UNIVERSITY OF LATVIA
FACULTY OF CHEMISTRY

DYNAMIC KINETIC RESOLUTION OF SECONDARY ALCOHOLS

MASTER THESIS

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RĪGA
2019

ANNOTATION

Dynamic kinetic resolution of secondary alcohols. Simonas Balkaitis. Supervisor: Dr. chem. Artis Kinēns. Master's thesis contains 63 pages, 10 figures, 31 scheme, 14 tables, 1 equation, 53 literature references. Written in English.

First, secondary alcohols' racemisation by various iridium, ruthenium and iron catalysts was investigated. Next, kinetic resolution of alcohols in most suitable (for racemisation) solvents was explored. With this knowledge in hands, a new procedure for dynamic kinetic resolution was sought.

Key words: RUTHENIUM, IRIDIUM, DKR, RACEMIZATION, KR, BIRMAN, SECONDARY ALCOHOLS.

ANOTACIJA

Antrinių alkoholių dinaminė kinetinė rezoliucija. Simonas Balkaitis. Darbo vadovas: Dr. chem. Artis Kinēns. Magistrinį darbą sudaro 63 puslapiai, 10 iliustracijų, 31 schema, 14 lentelių, 1 lygtis, 53 literatūros šaltiniai. Darbas parašytas anglų kalba.

Pirmiausia buvo ištirta antrinių alkoholių racemizacija įvairių iridžio, rutenio ir geležies katalizatorių pagalba. Tuomet, racemizacijai tinkamiausiuose tirpiklių variantuose buvo tiriama alkoholių kinetinė rezoliucija. Gauti duomenys buvo panaudoti naujos dinaminės kinetinės rezoliucijos procedūros paieškose.

Raktiniai žodžiai: RUTENIS, IRIDIS, DINAMINĖ KINETINĖ REZOLIUCIJA, RACEMIZACIJA, KINETINĖ REZOLIUCIJA, BIRMAN, ANTRINIAI ALKOHOLIAI.

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ABBREVIATIONS

Ac	acetyl group
ATH	asymmetric transfer hydrogenation
Bn	benzyl group
Cp*	pentamethylcyclopentadienyl
CV	column volume
DCM	dichloromethane
DKR	dynamic kinetic resolution
DP FC	direct phase flash chromatography
EA	ethylacetate
ee	enantiomeric excess
Et_2O	diethyl ether
FID	flame ionisation detector
GC	gas chromatography
KR	kinetic resolution
LC-MS	liquid chromatography mass spectrometry
MeCN	acetonitrile
MW	microwave
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
Novozyme (435)	lipase from Candida antarctica acrylic resin
p-Cymene	1-methyl-4-(propan-2-yl)benzene
Ph	phenyl group
RT	room temperature
t-Amyl alcohol	2-methylbutan-2-ol
t-BuOK	potassium *tert*-butoxide
TEA	triethylamine
TH	transfer hydrogenation
TLC	thin layer chromatography
TMS	trimethylsilyl group
TOF	turnover frequency
Tol	toluene
Ts	tosyl group
UPLC	ultra performance liquid chromatography

INTRODUCTION

Secondary alcohols exhibit valuable biological, physical and chemical properties [1, 2, 3, 4], leading to widespread use in food and drug industry. Optically pure secondary alcohols are an important subclass of secondary alcohol fragment containing compounds. For instance, enantiopure secondary alcohols are valuable intermediates for medicinal chemistry as highlighted by key intermediates required for the synthesis of anti-cancer drugs crizotinib [5a,b] and lorlatinib [5c] (fig. 1). High demand for enantiopure alcohols has attracted our attention and we decided to investigate their synthesis.

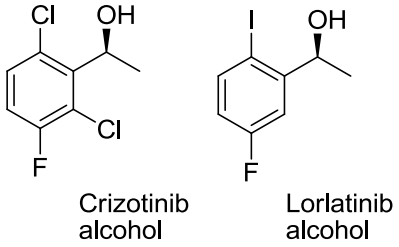
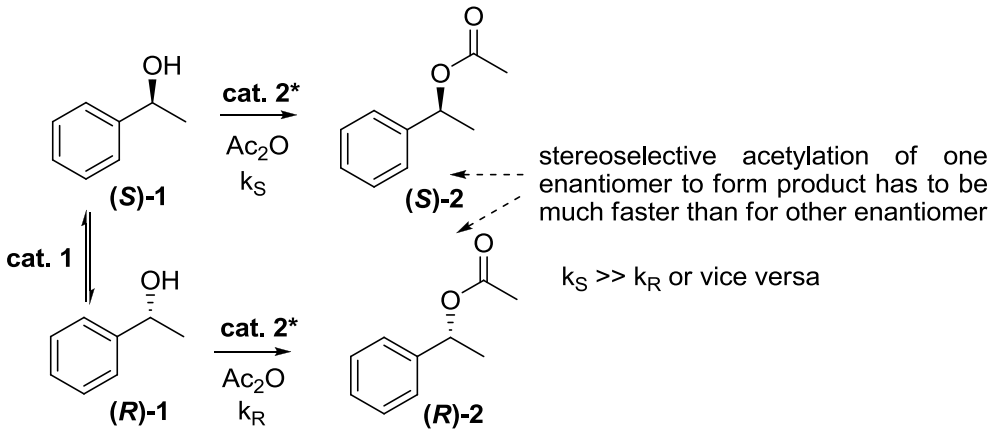


Figure 1. **Building blocks for Crizotinib and Lorlatinib.**

Various methods exist to obtain the alcohols in enantiopure form, for example, ketone reduction, followed by chiral chromatographic separation, which is problematic on industrial scale. Another choice is asymmetric reduction or asymmetric transfer hydrogenation, which ideally yields single enantiomer, whereas in practice products are enantiomerically impure and require further purification [6]. Yet another option is employment of enzymes (ketoreductases) as enantioselective reduction catalysts [7], however they perform well with only certain selected compounds, thus optimisation and even adjustments to enzyme must be performed. Dynamic kinetic resolution is a prominent method where a combination of two catalytic systems in one flask is used – transition metal catalysed racemisation of secondary alcohol coupled with enantioselective derivation of racemic secondary alcohol. This method theoretically allows converting racemic alcohol to enantiopure product in excellent yields, yet both cycles should not interrupt each other as interruption of racemisation cycle would lead to KR.

1. LITERATURE REVIEW

Dynamic kinetic resolution (DKR) typically employs a two-catalyst system (scheme 1) – one to racemise (**cat. 1**) and another one (**cat. 2***) to enantioselectively acylate the substrate. Below is represented such case: *S* enantiomer of 1-phenylethanol is acetylated faster by catalyst **cat. 2*** (* here to signify that this is single enantiomer), thus (*R*)-1-phenylethanol begins to build up as in kinetic resolution (KR), in order to retain selective KR – racemisation of enantioenriched alcohol by **cat. 1** becomes crucial. Virtually, at any time of reaction ee of 1-phenylethanol should be approximately zero. Consequently, highly selective towards one enantiomer acylation catalyst and a rapidly racemising catalyst are necessary for a successful DKR.



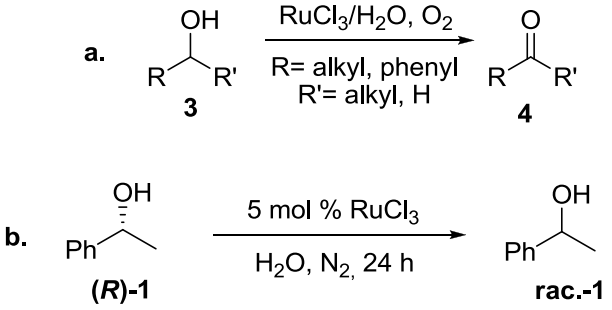
Scheme 1. **General DKR example**.

1.1 Racemisation – main mechanisms and catalyst types

Racemisation is transformation of enantiopure or enantioenriched compounds to racemates. It can happen spontaneously as a result of keto-enol tautomerisation leading to unwanted racemisation of various compounds. However, in some cases it is highly sought-after. For instance, racemisation of secondary alcohols is much more problematic in cases where racemisation inducing groups do not exist in the molecule. Then one must apply either oxidation with subsequent reduction or to use redox catalysts, which can perform both reactions in a single flask. Consequently, many complexes containing Rh, Pd, Ru, Al, V [8], Ti [9] metals and even transition metal free catalysts [10] have been investigated. It is important to pinpoint that most of them participate in redox at elevated temperatures.

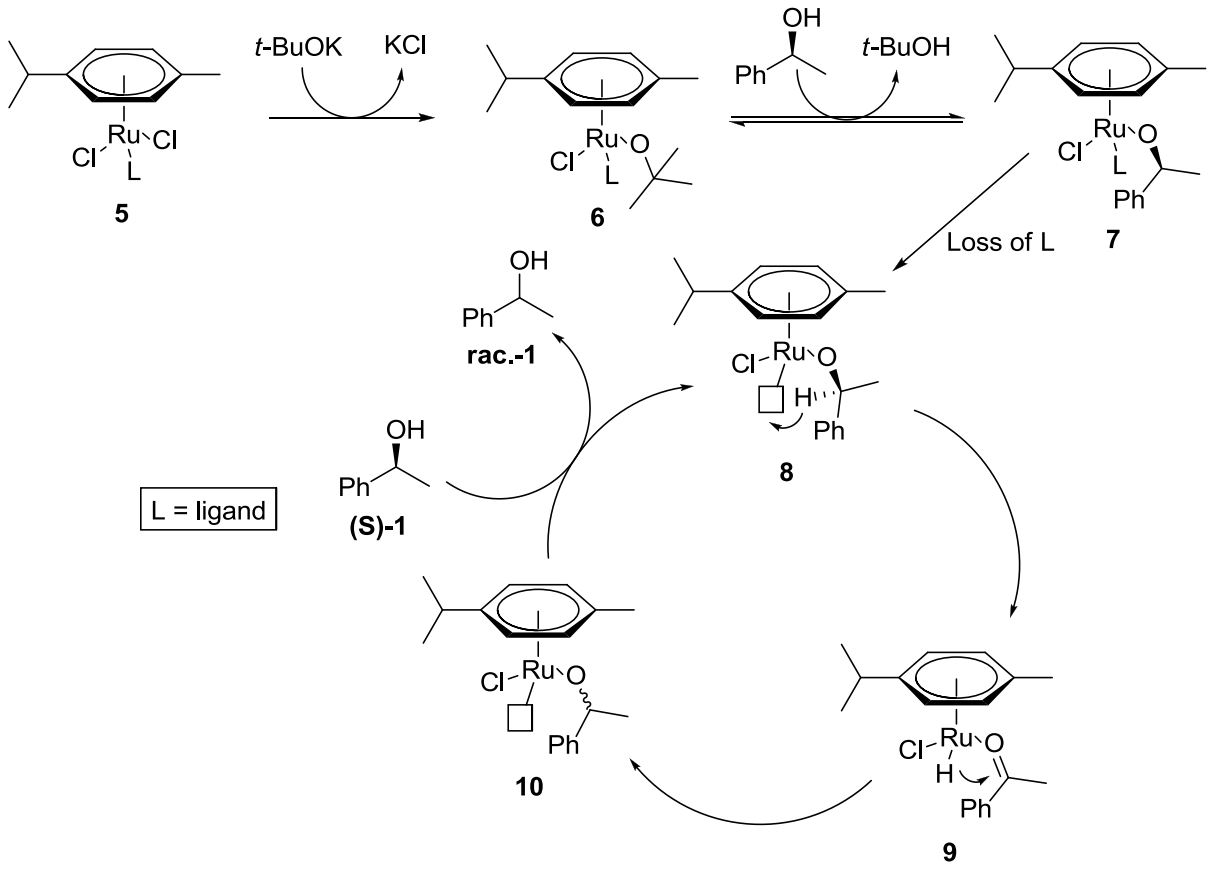
Out of the mass, ruthenium catalysts are amongst the most popular and most studied. Possibly the simplest – ruthenium (III) chloride – catalyst was reported by Wolfson's group

[11]. Under aerobic conditions at 90°C ruthenium (III) chloride was able to oxidise primary and secondary alcohols in water (scheme 2a). Upon further investigation it was noticed that under inert atmosphere the same catalytic system was able to racemise (*R*)-1-phenylethanol, however, information provided in the article was scarce.



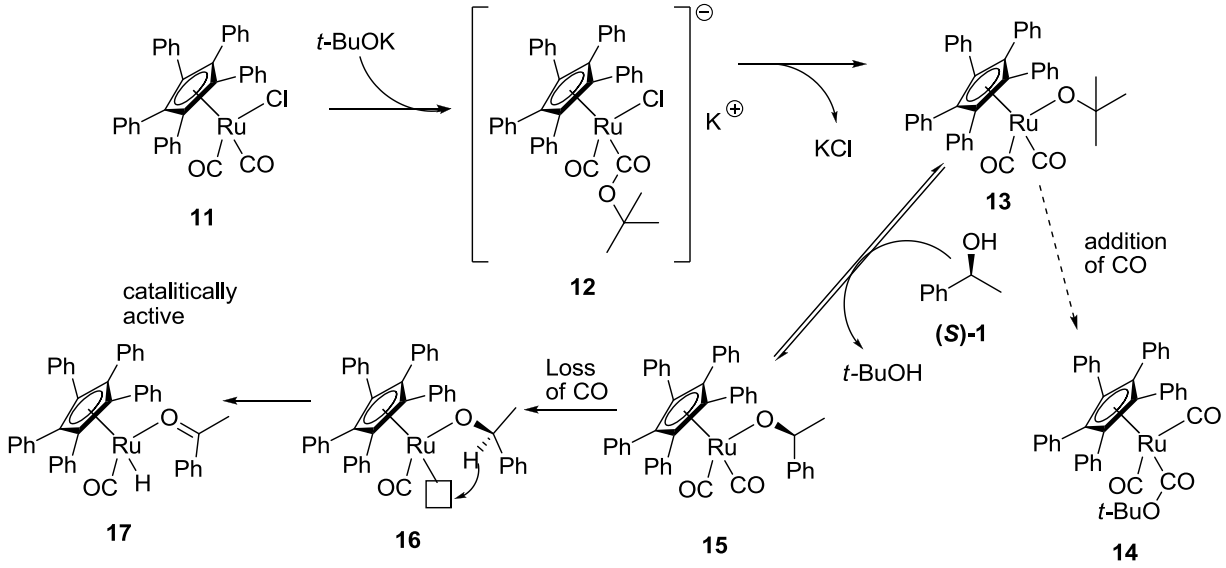
Scheme 2. **Aerobic oxidation and anaerobic DKR of secondary alcohols.**

Ruthenium (III) chloride is poorly soluble in organic solvents, hence various organo-ruthenium complexes are usually employed as increased solubility in turn improves reactivity. Ruthenium p-cymene complexes are amongst the most widely available and used. In depth mechanistic investigations of racemisation with ruthenium *p*-cymene complexes were reported by group from China, lead by Li and Hou who have performed synthesis of several ruthenium p-cymene ligated complexes and tested them in racemisation reactions [12]. Mechanistic studies and quantum-chemical density functional theory (DFT) based calculations were in accordance with each other and allowed to propose detailed reaction mechanism (scheme 3). Ruthenium complex **5** is activated by expelling chloride and attaching *tert*-butoxide in ligand exchange. Activated ruthenium species **6** can then undergo oxo-ligand exchange to form **7**. Catalytic cycle begins upon loss of ligand L during formation of **8**. 1-Phenylethanol is oxidised and subsequently reduced by inner-sphere mechanism, yielding racemized product. Inner-sphere mechanism is β-hydride elimination from alkoxide in **8**, leading to formation of ruthenium hydride species with ligated ketone **9**. Upon equilibrium – ruthenium hydride regenerates alkoxide ligand by reduction of ketone, however, in this case alkoxide can obtain any configuration – thus complex **10** becomes racemised. This type of mechanism is referred as inner-sphere mechanism.



Scheme 3. **Inner-sphere racemization mechanism.**

Ruthenium cyclopentadienyl complexes are another well established subclass of organo-ruthenium complexes. A very stable and reactive Bäckvall's **11** – a widely used catalyst – belongs to ruthenium Cp* complex subclass. Even though widely used, it took nearly a decade until Bäckvall was able to shed more light on operational mechanism of his ruthenium catalyst [13]. Activation of catalyst **11** by *tert*-butoxide takes place by carbonyl attack and complex **12** is formed. As soon as KCl precipitates out – activated complex **13** is obtained. It was shown, that in CO atmosphere – catalytic activity is inhibited as complex **14** forms. In inert atmosphere, complex **13** can undergo ligand exchange – *tert*-butoxide is expelled as *tert*-butanol while a newly formed *sec*-alkoxide ligand is introduced **15**. Complex **15** it-self is inactive towards racemisation as β-hydride elimination cannot happen. Initially it was hypothesised that η^5-η^3 ring slippage of Cp* takes place to free coordination site on ruthenium, however, authors were unable to verify or disprove experimentally, thus detailed DFT calculations were performed. Calculations supported a conclusion that loss of CO ligand (**15** to **16**) is a more energetically favourable path of mechanism and as soon as **16** is formed the inner-sphere mechanism (through **17**) follows (scheme 4). What is more, catalyst **11** is of high importance as it boasts of high stability under aerobic conditions, thus leading to it's vide-spread use.



Scheme 4. **Latest activation mechanism of the Bäckvall's catalyst**.

Several years after Bäckvall catalyst's introduction Koreans Kim and Park reported a similar structure and highly efficient room temperature racemisation catalyst **18** (fig. 2), it was made commercially available yet complex is unstable in presence of oxygen [14a], thus it has to be stored and used under inert atmosphere. In their subsequent article [14b] authors installed –OBn in **19** instead of –NH*i*-Pr in **18**, thus leading to a more stable catalyst that can be stored under air. While **18** could racemise secondary alcohol in less than 1 h, it took around 2.5 h with **19** until complete racemisation of (*S*)-1-phenylethanol could be achieved. Next it was shown that various benzylic and aliphatic alcohols can be successfully racemised. In order to promote **19** authors attached it to polymeric moiety and proved that it can be re-used at least three times, making it a catalyst of high interest. Apparently, compound **19** was not commercialized.

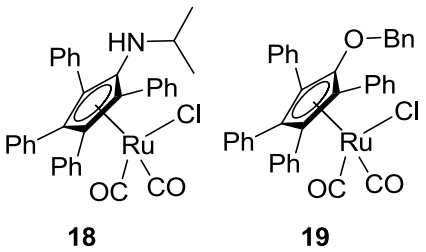
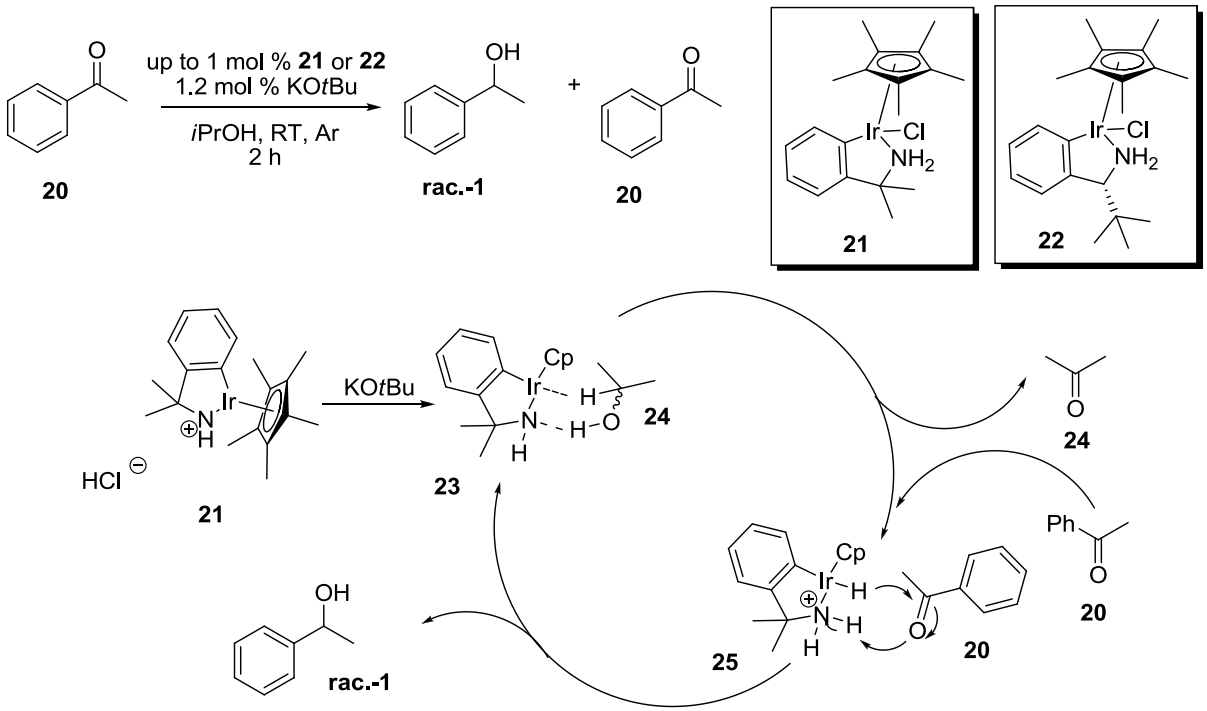


Figure 2. **Catalysts introduced by Koreans Park and Kim.**

Aside from inner-sphere mechanism catalysts, many more different types of catalysts have been reported and their operational mechanisms suggested [15], including the dihydride mechanism for Noyori's catalysts [16]. Others have reported heterogeneous racemisation catalysts, for example, the use of Ru deposited Al_2O_3 [17]. Another commonly accepted type

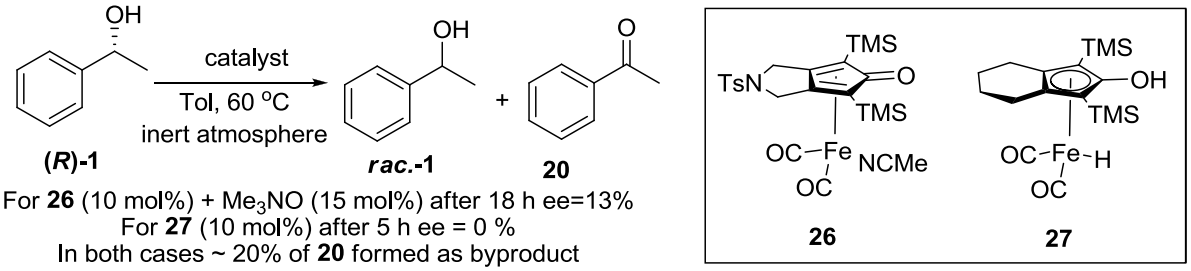
of mechanism is outer-sphere mechanism, for which a great example are highly efficient asymmetric transfer hydrogenation (ATH) Ir catalysts **21** and **22** (scheme 5) that were proposed by Takao et. al. [18a,b]. Transfer hydrogenation (TH) is a concept when hydrogen is abstracted from one alcohol (called sacrificial, usually *iso*-propanol) by a transition metal catalyst, hydride form of the catalyst is formed and then this catalyst hydrogenates the ketone to form another alcohol. It is an equilibrium reaction hence sacrificial alcohol is used in high excess (practically as a solvent) compared to ketone. It was shown that reduction can be successfully performed even at -30°C, highlighting activity of **21**. Both catalysts are thought to racemize in a dihydride – outer-sphere mechanism (scheme 5) In essence, complex **21** is activated by potassium *tert*-butoxide by formation of 16-electron complex **23**. Due to electron deficiency in **23** – sacrificial alcohol **24** first coordinates, it is then oxidised to ketone **24** and dihydride **25** is formed. This dihydride then upon equilibrium conditions can transfer hydrogen back to **24** or to **20**. Reduction of **20** leads to racemic **1**. While inner-sphere mechanism requires free coordination site for alkoxide to attach so that intramolecular redox could begin, the outer-sphere mechanism relies on six-membered intermolecular redox. Theoretically, any ATH (or TH) catalyst under certain conditions can be employed as a racemization agent. What is more, it is usually applied with lower catalyst loadings (up to 1 mol %) than ruthenium catalysts (typically 5 mol %), thus balancing out the price.



Scheme 5. **TH from isopropanol to acetophenone.**

On the other hand, much cheaper transition metals can as well be employed. A rather recent (2016) article by Rueping et al. introduced the first application of iron-based catalysts

in the race for faster racemisation [19a]. Synthesis of these complexes (discussed in detail in chapter 2.1) and application in reductive amination was first reported three years earlier by Renaud and Poater [19b]. Two best iron catalysts **26** and **27** and their reactivity is shown below (scheme 6), it is important to note the need to use inert atmosphere. It was measured, that formation of ketone **20** takes place in substantial amounts, however, authors did not suggest any workaround to this issue.



Scheme 6. **Iron complexes catalysed racemisation.**

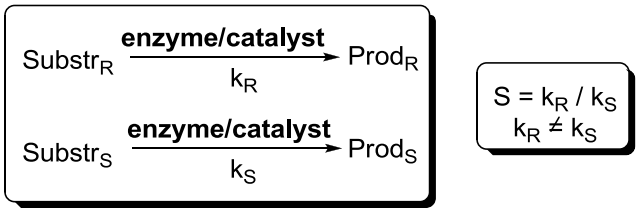
Each year many more new catalysts are introduced. Rapid room temperature or sub-room temperature racemisation continues to be an active field of investigation. And even though some of the mechanisms are known, generally, nobody can tell if any catalyst will perform well a priori to testing it as no uniformly accepted set of rules exists. Thus, it remains important to test as many complexes as possible and evaluate their suitability for specific set of conditions.

To conclude, a wide scope of catalysts was reviewed and selected ones were presented. Ruthenium complexes are the biggest group with several well known rapid and efficient catalysts. Iridium complexes have potential economic disadvantage, however, they can be of higher activity than ruthenium complexes. Iron compounds are of high interest due to their low price and safety. Thus, all these complexes must be employed in research of DKR.

1.2 KR – mechanism and applied catalysts

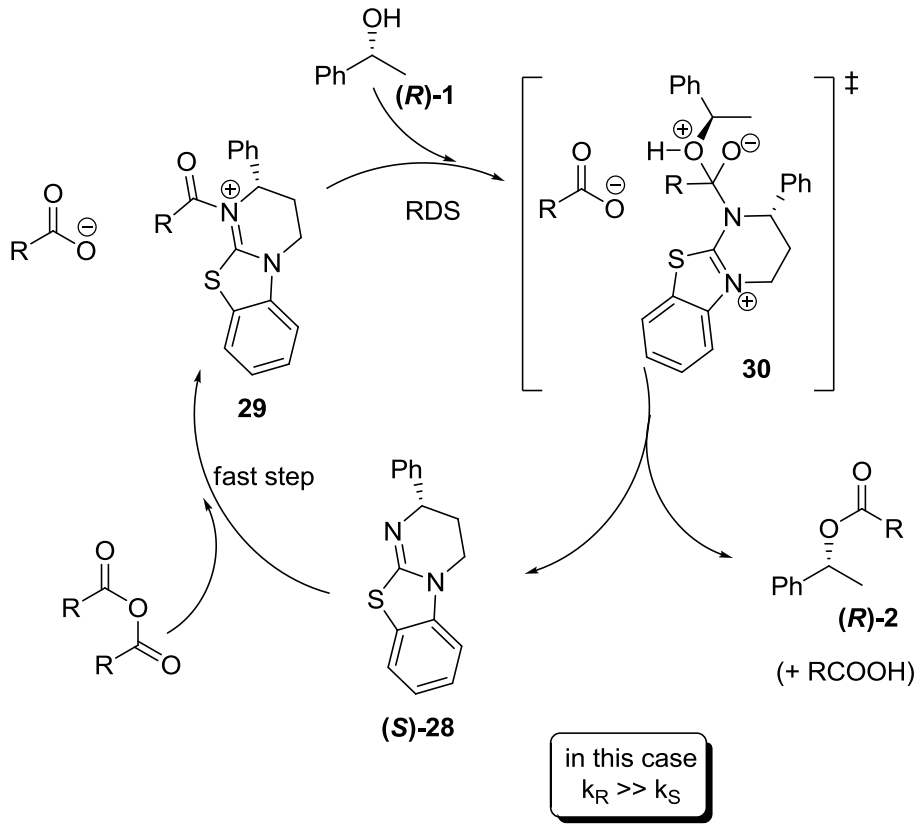
Kinetic resolution – similarly to racemisation/transfer hydrogenation – is a broadly researched field. Over decades, initial observations of catalytic acylation reactions have lead to chiral acylation catalysis. Chiral acylation catalysts, similarly to enzymes, can distinguish between different enantiomers and provide enantioselective acylation. In practice, both enantiomers are acylated but at different rates (scheme 7). Slower reacting enantiomer has a higher transition state energy than the faster reacting enantiomer. Thermodynamics states that at lower temperature the system has less energy, hence the smaller transition state energy reaction will be more favoured, in turn selectivity of acylation usually can be improved by

lowering the temperature. The field of KR now employs both – enzymatic catalysis and asymmetric organocatalysts – to fulfil the high demand of enantiopure materials. Due to abundance of natural sources, enzymes constitute an important part in resolution of secondary alcohols. Numerous lipases have been employed for this matter [20]. However, solubility issues and the need to screen multiple enzymes for certain alcohol remain as major drawbacks. The search for more general catalysts led various researchers to investigate synthetic catalysts in more detail.



Scheme 7. **General scheme of KR.**

Nucleophilic catalysts containing nitrogen, sulphur and phosphorous [21a-c] atoms have been reported. DMAPs and amidines are well established nitrogen based Lewis-base catalysts. Birman and co-workers introduced and thoroughly researched amidine based Lewis-base catalysts (ABCs) [22]. ABCs, especially (*S*)-**28**, proved to be very selective and active catalysts for KR of secondary alcohols. As a specific example with (*S*)-**28**, kinetic resolution by nucleophilic catalysts requires catalyst **28** to attack acylating reagent in order to form cationic complex, such as **29** (scheme 8). Cationic complex is necessary to alleviate alcohol addition to carbonyl as otherwise alcohol and acylating reagent would not react or reaction rate would be utterly slow. Alcohol adds to carbonyl via a tetrahedral diastereomeric transition state **30**, which is responsible for enantioselectivity – one enantiomer forms a slightly higher energy transition state than opposite enantiomer (thus, $k_R >> k_S$ or vice versa) and this energy difference determines selectivity factor of the catalyst [23]. Selectivity factor (S) is the ratio between k_R and k_S (or vice versa) rate constants, it is a numerical value useful for comparison of catalysts and for evaluation of catalyst suitability for certain set of reaction conditions. Selectivities can be easily calculated with knowledge of ee of starting materials or ee of products and conversion (eq. 1).



Scheme 8. **Mechanism of kinetic resolution with Birman's catalyst (*S*)-28.**

$$S = \frac{\ln[(1 - C) \cdot (1 - ee)]}{\ln[(1 - C) \cdot (1 + ee)]}$$

C – conversion, ee – enantiomeric excess of alcohol or ester

Equation 1. **Selectivity calculation formula.**

Connon's and Fu's groups devoted their attention to chiral DMAP derivatives. Connon's group was working on 4-pyrrolidino pyridine scaffold with proline based substituent at 3rd position of the pyridine [24] (fig. 3). KR reactions with Connon's catalyst, isobutyric anhydride and benzylic or aliphatic alcohols in DCM achieved selectivities ranging 2.7–10.1 in 6 h at room temperature. When this catalyst was applied at -78 ^{o}C, reactions achieved 10.8–20.0 selectivites and required 24 h. Whereas Fu went on to develop a DMAP-ferrocene complex which, pleasingly, boasts very high selectivity factors (up to S = 70) [25] (fig. 3). Reactions are performed in *t*-amyl alcohol with acetic anhydride and TEA as general base. Benzylic, aliphatic, allylic and propargylic substrates are suitable. High catalytic activity and enantioselectivity arise from electron rich DMAP unit and from substantial shielding on one side of DMAP, forcing the non-matching enantiomer to build-up and efficiently transferring acyl group onto matching enantiomer.

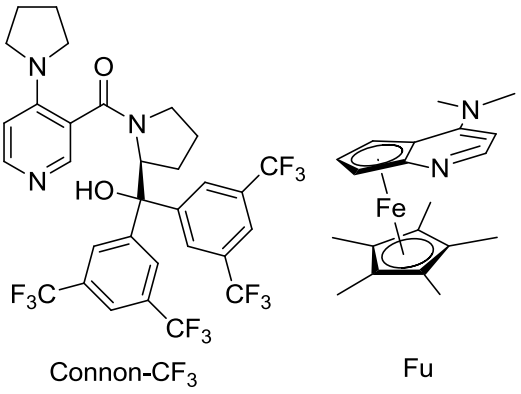


Figure 3. **Connon and Fu catalysts.**

Overall, out of multiplicity of KR catalysts several important cases were reported in this review. Generally, acylation reactions follow similar catalytic mechanism. Differences in catalyst substitution lead to differences in selectivities. Above mentioned catalysts are potential candidates for DKR due to their high enantioselectivities and, thus, should be tested.

1.3 DKR – enzymatic vs. non-enzymatic

KR has a potential to provide a 100 % ee product with 50 % yield limitation, which is a major disadvantage. On the other hand, a combination of racemisation and KR has a potential to provide a 100 % ee product in 100 % theoretical yield. Hence, numerous accounts on chemoenzymatic DKR began appearing around 2000's. Park and Kim from Korea, Bäckvall from Sweden and many other groups attempted to combine various immobilized lipases in combination with known racemisation catalysts in the pursuit of deracemisation. Shvo's catalyst (fig. 4) in chemoenzymatic procedure was reported by Bäckvall in one of the first papers [26], however procedure had inherited problems due to slow reactivity of Shvo's catalyst (several days reaction at 70 ^{o}C). Later Park and Kim announced a slow DKR which would take even up to weeks, while racemisation with their catalyst was due in 30 min [27]. Clearly it was not an easy feat and after a while Bäckvall combined his Ru catalyst with Candida antarctica lipase B (CALB) to accomplish rapid (3-72 h, substrate dependant), robust and successful chemoenzymatic DKR [28a,b]. Overall, there is a plethora of factors limiting the applicability of chemoenzymatic DKR: dependence on complicated structure enzymes, limited suitable substrate scope, high sensitivity of enzyme on various reaction conditions and even on what matrix (or support) the enzyme was immobilised [29].

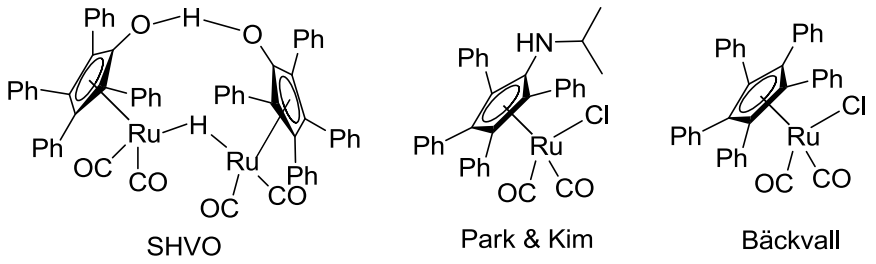
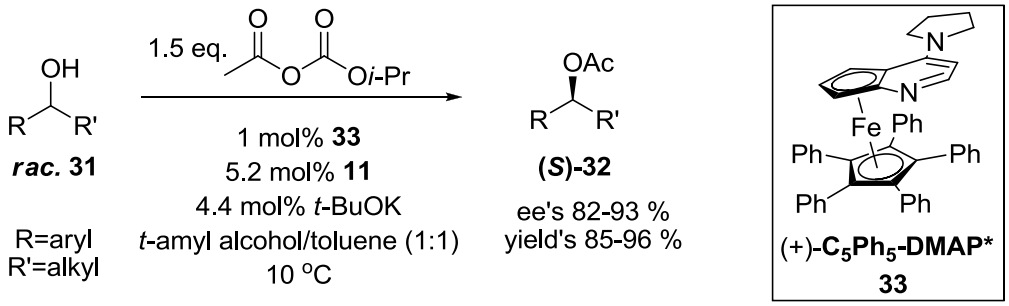


Figure 4. **Ruthenium racemisation catalysts.**

Issues associated with chemoenzymatic DKR call for an organocatalytic DKR. However, up to date there has been only one article about catalytic DKR, employing the above mentioned Bäckvall's ruthenium catalyst and Fu's iron based enantioselective acylation catalyst. It was reported in 2012 by Fu et al. [30]. This was a proof of principle that it is possible to achieve DKR by two different catalytic nonenzymatic systems (scheme 9), however reaction procedure is arduous (syringe pumping for days, synthesis of acyl donor and it's purification by vacuum distillation) and reaction set-up is sensitive to air, substrate scope was rather limited to simple aryl alkyl secondary alcohols. Authors began research with a much simpler reaction setup – acetic anhydride was employed. However, it was observed that the intended DKR rapidly stops racemising and turns into KR. In essence, some species present in reaction mixture were inactivating ruthenium complex. A throughout analysis revealed a serious problem – acetate ions were inactivating racemisation catalyst. To verify this, sodium acetate was introduced to a solution of *t*-BuOK activated Bäckvall's catalyst. The newly formed stable ruthenium acetate complex was purified and introduced into racemisation reaction flask, racemisation was not observed. This has lead to investigation of alternative acylating reagents. Only acyl carbonates (which are commercially unavailable) proved to be compatible with ruthenium catalyst in this DKR setup. Still, in order to improve selectivities a *t*-amyl alcohol – toluene (1:1) solvent mixture at 10 ^{o}C had to be used. Lastly, slow syringe pumping was introduced to overcome acetyl carbonate's disintegration and to limit acetylation rate. All these efforts afforded successful non-enzymatic DKR for a narrow scope of compounds with good to excellent yields (85 – 96 %) and 82 – 93 % ee values (scheme 9).



Scheme 9. **Dynamic kinetic resolution reaction established by Fu.**

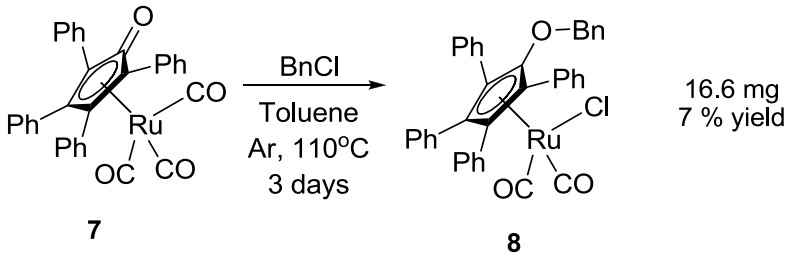
To sum up, simply KR is an uneconomic choice in most of the cases, chemoenzymatic DKR is a viable solution in specific cases as it allows achieving high yields and high ee values. Non-enzymatic DKR with more predictable chemistry and easily modifiable acylating catalyst suitable for a broad scope of substrates would be a significant advancement in the field. Thus, to achieve non-enzymatic DKR for a broad scope of substrates, a wide range of reported racemisation and acylation catalysts in combination with available acylating reagents must be thoroughly tested.

2. RESULTS AND DISCUSSION

The demand for enantiopure secondary alcohols and only a single non-enzymatic DKR procedure (requiring: syringe pumping, long reaction times, pre-synthesis of acetylation reagent and the use of glovebox and inert atmosphere, limited scope) provided by Fu fuelled our interest. DKR method is currently underdeveloped due to problem raising inhibition of one catalytic cycle by another cycle – racemisation is halted by carboxylates, as was shown by Fu. We hypothesised that rather broad scope of existing racemisation and acylation catalysts could eventually lead to a better DKR procedure. For this reason, a stepwise approach was adopted. Initially, it was search for best racemizing and acetylating catalysts. Followed by investigation of possible inhibition of racemisation cycle by other species (existing in DKR setup). Finally, attempts to combine the gained knowledge in order to build a successful non-enzymatic method. This all will be represented in separate subchapters to follow. Commercially available catalysts were purchased and those that were of high interest but commercially unavailable were synthesised. (*R*)-1-phenylethanol – a cheaper and less specific representation of alcohols seen in introduction (fig. 1) was chosen as model substrate.

2.1 Synthesis of racemisation catalysts

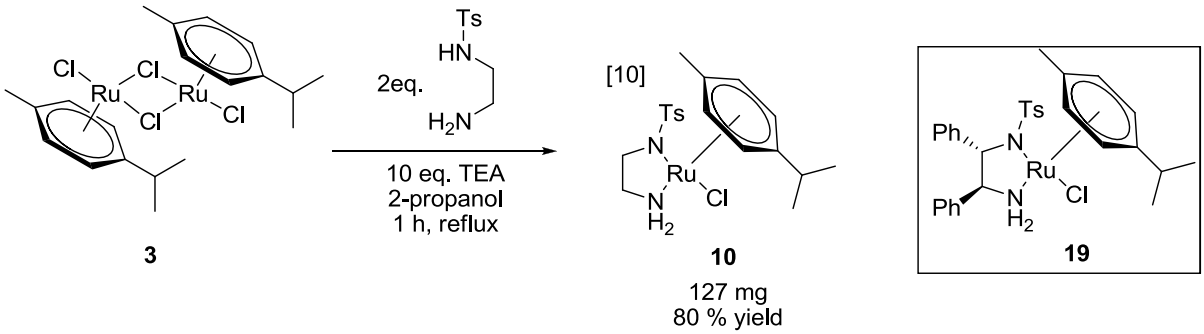
At first, our interest was caught by reportedly air-stable *O*-alkyl(tetraphenyl)cyclopentadienyl ruthenium complexes [14b]. According to authors, *O*-benzyl derivative was superior to other catalysts tested in this article. Synthesis of **8** was performed by repeating original procedure (scheme 10), however, reaction did not proceed as well as reported and after purification by direct phase flash chromatography only 16.6 mg of target compound **8** were obtained (7 % yield instead of reported 65 %). This was enough to perform several test reactions.



7 **8**

Scheme 10. **Synthesis of (*O*-benzyl(tetraphenyl) cyclopentadienyl) dicarbonyl ruthenium (II) chloride.**

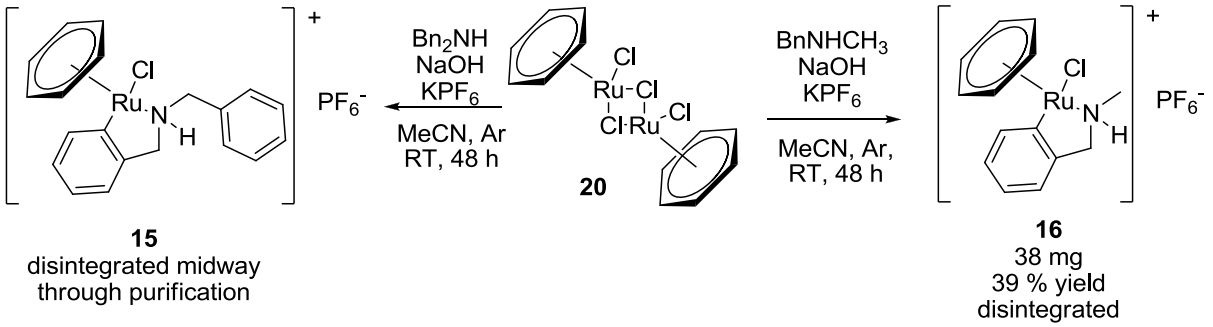
Next, it was hypothesised that high TOF asymmetric transfer hydrogenation catalyst **19** (scheme 11) by Noyori [16] could be deprived of chiral centres (scheme 11, compound **10**) and employed as racemisation catalyst. Apparently, this idea has already been investigated back in 2002 by Sheldon [31], hence catalyst synthesis was performed by following the reported procedure (scheme 11). Attempt to reproduce the original method was unsuccessful as reaction mixture became dark and contained unidentified mixture of compounds. Contrary to the reported procedure catalyst **10** was successfully obtained only after the reaction was performed under Ar atmosphere. Reaction mixture, when under Ar, obtained the red colour and after reflux and purification 127 mg of compound **10** were collected with increased yield (80 %, compared to 66 % in the original procedure).



Scheme 11. **Synthesis of (*N*-*p*-toluenesulfonylethylenediamine) (*p*-cymene) ruthenium (II) chloride (10) and structure of Noyori catalyst 19.**

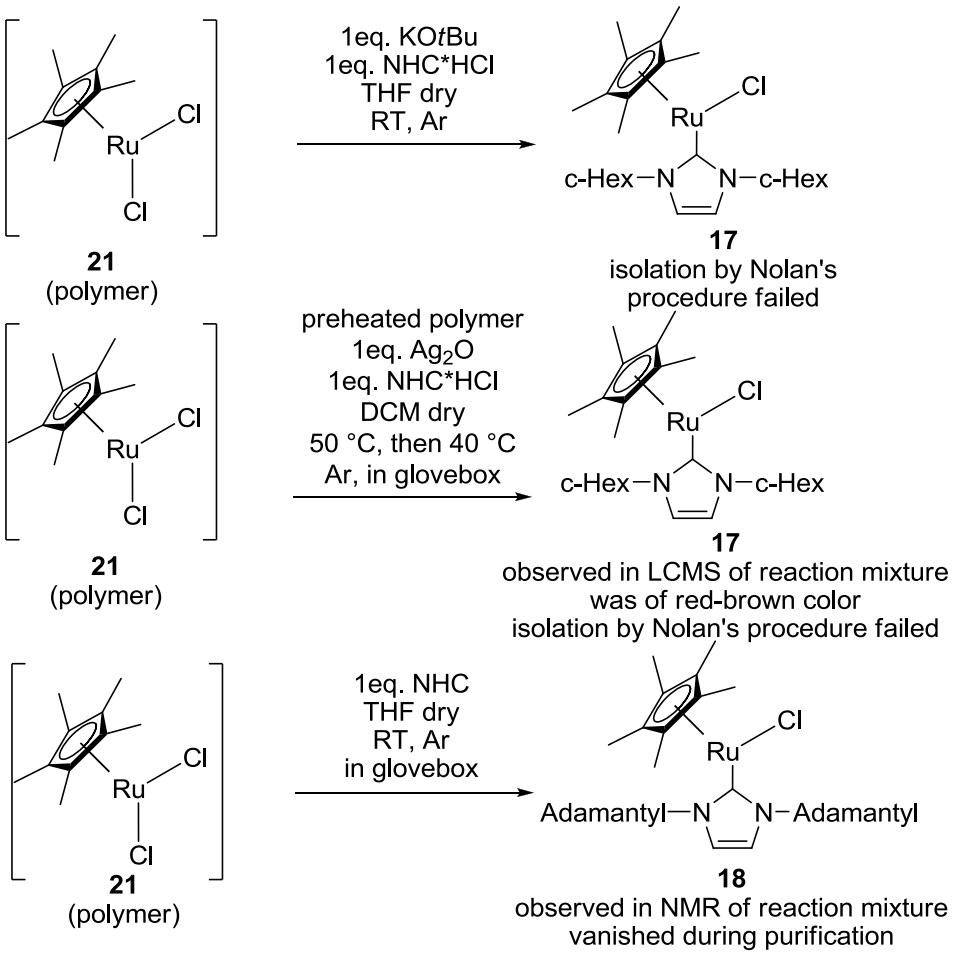
Vries and Feringa published an article on asymmetric transfer hydrogenation and racemisation with examples of η^6-benzene ruthenium complexes [32a]. As one ruthenium catalyst was applied for racemisation it immediately caught our attention because we were interested to compare Cp*, *p*-cymene and benzene ligated ruthenium complexes. Several years before Pfeffer reported a one step synthesis for catalyst **16** [32b] (scheme 12). Thus, we set out to perform syntheses with two different amines – dibenzylamine and benzylmethylamine. As soon as reaction with dibenzylamine was complete, reaction mixture was filtered and solvent was evaporated by reported procedure while trying to maintain lowest possible exposure to air (working fast during these procedures), unfortunately, the yellow residue turned dark and a slight odour of benzaldehyde appeared, compound **15** was not observed. In contrast, reaction with benzylmethylamine was successfully filtered, solvent was removed, solids where purified by dissolving them in MeCN and filtering over neutral alumina column. As yellow fraction was collected and solvent was removed – 38 mg (39 %) of compound **16** was collected. Unfortunately, the compound was unstable in the air even in solid phase and shortly after purification started disintegrating in the flask to form green solids (NMR sample as well turned green before NMR was completed, thus product could not

be confirmed), benzaldehyde smell was noticeable. Based on appearance of benzaldehyde smell and general ease of oxidation of benzylic position it was assumed that these catalysts were, most probably, inherently prone to oxidation and disintegration due to presence of unsubstituted benzylic position.

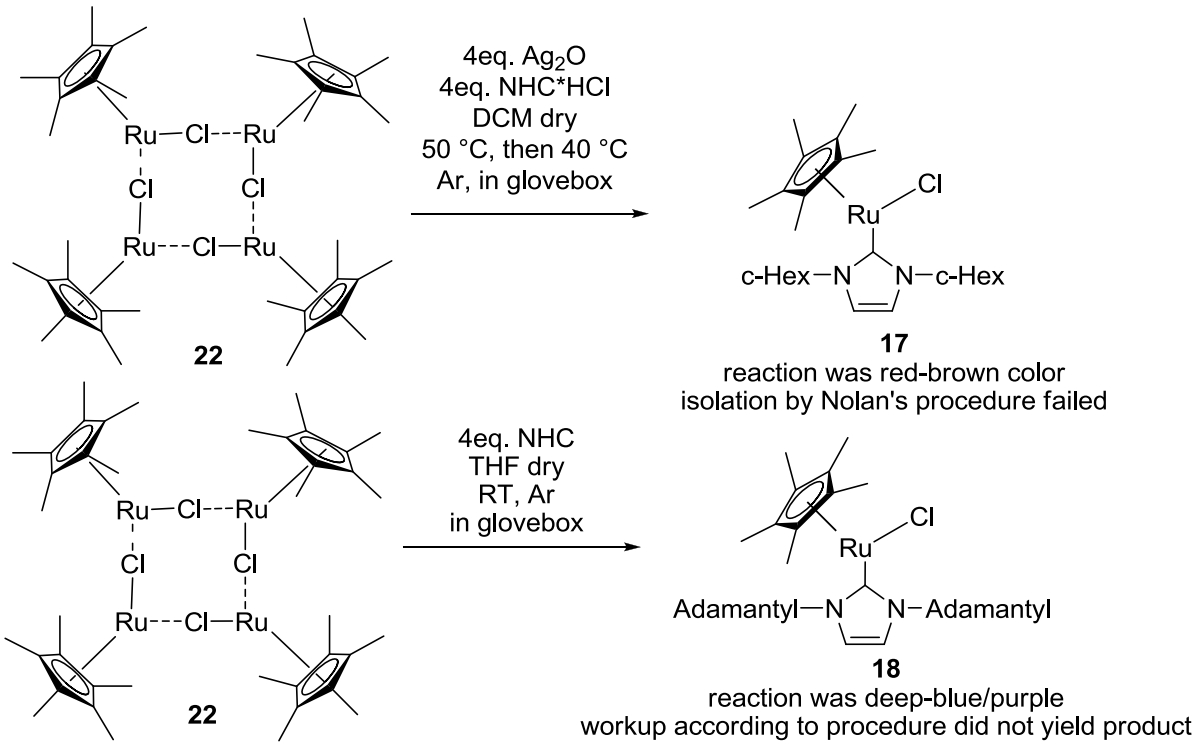


Scheme 12. **Synthesis of η^6-benzene ruthenium complexes.**

Last efforts towards synthesis of ruthenium complexes were devoted to persistent carbene ruthenium complexes. N-heterocyclic carbene (NHC) ruthenium Cp* complexes were of interest due to high electron density which could lead to faster racemisation. Nolan's catalysts **17** and **18** (scheme 13) [33a] were shown to perform rapid racemisation at room temperature [33b]. Hence, **17** and **18** had to be synthesised in order to compare them with other racemisation catalysts. We had ruthenium Cp* polymer **21** and NHC hydrochlorides in stock, thus we began by experimenting with these as starting materials (authors originally used free NHC's and **22**). To generate free NHC silver (I) oxide procedure from Joó [34a] and potassium *tert*-butoxide procedure from Arduengo [34b] were used. As ruthenium polymer decomposes to tetramer at elevated temperature we deliberately heated it for one experiment with heat-gun. Unfortunately, all efforts went to no avail (scheme 13) as ruthenium polymer had poor solubility and attempts to generate free NHC *in-situ* failed. As polymer **21** failed, we changed to ruthenium tetramer **22**. Two more experiments were performed (scheme 14), one with NHC hydrochloride and *in-situ* generation of free NHC to verify if this generation was problematic. Indeed, reaction mixture did not obtain the deep blue colour that was reported be Nolan and product was not isolated, thus proving the need to use free NHC. When free adamantyl-NHC was combined with ruthenium tetramer – the deep blue colour was seen, formation of complex was observed in ^{1}H NMR of reaction mixture, however, purification was unsuccessful and catalyst was not obtained.

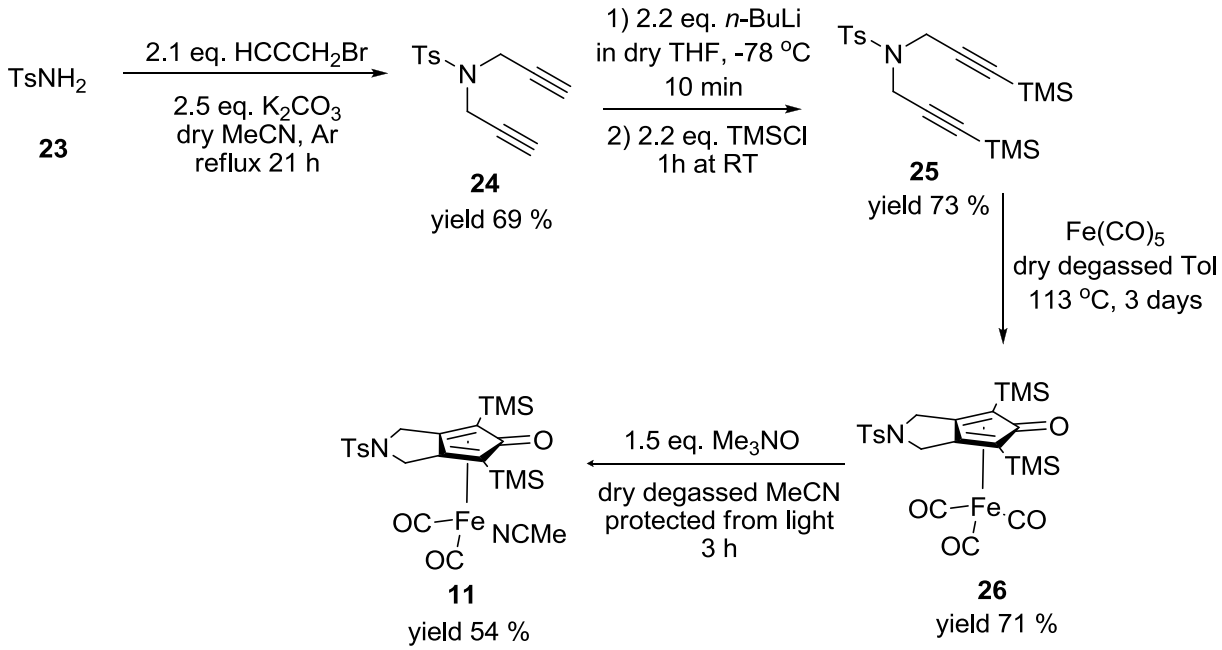


Scheme 13. **Experiments with ruthenium polymer.**



Scheme 14. **Experiments with ruthenium tetramer.**

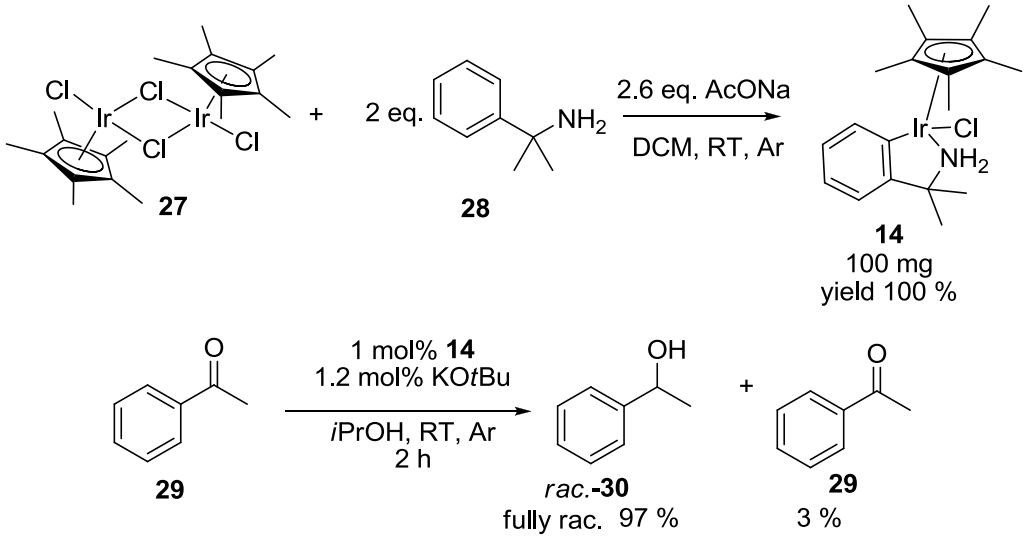
Compared to ruthenium, iron catalysts are less expensive and they exhibit less negative health and ecological properties. Due to these benefits it was important to synthesise and test iron based catalyst, thus Renaud and Poater's [19b] iron catalyst **11** was chosen. Original procedure was slightly modified as in synthesis of **24** dry MeCN (instead of dry acetone) and argon were used as other articles reported [35], whereas argon was introduced to decrease chances of by-product formation upon reflux (scheme 15). However, the reaction with diiron nonacarbonyl in these modified conditions was unsuccessful. We hypothesised that it was due to poor quality of diiron complex from an old batch that was used. Then we switched to a new good quality iron pentacarbonyl instead of diiron nonacarbonyl (these iron carbonyl complexes are interchangeable in this case) and the reaction proceeded smoothly. In total, 50 mg of activated catalyst **11** were obtained.



Scheme 15. **Synthesis of catalyst (2,4-bis(trimethylsilyl)-7-N-tosyl-bicyclo[3.3.0]hepta-1,4-dien-3-one)iron acetonitriledicarbonyl.**

Eventually it was decided to try iridium complexes. Even though iridium is several times more expensive than ruthenium, literature precedents on ATH suggested that price difference could be offset by significantly lower catalyst loadings and faster reaction rates. We decided to synthesise the iridium complex **14** that was very efficient for ATH, as reported by Ikariya [18a]. Synthesis and purification of **14** were as reported in the article (scheme 16, top). Catalyst appeared to be air stable in solid phase and in the solution (NMR sample did not disintegrate over several days). Catalyst was tested in reported transfer hydrogenation reaction (scheme 16, bottom) as an additional proof of catalyst's quality. Transfer hydrogenation from

iso-propanol to acetophenone was efficient and, as reported, provided nearly quantitative TH and yielded racemic product.



Scheme 16. **Synthesis of Ir complex 14 and catalytic reduction of acetophenone with 14.**

2.2 Racemisation reactions

As synthesis of catalysts was finished, we began to evaluate them. In depth analysis of literature revealed that successful DKR needs rapid racemisation catalyst that would not be inhibited by other species in reaction mixture and highly enantioselective derivatization catalyst with suitable derivatizing agent. Hence, we came to understand that racemisation is the key part and key problem and a lot of research was devoted for it. Below a complete list of all compounds that were tested for this purpose is given (fig. 5).

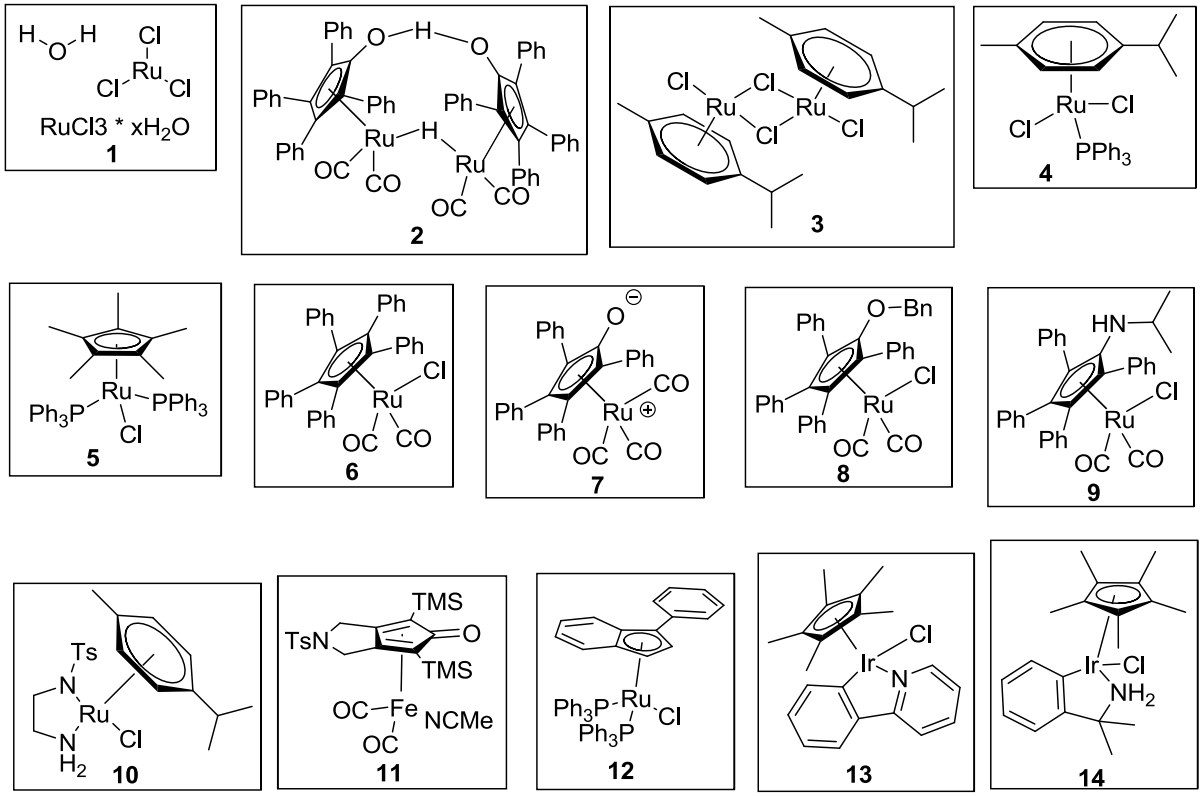


Figure 5. **Racemisation catalysts.**

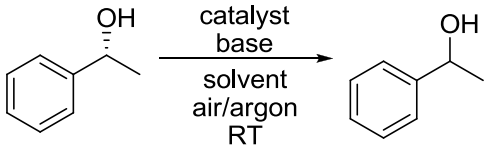
Initially, solvent had to be chosen. Most common solvents used for these reactions were toluene or mixtures of toluene with *t*-amyl alcohol [12, 17b, 30], for this reason it was decided to perform reactions with each catalyst in two different solvent systems. What is more, as some catalysts were known to be air-sensitive, raemisations had to be tested under aerobic and anaerobic conditions. That gave four different reaction condition combinations (ruthenium (III) chloride did not dissolve in pure toluene, hence reactions were performed in water instead):

- in toluene at room temperature
- in toluene at room temperature, under argon
- in toluene – *t*-amyl alcohol mixture (v:v = 2:3) at room temperature
- in toluene – *t*-amyl alcohol mixture (v:v = 2:3) at room temperature, under argon

Next, proper temperature for reaction had to be set. In order to eventually establish a DKR reaction we were limited to temperature which would not exceed room temperature (~25 ^{o}C) as kinetic resolution (KR) catalysts are more selective at lower temperatures and majority of them would fail at temperatures usual for enzymatic DKRs (50 – 70 ^{o}C). Room temperature was chosen for two main reasons – it was a comfortable temperature to perform

reactions at and it was convenient to compare racemisation rates of catalysts in this temperature.

One remaining important factor was concentration of substrate. Based on information, obtained from articles, 12 mg/ml (0,1 mol/L) concentration of model substrate (*R*)-1-phenylethanol in solvent was used. What is more, *t*-BuOK was used as standard base, however, several catalysts (fig. 5, compounds **1**, **2**, **11**) were reported to racemise under base free conditions, while complex **8** (fig. 5) was reported to perform best with equimolar amount of potassium phosphate. Finally, racemisation reactions were performed (scheme 17). Chiral cyclodextrin coated column equipped gas chromatograph was used for determination of ee. Samples were taken at certain time intervals, however, for convenience of the reader and clearer picture of the data – ee values only after 2 h and 24 h (omitted where unimportant) are provided (tables 2.1 – 2.4).



(*R*)-**30** *rac.*-**30**

Scheme 17. **Principal racemisation reaction scheme.**

Table 2.1.

Racemisations in toluene

# of cat.	cat./ base, in mol%	ee % (2 h)	ee % (24 h)
1‘	5 / 0	100.0	100.0
2	2 / 0	98.4	97.3
3	2 / 5	99.0	89.5
4	2 / 5	98.0	97.6
5	2 / 5	100.0	99.3
6	2 / 5	0.0	0.1
7	2 / 5	98.1	97.6
8	2 / 100‘‘	100.0	68.5
9	2 / 5	28.2	10.3
10	2 / 5	100.0	100.0
11	7 / 0	100.0	100.0

In tables 2.1-2.3: ‘reaction was performed in water; “K_3PO_4 was used instead of *t*-BuOK. In tables 2.1-2.4: negative ee values represent presence of bigger amounts of (*S*)-1-phenylethanol in reaction mixture.

Seemingly, almost all catalysts (**1**-**5**, **7**, **10**, **11**) were reluctant to racemise in toluene under air at room temperature (table 2.1). Furthermore, reaction mixtures containing Noyori type catalyst (**10**) became dark in a couple of minutes, which might represent some disintegration happening *in-situ*. Compound **8** did racemise but it was too slow to be useful.

Only Bäckvall's (**6**) and Park's (**9**) catalysts showed, respectively, excellent and good reactivity. This already allowed us to identify at least two catalysts are possible candidates for further research. Next, all of these compounds were tested in identical reaction conditions but under inert Ar atmosphere (table 2.2).

Table 2.2.

Racemisations in toluene, under argon

# of cat.	cat./ base, in mol%	ee % (2 h)	ee % (24 h)
1'	5 / 0	98.0	97.6
2	2 / 0	97.6	96.7
3	2 / 5	92.0	71.7
4	2 / 5	94.3	92.7
5	2 / 5	7.4	6.7
6	2 / 5	0.0	0.0
7	2 / 5	97.5	97.2
9	2 / 5	-1.5	-0.1
10	2 / 5	94.6	70.6
11	7 / 0	100.0	100.0

Much more promising results were gathered from reactions performed in toluene under argon (table 2.2). Evidently, some catalysts (**1**, **2**, **4**, **7**, **11**) still lacked energy (higher temperature was required) for racemisation. Compounds **3** and **10** did induce slow redox and catalyst **10** did not show instant disintegration (darkening in reaction mixture) as in previous case (table 2.1). Moreover, complex **5**, which has never been reported as racemising catalyst, proved to be an excellent room temperature racemisation catalyst. As expected, compounds **6** and **9** both performed excellent and after comparison of data from tables 1 and 2 for **9** it seems that it is quite air-sensitive in these reaction conditions. To see if these trends are intrinsic, toluene was switched to toluene – *tert*-amyl alcohol mixture and again reactions were first performed under air (table 2.3).

Table 2.3.

Racemisations in toluene – *t*-amyl alcohol mixture (v:v = 2:3)

# of cat.	cat./ base, in mol%	ee % (2 h)	ee % (24 h)
1	5 / 0	100.0	94.7
2	2 / 0	100.0	96.6
3	2 / 5	91.9	76.6
4	2 / 5	96.3	95.9
5	2 / 5	100.0	96.6
6	2 / 5	2.7	0.5
7	2 / 5	95.0	94.7
8	2 / 100‘‘	83.7	18.4
9	2 / 5	57.2	50.1
10	2 / 5	100.0	100.0
11	7 / 0	100.0	100.0
12	5 / 5	97.0	-
13	2 / 5	98.0	97.0

As soon as solvent was changed from toluene (table 2.1) to mixture of toluene and *t*-amyl alcohol (table 2.3), majority of compounds (**1**, **2**, **4**, **5**, **7**, **10**-**13**) did not express significant rate of redox at these conditions. Catalysts **3** and **9** did induce slow racemisation, although unexpectedly, **9** was more active in neat toluene. To our surprise, we were able to observe that catalyst **8** performed much better, however, it was unsuitable candidate for intended use in DKR as it was still too slow. Again, **6** was excellent in racemising (*R*)-1-phenylethanol. Lastly, reactions were performed in solvent mixture under Ar (table 2.4).

Table 2.4.

Racemisations in toluene – *t*-amyl alcohol mixture (v:v = 2:3), under argon

# of cat.	cat./ base, in mol%	ee % (2 h)	ee % (24 h)
1	5 / 0	100.0	94.7
2	2 / 0	100.0	96.9
3	2 / 5	94.2	88.1
4	2 / 5	86.5	84.3
5	2 / 5	8.0	-0.7
6	2 / 5	0.0	0.0
7	2 / 5	86.2	69.8
9	2 / 5	-1.3	0.0
10	2 / 5	84.8	51.4
11	7 / 0	100.0	100.0
12	5 / 5	0.0	-
13	2 / 5	98.0	97.0
14	1 / 1,2	87.0	-

Performing reactions in toluene – *t*-amyl alcohol mixture under argon proved to be the best combination as four catalysts were able to reach complete racemisation with reasonable rates - 5 h for complex **5** (only 8 % ee after 2 h) and in 2 h for **6**, **9** and **12** (**12** is highly air sensitive in solution, whereas in solid state – it can be handled outside glovebox). When data for selected catalysts (**5**, **6**, **9**, **12**) was compared for samples taken 30 minutes after beginning of reaction – catalyst **5** was shown to be less effective as it racemised alcohol to only 77,6 %, whereas it's competitors have already racemised alcohol completely. A more in depth analysis of the newly found **5** was necessary.

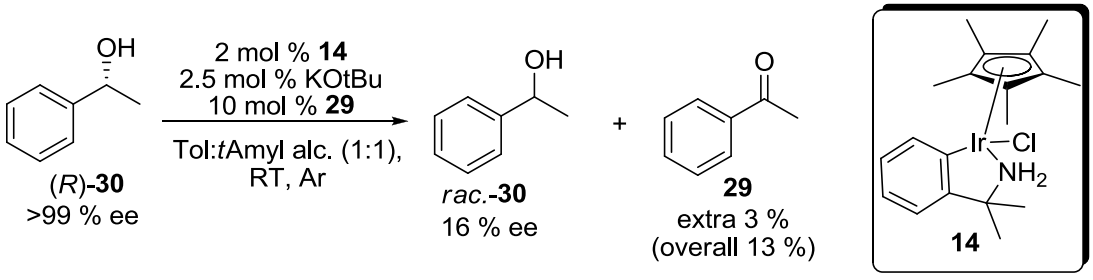
A set of reactions was planned and performed to evaluate compatibility and limitations of **5** (table 2.5.). First, it was important to answer the question of when does the catalyst disintegrate, for this reason **5** and *t*-BuOK were dissolved in solvents and vigorously stirred in open MW vial for 2 h, then vial was capped, thoroughly flushed with Ar and (*R*)-1-phenylethanol was injected (entry 5.2). Racemisation happened to be 10 times slower (compared to entry 5.1), meaning that roughly 90 % of catalyst was no longer active, thus, this has clearly shown that activated catalyst in solution is susceptible to air. Next the need for base was tested (entry 5.3) and reaction did not proceed without *t*-BuOK, meaning that base is crucial. This in turn has lead to exploration of other bases that could support racemisation – potassium carbonate and phosphate (entries 5.4 and 5.5), evidently, these bases do activate **5**, but with efficiency much lesser than potassium *tert*-butoxide. Then several inhibitors were tested: acetic and isobutyric anhydrides and isopropenyl acetate (entries 5.6-5.8) in combination with DMAP (to act as general acylation catalyst), all three racemisations were inhibited, even though no ester was formed in isopropenyl acetate's case, whereas acid anhydrides acylated very well. Finally, reaction in presence of isopropenyl acetate (entry 5.8) was rerun with inversed ratio of **5** and *t*-BuOK (entry 5.9) with the hypothesis that lower amount of base could possibly improve racemisation. Practically, racemisation was again inhibited by some species from reaction media. To conclude, this probing revealed that this newly found racemisation catalyst **5** as well follows the same trends that were reported for other ruthenium complexes and that they might be a general truth for all inner-sphere mechanism catalysts.

Table 2.5.

Racemisations with complex 5 in Tol-*t*Amyl alcohol (2:3) under Ar at RT.

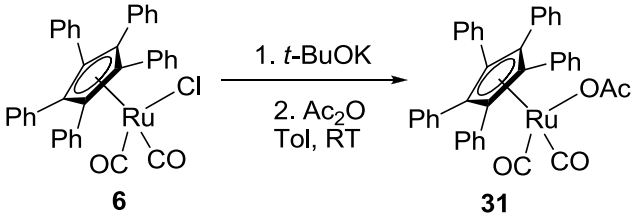
Entry	**5** / *t*-BuOK in mol %	ee % (2 h)	ee % (24 h)	modification/additives
5.1	2 / 5	8.7	0.0	-
5.2	2 / 5	82.0	n.d.	vigorously stirred 2 h under air, then Ar flushed and added (*R*)-1-phenylethanol
5.3	2 / 0	100.0	100.0	no base added
5.4	2 / 100	100.0	86.9	instead of *t*-BuOK added 1 eq. of K_2CO_3
5.5	2 / 100	100.0	84.7	instead of *t*-BuOK added 1 eq. of K_3PO_4
5.6	2 / 5	100.0	100.0	added 0.5 eq. DMAP and 1 eq. $(Ac)_2O$
5.7	2 / 5	100.0	100.0	added 0.5 eq. DMAP and 0.5 eq. $(i\text{PrCO})_2O$
5.8	2 / 5	100.0	100.0	added 0.5 eq. DMAP and 0.5 eq. isopropenyl acetate
5.9	5 / 3	100.0	97.5	added 0.5 eq. DMAP and 0.5 eq. isopropenyl acetate

Iridium complexes, on the other hand, should follow outer-sphere redox, which could lead to a slightly different reactivity and inhibitory patterns. Compound **13** was never reported for racemisation or TH, but it had similar structural features and was even cheaper than majority of ruthenium complexes, basically, due to that it was obtained and tested. Complex **14**, on the other hand, was a different story as it was reported to be rapid TH catalyst but underperforming in racemisation, which essentially is the same transfer hydrogenation but from alcohol to that alcohol's ketone. At this point we began hypothesising and some articles supported our hypothesis that racemisation can be slowed down by high abundance of alcohol and next to zero concentration of respective ketone. One way to test this hypothesis and to search for workaround is to deliberately add a small amount of ketone, for example 10 mol % of acetophenone **29** (scheme 18). To our delightment, upon introduction of acetophenone (*R*)-1-phenylethanol retained only 16 % ee after two hours (compared to 87 % ee, it should be noted, that this was achieved with 1 mol % loading of **14**) and almost no significant ketone formation was observed (10 mol % were added, after 2 h ~ 13 mol % were observed by GC). It should be noted that for simplicity toluene – *tert*-amyl alcohol mixture was set to 1:1 ratio, racemisations were not affected by this.

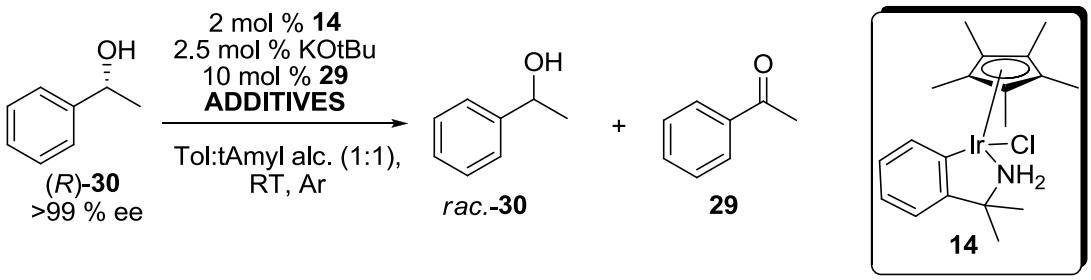


Scheme 18. **Iridium induced racemisation in presence of acetophenone.**

Excited by these findings, we set out to explore this catalyst further. It was known from Fu's work that ruthenium catalyst **6** is inhibited by sources of acetates (scheme 19) and that this newly formed complex **31** is no longer able to induce racemisation. For complexes **9** and **12** this compatibility was tested by dissolving complex in potassium pivalate and potassium *tert*-butoxide solution in toluene – *tert*-amyl alcohol mixture (1:1) and finally introducing (*R*)-1-phenylethanol. Unsurprisingly, both complexes were incompatible with carboxylates and racemisation did not proceed. However, when **14** was added to a solution of potassium acetate and potassium *tert*-butoxide, followed by (*R*)-1-phenylethanol and acetophenone (scheme 20), to our delight, racemisation was not inhibited and did proceed even slightly faster with 9 % ee after 2 h (compared to 16 % in absence of KOAc) with buildup of 6 % acetophenone (table 2.6, entry 6.2), the same was true for potassium pivalate (entry 6.5). Then various probable inhibitors were screened (table 2.6), apparently, acetic acid (entry 6.1) was inhibiting racemisation, similarly, *p*-nitro phenol (entry 6.3) slowed down racemisation, whereas potassium *p*-nitro phenolate (entry 6.4) did not. This allowed building a hypothesis that acidic proton is the biggest problem for iridium catalyst, hence, compatibility with several bases (entries 6.6-6.8) were tested, they were all compatible. Potassium cyanide (entry 6.9) was also evaluated, due to possible use of acetyl cyanide as acylating reagent, racemisation was unaffected. Since some acylating reagents decompose with escaping of CO_2, for example Fu's carbonates, it was necessary to test compatibility with carbon dioxide (entry 6.10). Addition of dry ice into reaction vial did not interrupt racemisation. These promising results with iridium complex **14** have expanded the list of racemisation catalysts to be tested for DKR.



Scheme 19. **Ruthenium acetate complex formation.**



Scheme 20. **Racemisations by 14 with different additives.**

Table 2.6.

Racemisations by 14 with different additives.

Entry	ee, %	**29**, % *	ADDITIVES
6.1	98	0	1 eq. AcOH
6.2	9	6	1 eq. KOAc
6.3	41	4	1 eq. *p*-nitro phenol
6.4	4	11	1 eq. potassium *p*-nitro phenolate
6.5	1	12	1 eq. PivOK
6.6	2	11	1 eq. K_2CO_3
6.7	5	10	1 eq. $NaHCO_3$
6.8	6	11	1 eq. TEA
6.9	3	5	1 eq. KCN
6.10	4	3	10 eq. CO_2

Acetophenone **29** and ee percentages were determined by chiral GC.

* buildup of ketone (initially added 10 % are subtracted)

Overall, it was concluded that ruthenium or iridium complexes could be employed for room temperature racemisation under inert atmosphere. Toluene – *t*-amyl alcohol mixture provided better results than pure toluene, however, in principle, both could be used. A list of suitable catalysts was assembled: robust **6** and air-sensitive **9** and **12** catalyse with similarly rapid rates of racemisation. Iridium complex **14** might be a viable alternative to ruthenium complexes as, most importantly, it is not inhibited by carboxylates. Newly discovered racemisation catalyst **5** would be the last choice due to air-sensitivity and slower redox rates, however, it is still much faster than most commercially available reported catalysts that were tested.

2.3 Investigation of KR

Plethora of different enantioselective acylation catalysts exists. Reports of the most suitable conditions for each catalyst for specific substrate(s) can be found in literature, however, comparison articles are less common. Thus, there was a need to obtain a collection of acylation catalysts and screen them in conditions suitable for racemisation of alcohol in order to evaluate and choose the most suitable catalyst. For simplicity and in order to have a finite number of catalysts to screen – nitrogen based catalysts were investigated. This was in part due to our expertise in nucleophilic DMAP catalysis and due to practical reason that they were commercially available (whereas phosphorous or sulphur based catalysts are less commercialised). Commercial availability was important as non-enzymatic DKR with of-the-shelf catalysts would be useful in industrial chemistry. Overall, general considerations and requirements for acylation catalyst were:

- unaffected by racemisation cycle;
- highly selective in racemisation conditions (toluene – *tert*-amyl alcohol mixture at RT, under Ar);
- commercially available and (preferably) inexpensive.

One particular acylation catalyst was of high interest as it was previously developed in our group and performed very well in DKR of azole hemiaminals [36]. However, the synthesis of this Vedej's type catalyst **45** (fig. 6) was problematic due to the use of *tert*-butyl lithium, long linear reaction sequence and poor yields in some of the steps. Thus, an alternative multi-gram pathway was necessary and it was successfully developed with *n*-butyl lithium, shorter reaction sequence, higher yields and key step of zinc chloride mediated chloride exchange to dimethylamino fragment on catalyst scaffold, all this work was published in an article, thus synthesis of it will not be discussed in detail here [37].

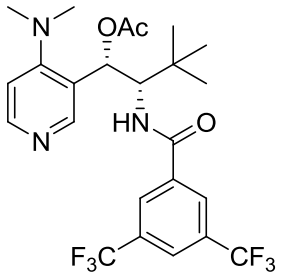


Figure 6. **Vedej's type acylation catalyst 45.**

A set of 12 compounds was assembled (fig. 7) with seven of them – three Birman's amidine, two Fu's ferrocene, Ishihara's imidazole and Connon's proline based catalysts – being commercially available. This assembly had to be tested with racemic 1-phenylethanol in toluene – *tert*-amyl alcohol mixture. Ideally, acylation should take place with as simple and as abundant acylating reagent as possible, hence, kinetic resolutions underwent with acetic and isobutyric anhydrides (scheme 21).

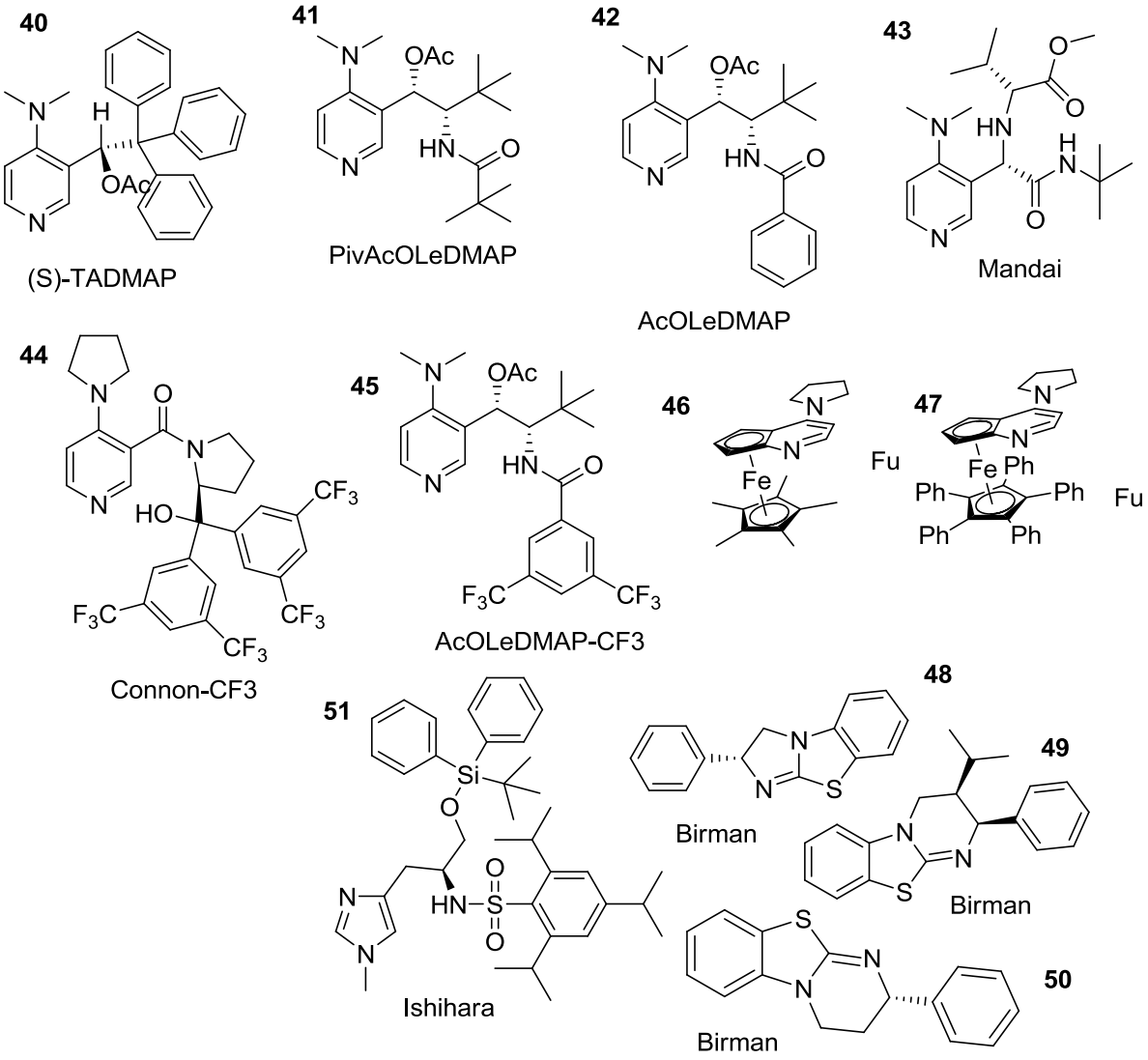
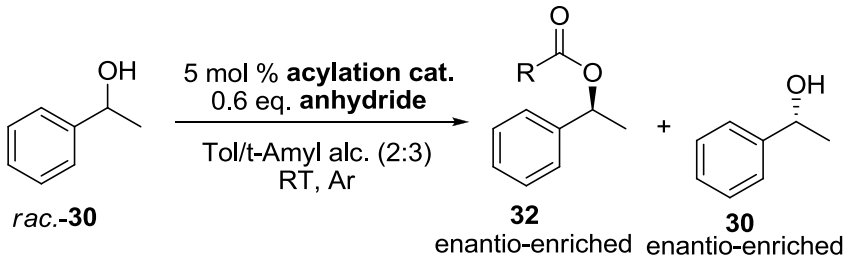


Figure 7. **Acylation catalysts.**



Scheme 21. **Principal kinetic resolution reaction scheme.**

KR reactions were performed in capped MW vials to avoid any loses of reagents or inert atmosphere. Inert atmosphere was used for two reasons – racemisations needed inert atmosphere and, even though organocatalysts (fig. 7) in solid state are air stable, Fu's ferrocenes might be prone to oxidation in solution, thus, it was reasonable to employ argon. Again, for analysis of reaction mixtures – chiral gas chromatography was utilized. Separation of acetylated products and starting alcohols was good, in contrast, isobutyrylated alcohols

showed poor separation in applied GC method but there was enough of information obtained from chromatograms since separation of alcohol enantiomers was not interrupted.

Table 2.7.

Selectivities of KR with isobutyric anhydride.

# of cat.	40	41	42	43	44	45
S (2h)	2.1	1.1	2.3	1.5	3.2	2.7
S (23h)	2.3	1.1	2.5	1.5	3.2	2.4
# of cat.	46	**47**	**48**	**49**	**50**	51
S (2h)	1.3	0.0*	3.3	6.2	2.9	1.2
S (23h)	1.2	4.6	6.4	9.5	4.1	1.2

*zero conversion

As reactions with isobutyric anhydride were setup, samples for GC were taken after 2 and 23 hours in order to track rate of conversion and to evaluate selectivity (table 2.7.). Remarkably, only Birman's catalysts showed moderate selectivity towards acylation of 1-phenylethanol. Fu's ferrocenes were rather slow, whereas remaining compounds poorly maintained enantioselectivity. These findings were somewhat concerning as generally it is accepted that the use of isobutyric anhydride slows down reaction and steric bulk improves enantioselectivity. Thus, it seemed that acetylation with acetic anhydride can lead to even worse outcome.

Table 2.8.

Selectivities of KR with acetic anhydride.

# of cat.	40	41	42	43	**44**	**45**
S (2h)	1.4	2.0	3.0	1.7	4.0	4.4
S (23h)	1.4	1.9	2.9	1.7	4.0	4.4
# of cat.	46	**47**	**48**	**49**	**50**	51
S (2h)	1.9	∞*	19.6	19.9	9.1	1.0
S (23h)	1.9	23.3	19.6	19.8	9.1	1.0

* 13 % conv., >99 % ee of S-ester

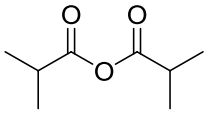
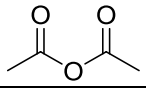
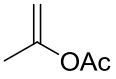
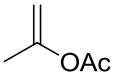
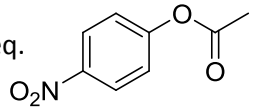
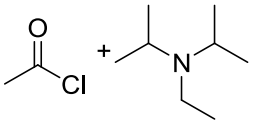
Delightfully, selectivities improved when isobutyryl group was exchanged to acetyl (table 2.8.). Even though Vedej's type catalysts displayed insignificant improvement, the Fu's and Birman's catalysts displayed very good selectivities. It should be noted, though, that Fu's pentaphenyl ferrocene had much slower rate of conversion (13 % in 2 h) as compared to Birman's amidines (~50 % in 2 h). On one hand, slower rate of acylation allows increasing selectivity and can, thus, be favourable. On another hand, Birman's catalysts can achieve approximately identical selectivity while maintaining significantly higher rate of acetylation (at least 5 times faster). In order to implement a more alluring method than the one reported

by Fu – method should be able to provide product more rapidly, hence, it seemed logical to choose faster and very selective Birman's catalyst as the best candidate for successful DKR.

Next, it was important to evaluate more commercially available acylating reagents (table 2.9.). Reactions employing Birman's catalyst **49** were setup to acylate racemic 1-phenylethanol. Isopropenyl acetate and *para*-chlorophenol acetate are two very common reagents used in enzymatic resolutions, however, we hypothesised that *para*-chlorophenol acetate might not be sufficiently rapid, hence, it was decided to use a more active *para*-nitrophenol acetate. In particular, isopropenyl acetate seemed as a very good candidate for DKR because, as it gives of acetyl group, remaining enolate abstracts proton from 1-phenylethanol and reforms into acetone, which should not inhibit racemisation. Unfortunately, the esterification did not proceed as it was used in combination with Birman's catalyst (entry 9.3) at room temperature. Then we thought that possibly higher temperature (which is a usual prerequisite to enzymatic KRs or DKRs) is required to alleviate dissociation of acetate from isopropenyl acetate, thus a reaction at 60 ^{o}C was performed (entry 9.4), however it still did not yield any product. Since these reaction conditions were suitable for racemisation and KR with other acylating reagents, it was decided not to make any changes to these conditions and to test other acylating reagents instead. In order to increase the pH of reaction mixture (as this might be necessary in DKR, to avoid inhibition of racemisation) *para*-nitrophenol acetate was employed in combination with TEA at room temperature (entry 9.5). Using a more active acylating reagent allowed to decrease the loading of Birman's catalyst fivefold and still retain reasonable rate of conversion (45 % in 23 h) with selectivity (6.5) that could be improved upon fine-tuning of reaction conditions. Last, it made sense to test if acetyl chloride in combination with *N,N*-diisopropylethylamine (DIPEA) could be used (entry 9.6) as chloride in reaction media should be compatible with racemisation. Interestingly, 22 % conversion in 23 h was rather low, this could have happened due to unknown quality of AcCl (AcCl was not distilled before use) and the minute amounts used (significant part of ~20 uL of AcCl can be easily lost during handling), but what was more interesting – selectivity of s = 9 was achieved, even though the background uncatalysed esterification reaction was very probable.

Table 2.9.

Comparison of different acylating reagents.

Entry	reagent and conditions	loading (mol %) of **49**	conv., % (23h)	selectivity (23h)
9.1	0.6 eq.  at RT	5	62	9.5
9.2	0.6 eq.  at RT	5	55	19.6
9.3	0.6 eq.  at RT	5	0	0
9.4	0.6 eq.  at 60°C	5	0	0
9.5	1 eq.  + TEA at RT	1	45	6.5
9.6	0.6 eq.  at RT	5	22	9

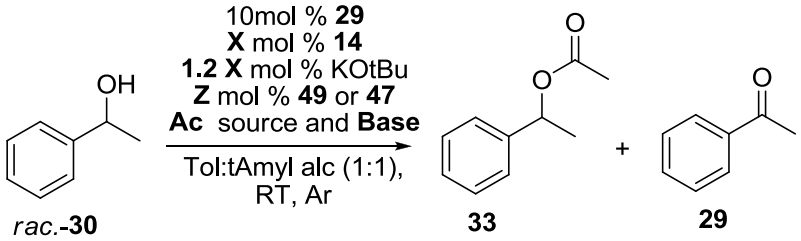
To sum up, kinetic resolution investigations have helped to identify the best candidates for enantioselective acylation of 1-phenylethanol – Fu's and Birman's catalysts. It was also shown that commercially available alternatives to carboxylic anhydrides could be used as acylating reagents. This data in combination with observations in racemisation subchapter allows exploring DKR in detail.

2.4 DKR reactions

With knowledge gathered during racemisations and kinetic resolutions it was time to test combinations for dynamic kinetic resolution reactions. It was shown that ruthenium complexes are incompatible with carboxylic anhydrides due to the formation of stable new complexes with carboxylates that are no longer catalytically active. What is more, it was identified that iridium complex **14** was unaffected by carboxylates and could catalyse redox in presence of carboxylic acid salts, but not the acid itself. Incited by this finding we decided to start with iridium DKR.

Since it was evident from previous experiments that formation of acetic acid during reaction is unfavourable, a workaround was implemented – TEA was introduced to negate the

formation of acetic acid (scheme 22). As first reaction with Birman's catalyst, potassium *tert*-butoxide activated **14**, TEA, acetophenone, 1-phenylethanol and acetic anhydride (table 2.10., entry 10.1) was set up, a discouraging result was obtained. For some reason, selectivity of acylation was very poor and 1-phenylethanol was non-racemised. This lead to a hypothesis that relative rates of acylation and racemisation might differ very much, hence, one should increase the loading of redox catalyst and decrease acylation catalyst percentage (entry 10.2). Enantioselectivity improved but 41 % ee was too low, acetophenone buildup reached significant value of 19 % (meaning that almost 20 % of initially added 1-phenylethanol was wasted in oxidation reaction) and alcohol was nowhere near to being racemic.



Scheme 22. **DKR setup with complex 14.**

Table 2.10.

DKR attempts with iridium complex 14.

Entry	Cat.	X	Z	Ac source (1,2 eq.)	Base (1,5 eq.)	Time, h	**33**:**30**, % of **33** (NMR)	ee, % **33** (GC)	ee **30**, % (GC)	**29**, % (GC)
10.1	**49**	2	5	Ac_2O	TEA	20,5	89	14	99	2
10.2	**49**	5	1	Ac_2O	TEA	29	83	41	89	19
10.3	**47**	5	1	Ac_2O	TEA	336	77	69	2	69
10.4	**47**	5	1	Ac_2O	TEA	24	7	40	0	57
10.5	**47**	2	10	Ac_2O	TEA	24	66	71	86	20
10.6	**47**	2	10	Ac_2O	Proton sponge	24	64	67	86	10
10.7	**47**	2	10	Ac_2O	$NaHCO_3$	24	63	68	84	12
10.8	**49**	5	3	*p*-nitrophenol acetate	TEA	122	<5	33	4	46
10.9	**49**	2	3	*p*-nitrophenol acetate	TEA	46	55	45	53	1

Note: **29** buildup percentage is given (10 % of initially added acetophenone was subtracted); entry 10.4 was under H_2 atmosphere; entries 10.1-10.8 were of the usual 0.1 M concentration (by 1-phenylethanol) and 10.9 was a heterogenous reaction mixture with ~ 1.3 M concentration.

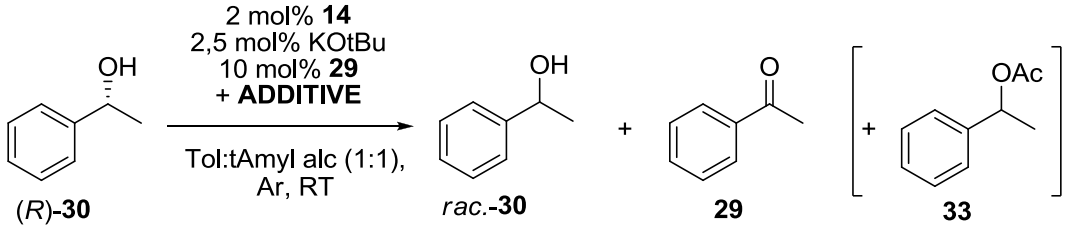
As Birman's catalyst failed in these conditions, it was necessary to test Fu's catalyst. Clearly, Fu's catalyst was much slower as 77 % of alcohol were converted into ester in 336 h

(Birman's catalyst converted 83 % in 29 h) and more selective (69 % ee of ester after 336 h, whereas Birman's catalyst achieved 41 % ee of ester after 29 h), as it might seem (entry 1.3), however, this reaction had almost 70 % of ketone buildup, making this catalytic system a successful method for oxidation and an unsuccessful DKR. It became evident that redox cycle is somehow interrupted, **14** abstracts hydrogen from 1-phenylethanol, acetophenone is formed and then hydrogen dissipates either in molecular form, or due to side reaction. Reaction mixture did not contain species that could be reduced easily, hence, it was hypothesised that molecular hydrogen dissociates from hydrido iridium complex. Consequently, reaction was repeated under hydrogen atmosphere (entry 10.4) and this did not reduce the buildup of ketone as even after 24 hours content of ketone (57 %) was similar to that of 336 hours (69 %) in reaction under inert atmosphere. Next, Fu catalyst's percentage was increased tenfold in order to speed up acylation (entry 10.5) and this, surprisingly, reduced buildup of ketone to only 20 % while at the same time leading to, in principle, kinetic resolution (71 % ee of ester and 86 % ee of alcohol are representative of KR). At this point it was decided to test two more bases – 1,8-Bis(dimethylamino)naphthalene (proton sponge) and sodium hydrocarbonate (entries 10.6-10.7). Both bases have lead to minor improvement as ketone buildup was diminished (compared to entry 1.5 with TEA), but only kinetic resolution was observed.

Acetic acid was incompatible with **14**, whereas *para*-nitrophenol at least partially was compatible. As a result, a reaction with Birman's catalyst and *para*-nitrophenol acetate as acylating reagent was performed (entry 10.8). Molar percentage of catalysts were modified to 5 mol % iridium **14** and 3 mol % Birman's catalysts' to balance their rates, this proved to be a very slow (traces of product after 122 h) kinetic resolution with high (46 %) ketone buildup. Drastically increased concentration and modification of catalysts' loadings were implemented (entry 10.9), yielding a heterogenous slurry, yet, with almost no ketone buildup and enantiomeric excesses representative of kinetic resolution. From all these reactions it was clear that some unknown reason was responsible for failure of DKR and a step by step approach was necessary to figure out where the problem was.

A matrix of twenty reactions was setup. In each of the 20 vials *t*-BuOK activated complex **14** was to racemise (*R*)-1-phenylethanol in presence of base, base with acetic anhydride, base with acetic acid or base with acetic anhydride and Birman's catalyst (scheme 23). Essentially, these experiments were performed to figure out which components lead to ketone buildup and at the same time to evaluate to what extent the background acetylation happens. Redox cycle was fast (1-phenylethanol was already racemic after 2 h) and ketone buildup over 21 hours was manageable at ~10 % in presence of potassium carbonate, sodium hydrocarbonate, TEA, potassium cyanide and potassium acetate (table 2.11., entries 11.1,

11.5, 11.9, 11.13, 11.17). Next, acetic anhydride was introduced in addition to the bases, in mixtures with potassium carbonate, sodium hydrocarbonate, TEA and potassium acetate (entries 11.2, 11.6, 11.10, 11.18) background acylations were quite slow, reaching 6 – 16 % in 21 h, however, alcohol was not racemised (68 – 81 % ee after 21 h) and ketone buildup of 25 – 46 % was significant. Interestingly, acetic anhydride in combination with potassium cyanide (entry 11.14) yield highest – 31 % – background acetylation and did not produce ketone buildup (only 3 %), but the alcohol remained nonracemised (81 % after 21 h). Evidently, acetic anhydride was in some way inhibiting reduction, but not oxidation by **14**. Then ability of the base to negate the effect of acetic acid was tested, for this acetic acid was combined with the bases. In all cases ketone buildup remained below 10 %, but none of the reaction mixtures had racemic alcohol after 21 hours (entries 11.3, 11.7, 11.11, 11.15, 11.19), rendering these bases insubstantially effective. As base and acetic anhydride addition was supported by 3 mol % of Birman catalyst's loading – rapid acetylations (75 – 82 % in 2 h) were observed (entries 11.4, 11.8, 11.12, 11.16, 11.20). Additionally, ketone buildup was negligible and remaining alcohol was not racemised, providing that redox cycle was completely off.



Scheme 23. **General reaction scheme for investigations with 14**.

Table 2.11.

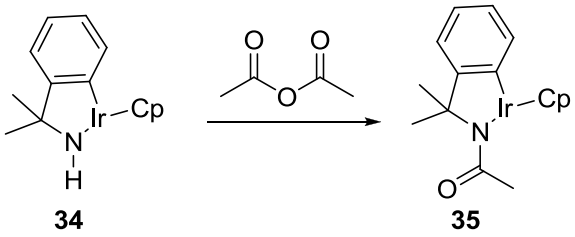
Racemisations with 14 in presence of additives.

Entry	Additives (in 1 eq., except 3mol% **49**)	ee of **30**, % (2h)	**29**, % (2h)	**33**, % (2h)		ee of **30**, % (21h)	**29**, % (21h)	**33**, % (21h)
11.1	K_2CO_3	2	11	0		-5	13	0
11.2	K_2CO_3 + Ac_2O	82	14	4		78	46	12
11.3	K_2CO_3 + AcOH	67	4	0		39	10	0
11.4	K_2CO_3 + Ac_2O + **49**	26	2	81		69	3	84
11.5	$NaHCO_3$	5	10	0		-7	11	0
11.6	$NaHCO_3$ + Ac_2O	77	12	2		74	25	7
11.7	$NaHCO_3$ + AcOH	70	4	0		62	7	0
11.8	$NaHCO_3$ + Ac_2O + **49**	20	1	80		69	1	86
11.9	TEA	6	11	0		4	14	0
11.10	TEA + Ac_2O	84	19	2		81	39	6
11.11	TEA + AcOH	79	8	0		67	9	0
11.12	TEA + Ac_2O + **49**	7	4	81		82	3	84
11.13	KCN	3	5	0		6	10	0
11.14	KCN + Ac_2O	83	4	8		81	3	31
11.15	KCN + AcOH	74	2	0		71	2	0
11.16	KCN + Ac_2O + **49**	6	2	75		17	2	77
11.17	KOAc	9	6	0		n.d.	n.d.	n.d.
11.18	KOAc + Ac_2O	70	12	5		68	30	16
11.19	KOAc + AcOH	71	5	0		50	7	0
11.20	KOAc + Ac_2O + **49**	17	2	82		99	2	85

Note: **29** buildup is reported (initially added 10 % are subtracted). Data was obtained from GC analysis.

Startled by the above-mentioned findings we began searching for any rationale. Iridium catalytic cycle (scheme 5) was readdressed and a hypothesis was proposed that activated iridium complex **34** could be susceptible to acylating agents (as well as other electrophiles) due to electron rich nitrogen atom, which, in theory, could be acylated (scheme 24). This was evaluated by NMR and MS experiments: complex **14** was mixed with *t*-BuOK in C_6D_6, ^1H and ^{13}C NMR spectra were obtained and a mass spectrum (MS) was measured, then acetic anhydride was added and identically ^1H, ^{13}C NMR spectra and MS were measured. Proton spectra had visible upfield shifts in aliphatic region (fig. 8), whereas in carbon spectra – a new possibly amide carbonyl peak appeared at 181 ppm (fig. 9) as well as a new aliphatic carbon. However, these were not fully conclusive findings and MS data was important. Activated complex **34** (fig. 10) had all expected isotopic masses (460 – 463 Da) while the sample with acetic anhydride had significant amounts of activated complex plus small amount of acetylated iridium complex **35** (504 Da) and a bigger count of 536 Da mass, which could only

be associated with acetylated iridium complex methanol adduct, even though MS was recorded on LC-MS with direct injection and the system was prewashed so that only MeCN would be the mobile phase. Findings that activated iridium complex **14** could be harmed by any acetyl group in combination with unsuccessful DKR attempts discouraged any additional investigations with **14** and further research focused on ruthenium complexes.



34 **35**

Scheme 24. **Proposed reaction.**

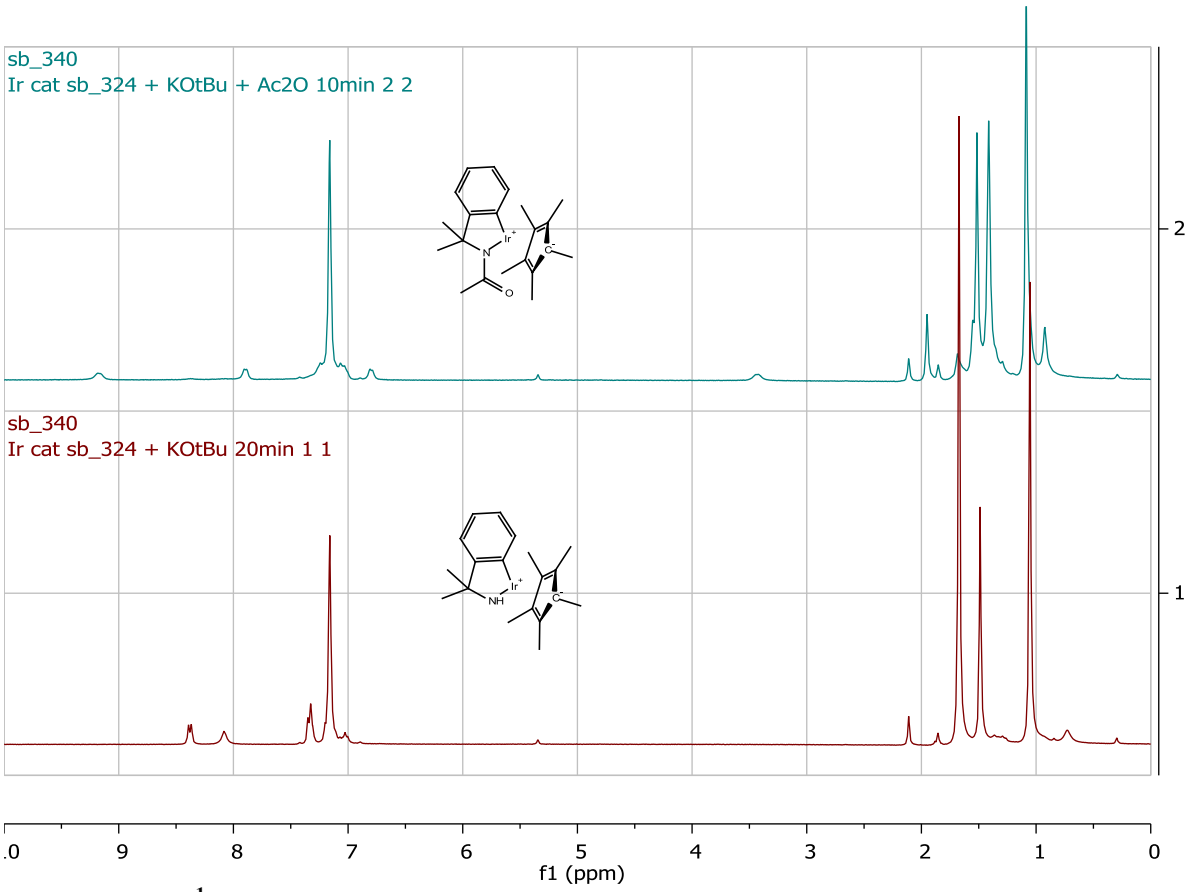


Figure 8. **^{1}H NMR spectra of acetylated 35 and activated 34 iridium complexes.**

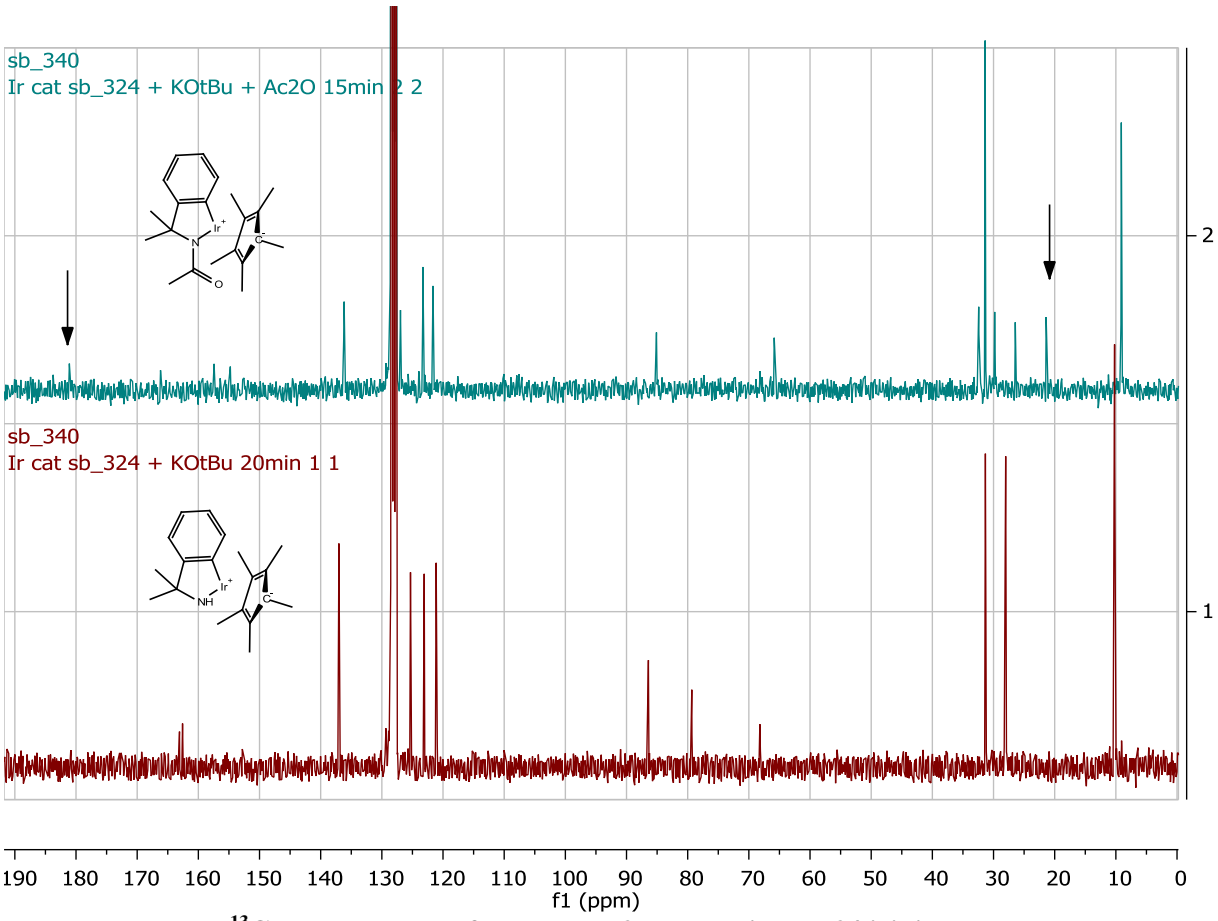


Figure 9. **^{13}C NMR spectra of acetylated 35 and activated 34 iridium complexes.**

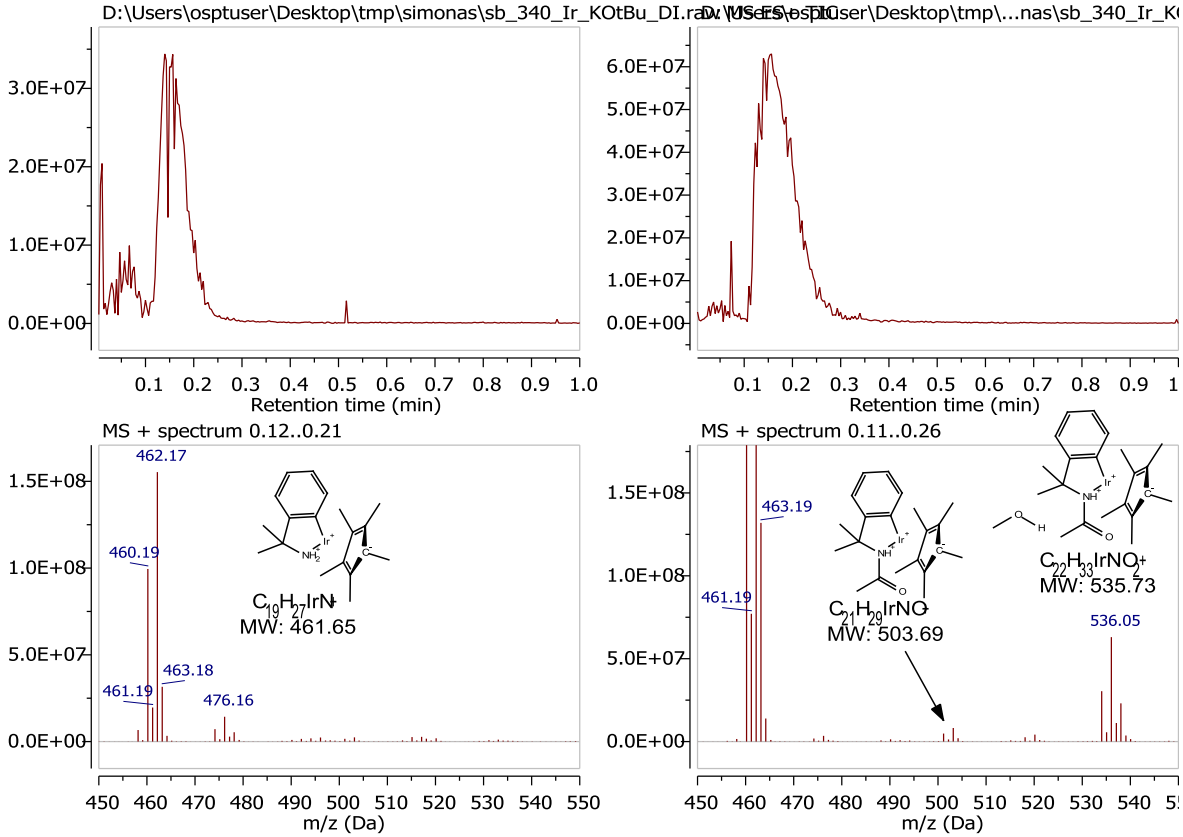
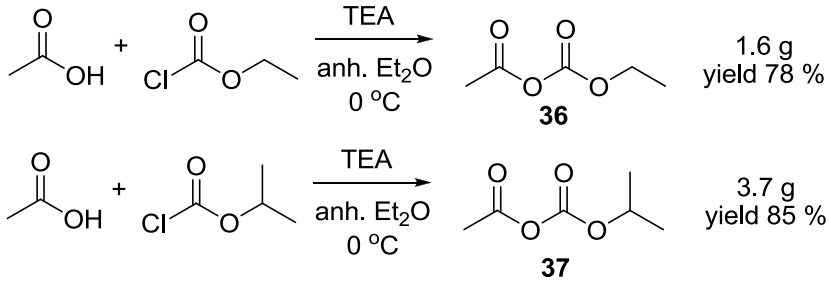


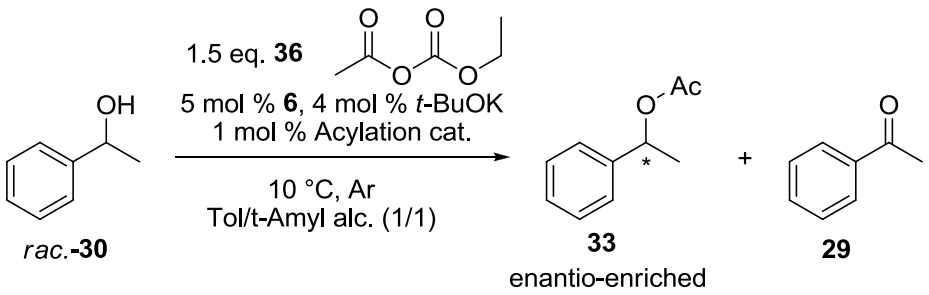
Figure 10. **Mass spectra of activated 34 and acetylated 35 iridium complexes.**

Fu has reported the first and only precedent of non-enzymatic DKR with ruthenium and ferrocene catalysts. Thus, it was important to first reproduce successful DKR with Backvall's complex **6** before setting up new DKRs with other ruthenium complexes. Since Fu's group observed that acetates inhibit racemisation catalyst, they employed organic carbonates such as acetic (ethyl carbonic) anhydride **36** and acetic (isopropyl carbonic) anhydride **37**. Under DKR conditions these anhydrides produce acetyl group, CO_2 and alkoxide, hence, self-acetylation is one possible side reaction, whereas second possible side reaction is addition of nucleophile to carbonate's carbonyl group by expelling acetate, which is known to harm racemisation catalyst. What is more, these carbonates are not available commercially and have to be synthesised, due to that these carbonates were successfully synthesised according to procedures reported by Fu (scheme 25).



Scheme 25. **Synthesis of carbonic anhydrides 36 and 37.**

To begin with, Fu's **47** and Birman's **49** catalysts were tested in parallel with Backvall's ruthenium complex **6** and acetic (ethyl carbonic) anhydride **36** (scheme 26). Acylating reagent, as it was reported in article, was automatically syringe-pumped over 20 hour period into 10 °C reaction mixture. Evidently, Birman's catalyst was outperforming Fu's catalyst in terms of speed, respectively, with 55 % and 6 % conversions in 21 hours, however, 1-phenylethanol was not racemic (88 % ee) in reaction with Birman's catalyst, while it was almost racemic (5 %) in reaction with Fu's catalyst (table 2.12., entries 12.1 and 12.3). Furthermore, 42 hour samples represented almost identical data (entries 12.2 and 12.4) as in 21 hour samples. These findings showed that racemisation in reaction with Birman's catalyst was inhibited and that both reactions stopped approximately when the syringe-pumping ceased. It was reported by Fu that acetic (isopropyl carbonic) anhydride **37** was better than acetic (ethyl carbonic) anhydride **36**, hence, we decided to test acetic (isopropyl carbonic) anhydride **37**.



Scheme 26. **DKR attempts with acetic (ethyl carbonic) anhydride 36.**

Table 2.12.

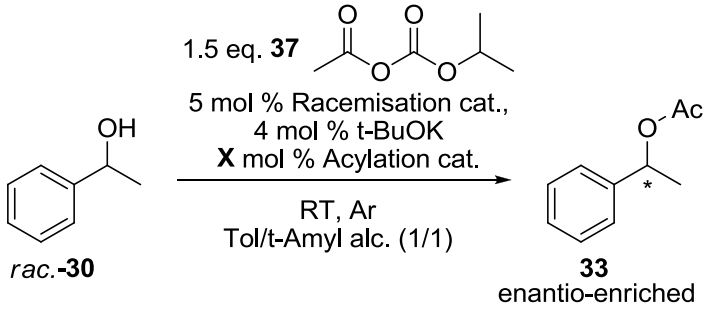
Results of DKR attempts with acetic (ethyl carbonic) anhydride.

Entry	Acylating cat.	Time, h	ee of **30**, %	ee of **33**, %	Conv., %
12.1	**47**	21	5	89	6
12.2	**47**	42	6	89	8
12.3	**49**	21	88	73	55
12.4	**49**	42	89	73	54

Note: data is based on chiral GC analysis. Ketone formation was 1-3 %. 20 hour syringe-pumping was done.

For reactions with acetic (isopropyl carbonic) anhydride **37** (scheme 27) we decided to expand acylation catalysts' list in order to obtain more data, hence Fu's **47**, Birman's **49** and Vedej's type **45** were tested. All reactions were performed with faster – 3 hour syringe-pump addition and at room temperature as opposed to original procedure which involved very slow addition of acylating reagent and unconvenient 10 ^{o}C reaction temperature. First of all, it was important to obtain data that DKR can be achieved in our laboratory. For this matter, three reactions with different acylating reagents were performed in combination with Backvall's catalyst **6** (table 2.13., entries 13.1-13.3). To our delight, reaction involving Fu's **47** clearly showed DKR character with 49 % ee of product and 1 % ee of remaining 1-phenylethanol at 67 % conversion after 51 h of reaction (entry 13.1). Analogous reaction with Birman's **49** was DKR for the initial 24 hours (71 % ee of ester and 12 % ee of remaining 1-phenylethanol at 58 % conversion) and then at some point switched to KR as 51 h sample had 65 % ee of ester at 84 % conversion and a significant 71 % ee of 1-phenylethanol (entry 13.2). Reaction with Vedej's type **45** was only KR, judging from data, as at all sampling times 1-phenylethanol was enantio-enriched (26-93 % ee), meaning that racemisation was halted (entry 13.3). We hypothesised that in second entry DKR could have switched to KR due to prolonged reaction time and possibly due to slow diffusion of air through puncture holes in the caps. Moreover, Nolan's catalyst **12** was a prominent alternative to **6**, thus, a set of reactions with 10 mol % loading of acylating catalysts and **12** was performed (entries 13.4-13.6). Unfortunately, these experiments resulted in purely kinetic resolutions as acetylation was happening much faster

(compared to 13.1-13.3) and racemisation was inhibited. Then, acylation catalyst loading was again diminished back to 1 mol % and reactions with **12** were set up (entries 13.7-13.9) in an attempt to control the relative rates of two cycles and avoid inhibition of redox cycle. As expected, acetylation rates in all three reactions had decreased, nonetheless, in all cases redox cycle was inhibited. Nolan's complex **12** was easily inactivated in reaction media, hence, it was decided to test another alternative – compound **9** (entries 13.10-13.12). Park's complex **9** is a very rapid racemisation catalyst sensitive to air even upon storage, hence, it is stored in glovebox and has to be weighed in it and carefully handled outside to prevent decomposition by air. As reactions were performed under argon and with 1 mol % of acetylation catalysts – all three reactions yielded dynamic kinetic resolutions as alcohol was being racemised and rapidly formed ester was enantio-enriched. Overall, Park's catalyst **9** in these conditions significantly outperformed Nolan's **12** and slightly Backvall's **6** (since **6** failed in entry 13.3, while **9** succeeded to racemise in entry 13.12). Complex **6** was chosen to be used in further reactions as most air-stable. Finally, it was shown that better enantioselectivities are achieved by increasing concentration and diminishing temperature (entry 13.13) – 1 mol % of **47** with 5 mol % of **6** at ~5 times bigger concentration in 10 ^{o}C yielded excellent DKR with improved 70 % ee of ester at 30 % conversion (entry 13.13 compared to maximum 59 % ee of ester at 6 % conversion in entry 13.1). In principle, Fu's conditions have potential to be improved, nevertheless, avoiding synthesis of acetic (alkyl carbonic) anhydrides and employing a commercially available acetylating reagent would be a big improvement.



Scheme 27. **DKR attempts with acetic (isopropyl carbonic) anhydride 37.**

Table 2.13.

Results of DKR attempts with acetic (isopropyl carbonic) anhydride.

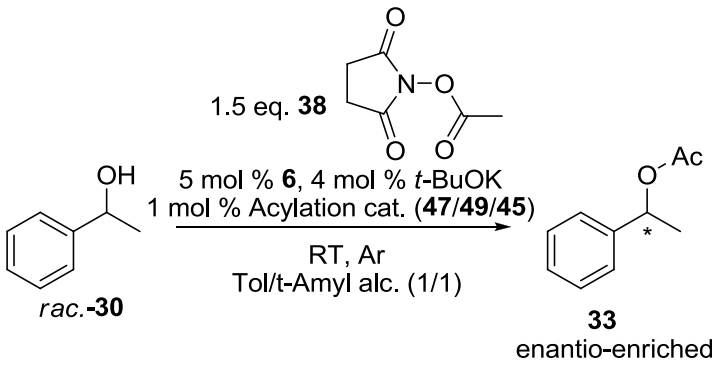
Entry	Acylation cat.	X	Racemisation cat.	Time, h	Conv., %	ee of **30**, %	ee of **33**, %
13.1	**47**	1	**6**	1.5	6	0	59
				3.5	19	3	44
				24	53	4	53
				51	67	1	49
13.2	**49**	1	**6**	1.5	34	14	85
				3.5	34	3	78
				24	58	12	71
				51	84	71	65
13.3	**45**	1	**6**	1.5	40	26	55
				3.5	63	67	34
				24	71	93	29
				51	70	78	29
13.4	**47**	10	**12**	1.6	35	27	74
				3.5	52	71	64
				24	63	98	45
13.5	**49**	10	**12**	1.6	48	88	71
				3.5	64	99	30
				24	73	99	30
13.6	**45**	10	**12**	1.6	49	43	48
				3.5	64	77	33
				24	67	77	33
13.7	**47**	1	**12**	1.6	21	6	46
				3.5	34	23	49
				24	56	28	40
13.8	**49**	1	**12**	1.6	35	33	75
				3.5	41	39	57
				24	64	47	44
13.9	**45**	1	**12**	1.6	40	29	49
				3.5	65	77	32
				24	69	79	30
13.10	**47**	1	**9**	1.6	17	0	33
				3.5	14	0	26
				24	45	0	29
13.11	**49**	1	**9**	1.6	27	0	68
				3.5	30	1	56
				24	50	13	54
13.12	**45**	1	**9**	1.6	39	19	56
				3.5	59	0	51
				24	67	11	54
13.13	**47**	1	**6**	4	22	1	64
				6	30	1	70

Note: ee's were determined by chiral GC, conversion was determined by NMR. Anhydride **37** was added over 3 h. Entry 13.13 was performed at 10 ^{o}C (all others at RT). All reactions were of 30 mg of 1-phenylethanol in 0.8 mL of solvents, except entry 13.13 which was 100 mg of 1-phenylethanol in 0.5 mL of solvents.

In search for alternative acetylating reagents multiple commercially available options were screened and some proved unsuitable. For example, several DKR attempts with AcCl and DIPEA mixture (with 5 mol % Birman's **49** in combination with varying loadings of Backvall's **6** or **5** in toluene / *t*-amyl alcohol = 2 / 3 mixture) were setup as we were intrigued by possibility to obtain enantioselective KR with AcCl. Unfortunately, all attempts resulted in kinetic resolutions and deeper investigations simply suggested that trace amounts of AcOH present in AcCl would possibly be responsible for inhibition of 5 mol % of redox catalyst. Next, based on previous knowledge in our laboratory, 4-nitrobenzoic anhydride was tested for DKR. However, chiral GC separation was problematic and product was almost racemic in all three reactions (with 1 mol % of Fu's **47**, Birman's **49** and Vedej's type **45** catalysts in combination with Backvall's **6** in toluene / *t*-amyl alcohol = 2 / 3 mixture), as a result, no further research was performed. Moreover, di-tert-butyl dicarbonate (Boc_2O) was employed with 5 mol % of Birman's **49** and Vedej's type **45** in combination with 5 mol % Backvall's **6** in toluene – *t*-amyl alcohol (2:3) mixture and both reactions did not yield any product. Synthesis of GC standards with equimolar 1-phenylethanol, Boc_2O and DMAP in the same toluene – *t*-amyl alcohol (2:3) mixture as well failed, hence, it was concluded that these conditions are unsuitable for addition of boc-group to 1-phenylethanol.

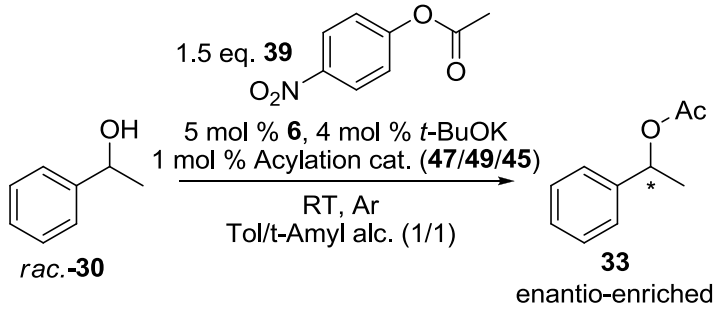
Furthermore, 2,5-dioxopyrrolidin-1-yl acetate **38** was to be tested, but the commercially obtained compound had noticeable acetic acid smell, proton NMR revealed that compound was indeed contaminated with acetic acid, hence, it was recrystallised from ethanol. Background reaction was checked by mixing equimolar amounts of 1-phenylethanol with **38** in toluene, this did not yield product in 24 h, thus it was concluded that no background reaction was running. Weak acid should be produced over the course of DKR and additional base might be necessary, hence two more background reaction checks were performed with addition of one equivalent of TEA or *t*-BuOK to a mixture of 1-phenylethanol and **38** in toluene. TEA did not induce background reaction, whereas addition of *t*-BuOK resulted in 21 % conversion after 40 min, interestingly, conversion did not change in further 24 hours. Then three DKR attempts were performed without extra base with Fu's **47**, Birman's **49** and Vedej's type **45** in combination with Backvall's **6** (scheme 28) and they all ended with only 1 % conversion in 22 h. As acetylation did not take place in DKR attempts, four reactions were setup to test if KR happens. For that matter 2 mol % Birman's **49** or Vedej's type **45** were added to mixtures of 1-phenylethanol with **38** and TEA or *t*-BuOK. Two KR attempts with TEA did not proceed at all, while both KR attempts in presence of *t*-BuOK yielded ~ 23 % of racemic ester **33**, meaning that only background reaction was present. With these two additional reactions we deduced that particular batch of *t*-BuOK was approximately 20 % *t*-

BuOK and remaining 80 % were some other potassium salts, thus it was discarded. Overall, we have witnessed that this particular acylating reagent was insufficiently reactive in these conditions and is not suitable for room temperature DKR.



Scheme 28. **DKR attempts with 2,5-dioxopyrrolidin-1-yl acetate 38.**

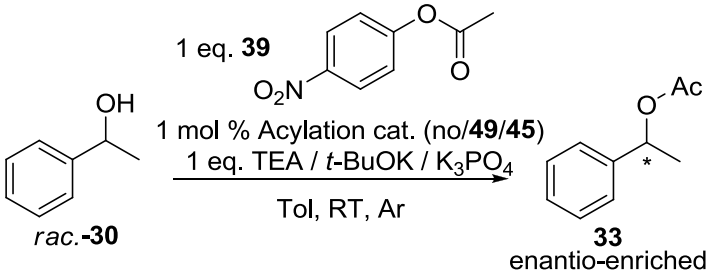
Only one acetylating reagent remained – 4-nitrophenyl acetate **39**. It was already known that kinetic resolution is feasible, thus it seemed a reasonable candidate for DKR. As in the case with acetic (isopropyl carbonic) anhydride **37**, it was decided to do syringe-pumping of 4-nitrophenyl acetate. 54 mg of acetylating reagent were dissolved in 0.4 mL of toluene – *t*-amyl alcohol mixture as reagent displayed poor solubility. As in previous cases, three reactions were setup with Fu's **47**, Birman's **49** and Vedej's type **45** acylation catalysts in combination with Backvall's **6**, overall reaction scale was 30 mg of 1-phenylethanol in 1.2 mL of solvents (scheme 29). Product **33** formation in all three cases was below 5 % in 23 hours, enantiomeric excesses in reactions with **47** and **45** were only 2 %, whereas in reaction with **49** ee was 58 %. Since product formation correlated to *t*-BuOK loading, background reaction had to be checked.



Scheme 29. **DKR attempts with 4-nitrophenyl acetate 39.**

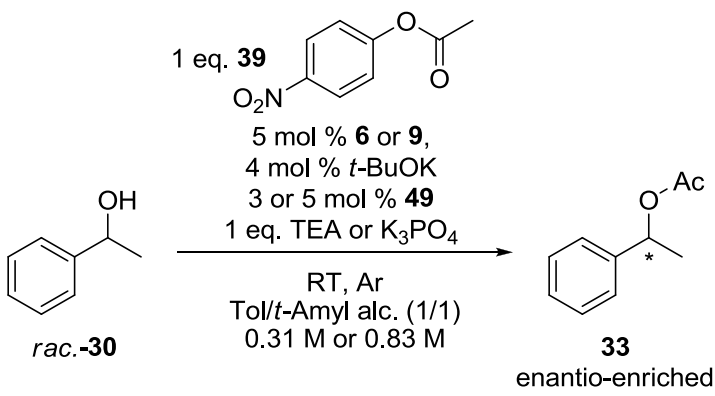
Background reaction was tested by running 25 hour reaction between 1-phenylethanol, 4-nitrophenyl acetate **39** and bases – TEA and *t*-BuOK with Birman's **49** and Vedej's type **45** catalysts and without catalyst (scheme 30). Reaction without catalyst with TEA yielded no product in 25 hours, whereas reaction without catalyst with *t*-BuOK resulted in 40 %

conversion in 25 hours. Reactions with Birman's catalyst **49** with both TEA and *t*-BuOK have resulted in 46 % conversions, however, ester's ee was 62 % in reaction with TEA and 10 % in reaction with *t*-BuOK. Reaction with catalyst **45** and TEA yielded 4 % of product with 22 % ee, whereas **45** with *t*-BuOK resulted in 40 % conversion and 0 % ee. All these findings were combined and it was concluded, that *t*-BuOK leads to rapid background reaction, whereas TEA supports KR, thus general base is necessary for a successful KR with **39** in combination with catalyst **49**. Potassium phosphate was also evaluated as another option for general base, hence one reaction with 4-nitrophenyl acetate **39**, K_3PO_4 and Birman's **49** was setup (note: in this case toluene – *t*-amyl alcohol (1:1) mixture was used). Potassium phosphate proved to be another candidate as general base for DKR as after 23 hours 57 % conversion was achieved with 56 % ee of ester.



Scheme 30. **Background reaction with 4-nitrophenyl acetate 39.**

Finally, dynamic kinetic resolutions were set up with additional general base (scheme 31). As KR with K_3PO_4 was faster, it was added to two DKR reactions with Park's **9** and Backvall's **6** (table 2.14., entries 14.1-14.2). Both reactions were slow as 48 % conversion was achieved in 6 days, furthermore, product was formed with lower that 60 % ee and reaction with **9** (entry 14.1) turned into KR after prolonged time (19 % ee of 1-phenyl ethanol after 50 h). Based on these findings it was decided to perform two more reactions in higher concentrations and with catalyst **6** in combination with potassium phosphate or TEA (entries 14.3 and 14.4). With increased concentration – reaction with K_3PO_4 became more rapid, reaching 64 % conversion in 53 h with 66 % ee of ester, however, 1-phenylethanol by that time already had accumulated 39 % ee (entry 14.3). On the other hand, reaction with TEA was much slower (29 % conversion in 24 h, compared to 49 % in reaction with K_3PO_4), but alcohol remained racemic and ester had slightly higher ee of 73 %. Concentration could not be increased further in order not to lose homogeneity of reaction mixtures as a result of poor solubility of acetylating reagent. Overall, slow DKR reactions were observed and after further in depth optimisation a new method of DKR with 4-nitrophenol acetate **39** could possibly be achieved.



Scheme 31. **DKR reactions with 4-nitrophenyl acetate 39 and general base.**

Table 2.14.

DKR reactions with 4-nitrophenyl acetate.

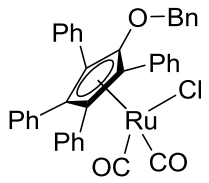
Entry	Rac. cat.	mol % of **49**	Base	Conc., M	Time, h	Conv., %	ee of **30**, %	ee of **33**, %
14.1	**9**	5	K_3PO_4	0.31	24	16	9	43
					50	27	19	50
					144	48	52	54
14.2	**6**				24	18	2	40
					50	26	4	49
					144	48	16	59
14.3		3		0.83	24	49	17	64
					53	64	39	66
14.4			TEA		24	29	2	73

Note: chiral GC was used for determination of ee; conversion was determined by proton NMR.

3. EXPERIMENTAL PART

General information. Unless otherwise noted, all chemicals were used as obtained from commercial sources. Analytical thin-layer chromatography (TLC) was performed on precoated silica gel F-254 plates. Nuclear magnetic resonance spectra were recorded on 300 MHz Bruker Avance NMR spectrometer at the following frequencies: ^{1}H, 300 MHz; $^{13}C\{^{1}H\}$, 75 MHz. Chemical shifts are reported in parts per million (ppm) relative to TMS or with the residual solvent peak as an internal reference. Liquid chromatography was performed on Waters LC-MS (gradient 10 % to 100 % MeCN in H_2O over 14 min) or Waters UPLC (gradient 10 % to 100 % MeCN in H_2O over 6 min). Gas chromatography analysis was performed on Agilent 6890N GC (temperature gradient 105 ^{o}C to 115 ^{o}C at 1 ^{o}C/min, then 115 ^{o}C to 150 ^{o}C at 5 ^{o}C/min) using Agilent J&W CP-Chirasil-Dex CB (0.25 mm ID, 25 m length, 0.25 μm film) column. All reactions were performed in 10 mL microwave tubes capped with penicillin vial caps to prevent evaporation and to preserve inert atmosphere, if needed. Solvents used were: dry toluene (ACROS 99.85 %), stored under inert atmosphere, extra dry DCM (ACROS 99.9 %), stored under inert atmosphere. *t*-amyl alcohol (TCI 98 % or ACROS 99 %) and deionised water.

3.1 Synthesis of catalysts

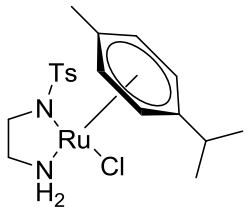


8

(*O*-Benzyl(tetraphenyl) cyclopentadienyl) dicarbonyl ruthenium (II) chloride (8)

A solution of η^4-$(C_4Ph_4CO)(CO)_3Ru$ (203 mg, 0.356 mmol, 1 equiv.) and benzyl chloride (41.1 uL, 45.1 mg, 0.357 mmol, 1 equiv.) in toluene (4 mL) was placed in a 10 mL MW vial, it was capped and flushed with argon. Reaction was heated at 110 °C under argon for 3 days, afterwards mixture was concentrated and purified by DP FC using 15 g silica-gel column (gradient 0% EA to 100% EA in PE in 15 CV), 17 mg (7 % yield) of sand coloured product was collected.

^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 4.87 (s, 2H), 6.97 – 7.30 (m, 21H), 7.55 – 7.57 (m, 4H) is in agreement with literature [14b].

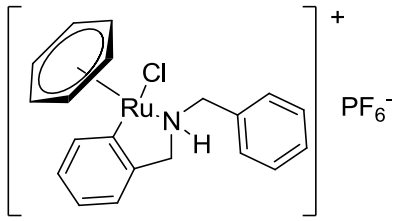


10

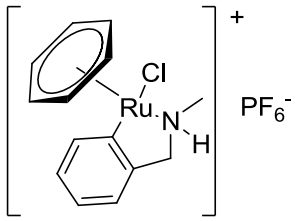
(*N*-*p*-Toluenesulfonylethylenediamine) (*p*-cymene) ruthenium (II) chloride (10)

N-p-toluenesulfonylethylenediamine (69.98 mg, 0.33 mmol, 2 equiv.), $[RuCl_2(p\text{-cymene})]_2$ (0.1 g, 0.16 mmol, 1 equiv.) and triethylamine (91 uL) and 2-propanol (3.3 mL) were added to a 10 mL MW tube. Tube was capped and flushed with Ar, reaction mixture was heated under reflux for 1 h. After cooling volatiles were removed in vacuo and the residue was dissolved in dichloromethane (5 mL). The red solution was washed two times with water (10 mL) and dried over Na_2SO_4. Removal of solvent yielded 127 mg (80 % yield) of red solid.

^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 1.22 (d, ^3J = 6.0 Hz, 6H), 2.13 (s, 3H), 2.33 (s, 3H), 2.64 – 3.00 (m, 5H), 5.43 – 5.63 (m, 4H), 7.16 (d, ^3J = 9.2 Hz, 2H), 7.75 (d, ^3J = 9.2 Hz, 2H) is in agreement with literature [20].



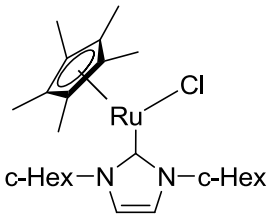
15



16

[(η^6-C_6H_6)Ru(C_6H_4-2-$CH_2NH(CH_2C_6H_5)$)($NCCH_3$)](PF_6) (15) and [(η^6-C_6H_6)Ru(C_6H_4-2-CH_2NH_2)($NCCH_3$)](PF_6) (16)

$[Ru(\eta^6\text{-}C_6H_6)Cl_2]_2$ (0.1 g, 0.2 mmol, 1 equiv.), NaOH (0.016 g, 0.4 mmol, 2 equiv.), and KPF_6 (0.147 g, 0.8 mmol, 4 equiv.) were weighed into 10 mL MW tube, capped, flushed with Ar and suspended in CH_3CN (5 mL). Then appropriate amine was introduced via syringe (dibenzylamine 0.039 g, 0.2 mmol, 1 equiv. for **15** and *N*-benzylmethylamine 0.024 g, 0.2 mmol, 1 equiv. for **16**), and the mixture was stirred at RT under inert atmosphere for 48 h. The dark yellow reaction mixture was filtered over Celite, concentrated under reduced pressure, and filtered over alumina plug with CH_3CN as eluent. The yellowish fraction was collected and concentrated on rotovap. Yellow residues of possibly **15** disintegrated to black solids under air soon after drying. 38 mg (39 %) of possibly **16** was collected, however, it rapidly disintegrated to green solids under air and NMR spectra were not obtained. Benzaldehyde smell was detected in both cases.



17

Chloro(1,3-dicyclohexyl-1,3-dihydro-2H-imidazol-2-ylidene)[(1,2,3,4,5-η)-1,2,3,4,5-pentamethyl-2,4-cyclopentadien-1-yl]ruthenium (17)

1st attempt in synthesis of **17**

ICy*HBF_4 (104.2 mg, 0.3 mmol, 1 equiv.) and *t*-BuOK (36.5 mg, 0.3 mmol, 1 equiv.) were added to 4 mL of dry THF under Ar, stirred for 1h and transfered to an Ar flushed flask containing ruthenium polymer **21** (100 mg, 0.3 mmol, 1 equiv.). Reaction mixture became green. After 5 h of stirring at RT, the reaction mixture was filtrated through a medium porosity frit and the filtrate was concentrated to dryness. The residue was then extracted with 50 mL of pentane, filtrated through a small porosity frit and concentrated under reduced pressure. Product was not obtained as only black tars were collected. Possibly the "activation" and formation of carbene did not proceed correctly or there might have been something that would degrade ruthenium polymer or complex.

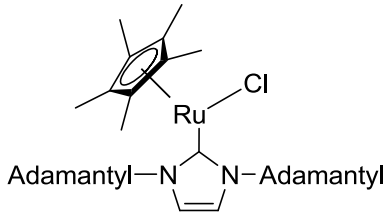
2nd attempt in synthesis of **17**

ICy*HCl (87.5 mg, 0.3 mmol, 1 equiv.) and Ag_2O (75.4 mg, 0.3 mmol, 1 equiv.) were dissolved in 6 mL of dry DCM under Ar, stirred and heated at 50 ^oC for 4 h. Ruthenium polymer **21** (100 mg, 0.3 mmol, 1 equiv.) was weighed in a separate MW tube, capped and flushed with Ar before being gently heated with a heat gun, some of the black powder turned to red coloured powder. As 4 hours elapsed, reaction mixture in DCM was transferred via syringe to the flask containing preheated ruthenium polymer **21**, reaction was heated at 40 ^oC for 4 h and then left to stir at RT for additional 72 h. LCMS analysis showed impure reaction mixture that contained product mass. Purification by pentane (as in 1st attempt) was unsuccessful. Then brown suspension was dissolved in minimal amount of DCM and hexane was added slowly, precipitation of orange-brown solid began, however, ^1H NMR analysis was inconclusive (peaks did not match those that were reported).

3rd attempt in synthesis of **17**

ICy*HCl (87.5 mg, 0.3 mmol, 3 equiv.) and Ag_2O (75.4 mg, 0.3 mmol, 3 equiv.) were dissolved in 6 mL of dry DCM under Ar, stirred and heated at 50 ^oC for 3 h. Ruthenium

tetramer **22** (100 mg, 0.1 mmol, 1 equiv.) was weighed in a separate MW tube, capped and flushed with Ar. As 3 hours elapsed, reaction mixture in DCM was transferred via syringe to the flask containing ruthenium tetramer **22**, solution became dark-red coloured. Reaction was then heated at 40 ^{o}C for 2 h and then left to stir at RT for additional 15 h, solution became dark-brown coloured. Purification by pentane (as in 1st attempt) was unsuccessful, product was not isolated.



18

Chloro[1,3-dihydro-1,3-bis(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-2H-imidazol-2-ylidene][(1,2,3,4,5-η)-1,2,3,4,5-pentamethyl-2,4-cyclopentadien-1-yl]ruthenium (18)

1st attempt to synthesise **18**

IAd (109.5 mg, 0.3 mmol, 1 equiv.) and ruthenium polymer **21** (100 mg, 0.3 mmol, 1 equiv.) were dissolved in 4 mL of dry THF under Ar, stirred at RT for 5 h. Proton NMR analysis of reaction mixture suggested that product was present in solution. Purification followed, reaction mixture was filtrated through a medium porosity frit and the filtrate was concentrated to dryness. The residue was then extracted with 50 mL of pentane, filtrated through a small porosity frit and concentrated under vacuo. Product was not obtained.

2nd attempt to synthesise **18**

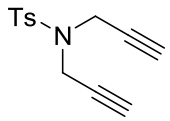
IAd (109.5 mg, 0.3 mmol, 3 equiv.) and ruthenium tetramer **22** (100 mg, 0.1 mmol, 1 equiv.) were dissolved in 9 mL of dry THF under Ar, a lot of starting material did not dissolve, stirred at RT for 2 h. Purification followed, reaction mixture was filtrated through a medium porosity frit and the filtrate was concentrated to dryness. The residue was then extracted with 50 mL of pentane, some insoluble black compound (similarly as with ruthenium polymer **21**) was observed, solution was filtrated through a small porosity frit and concentrated under vacuo. Product was not obtained. Insoluble black residue suggested a hypothesis that ruthenium tetramer **22** could be contaminated with ruthenium polymer **21**.

3rd attempt to synthesise **18**

Based on 2nd attempt we made an assumption: purchased tetramer was not entirely tetramer, this assumption was based on observation that some part of tetramer **21** did not dissolve. For

this reason 50.8 mg of tetramer complex **22** was weighed and dissolved in 4.5 mL dry THF, after stirring for 10 min it was centrifuged, liquid layer removed by syringe, solids were dried with Ar flow and weighed - 30 mg of undissolved leftovers. Remaining solution was dried by Ar flow and then it was used for further reaction.

IAd (24.8 mg, 0.07 mmol, 3 equiv.) and pre-purified ruthenium tetramer **22** (20 mg, 0.02 mmol, 1 equiv.) were dissolved in 1.8 mL of dry THF under Ar, everything dissolved and reaction mixture became deep-blue (as reported by Nolan). As an extra measure, reaction vial was covered with Al foil in order to prevent light and omit the chance of light-induced decomposition. It was left to stir at RT for 2 h, after which solution had become brown. Purification followed, reaction mixture was filtrated through a medium porosity frit and the filtrate was concentrated to dryness. The residue was then extracted with 50 mL of pentane, solution was filtrated through a small porosity frit and concentrated under reduced pressure. Small amount of product **18** was obtained, however, proton NMR spectra showed mixture of product (minor) and side products (major).

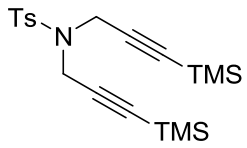


24

4-Methyl-*N*,*N*-di(prop-2-ynyl)benzenesulfonamide (24)

To a solution of p-toluenesulfonamide (1 g, 5.8 mmol, 1 equiv.) in dry acetonitrile (10 mL) in 20 mL MW tube was added potassium carbonate (2.02 g, 14.6 mmol, 2.5 equiv.), tube was capped and flushed with Ar. Propargyl bromide (80 % solution in toluene, 1.09 mL, 12.3 mmol, 2.1 equiv.) was injected and reaction was refluxed at 80 ^{o}C for 21 h. Afterwards MeCN was removed under reduced pressure and solid residue was dissolved in water (10 mL) and extracted with EA (30 mL), dried over Na_2SO_4. Purification on 100 g silica-gel DP FC (gradient 20 % EA to 100 % EA in PE in 15 CV) yielded 1 g (69 % yield) of white solid.

^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 2.15 (s, 2H), 2.43 (s, 3H), 4.17 (d, ^{4}J = 3.0 Hz, 4H), 7.31 (d, ^{3}J = 6.2 Hz, 2H), 7.72 (d, ^{3}J = 9.0 Hz, 2H) is in agreement with literature [18b].

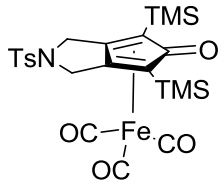


25

4-Methyl-*N*,*N*-bis(3-(trimethylsilyl)prop-2-ynyl)benzenesulfonamide (25)

To a solution of diyne **24** (150 mg, 0.61 mmol, 1 equiv.) in dry THF (1.2 mL), at –78 °C was injected n-BuLi (556 uL, 1.3 mmol, 2.4 M solution in hexanes, 2 equiv.). The reaction mixture was stirred for 10 minutes at –78 °C, and then 1 hour at room temperature. TMSCl (169 uL, 145 mg, 1.3 mmol, 2 equiv.) was added and the resulting solution was stirred at room temperature for 1 hour. Reaction was quenched with 1 mL of saturated NH_4Cl aqueous solution, then aqueous layer was extracted with ether (2x10mL). Organic phase dried over Na_2SO_4. Purification on 10 g silica-gel DP FC (gradient 5 % Et_2O to 15 % Et_2O in PE in 15 CV) yielded 174 mg (73 % yield) of yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 0.06 (s, 18H), 2.41 (s, 3H), 4.15 (s, 4H), 7.28 (d, ^3J = 6.0 Hz, 2H), 7.70 (d, ^3J = 9.0 Hz, 2H) is in agreement with literature [18b].

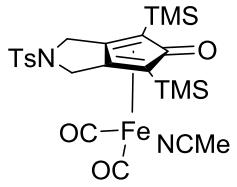


26

(2,4-bis(Trimethylsilyl)-7-*N*-tosyl-bicyclo[3.3.0]hepta-1,4-dien-3-one)iron tricarbonyl (26)

Diyne **25** (98 mg, 0.25 mmol, 1 equiv.) was dissolved in 2 mL of dry toluene (stored under Ar), MW tube was purged with Ar (needle in solution), then iron pentacarbonyl (101 uL, 147 mg, 0.75 mmol, 3 equiv.) was injected and reaction stirred for 2 days at 123 ^{o}C. After cooling solvent was evaporated, oil dissolved in PE and Et_2O mixture and filtered through syringe filter. Solvent was removed under reduced pressure and the yellow oil was then purified by DP FC using neutral alumina, as use of silica lead to some decomposition, (gradient 5 % Et_2O to 100 % Et_2O in PE in 15 CV) to give 100 mg (71 % yield) of yellow solid **26**.

^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 0.23 (s, 18H), 2.45 (s, 3H), 4.23 (d, ^2J = 15.0 Hz, 2H), 4.40 (d, ^2J = 15.0 Hz, 2H), 7.39 (d, ^3J = 9.2 Hz, 2H), 7.79 (d, ^3J = 6.0 Hz, 2H) is in agreement with literature [18b].

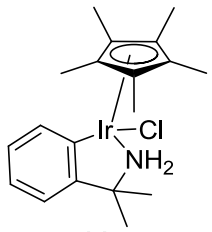


11

(2,4-bis(Trimethylsilyl)-7-*N*-tosyl-bicyclo[3.3.0]hepta-1,4-dien-3-one)iron acetonitrile dicarbonyl (11)

To a solution of iron complex **26** (56 mg, 0.1 mmol, 1 equiv.) in degassed MeCN (1.1 mL), was added Me_3NO (11.3 mg, 0.15 mmol, 1.5 equiv.). The 10 mL MW tube was protected from light with aluminium foil, and reaction mixture was stirred at room temperature for 3 hours. Then mixture was concentrated in vacuum. Crude product was purified on 10 g neutral alumina DP FC column using pure Et_2O as eluent to afford 33 mg (58 % yield) of yellow solid **11**.

^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 0.18 (s, 18H), 2.24 (s, 3H, CH_3CN), 2.44 (s, 3H), 3.93 – 4.07 (m, 4H), 7.35 (d, ^3J = 9.0 Hz, 2H), 7.73 (d, ^3J = 9.0 Hz, 2H) is in agreement with literature [18b].

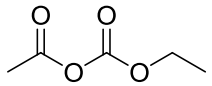


14

Cp*IrCl[κ^2(N,C)-($NH_2C(CH_3)_2$-2-C_6H_4)] (14)

[Cp*$IrCl_2$]$_2$ (80 mg, 0.1 mmol, 1 equiv.) and NaOAc (21.4 mg, 0.26 mmol, 2.6 equiv.) were weighed into 10 mL MW vial and capped, flushed with Ar. Then 4 mL of dry DCM and cumylamine (27.2 mg, 0.2 mmol, 2 equiv.) were introduced via syringe. Mixture was stirred at room temperature over-weekend (~70 h). Solvent was removed under reduced pressure. Solids were dissolved in toluene was filtered through 0.2 μm syringe filter, evaporation of the filtrate to dryness gave 100 mg (100 % yield) of orange crystalline iridacycle **14**.

^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 1.25 (s, 3H), 1.53 (s, 3H), 1.73 (s, 15H), 6.77 – 6.88 (m, 2H), 6.97 – 7.02 (m, 1H), 7.47 – 7.49 (m, 1H) is in agreement with literature [18a].

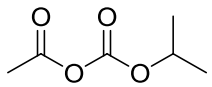


36

Acetic (ethyl carbonic) anhydride (36)

A 250 mL round-bottom flask was filled with 30 mL of anhydrous Et_2O and 2.1 mL TEA (15 mmol, 1 equiv.). Solution was cooled to 0 °C and 0.86 mL of acetic acid (15 mmol, 1 equiv.) were added added. Mixture was stirred for 10 min before adding 1.4 mL of ethyl chloroformate (15 mmol, 1 equiv.) dropwise over 5 min. Reaction was stirred for additional 40 min before quenching with 15 mL of 10 % citric acid solution. Organic layer was removed and extracted with additional 10 mL of 10 % citric acid, then 15 mL of saturated $NaHCO_3$ and 15 mL of brine before drying on Na_2SO_4. Evaporation of organic solution was done at ~300 mbar in order not to lose product **36**. 1.6 g of colourless liquid (79 % yield) were obtained.

^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 1.36 (t, ^3J = 7.2 Hz, 3H), 2.21 (s, 3H), 4.32 (q, ^3J = 7.2 Hz, 2H) is in agreement with literature [30].



37

Acetic (isopropyl carbonic) anhydride (37)

A 250 mL round-bottom flask was filled with 60 mL of anhydrous Et_2O and 4.1 mL TEA (30 mmol, 1 equiv.). Solution was cooled to 0 °C and 1.7 mL of acetic acid (30 mmol, 1 equiv.) were added added. Mixture was stirred for 10 min before adding 14.8 mL of 2 M isopropyl chloroformate (30 mmol, solution in Tol, 1 equiv.) dropwise over 10 min. Reaction was stirred for additional 45 min before quenching with 30 mL of 10 % citric acid solution. Organic layer was removed and extracted with additional 20 mL of 10 % citric acid, then 30 mL of saturated $NaHCO_3$ and 30 mL of brine before drying on Na_2SO_4. Evaporation of organic solution under reduced pressure afforded 3.7 g of slightly yellowish liquid **37** (85 % yield).

^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 1.35 (d, ^3J = 6.3 Hz, 6H), 2.21 (s, 3H), 4.99 (septet, ^3J = 6.3 Hz, 1H) is in agreement with literature [30].

3.2 Setup of racemisation, KR and DKR reactions

General racemisation reaction procedure: base and racemisation catalyst were weighed (only for air-sensitive catalyst **9** this was done in glovebox, the rest - under ambient atmosphere) into 10 mL MW tube. Then stir bar was added and the tube was capped (purged

with Ar, if needed). Afterwards, 1.5 mL of solvent (Tol or *t*-amyl alc.) and solution of (*R*)-1-phenylethanol in toluene (30 mg in 1 mL, alcohol in toluene) were added.

General KR reaction procedure: to a 10 mL MW tube acylation catalyst was weighed (5 mol %) and 1.5 mL *t*-amyl alcohol was added, followed by solution of rac. 1-phenylethanol (30 mg, 1 eq.) in toluene (30 mg in 1 mL, alcohol in toluene). Stir bar was added and tube was capped and flushed with Ar. 0.6 eq. of anhydride (13.9 uL acetic or 24.0 uL isobutyric) was added with micro syringe.

General DKR reaction procedure: acetylating reagent (if solid), acylation catalyst, general base (if required and if solid), *t*-BuOK, followed by racemisation catalyst were weighed (for air-sensitive catalysts this was done in glovebox, the rest - under ambient atmosphere) into 10 mL MW tube. Stir bar was added to the tube and the tube was capped (purged with Ar, if needed), then 1.5 mL of solvent (Tol or *t*-amyl alc.) was added, after 10 minutes solution of 1-phenylethanol (30 mg) in 1 mL of toluene, general base (if required and if liquid) and acetylating reagent (if liquid) were added to the coloured solution (reaction mixtures were suspensions in several cases with higher concentrations).

General procedure for preparation of GC samples: 0,15 – 0,18 mL of reaction mixture were taken, diluted with ~ 1 mL of Et_2O and extracted with 0,3 – 0,5 mL H_2O. Water phase washed with another portion of ~ 1mL of Et_2O. Organic phase dried over Na_2SO_4 in Pasteur pipette before GC analysis. Retention times: (*R*)-1-phenylethanol 14.36 min; (*S*)-1-phenylethanol 14.85 min; (*S*)-1-phenylethyl acetate 11.24 min; (*R*)-1-phenylethyl acetate 12.37 min; 1-phenylethyl isobutyrate 15.13 min and 15.17 min.

CONCLUSIONS

1. Majority of tested racemisation catalysts were unsuitable for nonenzymatic DKR. As rate of racemization of (*R*)-1-phenylethanol using these catalysts was too slow under experimental conditions.

2. Bäckvall's catalyst **6** is top choice for room temperature racemisation, being fast and non-sensitive to air. Complete racemization of secondary alcohol is achieved in less than 30 minutes.

3. Nolan's **12** and Park's **9** catalysts are as reactive as Bäckvall's catalyst **6**, but only under inert atmosphere. Complete racemization is achieved in less than 30 minutes, however, both catalysts are sensitive to air, hence, should be stored in glove-box and are less applicable.

4. Previously unreported racemisation catalyst **5** was found. The complex **5** achieved complete racemisation of (*R*)-1-phenylethanol within 2 h under inert atmosphere.

5. Iridium complex **14** is a rapid racemisation catalyst that is unaffected by carboxylates. However, it is unsuitable for DKR as it is inhibited by acylating reagent of amido group.

6. Fu's catalyst **47** (s = 23.3) and Birman's catalyst **49** (s = 19.8) showed highest enantioselectivities in KR of 1-phenylethanol. However, Birman's catalyst **49** is at least 5 times faster.

7. Commercially available 4-nitrophenyl acetate was shown to be compatible with Bäckvall's catalyst **6** and suitable for KR of 1-phenylethanol. Thus, it can be used in non-enzymatic DKR in combination with Bäckvall's catalyst **6** and Birman's catalyst **49**.

REFERENCES

1. Papageorgiou, V. P.; Assimopoulou, A. N.; Couladouros, E. A.; Hepworth, D.; Nicolaou, K. C. The chemistry and biology of alkannin, shikonin, and related naphthazarin natural products. *Angew. Chem. Int. Ed.*, **1999**, *38*, 270–301.
2. Meizer, R.; Meraner, D.; Meizer, E.; Radda, C.; Landsiedl, F.; Aigner, N. Outcome of painful bone marrow edema of the femoral head following treatment with parenteral iloprost. *Indian J Orthop*., **2009**, *43*, 36–39.
3. Boyd, M. Indinavir: the forgotten HIV-protease inhibitor. Does it still have a role? *Expert Opin. Pharmacother*., **2007**, *8*, 957–964.
4. Sharma, P.; Sharma, R. K. Platinum functionalized multiwall carbon nanotube composites as recyclable catalyst for highly efficient asymmetric hydrogenation of methyl pyruvate. *RSC Adv*., **2015**, *5*, 102481–102487.
5. For crizotinib: a) Kocienski, P. Synthesis of Crizotinib (PF-02341066). *Synfacts*, **2011**, *12*, 1274–1274 b) Qian, J.-Q.; Yan, P.-C.; Che, D.-Q.; Zhou, Q.-L.; Li, Y.-Q. A novel approach for the synthesis of Crizotinib through the key chiral alcohol intermediate by asymmetric hydrogenation using highly active Ir-Spiro-PAP catalyst. *Tet. Lett*., **2014**, *55*, 1528–1531. For lorlatinib c) Johnson, T. W.; Richardson, P. F.; Bailey, S.; Brooun, A.; Burke, B. J.; Collins, M. R.; Cui, J. J.; Deal, J. G.; Deng, Y. L.; Dinh, D.; Engstrom, L. D.; He, M.; Hoffman, J.; Hoffman, R. L.; Huang, Q.; Kania, R. S.; Kath, J. C.; Lam, H.; Lam, J. L.; Le, P. T.; Lingardo, L.; Liu, W.; McTigue, M.; Palmer, C. L.; Sach, N. W.; Smeal, T.; Smith, G. L.; Stewart, A. E.; Timofeevski, S.; Zhu, H.; Zhu, J.; Zou, H. Y.; Edwards, M. P. Discovery of (10*R*)-7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2H-8,4-(metheno)pyrazolo[4,3-h][2,5,11]-benzoxadiazacyclotetradecine-3-carbonitrile (PF-06463922), a macrocyclic inhibitor of anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1) with preclinical brain exposure and broad-spectrum potency against ALK-resistant mutations. *J. Med. Chem.*, **2014**, *57*, 4720–4744.
6. Klauck, M. I.; Patel, S. G.; Wiskur, S. L. Obtaining enriched compounds via a tandem enantioselective reaction and kinetic resolution polishing sequence. *J. Org. Chem.* **2012**, *77*, 3570−3575.
7. Truppo, M. D. Biocatalysis in the pharmaceutical industry: the need for speed. *ACS Med Chem. Lett.*, **2017**, *8*, 476−480.

8. For review Ahn, Y.; Ko, S.-B.; Kim, M.-J.; Park, J. Racemization catalysts for the dynamic kinetic resolution of alcohols and amines. *Coord. chem. Rev.*, **2008**, *252*, 647–658.
9. Xu, G.; Wang, L.; Chen, Y.; Cheng, Y.; Wu, J.; Yang, L. Highly efficient dynamic kinetic resolution of secondary aromatic alcohols using a low-cost solid super acid as a racemization catalyst. *Tet. Lett*., **2013**, *54*, 5026–5030.
10. a) Cheng, Y.; Xu, G.; Wu, J.; Zhang, C.; Yang, L. Highly efficient dynamic kinetic resolution of secondary aromatic alcohols with low-cost and easily available acid resins as racemization catalysts. *Tet. Lett*., **2010**, *51*, 2366–2369. b) Xu, G.; Chen, Y.; Wu, J.; Yang, L. Dynamic kinetic resolution of secondary aromatic alcohols with new efficient acyl donors. *Tet. Asym*., **2011**, *22*, 1373–1378.
11. Wolfson, A.; Yehuda, C.; Shokin, O.; Tavor, D. Simple and recyclable oxidation, racemization and dynamic kinetic resolution of activated alcohols catalyzed by hydrated ruthenium chloride in aqueous medium. *Lett. in Org. Chem*., **2006**, *3*, 107–110.
12. Cao, H.; Cai, L.-H.; Wang, C.-X.; Zhu, X.-H.; Li, Z.-M.; Hou, X.-F. Ligand effect in racemization and dynamic kinetic resolution of alcohols: mechanism on cymene ruthenium complexes. *J. Organom. Chem*., **2015**, *775*, 60–66.
13. a) Matute, B. M.; Edin, M.; Bogár, K.; Bäckvall, J.-E. Highly compatible metal and enzyme catalysts for efficient dynamic kinetic resolution of alcohols at ambient temperature. *Angew. Chem. Int. Ed.*, **2004**, *43*, 6535–6539 b) Warner, M. C.; Verho, O.; Bäckvall, J.-E. CO dissociation mechanism in racemization of alcohols by a cyclopentadienyl ruthenium dicarbonyl catalyst. *J. Am. Chem. Soc*., **2011**, *133*, 2820–2823 c) Stewart, B.; Nyhlen, J.; Matute, B. M.; Bäckvall, J.-E.; Privalov, T. A computational study of the CO dissociation in cyclopentadienyl ruthenium complexes relevant to the racemization of alcohols. *Dalton Trans*., **2013**, *42*, 927–934.
14. a) Choi, J. H.; Kim, Y. H.; Nam, S. H.; Shin, S. T.; Kim, M.-J.; Park, J. Aminocyclopentadienyl ruthenium chloride: catalytic racemization and dynamic kinetic resolution of alcohols at ambient temperature. *Angew. Chem. Int. Ed*., **2002** *41*, 2373–2376 b) Kim, N.; Ko, S.-B.; Kwon, M. S.; Kim, M.-J.; Park, J. Air-stable racemization catalyst for dynamic kinetic resolution of secondary alcohols at room temperature. *Org. Lett*., **2005**, *7*, 4523–4526.
15. Samec, J. S. M.; Bäckvall, J.-E.; Andersson, P. G.; Brandt, P. Mechanistic aspects of transition metal-catalyzed hydrogen transfer reactions. *Chem. Soc. Rev*., **2006**, *35*, 237–248.

16. Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. Asymmetric transfer hydrogenation of imines. *J. Am. Chem. Soc*., **1996**, *118*, 4916–4917.
17. a) Yamaguchi, K.; Mizuno, N. Supported ruthenium catalyst for the heterogeneous oxidation of alcohols with molecular oxygen. *Angew. Chem. Int. Ed*., **2002**, *41*, 4538–4542 b) Yamaguchi, K.; Mizuno, N. Scope, kinetics, and mechanistic aspects of aerobic oxidations catalyzed by ruthenium supported on alumina. *Chem. Eur. J*., **2003**, *9*, 4353–4361 c) Zsigmond, A.; Kecskemeti, A.; Bogar, K.; Notheisz, F.; Mernyak, E. Efficient heterogeneous racemization of secondary alcohols: convenient synthesis of 17α-estradiol 3-methyl ether. *Cat. Comm*., **2005**, *6*, 520–524.
18. a) Arita, S.; Koike, T.; Kayaki, Y.; Ikariya, T. Synthesis and Reactivities of Cp*Ir Amide and Hydride Complexes Bearing C−N Chelate Ligands. *Organom*., **2008**, *27*, 2795–2802 b) Sato, Y.; Kayaki, Y.; Ikariya, T. Comparative Study of Bifunctional Mononuclear and Dinuclear Amidoiridium Complexes with Chiral C−N Chelating Ligands for the Asymmetric Transfer Hydrogenation of Ketones. *Chem. Asian J*., **2016**, *11*, 2924–2931.
19. a) Sepelgy, O. E.; Alandini, N.; Rueping, M. Merging iron catalysis and biocatalysis—iron carbonyl complexes as efficient hydrogen autotransfer catalysts in dynamic kinetic resolutions. *Angew. Chem. Int. Ed*., **2016**, *55*, 13602–13605 b) Moulin, S.; Dentel, H.; Ozherelyeva, A. P.; Gaillard, S.; Poater, A.; Cavallo, L.; Lohier, J. F.; Renaud, J.-L. Bifunctional (cyclopentadienone)iron–tricarbonyl complexes: synthesis, computational studies and application in reductive amination. *Chem. Eur. J*. **2013**, *19*, 17881–17890.
20. Ghanem, A.; Aboul-Enein, H. Y. Application of lipases in kinetic resolution of racemates. *Chirality*, **2004**, *17*, 1–15.
21. a) Arias-Perez, M. S.; Cosme, A.; Galvez, E.; Sanz-Aparicio, J.; Fonseca, I.; Bellanato, J. Structural study of (±) alkyl 3-hydroxy-1-azabicyclo[2.2.2]octane-3-carboxylates. *J. Mol. Struct*. **2003**, *644*, 171-179 b) Aroyan, C.E.; Miller, S. J. Enantioselective Rauhut−Currier Reactions Promoted by Protected Cysteine. *J. Am. Chem. Soc*., **2007**, *129*, 256-257 c) Xiao, Y.; Sun, Z.; Guo, H.; Kwon, O. Chiral phosphines in nucleophilic organocatalysis. *Beilstein J. Org. Chem*., **2014**, *10*, 2089–2121.
22. Yang, X., Liu, P.; Houk, K. N.; Birman, V. B. Manifestation of Felkin-Anh Control in Enantioselective Acyl Transfer Catalysis: Kinetic Resolution of Carboxylic Acids. *Angew. Chem. Int. Ed*., **2012**, *51*, 9638–9642.

23. Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. Practical Considerations in Kinetic Resolution Reactions. *Adv. Synth. & Cat*., **2001**, *343*, 5–26.
24. Ó Dálaigh, C.; Connon, S. J. Nonenzymatic Acylative Kinetic Resolution of Baylis−Hillman Adducts. *J. Org. Chem*., **2007**, *72*, 7066–7069.
25. Ruble, J. C.; Fu, G. C. Chiral π-Complexes of Heterocycles with Transition Metals: A Versatile New Family of Nucleophilic Catalysts. *J. Org. Chem*., **1996**, *61*, 7230–7231.
26. Larsson, A. L. E.; Persson, B. A.; Bäckvall, J.-E. Enzymatic Resolution of Alcohols Coupled with Ruthenium- Catalyzed Racemization of the Substrate Alcohol. *Angew. Chem. Int. Ed.,* **1997**, *36*, 1211-1212.
27. Kim, M.-J.; Choi, Y. K.; Choi, M. Y.; Kim, M. J.; Park, J. Lipase/Ruthenium-Catalyzed Dynamic Kinetic Resolution of Hydroxy Acids, Diols, and Hydroxy Aldehydes Protected with a Bulky Group. *J. Org. Chem*., **2001**, *66*, 4736-4738.
28. a) Pàmies, O.; Bäckvall, J.-E. Chemoenzymatic dynamic kinetic resolution. *Trends Biotechnol*., **2004**, *22*, 130–135 b) Martín-Matute, B.; Edin, M.; Bogár, K.; Kaynak, F. B.; Bäckvall, J.-E. Combined Ruthenium (II) and Lipase Catalysis for Efficient Dynamic Kinetic Resolution of Secondary Alcohols. Insight into the Racemization Mechanism. *J. Am. Chem. Soc*., **2005**, *127*, 8817–8825.
29. Cabrera, Z.; Fernandez-Lorente, G.; Fernandez-Lafuente, R.; Palomo, J. M.; Guisan, J. M. Novozym 435 displays very different selectivity compared to lipase from Candida antarctica B adsorbed on other hydrophobic supports. J. Mol. Catal. B: Enzym., **2009**, *57*, 171–176.
30. Lee, S. Y.; Murphy, J. M.; Ukai, A.; Fu, G. C. Nonenzymatic dynamic kinetic resolution of secondary alcohols via enantioselective acylation: synthetic and mechanistic studies. *J. Am. Chem. Soc.*, **2012**, *134*, 15149–15153.
31. Dijksman, A.; Elzinga, J. M.; Li, Y. X.; Arends, I. W. C. E.; Sheldon, R. Efficient ruthenium-catalyzed racemization of secondary alcohols: application to dynamic kinetic resolution. A. *Tet. Asym*., **2002**, *13*, 879–884.
32. a) Sortais, J.-B.; Pannetier, N.; Holuigue, A.; Barloy, L.; Sirlin, C.; Pfeffer, M.; Kyritsakas, N. Cyclometalation of Primary Benzyl Amines by Ruthenium(II), Rhodium(III) and Iridium(III) Complexes. *Organom*., **2007**, *26*, 1856-1867 b) Jerphagnon, T.; Haak, R.; Berthiol, F.; Gayet, A. J. A.; Ritleng, V.; Holuigue, A.; Pannetier, N.; Pfeffer, M.; Voelklin, A.; Lefort, L.; Verzijl, G.; Tarabiono, C.; Janssen, D. B.; Minnaard, A. J.; Feringa, B. L.; Vries, J. G. Ruthenacycles and Iridacycles as Catalysts for Asymmetric Transfer Hydrogenation and Racemisation. *Top. Catal.*, **2010**, *53*, 1002–1008.

33. a) Huang, J.; Schanz, H.-J.; Stevens, E. D.; Nolan S. P. Stereoelectronic Effects Characterizing Nucleophilic Carbene Ligands Bound to the Cp*RuCl (Cp* = η^5-C_5Me_5) Moiety: A Structural and Thermochemical Investigation. *Organom*., **1999**, *18*, 2370–2375 b) Bosson, J.; Nolan, S. P. *N*-Heterocyclic Carbene-Ruthenium Complexes for the Racemization of Chiral Alcohols. *J. Org. Chem*., **2010**, *75*, 2039–2043.
34. a) Csabai, P.; Joó, F. Synthesis and Catalytic Properties of New Water-Soluble Ruthenium (II) N-Heterocyclic Carbene Complexes. *Organom*., **2004**, *23*, 5640–5643 b) Arduengo, A. J.; Harlow, R. L.; Kline, M. A Stable Crystalline Carbene. *J. Am. Chem. Soc*., **1991**, *113*, 361–363.
35. Saeidian, H.; Sadighian, H.; Arabgari, M.; Mirjafary, Z.; Ayati, S. E.; Najafi, E.; Moghaddam, F. M. Organocopper-based magnetically recoverable and reusable nanocatalyst for efficient synthesis of novel 1,2,3-triazole-based sulfonamides in green medium. *Res. Chem. Intermed.*, **2018**, *44*, 601–612.
36. Kinens, A.; Sejejs, M.; Kamlet, A. S.; Piotrowski, D. W.; Vedejs, E.; Suna, E. Development of a Chiral DMAP Catalyst for the Dynamic Kinetic Resolution of Azole Hemiaminals. *J. Org. Chem*., **2017**, *82*, 869–886.
37. Kinens, A.; Balkaitis, S.; Suna, E. Preparative-Scale Synthesis of Vedejs Chiral DMAP Catalysts. *J. Org. Chem*., **2018**, *83,* 12449–12459.

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