DNA-Based asymmetric catalysis as a synthetic tool

Megens, Rikkert Pepijn

Chapter 5
DNA-Based Catalytic Enantioselective Protonation in Water

Enantioselective protonation is an elegant method for introducing chirality in a molecule. In this chapter a new method for enantioselective protonation in water using DNA-based catalysis is described.

5.1 Introduction

Tertiary carbon stereocenters are common in natural products. Therefore, useful and easy methods for the enantioselective synthesis of these compounds are of utmost importance. One of the conceptually most straightforward methods for the selective preparation of compounds with a chiral tertiary carbon is the enantioselective introduction of a proton to a carbanion. However, protonation is difficult to control due to the small size of the proton. Furthermore, protonations are among the most rapid reactions and are often diffusion controlled.[1] Most examples of the enantioselective protonation in the literature involve the asymmetric protonation of metal enolates with chiral protonating agents (CPA's).[1-5] The choice of CPA, acidity of the CPA, E/Z ratio of the substrate and temperature need to be optimized in order to achieve enantioselective protonation with high selectivities. Here, these parameters will be discussed separately and illustrated with examples.

5.1.1 Chiral protonating agent

A variety of chiral protonating agents have been reported to induce high enantioselectivities in the asymmetric protonation of a variety of substrates. Especially CPA's consisting of a proton donor combined with a proton acceptor group in a *syn* arrangement have been shown to afford good enantioselectivities.[6] The proton acceptor group can coordinate via hydrogen bonding to the enol and thereby lock the position of the proton donor over the prochiral center (Figure 5.1). This approach can also be applied to a metal-enolate, however, in that case the proton acceptor group should be replaced by a metal binding moiety.

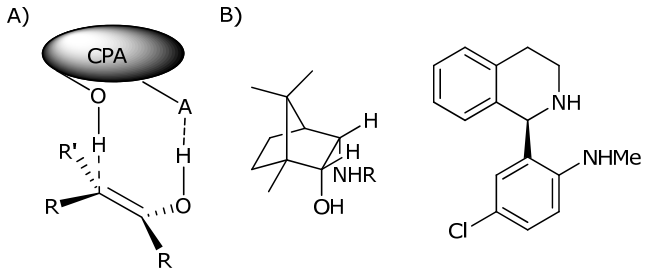


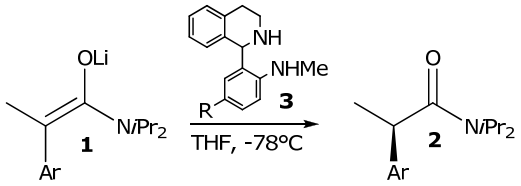
Figure 5.1. A; Induction of selectivity in enantioselective protonation, B; examples of CPA's with *syn* oriented donor and acceptor groups.

5.1.2 Acidity of the chiral protonating agent

The acidity of the protonating agent should be matched to the product: the protonating agent should be weakly acidic compared to the product. The reason for this is twofold, first of all when the difference of in pK_a is too large the protonation will proceed fast and the reaction proceeds a-selective. Therefore, in order to perform the reaction under kinetic control the ΔpK_a needs to be small. On the other hand, the

protonation needs to be as complete as possible, since otherwise it will result in an a-selective protonation during work-up. In practice, the best enantioselectivities and complete protonation are obtained when $2 < \Delta pK_a < 4$.[5]

This has been nicely demonstrated by Vedejs *et al.*,[7] who have investigated the selective protonation of lithium enolate **1** with a series of anilines (**3**) (Scheme 5.1). The best result (ee = 97%) was obtained when $\Delta pK_a = 3$, illustrating the importance of the choice of protonating agent.



pKa (DMSO) = 31

R	H	Cl	CF_3	CO_2Et	Ts	NO_2
pK_a **3** (DMSO)	29.0	27.7	25.5	24.8	23.3	19.3
Ee (%) **2**	90	97	93	40	37	0

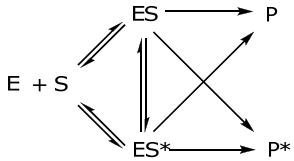
Scheme 5.1. Selective protonation of **1** by a series of anilines.

5.1.3 Temperature

Most enantioselective protonation reactions occur at low temperatures due to instability of the metal enolate and because in most cases then the enantioselectivity is higher. However, there are a few examples were the enantioselectivity goes through a maximum with increasing temperature. There are two possible explanations for this behavior. Firstly, it can be explained by C- versus O-protonation.[5] This means that at lower temperature the enolate is prefentially protonated on the oxygen. Then the enol is prefentially obtained, which will tautomerize during work-up and thereby cause formation of the racemic product.

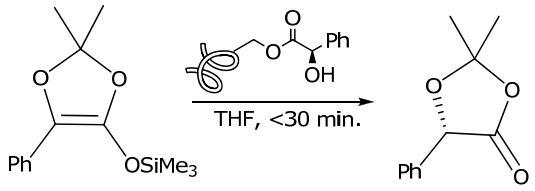
Secondly, it can be explained by the isoinversion principle proposed by Scharf and co-workers.[8] The isoinversion principle is a theoretical model that is designed to explain the selectivity of reactions containing two or more stages. It is a dynamic model, which takes all the reaction components and the optimization into consideration. The general kinetic scheme, which resembles enzyme kinetics, for this model involves a prochiral starting material which can react with a chiral substrate or catalyst to afford two diastereomeric intermediates (ES + ES*). These intermediates are in equilibrium with each other. These intermediates can then either react further to form P and P*, or revert back to the starting materials (Scheme 5.2). Since the selectivity is induced in two steps and each step has its own kinetic parameters, inversion points are

expected in the temperature dependent kinetics measurement. The inversion point is called the isoinversion temperature.



Scheme 5.2. General kinetics scheme for the isoinversion principle.

This type of kinetics was found in the enantioselective protonation of a silyl enol ether by a polymer supported CPA.[9] The maximum ee was obtained at -40 °C while lower selectivities where found at both higher and lower temperatures. (Scheme 5.3).



T (°C)	ee %	Yield %
-78	28	96
-40	94	95
-20	26	92

Scheme 5.3. Selective protonation of **4** by a polymer supported CPA.

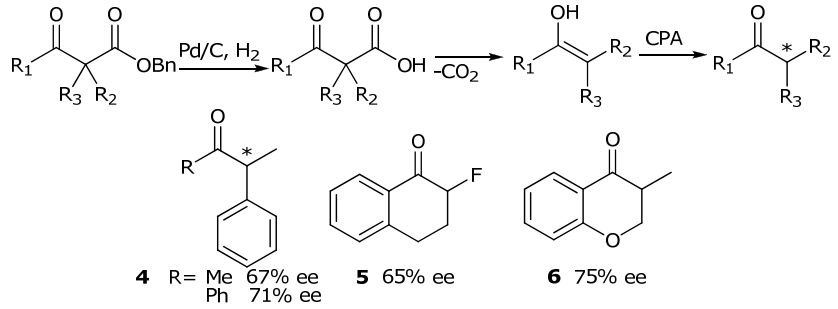
5.2 Catalytic enantioselective protonation

Enantioselective protonation can be performed catalytically via two different routes. First of all, via the regeneration of the chiral protonating agent and secondly, by forming the enolate catalytically.

The chiral protonating agent can be regenerated via different routes. Most examples make use of a preformed silyl enol ether in combination with a chiral Brønsted acid catalyst. After protonation of the silyl enol ether by the chiral Brønsted acid, the Brønsted acid can be regenerated by a proton donor, typically an alcohol.[7,10-15] For the catalytic formation of the enolate various approaches have been followed.

5.2.1 Enantioselective protonation via catalytic enolate formation.

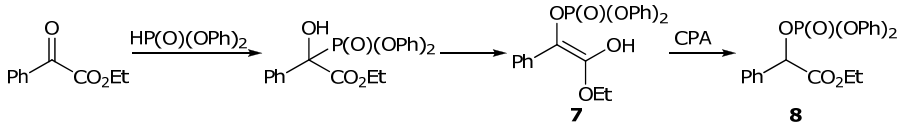
Hénin *et al.* performed a catalytic enantioselective protonation via a reaction cascade of deprotection/decarboxylation followed by asymmetric protonation (Scheme 5.4).[16-18]



Scheme 5.4. Deprotection/decarboxylation enantioselective protonation cascade.

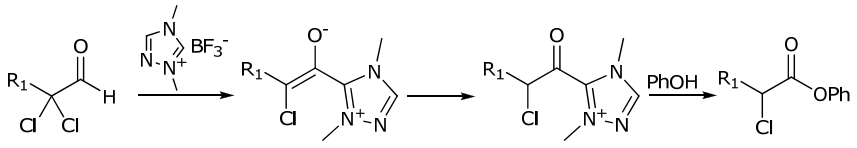
This methodology still requires the use of a chiral protonating agent, for example chiral amino alcohols such as cinchonidine and aminoborneol. However the CPA is regenerated in the course of the reaction by the enol intermediate. The cascade was used to form α-arylpropanones (**4**)[17], 2-fluorotetralones (**5**)[18] and 3-methylchromanones (**6**)[16]. It is thought that either the chiral protonating agent coordinates to proton on the enolate or a palladium enolate is formed, which is protonated by the CPA.[17]

An alternative method makes use of a rearrangement reaction to form an enol, the phospha-Brook rearrangement. In this cascade an α-ketoester is phosphonated which is followed by the rearrangement to form an α-phosphonyloxy enolate (**7**).[19] This is finally protonated by the chiral protonating agent to form α-phosphonyloxy ester (**8**) with up to 92% ee (Scheme 5.5).



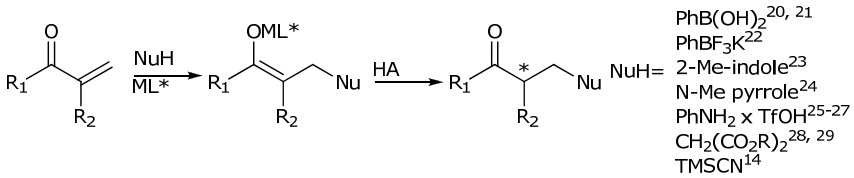
Scheme 5.5. Phophonylation/phospha-Brook rearrangement/ enantioselective protonation cascade.

An alternative method for the formation of the enolate is via the formation of an azolium salt/elimination of HCl followed by selective protonation and substitution of the azolium salt by phenol (Scheme 5.6).[20] By using a chiral azolium salt it was possible to form the α-chloroester with up to 93% ee, in cases that R_1 is a benzyl- or alkyl group.



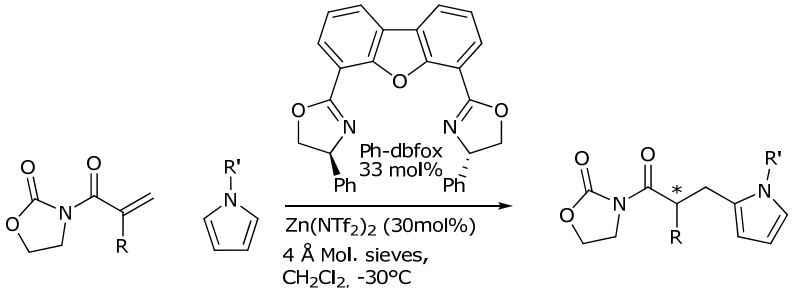
Scheme 5.6. Formation of an azolium salt/elimination of HCl followed by selective protonation and acylation with phenol.

Finally, the most often used stategy is formation of the enolate via conjugate additions. Various conjugate addition reactions have been performed in such a cascade process like rhodium catalyzed conjugate addition of organoboron reagents[21-23], conjugate additions of neutral π-nucleophiles[24,25], (aza)[26-28] Michael additions[29,30] or cyanation[15] (Scheme 5.7). In all these cases a chiral metal-ligand complex or organocatalyst is used for the induction of the chirality in the enantioselective protonation step. Furthermore, in most cases a proton source is used in stoichiometric amounts to obtain enantioselectivity.



Scheme 5.7. Conjugate addition-enantioselective protonation to α-substituted enones.

One of the key examples involves the Friedel-Crafts alkylation of N-methyl pyrrole with α-substituted oxazolidinone acrylates, followed by enantioselective protonation of the formed enolate, catalyzed by a chiral Lewis acid complex (Scheme 5.8).[24] Using a combination of a Ph-dbfox ligand in combination with zinc(II) salts at -30°C was found to give the product in good yield and excellent enantioselectivity. A wide range of α-substituents and N-alkyl pyrrole could be used with up to 98% ee.



R	R'	Time (h)	Yield (%)	ee (%)
Me	Me	1	98	93
Et	Me	2	89	97
CH_2CO_2Me	Me	3	90	98
CH_2OTIPS	Me	4	68	98
Ph	Me	48	74	97
Me	Et	1	92	91
Me	CH_2CH_2Br	2	84	90
Me	Bn	3	84	91
Me	Ph	16	70	73

Scheme 5.8. Friedel-Crafts alkylation of α-substituted oxazolidinone acrylates with N-substituted pyrrole followed by enantioselective protonation of the enolate.

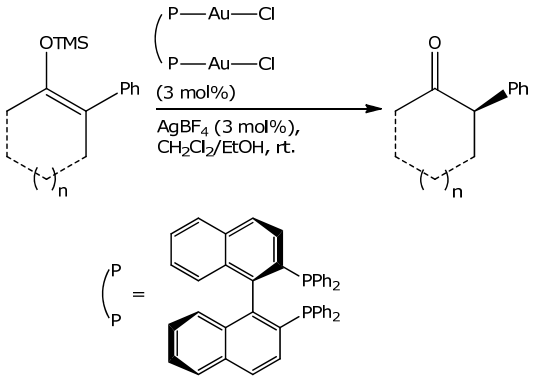
5.3 Enantioselective catalytic protonations in protic solvents

One of the major challenges in enantioselective catalytic protonations is the necessity to use stoichiometric amounts of proton donor. The reaction would be facilitated substantially if it could be carried out in a protic solvent, which also acts as the proton donor. However, the use of large amounts of proton donor will result in fast protonation of the enolate and therefore it will be difficult to achieve enantioselectivity.

5.3.1 Transition metal- or organocatalyzed enantioselective protonation in protic solvents

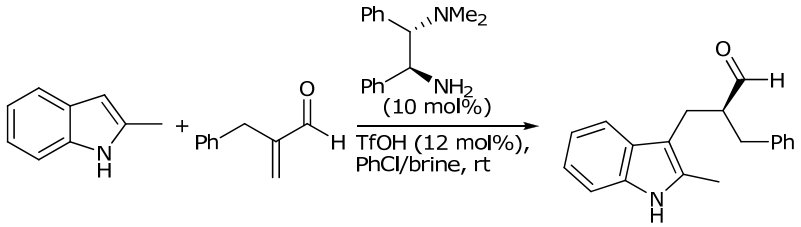
Examples of transition metal- or organocatalyzed enantioselective protonation in pure protic solvents are not known to date. However two examples are known, which use an excess of protic solvent. These strategies make use of positioning of the proton source above the face of the enolate.

The first example is a chiral Brønsted acid derived from a cationic gold(I) complex that is able to catalyze the enantioselective protonation of a silyl enol ether of ketones in a 1:1 mixture of dichloromethane and EtOH.[12] Generation of a cationic gold(I) catalyst with $AgBF_4$ proved essential, as no reaction was observed without $AgBF_4$. Cyclic and acyclic silyl enol ethers were converted with up to 95% ee. Moreover, different mixtures of E/Z isomers afforded the same enantioselectivity. It is thought that the gold derived Lewis acid-activated Brønsted acid (LBA)[12] discriminates between the two isomers and approaches both silyl ethers from the same prochiral face, which results in the high enantioselectivity regardless of the E/Z ratio. However, due to the high substrate content this 1:1 mixture of DCM/EtOH still resembles only 13.7 equivalents of protonating agent. Additionally, this approach requires the generation of the silyl enol ether prior to use.



Scheme 5.9. Catalytic enantioselective protonation of silyl enol ethers with a chiral Brønsted acid derived from a cationic gold(I) complex.

The second example involves a Friedel-Crafts alkylation/ enantioselective protonation catalyzed by a chiral primary amine (Scheme 5.10).[24] Using a 2:1 mixture of chlorobenzene and brine (50 eq. compared to substrate) resulted in 74% yield and 93% ee. The reaction could also be performed in brine alone, however, in that case the yield dropped to 34% with a small decrease in enantioselectivity. The reaction shows a wide substrate and nucleophile scope, although in many cases only 5 eq. of brine was used in order to obtain good yield and enantioselectivity. Mechanistic studies showed that water most likely is the proton donor in this reaction.

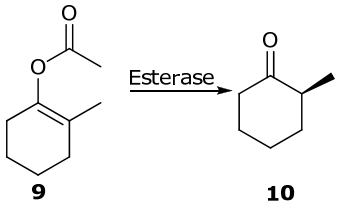


Scheme 5.10. Chiral primary amine catalyzed Friedel-Crafts alkylation/enantioselective protonation.

5.3.2 Enzymatic enantioselective protonation in protic solvents

Enzymes are most likely by far the best catalysts for the enantioselective protonation in a protic solvent. Generally, an enzyme contains a hydrophobic and well-defined catalytic pocket in which the proton can be directed via an amino acid or an isolated hydrogen bonded solvent molecule. Several enzymes are able to catalyze the enantioselective protonation reaction in protic solvents. These enzymes can be divided in two general classes, namely, esterases and decarboxylases.

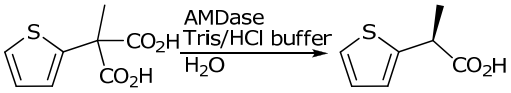
Esterases catalyze the enantioselective protonation reaction from enol acetates via an enolate to yield enantioenriched ketones. Live *Pichia miso* IAM 4682 yeast cells,[31] liverwort *Marchantia polymorpha* esterase I[32] and Lipase PS-C II[33] are able to convert enol acetate **9** into ketone (*S*)-**10** with 99%, 99% and -77% ee, respectively (Scheme 5.11). The yeast cells can also catalyze the enantioselective protonation of larger ring systems, up to 12-membered rings, with high enantioselectivities. The liverwort *Marchantia polymorpha* esterase I can use several different alkyl substituted enol acetates to produce the corresponding ketone with up to 99% ee. However in both cases the facial preference for proton delivery and, hence, which enantiomer is formed in excess, varied for different ring sizes and alkyl substitutions. In the case of Lipase PS-C II the enantioselectivity was highly dependent on the reaction temperature and proton source. The best results were obtained using a solid supported enzyme at 0 °C and EtOH as proton source.



9 **10**

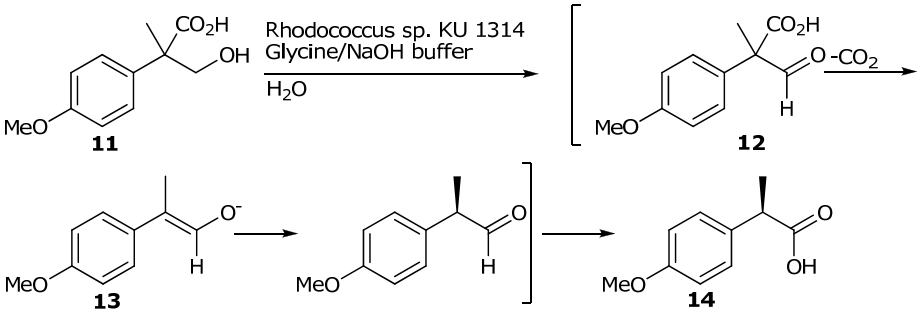
Scheme 5.11. Enzymatic hydrolysis followed by enantioselective protonation of enol acetates.

Decarboxylases generate enolates *in situ* by decarboxylation of malonic acid derivatives, which are subsequently protonated to form enantioenriched carboxylic acids. Ohta and co-workers have isolated arylmalonate decarboxylase (AMDase), which catalyzes the decarboxylation of α-methyl-α-thiophen-2-yl-malonates followed by enantioselective protonation to form α-thiofen-2-ylpropionic acid in 99% (Scheme 5.12).[34,35] The cysteine residue on position 188 was essential for activity as it is active in the decarboxylation and protonation step. By preparation of the double mutant AMDase G74C/C188S, the opposite enantiomer was obtained. These mutations remove the active site cysteine and place it at the opposite side of the catalytic pocket. Although the opposite enantiomer was obtained in 97% ee, the activity of the enzyme was several orders of magnitude lower.[36,37]



Scheme 5.12. Enzymatic decarboxylative protonation with AMDase.

Another example is the conversion of a β-hydroxyacid to α-arylpropionic acid by *Rhodococcus sp.* KU1314 via an oxidation/ decarboxylation/protonation/oxidation cascade.[38] In the proposed metabolic cycle the alcohol **11** is oxidized to the corresponding aldehyde (**12**), which is subsequently decarboxylated to form an enolate (**13**). After enantioselective protonation and oxidation, α-arylpropionic acid (**14**) was obtained in 74% ee. A variety of larger alkyl substituents could be used, giving rise to moderate enantioselectivities. However, in these cases the activity dropped significantly, indicating that the enzyme is sensitive to steric hindrance.



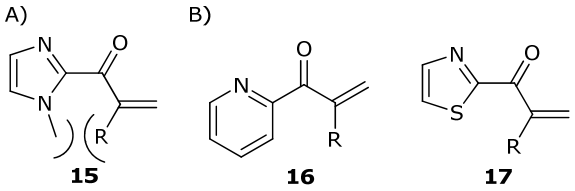
Scheme 5.13. Enzymatic oxidation/decarboxylation/protonation/ oxidation cascade.

In summary, a few examples of enantioselective protonation in protic solvent are known. However, in the enzymatic protonation the substrate scope is limited due to the tight enzymatic pocket. Moreover, for the transition metal catalyzed protonations a co-solvent is required in order to limit the amount of proton donor. Therefore, a more general method for the enantioselective protonation in protic solvents with a wide substrate scope is desirable. Here, the aim was the development of an enantioselective protonation reaction by using the DNA-based catalysis concept. This would combine the hydrophobic environment, created by the DNA, with a broad substrate scope by using transition metal catalysis.

5.4 DNA-based catalytic enantioselective protonation in water

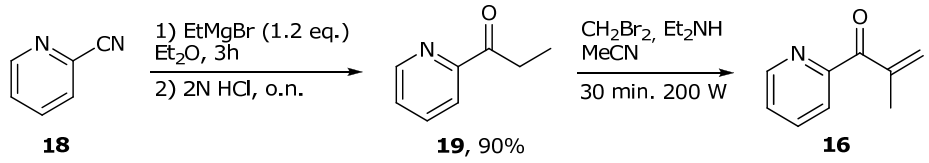
5.4.1 Substrate synthesis

α,β-Unsaturated 2-acyl imidazoles have been widely used for DNA-based asymmetric catalysis. To date, attention has been focused on the use of β-substituted substrates. However, in order to perform the enantioselective protonation reaction, an α-substituent is required. It has been shown that α-substituted α,β-unsaturated 2-acyl imidazoles (**15**) are not reactive in Cu^{II}-catalyzed conjugate additions.[39] This is probably due to steric hindrance between the α-substituent and the methyl group of the imidazole-moiety (Scheme 5.14A). As a result, the carbonyl group and the olefin are prevented from being co-planar and, therefore, the substrate cannot bind to the Cu^{II}-center in a bidentate fashion and thus the substrate is not activated. For this reason, two new types of substrates were designed. In these substrates, the imidazole moiety is replaced by either a 2-pyridinyl (**16**) or a 2-thiazolyl (**17**) moiety (Scheme 5.14B). These substrates can still coordinate in a bidentate fahion to the Cu^{II} catalyst but the steric hindrance is removed.



Scheme 5.14. A; α-substituted α,β-unsaturated 2-acyl imidazole, B; new α-substituted α,β-unsaturated substrates.

The α-substituted α,β-unsaturated 2-acylpyridine (**16**) was synthesized in a two step process starting from 2-cyano pyridine (**18**). The 2-cyano pyridine was reacted with EtMgBr followed by acidic workup to form **19** (Scheme 5.15).[40] This was then α-methenylated with bromoform in a closed vessel in the microwave to form the α,β-unsaturated substrate (**16**).[41] However, the conditions of the last step gave some problems. First of all, the reaction can only be performed in small scale (up to 100 mg) and, secondly, the reaction is exothermic and difficult to control. Therefore this class of enones was abandoned as substrates.

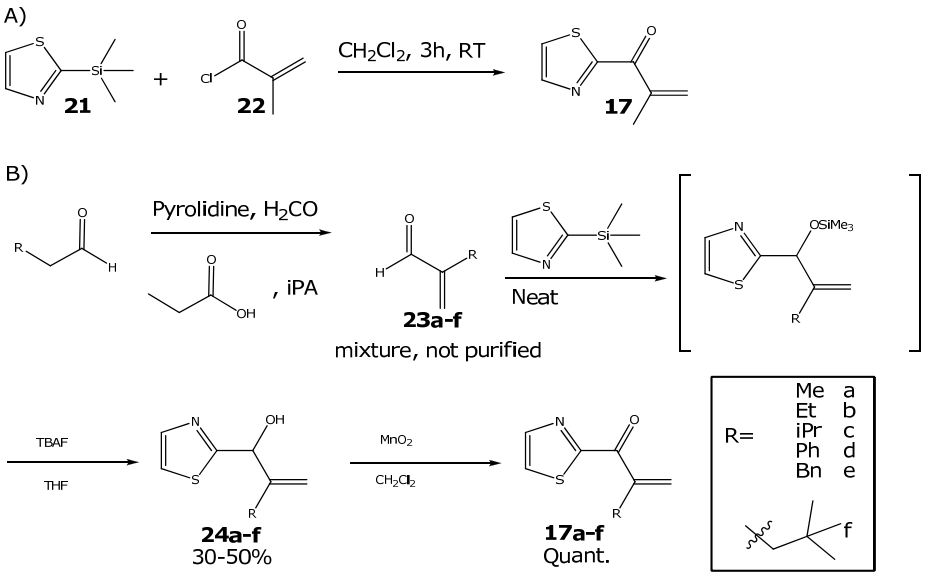


Scheme 5.15. Synthesis of α,β-unsaturated pyridine substrate.

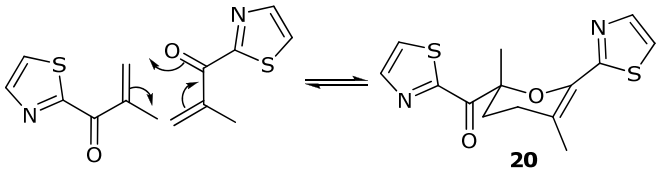
α,β-unsaturated acyl 2-thiazole substrate (**17**) was synthesized by the addition of the corresponding α,β-unsaturated acid chloride (**22**) to 2-trimethylsilyl thiazole, the so called Dondoni reagent (**21**; Scheme 5.16A).[42] However, the substrates bearing a terminal alkene are unstable and slowly form dimers (Scheme 5.17), which are the result of an intermolecular Diels-Alder reaction. The structure of the dimer has been confirmed by mass spectrometry, ^{1}H, ^{13}C, COSY and HSQC NMR.

The dimer is formed upon storing the enone over an extended period. The problem of dimerization could be overcome by preparation of the enone just before use in catalysis. For that purpose an α,β-unsaturated aldehyde was reacted with the Dondoni reagent (**21**) followed by deprotection of the formed silyl ether with tetrabutylammonium fluoride to yield the allylic alcohol **24** (Scheme 5.16B).[42] This was oxidized with MnO_2, after which the substrate was used immediately without extensive purifications. Not all α-substituted α,β-unsaturated aldehydes were commercially available. These were prepared from the corresponding aldehyde and α-methenylated using formaldehyde with a catalytic amount of propionic acid and pyrollidine and used without further purification.[43] The exception was 4,4-dimethyl-2-methylenepentanal (**23f**) which was prepared via an iridium-catalyzed

hydroformylation of 3,3-dimethylbutene,[44] followed by the α-methenylation with formaldehyde



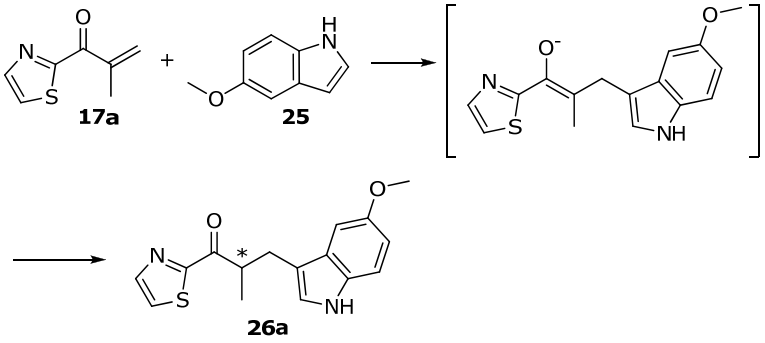
Scheme 5.16. Synthesis of α,β-unsaturated 2-thiazole substrates.



Scheme 5.17. Intermolecular Diels-Alder reaction of substrate.

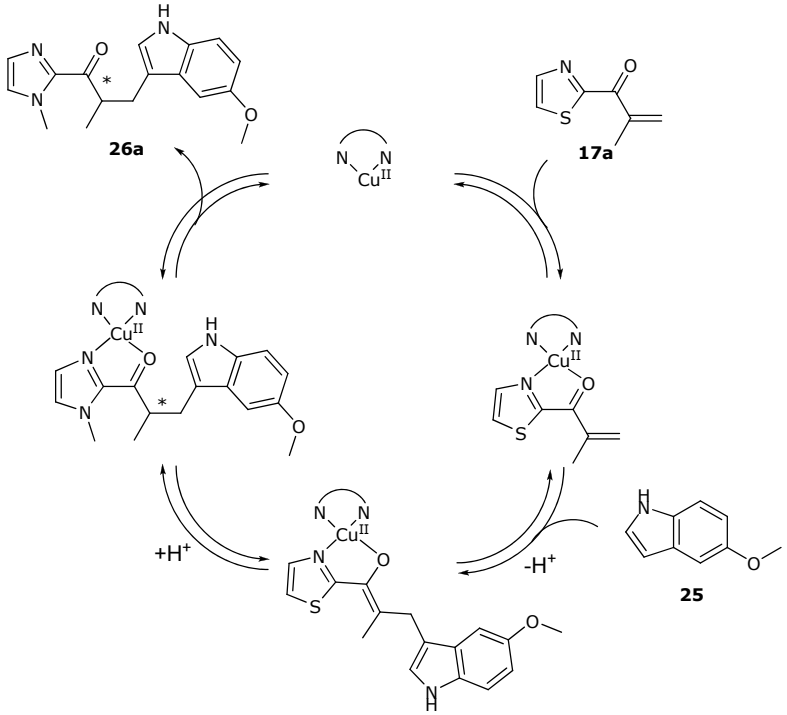
5.4.2 Reaction optimization

For the selective protonation of α-substituted α,β-unsaturated thiazoles, the Friedel-Crafts alkylation was chosen, which has been developed in our group.[24,25] This reaction proved to be strongly DNA accelerated. As model reaction for the optimization of the reaction conditions the Friedel-Crafts alkylation of 5-methoxyindole (**25**) with **17a**, followed by the enantioselective protonation of the formed enolate was selected (Scheme 5.18).



Scheme 5.18. Friedel-Crafts alkylation followed by selective protonation.

There are several challenges associated with this reaction when using DNA-based catalysis. Firstly, the reaction is performed in water. This implies that the concentration of the protonating agent, cq. water, is very high. Therefore, a major challenge is to control the protonation step. Secondly, in order to obtain enantioselectivity the protonation needs to be the rate determining step. Therefore, the conjugate addition step needs to be very fast, since protonations are in general quite rapid, especially in water (Scheme 5.19). Additionally, the reaction can also be Brønsted acid catalyzed which will result in a racemate.



Scheme 5.19. General reaction mechanism for the Friedel-Crafts alkylation followed by enantioselective protonation.

It was hypothesized that the enantioselective protonation in water using DNA-based catalysis might work because the copper catalyzed reaction takes place in the DNA-environment and since the DNA interior is relatively hydrophobic,[45,46] it provides a hydrophobic environment around the catalyst, thereby reducing the effective concentration of protonating agent. Furthermore, as was mentioned before, the DNA accelerates the Friedel-Crafts alkylation considerably which raised the prospect that the alkylation can be faster than the protonation.

First, the reaction in presence of st-DNA with different indole and catalyst loading was investigated. To our surprise we found reasonable conversion and enantioselectivities in the first attempts. It was found that a ratio of 1:1 of substrate to indole with 15 mol% of Cu-dimethylbipyridine (Cu-dmbipy) gave the best results in terms of enantioselectivity (Table 5.1).

Table 5.1. Optimization of reaction conditions.

ratio **17a**: **25**	15 mol% cat		30 mol% cat		30 mol% cat, no DNA	
	Conv.	ee	Conv.	ee	Conv.	ee
1:1	49%	49%	92%	42%	0%	Nd
1:2	74%	40%	88%	43%	12%	-
1:5	54%	38%	90%	34%	71%	-
1:10	55%	29%	79%	26%	98%	-

Conditions: 20 mM MOPS, pH 6.5, 0.67 mg/ml st-DNA, [Cu(dmbipy)$(NO_3)_2$], 1 mM **17a**, 4 °C, 1h.

The pH of the buffer was varied in order to make sure that the product is completely protonated but also no Brønsted acid catalysis takes place. It was found that lowering the pH to 5.0 increased the enantioselectivity to 59% (Table 5.2). Although pH 5.0 is slightly below the buffering capacity of MOPS, the pH did not change during the reaction. Lowering the pH requires changing of the buffer to acetate and phosphate buffers, which are weakly copper binding. At this pH a decrease of selectivity was found. There are several possible explanations for this drop in enantioselectivity, 1) the weak binding of the buffer to the active copper complex might interfere with the reaction, 2) due to the lower pH, Brønsted acid catalysis of the conjugate addition starts to play a role in addition to the copper catalyzed reaction or 3) due to the lower pH the protonation step is accelerated thus causing a lower ee.

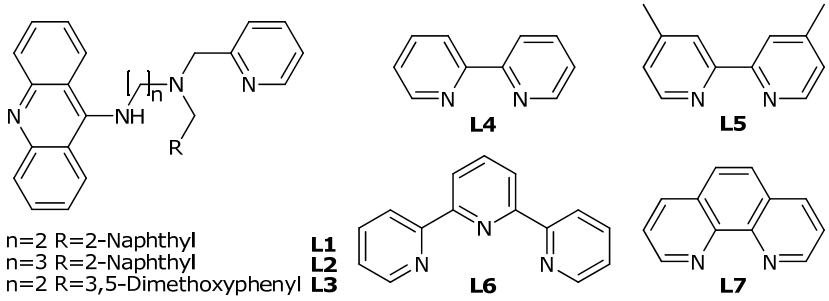
Table 5.2. Optimization of the pH.

Buffer	pH	Conv	ee
MOPS	7.5	Full	11%
MOPS	6.5	98%	27%
MES	5.5	87%	44%
MES	5.0	Full	59%
Phosphate	4.5	86%	44%
Acetate	4.5	61%	46%
Phosphate	4.0	94%	48%
Acetate	4.0	55%	51%

Conditions: 20 mM buffer, 0.67 mg/ml DNA, 0.15 mM [Cu(dmbipy)$(NO_3)_2$], 1 mM **17a**, 1mM **25**, 4 °C.

Finally, a variety of ligands was screened for their performance in the enantioselective protonation. First generation ligands (Table 5.3, Entry 1-3) afforded hardly any enantioselectivity. The Cu^{II} complex of 4,4'-dimethyl-2,2'-bipyridine (**L5**), which was also the ligand of choice for the enantioselective Friedel-Crafts alkylation, gave full conversion and 59% ee after 2 hours, whereas other second generation ligands (Entry 4,5 and 6) gave poor enantioselectivities. Combining all these results it was decided that Cu(dmbipy) with a MES buffer at pH 5.0 and 1 equivalent of indole were giving the best results.

Table 5.3. Screening of ligands.



Entry	Ligand	conv	ee
1[a]	**L1**	57%	-1%
2[a]	**L2**	67%	16%
3[a]	**L3**	63%	-17%
4	**L4**	34%	36%
5	**L5**	Full%	59%
6	**L6**	73%	9%
7	**L7**	98%	11%

Conditions: 20 mM MES pH 5.0, 0.67 mg/ml DNA, 0.15 mM [$Cu(NO_3)_2$], 0.15 mM ligand, 1 mM **17a**, 1 mM **25**, 4 °C. a; 0.165 mM ligand.

5.5 Substrate scope

With the optimal conditions in hand, a range of substrates (**17a-f**) was tested (Table 5.4). Using substrates with linear alkyl chains (**17a** and **b**) resulted in full conversion after 4h, with 59% and 58% ee, respectively. Using more bulky α-substituents (Entries 4-7; **17c-f**), no conversion was obtained after 4h. After extended reaction time, some conversion could be obtained in case of **17c**. Furthermore, the hetero Diels-Alder product (**20**) was formed in the course of the reactions that did not reach full conversion within 4h. DFT calculations were performed to check whether the thiazole and carboxyl group in these substrates are still co-planar.* In these calculations the minimal energy structure was determined for **17a** and **17c**. It was found that the dihedral angle between the thiazole and the carbonyl moieties was small for substrates bearing linear alkyl chains (22°) while the substrates with more bulky substituents showed a larger dihedral angle of 46° (Figure 5.2A). This geometry does not allow for a bidentate coordination of the substrate to the Cu^{II} center. Therefore, the α,β-unsaturated substrates with bulky substituents in the α position cannot be activated.

Table 5.4. Substrate scope.

Entry	Substrate	Time	Conv	ee	remarks
1	Me	2h	Full	59%	
2	Me[a]	4h	Full	50%	
3	Et	4h	Full	58%	
4	*i*Pr	3d	17%	32%	+ dimer
5	Ph	3d	0%	Nd	+ dimer
6	Bz	3d	0%	Nd	
7	$CH_2C(CH_3)_3$	3d	0%	Nd	

Conditions: 20 mM MES pH 5.0, 0.67 mg/ml DNA, 0.15 mM $[Cu(dmbipy)(NO_3)_2]$, 1 mM **17**, 1 mM **25**, 4 °C. a; reaction perfomed at -18 °C with 40% v/v MeOH.

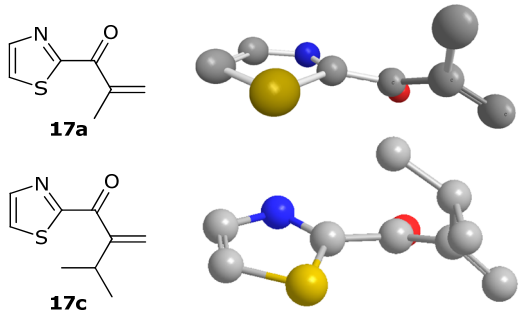


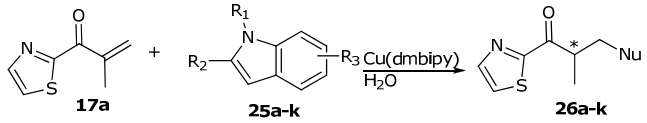
Figure 5.2. Substrate conformation calculations performed at the DFT B3-LYP 6-31G(d,p) level.

* Calculations were performed by Jos Kistemaker.

As has been shown in chapter 3, the addition of a co-solvent allows for a lower reaction temperature. Therefore, the reaction of **17a** with indole **25** has been perfomed at -18 °C. However a lower enantioselectivity was obtained in this case. This can either be caused by the addition of the co-solvent, or the isoinversion effect, as was explained in chapter 5.2.

5.6 Nucleophile scope

A large number of nucleophiles for the Friedel-Crafts alkylation (Scheme 5.20) was tested. The enantioselectivity decreased significantly when the electron donating group in the 5-position was removed (Entry 2-4). Furthermore, the enantioselectivity was completely lost when a N- or 2-substituted methylindole was used (Entry 5-7). The nucleophilicity of these indoles (**25b-g**) is lower compared to **25a**.[47] This results in a relatively slower alkylation and therefore the rates of the alkylation step approaches the rate of the protonation step. This will lead to a lower kinetic control over the protonation and thus enantioselectivity. Changing the electron donating group to either a hydroxyl, amino, chloride or bromide did give rise to enantioselectivity (Entry 8-11).



	R_1	R_2	R_3
a	H	H	5-MeO
b	H	H	H
c	H	H	6-MeO
d	H	H	7-MeO
e	Me	H	H
f	H	Me	H
g	H	Me	5-MeO
h	H	H	5-OH
i	H	H	5-NH_2
j	H	H	5-Cl
k	H	H	5-Br

Entry	Nucleophile	Product	time	Conv.	ee
1	**25a**	**26a**	2h	Full	59%
2	**25b**	**26b**	4h	Full	32%
3	**25c**	**26c**	1d	Full	11%
4	**25d**	**26d**	1d	Full	29%
5	**25e**	**26e**	4h	Full	6%
6	**25f**	**26f**	4h	Full	3%
7	**25g**	**26g**	1d	Full	5%
8	**25h**	**26h**	1d	Full	48%
9	**25i**	**26i**	1d	95%	52%
10	**25j**	**26j**	1d	Full	27%
11	**25k**	**26k**	1d	Full	29%

Conditions: 20 mM MES pH 5.0, 0.67 mg/ml st-DNA, 0.15 mM [$Cu(dmbipy)(NO_3)_2$], 1 mM **17a**, 1mM **25**, 4 °C.

Scheme 5.20. Nucleophile scope.

More importantly, in the reactions with indoles **25h-k** in the absence of DNA the desired product could not be obtained: only in the presence of DNA the desired product was formed. Additionally, in the reaction with **25i** in the absence of DNA the aza-Michael addition product, from addition of the 5-amino group, was formed. This demonstrates the essential role of DNA in catalysis by causing a large rate acceleration of the rate of the conjugate addition, consistent with previous observations.[48,49]

5.7 DNA sequence selectivity

A preliminary study of the DNA sequence dependence of the enantioselective protonation, using various self-complementary oligonucleotides as catalyst scaffold was performed (Table 5.5). The oligonucleotide with a central GGG tract gave similar results compared to st-DNA. However other GC rich sequences and AT rich sequences showed significantly lower enantioselectivities. As is known from previous studies, some DNA sequences accelerate the reaction more than others. However, in the enantioselective protonation two processes are taking place: the Friedel-Crafts alkylation and the enantioselective protonation. Both steps of the process will be affected by the DNA sequence. The rate acceleration of the protonation step needs to be smaller than the rate acceleration of the alkylation step in order to maintain the kinetic control over the protonation step. Hence, the effect of the DNA sequence is not as simple as is found for the Friedel-Crafts alkylation itself. Another possible explanation would be that the sequence containing the central GGG tract is accelerating the reaction to such an extent, that also in st-DNA, this sequence is dominating the outcome of the reaction. In that case it is unlikely that higher ee's can be found by using defined DNA sequences.

Table 5.5. Sequence selectivity.

Sequence	Conv.	ee
st-DNA	Full	59%
TCAGGGCCCTGA	96%	60%
GCGCGCGCGCGC	85%	34%
CGGGATCCCGA	72%	17%
TCGGGGCCCCGA	Full	24%
CAAAAATTTTTG	70%	26%
GCGCTATAGCGC	94%	10%

Conditions: 20 mM MES pH 5.0, DNA (1 mM in bp), 0.15 mM $[Cu(dmbipy)(NO_3)_2]$, 1 mM **17a**, 1 mM **25**, 4 °C, 2h.

5.8 Conclusions

Using the DNA-based catalysis concept, we have developed the first catalytic enantioselective Friedel-Crafts alkylation/protonation cascade

of enones to indoles mediated by transition metal complexes in a protic solvent, cq. water. Although the substrate scope is limited to enones carrying small substituents on the α-position, a large variety of indoles can be used with up to 59% ee. This might be related to the hydrophobic environment that the DNA creates around the copper complex. Furthermore, some products can only be obtained in the presence of DNA, illustrating the importance of the DNA acceleration effect.

5.9 Experimental section

General remarks

Salmon testes DNA was obtained from Sigma. Indoles were obtained from Aldrich and TCI Europe. Copper complexes[50], **16**[41], **19**[40], **23f**,[44] and ligands[51] were synthesized according to literature procedures. ^{1}H-NMR and ^{13}C-NMR were recorded on a Varian 400 (400 MHz). Chemical shifts (δ) are quoted in ppm using residual solvent as internal standard (δ_H 7.26 and δ_C 77.0 for $CDCl_3$). Enantiomeric excess determination was performed by HPLC analysis on a Shimadzu 10AD-VP system. Mass spectra were recorded on a LTQ ORBITRAP XL.

Computational details

The Gaussian 03W (rev. B.03) software package was used for all calculations.[52] The structures (**17a**, **c**) were optimized using the DFT B3-LYP 6-31G(d,p) level. In these calculations only the local minimal energy structure was determined for the structures in which the nitrogen and carbonyl are in cisoid formation Frequency analysis showed only positive eigenvalues, demonstrating that they are at energy minima.

DNA-based catalysis, representative procedure

A buffered solution (20 mM MES, pH 5.0) of DNA bound catalyst (1 mM salmon testes DNA in basepairs and 0.15 mM [Cu(dmbipy)$(NO_3)_2$]) was prepared by mixing a solution of salmon testes DNA (5 ml of a 2 mg/ml solution in 60 mM MES pH 5.0, prepared 24 h in advance) with an aqueous solution of catalyst (10 ml of a 0.225 mM solution of [Cu(dmbipy)$(NO_3)_2$] in water. 15 μmol of indole in 10 μL MeCN was added and the mixture was cooled to 5 °C. The reaction was started by addition of 15 μmol of substrate and mixed by continuous inversion for the indicated time, followed by extraction of the product with Et_2O, drying (Na_2SO_4) and removal of the solvent. The crude product was analyzed by ^{1}H-NMR and HPLC.

Enantioselective protonation, general synthesis of racemates

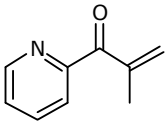
A buffered solution (20 mM MES, pH 5.0) of 0.15 mM $[Cu(NO_3)_2]\cdot 3\ H_2O$ and 1 mM of the corresponding indole was prepared. To this mixture 1 mM of enone dissolved in a appropriate amount of MeCN was added. The reaction was mixed by continuous inversion at room temperature, followed by extraction of the product with Et_2O. After drying (Na_2SO_4) and removal of the solvent the crude product was purified by column chromatography (EtOAc/heptane 1:4).

Reaction of 21 with acrylaldehydes, general procedure

2-(trimethylsilyl)thiazole (1 g; 6.4 mmol) and the acrylaldehyde (6.4 mmol) were added to a round bottom flask and stirred for 4h. The mixture was diluted with 100 ml THF and treated with tetrabutylammoniumfluoride (TBAF) in THF (1 eq.) and stirred for 1 h. The solvent was removed and the residue was dissolved in EtOAc (50 ml) and washed with sat. $NaHCO_3$, dried over Na_2SO_4 and the solvent was removed. The brownish oil was purified by column chromatography (silica; pentane/Et_2O, 7:3) to give the products as slightly yellow oils.

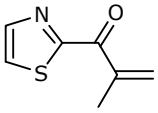
Oxidation of 24a-f to 25a-f, general procedure

10 eq of MnO_2 was added to a solutions of the 1-(thiazol-2-yl)prop-2-en-1-ol in 10 ml CH_2Cl_2 and stirred for 45 minutes. The black mixture was filtered over celite and the solvent was evaporated to afford the corresponding ketone.



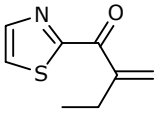
2-Methyl-1-(pyridin-2-yl)prop-2-en-1-one (16)

The product was obtained as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, J=4.6 Hz, 1H), 7.82 (m, 2H), 7.42 (m, 1H), 6.03 (d, J=14.7 Hz, 2H), 2.09 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 155.5, 148.4, 142.7, 136.9, 129.9, 125.7, 124.0, 18.5. HRMS: m/z: $C_9H_{10}NO^+$, Calcd. 148.07569; found: 148.07614.



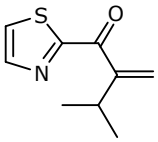
2-Methyl-1-(thiazol-2-yl)prop-2-en-1-one (17a)

The product was obtained as a slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 3.1 Hz, 1H), 7.64 (d, J = 3.1 Hz, 1H), 6.93 (br, 1H), 6.19 – 6.10 (br, 1H), 2.09 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.4, 167.5, 144.4, 141.6, 131.2, 125.6, 18.7. HRMS: m/z: $C_7H_8NOS^+$, Calcd. 154.03211; found 154.03219.



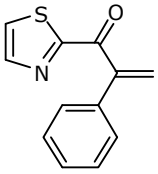
2-Methylene-1-(thiazol-2-yl)butan-1-one (17b)

The product was obtained as a slightly yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, J = 3.0 Hz, 1H), 7.64 (d, J = 3.1 Hz, 1H), 6.85 (br, 1H), 6.08 (br, 1H), 2.49 (q, J = 7.4 Hz, 2H), 1.12 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.7, 167.8, 147.4, 144.4, 129.0, 125.6, 24.9, 12.4. HRMS: m/z: $C_8H_{10}NOS$+, Calcd. 168.04776; found 168.04750.



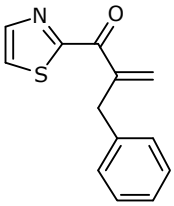
3-Methyl-2-methylene-1-(thiazol-2-yl)butan-1-one (17c)

The product was obtained as a slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 3.1 Hz, 1H), 7.65 (d, J = 3.1 Hz, 1H), 6.69 (br, 1H), 6.03 (br, 1H), 3.16 – 3.00 (m, 1H), 1.14 (d, J = 6.9 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.4, 168.0, 152.2, 144.4, 126.6, 125.7, 29.2, 21.6. HRMS: m/z: $C_9H_{12}NOS^+$, Calcd. 182.06341; found 182.06331.



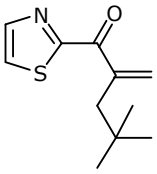
2-Phenyl-1-(thiazol-2-yl)prop-2-en-1-one (17d)

The product was obtained as a slightly yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, J=3.1 Hz, 1H), 7.64 (d, J=3.1 Hz, 1H), 7.26 (m, 5H), 7.07 (d, J=0.9 Hz, 1H), 6.02 (d, J=0.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.9, 167.4, 147.8, 143.4, 132.3, 131.9, 129.1, 128.7, 128.4, 124.2. HRMS: m/z: $C_{12}H_{12}NOS^+$, Calcd. 216.04831; found 216.05012.



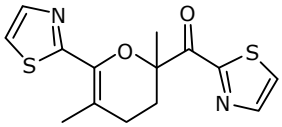
2-Benzyl-1-(thiazol-2-yl)prop-2-en-1-one (17e)

The product was obtained as a slightly yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, J = 3.1 Hz, 1H), 7.64 (d, J = 3.1 Hz, 1H), 7.43 – 7.18 (m, 5H), 7.07 (d, J = 0.5 Hz, 1H), 6.02 (d, J = 0.9 Hz, 1H), 3.83 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.1, 145.5, 144.8, 138.8, 132.2, 129.5, 129. 2, 128.7, 126.6, 126.1, 38.4. HRMS: m/z: $C_{13}H_{12}NOS^+$, Calcd. 230.06341; found 230.06359.



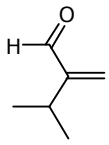
4,4-Dimethyl-2-methylene-1-(thiazol-2-yl)pentan-1-one (17f)

The product was obtained as a slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 2.9 Hz, 1H), 7.84 (d, J = 3.0 Hz, 1H), 6.85 (br, 1H), 6.16 (br, 1H), 2.69 (s, 2H), 1.09 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.6, 167.5, 144.5, 144.1, 131.6, 125.7, 45.1, 31.6, 29.4. HRMS: m/z: $C_{12}H_{16}NOS^+$, Calcd. 210.09471; found 210.09472.



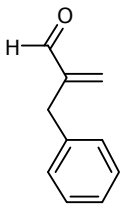
(2,5-Dimethyl-6-(thiazol-2-yl)-3,4-dihydro-2*H*-pyran-2-yl)(thiazol-2-yl) methanone (20)

The product was obtained as a slightly yellow oil.^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.01 (d, *J* = 3.1 Hz, 1H), 7.80 (d, *J* = 3.3 Hz, 1H), 7.64 (d, *J* = 3.1 Hz, 1H), 7.28 (d, *J* = 3.3 Hz, 1H), 3.05 – 3.01 (m, 1H), 2.19 – 2.14 (m, 1H), 2.09 (s, 3H), 2.07 – 2.06 (m, 1H), 2.04 – 2.03 (m, 1H), 1.85 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ = 191.9, 165.3, 163.9, 144.7, 142.6, 139.8, 126.3, 118.6, 111.3, 82.6, 30.7, 26.5, 24.7, 18.4. HRMS: m/z: $C_{14}H_{15}N_2O_2S_2^+$, Calcd. 307.05695; found 307.05653.



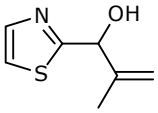
3-Methyl-2-methylenebutanal (23c)

The product was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, 1H), 6.23 (br, 1H), 5.94 (br, 1H), 2.92 – 2.61 (m, 1H), 1.07 (m, 6H).^{13}C NMR (100 MHz, $CDCl_3$) δ 194.7, 156.4, 132.2, 26.1, 21.3.



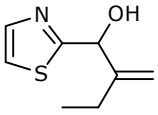
2-Benzylacrylaldehyde (23e).

The product was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (s, 1H), 7.24 (m, 5H), 6.09 (br, 1H), 5.29 (br, 1H), 3.57 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.0, 149.7, 142.2, 135.2, 129.1, 128.5, 126.4, 34.1. HRMS: m/z: $C_{10}H_{11}O^+$, Calcd. 169.06239; found 169.06220.



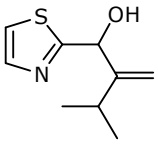
2-Methyl-1-(thiazol-2-yl)prop-2-en-1-ol (24a)

The product was obtained as a slightly yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, *J* = 3.2 Hz, 1H), 7.32 (d, *J* = 3.2 Hz, 1H), 5.45 (br, 1H), 5.25 (s, 1H), 5.05 (d, *J* = 1.2 Hz, 1H), 1.72 (s, 3H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.4, 145.4, 142.4, 119.8, 114.2, 76.0, 17.5. HRMS: m/z: $C_7H_{10}NOS^+$, Calcd. 156.04776; found: 156.04784.



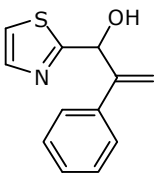
2-Methylene-1-(thiazol-2-yl)butan-1-ol (24b)

The product was obtained as a slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.31 (s, 1H), 5.48 (br, 1H), 5.30 (s, 1H), 5.06 (br, 1H), 3.62 (s, 1H), 2.16 (m, 1H), 1.96 (m, 1H), 1.03 (td, J = 7.3, 1.7, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 151.0, 142.1, 119.6, 111.5, 75.4, 23.6, 11.9. HRMS: m/z: $C_8H_{12}NOS^+$, Calcd. 170.06341; found 170.06283.



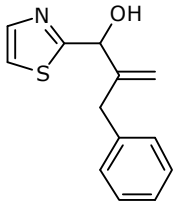
3-Methyl-2-methylene-1-(thiazol-2-yl)butan-1-ol (24c)

The product was obtained as a slightly yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, J = 3.3 Hz, 1H), 7.31 (dd, J = 3.1, 1.7 Hz, 1H), 5.52 (d, J = 3.8 Hz, 1H), 5.30 (s, 1H), 5.12 (br, 1H), 2.46 – 2.25 (m, 1H), 1.09 (d, J = 6.8 Hz, 3H), 1.00 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 156.4, 142.1, 119.6, 110.5, 74.6, 29.8, 22.9, 22.6. HRMS: m/z: $C_9H_{14}NOS^+$, Calcd. 184.07906; found 184.07851.



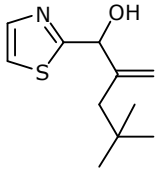
3-Phenyl-2-methylene-1-(thiazol-2-yl)butan-1-ol (24d)

The product was obtained as a slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J=3.1 Hz, 1H), 7.25 (m, 6H), 5.98 (d, *J* = 5.2 Hz, 1H), 5.58 (s, 2H), 5.23 (d, *J* = 5.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 153.4, 142.4, 139.6, 128.2, 127.1, 126.4, 118.6, 112.9, 81.5. HRMS: m/z: $C_{12}H_{12}NOS^+$, Calcd. 218.06341; found 218.06341.



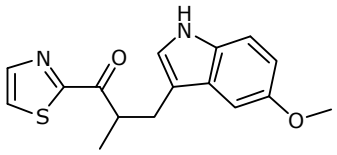
2-Benzyl-1-(thiazol-2-yl)prop-2-en-1-ol (24e)

The product was obtained as a slightly yellow oil. ^{1}H NMR (300 MHz, $CDCL_3$) δ 7.74 (d, *J* = 3.2 Hz, 1H), 7.33 (d, *J* = 3.2 Hz, 1H), 7.32 – 7.12 (m, 5H), 5.49 (d, *J* = 3.1 Hz, 1H), 5.37 (s, 1H), 4.93 (br, 1H), 3.49 (d, *J*=15.9 Hz, 1H), 3.30 (d, *J*=15.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 149.0, 142.2, 138.7, 129.3, 128.4, 126.3, 119.7, 114.7, 74.6, 38.0. HRMS: m/z: $C_{13}H_{14}NOS^+$, Calcd. 232.07906; found 232.07904.



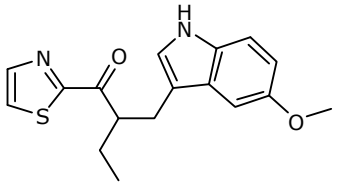
4,4-Dimethyl-2-methylene-1-(thiazol-2-yl)pentan-1-ol (24f)

The product was obtained as a slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 2.8 Hz, 1H), 7.30 (d, *J* = 2.9 Hz, 1H), 5.47 (d, *J* = 5.2 Hz, 2H), 5.09 (br, 1H), 3.52 (s, 1H), 2.07 (d, *J* = 13.8 Hz, 1H), 1.93 (d, *J* = 13.5 Hz, 1H), 0.95 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 147.3, 142.2, 119.6, 114.9, 74.6, 45.7, 31.7, 29.8. HRMS: m/z: $C_{11}H_{18}NOS^+$, Calcd. 212.11036; found 212.11031.



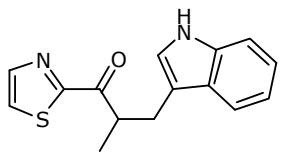
3-(5-Methoxy-1H-indol-3-yl)-2-methyl-1-(thiazol-2-yl)propan-1-one (26a)

Purification by column chromatography (SiO_2, EtOAC:heptane 1:4). The product was obtained as a slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 3.0 Hz, 1H), 7.83 (s, 1H), 7.66 (d, *J* = 3.0 Hz, 1H), 7.27 – 7.24 (m, 1H), 7.22 (d, *J* = 8.7 Hz, 1H), 7.00 (d, *J* = 2.4 Hz, 1H), 6.84 (dd, *J* = 8.7, 2.5 Hz, 1H), 4.23 (m, 1H), 3.91 (s, 3H), 3.37 (dd, J = 14.4, 5.9 Hz, 1H), 2.83 (dd, J = 14.4, 8.1 Hz, 1H), 1.29 (d, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.4, 167.0, 153.9, 144.6, 131.3, 127.9, 126.2, 123.3, 113.5, 112.3, 111.7, 101.0, 55.9, 42.3, 29.0, 16.5. HRMS: m/z: $C_{16}H_{17}N_2O_2S^+$, Calcd. 301.10052; found 301.10130. Ee's were determined by HPLC analysis (Chiralcel-AD, n-heptane/iPrOH 95:5, 1 mL/min). Retention times: 32.8 and 34.6 mins.



2-((5-Methoxy-1H-indol-3-yl)methyl)-1-(thiazol-2-yl)butan-1-one (26Et)

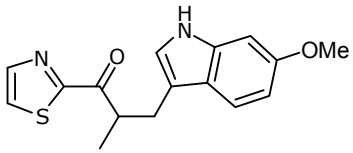
Purification by column chromatography (SiO_2, EtOAC:heptane 1:4). The product was obtained as a slightly yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) 7.17 (d, J = 8.75 Hz, 1H), 7.21 (d, J = 1.94 Hz, 1H), 6.82 (dd, J = 8.78, 2.24 Hz, 1H), 6.95 (s, 1H), 7.61 (d, J = 3.02 Hz, 1H), 7.97 (d, J = 3.01 Hz, 1H), 8.03 (s, 1H), 4.18 (td, J = 10.51, 6.29 Hz, 1H), 3.90 (s, 3H), 3.30 (dd, J = 14.48, 6.91 Hz, 1H), 2.91 (dd, J = 14.48, 7.18 Hz, 1H), 1.93 (m, 1H), 1.73 (m, 1H), 0.92 (t, J = 7.40 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.6, 168.0, 154.1, 144.9, 131.6, 128.2, 126.5, 124.0, 113.7, 112.4, 112.0, 101.2, 56.1, 49.5, 28.4, 24.9, 12.0. HRMS: m/z: $C_{17}H_{19}N_2O_2S^+$, Calcd. 315.11672; found 315.11584. Ee's were determined by HPLC analysis (Chiralcel-AD, n-heptane/iPrOH 95:5, 1 mL/min). Retention times: 14.1 and 15.6 mins.



3-(1*H*-Indol-3-yl)-2-methyl-1-(thiazol-2-yl) propan-1-one (26b)

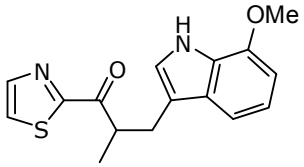
Purification by column chromatography (SiO_2, Et_2O:n-pentane 1:1). The product was obtained as a slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.02 (d, *J* = 2.9 Hz, 1 H), 7.94 (br, 1 H), 7.74 (d, *J* = 7.8 Hz, 1 H), 7.65 (d, *J* = 2.9 Hz, 1 H), 7.33 (d, *J* = 8.0 Hz, 1 H), 7.18 – 7.13 (m, 2 H), 7.02 (s, 1 H), 4.38 – 4.12 (m, 1 H), 3.40 (dd, *J* = 14.4, 6.3 Hz, 1 H), 2.90 (dd, *J* =14.4, 8.0 Hz, 1 H), 1.30 (d, *J* = 6.9 Hz, 3 H).^{13}C NMR (100 MHz, $CDCl_3$) δ = 197.4, 166.9, 144.7, 135.8, 127.6, 126.1, 122.5, 121.9, 121.2, 119.7, 119.3, 111.0, 42.4, 28.7, 16.8. HRMS: m/z: $C_{15}H_{15}N_2OS^+$, Calcd.

271.08996; found 271.09000. Ee's were determined by HPLC analysis (Chiralcel-AD, n-heptane/iPrOH 95:5, 1 mL/min). Retention times: 23.0 and 26.0 mins.



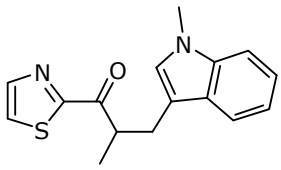
3-(6-Methoxy-1*H*-indol-3-yl)-2-methyl-1-(thiazol-2-yl)propan-1-one (26c)

The product was obtained as a slightly yellow oil. Purification by column chromatography (SiO_2, Et_2O:n-pentane 1:1). ^1H NMR (400 MHz, $CDCl_3$) δ = 8.01 (s, 1H), 7.85 (br, 1H), 7.69 (s, 1H), 7.60 (s, 1H), 7.58 (s, 1H), 6.89 (s, 1H), 6.81 (s, 1H), 4.27 – 4.17 (m, 1H), 3.83 (s, 3 H), 3.35 (dd, *J* = 14.5, 6.4 Hz, 1H), 2.84 (dd, *J* = 14.4, 8.0 Hz, 1H), 1.28 (d, *J* = 6.9 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$) 197.8, 167.2, 153.4, 144.6, 131.4, 127.1, 126.0, 123.5, 114.6, 111.4, 110.7, 100.5, 57.3, 41.3, 30.1, 17.5. HRMS: m/z: $C_{16}H_{17}N_2OS^+$, Calcd. 301.10052; found 301.10025. Ee's were determined by HPLC analysis (Chiralcel-OD, n-heptane/iPrOH 90:10, 1 mL/min). Retention times: 20.2 and 25.8 mins.



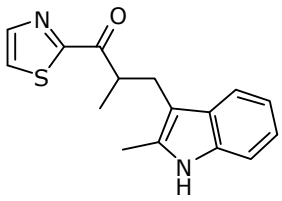
3-(7-Methoxy-1*H*-indol-3-yl)-2-methyl-1-(thiazol-2-yl)propan-1-one (26d)

Purification by column chromatography (SiO_2, Et_2O:n-pentane 1:1). The product was obtained as a slightly yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.16 (br, 1H), 8.01 (s, 1H), 7.64 (s, 1H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.04 (t, *J* = 7.9 Hz, 1H), 6.99 (s, 1H), 6.63 (d, *J* = 7.6 Hz, 1H), 4.23 – 4.21 (m, 1H), 3.94 (s, 3H), 3.37 (dd, *J* = 14.4, 6.1 Hz, 1H), 2.87 (dd, *J* =14.3, 8.0 Hz, 1H), 1.28 (d, *J* = 6.9 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ = 197.4, 167.0, 146.1, 144.7, 128.9, 126.7, 126.1, 122.1, 119.7, 114.2, 111.9, 101.8, 55.3, 42.5, 28.8, 16.8. HRMS: m/z: $C_{16}H_{17}N_2OS^+$, Calcd. 301.10052; found 301.10038. Ee's were determined by HPLC analysis (Chiralcel-OD, n-heptane/iPrOH 90:10, 1 mL/min). Retention times: 19.1 and 23.6 mins.



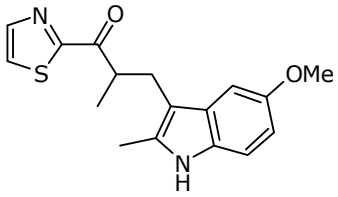
2-Methyl-3-(1-methyl-1*H*-indol-3-yl)-1-(thiazol-2-yl)propan-1-one (26e)

Purification by column chromatography (SiO_2, Et_2O:n-pentane 1:1). The product was obtained as a slightly yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.01 (d, *J* = 1.8 Hz, 1H), 7.72 (d, *J* = 7.9 Hz, 1H), 7.64 (d, *J* = 1.8 Hz, 1H), 7.25 (s, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.11 (t, *J* = 7.4 Hz, 1H), 6.87 (s, 1H), 4.28 – 4.14 (m, 1H), 3.72 (s, 3H), 3.38 (dd, *J* = 14.4, 6.2 Hz, 1H), 2.87 (dd, *J* = 14.4, 8.0 Hz, 1H), 1.29 (d, *J* = 6.9 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ = 197.4, 166.9, 144.7, 142.6, 136.9, 127.3, 126.1, 121.4, 119.2, 118.7, 112.1, 109.0, 42.7, 32.6, 28.6, 16.8. HRMS: m/z: $C_{16}H_{17}N_2OS^+$, calcd. 285.10561; found 258.10554. Ee's were determined by HPLC analysis (Chiralcel-OD, n-heptane/iPrOH 98:2, 1 mL/min). Retention times: 13.6 and 15.0 mins.



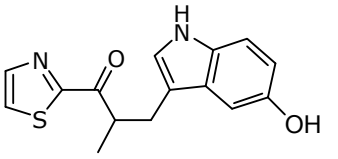
2-Methyl-3-(2-methyl-1*H*-indol-3-yl)-1-(thiazol-2-yl)propan-1-one (26f)

Purification by column chromatography (SiO_2, EtOAc:n-pentane 1:3). The product was obtained as a slightly yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.00 (d, *J* =3.0 Hz, 1H), 7.82 (br, 1H), 7.69 – 7. 67 (m, 1H), 7.62 (d, *J* = 3.0 Hz, 1H), 7.26 – 7.22 (m, 1H), 7.11 – 7.08 (m, 2H), 4.22 (dd, *J* = 14.0, 7.3 Hz, 1H), 3.30 (dd, *J* = 14.1, 5.6 Hz, 1H), 2.80 (dd, *J*=14.2, 8.9 Hz, 1H), 2,39 (s, 3H), 1.24 (d, *J* = 6.9 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.5, 165.9, 143.7, 134.2, 131.1, 127.8, 125.0, 119.9, 118.2, 117.4, 109.0, 108.3, 41.7, 27.0, 15.2, 10.8. HRMS: m/z: $C_{16}H_{17}N_2OS^+$, calcd. 285.10561; found 258.10551. Ee's were determined by HPLC analysis (Chiralcel-AD, n-heptane/iPrOH 95:5, 1 mL/min). Retention times: 16.9 and 19.2 mins.



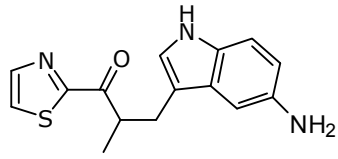
3-(5-Methoxy-2-methyl-1*H*-indol-3-yl)-2-methyl-1-(thiazol-2-yl)propan-1-one (26g)

Purification by column chromatography (SiO_2, EtOAc:n-pentane 1:3). The product was obtained as a slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.00 (s, 1H), 7.65 (s, 2H), 7.25 (s, 1H), (7.12 (dd, *J* = 8.7, 2.0 Hz, 1H), 6.76 (d, *J* = 8.7 Hz, 1H), 4.29 – 4.12 (m, 1H), 3.91 (s, 3H), 3.28 (dd, *J* = 14.2, 5.2 Hz, 1H), 2.73 (dd, *J* = 14.2, 9.0 Hz, 1H), 2.38 (s, 3H), 1.22 (d, *J* = 6.8 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ = 197.5, 167.0, 153.9, 144.6, 133.0, 130.3, 129.2, 126.1, 110.7, 109.4, 105.9, 100.9, 55.9, 42.6, 28.3, 15.9, 11.9. HRMS: m/z: $C_{17}H_{19}N_2O_2S^+$, calcd. 315.11617; found 315.11638. Ee's were determined by HPLC analysis (Chiralcel-AD, n-heptane/iPrOH 95:5, 1 mL/min). Retention times: 22.1 and 23.7 mins.



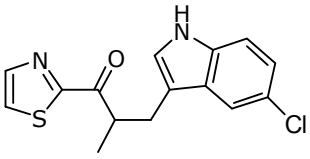
3-(5-Hydroxy-1*H*-indol-3-yl)2-methyl-1-(thiazol-2-yl)propan-1-one (26h)

Purification by column chromatography (SiO_2, Et_2O:n-pentane 3:2). The product was obtained as a slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.02 (d, *J* = 3.0 Hz, 1 H), 7.81 (br, 1 H), 7.65 (d, *J* = 3.0 Hz, 1 H), 7.18 (d, *J* = 8.6 Hz, 1 H), 7.13 (d, *J* = 2.0 Hz, 1 H), 6.99 (d, *J* = 2.1 Hz, 1 H), 6.75 (dd, *J* = 8.6, 2.5 Hz, 1 H), 4.58 (br, 1 H), 4.26 – 4.15 (m, 1 H), 3.32 (dd, *J* = 14.4, 6.4 Hz, 1 H), 2.82 (dd, *J* = 14.4, 7.9 Hz, 1 H), 1.28 (d, *J* = 7.0 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 197.3, 166.9, 149.2, 144.6, 131.4, 128.2, 126.1, 123.6, 113.1, 111.6, 111.5, 103.6, 42.2, 28.7, 16.7. HRMS: m/z: $C_{15}H_{15}N_2O_2S^+$, calcd. 287.08487; found 287.08248. Ee's were determined by HPLC analysis (Chiralcel-OD, n-heptane/iPrOH 90:10, 1 mL/min). Retention times: 40.1 and 46.0 mins.



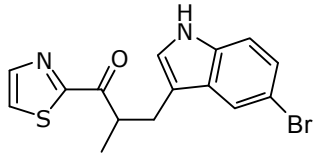
3-(5-Amino-1*H*-indol-3-yl)2-methyl-1-(thiazol-2-yl)propan-1-one (26i)

Purification by column chromatography (SiO_2, EtOAC:Et_2O:pentane 2:6:1 and 5 vol% Et_3N). The product was obtained as a slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.00 (d, *J* = 3.0 Hz, 1H), 7.91 (br, 1H), 7.63 (d, *J* = 3.0 Hz, 1H), 7.11 (d, *J* = 8.5 Hz, 1H), 7.01 (s, 1H), 6.91 (s, 1H), 6.63 (d, *J* = 8.5 Hz, 1H), 4.20 (m, 1H), 3.30 (dd, *J* = 14.3, 6.3 Hz, 1H), 2.80 (dd, *J* = 14.4, 8.0 Hz, 1H), 1.28 – 1.25 (m, 5H).^{13}C NMR (100 MHz, $CDCl_3$) δ = 197.5, 167.0, 144.7, 139.1, 131.1, 128.4, 126.2, 123.3, 112.8, 112.5, 111.6, 104.2, 42.4, 28.8, 16.8. HRMS: m/z: $C_{15}H_{15}N_3OS^+$, calcd. 286.10148; found 286.10201. Ee's were determined by HPLC analysis (Chiralcel-AD, n-heptane/iPrOH 93:7, 1 mL/min). Retention times: 76.8 and 80.4 mins.



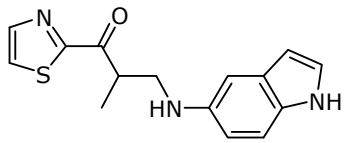
3-(5-Chloro-1*H*-indol-3-yl)2-methyl-1-(thiazol-2-yl)propan-1-one (26j)

Purification by column chromatography (SiO_2, Et_2O:n-pentane 1:2). The product was obtained as a slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.03 (s, 1 H), 7.99 (br, 1 H), 7.70 (s, 1 H), 7.66 (s, 1 H), 7.26 (s, 1 H), 7.23 (d, *J*=8.6, 1 H), 7.12 (d, *J* =8 .6, 1 H), 4.19 (dd, *J* = 14.0, 7.1 Hz, 1 H), 3.34 (dd, *J* = 14.4, 6.2 Hz, 1 H), 2.85 (dd, *J*=14.5, 7.7 Hz, 1 H), 1.29 (d, *J*=6.9, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 192.3, 162.0, 140.0, 129.7, 123.9, 121.5, 120.4, 119.1, 117.5, 114.0, 108.9, 107.2, 61.1, 37.7, 23.9. HRMS: m/z: $C_{15}H_{14}ClN_2OS^+$, calcd. 305.05156; found 305.05172. Ee's were determined by HPLC analysis (Chiralcel-AD, n-heptane/iPrOH 95:5, 1 mL/min). Retention times: 21.3 and 22.3 mins.



3-(5-Bromo-1*H*-indol-3-yl)2-methyl-1-(thiazol-2-yl)propan-1-one (26k)

Purification by column chromatography (SiO_2, Et_2O:n-pentane 1:1). The product was obtained as a slightly yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.04 (d, J = 3.0 Hz, 1H), 7.96 (br, 1H), 7.87 (s, 1H), 7.66 (d, J = 3.0 Hz, 1H), 7.24 (d, J = 1.8 Hz, 1H), 7.20 (s, 1H), 7.02 (d, J = 1.8 Hz, 1H), 4.23-4.12 (m, 1H), 3.33 (dd, J = 14.5, 6.4 Hz, 1H), 2.85 (dd, J =14.5, 7.7Hz, 1 H), 1.29 (d, J = 6.9 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 197.0, 166.8, 144.7, 134.8, 129.4, 126.2, 124.8, 123.6, 121.9, 113.6, 112.7, 112.4, 42.4, 28.6, 16.7. HRMS: m/z: $C_{15}H_{14}BrN_2OS^+$, calcd. 349.00047; found 349.00057. Ee's were determined by HPLC analysis (Chiralcel-AD, n-heptane/iPrOH 95:5, 1 mL/min). Retention times: 21.4 and 22.4 mins.



3-((1*H*-Indol-5-yl)amino-2-methyl-1-(thiazol-2-yl))propan-1-one (aza-Michael product)

Product isolated from the reaction between **17a** and **25i** in the absence of DNA. Purification by column chromatography (SiO_2, Et_2O:n-pentane 4:1). The product was obtained as a slightly yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.01 (d, *J* = 2.9 Hz, 1 H), 7.91 (br, 1 H), 7.65 (d, *J* = 2.9 Hz, 1 H), 7.16 (d, *J* = 8.6 Hz, 1 H), 7.09 (s, 1 H), 6.89 (s, 1 H), 6.59 (d, *J* = 8.6 Hz, 1 H), 6.37 (s, 1 H), 4.31 – 4.12 (m, 1 H), 3.69 (dd, *J* = 12.6, 7.6 Hz, 1 H), 3.38 (dd, *J* = 12.6, 5.5 Hz, 1 H), 2.43 (s, 1 H), 1.37 (d, *J* = 7.0 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.6, 167.0, 144.7, 141.8, 130.2, 128.8, 126.4, 124.4, 112.3, 111.6, 102.6, 101.8, 48.4, 41.7, 15.1. HRMS: m/z: $C_{15}H_{16}N_3OS^+$, calcd. 286.10141; found 286.10168 Ee's were determined by HPLC analysis (Chiralcel-AD, n-heptane/iPrOH 93:7, 1 mL/min). Retention times: 53.0 and 57.8 mins.

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