EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Squaramide Linked Chloramphenicol Base Hybrid Catalysts for Asymmetric Michael Addition of 2,3-dihydrobenzofuran-2-carboxylates to Nitroolefins

Authors: Fener Chen, Linjie Yan, Guanxin Huang, Haifeng Wang, Fangjun Xiong, and Haihui Peng

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201701485

Link to VoR: http://dx.doi.org/10.1002/ejoc.201701485

Supported by
ACES Asian Chemical Editorial Society

WILEY-VCH

10.1002/ejoc.201701485

WILEY-VCH

Squaramide Linked Chloramphenicol Base Hybrid Catalysts for Asymmetric Michael Addition of 2,3-dihydrobenzofuran-2-carboxylates to Nitroolefins

Linjie Yan,[a] Guanxin Huang, [a] Haifeng Wang, [a] Fangjun Xiong, [a] Haihui Peng, *[a] and Fener Chen *[a]

Abstract: A novel array of hybrid catalysts incorporating chloramphenicol base with another chiral scaffold using a squaramide linker have been developed and successfully applied in Michael addition of 2,3-dihydrobenzofuran-2-carboxylates to nitroolefins. The controlling experiments suggested that the hybrid catalysts were more reactive than non-hybridized bifunctional catalysts and the matching of chiralities between two scaffolds were crucial for high reactivity and stereoselectivity. This hybrid organocatalysts proved to be general for various substrates. In the presence of 0.5 mol% catalyst loading, a range of 2,3-dihydrobenzofuran-2-carboxylates derivatives bearing a quaternary-tertiary stereocenters were obtained in high yields (up to 98%) with excellent enantioselectivities (up to 99% *ee*) and moderate diastereoselectivities (up to 8/92 *dr*).

Introduction

Over the past decades, significant progress has been made in the area of bifunctional organocatalysis.[1] Remarkably, the vast majority of these bifunctionalities are based on natural product scaffolds, such as proline[2] and cinchona alkaloids,[3] whilst fully synthetic catalysts are much more limited.[4] While bifunctional organocatalysis greatly enriches the field of asymmetric catalysis, the modification toward these natural catalysts became difficult and exhausting, and new organocatalysts are still highly desirable.

Molecular hybridization, a pivotal strategy in new drug discovery,[5] provides an alternative opportunity for novel asymmetric organocatalysis via introduction of various privileged chiral scaffolds into the same structure with a proper linker.[6] Regarding the introduction of two distinctive chiral scaffolds into the hybrid catalyst, the biggest concern is the match-mismatch effects of the two chiral pools.[7] In theory, matching effect would facilitate new transformations with high reactivity and stereoselectivity. This is particularly important when using opposite configuration of one chiral scaffold, from which the configuration-reversed product may be obtained. To explore the possibility of this new hybrid catalyst, we selected the chloramphenicol base as a core structure via rational assembly with additional chiral framework.

[a] L. Yan, G. Huang, H. Wang, F. Xiong, H. Peng and F. Chen
Department of Chemistry
Fudan University
Shanghai 200433, PR China.
E-mail: haihui_peng@fudan.edu.cn, rfchen@fudan.edu.cn.

Supporting information for this article is given via a link at the end of the document.

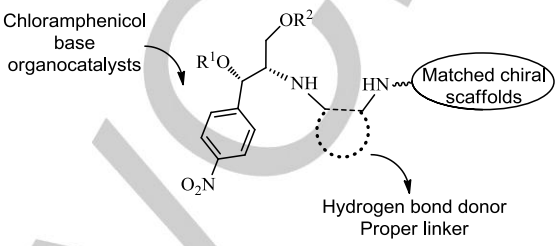
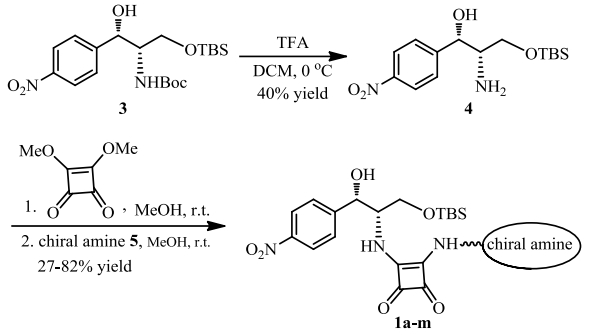


Figure 1. Design of new hybrid organocatalysts.

Chloramphenicol base, a by-product of chloramphenicol production, with easy structural modification, ready availability and substantially lower cost, has proven to be a useful bifunctional catalyst in various asymmetric transformations.[8] Extending the interest of this cost-efficient scaffold, based on the concept of molecular hybridization, may stimulate the development of more practical catalysis. Herein, we report a novel array of hybrid organocatalysts assembling chloramphenicol base with chiral amine scaffold by a squaramide linker.[9] Assessment of their catalytic behavior in the asymmetric Michael addition of 2,3-dihydrobenzofuran-2-carboxylates to nitroolefins with a quaternary stereocenter formation at C-2 was also described.[10] It is worth noting that the hybrid catalysts gave higher stereoselectivity and efficiency than a single chiral scaffold derived bifunctional catalysts through the controlling experiments.

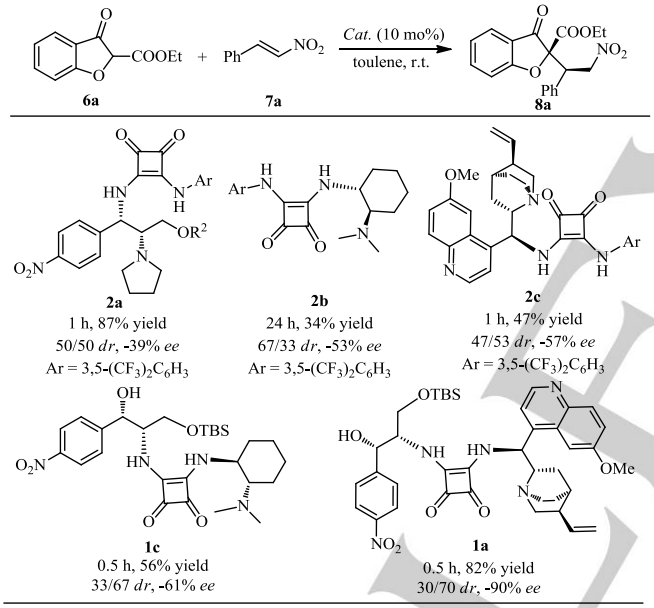
Results and Discussion

The chloramphenicol base hybrid catalysts (**1**) were readily prepared through a three-step procedure from Boc and TBS groups protected chloramphenicol base **3** (Scheme 1). Firstly, deprotection of Boc group was conducted in dichloromethane in the presence of trifluoroacetic acid at 0 °C to afford compound **4** in 40% yield. The obtained compound **4** was treated with dimethyl squarate in methanol to give the squaric monoamide monoester, followed by reaction with various chiral amines **5** to produce the chloramphenicol base hybrid catalysts.[11]



Scheme 1. Synthesis of squaramide linked chloramphenicol base hybrid catalysts.

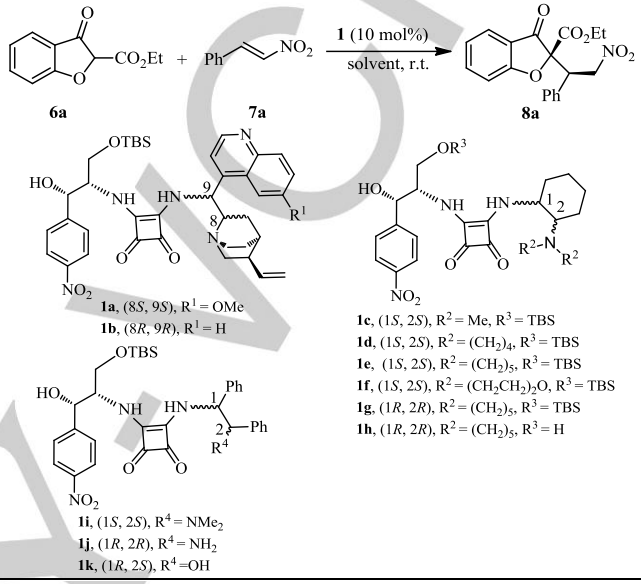
With the non-hybrid and hybrid catalysts, their catalytic activities and enantioselectivities were examined in the asymmetric Michael addition of 2,3-dihydrobenzofuran-2-carboxylates to nitroolefins.



Scheme 2. Controlling experiments.

As shown in Scheme 2, the addition proceeded smoothly to give the desired adduct product **8a** using non-hybridized organocatalysts **2a**-**2c**, among which chloramphenicol base derived catalyst **2a** performed to give **8a** within 1 h (39% *ee*, 87% yield, 50/50 *dr*). In comparison, quinine-based organocatalyst **2c** showed better stereocontrol but with lower yield (57% *ee*, 47% yield, 47/53 *dr*). Gratifyingly, using chloramphenicol base-diaminecyclohexane hybrid catalyst **1c**, both enantioselectivity and diastereoselectivity were improved (61% *ee*, 33/67 *dr*) and the reaction was completed within 0.5 h in 56% yield, suggesting the orthogonal effect of this hybrid catalyst by combining two chiral scaffolds together. Moreover, with chloramphenicol base-quinine hybrid catalyst **1a**, the reaction was further improved to 82% yield with 90% *ee* and 30/70 *dr* within 0.5 hour. These results implicated that matched hybrid catalyst could largely promote the reactivity and stereo-control over the reaction, which is in accordance with our previous hypothesis.

Table 1. Conditions screening.[a]



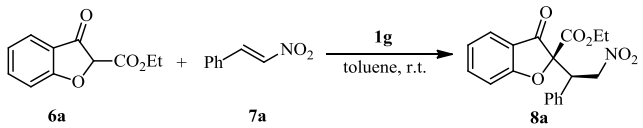
entry	cat.	solvent	t (h)	yield (%)[b]	dr[c]	ee (%)[c,d]
1	**1a**	toluene	0.5	82	30/70	-90
2	**1b**	toluene	0.5	83	18/82	46
3	**1c**	toluene	0.5	56	33/67	-61
4	**1d**	toluene	8	78	31/69	-74
5	**1e**	toluene	3	69	27/73	-84
6	**1f**	toluene	10	75	31/69	-82
7	**1g**	toluene	0.5	80	24/76	93
8	**1h**	toluene	4	89	47/53	92
9	**1i**	toluene	0.5	50	24/76	70
10	**1j**	toluene	5	48	50/50	0
11	**1k**	toluene	5	51	50/50	0
12	**1g**	CH_2Cl_2	0.5	59	29/71	85
13	**1g**	MTBE	0.5	61	52/48	89
14	**1g**	THF	7	81	51/49	83
15	**1g**	EtOH	7	68	58/42	83
16	**1g**	DMF	5	62	41/59	76

[a] Unless otherwise noted, all reactions were carried out with ethyl 3-oxo-2,3-dihydrobenzofuran-2-carboxylate **6** (0.2 mmol), nitroolefin **7** (0.24 mmol) and catalyst (10 mol%) in 2 mL solvent at r.t. [b] Yield of isolated product. [c] Determined by HPLC. [d] Refers to the major diastereoisomer.

Inspired by the above results, a series of hybrid catalysts assembled chloramphenicol base with cinchonine alkaloids (**1a**, **1b**), 1,2-diaminocyclohexane (**1c**-**1h**) or diphenyl ethylene diamine (**1i**-**1k**), were synthesized and evaluated, aiming to improve the selectivity. The results were displayed in Table 1.

Firstly, hybrid catalyst **1a** (chloramphenicol base-quinine) gave good reactivity and selectivity for this addition (entry 1). With the configuration-reversed quinine analogue **1b**, Michael addition proceeded to give opposite stereochemistry but with moderate selectivity (46% *ee*, 18/82 *dr*, entry 2). Various chloramphenicol base-cyclohexane diamine hybrid catalysts were also examined, among which bulkier piperidyl substituted hybrid catalyst **1c** gave the highest enantioselectivity of 84% *ee* (entries 3-6). Surprisingly, the configuration-reversed 1,2-diaminocyclohexane hybrid catalyst **1g** gave the configuration-reversed product in 80% yield with 93% *ee* and 24/76 *dr* (entry 7). Thus this method provided a general way to obtain the two opposite configuration products. Chloramphenicol base-diphenyl ethylene diamine hybrid catalyst was also investigated to give the desired product with moderate selectivity (**1i**, entry 9). However, when using free amine or alcohol substituted hybrid catalysts **1j** and **1k**, no stereoselectivity was observed (entries 10, 11). Various solvents were also investigated in this system, among which toluene performed the best (entries 12-16 *vs* entry 7).

Table 2. Investigation of the catalyst loading and concentration with **1g**.[a]



6a **7a** **8a**

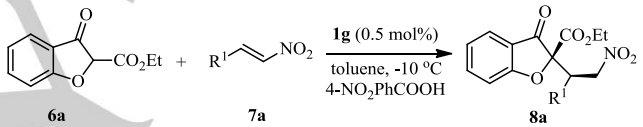
entry	cat. (mol %)	conc. (M)	t (h)	yield (%)[b]	dr	ee (%)[c, d]
1	10	0.1	0.5	80	24/76	93
2	5	0.1	0.5	81	29/71	94
3	1	0.1	0.5	83	28/72	94
4	0.5	0.1	0.5	80	27/73	94
5	0.1	0.1	7	35	25/75	80
6	0.5	1.0	0.5	88	26/74	94
7	0.5	0.5	0.5	90	24/76	95
8[e]	0.5	0.5	1	92	14/86	98

[a] Unless otherwise noted, all reactions were carried out with ethyl 3-oxo-2,3-dihydro benzofuran-2-carboxylate **6a** (0.2 mmol), nitroolefin **7a** (0.24 mmol) and catalyst **1g** (x mol%) in toluene at r.t. [b] Yield of isolated product. [c] Determined by HPLC. [d] Refers to the major diastereoisomer. [e] 4-NO_2PhCOOH (20 mol%) was used at -10 °C.

To further improve the diastereoselectivity, we investigated other parameters such as catalyst loading, temperature, concentration and additives. The results were summarized in Table 2. Notably, reactivities and stereoselectivties were maintained when changing the catalyst loading from 10 mol% to 1 mol% (entries 1-3) and the catalyst loading could be further decreased to 0.5 mol% with good reactivity and selectivity (0.5 h, 80% yield, 94% *ee*, 27/73 *dr*, entry 4). Further decreasing the catalyst loading led to prolonged reaction time with decreased yield and enantioselectivity (entry 5). Interestingly, increasing the concentration to 0.5 M gave higher yield (90%) and a marginal increase in stereoselectivity (95% *ee*, 24/76 *dr*, entry 7). Finally, with the assistance of Brønsted acids and decrease of the temperature to -10 °C, this reaction was improved with 92% yield, 98% *ee* and 14/86 *dr* (entry 8).

This bifunctional hybrid catalyst **1g** proved to be a highly active catalyst toward asymmetric Michael addition of various nitroolefins **7** with ethyl 3-oxo-2,3-dihydrobenzofuran-2-carboxylate (**6a**). As summarized in Table 3, in all cases, this addition proceeded with high yields and enantioselectivities. With electro-diversified aromatic nitroolefin **7**, both the electronic-rich and deficient aryl groups furnished the adducts in good yields (56-98%) and high enantioselectivities (82-99%) albeit with moderate diastereoselectivities (entries 1-13). 2-Naphthyl nitroolefin **7n** proved to be less reactive, which required the prolonged reaction time with decreased yield (70%), but the stereoselectivity was maintained (95% *ee*, 20/80 *dr*, entry 14). Heteroaromatic nitroolefins (**7o**, **7p**) were also compatible in these conditions to provide the corresponding products efficiently in good yields (78%, 86%) and high enantioselectivities (95%, 96% *ee*) (entries 15-16). Aliphatic nitroolefin was less reactive, which required prolonged reaction time with decreased yields (68%), but high enantioselectivities (89% *ee*) and diastereoselectivity were still obtained (8/92 *dr*, entry 17).

Table 3. Substrate scope of nitroolefins.[a]



6a **7a** **8a**

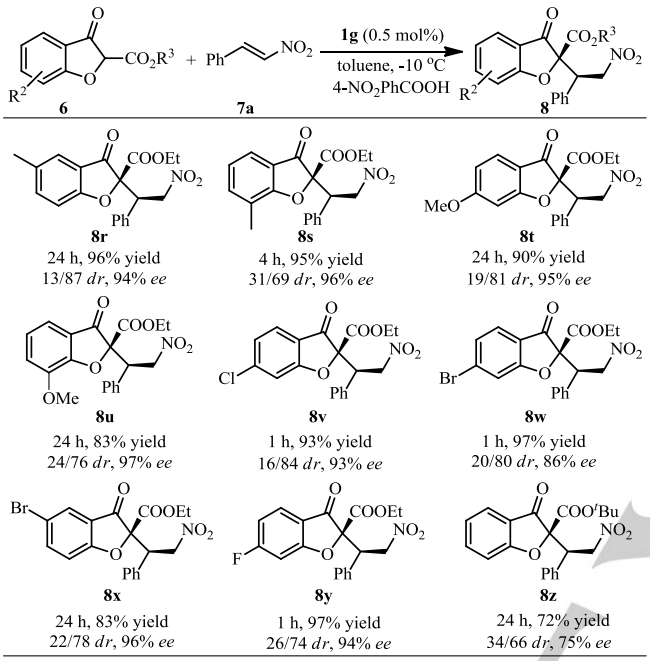
entry	R^1	t (h)	yield (%)[b]	dr[c]	ee (%)[c,d]
1	Ph	1	92 (**8a**)	14/86	98
2	3-ClPh	1	78 (**8b**)	19/81	94
3	4-CF_3OPh	1	97 (**8c**)	24/76	97
4	2-BrPh	1	92 (**8d**)	32/68	87
5	4-BrPh	1	80 (**8e**)	56/44	92
6	2-ClPh	1	84 (**8f**)	2674	95
7	3-BrPh	1	83 (**8g**)	17/83	98
8	2-CF_3Ph	1	85 (**8h**)	54/46	95/96
9	4-FPh	1	86 (**8i**)	21/79	99
10	4-ClPh	1	98 (**8j**)	22/78	97
11	4-MePh	1	56 (**8k**)	16/84	99
12	4-MeOPh	1	96 (**8l**)	29/71	82
13	3,4-Cl_2Ph	1	94 (**8m**)	25/75	98
14	2-Naphthyl	96	70 (**8n**)	20/80	95
15	2-Thienyl	1	78 (**8o**)	17/83	95
16	5-Cl-2-Thienyl	1	86 (**8p**)	17/83	96
17	$Ph(CH_2)_2$	96	68 (**8q**)	8/92	89

[a] Unless otherwise noted, all reactions were carried out with ethyl 3-oxo-2,3-dihydrobenzofuran-2-carboxylate **6a** (0.5 mmol), nitroolefin **7** (0.6 mmol), 4-NO_2PhCOOH (20 mol%) and **1g** (0.5 mol%) in 1 mL toluene at -10 °C. [b] Yield of the isolated product. [c] Determined by HPLC. [d] Refers to the major diastereoisomer.

The generality and scope of this methodology was further demonstrated in the Michael addition of nitroolefin **7a** with different 3-oxo-2,3-dihydrobenzofuran-2-carboxylate **6** (Table 4). Generally, excellent yields with high

enantioselectivities were obtained (**8r**-**8y**). The presence of either electron donating or electron withdrawing substitutes in various positions of the aromatic ring of **6** were found to be equally effective. However, with more bulky *tert*-butyl ester of the dihydrobenzofuran derivative, the desired product was obtained with longer reaction time in lower yield and selectivity (**8z**).

Table 4. Substrate scope.[a-d]



[a] Unless otherwise noted, all reactions were carried out with ethyl 3-oxo-2,3-dihydrobenzofuran-2-carboxylate **6** (0.5 mmol), nitroolefin **7a** (0.6 mmol), 4-NO_2PhCOOH (20 mol%) and catalyst **1g** (0.5 mol%) in 1.0 mL toluene at -10 °C. [b] Yields were isolated product. [c] The values of *dr* and *ee* were determined by HPLC. [d] The values of *ee* refer to the major diastereoisomer.

Single crystal X-ray analysis on the major diastereoisomer of compound **8h** enabled us to determine the absolute configuration of the stereocenter (Figure 2).[12]

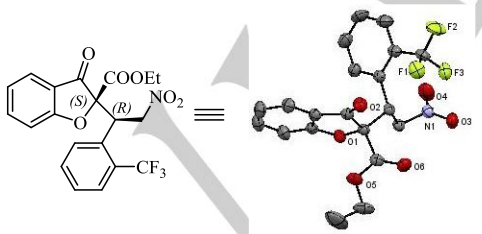
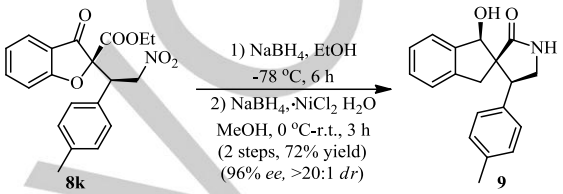


Figure 2. Determination of the absolute configuration by X-ray crystal analysis of the major diastereoisomer of compound **8h**.

Notably, 2,2-disubstituted-2,3-dihydrobenzofuran bearing a quaternary stereocenter at C-2 position was important building blocks in natural compounds and bioactive chemicals.[13] Using this scaffold to synthesize spiro-tricyclic dihydrobenzofuran moiety was thus performed to illustrate the synthetic utility. As shown in Scheme 3, the single isomer of adduct **8k** could be readily converted into spiro-tricyclic dihydrobenzofuran **9** by two simple procedures, including reduction of the keto group with sodium borohydride to the corresponding alcohol, followed by reducing the nitro group to amine group and sequential intramolecular amidation.[14] The spiro-tricyclic dihydrobenzofuran **9** was obtained as major diastereoisomer in 72% yield with 96% *ee* over two steps.



Scheme 3. Asymmetric synthesis of spiro tricyclic dihydrobenzofuran **9**.

Conclusions

In summary, we have designed and synthesized a novel series of chloramphenicol base hybrid catalysts using the hybridization strategy. Rational combining chloramphenicol base with alternative chiral scaffolds by a squaramide linker led to high catalytic efficiency and stereocontrol for the asymmetric Michael addition of 3-oxo-2,3-dihydrobenzofuran-2-carboxylates to nitroolefins. The controlling experiments showed the hybrid catalysts presenting better performance than the non-hybrid catalysts and provided the insight into their structure-catalytic activity relationship. Taking full advantage of the diversity-oriented character of hybridization, further exploitation of this capacity in discovering new catalysts with enhanced performances and expanded applications is undergoing.

Experimental Section

The 3-oxo-2,3-dihydrobenzofuran-2-carboxylates (**6**, 0.5 mmol), 4-NO_2PhCOOH (0.1 mmol) and catalyst (0.0025 mmol) were dissolved in toluene (1 mL) and cooled to -10 °C. Then nitroolefin (**7**, 0.6 mmol) was added to the reaction mixture, after addition the reaction mixture was stirred at -10 °C. The reaction was monitored by TLC, after consumption of **6**, solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography with PE/EtOAc = 8/1.

Keywords: Asymmetric Organocatalysis • Chloramphenicol base • Hybrid catalysts • Michael addition

References

[1] For selected reviews of bifunctional organocatalysis, see: a) M. Kanai, N. Kato, E. Ichikawa, M. Shibasaki, *Synlett.* **2005**, 1491; b) S. J. Connon, *Chem. Eur. J.* **2006**, *12*, 5418; c) T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2006**, *348*, 999; d) B. J. List, *Chem. Rev.* 2007, 107, 5413; e) S. J. Connon, *Chem. Commun.* **2008**, 2499; f) P. Chauhan, S. Mahajan, U. Kaya, D. Hack, D. Enders, *Adv. Synth. Catal.* **2015**, *357*, 253; g) X. Fang, C. Wang, *Chem. Commun.* **2015**, *51*, 1185; h) X. Zhao, B. Zhu, Z. Jiang, *Synlett.* **2015**, *26*, 2216; i) F. E. Held, S. B. Tsogoeva, *Catal. Sci. Technol.* **2016**, *6*, 645; j) Y.-L. Sun, Y. Wei, M. Shi, *ChemCatChem* **2017**, *9*, 718.

[2] a) M. Xie, X. Liu, X. Wu, Y. Cai, L. Lin, X. Feng, *J. Am. Chem. Soc.* **2013**, *135*, 10026; b) S. Dong, X. Liu, X. Chen, F. Mei, Y. Zhang, B. Gao, L. Lin, X. Feng, *J. Am. Chem. Soc.* **2010**, *132*, 10650; c) B. List, *Tetrahedron* **2002**, *58*, 5573.

[3] a) F. Du, J. Zhou, Y. Peng, *Org. Lett.* **2017**, *19*, 1310; b) X. Liu, Y. Wang, D. Yang, J. Zhang, D. Liu, W. Su, *Angew. Chem. Int. Ed.* **2016**, *55*, 8100; *Angew. Chem.* **2016**, *128*, 8232; c) M. Ryota, A. Keisuke, M. Seijiro, *J. Am. Chem. Soc.* **2015**, *137*, 6766; d) Y.-H. Lam, K. N. Houk, *J. Am. Chem. Soc.* **2014**, *136*, 9556; e) J. Lubkoll, H. Wennemers, *Angew. Chem. Int. Ed.* **2007**, *46*, 6841; *Angew. Chem.* **2007**, *119*, 6965; f) J. Song, Y. Wang, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 6048; g) S. H. McCooey, S. J. Connon, *Angew. Chem. Int. Ed.* **2005**, *44*, 6367; *Angew. Chem.* **2005**, *117*, 6525; h) J. Ye, D. J. Dixon, P. S. Hynes, *Chem. Commun.* **2005**, 4481; i) H. Li, Y. Wang, L. Deng, *J. Am. Chem. Soc.* **2004**, *126*, 9906.

[4] a) V. N. Wakchaure, B. List, *Angew. Chem. Int. Ed.* **2010**, *49*, 4136; *Angew. Chem.* **2010**, *122*, 4230; b) E. Smith, I. Schiffers, C. Bolm, *Tetrahedron*, **2010**, *66*, 6349; c) T. Honjo, T. Tsumura, S. Sano, Y. Nagao, K. Yamaguchi, Y. Sei, *Synlett.* **2009**, 3279; d) T. Honjo, S. Sano, M. Shiro, Y. Nagao, *Angew. Chem. Int. Ed.* **2005**, *44*, 5838; *Angew. Chem.* **2005**, *117*, 5988.

[5] For recent selected examples of hybrid chemistry in medicinal discovery, see: Z. Wan, Y. Tao, Y. Wang, T. Mao, H. Yin, F. Chen, H. R. Piao, E. D. Clercq, D. Daelemans, C. Pannecouque, *Bioorg. Med. Chem.* **2015**, *23*, 4248.

[6] For selected examples of hybrid catalysts, see: a) A. F. de la Torre, D. G. Rivera, M. A. B. Ferreira, A. G. Correa, M. W. Paixao, *J. Org. Chem.* **2013**, *78*, 10221; b) L. Weselinski, E. Slyk, J. Jurczak, *Tetrahedron Lett.* **2011**, *52*, 381; c) A. Patti, S. Pedotti, *Eur. J. Org. Chem.* **2014**, *3*, 624; d) P. Barrulas, M. Benaglia, A. J. Burke, *Tetrahedron: Asymmetry* **2014**, *25*, 923; e) M. Isik, C. Tanyeli, *J. Org. Chem.* **2013**, *78*, 1604; f) M. Isik, M. Y. Unver, C. Tanyeli, *J. Org. Chem.* **2015,** *80*, 828; g) J. Borges-Gonzalez, A. Feher-Voelger, F. P. Crisostomo, E. Q. Morales, T. Martin, *Adv. Synth. Catal.* **2017**, *359*, 576.

[7] M. Isik, H. U. Akkoca, I. M. Akhmedov, C. Tanyeli, *Tetrahedron: Asymmetry* **2016**, *27*, 384.

[8] a) S. Wang, F. Chen, *Adv. Synth. Catal.* **2009**, *351*, 547; b) H. Yang, F. Xiong, J. Li, F. Chen, *Chin. Chem. Lett.* **2013**, *24*, 553; c) H. Yang, F. Xiong, X. Chen, F. Chen, *Eur. J. Org. Chem.* **2013**, 4495; d) L. Yan, H. Wang, W. Chen, Y. Tao, K. Jin, F. Chen, *ChemCatChem* **2016**, *8*, 2249; e) H. Wang, L. Yan, F. Xiong, Y. Wu, F. Chen, *RSC Adv.* **2016**, *6*, 75470; f) X. Wang, L. Xu, L. Yan, H. Wang, S. Han, Y. Wu, F. Chen, *Tetrahedron* **2016**, *72*, 1787; g) X. Wang, L. Xu, F. Xiong, Y. Wu, F. Chen, *RSC Adv.* **2016**, *6*, 37701; h) H. Wang, L. Yan, Y. Wu, F. Chen, *Tetrohedron* **2017**, *19*, 2793; i) L. Yan, H. Wang, F. Xiong, Y. Tao, Y. Wu, F. Chen, *Tetrahedron: Asymmetry* **2017**, *28*, 921; j) Y. Wang, G. Huang, S. Hu, K. Jin, Y. Wu, F. Chen, *Tetrahedron* **2017**, *73*, 5055.

[9] J. Alemán, A. Parra, H. Jiang, K. A. Jørgensen, *Chem. Eur. J.* **2011**, *17*, 6890.

[10] During the preparation of this manuscript, a similar work has been reported, see: K. Sivamuthuraman, N. Kumarswamyreddy, V. Kesavan, *J. Org. Chem.* **2017**, *82*, 10812.

[11] C. Cornaggia, F. Manoni, E. Torrente, S. Tallon, S. J. Connon, *Org. Lett.* **2012**, *14*, 1850.

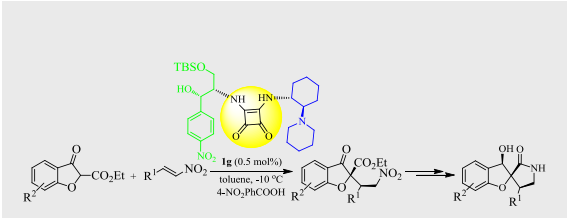
[12] CCDC 1543024 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[13] a) J. M.-Contelles, M. do C. Carreiras, C. Rodríguez, M. Villarroya, A. G. García, *Chem. Rev.* **2006,** *106*, 116; b) Y. Liu, M. Kubo, Y. Fukuyama, *J. Nat. Prod.* **2012**, *75*, 2152; c) P. Lan, M. G. Banwell, A. C. Willis, *J. Org. Chem.* **2014**, *79*, 2829; d) J. H. Chang, H.-U. Kang, I.-H. Jung, C.-G. Cho, *Org. Lett.* **2010**, *9*, 2016; e) X. Yao, X. Xie, C. Wang, L. Zu, *Org. Lett.* **2015**, *17*, 4356.

[14] H. Wang, J. Luo, X. Han, Y Lu, *Adv. Synth. Catal.* **2011**, *353*, 2971.

Entry for the Table of Contents

FULL PAPER



A novel hybrid catalysts incorporating chloramphenicol base with another chiral scaffold using a squaramide linker have been developed and successfully applied in Michael addition of 2,3-dihydrobenzofuran-2-carboxylates to nitroolefins. With 0.5 mol% catalyst loading, a range of 2,3-dihydrobenzofuran-2-carboxylates derivatives bearing a quaternary-tertiary stereocenters were obtained in high yields with excellent enantioselectivities and moderate diastereoselectivities.

* Organocatalysis

Asymmetric catalysis

Linjie Yan, Guanxin Huang, Haifeng Wang, Fangjun Xiong, Haihui Peng and Fener Chen **

Page No. – Page No.

Squaramide linked chloramphenicol base hybrid catalysts for asymmetric Michael addition of 2,3-dihydrobenzofuran-2-carboxylates to nitroolefins