Enantioselective Rh(I)-Catalyzed Conjugate Alkynylation of 5-Benzylidene Meldrum's Acid with TMS-acetylene

by

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AUTHOR'S DECLARATION

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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Abstract

The Rh-catalyzed conjugate addition of TMS-acetylene to alkylidene Meldrum's acids was developed. Exceptional ee's and yields were attained using chiral 3,5-Xylyl-BIPHEP ligand. The scope of the reaction was also shown to be very broad with functionalities including phenol, silyl ether, and boronates being tolerated. The successful deprotection and subsequent Sonogashira coupling reaction of the terminal alkyne was also developed.

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A very big thanks also has to go to the people in my life who are not work related, but indeed help me to get through every day. My mom and dad, and sisters Lisa, Joanna and Angela for their unconditional love and support; without them none of this would have been possible. They are always there when I need them and I know they will always be there. I also have to thank my girlfriend Bridget, who has been the source of so much encouragement, and is always willing to listen to me, even if the conversation is about chemistry. She is the reason that evenings and weekends always seem to short and her companionship has meant so much to me.

Dedicated to my Mom, Dad, sisters Angela,

Joanna, and Lisa and my girlfriend Bridget. Their love and support has been invaluable

over the past two years.

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List of Abbreviations

acac	acetylacetone or radical therof
B-1-alkynyl-9-BBN	*B*-1-alkynyl-9-borabicyclo[3.3.1]nonanes
BINAP	1,1′-Binaphthalene-2,2′-diyl-bis(diphenylphosphine)
BiPHEP	2,2′-Bis(diphenylphosphino)-6,6′-dimethoxy-1,1′-biphenyl
DME	1,2-dimethoxyethane
DTBM	di-*tert*-butyl-methoxy
EDG	electron donating group
ee	enantiomeric excess
EWG	electron withdrawing group
h	hour
HOMO	highest occupied molecular orbital
LUMO	lowest unoccupied molecular orbital
PGE_2	Prostaglandin E_2
Piv	pivalate
rt	room temperature
SEGPHOS	5,5′-Bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole, [4(*R*)-(4,4′-bi-1,3-benzodioxole)-5,5′-diyl]bis[diphenylphosphine]
TBAF	tetra-*n*-butylammonium fluoride
TBDMS	*tert*-butyl-dimethylsilyl
TES	triethylsilyl
TIPS	triisopropylsilyl
TMS	trimethylsilyl

Abbreviations for multiplicities of ^{1}H NMR and ^{13}C NMR signals

br s	broad singlet
d	doublet
m	multiplet
q	quartet
s	singlet
t	triplet

1 - Introduction

The 1,4-conjugate addition of carbon nucleophiles to α,β-unsaturated carbonyls is one of the most widely used methods in organic chemistry for the formation of carbon-carbon bonds.[1] The unique reactivities of this class of compounds arise from the conjugation of the carbon-carbon double bond with that of a carbonyl, forming the resonance structures shown in Figure 1.[2]

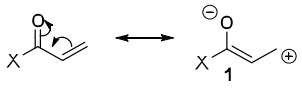


Figure 1. Resonance forms of α, β-unsaturated ketones

The conjugation of the two π systems works to make the β-carbon of **1** bear a partial positive charge, allowing it to react as an electrophile, forming carbon-carbon bonds as in Figure 2. The bond forming step of such a reaction involves the interaction of the HOMO of the nucleophile interacting with the LUMO of the electrophile, the enone in this case, thus forming the new bond.[2] Many different nucleophiles are capable of undergoing such conjugate addition reactions including amines, alcohols, and thiols.

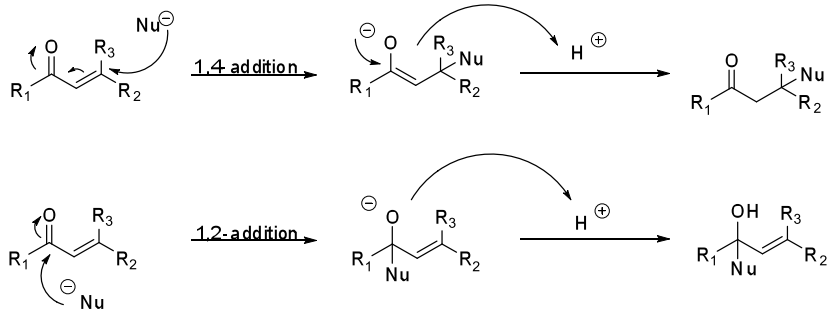


Figure 2. Possible mechanisms of 1,4-addition and 1,2-addition of a nucleophile to an enone

Many factors affect the regioselectivity of such reactions, as the nucleophile can add in either a 1,2- or a 1,4-fashion. To increase the selectivity towards the 1,4-addition several factors can be varied. One can run such reactions at higher temperatures, favouring the more

stable thermodynamic 1,4-addition product.[2] Using a less reactive carbonyl group such as an ester or amide tends to favour the 1,4-addition product, as the β-carbon is more reactive in such species.[2] Finally the nature of the nucleophile can be used to favour 1,2- or 1,4-addition. Such reactions tend to follow the hard and soft base guideline.[3] That is, a hard nucleophile, such as an alkoxide, will tend to favour the 1,2-addition since the carbonyl carbon is a hard electrophile. On the opposite end, a soft nucleophile, such as a thiol, will favour the 1,4-addition, as the β-carbon is a soft electrophile.[2]

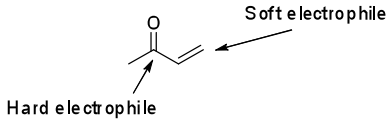


Figure 3. Hard and soft electrophilic positions of enones

Metal alkynylides have different properties depending on the metal that is used, and the hybridization of the carbon that is being activated. Harder carbon groups, like alkyl or alkenyl will favour the 1,2-addition more so than the softer alkynyl. Metals from the first columns of the periodic table; Li, Mg, or Al for example make for hard nucleophiles. Transition metals like Cu, Rh, or Ru make for softer nucleophiles.[3] Thus transmetallation of a hard metal alkynylide with a softer metal can be used to favour the 1,4-addition. This methodology will be discussed in more detail in future sections for metals such as Cu and Rh.

2 - Literature Review

2.1 - Conjugate addition of alkynes to α, β – unsaturated ketones

The addition of alkynes to α, β-unsaturated ketones remains an open area of research, despite the fact that these additions provide a ready route to γ, δ-alkynyl ketones.[4] These are synthetically useful intermediates for the synthesis of 1,4-diketones[5], furans[6] and pyrroles.[7] This gap in methodology can be attributed to the low reactivity of most copper-alkynyl complexes[8], which would be the obvious choice to perform such 1,4-additions. Fisher and House[8] first reported on this poor reactivity in 1969, after which Corey and co-workers were able to use alkynes as so called 'dummy' ligands on Cu for the conjugate addition of various alkyl groups to cyclohexenone, a reaction that, when performed without a 'dummy' ligand, meant a maximum of 50% yield based on ligand.[9]

Due to the low reactivity of alkynes in copper-catalyzed conjugate addition reactions, other metals have been screened for their usefulness in such reactions. Success has been attained using metals such as aluminium, boron and rhodium. Many of these reactions have now been performed asymmetrically with excellent enantiomeric excess (ee) reported. As well, the low reactivity of alkynyl copper species has been overcome by the use of highly activated acceptors like alkylidene Meldrum's acids.[10]

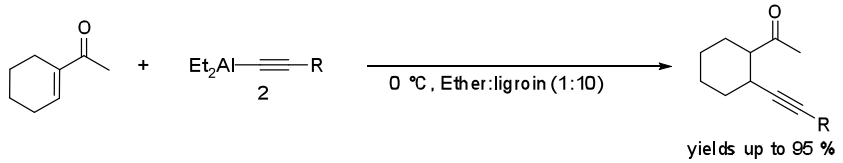
2.2 - Additions Stoichiometric in Metal

2.2.1 - Conjugate addition of alkynylaluminium species to α,β-unsaturated ketones

Up until the early 1970's there was no direct way to access the γ, δ-acetylenic ketones that were desired as synthetic intermediates.[4] In an effort to overcome this gap in methodology, Hooz[11] developed a method based on the Nagata hydrocyanation reaction, where an sp-hybridized cyano group was successfully added via Michael addition to an enone.[12] Hooz

reacted diethylalkynylalanes (**2**) with a range of α, β-unsaturated ketones, to form the desired 1,4-addition products. A representative example is shown in Scheme 1.

Scheme 1. Conjugate addition of alkynylalanes



The organoalane was prepared from the Li-acetylide and diethylaluminum chloride to give **2**. Though this methodology was a step in the right direction it had many drawbacks, the major one being that the reaction requires a ketone that is capable of adopting a cisoid conformation. Ketones that cannot adopt this cisoid confirmation give rise to the 1,2-addition product. A mechanism for this reaction has been suggested (Figure 4) to explain this reactivity pattern.

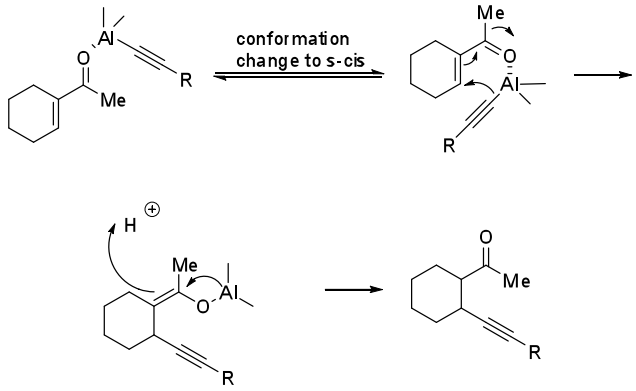
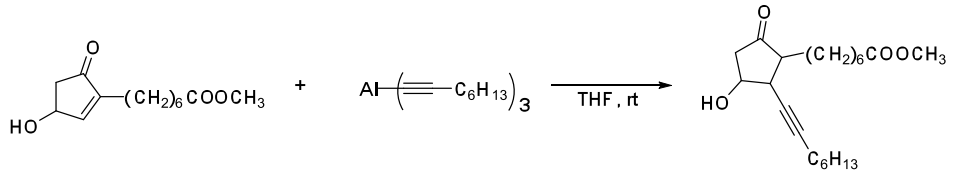


Figure 4. Suggested mechanistic rationale for observed reactivity pattern of organo aluminum alkynes

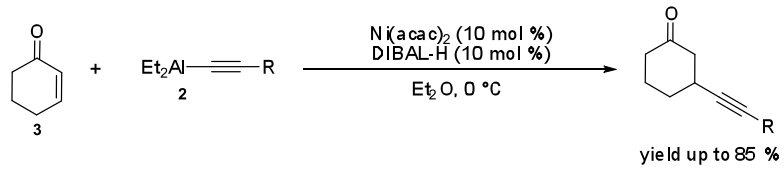
This methodology was quickly adapted by Collins and Pappo[13] who used it to form a key intermediate (Scheme 2) in their synthesis of prostaglandin analogs. It is worth noting the presence of the directing hydroxyl group, which enables this addition to occur via an intramolecular five membered transition state, similar to that depicted in Figure 4.

Scheme 2. Synthesis of intermediate for prostaglandin analog



The challenge of the direct addition of alkynes to the seemingly simple enone, cyclohex-2-ene-1-one (**3**), remained unmet until 1977 when it was discovered that the use of a Ni catalyst in conjunction with the organoalane **2**, allowed for the direct addition of the acetylene analog **2** to ketone **3**.[14] Schwartz and co-workers were able to attain yields up to 85% with no 1,2-addition product observed. When the reaction was carried out without the reduction of the Ni (II) complex to the Ni (I) complex, the authors noted that dimerization of the alkyne was observed. This was likely a result of a double ligand exchange of alkyne with the $Ni(acac)_2$ species followed by a reductive elimination to form the dimerized alkyne and the reduced Ni.

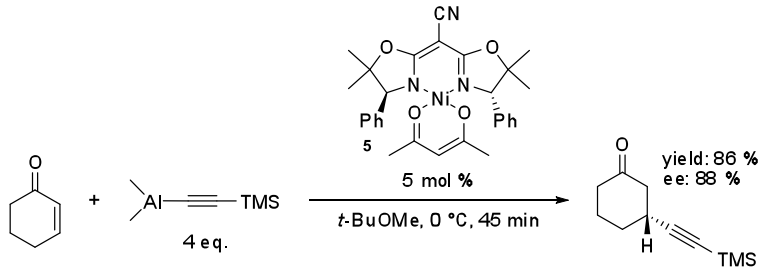
Scheme 3. Ni catalyzed conjugate addition of alkynylalanes



A variant of this reaction was investigated by Corey and Kwak,[15] who in 2004 developed an enantioselective variant. Corey and Kwak noted that the use of a Ni (II) species **4** rather than the Ni (I) species that was used by Schwartz was required to attain high yields and ee. Unlike Schwartz, Corey and Kwak did not note any dimerized alkyne product, suggesting that their bisoxazoline ligand was bound more tightly to the Ni than the acetylacetone (acac) ligand that Schwartz was using. This increased affinity for Ni prevented the formation of the bisalkynyl Ni (II) complex, thus preventing the formation of dimer. Using their newly

optimized system, Corey and Kwak were able to achieve yields of up to 86%, and ee's of up to 88% for cyclohexenone.

Scheme 4. Chiral Ni catalyzed conjugate addition of alkynylalanes

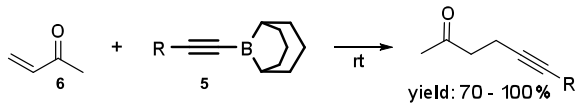


2.2.2 - Conjugate addition of alkynyl-boron species to α,β-unsaturated ketones

Similar chemistry has been performed using organoboranes. Pappo and co-workers were the first to use organoboranes to transfer terminal alkynes to α,β-unsaturated ketones.[16] In their quest to synthesize prostaglandin E2 (PGE_2) they used a trialkynylboron derivative to successfully add in a 1,4 fashion to methyl vinyl ketone, yielding 48 % of the desired product. They noted that when the organoalane was used for this reaction, a 1:1 mixture of the 1,2- and 1,4-addition products was obtained.

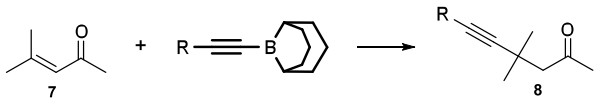
Brown, Molander and Sinclair[17] noted the shortcomings of this methodology, namely that in the Pappo transformation only one of the three acetylene groups on the boron are transferred, resulting in a maximum yield of 33% with respect to acetylene. This is especially critical if the acetylene subunit is a valuable intermediate. To overcome this drawback they developed a procedure in which *B*-1-alkynyl-9-borabicyclo[3.3.1]nonanes (*B*-1-alkynyl-9-BBN, **5**) were successfully added to methyl vinyl ketone (**6**) and related ketones, in a 1,4 addition reaction (Scheme 5).

Scheme 5. Alkynylboranes as alkyne source



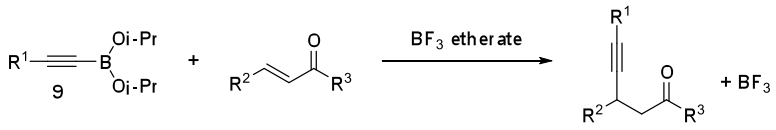
Yields of this reaction were generally quite good ranging from 70-100% depending on the enone that was used. One particularly interesting result was attained using mesityl oxide (**7**) as the enone, in which they successfully formed a quaternary carbon centre as in product ketone **8**.

Scheme 6. Formation of quaternary centre using alkynylborane



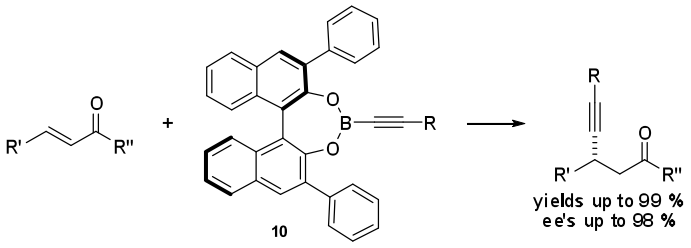
This methodology was expanded by the Suzuki group, used triisopropoxyborane (**9**) as the alkyne transfer reagent (Scheme 7). They were successful in attaining yields of up to 86%.[18]

Scheme 7. Triisopropoxyborane as the alkyne transfer reagent



Chong adapted the work done by Suzuki, adding a chiral ligand to the boron, thereby performing the first enantioselective 1,4-conjugate addition of alkynyl boronates.[19] It was found that with chiral ligand **10**, depicted in Scheme 8, high yields of up to 99% and exceptional ee's of greater than 98% could be obtained.

Scheme 8. Chiral addition of alkynyl boranes



The Chong group was able to take this methodology one step further, when they applied the same general principle, only this time they used an exchangeable chiral ligand, thereby making the reaction catalytic in ligand.[20] The general concept is shown in Figure 4, wherein an achiral unreactive boronate **11**, is made chiral through reaction with ligand **12**, forming intermediate **13**. This intermediate then undergoes a reaction with enone **14**, to generate intermediate **15**, where the transfer of the alkyne from boron to enone has taken place. Release of the chiral ligand by boron intermediate **15** gives the product, and regenerates the chiral ligand, which can now react with the boronic ester starting material to form intermediate **14**, thereby completing the catalytic cycle.

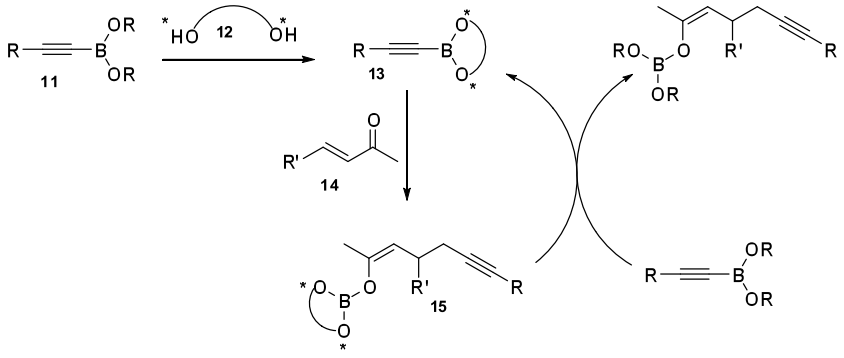


Figure 4. Proposed catalytic cycle for the 1,4-addition of alkynylboron to enone

The key to this proposed chemistry was that the starting alkynyl boronate had to be substantially less reactive than 'activated' alkynylboronate **13**. It was indeed found that the

starting alkynyl boronate did not provide any of the 1,4-addition product, but in the presence of the binaphthol ligand, yields of up to 95% were obtained, with excellent ee's from 83-96 %.

Although the reaction was compatible with many enones, substrates that were not able to adopt the required *s*-cis conformation were unreactive. As with the organoalane discussed earlier, this conformation was required for the reactions to proceed, as a cyclic six membered transition state was proposed. This procedure also required the stoichiometric use of Li to form the Li-alkynylide as a key intermediate in the formation of the alkynylboronate.

2.3 - Additions catalytic in metal

2.3.1 - Copper catalyzed conjugate addition of alkynes to α,β-unsaturated ketones

The reactions discussed up to this point have required the addition of a stoichiometric amount of at least one metal, that is either aluminium or boron, in order to form the active metal alkynylides. This is not ideal as it is not economical, and many of the alkynyl metal intermediates are sensitive to water or air, which makes the protocols less practical. The Carreira group applied methodology they had developed for the reaction of metal alkynylides with ketones and imines, and used a similar methodology to perform the conjugate addition to Meldrum's acid acceptors **16**.[10] They used Meldrum's acid acceptors for several reasons: firstly, Meldrum's acid derived Michael acceptors are easily prepared, with numerous methods being available; second, once the conjugate addition has taken place, the Meldrum's acid moiety can be converted to the corresponding β-alkynyl acid, amine, amide, or ester[21] (Figure 5); lastly the symmetrical nature of the Meldrum's acid acceptors makes the starting material geometry irrelevant.

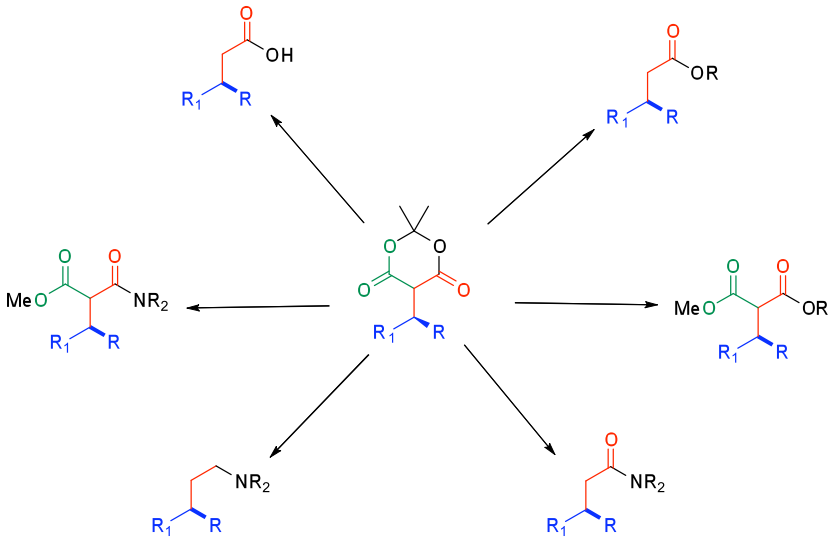
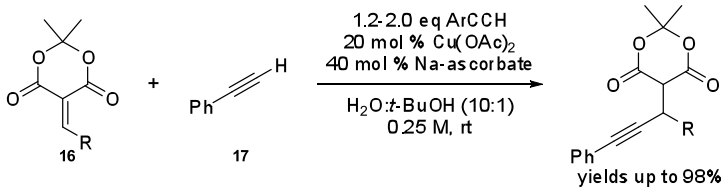


Figure 5. Transformations of Meldrum's acid

Carreira used a Cu (II) salt that was converted to the active Cu (I) species in situ using sodium ascorbate.[22] This was groundbreaking work, because at the time it was thought that Cu-alkyne complexes were unreactive due to the strength of the Cu-alkyne interaction. Under optimized conditions, they found that the conjugate addition of phenylacetylene (**17**) was general and was applied to numerous Meldrum's acid acceptors, including aromatic, heteroaromatic, branched and unbranched aliphatic alkylidenes, all with good yields.

Scheme 9. Cu-catalyzed conjugate addition of phenylacetylene

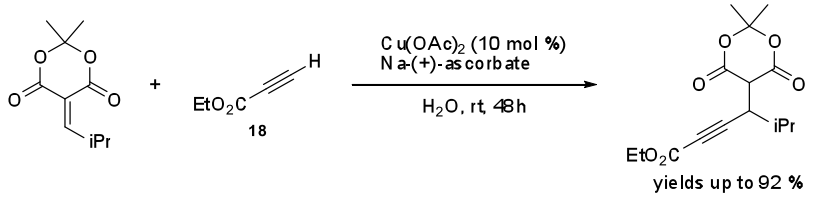


The importance of both Cu (II) and ascorbate was confirmed by control experiments. Most interestingly, a preformed Cu (I) alkynylide in degassed water did not add in the absence of ascorbate, suggesting that it plays a role in catalyzing the reaction aside from reduction of

copper. They also noted the importance of water as a solvent, as decreasing the amount of water in the system coincided with a decrease in conversion.

Recently the Carreira group was able to extend this chemistry to include alkynes other than phenylacetylene (**17**). [23] In 2007, they developed methodology very similar to that for phenylacetylene (**17**), with the main difference being the use of ethyl propiolate (**18**) as the terminal alkyne nucleophile (Scheme 10).

Scheme 10. Cu catalyzed conjugate addition of ethyl propiolate



This marked the first time that ethyl propiolate (**18**) was able to be activated using sub stoichiometric amounts of Cu. It was also the first example of using such propiolates in a Michael addition reaction under catalytic conditions. Of note is the chemoselectivity, as only 1,4 addition of the alkyne **18** to the Meldrum's alkylidene was observed, despite the fact that the propiolate and the product alkynoate are both good electrophiles.[24] One of the major drawbacks noted by the authors is the lack of reactivity of Meldrum's acceptors bearing aryl or alkenyl substituents, as efforts to perform such reactions under these standard conditions resulted only in recovery of starting material.

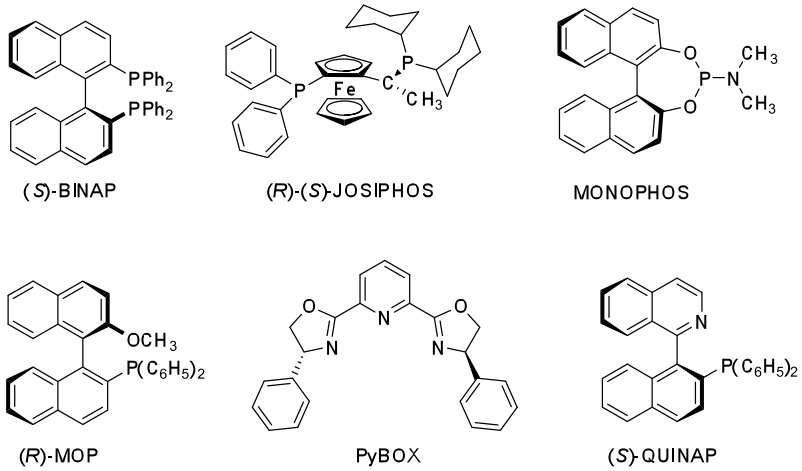
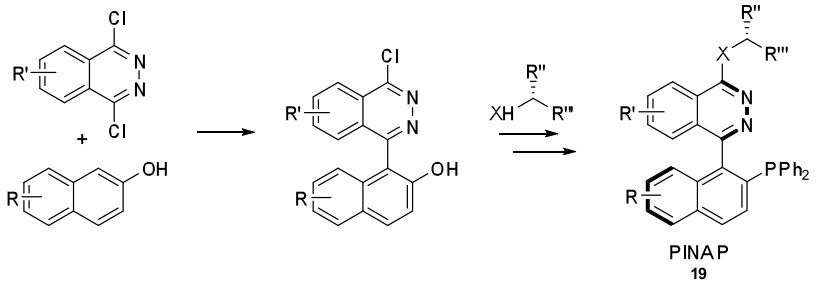


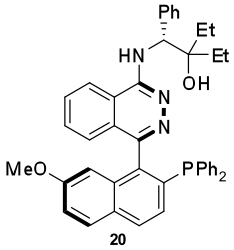
Figure 6. Ligands tested by Carreira Group

An impressive enantioselective variant of this reaction was reported by Carreira, using phenylacetylenes as nucleophiles. [25] Many ligand classes were screened during the initial experiments including phosphines, such as BINAP, JOSIPHOS, MONOPHOS, and MOP; they also screened donors like PYBOX (Figure 6). All but one of these ligands gave low ee's with the best being tol-BINAP with an ee of 25%. The only exception was that of QUINAP which yielded an ee of 42%. Due to difficulties in the modification of the QUINAP type ligands a new P, N-ligand was developed and termed PINAP (**19**).[26] Being easily accessible in a four step sequence (Scheme 11) various structural and electronic modifications on the ligand could be examined.

Scheme 11. Synthesis of PINAP ligands



A ligand, **20**, was finally discovered that provided satisfactory yield and ee (Figure 7). Surprising was the importance of the seemingly remote chiral amine group, where one diastereomer gave a far superior ee to the other (80% to 37%). This result suggested the importance of this chiral amine group and was the starting point for fine tuning of the ligand.

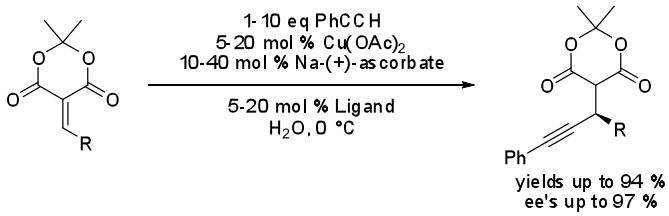


20

Figure 7. Chiral PINAP ligand

Using the optimized procedure (Scheme 12), high yields and ee's were attained in up to 94% and 97%, respectively. The scope of the reaction was examined and found that in the case of γ-branched acceptors reactions could be carried out with 10% catalyst loading. In cases where there was no γ-branching, the acceptors required higher catalyst loading of 20%. Aromatic groups in the R position were tolerated, but required longer reaction times to reach completion.

Scheme 12. Chiral conjugate addition of phenyl acetylene



The versatility of the Meldrum's acid acceptors in further chemistry has been limited by the scope of acetylenes that are compatible using this copper chemistry. It would be desirable to develop a method using silyl acetylenes which are easily manipulated by removal of the silyl protecting group, allowing for further transformations.

2.3.2 - Rhodium catalyzed conjugate addition of alkynes to α,β-unsaturated ketones

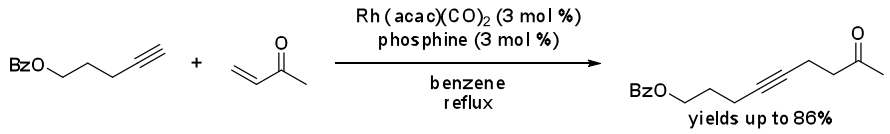
Aside from the copper catalyzed conjugate addition of alkynes to α,β-unsaturated ketones few other catalytic methods exist. One of the more promising metals being studied is Rh which is ideal for such reactions for numerous reasons. Unlike the more common metals employed for such reactions, namely Grignard reagents, organolithiums, or diorganozincs, Rh has fewer problems associated with chemoselectivity. This allows for greater substrate compatibility, including the use of aryl nucleophiles which are known to be problematic with copper catalysis.[27] The Rh catalyzed reactions also tend to be more tolerant of water than the Li, Zn, and Mg reagents, allowing for the potential of more environmentally friendly chemistry, since fewer harmful solvents are required.

Interestingly, though Rh is known to activate C-H bonds towards 1,4 additions, few examples exist for the activation of alkynes to α,β-unsaturated ketones. Nikishin and Kovalev reported the first such example in 1990.[28] They found that $RhCl(PMe_3)_3$ was an effective catalyst at performing the conjugate addition of terminal alkynes to unsaturated ketones. However, these reactions were extremely slow, requiring two to five days to go to completion. Increasing the temperature increased product formation, but also dramatically increased the undesired alkyne dimerization side reaction. The $RhCl(PMe_3)_3$ catalyst is not commercially available, and its synthesis is difficult and requires the use of trimethylphosphine, a toxic, air sensitive reagent.

In an effort to make a safer and more stable catalyst, Lerum and Chisholm opted to use a precatalyst in their work, $Rh(acac)(CO)_2$ complex.[29] This was easily converted to the active phosphine containing catalyst by the addition tris-(o-methoxyphenyl)phosphine, which easily displaces the CO ligand. Optimization revealed that temperatures above 50 °C were required,

and little difference in yield was noted between solvents such as benzene, toluene and dioxane. The reaction was also found to be relatively insensitive to water.

Scheme 13. Rh-catalyzed conjugate addition of terminal alkyne



A proposed reaction mechanism is as follows (Figure 8). Insertion of the Rh catalyst into the alkyne C-H bond generates Rh-alkynylide **21**. Complex **21** then coordinates to the enone, which is followed by migratory insertion of the alkyne to the olefin. Complex **22** then undergoes reductive elimination regenerating the active catalytic species **23**.

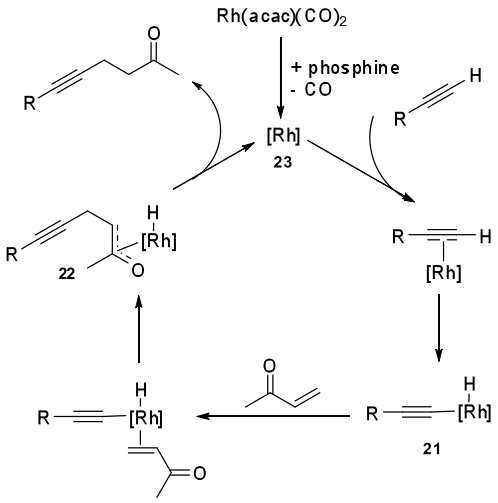
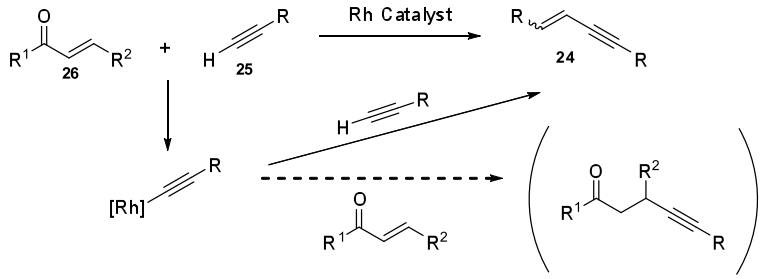


Figure 8. Proposed reaction mechanism for the Rh-catalyzed conjugate addition of alkynes to enones

A noted complication of this methodology is the requirement for high temperatures at which Rh-catalyzed dimerization of alkynes can become a competing pathway (Scheme 14). Both Kovalev and Lerum noted this tendency and explored various routes of overcoming it, none of which worked with great success.

Scheme 14. Dimerization as a competing reaction



Noting that the main problem appears to be the presence of a stoichiometric amount of terminal alkyne **25**, the Hayashi group began work to overcome this problem.[30,31] Since the terminal alkyne is more reactive than β-substituted enone **26**, formation of product **24** dominates. They showed that if they were able to keep the concentration of the alkyne low, then the 1,4-addition would be the preferred reaction.[30]

Their approach involved an asymmetric 1,3-rearrangement of alkynyl alkenyl carbinols (**27**). Though not a true 1,4-addition reaction, it is the synthetic equivalent. The proposed reaction pathway (Figure 9) is as follows: generation of the alkoxyrhodium species **28**, from the starting alkynyl alkenyl carbinol, this is followed by β-alkynyl elimination to give active alkynylrhodium species **29**. This alkynylrhodium species undergoes conjugate addition to the newly generated enone, resulting in oxa-π-allyl-rhodium intermediate **30**. Subsequent reaction of the Rh with an equivalent of water generated the desired final product and regenerates the [Rh]OH catalyst.

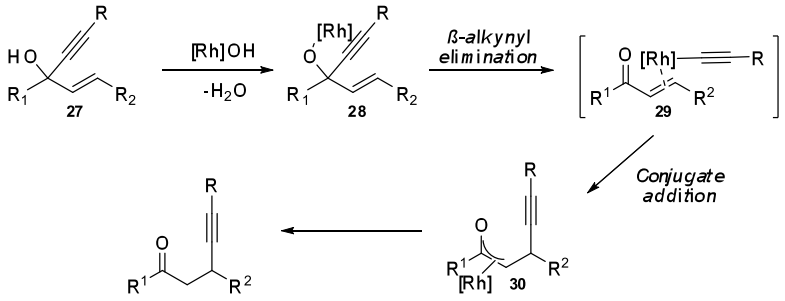
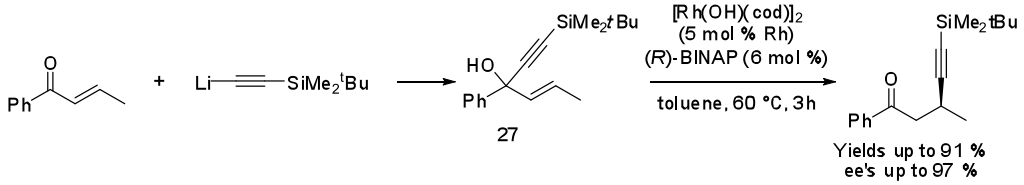


Figure 9. Proposed reaction pathway for β-alkynyl elimination

The reaction was successfully carried out with high ee's and yields. A general procedure is shown in Scheme 15. The starting alkynyl alkenyl carbinol **27** was easily accessed by 1,2-addition of the requisite lithium acetylide. This was followed by treatment with $[Rh(OH)(cod)]_2$ (5 mol % Rh), (*R*)-BINAP (6 mol %), in toluene at 60 °C, affording the desired product in up 98% yield and 91% ee.

Scheme 15. 1,3-alkyne migration



The second process which the Hayashi group developed to prevent the dimerization of the alkyne involves (triisopropylsilyl)-acetylene (TIPS-acetylene, **31**) combined with di-*tert*-butyl-methoxy-SEGPHOS (DTBM-SEGPHOS, **32**) as the chiral ligand.[31] This methodology is based on the assumption that the sterically bulky silicon, combined with the sterically bulky phosphine ligand should hinder dimerization (Figure 10).

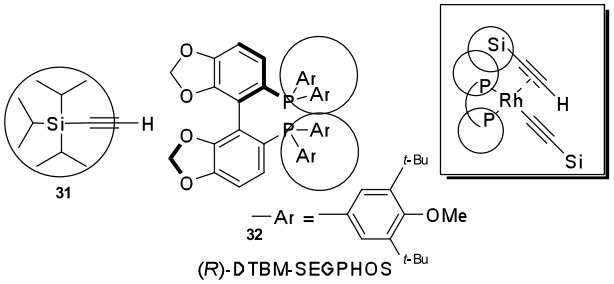


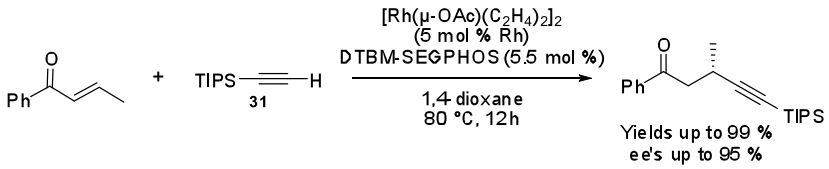
Figure 10. Rationale for decrease in dimerization of alkynes in presence of bulky ligand

Hayashi's group was successful in the application of this procedure, and obtained yields of up to 99% with ee's of up to 93%. To demonstrate that the hypothesis for steric bulkiness was correct, experiments were performed where the silyl acetylene was mixed with catalyst and

ligand. After reacting for 30 min at 40 °C. It was found that (*R*)-BINAP with either triethylsilyl-acetylene (TES-acetylene) or TIPS-acetylene (**31**) gave a high conversion to the dimer. When (*R*)-DTBM-segphos (**32**) was used in place of (*R*)-BINAP conversions to alkyne dimer (**24**) of 25% and 4% were obtained for TES-acetylene and TIPS-acetylene (**31**), respectively. This confirms that the bulky ligand and acetylene plays an important role in preventing dimerization of the alkyne.

Their methodology was successful for a number of α,β-unsaturated ketones (Scheme 16). For 1-propenyl ketones bearing aryl, alkenyl, or alkyl groups on the carbonyl carbon yields of 78-99 % were obtained, with ee's ranging from 91-95%. The reaction was also tolerant of linear enones possessing a longer alkyl chain at the β-position, providing excellent yields.

Scheme 16. Rh catalyzed conjugate addition of TIPS-acetylene



Demonstrating the versatility of the final product, Hayashi and co-workers were able to remove the silyl group using tetrabutylammonium fluoride (TBAF), yielding the alkynyl ketone without erosion of ee. This terminal acetylene was subjected to Sonogashira coupling with iodobenzene, as well as a copper catalyzed cycloaddition with 1-azido-4-chlorobenzene. Both gave the target compounds in high yields and ee.

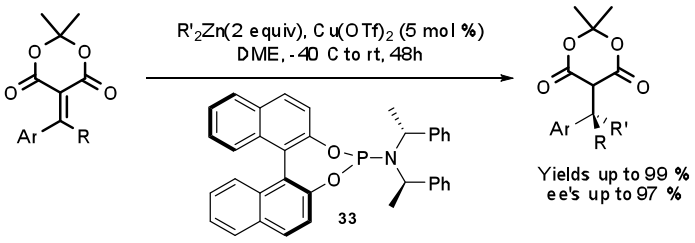
3 - Research Proposal

3.1 - Work of the Fillion Group

The Fillion group at Waterloo has focused on the unique reactivities of Meldrum's acid derivatives in conjugate addition reactions to develop new synthetic methodologies. One of the first examples of this type of methodology from our group was published by Fillion and Wilsily in 2006.[32]

They found that in the presence of the commercially available phosphoramidite ligand **33**, $Cu(OTf)_2$ catalyzed the addition of dialkylzinc reagents to disubstituted alkylidene Meldrum's acids in excellent yields and ee's (Scheme 17). Most important about this work was the ability to form all-carbon quaternary centres, a structural motif found in many natural products, but at that time understudied in the literature. This was attributed to the increased electrophilicity of the Meldrum's acid derivatives, allowing for the electrophile to overcome the sterically unfavourable environment associated with the formation of quaternary centres. More recently this work has been expanded to include other acceptors[33], as well the conjugate addition of dimethylzinc reagents to form quaternary all-carbon centres.[34]

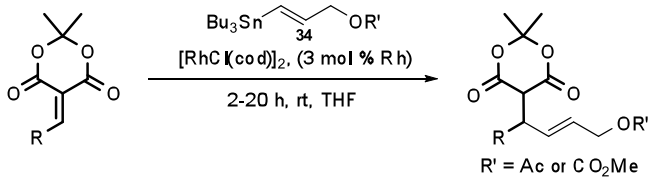
Scheme 17. Conjugate addition of organozincs to alkylidene Meldrum's acids



With this lead example in hand our group investigated the conjugate addition of other nucleophiles to alkylidene Meldrum's acids. In 2008 Fillion et al. published results in which

Rh catalyzed the conjugate addition of vinylstannanes **34** onto Meldrum's acid acceptors as shown in Scheme 18.[35]

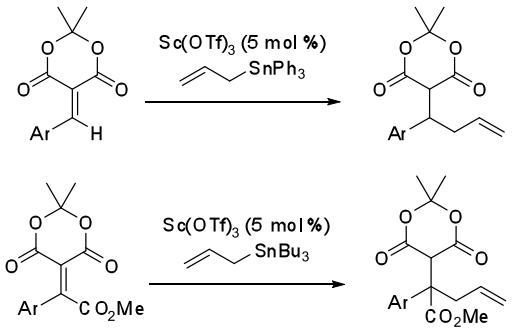
Scheme 18. Rh catalyzed conjugate addition of vinyltributyltin to alkylidene Meldrum's acids



Since excellent yields were obtained under mild conditions, this once again demonstrated the superior reactivity of Meldrum's acid acceptors to conjugate addition. The substrate scope was investigated, and found to be quite broad. Along with benzylidene acceptors it was found that ethylidene Meldrum's acid was tolerated giving the desired 1,4-addition product in good yield. In conjunction with the benzyl and ethyl substituents halo, cyano, nitro, and methyl ester substituents were also compatible. It was also noted that the addition of (*Z*)-stannyl acetate to Meldrum's acceptors afforded the corresponding 1,4-addition product with retention of the double-bond geometry.

Further examples from the Fillion group of conjugate addition on to alkylidene Meldrum's acids have more recently been published.[36] Dumas and Fillion were able to successfully add allyl tributyl and triphenyl tin reagents to numerous alkylidene Meldrum's acids under $Sc(OTf)_3$ catalyzed conditions to form both the tertiary and quaternary centres (Scheme 19). Yields for this reaction were generally quite good, with numerous substrates being tolerated including thiophene, furyl, and alkyl substituents.

Scheme 19. Conjugate addition of allyl tin to alkylidene Meldrum's acid

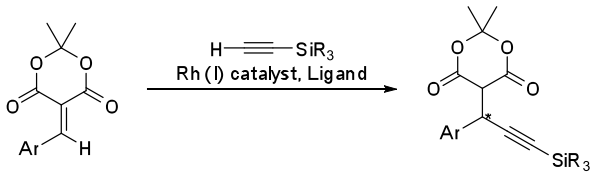


3.2 - Proposed Work

It was hypothesized that if one could apply the methodologies described above (1,4-addition onto alkylidene Meldrum's acids) in conjunction with a silyl protected

system similar to that of Hayashi and co-workers, it would be possible to perform the Rh catalyzed conjugate addition of alkynes onto alkylidene Meldrum's acids (Scheme 20) under mild conditions to form the propargylic stereocenter. The use of the silyl protected alkyne would present a handle for which further chemistry could be employed, a possibilty that was not viable with work performed by Carreira and co-workers (Scheme 12, page 13).

Scheme 20. Proposed general reaction



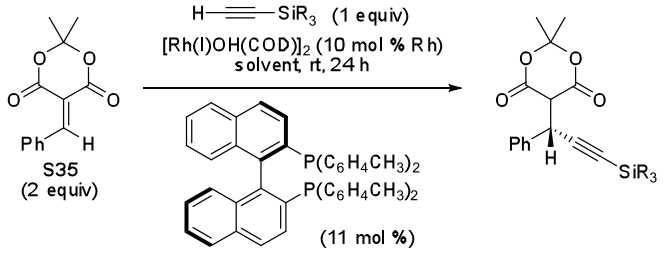
4 - Results and Discussion

4.1 - Development and Optimization of Reaction Conditions

4.1.1 - Optimization of Alkyne and Solvent

The first two aspects of the reaction to be optimized were solvent and silyl acetylene. The initial conditions, adapted from the work Hayashi had done previously involving the Rh catalyzed intramolecular rearrangement of alkynyl alcohols, were as follows; using $[RhOH(COD)_2]_2$ as the catalyst, and (*R*)-tol-BINAP as the ligand, various silyl acetylenes and solvent combinations were investigated, and are listed in Table 1.

Table 1. Optimization of alkyne and solvent. Conversion determined using mesitylene as internal standard



Solvent	H—≡—TMS **36**		H—≡—TBDMS		H—≡—TIPS **34**	
	Conversion	ee	Conversion	ee	Conversion	ee
PhMe	39 %	78 %	23 %	69 %	15 %	14 %
THF	41 %	66 %	26 %	62 %	23 %	3 %
1,4 Dioxane	30 %	67 %	23 %	66 %	20 %	38 %
DME	54 %	87 %	23 %	73 %	NR	N/A

Under the described conditions it was found that regardless of solvent the conversions seemed to increase with decreasing size of the silyl group present on the alkyne. That is to say that TIPS-acetylene gave the lowest conversions followed by *tert*-butyldimethylsilyl-acetylene (TBDMS-acetylene), while trimethylsilyl-acetylene (TMS-acetylene) gave the highest level of conversion. This is opposite to the trend noted by Hayashi, who required a bulky alkyne to reduce the amount of dimerization taking place. In the system described herein the conditions

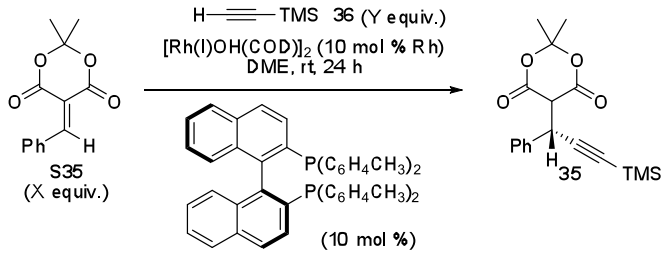
are much milder (rt vs 80 °C) and dimerization though still present is not as important as the competing pathway.

In looking at the various solvents, DME was found to give both the best conversion after 24 h, with 54%, and the best ee of 87%, when the TMS-acetylene was used as the alkyne source. The use of DME as solvent is in accord with previous results our group had attained for the conjugate addition of dimethylzinc to various alkylidene Meldrum's acids.[32]

4.1.2 - Determination of equivalents of reagents

Having determined an appropriate alkyne and solvent for the conjugate addition reaction, the various equivalents of each component were next investigated. The equivalents of the alkyne and Meldrum's alkylidene were found to have a major effect on the observed conversion of the reaction (Table 2).

Table 2. Effect of equivalents of alkyne versus alkylidene on conversion



MA:Alkyne	7:1	5:1	3:1	2:1	1:1	1:3	1:5	1:7
Conversion	86%	79%	78%	45%	45%	66%	69%	64%

Conversion determined using internal mesitylene standard

It was found that having higher equivalents of **S35** tended to give higher conversion to product **35**, with a maximum of 86 % conversion being observed when 7 equivalents of **S35** were used. On the opposite end of the spectrum, having an excess of alkyne **36**, gave lower conversions (relative to first three entries in Table 2), with a maximum of 69 % obtained when 1 equivalent of **S35**, and 5 equivalents of **36** were used. Though giving lower conversions relative to reactions where excess alkylidene was used, it was decided that the ease of

purification of these reactions, outweighed any potential loss in conversion, and TMS-acetylene (**36**) was used in 5-fold excess for all subsequent reactions.

It is worth noting that, in all the cases where excess alkyne was used, a significant amount of the dimerization product (described earlier in Scheme 14) was observed. Numerous efforts were made to decrease its formation, but in all cases dimerization persisted. Decreasing the concentration, as well as slow addition of the alkyne did not result in any appreciable decrease in amount of dimer being formed, and in both cases resulted in a decreased conversions. An additive of styrene was used in an effort to decrease the extent of dimerization that was occurring. The hypothesis was that having a second site where the alkynyl-Rh species could complex would decrease the frequency with which the alkynyl-Rh came in contact with TMS-acetylene (**36**), and would thus decrease the amount of dimerization. In cases where this additive was investigated, no difference in either conversion to product or dimer was observed.

4.1.3 - Effect of various ligands on conversion and ee

With general conditions available, the effect of various ligands were next investigated. Starting with a broad scope of ligands conversions and ee's were determined under the general reaction conditions shown in Figure 11.

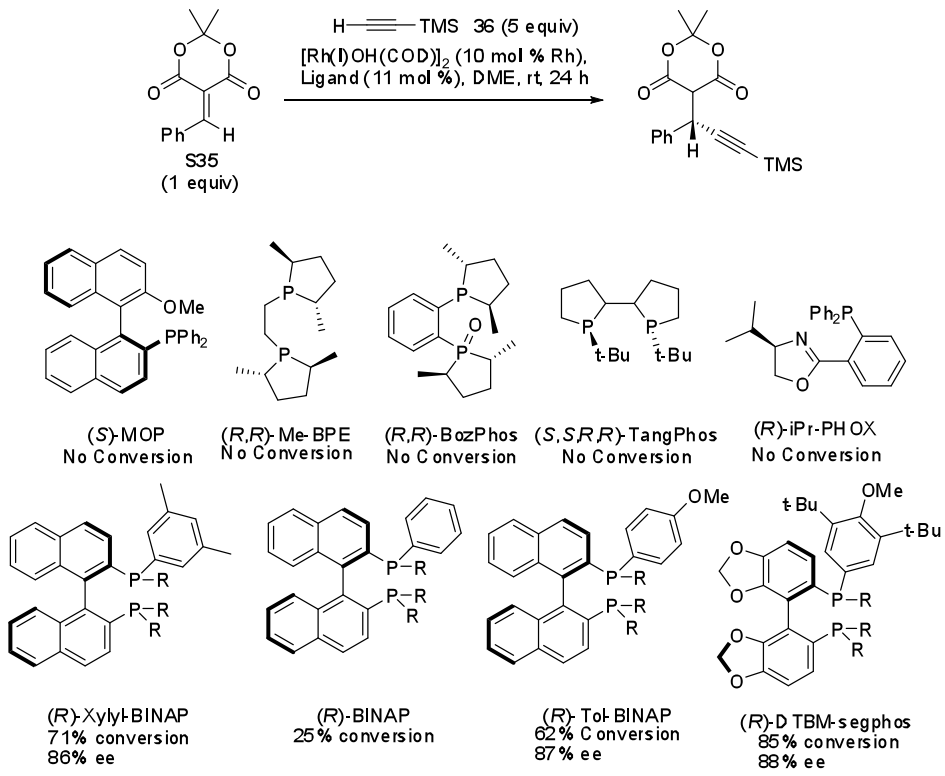


Figure 11. Initial ligands screened

Use of such a broad ligand scope allowed some general conclusions to be made about the conjugate addition reaction. It appeared that there were two general structural features of the ligand that were required if the conjugate addition reaction were to occur. Firstly, is the presence of a biphenyl backbone, as all ligands such as BozPhos and TangPhos, which do not have the biphenyl backbone did not give any conversion to product and only starting materials were recovered. The hypothesis is that the dialkylphosphine ligand is too basic and inhibited the catalyst. The second requirement appears to be the need for a biphosphine moiety. The MOP did not give any conversion, though it contains a biphenyl backbone. The ligands which contained both the biphenyl backbone and were bidentate gave conversion. While plain BINAP gave only 25% conversion, both Tol-BINAP and 3,5-Xylyl-BINAP gave conversions of 62 and 71% and ee's of 87 and 86%, respectively. The DTBM-Segphos, containing both the biphenyl backbone, and the biphosphine, also gave a good conversion of 85% and enantiomeric

excess of 88%. This result hinted at the importance of the ethereal oxygens on the backbone of the ligand. With this in mind we opted to investigate the BiPHEP family of ligands in detail due to the presence of the ethereal oxygens, biphenyl backbone, bidentate lignad and a relatively large number of commercially available derivatives. (There are nine BiPHEP derivatives and only three SEGPHOS derivatives commercially available).

After investigating all commercially available BiPHEP derivatives, some further general conclusions could be drawn (Figure 12). Overly bulky variants such as **37**, **38**, **39** give little to no conversion, as do electron rich derivatives such as **39**. The furyl substituted variant **41**, also gave low conversion and ee. Somewhat surprisingly the isopropyl derivative, **42**, gave a relatively high ee 82% and modest conversion of 68%. It was the phenyl substituted derivatives **43**, **44**, **45** that gave the best results in terms of ee. The plain phenyl derivative **43** gave 50% conversion and 83% ee after 24 h, while the 4-Me derivative (**44**) gave even better results with a conversion of 66% and ee of 88%. The 3,5-xylyl (**45**) gave the best result of the series with a still modest conversion of 70%, and high ee of 94%. Having investigated 18 ligands, we were satisfied with the results obtained with the 3,5-xylyl derivative, and selected this as the ligand for all future reactions

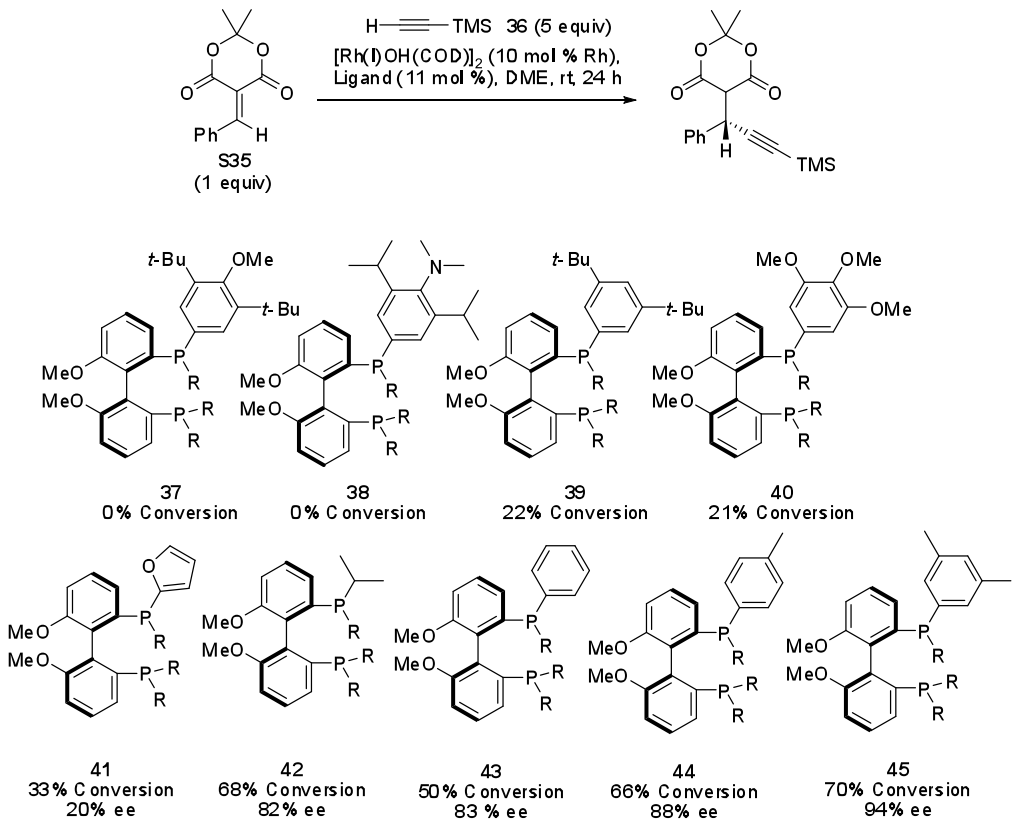


Figure 12. Biphep ligands investigated

4.1.4 - Effect of temperature on conversion

With a modest conversion of only 70% for the partially optimized conditions steps were undertaken to increase the conversion. Increasing the temperature as a means of increasing conversion was quickly ruled out as an option since this leads to increased dimerization of the alkyne.

4.1.5 - Effect of time and catalyst loading

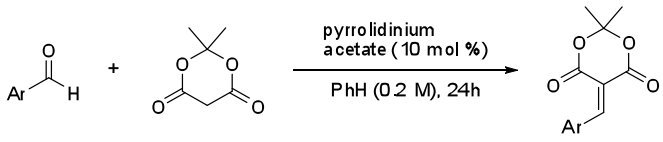
The effects of reaction time and catalyst loading to further increase conversion were also investigated. Both were found to be crucial if complete conversions were going to be obtained. Results are summarized in Table 3, with the optimal conditions being 15% catalyst loading, and a reaction time of 72 h. With virtually complete conversions now obtained, the scope of the reaction could be investigated.

Table 3. Effect of time and catalyst loading

Catalyst loading	Conversion After 24h	Conversion After 48h	Conversion After 72h
5%	50%	60%	N/A
10%	63%	70%	75%
12%	67%	76%	80%
15%	68%	79%	>95%
20%	N/A	N/A	>95%

4.2 - Substrate Preparation

All alkylidene Meldrum's acids were prepared according to the literature procedure developed by our group[37] (Scheme 21). Meldrum's acid is simply stirred with the desired aldehyde in the presence of a catalytic amount of pyrrolidinium acetate (prepared in-situ) in benzene for 24 h at rt or 50 °C. Once the reaction is complete benzene is removed and simple recrystallization from methanol yields the alkylidene Meldrum's acid as a bench stable crystalline solid.



Scheme 21. Preparation of alkylidene Meldrum's acids

4.3 - Scope of reaction

With a broad range of starting materials available, the scope of the reaction was investigated. All reactions were compared to the general case of the phenyl alkylidene Meldrum's acid (**S35**), which was used for the initial optimization reactions. In general the reaction was found to be sensitive to electronics, as electron donating groups (EDG) deactivated the alkylidene to addition and electron withdrawing groups (EWG) activated the alkylidene to generally give higher conversions.

4.3.1 - Effect of halogen substitution

The effect of halogen substitution was investigated for the substrates listed in Figure 13. Conversions of 66% and 60% were observed for the 4- and 3-fluoro substituted benzylidene Meldrum's acids (**S46** and **S47**), respectively. This appears to be in contradiction to the activation that each substituent would have on the alkylidene. Based on published[38] σ-values one would expect the 3-F (σ = 0.34) to be more activating and thus give higher conversions compared to the 4-F (σ = 0.06). This was not the case, and the discrepancies in conversion may be due to differences in solubility of each substrate. The low conversion of the 2-F substrate **S48** can likely be attributed to steric factors, as a substituent in the ortho position of the phenyl ring would likely cause steric interference on the approaching nucleophile.

In terms of ee the results suggested that F substitution in the 2- and 3- positions had little effect and good ee's of about 90% were achieved in each case. Substitution with fluoride in the 4-position on the other hand deteriorates the ee relative to the 2- and 3- substituted variants, with a maximum ee of 83% being observed.

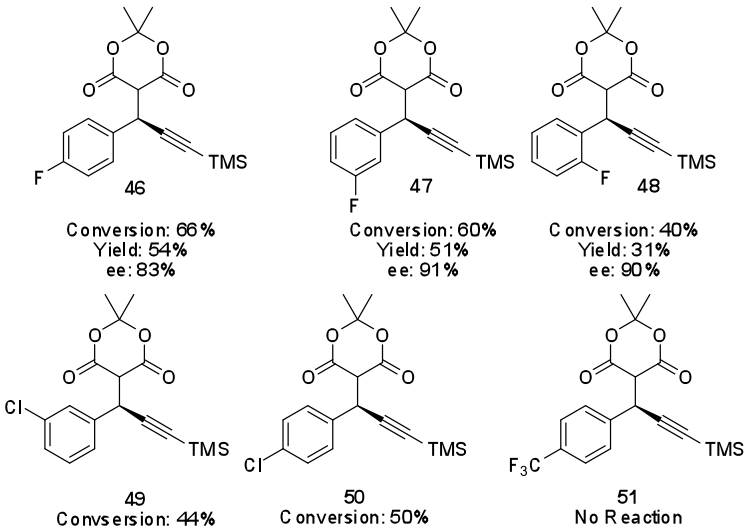


Figure 13. Effect of halogen substitution on conversion

All of the 4-Cl (σ = 0.23), 3-Cl (σ = 0.37), and the 4-CF_3 (σ = 0.54) **S49** – **S51** gave lower conversions than their σ values would suggest. In all three cases this can likely be

attributed to the low solubility of the starting material, which slows the reaction, and results in less conversion.

4.3.2 - Effect of phenol and protected phenols substitution

It was with the various protected and unprotected phenols that the effect of electronics was most pronounced (Figure 15). The 4-phenol and its protected variants, **S52** and **S53** (Figure 15) have σ values[38] of -0.27, and -0.37, respectively. Values in this range suggest that a large amount of electron donation is occurring (shown in Figure 14**)**. This electron donation may be increasing the electron density at the electrophilic site of the Meldrum's acid, thereby decreasing its reactivity towards nucleophiles. This decrease in reactivity can be seen in the conversions of the *para*-substituted phenol derivatives, which in all cases gave less than 20% conversion.

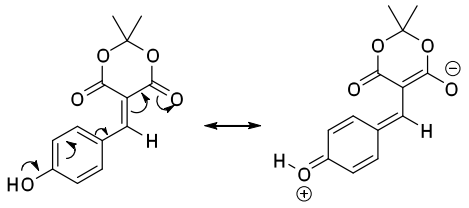


Figure 14. Effect of resonance on reactivity of Meldrum's alkylidene

Simply moving the phenolic oxygen from the *para* to the *meta* position drastically changed the observed conversions from under 20% to over 98% in all cases investigated. This drastic increase in conversion can be rationalized through the σ values[38] (0.12) of the *meta*-phenols (**S54** – **S56**). When the phenolic oxygen is moved from the 4- to the 3- position, the electrons cannot be delocalized into the Meldrum's alkylidene through resonance, and the inductive effects of the oxygen dominate. This results in less electron density about the alkylidene; increasing its reactivity to nucleophiles and resulting in higher conversions. In the cases of the **S54**, **S55** and **S56** high ee's were obtained regardless of protecting group, though

the unprotected phenol gave the highest ee of 97%, followed by the MeO with an ee of 91% and the OTIPS with an ee of 89%.

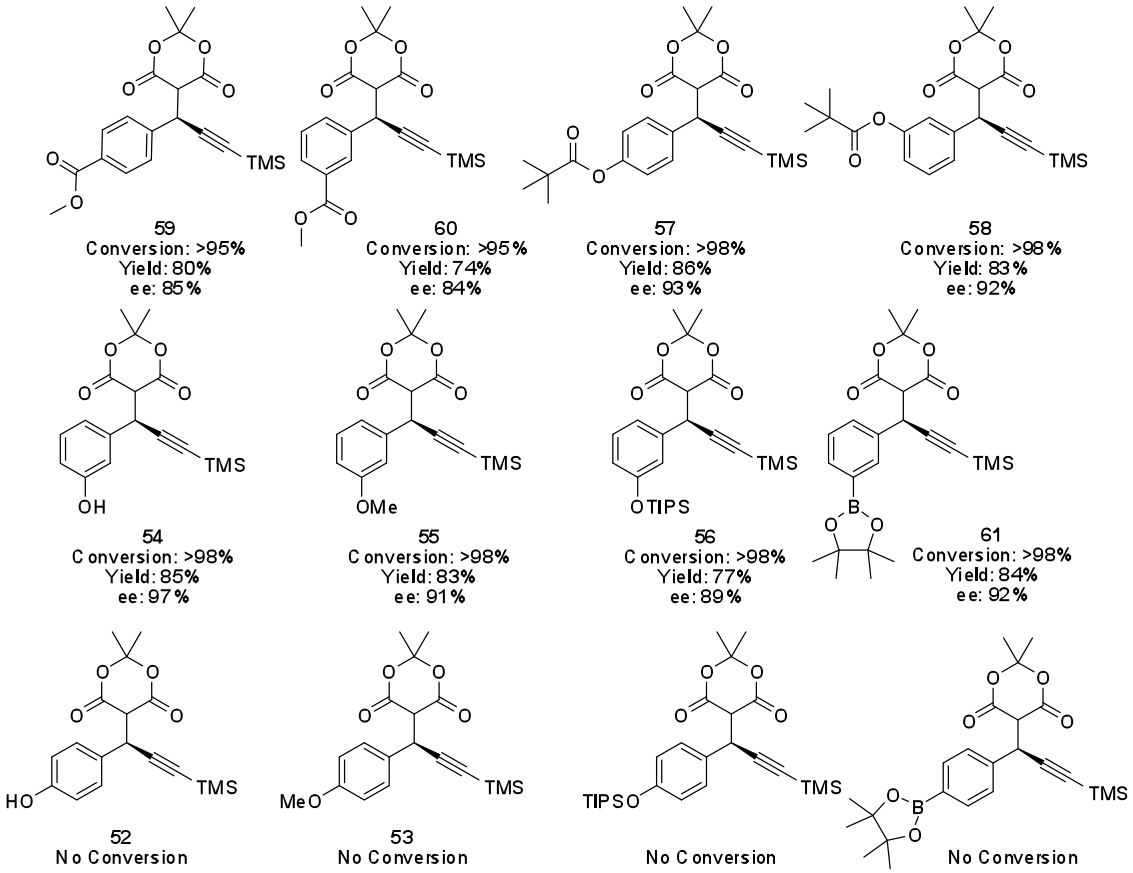


Figure 15. Phenolic substrates and the effect of substitution

The pivaloate-protected phenols, **S57** and **S58** gave complete conversion in both the *meta* and *para* positions. A similar reasoning to that above can be used to rationalize the conversion of the *meta*-pivaloate-protected phenol **S58**. Interestingly the *para*-Piv protected phenol **S57** gives complete conversion. This can be attributed to the new resonance form available (Figure 16). This change in resonance pattern decreases the amount of electron density present at the reacting carbon on the alkylidene Meldrum's acid, thereby increasing its electrophilicity and thereby the conversion.

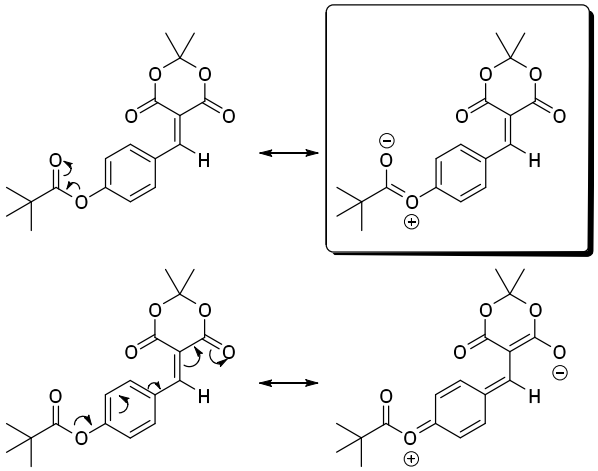


Figure 16. Resonance forms of Piv protected phenol

In conjunction with all of the various phenols, the *meta*- and *para*-substituted methyl esters, **S59** and **S60**, gave complete conversions and ee's of 85% and 84%, respectively. The reaction was also compatible with *meta*-boron substituent **S61**, but no reaction was observed for the *para*-substituted analogue **S62**. This further supports the electronics argument made previously (page 30). The mild reaction conditions allow for numerous substituents to be tolerated, from unprotected phenol, to silyl substituents to boronic ester. High conversions and ee's were typically attained when groups were present in electron withdrawing positions. Groups that can be considered electron donating to the reaction centre (*para*-substituted phenol derivatives) gave low conversions.

4.3.3 - Effect of carbon substitution

Under the standard conditions various alkylidene Meldrum's acids containing carbon substituents were investigated (Figure 17). The reaction was tolerant of the 2-naphthyl substituent **S63**, yielding 80% conversion and an exceptional ee of 99%. 1-Naphthyl, **S64**, on the other hand gave no conversion, and only starting material was observed. The lack of conversion can likely be attributed to the increased steric bulk that would be found at the

reacting centre of the alkylidene Meldrum's acid. The less than optimal conversion of **S63** (which is similar in size and electronics to the plain phenyl) can be attributed to low solubility of the starting material. The reaction was also compatible with 3- and 4-methyl substituted benzylidene Meldrum's acids, **S65** and **S66**. The difference in conversion between the two substituents can't be fully rationalized, other than to say that based on other results the system appears to be more tolerant of substitution in the *meta*- position. Both **S55** and **S56** have excellent ee's of 98%, suggesting that the ligand can easily differentiate between both substituents regardless of the position of the substitution. Unlike the fluoro derivatives, the *ortho*-methyl substituent **S67**, did not give any conversion, and only starting material was observed. This was precedented by other work in our group, where it was found that *ortho* substitution decreases conversion.[32] This is presumably due to the increased sterics that are present at the reaction centre of the electrophile, making it inaccessible to the approaching nucleophile. The reaction was also very tolerant of the 4-*t*-butyl substitution **S68**, which gave nearly complete conversion, and excellent ee of 94%. It was surprising to find that substrate **S69**, gave conversions of only 50%, as one would expect similar reactivities to those of the plain phenyl and naphthyl substrates.

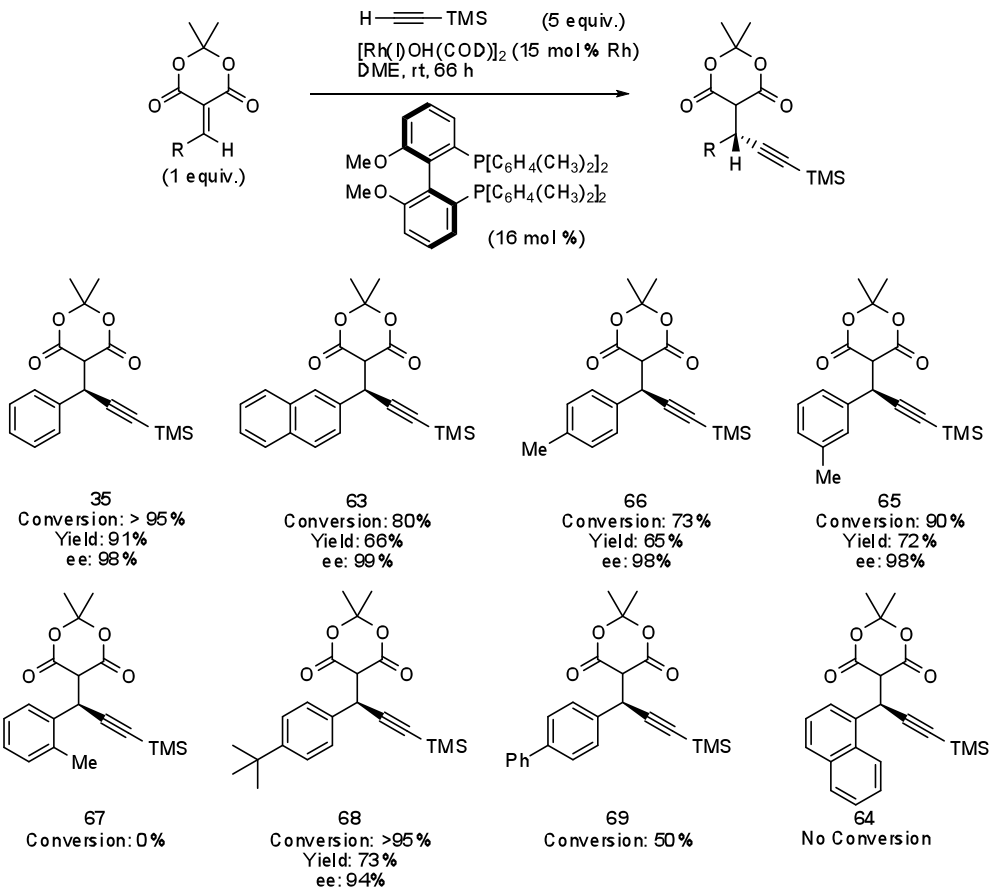


Figure 17. Effect of Carbon Substitution

4.3.4 - Non-aryl substituted alkylidenes

With the exception of the isopropyl alkylidene **S70**, it was found that non-aryl substituted alkylidenes (Figure 18) gave little to no conversion, and in most cases resulted in recovery of starting materials. The isopropyl derivative **S70** gave a conversion greater than 95%, with a modest ee of 74%. The furyl and thiophenyl alkylidenes likely have higher electron densities at the electrophilic centre of the alkylidene decreasing their reactivity (see ref. 36 for other examples), and as such resulted in no conversions.

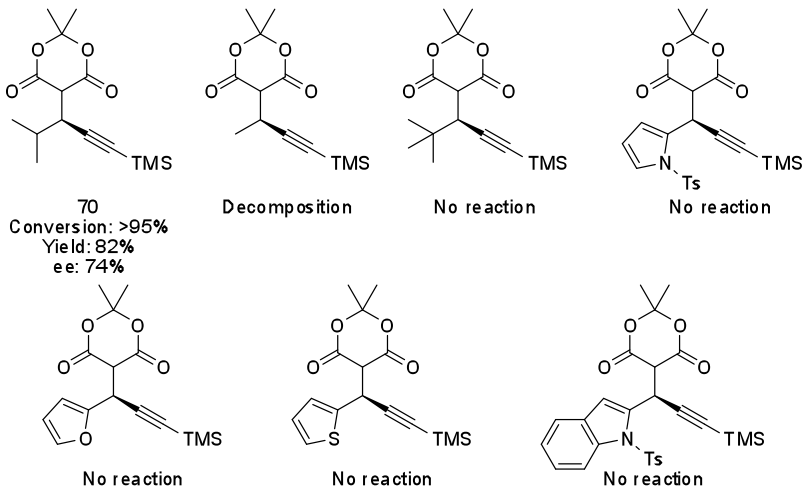


Figure 18. Non-aryl containing alkylidenes

4.3.5 - Quaternary carbon centres

At the outset of the project it was hoped that the highly activated nature of the alkylidene Meldrum's acid would allow for the conjugate addition of the Rh-alkynilides to yield quaternary carbon centres. In the past, our group has had success with similar additions, wherein diethyl[32] and dimethyl[34] zinc was successfully added to disubstituted alkylidene Meldrum's acids. It was decided that quaternary alkylidenes that were successful for the diethylzinc reactions would be tried under these conditions (Figure 19).

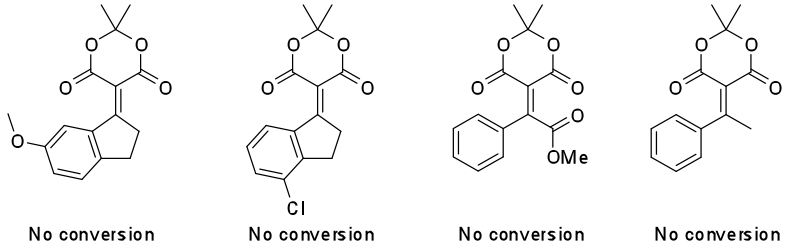


Figure 19. Attempts at the formation of quaternary carbon centres

As can be seen in Figure 19, regardless of the alkylidene, no conversion to any product was observed. It seems that the sterics or electronics of the alkylidene were too demanding for the Rh-alkynye to add.

4.4 - Changing the terminal alkyne

In conjunction with investigating the scope of the reaction with respect to various alkylidene Meldrum's acids, the investigation of various terminal alkynes was also undertaken. Using standard conditions and phenyl alkylidene Meldrum's acid as the standard substrate, several terminal alkynes were investigated and the results are summarized in Figure 20.

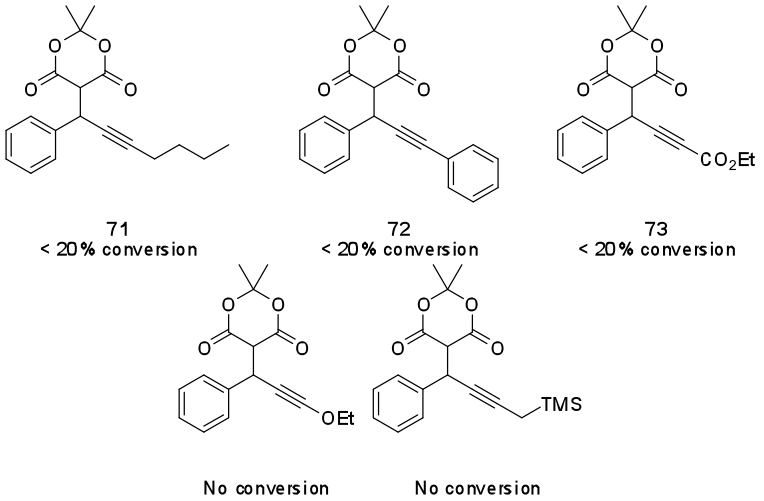


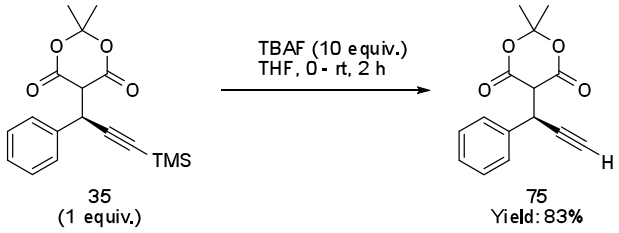
Figure 20. Scope of the source of terminal alkyne

Unfortunately, regardless of the terminal alkyne tested, none gave appreciable conversion. Using ethyl propiolate or TMS-propyne as terminal alkyne gave no conversion, and only starting material was observed. Slightly better conversion was observed for the less electron rich variants yielding products **71**, **72**, and **73** all in less than 20% conversion. It can thus be concluded that only the silyl acetylene variants give appreciable conversion.

4.5 - Transformations of products

4.5.1 - Deprotection of alkyne

With a broad scope of substrates investigated the next step was to investigate whether the alkynyl Meldrum's product **35** could be deprotected to yield the unprotected terminal alkyne. The deprotection was easily achieved (Scheme 22), by simply stirring the product with 10 eq of TBAF to yield deprotected product, **75** in 83% yield.

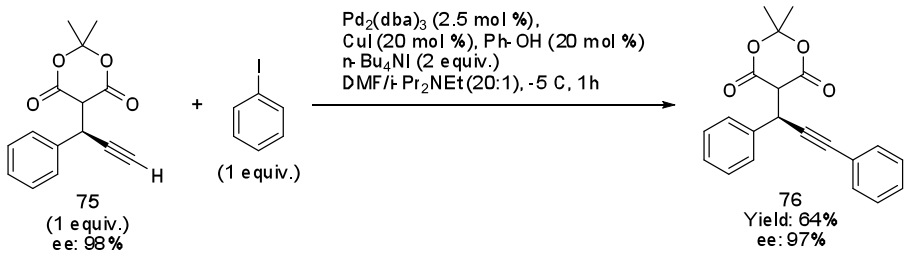


Scheme 22. Deprotection of alkyne

4.5.2 - Sonogashira coupling

With a simple and effective method for the deprotection of the TMS-alkyne in hand, chemistry was undertaken to use the newly formed terminal alkyne as a handle for further chemistry. Standard Sonogashira conditions using high temperature and amine solvent yielded decomposition of the starting Meldrum's alkylidene with no sign of the coupled product.

As it is well known within our group, the products of the conjugate addition tend not be heat stable, and as such a low temperature variant of the Sonogashira coupling was needed. By slightly modifying a known literature procedure for low temperature coupling[39], the coupled Sonogashira product was successfully isolated in modest yield and without loss of ee (Scheme 23).



Scheme 23. Low temperature Sonogashira coupling

This transformation also allowed for the determination of the absolute stereochemistry of the products, as chiral product **76** is a known compound.[25] It was found that the '*S*' enantiomer of the ligand gives the '*R*' enantiomer of the product.

4.6 - Potential commercial application

The control of diseases such as diabetes and dyslipidemia is of major interest to pharmaceutical companies. Recently Amgen has released several patents for small molecules (Figure 21) known to be effective at binding to GPR-40 receptor, giving potential drug targets of high importance.[40]

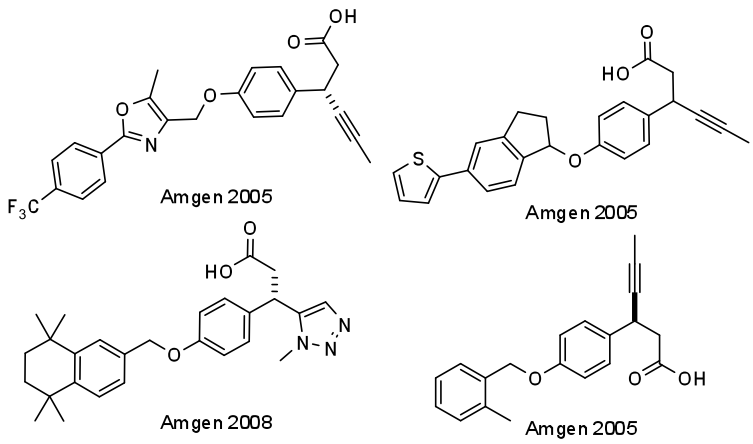
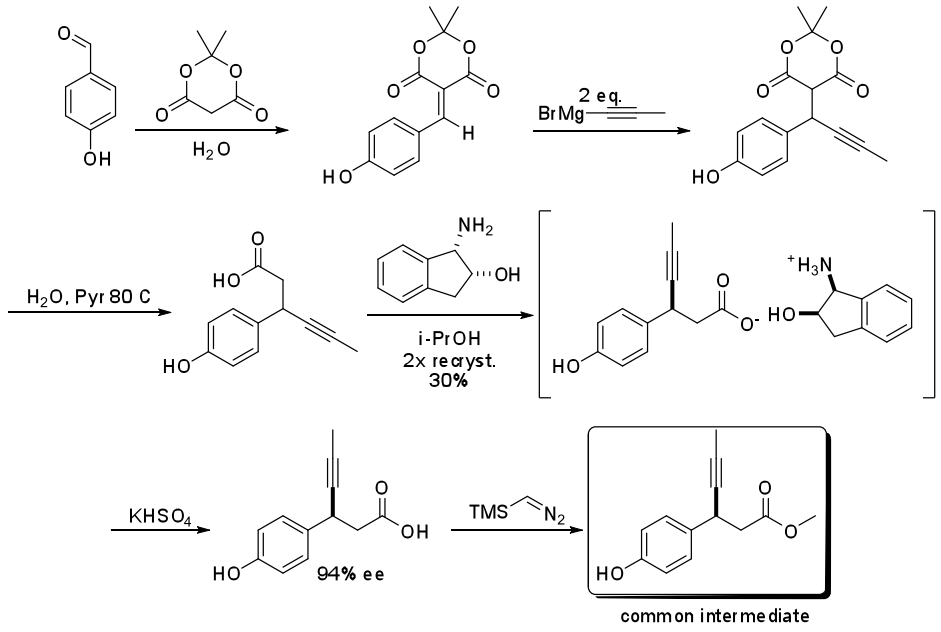


Figure 21. GPR-40 antagonists patented by Amgen in past 4 years

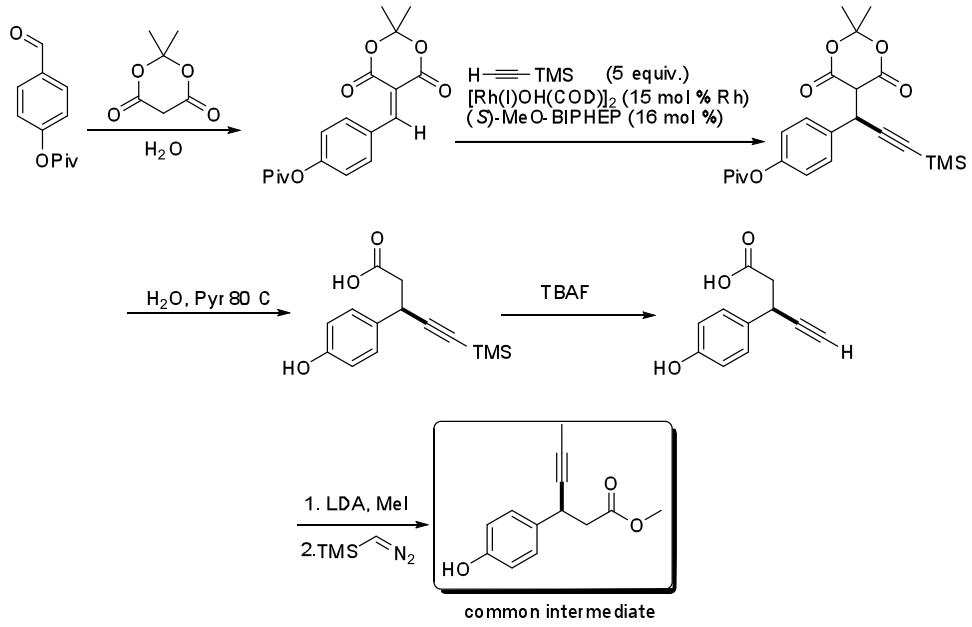
The current synthesis of these products is shown in Scheme 24, with a key step being the chiral resolution of the racemic mixture to yield the desired enantiomer. These chiral

resolutions are not desirable as they result in the loss of 50% of product thus increasing cost and waste.



Scheme 24. Amgen synthesis of GPR-40 receptor analogue

It is being proposed that the chemistry discussed in this thesis could be applied to form the product illustrated in Figure 21, without the need for chiral resolution. A proposed synthesis is shown in Scheme 25. The main difference for this pathway would be the need to deprotect the silyl-protected alkyne followed by subsequent methylation of the newly formed terminal alkyne.



Scheme 25. Proposed synthesis of GRP-40 receptors

5 - Conclusion

The successful development and optimization of the first chiral conjugate addition of TMS-acetylene (**36**) was performed. The scope of the reaction was investigated and found to be general for substrates containing electron neutral or electron withdrawing groups. Further transformations were performed on the chiral products and the absolute stereochemistry was determined. A family of recently patented biologically active compounds was also identified for which this chemistry may be of substantial use.

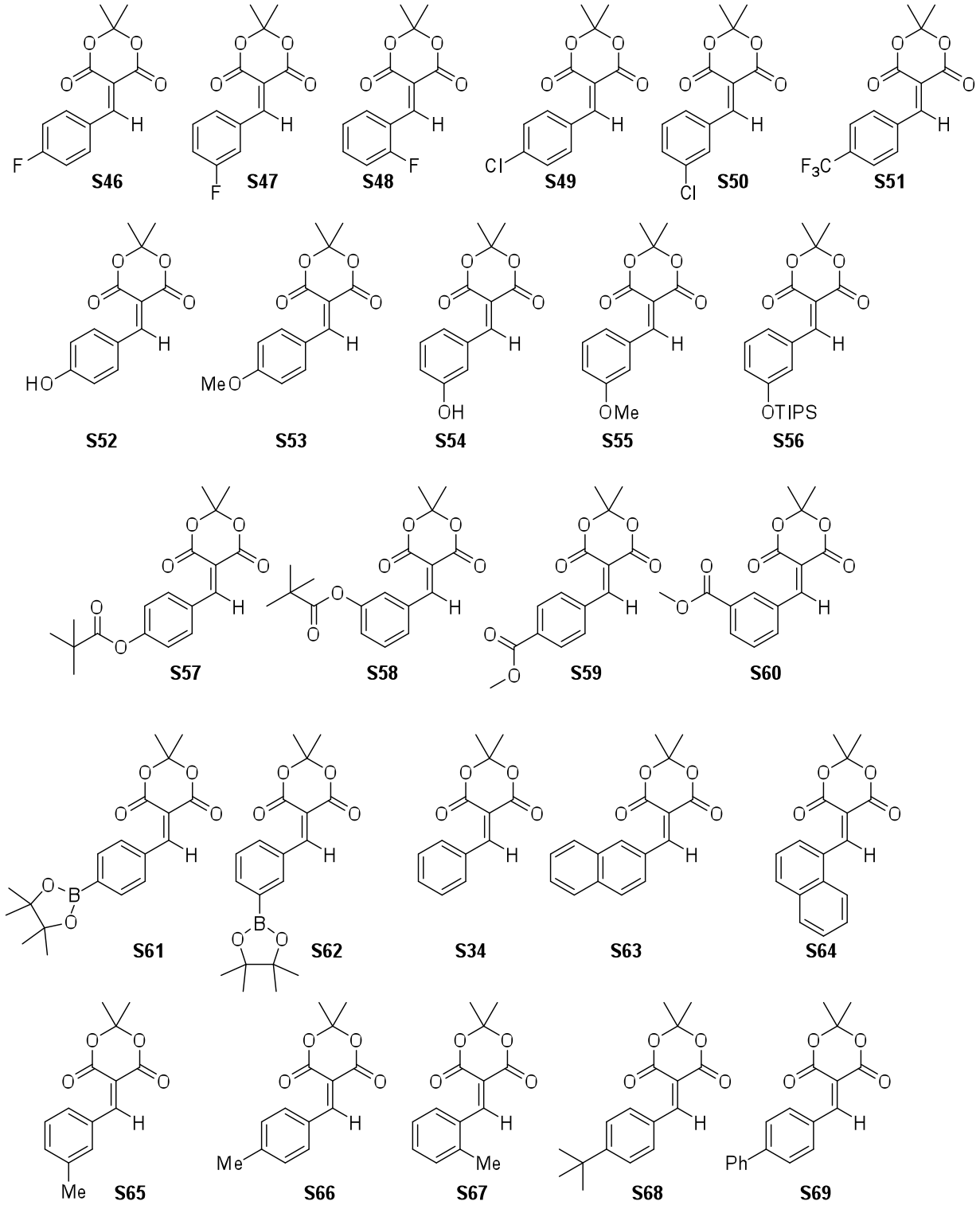


Figure 22. Starting materials used

6 - Experimental Section

General Considerations:
Reactions:
All reactions were performed in flame- or oven-dried glassware under a nitrogen atmosphere unless indicated otherwise. DME was distilled from Na/benzophenone and stored in a Schlenk flask in a nitrogen glove box. THF was obtained from a solvent purification system based on the published procedure.[41] Molecular sieves were activated by heating in an oven overnight (135 °C, 16h), and stored in a glove box. Known alkylidene Meldrum's acids were prepared by Knoevenagel condensation of the corresponding aldehydes with Meldrum's acid.[42] Unless indicated otherwise, all other reagents were used as received from commercial sources. Reactions were monitored by thin-layer chromatography and visualized by UV and/or by staining with ceric ammonium molybdate.

Characterization:

^{1}H and ^{13}C NMR spectra for all compounds were obtained in $CDCl_3$ at 300 MHz and 75 MHz, respectively. Chemical shifts are reported in parts per million (ppm, δ). Proton spectra were calibrated to residual $CHCl_3$ (7.24 ppm); carbon spectra were calibrated to $CDCl_3$ (77.0 ppm). Carbon multiplicities (C, CH, CH_2, CH_3) were determined by combined DEPT 90/135 experiments. Prior to measurement, some adducts were converted into the corresponding anilides: 5 mg of adduct was heated in 0.55 ml of DMF/aniline (10:1) at 100 °C for 1 h, cooled to 23 °C, the reaction mixture was extracted with Et_2O and washed three times with 1 M HCl, the organic phase was filtered through a plug of silica gel, eluted with hexane/EtOAc 4:1 to give the pure anilide.[25] Chiral HPLC analyses were performed using a Chiralcel ODH, or AD-

H column. High resolution mass spectrometry was performed at the University of Waterloo Mass Spectrometry facility. Melting points are uncorrected.

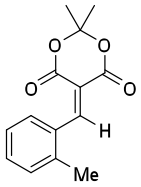
Preparation of Alkylidene Meldrum's Acids – General Procedure A. All known and unknown alkylidene Meldrum's acids were prepared according to the literature procedures.[42] Into a flamed dried round-bottom flask (RBF) equipped with magnetic stir bar was added the desired aldehyde (30.0 mmol, 1.2 equiv.), Meldrum's acid (3.6 g, 25.0 mmol, 1 equiv.) and dry benzene (distilled from Na/benzophenone, 125 mL, 0.2 M). To this solution was added 2.5 mL of a 0.5 mM solution of pyrrolidinium acetate in benzene (prepared by dropwise addition of AcOH to pyrrolidine in benzene, 2.5 mmol, 10 mol %) at room temperature. The RBF was capped with a rubber septa and placed in a preheated oil bath at 50 °C for 24 h. After 24 h, the RBF was removed from the heat and the suspension was filtered eluting with MeOH. The precipitate was discarded, and the mother liquor was concentrated to dryness in vacuo. The resulting solid was purified by recrystallization from MeOH.

Conjugate Addition of TMS-acetylene to Alkylidene Meldrum's Acids – General Procedure B. In a glove box, a 3 mL oven dried conical vial equipped with a magnetic spin vane was charged with hydroxy(1,5-cyclooctadiene)rhodium(I) dimer (7.5 mol % Rh), (*S*)-(-)-2,2'-Bis[di(3,5-xylyl)phosphino]-6,6'-dimethoxy-1,1'-biphenyl (16 mol %), and dry DME (distilled from Na/benzophenone, 125 μL, 0.6 M). This solution was then heated in a 50 °C oil bath for 5 min. In a glove box, to the resulting red-orange solution was added 6 mg of 4 Å molecular sieves, alkylidene Meldrum's acid (0.075 mmol, 1.0 equiv.), and TMS-acetylene (53 μL, 0.325 mmol, 5 equiv.). The conical vial was capped and removed from the glove box and stirred at room temperature for 66 h. Concentration and purification by flash chromatography on silica gel gave the pure products.

Preparation of racemates. To a flame dried RBF equipped with a magnetic stir bar was added 5 mL of dry THF under a nitrogen atmosphere. The THF was cooled to -78 °C, and TMS-acetylene (80 μL, 0.56 mmol, 1.1 equiv.) was added followed by the slow addition of *n*-BuLi (2.5 M solution, 0.2 mL, 0.51 mmol, 1.0 equiv.). This was allowed to stir at -78 °C for 5 min and a solution of the desired alkylidene Meldrum's acid (0.51 mmol, 1.0 equiv.) in 5 mL of dry THF was added dropwise. The mixture was allowed to stir from -78 °C to -10 °C for 4 hours. The reaction was diluted with EtOAc (5 mL), and quenched with aqueous NH_4Cl (5 mL, saturated). The organic phase was washed 2x with water and 1x with brine. The organic phase was then concentrated, and the resulting solid purified either by recrystallization from MeOH or by flash chromatography.

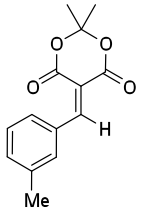
Starting materials used that were not previously characterized

2,2-Dimethyl-5-(2-methylbenzylidene)-1,3-dioxane-4,6-dione (S67)



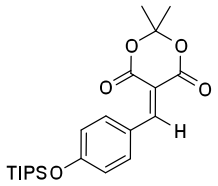
Following general procedure A, alkylidene Meldrum's acid was purified by recrystallization from methanol to give 54% (3.3 g) of **S67** an off white solid. M.p. 133-136 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.68 (s, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.37 (t, J = 7.4 Hz, 1H), 7.26-7.19 (m, 2H), 2.40 (s, 3H), 1.80 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 162.6 (C), 159.4 (C), 157.2 (CH), 139.2 (C), 132.4 (CH), 131.4 (C), 130.5 (CH), 130.2 (CH), 125.7 (CH), 116.2 (C), 104.7 (C), 27.7 (CH_3), 20.2 (CH_3); HRMS (EI) *m/z* calcd for $C_{14}H_{14}O_4$ (M^+): 246.0892. Found: 246.0896.

2,2-Dimethyl-5-(3-methylbenzylidene)-1,3-dioxane-4,6-dione (S65)



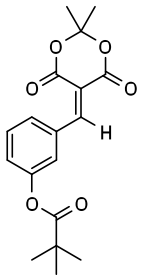
Following general procedure A, alkylidene Meldrum's acid was purified by recrystallization from methanol to give 85% (5.2 g) of **S65** an off white solid. M.p. 72-73 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.36 (s, 1H), 7.83-7.80 (m, 2H), 7.34 (d, *J* = 4.2 Hz, 2H), 2.37 (s, 3H), 1.78 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 163.2 (C), 159.7 (C), 158.3 (CH), 138.4 (C), 134.5 (CH), 134.0 (CH), 131.6 (C), 130.7 (CH), 128.5 (CH), 114.5 (C), 104.4 (C), 27.5 (CH_3), 21.2 (CH_3); HRMS (EI) *m/z* calcd for $C_{14}H_{14}O_4$ (M^+): 246.0892. Found: 246.0891.

2,2-Dimethyl-5-(4-(triisopropylsilyloxy)benzylidene)-1,3-dioxane-4,6-dione



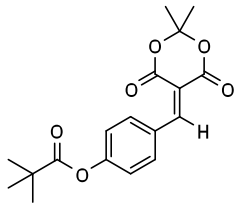
Following general procedure A, alkylidene Meldrum's acid was purified by recrystallization from methanol to give 70% (2.3 g) of a yellow solid. M.p. 67-69 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.34 (s, 1H), 8.16 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 1.76 (s, 6H), 1.25 (septet, *J* = 7.3 Hz, 3H), 1.09 (d, *J* = 7.2 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) 164.1 (C), 162.2 (C), 157.9 (CH), 137.7 (CH), 124.9 (C), 120.2 (CH), 110.6 (C), 104.1 (C), 27.4 (CH_3), 17.8 (CH), 12.7 (CH); HRMS (EI) *m/z* calcd for $C_{22}H_{32}O_5Si$ (M^+): 404.2019. Found: 404.2024.

3-((2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)methyl)phenyl pivalate (S58)



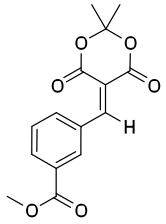
Following general procedure A, alkylidene Meldrum's acid was purified by recrystallization from methanol to give 56% (2.8 g) of **S58** an off white solid. M.p. 86 - 90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.36 (s, 1H), 7.86–7.83 (m, 2H), 7.47 (t, *J* = 8.2 Hz, 1H), 7.25 (d, *J* = 9.1 Hz, 1H), 1.78 (s, 6H), 1.33 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 176.8 (C), 163.0 (C), 159.4 (C), 156.6 (CH), 151.0 (C), 132.8 (C), 131.1 (CH), 129.5 (CH), 126.8 (CH), 126.0 (CH), 115.5 (C), 104.6 (C), 39.0 (C), 27.5 (CH_3), 27.0 (CH_3); HRMS (EI) *m/z* calcd for $C_{18}H_{20}O_6$ (M^+): 332.1260. Found: 332.1271.

4-((2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)methyl)phenyl pivalate (S57)



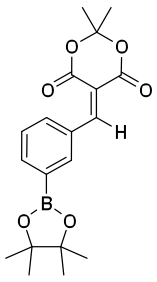
Following general procedure A, alkylidene Meldrum's acid was purified by recrystallization from methanol to give 42% (4.2 g) of **S57** a pale yellow solid. M.p. 88 - 90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.35 (s, 1H), 8.13 (d, *J* = 8.8 Hz, 2H), 7.17 (d, *J* = 8.7 Hz, 2H), 1.77 (s, 6H), 1.34 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 176.1 (C), 163.2 (C), 159.7 (C), 156.8 (CH), 155.2 (C), 135.6 (CH), 128.9 (C), 121.8 (CH), 114.1 (C), 104.4 (C), 39.1 (C), 27.5 (CH_3), 26.9 (CH_3); HRMS (EI) *m/z* calcd for $C_{18}H_{20}O_6$ (M^+): 332.1260. Found: 332.1259.

Methyl 3-((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)methyl)benzoate (S60)



Prepared with slight modification of general procedure A. Reaction was performed on a 3.0 mmol scale and alkylidene Meldrum's acid was purified by aqueous workup with saturated sodium bicarbonate followed by recrystallization from methanol to give 15% (0.13 g) of **S60** off white solid. M.p. 108-109 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.50 (s, 1H), 8.38 (s, 1H), 8.19 (d, J = 7.9 Hz, 1H), 8.13 (d, J = 7.8 Hz, 1H), 3.89 (s, 3H), 1.76 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 165.8 (C), 162.6 (C), 159.3 (C), 156.5 (CH), 136.6 (CH), 134.2 (CH), 133.8 (CH), 131.8 (C), 130.6 (C), 128.7 (CH), 116.0 (C), 104.7 (C), 52.3 (CH_3), 27.6 (CH_3); HRMS (EI) *m/z* calcd for $C_{15}H_{14}O_6$ (M^+): 290.0790. Found: 290.0795.

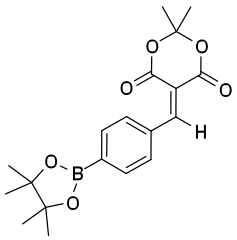
2,2-dimethyl-5-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzylidene)-1,3-dioxane-4,6-dione (S62)



Following general procedure A, but performed on a 10 mmol scale, alkylidene Meldrum's acid was purified by recrystallization from methanol to give 85% (3.0 g) of **S62** an off white solid. M.p. 94-95 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.45 (s, 1H), 8.31 (d, J = 8.0 Hz, 1H), 8.24 (s, 1H), 7.95 (d, J = 7.2 Hz, 1H), 7.47 (t, J = 7.6 Hz, 1H), 1.79 (s, 6H), 1.33 (s 12H); ^{13}C NMR (75 MHz, $CDCl_3$) 163.2 (C), 159.7 (C), 158.4 (CH), 140.8 (CH), 139.8 (CH), 135.2 (CH), 131.1

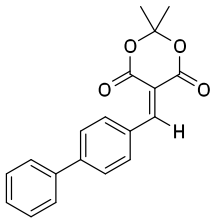
(C), 128.1 (CH), 114.7 (C), 104.5 (C), 84.2 (C), 27.6 (CH_3), 24.8 (CH_3); HRMS (EI) *m/z* calcd for $C_{19}H_{23}BO_6$ (M^+): 358.1588. Found: 357.1628.

2,2-dimethyl-5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzylidene)-1,3-dioxane-4,6-dione (S61)



Following general procedure A, alkylidene Meldrum's acid was purified by recrystallization from methanol to give 72% (2.8 g) of **S61** an off white solid. M.p. 167-169 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.41 (s, 1H), 7.93 (d, *J* = 7.9 Hz, 2H), 7.86 (d, *J* = 7.6Hz, 2H), 1.79 (s, 6H), 1.33(s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) 163.8 (C), 159.4 (C), 157.9 (CH), 134.8 (CH), 133.8 (C), 132.0 (CH), 115.5 (C), 104.6 (C), 84.2 (C), 27.6 (CH_3), 24.8 (CH_3); HRMS (EI) *m/z* calcd for $C_{19}H_{26}BO_6$ (M^+): 358.1588. Found: 357.1625.

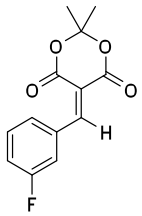
5-(biphenyl-4-ylmethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (S69)



Following general procedure A, alkylidene Meldrum's acid was purified by recrystallization from methanol to give 53% (4.1g) of **S69** a yellow solid. M.p. 141 - 146°C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.44 (s, 1H), 8.16 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 7.0 Hz, 2H), 7.49 – 7.39 (m, 3H), 1.80 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 163.3 (C), 159.9 (C), 157.5 (CH), 146.4 (C), 139.3 (C), 134.5 (CH), 130.5 (C), 128.9 (CH), 128.5 (CH), 127.2 (CH),

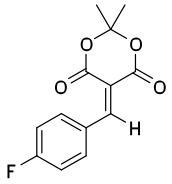
114.0 (C), 104.4 (C), 27.5 (CH_3); HRMS (EI) *m/z* calcd for $C_{19}H_{16}O_4$ (M^+): 308.1049. Found: 308.1044.

5-(3-fluorobenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (S47)



Following general procedure A, alkylidene Meldrum's acid was purified by recrystallization from methanol to give 64% (4.8 g) of **S47** a white solid. M.p. 117 - 119 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.34 (s,1H), 7.88 (d, *J* = 10.0 Hz, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.47-7.39 (m, 1H), 7.27 – 7.21 (m, 1H) 1.79 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 162.9 (C), 162.3 (d, *J* = 246.2 Hz, C), 159.3 (C), 156.3 (d, *J* = 2.5 Hz, CH), 148.3 (C), 133.4 (C), 130.2 (d, *J* = 8.2 Hz, CH), 129.7 (CH), 120.5 (d, *J* = 21.2 Hz, CH), 119.3 (d, *J* = 23.3 Hz, CH), 116.1 (C), 104.8 (C), 27.7 (CH_3); HRMS (EI) *m/z* calcd for $C_{13}H_{11}FO_4$ (M^+): 250.0641. Found: 250.0639.

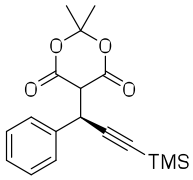
5-(4-fluorobenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (S46)



Following general procedure A, alkylidene Meldrum's acid was purified by recrystallization from methanol to give 58% (4.4 g) of **S46** a white solid. M.p. 139 - 140 °C; ^{1}H NMR (300 MHz, CDCl3) 8.36 (s, 1H), 8.17 – 8.11 (m, 2H), 7.14 (t, *J* = 8.6 Hz, 2H) 1.78 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 165.7 (d, *J* = 257.5 Hz, C), 163.2 (C), 159.8 (C), 156.7 (CH), 136.8 (d, *J* = 9.4 Hz, CH), 128.0 (d, *J* = 3.1 Hz, C), 116.1 (d, *J* = 21.8 Hz, CH), 114.1 (C), 104.6 (C), 27.6 (CH_3); HRMS (EI) *m/z* calcd for $C_{13}H_{11}FO_4$ (M^+): 250.0641 Found: 250.0649.

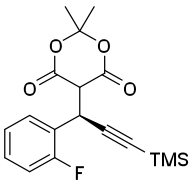
Product Specific Information

(*R*)-2,2-Dimethyl-5-(1-phenyl-3-(trimethylsilyl)prop-2-ynyl)-1,3-dioxane-4,6-dione (35)



Prepared according to general procedure B. Purification by flash chromatography (1:4 then 1:1 EtOAc:hexanes) gave 89% (22 mg) of **35** as an off white solid. M.p. 92 – 94 °C (racemate), 102 – 105 °C (chiral); ^{1}H NMR (300 MHz, $CDCl_3$) 7.51 (d, *J* = 7.3 Hz, 2H), 7.35-7.23 (m, 3H), 4.90 (d, *J* = 1.7 Hz, 1H), 3.86 (d, *J* = 2.4 Hz, 1H), 1.70 (s, 3H), 1.62 (s, 3H), 0.17 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 163.9 (C), 163.0 (C), 136.8 (C), 128.5 (CH), 128.4 (CH), 127.7 (CH), 105.2 (C), 102.4 (C), 90.7 (C), 52.7 (CH), 37.4 (CH), 28.4 (CH_3), 27.9 (CH_3), -0.17 (CH_3); An enantiomeric excess of 98% (*R*) was measured by chiral HPLC (AD-H, 1% *i*-PrOH/hexanes, 0.75 mL/min, t_{R1} = 18.0 min (minor), t_{R2} = 22.3 min (major)). HRMS (EI) *m/z* calcd for $C_{18}H_{22}O_4Si$ (M^+-acetone): 272.0947. Found: 272.0869.

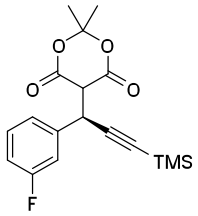
5-(1-(2-fluorophenyl)-3-(trimethylsilyl)prop-2-ynyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (48)



Purification by flash chromatography (1:3 EtOAc:hexanes) gave 31% (8.1 mg) of **48** a white solid. M.p. 119 - 120 °C (racemate), 113 – 116 °C (chiral); ^{1}H NMR (300 MHz, CDCl3) 7.85 (t, *J* = 7.2 Hz, 1H), 7.29-7.17 (m, 2H), 7.03 – 6.97 (m, 1H), 5.12 (d, *J* = 2.4 Hz, 1H), 3.93 (t, *J* = 2.4 Hz, 1H), 1.76 (s, 3H), 1.72 (s, 3H), 0.17 (s, 9H) ^{13}C NMR (75 MHz, $CDCl_3$) 164.2 (C), 162.5 (C), 159.8 (d, *J* = 243.3 Hz, C), 132.0 (d, *J* = 3.4 Hz, CH), 129.5 (d, *J* = 8.3 Hz, CH), 124.2 (d, *J* = 3.2 Hz, CH), 124.0 (C), 114.8 (d, *J* = 21.1 Hz, CH), 105.1 (C), 100.6 (C), 91.8

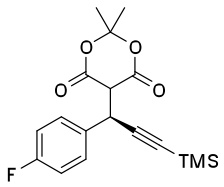
(C), 50.6 (d, J = 2.3 Hz, CH), 32.1 (d, J = 2.9 Hz, CH), 28.5 (CH_3), 27.7 (CH_3), -0.18 (CH_3) ; Enantiomeric excess of 90% was determined, after conversion into the corresponding anilide following a litterateur procedure[25], using chiral HPLC (OD, 10% *i*-PrOH/hexanes, 1.0 mL/min, t_{R1} = 7.61 min (major), t_{R2} = 10.52 min (minor)). HRMS (EI) *m/z* calcd for $C_{18}H_{21}FO_4Si$ (M^+ - methyl): 348.1193. Found: 333.0958.

5-(1-(3-fluorophenyl)-3-(trimethylsilyl)prop-2-ynyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (47)



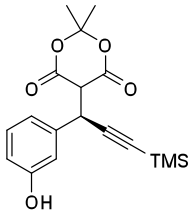
Purification by flash chromatography (1:3 EtOAc:hexanes) gave 51% (13.3 mg) of **47** a white solid. M.p. 108 - 110 °C (racemate), 115 – 117 °C (chiral); ^{1}H NMR (300 MHz, CDCl3) 7.29 – 7.24 (m, 3H), 6.96 – 6.94 (m, 1H), 4.92 (d, J = 2.4 Hz, 1H), 3.86 (d, J = 2.6 Hz, 1H), 1.71 (s, 3H), 1.67 (s, 3H), 0.17 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 163.7 (C), 162.9 (C), 162.7 (d, J = 244.6 Hz, C), 139.3 (d, J = 7.4 Hz, C), 129.9 (d, J = 8.1 Hz, CH), 124.0 (d, J = 2.9 Hz, CH), 116.0 (d, J = 22.7 Hz, CH), 114.7 (d, J = 20.9 Hz, CH), 105.3 (C), 101.7 (C), 91.2 (C), 52.6 (CH), 37.0 (CH), 28.4 (CH_3), 27.8 (CH_3), -0.19 (CH_3); An enantiomeric excess of 85% was measured by chiral HPLC (AD, 1.0% *i*-PrOH/hexanes, 1.0 mL/min, t_{R1} = 17.7 min (major), t_{R2} = 19.9 min (minor)). HRMS (EI) *m/z* calcd for $C_{18}H_{21}FO_4Si$ (M^+ - acetone): 290.0774. Found: 290.0772.

5-(1-(4-fluorophenyl)-3-(trimethylsilyl)prop-2-ynyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (46)



Purification by flash chromatography (1:3, 1:1 EtOAc:hexanes) gave 54% (14.1 mg) of **46** a yellow solid. M.p. 104 -105 °C (racemate), 98 -102 °C (chiral); ^{1}H NMR (300 MHz, CDCl3) 7.51 – 7.46 (m, 2H), 7.00 (t, *J* = 8.6 Hz, 2H), 4.91 (d, *J* = 2.4 Hz, 1H), 3.83 (d, *J* = 2.7 Hz, 1H), 1.70 (s, 3H), 1.64 (s, 3H), 0.17 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 163.6 (C), 163.1 (C), 162.2 (d, *J* = 245.3 Hz, C), 132.5 (d, *J* = 3.2 Hz, C), 130.5 (d, *J* = 8.1 Hz, CH), 115.3 (d, *J* = 21.4 Hz, CH), 105.2 (C), 102.4 (C), 90.8 (C), 52.8 (CH), 36.7 (C), 28.4 (CH_3), 27.8 (CH_3), -0.17 (CH_3) ; An enantiomeric excess of 85% was measured by chiral HPLC (AD, 1.0% *i*-PrOH/hexanes, 1.0 mL/min, t_{R1} = 16.8 min (major), t_{R2} = 18.7 min (minor)). HRMS (EI) *m/z* calcd for $C_{18}H_{21}FO_4Si$ (M^+ - acetone): 290.0774. Found: 290.0776

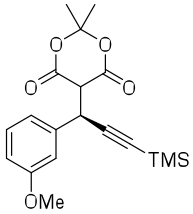
(*R*)-5-(1-(3-Hydroxyphenyl)-3-(trimethylsilyl)prop-2-ynyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (54)



Prepared according to general procedure B. Purification by flash chromatography (1:3 EtOAc:hexanes) gave 85% (22 mg) of **54** as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) 7.18 (t, *J* = 8.1 Hz, 1H), 7.03–7.01 (m, 2H), 6.74 (dd, *J* = 7.9, 2.0 Hz, 1H), 5.10 (very broad s, OH), 4.88 (d, *J* = 2.5Hz, 1H), 3.87 (d, *J* = 2.6 Hz, 1H), 1.70 (s, 3H), 1.63 (s, 3H) 0.17 (s, 9H) ^{13}C NMR (75 MHz, $CDCl_3$) 163.9 (C), 163.2 (C), 155.6 (C), 138.6 (C), 129.7 (CH), 120.7 (CH), 115.7 (CH), 114.8 (CH), 105.5 (C), 102.3 (C), 90.8(C), 52.6 (CH), 37.2 (CH), 28.4 (CH_3), 27.8

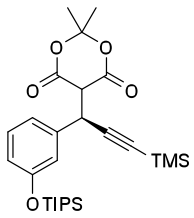
(CH_3), -0.13 (CH_3); Enantiomeric excess of 97% was determined, after conversion into the corresponding anilide[25], using chiral HPLC (OD-H, 10% *i*-PrOH/hexanes, 1.0 mL/min, t_{R1} = 10.5 min (major), t_{R2} = 13.9 min (minor)). HRMS (EI) *m/z* calcd for $C_{18}H_{22}O_5Si$ (M^+): 346.1237. Found: 346.1241.

(*R*)-5-(1-(3-Methoxyphenyl)-3-(trimethylsilyl)prop-2-ynyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (55)



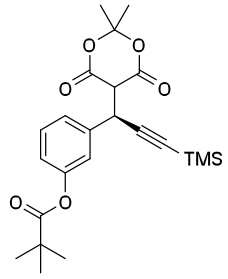
Prepared according to general procedure B. Purification by flash chromatography (1:3 EtOAc:hexanes) gave 83% (22 mg) of **55** as a yellow solid. M.p. 101-105 °C (racemate), 100 - 103 °C (chiral); ^{1}H NMR (300 MHz, $CDCl_3$) 7.29-7.26 (m, 1H), 7.16 (s, 1H), 7.09 (d, *J* = 7.6 Hz, 1H), 6.84 (d, *J* = 8.1 Hz, 1H) 4.94 (d, *J* = 2.2 Hz, 1H), 3.91 (d, *J* = 2.6 Hz, 1H), 3.83 (s, 3H), 1.73 (s, 3H), 1.67 (s, 3H), 0.21 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 163.8 (C), 162.9 (C), 159.4 (C), 138.3 (C), 129.3 (CH), 120.6 (CH), 114.2 (CH), 113.3 (CH), 105.1 (C), 102.3 (C), 90.7 (C), 55.1 (CH_3), 52.7 (CH), 37.4 (CH), 28.3 (CH_3), 27.9 (CH_3), -0.24 (CH_3); Enantiomeric excess of 95% was determined, after conversion into the corresponding anilide[25], using chiral HPLC (OD-H, 10% *i*-PrOH/hexanes, 1.0 mL/min, t_{R1} = 9.2 min (major), t_{R2} = 12.6 min (minor)). HRMS (EI) *m/z* calcd for $C_{19}H_{24}O_5Si$ (M^+): 360.1393. Found: 360.1389.

(*R*)-2,2-Dimethyl-5-(1-(3-(triisopropylsilyloxy)phenyl)-3-(trimethylsilyl)prop-2-ynyl)-1,3-dioxane-4,6-dione (56)



Prepared according to general procedure B. Purification by flash chromatography (1:3 EtOAc:hexanes) gave 77% (29 mg) of **56** as a clear oil; ^{1}H NMR (300 MHz, $CDCl_3$) 7.16–7.12 (m, 2H), 6.96 (d, J = 7.5 Hz, 1H) 6.77 (d, J = 7.8 Hz, 1H) 4.88 (s, 1H), 3.86 (d, J = 2.2 Hz, 1H), 1.69 (s, 3H), 1.61 (s, 3H), 1.21 (septet, J = 7.1Hz, 3H), 1.09 (d, J = 7.1 Hz, 18H), 0.16 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 163.8 (C), 163.0 (C), 156.0 (C), 138.1 (C), 129.2 (CH), 120.7 (CH), 120.4 (CH), 119.3 (CH), 105.1 (C), 102.5 (C), 90.4 (C), 52.6 (CH), 37.3 (CH), 28.4 (CH_3), 27.9 (CH_3), 17.9 (CH_3), 12.6 (CH), -0.19 (CH_3); Enantiomeric excess of 89% was determined, after conversion into the corresponding anilide[25], using chiral HPLC (OD-H, 10% *i*-PrOH/hexanes, 1.0 mL/min, t_{R1} = 4.8 min (major), t_{R2} = 5.9 min (minor)). HRMS (EI) *m/z* calcd for $C_{27}H_{42}O_5Si_2$ (M^+): 502.2571. Found: 502.2580.

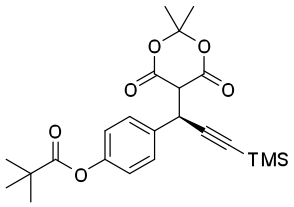
(*R*)-3-(1-(2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-3-(trimethylsilyl)prop-2-ynyl)phenyl pivalate (58)



Prepared according to general procedure B. Purification by flash chromatography (1:3 EtOAc:hexanes) gave 83% (27 mg) of **58** a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) 7.40 (d, J = 7.8 Hz, 1H), 7.31 (t, J = 7.9 Hz, 1H), 7.19 (s, 1H), 6.96 (d, J = 7.9 Hz, 1H), 4.90 (d, J = 2.3

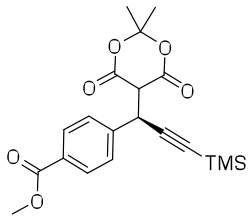
Hz, 1H), 3.89 (d, *J* = 2.6 Hz, 1H), 1.69 (s, 3H), 1.65 (s, 3H), 1.33 (s, 9H), 0.16 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 176.9 (C), 163.8 (C), 162.8 (C), 150.9 (C), 138.5 (C), 129.2 (CH), 125.8 (CH), 121.7 (CH), 120.9 (CH), 105.2 (C), 101.9 (C), 91.0 (C), 52.5 (CH), 39.0 (C), 37.0 (CH), 28.4 (CH_3), 27.7 (CH_3), 27.0 (CH_3), -0.24 (CH_3); Enantiomeric excess of 94% was determined, after conversion into the corresponding anilide[25], using chiral HPLC (OD-H, 10% *i*-PrOH/hexanes, 1.0 mL/min, t_{R1} = 5.1 min (major), t_{R2} = 6.2 min (minor)). HRMS (EI) *m/z* calcd for $C_{23}H_{30}O_6Si$ (M^+-acetone): 372.1393. Found: 372.1389.

(*R*)-4-(1-(2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-3-(trimethylsilyl)prop-2-ynyl)phenyl pivalate (57)



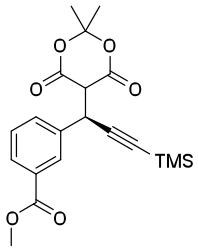
Prepared according to general procedure B. Purification by flash chromatography (1:3 EtOAc:hexanes) gave 86% (28 mg) of **57** a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) 7.52 (d, *J* = 8.6 Hz, 2H), 6.99 (d, *J* = 8.6 Hz, 2H), 4.91 (d, *J* = 2.5 Hz, 1H), 3.87 (d, *J* = 2.6 Hz, 1H), 1.69 (s, 3H), 1.63 (s, 3H), 1.32 (s, 9H), 0.16 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 176.9 (C), 163.6 (C), 162.9 (C), 150.5 (C), 134.0 (C), 129.8 (CH), 121.3 (CH), 105.1 (C), 102.3 (C), 90.5 (C), 52.6 (CH), 39.0 (C), 36.7 (CH), 28.3 (CH_3), 27.6 (CH_3), 27.0 (CH_3), -0.22 (CH_3); Enantiomeric excess of 93% was determined, after conversion into the corresponding anilide[25], using chiral HPLC (OD-H, 10% *i*-PrOH/hexanes, 1.0 mL/min, t_{R1} = 7.6 min (major), t_{R2} = 8.5 min (minor)). HRMS (EI) *m/z* calcd for $C_{23}H_{30}O_6Si$ (M^+-acetone): 372.1393. Found: 372.1397.

(*R*)-Methyl 4-(1-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-3-(trimethylsilyl)prop-2-ynyl)benzoate (59)



Prepared according to general procedure B. Purification by flash chromatography (1:3 EtOAc:hexanes) gave 80% (23 mg) of **59** as a white solid. M.p. 122 - 125 °C (racemate), 115 - 120 °C (chiral); ^{1}H NMR (300 MHz, $CDCl_3$) 7.99 (d, J = 8.3 Hz, 2H), 7.59 (d, J = 8.3 Hz, 2H), 4.98 (d, J = 2.5 Hz, 1H), 3.88 (app. s, 4H), 1.71 (s, 3H), 1.68 (s, 3H), 0.17 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 166.6 (C), 163.5 (C), 162.7 (C), 141.9 (C), 129.6 (CH), 129.4 (C), 128.5 (CH), 105.2 (C), 101.4 (C), 91.4 (C), 52.4 (CH), 52.0 (CH_3), 37.2 (CH), 28.3 (CH_3), 27.7 (CH_3), -0.29 (CH_3); An enantiomeric excess of 85% was measured by chiral HPLC (AD-H, 10% *i*-PrOH/hexanes, 1.0 mL/min, t_{R1} = 7.5 min (minor), t_{R2} = 8.3 min (major)). HRMS (EI) *m/z* calcd for $C_{20}H_{24}O_6Si$ (M^+-MeOH): 357.1158. Found: 357.1156.

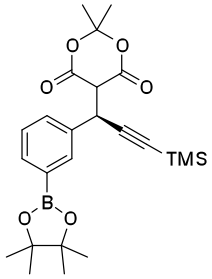
(*R*)-Methyl 3-(1-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-3-(trimethylsilyl)prop-2-ynyl)benzoate (60)



Prepared according to general procedure B. Purification by flash chromatography (1:3 EtOAc:hexanes) gave 74% (22 mg) of **60** as an off white solid M.p. 105-106 °C (racemate), 105-108 °C (chiral); ^{1}H NMR (300 MHz, $CDCl_3$) 8.12 (s, 1H), 7.94 (d, J = 7.8 Hz, 2H), 7.81 (d, J = 7.8 Hz, 2H), 7.42 (t, J = 7.8 Hz, 1H), 4.97 (d, J = 2.4 Hz, 1H), 3.89-3.88 (m, 4H), 1.72 (s, 3H), 1.70 (s, 3H), 0.18 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 166.7 (C), 163.8 (C), 162.7 (C),

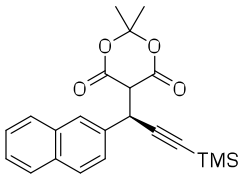
137.4 (C), 133.3 (CH), 130.2 (C), 129.2 (CH), 128.8 (CH), 128.5 (CH), 105.2 (C), 101.5 (C), 91.6 (C), 52.5 (CH), 52.1 (CH_3), 37.1 (CH), 28.4 (CH_3), 27.7 (CH_3), -0.29 (CH_3); Enantiomeric excess of 84% was determined, after conversion into the corresponding anilide[25], using chiral HPLC (OD-H, 10% *i*-PrOH/hexanes, 1.0 mL/min, t_{R1} = 5.2 min (major), t_{R2} = 13.7 min (minor)). HRMS(ESI) *m/z* calcd for $C_{20}H_{24}O_6Si$ $(M+H)^+$: 389.1420. Found: 389.1412.

(*R*)-2,2-Dimethyl-5-(1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3-(trimethylsilyl)prop-2-ynyl)-1,3-dioxane-4,6-dione (62)



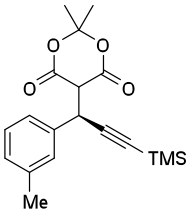
Prepared according to general procedure B. Purification by flash chromatography (1:3 EtOAc:hexanes) gave 84% (29 mg) of **62** a clear oil; ^{1}H NMR (300 MHz, $CDCl_3$) 7.80–7.78 (m, 2H), 7.70 (d, *J* = 7.3 Hz, 1H), 7.37 (t, *J* = 7.9 Hz, 1H), 4.93 (d, *J* = 2.3 Hz, 1H), 3.88 (d, *J* = 2.6 Hz, 1H), 1.70 (s, 6H), 1.32 (s, 12H) 0.17 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 164.3 (C), 162.7 (C), 136.4 (C), 134.0 (CH), 133.9 (CH), 132.0 (CH), 127.9 (CH), 105.1 (C), 102.1 (C), 91.3 (C), 83.8 (C), 52.8 (CH), 37.5 (CH), 28.5 (CH_3), 27.9 (CH_3), 24.9 (CH_3), 24.9 (CH_3), -0.17 (CH_3); Enantiomeric excess of 92% was determined, after conversion into the corresponding anilide[25], using chiral HPLC (OD-H, 10% *i*-PrOH/hexanes, 1.0 mL/min, t_{R1} = 5.2 min (major), t_{R2} = 6.3 min (minor)). HRMS(ESI) *m/z* calcd for $C_{24}H_{33}BO_6Si$ $(M+H)^+$: 457.2218. Found: 457.2216.

(*R*)-2,2-Dimethyl-5-(1-(naphthalen-2-yl)-3-(trimethylsilyl)prop-2-ynyl)-1,3-dioxane-4,6-dione (63)



Prepared according to general procedure B. Purification by flash chromatography (1:3 EtOAc:hexanes) gave 70% (20 mg) of **63** as a pale yellow solid. M.p. 127 – 129 °C (racemate), 120 – 121 °C (chiral); ^{1}H NMR (300 MHz, $CDCl_3$) 7.98 (s, 1H), 7.83-7.81 (m, 3H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.46 (d, *J* = 4.5 Hz, 1H), 7.45 (d, *J* = 2.4 Hz, 1H), 5.11 (d, *J* = 2.2 Hz, 1H), 3.97 (d, *J* = 2.4 Hz, 1H), 1.69 (s, 3H), 1.63 (s, 3H), 0.21 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 163.9 (C), 163.0 (C), 134.2 (C), 133.1 (C), 132.7 (C), 128.0 (CH), 127.8 (CH), 127.5 (CH), 126.2 (CH), 126.1(CH), 105.2 (C), 102.5 (C), 90.2 (C), 52.7 (CH), 37.5 (CH), 28.4 (CH_3), 27.8 (CH_3), -0.10 (CH_3) (2 overlapping carbons); An enantiomeric excess of 99% was measured by chiral HPLC (AD-H, 1% *i*-PrOH/hexanes, 1.0 mL/min, t_{R1} = 21.0 min (major), t_{R2} = 24.2 min (minor)). HRMS (EI) *m/z* calcd for $C_{22}H_{24}O_4Si$ (M^+): 380.1444. Found: 380.1440.

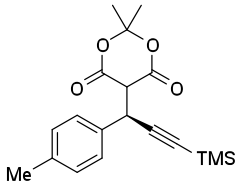
(*R*)-2,2-Dimethyl-5-(1-m-tolyl-3-(trimethylsilyl)prop-2-ynyl)-1,3-dioxane-4,6-dione (65)



Prepared according to general procedure B. Purification by flash chromatography (1:3 EtOAc:hexanes) gave 72% (19 mg) of **65** as an off white solid. M.p. 103 - 105 °C (racemate), 107 – 109 °C (chiral); ^{1}H NMR (300 MHz, $CDCl_3$) 7.33–7.29 (m, 2H), 7.24 – 7.19 (m, 1H), 7.07 (d, *J* = 7.4 Hz, 1H), 4.90 (d, *J* = 2.4 Hz, 1H), 3.86 (d, *J* = 2.7 Hz, 1H), 2.32 (s, 3H), 1.70 (s, 3H), 1.63 (s, 3H), 0.17 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 164.0 (C), 163.0 (C), 138.0 (C),

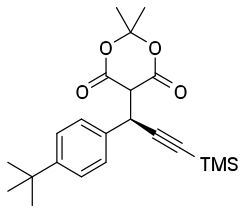
136.7 (C), 129.1 (CH), 128.4 (CH), 128.3 (CH), 125.6 (CH), 105.1 (C), 102.5 (C), 90.6 (C), 52.7 (CH), 37.4 (CH), 28.4 (CH_3), 27.9 (CH_3), 21.4 (CH_3), -0.17 (CH_3); An enantiomeric excess of 98% was measured by chiral HPLC (AD-H, 10% *i*-PrOH/hexanes, 0.5 mL/min, t_{R1} = 17.1 min (minor), t_{R2} = 23.8 min (major)). HRMS (EI) *m/z* calcd for $C_{19}H_{24}O_4Si$ (M^+-acetone): 286.1025. Found: 286.1022.

(*R*)-2,2-Dimethyl-5-(1-p-tolyl-3-(trimethylsilyl)prop-2-ynyl)-1,3-dioxane-4,6-dione (66)



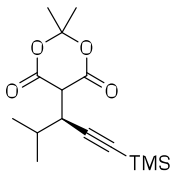
Prepared according to general procedure B. Purification by flash chromatography (1:3 EtOAc:hexanes) gave 65% (17 mg) of **66** as a white solid. M.p. 110 - 112 °C (racemate), 114 - 115 °C (chiral); ^{1}H NMR (300 MHz, $CDCl_3$) 7.39 (d, *J* = 7.9 Hz, 2H), 7.13 (d, *J* = 7.9 Hz, 2H), 4.90 (d, *J* = 2.3 Hz, 1H), 3.86 (d, *J* = 2.7 Hz, 1H), 2.31 (s, 3H), 1.69 (s, 3H), 1.63 (s, 3H), 0.17 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 163.9 (C), 163.0 (C), 137.3 (C), 133.7 (C), 129.1 (CH), 128.4 (CH), 105.1 (C), 102.7 (C), 90.3 (C), 52.7 (CH), 37.1 (CH), 28.3 (CH_3), 27.8 (CH_3), 21.0 (CH_3), -0.15 (CH_3); An enantiomeric excess of 98% was measured by chiral HPLC (AD-H, 10% *i*-PrOH/hexanes, 0.5 mL/min, t_{R1} = 20.9 min (major), t_{R2} = 23.8 min (minor)). HRMS (EI) *m/z* calcd for $C_{19}H_{24}O_4Si$ (M^+-acetone): 286.1025. Found: 286.1018.

(*R*)-5-(1-(4-*tert*-Butylphenyl)-3-(trimethylsilyl)prop-2-ynyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (68)



Prepared according to general procedure B. Purification by flash chromatography (1:3 EtOAc:hexanes) gave 73% (21 mg) of **68** as a yellow solid. M.p. 91 - 96 °C (racemate), 93 - 95 °C (chiral); ^{1}H NMR (300 MHz, $CDCl_3$) 7.43 (d, J = 7.4 Hz, 2H), 7.34 (d, J = 7.7 Hz, 2H), 4.90 (s, 1H), 3.85 (s, 1H), 1.69 (s, 3H), 1.59 (s, 3H), 1.28 (s, 9H), 0.17 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 163.9 (C), 163.0 (C), 150.5 (C), 133.7 (C), 128.1 (CH), 125.4 (CH), 105.1 (C), 102.7 (C), 90.3 (C), 52.7 (CH), 37.0 (CH), 34.4 (C), 31.2 (CH_3), 28.4 (CH_3), 27.8 (CH_3), -0.15 (CH_3); An enantiomeric excess of 94% was measured by chiral HPLC (AD-H, 1% *i*-PrOH/hexanes, 1.0 mL/min, t_{R1} = 9.4 min (minor), t_{R2} = 10.6 min (major)). HRMS (EI) *m/z* calcd for $C_{22}H_{30}O_4Si$ (M^+-acetone): 328.1495. Found: 328.1488.

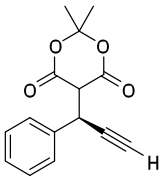
(*S*)-2,2-Dimethyl-5-(4-methyl-1-(trimethylsilyl)pent-1-yn-3-yl)-1,3-dioxane-4,6-dione (70)



Prepared according to general procedure B. Purification by flash chromatography (1:3 EtOAc:hexanes) gave 85% (18 mg) of **70** as an off white solid. M.p. 70 – 74 °C (racemate), 72 – 74 °C (chiral); ^{1}H NMR (300 MHz, $CDCl_3$) 3.59 (d, J = 2.8 Hz, 1H), 3.04 (dd, J = 10.4, 2.8 Hz, 1H), 2.37 (octet, J = 6.6 Hz , 1H), 1.78 (s, 3H), 1.73 (s, 3H), 1.12 (d, J = 6.6 Hz, 3H), 0.97 (d, J = 6.6 Hz, 3H) 0.09 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 165.7 (C), 163.7 (C), 105.2 (C), 104.3 (C), 89.0 (C), 47.3 (CH), 41.3 (CH), 30.1 (CH), 28.7 (CH_3), 28.2 (CH_3), 21.7 (CH_3), 20.2

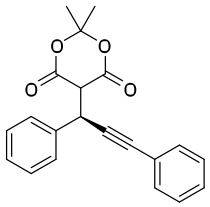
(CH_3), -0.17 (CH_3); Enantiomeric excess of 74% was determined, after conversion into the corresponding anilide following a literature procedure[25], using chiral HPLC (OD-H, 10% *i*-PrOH/hexanes, 1.0 mL/min, t_{R1} = 7.4 min (major), t_{R2} = 9.9 min (minor)). HRMS (EI) *m/z* calcd for $C_{15}H_{24}O_4Si$ (M^+- CH_3): 281.1209. Found: 281.1212.

(*R*)-2,2-Dimethyl-5-(1-phenylprop-2-ynyl)-1,3-dioxane-4,6-dione (71)



To an RBF equipped with a magnetic spin vane was added phenyl alkylidene Melrum's acid (240 mg, 0.72 mmol, 1.0 equiv.) and THF (100 mL, 0.0072M). The solution was cooled in an ice bath and tetra-*n*-butylammonium fluoride (1.0 M solution, 7.2 mL, 7.2 mmol, 10 equiv) was added. The mixture was allowed to warm to rt, and stirred for 2 h. The crude mixture was diluted with ether and the organic phase washed with aqueous NH_4Cl (20 mL, saturated), followed by water (3x 20 mL) gave a crude yellow oil. Purification by flash chromatography (1:3 EtOAc:hexanes) gave 83% (154 mg) of **71** as a white solid. M.p. 117-121 °C (racemate), 118 - 120 °C (chiral); ^{1}H NMR (300 MHz, $CDCl_3$) 7.54 (d, *J* = 7.3 Hz, 2H), 7.36 – 7.24 (m, 3H), 4.94 (t, *J* = 2.5 Hz, 1H), 3.92 (d, *J* = 2.6 Hz, 1H), 2.42 (d, *J* = 2.6 Hz, 1H), 1.71 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 163.5 (C), 162.8 (C), 136.2 (C), 128.5 (CH), 128.4 (CH), 127.9 (CH), 105.2 (C), 80.8 (C), 73.4 (CH), 52.5 (CH), 35.8 (CH), 28.2 (CH_3), 27.4 (CH_3); HRMS (EI) *m/z* calcd for $C_{15}H_{14}O_4$ (M^+-acetone): 200.0998. Found: 200.0466.

(*R*)-5-(1,3-Diphenylprop-2-ynyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (72)



Prepared by modification of literature procedure.[43] Under an argon atmosphere, an oven dried resealable Schlenk tube was charged with iodobenzene (40 μL, 0.38 mmol, 1.0 equiv.), cuprous iodide (22 mg, 0.11 mmol, 0.28 equiv.), tetra-n-butylammonium iodide (280.7 mg, 0.76 mmol, 2 equiv.), phenol (71.5 mg, 0.76 mmol, 2.0 equiv.), DMF (4 mL, 0.1 M), diisopropylamine (0.2 mL) were added. The mixture was degassed by three freeze pump thaw cycles. Then $Pd_2(dba)_3{\cdot}(CHCl_3)$ (9.8 mg, 0.009 mmol, 2 mol %) was added and the mixture was stirred at room temperature for 5 min. The mixture was cooled to -5 °C, and the deprotected alkylidene Meldrum's acid (**72**) (98 mg, 0.38 mmol, 1 equiv) was added, and stirring continued at -5 °C for 1 h. The reaction was then quenched with aqueous NH_4Cl (2 mL, saturated), and the organic materials were extracted twice with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by silica gel chromatography gave 64 % (81.2 mg), of **72**. All spectroscopic data are in accord with that found in literature.[25] Enantiomeric excess of 97% was determined, after conversion into the corresponding anilide[25], using chiral HPLC (OD-H, 10% *i*-PrOH/hexanes, 1.0 mL/min, t_{R1} = 9.2 min (major), t_{R2} = 12.6 min (minor)).

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