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方酰胺催化氮杂二烯和吡唑啉-5-酮的加成：含吡唑三芳基甲烷的不对称合成

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摘要 用金鸡纳碱衍生的手性双功能有机催化剂，实现了橙酮衍生的氮杂二烯和吡唑啉-5-酮的高对映选择性加成反应，最高对映选择性可达 99%. 该方法学为含吡唑手性三芳基甲烷衍生物合成提供一条简洁的途径.
关键词 三芳基甲烷；吡唑；有机催化；氮杂二烯；对映选择性加成

Enantioselective Synthesis of Triarylmethanes Bearing Pyrazole Moiety through Squaramide-Catalyzed Addition of Azadienes with Pyrazolin-5-ones

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Abstract Using cinchona-derived bifunctional squaramides as catalyst, an asymmetric addition of aurone-derived azadienes with pyrazolin-5-ones was developed, providing a series of chiral triarylmethanes bearing pyrazole moiety with up to 99% *ee*.
Keywords triarylmethane; pyrazole; organocatalysis; azadiene; enantioselective addition

1 Introduction

Triarylmethane moiety widely exists in natural products, medicinal and material molecules due to their unique structural and physical properties.[1-2] Among the triarylmethanes, heteroaryl-substituted triarylmethanes are the privileged architectures frequently founded in pharmaceuticals and bioactive molecules.[2-3] Pyrazole moiety, as a class of important nitrogen-containing heterocycles, is widespread in drugs and bioactive compounds[4] (Figure 1). Therefore, the enantioselective synthesis of triarylmethanes bearing pyrazole moiety is highly desirable.

Among the various synthetic routes of pyrazoles, using pyrazolin-5-ones as the starting material is undoubtedly a fast and straightforward method.[5] Over the past decades, some Michael acceptors such as *α*,*β*-unsaturated aldehydes,[6] ketones,[7] esters,[8] nitriles,[9] nitro-olefins,[10] imines,[11] azonaphthalenes[12] *etc*[13] have been successfully applied to enantioselective reactions with pyrazolin-5-ones. Notably, the reaction of *α*,*β*-unsaturated imines with pyrazolin-5-ones has not been reported so far.

As highly reactive intermediates, aurone-derived azadienes have attracted much attention in recent years because of their driving force of aromatization. Various reaction systems such as metal catalysis,[14] Lewis base catalysis,[15] *N*-heterocyclic carbene catalysis,[16] Brønsted acid catalysis,[17] inorganic acid and base-mediated reaction[18] have been successfully developed. What's more, chiral bifunctional bases have also been applied to the reactions of aurone-derived azadienes recently.[19] Considering the fact

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that aurone-derived azadienes are new kind of Michael acceptors for pyrazolin-5-ones, herein, we hope to realize the cinchona-derived chiral bifunctional base-catalyzed addition of aurone-derived azadienes with pyzarolin-5-ones to construct chiral triarylmethanes bearing pyrazole moiety.

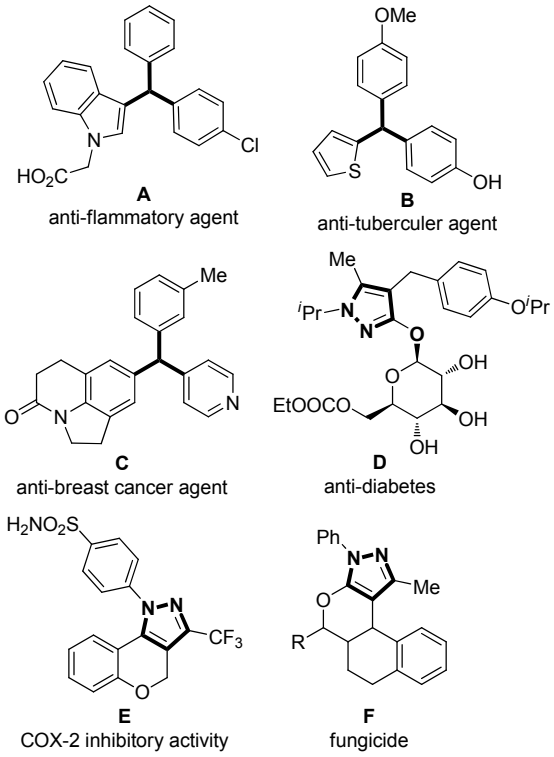
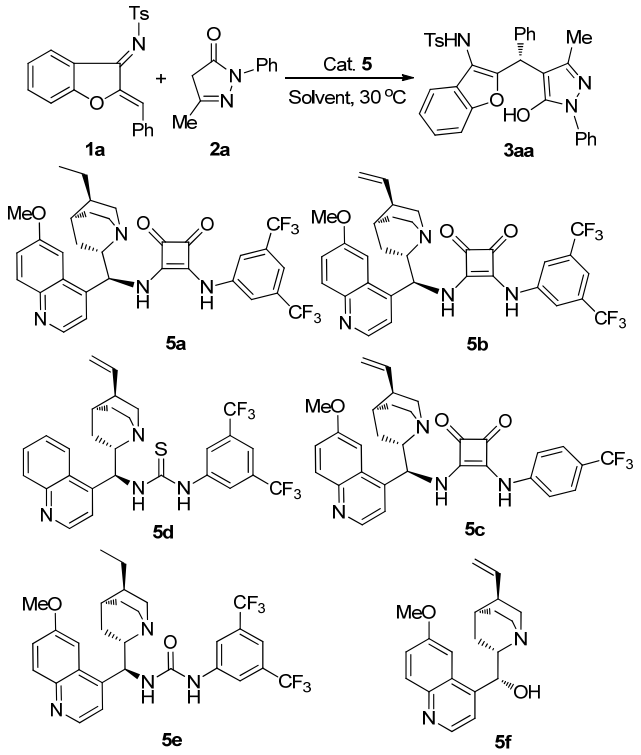


Figure 1 Representative bioactive heteroaryl-substituted triarylmethanes and pyrazoles

2 Results and discussion

At the outset, azadiene **1a** and pyrazolin-5-one **2a** were chosen as model substrates to explore reaction conditions in the presence of bifunctional squaramide catalyst **5a**. To our delight, the desired product was obtained in 86% yield and 98% *ee*. Then various solvents were evaluated. The results were depicted in Table 1, and indicated that the solvent had no obvious effect on the enantioselectivity (92%～98% *ee*). Among them, dichloromethane was the most favorable solvent in terms of yield and enantioselectivity (Entries 1～6). Then, several bifunctional catalysts were examined. It was found that cinchona-derived catalysts such as squaramide, thiourea and quinine had higher enantioselectivities than the urea catalyst. Among the screened catalysts, squaramide **5a** was the best, offering the desired compound in 86% yield and 98% *ee* (Entries 7～11). To further improve the reactivity, the amount of pyrazolin-5-one **2a** was improved to 1.1 equiv., the 91% yield was obtained (Entry 12). Thus, the optimal conditions for this reaction were established: using dichloromethane as the solvent and squaramide **5a** as catalyst to perform the reaction at 30 ℃.

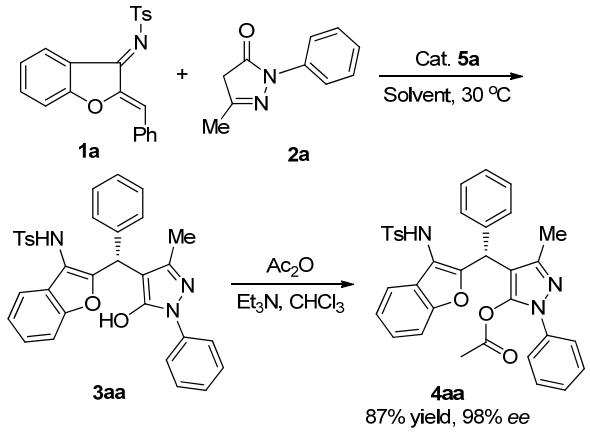
Table 1 Optimization of reaction conditions[a]



Entry	Catalyst	Solvent	Yield[b]/%	*ee*[c]/%
1	**5a**	CH_2Cl_2	86	98
2	**5a**	$CHCl_3$	83	98
3	**5a**	DCE	80	98
4	**5a**	Toluene	77	98
5	**5a**	Mestitylene	88	92
6	**5a**	THF	54	96
7	**5b**	CH_2Cl_2	87	96
8	**5c**	CH_2Cl_2	82	97
9	**5d**	CH_2Cl_2	65	94
10	**5e**	CH_2Cl_2	61	72
11	**5f**	CH_2Cl_2	87	96
12[d]	**5a**	CH_2Cl_2	91	98

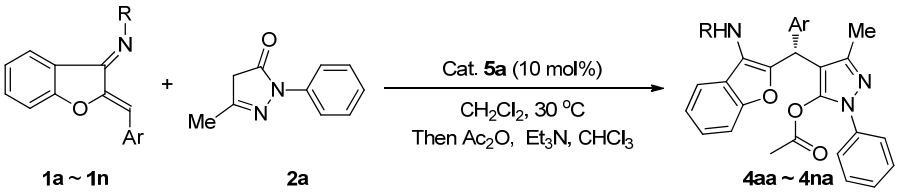
[a] Reaction conditions: **1a** (0.10 mmol), **2a** (0.10 mmol), Cat. **5** (10 mol%), solvent (1.5 mL), 2 h. [b] Isolated yields based on the azadiene. [c] Determined by HPLC. [d] 0.11 mmol of **2a** was added.

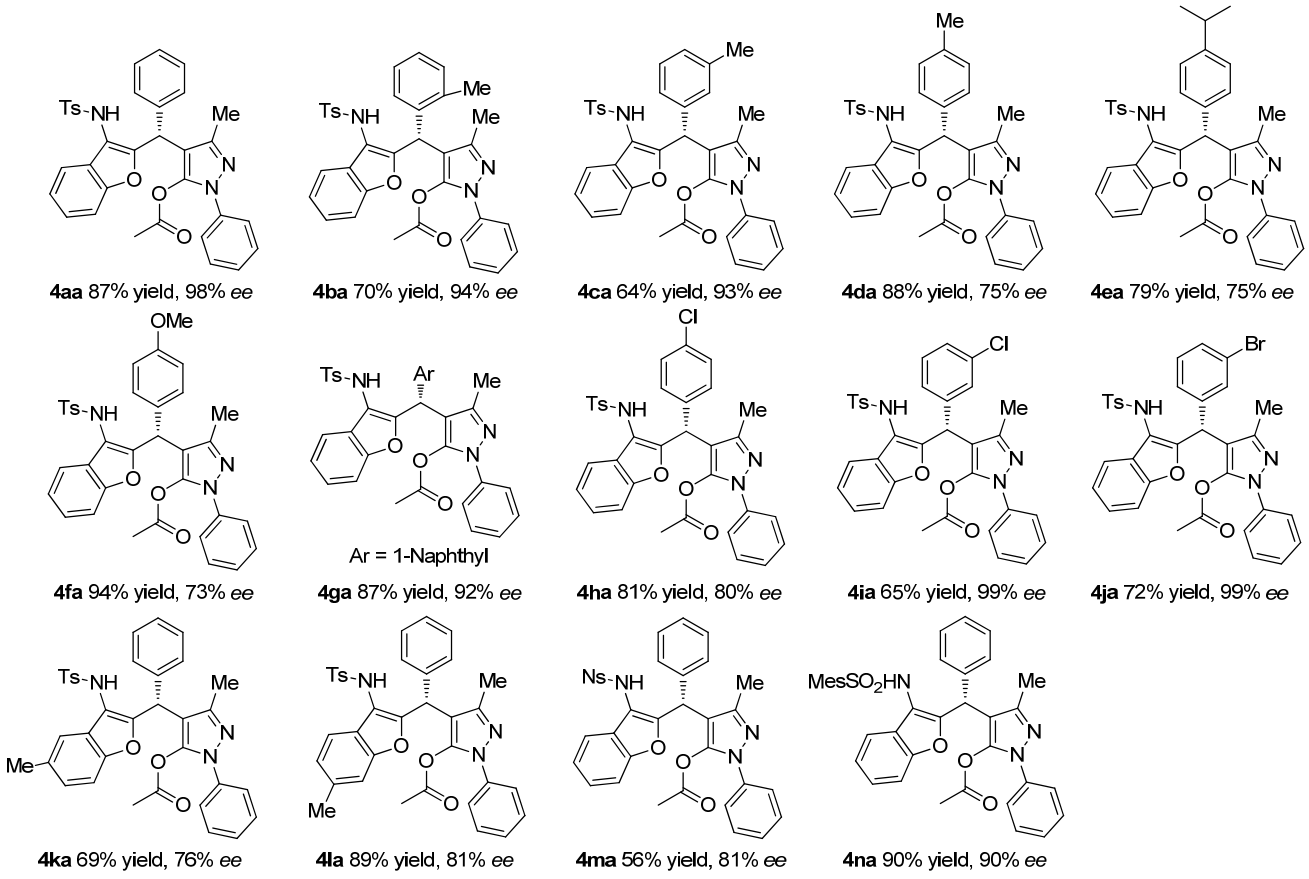
Owing to existence of enol-ketone isomerization[7c] of the addition product **3aa**, clean NMR spectra could not be obtained (clean HPLC spectra could be obtained). So, protection of **3aa** with acetic anhydride was employed. Initially, we attempted the protection *in situ*, however, the target compound was acquired only in 79% yield and the *ee* value dropped to 82%, which might ascribe to the reversible Michael addition to result in partial racemization in the presence of bifunctional squaramide catalyst **5**. So, the acetylation protection was performed after the isolation of **3aa** with chloroform as solvent. Delightedly, the acetylation product **4aa** could be obtained in 87% yield and 98% *ee* without any loss of optical purity (Scheme 1).



Scheme 1 Acetylation protection of addition product

With the optimal reaction conditions in hand, the substrate scope was investigated. Initially, a wide array of azadienes was explored (Scheme 2). It was found that the steric effect was obvious. When the methyl substituent was on the *ortho* or *meta*-position of the right phenyl ring of azadiene, the target products could be obtained in moderate yield and excellent enantioselectivities (**4ba** and **4ca**). With *para*-position methyl substituted azadiene, the reaction performed well, however, the *ee* value decreased to 75% (**4da**). The electronic properties of substituents on the phenyl ring were also exploited, which had no obvious influence on the enantioselectivity (**4ea**, **4fa**, **4ha**). For 1-naphthyl substituted azadiene (**2g**), the reaction proceeded smoothly, providing the corresponding product with 87% yield and 92% *ee*. When halogen substituents were on *meta*-position of right phenyl ring of azadienes, 99% enantioselectivities were obtained (**4ia** and **4ja**). The azadienes with methyl substituent at the 5- or 6-position of benzofuryl ring were also transformed with moderate to good yields and enantioselectivities (**4ka** and **4la**). When the tosyl group was replaced with 4-nitro-benzenesulfonyl, the desired product was obtained in moderate (56%) yield and 81% *ee* probably because of electron-withdrawing property. However, when bulky 2,4,6-trimethylbenzenesulfonyl was used, the desirable product (**4na**) was acquired with 90% yield and 90% *ee*.

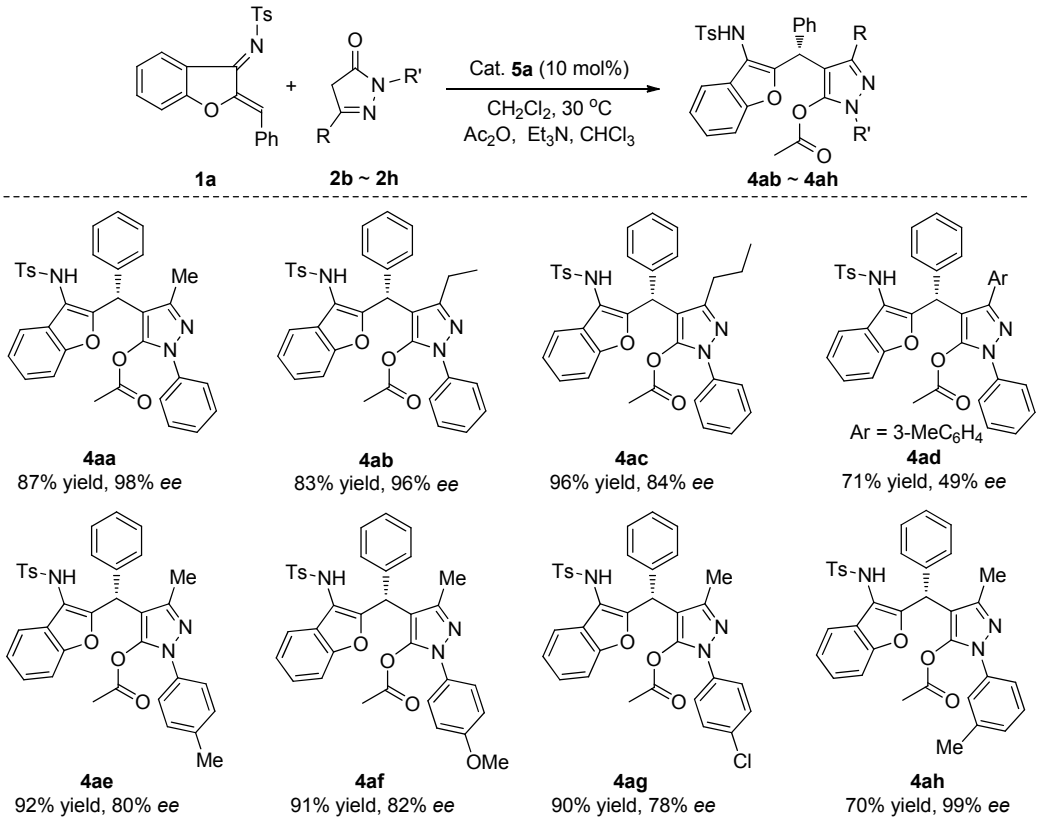




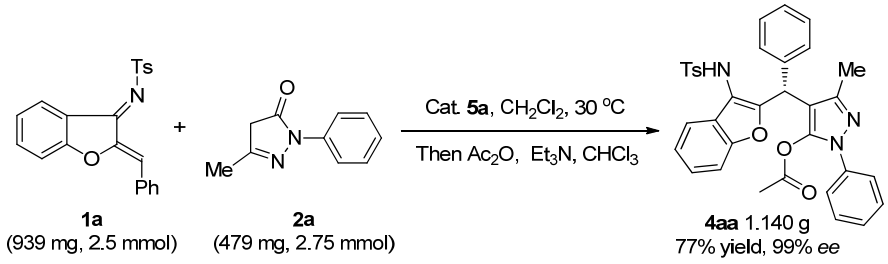
Scheme 2 Substrate scope of azadienes **1**

Next, we turned our attention to a series of pyrazolin-5-ones (Scheme 3). When alkyl substituent was introduced onto 3-position of pyrazolin-5-ones **2**, the reactions conducted smoothly, providing the desired products in good to excellent yields and enantioselectivities (**4aa**～**4ac**). While when 3-aryl substituted substrate **2d** was used, the *ee* value sharply dropped to moderate 49% (**4ad**), the reason is not clear. The effect of 1-aryl substituents of pyrazolin-5-ones **2** on reactivity and enantioselectivity was investigated. Moderate (78%～82%) *ee* were obtained (**4ae**～**4ag**) regardless of electronic properties of 4-substituents of 1-phenyl ring of **2**. Meanwhile, it was found that the substituents at the *meta*-position of 1-phenyl ring of pyrazolin-5-one **2** exhibited better enantioselectivity than that of *para*-position, such as **2h** bearing 3-methylphenyl, the reaction performed well and the best 99% *ee* could be obtained.

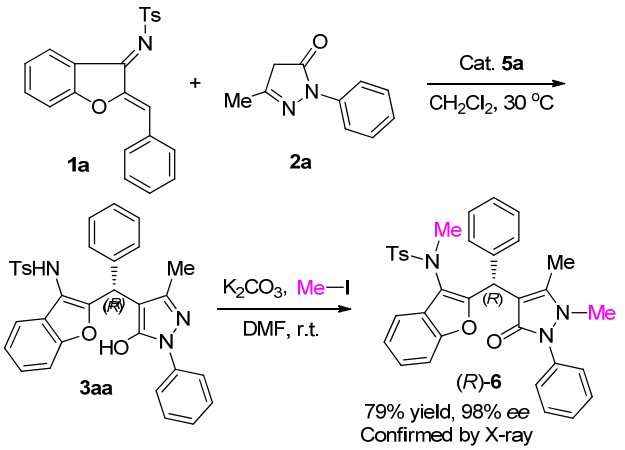
To further demonstrate the practicality of this methodology, the gram scale experiment was conducted, giving the desired product in 77% yield and without loss of enantioselectivity and activity (Scheme 4). To determine the absolute configuration of the addition product, firstly, we tried direct growth of single crystal of (−)-**4aa**, it is not successful. Next, the methylation of unprotected intermediate **3aa** was tried with iodomethane in the prsence of potassium carbonate in *N*,*N*-dimethylformamide (DMF).[20] Surprisingly, the *N*,*N*-dimethylation product **6** was obtained (the reason might ascribe to bulky steric hindrance and intramolecular hydrogen-bonding interaction of hydroxy group to inhibit the *O*-methylation), which could be easily recrystallized from the mixture solvents chloroform and *n*-hexane. On the basis of single crystal X-ray diffraction analysis (Figure 2), the absolute configuration of product (−)-**6** was assigned to be *R* (Scheme 5). The absolute configuration of addition product **4aa** was thus unambiguously determined to be *R*.



Scheme 3 Substrate scope of pyrazolin-5-ones **2**



Scheme 4 Gram-scale experiment



Scheme 5 Synthesis of compound (*R*)-**6**

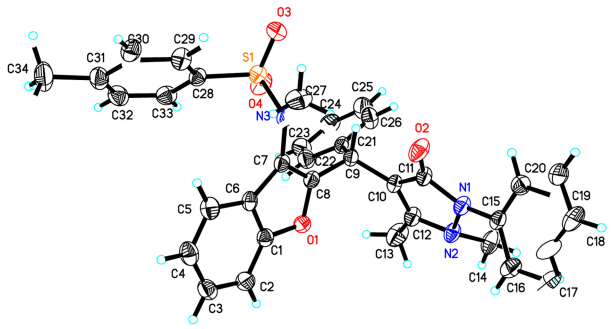


Figure 2 Single crystal X-ray diffraction analysis of compound *R*-**6**

Based on the above experiments and the X-ray diffraction results, a plausible mechanism was suggested and depicted in Scheme 6. As a dual-activating organocatalyst, the Brønsted base part of squaramide **5a** grabs the proton of enol tautomer of pyrazolin-5-one, then the Brønsted acid part of squaramide activates the azadiene via double hydrogen bonding, the simultaneous nucleophilic addition to lead a enantioselective Michael addition, followed by tautomerization to give the adduct **3aa** with *R* configuration.

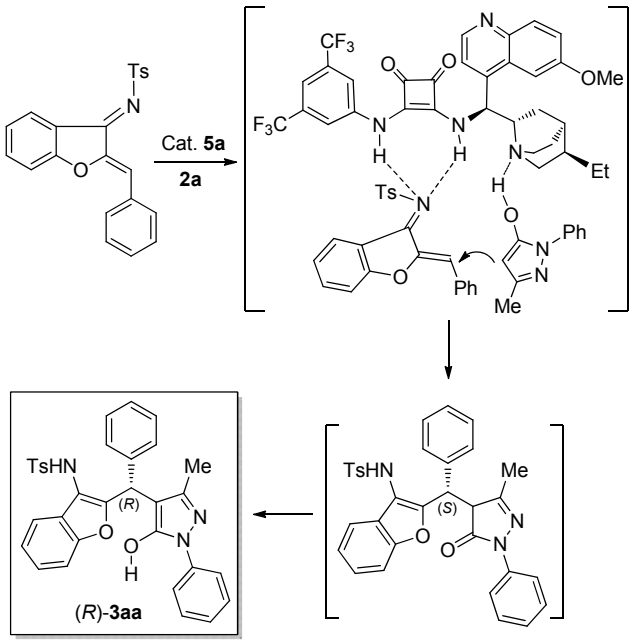
3 Conclusions

In summary, an enantioselective bifunctional squaramide-catalyzed addition of azadienes with pyrazolin-5-ones was successfully developed, providing a series of chiral triarylmethanes bearing pyrazole moiety in moderate to excellent yields and up to 99% *ee*. This methodology exhibited broad substrates scope and functional groups compatibility, and the experiment at gram scale could proceed smoothly without any loss of enantioselectivity and reactivity. The further exploration on development of novel asymmetric cycloaddition reaction of azadienes is currently on going in our laboratory.

4 Experimental section

4.1 Instruments and reagents

All reactions were carried out under an atmosphere of nitrogen using the standard Schlenk techniques, unless otherwise noted. Commercially available reagents were used without further purification. Solvents were treated prior to use according to the standard methods. ^{1}H NMR, ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz with the Brucker spectrometer. Chemical shifts are reported in ppm using tetramethylsilane as internal standard when using $CDCl_3$ as solvent for ^{1}H NMR spectra. The following abbreviations were used to symbolize the multiplicities: s＝singlet, d＝doublet, t＝triplet, m＝multiplet, br＝broad. Flash column chromatography was performed on silica gel (200～300 mesh). All reactions were monitored by TLC analysis. Optical rotations were measured by the polarimeter. Enantiomeric excess was determined by the HPLC analysis using chiral column described below in detail. Commercially available reagents were used throughout without further purification. Aurone-derived azadienes **1** could be synthesized from enones and sulfonamides according to the known literature procedures.[15,19,21-22] Pyrazolin-5-ones **2** were prepared according to the known procedure.[23]



Scheme 6 Proposed reaction mechanism

4.2 Typical procedure for the syntheses of triarylmethanes bearing pyrazole moiety

A mixture of azadienes **1** (0.20 mmol), pyrazolin-5-ones **2** (0.22 mmol) and bifunctional squaramide organocatalyst **5a** (12.6 mg, 0.02 mmol) in dichloromethane (3.0 mL) was stirred at 30 ℃ for 2 h. The crude product was directly purified by silica gel column chromatography [eluent: *V*(hexane)∶*V*(ethyl acetate)＝5∶1 to 2∶1]. To a solution of the product obtained above in chloroform (3.0 mL), acetic anhydride (22.5 mg, 0.22 mmol) and triethylamine (6.1 mg, 0.06 mmol) were added in sequence and the reaction mixture was stirred at ambient temperature for 2 h. After the completion of acylation reaction, the volatiles were

removed under the reduced pressure, and the residue was purified by column chromatography on silica gel by using hexane/ethyl acetate (V∶V=5∶1) as eluent to give the chiral triarylmethanes **4**.

(−)-3-Methyl-4-((3-((4-methylphenyl)sulfonamido)-benzofuran-2-yl)(phenyl)methyl)-1-phenyl-1*H*-pyrazol-5-yl acetate (**4aa**): 101 mg, 87% yield, viscous liquid. R_f= 0.30 [V(hexane) ∶ V(ethyl acetate) = 5 ∶ 1], 98% *ee* [HPLC: Chiralcel IA column, 254 nm, 30 ℃, V(*n*-Hexane) ∶ V(*i*-PrOH)=70∶30, flow=0.7 mL/min, retention time 13.3 min (minor) and 20.1 min (major)]. $[\alpha]_D^{20}$ −80.16 (*c* 0.60, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67 (d, J=8.3 Hz, 2H), 7.51～7.43 (m, 2H), 7.42～7.36 (m, 2H), 7.35～7.26 (m, 5H), 7.22～7.11 (m, 5H), 7.09～7.00 (m, 2H), 6.47 (s, 1H), 5.49 (s, 1H), 2.35 (s, 3H), 2.02 (s, 3H), 1.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.0, 154.8, 153.3, 148.4, 144.2, 141.9, 138.5, 137.9, 136.9, 129.8, 129.3, 128.6, 128.5, 127.6, 127.5, 127.1, 125.9, 124.7, 123.3, 122.9, 119.3, 113.6, 111.6, 107.7, 37.2, 21.7, 20.0, 13.7; HRMS calcd for $C_{34}H_{30}N_3O_5S$ $[M+H]^+$ 592.1901, found 592.1909.

(+)-3-Methyl-4-((3-((4-methylphenyl)sulfonamido)-benzofuran-2-yl)(*o*-tolyl)methyl)-1-phenyl-1*H*-pyrazol-5-yl acetate (**4ba**): 84 mg, 70% yield, viscous liquid. R_f= 0.29 [V(hexanes) ∶ V(ethyl acetate) = 3 ∶ 1], 94% *ee* [HPLC: Chiralcel IA column, 254 nm, 30 ℃, V(*n*-hexane) ∶ V(*i*-PrOH)=70∶30, flow=0.7 mL/min, retention time 11.6 min (minor) and 13.7 min (major)]. $[\alpha]_D^{20}$ +29.05 (*c* 0.84, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.63 (d, J=8.3 Hz, 2H), 7.50～7.43 (m, 2H), 7.42～7.32 (m, 3H), 7.33～7.29 (m, 1H), 7.23～7.04 (m, 9H), 6.28～6.21 (br, 1H), 5.61 (s, 1H), 2.34 (s, 3H), 2.18 (s, 3H), 1.99 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.5, 153.9, 153.2, 148.2, 144.1, 142.1, 138.0, 136.9, 136.6, 136.6, 130.7, 129.7, 129.3, 128.8, 127.6, 127.4, 127.4, 126.2, 126.1, 124.6, 123.3, 123.0, 119.4, 113.7, 111.7, 106.6, 35.3, 21.7, 19.8, 19.6, 13.2; HRMS calcd for $C_{35}H_{32}N_3O_5S$ $[M+H]^+$ 606.2057, found 606.2054.

(−)-3-Methyl-4-((3-((4-methylphenyl)sulfonamido)-benzofuran-2-yl)(*m*-tolyl)methyl)-1-phenyl-1*H*-pyrazol-5-yl acetate (**4ca**): 77 mg, 64% yield, viscous liquid. R_f= 0.19 [V(hexane) ∶ V(ethyl acetate) = 2 ∶ 1], 93% *ee* [HPLC: Chiralcel IA column, 254 nm, 30 ℃, V(*n*-hexane) ∶ V(*i*-PrOH)=70∶30, flow=0.7 mL/min, retention time 11.3 min (minor) and 15.2 min (major)]. $[\alpha]_D^{20}$ −120.72 (*c* 0.77, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69 (d, J=8.3 Hz, 2H), 7.49～7.44 (m, 2H), 7.42～7.32 (m, 3H), 7.31～7.27 (m, 1H), 7.21～7.14 (m, 4H), 7.10～7.03 (m, 3H), 6.89 (d, J=6.8 Hz, 2H), 6.25 (s, 1H), 5.39 (s, 1H), 2.36 (s, 3H), 2.31 (s, 3H), 2.02 (s, 3H), 1.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.9, 154.8, 153.2, 148.4, 144.1, 141.9, 138.3, 138.1, 137.9, 136.9, 129.8, 129.3, 129.2, 128.4, 127.9, 127.7, 127.4, 126.0, 125.7, 124.6, 123.3, 122.9, 119.3, 113.5, 111.7, 107.7, 37.1, 21.7, 21.6, 20.0, 13.7; HRMS calcd for $C_{35}H_{32}N_3O_5S$ $[M+H]^+$ 606.2057, found 606.2062.

(−)-3-Methyl-4-((3-((4-methylphenyl)sulfonamido)-benzofuran-2-yl)(*p*-tolyl)methyl)-1-phenyl-1*H*-pyrazol-5-yl acetate (**4da**): 106 mg, 88% yield, viscous liquid. R_f= 0.31 [V(hexane) ∶ V(ethyl acetate) = 3 ∶ 1], 75% *ee* [HPLC: Chiralcel IA column, 254 nm, 30 ℃, V(*n*-Hexane) ∶ V(*i*-PrOH)=70∶30, flow=0.7 mL/min, retention time 11.8 min (minor) and 17.4 min (major)]. $[\alpha]_D^{20}$ −82.82 (*c* 1.06, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.68 (d, J=8.3 Hz, 2H), 7.49～7.42 (m, 2H), 7.41～7.26 (m, 4H), 7.22～7.13 (m, 3H), 7.11～7.03 (m, 4H), 6.99 (d, J=8.0 Hz, 2H), 6.43～6.35 (br, 1H), 5.41 (s, 1H), 2.36 (s, 3H), 2.33 (s, 3H), 2.02 (s, 3H), 1.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.0, 155.0, 153.2, 148.4, 144.1, 141.9, 137.9, 136.9, 136.7, 135.4, 129.8, 129.3, 129.2, 128.5, 127.7, 127.4, 125.6, 124.6, 123.3, 122.9, 119.3, 113.5, 111.6, 107.8, 36.8, 21.7, 21.2, 20.0, 13.7; HRMS calcd for $C_{35}H_{32}N_3O_5S$ $[M+H]^+$ 606.2057, found 606.2060.

(−)-4-((4-Isopropylphenyl)(3-((4-methylphenyl)sulfonamido)benzofuran-2-yl)methyl)-3-methyl-1-phenyl-1*H*-pyrazol-5-yl acetate (**4ea**): 100 mg, 79% yield, viscous liquid. R_f=0.22 [V(hexane) ∶ V(ethyl acetate) = 3 ∶ 1], 75% *ee* [HPLC: Chiralcel IA column, 254 nm, 30 ℃, V(*n*-hexane) ∶ V(*i*-PrOH)=70∶30, flow=0.7 mL/min, retention time 11.4 min (minor) and 12.8 min (major)]. $[\alpha]_D^{20}$ −61.60 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.70～7.64 (m, 2H), 7.48～7.43 (m, 2H), 7.42～7.32 (m, 3H), 7.31～7.27 (m, 1H), 7.22～7.16 (m, 3H), 7.15～7.11 (m, 2H), 7.09～6.99 (m, 4H), 6.22 (s, 1H), 5.40 (s, 1H), 2.89 (hept, J=6.9 Hz, 1H), 2.37 (s, 3H), 2.02 (s, 3H), 1.75 (s, 3H), 1.24 (d, J=6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.0, 155.0, 153.2, 148.4, 147.6, 144.1, 141.9, 138.0, 136.9, 135.6, 129.8, 129.3, 128.5, 127.7, 127.4, 126.6, 126.0, 124.6, 123.3, 123.0, 119.3, 113.5, 111.7, 107.8, 36.9, 33.8, 24.1, 21.7, 20.0, 13.8; HRMS calcd for $C_{37}H_{36}N_3O_5S$ $[M+H]^+$ 634.2370, found 634.2369.

(−)-4-((4-Methoxyphenyl)(3-((4-methylphenyl)sulfonamido)benzofuran-2-yl)methyl)-3-methyl-1-phenyl-1*H*-pyrazol-5-yl acetate (**4fa**): 117 mg, 94% yield, viscous liquid. R_f=0.17 [V(hexane) ∶ V(ethyl acetate) = 3 ∶ 1], 73% *ee* [HPLC: Chiralcel IA column, 254 nm, 30 ℃, V(*n*-Hexane) ∶ V(*i*-PrOH)=70∶30, flow=0.7 mL/min, retention time 13.9 min (minor) and 24.2 min (major)]. $[\alpha]_D^{20}$ −74.95 (*c* 1.17, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.68 (d, J=8.3 Hz, 2H), 7.47～7.42 (m, 2H), 7.41～7.35 (m, 2H), 7.33 (d, J=8.3 Hz, 1H), 7.31～7.27 (m, 1H), 7.22～7.15 (m, 3H), 7.09～7.00 (m, 4H), 6.85～6.77 (d, J=8.8 Hz, 2H), 6.29～6.20 (br, 1H), 5.40 (s, 1H), 3.79 (s, 3H), 2.37 (s, 3H), 2.02 (s, 3H), 1.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.0, 158.7, 155.2, 153.2, 148.4, 144.2, 141.8, 138.0, 136.9, 130.5, 129.8, 129.7, 129.3, 127.7, 127.5, 126.0, 124.6, 123.4, 123.0, 119.3, 113.9, 113.3, 111.7, 107.9, 55.4, 36.5, 21.7, 20.0, 13.8; HRMS calcd for $C_{35}H_{32}N_3O_6S$ $[M+H]^+$ 622.2006, found 622.2009.

(−)-3-Methyl-4-((3-((4-methylphenyl)sulfonamido)-

benzofuran-2-yl)(naphthalen-1-yl)methyl)-1-phenyl-1*H*-pyrazol-5-yl acetate (**4ga**): 111 mg, 87% yield, viscous liquid. R_f=0.34 [*V*(hexane)∶*V*(ethyl acetate)=3∶1], 92% *ee* [HPLC: Chiralcel IA column, 254 nm, 30 ℃, *V*(*n*-hexane)∶*V*(*i*-PrOH)=70∶30, flow=1.0 mL/min, retention time 10.9 min (minor) and 22.9 min (major)]. $[\alpha]_D^{20}$ −7.21 (*c* 1.11, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.92～7.85 (m, 2H), 7.80 (d, *J*=8.2 Hz, 1H), 7.68 (d, *J*=8.3 Hz, 2H), 7.50～7.44 (m, 4H), 7.40～7.34 (m, 3H), 7.30～7.26 (m, 3H), 7.21～7.14 (m, 2H), 7.12～7.03 (m, 3H), 6.46 (s, 1H), 6.21 (s, 1H), 2.27 (s, 3H), 1.96 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 167.6, 154.2, 153.2, 148.2, 144.1, 142.2, 138.0, 137.0, 134.1, 133.9, 131.5, 129.7, 129.3, 128.9, 128.3, 127.6, 127.4, 126.7, 126.7, 126.1, 125.9, 125.4, 124.6, 123.4, 123.3, 123.0, 119.5, 113.7, 111.7, 107.3, 34.8, 21.6, 19.7, 13.3; HRMS calcd for $C_{38}H_{32}N_3O_5S$ $[M+H]^+$ 642.2057, found 642.2051.

(−)-4-((4-Chlorophenyl)(3-((4-methylphenyl)sulfonamido)benzofuran-2-yl)methyl)-3-methyl-1-phenyl-1*H*-pyrazol-5-yl acetate (**4ha**): 101 mg, 81% yield, viscous liquid. R_f=0.38 [*V*(hexane)∶*V*(ethyl acetate)=3∶1], 80% *ee* [HPLC: Chiralcel IA column, 254 nm, 30 ℃, *V*(*n*-hexane)∶*V*(*i*-PrOH)=70∶30, flow=0.7 mL/min, retention time 11.4 min (minor) and 22.0 min (major)]. $[\alpha]_D^{20}$ −87.12 (*c* 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.66 (d, *J*=8.3 Hz, 2H), 7.47～7.42 (m, 2H), 7.41～7.35 (m, 2H), 7.33 (d, *J*=8.3 Hz, 1H), 7.30～7.27 (m, 1H), 7.25～7.23 (m, 1H), 7.21～7.14 (m, 3H), 7.11～7.02 (m, 3H), 6.96 (d, *J*=7.8 Hz, 1H), 6.49 (s, 1H), 5.51 (s, 1H), 2.35 (s, 3H), 2.03 (s, 3H), 1.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 167.9, 154.5, 153.2, 148.2, 144.3, 141.9, 137.8, 137.2, 136.7, 132.9, 130.0, 129.8, 129.3, 128.6, 127.6, 127.5, 125.7, 124.8, 123.4, 122.9, 119.2, 113.7, 111.6, 107.4, 36.5, 21.6, 20.0, 13.8; HRMS calcd for $C_{34}H_{29}ClN_3O_5S$ $[M+H]^+$ 626.1511, found 626.1518.

(−)-4-((3-Chlorophenyl)(3-((4-methylphenyl)sulfonamido)benzofuran-2-yl)methyl)-3-methyl-1-phenyl-1*H*-pyrazol-5-yl acetate (**4ia**): 82 mg, 65% yield, viscous liquid. R_f=0.36 [*V*(hexanes)∶*V*(ethyl acetate)=3∶1], 99% *ee* [HPLC: Chiralcel IA column, 254 nm, 30 ℃, *V*(*n*-Hexane)∶*V*(*i*-PrOH)=70∶30, flow=0.7 mL/min, retention time 13.3 min (minor) and 16.1 min (major)]. $[\alpha]_D^{20}$ −107.43 (*c* 0.82, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.67 (d, *J*=8.3 Hz, 2H), 7.47～7.42 (m, 2H), 7.41～7.32 (m, 3H), 7.31～7.27 (m, 1H), 7.24～7.14 (m, 5H), 7.10～7.02 (m, 4H), 6.54 (s, 1H), 5.46 (s, 1H), 2.36 (s, 3H), 2.04 (s, 3H), 1.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 167.9, 154.2, 153.3, 148.2, 144.3, 142.0, 140.6, 137.8, 136.7, 134.3, 129.9, 129.8, 129.3, 128.6, 127.6, 127.6, 127.4, 126.9, 125.8, 124.9, 123.5, 123.0, 119.3, 113.9, 111.7, 107.2, 36.8, 21.7, 20.0, 13.8; HRMS calcd for $C_{34}H_{29}ClN_3O_5S$ $[M+H]^+$ 626.1511, found 626.1513.

(−)-4-((3-Bromophenyl)(3-((4-methylphenyl)sulfonamido)benzofuran-2-yl)methyl)-3-methyl-1-phenyl-1*H*-pyrazol-5-yl acetate (**4ja**): 97 mg, 72% yield, viscous liquid. R_f=0.29 [*V*(hexane)∶*V*(ethyl acetate)=3∶1], 99% *ee* [HPLC: Chiralcel IA column, 254 nm, 30 ℃, *V*(*n*-hexane)∶*V*(*i*-PrOH)=70∶30, flow=0.7 mL/min, retention time 14.4 min (minor) and 16.4 min (major)]. $[\alpha]_D^{20}$ −114.84 (*c* 0.97, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.68 (d, *J*=8.1 Hz, 2H), 7.45 (d, *J*=8.2 Hz, 2H), 7.42～7.32 (m, 4H), 7.32～7.27 (m, 1H), 7.24～7.13 (m, 5H), 7.13～7.02 (m, 3H), 6.66～6.41 (br, 1H), 5.45 (s, 1H), 2.36 (s, 3H), 2.05 (s, 3H), 1.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 167.9, 154.1, 154.1, 153.3, 148.2, 144.3, 142.0, 140.9, 137.8, 136.7, 131.4, 130.3, 130.1, 129.7, 129.3, 127.6, 127.6, 127.3, 125.8, 124.9, 123.5, 123.0, 122.6, 119.3, 113.9, 111.7, 107.2, 36.7, 21.7, 20.0, 13.8; HRMS calcd for $C_{34}H_{29}BrN_3O_5S$ $[M+H]^+$ 670.1006, found 670.1011.

(−)-3-Methyl-4-((5-methyl-3-((toluyl)sulfonamido)-benzofuran-2-yl)(phenyl)methyl)-1-phenyl-1*H*-pyrazol-5-yl acetate (**4ka**): 0.1 mmol, 42 mg, 69% yield, viscous liquid. R_f=0.48 [*V*(hexanes)∶*V*(ethyl acetate)=3∶1], 76% *ee* [HPLC: Chiralcel IA column, 254 nm, 30 ℃, *V*(*n*-hexane)∶*V*(*i*-PrOH)=70∶30, flow=0.7 mL/min, retention time 10.2 min (minor) and 13.3 min (major)]. $[\alpha]_D^{20}$ −75.71 (*c* 0.42, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.68 (d, *J*=8.2 Hz, 2H), 7.48～7.43 (m, 2H), 7.42～7.34 (m, 2H), 7.31～7.23 (m, 4H), 7.22～7.10 (m, 5H), 7.02～6.94 (m, 1H), 6.66 (s, 1H), 6.35 (s, 1H), 5.46 (s, 1H), 2.37 (s, 3H), 2.25 (s, 3H), 2.01 (s, 3H), 1.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 168.0, 155.2, 151.7, 148.4, 144.1, 141.9, 138.6, 138.0, 137.0, 132.8, 129.8, 129.3, 128.6, 128.5, 127.8, 127.4, 127.1, 126.0, 125.9, 122.9, 119.0, 113.3, 111.2, 107.7, 37.1, 21.6, 21.2, 20.1, 13.7; HRMS calcd for $C_{35}H_{32}N_3O_5S$ $[M+H]^+$ 606.2057, found 606.2066.

(−)-3-Methyl-4-((6-methyl-3-((toulyl)sulfonamido)-benzofuran-2-yl)(phenyl)methyl)-1-phenyl-1*H*-pyrazol-5-yl acetate (**4la**): 105 mg, 89% yield, yellow solid. m.p. 110～111 ℃, R_f=0.23 [*V*(hexanes)∶*V*(ethyl acetate)=3∶1], 81% *ee* [HPLC: Chiralcel IA column, 254 nm, 30 ℃, *V*(*n*-Hexane)∶*V*(*i*-PrOH)=70∶30, flow=0.7 mL/min, retention time 11.9 min (minor) and 14.4 min (major)]. $[\alpha]_D^{20}$ −85.44 (*c* 2.04, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.65 (d, *J*=8.2 Hz, 2H), 7.44 (d, *J*=7.6 Hz, 2H), 7.40～7.32 (m, 2H), 7.30～7.20 (m, 4H), 7.17～7.06 (m, 5H), 6.96～6.84 (m, 2H), 6.59 (s, 1H), 5.45 (s, 1H), 2.37 (s, 3H), 2.33 (s, 3H), 1.99 (s, 3H), 1.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 167.9, 153.8, 153.7, 148.4, 144.0, 141.9, 138.7, 137.9, 136.8, 134.9, 129.7, 129.2, 128.5, 128.4, 127.6, 127.4, 127.0, 124.7, 123.4, 122.9, 118.8, 113.5, 111.8, 107.8, 37.1, 21.7, 21.6, 20.0, 13.7; HRMS calcd for $C_{35}H_{32}N_3O_5S$ $[M+H]^+$ 606.2057, found 606.2058.

(−)-3-Methyl-4-((3-((4-nitrophenyl)sulfonamido)-benzofuran-2-yl)(phenyl)methyl)-1-phenyl-1*H*-pyrazol-5-yl acetate (**4ma**): 69 mg, 56% yield, yellow solid. m.p. 115～116 ℃; R_f=0.17 [*V*(hexanes)∶*V*(ethyl acetate)=3∶1], 81% *ee* [HPLC: Chiralcel IA column, 254 nm, 30 ℃, *V*(*n*-Hexane)∶*V*(*i*-PrOH)=70∶30, flow=0.7 mL/min, retention time 13.4 min (minor) and 18.6 min

(major)]. $[\alpha]_D^{20}$ −68.43 (*c* 1.02, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) *δ*: 8.09 (d, *J*=8.8 Hz, 2H), 7.87 (d, *J*=8.8 Hz, 2H), 7.41 (d, *J*=7.6 Hz, 2H), 7.38～7.31 (m, 3H), 7.28～7.17 (m, 6H), 7.15～7.11 (m, 2H), 7.07～6.99 (m, 1H), 6.91～6.86 (m, 1H), 5.53 (s, 1H), 2.01 (s, 3H), 1.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 168.0, 155.1, 153.2, 150.2, 148.4, 145.4, 141.9, 138.3, 137.7, 129.3, 128.8, 128.6, 128.4, 127.6, 127.3, 125.3, 125.1, 124.3, 123.6, 123.0, 118.7, 112.9, 111.9, 107.6, 37.2, 20.1, 13.6; HRMS calcd for $C_{33}H_{27}N_4O_7S$ $[M+H]^+$ 623.1595, found 623.1590.

(−)-4-((3-(Mesitylamino)benzofuran-2-yl)(phenyl)-methyl)-3-methyl-1-phenyl-1*H*-pyrazol-5-yl acetate (**4na**): 111 mg, 90% yield, yellow solid. m.p. 92～93 ℃; R_f= 0.43 [*V*(hexanes) ∶ *V*(ethyl acetate) = 3 ∶ 1], 90% *ee* [HPLC: Chiralcel IA column, 254 nm, 30 ℃, *V*(*n*-hexane) ∶ *V*(*i*-PrOH) = 70 ∶ 30, flow = 0.7 mL/min, retention time 8.4 min (minor) and 10.9 min. (major)]. $[\alpha]_D^{20}$ −109.72 (*c* 2.20, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) *δ*: 7.46～7.41 (m, 2H), 7.39～7.28 (m, 3H), 7.28～7.16 (m, 5H), 7.14～7.03 (m, 4H), 6.84 (s, 2H), 6.45 (s, 1H), 5.37 (s, 1H), 2.51 (s, 6H), 2.22 (s, 3H), 2.00 (s, 3H), 1.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 168.0, 155.4, 153.3, 148.2, 142.9, 141.8, 139.6, 138.4, 137.9, 134.1, 132.1, 129.3, 128.6, 128.4, 127.4, 127.1, 126.4, 124.6, 123.5, 122.8, 119.5, 113.4, 111.6, 107.6, 37.3, 23.3, 21.0, 20.0, 13.6; HRMS calcd for $C_{36}H_{34}N_3O_5S$ $[M+H]^+$ 620.2214, found 620.2211.

(−)-3-Ethyl-4-((3-((4-methylphenyl)sulfonamido)-benzofuran-2-yl)(phenyl)methyl)-1-phenyl-1*H*-pyrazol-5-yl acetate (**4ab**): 100 mg, 83% yield, viscous liquid. R_f= 0.35 [*V*(hexane) ∶ *V*(ethyl acetate) = 5 ∶ 1], 96% *ee* [HPLC: Chiralcel IA column, 254 nm, 30 ℃, *V*(*n*-Hexane) ∶ *V*(*i*-PrOH) = 70 ∶ 30, flow = 0.7 mL/min, retention time 10.1 min (minor) and 23.0 min (major)]. $[\alpha]_D^{20}$ −115.99 (*c* 1.30, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) *δ*: 7.68 (d, *J*=8.3 Hz, 2H), 7.49～7.44 (m, 2H), 7.42～7.35 (m, 2H), 7.34～7.23 (m, 5H), 7.22～7.16 (m, 3H), 7.15～7.02 (m, 4H), 6.17 (s, 1H), 5.46 (s, 1H), 2.47～2.37 (m, 2H), 2.37 (s, 3H), 1.67 (s, 3H), 1.09 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 167.9, 154.9, 153.3, 153.0, 144.2, 141.8, 138.7, 138.1, 136.9, 129.8, 129.3, 128.7, 128.5, 127.7, 127.4, 127.2, 126.0, 124.7, 123.4, 123.0, 119.3, 113.5, 111.6, 107.0, 37.1, 21.7, 21.1, 19.9, 12.6; HRMS calcd for $C_{35}H_{32}N_3O_5S$ $[M+H]^+$ 606.2057, found 606.2060.

(−)-4-((3-((4-Methylphenyl)sulfonamido)benzofuran-2-yl)(phenyl)methyl)-1-phenyl-3-propyl-1*H*-pyrazol-5-yl acetate (**4ac**): 119 mg, 96% yield, viscous liquid. R_f=0.40 [*V*(hexanes) ∶ *V*(ethyl acetate)=5 ∶ 1], 84% *ee* [HPLC: Chiralcel IA column, 254 nm, 30 ℃, *V*(*n*-Hexane) ∶ *V*(*i*-PrOH) = 70 ∶ 30, flow = 0.7 mL/min, retention time 10.8 min (minor) and 35.3 min (major)]. $[\alpha]_D^{20}$ −79.03 (*c* 2.08, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) *δ*: 7.68 (d, *J*= 8.3 Hz, 2H), 7.49～7.42 (m, 2H), 7.42～7.35 (m, 2H), 7.35～7.23 (m, 5H), 7.23～7.15 (m, 3H), 7.14～7.02 (m, 4H), 6.27 (s, 1H), 5.46 (s, 1H), 2.37 (s, 3H), 2.41～2.25 (m, 2H), 1.65 (s, 3H), 1.59～1.39 (m, 2H), 0.86 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 167.8, 154.7, 153.2, 151.9, 144.1, 141.6, 138.6, 138.0, 136.8, 129.7, 129.2, 128.6, 128.4, 127.6, 127.3, 127.0, 125.9, 124.5, 123.3, 122.9, 119.2, 113.4, 111.5, 107.2, 37.1, 29.7, 21.8, 21.6, 19.8, 14.2; HRMS calcd for $C_{36}H_{34}N_3O_5S$ $[M+H]^+$ 620.2214, found 620.2217.

(−)-4-((3-((4-Methylphenyl)sulfonamido)benzofuran-2-yl)(phenyl)methyl)-1-phenyl-3-(*m*-tolyl)-1*H*-pyrazol-5-yl acetate (**4ad**): 95 mg, 71% yield, yellow solid. m.p. 186～187 ℃; R_f = 0.21 [*V*(hexanes) ∶ *V*(dichloromethane) ∶ *V*(ethyl acetate)=2 ∶ 2 ∶ 0.1], 49% *ee* [HPLC: Chiralcel IA column, 254 nm, 30 ℃, *V*(*n*-hexane) ∶ *V*(*i*-PrOH)= 70 ∶ 30, flow=0.7 mL/min, retention time 9.6 min (minor) and 22.9 (major) min]; $[\alpha]_D^{20}$ −77.67 (*c* 1.76, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) *δ*: 7.57～7.47 (m, 3H), 7.44～7.37 (m, 4H), 7.32～7.13 (m, 11H), 6.92 (d, *J*=8.2 Hz, 4H), 5.89～5.79 (br, 1H), 5.19 (s, 1H), 2.32 (s, 3H), 2.24 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 167.0, 153.6, 153.3, 151.0, 143.9, 142.5, 138.5, 138.3, 137.9, 136.2, 132.8, 129.6, 129.5, 129.4, 129.3, 128.7, 128.5, 128.4, 127.9, 127.5, 127.0, 126.3, 125.7, 124.7, 123.5, 123.2, 120.2, 113.8, 111.4, 107.5, 37.6, 21.6, 21.5, 20.0; HRMS calcd for $C_{40}H_{34}N_3O_5S$ $[M+H]^+$ 668.2214, found 668.2210.

(−)-3-Methyl-4-((3-((4-methylphenyl)sulfonamido)-benzofuran-2-yl)(phenyl)methyl)-1-(*p*-tolyl)-1*H*-pyrazol-5-yl acetate (**4ae**): 111 mg, 92% yield, viscous liquid. R_f= 0.40 [*V*(hexanes) ∶ *V*(ethyl acetate) = 5 ∶ 1], 80% *ee* [HPLC: Chiralcel IA column, 254 nm, 30 ℃, *V*(*n*-hexane) ∶ *V*(*i*-PrOH) = 70 ∶ 30, flow = 0.7 mL/min, retention time 16.1 min (minor) and 23.5 min (major)]. $[\alpha]_D^{20}$ −89.99 (*c* 2.02, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) *δ*: 7.70 (d, *J*=8.3 Hz, 2H), 7.37～7.32 (m, 3H), 7.31～7.25 (m, 3H), 7.24～7.17 (m, 5H), 7.15～7.11 (m, 2H), 7.11～7.06 (m, 2H), 6.50 (s, 1H), 5.48 (s, 1H), 2.38 (s, 3H), 2.36 (s, 3H), 2.03 (s, 3H), 1.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 168.0, 154.9, 153.2, 148.0, 144.1, 141.9, 138.5, 137.4, 136.9, 135.5, 129.8, 129.8, 128.6, 128.5, 127.6, 127.1, 126.0, 124.6, 123.3, 122.9, 119.3, 113.6, 111.6, 107.4, 37.2, 21.7, 21.2, 20.0, 13.7; HRMS calcd for $C_{35}H_{32}N_3O_5S$ $[M+H]^+$ 606.2057, found 606.2053.

(−)-1-(4-Methoxyphenyl)-3-methyl-4-((3-((4-methyl-phenyl)sulfonamido)benzofuran-2-yl)(phenyl)methyl)-1*H*-pyrazol-5-yl acetate (**4af**): 113 mg, 91% yield, viscous liquid. R_f=0.30 [*V*(hexanes) ∶ *V*(ethyl acetate)=5 ∶ 1], 82% *ee* [HPLC: Chiralcel IA column, 254 nm, 30 ℃, *V*(*n*-hexane) ∶ *V*(*i*-PrOH) = 70 ∶ 30, flow = 0.7 mL/min, retention time 20.2 min (minor) and 32.8 min (major)]. $[\alpha]_D^{20}$ −88.33 (*c* 2.34, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) *δ*: 7.67 (d, *J*=8.2 Hz, 2H), 7.36～7.31 (m, 3H), 7.31～7.26 (m, 3H), 7.21～7.14 (m, 3H), 7.12～7.01 (m, 4H), 6.96～6.78 (m, 2H), 6.26 (s, 1H), 5.43 (s, 1H), 3.80 (s, 3H), 2.37 (s, 3H), 2.00 (s, 3H), 1.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 168.1, 159.0, 155.0, 153.3, 147.9, 144.2, 141.9, 138.5, 136.9, 131.0, 129.8, 128.6, 128.5,

127.7, 127.1, 126.0, 124.9, 124.7, 123.4, 119.3, 114.4, 113.6, 111.7, 107.1, 55.6, 37.2, 21.7, 20.0, 13.7; HRMS calcd for $C_{35}H_{32}N_3O_6S$ $[M+H]^+$ 622.2006, found 622.2008.

(−)-1-(4-Chlorophenyl)-3-methyl-4-((3-((4-methylphenyl)sulfonamido)benzofuran-2-yl)(phenyl)methyl)-1*H*-pyrazol-5-yl acetate (**4ag**): 113 mg, 90% yield, viscous liquid. R_f = 0.40 [*V*(hexane) : *V*(ethyl acetate) = 5 : 1], 78% *ee* [HPLC: Chiralcel IA column, 254 nm, 30 ℃, *V*(*n*-Hexane) : *V*(*i*-PrOH) = 70 : 30, flow = 0.7 mL/min, retention time 15.2 min (minor) and 22.9 min (major)]. $[\alpha]_D^{20}$ −78.70 (*c* 1.70, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.67 (d, *J* = 8.3 Hz, 2H), 7.44～7.37 (m, 2H), 7.37～7.31 (m, 3H), 7.31～7.25 (m, 3H), 7.23～7.10 (m, 5H), 7.08～7.03 (m, 1H), 7.01～6.95 (m, 1H), 6.42 (s, 1H), 5.51 (s, 1H), 2.36 (s, 3H), 2.02 (s, 3H), 1.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 167.8, 154.8, 153.2, 148.8, 144.2, 142.0, 138.4, 136.9, 136.5, 133.0, 129.8, 129.5, 128.6, 127.6, 127.2, 125.9, 124.7, 124.0, 123.4, 119.2, 113.6, 111.7, 108.1, 37.1, 21.7, 20.0, 13.7; HRMS calcd for $C_{34}H_{29}ClN_3O_5S$ $[M+H]^+$ 626.1511, found 626.1512.

(−)-3-Methyl-4-((3-((4-methylphenyl)sulfonamido)-benzofuran-2-yl)(phenyl)methyl)-1-(*m*-tolyl)-1*H*-pyrazol-5-yl acetate (**4ah**): 85 mg, 70% yield, pale yellow solid. m.p. 86～87 ℃; R_f = 0.40 [*V*(hexane) : *V*(ethyl acetate) = 5 : 1], 99% *ee* [HPLC: Chiralcel IA column, 254 nm, 30 ℃, *V*(*n*-hexane) : *V*(*i*-PrOH) = 70 : 30, flow = 0.7 mL/min, retention time 12.6 min (minor) and 20.2 min (major)]. $[\alpha]_D^{20}$ −86.89 (*c* 1.04, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.68 (d, *J* = 8.3 Hz, 2H), 7.37～7.27 (m, 4H), 7.26～7.14 (m, 6H), 7.14～7.02 (m, 5H), 6.38 (s, 1H), 5.46 (s, 1H), 2.36 (s, 3H), 2.35 (s, 3H), 2.01 (s, 3H), 1.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 168.0, 154.9, 153.3, 148.2, 144.2, 141.9, 139.5, 138.5, 137.8, 136.7, 129.8, 129.0, 128.6, 128.5, 128.3, 127.7, 127.1, 126.0, 124.7, 123.8, 123.3, 119.7, 119.3, 113.6, 111.7, 107.6, 37.2, 21.7, 21.5, 20.0, 13.7; HRMS calcd for $C_{35}H_{32}N_3O_5S$ $[M+H]^+$ 606.2057, found 606.2060.

4.3 Experiment at gram scale

A mixture of azadiene **1a** (939 mg, 2.50 mmol), pyrazolin-5-one **2a** (479 mg, 2.75 mmol) and bifunctional squaramide organocatalyst **5a** (158 mg, 0.25 mmol) in dichloromethane (37.5 mL) was stirred at 30 ℃ for 2 h. The crude product was directly purified by silica gel column chromatography [eluent: *V*(hexane) : *V*(ethyl acetate) = 5 : 1 to 2 : 1]. To a solution of the product obtained above in chloroform (37.5 mL), acetic anhydride (281 mg, 2.75 mmol) and triethylamine (76 mg, 0.75 mmol) were added in sequence and the reaction mixture was stirred at ambient temperature for 3 h. After the completion of the reaction, the volatiles were removed by the reduced pressure, and the crude product was purified by column chromatography on silica gel by using hexane/ethyl acetate (*V* : *V* = 5 : 1) as the eluent to give product **3aa**, 1.140 g, 77% yield, 99% *ee*.

4.4 Determination of the absolute configuration

A mixture of azadiene **1a** (37.5 mg, 0.10 mmol), pyrazolin-5-one **2a** (17.4 mg, 0.10 mmol) and bifunctional squaramide organocatalyst **5a** (6.3 mg, 0.01 mmol) in dichloromethane (1.5 mL) was stirred at 30 ℃ for 2 h. The reaction mixture was directly purified by silica gel column chromatography using hexanes/ethyl acetate (*V* : *V* = 5 : 1 to 2 : 1) as eluent to give the desirable adduct **3aa**, 47.0 mg, 86% yield, 97% *ee*. To a solution of **3aa** (47.0 mg, 0.086 mol) obtained above in *N*,*N*-dimethylformamide (2.0 mL), potassium carbonate (70.5 mg, 0.51 mmol) and iodomethane (72.4 mg, 0.51 mmol) were added in sequence and the reaction mixture was stirred at ambient temperature for overnight. The reaction was quenched by water (20 mL), then the reaction mixture was extracted with ethyl acetate (20 mL×3). The organic layer was washed by water (20 mL×3) and dried over anhydrous sodium sulfate. The solvent was removed by reduced pressure and the crude product was purified by column chromatography on silica gel by using hexanes/ethyl acetate (*V* : *V* = 5 : 1) as eluent to give the dimethylation product (−)-**6**, 39 mg, 79% yield, 98% *ee*.

(*R*)-(−)-*N*-(2-((1,5-Dimethyl-3-*oxo*-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)(phenyl)methyl)benzofuran-3-yl)-*N*,4-dimethylbenzenesulfonamide (**6**): 39 mg, 79% yield, white solid. m.p. 210 ～ 211 ℃; R_f = 0.20 [*V*(hexane) : *V*(ethyl acetate) = 5 : 1], 98% *ee* [HPLC: Chiralcel AD-H column, 254 nm, 30 ℃, *V*(*n*-hexane) : *V*(*i*-PrOH) = 60 : 40, flow = 0.7 mL/min, retention time 9.2 min (major) and 23.1 min (minor)]; $[\alpha]_D^{20}$ −22.83 (*c* 0.60, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.54 (m, 2H), 7.48～7.26 (m, 7H), 7.26～6.81 (m, 9H), 5.44 (s, 1H), 3.38 (s, 3H), 3.05 (s, 3H), 2.27 (s, 3H), 2.08 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) *δ*: 165.2, 155.1, 154.9, 153.4, 143.4, 139.9, 136.0, 135.3, 129.5, 129.2, 128.4, 128.3, 127.5, 126.6, 126.4, 124.3, 123.9, 123.0, 120.0, 119.7, 111.7, 109.5, 38.7, 36.8, 35.8, 21.6, 12.1; HRMS (ESI-TOF) calcd for $C_{42}H_{38}N_3O_5S_2$ $[M+H]^+$ 578.2108, found 578.2113.

To determine the absolute configuration of (−)-**6**, a single crystal was grown from its solution in chloroform and *n*-hexane. *n*-Hexane was slowly added into the solution of (−)-**6** in chloroform at room temperature, then the solvent was slowly evaporated and single crystal was obtained. The absolute configuration of (−)-**6** is *R*. The CCDC number is CCDC 1962887. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk. So, the absolute configuration of the addition product and acylated compound (−)-**4aa** were assigned to be *R*.

Supporting Information ^{1}H NMR spectra, ^{13}C NMR spectra and HPLC spectra for compounds **4**, **6**. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn/.

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