CHEMISTRY
AN ASIAN JOURNAL

DOI: 10.1002/asia.201200686

Asymmetric Formal [3+2] Cycloaddition Reaction of α-Aryl Isocyanoesters with *N*-Aryl Maleimides by Bifunctional Cinchona Alkaloids-Based Squaramide/$AgSbF_6$ Cooperative Catalysis

Mei-Xin Zhao,*[a] Deng-Ke Wei,[a] Fei-Hu Ji,[a] Xiao-Li Zhao,[b] and Min Shi*[a, c]

Cooperative catalysis, which combines two or more catalytic species that operate together within the same molecular environment to achieve an overall transformation through synergistic activation of reaction partners, have been shown to possess distinguished advantages in developing new chemical transformations or improving the efficiency and stereoselectivity of existing transformations.[1] The organo/metal mixed system, as one of the three main categories of cooperative systems, has been widely used in reactions such as α-functionalization of aldehydes or imines, conjugate addition to α,β-unsaturated carbonyl compounds, and carbonyl and imine 1,2-addition via the merger of enamine or imine catalysis and metal catalysis.[1j] Moreover, cinchona alkaloid scaffolds have proven to be privileged systems in the cooperative catalysis owing to their facile preparation, excellent stereoselective induction, commercial availability, and presence of multiple sites for further functionalization. Cinchona alkaloid-derived ethers, esters, amides, and thioureas have been widely applied in nucleophilic additions of aldehydes, imines, and olefins, through their Brønsted/Lewis basic property, to activate pro-nucleophiles via deprotonation or coordination, and ketene cycloaddition reactions by using them as Lewis basic/nucleophilic catalyst.[1k]

While the thiourea framework has been considered a gold mine in H-bonding involved bifunctional activation processes, squaramides has become another complementary or even superior H-bond donor catalyst in asymmetric organocatalysis in the past several years.[2] Squaramide's dual binding ability, structural rigidity, different H-bond spacing, and lower pK_a values of the *N*-H protons, may lead to a broader substrate scope, improved recognition, better stereoinduction, or rate enhancement compared to the thiourea or urea analogues in some cases. However, to the best of our knowledge, no example of organo/metal cooperative catalysis involving squaramide has been reported.

The cyclization reaction of isocyanides with carbon-carbon and carbon-heteroatom multiple bonds has proved to be a powerful tool for the synthesis of numerous important classes of nitrogen heterocyclic compounds due to the unique divalent features of the isocyano group that make isocyanides react smoothly with both electrophiles and nucleophiles.[3] Isocyanoacetates, owing to an acidic proton in the α-position originating from the ester group, have exhibited an exceptional reaction diversity and high synthetic potential. In light of the pioneering work by Ito and Hayashi, using chiral Au^I or Ag^I complexes as catalysts to promote the asymmetric addition of isocyanoacetates to aldehydes,[4] this type of addition had been widely used in the synthesis of some bioactive molecules and natural products in the 1980s.[5] However, this kind of asymmetric reaction was overlooked and received limited attention in the following twenty years[6,7] until Gong and co-workers described the first organocatalytic asymmetric reaction of α-aryl isocyanoacetates with nitroolefins in the presence of cinchona alkaloids.[8] Since then, organo- or organometallic-catalyzed asymmetric additions of isocyanoacetates with many electrophiles, such as aldehydes,[9] imines,[10] azodicarboxylates,[11] α,β-unsaturated carbonyl compounds,[12] and maleimides,[13] have been intensively investigated.

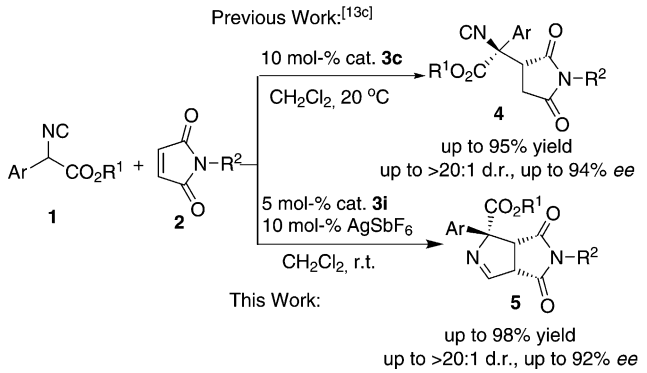
As part of our ongoing interest in the enantioselective addition reactions of α-aryl isocyanoacetates to unsaturated compounds, we have developed a highly diastereo- and enantioselective Michael addition reaction of α-aryl isocyanoacetates to *N*-aryl maleimides using quinine-derived squaramide as catalyst (Scheme 1).[13c] Different from those addition reactions of isocyanoacetates to nitroolefins or α,β-unsaturated carbonyl compounds, Michael adducts **4** rather than expected [3+2] cycloaddition products **5** were obtained in this reaction. Considering that silver acetate is an efficient catalyst for the cycloaddition reaction of isocyanoacetates with various Michael acceptors[14] and encouraged by the development in the field of cooperative catalysis using cincho-

[a] Dr. M.-X. Zhao, D.-K. Wei, F.-H. Ji, Prof. Dr. M. Shi
Key Laboratory for Advanced Materials and Institute of Fine Chemicals
East China University of Science and Technology
130 Meilong Road, Shanghai, 200237 (P. R. China)
Fax: (+86) 21-34201699
E-mail: mxzhao@ecust.edu.cn
Mshi@mail.sioc.ac.cn

[b] Dr. X.-L. Zhao
Department of Chemistry
East China Normal University
3663 N. Zhongshan Road, Shanghai, 200062 (P. R. China)

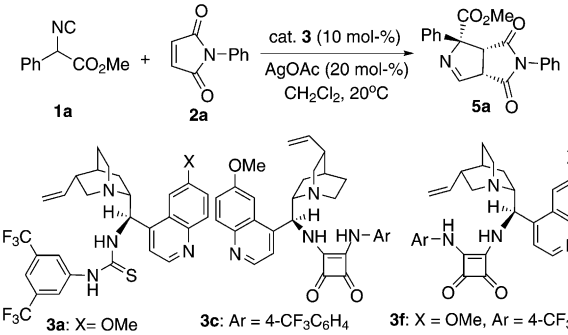
[c] Prof. Dr. M. Shi
State Key Laboratory of Organometallic Chemistry
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences
354 Fenglin Road, Shanghai 200032 (P. R. China)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/asia.201200686.



Scheme 1. Asymmetric reactions of α-aryl isocyanoacetates **1** with maleimides **2**.

Table 1. Screening of catalysts for the asymmetric [3+2] cycloaddition of α-phenyl isocyanoacetate **1a** with *N*-phenyl maleimide **2a**.[a]



Entry[a]	Catalyst **3**	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**3a**	75	>20:1	6
2	**3b**	82	>20:1	4
3	**3c**	80	>20:1	41[e]
4	**3d**	82	>20:1	40[e]
5	**3e**	90	>20:1	46[e]
6	**3f**	90	>20:1	63
7	**3g**	85	>20:1	67
8	**3h**	72	>20:1	65

[a] Unless noted otherwise, all reactions were carried out with **1a** (0.2 mmol), **2a** (0.1 mmol), AgOAc (0.02 mmol), and **3** (0.01 mmol) in CH_2Cl_2 (2 mL) at 20 °C for 2 h. [b] Yield of isolated product. [c] The d.r. of the purified product was determined by ^{1}H NMR spectroscopy. [d] The *ee* was determined by HPLC on a chiral stationary phase. [e] The opposite enantiomer was obtained.

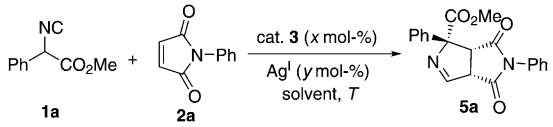
na alkaloid derivatives in combination with metal ions,[1k,9b,12a] we envisioned that cinchona alkaloid derivatives/Ag^I salt cooperative catalysis could facilitate the [3+2] cycloaddition reaction of isocyanoacetates with *N*-aryl maleimides, affording the expected optically active, substituted 1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole derivatives **5**. While one example has been reported very recently for the catalytic asymmetric [3+2] cycloaddition of α-substituted isocyanoacetates with *N*-phenyl maleimides using a cationic Au^I/DTBM-segphos complex as catalyst,[13b] to the best of our knowledge, no example of an organo/metal cooperative catalytic system for this kind of reaction has been reported. Herein, we wish to report our studies on this subject.

In our initial attempt we examined the reaction outcome of the asymmetric [3+2] cycloaddition reaction of α-phenyl isocyanoacetate **1a** with *N*-phenyl maleimide **2a** in dichloromethane at 20 °C. A variety of bifunctional cinchona alkaloid-derived thioureas or squaramides, in combination with 20 mol % of AgOAc, were examined in these model reactions, and the results of these experiments are summarized in Table 1. Quinidine- or cinchonine-derived thiourea catalysts **3a** and **3b** exhibited high catalytic activity, affording the desired adduct **5a** in high yield and good diastereoselectivity but with low enantioselectivity (Table 1, entries 1–2). However, the use of quinine- or quinidine-derived squaramides as organocatalyst significantly improved the enantioselectivity along with similar diastereoselectivity and yield (Table 1, entries 3–8). It should be noted that different from the cinchona alkaloid-derived squaramide-catalyzed asymmetric Michael addition of α-aryl isocyanoacetates to maleimides, in which quinine-derived squaramide **3c** gave the best results, quinidine-derived squaramide catalysts **3f**–**3h** in combination with AgOAc resulted in a better enantioselectivity as compared to that obtained with the corresponding quinine-derived squaramide catalysts **3c**–**3e**. Catalyst **3g** turned out to be a good catalyst for this reaction, affording the corresponding product **5a** in 85 % yield with >20:1 d.r. and 67 % *ee* (Table 1, entry 7).

To improve the enantioselectivity, further efforts were undertaken by examining other parameters, such as solvents, Lewis acid, temperature, reaction concentrations, and catalyst loading; representative results are summarized in Table 2 (for further details, see Table S1 in the Supporting Information). It was found that this [3+2] cycloaddition reaction can proceed smoothly in most of less polar solvents to give **5a** with moderate enantioselectivity (Table 2, entries 1–6). Dichloromethane and ethyl acetate (EA) gave the best stereoselecitivity with similar yield at 15 °C when **3g** was used as an organocatalyst (Table 2, entries 1 and 6). Using ethyl acetate as solvent, the enantioselectivity and yield can be further improved by lowering the reactant concentration and adding 3 Å molecular sieves as additive, respectively (Table 2, entries 7–8). Among the various Lewis acids screened (see Table S1 in the Supporting Information), $AgSbF_6$ was found to be the best metal catalyst (Table 2, entry 9).[15] Further screening with cinchonine-derived squaramide catalysts **3i** and **3j** revealed that **3i** afforded **5a** with a higher yield and enantioselecitivity than **3g** and **3j** (Table 2, entries 10 vs. 9 and 11). Considering that dichloromethane was another suitable solvent for this reaction, we next re-examined the cooperative catalytic system **3i**/$AgSbF_6$ in CH_2Cl_2. Different from **3g**/AgOAc, no obvious temperature effect was observed (Table 1, entries 12 and 13). Reducing the ratio of **1a**/**2a** from 2:1 to 1.5:1 still afforded similar enantioselectivity and a reasonable yield (Table 1, entry 14). Further examination of catalyst loading

CHEMISTRY
AN ASIAN JOURNAL

Table 2. Optimization of the reaction conditions for the asymmetric [3+2] cycloaddition reaction of α-phenyl isocyanoacetate **1a** with *N*-phenyl maleimide **2a**.[a]



1a 2a 5a

Entry	3	Ag (I)	Solvent	T [°C]	t [h]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**3g**	AgOAc	CH_2Cl_2	15	2	77	>20:1	71
2	**3g**	AgOAc	$CHCl_3$	15	2	80	>20:1	63
3	**3g**	AgOAc	DCE	15	2	81	>20:1	66
4	**3g**	AgOAc	Et_2O	15	2	86	>20:1	66
5	**3g**	AgOAc	THF	15	2	90	>20:1	62
6	**3g**	AgOAc	EA	15	2	92	>20:1	72
7[e]	**3g**	AgOAc	EA	15	2	80	>20:1	77
8[e,f]	**3g**	AgOAc	EA	15	2	90	>20:1	76
9[e,f]	**3g**	$AgSbF_6$	EA	15	2	93	>20:1	77
10[e,f]	**3i**	$AgSbF_6$	EA	15	2	92	>20:1	81
11[e,f]	**3j**	$AgSbF_6$	EA	15	2	67	>20:1	73
12[f,g]	**3i**	$AgSbF_6$	CH_2Cl_2	15	0.5	98	>20:1	85
13[f,g]	**3i**	$AgSbF_6$	CH_2Cl_2	25	0.5	98	>20:1	85
14[f,g,h]	**3i**	$AgSbF_6$	CH_2Cl_2	25	0.5	86	>20:1	86
15[f,g,h,i]	**3i**	$AgSbF_6$	CH_2Cl_2	25	0.8	94	>20:1	88
16[f,g,h,j]	**3i**	$AgSbF_6$	CH_2Cl_2	25	1.5	95	>20:1	89
17[f,g,h,k]	**3i**	$AgSbF_6$	CH_2Cl_2	25	1.5	86	>20:1	89
18[f,g,h,l]	**3i**	$AgSbF_6$	CH_2Cl_2	25	1.5	86	>20:1	89
19[f,g,h,m]	**3i**	$AgSbF_6$	CH_2Cl_2	25	1.5	58	>20:1	84
20[f,g,h,n]	**3i**	$AgSbF_6$	CH_2Cl_2	25	1.5	62	>20:1	73

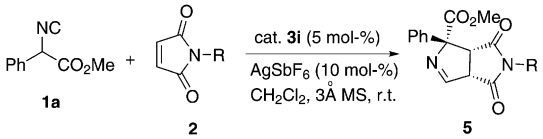
[a] Unless noted otherwise, all reactions were carried out with **1a** (0.2 mmol), **2a** (0.1 mmol), **3** (10 mmol%), and AgOAc or $AgSbF_6$ (20 mol%) in 2 mL of solvent. [b] Yield of isolated product. [c] The d.r. of the purified product was determined by ^{1}H NMR spectroscopy. [d] The *ee* was determined by HPLC on a chiral stationary phase. [e] Ethyl acetate (4 mL) was used. [f] 3 Å MS (30 mg) was added. [g] CH_2Cl_2 (4 mL) was used. [h] The ratio of **1a/2a** was 1.5:1. [i] **3i** (10 mmol%) and $AgSbF_6$ (10 mol%) were used. [j] **3i** (5 mmol%) and $AgSbF_6$ (10 mol%) were used. [k] **3i** (5 mmol%) and $AgSbF_6$ (5 mol%) were used. [l] **3i** (5 mmol%) and $AgSbF_6$ (1 mol%) were used. [m] **3i** (3 mmol%) and $AgSbF_6$ (1 mol%) were used. [n] **3i** (1 mmol%) and $AgSbF_6$ (1 mol%) were used.

revealed that reducing the equivalent of $AgSbF_6$ from 20 mol% to 1 mol% still afforded **5a** with high enantioselectivity, albeit with lower yield after a longer reaction time (Table 2, entries 15–18). However, upon reduction of the organocatalyst loading from 5 mol% to 1 mol%, a lower yield of **5a** along with a lower enantioselectivity was obtained (Table 2, entries 19–20). Considering both the yield and enantioselectivity, we identified 5 mol% of **3i** and 10 mol% of $AgSbF_6$ as the optimal catalyst loading.

With the optimized reaction conditions in hand, the scope of maleimides **2** was examined next; the results of these experiments are summarized in Table 3. Generally, most of the *N*-aryl substituted maleimides can undergo the [3+2] cycloaddition reaction smoothly to give the desired adducts **5a**–**g** in high yield (90–96%), excellent diastereoselectivity (> 20:1), and good enantioselectivity (74–89%). Both the electronic property of the substituents and the position of substitution play an important role in determining the reaction outcome. *N*-Aryl maleimides bearing with an electron-withdrawing group on the aromatic ring yielded the desired products in slightly lower enantioselectivity as compared to the corresponding substrates with no substituents or with electron-donating groups (Table 3, entries 2–3, 6 vs. 1, 4, 5, and 7). Substrate **2g**, bearing an electron-donating group at the *meta* position, afforded the corresponding product **5g** in much higher enantioselectivity than substrate **2e**, which bears an electron-donating group at the *para* position (Table 3, entries 7 vs. 5). For the less reactive *N*-alkyl-substituted maleimides **2h** and **2i**, the cycloaddition adducts **5h** and **5i** were obtained in good yield, high diastereoselectivity, and moderate enantioselectivity (Table 3, entries 8 and 9).

To broaden the substrate scope, a variety of isocyanoacetates bearing a variety of substituents with different electronic and steric proerties were also evaluated (Table 4). Generally, most of the reactions using these α-aryl isocyanoacetates reacted smoothly to afford the corresponding cycloaddition adducts in high yield and excellent diastereoselectivity. The enantioselectivity varied depending on the substituent's electronic property. α-Aryl-substituted isocyanoacetates bearing an electron-withdrawing group on the aromatic ring led to a better enantioselectivity than those bearing an electron-donating group (Table 4, entries 1–3, 5, and 7 vs. 4, 6, and 8). In the case of *ortho*-substituted isocyanoacetates **1h** and **1i**, which cannot react with maleimide **2a** in a Michael addition under catalysis of **3c**,[13c] the corresponding products **5p** and **5q** were also formed in high yield and good enantioselectivity (Table 4, entries 7 and 8). Different from benzyl α-phenyl isocyanoacetate **1j**, which could provide the corresponding adduct **5r** in high yield and good stereoselectivity, *t*-butyl α-phenyl isocyanoacetate **1k** afforded the product **5s** in moderate yield and similiar stereoselectivity, even after prolonged reaction times, presumably owing to steric hindrance

Table 3. Scope of *N*-substituted maleimides **2** for the asymmetric [3+2] cyclo- addition of isocyanoacetate **1a**.[a]

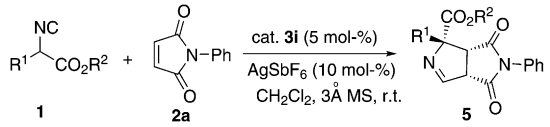


1a 2 5

Entry	2 (R)	5	t [h]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**2a** (Ph)	**5a**	1.5	95	>20:1	89
2	**2b** (4-FC_6H_4)	**5b**	0.5	90	>20:1	74
3	**2c** (4-BrC_6H_4)	**5c**	0.5	91	>20:1	78
4	**2d** (4-MeC_6H_4)	**5d**	0.5	92	>20:1	81
5	**2e** (4-$MeOC_6H_4$)	**5e**	0.5	92	>20:1	77
6	**2f** (3-ClC_6H_4)	**5f**	0.5	96	>20:1	77
7	**2g** (3-$MeOC_6H_4$)	**5g**	0.5	92	>20:1	86
8	**2h** (Bn)	**5h**	30	84	>20:1	65
9	**2i** (Me)	**5i**	10	76	>20:1	53

[a] All reactions were carried out with α-phenyl isocyanoacetate **1a** (0.225 mmol), maleimide **2** (0.15 mmol), **3i** (5 mol%), and $AgSbF_6$ (10 mol%) in CH_2Cl_2 (4.0 mL) at room temperature. [b] Yield of isolated product. [c] The diastereoisomeric ratio of the purified product was determined by ^{1}H NMR spectroscopy. [d] The *ee* was determined by HPLC on a chiral stationary phase.

Table 4. Scope of isocyanoacetates **1** for the asymmetric [3+2] cycloaddition with *N*-phenyl maleimide **2a**.[a]



1 2a 5

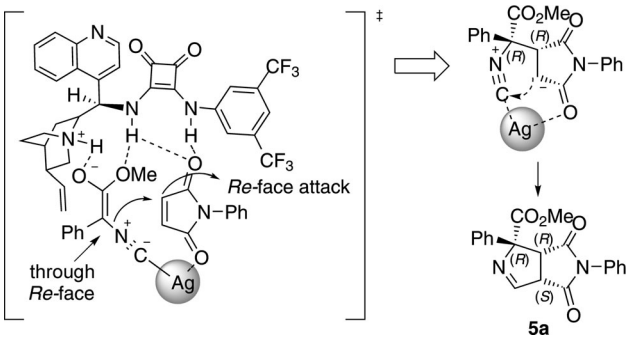
Entry	**1** (R^1/R^2)	**5**	*t* [h]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**1b** (4-FC_6H_4/OMe)	**5j**	0.5	93	>20:1	90
2	**1c** (4-ClC_6H_4/OMe)	**5k**	0.5	93	>20:1	90
3	**1d** (4-BrC_6H_4/OMe)	**5l**	0.5	91	>20:1	92
4	**1e** (4-MeC_6H_4/OMe)	**5m**	5	71	>20:1	74
5	**1f** (3-FC_6H_4/OMe)	**5n**	0.5	93	>20:1	89
6	**1g** (3-MeC_6H_4/OMe)	**5o**	2	97	>20:1	81
7	**1h** (2-BrC_6H_4/OMe)	**5p**	24	98	10:1	86
8	**1i** (2-MeC_6H_4/OMe)	**5q**	48	91	>20:1	79
9	**1j** (Ph/OBn)	**5r**	12	95	>20:1	80
10	**1k** (Ph/O*t*Bu)	**5s**	24	50	>20:1	80
11	**1l** (*i*Pr/OMe)	**5t**	96	85	>20:1	10
12	**1m** (Bn/OMe)	**5u**	44	83	>20:1	10
13	**1n** (H/OEt)	**5v**	4	67	>20:1	13

[a] All reactions were carried out with α-phenyl isocyanoacetate **1** (0.225 mmol), maleimide **2a** (0.15 mmol), **3i** (5 mol%), and $AgSbF_6$ (10 mol%) in CH_2Cl_2 (4.0 mL) at room temperature. [b] Yield of isolated product. [c] The diastereoisomeric ratio of the purified product was determined by ^{1}H NMR spectroscopy. [d] The *ee* was determined by HPLC on a chiral stationary phase.

(Table 4, entries 9 vs. 10). Moreover, α-alkyl- or non-substituted isocyanoacetates **1l**, **1m**, and **1n** are not suitable for this asymmetric [3+2] cycloaddition, affording the desired products **5t–v** in good yield, high diastereoselectivity along with very low stereoselectivity (only ca. 10% *ee*; Table 4, entries 11–13).

The absolute and relative configuration of **5** was unambiguously assigned by X-ray crystallographic analysis of the optically pure compound **5l**,[16] which was obtained by recrystallization from a mixture of dichloromethane and hexanes (Table 4, entry 3). The structure allowed the (1*R*, 3a*S*, 6a*R*) assignment of the newly formed stereogenic centers in **5l** (see Figure S1 in the Supporting Information). The configurations of other adducts were then assigned by analogy.

Although the mechanism of these reactions reported here remains to be clarified, a plausible transition-state model, based on the experimental results and commonly accepted mechanisms, is proposed in Scheme 2. In this model, one carbonyl group of maleimide **2a** is hydrogen-bonded to the squaramide motif, while the α-proton of isocyanoacetate **1a** is easily deprotonated by the quinuclidine nitrogen of catalyst **3i** due to the activation of Ag^I chelating to the terminal carbon of the isocyano group. A single hydrogen bond is then formed between the OH group of the enolized isocyanoacetate and the tertiary amine of quinine. A weak hydrogen bond between the OMe group of the enolized isocyanoacetate and the NH in the squaramide moiety, as well as an interaction between Ag^I and the other carbonyl group of the maleimide might be formed concurrently, thus forcing the isocyanoacetate enolate to attack the maleimide from the *Re*-face, thereby leading to the formation of two newly generated stereocenters with (*R, R*)-configuration. Subsequently, a *5-endo-dig* cyclization would take place assisted by electrophilic silver isocyanide activation. The third stereocenter is formed as *S*-configuration after the cyclization step.



Scheme 2. Proposed transition-state model.

In summary, we have developed the first example of a cinchona alkaloid-derived squaramide/$AgSbF_6$ cooperative catalytic system for the highly diastereo- and enantioselective formal [3+2] cycloaddition of α-aryl isocyanoacetates with *N*-aryl maleimides. A wide variety of *N*-aryl-substituted maleimides and α-aryl isocyanoacetates, with different electronic and steric properties, were tolerated in this catalytic enantioselective [3+2] cycloaddition reaction, leading to optically active 1,3a,4,5,6,6a-hexahydropyrrolo[3,4-c]pyrrole derivatives in high yield along with good to excellent diastereo- and enantioselectivities. Investigations aimed at fully understanding the reaction mechanism and expanding this kind of bifunctional organo/metal cooperative catalysis with cinchona alkaloid scaffolds to other valuable transformations are currently ongoing in our laboratory.

Experimental Section

*General procedure for the asymmetric [3+2] cycloaddition of isocyanoacetates **1** with maleimides **2** under the cooperative catalysis by **3i**/$AgSbF_6$*

A solution of isocyanoacetate **1** (0.225 mmol), **3i** (4.5 mg, 0.0075 mmol), $AgSbF_6$ (5.2 mg, 0.015 mmol), and 3 Å MS (30 mg) in CH_2Cl_2 (4 mL) was stirred at room temperature for 10 min, followed by addition of maleimide **2** (0.15 mmol). The resulting mixture was stirred at room temperature for 0.5–96 h until the reaction was complete (monitored by TLC). Subsequently, the mixture was concentrated and purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 4:1) to furnish the corresponding cycloaddition product **5**.

*(1R,3aS,6aR)-Methyl-1-(4-fluorophenyl)-4,6-dioxo-5-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**5j**)*

Yellow solid, yield: 50.8 mg (93%); d.r. >20:1; m.p. 192.2–193.7 °C; $[\alpha]_D^{25} = -110.1$ ($c = 1.0$, CH_2Cl_2); 90% *ee* (Chiralpak AD-H; hexane/2-propanol, 3:2; 0.8 mL min^{-1}; 230 nm; $t_{major} = 14.48$ min, $t_{minor} = 24.83$ min); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.02$ (d, $J = 1.6$ Hz, 1H, =CH), 7.61–7.58 (m, 2H, ArH), 7.50 (t, $J = 7.2$ Hz, 2H, ArH), 7.44 (d, $J = 7.2$ Hz, 1H, ArH), 7.32 (dd, $J = 7.2$, 1.2 Hz, 2H, ArH), 7.11 (t, $J = 8.4$ Hz, 2H, ArH), 4.44 (dd, $J = 9.2$, 1.2 Hz, 1H, CH), 3.85 (d, $J = 9.2$ Hz, 1H, CH), 3.65 ppm (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 174.2$, 170.9, 169.8, 162.3 (d, $J = 245.2$ Hz), 162.0, 136.4 (d, $J = 2.3$ Hz), 131.4, 129.3, 129.0, 128.8 (d, $J = 8.2$ Hz), 126.5, 115.3 (d, $J = 21.8$ Hz), 89.8, 59.9, 54.1,

53.7 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -113.7$ ppm. IR (film): $\tilde{\nu} =$ 1713, 1509, 1383, 1226, 1192 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{16}FN_2O_4$ $[M+H]^+$ 367.1094; found: 367.1093.

Acknowledgements

We are grateful for financial support from the National Natural Science Foundation of China (20772030, 21072056, 21272067), the Fundamental Research Funds for the Central Universities, Scientific Research Foundation for the Returned Overseas Chinese Scholars, and State Education Ministry and Shanghai Rising-Star Program (10QA1402000).

Keywords: [3+2] cycloaddition · cooperative catalysis · isocyanoacetates · maleimides · synthetic methods

[1] For selected recent reviews on cooperative catalysis and references cited therein, see: a) J.-A. Ma, D. Cahard, *Angew. Chem.* **2004**, *116*, 4666–4683; *Angew. Chem. Int. Ed.* **2004**, *43*, 4566–4583; b) M. Kanai, N. Kato, E. Ichikawa, M. Shibasaki, *Synlett* **2005**, 1491–1508; c) M. Kanai, N. Kato, E. Ichikawa, M. Shibasaki, *Pure Appl. Chem.* **2005**, *77*, 2047–2052; d) Y. J. Park, J.-W. Park, C.-H. Jun, *Acc. Chem. Res.* **2008**, *41*, 222–234; e) D. H. Paull, C. J. Abraham, M. T. Scerba, E. Alden-Danforth, T. Lectka, *Acc. Chem. Res.* **2008**, *41*, 655–663; f) Z. Shao, H. Zhang, *Chem. Soc. Rev.* **2009**, *38*, 2745–2755; g) J. Zhou, *Chem. Asian J.* **2010**, *5*, 422–434; h) A. S. K. Hashmi, C. Hubbert, *Angew. Chem.* **2010**, *122*, 1026–1028; *Angew. Chem. Int. Ed.* **2010**, *49*, 1010–1012; i) C. Zhong, X. Shi, *Eur. J. Org. Chem.* **2010**, 2999–3025; j) A. E. Allen, D. W. C. MacMillan, *Chem. Sci.* **2012**, *3*, 633–658; k) L. Stegbauer, F. Sladojevich, D. J. Dixon, *Chem. Sci.* **2012**, *3*, 942–958.

[2] For recent review and references cited therein, see: a) J. Alemán, A. Parra, H. Jiang, K. A. Jørgensen, *Chem. Eur. J.* **2011**, *17*, 6890–6899; For selected recent examples, see: b) Y.-F. Wang, R.-X. Chen, K. Wang, B.-B. Zhang, Z.-B. Li, D.-Q. Xu, *Green Chem.* **2012**, *14*, 893–895; c) J.-B. Ling, Y. Su, H.-L. Zhu, G.-Y. Wang, P.-F. Xu, *Org. Lett.* **2012**, *14*, 1090–1093; d) X. Wang, W. Yao, Z. Yao, C. Ma, *J. Org. Chem.* **2012**, *77*, 2959–2965; e) H.-J. Yang, L. Dai, S.-Q. Yang, F.-E. Chen, *Synlett* **2012**, 948–950; f) J.-Y. Qian, C.-C. Wang, F. Sha, X.-Y. Wu, *RSC Adv.* **2012**, *2*, 6042–6048; g) W. Yang, D.-M. Du, *Chem. Commun.* **2011**, *47*, 12706–12708; h) N. Hara, S. Nakamura, Y. Funahashi, N. Shibata, *Adv. Synth. Catal.* **2011**, *353*, 2976–2980; i) C. Min, X. Han, Z. Liao, X. Wu, H.-B. Zhou, C. Dong, *Adv. Synth. Catal.* **2011**, *353*, 2715–2720; j) V. Marcos, J. Aleman, J. L. Garcia Ruano, F. Marini, M. Tiecco, *Org. Lett.* **2011**, *13*, 3052–3055; k) J. P. Malerich, K. Hagihara, V. H. Rawal, *J. Am. Chem. Soc.* **2008**, *130*, 14416–14417.

[3] For recent review, see: a) A. V. Lygin, A. de Meijere, *Angew. Chem.* **2010**, *122*, 9280–9311; *Angew. Chem. Int. Ed.* **2010**, *49*, 9094–9124; b) A. V. Gulevich, A. G. Zhdanko, R. V. A. Orru, V. G. Nenajdenko, *Chem. Rev.* **2010**, *110*, 5235–5331.

[4] a) Y. Ito, M. Sawamura, T. Hayashi, *J. Am. Chem. Soc.* **1986**, *108*, 6405–6406; b) Y. Ito, M. Sawamura, T. Hayashi, *Tetrahedron Lett.* **1987**, *28*, 6215–6218; c) T. Hayashi, M. Sawamura, Y. Ito, *Tetrahedron* **1992**, *48*, 1999–2012; d) T. Hayashi, Y. Uozumi, A. Yamazaki, M. Sawamura, H. Hamashima, Y. Ito, *Tetrahedron Lett.* **1991**, *32*, 2799–2802.

[5] a) Y. Ito, M. Sawamura, T. Hayashi, *Tetrahedron Lett.* **1988**, *29*, 239–240; b) A. Togni, S. D. Pastor, G. Rihs, *Helv. Chim. Acta* **1989**, *72*, 1471–1478; c) M. D. Bachi, A. Melman, *J. Org. Chem.* **1997**, *62*, 1896–1898.

[6] a) Y. Ito, M. Sawamura, M. Kobayashi, T. Hayashi, *Tetrahedron Lett.* **1988**, *29*, 6321–6324; b) S. D. Pastor, A. Togni, *J. Am. Chem. Soc.* **1989**, *111*, 2333–2334; c) A. Togni, S. D. Pastor, *Tetrahedron Lett.* **1989**, *30*, 1071–1072; d) M. Sawamura, Y. Ito, T. Hayashi, *Tetrahedron Lett.* **1989**, *30*, 2247–2250; e) M. Sawamura, Y. Nakayama, T. Kato, Y. Ito, *J. Org. Chem.* **1995**, *60*, 1727–1732.

[7] Chiral cation Pd and Pt complex catalyzed asymmetric reactions, see: a) J. M. Longmire, X. Zhang, M. Shang, *Organometallics* **1998**, *17*, 4374–4379; b) F. Gorla, A. Togni, L. M. Venanzi, A. Albinati, F. Lianza, *Organometallics* **1994**, *13*, 1607–1616; c) Y. Motoyama, H. Kawakami, K. Shimozono, K. Aoki, H. Nishiyama, *Organometallics* **2002**, *21*, 3408–3416; d) S. Gosiewska, M. H. in't Vald, J. J. M. de Pater, P. C. A. Bruijnincx, M. Lutz, A. L. Spek, G. van Koten, R. J. M. Klein Gebbink, *Tetrahedron: Asymmetry* **2006**, *17*, 674–686; e) S. Gosiewska, S. M. Herreras, M. Lutz, A. L. Spek, R. W. A. Havenith, G. P. M. van Klink, G. van Koten, R. J. M. Klein Gebbink, *Organometallics* **2008**, *27*, 2549–2559.

[8] C. Guo, M.-X. Xue, M.-K. Zhu, L.-Z. Gong, *Angew. Chem.* **2008**, *120*, 3462–3465; *Angew. Chem. Int. Ed.* **2008**, *47*, 3414–3417.

[9] For recent examples on the asymmetric additions to aldehydes, see: a) M.-X. Xue, C. Guo, L.-Z. Gong, *Synlett* **2009**, 2191–2197; b) F. Sladojevich, A. Trabocchi, A. Guarna, D. J. Dixon, *J. Am. Chem. Soc.* **2011**, *133*, 1710–1713; c) H. Y. Kim, K. Oh, *Org. Lett.* **2011**, *13*, 1306–1309.

[10] For recent example on the asymmetric addition to imines, see: a) Z.-W. Zhang, G. Lu, M.-M. Chen, N. Lin, Y.-B. Li, T. Hayashi, A. S. C. Chan, *Tetrahedron: Asymmetry* **2010**, *21*, 1715–1721; b) S. Nakamura, Y. Maeno, M. Ohara, A. Yamamura, Y. Funahashi, N. Shibata, *Org. Lett.* **2012**, *14*, 2960–2963.

[11] For recent example on the asymmetric addition to azodicarboxylates, see: D. Monge, K. L. Jensen, I. Marín, K. A. Jørgensen, *Org. Lett.* **2011**, *13*, 328–331.

[12] For recent examples on the asymmetric additions to α, β-unsaturated carbonyl compounds, see: a) C. Arróniz, A. Gil-González, V. Semak, C. Escolano, J. Bosch, M. Amat, *Eur. J. Org. Chem.* **2011**, 3755–3760; b) J. Song, C. Guo, P.-H. Chen, J. Yu, S.-W. Luo, L.-Z. Gong, *Chem. Eur. J.* **2011**, *17*, 7786–7790; c) L.-L. Wang, J.-F. Bai, L. Peng, L.-W. Qi, L.-N. Jia, Y.-L. Guo, X.-Y. Luo, X. Xu, L.-X. Wang, *Chem. Commun.* **2012**, *48*, 5175–5177.

[13] For recent examples on the asymmetric additions to maleimides, see: a) J.-F. Bai, L.-L. Wang, L. Peng, Y.-L. Guo, L.-N. Jia, F. Tian, G.-Y. He, X.-Y. Xu, L.-X. Wang, *J. Org. Chem.* **2012**, *77*, 2947–2953; b) S. Padilla, J. Adrio, J. C. Carretero, *J. Org. Chem.* **2012**, *77*, 4161–4166; c) M.-X. Zhao, D.-K. Wei, T.-L. Dai, F.-H. Ji, H. Zhou, M. Shi, **2012**, unpublished results.

[14] R. Grigg, M. I. Lansdell, M. Thornton-Pett, *Tetrahedron* **1999**, *55*, 2025–2044.

[15] Compared with AgOAc, no isocyanoacetate cyclodimerization product was observed when $AgSbF_6$ was used as metal catalyst, which simplified the purification of the desired cycloaddition product **5a**.

[16] CCDC 887265 (for **5l**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Empirical formula: $C_{20}H_{15}BrN_2O_4$; formula mass: 427.25; temperature: 296 (2) K; crystal system: Monoclinic; space Group: $P2(1)$; lattice parameters: $a = 10.839(2)$, $b = 7.8459(16)$, $c = 11.009(2)$ Å, $\alpha = 90.00$, $\beta = 104.222(6)$, $\gamma = 90.00°$, $V = 907.5(3)$ Å^3; $Z = 2$; $\rho_{cald} = 1.564$ g cm^{-3}; absorption coefficient: 2.294 mm^{-1}; $F(000) = 432$; crystal dimensions: $0.47 \times 0.16 \times 0.08$ mm; 2θ range: 1.91–24.99°; goodness of fit on F^2: 1.030; data/restraints/parameters: 2757/1/244; final R Indices $[I > 2\sigma(I)]$: $R_1 = 0.0317$, $wR_2 = 0.0817$; R Indices (all data): $R_1 = 0.0357$, $wR_2 = 0.0841$.

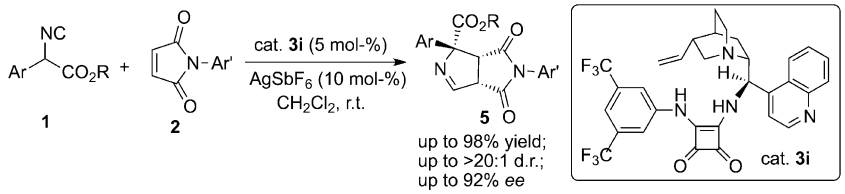
Received: July 28, 2012
Revised: August 16, 2012
Published online: ■■ ■■, 0000

COMMUNICATION

Cooperative Catalysis

Mei-Xin Zhao, Deng-Ke Wei, Fei-Hu Ji, Xiao-Li Zhao, Min Shi**

Asymmetric Formal [3+2] Cycloaddition Reaction of α-Aryl Isocyanoesters with *N*-Aryl Maleimides by Bifunctional Cinchona Alkaloids-Based Squaramide/$AgSbF_6$ Cooperative Catalysis



It is better to be cooperative: A highly diastereo- and enantioselective asymmetric [3+2] cycloaddition reaction of α-aryl isocyanoacetates with *N*-aryl maleimides through cooperative catalysis of cinchona alkaloid-derived squaramide/$AgSbF_6$ was developed. A wide range of optically active, substituted 1,3a,4,5,6,6a-hexahydropyrrolo-[3,4-c] pyrrole derivatives was obtained in high yields (up to 98%), high diastereoselectivities (>20:1 d.r.), and good to excellent enantioselectivities (up to 92% *ee*) under mild reaction conditions.