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Chiral Diamine Derivatives: Synthesis and Evaluation as Transient Directing Groups (TDGs) in C(sp3)-H activation reactions of α-keto amides

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Laburpena

Gradu Amaierako Lan hau Donostiako Kimika Fakultateko Kimika Organikoa I Sailean garatu da, Maria Antonia Mielgo Vicente irakaslearen zuzendaritzapean. Proiektu honetan planteatutako ikerketa Kimika Organikoaren arloan kokatzen da, zehazki, katalisi asimetrikoaren barruan. Lan honetan esploratu/aztertu da Pd-ak eta talde bideratzaile iragankorrek (Transient Directing Groups/TDGs ingelesez) bidez katalizatutako **K1** eta **K2** α-zeto amiden C(sp3)-H aktibazioa. Bereziki, β posiziotik haratago gelditzen diren posizioen arilazioan enfokatu da ikerketa, γ eta δ posizioetan, alegia. Erreakzioak bi motatako TDG-rekin gauzatu dira, lehenik katalizatzaile komertzial akiralekin (glizina eta β-alanina), eta ondoren diseinatutako TDG kiralekin. Lehenik eta behin, bi α-zeto amida substratuak (**K1** eta **K2**) sintetizatu dira taldean aurretik egindako protokoloetan oinarriturik. Ondoren, **L1**, **L2** eta **L3** TDG kiralen (diamina kiralen deribatuak) sintesia gauzatu da, bibliografian deskribatutako beste metodoetan egokitzapenak eginez. **L1** eta **L2** TDGak lortu eta karakterizatu egin dira. Aldiz, **L3** TDGa ez da lortu. **L1** eta **L2** ligandoak sintetizatzea lortu bada ere, haien sintesi protokoloak eta etekinak optimizatu behar dira oraindik. Azkenik, TDG ezberdinek katalizatutako C(sp3)-H arilazio erreakzioak esploratu dira, elektrozale bezala aril ioduroa komertziala erabiliz. Lehenik, erreakzio errazemikoak gauzatu dira: glizina eta β-alaninak katalizaturik. Ondoren diseinatutako **L1** eta **L2** TDGekin erreakzio asimetrikoak aztertu dira. Kasu guztietan erreakzioa ematen da, nahiz eta bakoitzak konbertsio ezberdina eman. Diseinaturiko TDGek erreakzioa ahalbidetzen dute, γ-arilazio selektiboa emanez, baina konbertsioa ez da totala, eta ez da espero zen enantioselektibitatea lortu.

Summary

This research project has been developed in the Department of Organic Chemistry I at the Faculty of Chemistry in Donostia, under the guidance of Professor Maria Antonia Mielgo Vicente. Research carried out in this project belongs to the Organic Chemistry field, more precisely, to the area of asymmetric catalysis. This work's aim has been to explore the reactivity of α-keto amides in C(sp3)-H activation reactions catalysed by Pd metal and transient directing groups (also abbreviated as TDG), more specifically, the direct arylation of more remote positions than the β site, in other words, the γ and δ positions. The reactions have been carried out with two types of ligands, first with commercially available achiral ligands (glycine and β-alanine), then with the designed chiral TDGs. Hence, first the α-keto amides (**K1** and **K2**) have been synthesised by adapting the protocols previously used in the research group. Afterwards, the synthesis of **L1**, **L2** and **L3** (chiral diamine derivatives) has been explored, adapting other methods described in the literature. **L1** and **L2** have been synthesised, although the protocols and yields require optimisation; however, **L3** has not been obtained. Lastly, the C(sp3)-H activation reactions have been explored using different TDGs and commercially available aryl iodide as the electrophile. The racemic reactions have been explored using achiral TDGs glycine and β-alanine. Then the designed **L1** and **L2** TDGs have also been tested. All TDGs analysed promote the C(sp3)-H arylation reaction with different conversions. Furthermore, the designed TDGs promote the selective γ-arylation of the α-keto amides but in the explored conditions the conversion is not complete and the observed enantioselectivity did not match the expected results.

Abbreviations and acronyms

Ac	Acetate
AcOH	Acetic acid
calcd.	Calculated
cat.	Catalyst/Catalytic
Cbz	Benzyl chloroformate
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
dr	Diastereomeric ratio
DCM	Dichloromethane
DMF	Dimethylformamide
ee	Enantiomeric excess
equiv.	Equivalent
Et	Ethyl
EtOAc	Ethyl acetate
EtOH	Ethanol
FG	Functional Group
FGI	Functional Group Interchange
h	Hour(s)
Hex	Hexane
HFIP	1,1,1,3,3,3-Hexafluoro-2-propanol
HPLC	High Performance Liquid Chromatography
IBX	2-Iodoxybenzoic acid
MeOH	Methanol
MHz	Megahertz
min	Minute(s)
m.p.	Melting point
nd	Not determined
ND	Not detected
NMR	Nuclear Magnetic Resonance
NSAID	Non-steroidal anti-inflammatory drugs
NR	No reaction
o.n.	Overnight
OTf_2	Trifluoromethanesulfonic anhydride
Ph	Phenyl

ppm	Parts per million
rt	Room temperature
t	Time
T	Temperature
*t*Bu	*tert*-Butyl
Et_3N	Triethylamine
TFA	Trifluoroacetic acid
THF	Tretrahydrofuran
TLC	Thin Layer Chromatography
TM	Transition metal
Tol	Toluene
δ	Chemical shift
λ	Wavelength

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1. INTRODUCTION

1.1. α-KETO AMIDES: INTEREST AND REACTIVITY

Aldehydes and ketones are ubiquitous molecules playing an important role as building blocks in organic synthesis, whose reactivity has been thoroughly studied throughout history by the chemical community. The functionalised derivatives of these compounds can be found as smaller units in biologically active molecules. For example, Streptomycin, which is used to treat several bacterial infections such as tuberculosis or plague; contains a α,β-functionalised aldehyde moiety. On the other hand, Nabumetone, a NSAID (non-steroidal anti-inflammatory drug) contains a β-functionalised ketone unit.[1] There are plenty of examples of other commercialised drugs which contain (β-) functionalised carbonylic substructures such as esters (or lactones as Warfarin), amides (or lactames, like Phenylpiracetam and Rolipram) or carboxylic acids (Baclofen) (Figure 1).[2, 3]

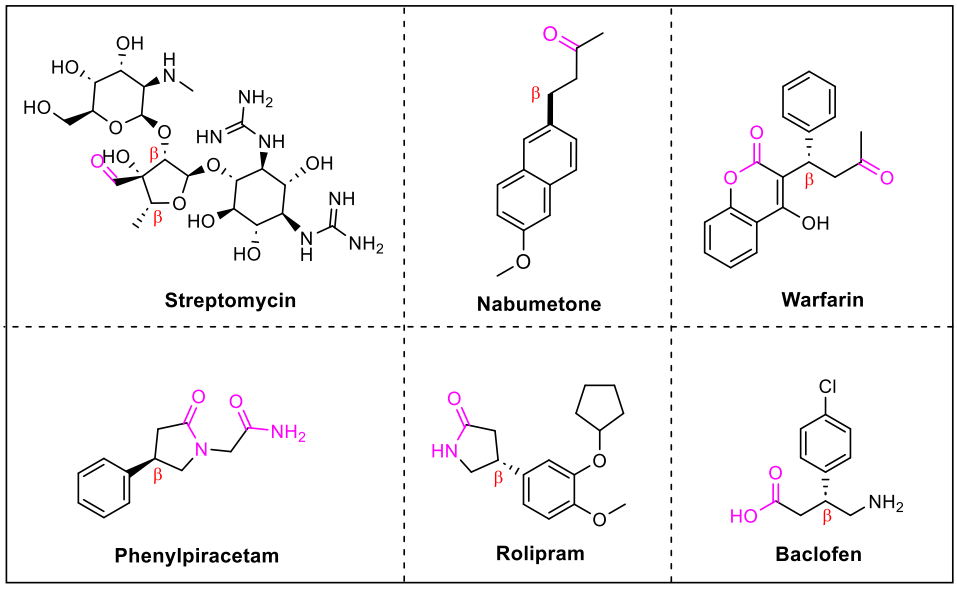


Figure 1. Bioactive compounds containing chiral β-functionalised carbonylic units.

On this basis, α-keto amides are a particular type of ketones that, as its name implies, contain an amide group at the α position adjacent to the ketone functional group (FG). α-keto amides are equally important building blocks in biology and synthetic organic chemistry as drug molecules or their key synthetic intermediates. The α-keto amide is known as a "privileged structure" as it is a useful ligand for different target proteins such as receptors, enzymes and so forth. These molecules can be classified into two

[1] Ge, H.; Yang, K.; Li, G., *Chem. Commun.* **2018**, *54*, 2759-2762.
[2] J. Ansell; J. Hirsh; L. Poller; H. Bussey; A. Jackobson; E. Hylek, *Chest*; **2004**, *126*, 204.
[3] W. Froestl, Future *Med. Chem.*; **2011**, *3*, 163-175

subgroups. The first group is made up by natural α-keto amides: for example, Complestatin (Figure 2, a), Eurystatin A and B (Figure 2, b) and Aplidine (Figure 2, c), which display HIV (human immunodeficiency viruses) replication inhibitor, prolyl endopeptidase inhibitor and antitumor activities respectively. The second subgroup, which consists of non-natural α-keto amides, have biological properties as well: epoxide hydrolase inhibitor, orexin receptor antagonist (Figure 2, e) and much more. This group of molecules has also been studied as replication inhibitors of Coronavirus and Enterovirus.[4]

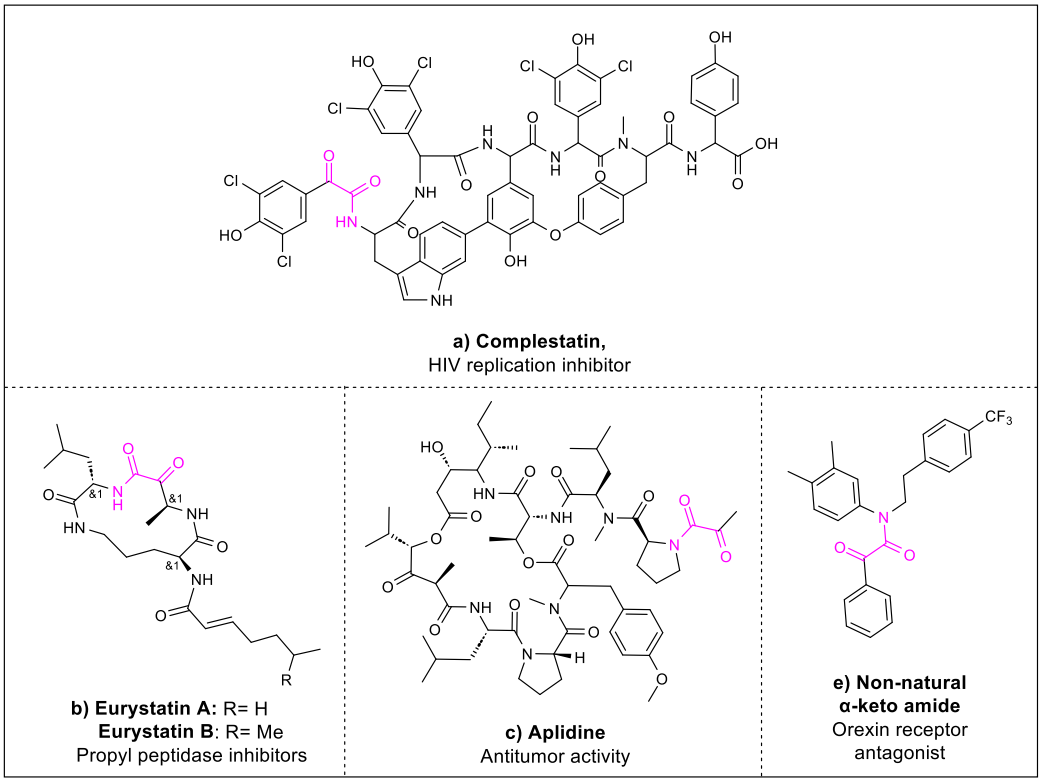


Figure 2. Bioactive compounds containing the α-keto amide moiety.

As a matter of fact, this group of molecules have unusually reactive ambident proelectrophile and pronucleophile moieties, containing five potentially active sites (Figure 3). Three of these are electrophilic, which are namely the ketone, the amide carbonyl and the (potentially) γ position carbon of its β,γ-unsaturated derivatives. The two remaining centres are nucleophilic: the amide nitrogen and the enolisable β-C-H. Nevertheless, the ketone carbon (ipso position) and the amide nitrogen are surely the most reactive sites, as the ketone is an activated carbonyl due to the presence of the electron-withdrawing amide group at the α-position. This property also increases the

[4] Robello, M.; Barresi, E.; Baglini, E.; Salerno, S.; Taliani, S.; Settimo, F. D., *J. Med. Chem.*; **2021,** 64, 3508-3545.

nucleophilicity of the nitrogen as the keto group is electron withdrawing and it facilitates the rotation of the C-N bond.[4]

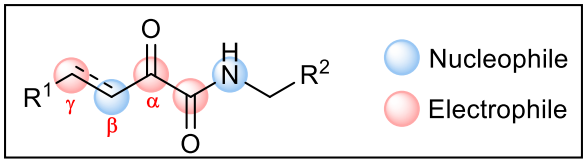


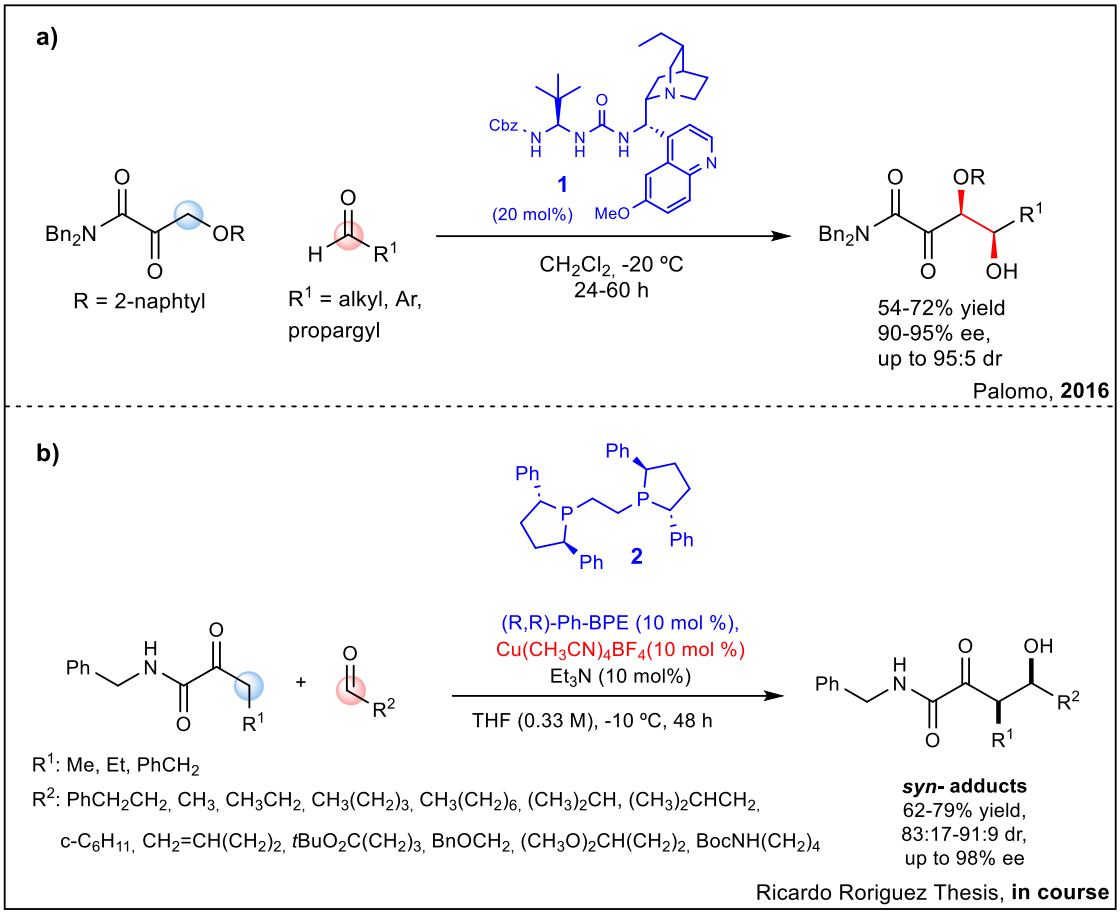
Figure 3. Chemically active sites on α-keto amides.

Due to the different reactive sites of these molecules, they can either be mono- di- or tri-functionalised, and the site of functionalisation can also be targeted by altering the reaction mechanisms and conditions. Most of the reactions explored have been done with cyclic α-keto amides, although there also are some advances in the functionalisation of aliphatic acyclic molecules. As previously stated, the keto functionality attached directly to the electron withdrawing amide carbonyl group is highly activated (electrophilic). This causes the ipso carbon and the γ position in β,γ-unsaturated derivatives to be very reactive electrophile sites. Hence, even if most of the reactivity of conventional ketones can be applied to α-keto amides, most studies concerning these molecules investigate the nucleophilic attack on the ipso carbon or Michael type additions; in both cases, the α-keto amide acts as the electrophile. [5] However, the behaviour of these α-keto amides as nucleophiles has been comparatively much less studied. Due to the high functionality of these molecules, the development of protocols for the regioselective functionalisation at one specific site is highly desirable.

In this context, our group has recently started to explore new methods for the direct functionalisation of α-keto amides in which the α-keto amides act as the nucleophile (via the nucleophilic β carbon).

In 2016, our group reported the diastereo- and enantioselective cross aldol reaction of β-alkoxy-α-keto amides with different aldehydes catalysed by the Brønsted Base **1** (Scheme 1, a).[6] These included enolisable, non-enolisable and FG-containing aldehydes to produce highly enantioenriched polyoxygenated aldol adducts without side-products (coming from dehydration, α-keto amide self-condensation, aldehyde enolisation or isotetronic acid formation).

[5] A. Muthukumar; S. Sangeetha; G. Sekar, *Org. Biomol. Chem.* **2018,** *16*, 7068-7083.
[6] H. Echave.; R. López; C. Palomo, *Angew. Chem. Int. Ed.* **2016,** *55*, 3364-3368.



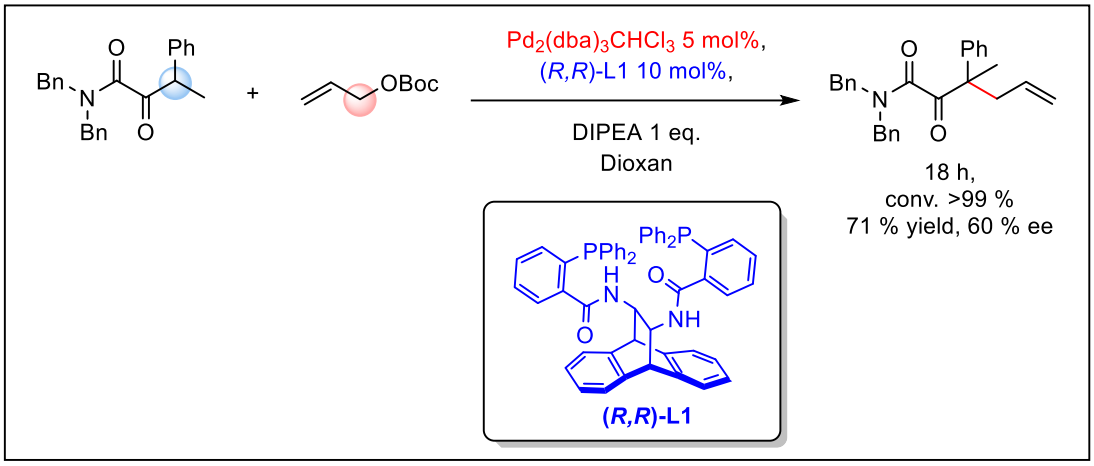
Scheme 1. Previous work of the group: a) Bronsted Base catalysed asymmetric aldol reactions of β-alkoxy-α-keto amides. Palomo, 2016. b) Cross aldol reaction of α-keto amides promoted by a chiral Cu(I) complex and Et_3N, Ricardo Rodriguez Thesis, ongoing.

More recently, the group has also expanded the pronucleophile scope of the α-ketoamides in the cross-aldol reaction (Scheme 1, b). In fact, under optimised conditions β-alkyl α-ketoamides react with different enolisable aldehydes in the presence of a Cu(I) salt, a tertiary amine and Pilkington's chiral biphosphine ligand **2** to afford the corresponding syn- aldols in good yields and very high enantioselectivity.[7]

In parallel, during the development of her PhD thesis, A. Vázquez in our group also explored the enantioselective β-allylation of the β-substituted α-ketoamides depicted in Scheme 2. The best results and conditions of this study provide the allyl derivative in 60% ee. This transformation is also currently being investigated and optimised in our

[7] R. Rodriguez, **2023**, *Asymmetric Direct Cross Aldol Reaction of α-Ketoamides Catalyzed by a Cu(I) Complex*, Unpublished results. Doctoral Thesis, *Universidad del País Vasco, UPV/EHU.*

group by M. Campo and I. Arburua. Preliminary results show that the reaction proceeds with only 10 mol% of base.[8]



Scheme 2. Asymmetric β-allylic allylation of α-keto amides, A. Vázquez PhD Thesis, 2020; M. Campo PhD Thesis, I. Arburua Master's Degree 2023.

Taking that into consideration, the development of efficient catalytic and asymmetric protocols for the regioselective functionalisation of α-ketoamides by using them as nucleophiles would be interesting and would open a whole range of possibilities for biological applications. In this context, the search of efficient protocols for the direct functionalisation via C(sp3)-H activation of more remote and less accessible γ (and hopefully δ) positions of α-keto amides is of high interest.

1.2. TRADITIONAL METHODS FOR THE FUNCTIONALISATION OF ALDEHYDES AND KETONES

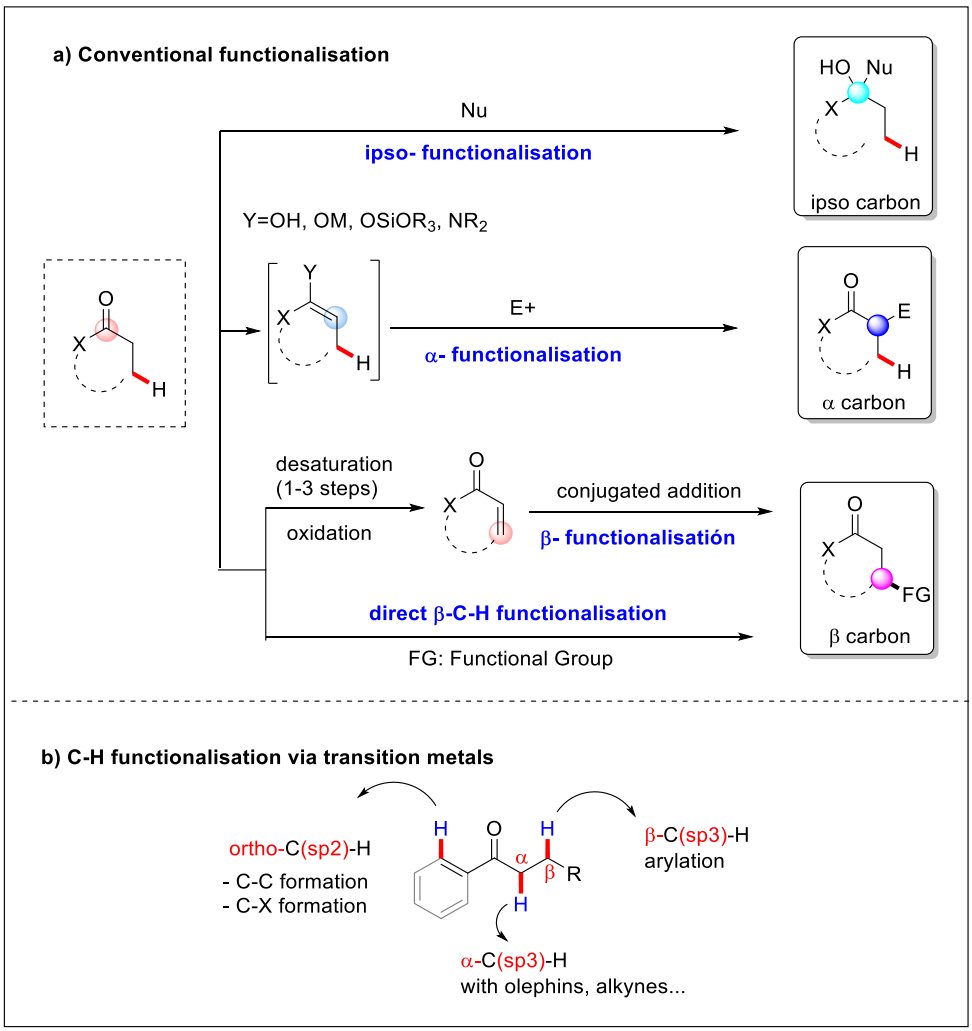
As previously mentioned, ketones and aldehydes are ubiquitous frames in natural products and synthetic intermediates. A wide range of transformations of aliphatic aldehydes and ketones rely on the reactivity of the ipso, α and β carbon centres (Scheme 3, a).

The enolisation of aldehydes and ketones and subsequent addition of these anionic species to other moieties is an extensively studied reaction and a very powerful tool in organic chemistry. This works via deprotonation of the carbon adjacent to the carbonyl group, creating a highly nucleophilic species, that partakes in many reactions: Aldol,

[8] a) A. Vázquez, **2020**, *Asymmetric β-allylic allylation of α-keto amides*, Doctoral Thesis, *Universidad del País Vasco UPV/EHU*. b) M. Campo, **2022**, Master's Thesis, *Universidad del País Vasco UPV/EHU*. c) I. Arburua, **2023**, Master's Thesis, *Universidad del País Vasco UPV/EHU*.

Claisen condensation, Michael addition, Robinson annulation and Reformatsky reactions to name a few.

While the ipso and α positions of aldehydes and ketones are generally more activated for their functionalisation, traditionally and in general, functionalisation of the β position is achieved through the conjugate addition of nucleophiles to the corresponding α,β-unsaturated carbonylic compounds. However, these α,β-unsaturated compounds have also to be previously synthesised, usually by stoichiometric oxidation of their saturated derivatives. Therefore, the development of direct methods to introduce functionalisation at the β position would significantly improve the efficiency of the preparation of these β-functionalised derivatives.

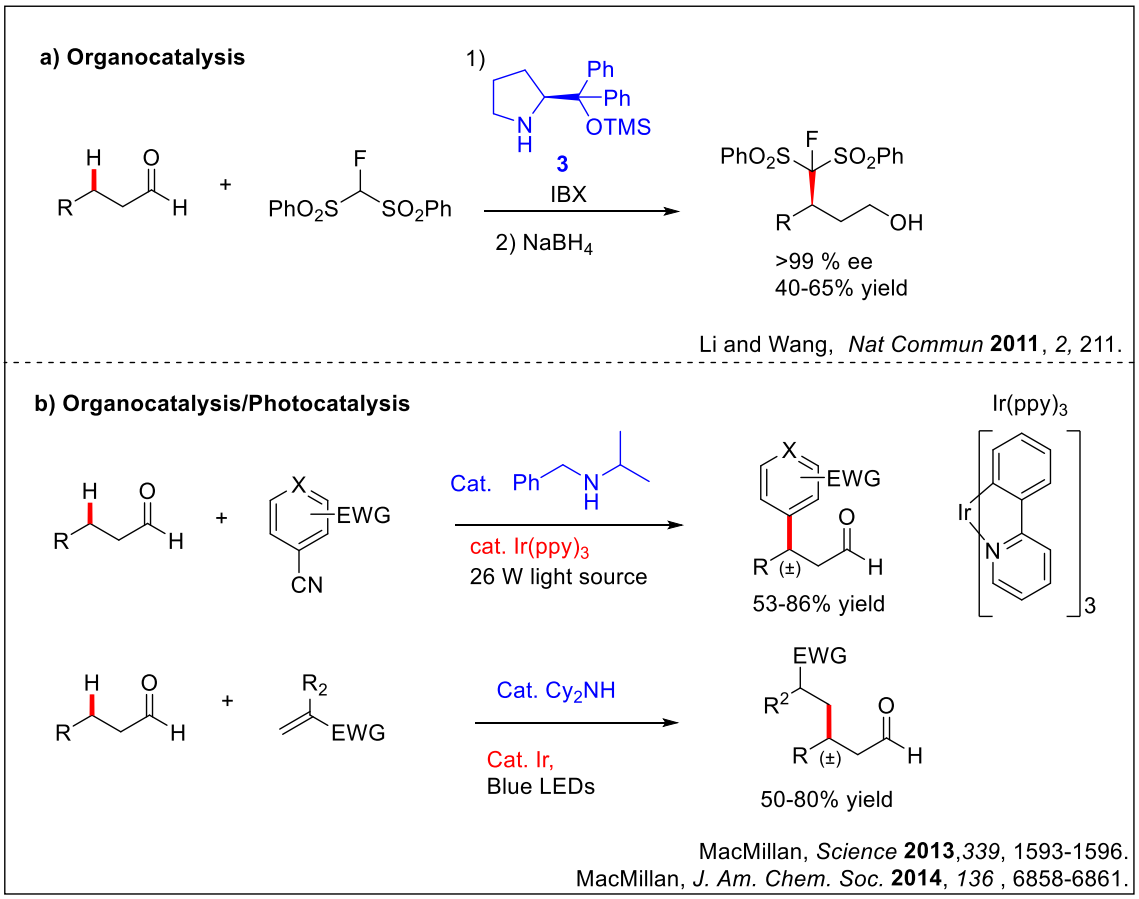


Scheme 3: Strategies for the functionalisation of aldehydes and ketones.

In recent years, new strategies have been developed for the functionalisation of carbonylic compounds at the β or γ positions which consist of C-H activation reactions by means of transition metal (TM) catalysts (cat.) (Scheme 3, b).

In the majority of stereoselective functionalisation reactions of aldehydes and ketones, one stereocenter is formed adjacent or very close to the site of catalysis. Very few examples have been described in which the stereocenter is directly achieved two, three, or more bonds away from the carbonylic group. Therefore, the remote stereochemical control in the functionalisation of these carbonyl derivatives represents an ambitious challenge in asymmetric catalytic synthesis.

Nevertheless, the direct functionalisation of the β position of aldehydes and ketones is still very underdeveloped and even more so for the enantioselective protocols.



Scheme 4. Methods for the direct β-functionalisation of aldehydes.

Two organocatalytic examples described for this purpose are shown in Scheme 4, the first one developed by Li and Wang in 2011 describes the enantioselective functionalisation of simple aldehydes (Scheme 4, a) in presence of the chiral amine cat. **3** and an IBX as the oxidant (2-Iodobenzoic acid), which involves the sequential formation of an enamine, oxidation process and nucleophilic addition, thus affording the

β-functionalised aldehydes, which were isolated as the alcohols due to their instability, in excellent enantioselectivity and from moderate to good yields.[9]

Subsequently, MacMillan's group developed the direct functionalisation of non-activated C(sp3)-H bonds of aliphatic aldehydes, by merging organocatalysis and photocatalysis (Scheme 4, b). Although this protocol provides β-functionalised aldehydes in moderate to good yields, the reaction is not enantioselective.[10] In this context, C(sp3)-H activation of carbonyl compounds at β or other remote positions is an interesting tool to open the range of accessible functionalised derivatives of this type.

1.3. C-H ACTIVATION: GENERAL CONCEPTS

Transition metal-catalysed activation and functionalisation of carbon-hydrogen bonds, also known as C-H activation, has undoubtably been one of the most revolutionary discoveries in the history of organic chemistry. This finding is highly interesting as it transforms carbon-hydrogen bonds that were deemed inert into new FGs, forming C-C and/or C-X bonds whilst bypassing intermediate FG installation and uninstallation. This innovation effectively reduces the steps of a synthetic route, which drives researchers and industries to create shortcuts in already familiar or standard synthetic pathways, channelling the scientific community towards a more efficient, greener chemistry. However, despite the many advances this chemistry has achieved since its preliminary reports, it is evident this new chemistry still has a lot of progress to make.

For instance, most of these reactions rely on the use of precious second-row and third-row TMs such as Palladium (Pd), Rhodium (Rh), Iridium (Ir) and Ruthenium (Ru), which, albeit efficient, are usually expensive and toxic.[11] These high-valent TMs like Pd^{II}, Rh^{III}, Ir^{III}, and Ru^{II} usually react via electrophilic pathways (normally aided by rendering them more electrophilic with solvents, ligands, and additives) like concerted metalation-deprotonation (CMD). Low-valent, electron-rich metals (Rh^{I}, Ir^{I}) on the other hand, normally undergo oxidative addition into C-H bonds, which kick-starts the reaction.[12] Thankfully, more and more researchers nowadays focus on the applications of inexpensive and abundant 3d TM(Cu, Co, Fe, Mn, and Ni).[11] Some other groups try to

[9] S.-L., Zhang S.-L.; H.-X., Xie; Zhu, J.; H. Li; X.-S., Zhang; J. Li; W. Wang, *Nat. Commun* **2011**, *2*, 211.
[10] a) M. T. Pirnot; D. A. Rankic; D. B. C. Martin; D. W. C. MacMillan, *Science* **2013,***339*, 1593-1596. b) J. A. Terrett; M. D. Clift; D. W. C. MacMillan, *J. Am. Chem. Soc.* **2014**, *136*, 6858-6861.
[11] P. Gandeepan; T. Müller; D. Zell; G. Cera; S. Warratz; L. Ackermann, *Chem. Rev.* **2019**, *119*, 2192–2452.
[12] T. Gensch; M. N. Hopkinson; F. Glorius; J. Wencel-Delord, *Soc. Rev.* **2016,** *45*, 2900-2936.

avoid the use of metal altogether and explore non-metal mediated C-H activation reactions.[13]

Not only do most of these experiments use precious metals, but the solvents used, which heavily influence the reactivity of the catalysts, are oftentimes toxic, flammable organic solvents (methanol, fluorinated alcohols...) and frequently expensive.[11, 14] Additionally, C-H bond activation reactions more often than not require additives (Lewis acids, Bronsted acids, metallic salts and/or different combinations of these compounds), which influence the conversion, selectivity or kinetics of the reactions.[11, 15]

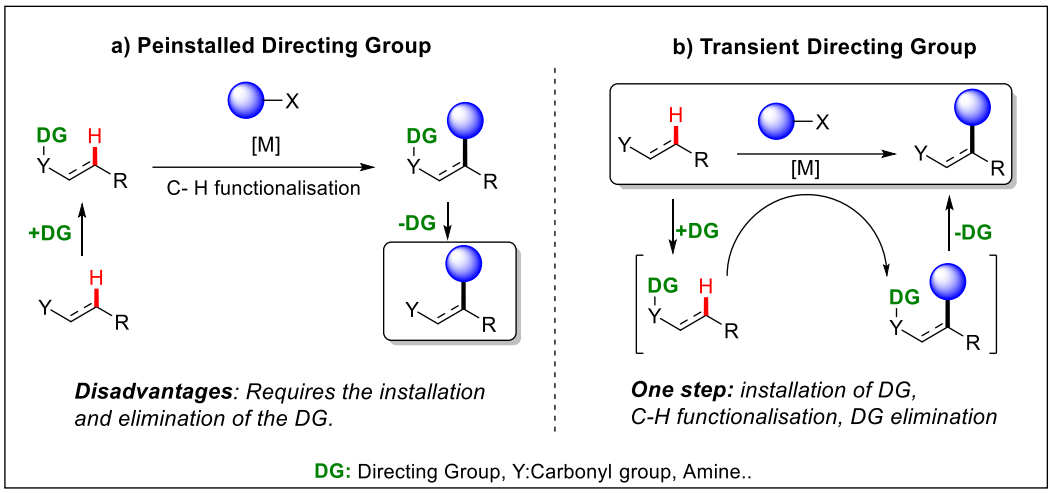
In spite of all this, nowadays C-H activation reactions are still appealing as well as interesting to access a range of C-functionalised compounds.

In this context, the ubiquity, and the high dissociation energy of C(sp3)-H bonds (100 kcal.mol^{-1}) poses the main problem in this field of research: the site-selectivity of carbon-hydrogen bond activation and functionalisation. There are two general solutions for this issue. In some reactions, inherent electronic and steric properties of the substrates such as the presence of FGs or chiral centres predetermine the regioselectivity (and in some cases, enantioselectivity) of the TM catalysts. This rule generally applies to molecules containing heteroatoms and heterocycles.[16]

The second method consists in the usage of directing groups (DGs), since arenes and aliphatic compounds do not contain such pronounced intrinsic reactivity gaps as mentioned in the last paragraph. These directing groups, which are located on the hydrocarbon reactant, are moieties that can coordinate to the metal catalyst. In consequence, this groups reacts as an "internal ligand" that attaches to the catalyst, directing it into the proximity of a specific C-H bond, channelling the activation reaction and accentuating the site-reactivity of the transformation (Scheme 5, a). These directing groups can either be monodentate, bidentate and even tridentate, depending on the distance of the C-H bond that wants to be modified from the coordinating atom. Despite this method's beneficial contribution to C-H activation reactivity, this strategy requires the covalent installation of the auxiliary directing group, which after the reaction must be eliminated from the product, which is inconvenient for its synthetic applications. Therefore, this strategy adds two additional steps to the synthetic sequence and

[13] A. Shamsabadi; V. Chudasama, *Org. Biomol. Chem.* **2019**, *17*, 2865-2872.
[14] F. Colobert; J. Wencel-Delord, *Org. Chem. Front.* **2016**, *3*, 394-400.
[15] M. Anand; R. B. Sunoj; H. F. Schaefer, III, *J.Am.Chem.Soc.* **2014**, *136*, 5535–5538.
[16] K. Murali; L. A. Machado; R. L. Carvalho; L. F. Pedrosa; R. Mukherjee; E. N. Da Silva Júnior; D. Maiti, *Chem.Eur.* J. **2021**, *27*, 12453–12508.

secondly, the conditions for the installation or/and elimination of directing groups might not be compatible with other FGs present in synthetic intermediate molecules.



Scheme 5. Strategies for the C-H functionalisation by means of Directing Groups (DGs).

A more appealing option consists of performing the installation and removal of the DG in situ (Scheme 5, b). In this case, the coordinating group is called a Transient Directing Group (TDG) and once the desired product is formed, the derivative is converted back into the original FG. So, after the C-H activation and the subsequent functionalisation, the directing group must dissociate from the product for it to temporarily attach to another substrate molecule. In this way, only a substoichiometric quantity of catalyst and ligand (TDG) would be needed, which would be an effective strategy to avoid the problems presented in the installation and elimination of the DGs we have mentioned before.[17]

In this context, C(sp2)-H activation has been thoroughly investigated in this area, since alkenes, heteroaromatics and aromatics and their derivatives are more reactive due to the presence of weaker π bonds. In contrast, relatively fewer reports of C(sp3)-H activation have been published due to the lower reactivity of these bonds. As a matter of fact, the high-level σ-CH* LUMO and the low-level σ-CH HOMO make the C(sp3)-H chemically inactive; and unlike the C-C double bond, the C(sp3)-H bond cannot pre-coordinate to the TM cat. due to the lack of stabilising π interactions that occur between the metal and the arene. The flexibility exhibited by the alkyl chains and the propensity of TM-alkyl intermediates to give an unwanted β-hydride elimination are additional obstacles. Because of this, C-H bonds with sp3 hybridisation are less prone to react and to be split by transition metals both from a kinetic, and thermodynamic point of view.

[17] P. Gandeepan; L. Ackermann, *Chem*, **2017**, 4, 199–222.

However, more and more research groups focus on the functionalisation of C(sp3)-H bonds nowadays.[18]

1.4. C(sp3)-H ACTIVATION IN ALDEHYDES AND KETONES BY IMINE-TYPE TDGs

As it has been stated earlier, a wide range of transformations of aliphatic aldehydes and ketones rely on the reactivity of the ipso- and α- carbon centres (Scheme 3, a). Nonetheless, recently some more research groups are getting involved in the investigation of direct functionalisation of the β position in aldehydes and ketones, and they do so by means of TM-catalysed C-H activation reactions.

Common FGs such as ketones or aldehydes are usually weakly coordinating and therefore, are poor candidates for TM-catalysed C-H activation reactions. Fortunately, these groups can easily be transformed into their better-donor derivatives such as imines, enamines, oximes, or hydrazones via Schiff base reactivity. These newly formed nitrogen-containing FGs are usually excellent chelating agents. Thus, they can act as nitrogen-containing DGs by coordinating to the TM catalyst and by drawing the desired C-H bond closer to the reactive site, allowing for a regioselective (or stereocontrolled) functionalisation reaction.[17] After the arylation (or the corresponding reaction) is complete, the imine (or corresponding N-containing FG) is hydrolysed back to the aldehyde or ketone, giving the desired final product. In other words, the TDG method relays heavily on the reversibility of the carbonyl-imine reactivity, which acts as the key-reaction to kickstart the catalytic cycle of the C-H activation reaction.

The functionalisation of C(sp3)-H in aliphatic ketones and aldehydes catalysed by TMs, which emerged almost a decade ago now, has been less explored than their more oxidised, analogous carboxylic compounds with a higher oxidation state. Analysing the described examples, most of the contributions to the processes of functionalisation of β-C(sp3)-H bonds are based on the reversible installation of a bidentate DG via an imine bond that favours a bicyclic cyclometallation intermediate.

Despite the benefits of using TDGs for the C(sp3)-H functionalisation of aldehydes and ketones, its application is not as developed as for other substrates or preinstalled DGs. The main contributions to this field of research are summarised below.

[18] T. Rogge; N. Kaplaneris; N. Chatani; J. Kim; S. Chang; B. Punji; L. L. Schafer; D. G. Musaev; J. Wencel-Delord; C. A. Roberts; R. Sarpong; Z. E. Wilson; M. A. Brimble; M. J. Johansson; L. Ackermann, *Nat Rev Methods Primers* **2021**, *1:43*.

The functionalisation of C–H bond catalysed by TMs provides a simple and effective way to synthesize differing aldehydes and ketones.[19] The TM-catalysed β-C–H bonds reaction based on TDG is credited as a most efficient method. In 1997, Jun et al. first proposed the concept of TDG in transformation of aldehydes to ketones with a Rh catalyst assisted by 2-amino-3-picoline.[20] In 2014, Dong's group reported Ru-catalysed alkylation of ketones using secondary amines as TDGs.[21]

The first explorations of palladium-catalysed C(sp3)-H arylation of aldehydes were published in 2016 almost simultaneously, by Yu on the one hand,[22] and Li and Ge on the other hand.[23]

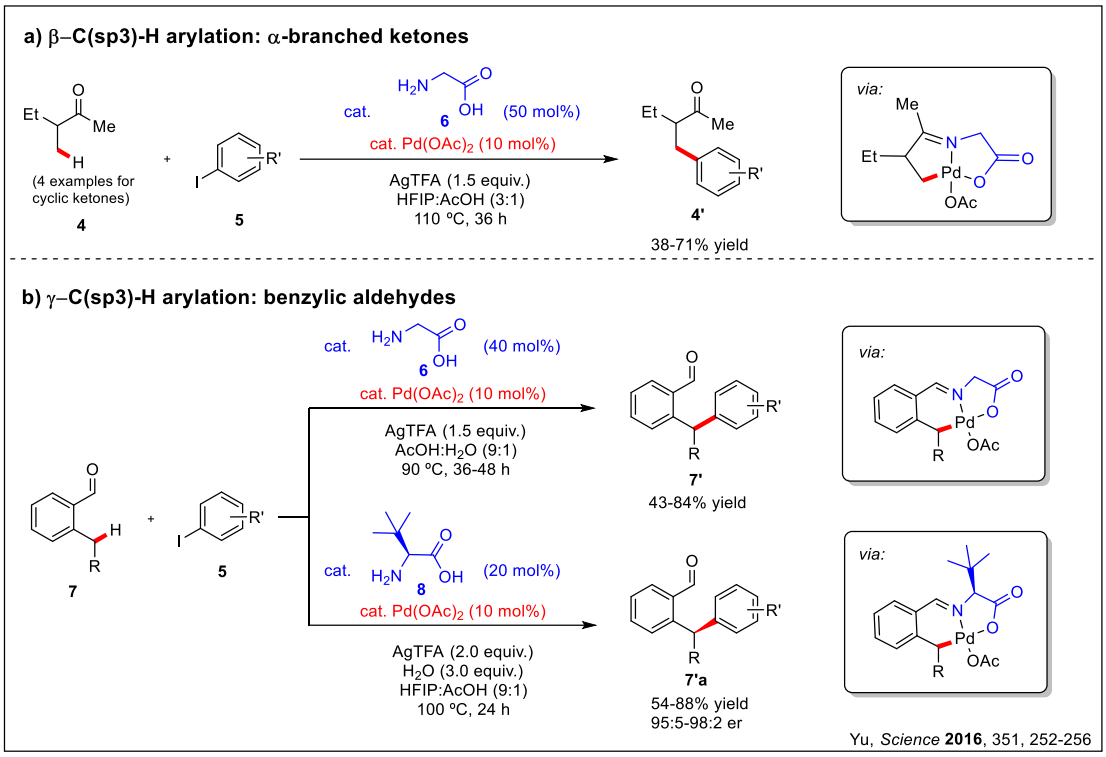
Prof. Yu described the Pd-catalysed β-arylation of α-branched aliphatic ketones (**4**, including 4 examples of cyclic ketones) on the one hand (Scheme 6, a); and on the other hand, the γ-arylation of benzaldehydes containing a methylene group at the ortho position (o-alkyl benzaldehydes **7**) (Scheme 6, b) while using glycine **6** as the TDG. In all three cases the arylated products were afforded in good yields in general via [5,5] and [5,6] fused byciclic palladium intermediates. [22] Additionally, when changing the glycine **6** by the enantiopure L-*tert*-leucine **8**, a broad range of **7** o-alkyl benzaldehydes were efficiently γ-arylated to provide the aryl derivatives in excellent enantioselectivity. It is important to note, that in this set of γ position activation reactions no competing β-C(sp3)-H bonds were available for functionalisation.

The group also did a set of control experiments in which they deduced that, firstly, in the reactions of the o-alkyl benzaldehydes the addition of H_2O improved the conversion as it reduced the quantity of imine intermediates that participated in competing side reactions that decomposed the starting material. They also concluded that the efficiency of the reaction did not specifically depend on the electronical character of the aryl iodide **5**, but more on the steric hindrance of both the substrate and the aryl iodide derivatives.

Although, glycine **6** was not a suitable TDG for Pd-catalysed C(sp3)-H activation of aliphatic aldehydes as side reactions lead to the decomposition of the accumulated

[19] For selected examples, see: a) S. Afewerki; A Córdova, *Chem. Rev.* **2016**, *116*, 13512–13570. b) X. -H. Zhang; D. W. C. MacMillan, *J. Am. Chem. Soc.* **2017**, *139*, 11353–11356. c) R.- Y, Zhu; Z.-Q. Li; H. S. Park; C. H. Senanayake; J.-Q. Yu, *J. Am. Chem. Soc.* **2018**, *140*, 3564–3568.
[20] C.-H. Jun; H. Lee; J.-B. Hong, *J. Org. Chem.* **1997**, *62*, 1200–1201.
[21] F.-Y. Mo; G.-B. Dong, *Science* **2014**, *345*, 68–72.
[22] F.-L. Zhang; K. Hong; T-J Li ; H. Park; J.-Q. Yu, *Science* **2016**, *351*, 252-256.
[23] K. Yang; Q. Li; Y. Liu ; G. Li ; H. Ge, *J. Am. Chem. Soc.* **2016**, *138*, 12775-12778.

imine intermediate. This would suppose that the proposed [5,5'] fused bicycle Pd intermediate would be suitable for aliphatic ketones but not for aliphatic aldehydes.

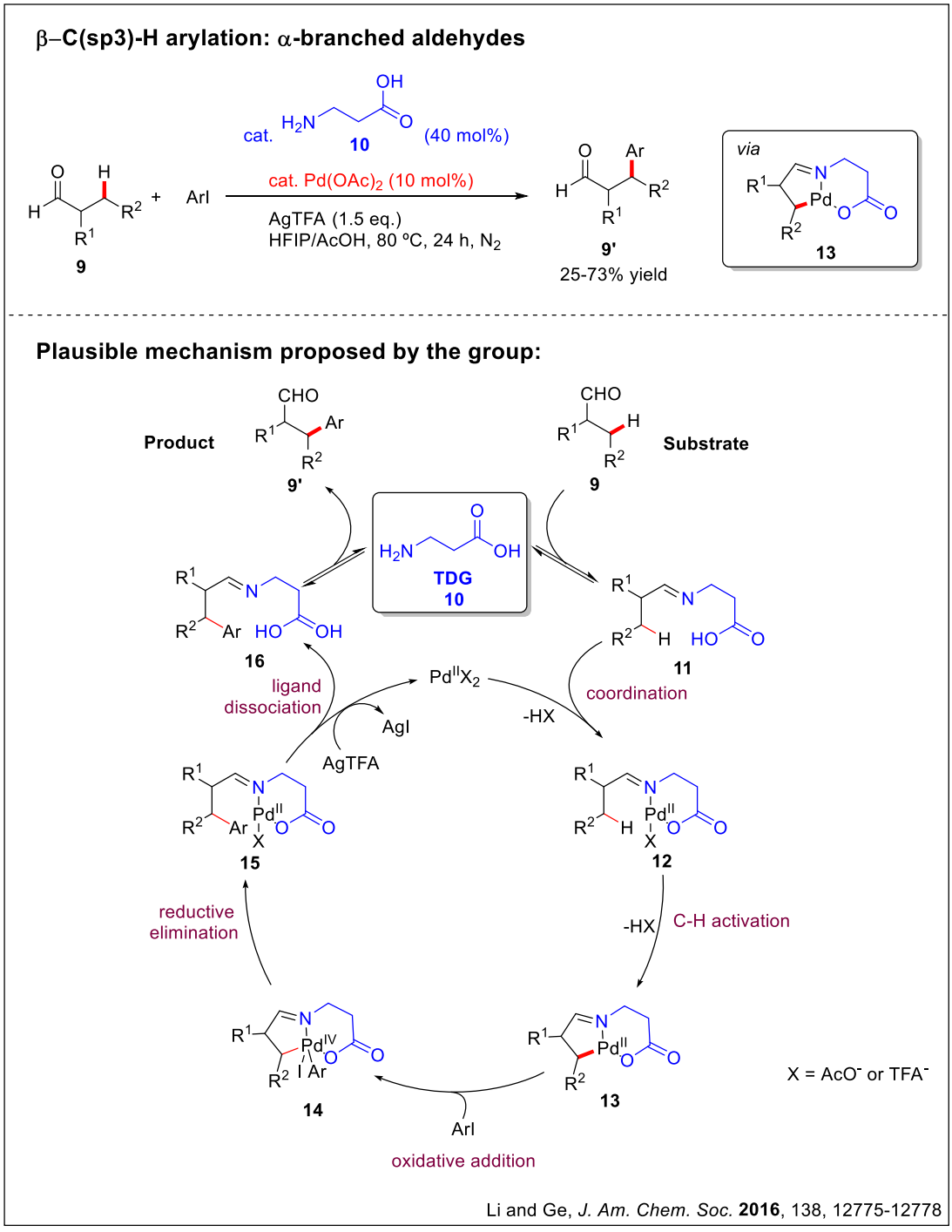


Scheme 6. Pioneering work on Pd catalysed C(sp3)-H activation of aldehydes and ketones via TDGs. Yu, 2016.

In the same year Li and Ge's group, however, solved this reactivity problem by using β-alanine **10** (and its substituted derivatives) as the TDG amino acid ligand (Scheme 7). They demonstrated that increasing the main chain of the TDG by one carbon (switching glycine for β-alanine), the desired arylated aldehydes were successfully obtained. They also successfully isolated the involved [5,6] bycyclic palladium intermediate.

With these results and previous literature reports at hand, they proposed a plausible mechanistic pathway for the reaction. The first step of the catalytic cycle is the formation of the imine **11** by reaction of the substrate **9** and the amino acid ligand **10**, which subsequently coordinates to the Pd(II) metal to form the corresponding six-member cyclic Pd(II) complex **12**. Then, this complex gives rise, by proximity, to a [5,6]-bicyclic intermediate **13** via a site-selective γ-C(sp3)-H bond activation process. Aryl iodide **5** undergoes oxidative addition to the palladium complex (forming the Pd(IV) species **14**), and the arylation of the γ position occurs via the reductive elimination of **14** to give molecule **15**, while the AgTFA salt additive serves to capture the iodide anions which could act as nucleophiles on the Pd catalyst. The reductive elimination of the Pd complex **15** is followed by the ligand dissociation from Pd to give the imine derivative **16** of the

desired product and the free active Pd(II) catalyst (Scheme 7). Finally, the product's derivative **16** is hydrolysed to give the desired final product **9'** and the free TDG **10**.[23] According to this mechanistic pathway, which authors believe to be most truthworthy until this day, the reaction would be driven by a Pd(II)-Pd(IV) catalytic cycle.



Scheme 7. Pioneering work on C(sp3)-H activation on α-branched aldehydes via TDGs. Li and Ge, 2016.[29]

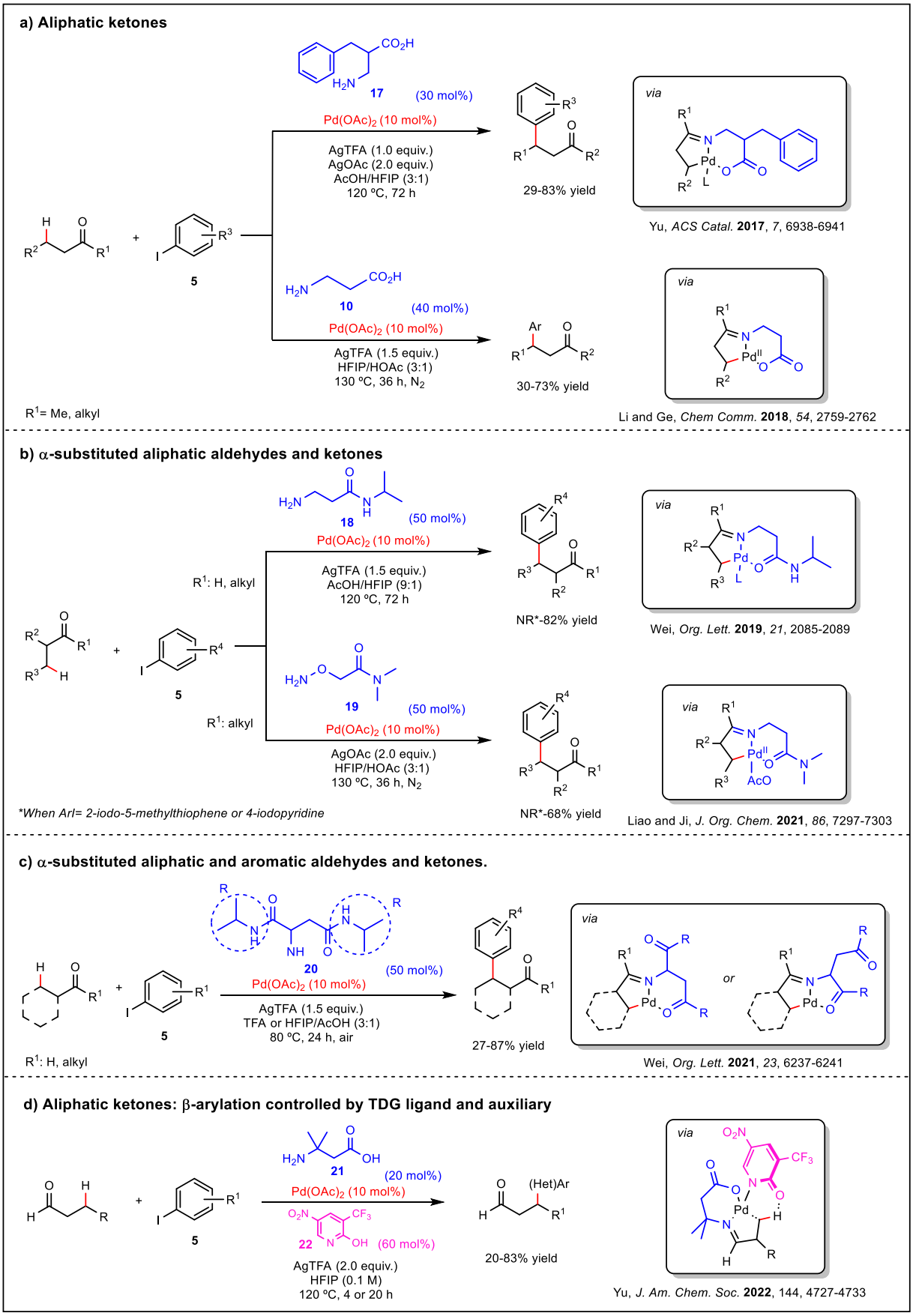
Since the publication of these first two pioneering projects and results, more research groups have become interested in this subject and its eventual application to a wider range of substrates. Because of this, several new works have been published concerning the β-C(sp3)-H and γ-C(sp3)-H activation in aldehydes and ketones since 2016. In the next section the main advances these publications have contributed to this field are reviewed. First the β position activating reactions are presented, and then the γ position activating ones.

One of the problems of these reactions was that the methylene β-C-H bonds were significantly less reactive than methyl carbons due to their steric hindrance. In this context, Yu and his group tried to find a better TDG for the regioselective activation of β methylene C(sp3)-H bonds of aliphatic ketones.[24] In this process they discovered, both computationally and experimentally, that the [5,6] bicyclic Pd intermediate was more effective than the [5,5'] chelation, which means that the [5,6] fused cycle is not exclusively important for aliphatic aldehydes (like Li and Ge reported) but also for aliphatic ketones. Subsequently, they designed various β-alanine based derived TDGs for the arylation of aliphatic α-non-substituted ketones, and the best results were provided by TDG **17** (Scheme 8, a) which afforded the arylated products in good yields for a wide scope of aliphatic ketones and aryl iodides. They also concluded that the yields depend on the bulkiness of the substrate ketone (which would affect in the formation of the imine), rather than the electronic properties of the reagents (ketones and aryl iodides).

In 2018 Li and Ge published an article following the same objectives as proposed by Yu in 2017 (Scheme 8, a).[25] In this case they used the commercially available β-alanine **10** as the TDG with aliphatic ketones, and they also slightly modified the reaction conditions (AgOAc as only additive, increase in temperature and inert atmosphere). They obtained very similar results to Yu's group and with a broad range of FG compatibility. This once again reinforces the [5,6] palladacycle theory proposed by the previous authors. This article is also the first one mentioning the role of the solvent, HFIP, which could be contributing to the formation of the imine intermediate, due to the low pKa of the fluorinated alcohol, which would condition the imine formation equilibrium.

Other reports, which are reviewed in Delord's work published in 2016 presume that the acidic character of HFIP prevents the decomposition of the starting material, or that

[24] K. Hong; H. Park ; J.-G. Yu, *ACS Catal.* **2017**, *7*, 6938-6941.
[25] L. Pan; K. Yang; G, Li; H. Ge, *Chem Comm.* **2018**, *54*, 2759-2762.



Scheme 8: Recent advances in the β-C(sp3)-H activation reactions in aldehydes and ketones.

HFIP could also form hydrogen bonds with the substrates, promoting it to a more activated state. Some other authors believe that the environment created by the extremely co-solvent mixture (HFIP:AcOH) assists the aryl group transfer from the aryl iodide to a palladacyclic intermediate. Not only that, but the use of HFIP also incredibly increased the site-selectivity of the reactions in some cases. Intriguingly enough, some authors noticed that the choice of the HFIP solvent is particularly beneficial if the targeted reaction occurs via a Pd(II)/Pd(IV) manifold (which relates to our reaction mechanism).[26] It becomes apparent, that in the publications cited up until now, authors *either* studied the reactivity of aldehydes *or* ketones, no TDG worked well for *both* types of substrates. Hence, a TDG that worked efficiently for the direct β-arylation of both aliphatic aldehydes and aliphatic ketones had yet to be discovered. In 2019, however, Wei and his group proposed a new range of amide based TDGs for these reactions.[27] For the first time, they efficiently synthesised the TDG **18** (an amide based TDG) that was efficient and gave good results for the β-functionalisation of both α-substituted aliphatic aldehydes and ketones (Scheme 8, b). In 2021 Liao and Ji reported a new group of 2-aminooxy acetamide based TDGs.[28] In this case, the TDG **19** gave good results for non-terminal β position carbons, which were previously considered harder to functionalise because of their higher steric hindrance. The two groups also noticed that some iodoaryl substrates (including 2-iodopyridine) gave no arylated product, since they were very good electron donating moieties and they deactivated the catalyst by coordinating to the palladium. Once again, all mechanisms proposed start by the formation of the corresponding imine-type (oxime ether in the case of Liao and Ji) intermediate which proceeds through a [5,6] palladacycle intermediate to give the desired products from moderate to good yields.

Based on his previous work published in 2019, in 2021 Prof. Wei designed a new range of different TDGs based on the structure of 2-amino-*N,N*-diisopropylsuccinamide (Scheme 8, c).[29] Just like in their previous work, this TDG **20** can mediate the β-arylation of different substrates such as α-substituted aliphatic and aromatic ketones but also α-substituted aliphatic and aromatic aldehydes in moderate to good yields. In addition, it also

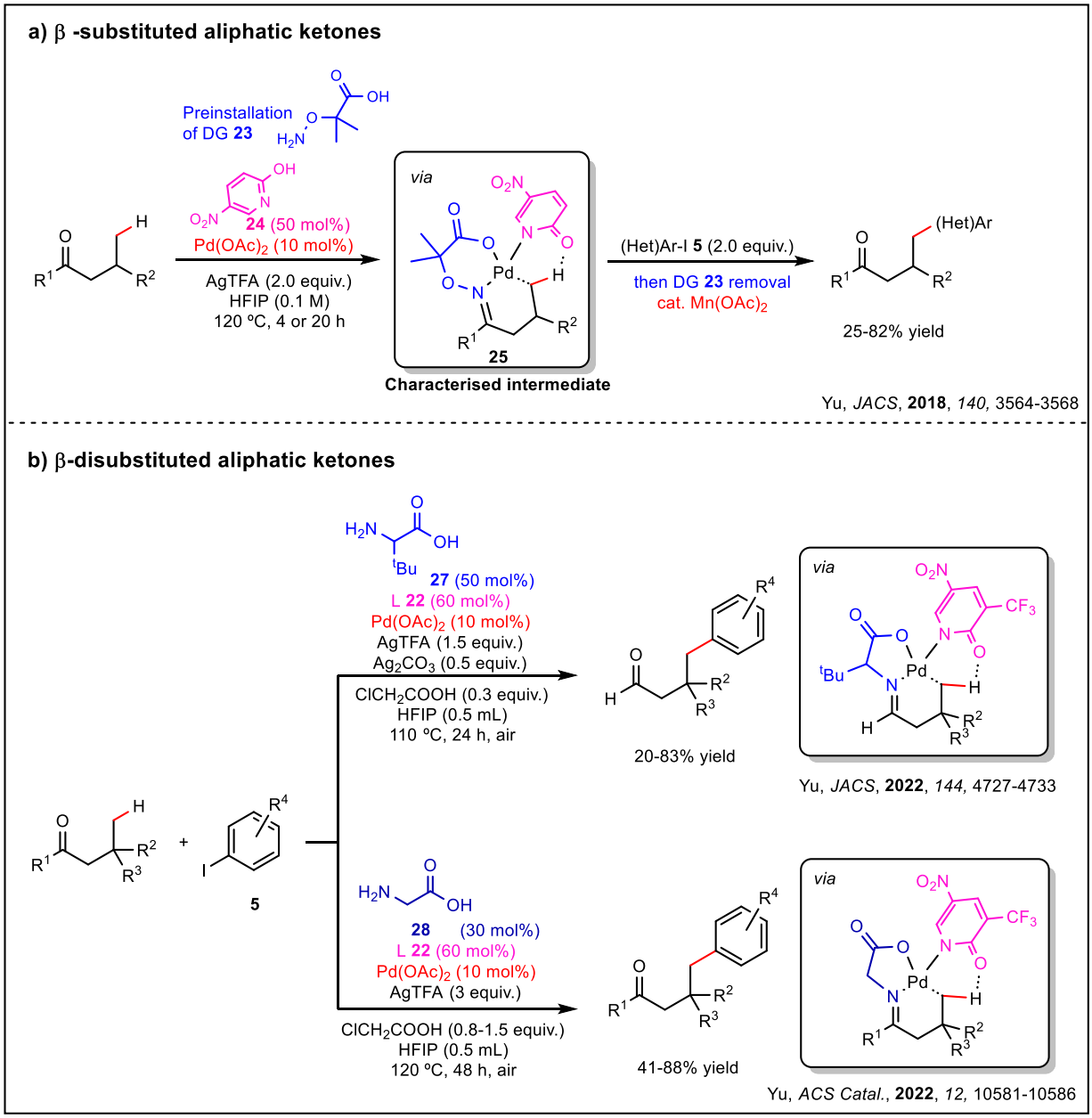
[26] a) Armaly, A.; Cacioppo, J.; Coombs, T.; Koehn, K.; Norwood IV, V.; Motiwala H.; Aubé, J., *Chem. Rev.* **2022**, *122*, 12544-12747. b) T. Bhattacharya; A. Ghosha; D. Maiti, *Chem. Sci.* **2021**, *12*, 3857-3870.
[27] C. Dong; L. Wu; J. Yao; K. Wei, *Org. Lett.* **2019**, *21*, 2085-2089.
[28] Y. Wang; G. Wu; X. Xu ; B. Pang ; S. Liao; Y. Ji, *J. Org. Chem.* **2021**, *86*, 7297-7303.
[29] L.-F. Wu; J.-W. Yao; X. Zhang; S.-Y. Liu; Z.-N Zhuang; K. Wei, *Org. Lett.* **2021**, *23*, 6237-6241.

efficiently guides the γ-arylation o-methylbenzaldehydes in good yields. Once again, the β-methyl activation is preferred over the β-methylene one.

When it comes to the last article published in this field (Yu, 2022), the technique is slightly different to the one used in the previous works. In Yu's work, apart from using TDG **21**, they also use an auxiliary molecule **22**, (5-nitro-3-(trifluoromethyl)pyridin-2-ol) to further guide the reaction towards the stereoselective β-functionalisation, by a speculated hydrogen bond formed between the substrate and the auxiliary molecule **22** (Scheme 8, d).[30] They also show the impact of the chelating ring size of the TDG via DFT calculations. They concluded that the site selectivity of C-H cleavage is controlled by the bite angle of the TDG, i.e., the C-H activation reaction will go through the formation of the less-strained palladacycle ring. This means that a fused [5,6] palladacycle is not always the key intermediate, as the intermediate's stability (and consequently, the site-selectivity of the reaction) also depends on the spatial configuration of the substrate and the TDG. This spatial structure has also to be considered when designing new TDGs for regioselective and enantioselective activation of β-C(sp3)-H bonds.

[30] Y.-H. Li; Y. Ouyang ; N. Chekshin ; J.-Q. Yu, *J. Am. Chem. Soc.* **2022**, *144*, 4727-4733.

Recently, works focused on the γ-C(sp3)-H activation of aldehydes and ketones via imine TDGs have also emerged. The main contributions on this subject are shown in Scheme 9.



Scheme 9: Recent advances in the γ-C(sp3)-H activation reactions in aldehydes and ketones.

The first example involving the γ-C(sp3)-H activation of ketones was published in the year 2018 by Yu and involved the use of β-substituted ketones as the substrates (Scheme 9, a).[31] In this work however, the DG **23** was not transient, and had to be preinstalled and then removed after the reaction. This DG **23** was also accompanied by an auxiliary ligand

[31] R.-Y Zhu; Zi.-Q. Li ; H. S. Park ; C. H. Senanayake ; J.-Q. Yu, *J. Am. Chem. Soc.* **2018**, *140*, 3564-3568.

24 (pyridionine X-type ligand) that coordinated to the TM, and then formed a hydrogen bond with the proximal hydrogen further activating the γ position. This reaction that would proceed through a [6,6] bicyclic palladacycle **25** gave good to moderate yields with different aryl iodides, and good yield for the 3-iodocyclopent-2-enone.

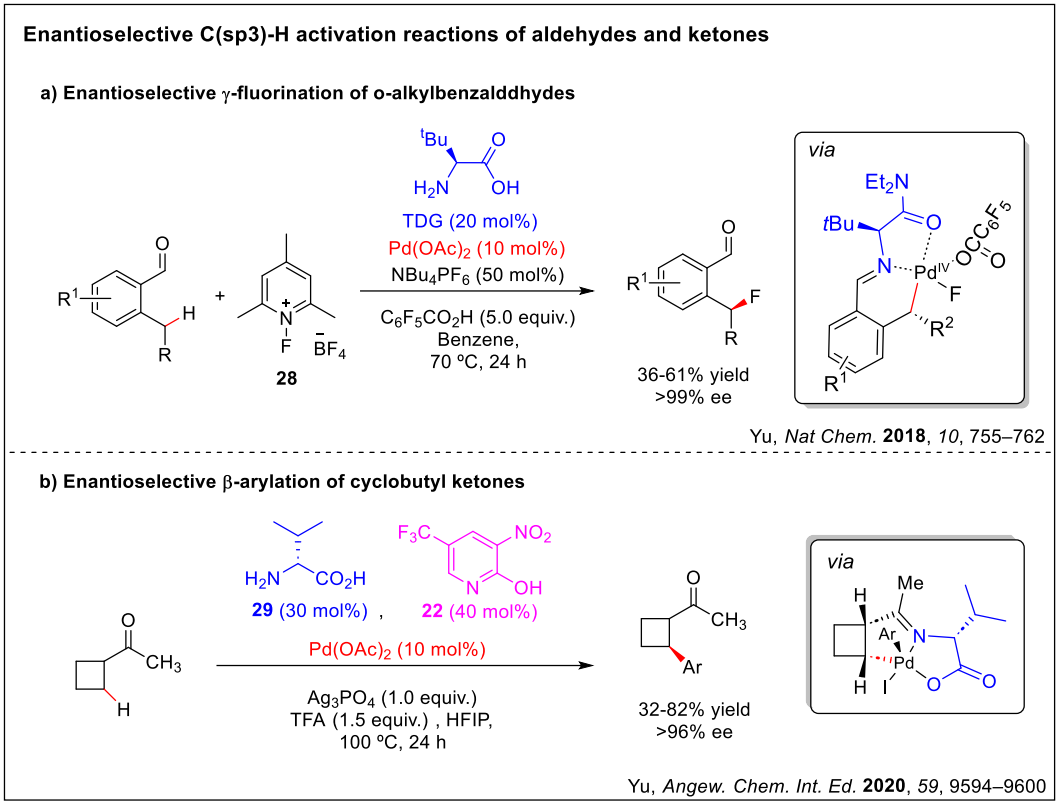
Lastly, Yu published two articles in 2022 in which they achieved the arylation of the γ position of β-disubstituted aliphatic ketones using auxiliary ligands and TDGs (whereas in 2018 they used preinstalled DGs).[30, 32] They also expanded the reactivity to primary aldehydes (Scheme 9, b). They did so by making use of TDGs **27** and **28** and the auxiliary ligand **22** to obtain good yields and compatibility with different FGs both in the aldehyde substrates and the aryl iodides.

Among the previously mentioned works, it is worth noting that only Yu's 2016 study introduced an enantioselective reaction, specifically utilising L-*tert*-leucine for the enantioselective γ-arylation of 2-methylbenzaldehydes (see Scheme 6, b). None of the other studies established a protocol for enantioselective arylation at the β-carbon of aldehydes or ketones. Nevertheless, a few articles have explored enantioselective β- or γ-functionalisation of aldehydes and ketones via C(sp3)-H activation reactions (Scheme 9, b).

In 2018, Yu also reported the appropriate conditions and reagents including the TDG (reversible imine formation), auxiliary and additives, for achieving the γ-fluorination of o-alkylbenzaldehydes in good yields and excellent enantioselectivity.(Scheme 10, a).[33] The reaction evolved by means of a Pd(II)/Pd(IV) catalytic cycle, in which the N-fluoro-2,4,6-

[32] Y.-H. Li; Y. Ouyang; N. Chekshin ; J.-Q. Yu, *ACS Catal.* **2022**, *12*, 10581-10586.
[33] H. Park; P. Verma; K. Hong; J.-Q. Yu, *Nat. Chem.* **2018**, *10*, 755-762.

trimethylpyridinium [F+] **28** served both as an oxidant for the Pd(II) precatalyst, and as a source of fluoride.



Scheme 10: Enantioselective β-functionalisation of o-alkylbenzaldehydes and cyclobutyl ketones.

Moreover, the enantioselective β-C(sp3)-H arylation of cyclobutyl ketones was reported by Yu in 2020 (Scheme 10, b).[34] This asymmetric reaction was catalysed by $Pd(OAc)_2$ and facilitated by D-valine **29** as the TDG. One of the interesting discoveries of this work was the crucial role of combining a silver salt with a 2-pyridone-type electron-deficient ligand **22** to achieve both high yields and enantioselectivity.

To date however, there is no published protocol for achieving enantioselective direct functionalisation of β- or γ-C(sp3)-H bonds in open-chain aliphatic aldehydes or ketones. Given the significance and potential of this innovative approach, it is essential to gather additional information, including experimental, theoretical, and mechanistic insights, to design and develop more efficient TDGs for enabling regio- and enantioselective direct functionalisation of C(sp3)-H bonds.

[34] L.-J. Xiao; K. Hong; F. Luo; L. Hu; W. R. Ewing; K.-S Yeung; J.-Q Yu, *Angew. Chem. Int. Ed.* **2020**, *59*, 9594-9600.

2. OBJECTIVES

In this context and taking into consideration the few reports on the enantioselective β-functionalisation and of other remote positions of aldehydes and ketones through the direct C(sp3)-H activation by means of TDGs, the main goal of this project has been to synthesise some new chiral diamine derived TDGs and explore them for the γ- or δ-functionalisation of α-ketoamides.

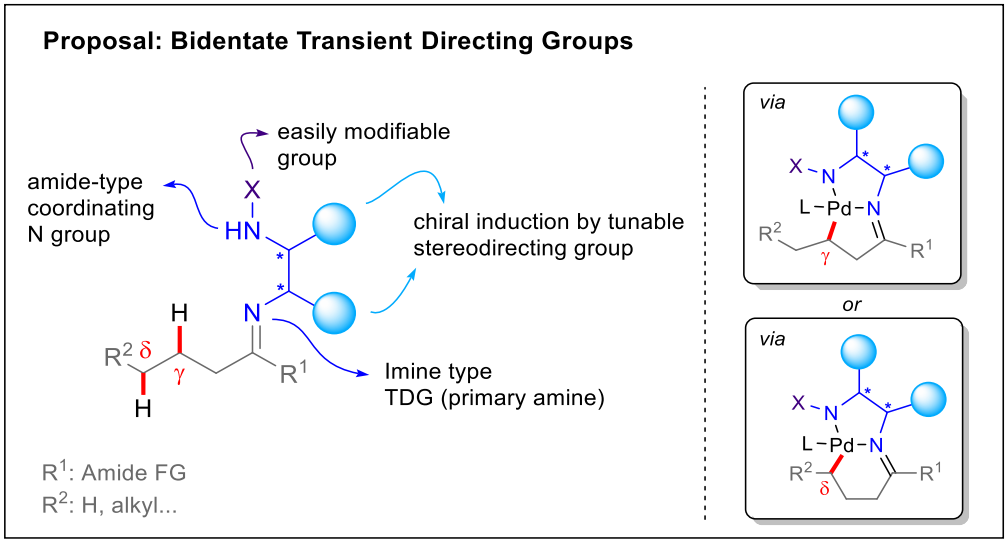


Figure 4. General structure of the proposed TDGs and the key palladacycle intermediates

On this basis, the proposed directing groups (Figure 4) would consist of a chiral diamine derivative containing the following elements: an amine group for imine formation, an easily modifiable amide-type coordinating group and one (or more) stereodirecting groups. Through this design, a thermodynamically stable [5,5'] or [5,6] bicyclic palladacycle would form to give either the γ- or δ- functionalised α-keto amides, which goes accordingly with the stability studies proposed by the authors from the literature.

In this manner, the designed TDGs would help to aim for a stereo- and enantioselective α-ketoamide functionalisation, that would not only be catalytic, but would also tolerate a wider range of FGs. Thus, it would be a very valuable tool to obtain new γ- or δ-functionalised α-keto amide derivatives with possible biological applications.

Therefore, according to the above proposal, the following specific objectives were considered:

1) Synthesis of the diamine TDGs. For the trials and, in a first instance, one single stereodirecting group was considered, which was that located closest to the C(sp3)-H bond to be activated. Three different TDGs were envisioned: **L1**, **L2** and **L3**. The first ligand, **L1** (Figure 5), would contain a trifluoromethyl sulfonyl substituent attached to the coordinating amine group. The second one, **L2** (Figure 5) would have a 3,5-bis(trifluoromethyl)benzenesulfonyl group. In this manner, the strong electron withdrawing nature of these groups would make the nitrogen scarcer in electronic charge, subsequently decreasing the electronic charge of Pd as well, making it more susceptible to activate the C(sp3)-H bond.[35] The **L3** TDG (Figure 5), on the other hand, would comprise the pyridine sulfonyl group. As pyridine is also electron donating, it would serve as a third anchoring point to hold onto the palladium metal, possibly facilitating the C(sp3)-H activation reaction.

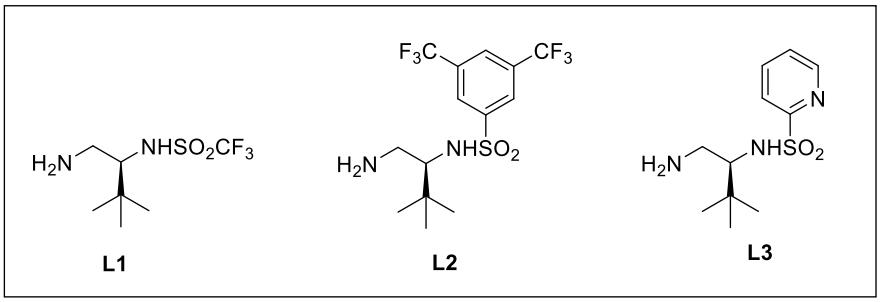


Figure 5. Proposed TDGs **L1**, **L2** and **L3**.

2) Synthesis of the α-keto amide substrates **K1** and **K2** (Figure 6). It was mandatory to consider a substrate which contained at least a two-carbon chain adjacent to the ketone group to study the γ-C(sp3)-H and δ-C(sp3)-H functionalisation reactions. Therefore, a three-carbon chain aliphatic substrate was selected, because in this way, we would be able to evaluate if the ligands designed would be prone to functionalise either the internal (methylene) γ position or the terminal δ position. α-Keto amide substrates could be synthesised according to protocols previously followed in the group.

[35] For some examples on the use of the sulfonyl 2-pyridyl group in Pd mediated C-H activation reactions see: a) Hernando, E.; Villalva, J.; Martínez, A. M.; Alonso, I.; Rodríguez, N.; Gómez Arrayá, R.; Carretero, J. C. *ACS Catal*. **2016**, *6*, 6868−6882. b) Rodríguez, N.; Romero-Revilla, J. A.; Fernández-Ibáñez, M. A.; C. Carretero, J. C., *Chem*. *Sci*. **2013**, *4*, 175.

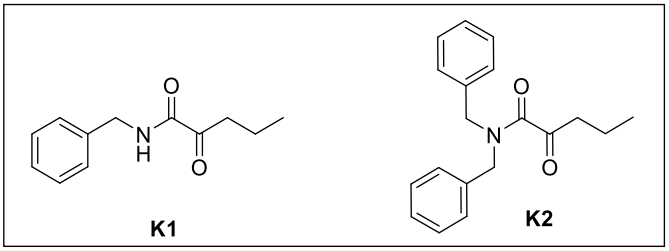


Figure 6. Proposed α-keto amides **K1** and **K2.**

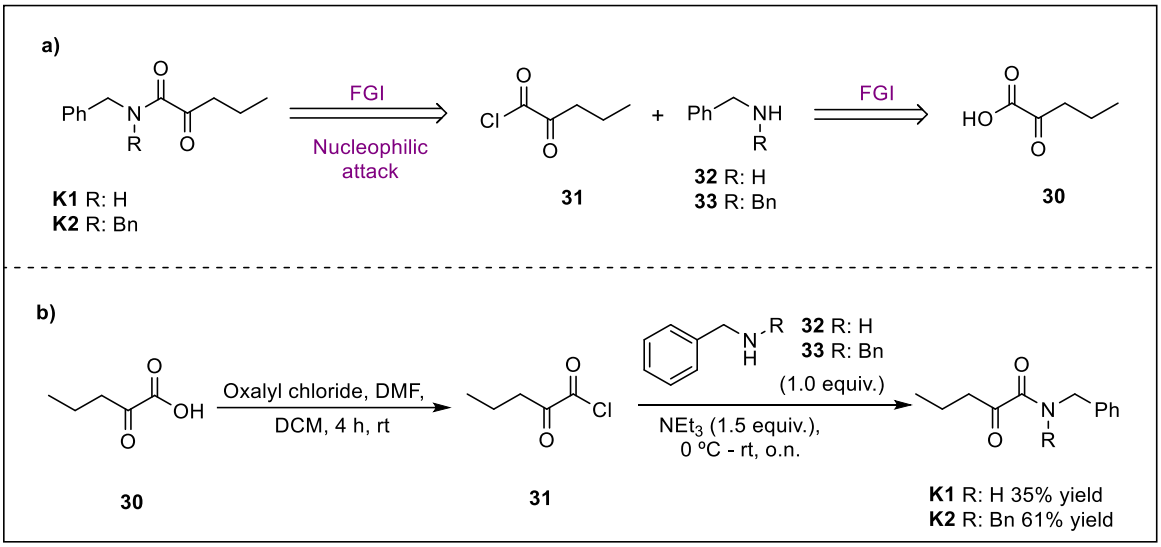
3) Exploration of the C(sp3)-H activation reaction of α-keto amides **K1** and **K2** with achiral ligands in order to identify the racemic products and determine the HPLC conditions for their separation.
4) Exploration of the C(sp3)-H activation reactions of α-keto amides assisted by the designed TDGs to check the regio- and enantioselectivity provided by the catalytic systems and reactants.

3. RESULTS AND DISCUSSION

In this chapter, the results of this research project are presented. First, the synthesis of both α-keto amides (**K1** and **K2**) which were the proposed substrates for the reaction, followed by the synthesis of the ligands **L1**, **L2** and **L3** are described. Finally, the results of the study of C(sp3)-H activation in α-keto amides with these ligands and some others will be documented.

3.1. SYNTHESIS OF THE α-KETO AMIDES

According to the objectives established, first the synthesis of the α-keto amides was considered. The synthesis of these structures was performed according to the precedents from our lab and adapting them when necessary.[36] Based on the following retrosynthetic analysis (Scheme 11, a) the synthesis of both α-keto amides could start off from the commercially available 2-oxopentanoic acid via the corresponding 2-oxopentanoyl chloride and further reaction with (di)benzyl amine.



Scheme 11. a) Retrosynthesis for α-keto amides **K1** and **K2**. b) Synthesis of α-keto amides **K1** and **K2**.

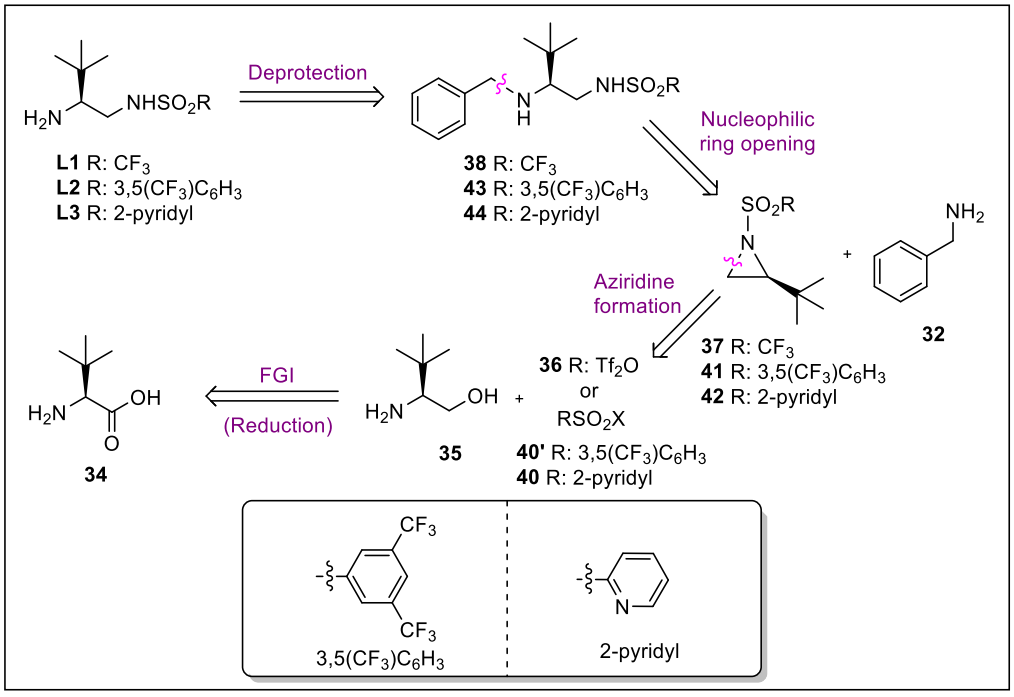
Therefore, the synthesis was started by reacting 2-oxopentanoic acid **30** with oxalyl chloride, with a few drops of DMF in DCM for four hours at room temperature. Then, 1 equivalent of the benzylamine **32** (or dibenzylamine **33**) and 1.5 equivalents of Et_3N were added to the mixture at 0 ° C. The mixture was allowed to stir overnight at room temperature and neutralised with the addition of 1M HCl. After work-up and flash

[36] Adapted from: S. Goudedranche ; D. Pierrot ; T. Constantieux ; D. Bonne ; J. Rodriguez, : *Chem. Commun.* **2014**, *50*, 15605-15608.

column chromatography purification, the products were obtained in 35% yield for **K1** and 61% for **K2**.

3.2. SYNTHESIS OF THE TDGs

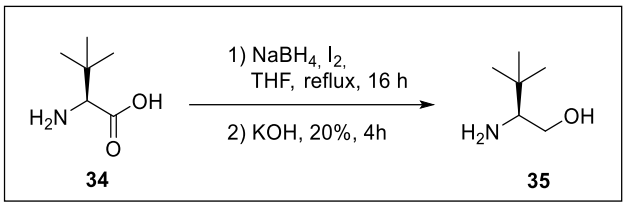
According to the objectives first established, the synthesis of TDGs **L1**, **L2** and **L3**, which contain an amine group, an *N*-coordinating easily modifiable group and a stereodirecting group was investigated. The retrosynthesis of the three ligands was proposed based on literature precedents and is shown in Scheme 12. These could be obtained upon *N*-deprotection of the benzylamine derivatives **38**, **43** and **44**. subsequent nucleophilic opening by benzyl amine **32**. These, in turn, would result from the aziridines' (**37**, **41**, **42**) nucleophilic ring opening by benzylamine **32**. The aziridine ring could be obtained from L-*tert*-Leucinol **35** by treatment with the appropriate sulfonyl chloride. L-*tert*-Leucinol **35** in turn, would be provided by reduction of commercial L-*tert*-leucine **34**. (Scheme 13).



Scheme 12. Retrosynthesic analysis fort the synthesis of **L1**, **L2** and **L3** TDGs.

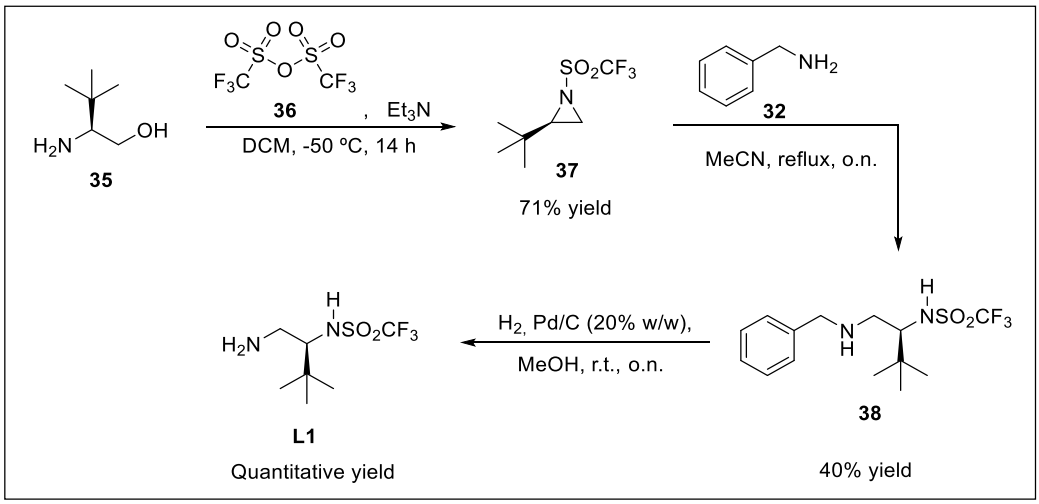
L-*tert*-Leucinol **35** was synthesised from the commercially available synthetic amino acid L-*tert*-Leucine **34**. This was done by reduction in the presence of $NaBH_4$ and I_2 in THF under reflux for 16 hours. After the quenching and workup, the desired L-*tert*-Leucinol **35** was obtained with 96% yield (Scheme 13).[37]

[37] Adapted from: C. Pezzetta; D. Bonifazi; R. W. M. Davidson, *Org. Lett.* **2019**, *21*, 8957–8961.



Scheme 13. Synthesis of the precursor L-tert-leucinol.

The next step was the formation of the aziridine ring. For **L1** (R= -CF_3) the aziridine **37** was prepared by treatment of aminoalcohol **35** with triflic anhydride **36** and Et_3N at -50 ° C in DCM for 14 hours (Scheme 14). The mixture was then neutralised by slowly adding cold 0.1 HCl and after the work-up, aziridine **37** was obtained in 71% yield and high purity and was used in the next step without further purification. The aziridine ring **37** was then opened via nucleophilic attack of benzylamine **32** by heating both compounds under reflux overnight in MeCN. After column chromatographic purification the desired protected product **38** was obtained in 40% yield. Finally, deprotection of **38** by hydrogenolysis under hydrogen and Pd/C catalyst in methanol, overnight at room temperature afforded **L1** in quantitative yield. [38]



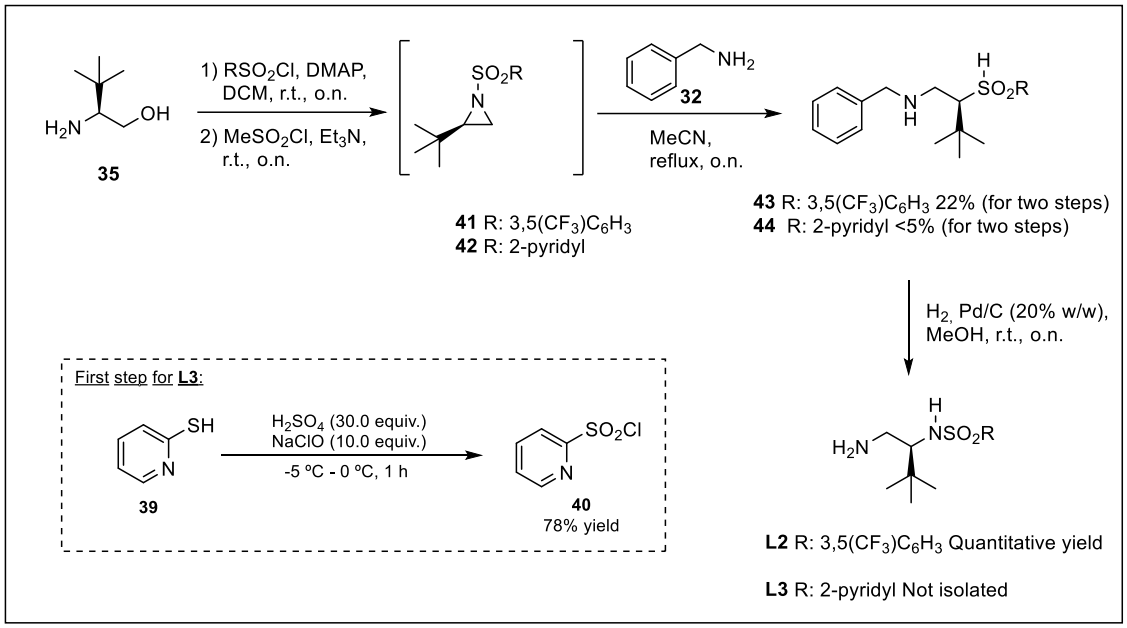
Scheme 14. Synthesis of **L1** TDG.

For ligands **L2** and **L3**, the synthesis was slightly different. In both cases L-*tert*-Leucinol **35** was treated with the corresponding sulfonyl chloride and DMAP, followed by mesylation of the free alcohol group (Scheme 15).

Previously, the sulfonyl chloride **40** needed for the synthesis of **L3** had to be prepared, since the commercial product was quite unstable and not accessible in the lab. For this purpose, sodium hypochlorite was added dropwise over 30 minutes to 2-

[38] Adapted from: I. J. Krauss; J. L. Leighton, *Org. Lett.* **2003**, *5*, 18, 3201–3203.

mercaptopyridine **39** in concentrated sulfuric acid and the mixture was allowed to react for an extra 30 minutes. After the workup, 2-pyridine sulfonyl chloride **40** was obtained in 78% yield.[39]



Scheme 15. Synthesis of the TDGs **L2** and **L3**.

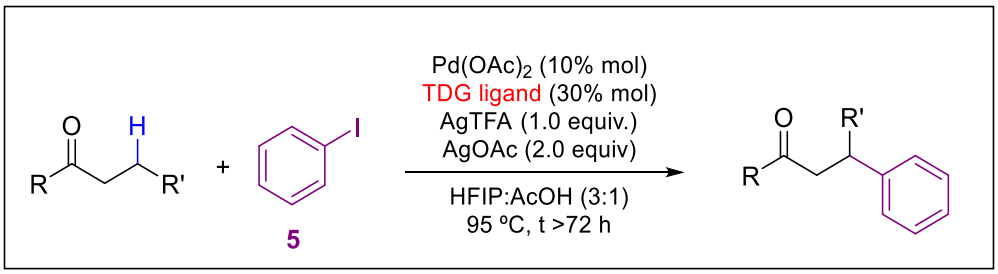
The aziridines **41** and **42** were built by the addition of the corresponding aryl sulfonyl chlorides and a few drops of DMAP to a solution of aminoalcohol **35** in DCM. The mixture was allowed to react overnight, methyl sulfonyl chloride and Et_3N were then added, and the mixture was stirred once again overnight at room temperature. Due to their instability the aziridines such obtained were used in the next step without further purification. The next steps were performed the same way as for ligand **L1**. First, the aziridine was opened by its treatment with benzylamine **32** in MeCN under reflux overnight. After the usual work-up **43** was obtained with a 22% yield (for two steps starting from L-*tert*-leucinol **35**). In the case of **44**, however, the desired product was detected in the ^1H NMR of the crude, but the quantity obtained after flash column chromatography was minimal (less than 5 mg). Finally, **L2** was obtained in quantitative yields by deprotection of the amine **43** via hydrogenolysis with H_2 and Pd/C in methanol by stirring at room temperature overnight. The designed **L2** ligand was obtained in 22% overall yield.[40]

[39] H. Zhang; D. Yang; X.-F. Zhao; J.-L. Niu; M.-P. Song, *Org. Chem. Front.* **2022**, *9*, 3723-3729.
[40] Aziridine formation procedure aadapted from : J. M. Apgar; R. R. Wilkening; D. L. Parker Jr.; D. Meng; K. J. Wildonger; D. Sperbeck; M. L. Greenlee; J. M. Balkovec; A. M. Flattery; G. K. Abruzzo; A. M. Galgoci; R. A. Giacobbe; C. J. Gill; M.-J. Hsu; P. Liberator; A. S. Misura; M. Motyl; J. Nielsen Kahn;

3.3. C-H ACTIVATION REACTION EXPLORATION

Once the substrates and the ligands were synthesised, it was time to test them in the C(sp3)-H activation reactions. In a first instance, the conditions previously reported by Yu for aliphatic ketones were selected.[24] This involved the use of $Pd(OAc)_2$ (10 mol%), AgTFA (1.0 equiv.), AgOAc (1.0 equiv.) with HFIP and AcOH (3:1) as solvents at 95 ° C for up to 72 hours.

GENERAL PROCEDURE



Scheme 16. General Procedure for the C-H activation reactions with different TDGs.

The reactions were performed at 0.2 mmol or 0.4 mmol scale in air-filled test tubes sealed with a septum with a balloon filled with argon gas.

A mixture of the substrate, iodobenzene **5**, silver salts, palladium catalyst, and TDG was prepared in HFIP and AcOH (all charged in the order they are listed in). The mixture was then sealed with a septum which had a balloon with argon gas attached to it and it was left stirring for ten minutes at room temperature. After the indicated time had passed, the vessel was put in an oil bath and was left to react for the indicated of time at 95 ˚C. After the indicated amount of time had passed, the reaction mixture was cooled to room temperature, diluted with EtOAc and filtered through a silica gel plug and concentrated in vacuo. The crude reaction was first purified by flash chromatography using Hex/EtOAc (98:2 to 95:5) as the eluent to afford both the starting product and final product in the same fraction. This fraction was then purified by preparative TLC using Tol:EtOAc 98:2 as the mobile phase to afford the desired arylated product.

3.3.1. Reactions with achiral TDGs

The reactions were first performed with natural amino acids previously reported/ as efficient TDGs for the reactions of aldehydes and ketones. The first trials mainly served

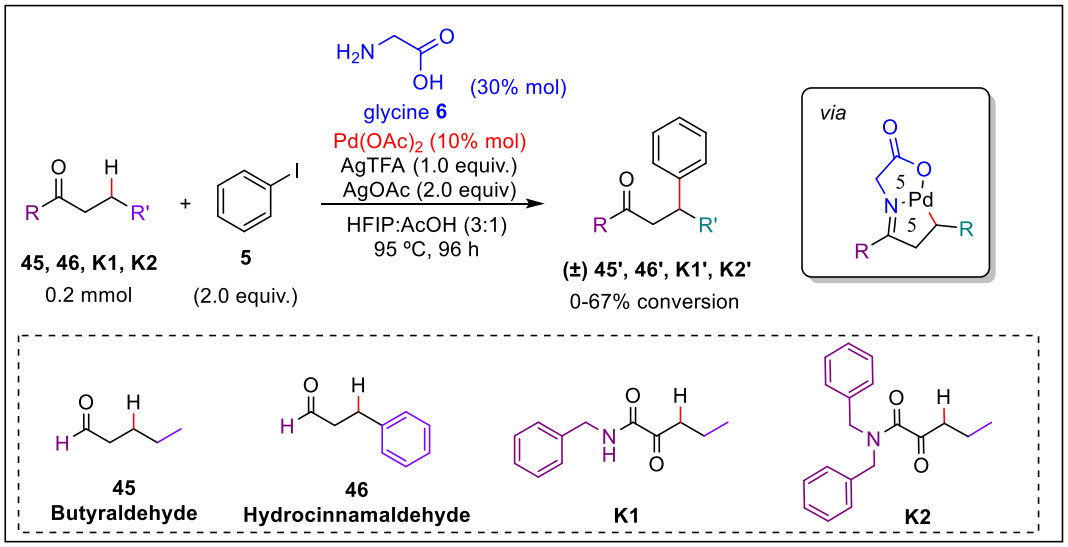
M. Powles; F. Racine; J. Dragovic; W. Fan; R. Kirwan; S. Lee; H. Liu; A. Mamai; K. Nelson. M. Peel, *Bioorg. Med. Chem. Lett.* **2021**, *32*, 1-9

to explore the setup, the how-tos of the reaction and workup, and to isolate and characterise the racemic arylated products.

Glycine as TDG

The study began following the research published by Yu et al. (2016) in which glycine was used as the TDG. To begin with, the reactions were first carried out with two different aldehydes: butyraldehyde and hydrocinnamaldehyde, as they were readily available and freshly distilled from our lab. The reaction was then performed with the α-keto amides previously synthesised: **K1** and **K2**. The general procedure was followed scaling everything to 0.2 mmol of the substrate. The conversion of the reaction was monitored by ^{1}H NMR spectroscopy using $CDCl_3$ as the solvent. In the next table are presented the times at which the samples were taken for every substrate and the corresponding reaction conversion.

Table 1. C(sp3)- arylation of aldehydes **45, 46**, **K1** and **K2** in the presence of **glycine 6** as the TDG.



	Conversion (%)			
Substrate	24 h	48 h	72 h	96 h
45	ND	ND	ND	ND
46	ND	ND	ND	ND
K1	60%	70%	73%	79%
K2	59%	60%	63%	73%

[a] Reactions carried out at 0.2 mmol scale (mmol ratio substrate:aryl iodide **5** 1:2) and with the mmol ratio shown in the scheme above the table. ND: Product Not detected.

As the results in Table 1 show, for aldehydes **45** and **46** no reaction was observed; however, for α-keto amides **K1** and **K2** the presence of a new arylated product was detected, which were assigned as the γ-arylated α-keto amide products **K1'** and **K2'**.

In these cases, the conversion was calculated by using different sets of signals. For **K1**, the conversion was calculated using the signals of protons **a** (Figure 7) from the starting α-keto amide and protons **b**, **c**, and **d** (whose signals overlapped) from the arylated product **K1'**. In the case of **K2**, the conversion was calculated with the signals from the protons **a** from sarting α-keto amide **K2** and **d** from the arylated α-keto amide **K2'** (Figure 8). Figures 7 and 8 show the ^{1}H NMR spectra corresponding to the samples taken at 48 h for **K1** and for **K2** with glycine **6** as the TDG.

Looking at the results in Table 1 it can be observed that aldehydes **45** and **46** do not react with Glycine as the TDG, just like Yu et al. had reported in their first C-H activation study on ketones and aldehydes, which the authors attributed to the instability of the [5,5'] palladacycle. The synthesised α-keto amides did however react in the presence of glycine to give the subsequent (speculated) [5,5'] intermediate palladacycle which then lead exclusively to the γ-monoarylated product. The conversion is already quite high at 24 hours of running time, and it progresses increasingly as reaction time increases. It can also be seen that at low reaction times **K2** appears to be slightly less reactive than **K1**, but at longer reaction times both conversions converge. Thus, to summarise, both α-keto amides **K1** and **K2** show similar reactivity with glycine as the TDG, for they provide the γ-arylated products **K1'** and **K2'** in good yields and with no trace of subproducts. As these reactions were performed in low scale, once the reaction stopped, an ^{1}H NMR spectra was recorded, and the reaction products were not isolated.

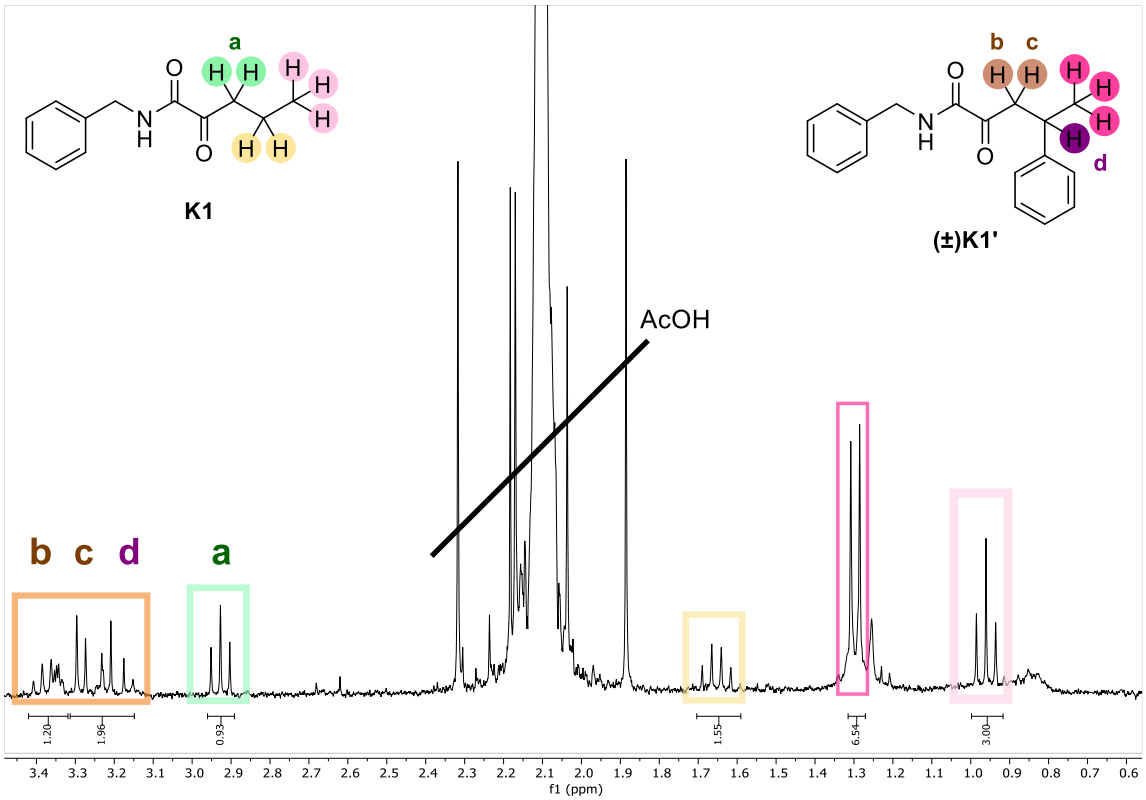


Figure 7. ^{1}H NMR spectra signals used for the determination of conversion of **K1** to **K1'**.

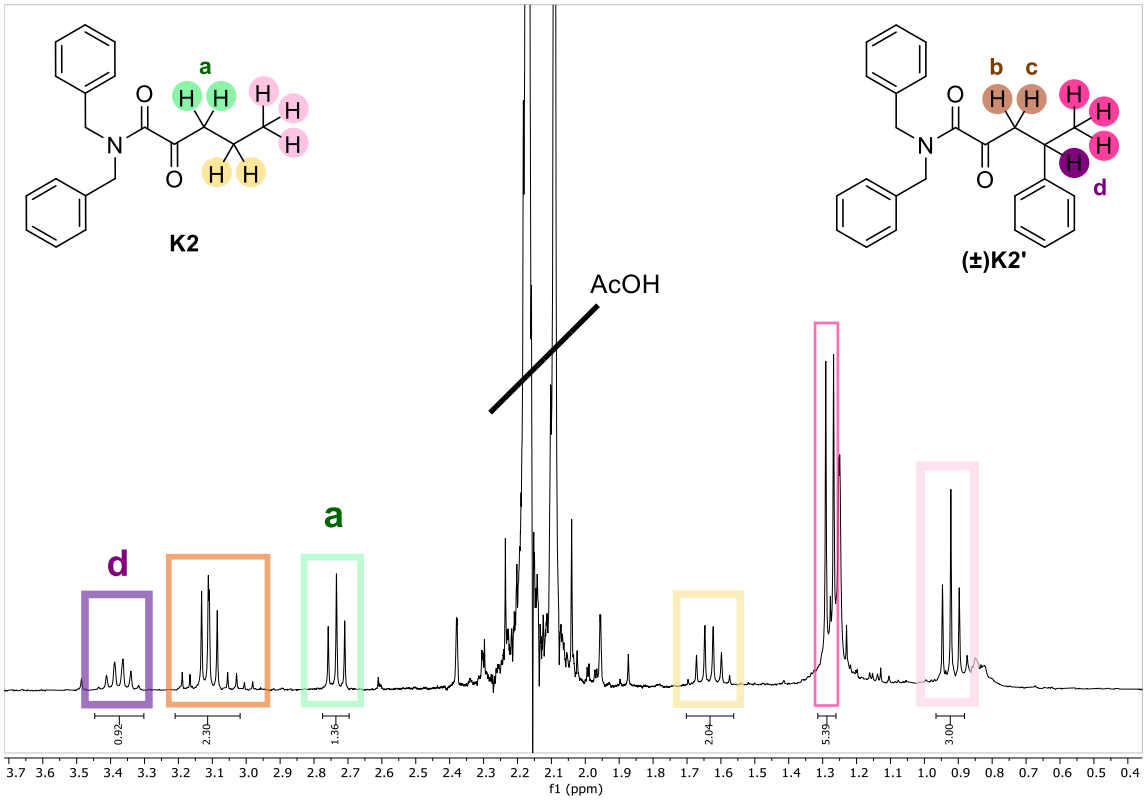
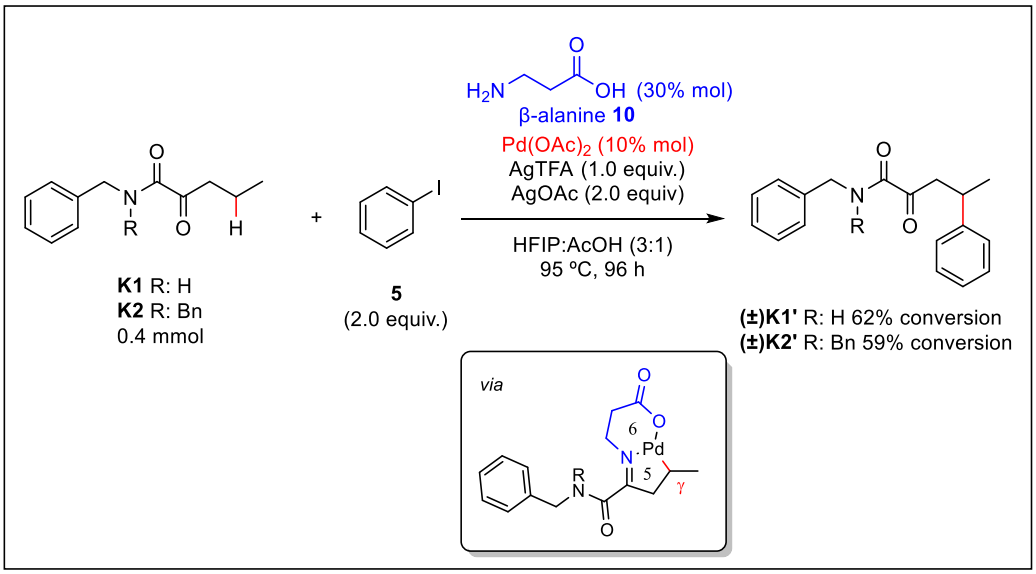


Figure 8. ^{1}H NMR spectra signals used for the determination of conversion of **K2** to **K2'**.

β-Alanine as TDG

After the exploration of the first experiments with glycine, the reactions with the α-keto amides **K1** and **K2** using β-alanine as the TDG were tested (Table 2). The general procedure was followed at 0.4 mmol scale of the starting product. The reaction mixtures were treated after 96 hours of stirring and a sample was taken every 24 hours from the start of the reaction.

Table 2. C(sp3)-H arylation of **K1** and **K2** in the presence of β-alanine as the TDG[a].



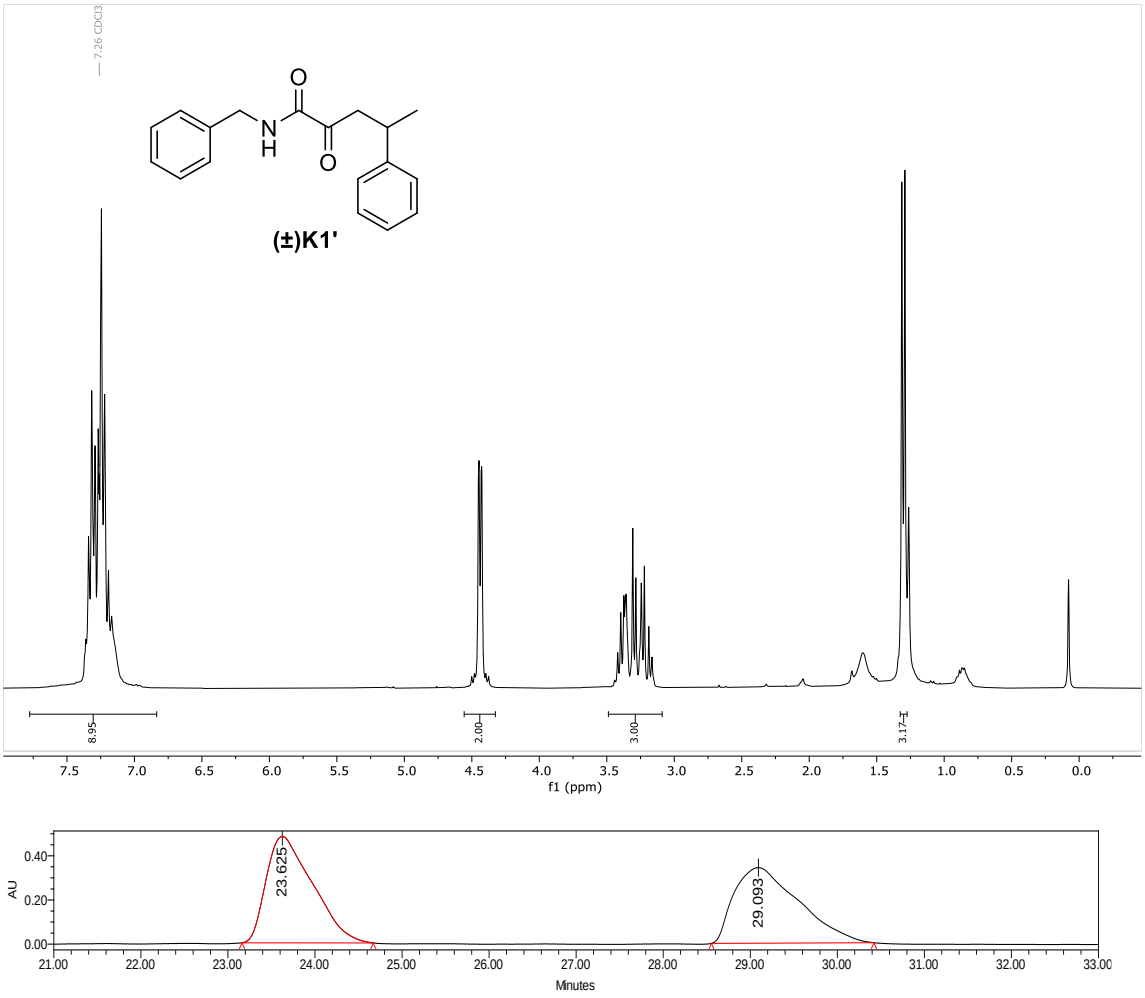
	Conversion (%)			
Substrate	24 h	48 h	72 h	96 h
K1	-	-	-	62%
K2	-		-	59%

[a] Reactions carried out at 0.4 mmol scale (mmol ratio α-keto amide:aryl iodide **5** 1:2) and with 3 mL HFIP, 1 mL AcOH and the mmol ratio shown in the scheme above the table. -: unreliable measurements or calculations. *Blank space:* missing sample.

Table 2 shows the conversion obtained for every sample, which were calculated using the same sets of signals and technique as before. Regrettably, the initial conversions of these reactions were too low to calculate a genuine conversion, and so only the last measuring was deemed reliable (at 96 hours).

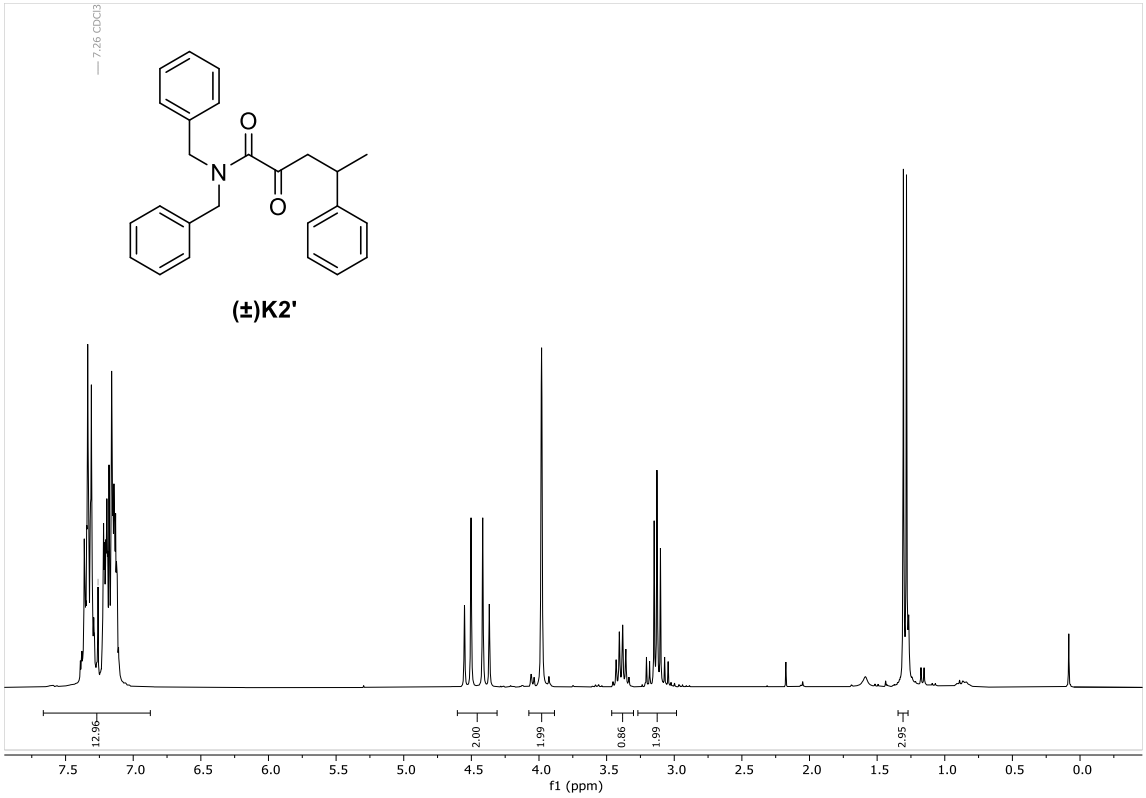
As it can be observed in Table 2**,** the C(sp3)-H activation reaction with β-alanine as the TDG has a slower initial rate compared to glycine, since the calculated conversion was so low that it could not be considered reliable until 96 hours of running time. However, at the end of the reaction (at 96 hours), both substrates **K1** and **K2** show similar results, although a little bit lower compared with that of glycine as the TDG. For **K1**, an unidentifiable subproduct could be detected in the ^{1}H NMR spectra from the start of the

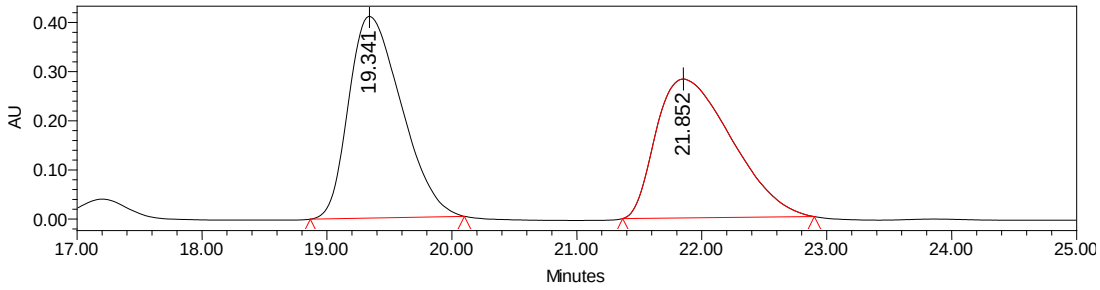
reaction at 24 hours (some signals at around 3.6 ppm). In the case of **K2** on the other hand, no subproduct is observed in the samples' ^{1}H NMR spectra, even at 96 hours of running time. From the results above, **K2** was considered a more suitable β-keto amide substrate for the TDGs designed in this project. As total conversions were not reached in these cases, the starting α-keto amides had to be separated from the α-arylated product. However, they exhibited similar Rf values in TLC. Therefore, after work-up and purification by flash chromatography column (EtOAc:Hex 98:2), preparative TLC (98:2 Tol/EtOAc) was performed and the γ-arylated compounds were isolated (8.0 mg of **K1'** and 5.0 mg of **K2'**). Both products were analysed by HPLC chromatography (ID column at 80:20 Hex:^{i}PrOH and 0.5 mL/min flow) to show that both enantiomers could be separated efficiently (Figures 9 and10).



Peak	Retention Time (min)	Area (%)
1	23.625	50.24
2	29.093	49.76

Figure 9. ^{1}H NMR spectrum of the γ-arylated α-ketoamide **(±)K1'** and HPLC chromatogram from the racemic reaction with β-alanine as the TDG. (HPLC: ID column, Hex:iPrOH 80:20, 0.0.5 mL/min flow).





Peak	Retention Time (min)	Area (%)
1	19.341	50.36
2	21.852	49.64

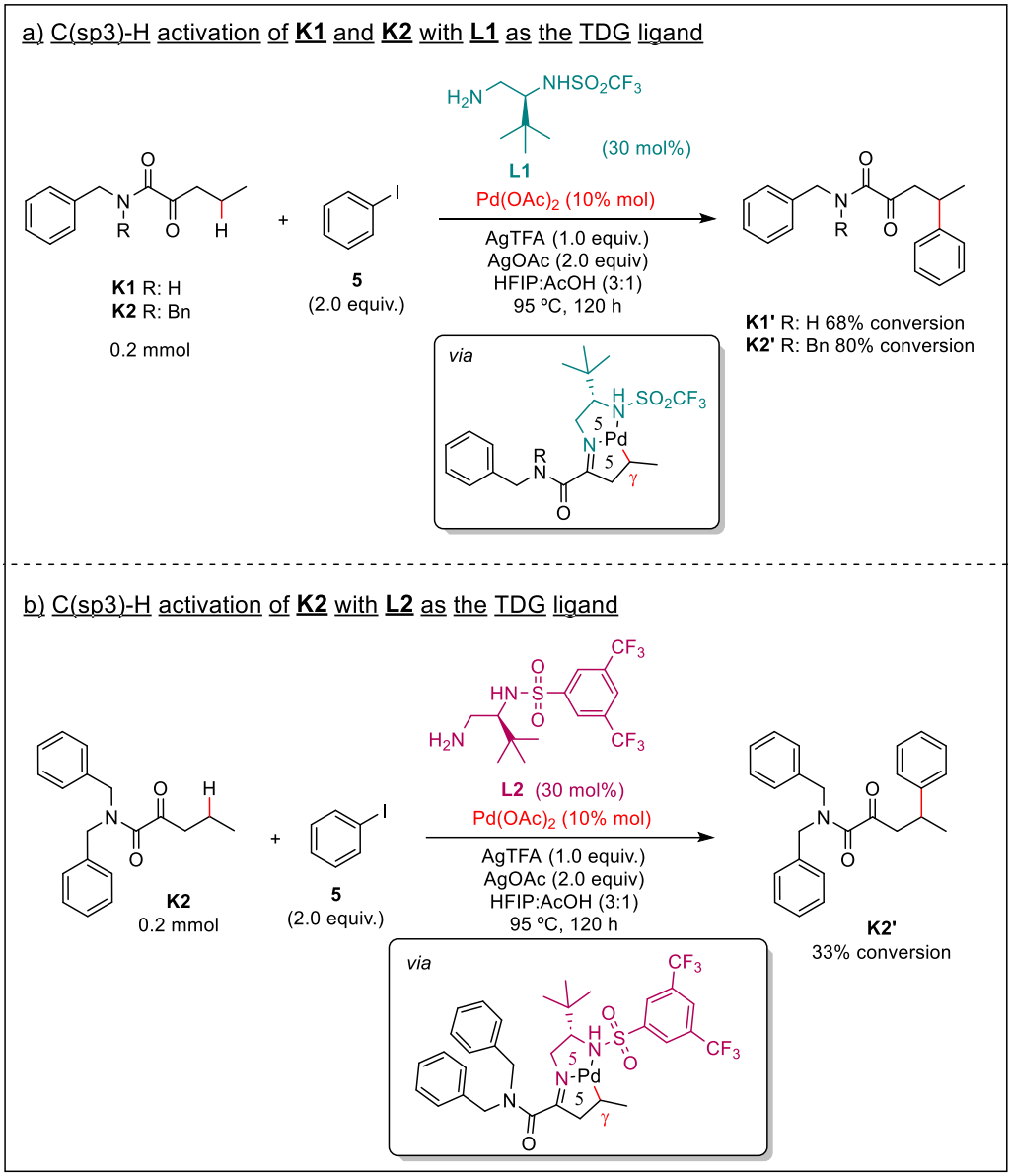
Figure 10. ^{1}H NMR spectrum of the γ-arylated α-ketoamide **K2'** and HPLC chromatogram from the racemic reaction with β-alanine as the TDG. (HPLC: ID column, Hex:iPrOH 80:20, 0.0.5 mL/min flow).

3.3.2. Reactions with chiral TDG L1 and L2

Once the results with the achiral TDGs were obtained, the reactions were explored with **L1** as the TDG. These experiments were carried out by following the general procedure at 0.2 mmol scale of the starting product. Samples for reactions of **L1** with **K1** and **K2** were taken at 24 hours, 96 hours, and 120 hours (crude product) of running time. The technique and signals used to calculate the conversion were the same as in the previous

cases, both for **K1** and **K2**. Reliable results were obtained which are shown in the Table 3 below.

Table 3. a) C(p3)-H arylation of **K1** and **K2** with **L1** as the TDG. b) C(p3)-H arylation of **K2** with **L2** as the TDG [a].



		Conversion (%)			
Ligand	**Substrate**	**24 h**	**96 h**	**120 h**	**ee**
L1	**K1**	13%	59%	68%	racemic
	K2	‹10%	76%	80%	racemic
L2	**K2**	‹10%	20%	33%	not det.

*[a] Reactions carried out at 0.2 mmol scale (mmol ratio α-keto amide:aryl iodide **5** 1:2) and with 1.5 mL HFIP, 0.5 mL AcOH and the mmol ratio shown in the scheme above the table.*

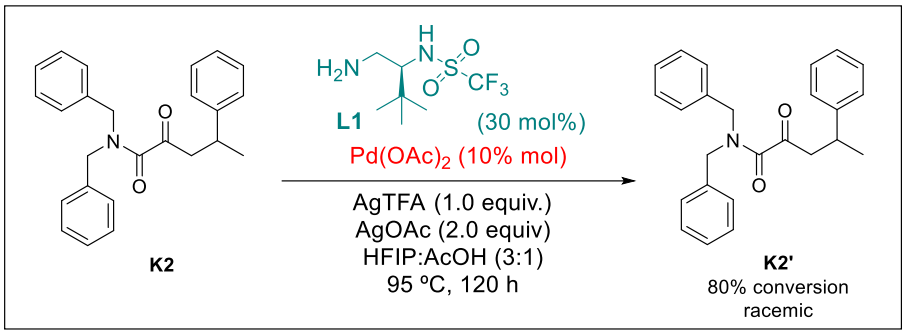
As the results from Table 3 show, the initial rate of the reactions with **L1** and **L2** are lower than that of glycine as the TDG; however, they are faster than with β-alanine. With **L1**, **K2** was more reactive than **K1** (although its initial rate was lower than **K1**'s), reaching a conversion of 80% at 120 hours whereas **K1** got a conversion of 68%. It could also be considered that **K2** reaches a plateau between 96 hours and 120 hours because the difference in conversion between the two samples is not as remarkable. With **L2**, by contrast, the arylation of **K2** is not as efficient as it reaches a conversion of 33% after 120 hours of reaction. This is probably linked to steric hindrance caused by the substituent of the sulfonyl group in **L2**. The crude mixtures were purified via flash column chromatography then preparative TLC to obtain 14 mg of **K1'** and 17 mg of **K2'**. Then the stereoselectivity of the reactions was analysed via HPLC analysis. Unfortunately, the stereocontrol was not good as both products were racemic.

These preliminary results would indicate that the reactivity does not only depend on the size of the bicyclic palladacycle intermediates formed in the process, but that the electronic and structural nature of the TDGs are also important factors in the C(sp3)-H activation reactions. This is proven by the fact that for both α-keto amides **K1** and **K2**, a postulated [5,5']-palladacycle intermediate is more beneficial to drive the reaction (comparing glycine to β-alanine), whereas according to the literature a [5,6]-palladacycle would be more advantageous. It goes without saying that the structural and electronical properties of the substrates (α-keto amides) also modulate the reactivity to some extent.

4. CONCLUSIONS

These are the conclusions which can be drawn from this research project:

- Synthesis of both α-keto amide substrates **K1** and **K2** has been achieved and both compounds have been characterised.
- TDGs **L1** and **L2** purposefully designed for C(sp3)-H reactions have been synthesised in the sufficient amount to be characterised and to perform the reactions. TDG **L3** could not be synthesised as its aziridine intermediate was very unstable. The synthesis of both **L1** and **L2** as well as **L3** need further investigation and optimisation.
- In the presence of glycine, butyraldehyde and hydrocinnamaldehyde didn't react, in accordance with literature precedents. In all cases, the C(sp3)-H reactions with α-keto amides **K1** and **K2** have displayed remarkable regioselectivity, consistently yielding the γ-arylated products (**K1'** and **K2'**), which have been subsequently isolated and characterized.
- In the case of racemic C(sp3)-H arylation reactions glycine was deemed a better TDG than β-alanine for the α-keto amide substrates as after 96h glycine provided higher conversions, while **K1** and **K2** showed similar behaviours.^{1}H NMR signals of aliquots in the racemic reactions of **K1** with β-alanine showed the presence of an unidentified subproduct.
- In the asymmetric reactions with **L1**, substrate **K2** was more reactive than **K1** (conversion of 80% and 68% respectively, after 120h). TDG **L2** appears to be less effective than **L1**, but this aspect needs further investigation. Both TDGs **L1** and **L2** give excellent regioselectivity, the only arylation products detected being γ-arylated α-keto amide products. However, the reaction was not optimised; the conversion is not total, which adds additional steps to the purification process and ee is lower than expected. In summary, further investigation is required in order to improve the reactivity and stereocontrol of the reaction. Based on this study, the best conditions for the γ-arylation of the α-keto amides seem to be the following ones:



Scheme 17. Best conditions for the γ-arylation of the α-keto amides.

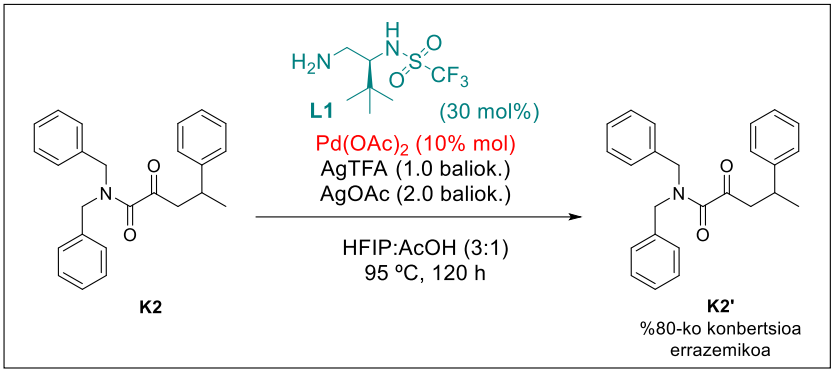
- Conditions for the enantiomers' separation by HPLC of compounds **K1'** and **K2'** were established.

4. ONDORIOAK

Hona hemen ikerketa proiektu honetatik atera daitezken ondorioak:

- Bi **K1** eta **K2** α-zeto amida substratuen sintesia lortu da eta bi konposatuak karakterizatu dira.
- C(sp3)-H erreakzioentzat bereziki diseinatutako **L1** eta **L2** TDGak sintetizatu dira. Kantitate nahikoa lortu da bi molekulak karakterizatzeko, baita behar izan diren C(sp3)-H erreakzioak burutzeko ere. **L3** TDGa ezin izan da sintetizatu, haren bitarteko aziridina oso ezegonkorra baita. **L1** eta **L2** TDGen sintesiek eta baita **L3** TDGarenak ere optimizazio eta ikerketa gehiagoren beharra dute.
- Glizinaren presentzian butiraldehido eta hidrozinamaldehidoak ez dute erreakzionatu, literaturako aurrekariekin bat datorrena kasu guztietan. **K1** eta **K2** α-zeto amidekin esploratutako erreakzioetan erregioselektibotasun bikaina ikusi da, γ-arilazio produktuak antzeman baitira bakarrik (**K1'** eta **K2'**), zeintzuk isolatu eta karakterizatu diren.
- C(sp3)-H arilazio erreakzio errazemikoen kasuan, diseinatutako α-zeto amidentzat glizina β-alanina baino TDG hobea dela ikusi da, erreakzioaren 96h ondoren glizinak konbertsio altuagoak eman dituelako, **K1** eta **K2**-k antzeko portaera erakusten dutelarik. β-Alaninak katalizaturiko **K1**-en erreakzio errazemikoan, alikuoten ^{1}H RMN seinaleek identifikatu gabeko azpiproduktu baten formazioa erakusten dute.
- TDG kiralekin eginiko erreakzioetan; **L1** TDGarekin **K2** erreaktiboagoa izan da **K1** baino (120 h ondoren, %80-ko eta %68-ko konbertsioak izan dituzte hurrenez hurren). Lehen saiakeraren arabera badirudi **L2** TDGa ez dela **L1** bezain eraginkorra, hala ere, TDG honen erreaktibitatea gehiago ikertu beharko litzateke. Diseinaturiko bi TDGek erregioselektibitate bikaina ematen dute, soilik α-zeto amida γ-arilatuak detektatu direlarik. Hala eta guztiz, erreakzioa ezin izan da optimizatu; erreakzioaren konbertsioa totala ez denez, purifikazio etapari urratsak gehitzen dizkio, gainera, ez da esperotako ee-a lortu. Ondorioz, ikerketa gehiagoren beharra dago errakzioaren erreaktibitatea eta estereokontrola hobetzeko.

Ikerketa honetan oinarriturik, badirudi α-zeto amiden γ-C(sp3)-arilaziorako baldintza egokienak hurrengoak direla:



18.eskema. α-Zeto amiden γ-arilaziorako baldintza egokienak.

- **K1** eta **K2'**ren enantiomeroen HPLC bidezko banaketarako baldintzak finkatu dira.

5. EXPERIMENTAL SECTION

5.1. TECHNIQUES AND MATERIAL

5.1.1. Nuclear Magnetic Resonance (NMR)

NMR spectra were recorded using a Bruker Avance DPW 300 (300 MHz for ^{1}H, 75 MHz for ^{13}C) spectrometer. The solvent used was $CDCl_3$ except for the ligands for which MeOD was used. Chemical shifts (δ) are quoted in parts per million and referenced to the residual $CDCl_3$ (or MeOD) peak, ^{1}H (δ = 2.50) and ^{13}C (δ = 77.0) and ^{1}H (δ = 3.35) and ^{13}C (δ = 49.3) for MeOD. The multiplicity of each signal is designated using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet; dd, double doublet. Coupling constants (J) are reported in Hertz (Hz).

For the processing and interpretation of the obtained spectra the software MestReNova (v.14.3.2-32681) was used.

5.1.2. Chromatography

Flash Chromatographic columns were monitored by thin layer chromatography (TLC) using Merck silica gel 60 F254 plates and visualized by fluorescence quenching under UV light, Fisher Bioblock lamp VL-4LC, λ= 254 nm and λ= 365 nm. The TLC plates were stained (if necessary) with a dipping solution of potassium permanganate (1 g KMnO4, 100 mL H2O), followed by heating.

Chromatographic purification (With Flash Chromatography Columns) was performed on Merck ROCC 60 silica gel 40-63 m as the stationary phase and a suitable mixture of solvents (Hex/EtOAc or DCM/MeOH) as eluent, which is specified for each of the reactions.

Preparative TLC was also performed using Merck silica gel 60 F254 plates and a mixture of Tol/EtOAc as the mobile phase. The plates were visualized by fluorescence light (Bioblock Lamp VL-4LC). The desired products were extracted from the previously carved and ground (with a mortar) stationary phase with a mixture of DCM and a few drops of methanol.

5.1.3. Determination of enantiomeric excess

Enantiomeric excesses (ee) were determined using analytical high performance liquid chromatography (HPLC) performed on Waters 600 (equipped with Photodiode Array Detector Waters 2996). The used column and solvent flow conditions are specified for each compound.

5.1.4. Optical rotation

Optical rotation was measure using a Jasc P-2000 High Accuracy Digital Polarimeter. The specific rotation ($[\ ]_D$) is given in 10^{-1} deg·cm^2·g^{-1}; temperature is given in °C and concentration is measured in g/100 mL. D corresponds to the sodium D-line (589 nm sodium doublet).

5.1.5. Mass Spectrometry

MS spectra were recorded on an ESI-ion trap Mass spectrometer Agilent 1100 series LC/MSD, SL model, on and UPCL-DAD-QTOF, Ultra High-Performance Liquid Chromatograpy-Mass spectrometer, Waters UPLC ACQUITY, Waters PDA detector, Waters SUnapt G2 or on an Agilent Thermoquest LCT spectrometer. Mass spectrometry analyses were performed in the General Research Service (SGIker) of the University of the Basque Country (UPV/EHU).

5.1.6. Reagent and Solvents

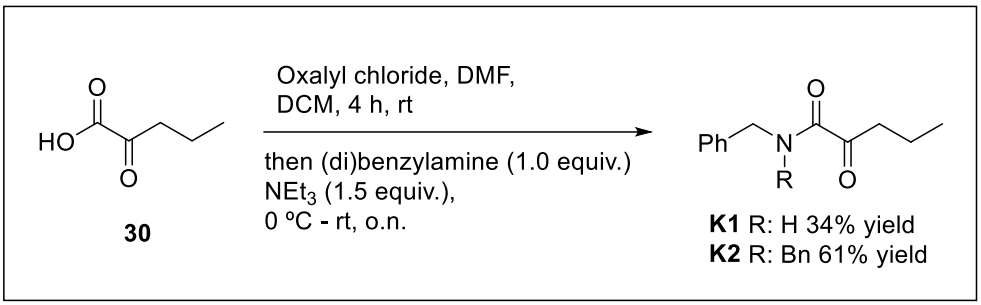
Reagents were purchased from different commercial suppliers (Sigma-Aldrich, ACros Organics, Alfa Aesar, Fluka, TCL, Merck, Fluuorochem, etc.) stored as specified by the manufacturer and used without previous purification unless otherwise stated.

The acetonitrile (MeCN) and dichloromethane (DCM) were distilled over CaH_2. The THF, on the other hand, was purchased from Scharlau and distilled over Na. The rest of the solvents (acetone, hexane, methanol) were purchased from OPPAC and were used without previous drying. Finally, the solvents used in HPLC (hexane, iPrOH) were obtained with chromatography purity (≥99%) from Sigma-Aldrich.

For the drying of the organic phases after extraction Na_2SO_4 was utilised. The removing of the reaction, extraction or chromatography solvents was done with Büchi R-110, R-200 and R-210 rotavapors under reduced pressure. The crudes and pure products were further dried using vacuum pumps (0,5 mmHg approx.).

5.2. SYNTHESIS OF THE KETOAMIDE REACTANTS:

GENERAL PROCEDURE[35]



To a solution of 2-oxopentanoic acid **30** (10 mmol, 1.2 mL, 1 equiv.) in dry DCM ([0.2 M], 50 mL total) under Ar gas was added oxalyl chloride (10 mmol, 1.3 mL, 1 equiv.). The resulting mixture was left to react for 4 h, until the HCl bubbles had stopped forming. The mixture was then cooled to 0 °C and both the Et_3N (15 mmol, 2.1 mL, 1.5 equiv.) and the nucleophilic amine (10 mmol, 1 equiv.) were added simultaneously, and the mixture was allowed to react overnight at room temperature. The reaction was then quenched by addition of a 1 M solution of HCl (40 mL). The aqueous phase was extracted with DCM (3×30 mL), then the organic phases were combined and brin (1×40 mL). The combined organic layers were then dried over Na_2SO_4, filtered, and evaporated under vacuo to obtain the crude product. The desired product was purified by flash column chromatography (Hexane:EtOAc, 95:5→80:20).

N-Benzyl-2-oxopentanamide **K1**

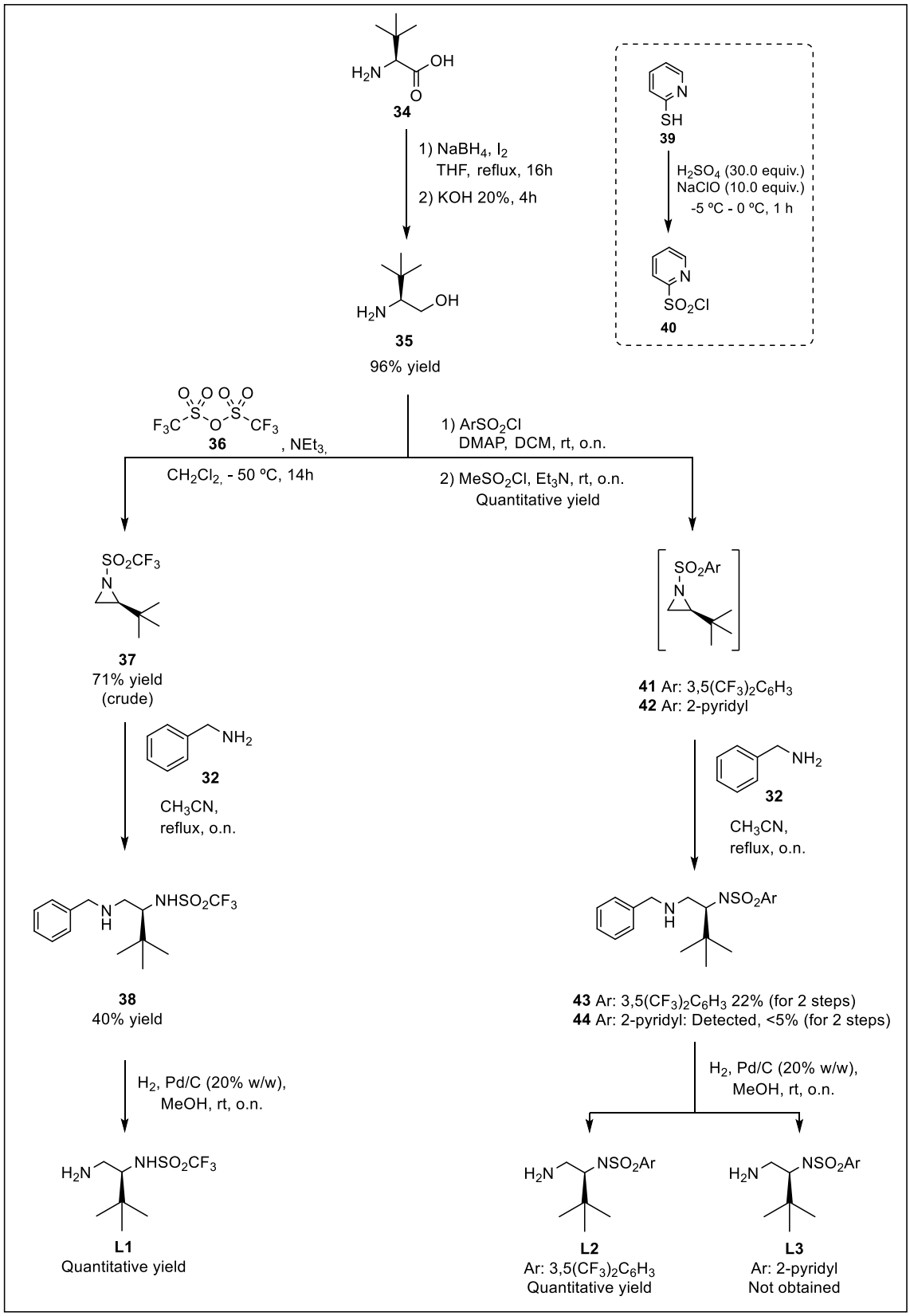
The title product **K1** was synthesised following the general procedure using benzylamine **32** (1.1 mL). After flash chromatography the product **K1** was obtained as white yellowish crystals. (0.7127 g, 3.5 mmol, 34%). The spectroscopic data were coincident with those previously reported.[36] m.p.=41,3-41,7 °C. ^{1}H NMR (300 MHz, Chloroform-d) 7.41 – 7.22 (m, 5H), 4.47 (d, *J* = 6.1 Hz, 2H), 2.93 (t, *J* = 7.2 Hz, 2H), 1.75 – 1.55 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H).

N,N-Dibenzyl-2-oxopentanamide **K2**

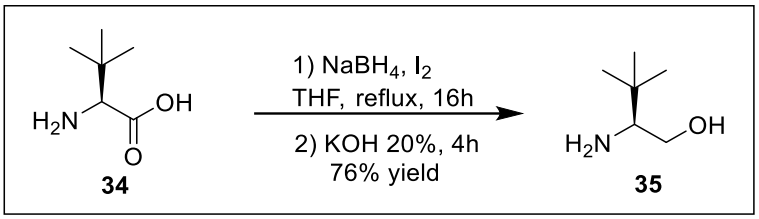
The product **K2** was obtained by following the general procedure and using dibenzylamine (2.0 mL) and the product **K2** was purified by flash chromatography to provide the product as a white crystal. (1.8098 g, 6.1 mmol, 61%). ^{1}H NMR (300 MHz, Chloroform-d) δ 7.42 – 7.16 (m, 10H), 4.54 (s, 2H), 4.36 (s, 2H), 2.74 (t, *J* = 7.3 Hz, 2H), 1.64 (h, *J* = 7.3 Hz, 2H), 0.93 (t, *J* = 7.4 Hz, 3H) ^{13}C NMR (75 MHz, Chloroform-d) δ 201.28, 167.99,

135.97, 135.58, 128.98, 128.91, 128,58, 128.20, 127.91, 49.97, 47.10, 42.12, 16.44, 13.68. m.p.=30 °C (≈rt). UPLC-DAD-QTOF: $C_{19}H_{21}NO_2$ [M+H]+ calcd.: 295,1572, found: 295,1583.

5.3. SYNTHESIS OF THE DIRECTING TRANSIENT GROUP LIGANDS



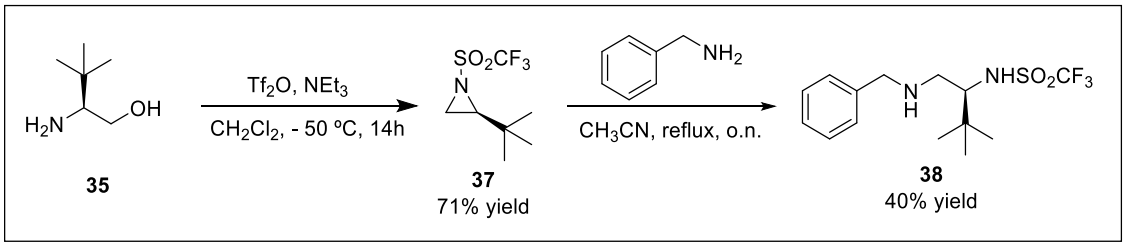
5.3.1. Precursor *(2S)*-2-Amino-3,3-dimethyl-1-butanol[3]



A dry flask containing anhydrous THF (120 mL) and $NaBH_4$ (4.78 g) under Argon gas was cooled to 0 °C. Then L-*tert*-leucine **34** (50 mmol, 6.56 g, 1 eq.) was slowly added. A second solution of I_2 (50.0 mmol, 12.7 g) in THF (30 mL) was added to it drop-wise for 15 minutes at the same temperature. The resulting mixture was stirred at room temperature until the formation of bubbles stopped, after which It was left to react overnight under reflux. The mixture was then cooled to 0 °C and quenched drop by drop with 20% KOH (100 mL) (caution as it is very reactive), and it was left to stir for 4 hours. The reaction mixture was then extracted with DCM (5 × 50 mL), and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo obtaining a colourless oil. (4.4532 g, 38 mmol, 76%). The spectroscopic data were coincident with those previously reported for **35**.[37] ^{1}H NMR (300 MHz, Chloroform-d) δ 3.78 – 3.68 (m, 1H), 3.22 (t, J = 9.2 Hz, 1H), 2.52 (d, J = 9.7 Hz, 1H), 1.96z (br. s, 3H), 0.90 (s, 9H).

5.3.2. Aziridine formation and Ring opening:

PROCEDURE A:



(2S)-2-Amino-3,3-dimethyl-1-butanol **35** (2.96 g, 25 mmol, 1 eq.) was dissolved in DCM (50 mL) and cooled to -78 °C under Argon atmosphere. A solution of Tf_2O **36** (9.3 mL, 55 mmol, 2.2 eq.) in DCM (100 mL) was then added dropwise. The reaction mixture was stirred at the same temperature for one hour after which it was left to stir overnight at -50 °C. Then, it was quenched by the addition of 0.1M HCl (50 mL) and washed with $NaHCO_3$ (sat.) (2×50 mL). The organic phase was dried with Na_2SO_4, filtered and the solvent was evaporated in vacuo to afford the product **37** as a brown oil. (4.1046 g, 17.8 mmol, 71%. ^{1}H NMR (300 MHz, Chloroform-d) δ 3.01 – 2.92 (m, 1H), 2.81 (dd, J = 7.3, 1.0,

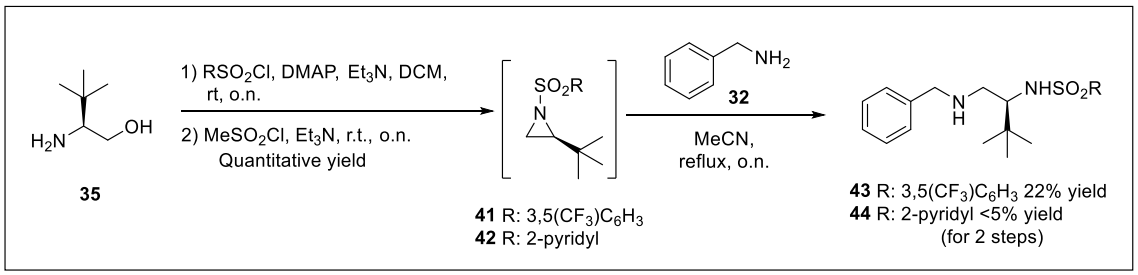
0.5 Hz, 1H), 2.53 (dd, J = 5.3, 0.9 Hz, 1H), 1.00 (s, 9H). The compound was pure enough and was used in the next step without further purification.

(S)-*N*-(2-(Benzylamino)-3,3-dimethylbutyl)-1,1,1-trifluoromethanesulfonamide

Benzylamine **32** (0.33 mL, 3mmol, 0.5 eq.) was added to a solution of *(2S)*-2-(1,1-Dimethylethyl)-1-[(trifluoromethyl)sulfonyl]aziridine **37** (1,39 g, 6 mmol, 1 eq.) in MeCN (9 mL) under Argon. The reaction mixture was stirred under reflux overnight. The solvent was evaporated under vacuo and the crude was directly submitted to flash column chromatography and eluted with (95:5 Hex:EtOAc) to obtain the product **38** as a yellow solid. (0.4073 g, 1.20 mmol, 40% yield). ^{1}H NMR (300 MHz, Chloroform-d) δ 7.45 – 7.23 (m, 5H), 4.20 (d, J = 13.8 Hz, 1H), 3.57 – 3.45 (m, 2H), 2.83 (dd, J = 14.0, 8.9 Hz, 1H), 2.61 (dd, J = 14.0, 4.3 Hz, 1H), 0.94 (s, 9H).

GENERAL PROCEDURE B:[28]

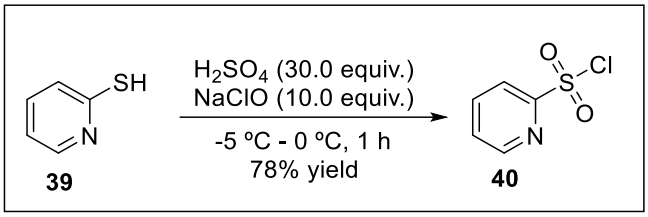
(2S)-1-[[3,5-Bis(trifluoromethyl)phenyl]sulfonyl]-2-(1,1-dimethylethyl)aziridine:



(S)-2-Amino-3,3-dimethylbutan-1-ol **35** (1.20g, 10.2 mmol, 1 eq.), Et_3N (2.1 mL, 15 mmol, 1.5 eq.) and DMAP (0.11 g, 1 mmol, 0.1 eq.) were dissolved in DCM (22 mL) under Argon atmosphere. The reaction mixture was cooled to -10 °C. A solution of the corresponding sulfonyl chloride (11 mmol, 1.1 eq.) in DCM (10 mL) was then added drop by drop. The reaction mixture was stirred overnight at room temperature. The mixture was then cooled to -10 °C and $MeSO_2Cl$ (0.85 mL, 11 mmol, 1.1 eq.) and Et_3N (2.1 mL, 15 mmol, 1.5 eq.) were added successively. After 10 minutes, the mixture was brought to room temperature and stirred overnight. The reaction mixture was washed with H_2O (2 × 50 mL) and the aqueous phase was extracted with DCM (2 × 25 mL). The combined organic phases were dried over Na_2SO_4, filtered and the solvent was evaporated in vacuo to afford the product as a brown oil in quantitative yield which was used for the next step without further purification.

In the case of sulfonyl aziridine **42** (R: 2-pyridyl), the required pyridine-2-sulfonyl chloride **40** is not commercial and was prepared as follows.

Pyridine-2-sulfonyl chloride **40**:[5]



Following the procedure in the literature, a multi-neck flask fitted with an addition funnel was charged with 2-mercaptopyridine **39** (1.1166 g, 10mmol, 1 equiv.) and sulfuric acid (16.7 mL, 30 equiv.) leaving it open to the atmosphere. The mixture was cooled to -8 ° C using a brine/ice bath. After that, aqueous sodium hypochlorite (13%, 47.8 mL, 10 equiv.) was added to it dropwise, over 30 minutes approximately, while keeping the fume hood closed and the room well ventilated (*THIS ADDITION GENERATES CHLORINE GAS!*). After the addition, the mixture was left to react for an additional 30 minutes, after which it was diluted with 50 mL and extracted twice with EtOAc (2×50 mL). The collected organic phase was dried with sodium sulphate, filtered, and concentrated in vacuo to obtain the crude product **40** as a yellow oil (0.3467 g, 1. 95 mmol, 66% yield). The spectroscopic data were coincident with those previously reported.[39] 1H NMR (300 MHz, Chloroform-d) 8.83 (dd, *J* = 2.9, 0.9 Hz, 1H), 8.12 (dt, *J* = 8.0, 1.3 Hz, 1H), 8.06 (td, *J* = 7.7, 1.7 Hz, 1H), 7.69 (ddd, *J* = 7.4, 4.7, 1.4 Hz, 1H).

(S)-N-(2-(Benzylamino)-3,3-dimethylbutyl)-3,5-bis(trifluoromethyl)benzenesulfonamide **43**:

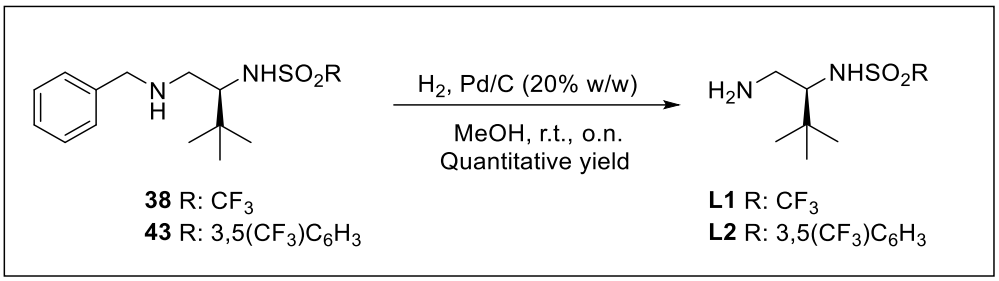
The title compound was prepared following General Procedure B starting from 3,5-bis(trifluoromethyl)benzene sulfonyl chloride (3.50 g, 11 mmol, 1.1 equiv.). The crude product was submitted to flash column chromatography and eluted with 90:10 Hex:EtOAc to afford the title product as a yellow oil (0.515 g, 1.07 mmol, % yield over two steps). ^{1}H NMR (300 MHz, Chloroform-d) δ 8.40 (d, J = 1.6 Hz, 2H), 8.05 (s, 1H), 7.51 – 7.23 (m, 5H), 4.36 (d, J = 13.1 Hz, 1H), 3.75 (dd, J = 10.4, 4.7 Hz, 1H), 3.42 – 3.24 (m, 1H), 2.78 (dd, J = 13.2, 10.5 Hz, 1H), 2.45 (dd, J = 13.2, 4.8 Hz, 1H), 0.71 (s, 9H).

(S)-2-((2-(tert-Butyl)aziridin-1-yl)sulfonyl)pyridine **44**:

The title was prepared following General Procedure B starting from freshly prepared pyridine-2-sulfonyl chloride **40** (1.20 g, 10.2 mmol, 1.0 equiv.). After the work-up only ‹5 mg of the crude were obtained, which were not enough for chromatographic purification.

5.3.3. Hydrogenolysis

GENERAL PROCEDURE



To a solution of Pd/C (20% w/w, 60 mg) in MeOH (8 mL) the corresponding benzyl derivative (0.84 mmol, 1,0 eq.) was added. The reaction mixture was then stirred at room temperature under Ar atmosphere for 16 hours. The reaction mixture was filtered through celite and the MeOH was evaporated in vacuo.

(S)-N-(2-Amino-3,3-dimethylbutyl)-1,1,1-trifluoromethanesulfonamide **L1**

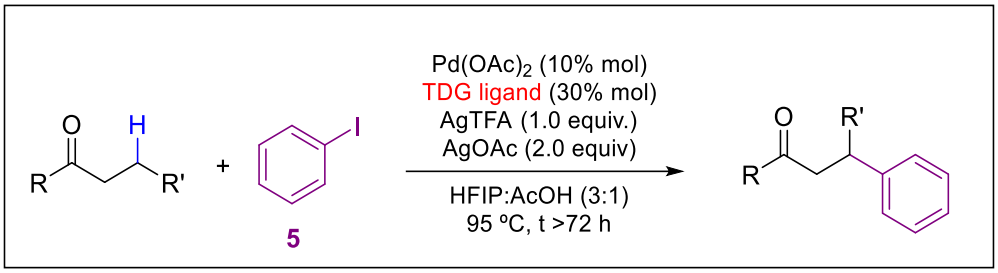
The title product was obtained from **38** (0.284 g, 0.84 mmol, 1.0 equiv.) following the general procedure and after the work-up **L1** was obtained as a white solid in a quantitative yield: $[\alpha]_D$=+1.72° (c 1.02, MeOH). m.p.= Decomposes before m.p. at 180 °C. ^1H NMR (300 MHz, Methanol-d^4) δ 3.69 (d, J = 10.2 Hz, 1H), 3.41 (dd, J = 13.5, 1.8 Hz, 1H), 3.20 (dd, J = 13.5, 10.0 Hz, 1H), 1.10 (s, 9H). ^{13}C NMR (75 MHz, Methanol-d4) δ 121.2 (q, J =318.8 Hz), 62.8, 53.5, 35.7, 26.9. UPLC-DAD-QTOF: $C_7H_{16}F_3N_2O_2S$ [M+H]+ calcd.: 249.0879, found: 249.0892.

(S)-N-(2-Amino-3,3-dimethylbutyl)-3,5-bis(trifluoromethyl)benzenesulfonamide **L2**:

The title product was obtained from **43** (0.515 g, 1,07 mmol, 1,0 eq.) following the general procedure and after the work-up **L2** was obtained as a white solid in a quantitative yield: $[\alpha]_D$=-15.1° (c 1.02, MeOH). m.p.=62.8-64.0 °C. ^1H NMR (300 MHz, Methanol-d^4) δ 8.48 (s, 2H), 8.28 (s, 1H), 3.32 – 3.24 (m, 1H), 2.96 (d, J = 13.1 Hz, 1H), 2.70 (t, J = 11.5 Hz, 1H), 0.78 (s, 9H). ^{13}C NMR (75 MHz, Methanol-d4) δ 146.3, 133.67 (q, J = 34.2 Hz), 128.8, 127.0, 124.2 (q, J = 273.4 Hz), 63.0, 51.5, 35.4, 27.6. ^{19}F NMR (400MHz, Methanol-d^4) δ 77.4 (s, 3F). UPLC-DAD-QTOF: $C_7H_{16}F_3N_2O_2S$ [M+H]+ calcd.: 393.1066, found: 393.1075.

5.4. β-C(sp3)-H ACTIVATION REACTION

5.4.1. General Procedure[41]



In air, a reaction tube with a stir bar was charged with the carbonylic reactant (aldehyde, ketone or α-ketoamide) (1 equiv.), iodobenzene **5** (2 equiv.), silver trifluoroacetate (1 equiv.), silver acetate (2 equiv.), palladium acetate (10% mmol) and the indicated TDG (30% mmol), followed by HFIP and AcOH (3:1) as indicated. The reaction tube was sealed, and a balloon with argon gas was added to avoid the solvent from evaporating and the mixture drying out. The mixture was left to react at ambient temperature for ten minutes, after which it was submerged in an oil bath and left to react for the indicated time at the indicated temperature. Then the reaction mixture was cooled to room temperature, diluted with EtOAc, filtered through a silica gel plug, and concentrated in vacuo to obtain the crude product as a dark brown oil. The crude mixture was then submitted to flash column chromatography with a mixture of Hex:EtOAc (different proportions). However, in the case of the α-keto amides, the reactant and the product could not be separated with this method, which led to first perform Preparative TLC on aluminium silica gel plaques with Tol:EtOAc (98:2) to successfully isolate the arylated final product.

5.4.2. Racemic Reactions

WITH GLYCINE

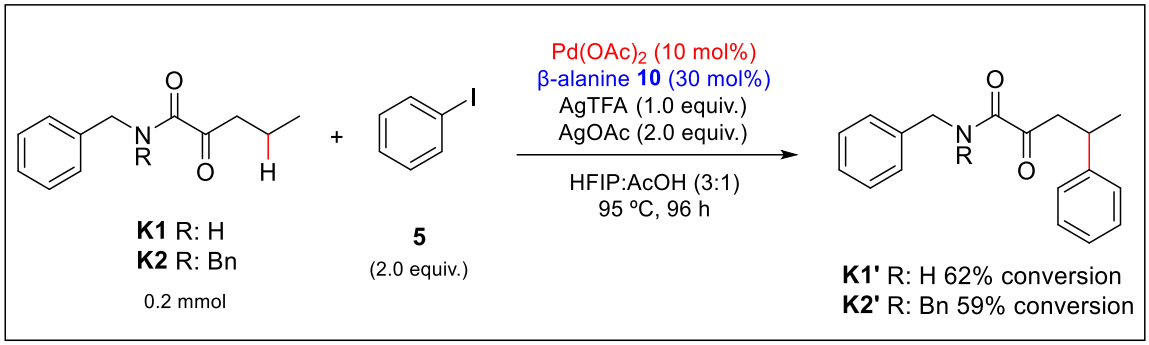
This reaction was performed using four different starting products. First, butyraldehyde **45**, then hydrocinnamaldehyde **46** and finally both α-keto amides **K1** and **K2** proposed for the reaction.

Each of the reaction tubes was charged with 0.2 mmol of the starting product, aryl iodide **5** (45.0 µL, 0.40 mmol, 2 equiv.) and then AgTFA (0.044 g, 0.20 mmol, 0.1 equiv.), AgOAc (0,067 g, 0.40 mmol, 2 equiv.), $Pd(OAc)_2$ (0.0045 g, 0.020 mmol, 10% mol) and glycine

[41] K. Hong; H. Park ; J.-G. Yu, *ACS Catal.* **2017**, *7*, 6938-6941.

(0.0046 g, 0.060 mmol, 30% mol). After adding the catalysts and the reactants, the solvents HFIP (1.5 mL) and AcOH (0.5 mL) were added. The mixture was left to react at a temperature of T_{bath}=95 °C for the indicated time. In the case of aldehydes **45** and **46**, no reaction was observed (no arylated product detected via ^{1}H NMR) and the initial unaltered aldehydes were identified. For **K1** and **K2** α-keto amides, different samples were analysed by ^{1}H NMR (see Chapter 3: Results and Discussion), the γ-arylated products were detected but not isolated.

WITH β-ALANINE



In these cases, because of the lack of reactivity with the aldehydes (**45** and **46)**, the reaction was only performed with the designed α-ketoamides **K1** and **K2** at 0.4 mmol scale.

The vials were charged with 0.4 mmol of the starting product and aryl iodide **5** (89.5 µL, 0.80 mmol, 2.0 equiv.). Subsequently, the catalyst and additives AgTFA (0.088 g, 0.40 mmol, 1.0 equiv.), AgOAc (0,134 g, 0.80 mmol, 2.0 equiv.), $Pd(OAc)_2$ (0.0090 g, 0.040 mmol, 10% mol) and β-alanine **10** (0.0171 g, 0.120 mmol, 30% mol) and the solvents HFIP (3.0 mL) and AcOH (1.0 mL) were added. The mixture was left to react at a temperature of T_{bath}=95 °C for 96 hours.

N-Benzyl-2-oxo-4-phenylpentanamide **K1'**:

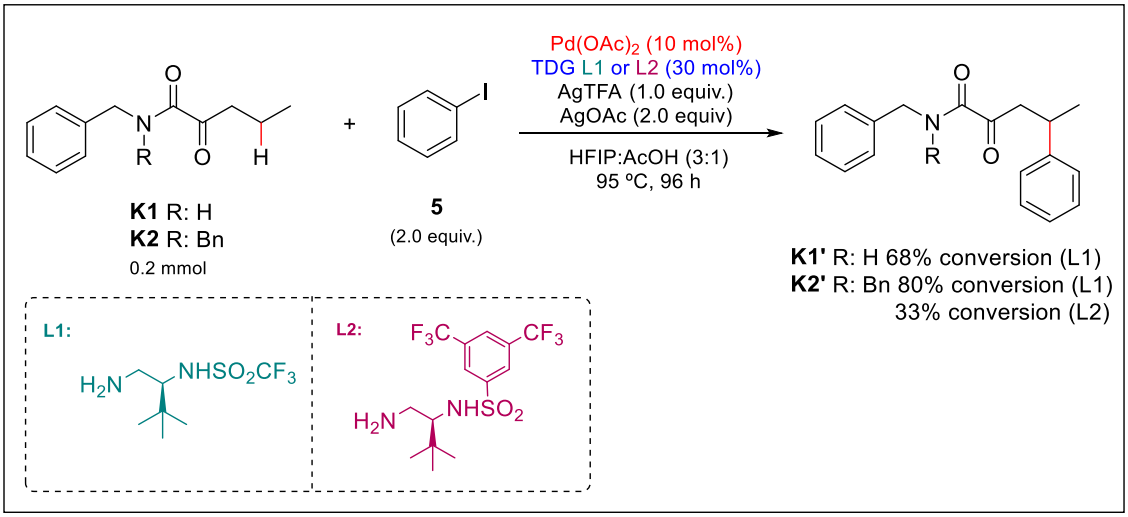
The general procedure was followed starting from *N*-benzyl-2-oxo-pentanamide **K1** (0.0847 g, 0.40 mmol, 1.0 equiv.). After 96 h of reaction the conversion was found to be 79%. After work-up (see General Procedure) the crude product was purified by flash column chromatography (eluent Hex:EtOAc 98:2→97:3). Unfortunately, this method was not enough to separate the starting product from the arylation product. After Preparative TLC separation (Tol:EtOAc 98:2), 8 mg of the pure title compound **K1'** were isolated as an off-white solid. m.p.=not determined. ^{1}H NMR (300 MHz, Chloroform-d4)

δ 7.45 – 7.01 (m, 10H), 4.44 (d, *J* = 6.2, 1.8 Hz, 2H), 3.47 – 3.12 (m, 3H), 1.30 (d, *J* = 6.8 Hz, 3H).^{13}C NMR (75 MHz, Chloroform-d4) δ 198.0, 160.1, 145.8, 137.0, 128.9, 128.7, 128.0, 127.0, 126.5, 45.0, 43.5, 35.3, 22.4. UPLC-DAD-QTOF: $C_{18}H_{20}NO_2$ [M+H]+ calcd.: 282.1489, found: 282.1488. A sample was analysed by Chiral HPLC (ID column, 80:20 Hex:^{i}PrOH, 0.5 mL/min flow. Retention times: 23.625 min; 29.093 min) which led to the separation of the two enantiomers.

N,N-Dibenzyl-2-oxo-4-phenylpentanamide **K2'**:

The general procedure was followed starting from *N,N*-dibenzyl-2-oxopentanamide **K2** (0.1210 g, 0.40 mmol, 1.0 equiv.) After 96 h of reaction conversion was found to be 59%. After work-up ,the crude product was purified via flash column chromatography (Hex:EtOAc 98:2→97:3) and then by Preparative TLC (Tol:EtOAc 98:2) to obtain 5.0 mg of **K2'** as an off-white solid. m.p.=not determined. ^{1}H NMR (300 MHz, Chloroform-d4) δ 7.42 – 7.06 (m, 15H), 4.69 – 4.21 (dd, 2H), 3.39 (h, *J* = 7.0 Hz, 1H), 3.24 – 2.99 (m, 2H), 1.29 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, Chloroform-d4) δ 200.0, 167.5, 145.5, 135.9, 135.5, 128.9, 128.9, 128.1, 127.8, 126.9, 126.6, 49.4, 48.2, 46.9, 35.00 22.7. UPLC-DAD-QTOF: $C_{25}H_{26}NO_2$ [M+H]+ calcd.: 372.1958, found: 372.1969. A sample was analysed by chiral HPLC analysis which led to the separation of both enantiomers (ID column, 80/20 Hex/iPrOH, 0.5 mL/min flow. Retention times: 19.341 min; 21.852 min).

5.4.3. Asymmetric Reactions



The same procedure employed with β-alanine **10** was followed but using TDG **L1** or **L2** (0.06 mmol, 30 mol%) instead of β-alanine. The reaction mixture was allowed to react at 95 °C for 96 h. Since complete conversion was not achieved, a small amount of the pure

arylated compound was isolated by flash chromatography column (eluent: Hex:EtOAc 98:2→97:3) followed by preparative TLC (Tol:EtOAc 98:2).

N-Benzyl-2-oxo-4-phenylpentanamide **K1'**:

The general procedure was followed starting from *N*-benzyl-2-oxo-pentanamide **K1** (0.0847 g, 0.20 mmol, 1.0 equiv.) and using **L1** (0.0156 g, 0.06 mmol, 30 mol%) as the TDG. After 96 h of reaction the conversion was found to be 68%. After work-up, flash column chromatography and subsequent preparative TLC afforded 14 mg of the pure title compound with **L1**. Spectroscopic data were coincident with those of the racemic product. A sample was analysed via chiral HPLC which revealed the product to be racemic. (ID column, 80:20 Hex:iPrOH, 0.5 mL/min flow. Retention times: 23.112 min; 29.726 min).

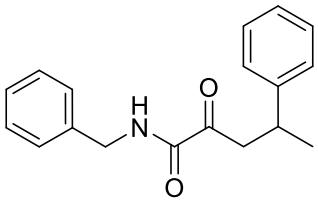
N,N-Dibenzyl-2-oxo-4-phenylpentanamide **K2'**:

The general procedure was followed starting from *N,N*-dibenzyl-2-oxopentanamide **K2** (0.1210 g, 0.20 mmol, 1.0 equiv.) and using **L1** (0.0156 g, 0.06 mmol, 30 mol%) as the TDG. After 96 h of reactions the conversions were found to be 80% for **L1** and 33% for **L2**. Flash column chromatography and subsequent preparative TLC purification afforded 17 mg of the pure title compound as an off-white solid for **L1**. Spectroscopic data were coincident with those of the racemic reaction. A sample was analysed by chiral HPLC analysis which showed the product to be racemic. (ID column, Hex:^{i}PrOH 80:20, 0.5 mL/min flow. Retention times: 19.223 min; 21.642 min). The γ-arylated product **K2'** from the reaction with **L2** as TDG was not isolated.

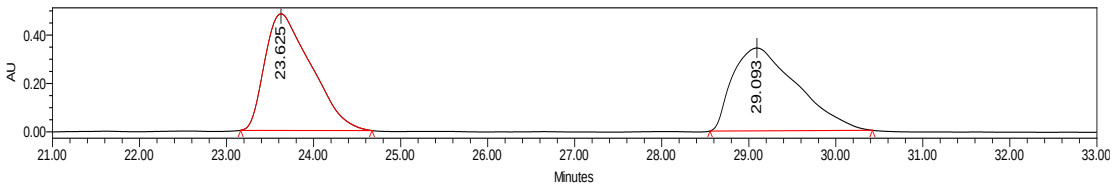
6. APPENDIX

6.1. HPLC Chromatograms

ID column, Hex:iPrOH 80:20, 0.0.5 mL/min flow.

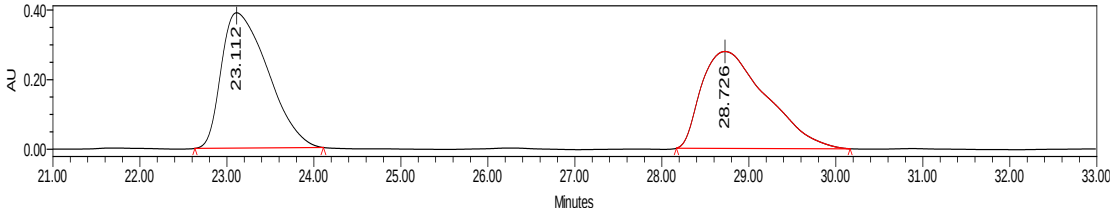


N-benzyl-2-oxo-4-phenylpentanamide **K1'** (β-alanine **10** TDG)

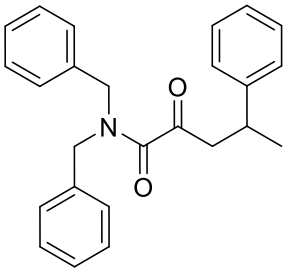


Peak	Retention Time (min)	Area (%)
1	23.625	50.24
2	29.093	49.76

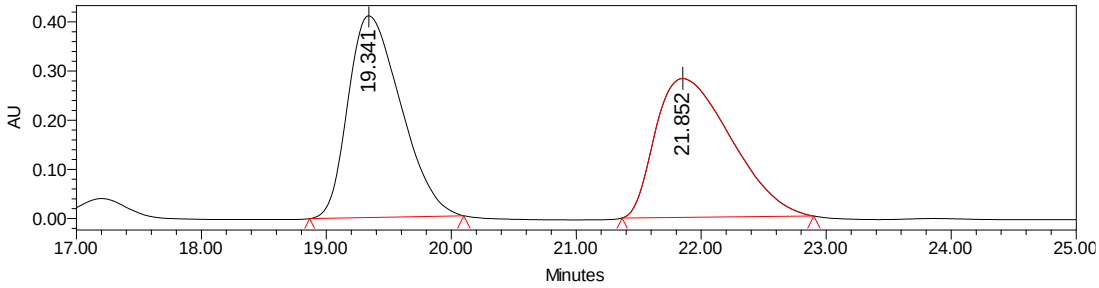
N-benzyl-2-oxo-4-phenylpentanamide **K1'** (**L1** TDG)



Peak	Retention Time (min)	Area (%)
1	23.112	50.02
2	28.726	49.98

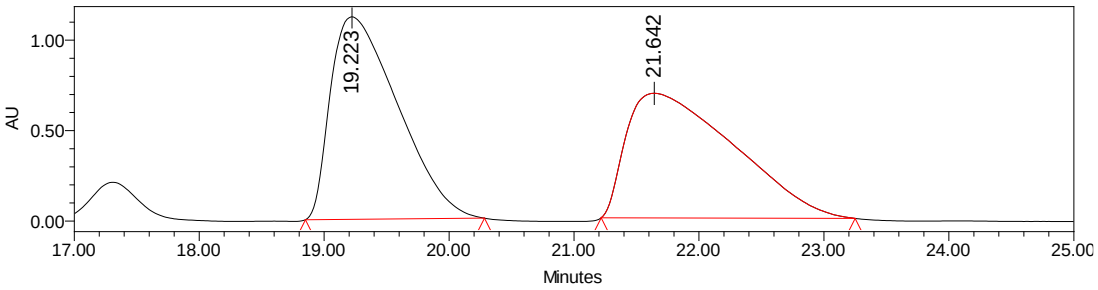


N,N-dibenzyl-2-oxo-4-phenylpentanamide **K2'** (β-alanine **10** TDG)



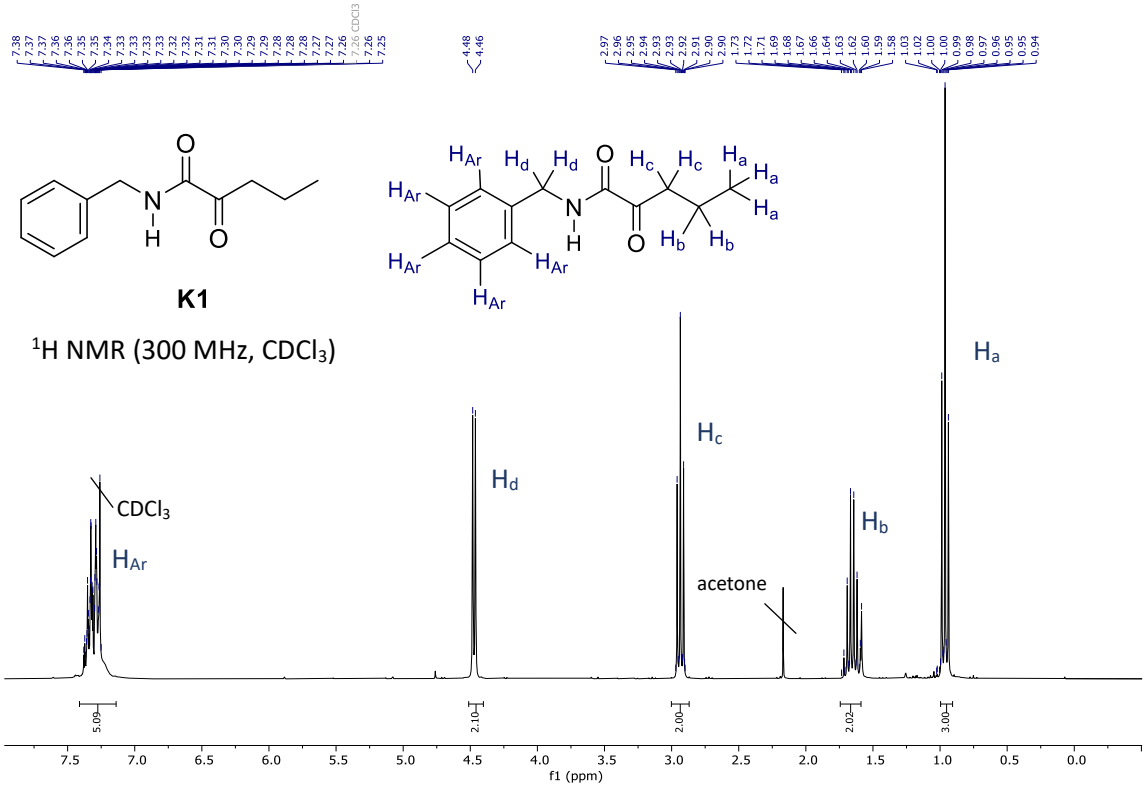
Peak	Retention Time (min)	Area (%)
1	19.341	50.36
2	21.852	49.64

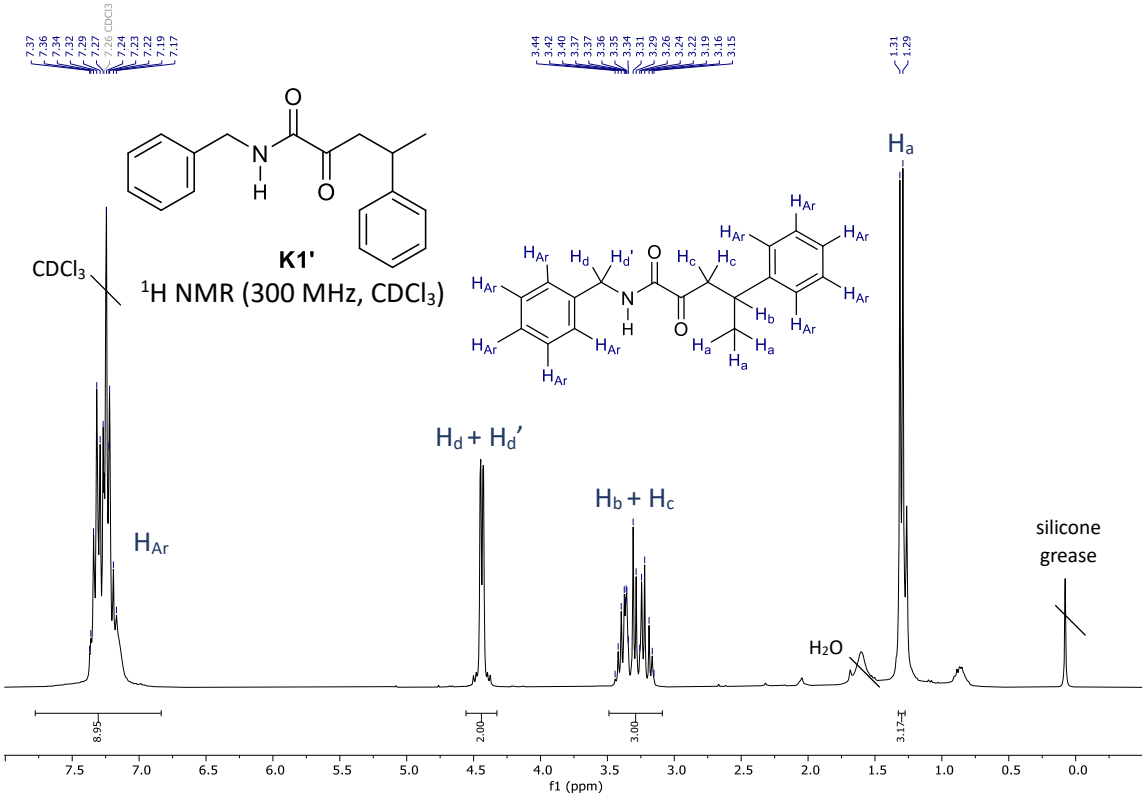
N,N-dibenzyl-2-oxo-4-phenylpentanamide **K2'** (**L1** TDG)

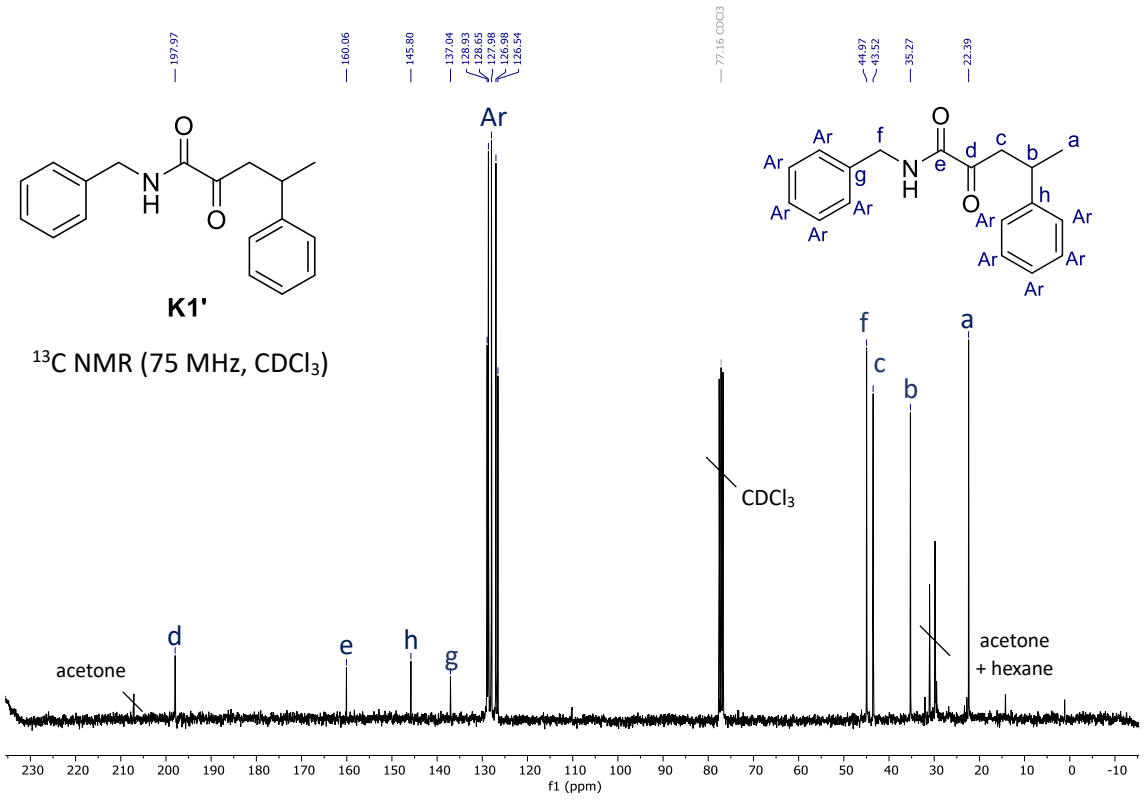


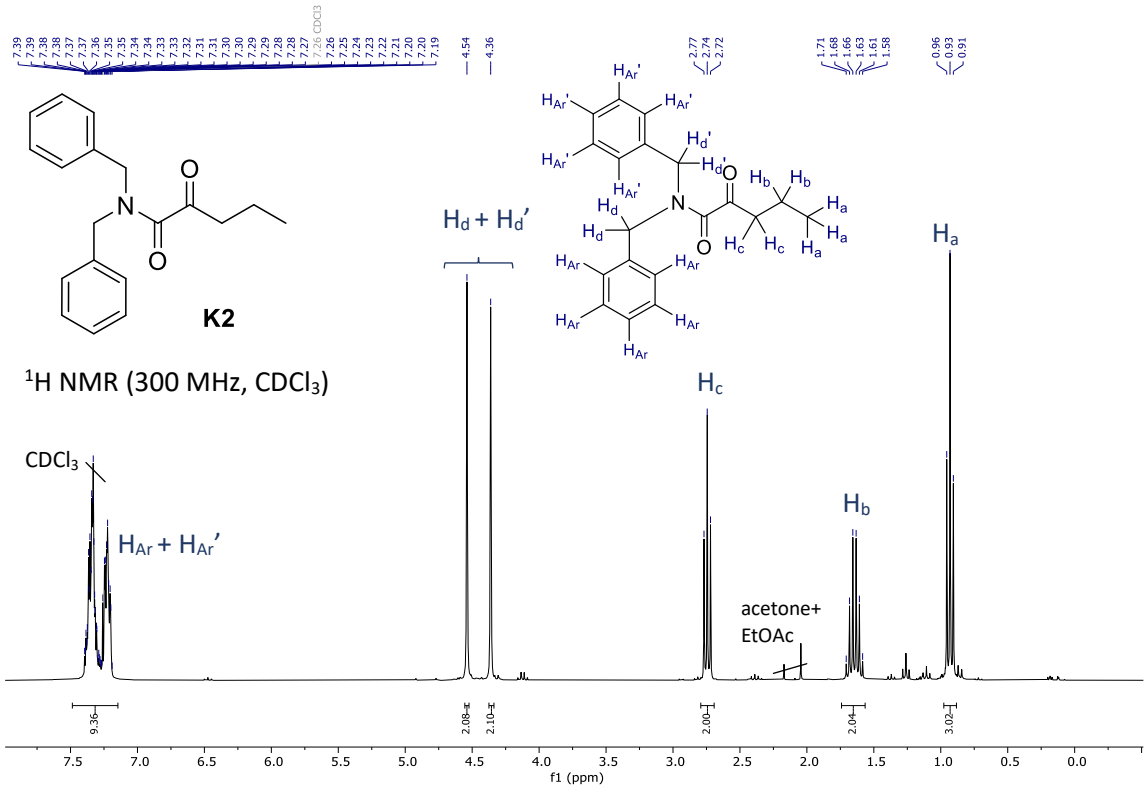
Peak	Retention Time (min)	Area (%)
1	19.223	50.38
2	21.642	49.62

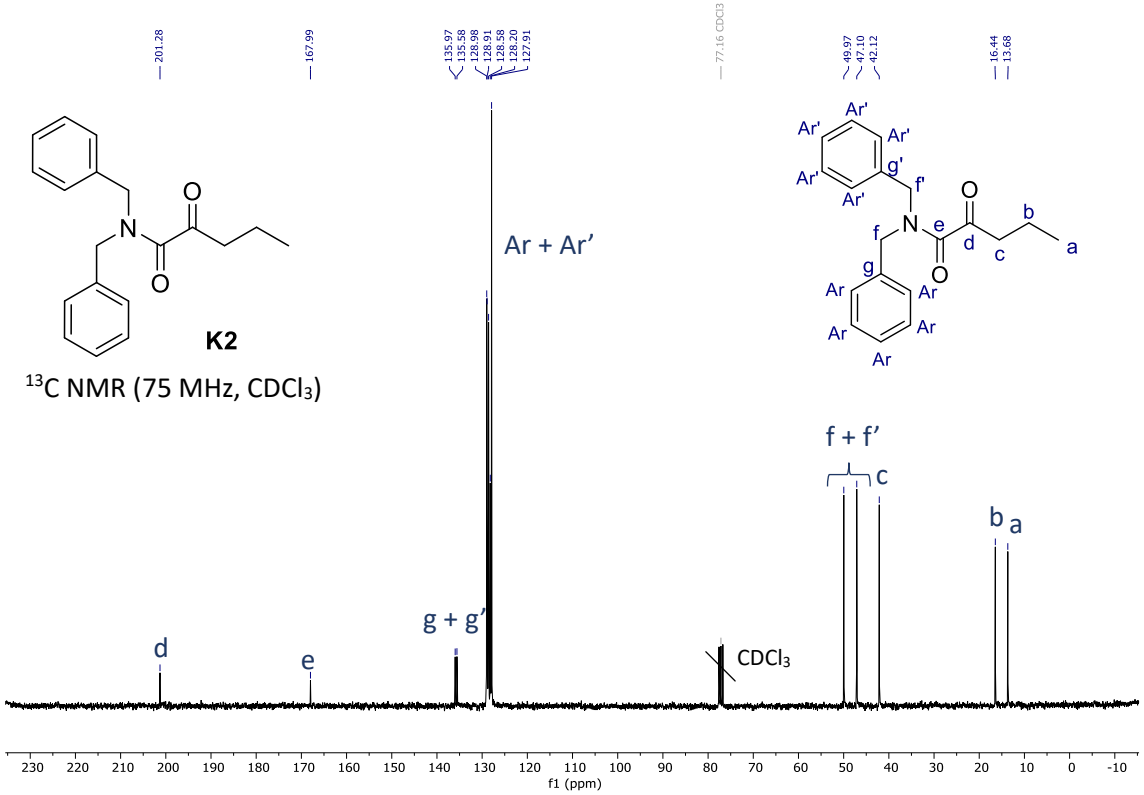
6.2. NMR Spectra

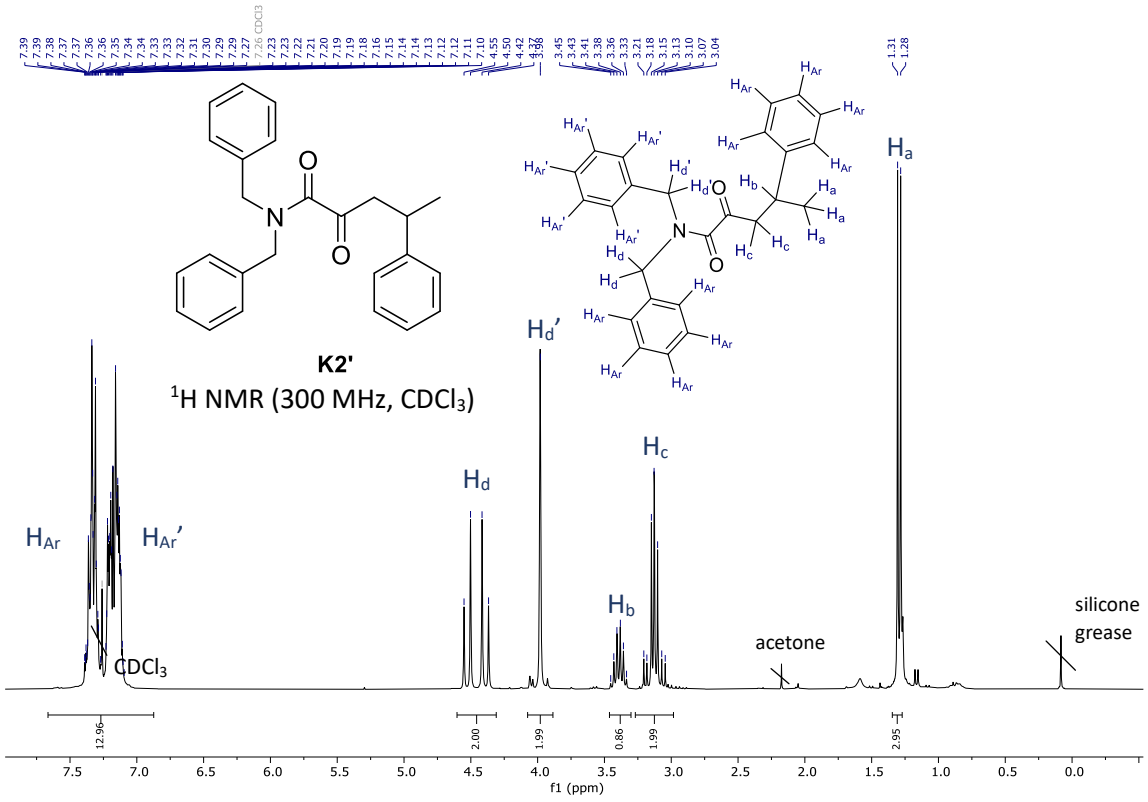


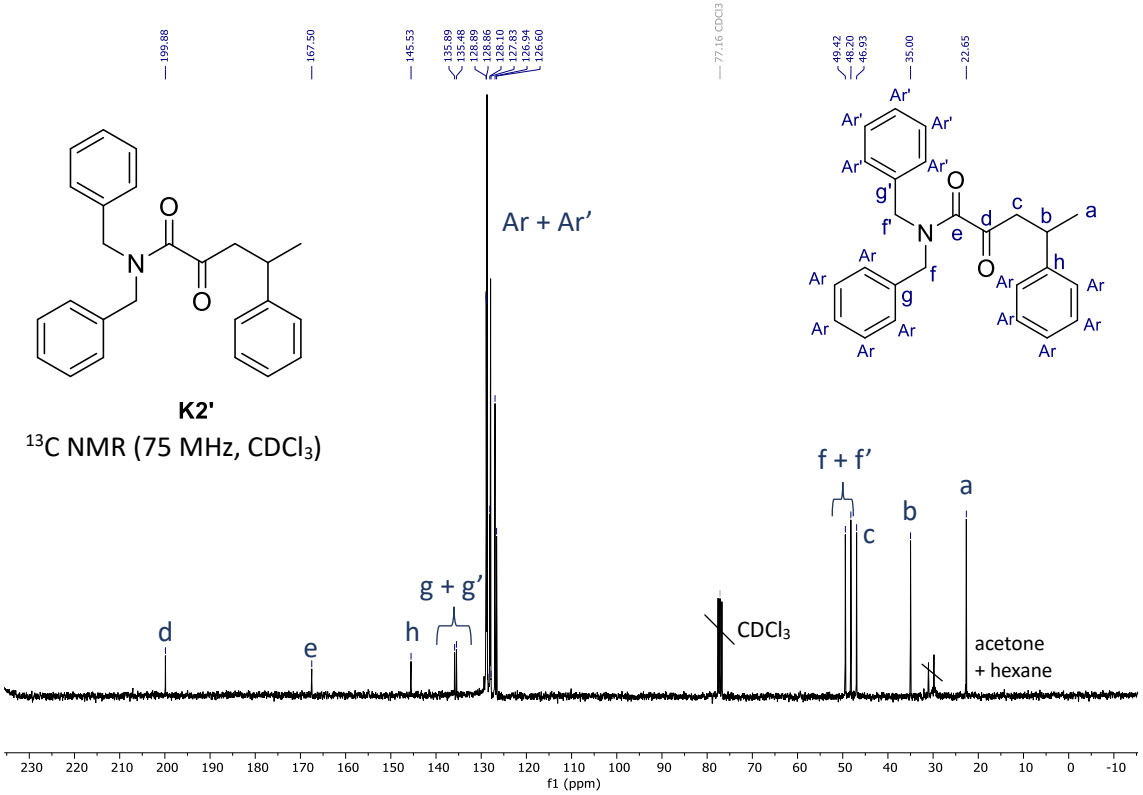



K1'
13C NMR (75 MHz, CDCl3)
CDCl3
acetone
acetone
+ hexane
f1 (ppm)


K2
1H NMR (300 MHz, CDCl3)
Hd + Hd'
Ha
Hc
Hb
CDCl3
HAr + HAr'
acetone+
EtOAc
f1 (ppm)

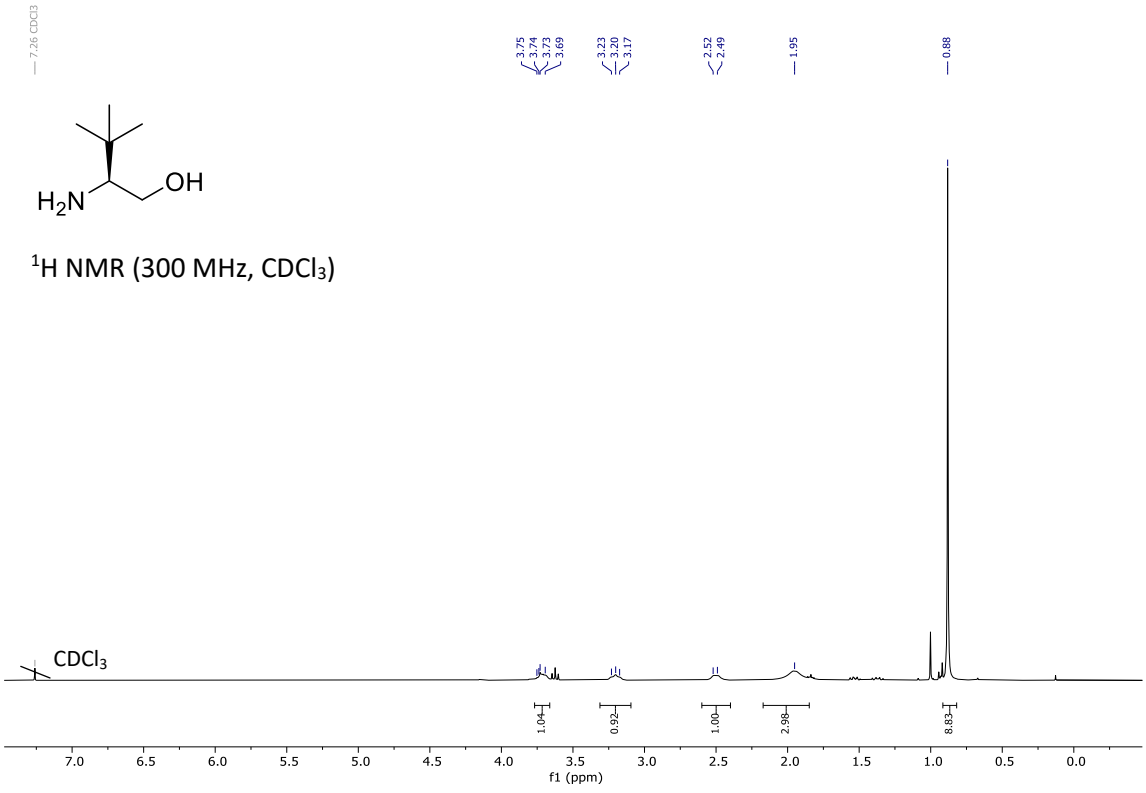

K2
^{13}C NMR (75 MHz, $CDCl_3$)
Ar + Ar'
f + f'
g + g'
CDCl3
f1 (ppm)


K2'
^{1}H NMR (300 MHz, $CDCl_3$)
H_{Ar}
H_{Ar}'
H_d
H_d'
H_c
H_b
H_a
$CDCl_3$
acetone
silicone grease
f1 (ppm)

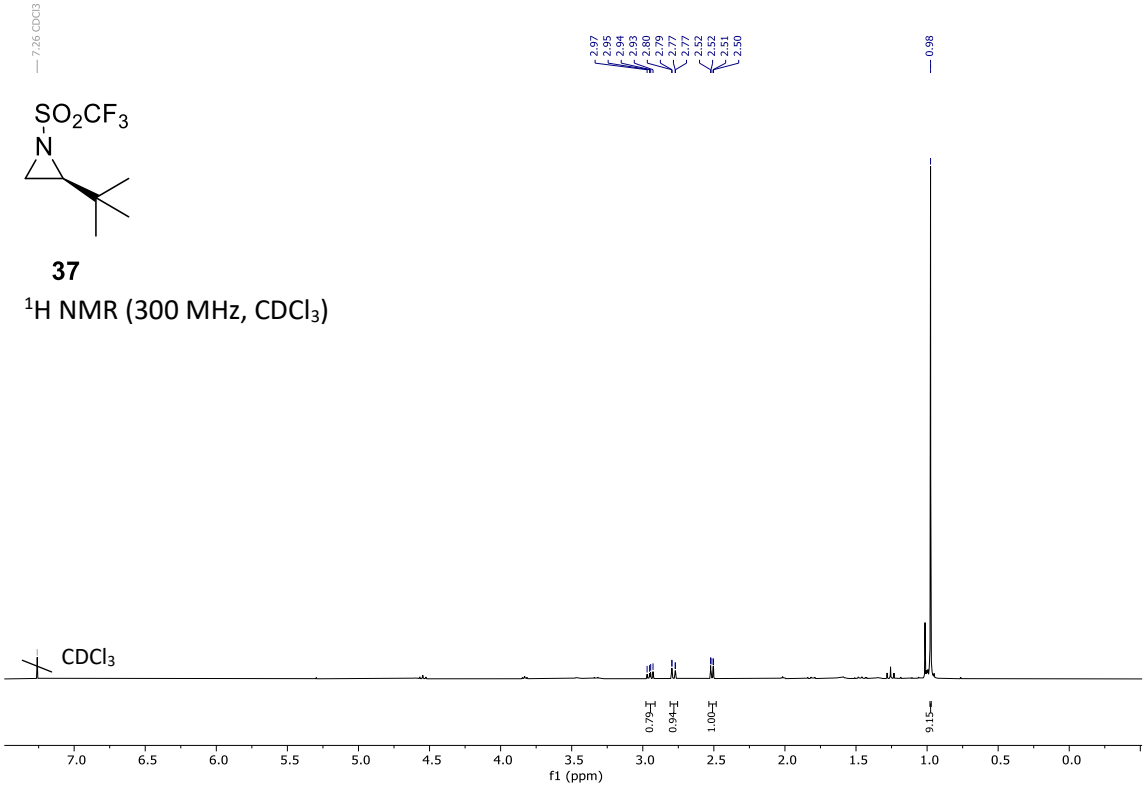


K2'

^{13}C NMR (75 MHz, $CDCl_3$)

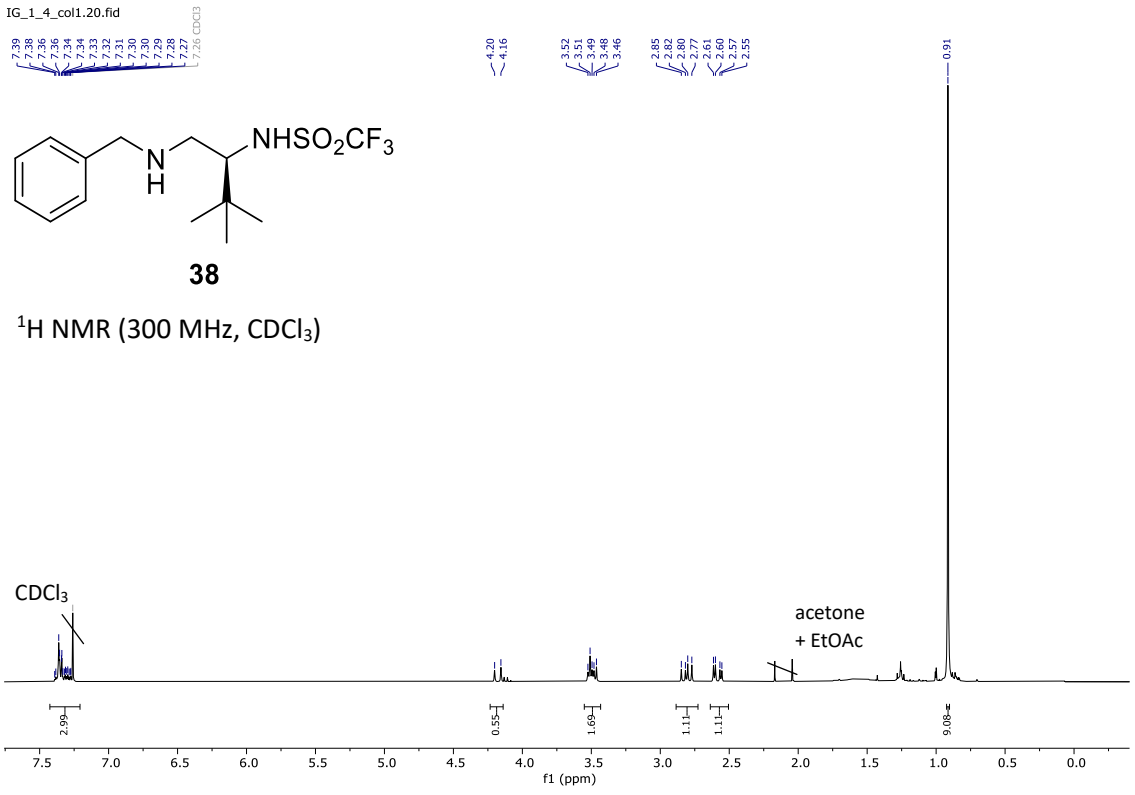


^{1}H NMR (300 MHz, $CDCl_3$)



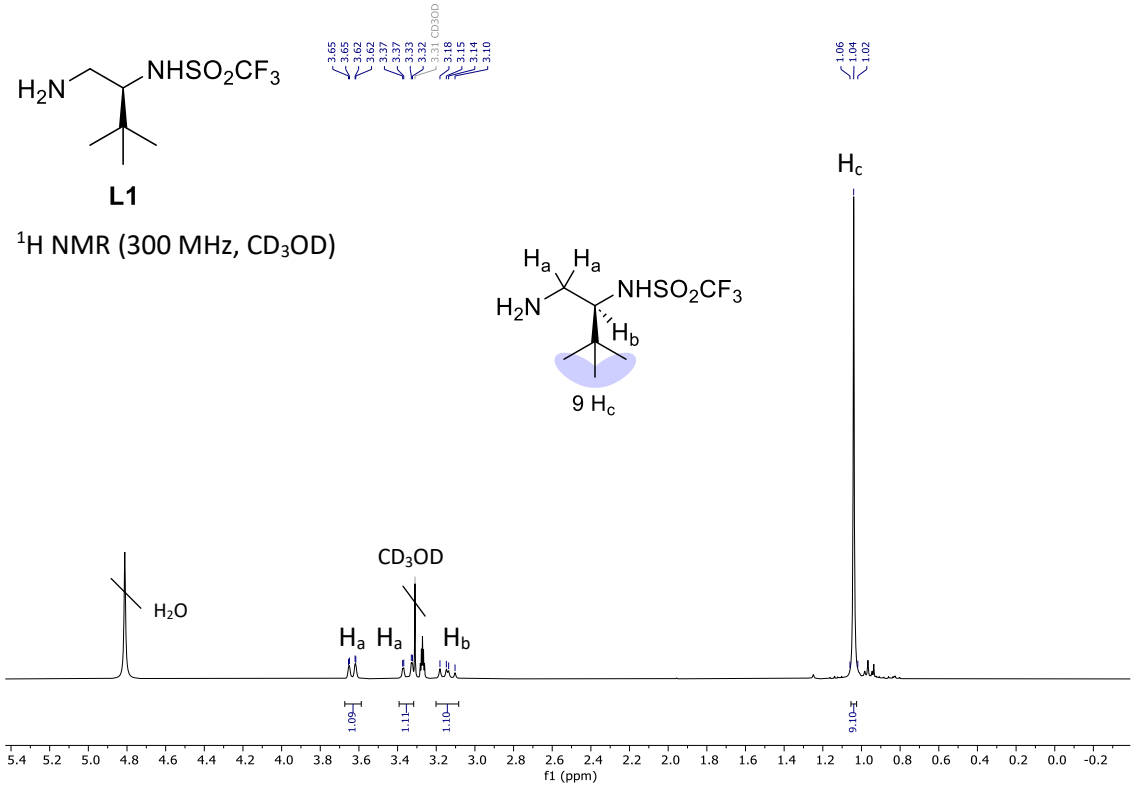
37

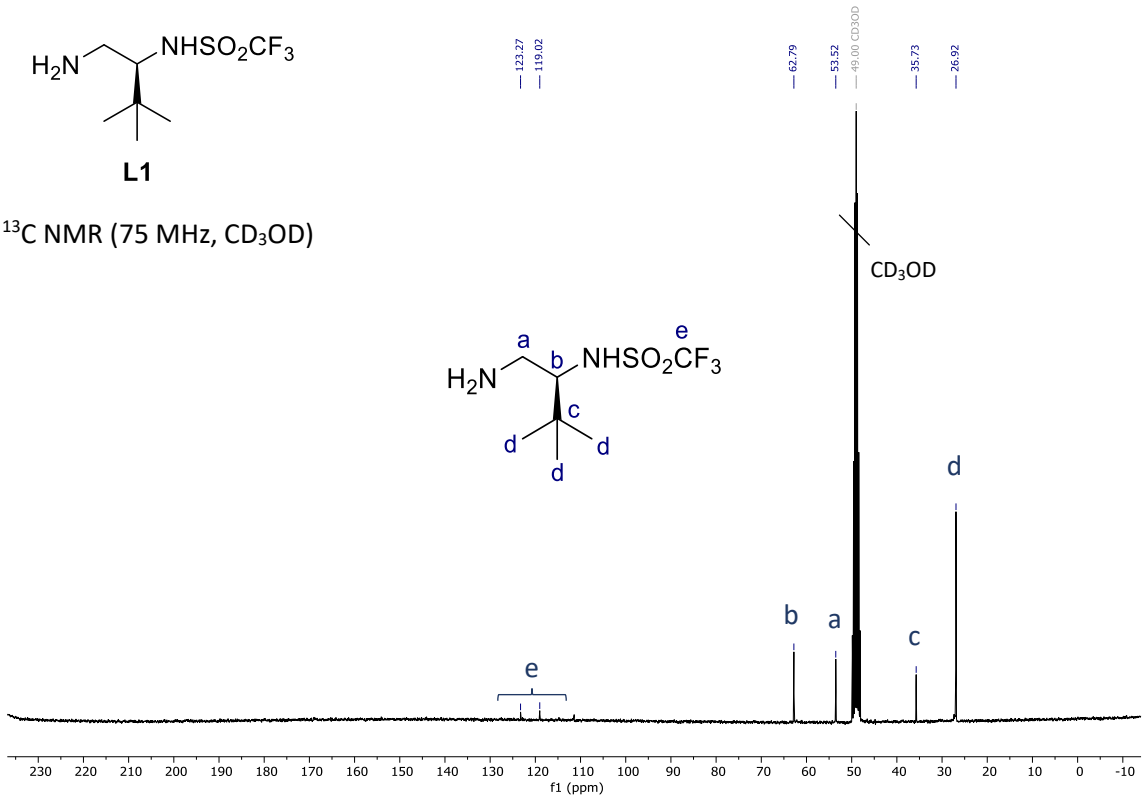
^{1}H NMR (300 MHz, $CDCl_3$)

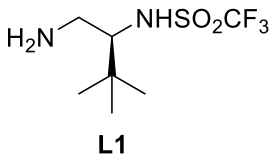


38

^{1}H NMR (300 MHz, $CDCl_3$)

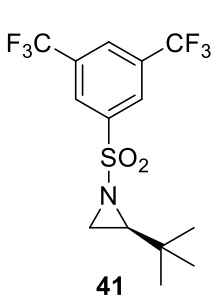

H2N
NHSO2CF3
L1
1H NMR (300 MHz, CD3OD)
Ha Ha
NHSO2CF3
H2N
Hb
9 Hc
Hc
H2O
CD3OD
Ha Ha
Hb
f1 (ppm)


H2N
NHSO2CF3
L1
13C NMR (75 MHz, CD3OD)
a
b
e
NHSO2CF3
H2N
c
d
d
d
CD3OD
b
a
c
d
e
f1 (ppm)



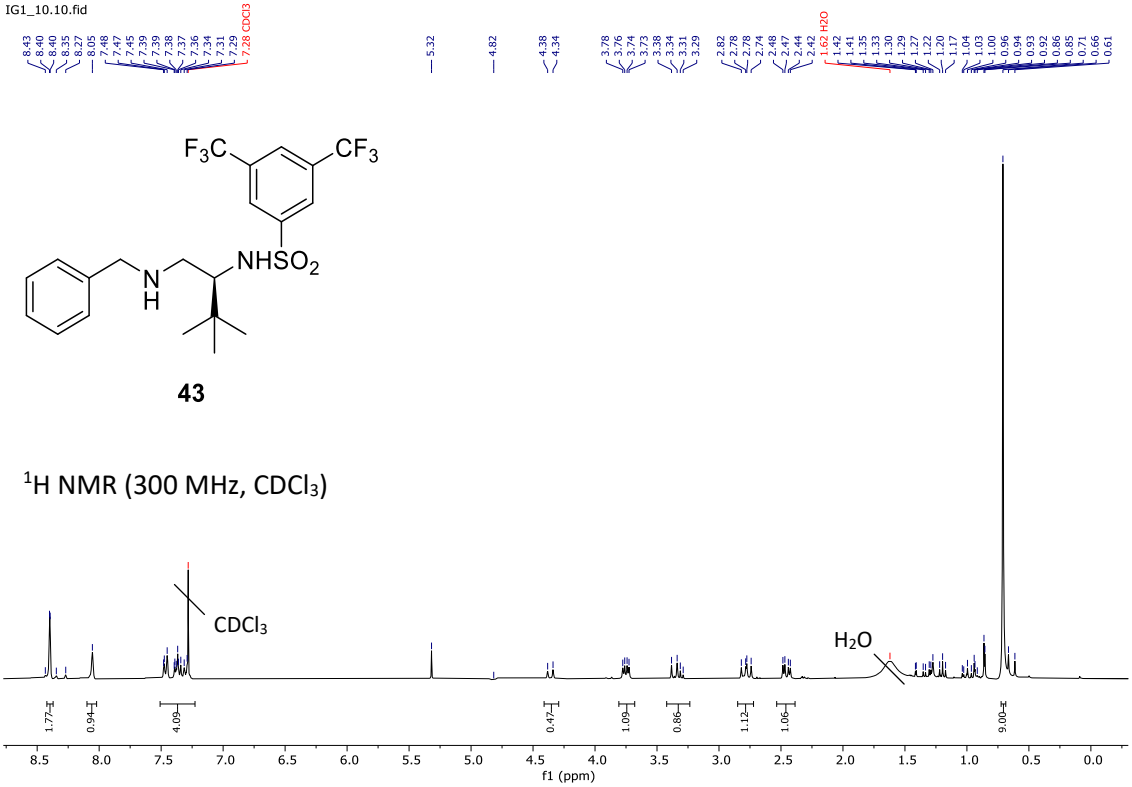
L1

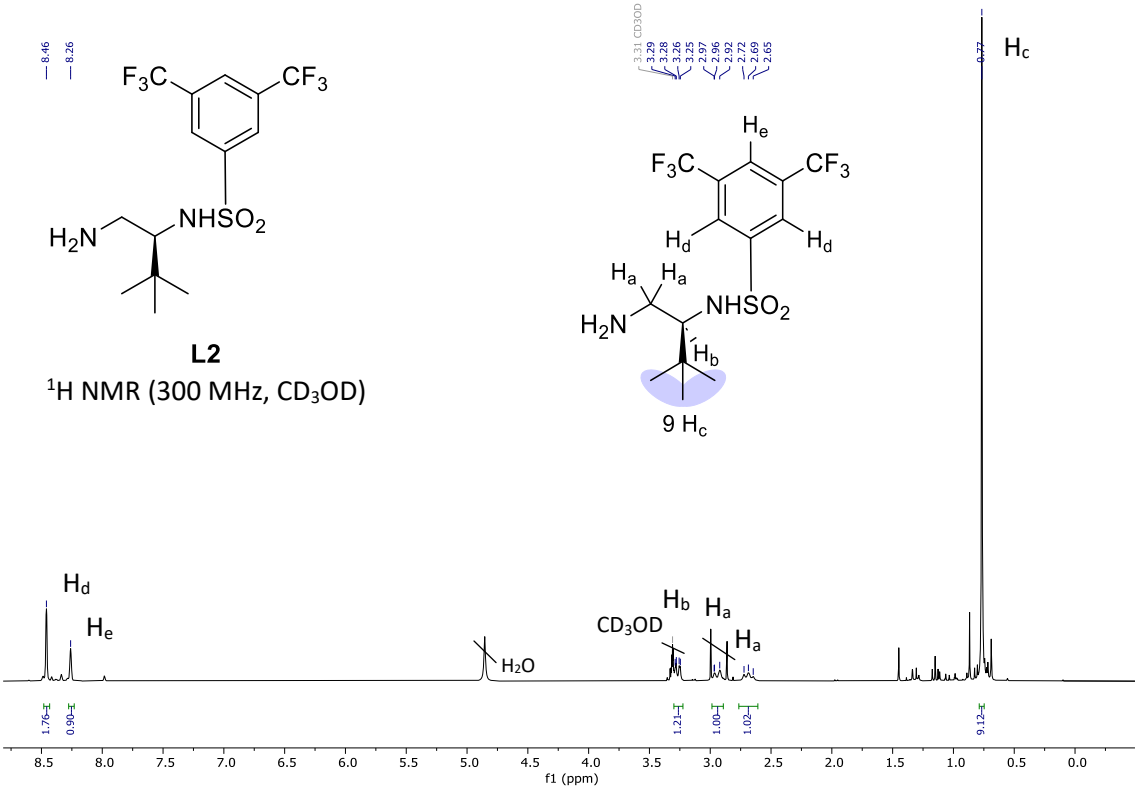
^{19}F NMR (400 MHz, CD_3OD)

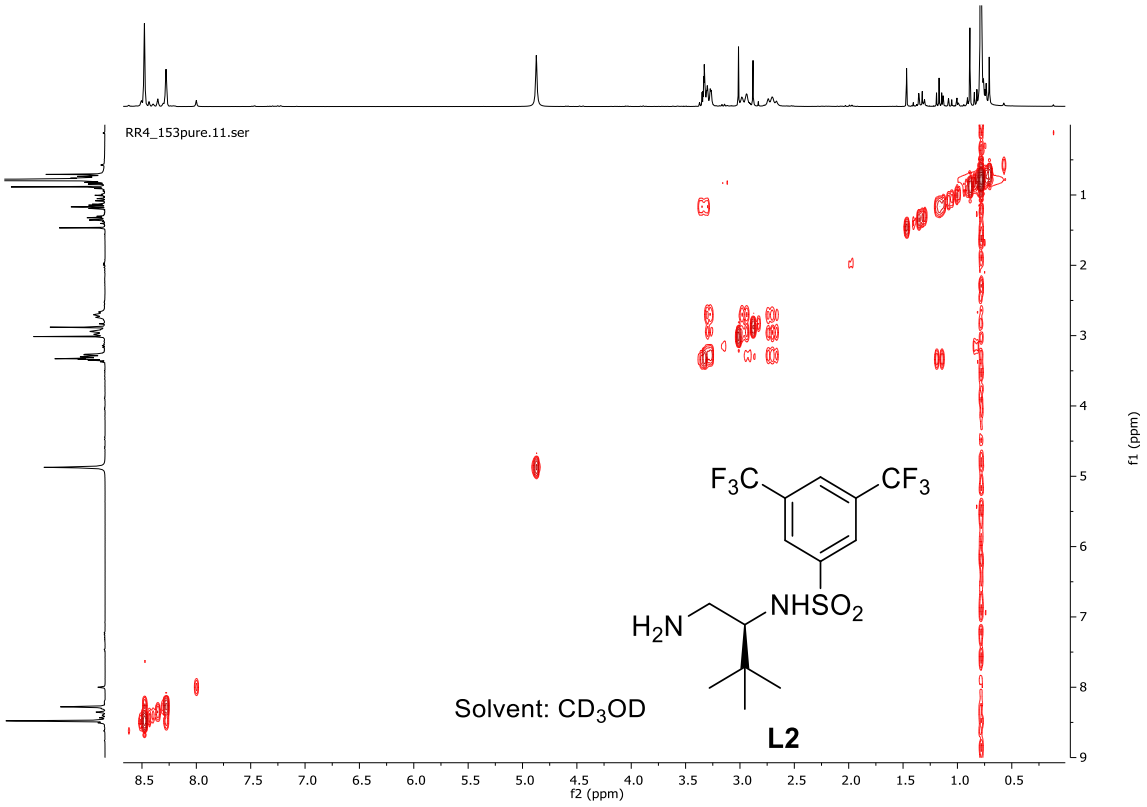


41

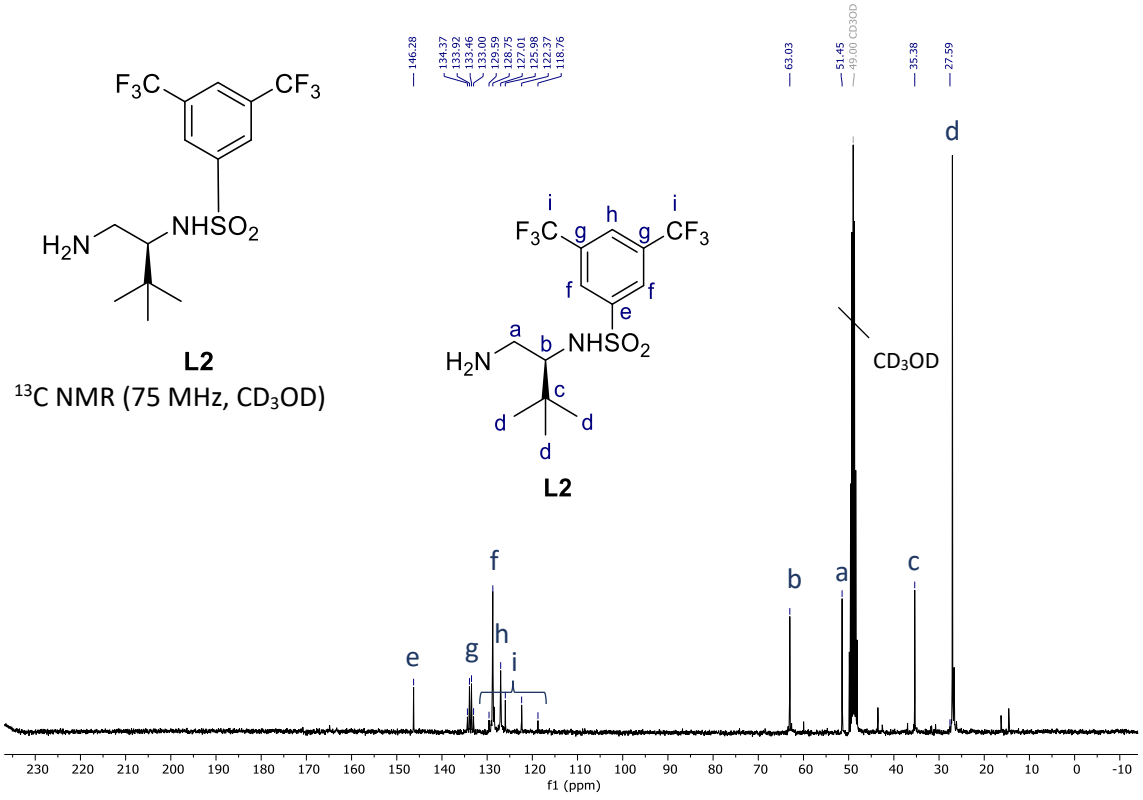
^{1}H NMR (300 MHz, $CDCl_3$)

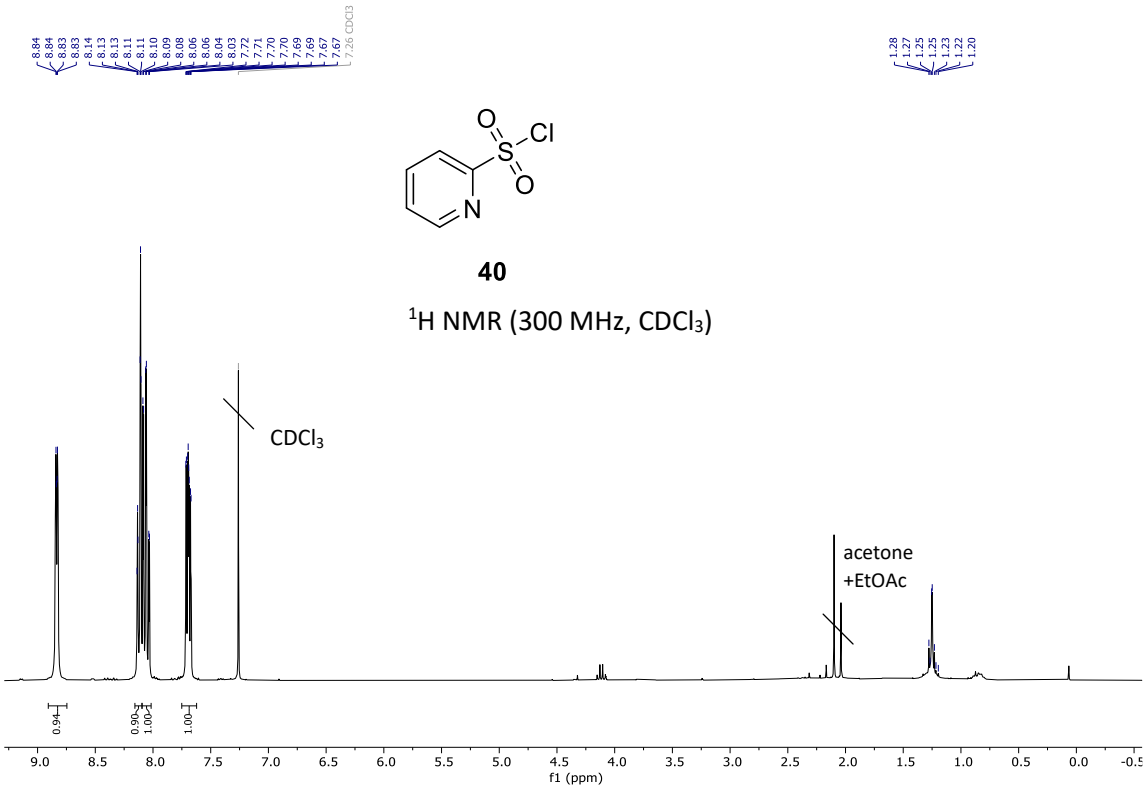

IG1_10.10.fid
F3C
CF3
NHSO2
N
H
43
1H NMR (300 MHz, CDCl3)
CDCl3
H2O
f1 (ppm)

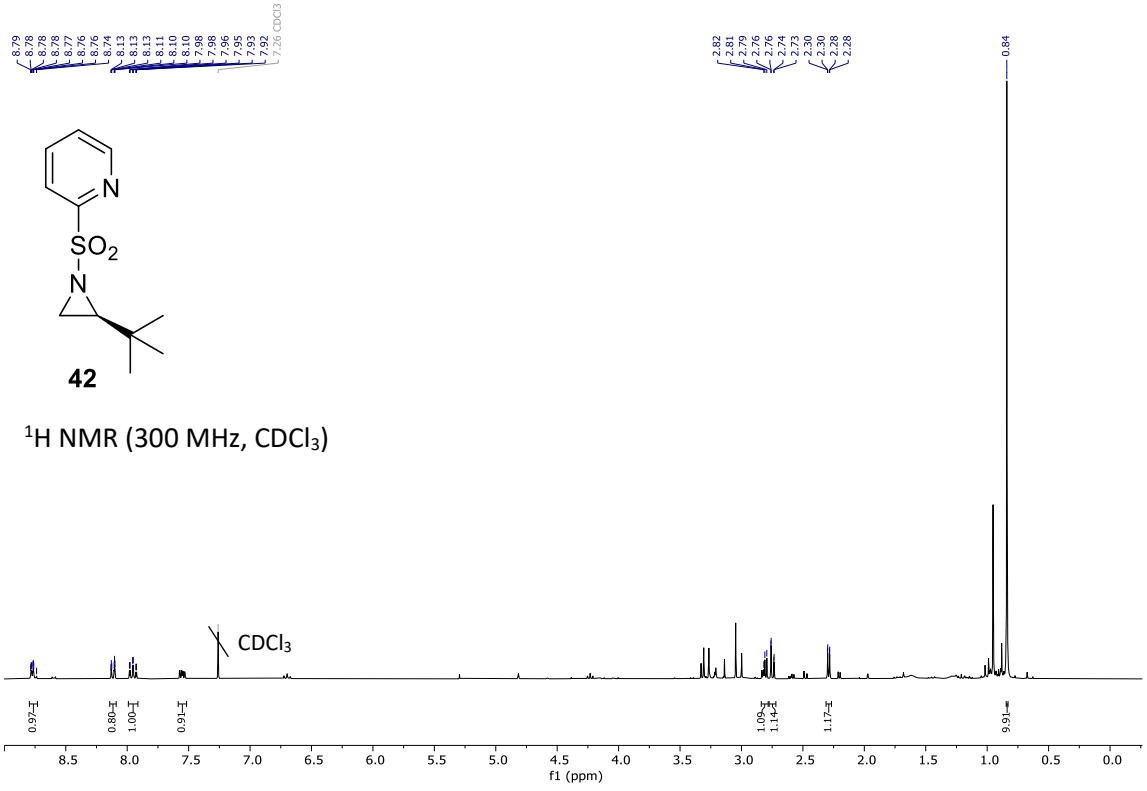

F3C
CF3
NHSO2
H2N
L2
1H NMR (300 MHz, CD3OD)
He
Hd
Ha
Hb
Hc
9 Hc
CD3OD
H2O
f1 (ppm)


RR4_153pure.11.ser
Solvent: CD3OD
L2
f2 (ppm)
f1 (ppm)

f


L2
13C NMR (75 MHz, CD3OD)
CD3OD
f1 (ppm)


8.84
8.84
8.83
8.83
8.14
8.13
8.13
8.11
8.11
8.10
8.09
8.08
8.06
8.06
8.04
8.03
7.72
7.71
7.70
7.70
7.69
7.69
7.67
7.67
7.26 CDCl3
1.28
1.27
1.25
1.25
1.23
1.22
1.20
O
Cl
S
O
N
40
1H NMR (300 MHz, CDCl3)
CDCl3
acetone
+EtOAc
0.94
0.90
1.00
1.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


8.79
8.78
8.78
8.78
8.77
8.76
8.76
8.74
8.13
8.13
8.13
8.11
8.10
8.10
7.98
7.98
7.96
7.95
7.93
7.92
7.26 CDCl3
2.82
2.81
2.79
2.79
2.76
2.74
2.73
2.30
2.30
2.28
2.28
0.84
N
SO2
N
42
1H NMR (300 MHz, CDCl3)
CDCl3
0.97
0.80
1.00
0.91
1.09
1.14
1.17
9.91
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)