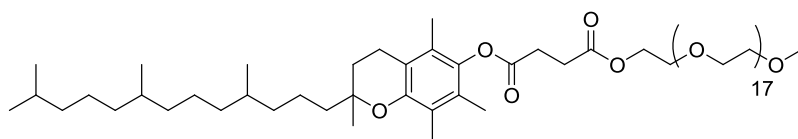
that the phases were mixing vigorous stirring was done after each addition of hexanes and stopped before removing the top hexane layer via syringe. The extracts were combined and filtrated through a pad of silica gel using EtOAc as the mobile phase, the solvent was evaporated *in vacuo* and the crude reaction mixture was analyzed by GC-MS to determine conversion. A small aliquot was removed using a pipette from the reaction mixture after the final extraction to ensure the product and any starting materials were completely removed. The small aliquot taken was filtrated through a pad of silica gel using EtOAc as the mobile phase and analyzed by TLC and GC-MS. Next the round-bottom was purged with a high flow of Ar with a vent needle for 15 minutes to ensure all removal of hexanes from the reaction media. Next the solution in the round-bottom flask was charged zinc dust (135 mg, 2 mmol), 5-phenyl-2-cyclohexenone (86 mg, 0.50 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 150  $\mu$ L, 1.0 mmol). The septum was replaced with a new one and then the solution was stirred for several minutes. Next, via syringe bromocyclohexane (92  $\mu$ L, 0.75 mmol) was added. The resulting mixture was stirred vigorously at rt for 6h. Another 92  $\mu$ L bromocyclohexane was added and the reaction was stirred continuously for 18 h. Repeat the aforementioned procedure for the extraction.

#### 2.4.4 Procedure for synthesis of TPGS-750-M:



**DL - $\alpha$ -Tocopherol Succinate, <10 g Scale:** To a solution of DL- $\alpha$ -tocopherol (4.30 g, 10.00 mmol) and succinic anhydride (1.50 g, 15.00 mmol) in toluene (20 mL) was added Et<sub>3</sub>N (0.35 mL, 2.50 mmol) at rt with stirring, and the stirring was continued at 60°C for 5 h. Water was added to the reaction mixture, which was then extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with 1 N HCl (3 x 50 mL) and water (2 x 30 mL),

dried over anhydrous  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo* affording a yellow liquid, which was purified by flash column chromatography on silica gel eluting with a 10% EtOAc/hexane to 35% EtOAc/hexanes gradient to afford DL- $\alpha$ -tocopherol succinate (5.25 g, 99%) as a white solid, mp 68 – 71 °C, lit. 22 mp 64 - 67 °C. IR (neat) 2926, 1757, 1714, 1576, 1463, 1455, 1415, 1377, 1251, 1224, 1151, 1110, 1078, 926  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.94 (t,  $J = 6.8$  Hz, 2H), 2.84 (t,  $J = 6.8$  Hz, 2H), 2.59 (t,  $J = 6.8$  Hz, 2H), 2.09 (s, 3H), 2.02 (s, 3H), 1.98 (s, 3H), 1.85 - 1.71 (m, 2H), 1.56 - 1.50 (m, 3H), 1.43 - 1.05 (m, 21H), 0.88 - 0.84 (m, 12H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  178.6, 171.0, 149.7, 140.7, 126.9, 125.1, 123.2, 117.6, 75.2, 39.6, 37.8, 37.7, 37.6, 37.5, 33.0, 32.9, 31.3, 29.2, 28.8, 28.2, 25.0, 24.6, 24.0, 22.9, 22.8, 21.2, 20.8, 19.95, 19.88, 13.0, 12.2, 12.0; MS (ESI)  $m/z$  554 (M+Na); HRMS (ESI) calcd for  $\text{C}_{33}\text{H}_{54}\text{O}_5\text{Na}$  [M + Na] $^+$  553.3869, found 553.3876.



**TPGS-750-M:** A mixture containing DL- $\alpha$ -tocopherol succinate (2.97 g, 5.60 mmol), poly(ethylene glycol) monomethylether-750 (4.00 g, 5.33 mmol) and p-TsOH (0.15 g, 0.79 mmol) in toluene (20 mL) was refluxed for 5 h using a Dean - Stark trap. After cooling to rt, the mixture was poured into saturated aqueous  $\text{NaHCO}_3$  solution and extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic layers were washed with saturated  $\text{NaHCO}_3$  (3 x 50 mL), brine (2 x 30 mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo* to afford the title compound (6.60 g, 98%) as a waxy solid. IR (neat) 2888, 1755, 1739, 1465, 1414, 1346, 1281, 1245, 1202, 1109, 947, 845  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.28 - 4.26 (m, 2H), 3.71 - 3.54 (m, PEG), 3.38 (s, 3H), 2.93 (t,  $J = 7.2$  Hz, 2H), 2.79 (t,  $J = 7.2$  Hz, 2H), 2.58 (t,  $J = 6.8$  Hz, 2H), 2.08 (s, 3H), 2.01 (s, 3H), 1.97 (s, 3H), 1.84 - 1.70 (m, 2H), 1.55 - 1.04 (m, 24H), 0.87 - 0.83 (m, 12H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  172.2, 170.9,

149.5, 140.6, 126.7, 125.0, 123.0, 117.4, 94.5, 75.1, 72.0, 70.64, 70.56, 69.1, 64.0, 59.0,  
39.4, 37.6, 37.5, 37.4, 37.3, 32.8, 32.7, 31.1, 29.2, 28.9, 28.0, 24.8, 24.5, 22.8, 22.7, 21.1,  
20.6, 19.8, 19.7, 13.0, 12.1, 11.8; MS (ESI) m/z 1272 (M + Na).

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## CHAPTER 3:

Organocatalyzed Reactions in Aqueous Media:

*N*-Heterocyclic Carbene Catalyzed reactions

involving Enals in Water

### 3.1 NHC-catalyzed reactions

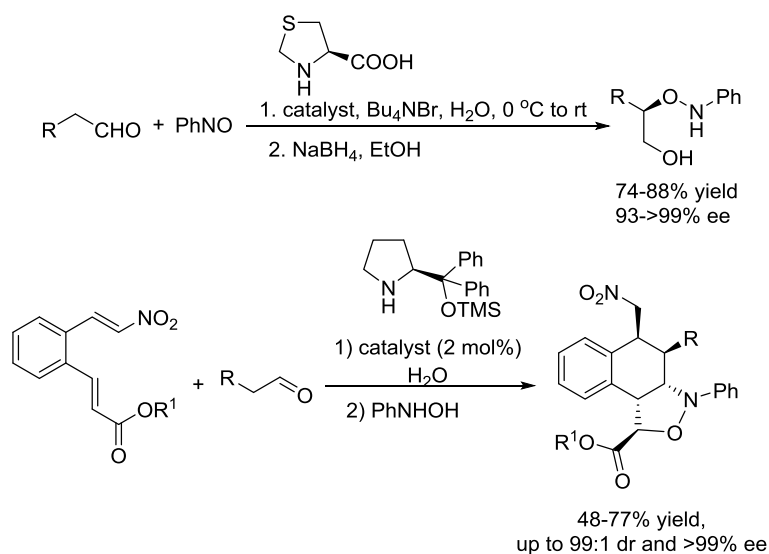
Organocatalysis, the use of a substoichiometric amount of an organic compound which does not contain a metal to accelerate a reaction, has received growing attention over the years.<sup>1</sup> Due to the advances made, it is now possible to apply the use of organocatalysts in various complex reactions, including key steps towards the synthesis of biologically active molecules and drugs.<sup>2</sup> In addition, they can take part in domino and/or cascade reactions, and generate multiple stereogenic centers at once.<sup>3</sup>

The concept of green chemistry has gained increasing importance nowadays and this has led to effort being made to develop organocatalytic reactions that can occur efficiently using water as reaction medium.<sup>4</sup> In the past, water was believed to have been an unsuitable solvent for organocatalytic reactions because the water molecules may interfere with the transition state formed between the organocatalyst and reactants. Consequently, disruption of the hydrogen bonds and other polar interactions may occur, which may lead to a slower reaction and lower isolated yields of the product.<sup>5</sup> However, since the seminal work by Breslow and Sharpless, the use of water as a solvent in organocatalytic reactions has experienced a great development.<sup>6</sup> In these studies, even though water does not dissolve the organic reagents, a rate acceleration was observed due to the hydrophobic effect.

Highly efficient organocatalytic reactions in water such as aldol, cycloadditions, Michael, Mannich, and Hantzsch reactions have been developed, and a few examples were highlighted in Chapter 1.<sup>7</sup> In 2009, our laboratory (Zhong) contributed to the growing interest of carrying out organocatalytic reactions in water by reporting a highly enantioselective  $\alpha$ -aminoxylation of aldehydes in aqueous media (Scheme 3.1).<sup>8</sup> By using *L*-thiaproline as the catalyst in the presence of tetrabutylammonium bromide as the phase transfer catalyst, good to high yields and excellent enantioselectivities of the desired products were obtained. Later on, we reported an efficient organocatalytic tandem

Michael/nitrone formation/intramolecular [3+2] nitrone-olefin cycloaddition reaction in aqueous media.<sup>7h</sup> This methodology provided access to tetrahydronaphthalene skeletons with multiple stereogenic centers with in good yields and high selectivities (Scheme 3.1).

**Scheme 3.1** (a) Enantioselective  $\alpha$ -aminoxylation of aldehydes; (b) Organocatalytic tandem Michael/nitrone formation/intramolecular [3+2] nitrone-olefin cycloaddition in aqueous media.



As mentioned earlier, NHCs are not only excellent ligands for metal-based catalysis, but also efficient organocatalysts for many reactions.<sup>3,9</sup> Compared to other organocatalysts like proline derivatives, studies that involve the employment of water as the solvent in *N*-heterocyclic carbene (NHC)-catalyzed reactions is relatively limited. In 2004, Bode and co-workers reported an NHC-catalyzed annulation of enals and aldehydes in an organic/solvent co-solvent (10:1 THF: $H_2O$  mixture).<sup>10</sup> This report showed that the presence of water in NHC-catalyzed reactions can be tolerated. Subsequently, the same group made use of water as a nucleophile in redox esterifications of chiral formylcyclopropanes to prepare the corresponding acid, and later as a co-solvent for the NHC-catalyzed activation of  $\alpha$ -chloroaldehyde bisulfite salts.<sup>11</sup> In 2010, Rovis and co-workers reported the synthesis

of  $\alpha$ -chloro and  $\alpha$ -fluoro carboxylic acids through a mild biphasic redox process using a toluene/water biphasic solvent containing 1.0 equiv of 1M aqueous  $K_2CO_3$  and 10 mol% of brine/ $Bu_4NI$  as additive.<sup>12</sup> Moreover, experimental and theoretical studies from the groups of Amyes, Diver, Gudat, and Nyulási showed that NHCs are reasonably stable in aqueous media.<sup>13</sup> More recently, Hoveyda and co-workers demonstrated the NHC-catalyzed enantioselective silyl conjugate addition to enones in an aqueous medium (3:1 THF:H<sub>2</sub>O mixture).<sup>14</sup>

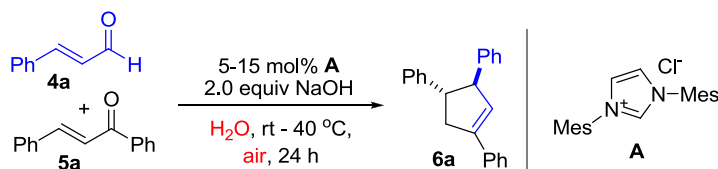
Despite the existence of these studies that have demonstrated the compatibility of water with NHC catalysis, the use of water as the sole solvent for NHC-catalyzed reactions remains undisclosed. This is surprising considering that the naturally occurring *N*-heterocyclic carbene precursor, thiamine, catalyzes many biological processes predominantly in an aqueous environment.<sup>15</sup> We surmised that following nature's lead, water should be a suitable solvent for *N*-heterocyclic carbene catalyzed reactions. In view that our laboratory (Chi) has been exploring the use of enals in various reactions,<sup>16</sup> we decided to carry out a study of organocatalytic NHC-catalyzed reactions involving  $\alpha,\beta$ -unsaturated aldehydes with water as the sole solvent.

## 3.2 Results and Discussion

We initiated our studies by investigating the reaction between chalcones and enals, which has been reported by the groups of Nair, Bode and Scheidt, and our laboratory (Chi).<sup>16b,17</sup> In the pioneering work by Nair, the use of an achiral carbene, 3-dimesityl imidazol-2-ylidene (IMes•HCl) **A**, led to the formation of ( $\pm$ ) trans-1,3,4-trisubstituted cyclopentenes as a single diastereomer in dry THF.<sup>17a</sup> In our case, the reaction of cinnamaldehyde **4a** and chalcone **5a** with a catalytic amount of NHC pre-catalyst **A**, in the

presence of the designer surfactant, TPGS-750-M, led to the formation of some product (Table 3.1, entry 1).<sup>18</sup>

**Table 3.1** Optimization of reaction conditions. <sup>a</sup>



entry	conditions	solvent	yield (%) <sup>b</sup>	dr <sup>b</sup>
1	15 mol% <b>A</b> , 0.45 equiv NaOH, rt	TPGS-750-M/H <sub>2</sub> O	18	N.D
2	15 mol% <b>A</b> , 2.0 equiv NaOH, rt	TPGS-750-M/H <sub>2</sub> O	83	10:1
3	15 mol% <b>A</b> , 2.0 equiv NaOH, rt	H <sub>2</sub> O	74	10:1
4	15 mol% <b>A</b> , 2.0 equiv NaOH, 40 °C	H <sub>2</sub> O	94	9:1
5	15 mol% <b>A</b> , 2.0 equiv NaOH, 60 °C	H <sub>2</sub> O	81	9:1
6	10 mol% <b>A</b> , 2.0 equiv NaOH, 40 °C	H <sub>2</sub> O	89	9:1
7	5 mol% <b>A</b> ,	H <sub>2</sub> O	94(80) <sup>c</sup>	11:1

2.0 equiv NaOH,				
40 °C				
8	5 mol% <b>A</b> ,	THF	100	7:1
2.0 equiv NaOH,				
40 °C				

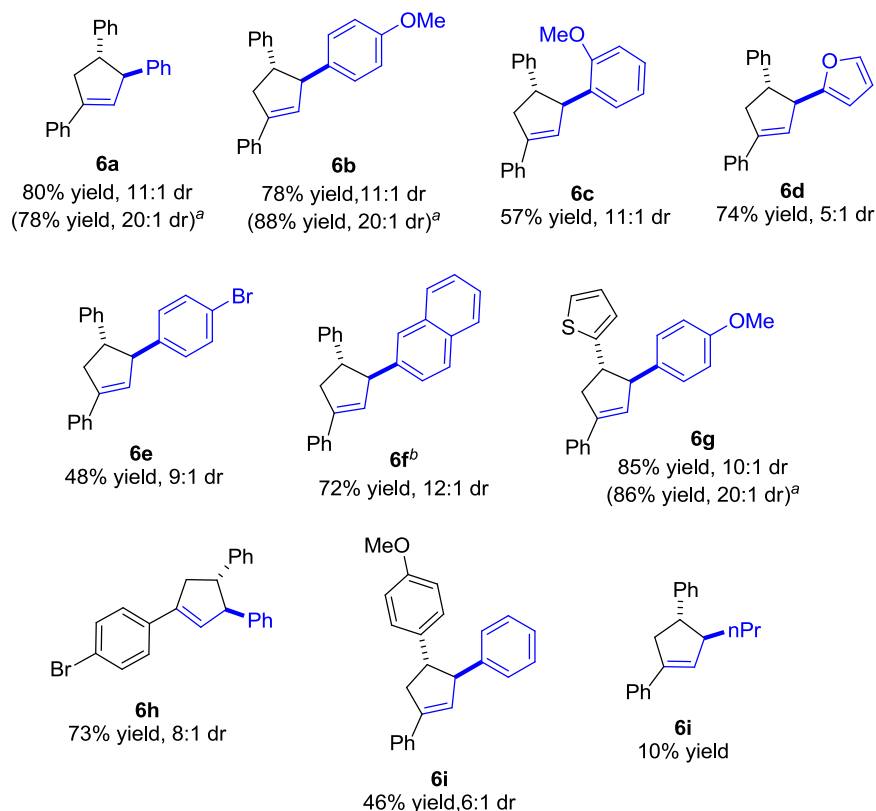
<sup>a</sup> Reaction conditions: **4a** (0.37 mmol), **5a** (0.25 mmol), catalyst, base, 0.5 mL solvent (0.5 M). <sup>b</sup> Estimated via <sup>1</sup>H NMR analysis of unpurified reaction mixture.

<sup>c</sup> Isolated yield after SiO<sub>2</sub> column chromatography. N.D = not determined.

Screening of the base revealed that the amount of the base was crucial for this reaction to occur with high conversions (Table 3.1, entries 1 and 2). In general, inorganic bases gave better conversions than organic bases (such as DBU), which are typically used for NHC-catalyzed reactions in organic solvents. Due to the reversible nature of the deprotonation of the azolium NHC precatalyst, it was observed that an excess amount of base was required to ensure a basic aqueous environment for the formation of the NHC catalyst from precursor **A**. Consequently, the use of 2 equivalents of NaOH led to the formation of the cyclopentene product **6a** in 83% yield with 10:1 dr (Table 3.1, entry 2). When a control reaction was carried out without the use of the surfactant, high conversions were also observed, which prompted us to carry out subsequent reactions “on water” (Table 3.1, entry 3). A survey of the reaction temperature showed that the desired product was obtained with excellent selectivity and yield at 40 °C (Table 3.1, entry 4). The slightly higher temperature led to an acceleration of the reaction, whereas lower conversions were observed at an higher temperature of 60 °C, possibly due to increased oxidation of the enal (Table 3.1, entry 5).<sup>19</sup> Lowering of the catalyst loading showed that 5 mol% catalyst loading was sufficient to obtain **6a** with good yield and diastereoselectivity (80% isolated yield, 11:1 dr, entry 7). Although a lower selectivity was observed “on water”, the yield was comparable to that in organic solvent, thereby making the change from organic to aqueous

solvent a viable strategy to construct cyclopentenenes. It is particularly noteworthy that this reaction could be carried out efficiently despite being completely in air, given that most NHC-catalyzed reactions are conducted in an inert atmosphere.<sup>19,20</sup>

**Scheme 3.2** Examples of enals and chalcones. <sup>a</sup>



<sup>a</sup> Reaction conditions: Enal **4** (0.37 mmol), chalcone **5** (0.25 mmol), catalyst **A** (5 mol%), NaOH (0.5 mmol), and water (0.5 mL, 0.5 M). <sup>b</sup> 1.0 mL of water used. Yields are isolated yields after SiO<sub>2</sub> column chromatography; dr values were determined via <sup>1</sup>H NMR analysis of unpurified in reaction mixture. <sup>a</sup> Literature values for reactions in organic solvents.

With the optimized reaction conditions in hand, the substrate scope was evaluated (Scheme 3.2). A variety of aromatic enals bearing electron-donating, electron-withdrawing and heteroaromatic groups were well tolerated. The desired products were afforded with good to excellent diastereoselectivities and yields. Furthermore, modified chalcones bearing different substituents (**6g**, **6h**, **6i**) also worked well. The yields and

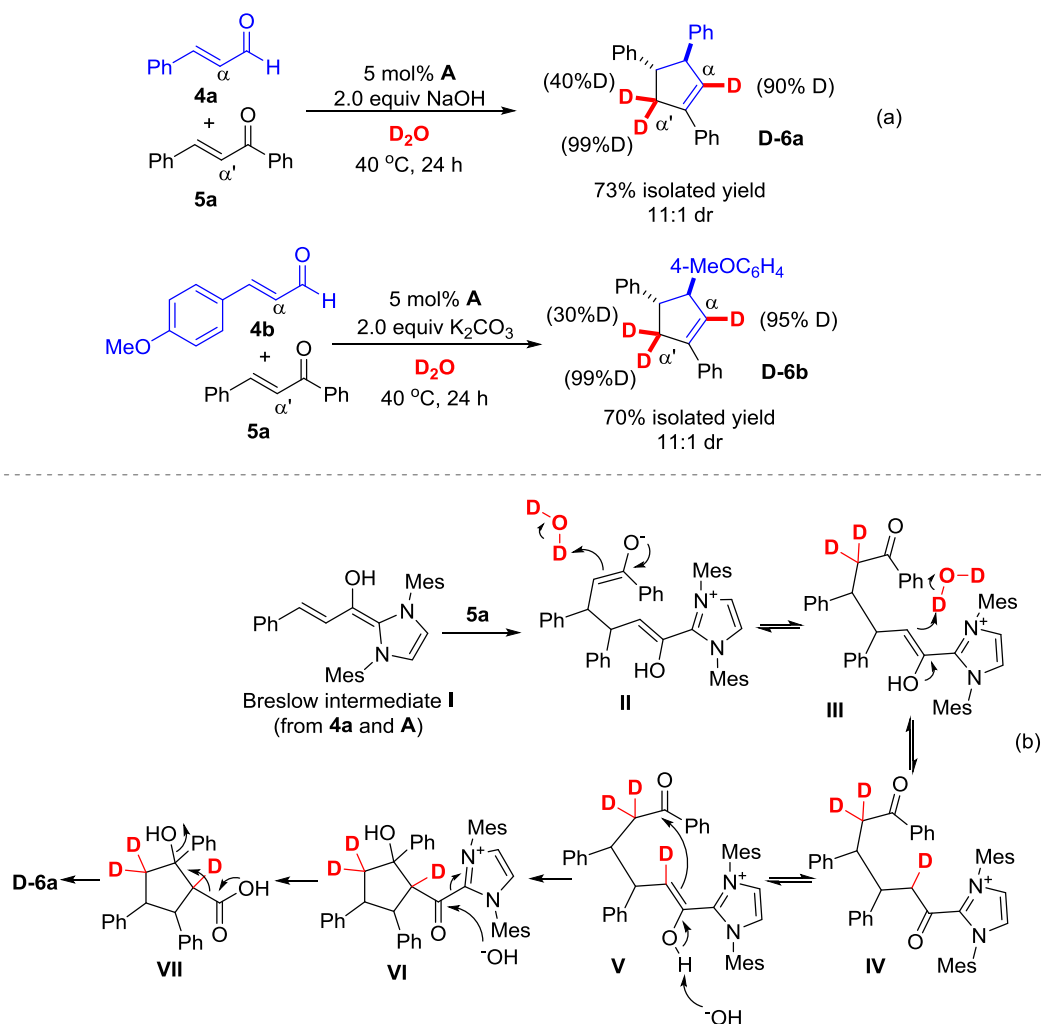
diastereoselectivities obtained under our aqueous environment are comparable to those reported in the literature using organic solvents.<sup>17a,17c</sup> However, alkyl enals were found to be unsuitable substrates, even with a higher catalyst loading (**6j**). Analysis of the crude mixture by <sup>1</sup>H NMR and TLC revealed a complex mixture which was not purified by column chromatography. It was observed that in all these reactions, as in other reactions involving similar chemistry, good stirring was crucial for good conversions.<sup>6b</sup> In some cases like **6f**, more water had to be added in order for there to be good stirring. Attempts to improve the diastereoselectivity of **6d** by varying the amount of water, amount and identity of base, and use of a surfactant led to no improvements in the diastereoselectivity.

The versatility of this methodology was demonstrated through the selective synthesis of deuterated cyclopentenones by carrying out the reaction in D<sub>2</sub>O. This may be an extremely useful methodology for making stable deuterated compounds, which are very important in analytics, pharmacology, material sciences, and the life sciences.<sup>21</sup> As illustrated in Scheme 3.3a, when the reaction between enal **4a** and chalcone **5a** was carried out in D<sub>2</sub>O, deuterated cyclopentenone (**D-6a**) was obtained. The deuterium isotopes were incorporated into the former  $\alpha$ -carbons of the enal and enone. It was determined that an inert atmosphere was required to ensure high conversions. When *para*-methoxycinnamaldehyde (**4b**) was used as the substrate, only 70% deuteration was observed at the  $\alpha$ -carbon of the enal. However, switching the base to K<sub>2</sub>CO<sub>3</sub> resulted in 95% deuteration at the  $\alpha$ -carbon of the enal (Scheme 3.3a, **D-6b**).

The proposed mechanism of this deuterium incorporation is shown in Scheme 3.3b. The incorporation of the deuterium into the former  $\alpha$ -carbon of enone **5a** involved a deuteration of intermediate **II**, which bears an acidic proton adjacent to the ketone group. The incorporation of deuterium into the former  $\alpha$ -carbon of the enal may occur at a few different stages. One possibility, which is shown in Scheme 3.3b, involves a deuteration of the NHC-bounded enolate intermediate **III** via a reversible process. Intermediate **IV** may

then tautomerize, and a 5-membered ring is formed via attack of the carbonyl group by the hydroxyl group on intermediate V. Due to the basic conditions, a hydroxide ion may attack the carbonyl group on intermediate VI to form a carboxylic acid, thereby regenerating the catalyst. Lastly, a decarboxylation step occurs to afford the desired product **D-6a**.

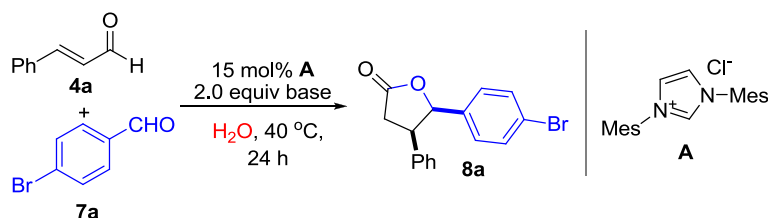
**Scheme 3.3** (a) Isotope incorporation and (b) the postulated pathway.



The next reaction that was investigated involves the direct annulation of enals and aldehydes to give  $\gamma$ -butyrolactones.<sup>10</sup> Our studies to explore this reaction using water as the only solvent began by using cinnamaldehyde and *p*-bromobenzaldehyde. Once again, the identity of the base used significantly affected the outcome of the reaction (Table

3.2). It was determined that this reaction occurred optimally with 2 equivalents of  $K_2CO_3$ , and only 5 mol% catalyst loading (Table 3.2, entry 8). This time, an inert atmosphere was necessary to ensure good conversions.

**Table 3.2** Optimization of reaction conditions. <sup>a</sup>



entry	base	dr ( <i>cis:trans</i> ) <sup>b</sup>	yield (%) <sup>c</sup>
1	NaOH	-	N.R.
2	DBU	-	N.R.
3	$K_2CO_3$	3:1	74
4	$Et_3N$	3:1	70
5	$K_3PO_4$	3:1	62
6	DMAP	3:1	56
7	DIEA	3:1	72
8 <sup>d</sup>	$K_2CO_3$	3:1	80

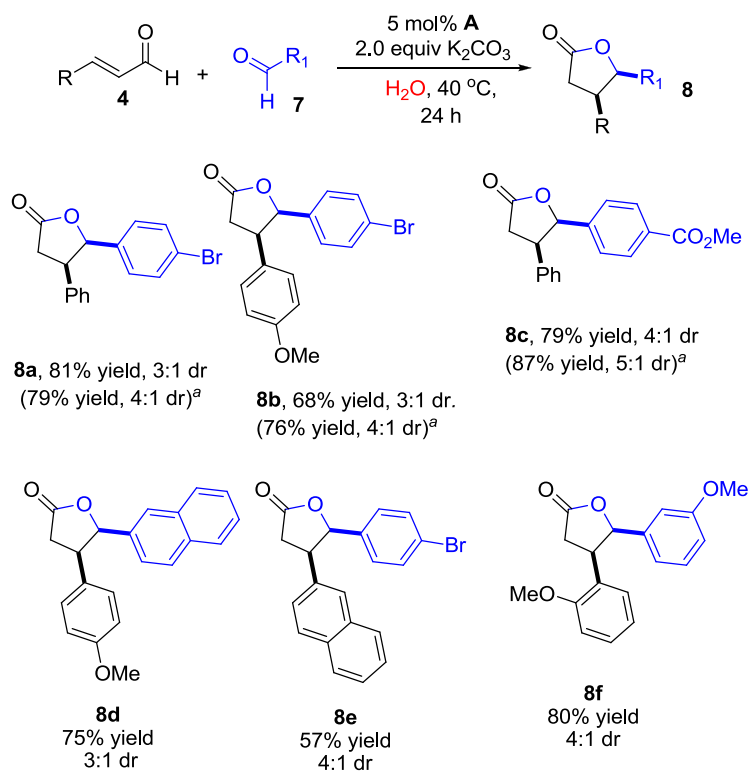
<sup>a</sup> Reaction conditions: **4a** (0.1 mmol), **7a** (2 equiv), catalyst **A** (15 mol%), base (2.0 equiv), and water (0.5 mL, 0.2 M). <sup>b</sup> Determined by  $^1H$  NMR analysis of crude mixture.

<sup>c</sup> Yield estimated by  $^1H$  NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard. <sup>d</sup> 5 mol% catalyst loading.

Having established the optimal catalytic reaction condition, the generality of the reaction was examined (Scheme 3.4). A variety of enals and aldehydes were found to work well in these conditions, with the desired products being afforded in good selectivities and yields. Aliphatic aldehydes were found to be unsuitable for this reaction. Essentially, the

substrate scope and results are comparable to the corresponding reactions carried out in organic solvents.<sup>10</sup>

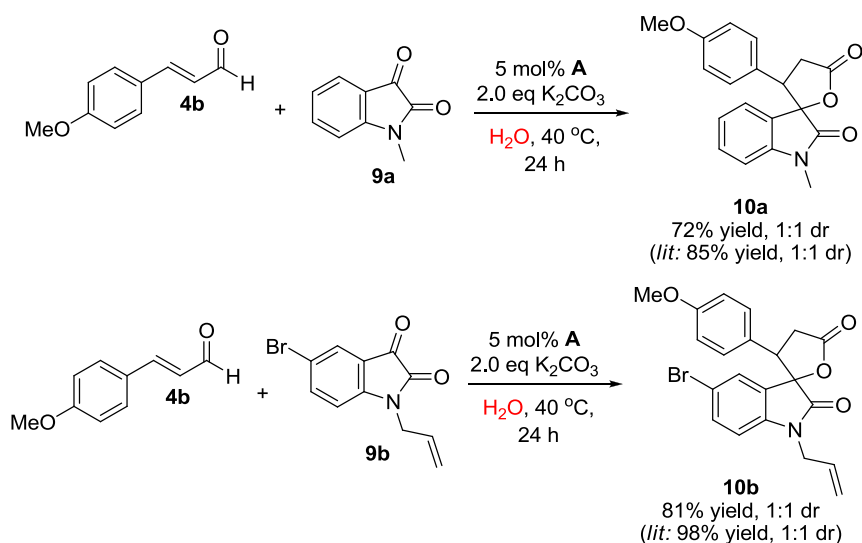
**Scheme 3.4** Examples of enals and aldehydes.



Reaction conditions: Enal **4** (0.1 mmol), aldehyde **7** (0.2 mmol), catalyst **A** (5 mol%),  $K_2CO_3$  (0.2 mmol), and water (0.5 mL, 0.2 M). Yields are isolated yields after  $SiO_2$  column chromatography; dr values were determined via  $^1H$  NMR analysis of unpurified reaction mixture. <sup>a</sup> Literature values for reactions in organic solvents.

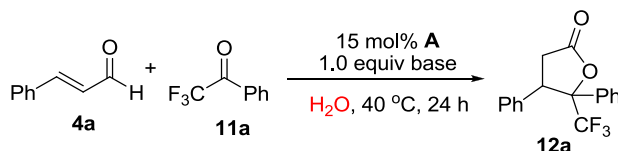
We next turned our attention to the reaction between enals and isatins, with a view to synthesize spiro isatin  $\gamma$ -lactones, which are an important structural unit of biologically active natural products, such as the mycotoxin triptoquivaline (Scheme 3.5).<sup>22</sup> Once again, it was demonstrated that this reaction could occur efficiently in aqueous media, and gave the desired products in 72-81% yield, and 1:1 d.r.

**Scheme 3.5**  $\gamma$ -Butyrolactone synthesis from 1,2-dicarbonyl compounds.



Attempts to use ketones like 2,2,2-trifluoro-1-phenylethanone as electrophiles with  $\alpha,\beta$ -unsaturated aldehydes in water as the solvent led to no product formation (Scheme 3.6).<sup>23</sup>

**Scheme 3.6** NHC-catalyzed reaction between ketones and enals.<sup>a</sup>



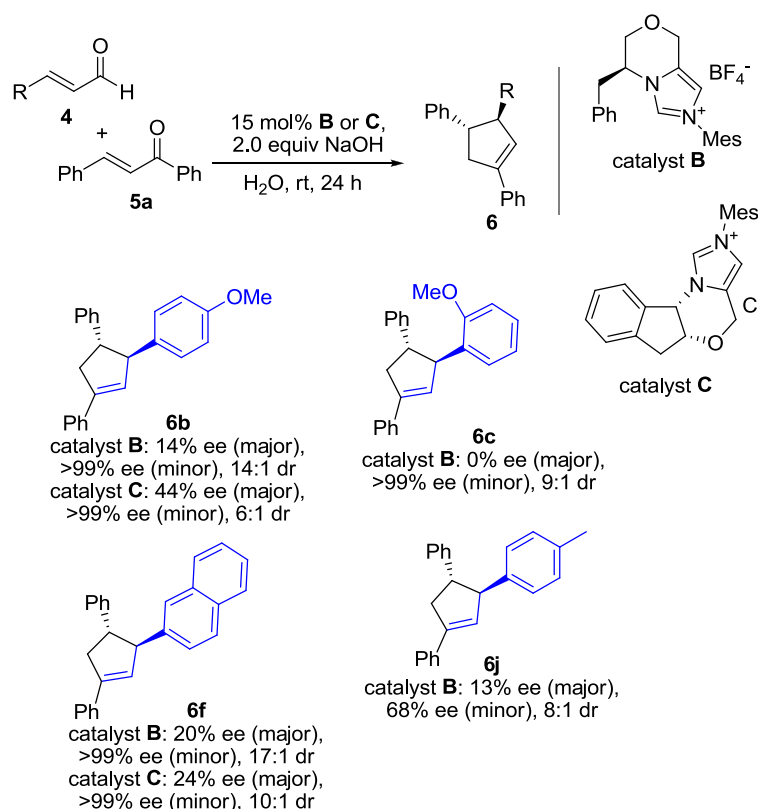
entry	base	dr ( <i>cis:trans</i> ) <sup>b</sup>	yield (%) <sup>c</sup>
1	NaOH	-	N.R.
2	DBU	-	N.R.
3	K <sub>2</sub> CO <sub>3</sub>	-	N.R.
4	DABCO	-	N.R.
5	MgO <i>t</i> Bu	-	N.R.

<sup>a</sup> Reaction conditions: **4a** (0.25 mmol), **11a** (2 equiv), catalyst **A** (15 mol%), base (1.0 equiv), and water (0.5 mL, 0.5 M). <sup>b</sup> Determined by <sup>1</sup>H NMR analysis of crude mixture.

<sup>c</sup> Yield estimated by <sup>1</sup>H NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard.

The enantioselective version of the reaction between enals and chalcones in water was also attempted (Scheme 3.7). However, despite the use of chiral catalysts that are typically efficient in organic solvent, low enantioselectivity of the major product was observed with various substrate combinations. Interestingly, in a few cases, the minor product was observed to have excellent enantioselectivity (**6b**, **6c**, **6d**).

**Scheme 3.7** Enantioselective NHC-catalyzed reaction between chalcones and enals. <sup>a</sup>



<sup>a</sup> Reaction conditions: Enal **4** (0.37 mmol), chalcone **5a** (0.25 mmol), catalyst **B** or **C** (15 mol%), NaOH (0.5 mmol), and water (0.5 mL, 0.5 M). dr values were determined via <sup>1</sup>H NMR analysis of unpurified in reaction mixture.

### 3.3 Conclusion

Water was shown to be a suitable solvent in NHC-catalyzed reactions, leading to the synthesis of ( $\pm$ ) trans-1,3,4-trisubstituted cyclopentenes and  $\gamma$ -butyrolactones with good to excellent selectivities and yields. The simple and mild reaction conditions, often without the need for an inert atmosphere, low catalyst loading and desirable characteristics of the solvent, make this an attractive methodology for large scale synthesis. Furthermore, the use of inexpensive inorganic bases (such as NaOH) were found to be optimal, and deuterated compounds can be synthesized easily and inexpensively by using D<sub>2</sub>O as the solvent. Preliminary studies were carried out to study the feasibility of NHC-catalyzed synthesis of enantioselective products in water. Although the major product was found to have low enantioselectivity, the possibility of carrying out highly enantioselective NHC-catalyzed reactions in water cannot be ruled out, as evidenced by the excellent enantioselectivities obtained for the minor product.

### 3.4 Experimental Section

#### 3.4.1 General Information

Commercially available materials purchased from Alfa Aesar or Aldrich were used as received. Proton nuclear magnetic resonance (<sup>1</sup>H NMR) spectra were recorded on Bruker AMX 400 (400 MHz) and Bruker BBFO (400 MHz) spectrometers. Chemical shifts were recorded in parts per million (ppm,  $\delta$ ) relative to tetramethylsilane ( $\delta$  0.00) or chloroform ( $\delta$  = 7.26, singlet). <sup>1</sup>H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets), m (multiplets), and etc. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Carbon nuclear magnetic resonance (<sup>13</sup>C NMR) spectra were recorded on Bruker BBFO

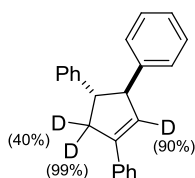
(100 MHz) spectrometer. High resolution mass spectral analysis (HRMS) was performed on a Finnigan MAT 95 XP mass spectrometer (Thermo Electron Corporation). Analytical thin-layer chromatography (TLC) was carried out on Merck 60 F254 pre-coated silica gel plate (0.2 mm thickness). The deionized water used for the reactions was degassed with N<sub>2</sub> prior to use. Visualization was performed using UV radiation (254 nm). Compounds **6a-h**,<sup>17a, 17c</sup> **8a-c**,<sup>10</sup> and **10a**<sup>22</sup> have been previously reported in the literature.

### 3.4.2 Procedure for catalytic reactions between enals and chalcones:

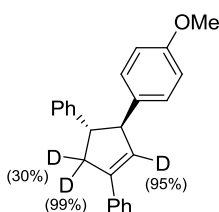
A borosilicate glass O.D. 16 x length 150 mm test tube containing a stir bar was successively charged with enal **4** (0.37 mmol), chalcone **5** (0.25 mmol), catalyst **A** (8.6 mg, 0.0125 mmol), NaOH (20 mg, 0.5 mmol) and water (0.5 mL). The test tube was capped with a rubber septum and the resulting milky emulsion was stirred vigorously at 40 °C for 24 h. The reaction mixture was cooled to room temperature and extracted using minimal amount of EtOAc, dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated under vacuum. The crude product was purified by flash column chromatography to afford the pure cyclopentene product **6**.

### 3.4.3 Procedure for deuteration reactions between enals and chalcones:

A dry 10 mL Schlenk tube equipped with stir bar was successively charged with enal **4** (0.375 mmol), chalcone **5** (0.25 mmol), catalyst **A** (8.6 mg, 0.0125 mmol), and NaOH (20 mg, 0.5 mmol). The flask was then evacuated and refilled with N<sub>2</sub> and D<sub>2</sub>O (0.5 mL) was added via a syringe. The resulting mixture was stirred vigorously at 40 °C for 48 h. The reaction mixture was cooled to room temperature and extracted using minimal amount of EtOAc, dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated under vacuum. The crude product was purified by flash column chromatography to afford the deuterated cyclopentene product **D-6a**.



**Deuterated compound (D-6a):** Colorless oil, *trans:cis* = 11:1, 73% combined yield of both isomers;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.59-7.53 (m, 2H), 7.40-7.14 (m, 13H), 6.27 (s, 0.1H), 4.13 (d,  $J = 7.2$  Hz, 1H), 3.44 (t,  $J = 8.3$  Hz, 1H), 3.33 (d,  $J = 9.2$  Hz, 0.6H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  145.7, 145.2, 142.3, 136.2, 128.7, 127.7, 127.6, 127.5, 126.6, 126.5, 126.0, 61.0, 57.0, 54.6, 54.5, 42.0, 41.8, 41.6; HRMS (ESI) calcd for  $\text{C}_{23}\text{H}_{18}\text{D}_3$ [ $\text{M}+1$ ] $^+$ : 300.1832, Found: 300.1828.

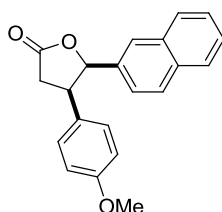


**Deuterated compound (D-6b):** Colorless oil, *trans:cis* = 11: 1, 70% yield of both isomers;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.53 (d,  $J = 7.5$  Hz, 2H), 7.36 (t,  $J = 7.4$  Hz, 2H), 7.29- 7.21 (m, 6H), 7.06 (d,  $J = 8.5$  Hz, 2H), 6.82 (d,  $J = 8.6$  Hz, 2H), 4.08 (d,  $J = 7.12$ , 1H), 3.78 (s, 3H), 3.40 (t,  $J = 8.4$  Hz, 1H), 3.31 (d,  $J = 8.9$  Hz, 0.7H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  158.4, 145.7, 141.9, 137.3, 136.2, 129.9, 128.7, 128.6, 127.8, 127.7, 127.5, 126.4, 126.0, 114.1, 113.3, 60.2, 55.5, 55.8, 41.9, 41.7, 41.5; HRMS for  $\text{C}_{24}\text{H}_{19}\text{D}_3\text{O}$  [ $\text{M}+1$ ] $^+$  Calculated: 327.1749, Found: 327.1735.

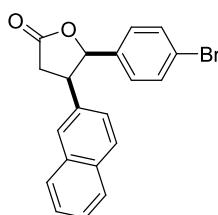
### 3.4.4 General Procedure for reaction between enals and aldehydes:

A borosilicate glass O.D. 16 x length 150 mm test tube containing a stir bar was successively charged with enal **4** (0.1 mmol), aldehyde **7** (0.2 mmol), catalyst **A** (3.4 mg, 0.005 mmol) and  $\text{K}_2\text{CO}_3$  (28 mg, 0.2 mmol). The test tube was capped with a rubber septum, flushed with  $\text{N}_2$ , and water (0.5 mL) was added via a syringe. The resulting milky emulsion

was stirred vigorously at 40 °C for 24 h. The reaction mixture was cooled to room temperature and extracted using minimal amount of EtOAc, dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated under vacuum. The crude product was purified by flash column chromatography to afford the pure lactone products **8**.

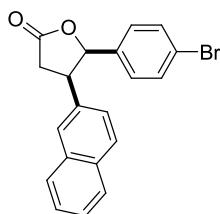


**cis-4-(4-methoxyphenyl)-5-(naphthalen-2-yl)dihydrofuran-2(3H)-one (8d):** White solid, cis:trans = 4:1, 75% combined yield of both isomers; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.74-7.71 (m, 1H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.46-7.43 (m, 2H), 6.82 (dd, *J* = 8.4, 1.6 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 2H), 6.57 (d, *J* = 6.8 Hz, 2H), 5.94 (d, *J* = 7.2 Hz, 1H), 4.13-4.08 (m, 1H), 3.65 (s, 3H), 3.07 (dd, *J* = 17.6, 8.2 Hz, 1H), 2.94 (dd, *J* = 17.2, 6.8 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 177.0, 159.0, 133.4, 133.0, 129.2, 128.7, 128.2, 127.8, 126.4, 126.3, 125.0, 123.9, 114.0, 85.0, 55.3, 46.4, 35.4; HRMS (ESI) calcd for C<sub>21</sub>H<sub>19</sub>O<sub>3</sub>[M+1]<sup>+</sup>: 319.1334, Found: 319.1331.



**cis-5-(4-bromophenyl)-4-(naphthalen-2-yl)dihydrofuran-2(3H)-one (8e):** White solid, cis:trans = 3:1, 57% yield of both isomers; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.72-7.68 (m, 2H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.47-7.39 (m, 3H), 7.20 (d, *J* = 8.4 Hz, 2H), 6.83-6.80 (m, 3H), 5.85 (d, *J* = 6.8 Hz, 1H), 4.23-4.19 (m, 1H), 3.14 (dd, *J* = 17.5, 8.2 Hz, 1H), 3.03 (dd, *J* = 17.5, 5.9 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 176.5, 134.8, 134.2, 133.2, 132.7,

131.4, 128.4, 127.9, 127.8, 127.6, 127.0, 126.6, 126.4, 125.9, 122.2; HRMS (ESI) calcd for  $C_{20}H_{16}BrO_2[M+1]^+$ : 369.0313, Found: 369.0310.



**cis-4-(2-methoxyphenyl)-5-(3-methoxyphenyl)dihydrofuran-2(3H)-one (8f):** White solid, cis: trans = 4:1, 80% combined yield of both isomers;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.15-7.10 (m, 1H), 7.04-7.00 (m, 1H), 6.81-6.73 (m, 2H), 6.69-6.62 (m, 2H), 6.57 (d,  $J$  = 7.6 Hz, 1H), 6.40 (s, 1H), 5.90 (d,  $J$  = 7.2 Hz, 1H), 4.45-4.40 (m, 1H), 3.69 (s, 3H), 3.58 (s, 3H), 3.08-2.70 (m, 2H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  177.3, 159.2, 157.2, 137.8, 128.8, 128.1, 125.7, 120.6, 118.3, 114.0, 111.0, 110.3, 83.8, 55.3, 41.4, 33.5; HRMS (ESI) calcd for  $C_{18}H_{19}O_4[M+1]^+$ : 299.1283, Found: 299.1281.

### 3.4.5 General Procedure for reaction between enals and isatins:

A borosilicate glass O.D. 16 x length 150 mm test tube containing a stir bar was charged with catalyst **A** (5 mol%), isatin derivative **9** (0.1 mmol), enal **4** (0.2 mmol),  $K_2CO_3$  (0.2 mmol) and water (0.5 mL). The test tube was capped with a rubber septum and the resulting milky emulsion was stirred vigorously at 40°C for 24 h. Extraction was carried out using EtOAc and the solvent was evaporated *in vacuo* and the crude reaction mixture was analyzed by NMR. Flash column chromatography provided the pure product. Analysis of the pure product by NMR showed that the product obtained is similar to that reported in literature.<sup>22</sup>

### 3.5 References

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## CHAPTER 4:

Polyethyleneglycol Ubiquinol Sebacate (PQS)

as a Surfactant Platform

for Catalytic Reactions in Water

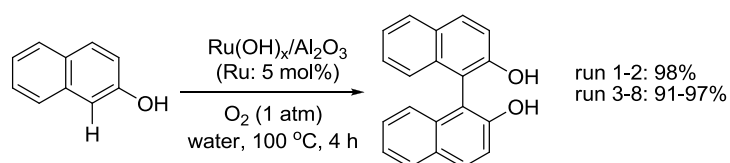
## 4.1 Introduction

### 4.1.1 Catalyst recycling

Since the introduction of the 12 Principles of Green Chemistry by Anastas and Warner in 1998, many chemical processes have been developed in accordance to these guidelines.<sup>1</sup> Besides the use of safer solvents, one of the guidelines highlights the importance of catalytic reagents, and it was implied that a highly desirable feature would be the recyclability of the catalysts employed. For reactions that make use of transition metal-based catalysts, many of these catalysts are derived from expensive and scarce metals that may also be toxic. Thus, employment of such catalysts should be minimized or optimized in such a way that recovery and recycling of the catalyst is feasible.<sup>2</sup>

Various research groups have attempted to recycle catalysts by the use of heterogeneous catalysts. An example is the use of a supported ruthenium catalyst by Mizuno and co-workers, to carry out oxidative homocoupling of 2-naphthol (Scheme 4.1).<sup>3</sup> In that study, the catalyst could be recycled up to seven times without any significant loss in the catalytic activity and an impressive turnover number (TON) of 160 was achieved, making it superior to other homogeneous or heterogeneous catalytic systems.

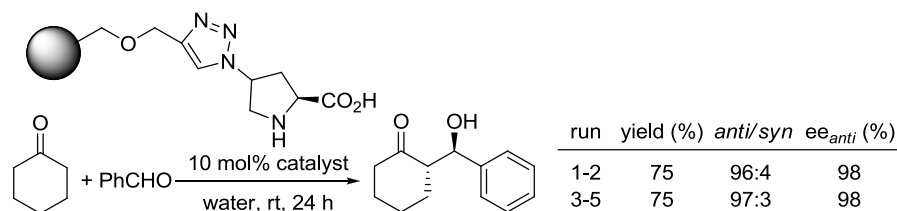
**Scheme 4.1** Oxidative homocoupling of 2-naphthol in water.



The group of Pericàs showed that 4-substituted proline immobilized onto a Merrifield resin could catalyze an aqueous asymmetric aldol reaction between cyclohexanones and benzaldehydes in good yields and excellent selectivities, and the

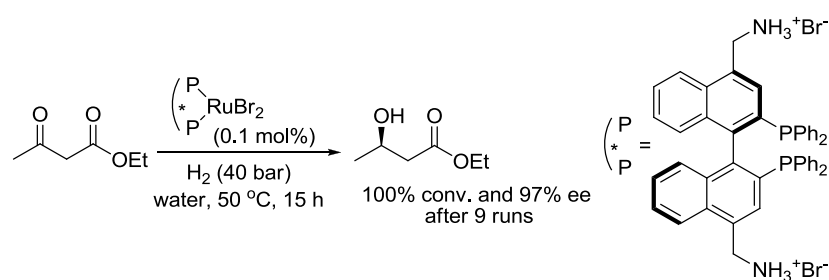
catalyst could be recycled up to five times without any detrimental effect on the reaction yield and selectivity (Scheme 4.2).<sup>4</sup>

**Scheme 4.2** Asymmetric aldol reaction catalyzed by a resin supported proline catalyst.



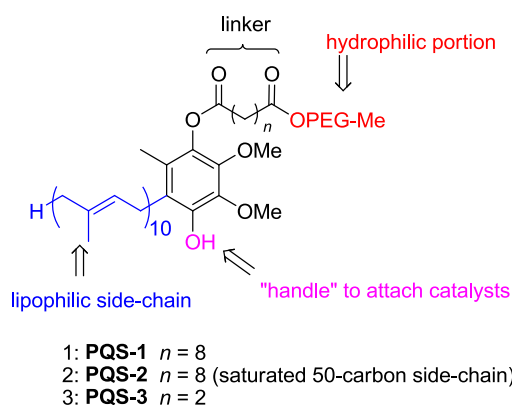
In addition, Lemaire and co-workers reported the use of ammonium groups to design water-soluble BINAP analogues for the aqueous ruthenium-catalyzed asymmetric hydrogenation of ethyl acetoacetate (Scheme 4.3). The catalyst could be recycled up to eight times, and the desired product was obtained with excellent conversion and enantioselectivity.

**Scheme 4.3** Asymmetric hydrogenation of  $\beta$ -ketoesters in water.



As mentioned earlier in Chapter 1, Lipshutz and co-workers developed a few versions of the “designer surfactant”, polyethyleneglycol ubiquinol sebacate (PQS), which is comprised of: (1) a lipophilic part that acts as the “solvent” for water insoluble organic reactants; (2) a hydrophilic component that results in aqueous solubility; and (3) an unbound -OH functionality inside the hydrophobic nucleus capable of covalent binding to a catalyst (Figure 4.1).<sup>5</sup> Following another principle in the 12 Principles of Green

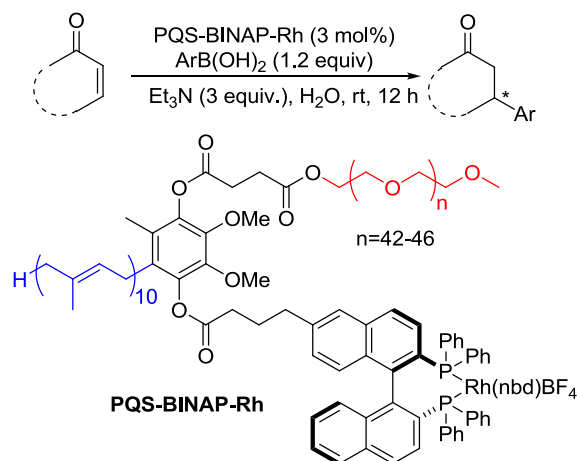
Chemistry, in which the use of “safer chemicals” of minimal toxicity is encouraged, PQS was synthesized from: (1) a polyethyleneglycol (PEG-2000); (2) the reduced form of the easily available coenzyme Q<sub>10</sub>, i.e., ubiquinol, and (3) a linker unit which is either sebacic acid (n = 8), or succinic acid, (n = 2). It spontaneously aggregates in water, and the nanomicelles consequently enable reactions to occur within their lipophilic hydrocarbon cores.



**Figure 4.1** Structure of PQS.

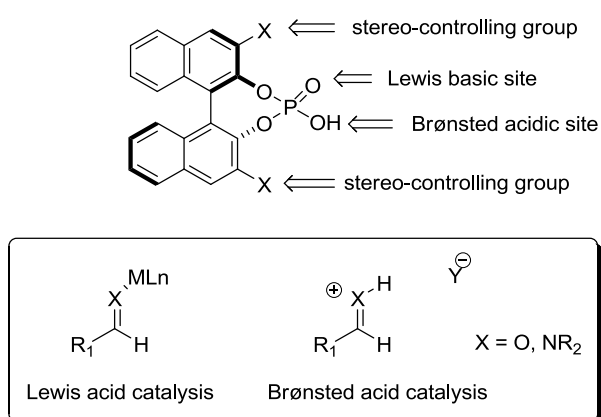
It was shown that olefin ring-closing and cross-metathesis reactions could be carried out in water by the independent covalent attachment of Grubbs-Hoveyda’s first- and second-generation catalysts.<sup>5a,5d</sup> Catalyst recycling of up to ten times could be achieved before a decrease in reactivity of the catalyst was observed. In a related study, 4-hydroxy proline was attached to PQS, which facilitated aldol reactions involving water-soluble and insoluble substrates in water, with high yields and selectivities.<sup>6</sup> More recently, (*R*)-BINAP was covalently attached to PQS, and subsequent addition of a rhodium(I) complex, [Rh(nbd)<sub>2</sub>]BF<sub>4</sub>, led to the formation of the catalyst, PQS-BINAP-Rh.<sup>5c</sup> This catalyst was successfully applied to the asymmetric conjugate addition reactions of arylboronic acids to enones to afford the desired products with high yields and enantioselectivities (Scheme 4.4).

**Scheme 4.4** Aqueous asymmetric conjugate addition catalyzed by PQS-BINAP-Rh.



**4.1.2 Brønsted acid catalysis**

In 2004, the groups of Akiyama and Terada independently reported highly efficient and enantioselective Mannich-type reactions involving imines using chiral phosphoric acids derived from (*R*)-BINOL.<sup>7</sup> After these seminal findings, chiral phosphoric acids were recognized as a novel class of organocatalysts, and attracted the attention of several synthetic organic chemists from around the world (Figure 4.2).<sup>8</sup>

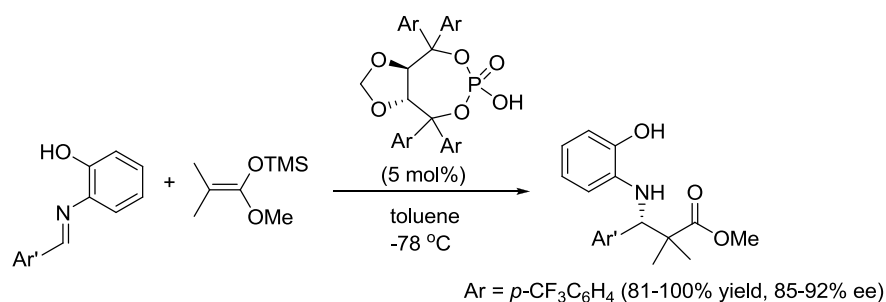


**Figure 4.2** Chiral Brønsted acids derived from (*R*)-BINOL.

It was determined that phosphoric acids are bifunctional catalysts that possess both a Brønsted-acidic site and a Lewis-basic site, and the substituents on the 3,3'-positions of the aromatic backbone play a crucial role for achieving excellent enantioselectivity. As a catalyst, their main role is to activate the nucleophile or electrophile. This is done by proton transfer from the Brønsted acid to the electrophile, which leads to a lowering of the energy of the lowest unoccupied molecular orbital (LUMO), thereby activating the electrophile towards nucleophilic attack. Alternatively, addition of Brønsted acids to the nucleophile leads to activation by way of keto–enol tautomerism. Unlike Lewis acids, that are usually prepared *in situ* from a Lewis acid and chiral ligand, and typically require stringent reaction conditions, Brønsted acids exhibit catalytic activity as they are, and tend to be moisture and air stable. In addition, they can be stored for a long period of time without decomposition.

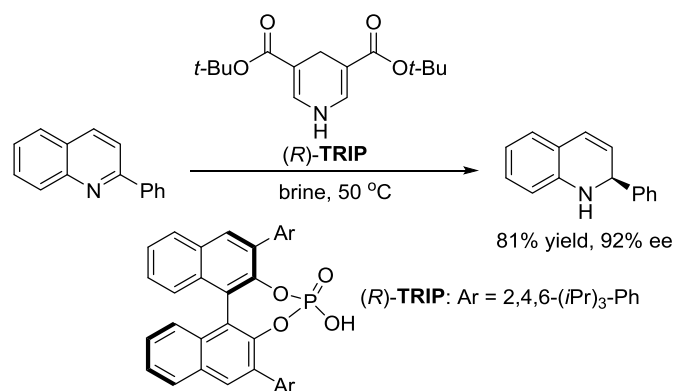
Several novel phosphoric acids have been reported, with some of them possessing the  $\alpha,\alpha,\alpha,\alpha$ -tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL) scaffold. Phosphoric acids bearing the TADDOL backbone, are derived from the cheap and readily available, (+)-*L*-tartaric acid, and are expected to have different electronic and steric properties from those bearing the BINOL scaffold. Akiyama and co-workers demonstrated the efficacy of this class of catalysts in the Mannich-type reaction of a ketene silyl acetal with aldimines (Scheme 4.5).<sup>9</sup>

**Scheme 4.5** Mannich-type reaction catalyzed by TADDOL-based phosphoric acids.



As mentioned in Chapter 1 and the previous chapters, a desirable property in many organic reactions that is currently being applied today is the successful employment of water as the medium for chemical reactions. It would therefore be extremely advantageous if chiral phosphoric acids can also be employed as catalysts for organic reactions in aqueous medium. This concept was virtually unknown until 2010, when Rueping and Theissmann made a scientific breakthrough by developing the first highly enantioselective phosphoric acid catalyzed reaction with water as the only solvent (Scheme 4.6).<sup>10</sup> To our knowledge, this is the only report that allows for highly enantioselective phosphoric-acid catalyzed reactions in water.

**Scheme 4.6** First phosphoric acid catalyzed reaction in water.

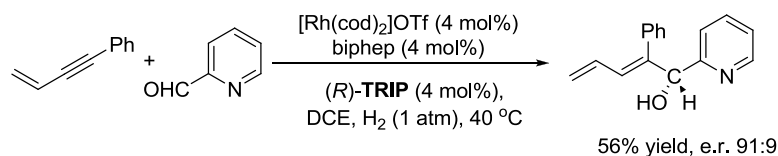


### 4.1.3 Cooperative catalysis between organo- and metal-catalysis

The combination of metal- and organocatalysis has recently emerged as a powerful strategy in asymmetric catalysis and organic synthesis.<sup>11</sup> The efficacy and scope of chiral phosphoric acids has been found to be greatly enhanced by the introduction of transition metals, and many research groups have reported the use of such cooperative catalysis. One of the first reports that made use of cooperative transition-metal and Brønsted acid catalysis was from Komanduri and Krische,<sup>12</sup> and involved the employment of an achiral Rh complex and (*R*)-3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diylhydrogen

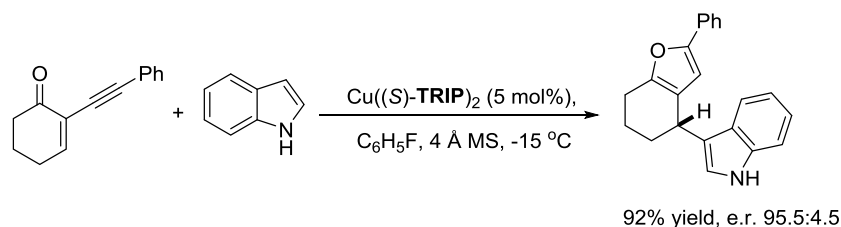
phosphate (TRIP),<sup>13</sup> which is one of the most versatile phosphoric acid developed so far. This seminal work described a highly enantioselective reductive coupling between conjugated heteroaryl-substituted aldehydes/ketones and 1,3-enynes (Scheme 4.7).

**Scheme 4.7** Rh-catalyzed asymmetric reductive coupling.



More recently, Toste and co-workers developed a Cu(II)-TRIP-catalyzed cycloisomerization/indole addition sequence between alkynes and indoles to give products with high yields and enantioselectivities (Scheme 4.8).<sup>14</sup>

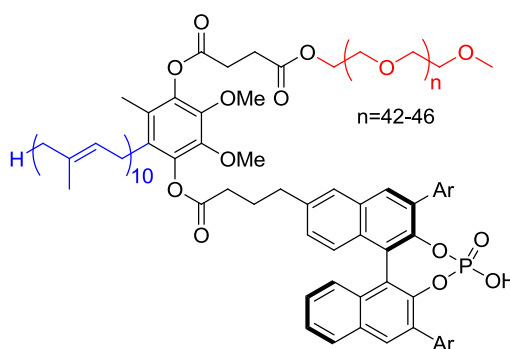
**Scheme 4.8** Cu-TRIP-catalyzed cycloisomerization and indole addition.



## 4.2 Design plan: PQS-attached phosphoric acid catalyst

Inspired by the promising results of PQS as a platform for which various catalysts can be covalently attached to, as reported by Lipshutz and Ghorai in 2010,<sup>15</sup> and building on the experience of our group in the field of organocatalysis,<sup>16</sup> we envisioned to make use of PQS as a surfactant platform to covalently attach phosphoric acids (such as BINOL-based phosphoric acid derivative **PQS-PA1**) for applications in asymmetric reactions with water as the solvent (Figure 4.3). Additionally, after the pioneering work by Akiyama et al.

(Scheme 4.5), there have been no further studies on the use of TADDOL-based phosphoric acids as efficient organocatalysts in organic reactions. It is therefore desirable to synthesize other analogues of TADDOL-based phosphoric acids, and evaluate their potential as organocatalysts in asymmetric organic reactions. It is hoped that the investigation of TADDOL-based phosphoric acids in organic solvent would provide us with a better understanding of phosphoric acid catalysis, and consequently aid in the development of phosphoric acid catalysis in water. In addition, investigation of the PQS-BINAP-Rh catalyst in various reactions would aid in the understanding of carrying out Rh-catalyzed reactions in water, and may lead to their application in phosphoric acid catalyzed reactions in water. Consequently, this chapter is comprised of: (1) the synthesis of various TADDOL-based chiral phosphoric acid catalysts and evaluation of their applications in organic solvent; and (2) the synthesis of the PQS-BINAP-Rh catalyst and its evaluation for the asymmetric hydrogenation and 1,4-addition of fumaric diesters. The ultimate goal is to expand the scope of asymmetric phosphoric-acid catalyzed reactions in water, possibly with the assistance of transition metals like Rh.



**Figure 4.3** BINOL-based phosphoric acid derivative **PQS-PA1**.

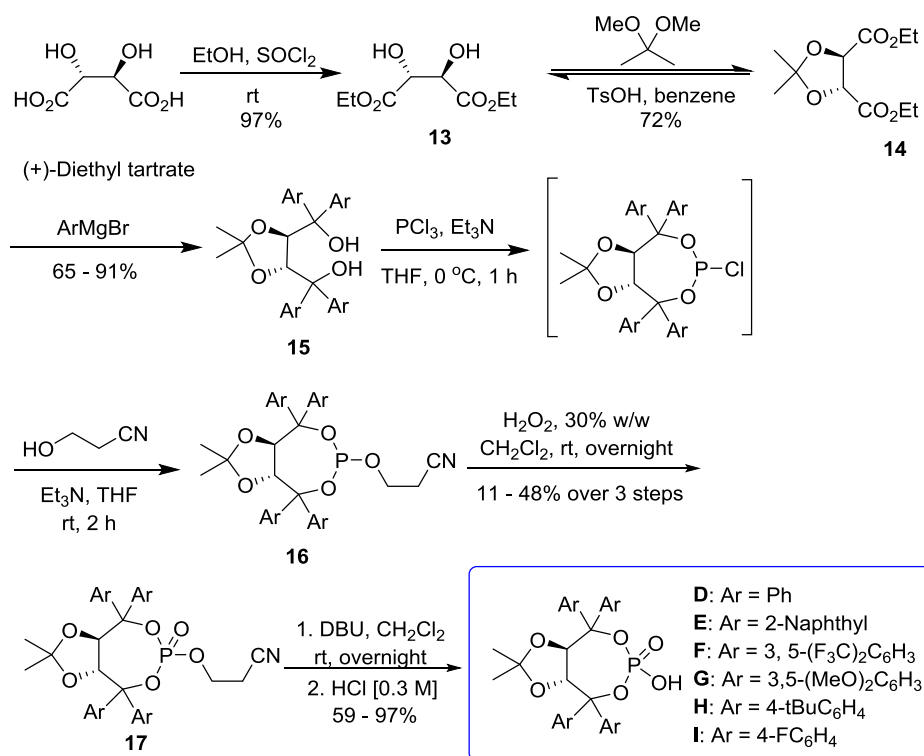
## 4.3 Development of Brønsted acid catalysis in organic solvent

### 4.3.1 Synthesis of TADDOL-based phosphoric acids

As mentioned in the earlier section, the first part of this project involves the synthesis of TADDOL-based phosphoric acids and evaluation as catalysts for different reactions in organic solvent. The chiral TADDOL-based phosphoric catalysts were prepared starting from the cheap and readily available (+)-*L*-tartaric acid (Scheme 4.9). Diester **13** was synthesized according to literature by esterification of (+)-*L*-tartaric acid with ethanol and thionyl chloride,<sup>17</sup> after which protection of the diol functionality was carried out by treatment with 2,2-dimethoxypropane in the presence of a catalytic amount of *p*-TsOH in benzene and azeotropic removal of water. Solvents like ethanol (43% yield), methanol (4% yield) and acetone (37% yield) were initially used as the solvent, but benzene proved to be the best amongst them as it furnished the desired product with the highest yield (72%). A Grignard reaction to form the TADDOL scaffold was subsequently conducted, after which the typical method used to synthesize phosphoric acids (POCl<sub>3</sub>, Et<sub>3</sub>N and then H<sub>2</sub>O) was carried out. Unfortunately, this method failed to afford the desired TADDOL-based phosphoric acids. An alternative protocol that makes use of a three step procedure was adopted instead.<sup>18</sup> This involves treatment of the TADDOL derivative with phosphorus trichloride under basic conditions, addition of 3-hydroxypropionitrile, followed by oxidation with a 30% w/w solution of hydrogen peroxide. Purification of intermediate **16** by flash chromatography was attempted to improve the yield of **17** (<50%). However, such attempts were unsuccessful due to the relative instability of the phosphite. Various attempts to synthesize the derivatives of compound **17** via this 3-step procedure were made because early attempts gave negligible amounts of the desired catalyst intermediate. It has to be emphasized that it is crucial that all reagents and solvents were distilled or dried prior to use, and that the hydrogen peroxide is in good condition. Subsequent treatment of compound **17** with 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU), followed by an acidic

work-up furnished the phosphoric acids **D-I** in good to excellent yields, two of which are novel catalysts (**G, H**).

**Scheme 4.9** Synthesis of TADDOL-based phosphoric acids.

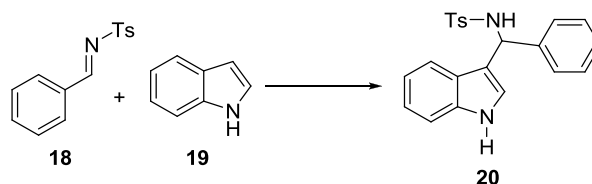


### 4.3.2 Use of phosphoric acids in the Friedel-Crafts reaction

With these phosphoric acids in hand, we next examined their efficiency for several reactions. We started our study with the Friedel-Crafts (F-C) reaction of indoles with imines, which furnishes products with an indole framework that is a privileged motif in a huge number of therapeutic agents and natural products.<sup>19</sup> Being an electron-rich heteroaromatic, the indole is activated toward electrophilic substitution, making it a suitable substrate for the asymmetric F-C reaction. Carrying out this reaction in the presence of 10 mol% catalyst showed that catalyst **D** afforded the desired product with the highest enantioselectivity (Table 4.1, entry 1). The use of catalyst **E**, which contains a bulky substituent led to a lower yield of the product, with no improvements in the enantioselectivity (entry 2). In addition,

electron-donating or electron-withdrawing substituents also led to lower yields and enantioselectivities (entries 3-6).

**Table 4.1** Screening of various catalysts.<sup>a</sup>

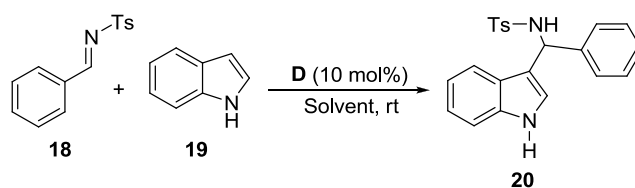


entry	catalyst	yield (%) <sup>b</sup>	ee (%) <sup>c</sup>
1	<b>D</b>	75	31
2	<b>E</b>	60	20
3	<b>F</b>	65	26
4	<b>G</b>	30	21
5	<b>H</b>	35	20
6	<b>I</b>	40	28

<sup>a</sup> Reaction conditions: Imine **18** (0.2 mmol), indole **19** (5 equiv), catalyst (10 mol%), toluene (1 mL, 0.2 M), rt. <sup>b</sup> Yields are isolated yields after SiO<sub>2</sub> column chromatography.

<sup>c</sup> Determined by chiral HPLC analysis (Chiralcel OD-H).

Next, the effect of various solvents on the reaction outcome was investigated using catalyst **D** as the catalyst of choice (Table 4.2). It was observed that the reaction proceeded smoothly in ethereal (entries 3 and 4), and chlorinated (entries 2 and 6) solvents. On the other hand, racemic product was obtained with the use of polar, protic solvents such as methanol (entry 5), and aprotic solvents like DMF and DMSO (entries 8 and 9). It was eventually determined that DCM was the optimal solvent, affording the product with the highest enantioselectivity and moderate yield (entry 2).

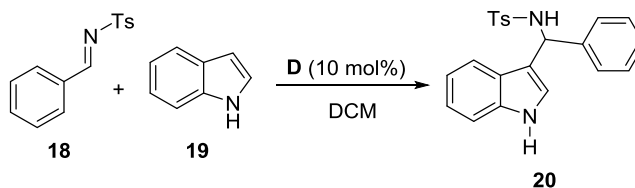
**Table 4.2** Screening of solvent.<sup>a</sup>

entry	solvent	yield (%) <sup>b</sup>	ee (%) <sup>c</sup>
1	toluene	75	31
2	DCM	64	41
3	ether	70	31
4	THF	35	29
5	MeOH	60	0
6	CHCl <sub>3</sub>	55	21
7	CH <sub>3</sub> CN	56	16
8	DMF	23	0
9	DMSO	24	0

<sup>a</sup> Reaction conditions: Imine **18** (0.2 mmol), indole **19** (5 equiv), catalyst **D** (10 mol%), solvent (1 mL, 0.2 M), rt. <sup>b</sup> Yields are isolated yields after SiO<sub>2</sub> column chromatography.

<sup>c</sup> Determined by chiral HPLC analysis (Chiralcel OD-H).

Having identified the optimal catalyst and solvent, the reaction temperature was then varied (Table 4.3). It was observed that lowering the reaction temperature resulted in a slower reaction and lower enantioselectivity (entry 1), while increasing the reaction temperature to 40 °C resulted in a faster reaction and higher enantioselectivity (entry 4). Decreasing the amount of indole used to 2 equivalents led to an improvement in the enantioselectivity to 83% (entry 5).

**Table 4.3** Further optimization of reaction conditions.<sup>a</sup>

entry	temperature (°C)	yield (%) <sup>b</sup>	ee (%) <sup>c</sup>
1	- 25	60	27
2	0	61	0
3	rt	64	41
4	40	67	50
5 <sup>d</sup>	rt	60	83

<sup>a</sup> Reaction conditions: Imine **18** (0.2 mmol), indole **19** (5 equiv), catalyst **D** (10 mol%), DCM (1 mL, 0.2 M), rt. <sup>b</sup> Yields are isolated yields after SiO<sub>2</sub> column chromatography.

<sup>c</sup> Determined by chiral HPLC analysis (Chiralcel OD-H). <sup>d</sup> 2 equiv indole used.

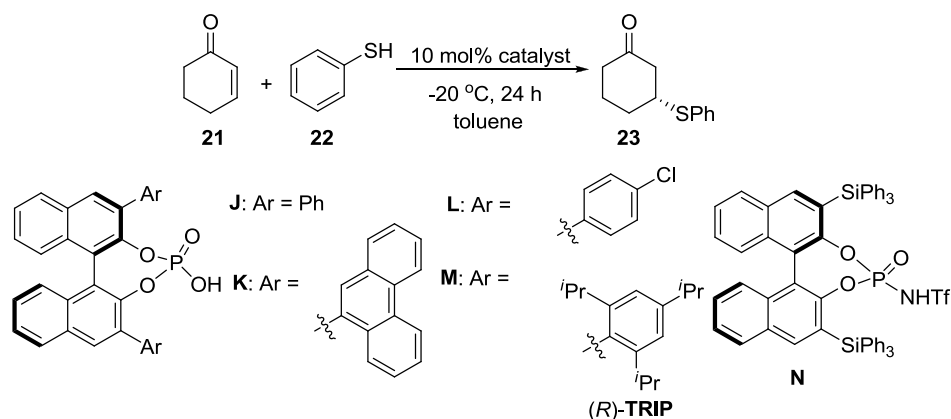
In the field of organocatalysis, various groups have made use of different catalysts to facilitate efficient F-C reactions. Despite the extensive optimization carried out as shown above, the results obtained with phosphoric acids bearing the TADDOL scaffold did not perform as well as those bearing the BINOL scaffold. It was reported by You and co-workers that the use of BINOL-based phosphoric acids efficiently furnish the desired products with up to >99% ee.<sup>20</sup>

### 4.3.3 Use of phosphoric acids in the Michael reaction

Another reaction that was studied in detail was the Michael addition reaction of thiols to  $\alpha,\beta$ -unsaturated ketones. This reaction was chosen as it provides direct access to optically active sulphides that are versatile building blocks for the synthesis of biologically important compounds.<sup>21</sup> Screening of various TADDOL- and BINOL-based phosphoric acid catalysts was carried out (Table 4.4). Carrying out this reaction in the presence of 10

mol% catalyst showed that among the TADDOL-based phosphoric acids, catalyst **D** afforded the desired product with the highest enantioselectivity (24% ee, entry 1). The use of catalyst **E**, which contains a bulky substituent led to a slightly higher yield of the product, with no improvements in the enantioselectivity (entry 2). Furthermore, electron-donating or electron-withdrawing substituents also led to lower yields and enantioselectivities (entries 3-6). It was observed that catalysts bearing the BINOL backbone generally gave a higher yield (entries 7, 9-11). Furthermore, the use of BINOL-based phosphoric acids bearing an electron-donating, electron-withdrawing, or bulky substituent did not lead to a higher enantioselectivity (entries 7-10). It seemed that acidity played an important role in influencing the enantioselectivity of this reaction, as seen by the highest enantioselectivity observed with the use of BINOL-based catalyst **N**, which possesses an *N*-triflyl phosphoramidate group (-54% ee, entry 11). This catalyst turned out to be the best catalyst, affording the product in 71% yield and -54% ee.

**Table 4.4** Screening of various catalysts.<sup>a</sup>



entry	catalyst	ee (%) <sup>b</sup>	yield (%) <sup>c</sup>
1	<b>D</b>	24	43
2	<b>E</b>	15	47
3	<b>F</b>	12	43

4	<b>G</b>	-5	41
5	<b>H</b>	-2	24
6	<b>I</b>	23	42
7	<b>J</b>	12	63
8	<b>K</b>	21	40
9	<b>L</b>	22	72
10	<b>M</b>	15	78
11	<b>N</b>	-54	71

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<sup>a</sup> Reaction conditions: **21** (0.1 mmol), **22** (0.12 mmol), catalyst (10 mol%), toluene (0.5 mL, 0.2 M). <sup>b</sup> Isolated yield after SiO<sub>2</sub> column chromatography. <sup>c</sup> Determined by chiral HPLC analysis.

#### 4.4 PQS-BINAP-Rh-catalyzed reactions in water

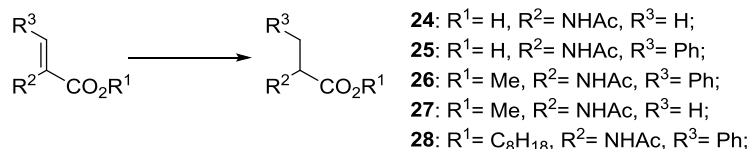
As a build up to the eventual goal of carrying out an asymmetric reaction in water using PQS-bound phosphoric acids, the PQS-BINAP-Rh catalyst was synthesized according to literature, with slight modifications.<sup>5c</sup> Having synthesized the catalyst, we applied it towards the asymmetric hydrogenation and asymmetric 1,4-addition of aryl boronic acids to fumaric ester compounds.

##### 4.4.1 Use of PQS-BINAP-Rh in asymmetric hydrogenation

Transition metal-mediated asymmetric hydrogenation is an efficient method for the catalytic reduction of prochiral alkenes, ketones, and imines into the corresponding chiral products with hydrogen gas.<sup>22</sup> Hydrogenation of acrylic acids using the PQS-Rh-BINAP catalyst was found to be sluggish (Table 4.5, entries 1 and 2). This may be due to the high polarity of the substrates, which would make them more likely to be outside the micelle and unable to interact with the catalyst. When hydrogenation of the corresponding esters were carried out (entries 3 and 4), the conversion was significantly increased, and an

improvement in enantioselectivity as compared to that in organic solvent was observed for (Z)-methyl 2-acetamido-3-phenylacrylate (entry 3). When a more lipophilic substrate was used, an improvement in conversion was also observed, albeit with loss of enantioselectivity (entry 5).

**Table 4.5** Selected results of hydrogenation using PQS- BINAP-Rh.<sup>a</sup>



entry	substrate	pressure (psi)	conversion (%) <sup>b</sup>	ee (%) <sup>c</sup>	conc. (M)
1	<b>24</b>	100	<10 (100)	N.A. (30.3)	0.05 (0.067)
2	<b>25</b>	100	<10 (99)	N.A. (84)	0.05 (0.025)
3	<b>26</b>	100 (15)	47 (100)	30 (15)	0.1 (0.067)
4	<b>27</b>	44	77 (77)	5 (24) <sup>d</sup>	0.5 (0.05)
5	<b>28</b>	44	50 (N.R.)	0 <sup>d</sup>	0.05

<sup>a</sup> Reaction conditions: Substrate (0.1 mmol), PQS-BINAP-Rh catalyst (2 mol%), water, rt. <sup>b</sup> Estimated by crude <sup>1</sup>H NMR. <sup>c</sup> Determined by HPLC. <sup>d</sup> Determined by GC. Values found with homogeneous catalyst in parentheses.

#### 4.4.2 Use of PQS-BINAP-Rh in the asymmetric 1,4-addition of aryl boronic acids to fumaric ester compounds

The asymmetric 1,4-addition of aryl boronic acids to fumaric ester compounds was also carried out. 1,4-Additions to electron-poor alkenes is a useful methodology for the construction of carbon-carbon bonds.<sup>23</sup> In contrast to  $\alpha,\beta$ -unsaturated ketones (e.g., 2-cyclohexen-1-one), the asymmetric conjugate addition of fumaric ester compounds have met with much less success, even though the corresponding products are synthetically useful 2-substituted 1,4-dicarbonyl compounds.<sup>24</sup> In a study carried out by Hayashi and co-



## 4.5 Conclusions

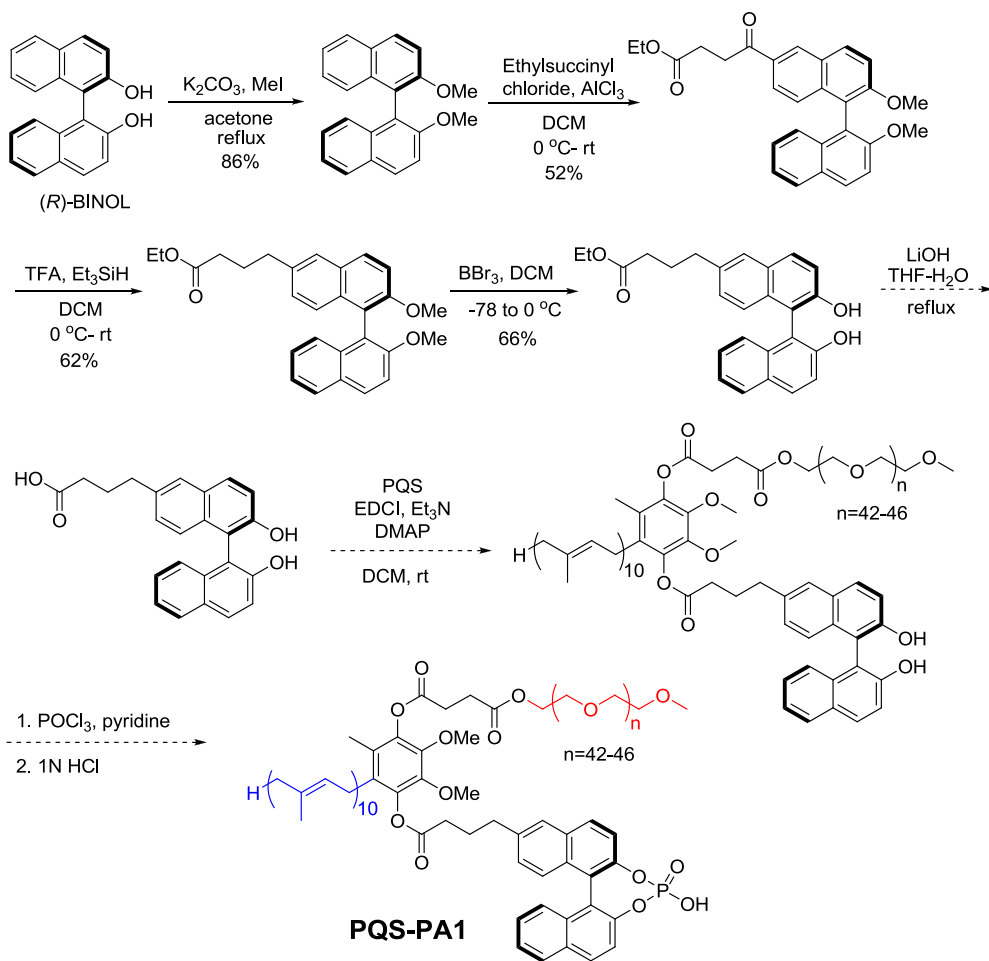
Six chiral phosphoric acids based on the TADDOL scaffold have been synthesized, two of which are novel catalysts (**G**, **H**). The catalytic ability of these catalysts were investigated in various reactions and the desired products were afforded in low enantioselectivities. In the case of the Michael addition reaction of thiols to  $\alpha,\beta$ -unsaturated ketones, these catalysts, as well as BINOL-based phosphoric acid catalysts, were screened and it was determined that a BINOL-based phosphoric acid catalyst (**N**) performed the best (71% yield, -54% ee).

The PQS-BINAP-Rh catalyst was synthesized and applied to the asymmetric hydrogenation and 1,4-addition of arylboronic acids to fumaric compounds. The use of water as a solvent in asymmetric hydrogenations is promising, as seen from the improvement in enantioselectivity for (*Z*)-methyl 2-acetamido-3-phenylacrylate. In the case of the asymmetric 1,4-addition of arylboronic acids to fumaric compounds, the selectivity of the reaction was significantly improved, especially with the addition of a lithium salt.

## 4.6 Outlook

After investigation of phosphoric acid catalysis in organic solvent and Rh-catalyzed reactions in water using the surfactant platform, PQS, the synthesis of PQS-bound phosphoric acids was attempted. The proposed synthesis of BINOL-based phosphoric acid derivative **PQS-PA1** starts with the conversion of commercially available and enantiomerically pure (*R*)-BINOL and follows published protocol (Scheme 4.11).<sup>25</sup> The first four steps have been successfully carried out and its complete synthesis, followed by application in asymmetric reactions in water will be explored in due course.

**Scheme 4.11** Synthesis of BINOL-based phosphoric acid derivative **PQS-PA1**.



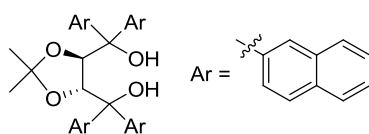
## 4.7 Experimental Section

### 4.7.1 General Information

$^1\text{H}$ -NMR,  $^{13}\text{C}$ -NMR and  $^{31}\text{P}$ -NMR spectra were recorded on a Bruker Avance DPX 300, Bruker AMX 400, Varian UNITY INOVA Avance at 400 or 500 spectrophotometer with  $\text{CDCl}_3$  as solvent. Chemical shifts for  $^1\text{H}$  NMR spectra are reported as  $\delta$  in units of parts per million (ppm) downfield from  $\text{SiMe}_4$  ( $\delta$  0.00) and relative to the signal of chloroform-*d* ( $\delta$  7.26).  $^{13}\text{C}$  NMR spectra are reported as  $\delta$  in units of parts per million (ppm) downfield from  $\text{SiMe}_4$  ( $\delta$  0.00) and relative to the signal of chloroform-*d* ( $\delta$  77.0). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad), coupling constant in Hz and integration. Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 pre-coated silica gel plate (0.2 mm thickness). Subsequent to elution, plates were visualized using UV radiation (254 nm). Visualization of the developed chromatogram was followed by UV absorbance, iodine, aqueous ammonium molybdate or aqueous potassium permanganate. Flash chromatography was performed using Merck silica gel 60 with freshly distilled solvents. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use. High resolution mass spectrometry (HRMS) was recorded on Finnigan MAT 95  $\times$  P spectrometer. Enantioselectivities were determined by High Performance Liquid Chromatography (HPLC) analysis employing a Daicel Chirapak Chiracel OD-H (0.46cm x 25 cm) column or a Shimadzu SPD-m20a Prominence diode array detector. Chiral GC analysis was performed using a Restek RT-*beta*DEXcst column (30 m x 0.250 mm, 0.25 micron). Retention times ( $t_{\text{R}}$ ) are from compound dependent temperature programs; split-inlet at 200 °C at 11.60 psi ( $\text{H}_2$ , constant pressure) with 20:1 split, FID 290 °C. The phosphoric acid catalysts and PQS-BINAP-Rh were synthesized according to literature procedures.<sup>5c,17,18</sup>

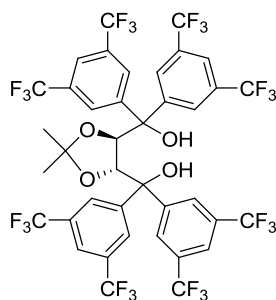
#### 4.7.1 Procedure for the preparation of TADDOL Derivatives 15a-f:

Magnesium (16.2 mmol, 8 equiv), anhydrous THF (6 mL), and a grain of iodine were added to a flame-dried two-necked round bottomed flask. Alky bromide (16.2 mmol, 8 equiv) in THF (3 mL) was then added dropwise such that a gentle reflux is maintained. The reflux was continued for 1 hr, followed by cooling to room temperature. (4*R*,5*R*)-diethyl 2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (0.5g, 2.03 mmol) in THF (3mL) was then added and stirred at room temperature overnight. Aqueous saturated ammonium chloride (10 mL) was carefully added to quench the reaction. The organic layer was separated, and the aqueous phase was extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with brine, then dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The crude product was purified by flash column chromatography to afford the pure TADDOL derivatives.



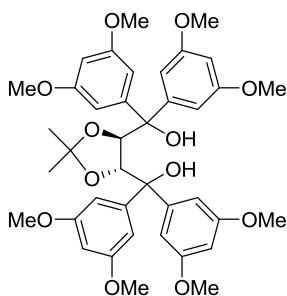
##### (4*R*,5*R*)-2,2-Dimethyl-- $\alpha,\alpha,\alpha',\alpha'$ -tetra(naphth-2-yl)-1,3-dioxolane-4,5-dimethanol

**(15b):** White solid, 63 % yield; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.34 - 7.64 (m, 28H), 4.94 (s, 2H), 4.69 (br, 2H), 1.15 (s, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  142.7, 140.7, 132.9, 132.8, 129.2, 128.8, 128.4, 128.3, 128.1, 127.7, 127.6, 127.5, 127.3, 127.0, 126.5, 126.4, 126.3, 126.1, 126.0, 110.1, 81.6, 78.8, 27.6.



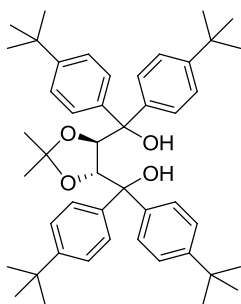
**(4R,5R)-2,2-dimethyl- $\alpha,\alpha,\alpha',\alpha'$ -tetrakis[3,5-bis(trifluoromethyl)phenyl]-1,3-**

**dioxolane-4,5-dimethanol (15c):** White solid, 71% yield;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.11 (s, 4H), 7.94 (s, 2H), 7.82 (s, 6H), 6.98 (s, 2H), 4.16 (s, 2H), 1.11 (s, 6H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  146.4, 143.7, 132.7, 132.4, 132.3, 132.1, 131.9, 131.7, 131.6, 131.3, 128.7, 127.8, 127.5, 127.3, 124.8, 124.6, 122.7, 122.1, 121.9, 119.3, 119.2, 111.0, 81.5, 25.4.



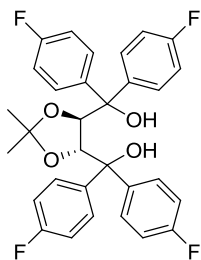
**(4R,5R)-2,2-dimethyl- $\alpha,\alpha,\alpha',\alpha'$ -tetrakis[3,5-bis(dimethoxy)phenyl]-1,3-dioxolane-**

**4,5-dimethanol (15d):** White solid, 87% yield;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.75(s, 4H), 6.53(s, 4H), 6.37(s, 2H), 6.28(s, 2H), 4.53(s, 2H), 4.24(s, 2H), 3.73 (s, 12H), 3.67 (s, 12H), 1.16 (s, 6H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  160.4, 160.0, 147.7, 145.1, 109.3, 106.9, 106.2, 99.5, 99.2, 81.7, 78.2, 55.5, 55.3, 27.5; HRMS (ESI) Calcd. for  $\text{C}_{39}\text{H}_{47}\text{O}_{12}$ ,  $m/z$  706.3068  $[\text{M}+\text{H}]^+$ ; Found: 707.3068.



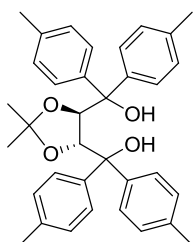
**(4R,5R)-2,2-dimethyl- $\alpha,\alpha,\alpha',\alpha'$ -tetrakis[3,5-bis(1,1-dimethylethyl)phenyl]-1,3-**

**dioxolane-4,5-dimethanol (15e):** White solid, 86% yield;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.29- 7.33 (m, 12H), 3.92 (s, 2H), 1.33 (s, 18H), 1.27 (s, 18H), 1.01 (s, 6H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  150.1, 149.9, 143.5, 139.8, 128.5, 127.5, 125.1, 124.2, 109.4, 81.3, 77.9, 34.6, 31.7, 31.5, 27.2.



**(4R,5R)-2,2-dimethyl- $\alpha,\alpha,\alpha',\alpha'$ -tetrakis(4-fluorophenyl)-1,3-dioxolane-4,5-**

**dimethanol (15f):** White solid, 56% yield;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.43 (q,  $J = 4.7$  Hz, 4H), 7.24 (q,  $J = 4.7$  Hz, 4H), 7.00 (t,  $J = 8.6$  Hz, 4H), 6.91 (t,  $J = 8.6$  Hz, 4H), 4.55 (s, 2H), 4.40 (s, 2H), 1.04 (s, 6H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  163.6, 163.5, 161.2, 161.0, 141.5, 138.2, 138.1, 130.5, 130.4, 129.6, 115.3, 115.1, 114.6, 114.4, 109.9, 81.0, 77.8, 27.3.



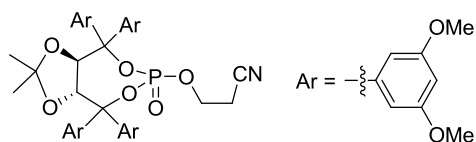
**(4R,5R)-2,2-dimethyl- $\alpha,\alpha,\alpha',\alpha'$ -tetrakis(4-methylphenyl)-1,3-dioxolane-4,5-**

**dimethanol (15g):** White solid, 91% yield;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.38 (d,  $J = 8.0$  Hz, 4H), 7.19 (d,  $J = 8.1$  Hz, 4H), 7.10 (d,  $J = 7.9$  Hz, 4H), 7.02 (d,  $J = 8.0$  Hz, 4H), 4.53 (s, 2H), 4.15- 4.18 (br, 2H), 2.34 (s, 6H), 2.26 (s, 6H), 1.04 (s, 6H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  143.4, 140.1, 137.2, 136.7, 128.9, 128.7, 128.1, 127.7, 109.4, 81.2, 78.0, 27.4, 21.3, 21.2.

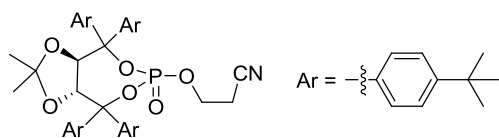
#### 4.7.2 Procedure for the synthesis of 17a-f:

To a stirred solution of the respective TADDOL derivatives (1.00 mmol) and  $\text{NEt}_3$  (3.40 mmol, 3.4 equiv) in dry THF (5 mL) at 0 °C was added dropwise  $\text{PCl}_3$  (1.05 mmol, 1.05 equiv). The resulting mixture was stirred at 0 °C for 30 min. 3-hydroxypropionitrile (1.1 mmol, 1.1 equiv) in dry THF (5 mL) was then added dropwise *via* cannula. The

reaction mixture was allowed to warm to room temperature and stirred for 2 h, after which it was diluted with dry THF and filtered through celite. The solvent was removed *in vacuo* to give a light yellow solid which was directly used without purification. To the crude phosphite in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added 30% aqueous H<sub>2</sub>O<sub>2</sub> (6.2 mmol, 6.2 equiv). The biphasic mixture was stirred vigorously overnight and then quenched by the addition of 20 mL of saturated aqueous NaHCO<sub>3</sub>. The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (20 mL) and the combined organic extracts were washed with saturated aqueous NaCl, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography to afford the pure product.

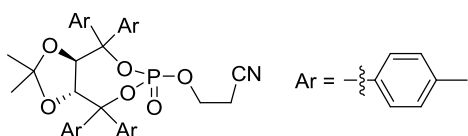


**TADDOL precatalyst (17d):** White solid (11 %); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.37-6.74 (m, 12H), 5.29 (d, *J* = 7.6 Hz, 1H), 5.12 (d, *J* = 7.6 Hz, 1H), 3.53- 3.89 (m, 25H), 3.91-4.01 (m, 1H), 2.32- 2.37 (m, 1H), 2.19- 2.31 (m, 1H), 0.96 (s, 3H), 0.65 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 116.0, 113.5, 107.7, 107.1, 105.7, 105.5, 99.8, 99.6, 99.4, 87.9, 88.6, 88.5, 80.1, 78.8, 62.2, 55.4, 55.3; <sup>31</sup>P NMR (162 MHz, CDCl<sub>3</sub>) δ - 12.7; HRMS (ESI) Calcd. for C<sub>42</sub>H<sub>48</sub>NO<sub>14</sub>P, *m/z* 822.2891 [M+H]<sup>+</sup>; Found: 822.2883.



**TADDOL precatalyst (17e):** White solid (30 %); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.52 (d, *J* = 8.0 Hz, 2H), 7.47- 7.42 (m, 4H), 7.38- 7.25 (m, 10H), 5.42 (d, *J* = 8.0 Hz, 1H), 5.10 (d, *J* = 8.0 Hz, 1H), 3.88- 3.80 (m, 1H), 3.38- 3.30 (m, 1H), 2.07- 2.00 (m, 1H), 1.86- 1.78 (m, 1H), 1.33- 1.27 (m, 36H), 0.82 (s, 3H), 0.42 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 151.6,

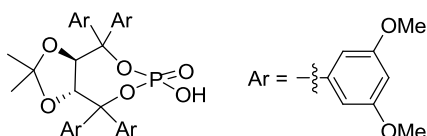
151.0, 150.9, 149.9, 141.0, 140.4, 136.9, 136.8, 136.3, 136.2, 128.8, 128.2, 127.2, 126.7, 125.4, 125.2, 124.5, 124.2, 116.2, 116.1, 113.8, 89.3, 89.2, 88.5, 88.4, 80.3, 78.4, 61.9, 34.8, 34.6, 31.5, 31.4, 26.9, 26.0, 18.8;  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ )  $\delta$  - 12.7; HRMS (ESI) Calcd. for  $\text{C}_{50}\text{H}_{65}\text{NO}_6\text{P}$ ,  $m/z$  806.4471  $[\text{M}+\text{H}]^+$ ; Found: 806.4480.



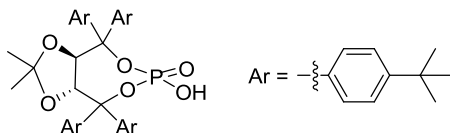
**TADDOL precatalyst (17g):** White solid (36 %);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.41-7.28 (m, 4H), 7.25- 7.04 (m, 13H), 5.35 (d,  $J = 8.0$  Hz, 1H), 5.12 (d,  $J = 8.0$  Hz, 1H), 3.94-3.87 (m, 1H), 3.48- 3.41 (m, 1H), 2.36- 2.18 (m, 13H), 2.06- 1.99 (m, 1H), 0.83 (s, 3H), 0.54 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  138.5, 138.1, 137.8, 137.7, 137.0, 136.9, 136.6, 136.5, 129.2, 129.1, 128.5, 128.4, 128.1, 127.4, 126.9, 116.3, 116.1, 113.9, 89.2, 89.1, 88.7, 80.1, 78.5, 62.1, 62.0, 27.0, 26.5, 21.3, 21.2, 19.1, 19.0;  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ )  $\delta$  - 12.7; HRMS (ESI) Calcd. for  $\text{C}_{38}\text{H}_{40}\text{NO}_6\text{P}$ ,  $m/z$  637.2593  $[\text{M}+\text{H}]^+$ ; Found: 637.2586.

#### 4.7.3 Procedure for the synthesis of chiral phosphoric acids (D-I):

To a stirred solution of the crude phosphate (1.00 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (10 mL) was added, dropwise at room temperature, DBU (150 mL, 1.0 mmol, 1.0 equiv). The solution was stirred 5 min at room temperature and when the reaction was complete by TLC, AcOH (50 mL) was added, followed by  $\text{H}_2\text{O}$  (10 mL). The organic layer was then washed two times with a 0.3 M HCl solution, saturated aqueous NaCl, and dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo* to afford the pure product.



**Chiral phosphoric acid (G):** White crystals (59 %);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.77 (br, 1H), 6.76 (d,  $J = 8.0$  Hz, 4H), 6.62 (d,  $J = 8.0$  Hz, 4H), 6.39 (d,  $J = 8.0$  Hz, 4H), 5.16 (s, 2H), 3.73 (s, 12H), 3.69 (s, 12H), 0.77 (s, 6H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  160.6, 159.9, 145.6, 141.5, 113.9, 107.6, 105.7, 99.8, 99.7, 88.3, 88.2, 79.7, 55.5, 27.0;  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ )  $\delta$  - 8.75; HRMS (ESI) Calcd. for  $\text{C}_{39}\text{H}_{45}\text{O}_{14}\text{P}$ ,  $m/z$  769.2625  $[\text{M}+\text{H}]^+$ ; Found: 769.2608,  $[\alpha]_{\text{D}}^{21} = -195.7$  ( $c = 1.16$ ,  $\text{CHCl}_3$ ).



**Chiral phosphoric acid (H):** White crystals (80 %);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.07 (br, 1H), 7.43 (d,  $J = 8.0$  Hz, 2H), 7.28- 7.24 (m, 10H), 7.18 (d,  $J = 8$  Hz, 4H), 5.15 (s, 2H), 1.25- 1.20 (m, 36H), 0.54 (s, 6H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  150.6, 150.4, 140.8, 137.2, 137.1, 128.6, 126.8, 125.1, 124.1, 113.6, 79.8, 34.7, 34.6, 31.6, 31.5, 26.6;  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ )  $\delta$  -7.40; HRMS (ESI) Calcd. for  $\text{C}_{39}\text{H}_{45}\text{O}_{14}\text{NaP}$ ,  $m/z$  775.4103  $[\text{M}+\text{Na}]^+$ ; Found: 775.4126.

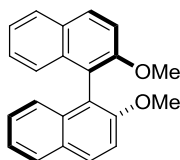
#### 4.7.4 Procedure for the Catalytic Asymmetric Friedel-Crafts Reaction:

To a 4 mL vial was added *N*-sulfonyl imine **18** (0.1 mmol), catalyst (10 mol%), and dry DCM (0.5 mL) under nitrogen. The reaction mixture was stirred for 10 min at rt and then for another 5 min at the stated temperature. Subsequently, indole **19** (0.2 mmol) was added in one portion and the reaction was left to stir until TLC indicated that the reaction was complete. The reaction was quenched using 10%  $\text{NaHCO}_3$  (1.2 mL), extracted with EtOAc (3 x 0.5 mL), and the solvent was evaporated *in vacuo*. Flash column chromatography using gradient elution of EtOAc/Hexane = 1 / 1 afforded the pure product.

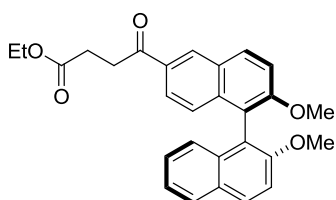
#### 4.7.5 Procedure for the phosphoric acid catalyzed Michael additions of thiols to $\alpha,\beta$ -unsaturated ketones:

To a 2 mL vial was added cyclohexenone **21** (0.1 mmol), thiol **22** (0.12 mmol), catalyst (10 mol%), and 0.5 mL toluene (0.2 M) under nitrogen. The reaction mixture was stirred at rt overnight, after which the solvent was removed *in vacuo* to afford the crude product. Analysis of the mixture by  $^1\text{H}$  NMR and HPLC was subsequently carried out.

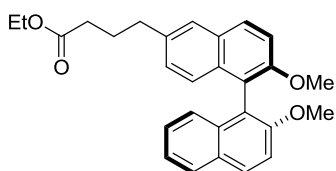
#### 4.7.6 Procedure for the synthesis of PQS-BINAP-Rh:



**(R)-2,2'-Dimethoxy-1,1'-binaphthalene:** To a well-stirred solution of (*R*)-binaphthol (2.50 g, 8.73 mmol) in anhydrous acetone (80 mL) were added anhydrous  $\text{K}_2\text{CO}_3$  (3.62 g, 26.2 mmol) and methyl iodide (1.65 mL, 26.2 mmol). The mixture was heated at reflux for 18 h. After cooling, the volatiles were removed *in vacuo* and the residual solids dissolved in  $\text{CH}_2\text{Cl}_2$  and  $\text{H}_2\text{O}$ . The layers were separated, and the aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 30 mL). The combined organic layers were dried over anhydrous  $\text{Na}_2\text{SO}_4$ , and the solvent was removed *in vacuo* to leave a pale yellow solid which was purified by washing with MeOH (3 x 10 mL) and concentrated *in vacuo* to afford the title compound (2.74 g, 99%) as a white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.99 (d,  $J = 9.2$  Hz, 2H), 7.87 (d,  $J = 8.4$  Hz, 2H), 7.47 (d,  $J = 9.2$  Hz, 2H), 7.32 (ddd,  $J = 8.0, 6.8, 1.2$  Hz, 2H), 7.22 (ddd,  $J = 8.4, 6.8, 1.2$  Hz, 2H), 7.11 (d,  $J = 8.4$  Hz, 2H), 3.78 (s, 6H).

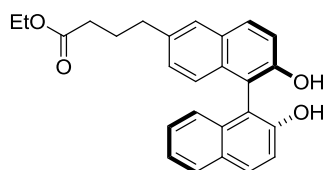


**(R)-Ethyl 4-(2,2'-Dimethoxy-1,1'-binaphth-6-yl)-4-oxobutanoate:** To a cooled (0 °C) solution of (R)-2,2'-dimethoxy-1,1'-binaphthalene (2.67 g, 8.49 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (65 mL) under argon was added solid AlCl<sub>3</sub> (1.36 g, 10.19 mmol). The red solution was stirred for 10 min, and to this was added dropwise ethyl succinyl chloride (1.33 mL, 9.34 mmol). The resulting brown solution was warmed to rt, stirred for 18 h, and poured carefully onto H<sub>2</sub>O (60 mL). The layers were separated, and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 30 mL). The combined organic layers were washed with H<sub>2</sub>O (2 x 30 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to afford the crude product which was subsequently purified by flash chromatography on silica gel (eluting with 30% EtOAc/hexanes) to afford the product as a white solid (2.63 g, 70%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.57 (d, *J* = 1.6 Hz, 1H), 8.12 (d, *J* = 8.8 Hz, 1H), 8.01 (d, *J* = 8.8 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.78 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.53 (d, *J* = 9.2 Hz, 1H), 7.47 (d, *J* = 9.2 Hz, 1H), 7.33 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 7.23 (ddd, *J* = 8.4, 6.8, 1.2 Hz, 1H), 7.16 (d, *J* = 8.8 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.82 (s, 3H), 3.77 (s, 3H), 3.42 (t, *J* = 6.8 Hz, 2H), 2.80 (t, *J* = 6.8 Hz, 2H), 1.28 (t, *J* = 7.2 Hz, 3H).



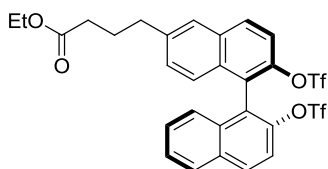
**(R)-Ethyl 4-(2,2'-Dimethoxy-1,1'-binaphth-6-yl)butanoate:** To a solution of (R)-ethyl 4-(2,2'-dimethoxy-1,1'-binaphth-6-yl)-4-oxobutanoate (3.80 g, 8.60 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5.3 mL) under an argon atmosphere, trifluoroacetic acid (10.6 mL) and triethylsilane (3.5 mL) were added dropwise at 0 °C. The mixture was stirred at rt for 7 h. The reaction was

quenched with water (5 mL) in an ice bath and then neutralized with saturated aqueous Na<sub>2</sub>CO<sub>3</sub> (10 mL), and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 30 mL). The combined organic layers were washed with brine (2 x 30 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to afford the crude product which was subsequently purified by flash chromatography on silica gel (eluting with 15% EtOAc/hexanes) to afford the product as a colorless oil (3.50 g, 95%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.98 (d, *J* = 8.8 Hz, 1H), 7.91 (d, *J* = 8.8 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.64 (s, 1H), 7.45 (t, *J* = 8.8 Hz, 2H), 7.32 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 7.29-7.25 (m, 1H), 7.21 (ddd, *J* = 8.4, 6.8, 1.2 Hz, 2H), 7.01-7.11 (m, 2H), 4.11 (q, *J* = 7.2 Hz, 2H), 3.78 (s, 3H), 3.76 (s, 3H), 2.75 (t, *J* = 7.6 Hz, 2H), 2.34 (t, *J* = 7.6 Hz, 2H), 2.00 (quint, *J* = 7.6 Hz, 2H), 1.24 (t, *J* = 7.2 Hz, 3H).

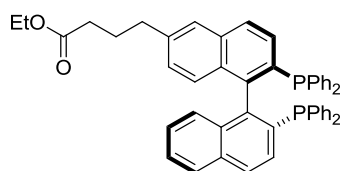


**(R)-Ethyl 4-(2,2'-Dihydroxy-1,1'-binaphth-6-yl)butanoate:** To a cooled (-78 °C) solution of (*R*)-ethyl 4-(2,2'-dimethoxy-1,1'-binaphth-6-yl)butanoate (3.35 g, 7.82 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (54 mL) was added dropwise a 1.0 M CH<sub>2</sub>Cl<sub>2</sub> solution of BBr<sub>3</sub> (17.3 mL, 17.3 mmol). The mixture was warmed over 7 h to 0 °C and then poured carefully onto saturated aqueous NaHCO<sub>3</sub> (50 mL). The layers were separated, and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 20 mL). The combined organic layers were washed with H<sub>2</sub>O (2 x 30 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to afford the crude product which was subsequently purified by flash chromatography on silica gel (eluting with 20% EtOAc/hexanes) to afford the pure product as a white solid (3.10 g, 99%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.99 (d, *J* = 8.8 Hz, 1H), 7.93-7.90 (m, 2H), 7.68 (s, 1H), 7.41-7.36 (m, 3H), 7.32 (ddd, *J* = 8.4, 6.8, 1.6 Hz, 1H), 7.17 (d, *J* = 8.8 Hz,

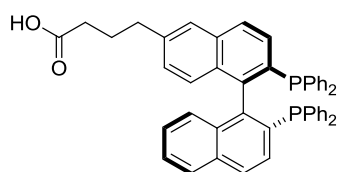
2H), 7.09 (d,  $J = 8.4$  Hz, 1H), 5.08 (s, 1H), 5.02 (s, 1H), 4.12 (q,  $J = 7.2$  Hz, 2H), 2.78 (t,  $J = 7.6$  Hz, 2H), 2.35 (t,  $J = 7.6$  Hz, 2H), 2.02 (quint,  $J = 7.6$  Hz, 2H), 1.25 (t,  $J = 7.2$  Hz, 3H).



**(R)-Ethyl 4-[2,2'-bis(trifluoromethanesulfoxy)-1,1'-binaphth-6-yl]butanoate:** To a cooled ( $0^{\circ}$  C) mixture of (*R*)-ethyl 4-(2,2'-dihydroxy-1,1'-binaphth-6-yl)butanoate (2.59 g, 6.47 mmol), 2,6-lutidine (2.26 mL, 19.4 mmol), and DMAP (0.16 g, 1.31 mmol) was added dropwise trifluoromethanesulfonic anhydride (2.8 mL, 16.9 mmol). The resulting orange solution was warmed to rt, stirred for 20 h, and then poured onto saturated aqueous  $\text{NaHCO}_3$  (20 mL). The layers were separated, and the aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 15 mL). The combined organic layers were washed with 0.5 M aqueous HCl (20 mL),  $\text{H}_2\text{O}$  (2 x 30 mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo* to afford the crude product which was subsequently purified by flash chromatography on silica gel (eluting with 10% EtOAc/hexanes) to afford the pure product as a colorless oil (4.17 g, 97%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.15 (d,  $J = 8.8$  Hz, 1H), 8.07 (d,  $J = 9.2$  Hz, 1H), 8.02 (d,  $J = 8.4$  Hz, 1H), 7.79 (s, 1H), 7.63-7.58 (m, 3H), 7.43 (t,  $J = 8.4$  Hz, 1H), 7.28-7.25 (m, 2H), 7.18 (d,  $J = 8.8$  Hz, 1H), 4.14 (q,  $J = 7.2$  Hz, 2H), 2.84 (t,  $J = 7.6$  Hz, 2H), 2.37 (t,  $J = 7.6$  Hz, 2H), 2.06 (quint,  $J = 7.6$  Hz, 2H), 1.26 (t,  $J = 7.2$  Hz, 3H).

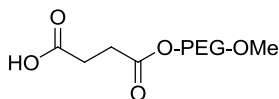


**(R)-Ethyl 4-[2,2'-(Diphenylphosphino)-1,1'-binaphth-6-yl]butanoate:** To a solution of NiCl<sub>2</sub>dppf (0.122 g, 0.23 mmol) in anhydrous DMF (3 mL) was added diphenylphosphine (0.16 mL, 0.92 mmol). The dark brown solution was then heated to 110 °C for 1 h. A solution of (R)-ethyl 4-[2,2'-bis(trifluoromethanesulfoxy)-1,1'-binaphth-6-yl]butanoate (1.02 g, 1.53 mmol) and DABCO (0.69 g, 6.15 mmol) in anhydrous DMF (4.5 mL) was added in one portion to the reaction flask and the resulting dark green solution is kept at 110 °C. Three additional portions of diphenylphosphine (3 x 0.16 mL) are added by syringe after 1 h, 3 h, and 7 h. Heating and stirring was continued for 72 h. The reaction was allowed to cool to rt and the DMF distilled from the reaction mixture. The resulting brown solid was stirred for 30 min in MeOH (20 mL) and filtered. The crude product was washed with methanol and dried *in vacuo* which was subsequently purified by flash chromatography on silica gel (eluting with 10% EtOAc/hexanes) to afford the pure product as a white solid (0.84 g, 75%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.90 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 8.8 Hz, 1H), 7.61 (s, 1H), 7.44 (dt, *J* = 8.4, 2.4 Hz, 2H), 7.36 (t, *J* = 8.0 Hz, 1H), 7.22-7.05 (m, 20H), 6.94 (t, *J* = 8.4 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 6.72 (s, 2H), 4.15 (q, *J* = 7.2 Hz, 2H), 2.71 (t, *J* = 7.2 Hz, 2H), 2.31 (t, *J* = 7.2 Hz, 2H), 1.96 (quint, *J* = 7.2 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H).

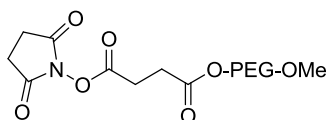


**(R)-4-[2,2'-(Diphenylphosphino)-1,1'-binaphth-6-yl]butanoic acid:** To a solution of (R)-ethyl 4-[2,2'-(diphenylphosphino)-1,1'-binaphth-6-yl]butanoate (0.71 g, 0.96 mmol) in

THF (8 mL) was added 8 mL of aqueous LiOH·H<sub>2</sub>O (2.02 g, 48.00 mmol) and the mixture heated at reflux for 20 h. After being cooled to rt, the solution was acidified to pH 3 with 2.0 M aqueous HCl and extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and the solvent was removed *in vacuo*. Recrystallization from methanol afforded the title compound as a white solid (0.67 g, 99%).  
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.89 (d, *J* = 8.4 Hz, 1H), 7.85-7.82 (m, 2H), 7.60 (s, 1H), 7.44 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.36 (t, *J* = 8.0 Hz, 1H), 7.21-7.06 (m, 20H), 6.94 (t, *J* = 8.4 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 6.71 (s, 2H), 2.73 (t, *J* = 7.2 Hz, 2H), 2.35 (t, *J* = 7.2 Hz, 2H), 1.97 (quint, *J* = 7.2 Hz, 2H).

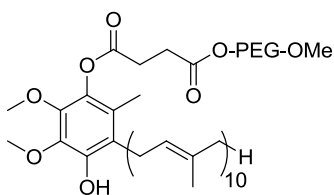


**Synthesis of mono-PEGylated succinic acid:** To a solution of poly(ethylene glycol) monomethyl ether-2000 (15.00 g, 7.50 mmol) and succinic anhydride (1.50 g, 15.00 mmol) in toluene (7.5 mL), Et<sub>3</sub>N (0.53 mL, 3.75 mmol) was added at rt with stirring, and the stirring was continued at 60 °C for 8 h. Water was added to the reaction mixture and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with 1 N HCl (3 x 50 mL), brine (2 x 30 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to afford the poly(ethylene glycol) monomethyl ether-2000 succinate (15.6 g, 99%) as a white solid. IR (thin-film): 3512, 2874, 1734, 1647, 1468, 1349, 1284, 1250, 1109, 949, 844 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 4.28-4.25 (m, 2H), 3.83-3.46 (m, PEG), 3.38 (s, 3H), 2.69-2.61 (m, 4H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 173.1, 171.7, 71.4-68.5 (m, PEG), 63.2, 58.5, 28.6, 28.2; MS (ESI): *m/z* ~ 551 (M + 4Na)<sup>+4</sup>.



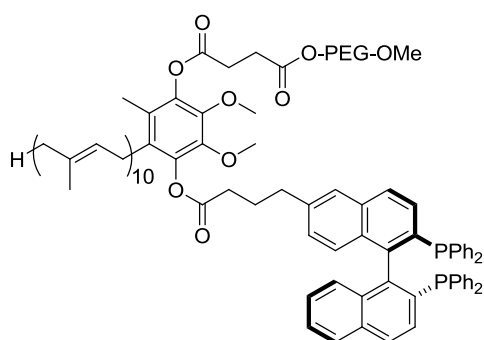
**Synthesis of activated PEGylated succinic acid:** Poly(ethylene glycol) monomethyl ether-2000 succinate (2.10 g, 1.00 mmol) was dissolved in  $\text{CH}_2\text{Cl}_2$  (10 mL) and cooled to  $0^\circ\text{C}$ . N-Hydroxysuccinimide (0.14 g, 1.20 mmol) and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide (EDCI, 0.25 g, 1.30 mmol) were then directly added in succession to the mixture as solids. The resulting mixture was stirred at rt for 12 h. Water was added to the reaction mixture and extracted with  $\text{CH}_2\text{Cl}_2$ .

The combined organic layers were washed with water, brine, dried, and concentrated *in vacuo* to afford the pure product (2.17 g, 99%) as a white waxy solid. IR (thin-film): 2883, 1814, 1784, 1739, 1645, 1468, 1360, 1280, 1234, 1205, 1147, 1116, 1062, 947, 843  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  4.29-4.27 (m, 2H), 3.83-3.46 (m, PEG), 3.38 (s, 3H), 2.97 (t,  $J = 7.2$  Hz, 2H), 2.84 (br s, 4H), 2.79 (t,  $J = 7.2$  Hz, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  170.9, 168.9, 167.6, 71.8-68.8 (m, PEG), 64.1, 59.0, 28.6, 26.2, 25.5; MS (ESI):  $m/z \sim 576$  ( $\text{M} + 4\text{Na}$ ) $^{+4}$ .



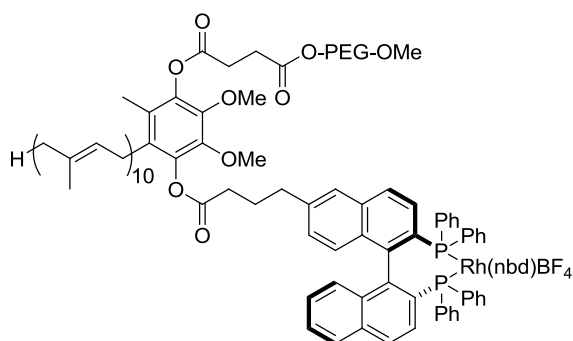
**Synthesis of PQS:** NaH (0.026 g, 0.65 mmol, 60% suspension in mineral oil) was added to a stirred solution of ubiquinol (0.52 g, 0.60 mmol) in THF (5.0 mL) at  $0^\circ\text{C}$ . After addition, the reaction mixture was stirred at  $22^\circ\text{C}$  for 1 h. A solution of PEGylated succinic acid (1.10 g, 0.50 mmol) in THF (5.0 mL) was added to the mixture at  $0^\circ\text{C}$ , and the stirring was continued for 30 min. The mixture was then stirred for another 8 h at rt. It was then cooled to  $0^\circ\text{C}$  and saturated aqueous  $\text{NH}_4\text{Cl}$  was added and then extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic layers were washed with water, brine, dried,

and concentrated *in vacuo* affording a yellowish liquid, which was purified by flash column chromatography on silica gel eluting with a CH<sub>2</sub>Cl<sub>2</sub> to 1:19 MeOH/CH<sub>2</sub>Cl<sub>2</sub> gradient to afford PQS-3 (0.95 g, 65%, mixture of two regioisomers) as a white waxy solid. IR (thin-film): 3518, 2885, 2740, 1761, 1738, 1663, 1467, 1360, 1343, 1280, 1242, 1147, 1114, 1062, 964, 843 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 5.78 (s, 0.3H), 5.74 (s, 0.7H), 5.12-5.06 (m, 9H), 4.98-4.93 (m, 1H), 4.27-4.24 (m, 2H), 3.89 (s, 3H), 3.78 (s, 3H), 3.70-3.44 (m, PEG), 3.37 (s, 3H), 3.31 (d, *J* = 6.4 Hz, 1.4H), 3.16 (d, *J* = 6.4 Hz, 0.6H), 2.94-2.89 (m, 2H), 2.80-2.75 (m, 2H), 2.11-1.96 (m, 39H), 1.74 (s, 2.1H), 1.72 (s, 0.9H), 1.66 (s, 3H), 1.58-1.56 (m, 27H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 172.04, 171.96, 170.9, 170.7, 145.4, 145.0, 142.1, 141.9, 137.8, 137.6, 135.3, 135.1, 135.0, 134.9, 134.8, 131.1, 128.4, 124.9, 124.4, 124.2, 124.1, 124.0, 121.9, 121.6, 117.9, 71.9-69.0 (m, PEG), 63.9, 60.9, 60.8, 60.6, 60.5, 59.0, 39.7, 29.0, 28.8, 28.7, 26.7, 26.6, 26.0, 25.7, 25.3, 17.7, 16.3, 16.2, 16.0, 12.0, 11.3; MS (ESI): *m/z* ~ 763 (M + 4Na)<sup>+4</sup>.



**PQS-BINAP:** PQS-3 (1.00 g, 0.34 mmol) and BINAP acid 22 (0.31 g, 0.44 mmol) were dissolved in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and cooled to 0 °C. 1-(3-Dimethylaminopropyl)-3-ethyl carbodiimide (EDCI) (0.10 g, 0.52 mmol), and DMAP (0.02 g, 0.16 mmol) were then directly added in succession to the mixture as solids. Et<sub>3</sub>N (0.08 mL, 0.57 mmol) was added through a syringe. The resulting mixture was stirred at 22 °C for 20 h. Water was added to the reaction mixture and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with saturated NaHCO<sub>3</sub>, water, brine, dried and concentrated *in vacuo*

affording a colorless liquid, which was purified by flash column chromatography on silica gel, eluting with Et<sub>2</sub>O, followed by 10% MeOH/CH<sub>2</sub>Cl<sub>2</sub> afforded PQS-BINAP (1.20 g, 98%) as a white foam. IR (thin-film): 3051, 2872, 1764, 1738, 1647, 1457, 1350, 1301, 1250, 1116, 951, 846 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.89 (d, *J* = 8.8 Hz, 1H), 7.85-7.82 (m, 2H), 7.64 (s, 1H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.21-7.05 (m, 20H), 6.93 (t, *J* = 8.0 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 6.73 (s, 2H), 5.13-4.97 (m, 10H), 4.29-4.26 (m, 2H), 3.81-3.80 (m, 6H), 3.72-3.46 (m, PEG), 3.39 (s, 3H), 3.21-3.19 (m, 2H), 2.97-2.92 (m, 2H), 2.84-2.77 (m, 4H), 2.63-2.56 (m, 2H), 2.10-1.92 (m, 41H), 1.73-1.55 (m, 33H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 171.9, 171.8, 171.3, 171.2, 170.3, 170.2, 145.1, 144.8, 143.3, 143.1, 140.6, 140.5, 140.3, 140.2, 139.3, 137.9, 137.8, 137.7, 137.5, 137.4, 137.1, 137.0, 135.7, 135.5, 135.4, 134.9, 134.7, 134.5, 134.3, 134.1, 133.9, 133.3, 133.1, 132.8, 132.7, 132.6, 131.9, 131.0, 130.6, 130.3, 128.3, 128.0, 127.9, 127.6, 127.5, 127.3, 126.9, 126.4, 125.7, 124.9, 124.7, 124.3, 124.1, 123.8, 121.1, 71.8-68.9 (PEG), 63.8, 60.6, 60.5, 58.9, 39.6, 34.8, 33.0, 28.9, 28.6, 26.6, 26.5, 26.3, 26.1, 25.6, 17.6, 16.2, 15.9, 12.1, 12.0; <sup>31</sup>P NMR (160 MHz, CDCl<sub>3</sub>, UNREFERENCED) δ 2.2; MS (ESI): *m/z* ~ 936 (M + 4Na)<sup>+4</sup>. Note: The extra peak near 45 ppm on the <sup>31</sup>P NMR spectrum is thought to be from trace amounts of the oxidized complex present.



**PQS-BINAP-Rh(nbd)BF<sub>4</sub>**: To a 10 mL round bottom flask purged with argon and equipped with a stir bar was added PQS-BINAP (600 mg, 0.164 mmol) and Rh(nbd)<sub>2</sub>BF<sub>4</sub> (48 mg, 0.131 mmol). Degassed CH<sub>2</sub>Cl<sub>2</sub> (8.0 mL) was added via syringe and the

mixture was stirred at rt.  $^{31}\text{P}$  NMR analysis confirmed instantaneous complexation. The solvent was removed *in vacuo* to yield PQS-BINAP-Rh(nbd)BF<sub>4</sub> as a dark-red solid (622 mg, 96%).  $^{31}\text{P}$  NMR (160 MHz, CDCl<sub>3</sub>, UNREFERENCED)  $\delta$  43.3, 42.6. Note: The extra peak near 45 ppm on the  $^{31}\text{P}$  NMR spectrum is thought to be from trace amounts of the oxidized version of PQS-BINAP present. The presence of PQS-BINAP (peak at 2.2 ppm) unbound to rhodium is important for high enantioselectivity, as the catalyst is active without a chiral ligand bound, thus degrading selectivity.

#### 4.7.6 Procedure for the PQS-BINAP-Rh catalyzed hydrogenations:

Under an atmosphere of argon, a 5 mL microwave vial was charged with PQS-BINAP-Rh (10 mg, 0.002 mmol), substrate (0.1 mmol) and water. The vial was then put into the stainless steel autoclave, flushed with hydrogen, and the desired pressure was kept constant throughout the whole experiment. The reaction mixture was then diluted with EtOAc (0.5 mL), filtered through a bed of silica gel, and washed with EtOAc (3 x 2 mL). The volatiles were removed *in vacuo* to afford the crude product, which was subsequently analyzed by  $^1\text{H}$  NMR/GC/HPLC.

#### 4.7.6 Procedure for the PQS-BINAP-Rh catalyzed 1,4-addition of boronic acids to fumaric esters:

Under an atmosphere of argon, a 5 mL microwave vial was charged with PQS-BINAP-Rh (10 mg, 0.002 mmol), phenylboronic acid (14.6 mg, 0.12 mmol), and fumaric ester (22.8 mg, 0.1 mmol). Water (0.5 mL) and Et<sub>3</sub>N (42  $\mu\text{L}$ , 0.6 mmol) were added to the vial and stirred at rt overnight. The homogeneous reaction mixture was then diluted with EtOAc (0.5 mL), filtered through a bed of silica gel, and washed with EtOAc

(3 x 2 mL). The volatiles were removed in vacuo to afford the crude product which was subsequently purified by flash chromatography on silica gel and then analyzed by HPLC.

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