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Intermolecular Pauson-Khand reaction:

Regioselectivity, stereoselectivity and promotion methods

Erika Fager-Jokela

Academic Dissertation

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Abstract

The Pauson-Khand reaction (PKR) is a very efficient method of synthesising cyclopentenones. In the reaction, an alkene, an alkyne and carbon monoxide combine to form a cyclopentenone ring, mediated or catalysed by a transition metal complex in one pot. In the cyclisation, three new carbon-carbon bonds are created. This thesis concentrates on the intermolecular variant of a cobalt(0)-mediated Pauson-Khand reaction.

The development of intermolecular cyclisation has been slow over the past decade, due to the lack of reactive alkenes and the lack of regioselectivity for substituted alkynes. Despite the publication of numerous studies, the electronic effects involved are not yet completely understood. In this study, our purpose was to gain a greater understanding of the interplay between steric and electronic factors in determining the regioselectivity of the Pauson-Khand reaction.

The electronic guidance regarding the alkyne regioselectivity of the Pauson-Khand reaction was studied with both conjugated aromatic alkynes and non-conjugated propargylic alkynes. It was demonstrated that, in the absence of steric effects, alkyne polarisation dictates the regiochemical selectivity of PKR. In conjugated systems, like diarylalkynes, Hammett values can be utilised in estimation of the polarisation of the alkyne. With nonconjugated alkynes, on the other hand, electronegativity of the substituent group designates the major regioisomer, as the charge differences are created via inductive effect.

In addition to investigating regioselectivity, additive-free methods for promotion of Pauson-Khand reaction were developed and utilised, and Pauson-Khand reaction was applied in the synthesis of estrone E-ring extension. With microwaves (MW) used in promotion, the heat was effectively transferred to the reaction, saving energy and time without affecting the selectivity of the reaction.

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Contents

List of original publications

This thesis is based on the following publications, which are referenced in the text by their Roman numerals:

I Erika Fager-Jokela, Emmi Kaasalainen, Kirsi Leppänen, Jan Tois and Juho Helaja, Development of intermolecular additive free Pauson-Khand reactions for estrone E-ring extension using microwaves. *Tetrahedron* **2008**, *64*, 10381-10387.

II Erika Fager-Jokela, Mikko Muuronen, Michael Patzschke and Juho Helaja, Electronic Regioselectivity of Diarylalkynes in Cobalt-Mediated Pauson-Khand Reaction: An Experimental and Computational Study with Para- and Meta-Substituted Diarylalkynes and Norbornene. *Journal of Organic Chemistry* **2012**, *77*, 9134-9147.

III Erika Fager-Jokela, Mikko Muuronen, Héléa Khaizourane, Ana Vázquez-Romero, Xavier Verdaguer, Antoni Riera and Juho Helaja, Regioselectivity of intermolecular Pauson-Khand reaction of aliphatic alkynes: experimental and theoretical study of the effect of alkyne polarization. *Journal of Organic Chemistry* **2014**, *79*, 10999-11010.

Author’s contribution to the articles

I EFJ performed all synthesis, analysis and characterisation in the study. KL performed the WAXS measurements. JH and EFJ drafted and edited the manuscript together.

II EFJ designed the research, and performed all syntheses, analyses and characterisations in the study. MM detailed and performed all calculations with help from MP. All authors drafted and edited the manuscript together.

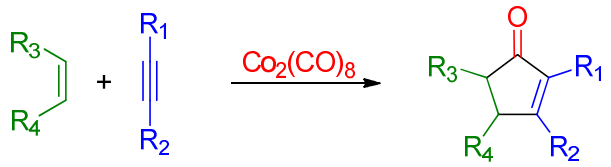
III EFJ performed the experimental work of reaction conditions study, and the experimental work with varying alkynes was done equally by EFJ and HK. All calculations were detailed and performed by MM. EFJ, MM, AR and JH drafted and edited the manuscript together.

List of abbreviations

Bn	Benzyl
Bu	Butyl
Cp	Cyclopentadiene
DCE	1,2-dichloroethane
DCM	Dichloromethane
DFT	Density functional theory
DMS	Dimethyl sulphide
DMSO	Dimethyl sulphoxide
dr	diastereomeric ratio
EDG	Electron donating group
ee	enantiomeric excess
Et	Ethyl
EWG	Electron withdrawing group
HPLC	High-performance liquid chromatography
IR	Infrared
Me	Methyl
MeCN	Acetonitrile
MW	Microwave
NBD	Norbornadiene (Bicyclo[2.2.1]hepta-2,5-diene)
NBN	Norbornene (Bicyclo[2.2.1]hept-2-ene)
NBO	Natural bond orbital
NMO	*N*-methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
PK	Pauson-Khand
PKR	Pauson-Khand reaction
TEA	Triethylamine
THF	Tetrahydrofurane (Oxolane)
TMANO	Trimethylamine *N*-oxide
TMEDA	N^1,N^1,N^2,N^2-tetramethylethane-1,2-diamine
TS	Transition state
WAXS	Wide-angle X-ray scattering

1. Introduction to Pauson-Khand reaction

The Pauson-Khand reaction (PKR) is, formally, a [2+2+1] cycloaddition first reported in the early 1970s by Pauson and Khand.[1-3] In this one-pot reaction, shown in Scheme 1, an alkene, an alkyne and carbon monoxide form a five-membered ring mediated or catalysed by a transition metal, typically and originally Co(0), complex.

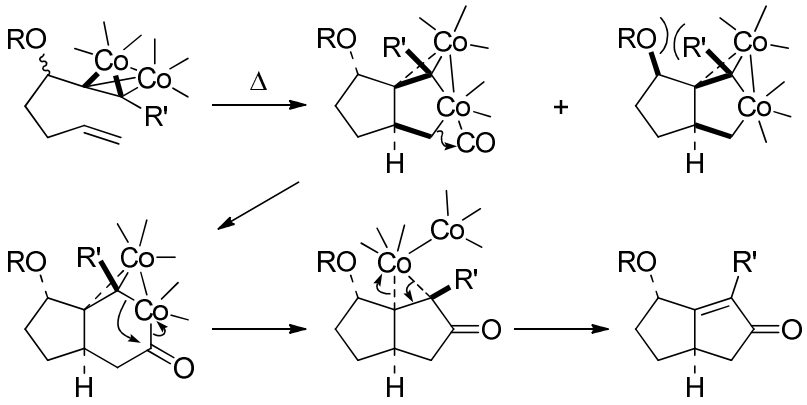


Scheme 1. Cobalt-mediated, intermolecular Pauson-Khand reaction.

The PKR has been considered as one of the most powerful tools in the synthesis of cyclopentenones and has been widely used in the synthesis of several natural products[4-12] and their building blocks[13,14]. In addition to the stoichiometric reaction, a catalytic version or PKR has also been applied.[15-17] Although the reaction was first promoted by cobalt and this is still the most common transition metal used, PKR can also be performed with rhodium[18], iridium[19], iron[20,21], ruthenium[22,23], chromium[24], molybdenum[25,26] and tungsten[27,28]. In this thesis, only intermolecular, cobalt(0)-mediated reactions are covered unless otherwise noted. Selected catalytic PKRs, as well as some intramolecular reactions, are also briefly described when significant to the topic.

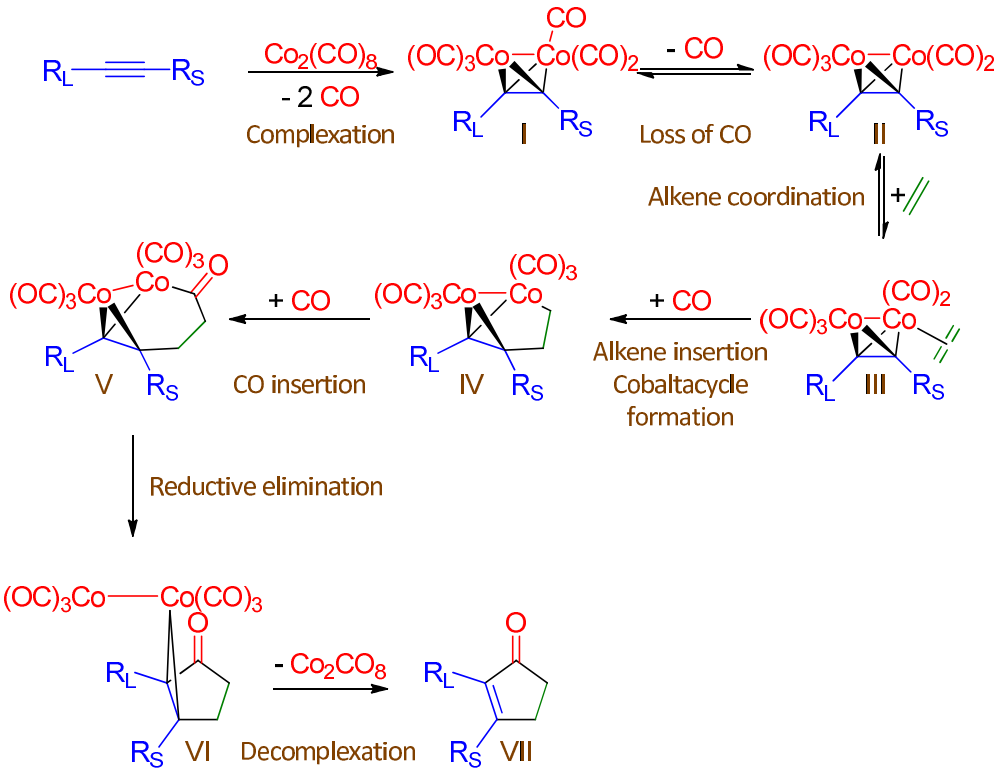
1.1 Mechanism

The PK reaction proceeds through several steps and transition states. A generally agreed-upon mechanism for the stoichiometric PKR, presented in Scheme 2, was originally proposed by Magnus[29,30] and, more recently, further confirmed with theoretical studies by Nakamura[31] and Pericàs[32]. Although the purpose of Magnus's hypothesis was to explain the observed stereoselectivity of certain intramolecular reactions and was based on general organometallic knowledge, it fits well into other experimental results and provides an explanation, together with other studies, of more recent problems as well.



Scheme 2. Magnus's mechanism for PKR.[29,30]

The mechanism is presented in a general form and with more details in Scheme 3. The reaction starts with the formation of alkyne-cobalt complex I, which are usually red and stable. The hexacarbonyl complex then loses one CO ligand in a reversible step, and pentacarbonyl complex II with a vacant coordination site is formed. The free site is reversibly occupied by coordination of an alkene (III). The next step in the mechanism, the cobaltacycle formation, is the most important since both regiochemistry and stereochemistry of the product are determined here. At this point, alkene insertion occurs between cobalt and the formerly alkyne carbon, forming five-member ring IV. After the alkene insertion, there is a carbonyl insertion to the bond between the former alkene and the cobalt (V), followed by reductive elimination, in which a bond is formed between the carbonyl carbon and the other end of the former alkyne so that five-member carbon cycle VI is closed. The final step is decomplexation of the weakly bonded cyclopentenone-cobalt complex, after which PKR is complete.



Scheme 3. General formulation of Magnus's PKR mechanism in detail.

The only isolated and fully characterised intermediate of the reaction is the alkyne-cobalt complex I. Examples of complexes like II have been detected by IR[33,34] and even isolated[35,36], but the isolated complexes had the unusual feature of a sulphur atom in the alkyne moiety coordinating to the cobalt and, thus, stabilising the complex. Also, a complex like IV has been detected by EI-MS.[37] A couple of complexes like III have also been isolated and characterised,[38-40] but none of these isolated type-III complexes was capable of continuing the PK reaction towards cyclopentenones.

The lack of experimental details regarding the mechanism and intermediates of PKR can be explained with reaction energies. Nakamura *et al.*[31] reported the first DFT calculations of the PKR mechanism in 2001. A schematic model of energies during PKR, based on their studies, is presented in Figure 1. Acetylene-cobalt complex formation, and release of two gaseous CO molecules, is an endothermic reaction with an activation energy of approximately 10 kcal/mol. The next step, removal of one CO ligand and formation of pentacarbonyl complex II with a vacant coordination site, is the reaction-rate determining step with an activation energy of 26 kcal/mol, and the following coordination of alkene produces intermediate III, which is only 12 kcal/mol lower in energy. The next transition state, the formation of four member ring leading to

cobaltacycle, is the highest-energy point of the mechanism with an activation energy of 15 kcal/mol. After alkene insertion, the reaction energies go rapidly downhill until, finally, cyclopentenone is formed.

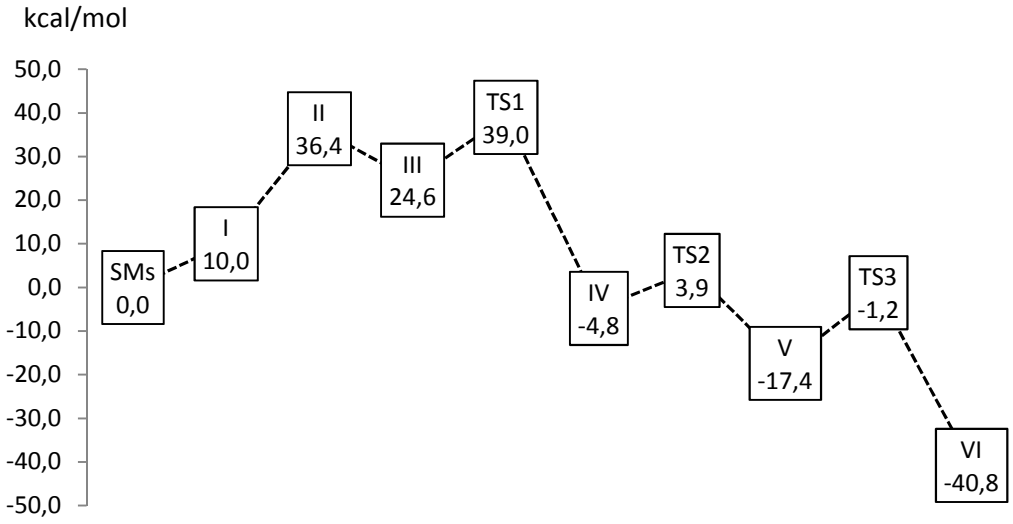


Figure 1. Energies of PKR by Nakamura.[31] These values were calculated for acetylene as an alkyne and ethene as an alkene with DFT methods. Exact values depend on methods and calculation levels chosen and vary between substrates, but general trends remain. Roman numbers identifying intermediates are presented in Scheme 3.

2. Selectivity in the Pauson-Khand reaction

In intermolecular Pauson-Khand reactions, an alkene, an alkyne and a carbon monoxide, mediated or catalysed by a transition metal complex, form three new carbon-carbon bonds and, depending on the alkene, two new stereocentres in a very controlled way, as presented in Figure 2.

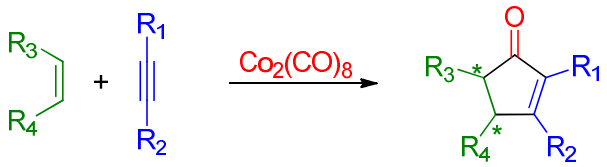


Figure 2. Pauson-Khand reaction.

In theory, there can be eight different isomeric products formed in the reaction: two are related to alkyne regioselectivity (R_1 and R_2 in Figure 2) and two to alkene regioselectivity (R_3 and R_4 in Figure 2); additionally, all four regioisomers have two enantiomers (two stereocentres in Figure 2). The number of possible stereoisomers is limited to two because of the reaction mechanism; the alkene stereochemistry is intact. In *cis*-alkene the groups in stereocentres R_3 and R_4 are always on the same side of the ring. Usually some of the possible isomeric products are ruled out by choosing symmetric starting materials, and this results in fewer theoretical products. However, selectivity often is a problem for the synthetic usability of PKR and a great deal of effort has gone into estimating and controlling the selectivity.

This chapter will focus on PKR selectivity. Section 2.1 will examine the regioselectivity originating from the alkyne, and section 2.2 will treat the alkene. Then, in section 2.3, aspects of PKR stereoselectivity will be discussed.

2.1 Regioselectivity regarding the alkyne

In intermolecular PK reactions the alkene always has two different alkyne carbons to bond with (from III to IV in Scheme 3), and therefore, there is a possibility of forming two different regioisomeric products. The only exception to this rule is if the alkyne is symmetric in relation to the triple bond. In such cases, only one product is formed because the two regioisomeric products are identical. According to Magnus's mechanism, the carbon that bonds with alkene carbon ends up in the resulting

cyclopentenone's β-position, the regiochemistry being determined in the first carbon-carbon bond formation.

There are two different primary factors affecting the regiochemistry determination: the steric and the electronic. Usually large groups prefer the α-position in the resulting cyclopentenone, leaving small groups in the β-position. Similarly, electron-donating groups tend to favour the α-position, and electron-withdrawing groups favour the β-position. These trends are shown in Figure 3.

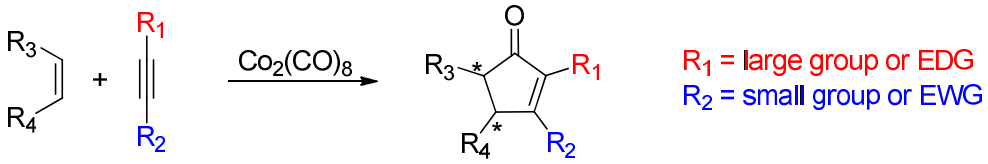


Figure 3. Alkyne-related regiochemistry in PKR.

With terminal alkynes, the regioselectivity of PKR is complete and the terminal carbon always ends up in the β-position, the substituent being situated in the α-position (Figure 4). This selectivity is due to the larger steric hindrance of any substituent compared with hydrogen. Theoretical calculations performed with propyne reveal that formation of an α-isomer is also electronically favourable.[41]

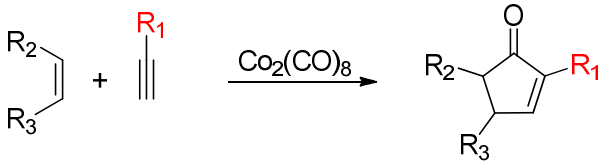


Figure 4. PKR of terminal alkynes.

With internal alkynes, the regiochemical selectivity is more complicated. In Magnus's reaction mechanism, the regiochemistry is determined in the step wherein the alkene is inserted into the Co-C bond. After coordination to the cobalt, the alkene has two possible Co-C bonds its insertion can occur between, and the one next to larger substituent is disfavoured due to steric hindrance (Figure 5).

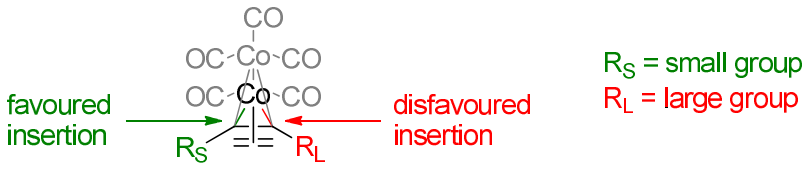


Figure 5. Regiochemistry determining step in the PKR mechanism. Alkene insertion is favoured next to the smaller alkyne substituent.

On the other hand, and in addition to steric factors, electronic differences between alkyne substituents also play a role in regiochemistry determination. The alkene forms bond with the end of the alkyne carrying more electron density.[42] The following sections will use case studies to examine the selection process in greater detail and see how steric and electronic factors outweigh each other. Examples of unexpected or borderline selectivity will be presented, and reasons for the observed results will be suggested.

2.1.1 Competition between steric and electronic factors

In the early reports of electron-deficient alkynes in PKR, reactions yielded PK cycloaddition products **1**-**5**, with EWGs in the β-position (Figure 6).[43,44] The unexpected regiochemistry, having the larger group in the β-position, was rationalised by alkyne polarisation.[43] It should be noted that each EWG in these PK products **1**-**5** is conjugated to the enone system, meaning that all alkynes were also conjugated.

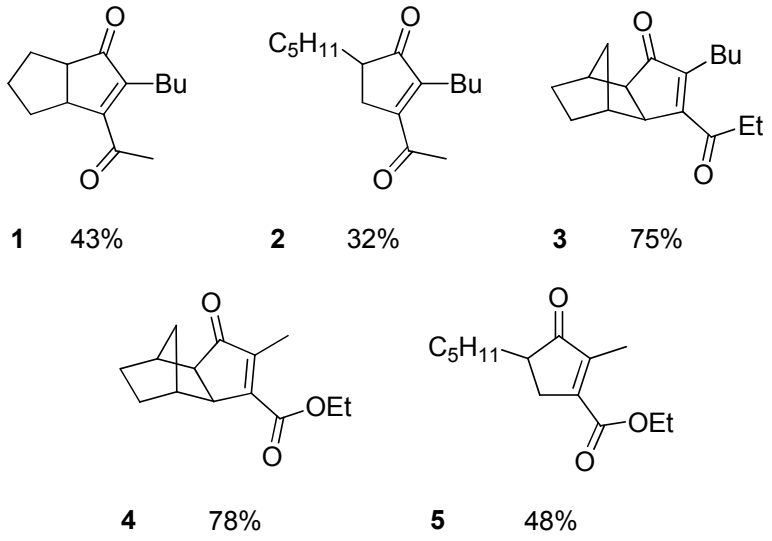


Figure 6. Products of PKRs with electron-deficient alkynes.[43,44]

In 1995, Krafft studied experimentally steric versus electronic effects in PKR with ethyl propiolate and ethyl butynoate[45], and later, Gimbert, Milet *et al*.[41,42] did theoretical calculations on the corresponding methyl ester compounds. By combining these results we have interesting example of two closely similar structures with opposite selectivity. When compared PKRs of **6** and **8** (Figure 7), it is obvious that regioselectivity is reversed between these two compounds. At the time, Krafft proposed that this is because steric interactions overrule in regiochemistry determination.[45] It is true with **6**, but it is worth noting that the triple bond in the alkyne of **6** is devoid of polarisation, and therefore

steric factors are the only determining factors present in the **6** system.[41] With **8**, in contrast, the triple bond is clearly polarised,[41] and it can be stated that, despite the size of the ester group, it is not large enough to overrule electronic polarisation of the alkyne C≡C bond, that determines the regiochemistry of the reaction.[41,42]

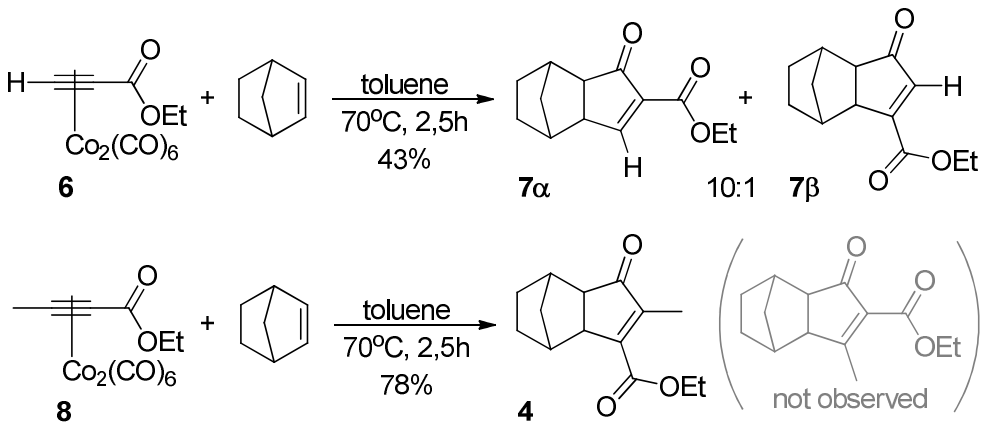


Figure 7. PKR of **6** and **8**.[45] The regiochemistry of **7** is reversed if the terminal alkyne is changed into a methylated one, as in **4**.

As in the case of **6**, steric effects overcome electronic effects with some propargylic acetals as well (Figure 8). In reaction of **9**, the reason for the observed selectivity is clear: both steric and electronic factors favour the acetyl group in the α-position as is typical for terminal alkynes. The electronic effect of the acetals in **11** and **13** is not as powerful as the effect of the conjugated ester in **8** (Figure 7), resulting in a weaker polarisation of the alkyne. Despite this, electronic reasons would support the acetyl ending up in the β-position in **12** and **14**, but if the other alkyl group is small, like the methyl in **11**, steric reasons become more important and electronics are dismissed. With the larger *n*-propyl group in **13**, the stereoisomers are almost in equilibrium. One explanation for the observed opposite selectivity between **8** and **11** and the weaker polarisation of the alkyne lies in the type of bonding; **8** is conjugated whilst **11** and **13** are not. However, internal propargylic silyl ethers have been reported to provide complete β-regioselectivity in PKR with ethane, despite the large size of the functionality.[46,47] These examples show how seemingly small issues have huge impact on the selectivity.

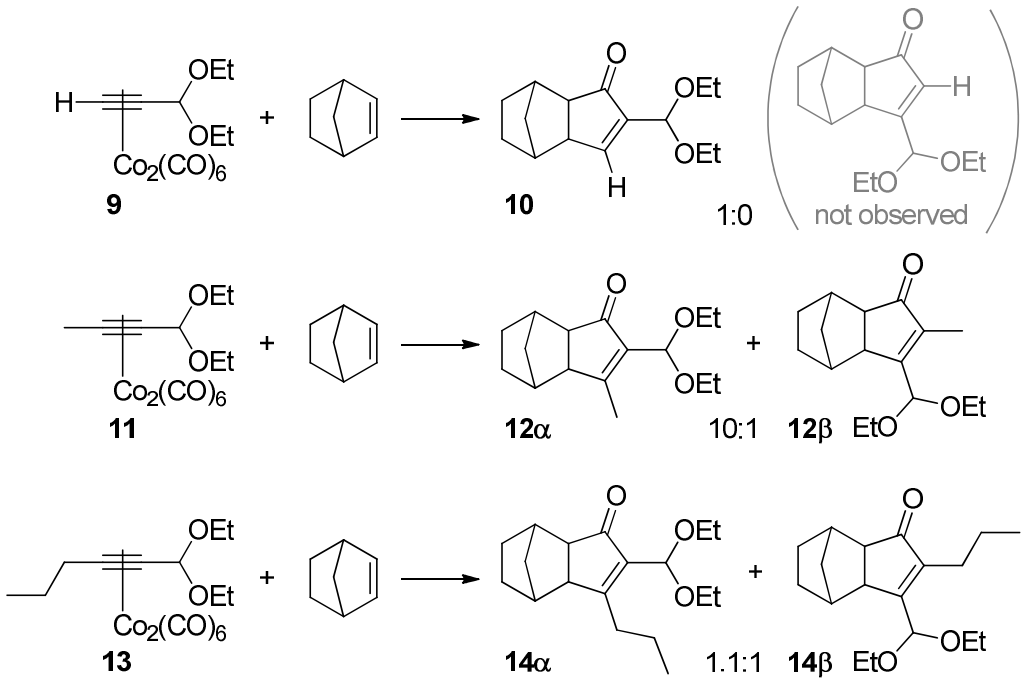


Figure 8. Steric effects overcoming electronic influence in the regioselectivity determination of some acetals.[45]

Regiochemistry determination is a complex issue and the dividing line between complete selectivity and unselective reaction can be narrow. The previously mentioned PKR of **8** has been repeated several times using both norbornene (NBN) and norbornadiene (NBD) as an alkene, and in each case, the outcome is similar: the electron-withdrawing ester group prefers the β-position.[48,49] However, if the methyl group at the end of a triple bond is changed into a strongly electron-withdrawing and sterically demanding trifluoromethyl group, as in complex **15**, the reaction outcome still remains the same (Figure 9).[49] For electronic reasons the trifluoromethyl in **15** would prefer the β-position, but in this case, steric factors, resulting from the electronic repulsion of fluorine atoms, overrule electronics in the regioselectivity process.

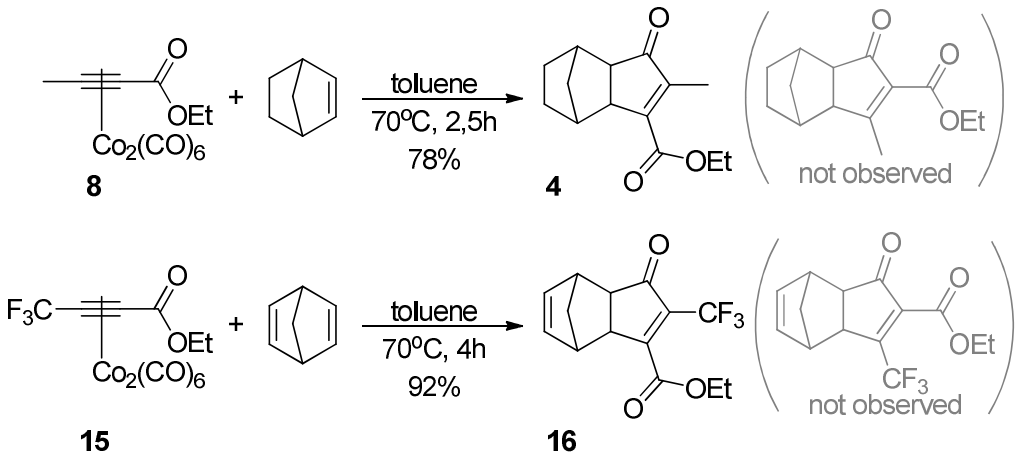


Figure 9. In PKR of **8**[45] and **15**[49] the regioselectivity stays intact despite the replacement of the methyl group with electronically different trifluoromethyl.

On one hand, reactions with trifluoromethyl-substituted alkynes seem straightforward, as sterically demanding CF_3 is occupying the α-position regardless of electronic effects. Riera *et al*.[50] have run a series of experiments with **17**, varying the other end of the alkyne (Figure 10). In reactions with NBD, they exclusively received **18** with a trifluoromethyl group in the α-position. On the other hand, Konno *et al*.[51] ran another set of experiments with **17**, presented in Figure 11, with regioisomeric mixtures of cyclopentenones **19α** and **19β** as products. The reaction conditions for both experiments were very close to each other, the main differences being the alkenes and solvents used (NBD vs. NBN and toluene vs. DCE, respectively) and the temperature (70°C vs. 84°C). The reason for this unexpected difference in results is not apparent, then, but it might indicate that the more reactive NBD is, for some reason, more regioselective compared with the slightly less-reactive NBN.

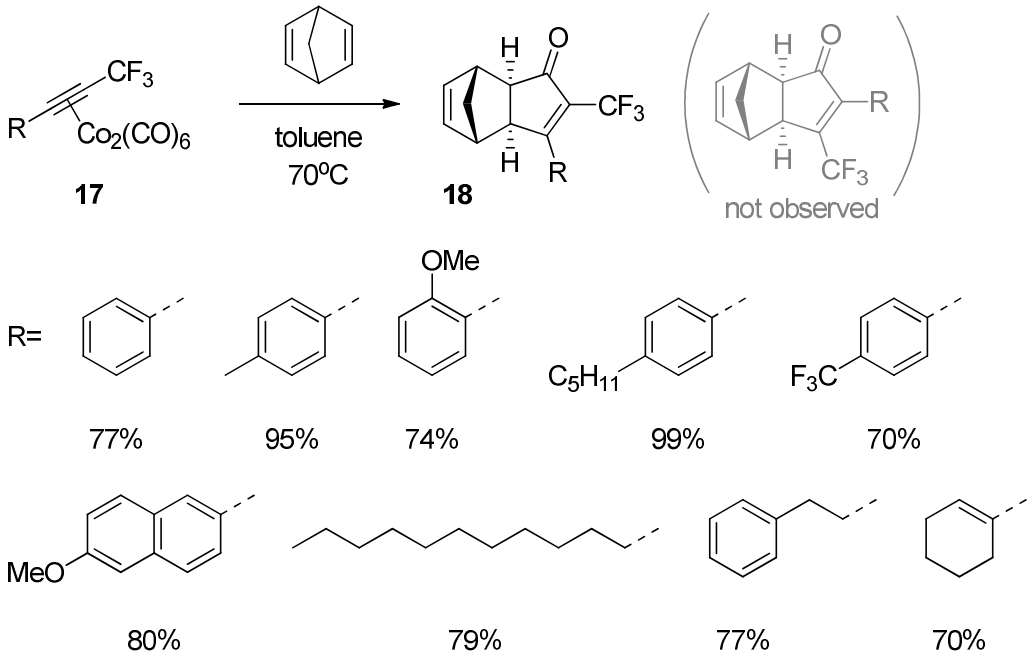


Figure 10. Reactions of trifluoromethyl-substituted internal alkynes with NBD by Riera *et al.*[50] In this study regioselectivity was total.

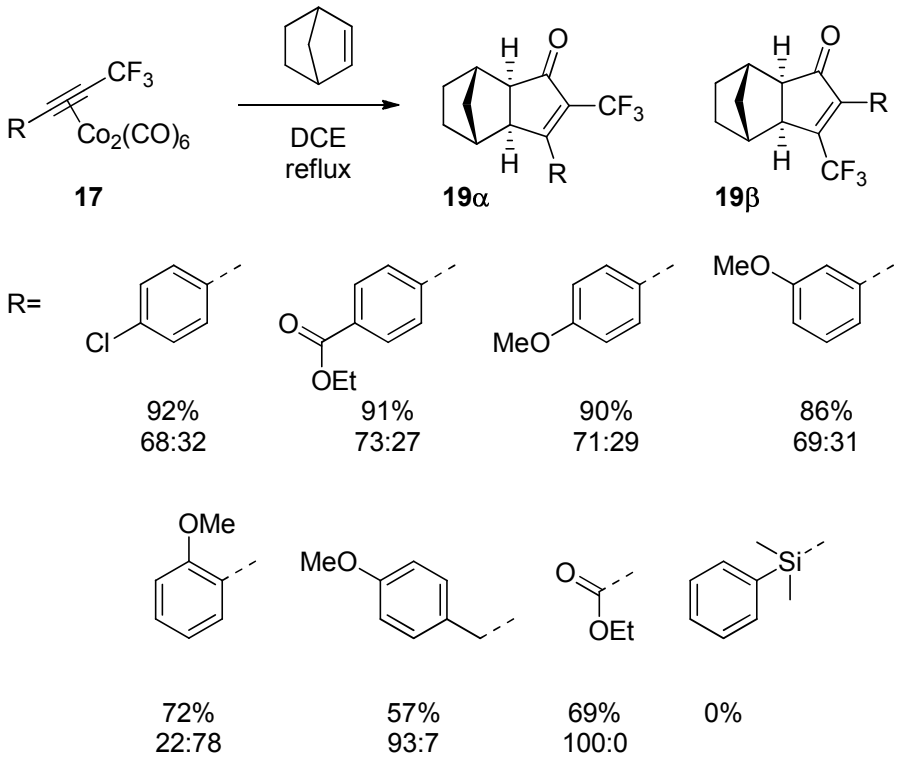


Figure 11. Reactions of trifluoromethyl-substituted internal alkynes with NBN by Konno *et al.*[51] Both regioisomers **19α** and **19β** were formed with varying ratios and the α:β ratios are presented below yields.

2.1.2 Regiochemistry determination with sterically near-equivalent alkynes

The examples above show how the result of the competition between steric and electronic factors is difficult to predict. In order to get more information on purely electronic guidance, the steric effect has been minimised. A few studies with sterically equivalent or near-equivalent diarylalkynes have been reported. Fairlamb *et al*.[52-54] have reported PKRs of heteroaromatic diarylalkynes with interesting results. In general, these results could not be fully explained by the electronic properties of the alkynes. The alkynes were classified as π-deficient (**20d**-**i**, red in Figure 12) and π-excessive (**20a**-**c** and **20j**-**l**, blue in Figure 12) heteroaromatics. All π-deficient heteroaromatics preferred the β-position, but results varied with alkynes having π-excessive substituents. They suggest that, aside from steric and electronic effects, dynamic ligand effects and stabilisation provided by the aromatic or heteroaromatic group might also influence the regiochemical outcome of intermolecular PKRs.[55]

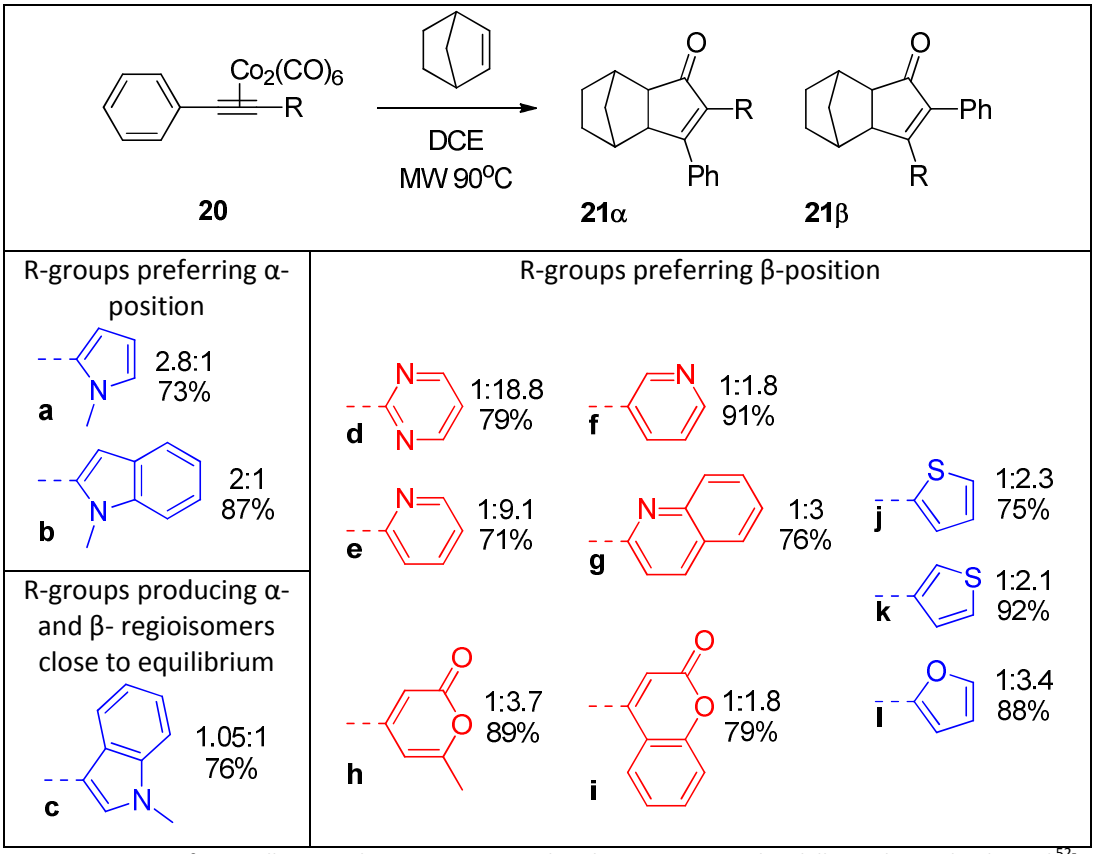


Figure 12. PKRs of sterically equivalent or near-equivalent heteroaromatic diarylalkynes by Fairlamb *et al.*[52-54] π-deficient substituents are marked with red and π-excessive substituents with blue.

One of the most cited PKRs of diaromatic alkynes is the reaction reported by Gimbert, Greene and co-workers, of **22** with NBN (Figure 13), in which the ethyl benzoate in **23** was found exclusively in the β-position.[41] Similar experiments were performed by Riera

et al.[56] with **24** and NBD. In this reaction, the product obtained was a 1:2.5 mixture of regioisomers **25α** and **25β** with benzoate correspondingly in their α- or β-positions (Figure 13). The previous, completely selective reaction has often been cited as an example of electronically determined regioselectivity[54,57,58], it will be discussed again in section 5.2.

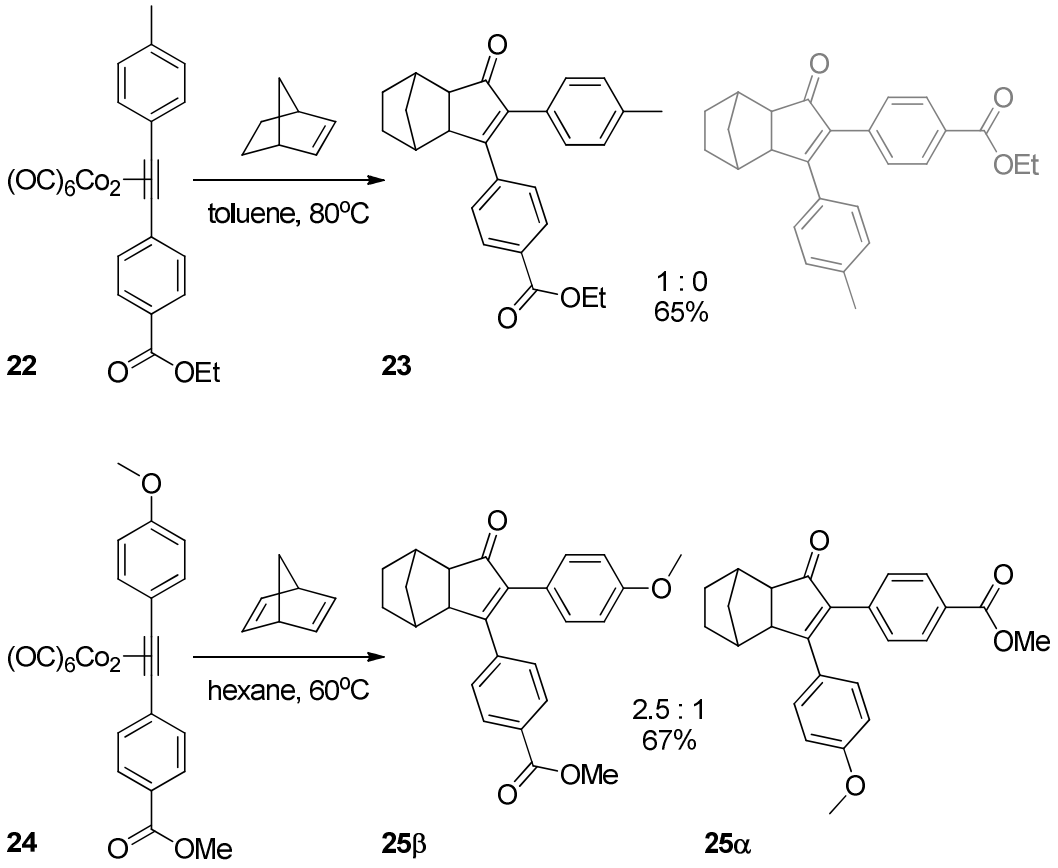


Figure 13. PKRs of **22**[41] and **24**[56]. The former reaction yields only one regioisomeric product whereas a 2.5:1 regioisomeric mixture is isolated from the latter reaction.

2.1.3 Theoretical approaches to alkyne regioselectivity

Computational studies related to the regiochemistry of PKR are rare, and this is partially due to the lack of experimental evidence related to the reaction mechanism making computational studies much more demanding. In 2001, Gimbert, Greene *et al*. reported a DFT study with alkyne-dicobalt hexacarbonyl complexes, claiming the *trans* effect to be heavily affecting the olefin initial coordination position and, consequently, the insertion, resulting in regioselective PKRs governed entirely by electronic differences in alkynes.[41] They present a theory that acetylenic carbons have electronic differences as a

result of the differing electronic natures of the substituents connected to the triple bond. These electronic differences have actually been observed by ^{13}C-NMR.[59-61] Due to electronic differences, the CO ligands are also dissimilar. The pseudo-equatorial CO ligand positioned *trans* to the acetylenic carbon, with more electron density, is reported to be the most stable, leaving the cis positioned CO relatively labile. This labile CO is claimed to be replaced by olefin, followed by an insertion to the same position, resulting in certain regioselectivity in the cyclopentenone. The weakness of this theory is that the coordinated alkene is free to rotate and relocate between pseudo-equatorial and pseudo-axial positions.[59,62-64] In addition to the insignificance of the initial coordination position, even the configuration of the stablest alkene-cobalt complex is not relevant, as the regiochemistry is determined in the insertion step, which is controlled by kinetics.

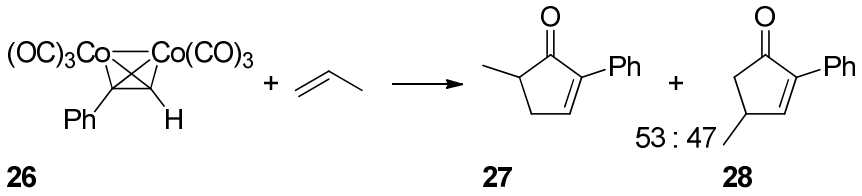
Gleiter *et al.*[65] have also tried to predict the regiochemical outcome of PKR. They compared experimental product ratios of S-alkyl substituted alkynes' PKRs with theoretical results derived from both X-ray data and charge distribution calculations performed at the DFT level. They relied on two different theories regarding the coordination and insertion, but neither measured bond length nor polarisation of the former triple bond correlated satisfactorily with the experimental results. Based on these studies Gleiter *et al.* conclude that the regioselectivity of PKR cannot be theoretically predicted based on the ground state of the alkyne dicobalthexacarbonyl complexes.

Milet, Gimbert and co-workers[64] have studied the transition states of PKR between ethylene and propyne, leading to different isomers. They found out that, unexpectedly, the TS with the lowest activation energy is derived from a complex having an alkene in a pseudo-axial position, which is higher in energy than the pseudo-equatorial positions. However, Milet, Gimbert and co-workers suggest that the stability of transition states is related to polarisation of the alkyne. Following studies with the same approach also explained the observed selectivity of methyl propiolate and methyl butynoate[42], already discussed in section 2.1.1.

In summary, it has been theoretically shown that alkyne polarisation can be, in some cases, used as a rationalisation of observed PKR regioselectivity. However, several other factors should be taken into account, steric issues being the most important ones.

2.2. Regioselectivity regarding the alkene

Regioselectivity for an alkene is even more complicated than it is for an alkyne. The selection occurs in the same reaction step as with an alkyne: during the insertion of the alkene to the alkyne dicobaltpentacarbonyl complex. In general, as the alkene double bond has two carbons, it has two regioisomeric ways to insert. For example, the PKR of a terminal, aliphatic alkene and a phenyl acetylene results in two regioisomers without selectivity, as presented in Scheme 4.[31,66]



Scheme 4. Regioselectivity of propene in PKR with phenyl acetylene.[31]

However, lack of regioselectivity regarding alkenes is not preventing the use of PKR as much as alkyne selectivity, as terminal aliphatic alkenes are not only poor in selectivity but, furthermore, usually provide low yields. The alkene regioselectivity is mostly dependent, then, on steric factors, and it is dramatically improved if a non-terminal alkyne is used in the reaction (Figure 14). And yet, whenever selectivity is improved, yield is negatively affected.[67]

The dependence of alkene selectivity and terminal alkynes is due to steric interactions and can easily be seen when looking at the mechanism.[29,30,66,67] The related parts of the mechanism are presented in Figure 15. If the alkyne is terminal the H at the end of the alkyne is too small to create steric crowding, and this results in a lack of regioselectivity for the product. Internal alkynes constrain the freedom of the alkene's alkyl tail to orientate in space, evoking selectivity to the alkene insertion.

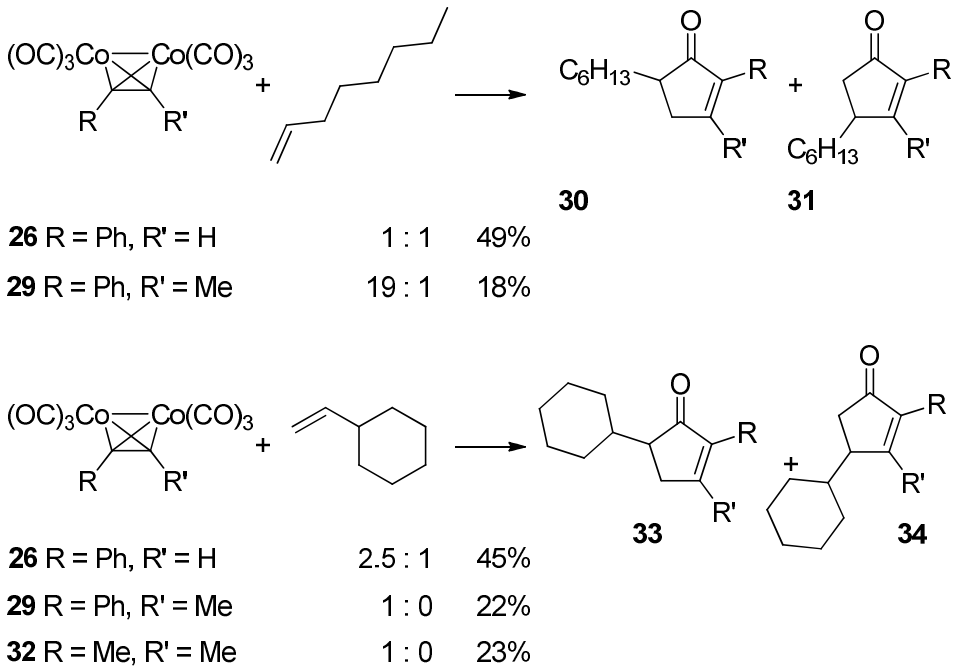


Figure 14. Difference in alkene regioselectivity between PKRs of terminal and internal alkynes.[66]

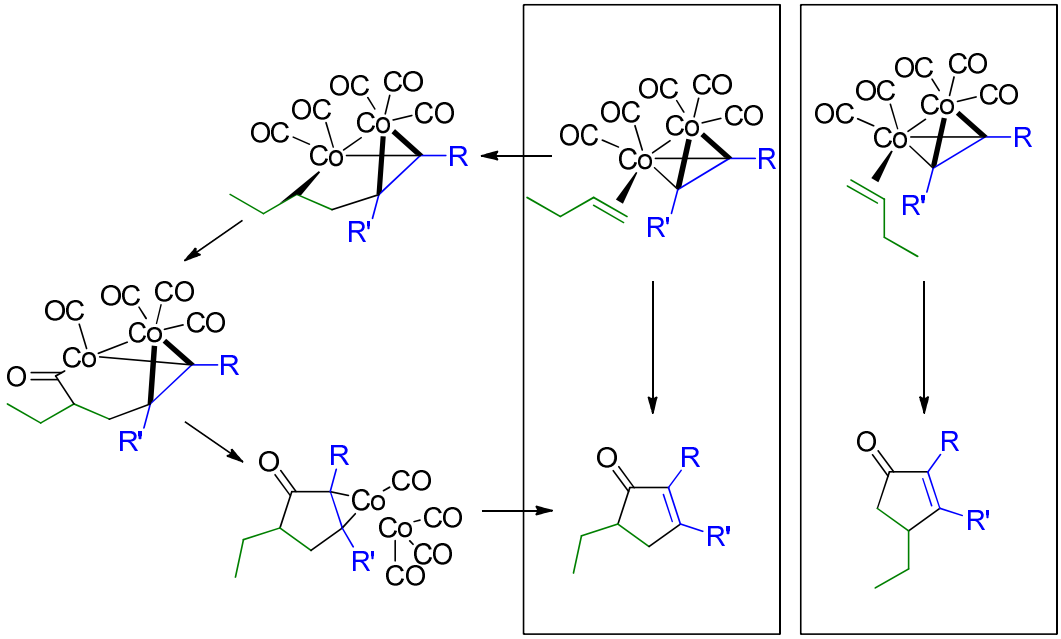


Figure 15. Steric reasoning for the observed alkene regioselectivity. With terminal alkynes (R'=H) steric interactions do not interfere with alkene insertion and both regioisomers are almost equally favoured. In PKR with internal alkynes, R'≠H, and steric hindrance limits the formation of a 4-substituted isomer.[67]

Selectivity can also be introduced by ligand coordination. If suitable coordinating groups are present in the alkene these groups can replace CO ligands and orientate the alkene for insertion. This idea was first noted in 1988 by Krafft[66] who presented a series of amines and sulphides with high degrees of regioselectivity. Selected examples are presented in Figure 16.

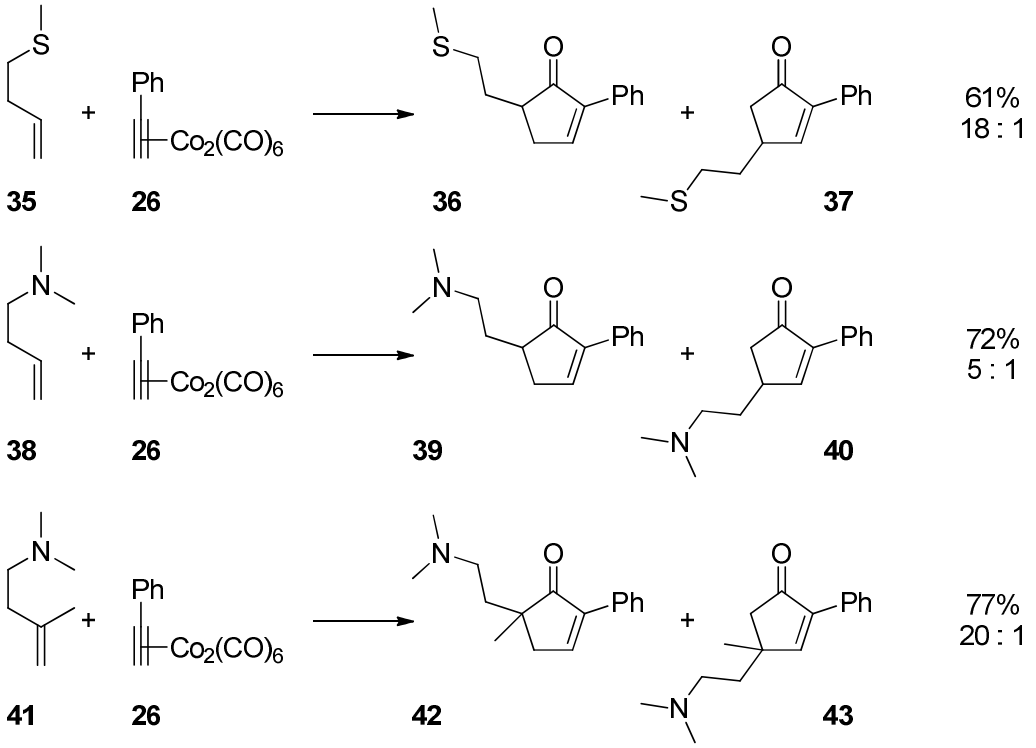
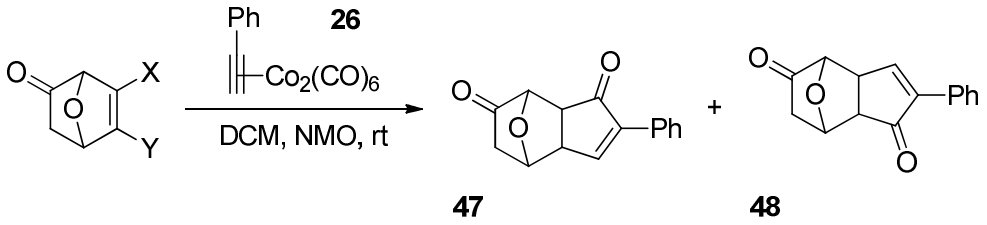


Figure 16. Regioguidance by remote heteroatoms.[66]

Even though the regioselectivity of alkenes is usually thought to be purely determined by steric factors, electronic variations in the alkene double bond can also be used in regioguidance. Reactions of 2-substituted 7-oxanorbornenes[68], 7-azanorbornenes[69] and norbornenes[70,71] showed clear evidence of regioselectivity related to functional groups in the alkene. The regioselectivity was increased with more electron withdrawing substituents, and theoretical calculations showed a connection between the experimentally observed regioselectivities and a polarisation of double bond carbons, induced by the inductive effect of the substituent in the 2-position.[71]

Moreover, bromine attached to the double bond can be used to choose between regioisomers. In alkenes **45** and **46** (Figure 17) the olefin carbon in which the bromine is situated prefers to bond to cobalt instead of carbon in the alkene insertion step, resulting in its position next to a carbonyl in the forming cyclopentenones **47** and **48**.

Without a halogen atom (**44**), both cyclopentenones **47** and **48** are formed almost equally. The bromine is spontaneously dehalogenated in the reaction.[68]



44 X,Y = H	60 : 40	80%
45 X = Br, Y = H	100 : 0	75%
46 X = H, Y = Br	20 : 80	70%

Figure 17. Effect on the regioselectivity of PKR when bromine is attached to the double bond.[68]

In addition to differences in alkenes and alkynes, reaction conditions have also been shown to affect the regioisomeric ratios of PKRs. Allylphosphonates have been used in regioselective PKRs, but their selectivity is highly dependent on reaction conditions. In reactions between **26** and **49** (Figure 18) both regioisomers **50** and **51** were formed. The ratio of **50** to **51** varied between 4:1 and 11:1, and the selectivity depended on both the solvent and the activation mechanism. Interestingly, the reaction did not proceed at all if performed without a promoter or if promoted with amine.[72]

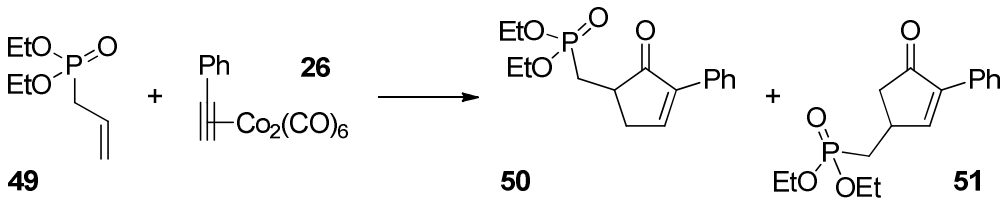


Figure 18. PKR of **26** and diethylallylphosphonate **49**.

Dependence of alkene regioselectivity on reaction conditions has also been observed with other alkenes.[73,74] The selectivity in a PKR between **53** and **52** (Figure 19) could be controlled by adjusting temperature. In DCE, the ratio could be turned from 90:10 to 48:52 of the regioisomers **54** and **55** shown in Figure 19, correspondingly, by raising the temperature from -20 °C to 40 °C. In toluene the same ratio could be turned from 95:5 to 23:77 and further to 12:88 by raising the temperature from -25 °C to 20 °C and, further, to 120 °C correspondingly. These reactions were promoted with *N*-methylmorpholine *N*-oxide (NMO), but this did not seem to affect the regioisomeric ratio when compared with reactions performed without additives at the same temperatures; however, yields were dramatically affected.[73] Additionally, in PK reactions

between **26** and allyl alcohol, changes in solvent and reaction temperature had a major impact on regioisomeric ratio. The product ratio varied from 2:1 to 1:2.6 (2,5-substituted versus 2,4-substituted correspondingly), depending on reaction conditions.[74]

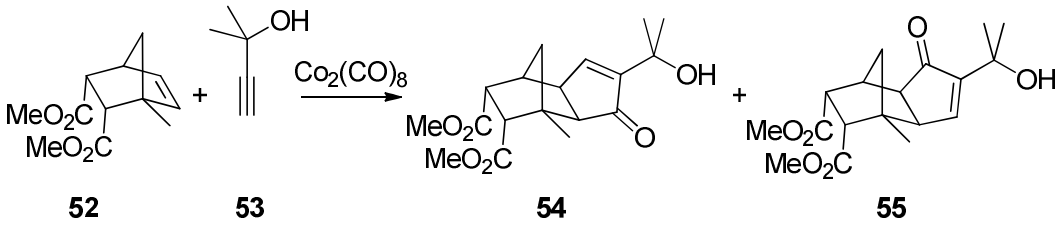


Figure 19. Regioselective PKR of a norbornene ester **52** and 2,2-dimethylpropargylalcohol **53**. The selectivity could be tuned by altering reaction conditions.

To conclude, the studies demonstrate that alkene-related regioselectivity is at least as complex as that of alkynes. It is even less-studied and less-controllable but often symmetric alkenes are used to prevent this problem.

2.3. Stereoselectivity

Insertion of the alkene into the cobalt-alkyne complex is a key step in PKR. It not only determines the regioselectivity of both the alkene and alkyne, but the stereochemistry of the product is also decided in that step. In PKR, two new stereocentres are formed (Figure 20). Once insertion of the alkene has occurred and the cobaltacycle has formed, both regio- and stereoselectivities are final.

In general, PKR is stereospecific with regards to the alkene. In the reaction product, *cis*-alkene substituents are situated on the same side of the formed cyclopentenone ring and *trans*-alkene substituents stand on the opposite sides, relative to each other.

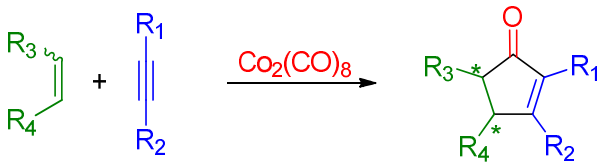


Figure 20. In PKR, two new stereocentres (marked with asterisks) are formed.

There are a two of different aspects related to stereochemistry in intermolecular PKR: diastereoselectivity and enantioselectivity. A commonly encountered special case of

diastereoselectivity in PKR is *exo* and *endo* selectivity, due to widely used and reactive bridged bicycles. This chapter will begin by treating this; then, it will examine the various methods for introducing other forms of diastereoselectivity and enantioselectivity into PKR.

2.3.1 *Exo* and *endo* selectivity

Bicyclic bridged alkenes, like NBN and NBD, are commonly used in PKR because of their high reactivities. Because of their bridged structures, they have two different faces to react from, and in PKR they produce both *exo* and *endo* fused polycycles. In the process, two additional stereocentres are formed as a result of desymmetrisation of the alkene (Figure 21). The selectivity is mostly determined by steric hindrance, but electronic factors might also influence the process, as will be seen a below.

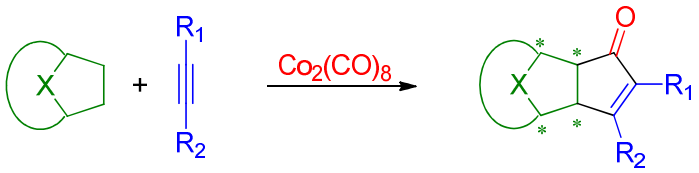


Figure 21. Four new stereocentres are formed in a single reaction; two are generated as a consequence of desymmetrisation of the alkene.

Endo and *exo* selectivity of NBN are presented in Figure 22. For steric reasons, the less hindered face of the alkene is preferred resulting in the formation of an *exo* adduct, and often the minor *endo* isomer cannot be observed.

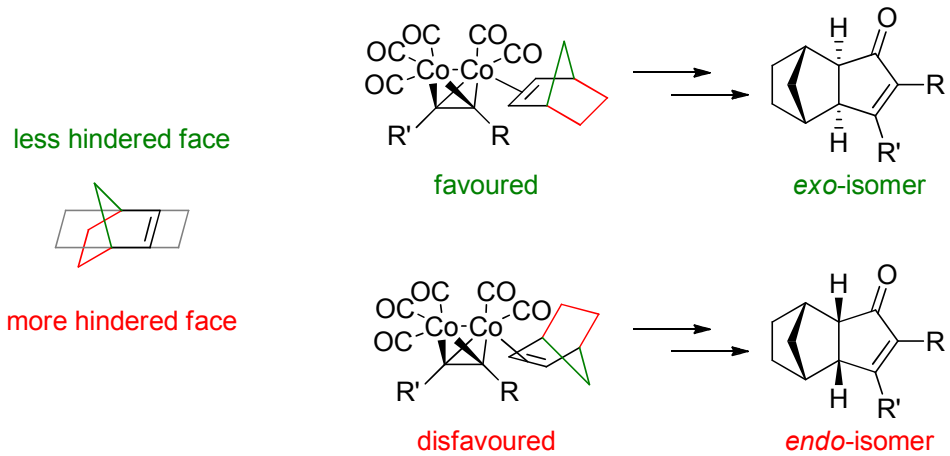


Figure 22. Steric reasoning for *exo* and *endo* selectivity of norbornene.

Despite the *exo* selectivity usually observed, a couple of interesting examples of *endo* isomer formation exist, providing valuable information about selectivity mechanisms.

For example, PKR between acetylene and NBD has been reported to produce significant amounts of *endo* product, in addition to the major *exo* product.[2,75,76] Interestingly, trimethylsilylacetylene also yielded some *endo* products in microwave- and NMO-promoted reactions.[76] Jeong, Chung and co-workers[77] reported TMANO-promoted PKRs of NBD and phenyl acetylene, propargyl alcohol and 4-pentyn-1-ol yielding a mixture of diastereoisomers with *exo*:*endo* ratios of 83:17, 80:20 and 88:12, respectively. All these examples are reactions of commonly used alkenes and alkynes yielding unexpected amounts of *endo* products in addition to the major *exo* products.

Still, there are also *endo* selective PKRs reported. In PKRs of NBD and certain chiral ynamides, the *endo* cycloadducts were synthesised as either the major or sole isomers, as shown in Figure 23.[78] The unusual selectivity of **56** was reasoned with steric issues[78], as no *endo* products have been observed with terminal ynamides or ynamines[78-81]. Moreover, the selectivity was not even close to complete if the phenyl in **56** was replaced by *n*-hexyl or *n*-butyl.[78] In addition to steric factors, the possibility of double bond coordination to both Co metals in the case of NBD was also suggested.[78]

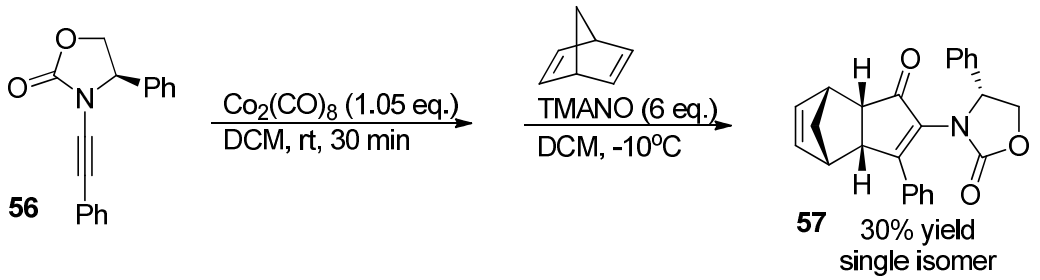
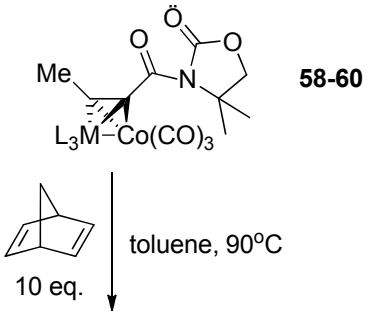
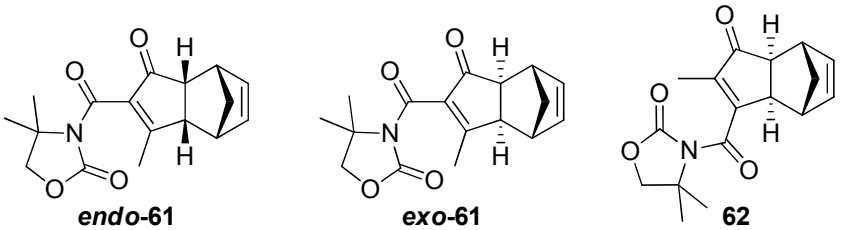


Figure 23. PKR of a chiral ynamine and norbornadiene resulting in the *endo* isomer as only product with 30% yield.[78]

Endo selectivity has also been observed in heterobimetallic PKRs, in which one of the cobalts in the alkyne hexacarbonyl complex is replaced with molybdenum or tungsten and one carbonyl with cyclopentadiene (Cp). While the reactions of some *N*-(2-alkynoyl)oxazolidinonen and sultams as heterobimetallic complexes, like **58** and **59** in Figure 24, yielded the *endo* adduct **61** as the major or only isomers, the corresponding dicobalt complex, **60**, yielded only *exo* cycloadducts ***exo* 61** and **62**.[82,83] This selectivity is explained as resulting from steric issues as the Cp coordinated to the W or Mo creates more hindrance, and coordination in the *endo* face alleviates these steric repulsions (Figure 25).





	ML_3	*endo*-61	*exo*-61	62
58	$Mo(CO)_2Cp$	80%	7%	10%
59	$W(CO)_2Cp$	65%	8%	7%
60	$Co(CO)_3$	0%	43%	56%

Figure 24. PKR of norbornadiene with a heterobimetallic or dicobalt complex of *N*-(butynoyl)-4,4-dimethyl-1,3-oxazolidin-2-one. Reversed selectivity is observed with heterobimetallic complexes **58** and **59**.[82,83]

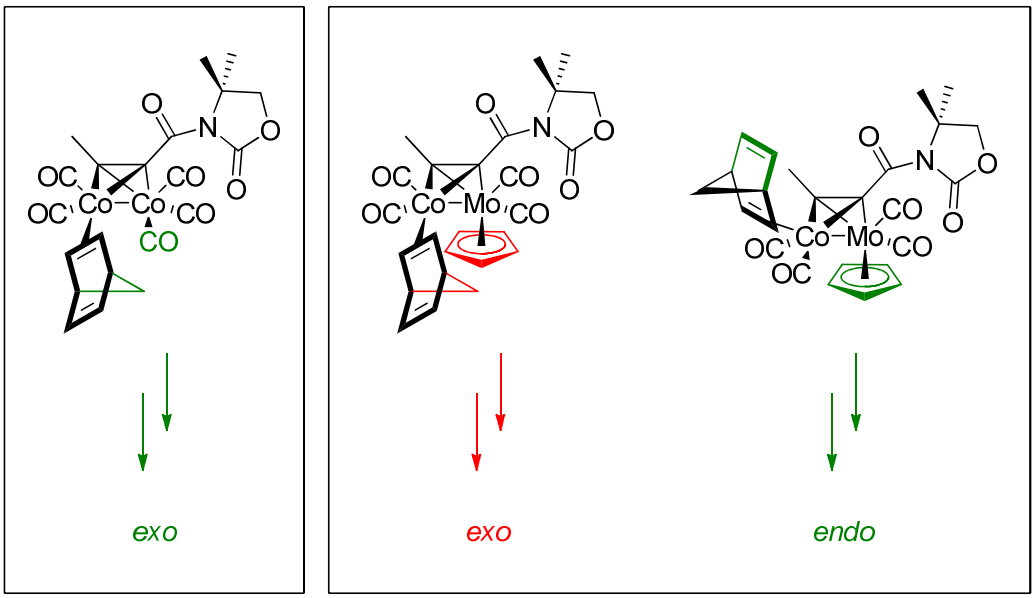


Figure 25. Steric reasoning for the observed *endo* selectivity within heterobimetallic complexes. On the left, there is a traditional dicobalt complex resulting in *exo* selectivity, as seen in Figure 22. On the right, the similar coordination to the heterobimetallic cobalt-molybdenium complex resulting that an *exo* isomer is disfavoured due to steric repulsion between the norbornadiene methylene bridge and Cp. This repulsion can be avoided with *endo* coordination.[82]

The two examples above are of electron deficient alkynes but were explained as resulting from steric issues. Riera, Verdaguer and co-workers studied whether electronic factors also play a role in *endo*/*exo* stereoselectivity by synthesising a series of sulphur- and amido-substituted alkynes with increasing electron deficiency. In reaction with NBD, relatively high yields of *endo* adducts were achieved using electron-deficient, terminal alkynes, with an *exo*:*endo* ratio of up to 74:26 and the *exo* being the main isomer. The relation between electron deficiency and the relative amount of *endo* isomer was not linear, though the least electron-deficient alkynes provided only *exo* isomers. Also NBN did not yield any *endo* isomer. They suggest that electronic differences do indeed play a role in selectivity and are responsible of the observed, uncommon *endo* isomer formation.[84] And yet, no following results or studies providing deeper insight have been reported so far.

2.3.2 Other diastereoselectivity and enantioselectivity

In theory, NBD and an alkyne dicobalt complex have four possible ways for complex formation, depending on the face of the olefin and its orientation. Two of these complexes lead to the formation of *endo* isomers—which the present study has already covered above—and the other two lead to *exo* products. Pathways leading from these two complexes to each enantiomer are presented in Figure 26.

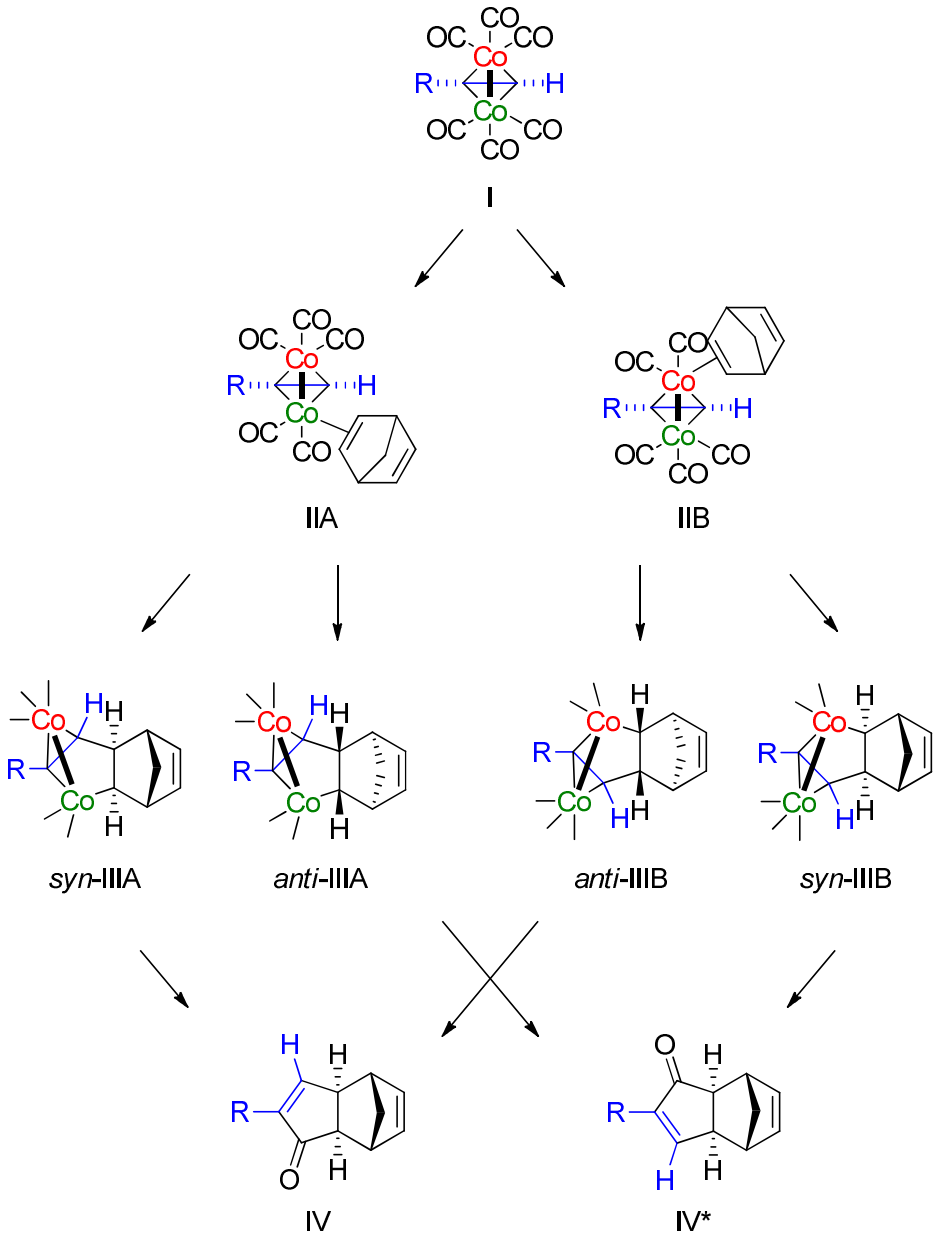


Figure 26. A schematic picture of the mechanistic pathways leading to each *exo* enantiomer. CO ligands of complexes III have been omitted to simplify the picture.

In general, there are several ways to control the stereoselectivity of PKR: chiral precursors, chiral auxiliaries, chiral ligands and chiral additives. This section will begin its explanation of each by discussing chiral precursors; then, it will treat the various auxiliaries, followed by chiral ligands. In the last subsection it will examine the various chiral PK additives. A more general view on additives will be presented in chapter 3.

2.3.2.1 Chiral substrates

Examples of intermolecular PKRs with chiral substrates are rare. In addition to the *exo endo* selective examples above, which in some cases yield other diastereoselectivity as well, there are a couple of examples: PKR of racemic cyclopropenes like **63** resulted in the formation of only one diastereomeric product like **64**, and in the case of enantiopure cyclopropenes, like **65**, the reaction was also enantioselective (Figure 27).[85]

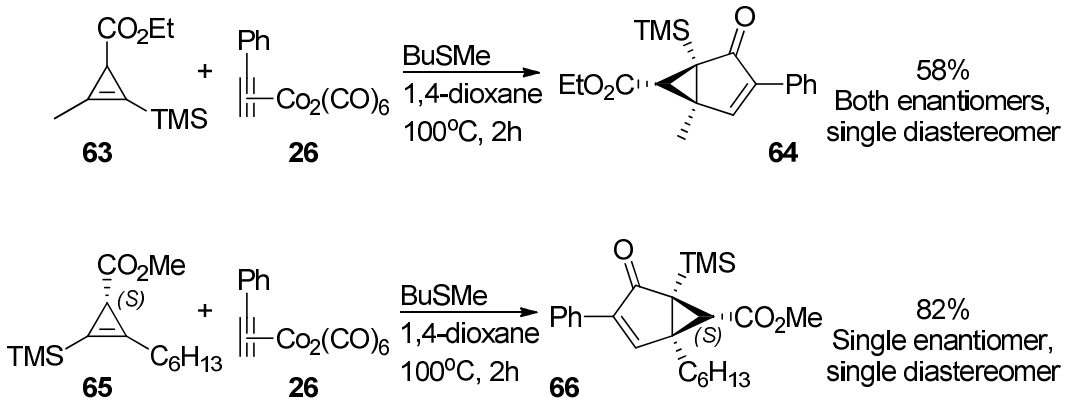


Figure 27. Diastereoselective PKRs of cyclopropenes. Reaction with racemic alkene **C62** yielded the single diastereoisomeric product **64** in racemic form, while enantiomerically pure cyclopropene **65** yielded enantiomerically enriched product **66**.[85]

Total diastereocontrol was achieved in PKRs of both NBN and NBD with sugar-derived azaenynes **67**, even though absolute stereochemistry of the product remained unclear (Figure 28).[86]

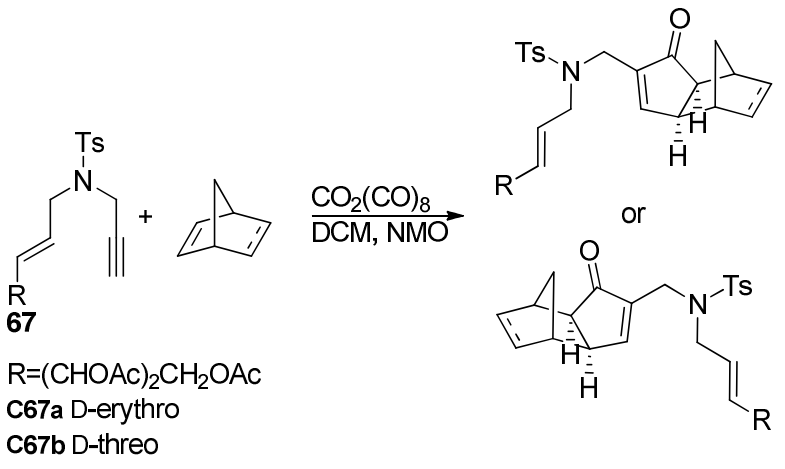


Figure 28. Total stereocontrol of sugar-derived azaenynes. Both alkynes yielded complete diastereoselectivity with both NBN and NBD with 62-80% yields.[86]

2.3.2.2 Chiral auxiliaries

If chiral substrates are rare in PKR, attempts to utilise chiral auxiliaries are more popular. The idea behind chiral auxiliaries is to favour one of the possible diastereomeric transition states, leading to an enantiopure product after the removal of the auxiliary. Chiral auxiliaries can be utilised in several ways. First, the auxiliary can be attached to the alkene or to the alkyne, use of alkynes being far more common approach. Attaching a chiral auxiliary to the alkyne has been widely used with varying success. It was first introduced in 1994 with chiral alkoxyethynes, which reacted with NBN and cyclopentene regioselectively and produced only *exo* isomers. Otherwise, the diastereoselectivities varied from nonselective to a diastereomeric ratio (dr) of >10:1. The best diastereoselectivities were achieved with *trans*-2-(9-phenanthryl)cyclohexanol as an auxiliary, but due to difficulties in its preparation in enantiopure form, *trans*-2-phenylcyclohehanol **72** was chosen for further studies. The auxiliary could also be easily removed in a two-step synthesis and the PK-retro-Diels-Alder domino sequence[87] afforded the enantiopure chiral cyclopentenone **73** (Figure 29).[88]

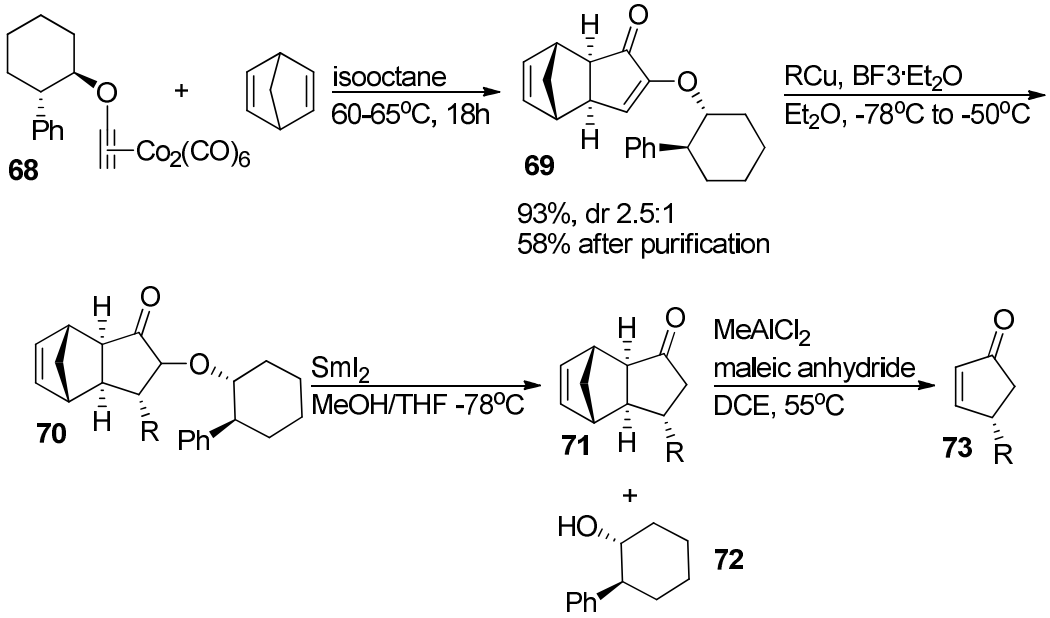


Figure 29. Diastereoselective PKR using chiral *trans*-2-phenylcyclohehanol **72** as a chiral auxiliary. The auxiliary can be recovered for reuse with reductive removal by samarium (II) iodine, and a retro-Diels-Alder reaction provided the final chiral cyclopentenone **73** with an ee 95% (R=Hept).[88]

The selectivity of alkoxyacetylenes could be improved by adding a suitable chelating group to the alcohol. With 10-methylthioisoborneol as an auxiliary, varying diastereoselectivities were observed. It turned out that the dicobalt hexacarbonyl complex of the alkoxy acetylene itself gave poor selectivities (dr 60:40 with NBD). Yet if a

chelated pentacarbonyl complex was formed prior to the cycloaddition reaction, the selectivities increased dramatically (up to dr 96:4 with NBD) (Figure 30).[36,63]

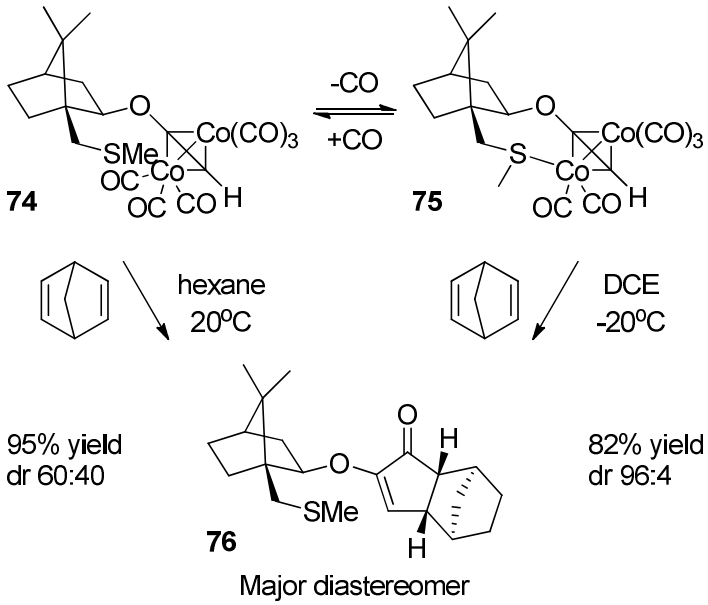
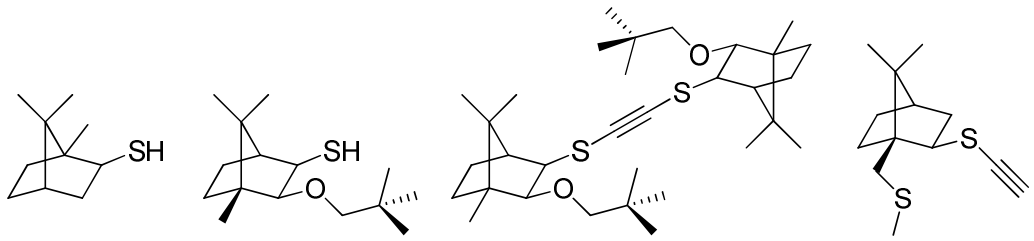


Figure 30. Diastereoselective PKR with cobalt-chelating alkoxyalkyne complex. The reaction of the non-chelated hexacarbonyl complex **74** is significantly less-selective than the reaction of the chelating pentacarbonyl complex **75**. **75** can be formed either chemically with NMO, or thermally by heating **74** under N_2. The latter method yields less selective cycloaddition reaction as the removal of CO and chelation are not complete and some amount of less-selective hexacarbonyl complex always remains.[36,63]

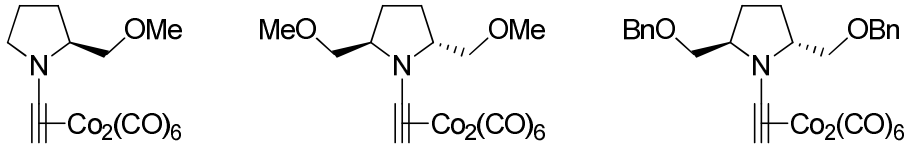
Corresponding reactions of acetylene thioethers yielded varied diastereoselectivities. On one hand, using thiol **77** (Figure 31) as an auxiliary yielded non-selective reactions when attached to either terminal or internal acetylenes. Thiol **78**, on the other hand, gave diastereoselectivities between 1:1 and 4.6:1 in moderate to good yields. The best selectivity was achieved with non-strained cyclopentene in an NMO-promoted reaction.[89] The diastereoselectivities were increased to 6:1 with corresponding dithioether **79**, but the yields dropped to the level of 25%.[90] The thioether analogue of internally chelating 10-methylthioisoborneol, **80**, yielded the best results of all the thioethers, with a maximum selectivity of 95:5, but it did not reach the potential of an oxygen analogue, as the yields were usually lower.[91] In general, then, replacing ethers with the aforementioned thioethers did not provide improvements to diastereoselective PKRs.



77 **78** **79** **80**

Figure 31. Auxiliaries **77** and **78** and alkynes **79** and **80** used in acetylene thioether studies.[89-91]

Chiral ynamines and ynamides, as they relate to *exo* and *endo* selectivity, were discussed already in section 2.3.1. A series of terminal ynamines as cobalt complexes **81**-**83** (Figure 32), derived from chiral secondary amines, gave moderate to good diastereoselectivities with poor to moderate yields. These ynamines were unusually reactive in PKR, providing thermal reactions with strained alkenes at even -35°C. Related DFT calculation revealed unexpectedly easy dissociative loss of CO from the complex, assisted by a planar nitrogen atom able to partially delocalise into the C-Co σ* orbital, resulting in increased reactivity of these ynamines in PKR.[79]



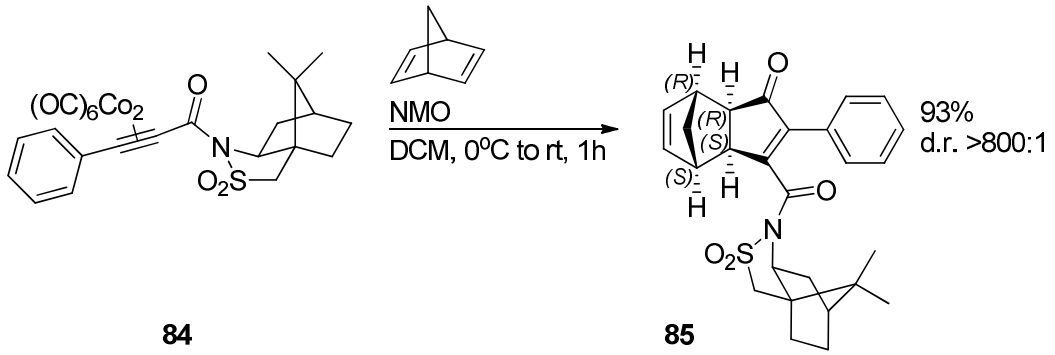
81 **82** **83**

Figure 32. Ynamine cobalt complexes **81**-**83** provide exceptional reactivity but poor yields and moderate to good diastereoselectivities.[79]

However, poor yields, combined with the diastereomer mixtures' inseparability, do not encourage this method's use in syntheses from practical standpoint. Chiral alkynyl amides provided slightly higher yields, but as a mixture of *endo* and *exo* isomers as discussed in 2.3.1. Minor *exo* adducts were 1:1 mixtures of diastereoisomers, while major *endo* adducts were formed as single diastereomers (Figure 23).[78]

Initial studies of PKRs with chiral 2-alkynoic esters offered depressing results, as albeit yields were good, diastereoselectivities were commensurately low.[92] However, *N*-(2-alkynoyl)oxazolidinones provided higher diastereoselectivities[93], and a new level of selectivity was achieved when *N*-(2-alkynoyl) sultams were tested in PKR. The cobalt hexacarbonyl complex **84** in a reaction with NBD (Figure 33) gave **85** at a higher diastereomeric ratio than HPLC detection could measure (>800:1) and in high yield.

Other alkylpropynoyl derivatives of the same sultam provided similar diastereoselectivities with slightly lower yields.[48] The reaction of **84** with NBN, instead of NBD, was highly selective as well with dr 125:1.[94] The practically complete diastereoselectivity was explained, with DFT calculations, as a result of similar chelation to the cobalt atom as with 10-(alkylthio)isoborneols like **75**[63] and 10-(alkylthio)isobornanethiols like **80**[91,94].



84 **85**

Figure 33. The highly diastereoselective PKR of **84** with dorbornadiene.[48]

Among others, also sulphoxides have been tested as chiral auxiliaries. When attached to alkynes, the resulting dicobalt hexacarbonyl complexes showed unexpected racemisation at sulphur and provided only low diastereoselectivities.[95] And yet, when sulphoxide was attached to the alkene, high diastereoselectivities and reasonable yields were achieved. In fact, **86** gave the best results, and it was also utilised in a synthesis of (-)-Pentenomysin I (**91**) as shown in Figure 34. This short synthesis also demonstrates well the easy removal of the sulphoxide auxiliairy.[96] The observed high reactivity and selectivity is suggested to be connected to the ability of the amine group to ligandate to the cobalt.[97]

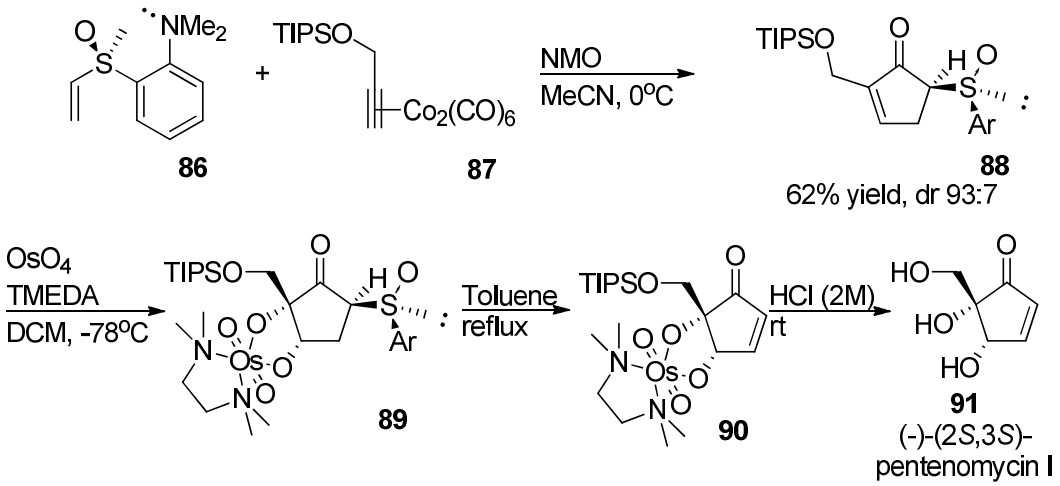


Figure 34. PKR using a vinyl sulphoxide as a chiral auxiliary and utilisation of the PK product in synthesising an antibiotic (-)-(2*S*,3S)-pentenomycin I (**91**). The PK product was purified by precipitation with hexane to give the (5*S*,*SR*)-adduct in ee>99% prior to continuation of the synthesis.

2.3.2.3 Chiral ligands

As explained above, the most diastereoselective auxiliaries did affect, at least partly, through chelation to the cobalt complex. This leads to the examination of chiral ligands in cobalt complexes, which also have the additional benefit of providing auxiliary-free products. The first example of a chiral ligand's use in PKR was published in 1988 by Pauson, Brunner and their groups[98]. They used Glyphos as a ligand and got a 6:4 diastereomeric mixture of the two alkyne cobalt complexes. After diastereomeric separation of the complexes, the PKR itself was totally enantioselective at 45°C and provided 90% ee at 90°C as a result of racemisation of the complex at high temperatures. Simple mixing of the hexacarbonyl complex and optically active Glyphos in situ in the reaction did not yield any notable enantioselectivity. A solid-state reaction on silica of the same complex with 2,5-dihydrofuran gave up to 59% ee at 59°C.[99] The low yields could be improved with NMO without losing any enantioselectivity.[100] An interesting point is that both enantiomers could be synthesised separately with (*R*)-(+)-Glyphos by choosing one of the two diastereomeric complexes, revealing that the selectivity actually derived from the chiral cobalt complex core and not from the chirality of the ligand.

Different kinds of bidentate ligands have been studied over years without any, or with only minimal improvements to the enantioselective reaction. Bidentate ligands with Co-P and Co-N coordination provide good enantioselectivities only in monocoordinated forms.[101,102] Bridging diphosphoamines or BINOL-derived phosphoramidites with a

double substitution, one to each cobalt in the axial positions, provide poor to good yields but poor selectivity with 0-38% ee depending on the ligand.[103,104] Results with (*S*)-BINAP or other chiral bidentate phosphines are not any better, giving <10% ee,[105] or in the case of (*R*)-BINAP, no reaction as a bridged ligand[58] and low yields without selectivity as a chelating alkyne-$Co(CO)_3$-Co(CO)BINAP complex.[106] However, the mode of ligand binding seems to play an important role in both the activity and selectivity of the reaction.

An exception to other bidentate ligands are P,S ligands, which according to their name, coordinate through phosphorus and sulphur. The first type of P,S ligands, presented in Figure 35, have a chiral carbon skeleton, providing stereoselectivity to both the formation of the complex and the PK reactions. In general, these complexes gave good to excellent yields and moderate to excellent enantioselectivities, depending on the ligand and reaction conditions (Figure 36).[107-110]

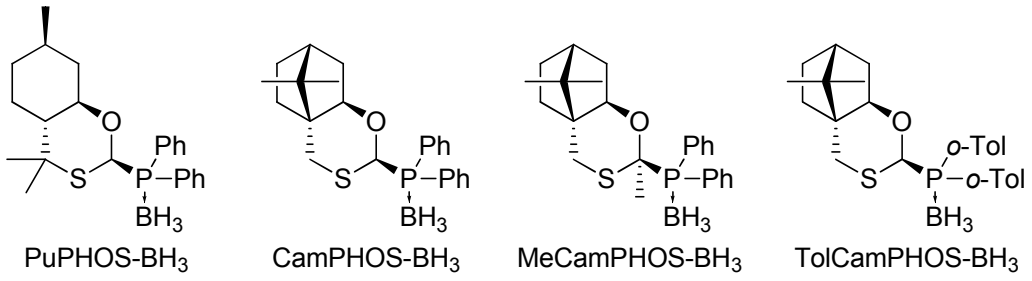


Figure 35. Selected chiral P,S ligands with a chiral carbon skeleton. PuPHOS is derived from (+)-pulegone, and CamPHOS and the related ligands from camphor.

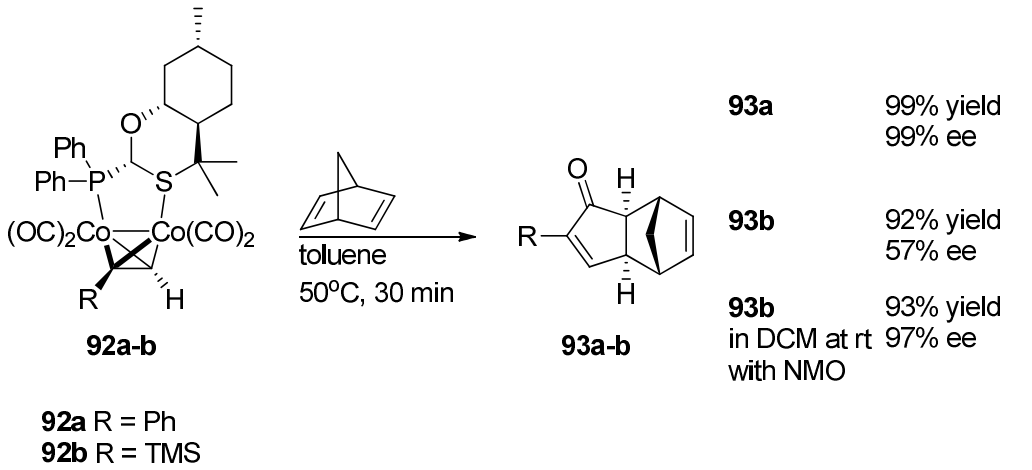


Figure 36. Selected PKRs of a chiral PuPHOS complex **C91**. In some cases, excellent yields and enantioselectivities were achieved.[107]

In another type of chiral P,S ligands, presented as alkyne cobalt complexes **94** and **95** in Figure 37, the sulphur is chiral, and they are often called PNSO ligands, as there is an amine bridge between the phosphorus and sulphur. These ligands are easier to synthesise, readily available as both enantiomers, and usually provide even higher diastereoselectivity.[111-113] Also, a complex with features of both types, chiral camphor-derived skeleton and chiral sulphur, has been reported, but it did not provide any cyclopentenone in a reaction with NBD.[114]

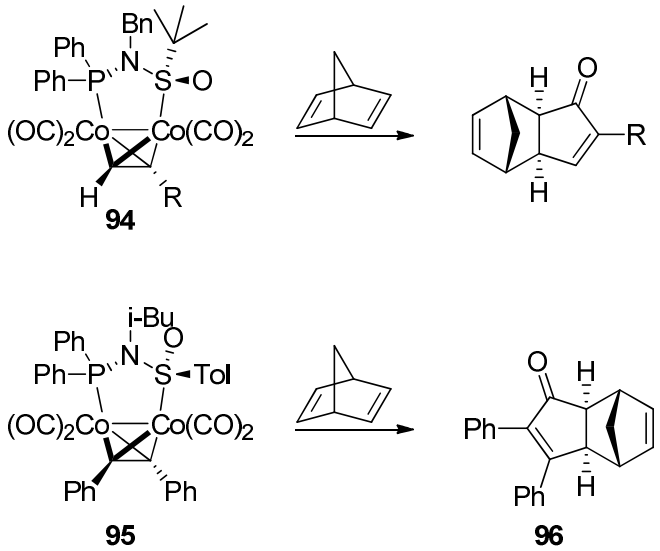


Figure 37. Two PKRs with chiral PNSO ligands.[111,113]

2.3.2.4 Chiral additives

Chirality can also be introduced to a cobalt complex using chiral promoters. Chiral amine *N*-oxides, such as brucine *N*-oxide[115], remove one CO from the prochiral alkyne-cobalt complex selectively, thus creating a desymmetrisised complex that favours either a *Re* or *Si* face coordination of alkene to the complex, each leading to one enantiomer. Additionally, other chiral amine *N*-oxides like quinine *N*-oxide[116] and sparteine *N*-oxides[117] have been used for this purpose. The selectivity of this method is moderate. However, a clever methodology reversing the selectively of the amine *N*-oxide has been presented, enabling synthesis of both enantiomers with the same catalyst. Enantiomer A is normally synthesised by adding chiral amine *N*-oxide to the complex. Enantiomer B, in contrast, is achieved by first forming the chiral pentacarbonyl complex with chiral amine *N*-oxide, then adding one equivalent of a phosphine ligand to occupy the free coordinating site. The following activation by NMO leads to decarbonylation of the other, phosphite-free cobalt, resulting in the formation of the other enantiomer.[118-120]

3. Promoters and other ways to accelerate PKR

Traditionally PK reactions are promoted thermally by refluxing the alkyne cobalt complex solution in the presence of the alkene. In many cases, the reaction times have been long, temperatures have been relatively high (70°-120°C), and yields have been only satisfactory. Consequently, several methods for accelerating the reaction and improving yields have been developed. In general, all additives or other promotion methods try to affect the rate limiting step (i.e., dissociation of CO), but different methods achieve this goal in different ways. This section will first examine nitrogen-based promoters—including, mainly, *N*-oxides and amines. It will then discuss compounds with sulphur and phosphorus, followed by microwave promotion and, in the closing, survey other chemical and physical methods for PKR promotion.

3.1 Nitrogen-based PKR promoters

Use of tertiary amine oxides, especially NMO, is currently a popular way to accelerate PKR (Figure 38). Tertiary amine oxides as PKR promoters were first introduced for intramolecular reactions by Schreiber *et al.*[121] and, soon thereafter, for intermolecular reactions by Jeong, Chung and co-workers[77]. Amine *N*-oxides oxidise one CO ligand into a weakly coordinating CO_2[122], thus aiding in dissociation and creating a free site for the alkene to coordinate. The main disadvantage of this method, the need of several equivalents excess of the *N*-oxides to achieve desired yields, is not yet fully understood.

Other *N*-oxides used in PKR include brucine *N*-oxide[115,119], quinine *N*-oxide[116], sparteine *N*-oxides[117] and TEMPO[123], of which the first three are used for asymmetric purposes. Solid support bound amine *N*-oxides have also been employed [124,125] and *N*-oxide has been prepared in situ from commercially available polymer-supported amine using *N*-(phenylsulphonyl)phenyloxaziridine (Davis' reagent)[126] as a co-oxidant.[124]

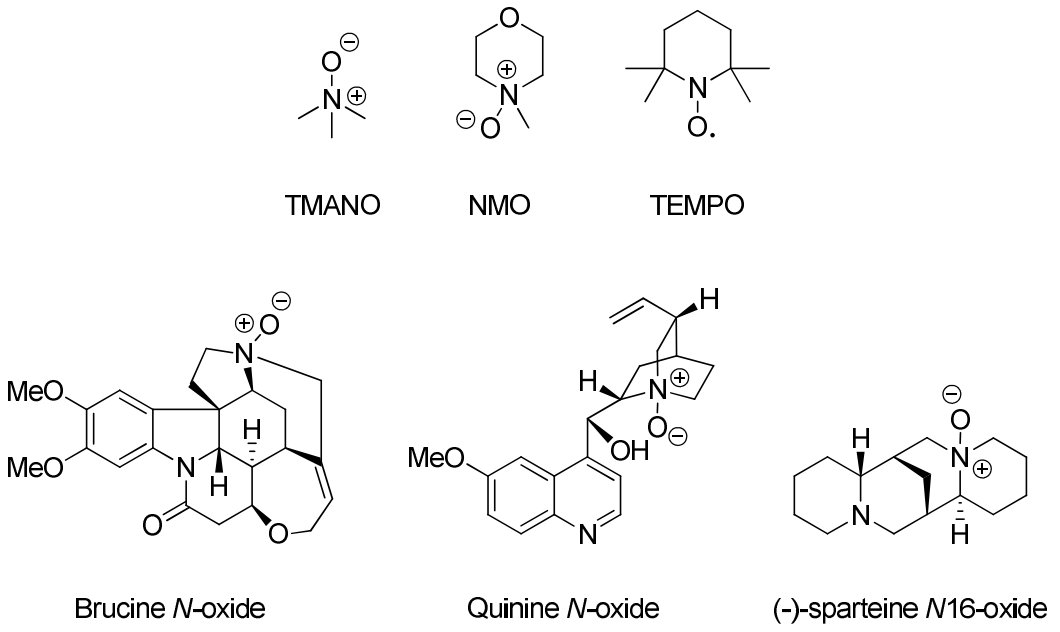


Figure 38. Selected amine *N*-oxides used in PKR promotion.

Sometimes, the effect of NMO is dependent on the alkyne. Alkynes bearing sulphur in a homopropargylic position, or in some cases even a bit farther from the triple bond, reacted considerably more slowly with NMO than without it, compared with other alkynes.[35] What occurs is that a relatively stable complex (**97** in Figure 41a), with a CO replaced by sulphur with intramolecular coordination, is formed. The relative stability of this complex at low temperatures reduces reaction rates, compared with thermal reactions, in which the stability of the complex is lower.

Promotion of PKR by amines has also been reported (Figure 39). In 1998, Pesiasamy and Rajesh[127] reported PKRs induced by TMEDA, α-methylbenzylamine and DMF at room temperature; although the yields were lower than with thermal promotion or other additatives. Kerr *et al*.[128] promoted PKR with a combination of TEA and ultrasound, but the yields were not as substantial as with TMANO. Sugihara, Yamaguchi and co-workers[129] compared different tertiary, secondary and primary amines and concluded that primary amines with secondary alkyl groups were the optimal choice for PKR at 35°C. With a tertiary amine the reaction did not proceed; the reaction was slow with secondary amines and primary amines with tertiary alkyl chains; and reactions promoted by primary amines with primary alkyl groups resulted in lower yields. However, in catalytic PK reactions the results were the opposite: using primary cyclohexylamine was ineffective and using tertiary diisopropylethylamine resulted in high yields.[130] It is assumed that in catalytic PKRs, amines might react with dicobalt

octacarbonyl or intermediate species in the catalytic cycle, instead of the alkyne dicobalt hexacarbonyl complex as in stoichiometric reactions. It has also been proposed that, in stoichiometric reactions, the accelerative effect of amines arises from their stabilisation of the pentacarbonyl complex.[131]

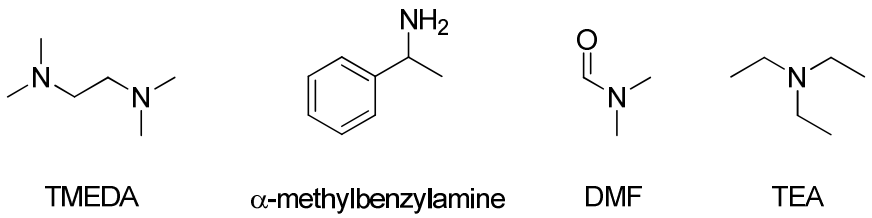


Figure 39. Selected amines used in PKR promotion.

3.2. Phosphorus- and sulphur-based PKR promoters

The use of phosphines, phosphites and phosphine-oxides as PKR promoters has also been studied (Figure 40). Billington, Pauson and co-workers[75] replaced one CO ligand of the alkyne cobalt hexacarbonyl complex with either phosphines or phosphites, but they observed only reduced reaction rates and lower yields, regardless of whether the complex was isolated prior to the reaction or prepared in situ. Surprisingly, the addition of phosphine oxide increased yields in intermolecular reactions. Phosphine oxides are inferior oxidants compared with *N*-oxides, and they therefore do not oxidise CO into CO_2 similarly to NMO and TMANO. They can, however, coordinate to the cobalt and replace a CO. As a weaker bonding ligand than CO, they are then more readily removed for alkene coordination.

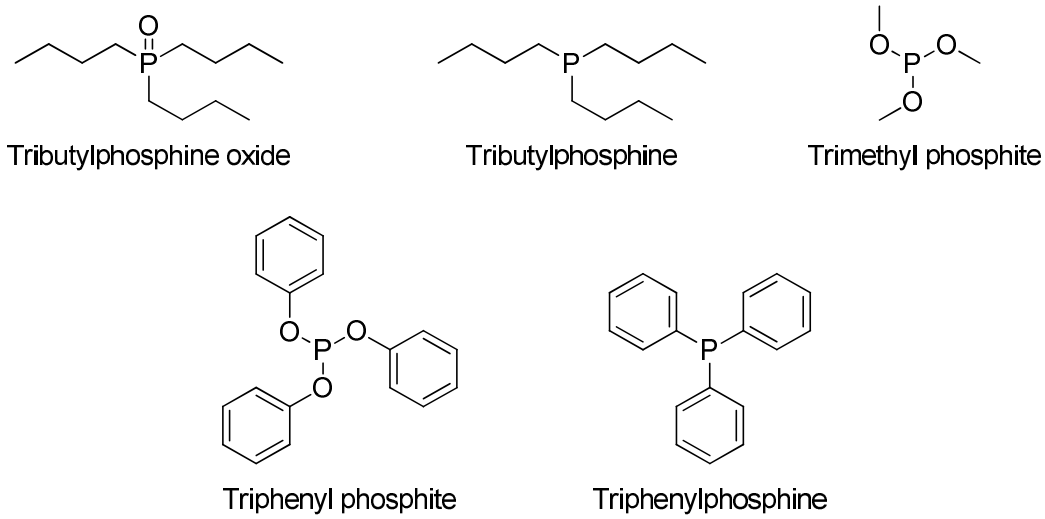


Figure 40. A phosphine oxide, phosphines and phosphites tested for PKR promotion.

The use of alkyl sulphides as PKR promoters was first introduced by Sugihara *et al*.[132] in 1999. The concept is derived from Krafft's study[35], in which alkyne dicobalt pentacarbonyls were formed with the aid of NMO and trapped with internal sulphides like **97** (Figure 41a). By heating these complexes in toluene a PK product was formed. This gave Sugihara *et al*. the idea of attempting externally added sulphides as PKR promoters. They tested different aromatic and aliphatic sulphides and showed that sulphides do indeed promote PKR, and *n*-butyl methyl sulphide was the most potent for this purpose. Overall, more than three equivalents of the sulphide were needed for efficient promotion, and steric hindrance around sulphur increased the reaction times and reduced yields (Figure 41b). A polymer-supported *n*-butyl methyl sulphide has also been successfully employed, with the benefit that it does not have the unpleasant odour like small sulphides, and the work-up and recycling require less effort.[133]

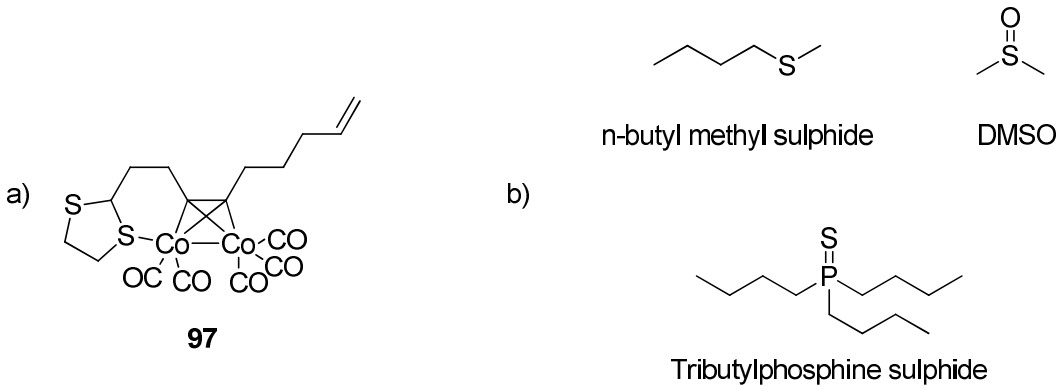


Figure 41. a) Alkyne dicobaltpentacarbonyl complex **97** with intramolecular coordination of sulphur.[35] b) Sulphide, sulphoxide and phosphate sulphide used in PKR promotion.

In addition to sulphides, also sulphoxides have been exploited in PKR promotion (Figure 41b). In a study by Pauson, Jeong and co-workers[74], DMSO was shown to accelerate PKR at 40°C with good to excellent yields. Even one equivalent of DMSO was enough to achieve good conversion. A 1:1 mixture of DMSO and dimethyl sulphide (DMS) has also been applied successfully with the idea of DMSO working as a promoter and DMS serving as a ligand.[134]

Finally, phosphane sulphides have been used to promote catalytic PKRs as well.[135,136] It has been proposed that they behave like amines—that is, by assisting the ligand exchange process of CO dissociation and alkene coordination.[135] With Bu_3PS, catalytic PKR is successful with only 3 mol% of $Co_2(CO)_8$ in atmospheric carbon monoxide pressure.

3.3. Microwave promotion

Microwaves in organic synthesis were introduced by Gedye, Smith, Westaway and co-workers[137] in 1986 by performing four different types of syntheses in a domestic microwave oven. They noticed a significant reduction in reaction times with comparable yields.

Microwaves as a promoter or a heating source result from the interactions between molecules and microwaves. Polar molecules try to orientate according to the rapidly changing electromagnetic field, because of dipole-dipole interactions, and this constant motion from reorientation creates heat (Figure 42). This method is in contrast with traditional thermal heating, in which heat is transferred from a heating source to the reaction mixture by conduction and convection. The transformation of electromagnetic energy into heat by dielectric losses also means that the temperature and heating of the reaction is dependent of the media. In polar solvents, the solvent itself is capable of absorbing electromagnetic energy and creating heat, which means that, in practice, in polar reaction media the temperature in the reaction is relatively homogenous and, from the reactant point of view, the heating resembles conventional thermal heating. Non-polar solvents, on the other hand, are transparent to the MW. The electromagnetic energy is absorbed by reactants, reagents or catalysts, and energy transfer occurs from these to solvent. This also means that the temperature might be heterogeneous within the reaction mixture, and local hot spots might form.[138]

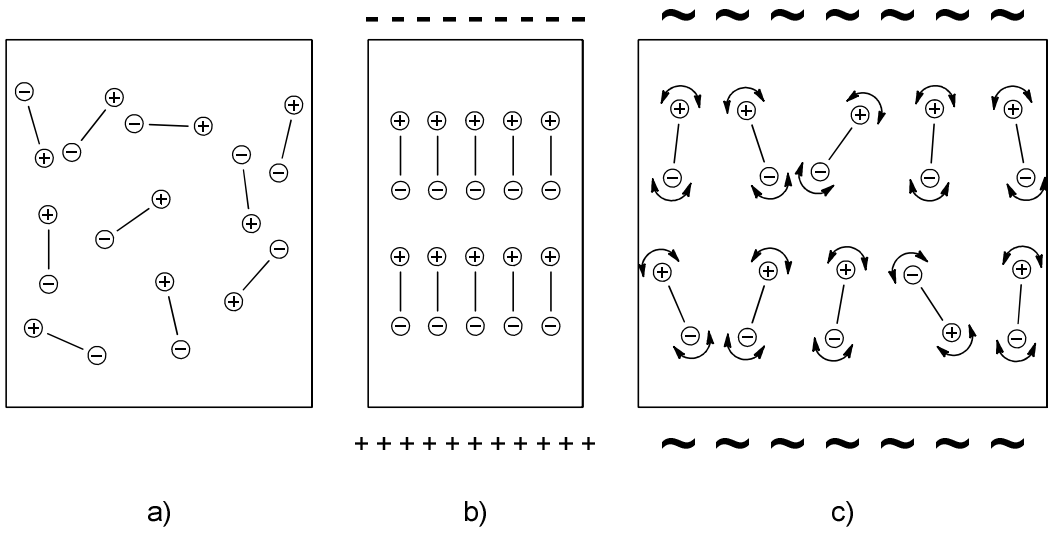


Figure 42. Dipoles in different environments. a) Without external electric field dipoles can have any position. b) When submitted to external electric field dipoles orientate according to the field. c) Microwaves make dipoles to continuously reorientate according to the quickly alterning field.

Other microwave-specific phenomena include overheating of the solvent and selective heating of specific compounds in the reaction. Overheating, or superheating, means that in atmospheric pressure, solvents heated with microwaves have higher boiling points than when they are heated conventionally. With many typical organic solvents the difference between these temperatures is 13°-26°C.[139] Reasoning for the overheating can be found in the temperature profile within the reaction flask. In traditional heating the heat comes to the reaction mixture through the reaction vessel, and the vessel is at least as warm as the solution inside it. In that warm flask surface, vapour bubbles can grow until they detach from the surface. With microwaves, in contrast, heating occurs in the reaction mixture and is transferred from the solution to the reaction vessel, which is made of microwave-transparent borosilicate glass. The reaction vessels are often cooled with air flow or are otherwise a bit colder than the reaction mixture, and therefore organic solvents can wet the surface or, in other words, form a film on the flask's surface covering cavities, pits and scratches in the glass, which are essential for the vapour-bubble growth process. As the number of potential vapour-trapping sites is reduced, the efficient boiling point, or nucleation limited boiling point, is increased.[139]

Selective heating with microwaves is based on the fact that most polar substances are heated rapidly and effectively and apolar compounds that do not absorb microwaves are heated only by convection and conduction from surrounding molecules. For

example, by choosing an appropriate biphasic solvent system, the solvents can have different temperatures in the same reaction vessel.[140-142]

Microwaves were first used in PKR promotion by Evans *et al*. in 2002.[76] In effect, they ran a series of stoichiometric inter- and intramolecular reactions with excellent yields in toluene and DCE and observed dramatically reduced reaction times compared with traditional thermal heating. Selected reactions with **98** and **100** are presented in Figure 43.

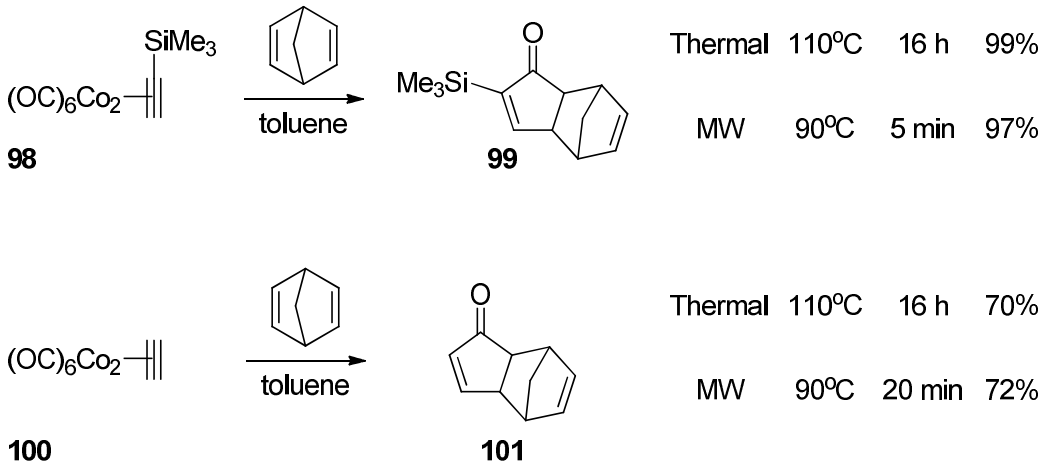


Figure 43. Comparision of PKRs of C97 and C99 performed with MWs and traditional thermal promotion.

The same year, Groth *et al*.[143] published an article examining a series of catalytic, MW irradiated and amine-promoted PK reactions in different solvents and temperatures. Fairlamb, with his group,[52-54] has also reported several PKRs heated with microwaves.

3.4. Other methods to promote PKRs

The first improvement to the standard methodology of PKR was introduced by Smith *et al*.[144,145] for intramolecular reactions. They adsorbed the alkyne-cobalt complex into a solid support, like silica or alumina, ran reactions without solvents, and got increased yields and dramatically shorter reaction times at lower temperatures. This promotion was independent of the pH in alumina, and in silica the optimal water content was between 10-20%. They assumed the promotion effect arose from solid supports assistance in the formation of preferred conformation, thus either reducing the entropy barrier of cyclisation[145] or facilitating the ligand exchange from CO to the alkene with the interaction between the support and alkyne[146]. The methodology was later expanded to both intermolecular reactions and zeolites as solid support[146].

Additionally, ultrasound has been shown to reduce reaction times in lower temperatures, but Billington, Pauson and co-workers[75] claimed that it has little effect on the yields. Kerr *et al*. got similar results with high-intensity ultrasound, but when ultrasound was combined with TMANO or TEA, the yields rose dramatically. In general, optimal conditions were considered to be a combination of TMANO and high-intensity ultrasound, which jointly produced good yields at low temperatures and in short reaction times. They assumed that the ultrasound effect is created as a combination of localised pressures and temperatures[147], and, especially with amine *N*-oxide, this method assists with the formation of the pentacarbonyl complex[128].

Among more unusual methods, molecular sieves have shown encouraging results in promoting PKR.[148] Photochemical induction has also been applied to both stoichiometric[149,150] and catalytic[17] reactions. Several hard Lewis bases, such as water and 1,2-dimethoxyethane, have also been shown to be valuable in promoting catalytic PKRs as well, but these methods were ineffective in stoichiometric reactions.[130] Lastly, water has also been used as a solvent combined with either surfactants[151] or ionic liquids[152] providing satisfactory yields.

4. Aims of the study

The Pauson-Khand reaction is a very efficient method for the synthesis of cyclopentenones. However, development of an intermolecular variant of this cyclisation has been very slow over the past decade, due to the lack of reactive alkenes and the lack of regioselectivity for substituted alkynes. In spite of the numerous studies published, the electronic effects involved are still not entirely understood.

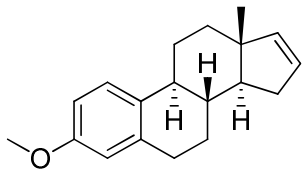
In this study, our purpose has been to

- Gain a greater understanding of the electronic guidance and interplay between steric and electronic factors in determining the regioselectivity of the Pauson-Khand reaction. (Publications II and III)
- Develop and utilise additive-free methods for PKR-promotion. (Publications I-III)
- Use PKR in syntheses of estrone E-ring extensions. (Publication I)

5. Results and discussion

5.1 Additive-free PKR: estrone E-ring extension with PKR and regiochemistry related to the alkene [I]

In most PKRs, alkenes are used in excess in order to push the reaction towards completion. It is not a problem as long as affordable and easily removable alkenes like NBN and NBD are used, but it might limit the utilisation of PKR in natural product synthesis. In this study we used the relatively expensive estrone derivative **102** (Figure 44) and introduced an additional E-ring to the steroid structure by PKR. Previously, the E-ring extended estrones have been synthesised by modifying the C17-ketone located in the D-ring.[153-156] The steroid D-ring has been modified with cycloaddition reactions before,[157-159] but the first E-ring extension by intermolecular PKR was published in a previous study from our group, in which the E-ring was introduced by the PKR of aromatic alkynes in DCM with sulphide activation[160]. However, these conditions did not provide any products when aliphatic propargylic alkynes were employed. In this study, then, alternative reaction conditions were explored in order to achieve, using PKR, the E-ring extension carrying aliphatic substituents. We decided to perform the reaction without chemical additives assisting the reaction, but instead we used microwaves for the promotion.

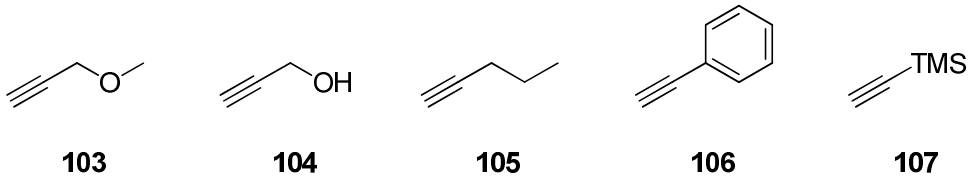


102

Figure 44. Structure of estrone derived alkene **102**.

As estrone is relatively expensive, we first performed a set of test reactions with NBN to determine proper conditions, then confirmed the results with cyclopentene and finally performed the experiments with estrone derivative **102**. Five different alkynes were chosen, methyl propargyl ether **103**, propargyl alcohol **104**, 1-pentyne **105**, phenyl acetylene **106** and trimethylsilyl acetylene **107**, shown in Figure 45. Contrary to conventional practice in intermolecular PKRs, only one equivalent of a norbornene or alkene **102** was used in the reactions. This probably negatively affected the resulting

yields, but we were more interested in the conversion of **102** and possibility of recycling the unreacted **102** after a reaction.



103 **104** **105** **106** **107**

Figure 45. Alkynes **103**-**107** used in this study.

All reactions were performed in DCE, except the cyclopentene reactions as neat, at 100°C and with microwave promotion. The results of the PKRs of alkynes **103**-**107** with norbornene, cyclopentene and estrone derivative **102** are presented in Figures 46, 47 and 48, respectively. In general, reactions with norbornene gave best yields, as expected, and only *exo* isomers were detected. Yields with cyclopentene were modest, and it did not react with usually reactive **107** at all. The PKR of estrone derivative **102** and both formed isomers are presented in Figure 49. Yields are reported as the combined yield of both regioisomers. Yields from **102** varied a lot, and it should be noted that **102** reacted unexpectedly poorly with **107**. Even though the yields with **102** were only in fair-good level, practically all the unreacted **102** could be recovered in purification by column chromatography.

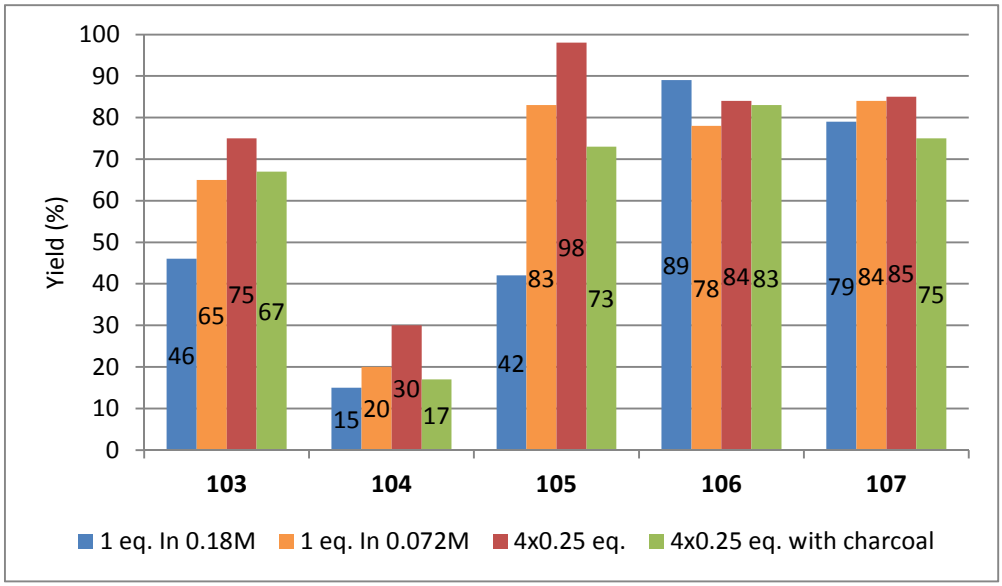


Figure 46. PKRs of alkynes **103**-**107** with norbornene. The addition method of alkyl-cobalt complex is presented with different colours. With blue, all complex is added at once and the concentration of the reaction mixture is 0.18 M. With orange the reaction mixture is diluted, the concentration being 0.072 M. With red, the complex is added in four equal portions to the solution and the final concentration is 0.18 M. Green columns represent reactions performed in charcoal suspension.

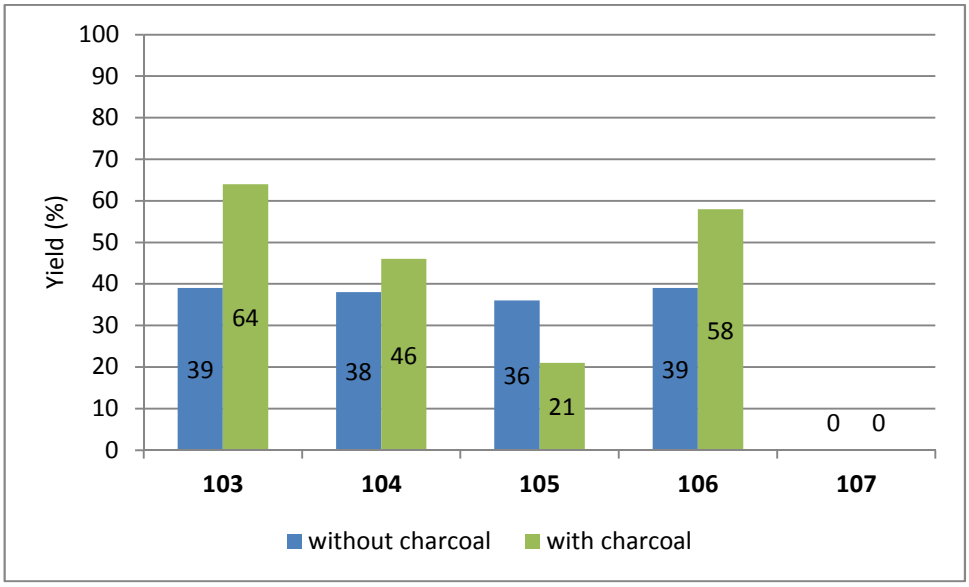


Figure 47. PKRs of alkynes **103**-**107** with cyclopentene. Blue columns represent standard reactions, and green columns represent reactions that were performed in a charcoal suspension.

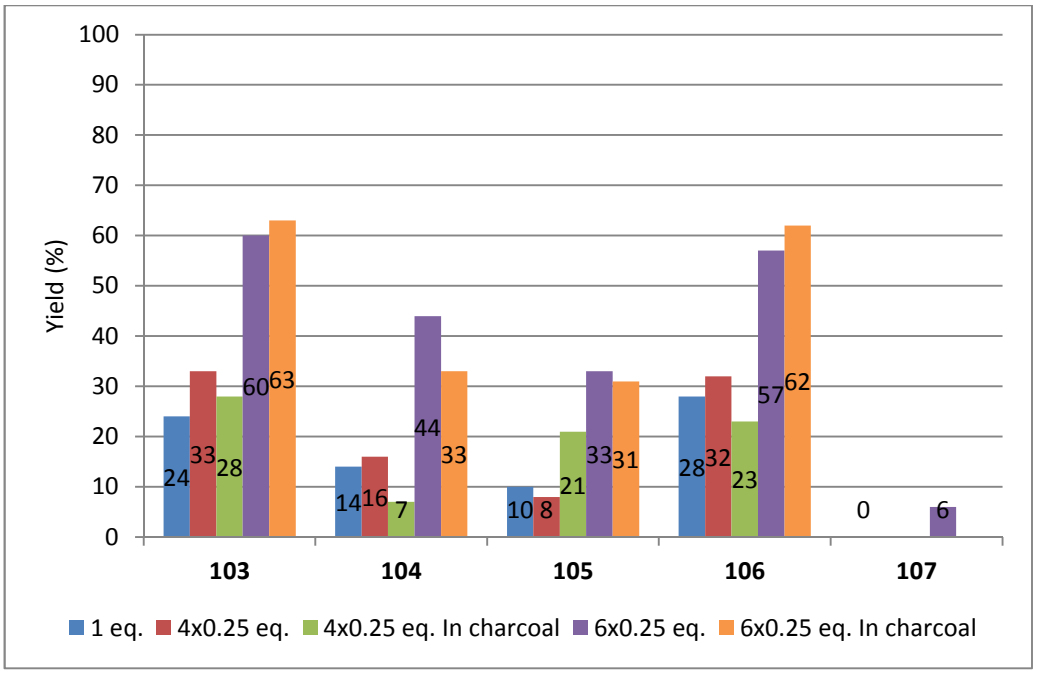
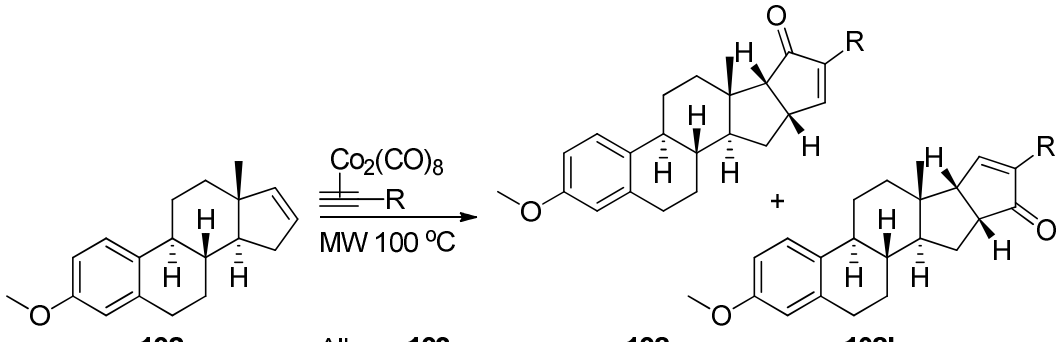


Figure 48. PKRs of alkynes **103**-**107** with estrone derivative **102**. Blue columns represent reactions in standard conditions. In the red columns the complex has been added in four equal portions, and in the purple columns 1.5 equivalents of the complex have been added in six equal portions. Green and orange columns represent reactions with charcoal suspended in the reaction mixture.



102

Alkyne **103**	**108a**	**108b**
Alkyne **104**	**109a**	**109b**
Alkyne **105**	**110a**	**110b**
Alkyne **106**	**111a**	**111b**
Alkyne **107**	**112a**	**112b**

Figure 49. PKR of estrone derivative **B6**. Two regioisomers, which differ in the orientation of the former alkene, are formed in the reaction.

In addition to the successful introduction of an E-ring, there were a couple of interesting findings during the study. As PKRs are usually run with an excess of alkene, simulating of the same situation by adding the alkyne cobalt complex in several portions—and, thus, having excess of alkene in the reaction mixture—improved yields with the norbornene (blue versus green columns in Figure 46) but did not have any notable effect with estrone derivative **102** (blue versus red columns in Figure 48). Still, the stepwise addition of a total 1.5 eq. of the complex (purple columns in Figure 48) provided the E-ring extended estrone derivative in fair to good yields. Without excess of the complex, we were not able to push the reaction into completion but had some of both alkene and complex in the reaction mixture, no matter how long the reaction time had been. Based on this study, a small overloading of the complex, combined with the stepwise addition of it, might provide a reasonable method if excess of alkene is not an option.

We also found that the addition of charcoal to the reaction mixture makes the reaction mixture cleaner, free of colourful organocobalt species and easier to purify. For reactions of estrone derivative **102**, this finding simplified the recovery of alkene.

The regiochemistry of alkene insertion was also studied. Interestingly, the regioselectivity of **102** in PKR with alkyne **106** was the opposite of a previous study from our group.[160] Previously, the ratio between **111a** and **111b** was 1.6:1, but in the present study it was 1:1.3. Reaction conditions have been shown to affect the regioselectivity of alkenes.[72-74] The main differences in the reaction conditions were the promotion method

(*t*-BuSMe vs. MW), temperature (40 ° vs. 100 °C) and solvent (DCM vs. DCE). As both solvents are aprotic chlorinated solvents with relatively similar polarities, the reason for the observed change in selectivity probably lies in either the promotion or the temperature.

5.2 Regioselectivity of sterically equivalent, conjugated alkynes [II]

This study was inspired by our reactions with carbamate-protected propargylic amines and problems of not having a way to find out whether the observed selectivity and high reactivity were arising from the large size of the carbamate group or from a kind of coordination. We encountered this problem while synthesising derivatives of estrone and its model compound discussed in the section 5.1. We came back to it several times over the years and finally realised that there is a general lack of knowledge about regioguidance in PKR. There was no way to reliably estimate the regiochemical outcome of sterically equivalent or even near-equivalent alkynes. About the same time as this occurred to us, an article of PKRs of heteroaromatic alkynes was published[54], pointing out the same problem and inspiring us even more.

We chose diaromatic alkynes for the study because they are easy to modify electronically without changing their steric properties. They also provide an easy way to confirm that the possibly coordinating functionalities are far away from the reaction centre. The electronic variation was made in two ways: by choosing different functional groups and by placing them in different positions in the aromatic ring. *o*-positions were not utilised because of the possible steric effects to the reaction centre. The alkynes were synthesised by Sonogashira coupling and their dicobalt hexacarbonyl complexes were prepared in situ before the PKR. The PKRs were performed with norbornene and promoted with microwaves to avoid any doubt about the influence of the additive on selectivity. The alkynes chosen are presented in Figure 50.

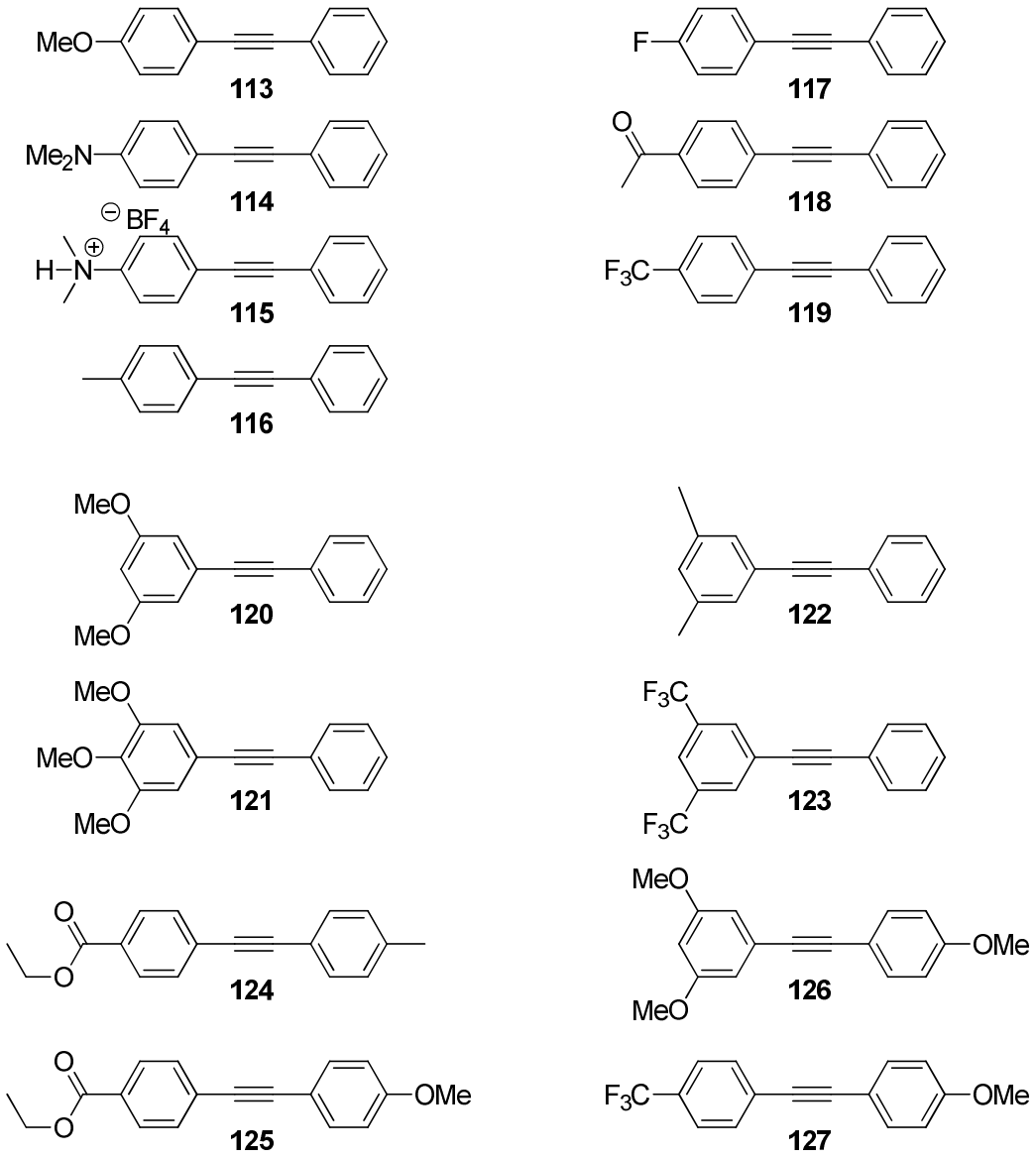


Figure 50. Alkynes **113**-**127** were chosen for the regioselectivity study.

The regiochemical outcomes are reported relative to the substituted aromatic ring, or in the case of alkynes **124**-**127**, relative to the left hand side of the compound in Figure 50. Regioselectivity of the PKRs of *p*-substituted alkynes were qualitatively as expected and the major isomer could be predicted based on Hammett-values of the substituents in the aromatic ring. The yields and ratios are presented in Figure 51 and the correlations between selectivity and Hammett-values are presented in Figure 52. It is worth pointing out, as well, that the regioselectivity could be switched from α to β by converting amine **114** into the corresponding BF_4^- salt **115**. However, we expected the selectivity to be much more visible. Also, throughout this study, we observed only *exo* isomers, and no *endo* isomers were detected. This was predictable, as *endo* isomers are much more

common in reactions of NBD, and with NBN only traces of *endo* isomers, if any, are usually seen.

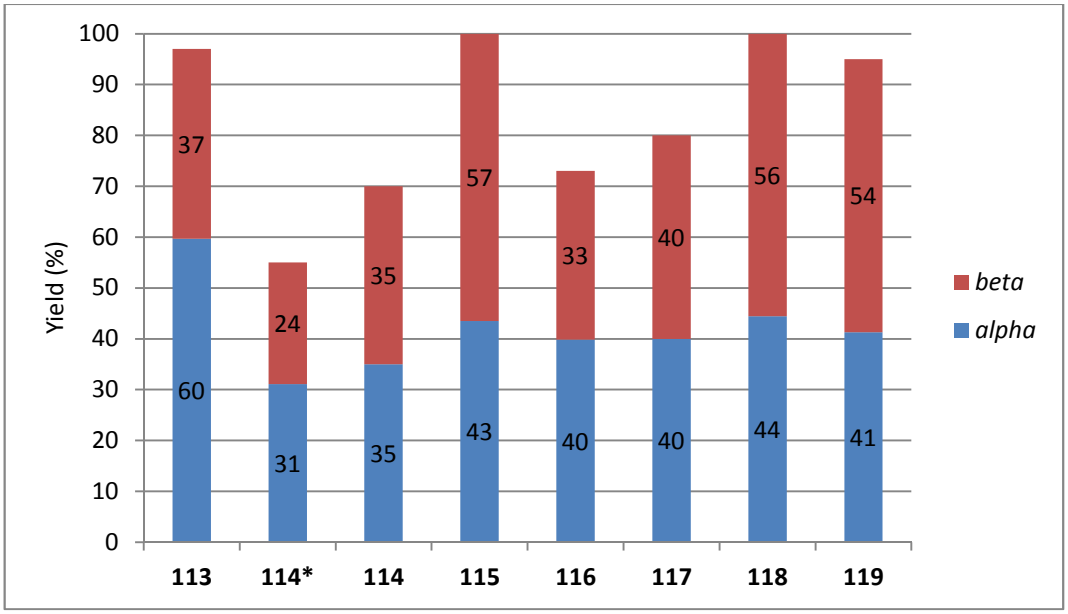


Figure 51. PKRs of *p*-substituted alkynes **113**-**119**. Reaction of **114** marked with an asterisk is performed with 1 equivalent of TEA present in the reaction mixture to minimise a possible reaction between the amine and Lewis-acidic cobalt complex.

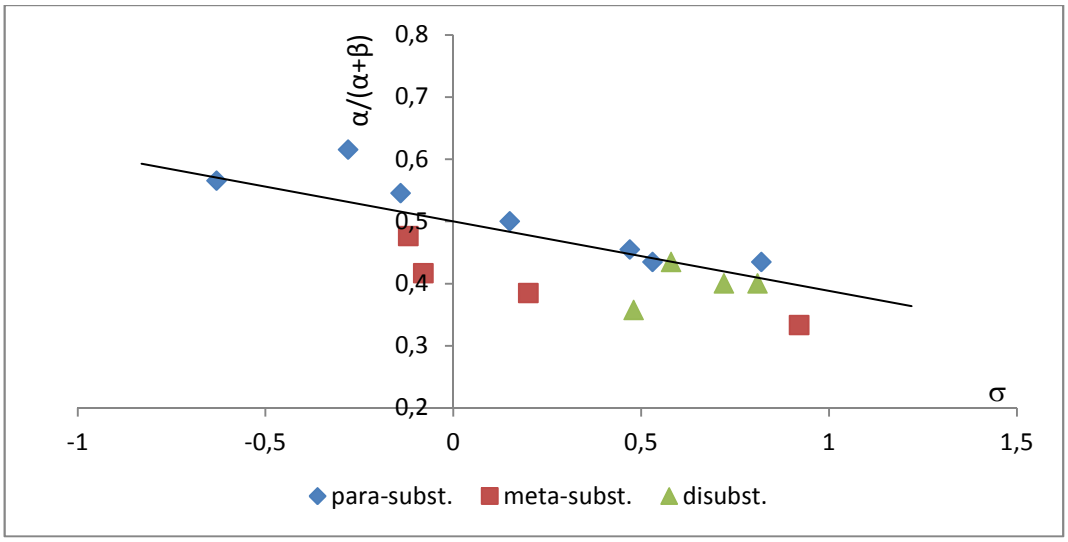


Figure 52. Correlations of Hammet $\sigma_{p/m}$ values to the regioisomeric outcome (α/α+β) of the reactions.

One of our most interesting findings, though, was the reactivity of alkyne **124**, which is the same that Greene *et al*. used as dicobalt octacarbonyl complex **22** when obtaining a single β isomer, as illustrated in Figure 13 and discussed in section 2.1.2. We repeated the reaction in our reaction conditions, and also as a thermal reaction in toluene at 80°C, but received, in both conditions, a 1:1.3 mixture of α and β, respectively, as a product.

Based on our results, the reported complete regioselectivity of **124**, which has had a major impact on PKR studies during the past decades, seems to be an overstatement. Even when the methyl group was changed into a more electron-donating methoxy group, the ratio was only slightly increased to 1:1.5 (Figure 53). On the other hand, the differences in regioselectivity between **24** (Figure 13) and **125** can be explained by different alkenes used in the reactions. As norbornadiene seems to be more selective than norbornene,[III] the observed selectivities are in accordance with each other.

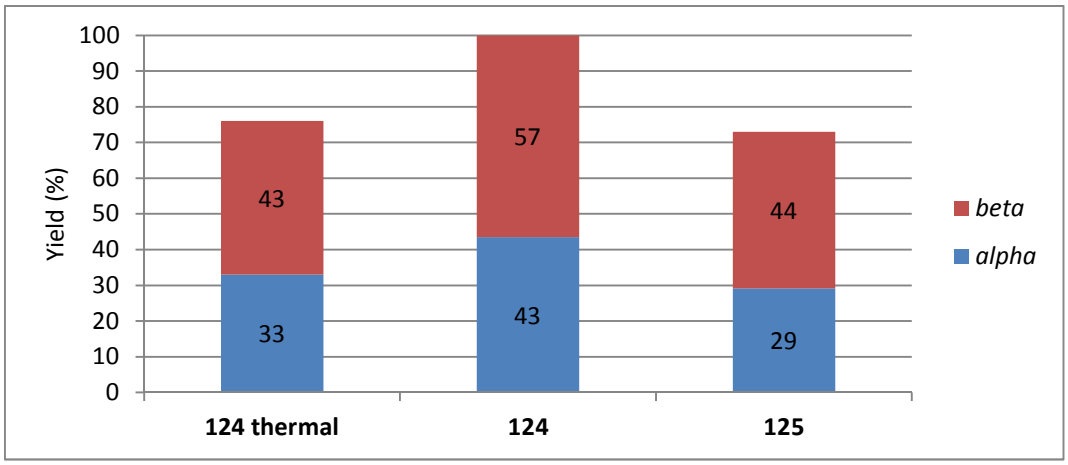


Figure 53. PKRs of alkynes **124** and **125**.

The effect of the substituent position in the aromatic ring was tested with three different groups: methoxy, which is EDG and has a free electron pair in the oxygen, methyl, which is also EDG but only through inductive effect, and trifluoromethyl, which is EWG. Results of the methyl and trifluoromethyl substituted alkynes are presented in Figure 54. As can be seen from this data, the major isomer stays the same with trifluoromethyl-substituted alkynes **119** and **123**, and the selectivity is more pronounced with double-substituted **123**. This is in agreement with the Hammett values and is easily explained with the inductive effect of CF_3. Unexpectedly, the 1.2:1 α-selectivity of *p*-substituted **116** is turned to 1:1.1 β-selectivity when the methyl is moved into *meta* positions, as in **122**.

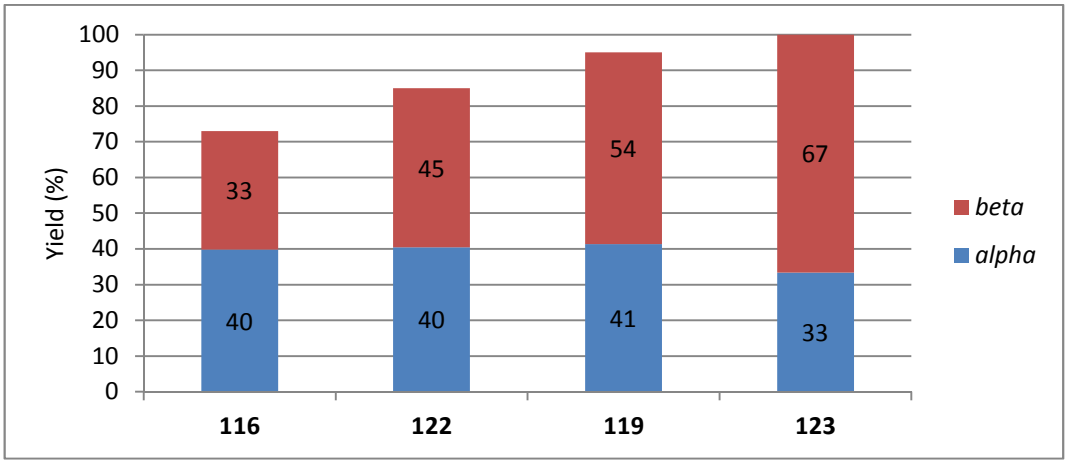


Figure 54. PKRs of methyl and frifluoromethyl-substituted diaromatic alkynes.

With methoxy-substituted alkynes (Figure 55), the 1.6:1 α-selectivity of **113** could be turned into a 1:1.4 β-selectivity by adding two methoxy groups into *meta* positions, as in **121**. By removing the substituent from the *para* position, the selectivity was fully inverted into 1:1.6 (**120**). The selectivity could be increased by combining the substituted rings of **113** and **120**, thus creating **126**, which resulted a 1:1.8 selectivity with regards to the *m*-substituted ring.

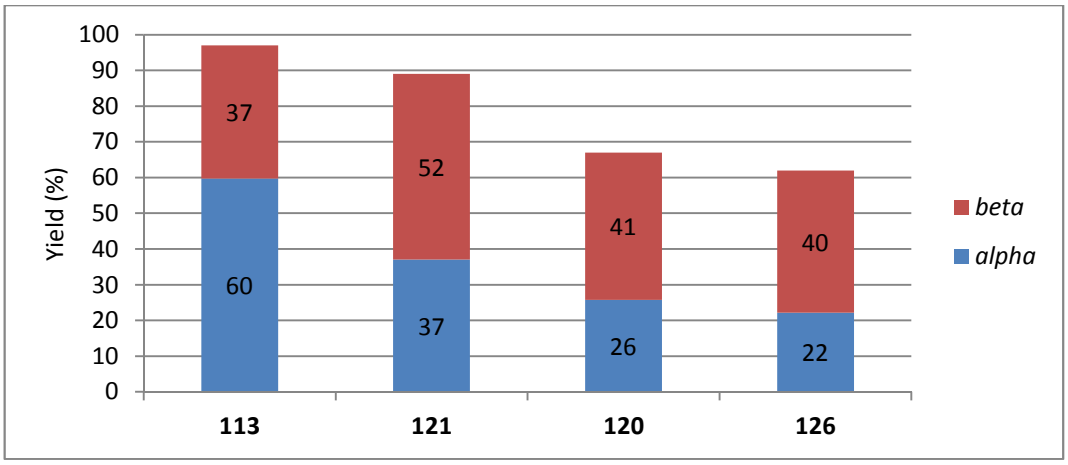


Figure 55. PKRs of methoxy-substituted alkynes. The selectivity is inverted by changing the substituent position (**113**, **121** and **120**) and increased by adding substituents into both aromatic rings at suitable positions (**126**).

The push-pull effect in PKR regioselectivity has been an unquestioned, widely discussed topic[41,54,161]. Encouraged by the results with the methoxy group we chose the most promising EDG and EWG to test the phenomena. We combined these substituents in the opposite aromatic rings of the alkyne, thereby creating **127**. To our disappointment, we were unable to find any experimental support for the theory (Figure 56). The selectivity

of alkyne **127** with an EWG and an EDG was 1:1.5, which is even less than the selectivity of the same EDG alone in **113**.

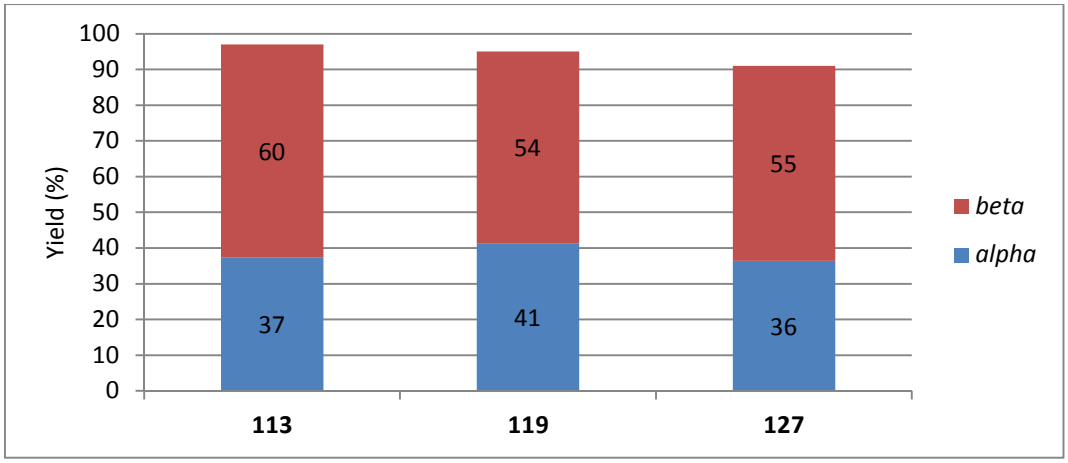


Figure 56. PKRs of methoxy-substituted **113**, CF_3-substituted **119** and **127** having both OMe and CF_3 in *p*-positions in the aromatic rings. The regioisomeric outcome of **113** is expectionally reported in respect to the non-substituted ring to clarify the hypothetical push-pull effect and facilitate the comparison of the alkynes.

In addition to the experimental results above and their comparison to the Hammett values, theoretical calculations were also performed to support our theory. Details of the calculations are presented in publication II. As a result we found out that the NBO charges of the α-alkyne carbons correlate well with the experimental selectivities (Figure 57). This provides a useful tool in predicting the regioselectivity of diaromatic alkynes in PKR. The calculations and experimental results together also showed that the general assumption of the dictating relationship between alkyne triple bond polarisation and the regioselective outcome of the reaction is valid and it can be utilised in regioselectivity estimations.

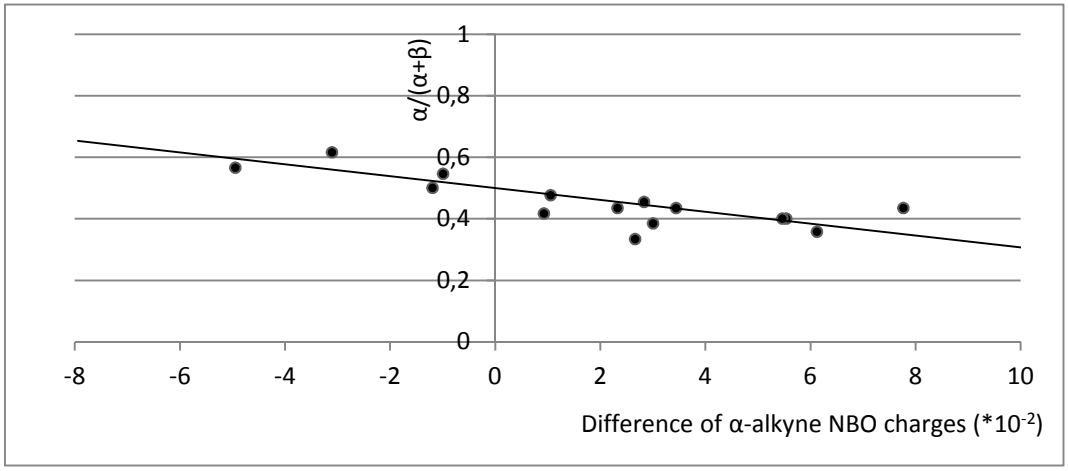


Figure 57. Correlation between experimental regioselectivity and computed NBO charge differences between α-alkyne carbons. The linear fitting is forced via origin (0, 0.5).

5.3 Regioselectivity of sterically near-equivalent propargylic alkynes [III]

Despite finding several answers to regioguidance with diaromatic alkynes, numerous questions, still remained. Next, we expanded the scope of the alkynes from conjugated diaromatic into non-conjugated alkynes, for which the polarisation of the triple bond is achieved via inductive effect. Also, because of our earlier results with changed regioselectivity related to the alkene in different reaction conditions, we wanted to confirm the general assumption that the regioselectivity of the alkyne stays relatively constant with respect to different reaction variables.

The chosen alkynes, a series of 1-substituted-2-hexynes, are presented in Figure 58. The oxygenated derivatives **129**-**131** were prepared from 2-hexyn-1-ol (**128**) by standard procedures. The nitrogenated derivatives **132**-**135** were prepared also from **128** by mesylation, followed by a substitution either with dimethyl amine (**132-133**) or with sodium azide, followed by reduction and functionalization of the primary amine by standard procedures (**134**-**135**). Alkyne **136** with an electron-withdrawing methyl ester was prepared from hept-3-yn-1-ol by oxidation followed by esterification. Alkyne **137** with a trimethylsilyl group, which was pursued to have a more electropositive atom at the propargylic position, was prepared by alkylation of tridec-1-yne with (chloromethyl)-trimethylsilane. For comparison, **138** was prepared as a carbon analogue of **137**. We also prepared an alkyne with both TMS- and *t*-Bu- substituents in propargylic positions in opposite ends of the triple bond, but PKRs of this compound turned out to be unsuccessful. Disubstituted alkyne **139** was prepared from but-2-yne-1,4-diol as a test to measure the directing effect of two similar substituents.

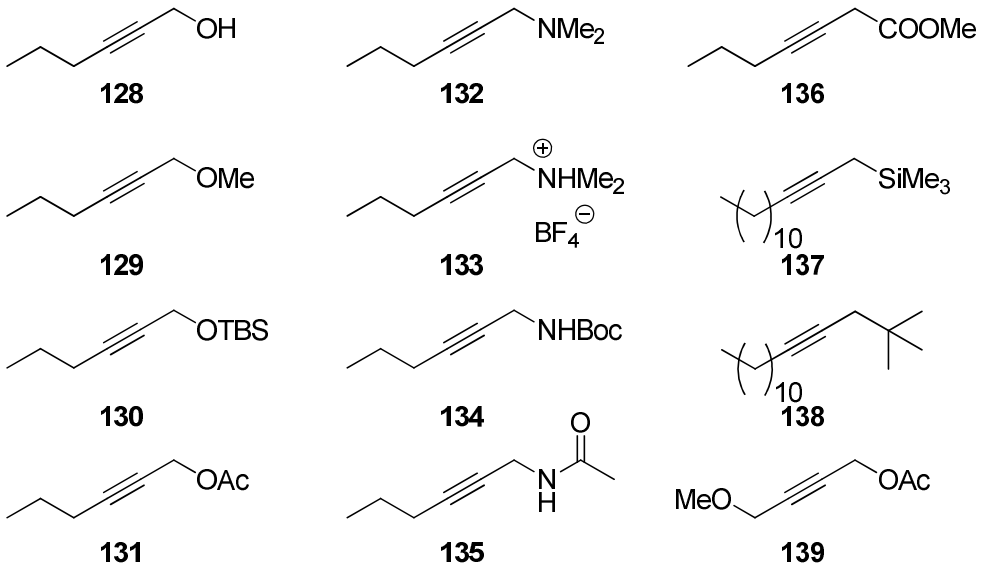
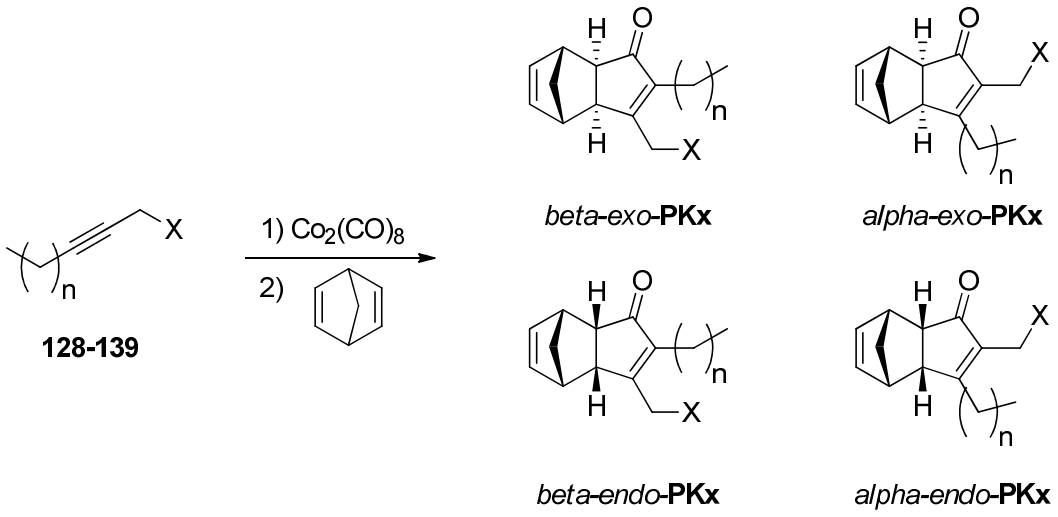


Figure 58. Alkynes chosen for this study.

The PK reactions with NBD were performed in thermal conditions at 70 °C. The crude products were chromatographed, and the ratio of the four possible PK adducts, presented in Scheme 5, was measured by NMR. In addition to the experimental study, the PKRs of these alkynes were studied computationally. Details of these calculations are presented in publication III.



Scheme 5. PKR of alkynes **128**-**139** with four possible products.

Both the experimental results and theoretical calculations supported the theory that electronic polarisation alone can result in significant regioselectivity in PKR. Experimentally, electronegative groups in a propargylic position caused β-selectivity to dominate in the reaction product distribution. This can be seen in the reactions of alkynes **128**-**136** (Figure 59). Theoretically, the carbon-carbon bond is formed with the

carbon having more electron density. The computational NBO charges indicate polarisation of alkyne, which is inductively mediated from the heteroatom. Protonation of the dimethyl amine group (**132** versus **133**) does not inverse the alkyne polarisation but intensifies it. This can be explained by the σ-bond mediated inductive effect that contrasts the π-bond mediated resonance effect that prevailed in the related aromatic amines **114** and **115** in publication II. In publication II, amine **114** provided non-selective reaction without TEA added to the reaction mixture, probably due to partial protonation of the amine. The same kind of protonation in situ in the reaction mixture might explain the unexpectedly high selectivity of **132** yielding only one PK adduct.

The electropositive group, as TMS in **137**, on the other hand, occupied the α-position. The selectivity of **137**, however, can also arise from steric reasons, as alkyne **138** also showed a clear α-selectivity. Nevertheless, NBO charges of the alkyne carbons in both alkynes **137** and **138** show bond formation to the more electron-rich carbon, resulting in both electronic and steric factors supporting formation of the same α-isomer.

Disubstituted aliphatic alkyne **139** provided a product mixture with both regioisomers almost in equilibrium. Meanwhile, despite the higher regioselectivity of acetylated derivative **131** compared to the methoxy derivative **129**, the methoxy substituent slightly dominated in the β-position in the PKR of **139**. The alkynyl NBO charges supported the outcome even though the selectivity was much lower than could be expected based on the theoretical calculations.

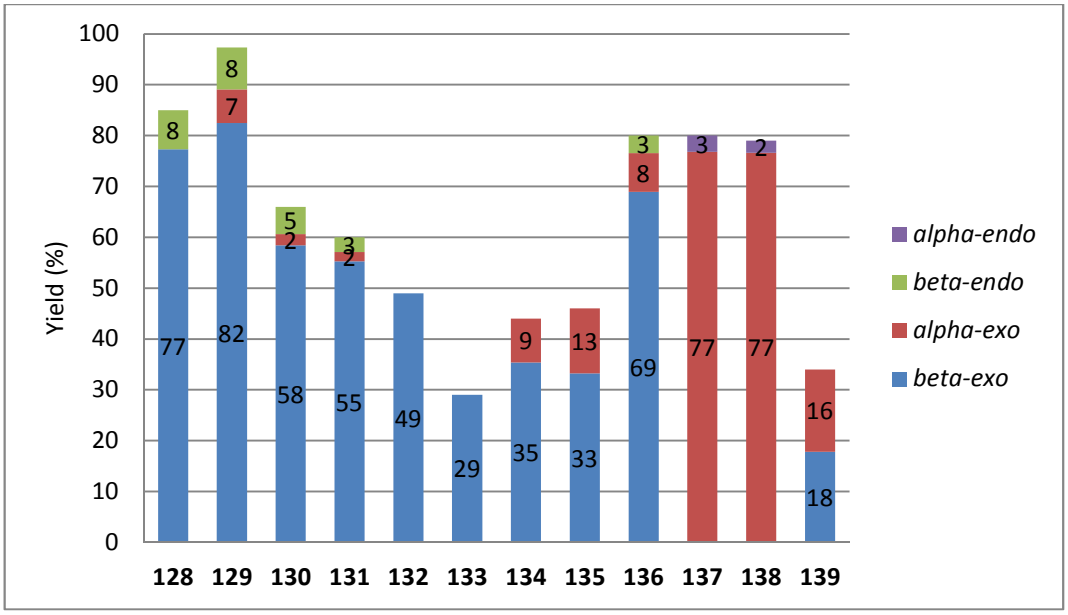


Figure 59. Product distribution in PKRs of aliphatic alkynes **128**-**139**.

In general, the polarisation and calculated NBO charges could be used to estimate the reaction outcomes qualitatively, but quantitative predictions could not be made. The difficulty in making qualitative conjectures is mostly because, unlike in aromatic systems, steric effects and different kinds of attractive and repulsive forces are usually present in aliphatic systems. By using simplified model compounds for the calculations, we were able to show the existence of an attractive force between the oxygen in the methoxy substituent and hydrogen in the NBD double bond. For the model compound, this hydrogen bond is present in both two major transition states leading to the formation of β-substituted cyclopentenone, and it is absent in other TSs. It serves as an example of a seemingly minor detail having unexpectedly large effect in regiochemistry determination.

To confirm the generalisability of our experimental results we performed the PKR of **129** in 15 different reaction conditions. The results are presented in Figure 60 and reaction c represents the standard conditions applied in reactions of other alkynes as well. We varied the amount of alkene (a-b, d), concentration of the solution (e-f), reaction temperature (g-h) and solvent (k-p). Furthermore, we also performed the reaction with MW heating (i) and with NBN as an alkene (j).

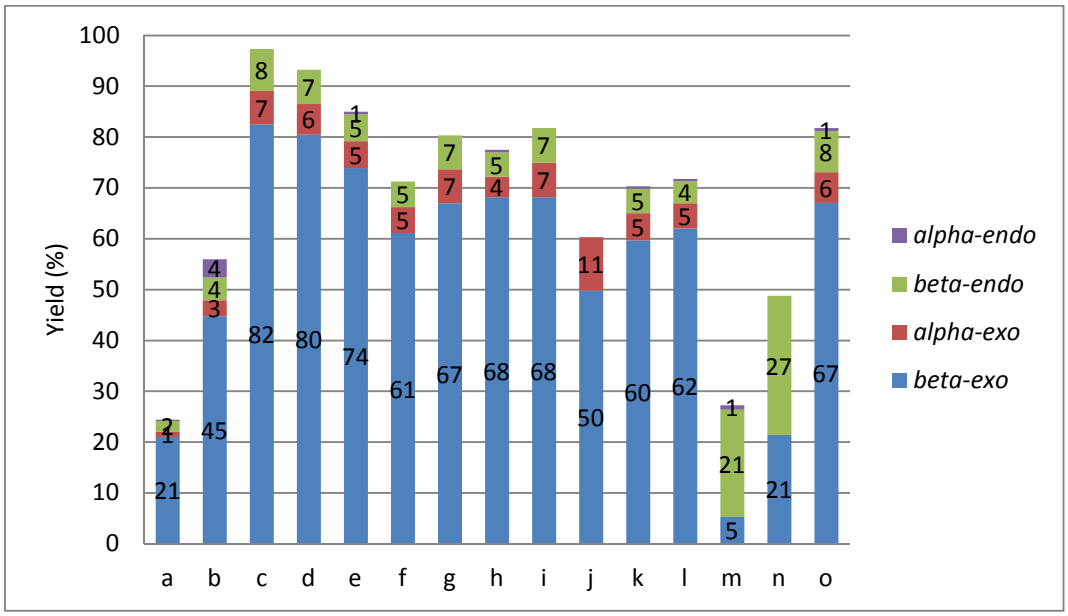


Figure 60. PKR of **129** in different reaction conditions. Standard conditions: 3 mmol of isolated alkyne-cobalt complex, 5 eq. NBD, 3 ml toluene, 70°C thermal heating. To these conditions the following variables were introduced: a-d amount of alkene: a=1 eq., b=3 eq., c=5 eq., d=10 eq.; e-f solvent amount: e=6 ml, f=1.5 ml; g-h reaction temperature: g=90°C, h=50°C; i heat source: MW (70°C); j alkene: NBN; k-p solvent: k=DCE, l=THF, m=MeCN, n=1:1 toluene/MeCN, o=9:1 toluene/MeCN.

As seen in Figure 60, the reaction conditions in general did not affect the regioisomeric ratio of the products substantially. The yields were significantly lower if smaller amounts of alkyne complex were used, and in the NBN reaction the *endo* isomers were absent. With NBN the regioselectivity was a bit lower than with NBD. The same difference in the behaviour of these alkenes in PKR has been also reported previously.[162] As an exception to the uniformity, when the reaction was realised in MeCN the major product was β-*endo* isomer, instead of the usual *exo* isomer. However, despite the fact that the reaction was relatively fast, the yield was significantly low. We tried to optimise the reaction to have a reasonably substantial source of the *endo* isomer, yet the relative amount of *endo* product decreased as toluene was added to the reaction mixture in order to increase the yields. We do not have an explanation for this unexpected *endo* selectivity, but one possible factor might be the combination of the small size and narrow, straight shape of MeCN, together with its strong ability to coordinate. Such behaviour has not been reported before.

6. Conclusions

In this study we aimed to gain more understanding of the interplay between steric and electronic factors in determining the regioselectivity of the Pauson-Khand reaction, and achieved several results related to this.

In the absence of steric effects, alkyne polarisation dictates the regiochemical selectivity of PKR. In conjugated systems, like diarylalkynes, the major isomer can usually be predicted based on general organic chemistry knowledge, keeping in mind the connection between alkyne polarisation and selectivity. EWGs and EDGs affect the outcome logically, and in aromatic systems, Hammett values can usually be utilised when estimating the polarisation of an alkyne. The NBO charges of the α-alkyne carbons correlated well with the experimental selectivity providing a useful tool in the prediction of regiochemistry.

With non-conjugated alkynes, on the other hand, electronegativity of the substituent group dictates the major regioisomer. With a lack of conjugation between the substituent and the triple bond, charge differences are created via inductive effect. The electron-donating or -withdrawing character of the group, if realised as a free electron pair or resonance stabilisation, does not have impact over sp^3-hybridised carbon. In addition to the results related to regioselectivity, we also observed the unexpected formation of an *endo* isomer as the major product while performing the PKR in MeCN.

The PK reaction of substituted alkynes is not solely governed by electronic parameters, but steric hindrance and hydrogen bonding can overrule these electronic effects. This complexity of the affecting mechanisms creates major challenges in PKR utilisation and offers still several new findings to uncover. However, PKR can be and has been used in several synthetic applications. Despite its limitations, it is one of the most powerful tools for the synthesis of five-membered rings. We have utilised it in a dexterous E-ring extension of estrone and developed an additive-free method for PKR that does not require excess of alkene. Our method saves the environment and valuable chemicals on one hand by spending only an equivalent amount of precious alkenes, and on the other hand, it also omits unnecessary chemical promoters and thereby creating less waste. By using MW in promotion, the heat is effectively transferred to the reaction, saving energy and time without affecting the selectivity of the reaction.

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