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Chiral Squaramide Catalyzed Synthesis of C4 Substituted Chiral Pyrazol-3-ol Derivatives via A Facile Asymmetric Michael addition of 3-Methyl-2-pyrazolin-5-one to β-Nitrostyrenes

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ABSTRACT

Asymmetric Michael addition of 3-methyl-2-pyrazolin-5-one to β-nitrostyrenes, catalyzed by a series of chiral squaramide bifunctional catalysts derived from cinchona alkaloids, yielded chiral pyrazol-3-ol derivatives. These pyrazol-3-ol derivatives were obtained in moderate to high yields with good enantioselectivities under mild conditions by using 1 mol% of the catalyst. This reaction affords valuable and easy access to chiral 5-methyl-4-(2-nitro-1-arylethyl) pyrazol-3-ol derivatives.

1. Introduction

The structural scaffolds of five-membered heterocyclic compounds containing two adjacent nitrogen atoms, such as pyrazoles, pyrazolones and pyrazolols are predominantly found in numerous bioactive compounds.[1] Among them, pyrazolone derivatives[2] are well known five-membered heterocyclic lactams widely found in medicinal drugs, and have a wide range of biological and pharmaceutical activities, such as analgesic, anti-inflammatory,[3] antibacterial,[4] anti-viral,[4b] antifungal,[5] anti-pyretic,[3,4a] anti-ischemic effects,[6] antitumor[7] and other useful properties (Fig. 1). Pyrazolones themselves provide a platform for the synthesis of a myriad of compounds by virtue of their highly reactive structural functionalities.[8] Particular attention has been paid for the synthesis of C4 substituted pyrazolone derivatives which are synthetic scaffolds in combinatorial and medicinal chemistry.[9] Polysubstituted 1-alkyl-3-hydroxypyrazole derivatives are known to be potent enzyme inhibitors and activators.[10] There are several examples reported in the literature for the 1-alkyl derivative whereas those for the 1-*H*-3-hydroxypyrazole are scarce. For instance, it has been reported that *O*-pyrazole glucopyranoside and galactopyranoside derivatives, such as remogliflozin etabonate display inhibitory action against human sodium-glucose cotransporters 1 and 2 (SGLT1 and SGLT2) to function as antidiabetic agents (Fig. 1).[10] Recently, 4-benzyl-5-methyl-1*H*-pyrazol-3-ols have been recognized as efficient and selective inhibitors of rat L-2-hydroxy acid oxidase (Fig. 1).[11] 3-Methyl-1-phenyl-2-pyrazolin-5-one, (Edaravone, MCI-186), a pyrazolone compound, has been an effective drug for ischemia related ailment such as brain ischemia[12a,b] and myocardial ischemia.[6] Moreover, Edaravone has also exhibited antidepressant activity.[12c]

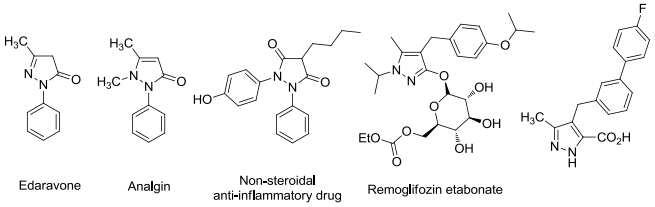


Figure 1. Biologically active pyrazole, pyrazolone and pyrazolol derivatives.

In recent years, the organocatalytic asymmetric Michael addition reaction for the synthesis of C4 substituted pyrazolone derivatives has gathered considerable interest as a convenient methodology for the C-C bond formation protocol.[13] Bifunctional *H*-bond catalysts derived from thiourea and squaramide moieties have proven efficiency for the asymmetric Michael additions of a variety of nucleophiles to nitroolefins.[14,15] In 2010, Yuan and co-workers have reported a highly diastereo- and enantioselective pyrazol-3-one addition to nitroalkenes using thioureas as bifunctional catalysts.[16] Recently, Du *et al*. reported an efficient chiral squaramide-catalysed enantioselective Michael addition of 1-Ph-pyrazolin-5-ones to nitroalkenes.[17] To the best of our knowledge, there is no study on asymmetric Michael addition of unprotected pyrazolines to β-nitrostyrenes. In continuation of our work on squaramide bifunctional catalysts,[15l] we were interested to study the Michael addition of 1*H*-pyrazolin-5-ones to β-nitroalkenes using cinchona alkaloid and bis CF_3 benzylamine

derived squaramide catalyst. Herein, we report our successful application of squaramide organocatalysts in the enantioselective Michael addition of pyrazolin-5-ones to nitroalkenes, where the corresponding C4-substituted chiral pyrazol-3-ol derivatives can be obtained in high to excellent yields (up to 95%) with moderate to high enantioselectivities (up to 96% ee).

2. Results and discussion

The preliminary reaction of 3-methyl-1*H*-pyrazol-5-one with β-nitrostyrene in dichloromethane in the presence of 10 mol% catalysts was conducted at room temperature, and results are given in Table 1. The screening studies revealed that the squaramides (**1a-c)** derived from the CF_3 substituted anilines gave the product (**4a)** in good yield with moderate enantioselectivities, (Table 1, entries 1-3) while the squaramides (**1d-i)** derived from benzylamines and bis-CF_3 benzylamines gave the desired product (**4a)** in excellent yield with good to moderate enantioselectivities (Table 1, entries 4-9). Further, the ferrocene derived squaramide catalysts (**1j-m),**[15l] afforded Michael product (**4a)** in good yield with moderate to low enantioselectivities, over an extended reaction time (Table 1, entries 10-13). On completion of the screening experiments, the performance of the catalyst **1i** was found to be the best for this model reaction among all the catalysts (**1a-m)**.

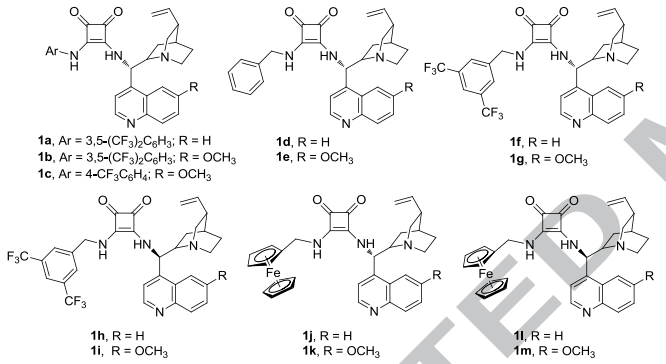
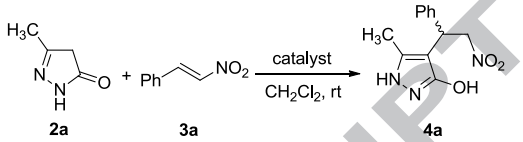


Figure 2. Different types of squaramide based bifunctional catalysts used in this study.

In continuation, different parameters such as the effect of solvents, temperature and catalyst loading were examined to arrive at the optimal reaction condition. Subsequently, the solvent screening studies revealed that solvents such as dichloromethane, chloroform, THF, toluene and acetonitrile favored good yields and moderate enantioselectivities (Table 1, entries 9 and 14-17) while, the reactions performed in diethyl ether resulted in moderate yield with poor enantioselectivity (Table 1, entry 18). The interference of a protic solvent like methanol, on the hydrogen-bond controlled organocatalysis, resulted in moderate yield and very poor enantioselectivity. (Table 1, entry 19). Among various solvents, dichloromethane was found to be the best choice as a solvent to achieve good yield and enantioselectivities. Upon screening over a range of temperatures, the reaction conducted at room temperature gave the desired product in good yield and enantioselectivity and a lower temperature had little or no effect on yield and enantioselectivity (Table 1, entries 20 and 21). The catalyst loading in the range of 0.5-5 mol% was examined for obtaining the optimal condition. Interestingly, 1mol% of the catalyst was found to be the most promising loading having achieved 95% yield of the product with 70% enantioselectivity. However, lowering of the catalyst loading further led to a drastic decrease in the yield even after prolonged reaction time (Table 1, entries 22-25). Based on all of the above results, the optimized reaction conditions as established were, 3-methyl-1*H*-pyrazol-5-one **2** (0.3 mmol) and nitroalkenes **3** (0.3 mmol) in 1.5 ml CH_2Cl_2 with 1 mol% of catalyst **1i** at room temperature.

Table 1. Catalyst screening and optimization of reaction conditions for the asymmetric Michael addition of 3-methyl-1*H*-pyrazol-5-one to β-nitrostyrene[a]



Entry	Catalyst (mol%)	Solvent	Temp (°C)	Time (h)	Yield[b] (%)	ee[c,d] (%)
1	**1a** (10)	CH_2Cl_2	rt	12	87	53 (*S*)
2	**1b** (10)	CH_2Cl_2	rt	12	89	58 (*S*)
3	**1c** (10)	CH_2Cl_2	rt	12	88	48 (*S*)
4	**1d** (10)	CH_2Cl_2	rt	14	83	54 (*S*)
5	**1e** (10)	CH_2Cl_2	rt	14	90	60 (*S*)
6	**1f** (10)	CH_2Cl_2	rt	12	93	46 (*S*)
7	**1g** (10)	CH_2Cl_2	rt	12	92	52 (*S*)
8	**1h** (10)	CH_2Cl_2	rt	12	85	48 (*R*)
9	**1i** (10)	CH_2Cl_2	rt	12	93	63 (*R*)
10	**1j** (10)	CH_2Cl_2	rt	16	86	40 (*S*)
11	**1k** (10)	CH_2Cl_2	rt	16	89	46 (*S*)
12	**1l** (10)	CH_2Cl_2	rt	16	84	42 (*R*)
13	**1m** (10)	CH_2Cl_2	rt	16	91	51 (*R*)
14	**1i**(10)	$CHCl_3$	rt	16	90	60 (*R*)
15	**1i** (10)	THF	rt	18	82	52 (*R*)
16	**1i** (10)	$PhCH_3$	rt	26	86	61 (*R*)
17	**1i** (10)	CH_3CN	rt	20	89	58 (*R*)
18	**1i** (10)	Et_2O	rt	48	73	45 (*R*)
19	**1i** (10)	CH_3OH	rt	12	78	11 (*R*)
20	**1i** (10)	CH_2Cl_2	0	36	94	60 (*R*)
21	**1i** (10)	CH_2Cl_2	-20	48	96	62 (*R*)
22	**1i** (5)	CH_2Cl_2	rt	15	93	59 (*R*)
23	**1i** (3)	CH_2Cl_2	rt	19	92	63 (*R*)
24	**1i** (1)	CH_2Cl_2	rt	24	95	70 (*R*)
25	**1i** (0.5)	CH_2Cl_2	rt	48	88	58 (*R*)

[a]Unless otherwise indicated, reactions were carried out with 3-methyl-1*H*-pyrazol-5-one **2a** (0.4 mmol) and β-nitrostyrene **3a** (0.33 mmol) in solvent (1.5 ml) at room temperature.

[b]Isolated yield after column chromatography purification.

[c]The ee values were determined by chiral HPLC analysis using a Daicel Chiralpak AD-H.

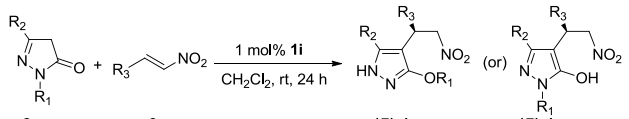
[d]The absolute configuration of the product **4a** was determined by comparison of its retention time with literature data according to ref. 13f.

Under the optimal reaction conditions, the Michael addition reaction of 3-methyl-2-pyrazolin-5-ones (**2a-c**) to a wide variety of nitroolefin substrates (**3a-q**) was examined. The results are shown in Table 2. Various nitroalkenes bearing electron donating and withdrawing groups reacted smoothly with 3-methyl-1*H*-pyrazol-5-one (**2a**) giving the desired products with high yields and moderate to good enantioselectivities. Notably, nitroalkenes bearing electron releasing groups such as Me and OMe at *para* or *ortho* position gave the desired products in good yield and enantioselectivity (Table 2, entries 2-4). Nitroalkenes bearing halogens such as fluoro, chloro and bromo at *ortho* or *para* position reacted smoothly with 3-methyl-1*H*-pyrazol-5-one (**2a**) to give the Michael adducts with good yield and moderate to good enantioselectivities (Table 2, entries 5-10). Interestingly fluorine at ortho position gave the corresponding Michael adduct

with high yield (90%) and good enantioselectivity (85% ee) (Table 2, entry 8).

Further, we have examined the reaction of nitroalkenes with nitro group at *ortho* or *meta* position on the phenyl ring. Nitroalkene **3k** gave a good yield and moderate enantioselectivity (89% yield and 75% ee), however, a high yield and good enantioselectivity (91% yield and 85% ee) was observed for nitroalkene **3l** (Table 2, entries 11 and 12). Napthyl nitroalkenes such as **3m** and **3n** gave corresponding Michael adduct with good yields and moderate enantioselectivities (Table 2, entries 13 and 14).

Table 2. Scope of the asymmetric Michael addition of pyrazolinones to nitroalkenes[a]



2a-c **3** **(*R*)-4a-q** R_1 = H **(*R*)-4r-u** R_1 = Ph

2a, R_1 = H; R_2 = CH_3
2b, R_1 = Ph; R_2 = CH_3
2c, R_1 and R_2 = Ph

Entry	R_1	R_2	R_3	Product	Yield[b] (%)	ee[c,d] (%)
1	H	CH_3	C_6H_5 (**3a**)	**4a**	95	70
2	H	CH_3	4-$CH_3C_6H_4$ (**3b**)	**4b**	86	66
3	H	CH_3	4-$CH_3OC_6H_4$ (**3c**)	**4c**	84	69
4	H	CH_3	2-$CH_3OC_6H_4$ (**3d**)	**4d**	89	77
5	H	CH_3	4-FC_6H_4 (**3e**)	**4e**	86	70
6	H	CH_3	4-ClC_6H_4 (**3f**)	**4f**	85	77
7	H	CH_3	4-BrC_6H_4 (**3g**)	**4g**	80	35
8	H	CH_3	2-FC_6H_4 (**3h**)	**4h**	90	85
9	H	CH_3	2-ClC_6H_4 (**3i**)	**4i**	84	67
10	H	CH_3	2-BrC_6H_4 (**3j**)	**4j**	82	71
11	H	CH_3	2-$NO_2C_6H_4$ (**3k**)	**4k**	89	75
12	H	CH_3	3-$NO_2C_6H_4$ (**3l**)	**4l**	91	85
13	H	CH_3	1-Naphthyl (**3m**)	**4m**	83	66
14	H	CH_3	2-Naphthyl (**3n**)	**4n**	79	65
15	H	CH_3	2-Furanyl (**3o**)	**4o**	92	83
16	H	CH_3	2-Thienyl (**3p**)	**4p**	88	76
17	H	CH_3	3,4-$(O_2CH_2)C_6H_3$ (**3q**)	**4q**	90	78
18	C_6H_5	CH_3	C_6H_5 (**3a**)	**4r**	96	96
19	C_6H_5	CH_3	2-Furanyl (**3o**)	**4s**	92	93
20	C_6H_5	CH_3	2-Thienyl (**3p**)	**4t**	95	96
21	C_6H_5	C_6H_5	C_6H_5 (**3a**)	**4u**	89	75

[a]Unless otherwise indicated, reactions were carried out with pyrazolin-5-one **2** (0.4 mmol), nitroalkenes **3** (0.33 mmol) and catalyst **1i** (1 mol%) in CH_2Cl_2 (1.5 ml) at room temperature.

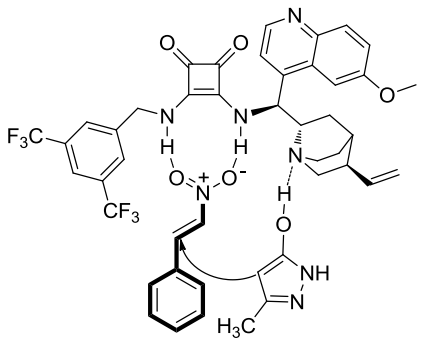
[b]Isolated yield after column chromatography purification.

[c]The ee values were determined by chiral HPLC analysis using a Daicel Chiralpak AD-H, IC column.

[d]The absolute configuration of the product **4a** was determined by comparison of its retention time with literature data according to ref. [13f] and the configurations of other products were tentatively assigned by analogy.

Heteroaromatic nitroalkenes such as nitro olefins with furyl (**3o**) and thienyl moieties (**3p**) reacted smoothly with 3-methyl-2-pyrazolin-5-one (**2a**) to provide the desired products with high yields and good to moderate enantioselectivities (Table 2, entries 15 and 16). 3,4-Methylenedioxy-substituted nitroalkene **3q** was also used as an acceptor, it afforded the corresponding Michael adduct with good yield (90%) and moderate enantioselectivity (78% ee) (Table 2, entry 17). In order to compare the efficiency of catalyst **1i** on the N-Phenyl substituted pyrazolones, the asymmetric Michael addition reaction was conducted under the optimized conditions (using 1mol% of the catalyst). Interestingly, the reaction of 1-Ph-pyrazolin-5-one (**2b**) with β-nitrostyrene (**3a**) afforded the product **4r** in high yield and excellent enantioselectivity, which were comparatively higher than those reported by Du and co-workers (Table 2, entry 18).[17] Similarly, heteroaromatic nitroalkenes such as furyl (**3o**) and thienyl (**3p**) nitro olefins reacted smoothly with 1-Ph-pyrazolin-5-one (**2b**) to give the desired products with high yield and excellent enantioselectivities (Table 2, entries 19 and 20). It is noteworthy to mention that the reaction was also conducted with 1,3-diphenyl-2-pyrazolin-5-one (**2c**) using the catalyst **1i** to afford the corresponding Michael adduct **4u** with good yield (89%) and moderate enantioselectivity (75% ee) (Table 2, entry 21).

Figure 3 depicts a possible transition state model on the basis of the observed experimental results. A hydrogen bonding interaction of the NH groups of rigid squaramide moiety of the catalyst with the nitro group of β- nitroalkene should increase the electrophilicity of the α-carbon of the styrene moiety. In other words, dual hydrogen bonding between the NH group and the nitro group activates the nitroalkene for a nucleophilic attack at the α-carbon atom. Simultaneous nucleophilic activation of the methylene carbon takes place (via tautomerism) due to the deprotonation of 3-methyl-2-pyrazolin-5-one by the basic nitrogen atom of the tertiary amine of cinchona alkaloid component. The R-configured product is then formed due to the attack of the deprotonated 3-methyl-2-pyrazolin-5-one on the activated nitroalkene from the *Si*-face which is commensurate with the observed enantioselective results.



Si face attack

Figure 3. Proposed transition state model

3. Conclusion

In summary, we describe the synthesis of a series of chiral bifunctional squaramides **1a-m** derived from Cinchona alkaloids constituting bis CF_3-anilines, bis CF_3-benzylamines and ferrocene. The catalytic activity of **1a-m** was studied successfully for asymmetric Michael addition of 3-methyl-2-pyrazolin-5-one to nitroalkenes in dichloromethane. Under the optimized reaction conditions, bifunctional catalyst **1i** exhibited better efficiency and good enantioselectivity. Moreover, the catalyst has displayed its versatility and ability over a broad substrate scope. The corresponding Pyrazol-3-ol derivatives were obtained in high to excellent yields with moderate to good enantioselectivities under mild conditions with low catalyst loading (1 mol%). This reaction affords valuable and easy access to enantiomerically pure 5-methyl-4-(2-nitro-1-arylethyl) pyrazol-3-ol derivatives. Further investigation on chiral bifunctional squaramides is currently being carried out in our laboratory to extend their application in asymmetric catalysis.

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