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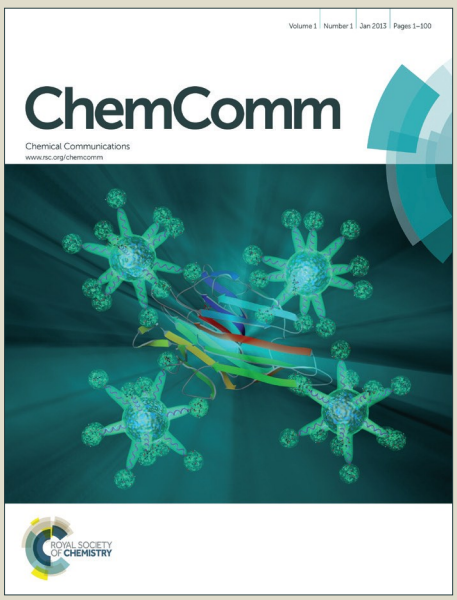

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Feature Article

Asymmetric synthesis of pyrazoles and pyrazolones employing the reactivity of pyrazolin-5-one derivatives

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Due to the frequent occurance of the pyrazole core in many important naturally occuring and synthetic molecules, tremendous efforts have been made for their synthesis. The pyrazolin-5-one derivatives have emerged as the most effective substrates for the synthesis of useful pyrazoles and their corresponding pyrazolone derivatives. Recently, the reactivity of pyrazolin-5-ones has been used for the asymmetric synthesis of highly functionalised pyrazole and pyrazolone derivatives by employing organo- and metal-catalysts. This feature article focuses on the progress in the catalytic asymmetric synthesis of pyrazoles and pyrazolones using pyrazolin-5-one derivatives.

1. Introduction

Among various heterocycles, pyrazole derivatives represent an important class of nitrogen containing five membered heterocyclic compounds that has attracted huge attention in recent years due to wide spread applications as pharmaceutical agents, synthetic scaffolds in combinatorial and medicinal chemistry, photographic couplers, chelating agents in coordination chemistry and agrochemical products.[1] The pyrazole unit is an integral part of many biologically active natural products such as l-α-Amino-β-(pyrazolyl-*N*)-propanoic acid (**1**), withasomnine (**2**), 4-hydroxywithasomnine (**3**), 4-methoxywithasomnine (**4**), pyrazofurin (**5**) and formycin (**6**) (Figure 1).[2] Many synthetic pyrazole derivatives also possess medicinal value. For example, remogliflozin etabonate (**7**) is a drug proposed for the treatment of type 2 diabetes,[3] whereas celecoxib (**8**)[4] and mavacoxib (**9**)[5] are COX-2 inhibitors. The latter, a veterinary drug with the trade name Trocoxil, is used to treat pain and inflammation in dogs with a degenerative joint disease.[6] Other synthetic compounds bearing a pyrazole ring possess different bioactivities such as the dihydropyrano[2,3-c]pyrazole derivative **10**, which is a human chk1 kinase inhibitor,[7] whereas the pyranopyrazoles **11**, **12** and **13** show antibacterial,[8] analgesic[9] and antiplatelet activities,[10] respectively. The annulated pyrazole **14** is an AMPA receptor activity enhancer[11] and **15** is a fungicide[12].

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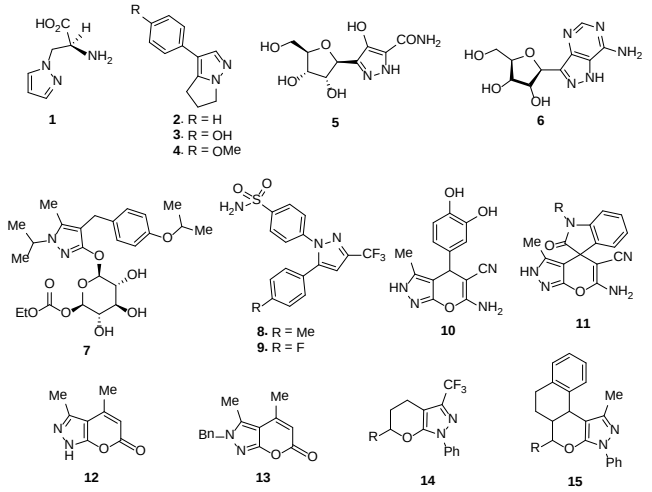

Figure 1. Pyrazole ring containing natural products, drugs and synthetic bioactive molecules.

Pyrazolones are another important class of pyrazole heterocycles possessing important biological properties and they have been known for more than one century.[13] The pyrazolone phenazone (**16**),[14] synthesized in 1883 by Ludwig Knorr, is the very first synthetic antipyretic and analgesic drug, and metamizole (**17**), developed somewhat later, is considered the strongest antipyretic (Figure 2).[15] The pyrazolone edaravone (**18**) is a neuroprotective agent.[16] The pyrazolone derivatives **19-22** act as p38 inhibitors,[17] HIV integrase inhibitors,[18] type 4-phosphodiesterase inhibitor,[19] and antibacterial agent,[20] respectively.

In the last few years, various catalytic asymmetric strategies employing organo- and metal-catalysts utilized pyrazolin-5-one derivatives for the synthesis of new, potentially bioactive enantiopure pyrazolone and pyrazole derivatives. The unique feature of the pyrazolin-5-one substrates is the

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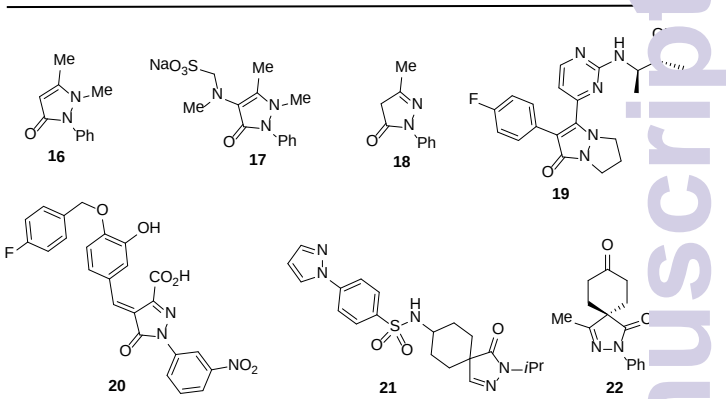
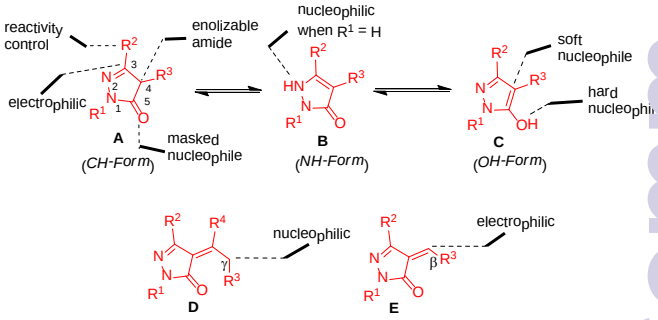


Figure 2. Pyrazolone drugs and bioactive compounds.

availability of many reactive centers, which can be manipulated in order to get valuable compounds. The pyrazolin-5-ones exist in three tautomeric forms **A**, **B** and **C** (Scheme 1). The main strategy for the asymmetric synthesis of pyrazoles and pyrazolones involves the nucleophilic addition of pyrazolin-5-ones **A** from C-4 to various acceptors to give tetrasubstituted carbon bearing pyrazolones (when R^3 = alkyl, aryl), or pyrazole derivatives (when R^3 = H). The latter can also undergo a subsequent reaction (cyclisation) with another electrophile through the C-4 and the C-5 OH functionality. Moreover, the N1-unsubstituted pyrazolin-5-one derivatives (R^1 = H) are suitable substrates for aza-Michael additions reactions. The α,β-unsaturated pyrazolones **D** bearing a γ hydrogen have been exploited for asymmetric vinylogous additions, whereas other α,β-unsaturated pyrazolones such as **E**, especially those derived from aldehydes, served as powerful Michael acceptors for various nucleophiles and these also undergo subsequent cascade sequences through C-4 addition and O-cyclisations. Moreover, the CN double bond in pyrazolones **A** served as an acceptor for the addition of small nucleophiles such as a hydride.



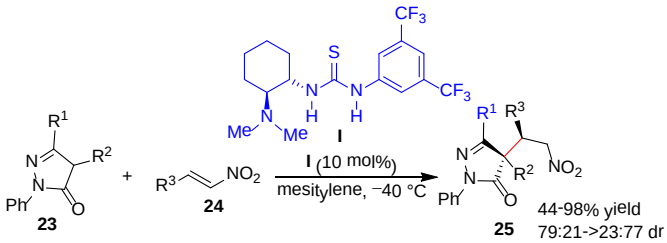
Scheme 1 Tautomerism and reactive centers on the pyrazolin-5-ones.

This *feature article* describes all those examples from the literature, where the above mentioned reactivity of the pyrazolin-5-ones was used for the synthesis of enantiopure pyrazolone and pyrazole derivatives by employing the catalytic potential of organo- and metal-catalysts. For a better understanding and a convenient presentation this *feature article* is classified according to the nature of the pyrazolin-5-one substrates.

2. Addition from C-4 of the pyrazolin-5-ones

2.1 Addition to nitroalkenes

The Michael addition to nitroolefins is certainly the most common and widely studied conjugate addition due to the high synthetic value of the corresponding nitroalkanes as a versatile scaffold for various other functionalities.[21] In 2010 Yuan and co-workers described the first stereoselective Michael addition of 4-substituted-pyrazolin-5-ones **23** to β-nitroalkenes **24** catalyzed by the bifunctional aminothiourea catalyst **I** (Scheme 2).[22] Diversely substituted aromatic and heteroaromatic nitroalkenes reacted well with 3,4-dimethyl-1-phenyl-1,2-dihydropyrazol-5-one to afford multi-substituted pyrazolin-5-one derivatives **25** with vicinal quaternary and tertiary stereocenters in consistently high yields with moderate to good enantioselectivities albeit low diastereoselectivities. Aliphatic nitroolefins were found to be quite sluggish substrates that provided the desired products in lower yields with good ee and poor dr in a prolonged reaction time. The *N*-phenyl pyrazolin-5-one, bearing a methyl group at R^2 and an ethyl or allyl group at R^1 reacted well with nitroalkenes to give the desired products. The major limitation of this method is that when instead of a phenyl group, a pyrazolin-5-one containing a H or a Ts group at nitrogen atom was employed, the desired products were obtained only in trace amounts.

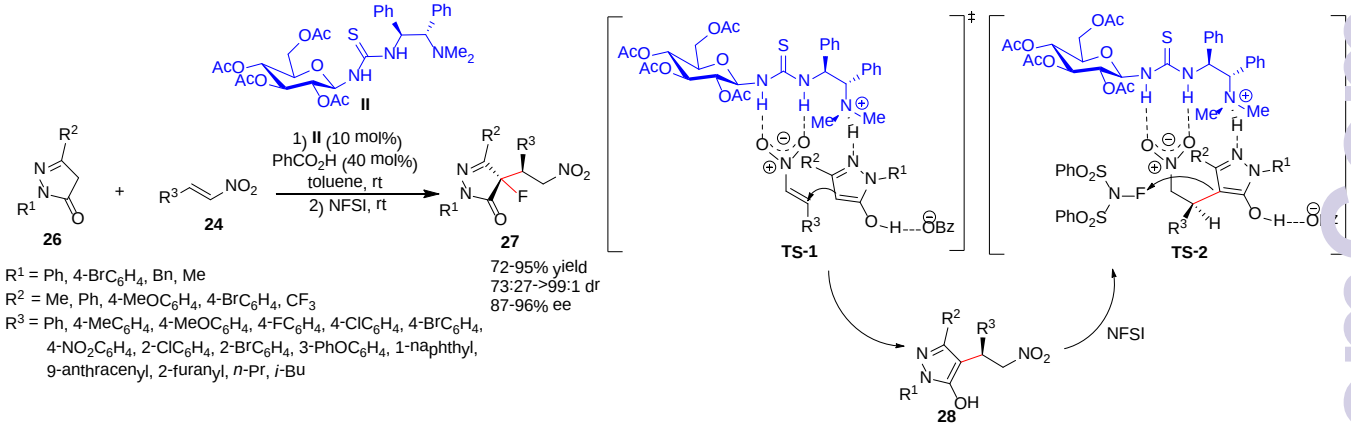


R^1 = Me, Ph
R^2 = Me, Et, allyl
R^3 = Ph, 4-ClC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 4-BrC$_6$H$_4$, 4-FC$_6$H$_4$, 4-CNC$_6$H$_4$, 2-BrC$_6$H$_4$, 2-MeOC$_6$H$_4$, 2-NO$_2$C$_6$H$_4$, 2-ClC$_6$H$_4$, 3-MeC$_6$H$_4$, 3-NO$_2$C$_6$H$_4$, 3-BrC$_6$H$_4$, 3-CF$_3$C$_6$H$_4$, 3,4-(MeO)$_2$C$_6$H$_3$, 2-furanyl, 2-thienyl, 1-naphthyl, (CH$_3$)$_2$CHCH$_2$, cyclohexyl

Scheme 2. Thiourea catalyzed Michael addition of 4-substituted-pyrazolin-5-ones to β-nitroalkenes.

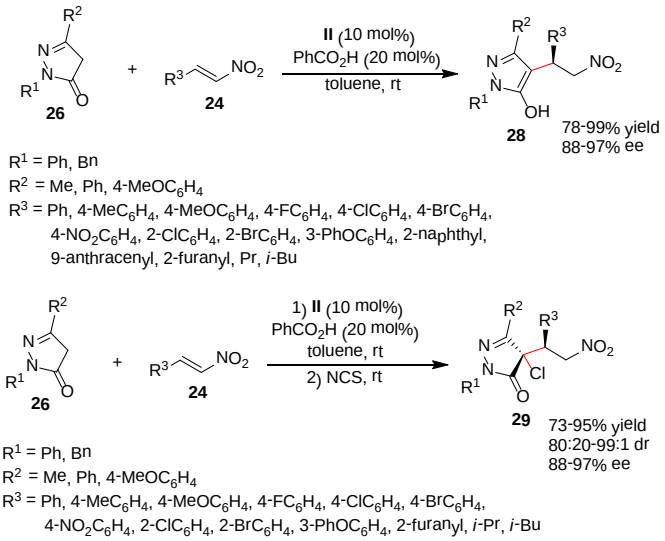
Ma's research group reported an organocatalytic sequential 1,4-addition/dearomative-fluorination reaction of pyrazolones with nitroolefins and *N*-fluorodibenzenesulfonamide (NFSI) (Scheme 3).[23] The process involves the initial enantioselective Michael addition of pyrazolones **26** to the various nitroolefins **24** catalyzed by a aminothiourea **II** and benzoic acid, followed by the addition of NFSI to complete the dearomative-fluorination reaction. A wide range of pyrazolones **27** bearing adjacent tertiary and fluorinated tetrasubstituted carbon centers could be easily synthesized in good to high yields and high stereoselectivities except for the β-furanyl nitroalkene, which gives the desired product only in moderated dr. A proposed mechanism for the one-pot sequential 1,4-addition/dearomative-fluorination transformation involves the activation of the nitroalkene with the thiourea unit through hydrogen-bonding and simultaneously the enol form of the pyrazolone substrate gets hydrogen-bonded to the ammonium cation of the catalyst, which in turn is formed by protonation with benzoic acid (**TS-1**). The corresponding benzoate anion assists the generation of the pyrazole enolate which then adds to the nitroalkenes, thus affording the Michael adduct **28**, which can be isolated. Then the latter undergoes subsequent diastereoselective electrophilic-fluorination *via* **TS-2** in the presence of NFSI.

The cooperative catalytic system consisting of a chiral aminothiourea **II** and an achiral organic acid also facilitated the Michael addition of 4-non-substituted pyrazolones **26** to the nitroolefins **24** to afford the corresponding pyrazole derivatives **27** in good to excellent yields and high enantioselectivities (Scheme 4).[24] The one-pot Michael additions and subsequent dearomative chlorination with *N*-chlorosuccinimide (NCS) catalyzed by the aminothiourea **II** and benzoic acid led to the formation of the chlorinated pyrazolones **29** bearing a tertiary and a tetrasubstituted chlorinated stereogenic center with excellent yields and ee-values and with moderate to excellent diastereomeric ratios.



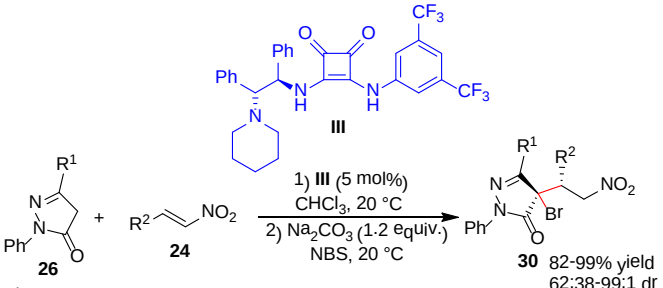
R^1 = Ph, 4-BrC$_6$H$_4$, Bn, Me
R^2 = Me, Ph, 4-MeOC$_6$H$_4$, 4-BrC$_6$H$_4$, CF$_3$
R^3 = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 2-ClC$_6$H$_4$, 2-BrC$_6$H$_4$, 3-PhOC$_6$H$_4$, 1-naphthyl, 9-anthracenyl, 2-furanyl, *n*-Pr, *i*-Bu

Scheme 3. Organocatalytic sequential 1,4-addition/dearomative-fluorination reaction of pyrazolones with nitroolefins and NFSI.



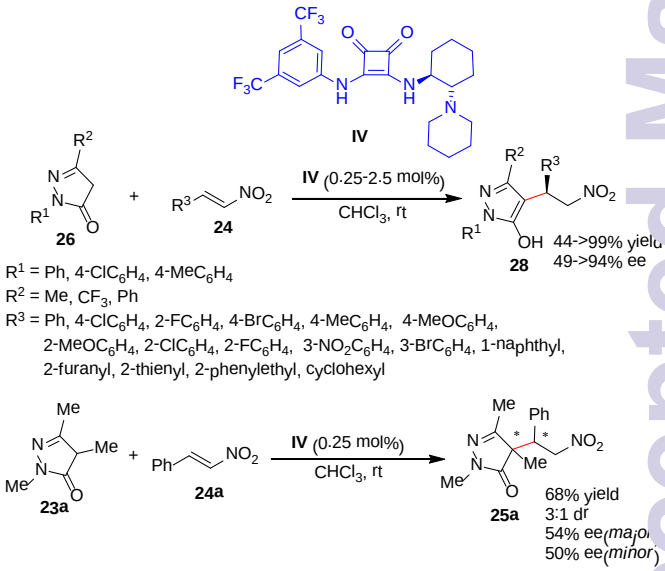
Scheme 4. Organocatalytic Michael addition of pyrazolones to nitroolefins and subsequent dearomative-chlorination with NCS.

A similar one-pot asymmetric sequential reaction involving a Michael addition/dearomative bromination reaction between pyrazol-5-ones **26**, nitroalkenes **24** and *N*-bromosuccinimide (NBS) provided a wide range of brominated pyrazol-5-one derivatives **30** with adjacent tetrasubstituted and tertiary stereocenters (Scheme 5).[25] The initial Michael addition was catalyzed by a bifunctional aminosquaramide **III**, whereas bromination takes place in the presence of an additional base to obtain the desired products in high yields with good to excellent stereoselectivities for most of the aromatic and heteroaromatic nitroalkenes. The aliphatic nitroalkenes were found to be less reactive, hence they required a longer reaction time to provide a good yield and ee, albeit with a lower dr.



Scheme 5. Organocatalytic sequential Michael addition/dearomative-bromination of pyrazolones with nitroolefins and NBS.

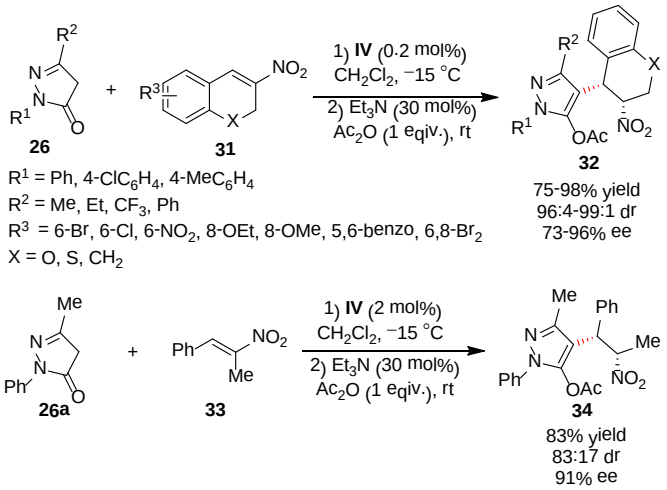
A very low loading of the squaramide **IV** catalyzed the enantioselective Michael addition of pyrazolin-5-ones **26** to the nitroalkenes **24** to afford the pyrazol-3-ol derivatives **28** in moderate to excellent yields and moderate to good enantioselectivities (Scheme 6).[26] This transformation worked well for a wide range of aromatic nitroalkenes bearing electron-withdrawing and electron-releasing substituents as well as for the nitroalkenes bearing heteroaryl and alkyl groups, although the latter required a considerably higher catalyst loading (2 mol%). The pyrazolones bearing a C-3 CF_3 group showed lower reactivity with lower yields and ee-values. With 3-methyl-1-(2,4-dinitrophenyl)-pyrazolin-5-one (R^1 = R^2 = Ph) the reaction could not take place whereas when using 1,3-diphenyl-2-pyrazolin-5-one (R^1 = Ph, $(NO_2)_2C_6H_3$ R^2 = Me) as a donor the corresponding product was not isolated through column chromatography due to the similar polarity of pyrazolone and the product. The squaramide **IV**-catalyzed Michael addition of 3,4-dimethyl-1- phenyl-2-pyrazolin-5-one (**23a**) with β-nitrostyrene **24a** provided a pyrazolone **25a** bearing a quaternary and a tertiary stereogenic center in moderate yield, diastereoselectivity and enantioselectivity. Under the standard reaction conditions a successful gram-scale reaction could also be performed in the presence of only 0.25 mol% of catalyst.



Scheme 6. Squaramide-catalyzed enantioselective Michael addition of pyrazolin-5-ones to nitroalkenes.

An enantioselective Michael addition of pyrazolin-5-ones **26** to the 3-nitro-2H-chromenes **31** provided an efficient entry to the heterocyclic system **32** containing chroman and pyrazolone units (Scheme 7).[27] This transformation catalyzed by a low loading of a squaramide catalyst **IV** afforded the desired products **32** in good to high yields, enantioselectivities and diastereoselectivities. However, a one-pot acetylation is required to resolve the problem of the tautomerization of the product. The nitroalkenes, in which a methylene or a sulfur atom is present instead of an oxygen atom, react efficiently with a pyrazolone to afford the corresponding products in good yields with excellent diastereoselectivity, however with X = CH_2 only 71% ee and with X = S 88% ee was obtained. In addition, an acyclic nitroalkene *i.e.* α-methyl-β-nitrostyrene (**33**) possesses lower reactivity and hence 2.0 mol% of the catalyst was used to obtain the desired product **34** in 83% yield with 83:17 dr and 91% ee. A gram-scale reaction also worked well without any loss in the chemical yield and stereochemical outcome of the reactions.

Recently, our research group disclosed the asymmetric synthesis of pyrano-annulated pyrazoles **36** by combining organo- and metal catalysis (Scheme 8).[28] This sequential catalytic reaction



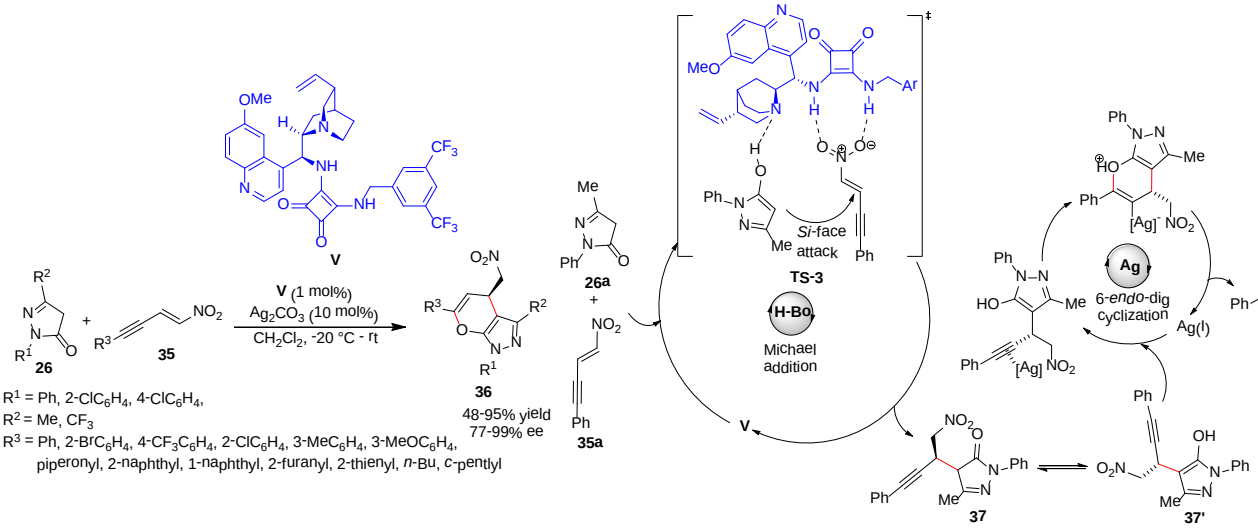
Scheme 7. Enantioselective Michael addition of pyrazolin-5-ones to the 3-nitro-2H-chromenes and α-methyl-β-nitrostyrene.

involves a squaramide **V**-catalyzed enantioselective Michael addition of pyrazolones **26** to the alkyne-tethered nitroolefins **35** followed by a subsequent silver catalyzed hydroalkoxylation. Both catalysts could be used together from the beginning without affecting the chemical yield or the enantioselectivity of the reaction. A series of potentially bioactive pyrano-annulated pyrazoles **36** was synthesized in good yields and moderate to high enantioselectivities. The virtually enantiopure pyrano-annulated pyrazoles could also be easily made available by a single crystallization from ethyl acetate:*n*-pentane. In this process, the squaramide acts as a bifunctional catalyst by activating the nitroalkene through hydrogen-bonding with the squaramide moiety, while the quinuclidine part of the catalyst assists the formation of the enolate, which adds to the nitroalkene through the *Si*-face (**TS-3**). The corresponding Michael adduct **37** then enters another catalytic cycle, where the silver-catalyzed 6-*endo-dig* cyclization of the enol **37'** to the alkyne proceeds *via* stereoselective *anti*-addition to form a vinylsilver intermediate, which under the reaction conditions undergoes fast protodeargentation to yield the pyrano-annulated pyrazole.

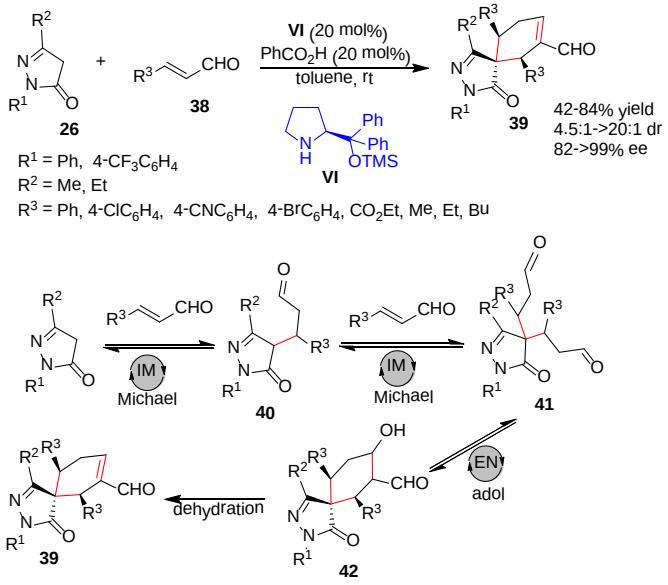
2.2 Addition to α,β-unsaturated carbonyl compounds

Rios and co-workers achieved an organocatalyzed triple domino Michael/Michael/aldol reaction between pyrazolones **26** and two molecules of enals **38** to furnish highly functionalized spiropyrazolone derivatives **39** (Scheme 9).[29] With diphenylprolinol trimethylsilyl ether **VI** as catalyst and benzoic acid as an additive the spiropyrazolones could be obtained in good yields and good to perfect stereoselectivities. The triple cascade sequence exhibits a wide substrate scope including various aryl or alkyl enals and nitroalkenes as well as substituted pyrazolones. The latter substrate, however bearing bulky substituents such as phenyl or *tert*-butyl as well as electron-withdrawing groups, such as trifluoromethyl, resulted in no desired product. This cascade reaction showed a strong nonlinear effect by plotting the ee of the catalyst against the ee of the product. Remarkably, when a catalyst with 70% ee was used, a virtually diastereo- and enantiopure spiropyrazolone was obtained. This triple domino reaction is initiated by the iminium ion formation between the catalyst and the enal, to which the pyrazolone first undergoes a Michael addition. The resulting Michael adduct **40** then adds to the iminium ion generated from the second molecule of the enal to afford a disubsituted pyrazolone **41**, which then undergoes an intramolecular aldol reaction through the enamine intermediate to provide **42**, which after subsequent dehydration provides the desired spiropyrazolone.

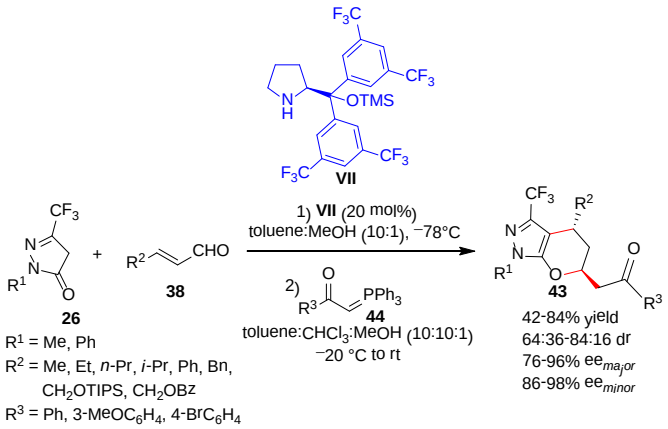
Our group reported an efficient asymmetric synthesis of tetrahydropyrano[2,3-c]pyrazoles **43** *via* a one-pot Michael/Wittig/oxa-Michael reaction (Scheme 10).[30] This sequence was initiated by a secondary amine **VII**-catalyzed Michael addition of 3-trifluoromethyl pyrazolones **26** to the various α,β-unsaturated aldehydes **38**, followed by the addition of the Wittig reagent **44** to accomplish the biologically active tetrahydropyrano[2,3-c]pyrazoles **43** *via* a subsequent Wittig/oxa-Michael reaction.



Scheme 8. Enantioselective Michael addition/hydroalkoxylation of pyrazolones with the alkyne-tethered nitroolefins by combining a squaramide with a silver catalyst.

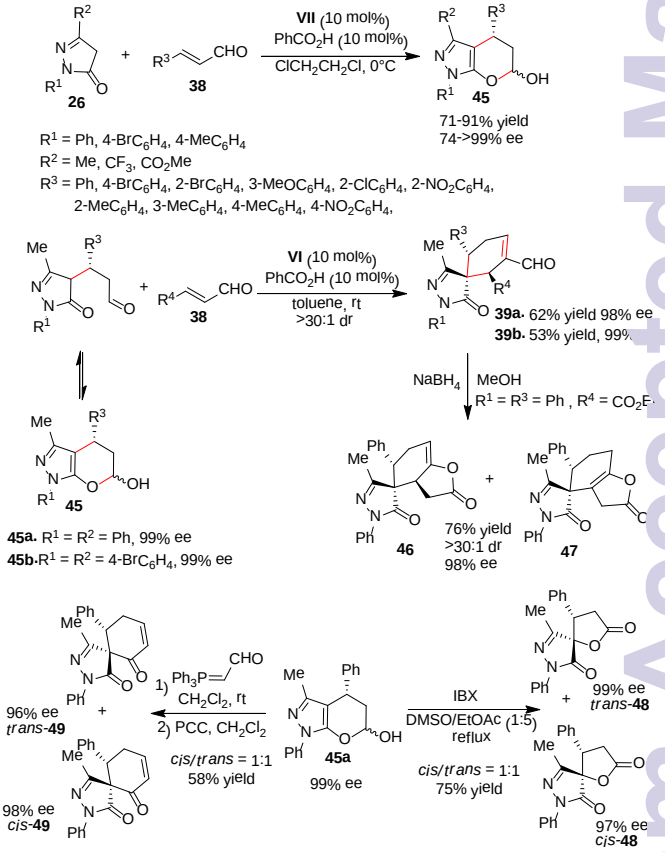


Scheme 9. Organocatalytic triple domino Michael/Michael/aldol condensation reaction between pyrazolones and enals.



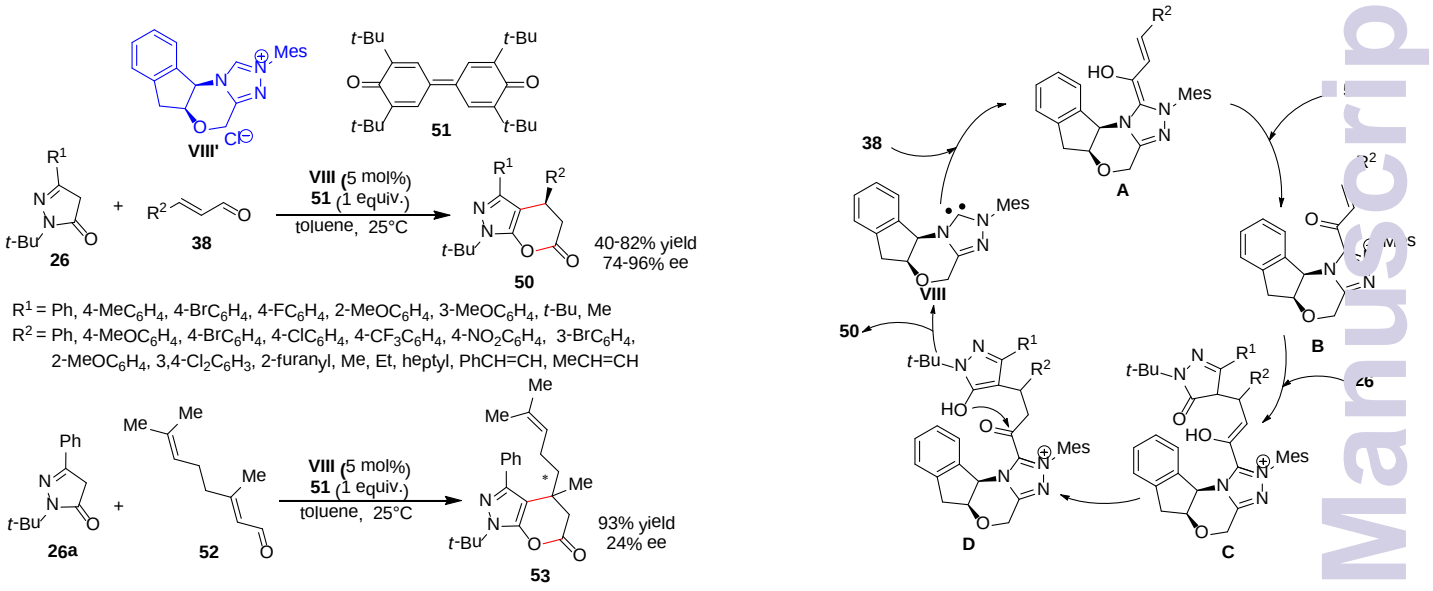
Scheme 10. Asymmetric synthesis of tetrahydropyrano[2,3-c]pyrazoles *via* a one-pot Michael/Wittig/oxa-Michael reaction.

Recently tetrahydropyrano[2,3-c]pyrazol-6-ols **45** have been synthesized by a Michael addition/hemiacetalization sequence using the secondary amine catalyst **VII** and benzoic acid as an additive (Scheme 11).[31] Good yields (71–91%) and good to high enantioselectivities were obtained with different pyrazolol-5-ones and α,β-unsaturated aldehydes. An extremely low ee value (10% ee) was observed when a phenyl group was present at the 3-position of the pyrazolol-5-one, probably due to steric reasons and no product was observed for an alkyl-substituted α,β-unsaturated aldehyde. The enantiomer of the catalyst also gave the desired product in 91% yield and perfect ee of the opposite enantiomer. The tetrahydropyrano[2,3-c]pyrazol-6-ols **45a** and **45b** were used for the construction of spiropyrazolones **39a** and **39b** through a Michael/aldol cascade sequence catalyzed by the Jørgensen-Hayashi catalyst **VI** in acceptable yields and excellent stereoselectivities. The corresponding spiro compound **39** was further converted into new lactones **46** and **47** through a reduction/lactonization reaction. The pyrazolone-derived spirolactones **48** were accessible through a IBX mediated hydroxylation/acetalization/oxidation reaction sequence. The reaction of **45a** with (triphenylphosphoranylidene)acetaldehyde did not undergo the Wittig/oxa-Michael reaction analogous to that previously reported by our group, instead, a Wittig/aldol sequence occurs to provide spiropyrazolone **49** in 58% yield after PCC mediated oxidation. The molecules synthesized in this diversity oriented synthesis (DOS) approach were examined for anti-tumor activity on three human cancer cell lines (*i.e.* A549 lung carcinoma cells, MDA-MB-231 breast cancer cells, and HCT116 colon cancer cells).The compounds **39a**, *trans*-**49**, and *cis*-**49** showed inhibitory activity against all three cancer cell lines and *trans*-**49** possess the best antitumor activity, with IC 50 values in the range of 4.4 to 8.5 µm.



Scheme 11. Asymmetric synthesis of tetrahydropyrano[2,3-c]pyrazol-6-ols and their transformation to spiropyrazolones.

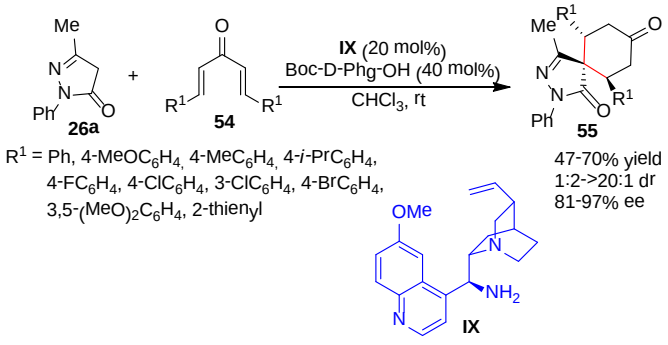
Very recently Biju and co-workers devised a new route for the synthesis of the dihydropyrano[2,3-c]pyrazol-6-(1*H*)-one core by employing the approach of base free NHC catalysis (Scheme 12).[32] The *N*-heterocyclic carbene (NHC)-catalyzed enantioselective annulation reaction of pyrazolones **26** with α,β-unsaturated aldehydes **38** proceeded *via* the formation of α,β-unsaturated acyl azolium intermediates under oxidative conditions. With this transformation various dihydropyranone-fused pyrazoles **50** were synthesized in good yields and enantioselectivities. An NHC catalyzed reaction of pyrazolone **26a** with a β,β-substituted enal **51** furnished the desired product **53** in 93% yield with poor ee of 24%. The possible mechanism for this NHC-catalyzed annulation involves



Scheme 12. N-heterocyclic carbene (NHC)-catalyzed enantioselective annulation reaction of pyrazolones with α,β-unsaturated aldehydes.

the chloride counterion assisted generation of the free NHC **VIII** from the precursor **VIII'**, which undergoes a nucleophilic 1,2-addition to the enal to generate the nucleophilic Breslow intermediate **A**. The latter is subsequently transformed into the key α,β-unsaturated acyl azolium intermediate **B** in the presence of oxidant **51**, to which pyrazolone is added in 1,4-fashion to get the enol **C**, which undergoes a proton transfer generating the acyl azolium intermediate **D**. This acyl azolium intermediate provides the desired product *via* an intramolecular acylation with the release of the carbene catalyst.

The asymmetric double Michael addition of *N*-phenyl-protected pyrazolones **26** to the divinyl ketones **54** provide an efficient access to the spirocyclohexanone pyrazolones **55** (Scheme 13).[33] The reaction was catalyzed by 9-amino-9-deoxy-epiquinine **IX** with *N*-Boc-D-phenylglycine as an acidic additive to furnish the desired spiro adducts **55** with acceptable yields and moderate to good stereoselectivities. This transformation worked well with various aryl substituted dienones, however a switch in the diastereoselectivity (1:2 dr) was observed with a heteroaryl (2-thienyl) substituted dienone. In contrast, the dienone

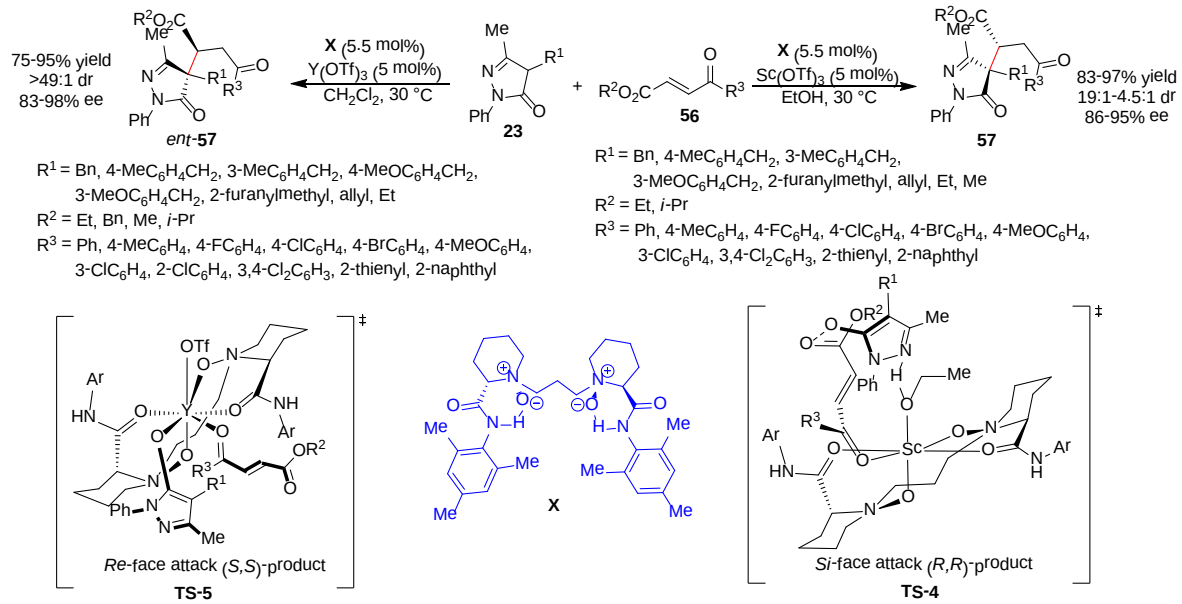


Scheme 13. Asymmetric double Michael addition of *N*-phenyl-protected pyrazolones to divinyl ketones.

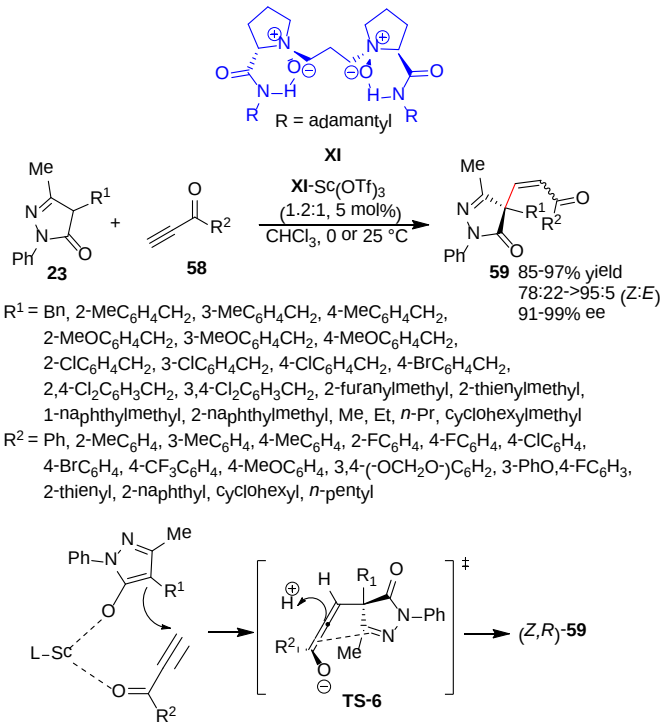
substrates bearing *ortho*-substituents proved non-reactive under the standard reaction conditions.

The metal/*NN'*-dioxide complexes catalyzed enantioselective Michael addition of 4-substituted pyrazolones **23** to the 4-oxo-4-arylbutenoates **56** gives rise to a range of 4-substituted-5-pyrazolone derivatives **57** (Scheme 14).[34] Using the same ligand **X** and only by switching the metal (Sc or Y) both enantiomers of the products could be obtained in good to excellent enantio- and diastereoselectivities. Furthermore, the scale up reaction proceeded with excellent ee and yields, thus showing the preparative value of this catalyst system. Poor nonlinear effects were observed for both catalytic systems, by plotting the ee value of the ligand **X** and the product, which suggests that monomeric oligomeric aggregates of $Sc(OTf)_3$/**X** and $Y(OTf)_3$/**X** might exist in the reaction system. In ethanol, the enantioselectivity of the yttrium(III)-catalyzed reaction was lower; however, in the scandium(III)-catalyzed case the presence of ethanol not only accelerated the reaction rate but also resulted in an improved enantioselectivity. The reversal of the enantioselectivity could be interpreted on the basis of the difference in the ionic radii of scandium (III) and yttrium (III), which leads to solvent effects. Scandium (III) has a smaller ionic radius than yttrium(III) (0.754 Å versus 0.93 Å), hence the alcohol is expected to coordinate to scandium(III) rather than to the sterically hindered pyrazolones. This coordinated alcohol gets hydrogen bonded to the nitrogen atom of the enolized pyrazolone. In contrast, in the case of yttrium(III) catalysis both reactants would be coordinated to the metal due to the larger ionic radius. The enantio-switchable conjugate addition was proposed to proceed *via* the **TS-4** and **TS-5**.

A *Z*-selective asymmetric 1,4-addition reaction of 4-substituted pyrazolones **23** to the alkynones **58** catalyzed by an *N,N'*-dioxide **XI**-scandium(III) complex resulted in the formation of 4-alkenyl-pyrazol-5-ones **59** with high geometric control, good to high yields,



Scheme 14. Enantioselective Michael addition of 4-substituted pyrazolones to 4-oxo-4-arylbutenoates

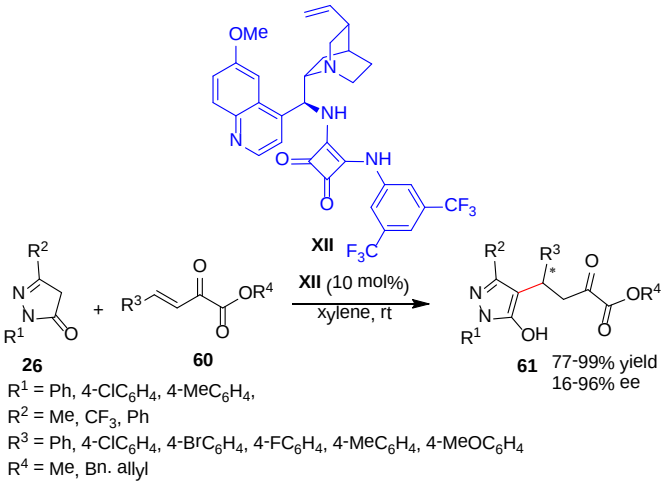


Scheme 15. Asymmetric 1,4-addition of 4-substituted pyrazolones to alkynones.

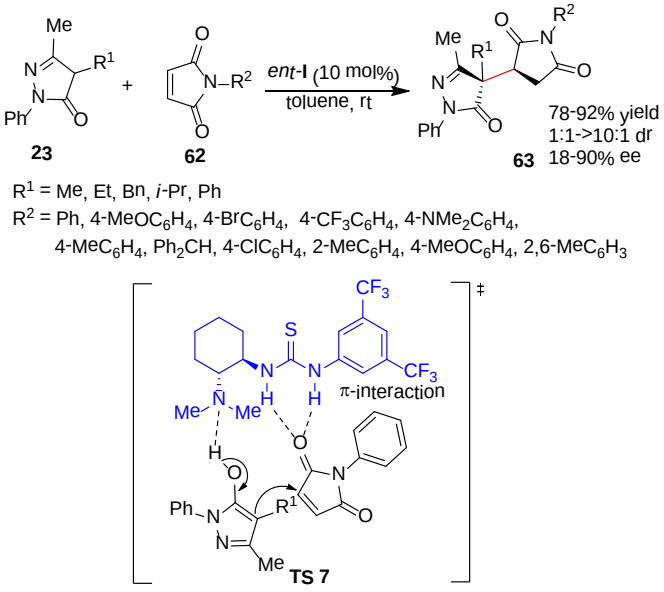
and excellent enantioselectivities (Scheme 15).[35] Various benzylic and alkyl groups at C4 of the pyrazolones as well as various aryl, hetereoaryl and alkyl groups on the alkynones are tolerated under the standard reaction conditions, and excellent results were obtained even with a gram scale reaction. The thermodynamically stable *E*-isomer could also be generated through a Ph_2MeP mediated isomerization reaction. A straight linear effect by plotting the ee of the catalyst against the ee of the products and the HRMS analysis of the catalyst suggests that the monomeric catalyst might be the major catalytically active species. The reaction was proposed to proceed through the formation of an enolate intermediate *via* the coordination of the carbonyl group of the 4-substituted pyrazol-5-one with the active **XI**–Sc(III). Simultaneously, the alkynone is coordinated to the central metal atom at a favourable position which leads to the subsequent electrophilic attack on the alkynone by the enolate *via* **TS-6**. In the transition state one side of the dienolate is shielded by the pyrazoline ring because of the interaction between the electron-enriched π-orbital of the dienolate and the electron-deficient carbon atom at the 3-position of the pyrazolone ring, in which the protonation occurs from the opposite side to afford the *Z*-isomer.

An aminosquaramide **XII**-catalyzed enantioselective Michael addition of pyrazolin-5-ones **26** to aryl substituted β,γ-unsaturated α-ketoesters **60** provides a straightforward entry to the optically active pyrazolone derivatives **61** in good to excellent yields and low to high enantioselectivities (Scheme 16).[36]

A bifunctional aminothiourea *ent*-**I** promoted enantioselective addition of pyrazolones **23** to *N*-aryl maleimides **62** afforded the corresponding pyrazolones **63** bearing vicinal quaternary and tertiary sterocenters in excellent yields, with none to good diastereodifferentiation and low to good enantioselectivities (Scheme 17).[37] With an alkyl substituted maleimide, the desired product was obtained in 93% yield, 3:1 dr and only poor ee of the major diasteromer. This can serve as evidence of π-stacking interactions between the *N*-aryl substituent of the maleimide and the (3,5-bistrifluoromethyl)phenyl moiety in the transition state **TS-7**, where the simultaneous activation of maleimide and pyrazolones with the thiourea and the tertiary amine of the catalyst occurs through hydrogen-bonding.



Scheme 16. Aminosquaramide catalyzed enantioselective Michael addition of pyrazolin-5-ones to aryl substituted β,γ-unsaturated α-ketoesters.

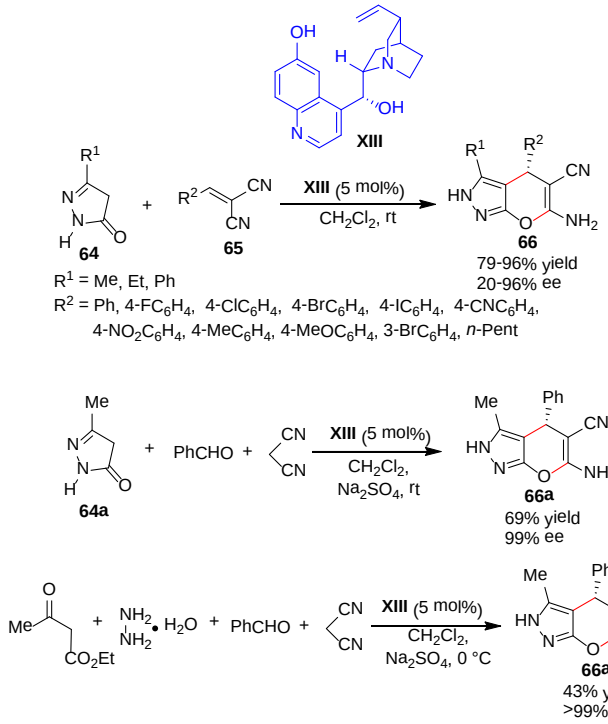


Scheme 17. Stereoselective Michael addition of pyrazolones to maleimides.

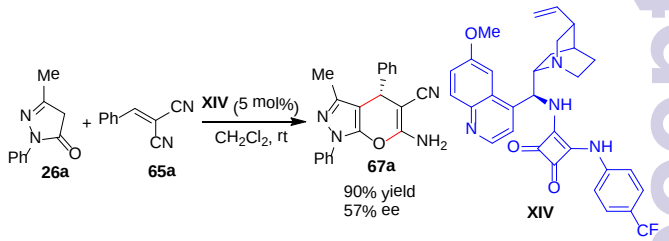
2.3 Addition to arylidenemalononitriles

In 2009 Zhao and co-workers developed a cupreine **XIII**- catalyzed domino Michael/Thorpe-Ziegler type reaction of *N*-unsubstituted 2-pyrazolin-5-ones **64** and benzylidenemalononitriles **65**, which led to the formation of 6-amino-5-cyanodihydropyrano[2,3-c]pyrazoles **66** in pretty good yields and low to excellent enantioselectivities (Scheme 18).[38] A three-component reaction between 2-pyrazolin-5-one **64a**, benzaldehyde and malononitrile (the latter two generate **65** *in situ*) and a four-component reaction involving hydrazine hydrate, a β-ketoester, benzaldehyde and malononitrile resulted in the same pyrazole product **66a**, with even better enantioselectivity using sodium sulfate as an additive to absorb the water generated during the reaction.

A similar type of enantioselective Michael addition/cyclization reaction between pyrazolone **26a** and benzylidene malononitrile **65a** catalyzed by a squaramide **XIV** provided the dihydropyrano[2,3-c]pyrazoles **67a** in 90% yield with moderate ee (Scheme 19).[39]



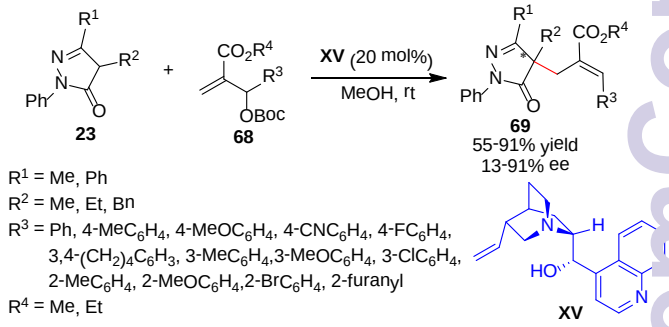
Scheme 18. Cupreine-catalyzed domino Michael/Thorpe-Ziegler type reaction 2-pyrazolin-5-ones with benzylidenemalononitriles.



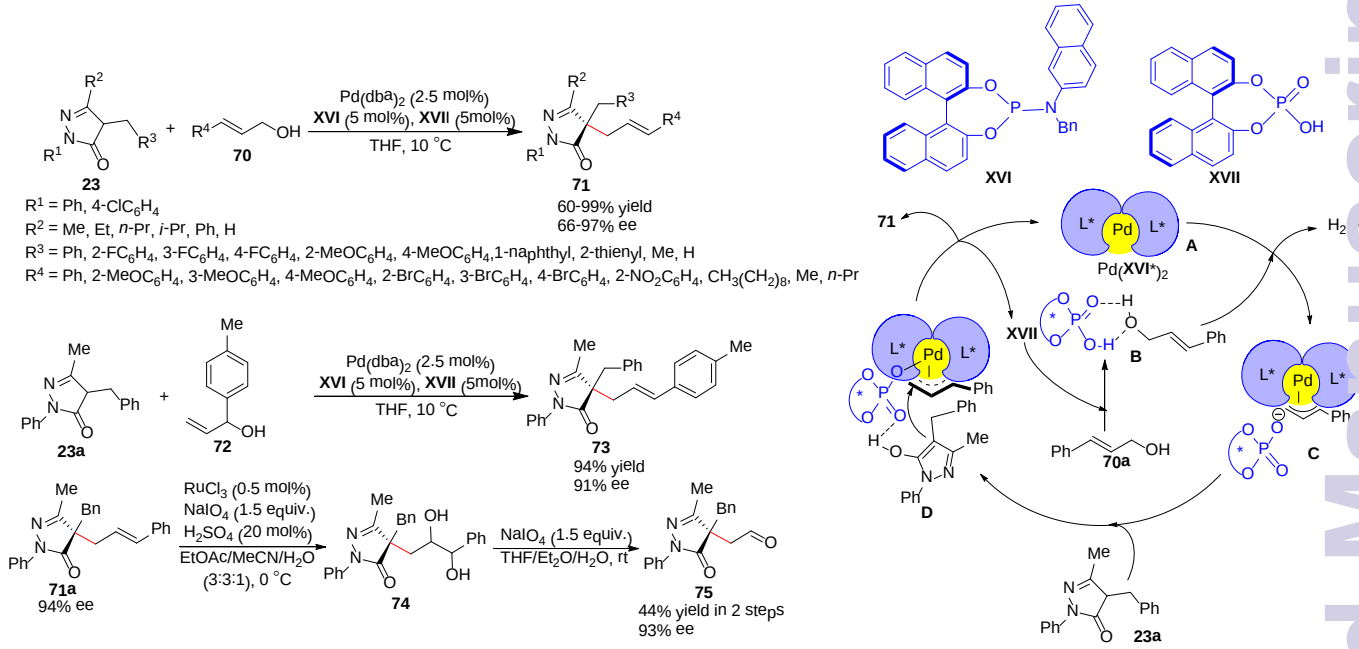
Scheme 19. Squaramide-catalyzed domino Michael/Thorpe-Ziegler type reactio of 2-pyrazolin-5-one with benzylidenemalononitrile.

2.4 Allylic alkylation

The asymmetric allylic alkylation of Morita-Baylis-Hillman (MBH) carbonates **68** using pyrazolones **23** as nucleophiles catalyzed by cinchonine (**XV**) gave the β-selective allylic alkylation products **69** in good yields and enantioselectivities (Scheme 20).[40] However, a low yield (55%) and poor enantioselectivity (13% ee) for the MBH carbonate bearing a heteroaryl group (R^3 = 2-furanyl) were observed.



Scheme 20. Asymmetric allylic alkylation of MBH carbonates with pyrazolones.



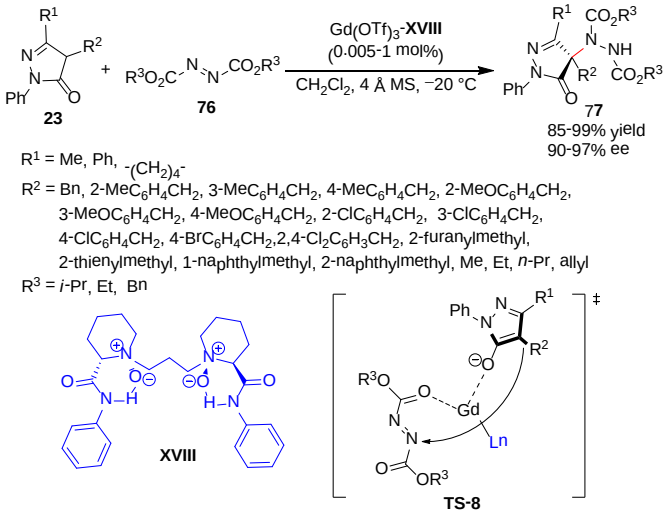
Scheme 21. Enantioselective allylic alkylation of pyrazol-5-ones with primary allylic alcohols.

A highly enantioselective allylic alkylation of pyrazol-5-ones with allylic alcohol was described by Gong and co-workers (Scheme 21).[41] A combination of a palladium complex with a chiral phosphoramidite ligand **XVI** and a chiral phosphoric acid **XVII** efficiently catalyzed the allylic alkylation of various pyrazol-5-ones **23** with primary allylic alcohols **70** to furnish the desired products **71** in high yields with excellent enantioselectivities. The pyrazolone with a phenyl group at C3 (R^2 = Ph) resulted in a good yield but with only 66% ee, whereas C3 unsubstituted pyrazolone (R^2 = H) gave 92% ee albeit with a medium yield of 60%. Under the standard reaction conditions a secondary allylic alcohol **72** also afforded the corresponding allylic adducts **73** in high yield and ee. The allylic alkylation products could be transformed into other valuable multi-functionalized pyrazol-5-one derivatives **74** and **75**. High-resolution mass spectrometry (HRMS) analysis of a mixture of the palladium complex with allylic alcohol **70a** (R^4 = Ph) and phosphoric acid showed that two molecules of the chiral ligand **XVI** are coordinated to palladium. Hence in the proposed reaction pathway, the Pd(**XVI***)$_2$complex **A** initially reacts with the allylic alcohol which in turn is activated by phosphoric acid through hydrogen bonding leading to the elimination of the hydroxy group thus providing the π-allylpalladium(II) complex **C**. Subsequently, the enolizable pyrazol-5-one enters into the catalytic cycle to form the intermediate **D**, where the chiral palladium complex and phosphate counteranion provide the hydrogen-bonding activation and orientation to give rise to the product with high ee, and the chiral palladium(0) complex **A** and phosphoric acid are regenerated for the next catalytic cycle.

2.5 α-Amination

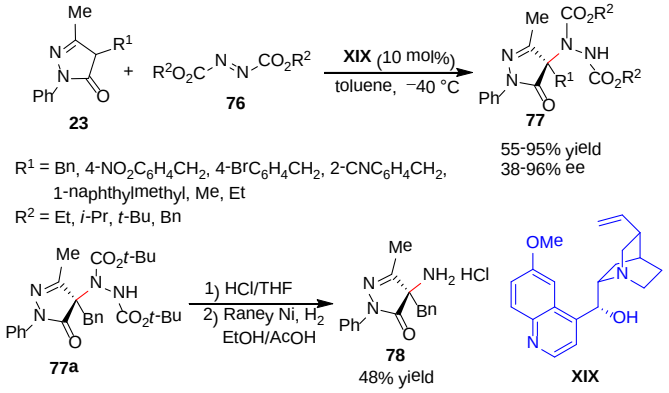
The enantioselective α-amination of 4-substituted pyrazolones was achieved by using chiral organo- and metal catalysts. In 2011 Feng and co-workers developed the first enantioselective α-amination of 4-substituted pyrazolones **23** with azodicarboxylates **76** catalyzed by a N,N′-dioxide **XVIII** gadolinium (III) complex (Scheme 22).[42] This procedure tolerated a wide range of substrates, and high yields and enantioselectivities of 4-amino-5-pyrazolones could be obtained even in the presence of 0.05 mol% of the catalyst. A non-linear relationship between the enantiomeric excess of the ligand **XVIII** and the product suggested that oligomeric aggregates of **XVIII**-$Gd(OTf)_3$ might exist in the reaction system. A successful gram-scale reaction using 0.05 mol% also demonstrates a high turnover number and hence the preparative utility of the process. The reaction was proposed to proceed *via* coordination of the carbonyl group of the pyrazolone with the active **XVIII**-Gd complex to generate an enolate. Simultaneously, the azodicarboxylate also coordinated to the Gd ion through an ester carbonyl group thus facilitating a *Re*-face attack of the enolate to the electrophilic diethyl azodicarboxylate to afford the desired *R*-configured product (**TS-8**).

An enantioselective amination of pyrazolones **23** with dibenzyl azodicarboxylate **76** catalyzed by a commercially available organocatalyst *i.e.* quinine (**XIX**) proceeded with good yields and good to very high enantioselectivities (Scheme 23).[43] The methyl substituted pyrazolone resulted in good yield albeit poor ee, whereas the dibenzyl azodicarboxylate provided the desired product in lower yield and good ee. The steric bulkiness of the alkyl group in the pyrazolone and the azodicarboxylate dramatically affected the



Scheme 22. Enantioselective α-amination of 4-substituted pyrazolones with azodicarboxylates catalyzed by a *N,N'*-dioxide gadolinium (III) complex.

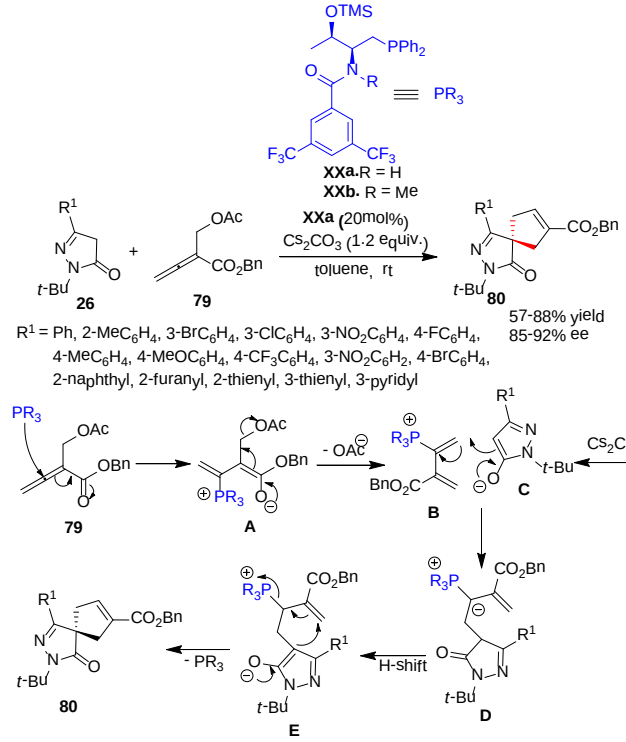
ee of the products as the reaction of methyl or ethyl substituted pyrazolone with diethyl azodicarboxylate instead of diisopropyl azodicarboxylate resulted in an almost racemic product. The aminated product could be converted into amines in acceptable yields without any loss of the enantiomeric purity *via* decarboxylation/reduction.



Scheme 23. Enantioselective α-amination of 4-substituted pyrazolones with azodicarboxylates catalyzed by quinine.

A phosphine **XXa**-catalyzed enantioselective [4+1] annulation reaction of allenoate-derived MBH acetates **79** and pyrazolones **26** led to the formation of the spiropyrazolones **80** in good yields and enantioselectivities (Scheme 24).[44] This [4+1] annulation strategy could be used to synthesize a precursor for the inhibitors of type-4 phosphodiesterase. The proposed mechanism for this annulation reaction involves the nucleophilic addition of the phosphine catalyst to the 2,3-butadienoate, leading to the formation of the intermediate **A**, which by the elimination of an acetate group forms the intermediate **B**. Then the enolate **C** derived from the pyrazolone adds to the γ-carbon position of the intermediate **B**, thus forming a phosphonium ylide **D**, which undergoes a proton transfer to give the intermediate **E**, where an intramolecular Michael addition and elimination of the phosphine catalyst occurs to provide the [4+1] annulation adduct.

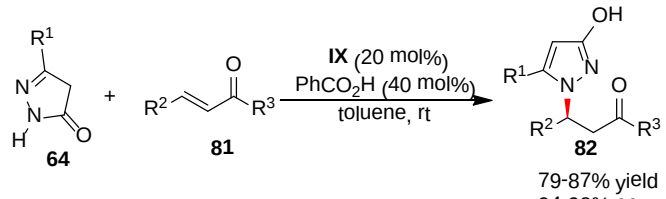
When the reaction was carried out with different amounts of D_2O, the incorporation of deuterium at the β-position of the cycloadduct was observed. These reactions proceeded at a slightly faster reaction rate leading to a lowering of the ee value. However, when the annulation product **80a** (R^1 = Ph) was treated with D_2O, no deuterium incorporation was observed. The reaction performed with a *N*-methylated catalyst led to the formation of the desired product in a significantly reduced yield (36%) and ee-value (19%), which suggests that hydrogen-bonding plays a crucial role in the stereochemical outcome and the reaction rate. This fact was further confirmed by the loss of enantioselectivity when water was added to the reaction. Based on these results, it was proposed that a water molecule participates in the 1,3-proton shift.



Scheme 24. Enantioselective [4+1] annulation reaction of allenoate-derived MBH acetates with pyrazolones.

2. Addition from N-2 of the pyrazolin-5-ones

Zhao and co-workers presented an aza-Michael addition reaction between 2-pyrazolin-5-ones **64** and aliphatic acyclic enones **81** (Scheme 25).[45] Using 9-*epi*-9-amino-9-deoxyquinine (**IX**) as the catalyst and benzoic acid as an additive, β-(3-hydroxypyrazol-1-yl) ketones **82** were easily accessible in good yields and very good enantioselectivities (94-98% ee). However, due to the low reactivity of (*E*)-chalcone and (*E*)-crotonophenone (R^2 = Me), the reaction completely failed to proceed. Furthermore the cyclic enone, cyclohexenone, resulted in the formation of a complex mixture of unidentified products.

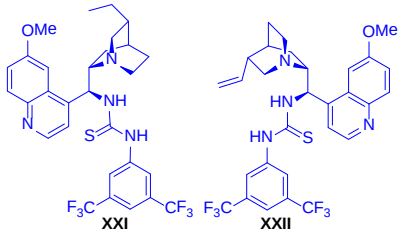


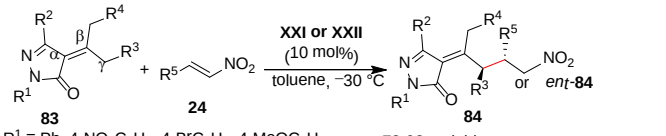
R^1 = Me, Et
R^2 = *n*-Pent, Me, Et, *n*-Bu, n-Hex, *i*-Pr, Bn, $PhCH_2CH_2$
R^3 = Me, Et, *n*-Pr

Scheme 25. Enantioselective aza-Michael addition reaction of 2-pyrazolin-5-ones with aliphatic acyclic enones.

3. Addition from the γ-carbon of the α,β-unsaturated pyrazolones

The group of Rassu and Zanardi used α-alkylidenepyrazolinones **83** as an electron-rich nucleophilic species in an asymmetric vinylogous Michael addition reaction (Scheme 26).[46] In the presence of cinchona-derived aminothiourea catalysts **XXI** and **XXII**, the enolizable α-alkylidenepyrazolinones **83** add efficiently at the β-position to the nitroolefins **24** to afford the adducts **84** in good yields and high levels of stereo- and geometrical selectivities. γ-Substituted α-alkylidenepyrazolinones also provide high enantioselectivities with excellent dr in favour of the *anti*-adduct. Both enantiomeric adducts were easily accessible by employing a *quasi*-enantiomeric quinine- or quinidine-based thiourea catalyst. It was proposed that the tertiary amine of the catalyst first

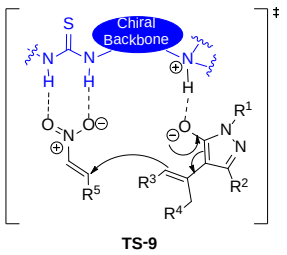




R^1 = Ph, 4-$NO_2C_6H_4$, 4-BrC_6H_4, 4-$MeOC_6H_4$,
R^2 = Me, *n*-Pr, Ph
R^3 = Me, Et
R^4 = Me, Et
R^5 = Ph, 4-BrC_6H_4, 2-FC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-furanyl

73-93% yield
94-99% ee
12:1->20:1 *E*:*Z*
>20:1 dr (*anti*:*syn*)

69-91% yield
69-99% ee
11:1->20:1 *E*:*Z*
>20:1 dr (*anti*:*syn*)

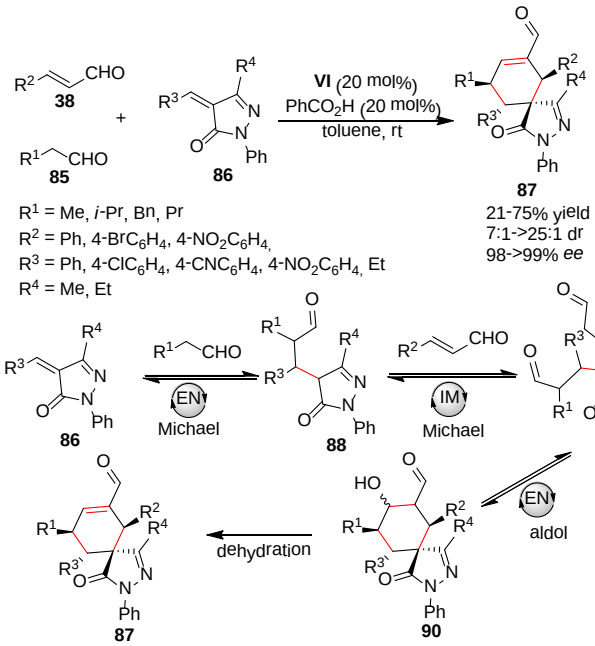


Scheme 26. Aminothiourea catalyzed vinylogous Michael addition of α-alkylidenepyrazolinones to nitroolefins.

deprotonates the alkylidenepyrazolones at the γ-position, and the protonated catalyst then brings the dienolate nucleophile closer to the nitroalkenes, which in turn are activated through hydrogen bonding with the thiourea moiety to facilitate a *Re*-face addition in case of catalyst **XXI** (**TS-9**).

4. Addition to the β-carbon of the α,β-unsaturated pyrazolones

Rios' research group reported a highly stereoselective synthesis of spiropyrazolones *via* a three component organocatlytic Michael/Michael/aldol reaction of aliphatic aldehydes **85**, enals **38** and α,β-unsaturated pyrazolones **86** (Scheme 27).[47] This triple domino sequence provided spiropyrazolonecyclohexenes **87** bearing four contiguous stereocenters in moderate to good yields, good to excellent dr and excellent enantioselectivities. However the presence of a bulky substituent at C-3 (R^4) did not provide any desired product. Another drawback of this methodology includes the formation of complex mixtures of products when aliphatic enals or a glyoxylate-derived enal were used under standard reaction conditions. This domino sequence is initiated by the addition of the aliphatic aldehydes **85** to the unsaturated pyrazolones **86** through the enamine intermediate followed by Michael addition of the corresponding adduct **88** to the enals **38** through an iminium intermediate to afford **89**. This intermediate then undergoes an intramolcular aldol reaction through enamine formation to afford **90** which upon dehydration resulted in the desired product **87**.

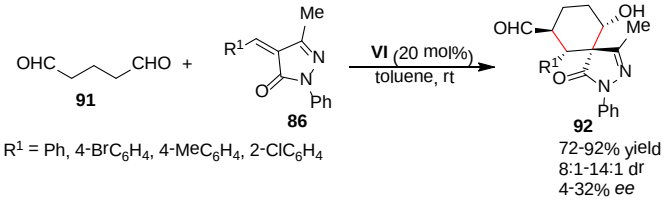


R^1 = Me, *i*-Pr, Bn, Pr
R^2 = Ph, 4-BrC_6H_4, 4-$NO_2C_6H_4$,
R^3 = Ph, 4-ClC_6H_4, 4-CNC_6H_4, 4-$NO_2C_6H_4$, Et
R^4 = Me, Et

21-75% yield
7:1->25:1 dr
98->99% *ee*

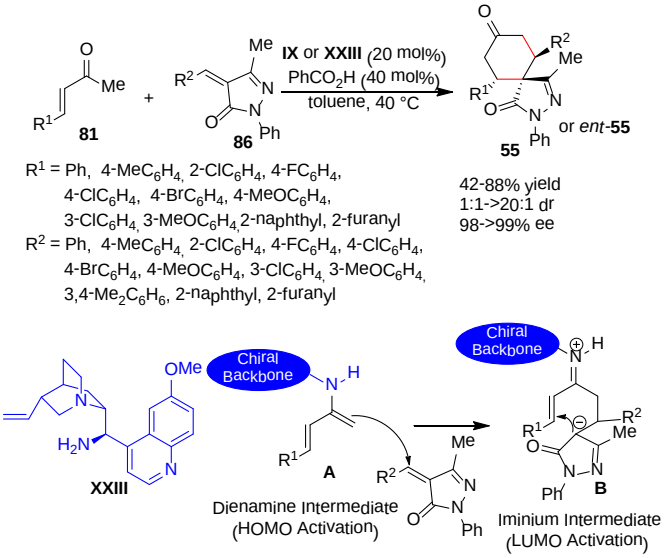
Scheme 27. Stereoselective Michael/Michael/aldol reaction between aliphatic aldehydes, enals and unsaturated pyrazolones.

A secondary amine **VI**-catalyzed domino Michael/aldol reaction between a dialdehyde **91** and α,β-unsaturated pyrazolones **86** resulted in the formation of spirocyclohexanepyrazolones **92** bearing four stereogenic centers with good dr values but with poor enantio-differentiation (Scheme 28).[48]



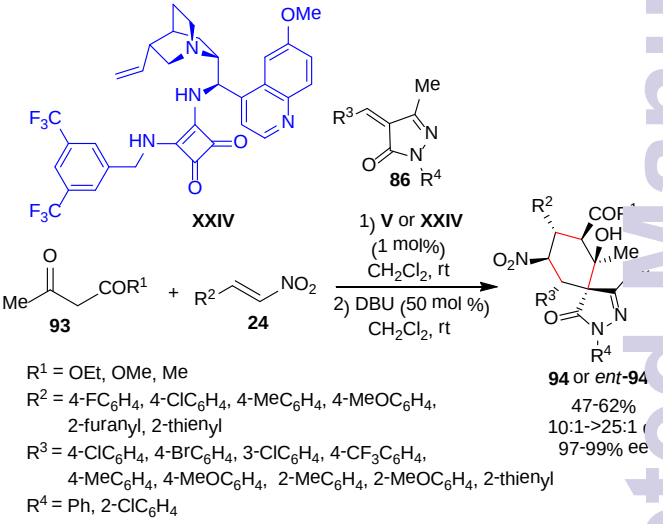
Scheme 28. Domino Michael/aldol reaction between a dialdehyde and α,β-unsaturated pyrazolones.

A double Michael reaction of α,β-unsaturated ketones **81** with α,β-unsaturated pyrazolones **86** provided a simple and effective entry to the spiropyrazolonecyclohexanones **55** with three consecutive stereogenic centers (Scheme 29).[49,50] The reaction pathway of this domino sequence involves HOMO-activation *via* dienamine **A** formed between the α,β-unsaturated ketone and the primary amine catalyst. This dienamine adds to the unsaturated pyrazolones to initiate another Michael addition to the resulting iminium ion **B** (LUMO-activation). With the pseudo-enantiomeric primary amine catalysts **IX** or **XXIII** and benzoic acid as an additive, the reactions proceeded well in most of the cases to provide both enantiomer of the products **55** in excellent stereoselectivities, with the exception of the alkyl-and 4-methyl phenyl substituted unsaturated ketones, which gave a diasteromeric mixture with a ratio of 2:1 dr and 1:1 dr, respectively.[49] The quinidine derived primary amine **XXIII** and 2-fluorobenzoic acid as an additive also catalyzed the similar double Michael reaction with good yields, excellent enantioselectivities and good diastereoselectivities.[50]



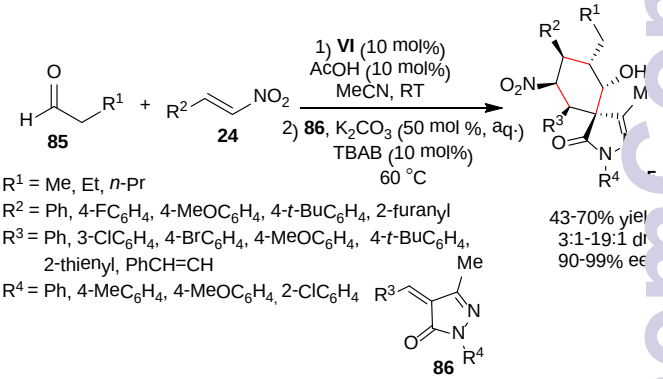
Scheme 29. Stereoselective double Michael reaction of unsaturated ketones and α,β-unsaturated pyrazolones.

Recently our group reported a one-pot sequential Michael/Michael/1,2-addition reaction involving β-dicarbonyl compounds **93**, nitroalkenes **24** and α,β-unsaturated pyrazolones **86** to provide an efficient entry to a new series of spirocyclohexanepyrazolones **94** (Scheme 30).[51] This transformation involves a low loading of the squaramide **V** to catalyze a Michael addition of the β-dicarbonyl compounds to the nitroalkenes followed by a DBU promoted Michael/1,2-addition reaction to afford various spirocyclohexanepyrazolones **94** bearing 3 stereocenters including two tetrasubstituted ones in good yield and excellent stereoselectivities (Scheme 48). The opposite enantiomer of the spirocyclohexanepyrazolones *ent*-**94** could be synthesized with the same level of asymmetric induction just by switching to the *pseudo*-enantiomeric squaramide catalyst **XXIV**. This cascade transformation could be scaled up to a gram level even with a lower loading of the squaramide and without affecting the stereochemical outcome of the reaction.



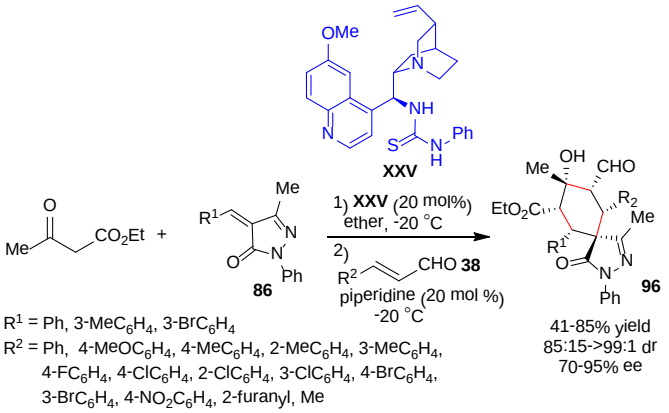
Scheme 30. Stereoselective Michael/Michael/1,2-addition sequence between β-dicarbonyl compounds, nitroalkenes and unsaturated pyrazolones.

Working on a similar project, Peng's group synthesized various fully functionalized spirocyclic cyclohexanes bearing medicinally important pyrazolone, rhodanine, barbituric acid or indandione moieties.[52] In this sequential reaction, the initial Michael addition of the aliphatic aldehydes **85** to the β-nitroalkenes **24** was catalyzed by the α,α-diphenyl prolinol trimethylsilyl ether and followed by the addition of unsaturated pyrazolones **86**, rhodanines, barbituric acids or indandiones under phase transfer conditions to accomplish the subsequent Michael/aldol addition sequence. A series of spirocyclohexanepyrazolones **95** were obtained in good yields, moderate to good dr and high ee (Scheme 31).



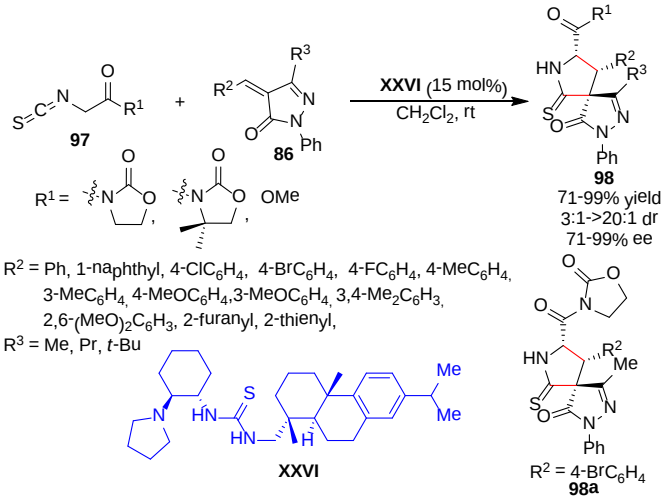
Scheme 31. Stereoselective Michael/Michael/1,2-addition sequence between aliphatic aldehydes, nitroalkenes and α,β-unsaturated pyrazolones.

Similar types of spirocyclohexanepyrazolones **96** could be synthesized by a slightly different one-pot sequential Michael/Michael/aldol reaction sequence involving an initial thiourea **XXV**-catalyzed asymmetric addition of ethyl acetoacetate to unsaturated pyrazolones **86**, followed by the piperidine catalyzed Michael/aldol addition sequence between the corresponding Michael adducts and the α,β-unsaturated aldehydes **38** (Scheme 32).[53] This method provided an efficient entry to the spirocyclohexanepyrazolones bearing six consecutive stereogenic centers with moderate to good enantioselectivities and good to excellent diastereoselectivities.



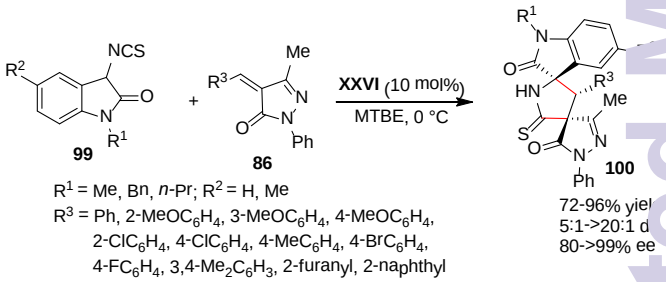
Scheme 32. Stereoselective Michael/Michael/1,2-addition sequence between a β-ketoester, α,β-unsaturated pyrazolones and enals.

Wang and co-workers developed a rosin-derived tertiary amine-thiourea **XXVI**-catalyzed stereoselective Michael addition/cyclization of α-isothiocyanato imides and esters **97** with a variety of α,β-unsaturated pyrazolones **86** to afford the functionalized spiropyrazolones **98** containing three vicinal stereogenic centers in good to high levels of diastereo- and enantioselectivity (up to 20:1 dr and 99% ee) (Scheme 33).[54] The evaluation of these new spiropyrazolones for their cytotoxicity *in vitro* towards the human T-cell leukemia cell line (jurkat), human cervical cancer cell line (Hela), and human bladder cancer cell line (5637) showed that spiropyrazolone **98a** exhibited noticeable antiproliferative activity.



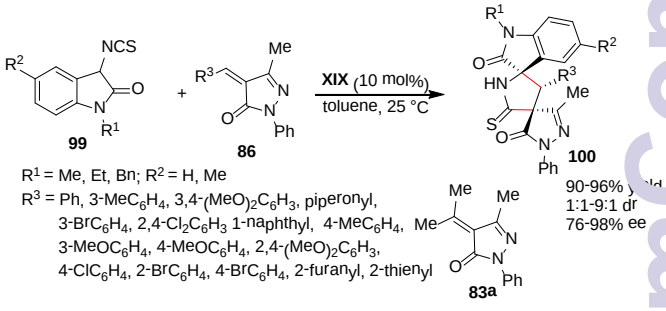
Scheme 33. Asymmetric Michael addition/cyclization of α-isothiocyanato imides and esters with α,β-unsaturated pyrazolones.

A closely related asymmetric domino Michael addition/cyclization reaction of 3-isothiocyanato-2-oxindoles **99** with various aryl substituted α,β-unsaturated pyrazolones **86** catalyzed by the same tertiary amine-thiourea **XXVI** provided spiro[oxindole/thiobutyrolactam/pyrazolone] derivates **100** containing three contiguous stereogenic centers, in good to high yields and good to excellent stereoselectivities (Scheme 34).[55] The alkyl substituted unsaturated pyrazolones **86** gave the desired product in good yield (82%) and high diastereoselectivity (20: 1 dr) albeit poor enantioselectivity (11% ee). It is worth mentioning that the catalyst loading of only 0.2 mol% was sufficient for a relatively large-scale reaction without a noticeable alteration in the enantioselectivity.



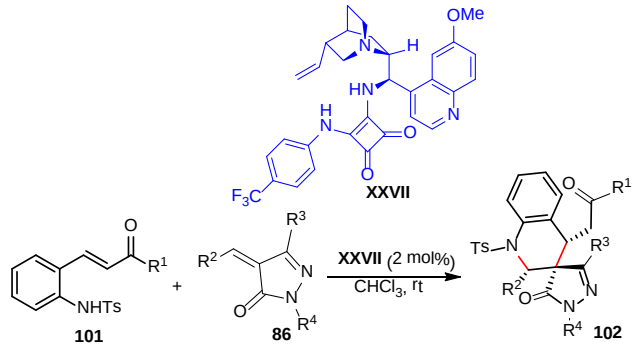
Scheme 34. Thiourea catalyzed asymmetric Michael addition/cyclization reaction of isothiocyanato oxindoles with α,β-unsaturated pyrazolones.

A similar asymmetric Michael/cyclization reaction of 3-isothiocyanato-2-oxindoles **99** with α,β-unsaturated pyrazolones **86**, promoted by commercially available quinine **XIX** as the catalyst under mild reaction conditions, provides the same spiro[oxindole/thiobutyrolactam/pyrazolone] derivatives **100** in excellent yields with none to good diastereo-differentiation and moderate to high enantioselectivities (Scheme 35).[56] The quinine catalyzed reaction of β,β-dialkyl α,β-unsaturated pyrazolones **83a** with 3-isothiocyanato-2-oxindole gave the corresponding product in 98% yield and >99:1 dr, but with only 2% ee. Quinine also catalyzed the asymmetric Michael addition/cyclization reaction of 3-isothiocyanato-2-oxindoles with α,β-unsaturated isoxazolones to give the spiroisoaxzole derivatives.



Scheme 35. Ouinine catalyzed asymmetric Michael addition/cyclization reaction of isothiocyanato oxindoles with α,β-unsaturated pyrazolones.

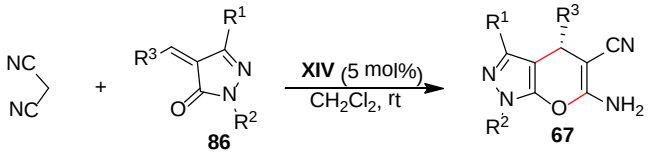
An aminosquaramide catalyzed stereoselective domino aza-Michael/Michael addition of 2-tosylaminoenones **101** with unsaturated pyrazolones **86** afforded a new series of spiropyrazolones **102** with a tetrahydroquinoline ring bearing three contiguous stereocenters in good to excellent yields, excellent diastereoselectivities and good enantioselectivities (Scheme 36).[57] The aryl-substituted unsaturated pyrazolones worked very well under the standard reaction conditions, however, an alkyl (R^2 = *i*-Pr) substituted pyrazolone resulted in a lower yield (43% yield) and stereoselectivity (9:1 dr and 60% ee).



R^1 = Ph, 4-ClC_6H_4, 4-BrC_6H_4, 4-$MeOC_6H_4$, 2-$MeOC_6H_4$, *t*-Bu
R^2 = Ph, 4-ClC_6H_4, 4-BrC_6H_4, 4-FC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 2-BrC_6H_4, 2-$MeOC_6H_4$, 2-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, *i*-Pr
R^3 = Me, Ph
R^4 = Ph, 4-ClC_6H_4, 4-MeC_6H_4,

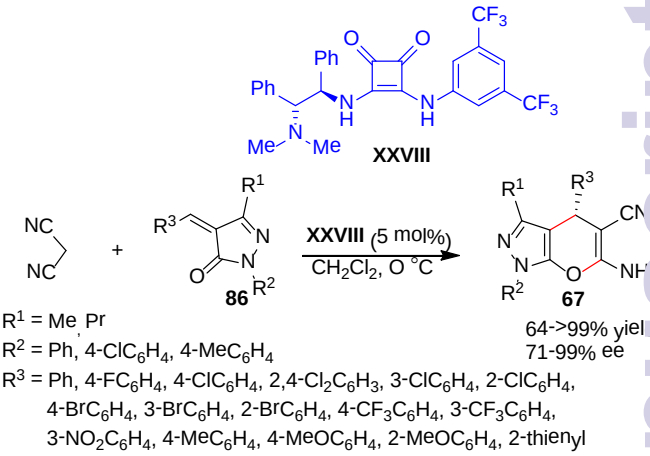
Scheme 36. Domino aza-Michael/Michael reaction of 2-tosylaminoenones with α,β-unsaturated pyrazolones.

An enantioselective domino Michael/Thorpe-Ziegler type reaction of α,β-unsaturated pyrazolones with malononitrile provided a direct entry to dihydropyrano[2,3-c]pyrazole derivatives. With a cinchona derived squaramide **XIV**, a variety of arylidenepyrazolones **86** reacted with malononitrile to give a series of dihydropyano[2,3-c]pyrazoles **67** in high yields and moderate enantioselectivities in a very short reaction time (Scheme 37),[39] whereas the squaramide **XXVIII** derived from (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine furnished the desired pyrano[2,3-c]pyrazoles **67** in moderate to excellent yields and enantioselectivities (Scheme 38).[58] The diaminocyclohexane-thiourea catalyzed enantioselective Michael addition and Thorpe-Ziegler type cyclisation also leads to the synthesis of functionalized fluorinated dihydropyrano[2,3-c]pyrazoles.[59]



R^1 = Me, Ph, CF_3
R^2 = Ph, 4-ClC_6H_4, 4-MeC_6H_4
R^3 = Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 2-BrC_6H_4, 2-$NO_2C_6H_4$, 3-$MeOC_6H_4$, 3-$NO_2C_6H_4$,

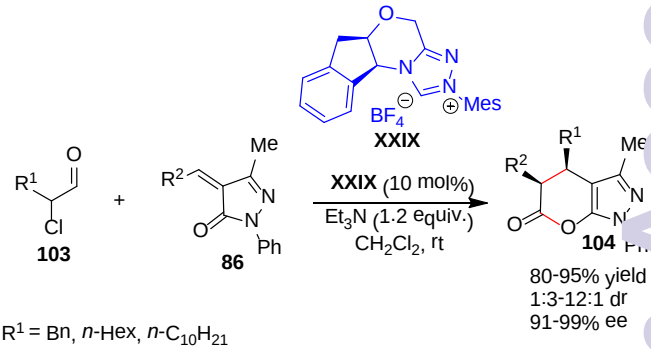
Scheme 37. Cinchona derived squaramide catalyzed enantioselective domino Michael/Thorpe-Ziegler type reaction.



R^1 = Me, Pr
R^2 = Ph, 4-ClC_6H_4, 4-MeC_6H_4
R^3 = Ph, 4-FC_6H_4, 4-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 3-ClC_6H_4, 2-ClC_6H_4, 4-BrC_6H_4, 3-BrC_6H_4, 2-BrC_6H_4, 4-$CF_3C_6H_4$, 3-$CF_3C_6H_4$, 3-$NO_2C_6H_4$, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-$MeOC_6H_4$, 2-thienyl

Scheme 38. (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine derived squaramide catalyzed enantioselective domino Michael/Thorpe-Ziegler type reaction.

An asymmetric NHC-catalyzed [4+2] annulation of α-chloroaldehydes **103** and 4-arylidenylpyrazolones **86** was developed by Ye's group (Scheme 39).[60] Using triazolium salt **XXIX** as NHC precursor, the chloroaldehydes **103** reacted well with unsaturated pyrazolones **86** to yield the dihydropyrano[2,3-c]pyrazol-6-(1*H*)-ones **104** in high yields with good diastereoselectivities and excellent enantioselectivities. Generally *cis*-cycloadducts were formed, however when o-chlorophenyl and 1-naphthyl bearing arylidenylpyrazolones were used, the diastereoselectivity switched to favor the *trans*-cycloadduct.

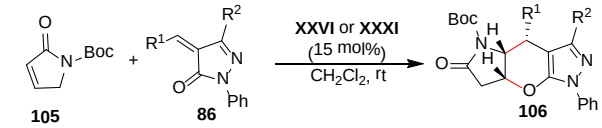


R^1 = Bn, *n*-Hex, *n*-$C_{10}H_{21}$
R^2 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-FC_6H_4, 4-BrC_6H_4, 4-CNC_6H_4, 3-MeC_6H_4, 3-$MeOC_6H_4$, 3-ClC_6H_4, 2-ClC_6H_4, 1-naphthyl

Scheme 39. NHC-catalyzed [4+2] annulation of α-chloroaldehydes with 4-arylidenylpyrazolones.

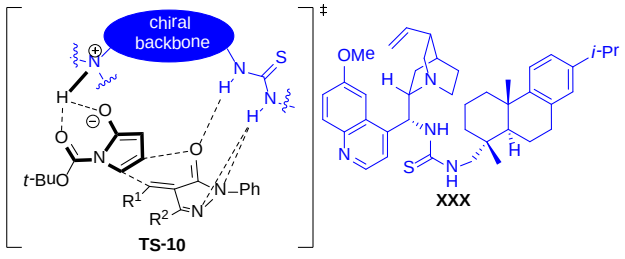
Wang and co-workers described a highly efficient β,γ-selective [4+2] cycloaddition of α,β-unsaturated γ-butyrolactams **105** with unsaturated pyrazolones **86**.[61] This strategy employs a rosin-derived aminothiourea **XXVI** as the catalyst to afford various bridged bi- or tricyclic dihydropyranopyrrolidin-2-one skeletons **106** (Scheme 40). The thiourea catalyst **XXVI** worked well for the unsaturated pyrazolone bearing a C3 phenyl group, whereas the cinchona derived catalysts **XXX** provided better enantioselectivity in the case of C3 alkyl substituted pyrazolones. The various 4-aryl substituted pyrazolones gave the desired products in good yields with high ee and excellent dr, and the 2-thienyl substituted pyrazolone gave good yields with >20:1 dr albeit lower ee-value of

56%. On the other hand a lactone was proved to be inactive for the [4+2] annulation. In the proposed transition state **TS-10**, the thiourea moiety activates the unsaturated pyrazolone through weak hydrogen bonds (lowering of the LUMO energy), while simultaneously the tertiary amine of the catalyst forms a dienolate, thus activating the β,γ-positions of α,β-unsaturated γ-butyrolactams (raising of the HOMO energy), which may enforce a high *Re*-face and *endo*-β,γ-selectivity to afford the desired products with the observed absolute configuration.



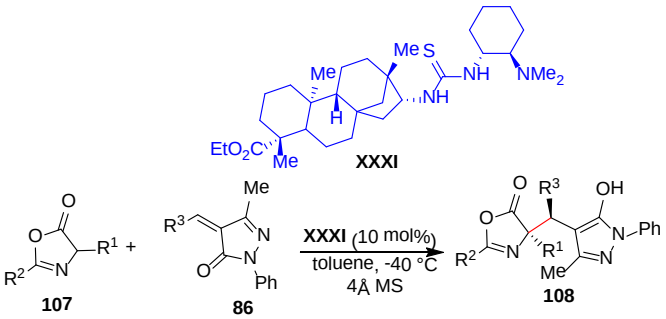
R^1 = Ph, 4-FC_6H_4, 4-ClC_6H_4, 2-BrC_6H_4, 2-ClC_6H_4, 4-BrC_6H_4, 3-BrC_6H_4, 4-MeC_6H_4, 3-MeC_6H_4, 3,4-$Me_2C_6H_4$, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 2-thienyl, 2-naphthyl

R^2 = Ph, Me, *n*-Pr, *t*-Bu



Scheme 40. Stereoselective β,γ-selective [4+2] cycloaddition of α,β-unsaturated β-butyrolactams with α,β-unsaturated pyrazolones

A bifunctional amine thiourea **XXXI**, derived from isosteviol catalyzed the enantioselective Michael addition of azlactones **107** to α,β-unsaturated pyrazolones **86** with complete C-4 regioselectivity.[62] A series of heterocyclic adducts **108** bearing a pyrazole moiety and azlactone - a masked amino acid structure, was easily synthesized in good yields with moderate to high enantioselectivities and very good dr. The azlactone bearing an alkyl group at the R^2 position however failed to provide the desired product, even when using a higher catalyst loading of 30 mol% at room temperature.



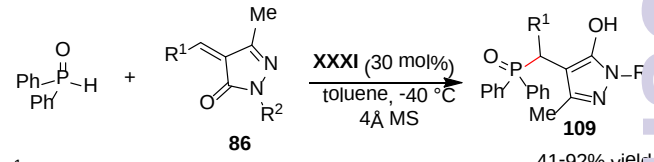
R^1 = Bn, *i*-Bu, *i*-Pr, 2-(methylthio)ethyl

R^2 = Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-MeC_6H_4

R^3 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$MeSC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 2-naphthyl, 2,4-$Cl_2C_6H_3$

Scheme 41. Enantioselective Michael addition of azlactones to the α,β-unsaturated pyrazolones.

The addition of diphenylphosphane oxide to the α,β-unsaturated pyrazolones **86** proceeded rapidly at room temperature with high yields under catalyst-free conditions however with an isosteviol derived thiourea **XXXI** a similar phosphine Michael addition led to the formation of pyrazole product **109** in moderate to good yields and moderate enantioselectivities.[63]



R^1 = Ph, 4-ClC_6H_4, 4-BrC_6H_4, 3-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$MeSC_6H_4$, 2-naphthyl, 2-furanyl

R^2 = Ph, 4-BrC_6H_4, 4-ClC_6H_4

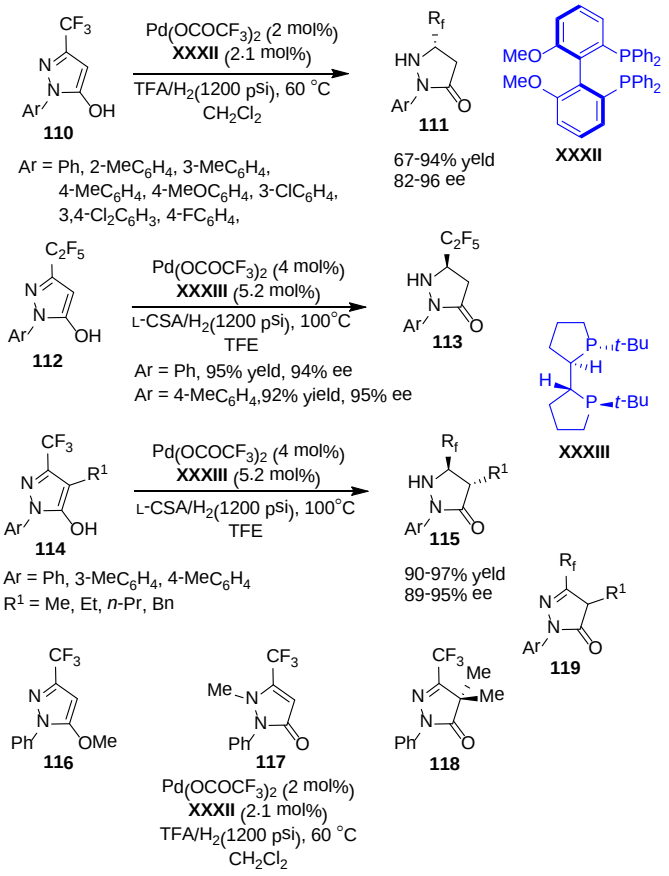
Scheme 42. Enantioselective Michael addition of diphenylphosphane oxide to α,β-unsaturated pyrazolones.

5. Asymmetric hydrogenation of pyrazol-5-ones

Very recently highly efficient palladium-catalyzed asymmetric hydrogenations of fluorinated pyrazol-5-ols have been published (Scheme 43).[64] The enantioselective hydrogenation of trifluoromethylated aromatic pyrazol-5-ols **110** takes place in the presence of (*S*)-MeO-Biphep ligands **XXXII** to afford a wide variety of 2,5-disubstituted pyrazolidinones **111** in high yields and enantioselectivities. However, the hydrogenation of 2-*o*-tolyl-substituted pyrazol-5-ol proceeded with moderate enantioselectivity of 82% ee and 67% yield even with a higher catalyst loading. In the presence of TangPhos **XXXIII**, the hydrogenation of pentafluoroethyl substituted pyrazol-5-ols **112** and 4-substituted 3-(trifluoromethyl)-1H-pyrazol-5-ols **114** occured at higher temperature to provide the corresponding pyrazolidinones **113** and **115** with high stereocontrol. In order to evaluate the mechanism, the hydrogenation of the substrates **116-118** were carried out under optimized reaction conditions. No reaction was observed with substrate **116** whereas substrate **117** gave a low yield (14%) and ee-value (10%). On the other hand, the substrate **118** gave an excellent ee of 91% with 89% yield. Based on these experimental results it was proposed that the reaction occurs *via* Brønsted acid promoted tautomerization to form the CH–form tautomer **119**, followed by the Pd-catalyzed asymmetric hydrogenation of the active tautomer to give the enantiopure pyrazolidinones.

Conclusions

The examples described in this feature article demonstrate the usefulness of the pyrazolin-5-one substrates for the asymmetric synthesis of valuable pyrazole and pyrazolone derivatives. Due to the presence of many reactive cites, these substrates offer numerous possibilities for functionalisation and hence, within a short span of five years a significant number of relevant publications has been reported in the



Scheme 43. Asymmetric hydrogenations of fluorinated pyrazol-5-ols.

literature. Using chiral organo- and metal catalysts, various simple C-C and C-X bond formations as well as cascade sequences involving the pyrazolin-5-one substrates provide diversely functionalised pyrazoles and pyrazolones in high stereoselectivities. The enantiopure pyrazolones, especially the spirocyclic ones, when tested for their bioactivities, showed great potential. Further applications of these pyrazolin-5-one substrates in asymmetric transformations can be expected in the near future.

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