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Bifunctional Thiourea Catalyzed Asymmetric Michael Addition of Anthrone to Methyleneindolinones

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Biologically significant hybrid derivatives of oxindoles and anthrones were prepared in high yield, high regioselectivity and high stereoselectivity via bifunctional thiourea catalyzed asymmetric conjugate addition of anthrone to methylene-indolinones. The regioselectivity and stereoselectivity could be finely tuned via change of substituents in methyleneindolinones.

The oxindole framework bearing a stereogenic C3 carbon center is an important fragment in many natural products and pharmaceutically significant molecules, such as strychnofoline,[1] spirotryprostatin B,[2] welwitindolinone C isothiocyanate,[3] and maremycin A[4] (Figure 1). Due to its ubiquity in biologically active compounds, a plethora of strategies have been developed for asymmetric synthesis of 3,3'-disubstituted oxindole frameworks[5] for further synthesis of natural products and biologically important compounds. Among these methods, methyleneindolinones have distinguished themselves as versatile reactants for preparation of 3,3'-disubstituted oxindole frameworks. Anthrone is a privileged motif that constitutes core structures of a large family of natural products and pharmaceutically active compounds such as variecolortide B and C (Figure 1).[6] A lot of methods have been developed to access this significant motif.[7] Based on the principle of superposition, new compounds with higher biological activity might be found by merging these two pharmaceutically significant moieties. However, to the best of our knowledge, no protocol is available to combine these two biologically intriguing moieties up to now although it holds great potential for finding novel pharmaceutically significant agents.

Both C3 and C4 of methyleneindolinone can be attacked by a nucleophile as both they are substituted with electron-withdrawing groups, furnishing two different Michael addition product **3** or **4** (Scheme 1). However, the reports concerning C3 attack are rather rare and the traditional strategy to achieve the regiospecific nucleophilic attack on C3 depends on introducing two electron-withdrawing substituents to C4, such as cyano groups.[8] As C3 and C4 substituted adducts are both significant agents in natural products and therapeutic agents (Figure 1), it is highly desirable to develop the stereoselective and regioselective strategy for construction of oxindole derivatives carrying tertiary or quaternary C3 carbon center. As a continuation of our interest in developing organocatalytic asymmetric reactions and green chemistry,[9] herein we report a chiral bifunctional thiourea catalyzed asymmetric Michael addition of anthrone to methyleneindolinones with high regioselectivity and stereoselectivity.

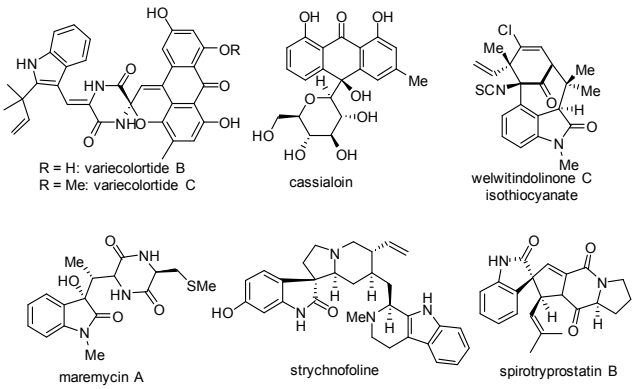
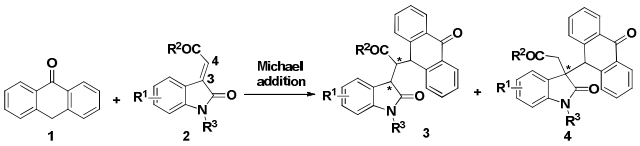


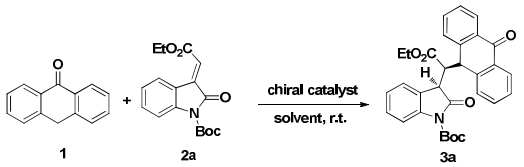
Figure 1. Natural products and bioactive molecules possessing moieties of oxindole and/or anthrone.

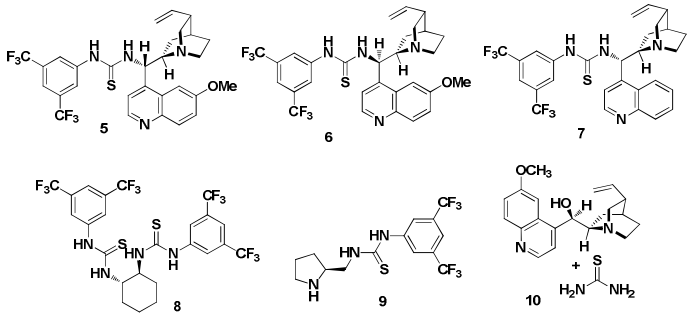


Scheme 1. Preparation of C3 and C4 substituted adducts via nucleophilic attack on C3 or C4.

Initially, the asymmetric conjugate addition was investigated with anthrone **1** and methyleneindolinone **2a** as model substrates. A series of chiral organocatalysts **5-10** were examined using methylene chloride as solvent. The desired adduct could be furnished in good yield with 20 mol% catalyst loading of cinchona alkaloid-derived bifunctional thiourea catalysts **5-6**, whereas the enantioselectivity was not satisfactory (Table 1, entries 1-2). Gratifyingly, the enantioselectivity and diastereoselectivity could be dramatically increased when catalyst loading of **5** and **6** was decreased to 10 mol% (Table 1, entries 3-4). The low enantioselectivity at higher catalyst loading (20 mol%) might be ascribed to the catalyst self-association which would drastically block the association of the catalyst with substrates.[10] Afterwards, the thiourea catalysts **7-9** and combinational catalyst of quinine with thiourea **10** were evaluated at 10 mol% catalyst loading, whereas only inferior results were

Table 1. Examination of various chiral catalysts in the Michael addition of methyleneindolinone and anthrone[a]





ntry	Cat. (mol%)	Solvent	T (℃)	Time (h)	ee (%)	d.r.[b]	Yield (%)[c]
1	**5** (20)	CH_2Cl_2	r.t.	5	-5	20:1	90
2	**6** (20)	CH_2Cl_2	r.t.	5	5	2:1	93
3	**5** (10)	CH_2Cl_2	r.t.	5	-75	14:1	90
4	**6** (10)	CH_2Cl_2	r.t.	5	70	>99:1	87
5	**7** (10)	CH_2Cl_2	r.t.	5	57	23:1	63
6	**8** (10)	CH_2Cl_2	r.t.	5	41	35:1	74
7	**9** (10)	CH_2Cl_2	r.t.	12	-	-	0
8	**10** (10)	CH_2Cl_2	r.t.	5	8	94:1	70
9	**5** (5)	CH_2Cl_2	r.t.	5	-11	8:1	90
10	**6 (5)**	CH_2Cl_2	r.t.	**5**	**80**	**>99:1**	**95**
11	**6** (3)	CH_2Cl_2	r.t.	5	68	28:1	83
12	**6** (5)	CH_2Cl_2	0	48	73	>99:1	95
13	**6** (5)	CH_2Cl_2	-10	50	84	63:1	93
14	**6** (5)	CH_2Cl_2	-15	48	31	28:1	84
15	**6** (5)	toluene	r.t.	12	80	69:1	87
16	**6** (5)	$CHCl_3$	r.t.	24	-2	22:1	73
17	**6** (5)	THF	r.t.	24	45	42:1	69
18	**6** (5)	Et_2O	r.t.	24	25	14:1	75
19	**6** (5)	DCE	r.t.	12	24	32:1	87
20	**6** (5)	EtOAc	r.t.	24	-4	71:1	85
21	**6** (5)	ethylene glycol	r.t.	24	1	10:1	54

[a] Reaction conditions: **1** (0.18 mmol), **2a** (0.15 mmol), 1 mL solvent.
[b] The diastereoselectivities of products **3** was measure by HPLC.
[c] Isolated yield after column chromatography.

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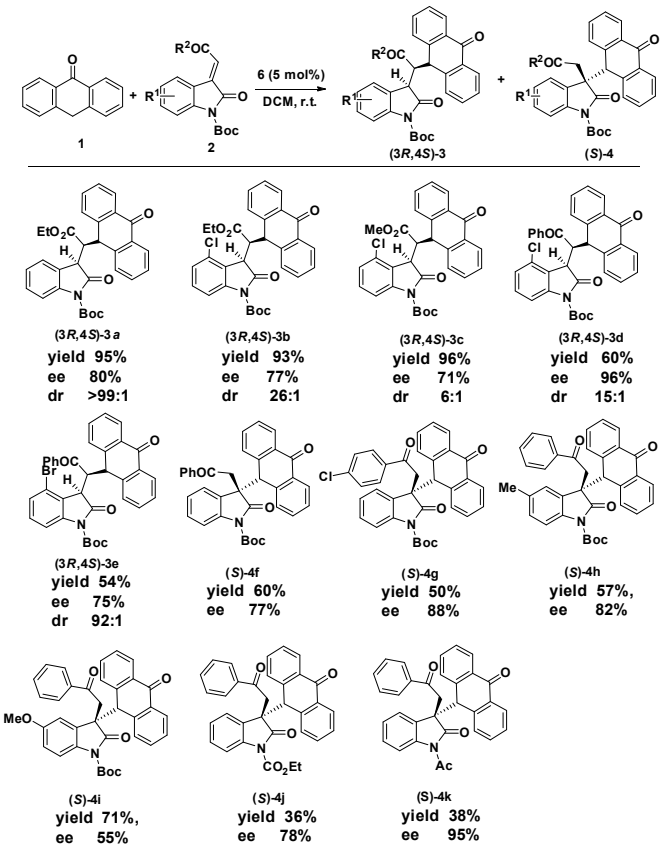
achieved (Table 1, entries 5-8). Further decreasing the catalyst loading to 5 mol% resulted in lower enantioselectivity for catalyst **5**, but higher enantioselectivity for catalyst **6** (Table 1, entries 9-10). The lower yield and lower enantioselectivity were observed with the catalyst loading further decreased to 3 mol% (Table 1, entry 11). Decreasing the temperature resulted in lower yields or lower enantioselectivity (Table 1, entries 12-14). The option of solvents had significant impact on the enantioselectivity and non-polar solvents were superior to polar solvents such as ethylene glycol and ethyl acetate (Table 1, entries 15-21), which might be rationalized that the association of catalyst and substrates could be severely blocked by the H-bonding interactions between chiral thiourea catalyst and the polar solvents.

With the optimized condition in hand, the substrate scope of the asymmetric conjugate addition was investigated. Gratifyingly, the



Scheme 2. Chiral thiourea catalyzed asymmetric Michael addition of methyleneindolinones and anthrone.

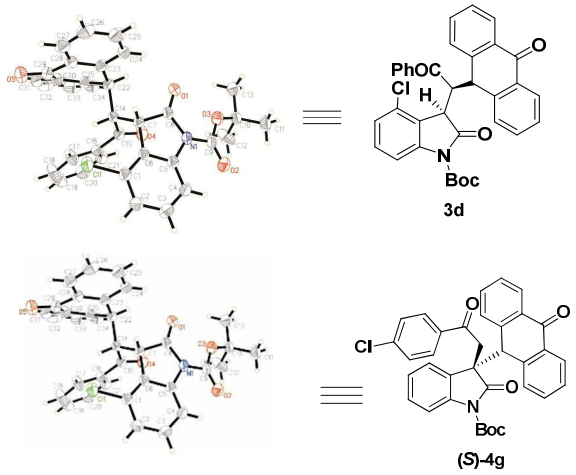
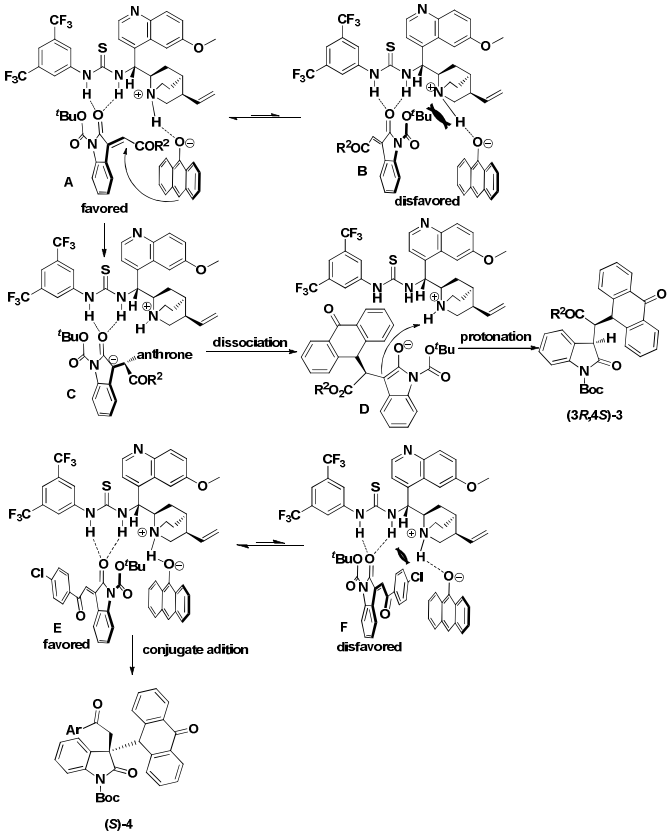


Figure 2. The single crystal structure of **3d** and **(*S*)-4g**.

products **3a-e** resulted from C4 attack could be furnished in high yields, high diasteroselectivity and high enantioselectivity. When C4 was substituted with a carboxylate group, the C4 addition products **3** were exclusively obtained in high yields. When carboxylate group at C4 was replaced with benzoyl groups, product **4g-4k** were observed as major product (Scheme 2). The relative configuration of **3d** and the absolute configuration of adduct (*S*)-**4g** have been unambiguously verified by X-ray crystal analysis (Figure 2). The decomposition of enantioenriched **3d** to starting materials was observed in the course of crystal cultivation, and presumably the racemic **3d** could be regenerated via the reversible conjugate addition. Namely, the enantioenriched **3d** could be racemerized gradually to the racemic **3d** in the course of crystal cultivation, hence only the single crystal structure of racemic **3d** was available.

On the basis of the above experimental results, the plausible reaction pathway and activation mode were proposed. As illustrated in Scheme **3**, the enolate generated from anthrone forms a strong H-bond with the *tert*-aminium moiety of catalyst **6**. Meanwhile, the oxygen atom of indolinone is chelated by dual H-bonds of thiourea moiety and dihedral angles between methyleneindolinone and thiourea moiety would approximate to be perpendicular [11] as shown in the transition states **A** and **B**.[12] Due to severe steric repulsion between bulky *tert*-amino group of catalyst **6** and *tert*-butoxyl group, transition state **B** is disfavoured. In addition to electronic factors, the nucleophilic enolate of anthrone chelated by the *tert*-aminium moiety is much closer to C4, therefore, the enolate would preferentially attack the *Si* face of C4 *via* well-defined transition state **A**, leading to carbanionic intermediate **C** which is tautomerized to the enolate **D**. In this process, electron-withdrawing groups in oxindole moiety like chlorine and bromine would make C4 much more electron-deficient, thus favoring the C4 attack (Scheme 2, **3b-e**). Smaller R^2 group was also much favourable for C4 attack due to its weakening the steric repulsion (Scheme 2, **3a-c**). In the following protonation step, as C4 stereocenter is substituted by bulky anthrone and ester group, the *tert*-aminium moiety of catalyst **6** which serves

as a proton source would approach the enolate intermediate **D** from the opposite side of anthrone, furnishing the final products (3*R*, 4*S*)-**3**. Additionally, the lifetime of anionic intermediate **C** and enolate intermediate **D** strongly depend on the electronic characteristics of substituents. Obviously, electron-withdrawing groups on the phenyl ring would stabilize these anionic intermediates, thus in favor of C4 attack, which is consistent with the experimental results. While if a stronger withdrawing group such as phenyl ketone was introduced to C4, the C3 would be more electron deficient than C4, thus it will favor the nucleophilic attack on C3. The electron-donating groups also decreased the possibility of attack on C4. When carboxylate group substituted at C4 is replaced with phenyl ketone which is bulkier than *tert*-butyl carbamate, the transition state **E** is more favoured than transition **F** in which severe steric repulsion exists between phenyl ketone and *tert*-aminium moiety of catalyst **6**. In addition to electronic effect, the C3 is much closer to enolate sterically as shown in transition state **E**, resulting in preferential nucleophilic attack from *Si* face of C3 to furnish the adducts **4** in (*S*)-configuration. In brief, the regioselectivity and stereoselectivity are controlled by both electronic effect and steric effect of the substrates as well as the chiral catalyst in the process of conjugate addition.



Scheme 3. Proposed reaction pathway.

Conclusions

In conclusion, the asymmetric conjugate addition of anthrone to methyleneindolinones was successfully implemented under the catalysis of bifunctional chiral thiourea catalyst to produce two types of adducts in high yield, high stereoselectivity and regioselectivity. The electronic and steric effect had a dramatic influence on the stereoselectivity and regioselectivity, which can be readily tuned by modification of substituents.

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Notes and references

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[b] Open Project Program of Hubei Key Laboratory of Drug Synthesis and Optimization, Jingchu University of Technology (Nos. OPP2015YB01 and OPP2015ZD02)

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† Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

1. (a) A. Lerchner and E. M. Carreira, *J. Am. Chem. Soc.*, 2002, **124**, 14826; (b) A. Lerchner and E. M. Carreira, *Chem. Eur. J.*, 2006, **12**, 8208.
2. (a) F. v. Nussbaum and S. J. Danishefsky, *Angew. Chem. Int. Ed.*, 2000, **39**, 2175; (b) L. E. Overman and M. D. Rosen, *Angew. Chem. Int. Ed.*, 2000, **39**, 4596; (c) C. Meyers and E. M. Carreira, *Angew. Chem. Int. Ed.*, 2003, **42**, 694; (d) P. R. Sebahar and R. M. Williams, *J. Am. Chem. Soc.*, 2000, **122**, 5666; (e) C. Marti and E. M. Carreira, *J. Am. Chem. Soc.*, 2005, **127**, 11505; (f) T. D. Bagul, G. Lakshmaiah, T. Kawabata and K. Fuji, *Org. Lett.*, 2002, **4**, 249.
3. J. M. Ready, S. E. Reisman, M. Hirata, M. M. Weiss, K. Tamaki, T. V. Ovaska and J. L. Wood, *Angew. Chem. Int. Ed.*, 2004, **43**, 1270.
4. F. Zhou, Y.-L. Liu and J. Zhou, *Adv. Synth. Catal.*, 2010, **352**, 1381.
5. (a) L. Hong and R. Wang, *Adv. Synth. Catal.*, 2013, **355**, 1023; (b) F. Manoni and S. J. Connon, *Angew. Chem. Int. Ed.*, 2014, **53**, 2628; (c) J. L. Li, B. Sahoo, C. G. Daniliuc and F. Glorius, *Angew. Chem. Int. Ed.*, 2014, **53**, 10515; (d) B. Tan, N. R. Candeias and C. F. Barbas, 3rd, *Nat. Chem.*, 2011, **3**, 473; (e) Y. Wang, J. O. Bauer, C. Strohmann and K. Kumar, *Angew. Chem. Int. Ed.*, 2014, **53**, 7514; (f) D. F. Chen, F. Zhao, Y. Hu and L. Z. Gong, *Angew. Chem. Int. Ed.*, 2014, **53**, 10763; (g) Z. Li, Y. Zhang, L. Zhang and Z. Q. Liu, *Org. Lett.*, 2014, **16**, 382.
6. (a) C. A. Kuttruff, H. Zipse and D. Trauner, *Angew. Chem. Int. Ed.*, 2011, **50**, 1402; (b) Y. Koyama, R. Yamaguchi and K. Suzuki, *Angew. Chem. Int. Ed.*, 2008, **47**, 1084; (c) L. F. Tietze, R. R. Singidi and K. M. Gericke, *Chem. Eur. J.*, 2007, **13**, 9939; (d) E. E. Podlesny and M. C. Kozlowski, *Org. Lett.*, 2012, **14**, 1408; (e) L. F. Tietze, R. R. Singidi and K. M. Gericke, *Org. Lett.*, 2006, **8**, 5873.
7. (a) C. Wu, W. Li, J. Yang, X. Liang and J. Ye, *Org. Biomol. Chem.*, 2010, **8**, 3244; (b) A. Zea, G. Valero, A.-N. R. Alba, A. Moyano and R. Rios, *Adv. Synth. Catal.*, 2010, **352**, 1102; (c) H.-J. Lee, Y.-M. Chae and D.-Y. Kim, *Bull. Korean Chem. Soc.*, 2011, **32**, 2875; (d) J.-F. Bai, Y.-L. Guo, L. Peng, L.-N. Jia, X.-Y. Xu and L.-X. Wang, *Tetrahedron*, 2013, **69**, 1229; (e) J. Shen, T. T. Nguyen, Y.-P. Goh, W. Ye, J. X. Xiao Fu and C.-H. Tan, *J. Am. Chem. Soc.*, 2006, **128**, 13692.
8. (a) V. P. Reddy Gajulapalli, P. Vinayagam and V. Kesavan, *RSC Adv.*, 2015, **5**, 7370; (b) A. Kumar and S. S. Chimni, *Beilstein J.*

Org. Chem., 2014, **10**, 929; (c) X.-W. Wang, C. Qiao, F.-F. Pan, W. Yu and Z.-H. Qi, *Synthesis*, 2014, **46**, 1143; (d) X. F. Huang, Y. F. Zhang, Z. H. Qi, N. K. Li, Z. C. Geng, K. Li and X. W. Wang, *Org. Biomol. Chem.*, 2014, **12**, 4372.

9. (a) J. Xiao, *Org. Lett.*, 2012, **14**, 1716; (b) J. Xiao, Y.-P. Lu, Y.-L. Liu, P.-S. Wong and T.-P. Loh, *Org. Lett.*, 2011, **13**, 876; (c) J. Xiao, Z. Z. Wong, Y. P. Lu and T. P. Loh, *Adv. Synth. Catal.*, 2010, **352**, 1107; (d) J. Xiao, K. Zhao and T. P. Loh, *Chem. Asian. J.*, 2011, **6**, 2890; (e) J. Xiao, K. Zhao and T. P. Loh, *Chem. Commun.*, 2012, **48**, 3548; (f) L. Xu, Z. Shao, L. Wang and J. Xiao, *Org. Lett.*, 2014, **16**, 796; (g) J. Xiao, Y. Chen, S. Zhu, L. Wang, L. Xu and H. Wei, *Adv. Synth. Catal.*, 2014, **356**, 1835; (h) Z. Shao, L. Xu, L. Wang, H. Wei and J. Xiao, *Org. Biomol. Chem.*, 2014, **12**, 2185; (i) Z. Shao, L. Wang, L. Xu, H. Zhao and J. Xiao, *RSC Adv.*, 2014, **4**, 53188; (j) R. Niu, J. Xiao, T. Liang and X. Li, *Org. Lett.*, 2012, **14**, 676; (k) T. Liang, J. Xiao, Z. Xiong and X. Li, *J. Org. Chem.*, 2012, **77**, 3583; (l) H. Wen, L. Wang, L. Xu, Z. Hao, C.-L. Shao, C.-Y. Wang and J. Xiao, *Adv. Synth. Catal.*, 2015, DOI: 10.1002/adsc.201500500; (m) J. Xiao, H. Wen, L. Wang, L. Xu, Z. Hao, C.-L. Shao and C.-Y. Wang, *Green Chem.*, 2016, DOI: 10.1039/c5gc01838b.

10. (a) H. S. Rho, S. H. Oh, J. W. Lee, J. Y. Lee, J. Chin and C. E. Song, *Chem. Commun.*, 2008, 1208; (b) A. Berkessel, F. Cleemann, S. Mukherjee, T. N. Muller and J. Lex, *Angew. Chem. Int. Ed.*, 2005, **44**, 807; (c) T. Okino, Y. Hoashi, T. Furukawa, X. Xu and Y. Takemoto, *J. Am. Chem. Soc.*, 2005, **127**, 119; (d) G. Tarkanyi, P. Kiraly, S. Varga, B. Vakulya and T. Soos, *Chem. Eur. J.*, 2008, **14**, 6078; (e) A. Berkessel, S. Mukherjee, F. Cleemann, T. N. Muller and J. Lex, *Chem. Commun.*, 2005, 1898.

11. H.-Y. Liao and S.-Y. Chu, *New J. Chem.*, 2003, **27**, 421.

12. (a) M. P. Lalonde, Y. Chen and E. N. Jacobsen, *Angew. Chem. Int. Ed.*, 2006, **45**, 6366; (b) D. A. Yalalov, S. B. Tsogoeva and S. Schmatz, *Adv. Synth. Catal.*, 2006, **348**, 826.

Bifunctional Thiourea Catalyzed Asymmetric Michael Addition of Anthrone to Methyleneindolinones

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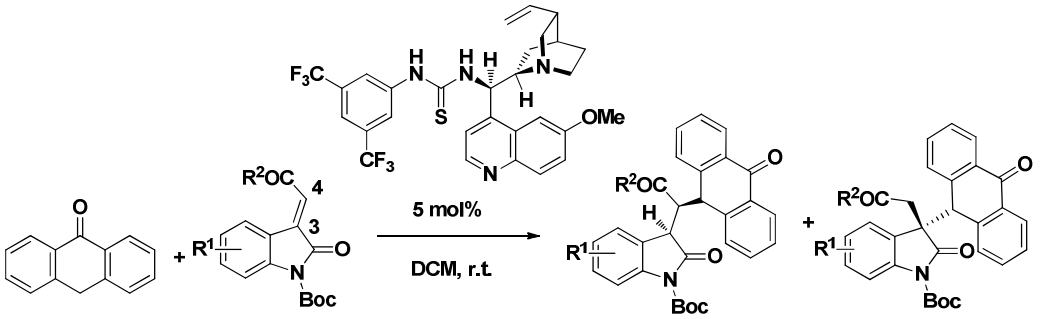
Biologically significant hybrid derivatives of oxindoles and anthrones were prepared in high yield, high regioselectivity and high stereoselectivity via bifunctional thiourea catalyzed asymmetric conjugate addition of anthrone to methylene-indolinones. The regioselectivity and stereoselectivity could be finely tuned via change of substituents in methyleneindolinones.



substituents tuned C3 and C4 addition products in high regioselectivity and stereoselectivity