Advanced Synthesis & Catalysis

Accepted Article

Title: Enantioselective Construction of Spirooxindole-Fused Cyclopenta[c]chromen-4-ones Bearing Five Contiguous Stereocenters via a Stepwise (3+2) Cycloaddition

Authors: Sandip Sambhaji Vagh, Praneeth Karanam, Cheng-Chieh Liao, Ting-Han Lin, Yan-Cheng Liou, Athukuri Edukondalu, Yi-Ru Chen, and Wenwei Lin

To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201901655

Link to VoR: http://dx.doi.org/10.1002/adsc.201901655

10.1002/adsc.201901655

COMMUNICATION

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Enantioselective Construction of Spirooxindole-Fused Cyclopenta[*c*]chromen-4-ones Bearing Five Contiguous Stereocenters via a Stepwise (3+2) Cycloaddition

Sandip Sambhaji Vagh,[a,†] Praneeth Karanam,[a,†] Cheng-Chieh Liao,[a] Ting-Han Lin,[a] Yan-Cheng Liou,[a] Athukuri Edukondalu,[a] Yi-Ru Chen[a] and Wenwei Lin[a,*]

[a] Department of Chemistry, National Taiwan Normal University, 88, Sec. 4, Tingchow Road, Taipei 11677, Taiwan, R.O.C. Fax: (+886) 2-2932-4249; Email: wenweilin@ntnu.edu.tw

[†] These authors contributed equally.

Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. The bifunctional quinine-catalyzed stepwise (3+2) cycloaddition for the enantioselective construction of spirooxindole-fused cyclopenta[*c*]chromen-4-ones is developed. The reactions of 3-homoacylcoumarins and alkylidene oxindole electrophiles generate aforementioned spirooxindole-chromenone adducts bearing five contiguous stereocenters, of which one is the spiro all-carbon quaternary stereocenter in high yields (up to 99%) with excellent stereoselectivities (up to >20:1 dr and 99% ee). This methodology was investigated for three different alkylidene oxindole electrophiles and could also be practically demonstrated on a gram scale. Mechanistic investigations revealed that the (3+2) cycloaddition for the enantioselective synthesis of spirooxindole-fused cyclopenta[*c*]chromen-4-ones is proceeding via a stepwise reaction pathway.

Keywords: spiro compounds; cyclopenta[*c*]chromen-4-ones; stepwise (3+2) cycloaddition; organic catalysis; 3-homoacylcoumarins

The spirooxindole skeleton has immense importance in modern organic chemistry because of its prevalence in both natural products and biologically active molecules.[1] Consequently, intensive investigation regarding their synthesis has been going on recently.[2] Although various elegant methods have been documented for the synthesis of these privileged motifs,[3] contrastingly, the methods to access spirooxindole scaffolds bearing an all-carbon quaternary spiro-stereocenter on the cyclopentane ring are underdeveloped.[4] The key challenge en route to chiral spirooxindole is formation of multiple stereocenters with a quaternary spiro-stereocenter in highly enantioselective manner. More importantly, enantioselective methods for the generation of spirocyclopentane oxindoles which forms the core of many potent drugs are very scarce.[5] On the other hand, coumarin derivatives such as cyclopentane-fused coumarins are considered as important motifs in medicinal chemistry and feature in many alkaloids and sesquiterpenes.[6] The fusion of spirooxindole and coumarin would give rise to new templates which may hold potential for drug discovery based on the individual medicinal strength of spirooxindole- and coumarin-based drugs.

Our group has long been working toward the development of novel organocatalytic reactions in generating complex molecular architectures.[7] In 2018, we reported a quinine-derived bifunctional thiourea-catalyzed concerted (3+2) cycloaddition reaction for the highly stereoselective synthesis of five membered coumarin/indanedione-fused spirocyclopentanes bearing four contiguous stereocenters.[8] Inspired from our previous work, we were keen on developing a (3+2) cycloaddition reaction for spirooxindole scaffolds, utilizing 3-homoacylcoumarin and alkylidene oxindole electrophiles. The supposed cycloaddition reaction would lead to less explored hybrid scaffolds that comprise both the privileged moieties and also bear five contiguous stereocenters, including a quaternary spiro-stereocenter. In this context, we report a bifunctional quinine derivative-catalyzed, highly enantioselective (3+2) cycloaddition reaction for the generation of complex spirooxindole-fused cyclopenta[*c*]chromen-4-ones in high yields and excellent enantioselectivities.

10.1002/adsc.201901655

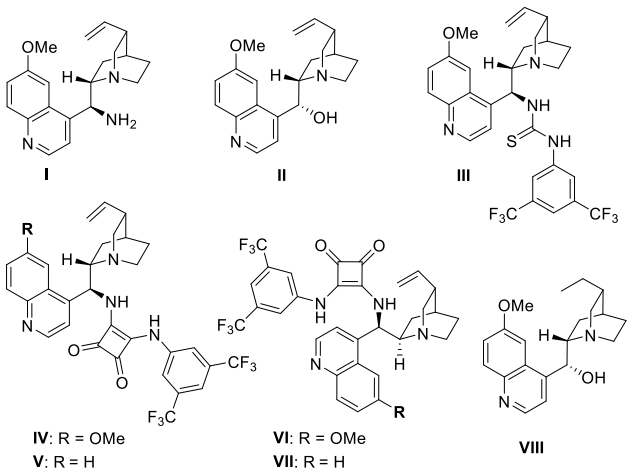
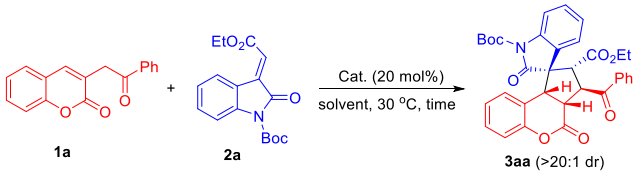


Figure 1. Chiral Catalysts Screened for the Reaction.

Table 1. Optimization of Reaction Conditions.[a]



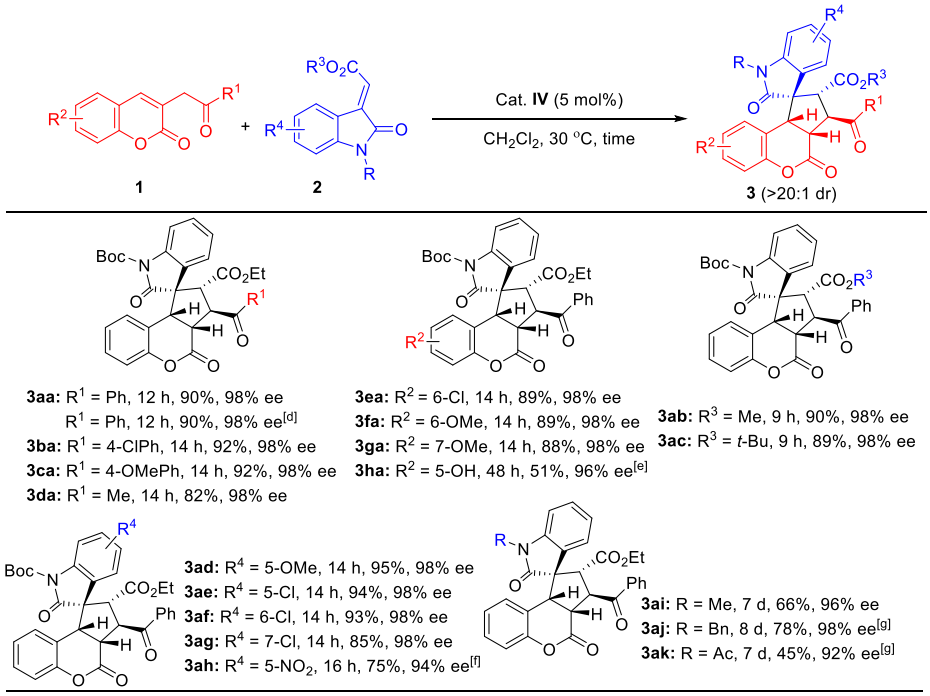
entry	catalyst	solvent	*t* (h)[b]	**3aa** (%)[c]	ee (%)[d]
1	DABCO	CH_2Cl_2	12	99	*rac*
2	**I**	CH_2Cl_2	12	59	20
3	**II**	CH_2Cl_2	2	89	73[e]
4	**III**	CH_2Cl_2	2	86	96
5	**IV**	CH_2Cl_2	2	93	98
6	**V**	CH_2Cl_2	2	87	94
7	**VI**	CH_2Cl_2	2	83	95[e]
8	**VII**	CH_2Cl_2	2	78	91[e]
9	**IV**	$CHCl_3$	2	92	97
10	**IV**	CH_3CN	2	73	95
11	**IV**	THF	3	92	97
12	**IV**	EtOAc	2	93	97
13	**IV**	EtOH	5	67	82
14[f]	**IV**	CH_2Cl_2	6	93	98
15[g]	**IV**	CH_2Cl_2	12	93	98

[a] Unless otherwise specified, all the reactions were carried out using **1a** (0.1 mmol), **2a** (1.1 equiv) and catalyst (20 mol%) in the given solvent (0.5 mL) at 30 °C. [b] The indicated time after which no considerable improvement in the yield of **3aa** was observed. [c] Yield of the **3aa** was determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3-dinitrobenzene as an internal standard. [d] Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase. [e] Enantiomer of **3aa** was obtained. [f] Catalyst **IV** (10 mol%) was used. [g] Catalyst **IV** (5 mol%) was used.

Table 2. Substrate Scope of (3+2) Cycloaddition Reaction.[a,b,c]

Initially, the (3+2) cycloaddition reaction between 3-homoacylcoumarin (**1a**) and *N*-Boc protected methyleneindolinone (**2a**) was carried out with 20 mol% of 1,4-diazabicyclo[2.2.2]octane (DABCO) in CH_2Cl_2 at 30 °C. We were pleased to notice the formation of spiroxindole **3aa** in 99% yield after 12 h (entry 1, Table 1). Encouraged by this result, we next examined a series of bifunctional hydrogen-bonding catalysts (entries 2-5). Among them (Figure 1), catalyst **IV** was found to be better interms of both yield and enantioselectivity (93% yield and 98% ee, entry 5). To test the influence of hydrogen-bonding activation, several other squaramide derivatives (entries 6-8) were screened (see Supporting Information for detailed optimization). Although all of them are found to effectively catalyze the (3+2) cycloaddition reaction, catalyst **IV** was still found to be superior. Interestingly, the pseudo enantiomeric catalyst **VI** also showed very good catalytic activity to afford the enantiomer of the product **3aa** in good yield and high enantioselectivity (83% yield and 95% ee, entry 7). Having found the choice of catalyst, solvent screening was carried out (entries 9-13). While the solvents such as $CHCl_3$, CH_3CN, THF and EtOAc, provided comparable results, EtOH as solvent, afforded the product in relatively poor yield and ee, presumably due to the disruption of hydrogen-bonding between the catalyst and the substrates by the solvent. It is worthy to note that in all cases, the diastereoselectivity was found to be excellent (>20:1). Decreasing the catalyst loading also resulted in similiar yields and ee values, albeit after longer reaction times (entries 14 and 15). Thus, the optimal conditions for **3aa** were established with 5 mol% of catalyst **IV** and CH_2Cl_2 as the solvent at 30 °C (entry 15).

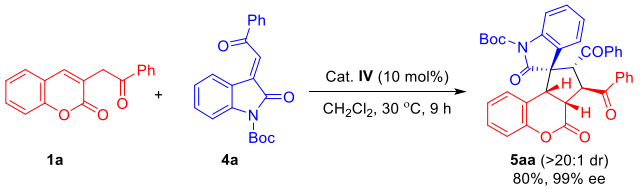
10.1002/adsc.201901655



[a] Unless otherwise specified, all the reactions were carried out using **1** (0.3 mmol), **2** (1.1 equiv) and catalyst **IV** (5 mol%) in CH_2Cl_2 (1.5 mL) at 30 °C. [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase. [d] Reaction was performed on a gram scale of **1a** (4 mmol, 1.05 g). [e] Catalyst **IV** (30 mol%) was used. [f] Diastereomeric ratio was 6:1. [g] Diastereomeric ratio was 10:1.

Having the optimized conditions in hand, we set out to investigate the substrate scope of the (3+2) cycloaddition reaction with respect to both the substrates (Table 2). Initially, the scope of 3-homoacylcoumarin **1** bearing various R^1 and R^2 groups were tested. In general, all the tested substrates **1** reacted smoothly with **2a** to give the products **3aa**-**3ha** in high yields and excellent enantioselectivites, regardless of their electronic nature. Notably, the substrate **1d** bearing a R^1 = Me substitution, afforded **3da** in relatively lower yield, although excellent enantioselectivity was maintained. Additionally, the substrate **1h** with R^2 = 5-OH substitution on the coumarin ring required higher loading of the catalyst (30 mol%) to result corresponding product **3ha**. This further demonstrates that the hydrogen-bonding between the substrate and the catalyst has great influence on the reaction. Next, various alkylidene oxindole esters **2** bearing different R^3 and R^4 groups were tested for the reaction with **1a**. Substrates bearing Me and *t*-Bu esters, such as **2b** and **2c**, also afforded corresponding products **3ab** and **3ac** with excellent enantioselectivities. Furthermore, the effect of various R^4 substituents on the aromatic ring of oxindole esters was also investigated. It was delightful to observe the formation of corresponding products **3ad**-**3ag** in excellent yields and enantioselectivities, regardless of the nature and position of the substitution. The substrate with a strong electron-withdrawing group, such as **2h** (R^4 = 5-NO_2), also furnished the desired product **3ah** in 75% yield and 94% ee, albeit with moderate diastereomeric ratio (6:1). Finally, for the generality of the reaction, substrates with other *N*-protecting groups, such as methyl, benzyl and acetyl groups, were also investigated. All the substrates were tolerated well in the reaction to afford the corresponding products **3ai**-**3ak**, albeit requiring much longer reaction times. These substrates were furnished with lower yields and diastereoselectivities when compared to those of the substrates bearing a *N*-Boc substitution. It is worth noting that the reaction for **3aa** could be performed on a gram scale with similar efficiency.

After successful application of alkylidene oxindole esters **2** in (3+2) cycloaddition reaction, we wish to explore the utility of alkylidene oxindoles bearing a ketone group. Accordingly, the substrate **4a** was examined with **1a** under the optimized conditions (see Supporting Information for detailed optimization). Although the same catalytic system (catalyst **IV**) was effective in delivering **5aa** bearing five contiguous stereocenters, the catalyst loading had to be doubled in CH_2Cl_2 (0.1 M) to obtain the optimal results as shown in Scheme 1.

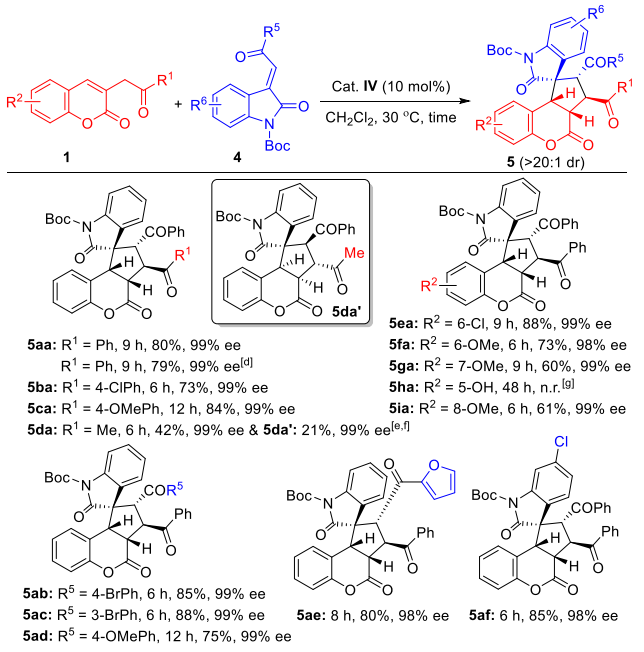


Scheme 1. Optimal Conditions for **5aa**.

10.1002/adsc.201901655

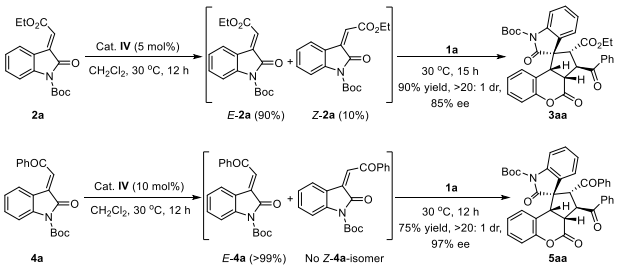
Examination of the substrate scope with respect to both the substrates **1** and **4** revealed slightly lower yields for most of the products **5**, when compared to the adducts **3** formed from **1** and **2**, albeit with excellent ee values (Table 3). Again, the substrate **1d** showed less reactivity towards **4a** to afford adduct **5da** in poor yield, along with formation of a diastereomer **5da'** in 2:1 ratio. It is worth noting that ee was still excellent and the diastereomer **5da'** was easily separated by using flash chromatography and subsequently confirmed by X-ray analysis.[9] The less reactive substrate **1h** bearing a R^2 = 5-OH group was found to be unreactive after 48 h, even usage of higher loading of the catalyst (30 mol%). The low reactivity of the alkylidene oxindole ketone **4a** compared to the alkylidene oxindole ester **2a** could be the reason. Furthermore, substrates bearing different R^5 and R^6 groups on **4** also afforded the desired products **5ab-5af** in good yields and excellent enantioselectivities under the optimized conditions. The alkylidene oxindole substrate bearing a heteroaryl substitution such as **4e** (2-furyl) also afforded the corresponding product **5ae** in good yield and excellent stereoselectivities (80% yield, >20:1 dr and 98% ee). In addition, the preparative utility of this (3+2) cycloaddition reaction, was also demonstrated by performing a gram scale reaction for **5aa** under the same conditions.

Table 3. Substrate Scope of **5**.[a,b,c]



[a] Unless otherwise specified, all the reactions were carried out using **1** (0.2 mmol), **4** (1.1 equiv) and catalyst **IV** (10 mol%) in CH_2Cl_2 (2 mL) at 30 °C. [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase. [d] Reaction was performed on a gram scale of **1a** (3.8 mmol, 1.0 g). [e] Reaction was performed on 0.4 mmol scale. [f] Diastereomeric ratio of **5da** and **5da'** was 2:1. [g] Catalyst **IV** (30 mol%) was used. n.r. = No reaction with the recovery of **1h** and **4a**.

Next, several control experiments have been performed to investigate the mechanism. The reaction of the alkylidene oxindole ester **2a** and the catalyst **IV** has been examined in CH_2Cl_2 at 30 °C for 12 h. *E*/*Z*-isomerization was observed by the analysis of ^{1}H NMR spectrum, and the ratio of *E*/*Z*-isomers of alkylidene oxindole ester **2a** was 90:10. Furthermore, subsequent addition of 3-homoacylcoumarin (**1a**) to the reaction mixture furnished the desired product **3aa** in 90% yield and lower enantioselectivity (85% ee) after 15 h. Interestingly, the reaction of the alkylidene oxindole ketone **4a** with the catalyst **IV** shows no *E*/*Z*-isomerization in CH_2Cl_2 after 12 h, and further treatment with 3-homoacylcoumarin **1a** afforded the desired product **5aa** in 75% yield and 97% ee which is almost similar ee as standard condition (Scheme 2). It could be understood that the reaction of *E*-isomer of **2a**/**4a** with **1a** provides the desired products **3aa** and **5aa** with high ee values, but the enantioselectivity of the product **3aa** has been diminished by the formation of *Z*-isomer of **2a**.

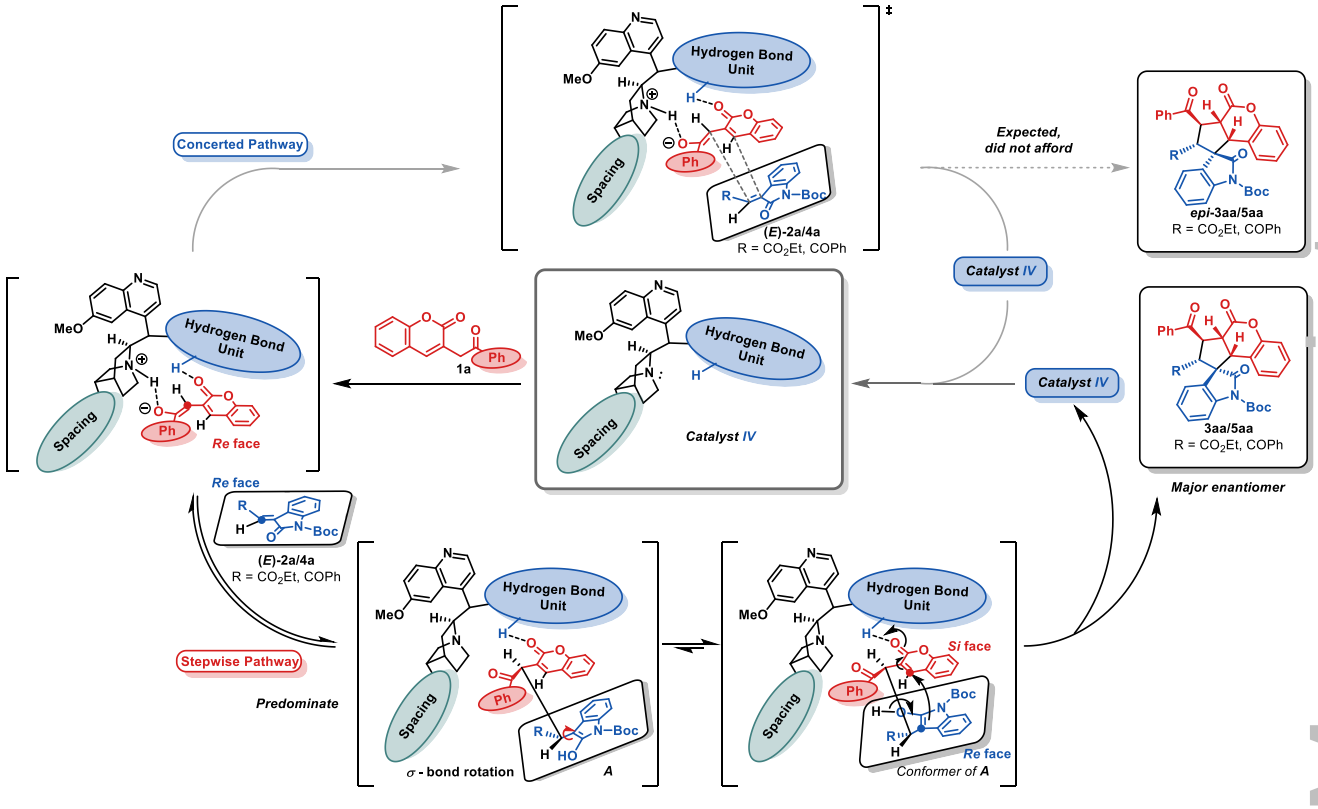


Scheme 2. Isomerization of **2a**/**4a** with Catalyst **IV**.

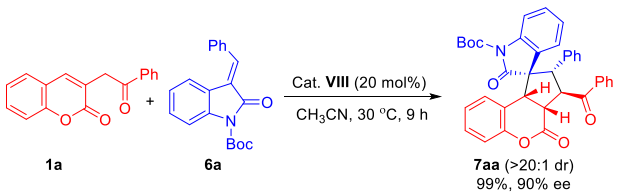
Generally, the (3+2) cycloaddition could proceed either via a concerted pathway or a stepwise double Michael cascade pathway. Based on the absolute configurations of products **3aa**/**5aa**, we have constructed possible reaction models in the concerted reaction pathway for formation of **3aa**/**5aa** from *E*-isomer of **2a**/**4a** and **1a** in presence of the catalyst. But we could not find the exact configurations of **3aa**/**5aa** from that of the possible proposed concerted product. Instead, the epimer of the desired product (*epi*-**3aa**/**5aa**) should observed in the concerted pathway (Scheme 3). Notably, even the exact configuration of proposed concerted product provided from the *Z*-isomer of **2a**/**4a** with **1a** is contradictory to the results in control experiments (Scheme 2). Therefore, one of the possibilities of formation of the aforementioned products from *E*-isomer in (3+2) cycloaddition via a concerted pathway is ruled out. Next, we have considered (3+2) cycloaddition reaction through a stepwise double Michael cascade reaction pathway to lead the desired products from the *E*-isomer of **2a**/**4a** and **1a**.

Based on all these results and the absolute configurations of products, a plausible reaction mechanism is presented in Scheme 3. Initially, chiral catalyst **IV** activates the 3-homoacylcoumarin **1a** by deprotonation to provide a conjugate acid-base pair with H-bonding interactions. The first Michael

addition from the *Re* face attack of **1a** to the *Re* face of the alkylidene oxindole ester **2a** or ketone **4a** provides the Michael adduct **A**. The squramide NH group of **IV** forms the hydrogen bonding with the carbonyl group of Michael adduct **A**. The H-bonding interactions along with the steric hindrance would lead to the favorable confirmer of the Michael adduct **A** to provide **3aa**/**5aa** with observed configurations. Subsequently, second Michael addition of oxindole with its *Re* face to the *Si* face of coumarin to afford **3aa**/**5aa** in good yields with high enantioselectivities.



Scheme 3. Plausible Mechanism for **3aa** and **5aa**.



Scheme 4. Optimal Conditions for **7aa**.

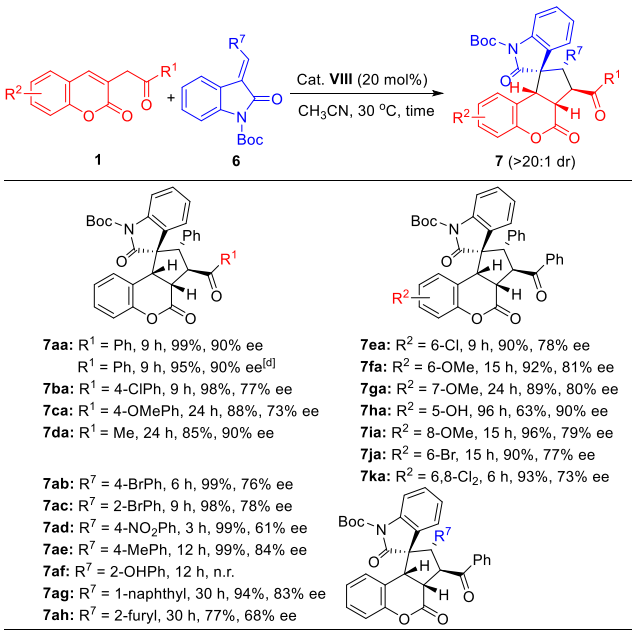
Having successfully extended the scope of alkylidene oxindole electrophiles, we further tested the applicability of benzylidene oxindoles in the (3+2) cycloaddition reaction. Accordingly, *E*-benzylidene oxindole **6a** was tested for the reaction with **1a**. However, our previous choice of the catalyst **IV** was not efficient. Therefore, further detailed optimization studies had to be carried out (see Supporting Information). Subsequently, the optimal yield of the adduct **7aa** (99% yield, >20:1 dr, 90% ee) was obtained when **1a** and **6a** (1.2 equiv) were reacted in the presence of the catalyst **VIII** (20 mol%) in CH_3CN (0.2 M) as solvent at 30 °C in 9 h (Scheme 4).

Again, substrates **1** and **6** possessing different substitutions were examined for their applicability. In general, all reactions resulted in good to excellent yields and good enantioselctivites irrespective of nature of the substrates and position of the substitution (Table 4). Substrates bearing different R^1 and R^2 groups on **1** reacted well with **6a** to provide the corresponding products **7aa-7ka** in 63-99% yields and 73-90% ee values. The substrate **1h** (R^2 = 5-OH) also well tolerated with **6a** to furnish the corresponding product **7ha** in 63% yield and 90% ee. Notably, the benzylidene oxindole **6f** bearing an *ortho*-OH substituent was found to be unreactive. Delightfully, the substrate bearing the naphthyl (**6g**) group also furnished the corresponding product **7ag** in good yield and selectivity, albeit requiring longer reaction time. In addition, the substrate **6h** bearing a furyl group was tolerated to afford the desired product **7ah** in relatively lower yield and

10.1002/adsc.201901655

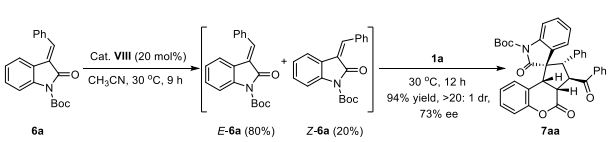
enantioselectivity. Furthermore, a gram scale preparation of **7aa** was found to be equally efficient.

Table 4. Substrate Scope of **7**.[a,b,c]



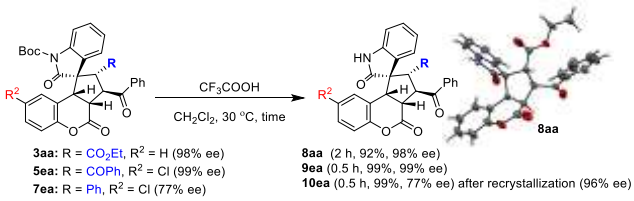
[a] Unless otherwise specified, all the reactions were carried out using **1** (0.2 mmol), **6** (1.2 equiv), catalyst **VIII** (20 mol%) in CH_3CN (1 mL) at 30 °C. [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase. [d] Reaction was performed on a gram scale of **1a** (3.8 mmol, 1.0 g). n.r. = No reaction with the recovery of **1a** and **6f**.

To investigate the differentiation between enantioselectivities of desired products from alkylidene oxindole carbonyl derivatives **2**/**4** and benzylidene oxindole derivatives **6**, we have performed crucial control experiments. The reaction of benzylidene oxindole (**6a**) and catalyst **VIII** in CH_3CN provided the ratio of *E*/*Z*-isomers of **6a** in 80:20 within 9 h. Furthermore, addition of 3-homoacylcoumarin (**1a**) to the reaction mixture furnished the desired product **7aa** with 73% ee which is lower than that obtained in the standard condition (Scheme 5). It was found that the predominating factor for the diminished enantiomeric ratios of the final products **7** in comparison with **3** and **5**, is the isomerization ability of their benzylidene oxindole derivatives **6**. In the presence of chiral catalyst, isomerization of alkylidene oxindole ester **2** and ketone **4** derivatives to their *Z*-isomers are much slower than the benzylidene oxindole derivatives **6**.



Scheme 5. Isomerization of **6a** with Catalyst **VIII**.

The removal of Boc group from **3aa**, **5ea** and **7ea** was conducted smoothly by treatment with TFA in CH_2Cl_2 at 30 °C to result the corresponding products **8aa**, **9ea** and **10ea** in high yields without erosion of enantioselectivity (Scheme 6). The absolute configurations of products **3**, **5** and **7** were established by single crystal X-ray diffraction analysis of the corresponding Boc-deprotected compounds **8**-**10**.[9]



Scheme 6. Deprotection of Compounds **3aa**/**5ea**/**7ea**.

In conclusion, we have developed a bifunctional quinine derivative-catalyzed stepwise (3+2) cycloaddition reaction for the generation of complex spirooxindole adducts in high yields (up to 99%), good to excellent diastereoselectivities (up to >20:1 dr) and excellent enantioselectivities (up to 99% ee). Apart from bearing five contiguous stereocenters, including a spiro all-carbon quaternary stereocenter, the products also incorporate a biologically active spirooxindole moiety as well as a cyclopenta[*c*]chromen-4-one core which are core structures of many natural products. Different Michael acceptors such as alkylidene oxindole esters, ketones and benzylidene oxindoles were investigated for the substrate scope of this stepwise (3+2) cycloaddition reaction. In addition, the reaction could be performed on a gram scale with similar efficacy. The mechanistic investigations proved that this is a (3+2) cycloaddition reaction via a stepwise Michael/Michael cascade pathway instead of concerted pathway. We have found that 3-homoacylcoumarin as 1,3-dipole precursor proceeds the stepwise (3+2) cycloaddition reaction with unsymmetrical alkylidene oxindole electrophiles whereas a concerted (3+2) cycloaddition has been reported with symmetric indandione alkylidenes.[8] Further studies regarding the application of 3-homoacylcoumarin in other organocatalytic reactions are underway in our laboratory.

Experimental Section

Typical procedure for the synthesis of spirooxindole-fused cyclopenta[*c*]chromen-4-ones 3: A capped glass vial equipped with a magnetic stir bar was charged with **1** (0.3 mmol), **2** (1.1 equiv), catalyst **IV** (9.4 mg, 5 mol%) and CH_2Cl_2 (1.5 mL) and stirred at 30 °C. The progress of the reaction was monitored by TLC and ^1H NMR data analysis. After the completion of reaction, 1N HCl (5 mL) was added and extracted with CH_2Cl_2 (2x3 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in *vacuo* and the crude residue was subjected to flash column chromatography over silica gel (hexanes/EtOAc) to afford pure spirooxindole-fused cyclopenta[*c*]chromen-4-ones **3**.

Typical procedure for the synthesis of spirooxindole-fused cyclopenta[*c*]chromen-4-ones 5: A capped glass vial equipped with a magnetic stir bar was charged with **1** (0.2 mmol), **4** (1.1 equiv), catalyst **IV** (12.6 mg, 10 mol%) and CH_2Cl_2 (2.0 mL) and stirred at 30 °C. The progress of the reaction was monitored by TLC and ^{1}H NMR data analysis. After the completion of reaction, the reaction mixture was concentrated in *vacuo* and the crude residue was subjected to flash column chromatography over silica gel (hexanes/EtOAc) to obtain pure spirooxindole-fused cyclopenta[*c*]chromen-4-ones **5**.

Typical procedure for the synthesis of spirooxindole-fused cyclopenta[*c*]chromen-4-ones 7: A capped glass vial equipped with a magnetic stir bar was charged with **1** (0.2 mmol), **6** (1.2 equiv), catalyst **VIII** (13.1 mg, 20 mol%) and CH_3CN (1.0 mL) and stirred at 30 °C. The progress of the reaction was monitored by TLC and ^{1}H NMR data analysis. After the completion of reaction, the reaction mixture was concentrated in *vacuo* and the crude residue was subjected to flash column chromatography over silica gel (hexanes/EtOAc) to obtain pure spirooxindole-fused cyclopenta[*c*]chromen-4-ones **7**.

Acknowledgements

The authors thank the Ministry of Science and Technology of the Republic of China (MOST 107-2628-M-003-001-MY3) for financial support.

References

[1] a) T. L. Pavlovska, R. G. Redkin, V. V. Lipson, D. V. Atamanuk, *Mol. Diversity.* **2016**, *20*, 299-344; b) N. Ye, H. Chen, E. A. Wold, P.-Y. Shi, J. Zhou, *ACS Infectious Diseases.* **2016**, *2*, 382-392; c) B. Yu, D.-Q. Yu, H.-M. Liu, *Eur. J. Med. Chem.* **2015**, *97*, 673-698; d) B. M. Trost, D. A. Bringley, T. Zhang, N. Cramer, *J. Am. Chem. Soc.* **2013**, *135*, 16720-16735; e) B. K. S. Yeung, B. Zou, M. Rottmann, S. B. Lakshminarayana, S. H. Ang, S. Y. Leong, J. Tan, J. Wong, S. Keller-Maerki, C. Fischli, A. Goh, E. K. Schmitt, P. Krastel, E. Francotte, K. Kuhen, D. Plouffe, K. Henson, T. Wagner, E. A. Winzeler, F. Petersen, R. Brun, V. Dartois, T. T. Diagana, T. H. Keller, *J. Med. Chem.* **2010**, *53*, 5155-5164; f) C. V. Galliford, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2007**, *46*, 8748-8758; g) C. Marti, Erick M. Carreira, *Eur. J. Org. Chem.* **2003**, *2003*, 2209-2219.

[2] a) Z.-J. Zhang, L. Zhang, R.-L. Geng, J. Song, X.-H. Chen, L.-Z. Gong, *Angew. Chem. Int. Ed.* **2019**, *58*, 12190-12194; b) Q. Liu, X.-Y. Chen, S. Li, K. Rissanen, D. Enders, *Adv. Synth. Catal.* **2019**, *361*, 1991-1994; c) G.-J. Mei, F. Shi, *Chem. Commun.* **2018**, *54*, 6607-6621; d) Q. Liu, S. Li, X.-Y. Chen, K. Rissanen, D. Enders, *Org. Lett.* **2018**, *20*, 3622-3626; e) Y. Lin, B.-L. Zhao, D.-M. Du, *J. Org. Chem.* **2018**, *83*, 7741−7750; f) L. Wang, S. Li, M. Blümel, R. Puttreddy, A. Peuronen, K. Rissanen, D. Enders, *Angew. Chem. Int. Ed.* **2017**, *56*, 8516-8521; g) N.-K. Li, J.-Q. Zhang, B.-B. Sun, H.-Y. Li, X.-W. Wang, *Org. Lett.* **2017**, *19*, 1954−1957; h) Y. Wang, M.-S. Tu, L.Yin, M. Sun, F. Shi, *J. Org. Chem.* **2015**, *80*, 3223−3232; i) W. Dai, X.-L. Jiang, Q. Wu, F. Shi, S.-J. Tu, *J. Org. Chem.* **2015**, *80*, 5737−5744.

[3] a) Y.-C. Zhang, F. Jiang, F. Shi, *DOI: 10.1021/acs.accounts.9b00549*; b) X. Xie, W. Huang, C. Peng, B. Han, *Adv. Synth. Catal.* **2018**, *360*, 194-228; c) X. Fang, C.-J. Wang, *Org. Biomol. Chem.* **2018**, *16*, 2591-2601; d) J.-B. Chen, Y.-X. Jia, *Org. Biomol. Chem.*, **2017**, *15*, 3550–3567; e) Y. Wang, H. Lu, P.-F. Xu, *Acc. Chem. Res.* **2015**, *48*, 1832-1844; f) W.-Y. Han, J.-Q. Zhao, J. Zuo, X.-Y. Xu, X.-M. Zhang, W.-C. Yuan, *Adv. Synth. Catal.* **2015**, *357*, 3007-3031; g) D. Cheng, Y. Ishihara, B. Tan, C. F. Barbas III, *ACS Catalysis.* **2014**, *4*, 743-762; h) L. Hong, R. Wang, *Adv. Synth. Catal.* **2013**, *355*, 1023-1052; i) N. R. Ball-Jones, J. J. Badillo, A. K. Franz, *Org. Biomol. Chem.* **2012**, *10*, 5165-5181; j) F. Zhou, Y.-L. Liu, J. Zhou, *Adv. Synth. Catal.* **2010**, *352*, 1381-1407.

[4] a) P. D. Chaudhari, B.-C. Hong, G.-H. Lee, *Org. Lett.* **2017**, *19*, 6112-6115; b) B.-L. Zhao, D.-M. Du, *Chem. Commun.* **2016**, *52*, 6162-6165; c) Q.-S. Sun, H. Zhu, Y.-J. Chen, X.-D. Yang, X.-W. Sun, G.-Q. Lin, *Angew. Chem. Int. Ed.* **2015**, *54*, 13253-13257. d) N. R. Ball-Jones, J. J. Badillo, N. T. Tran, A. K. Franz, *Angew. Chem. Int. Ed.* **2014**, *53*, 9462-9465; e) W. Sun, L. Hong, G. Zhu, Z. Wang, X. Wei, J. Ni, R. Wang, *Org. Lett.* **2014**, *16*, 544-547; f) B. Tan, N. R. Candeias, C. F. Barbas III, *Nature Chemistry* **2011**, *3*, 473; g) B. M. Trost, N. Cramer, S. M. Silverman, *J. Am. Chem. Soc.* **2007**, *129*, 12396-12397.

[5] a) E. V. Mercado-Marin, P. Garcia-Reynaga, S. Romminger, E. F. Pimenta, D. K. Romney, M. W. Lodewyk, D. E. Williams, R. J. Andersen, S. J. Miller, D. J. Tantillo, R. G. S. Berlinck, R. Sarpong, *Nature.* **2014**, *509*, 318; b) Z. Bian, C. C. Marvin, M. Pettersson, S. F. Martin, *J. Am. Chem. Soc.* **2014**, *136*, 14184 14192; c) T. Mugishima, M. Tsuda, Y. Kasai, H. Ishiyama, E. Fukushi, J. Kawabata, M. Watanabe, K. Akao, J. i. Kobayashi, *J. Org. Chem.* **2005**, *70*, 9430-9435; d) H. L. Byung, F. C. Michael, E. D. Fred, J. N. Stephen, S. J. Sandra, P. T. David, G. G. Timothy, D. W. Howard, L. H. Christopher, P. M. Vincent, I. K. Gabe, L. M. Patty, I. C. Joyce, G. M. David, W. B. Jerry, A. B. Carol, M. C. Eileen, J. A.-B. Susan, P. D. John, W. Z. Erich, W. Veronica, F. L. Michael, A. M. Michael, *Curr. Top. Med. Chem.* **2002**, *2*, 779-793; e) R. F. Bond, J. C. A. Boeyens, C. W. Holzapfel, P. S. Steyn, *J. Chem. Soc., Perkin Trans. 1.* **1979**, 1751-1761.

[6] a) M. I. L. Soares, C. S. B. Gomes, S. C. C. Nunes, A. A. C. C. Pais, T. M. V. D. Pinho e Melo, *Eur. J. Org. Chem.* **2019**, *2019*, 5441-5451; b) Q. Liu, X.-Y. Chen, R. Puttreddy, K. Rissanen, D. Enders, *Angew. Chem Int. Ed.* **2018**, *57*, 17100-17103; c) M. Michalak, K. Michalak, J. Wicha, *Nat. Prod. Rep.* **2017**, *34*, 361-410; d) P. Kamat, S. G. Tilve, V. P. Kamat, J. K. Kirtany, *Org. Prep. Proced. Int.* **2015**, *47*, 1-79; e) A. Srikrishna, B. Vasantha Lakshmi, *Tetrahedron Lett.* **2005**, *46*, 4879-4881; f) D. Ng, Z. Yang, M. A. Garcia-Garibay, *Org. Lett.* **2004**, *6*, 645-647; g) A. Matsuo, S. Yuki, M. Nakayama, *J. Chem. Soc., Perkin Trans. 1* **1986**, 701-710.

[7] a) S.-M. Yang, P. Karanam, M. Wang, Y.-J. Jang, Y.-S. Yeh, P.-Y. Tseng, M. R. Ganapuram, Y.-C. Liou, W.

10.1002/adsc.201901655

Lin, *Chem. Commun.* **2019**, *55*, 1398-1401; b) J.-K. Yu, H.-W. Chien, Y.-J. Lin, P. Karanam, Y.-H. Chen, W. Lin, *Chem. Commun.* **2018**, *54*, 9921-9924; c) S.-M. Yang, G. M. Reddy, T.-P. Wang, Y.-S. Yeh, M. Wang, W. Lin, *Chem. Commun.* **2017**, *53*, 7649-7652; d) L. Möhlmann, G.-H. Chang, G. Madhusudhan Reddy, C.-J. Lee, W. Lin, *Org. Lett.* **2016**, *18*, 688-691; e) C.-H. Chen, C.-T. Ko, G. M. Reddy, C.-J. Lee, W. Lin, *Eur. J. Org. Chem.* **2015**, *2015*, 5254-5265; f) U. Das, C.-H. Huang, W. Lin, *Chem. Commun.* **2012**, *48*, 5590-5592.

[8] Y.-R. Chen, M. R. Ganapuram, K.-H. Hsieh, K.-H. Chen, P. Karanam, S. S. Vagh, Y.-C. Liou, W. Lin, *Chem. Commun*. **2018**, *54*, 12702-12705.

[9] See Supporting Information for crystal data of compounds **5ac** (CCDC 1962249), **8aa** (CCDC 1948942), **9ea** (CCDC 1911409), **10ea** (CCDC 1893243) and **5da'** (CCDC 1959572). It is worth noting that the stereo-configuration of **5da'**is different from that of the proposed concerted product *epi*-**5da**.

10.1002/adsc.201901655

COMMUNICATION

Enantioselective Construction of Spirooxindole-Fused Cyclopenta[*c*]chromen-4-ones Bearing Five Contiguous Stereocenters *via* a Stepwise (3+2) Cycloaddition

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

Sandip Sambhaji Vagh,† Praneeth Karanam,† Cheng-Chieh Liao, Ting-Han Lin, Yan-Cheng Liou, Athukuri Edukondalu, Yi-Ru Chen and Wenwei Lin*