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

Pankaj Chauhan, Suruchi Mahajan and Dieter Enders*

Due to the frequent occurrence of the pyrazole core in many important naturally occurring 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 have 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. 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). Many synthetic pyrazole derivatives also possess medicinal value. For example, remogliflozin etabonate (7) is a drug proposed for the treatment of type 2 diabetes, whereas celecoxib (8) and mavacoxib (9) 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. Other synthetic compounds bearing a pyrazole ring possess different bioactivities such as the dihydropyran[2,3-c]pyrazole derivative 10, which is a human chk1 kinase inhibitor, whereas the pyranopyrazoles 11, 12 and 13 show antibacterial, analgesic and antiplatelet activities, respectively. The annulated pyrazole 14 is an AMPA receptor activity enhancer and 15 is a fungicide.

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Pyrazolones are another important class of pyrazole heterocycles possessing important biological properties and they have been known for more than one century. The pyrazolone phenazone (16), 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). The pyrazolone edaravone (18) is a neuroprotective agent. The pyrazolone derivatives 19-22 act as p38 inhibitors, HIV integrase inhibitors, type 4-phosphodiesterase inhibitor, and antibacterial agent, 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 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 $R^1 = \text{alkyl}$ or aryl), or pyrazole derivatives (when $R^3 = \text{H}$). The latter can also undergo a subsequent reaction (cyclisation) with another electrophile through the C-4 and the C-5 OH functionalities. Moreover, the N1-unsubstituted pyrazolin-5-one derivatives (R$^3 = \text{H}$) are suitable substrates foraza-Michael additions. The α,β-unsaturated pyrazolones D bearing a vinylhydrogen have been exploited for asymmetric vinylogous Michael 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.

Dieter Enders was born in 1946 in Butzbach, Germany, studied chemistry at the University of Giessen and completed his PhD under the supervision of Professor D. Seebach in 1974. After postdoctoral research at Harvard University with Professor E. J. Corey he returned to Giessen and obtained his habilitation in 1979. In 1980 he moved to the University of Bonn as an Associate Professor, and in 1985 to his present position as Professor of Organic Chemistry at the RWTH Aachen University. His research interests are asymmetric synthesis, the synthesis of biologically active compounds and organocatalysis. He has been the recipient of many awards including the Leibniz Prize, the Yamada Prize, the Max Planck Research Award, the Emil Fischer Medal, the Arthur C. Cope Senior Scholar Award, the Robert Robinson Award, the ERC Advanced Grant, and the Ryöji Noyori Prize. He is a member of the German Academy of Sciences Leopoldina.

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

Figure 2. Pyrazolone drugs and bioactive compounds.

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. 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). 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 R² and an ethyl or allyl group at R¹ 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.

Ma's research group reported an organocatalytic sequential 1,4-addition/dearomative-fluorination reaction of pyrazolones with nitroolefins and N-fluorobenzensulfonylamide (NFSI) (Scheme 3). The process involves the initial enantioselective Michael addition of pyrazolones 26 to the various nitroolefins 24 catalyzed by an 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-furan-substituted nitroalkene, which gives the desired product only in moderated diastereoselectivities. 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 pyrazoline 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 nitroalkene, 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 28 in good to excellent yields and high enantioselectivities (Scheme 4). The one-pot Michael additions and subsequent dearomative chlorination with N-chlorosuccinimidine (NCS) catalyzed by the aminothiourea II and benzoic acid led to the formation of the chlorinated pyrazolones 29 bearing a tertiary and tetrasubstituted chlorinated stereogenic center with excellent yields and ee-values and with moderate to excellent diastereomeric ratios.

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

Scheme 3. Organocatalytic sequential 1,4-addition/dearomative-fluorination reaction of pyrazolones with nitroolefins and NFSI.
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R3
R3
R3
NO2
O
NO2
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Moderate to excellent yields and moderate to good enantioselective Michael addition of pyrazolin-5-ones between pyrazolones bearing tertiarystereocenters (Scheme 5).25 The initial Michael addition was catalyzed by a bifunctional aminosquaramide catalyst. 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.

A very low loading of the squaramide catalyzed the enantioselective Michael addition of pyrazolin-5-ones to nitroalkenes. 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 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.

An 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 containing chroman and pyrazolone units (Scheme 7).27 This transformation catalyzed by a low loading of a squaramide catalyst afforded the desired products with 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 = CH2 only 71% ee and with X = S 88% ee was obtained. In addition, an acyclic nitroalkene i.e. α-methyl-β-nitrostyrene (13) possesses lower reactivity and hence 2.0 mol% of the squaramide 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 by combining organo- and metal catalysis (Scheme 8).28 This sequential catalytic reaction...
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 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 disubstituted 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).

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 tetrahydropyran[2,3-c]pyrazoles 43 via a subsequent 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). Good yields (71–91%) and good to high enantioselectivities were obtained with different pyrazolone-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 pyrazolone-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 enantomer. 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/oxytocin 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 divergent 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 IC50 values in the range of 4.4 to 8.9 μM.

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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 S1, 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 spirocyclohexane pyrazolones 55 (Scheme 13). 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 variousaryl substituted dienones, however a switch in the diastereoselectivity (1:2 dr) was observed with a heteroaryl (2-thienyl) substituted dienone. In contrast, the dienone VIII (5 mol%) and VIII (1 equiv.) toluene, 25°C+

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

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

The metal/NW 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-pyrazolone derivatives 57 (Scheme 14). 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 reactions 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 more oligomeric aggregates of Sc(OEt)3/X or Y(OEt)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 radius 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 alkynes 58 catalyzed by an N,N'-dioxide XI-scandium(III) complex resulted in the formation of 4-alkenylpyrazol-5-ones 59 with high geometric control, good to high yields.

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

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be the major catalytically active derivatives. 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 alkyne 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 aminosquaric acid XII-catalyzed enantioselective Michael addition of pyrazolin-5-ones 26 to aryl substituted β,y-unsaturated α-ketoesters 60 provides a straightforward entry to the optically active pyrazoline derivatives 61 in good to excellent yields and low to high enantioselectivities (Scheme 16).36

A bifunctional aminothiourea ent-l promoted enantioselective addition of pyrazolones 23 to N-aryl maleimides 63 afforded the corresponding pyrazolones 66 bearing vicinal quaternary and tertiary stereocenters 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 diastereomer. 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 the maleimide and pyrazolones with the thiourea and the tertiary amine of the catalyst occurs through hydrogen-bonding.
2.3 Addition to arylidenemalononitriles

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.

2.4 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). However, a low yield (55%) and poor enantioselectivity (13% ee) for the MBH carbonate bearing a heteroaryl group (R² = 2-furanyl) were observed.

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

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

Scheme 20. Asymmetric allylic alkylation of MBH carbonates with pyrazolones.
A highly enantioselective allylic alkylation of pyrazol-5-ones with allylic alcohol was described by Gong and co-workers (Scheme 21). A combination of a palladium complex with a chiral phosphoric acid \( \text{XVI} \) and a chiral phosphoric acid \( \text{XVII} \) efficiently catalyzed the allylic alkylation of various pyrazol-5-ones \( \text{23a} \) with primary allylic alcohols \( \text{70} \) to furnish the desired products \( \text{71} \) in high yields with excellent enantioselectivities. The pyrazolone with a phenyl group at C3 \( (R^2 = \text{Ph}) \) resulted in a good yield but with only 66% ee, whereas C3 unsubstituted pyrazolone \( (R^2 = \text{H}) \) gave 92% ee albeit with a medium yield of 60%. Under the standard reaction conditions a secondary allylic alcohol \( \text{72} \) also afforded the corresponding allylic adducts \( \text{73} \) in high yield and ee. The allylic alkylation products could be transformed into other valuable multifunctionalized pyrazol-5-one derivatives \( \text{74} \) and \( \text{75} \). High-resolution mass spectrometry (HRMS) analysis of a mixture of the palladium complex with allylic alcohol \( \text{70a} \) \( (R^2 = \text{Ph}) \) and phosphoric acid showed that two molecules of the chiral ligand \( \text{XVI} \) are coordinated to palladium. Hence in the proposed reaction pathway, the \( \text{Pd(XVI)2} \) complex \( \text{A} \) 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 \( \pi \)-allyl palladium(II) complex \( \text{C} \). Subsequently, the enolizable pyrazol-5-one enters into the catalytic cycle to form the intermediate \( \text{D} \), 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 \( \text{A} \) and phosphoric acid are regenerated for the next catalytic cycle.

2.5 \( \alpha \)-Amination

The enantioselective \( \alpha \)-amination of 4-substituted pyrazolones was achieved by using chiral organo- and metal catalysts. In 2011 Feng and co-workers developed the first enantioselective \( \alpha \)-amination of 4-substituted pyrazolones \( \text{23} \) with azodicarboxylates \( \text{76} \) catalyzed by a N,N'-dioxide \( \text{XVIII} \) gadolinium (III) complex (Scheme 22). 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 \( \text{XVIII} \) and the product suggested that oligomeric aggregates \( \text{XVIII-Gd(OTf)3} \) 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. This reaction was proposed to proceed via coordination of the carbon group of the pyrazolone with the active \( \text{XVIII-Gd} \) complex to generate an enolate. Simultaneously, the azodicarboxylate also coordinate 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 \( \text{TS-8} \).

An enantioselective amination of pyrazolones \( \text{23} \) with dibenzyl azodicarboxylate \( \text{76} \) catalyzed by a commercially available organocatalyst i.e. quinine \( \text{XIX} \) proceeded with good yields and in good to very high enantioselectivities (Scheme 23). The method 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
When the reaction was carried out with different amounts of D$_2$O, the incorporation of deuterium at the β-position of the cycloadduct was observed. These reactions proceeded at 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$_2$O, 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.


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).\cite{26} Using 9-epi-9-amino-9-deoxyquinine (IX) as the catalyst and benzoic acid as an additive, 6-(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 ($R^1 = Me$), the reactions completely failed to proceed. Furthermore the cyclic enone cyclohexenone, resulted in the formation of a complex mixture of unidentified products.

A phosphine XXa-catalyzed enantioselective [4+1] annihilation 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).\cite{44} This [4+1] annihilation strategy could be used to synthesize a precursor for the inhibitors of type-4 phosphodiesterase. The proposed mechanism for this annihilation 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] annihilation adduct.
3. Addition from the γ-carbon of the α,β-unsaturated pyrazolones

The group of Rassu and Zanardi used α-alkyldene pyrazolinones 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-alkyldene pyrazolinones 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-alkyldene pyrazolinones 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 deprotonates the α-alkyldene pyrazolinones at the γ-position, and the protonated catalyst then brings the dienolate nucleophile closer to the nitroalkene, which in turn are activated through hydrogen bonding with the thiourea moiety to facilitate a Re-face addition of the 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 organocatalytic Michael/Michael/aldol reaction of aliphatic aldehydes 85, enals 28 and α,β-unsaturated pyrazolones 86 (Scheme 27).47 This triple domino sequence provides spiropyrazolone cyclohexenes 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 (R4) 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 intramolecular aldol reaction through enamine formation to afford 90 which upon dehydration resulted in the desired product 87.

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

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

**Scheme 26.** Aminothiourea catalyzed vinylogous Michael addition of α-alkyldene pyrazolinones to nitroolefins.

**Scheme 27.** Stereoselective Michael/Michael/aldol reaction between aliphatic aldehydes, enals and unsaturated pyrazolones.
addition of the compounds 86 involves a low loading of the squaramide Michael/Michael/1,2-addition reaction. The exception of the alkyl- and 4-methyl phenyl substituted enantiomer of the products, 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. The quinidine derived primary amine catalysts IX or XXIII and 2-fluorobenzoic acid as an additive also provided a simple and effective entry to the spiropyrazolone cyclohexanones effective entry to the spiropyrazolone cyclohexanones. This 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.

Working on a similar project, Peng’s group synthesized various fully functionalized spirocyclohexanones bearing medicinally important pyrazolone, rhodanine, barbituric acid or indandione moieties. In this sequential reaction, the initial Michael addition of the aliphatic aldehydes 85 to the β-nitroalkenes 24 was catalyzed by the α,β-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).

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). This transformation involves 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 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.

A double Michael reaction of α,β-unsaturated ketones 81 with α,β-unsaturated pyrazolones 86 provided a simple and effective entry to the spiroprazolone cyclohexanones 55 with three consecutive stereogenic centers (Scheme 29). 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. 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. Working on a similar project, Peng’s group synthesized various fully functionalized spirocyclohexanones bearing medicinally important pyrazolone, rhodanine, barbituric acid or indandione moieties. In this sequential reaction, the initial Michael addition of the aliphatic aldehydes 85 to the β-nitroalkenes 24 was catalyzed by the α,β-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).
Similar types of spirocyclohexane pyrazolones 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). This method provided an efficient entry to the spirocyclohexane pyrazolones bearing six consecutive stereogenic centers with moderate to good enantioselectivities and good to excellent diastereoselectivities.

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). 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.

A closely related asymmetric domino Michael addition/cyclization reaction of 3-isothiocyanato-2-oxindoles 86 with various aryl substituted α,β-unsaturated pyrazolones 86 catalyzed by the same tertiary amine-thiourea XXVI provided spiro[oxindole/thiobutyrolactam/pyrazolone] derivatives 100 containing three contiguous stereogenic centers, in good to high yields and good to excellent stereoselectivities (Scheme 34). The alky 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.

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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 (R2 = i-Pr) substituted pyrazolone resulted in a lower yield (43% yield) and stereoselectivity (9:1 dr and 60% ee).

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 dihydropyranopyrrolidin-2-one skeletons with contiguous stereocenters under the standard reaction conditions, however, an alkyl (R2 = i-Pr) substituted pyrazolone resulted in a lower yield (43% yield) and stereoselectivity (9:1 dr and 60% ee).

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

Wang and co-workers described a highly efficient β,γ selective [4+2] cycloaddition of α,β-unsaturated γ-butylolactams 105 with unsaturated pyrazolones 86.61 This strategy employed 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 43-99% yield and 67-91% ee.

Scheme 38. (1R,2R)-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-arylideneypyrazolones 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 dihydropyranopyrazol-6-(1H)ones 104 in high yields with good diastereoselectivities and excellent enantioselectivities. Generally cis-cycloadducts were formed, however when o-chlorophenyl and 1-naphthyl bearing arylideneypyrazolones were used, the diastereoselectivity switched to favor the trans-cycloadduct.
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 βγ-positions of αβ-unsaturated γ-butyrolactams (raising of the HOMO energy), which may enforce a high Re-face and endo βγ-selectivity to afford the desired products with the observed absolute configuration.

\[
\text{Scheme 40. Stereoselective [B,γ-selective [4+2] cycloaddition of αβ-unsaturated β-butyrolactams with αβ-unsaturated pyrazolones}
\]

A bifunctional amine thiourea XXXI, derived from isosteviol catalyzed the enantioselective Michael addition of azlactones to αβ-unsaturated pyrazolones 86 with complete C-4 regioselectivity. 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 R1 position however failed to provide the desired product, even when using a higher catalyst loading of 30 mol% at room temperature.

\[
\text{Scheme 41. Enantioselective Michael addition of azlactones to the αβ-unsaturated pyrazolones}
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The addition of diphenylphosphane oxide to the αβ-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.

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\text{Scheme 42. Enantioselective Michael addition of diphenylphosphane oxide to αβ-unsaturated pyrazolones}
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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). 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-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 pentfluoroethyl substituted pyrazol-5-ols 112 and 4-substituted 3-(trifluoromethyl)-1H-pyrazol-5-ols 114 occurred 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 functionalisations and hence, within a short span of five years a significant number of relevant publications has been reported in the
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.

Notes and references


