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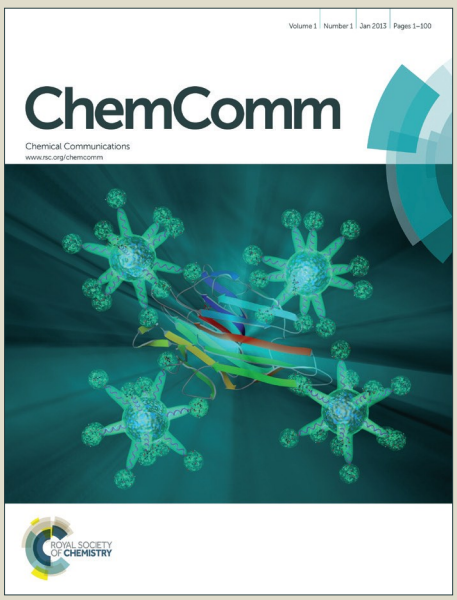

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Bifunctional Tertiary Amine-Squaramide Catalyzed Asymmetric Catalytic 1,6-Conjugate Addition/Aromatization of *para*-Quinone Methides with Oxindoles

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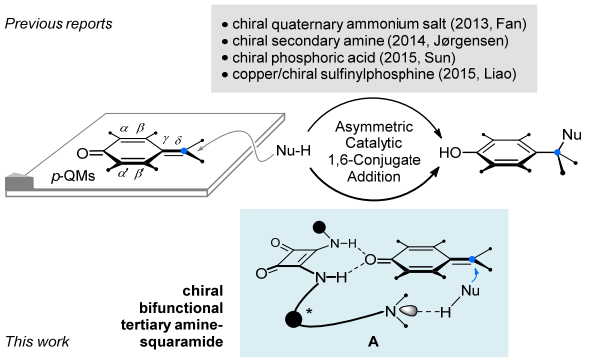
Asymmetric catalytic 1,6-addition of *p*-QMs with racemic oxindoles under the bifunctional catalysis of C_2-symmetric dimeric *Cinchona*-derived squaramide is described. This tertiary amine-squaramide catalyzed reaction provides a diastereoselective and enantioselective approach to the effective assembly of diverse diarylmethine-substituted oxindoles having vicinal tertiary and quaternary stereocenters.

para-Quinone methides (*p*-QMs) featuring a unique bisvinylogous enone system have been known for more than one century in organic chemistry.[1,2] Such structural units not only constitute the architectural framework of many natural products,[3] but also are involved in the molecular core of many transient entities *in-situ* formed in the chemical, medicinal and biological progresses.[4] Due to its intrinsic electrophilic property, *p*-QMs have been widely explored in organic synthesis, especially in the mode of 1,6-conjugate addition,[5] which was chemoselectively driven by the rearomatization. Despite the fact that the vast majority of methodologies of *p*-QMs was highlighted by 1,6-conjugate addition,[5] surprisingly, less attention has been paid to its asymmetric catalytic version.[6] Focusing on this challenge, several recent reports (Scheme 1) have been elegantly recorded, mainly including the phase transfer catalysis by chiral quaternary ammonium salt,[6a] the enamine catalysis by chiral secondary amine,[6b] the hydrogen-bonding catalysis by chiral phosphoric acid,[6d] and the transition metal catalysis by copper/chiral sulfinylphosphine.[6c] Therefore, the development of new model for the asymmetric catalytic 1,6-addition reaction of *p*-QMs is highly appealing in modern asymmetric synthesis.



Scheme 1. Asymmetric Catalytic 1,6-Addition of *p*-QMs

To address this topic, recently we developed a novel catalytic enantioselective 1,6-addition of *p*-QMs with oxindoles on the basis of bifunctional organocatalysis,[7] in which a new mode **A** (Scheme 1) using chiral tertiary amine-squaramide has been designed. To our knowledge, such enantioselective mode is yet to be reported in the design of catalytic asymmetric methodology for 1,6-conjugate addition of *p*-QMs.[6e] Herein we present our preliminary results on this aspect.

Initial model for our asymmetric catalytic 1,6-addition reaction was tested by using *p*-QM **1a** as acceptor and 3-phenyloxindole **2a** as donor. Inspired by the mode of the bifunctional catalysis,[7] as described in Table 1, a series of chiral organocatalysts consisting of the tertiary amine units (hydrogen bond acceptors) and the thiourea/squaramide moieties (hydrogen bond donors) were firstly investigated in this reaction employing K_2CO_3 as base and CH_2Cl_2 as solvent (entries 1–10). Generally, all catalysts examined in this model showed good reactivities (8-28 h, 87–97% yield), but the stereoselectivities (*dr* and *ee*) in these cases were quite dependent on the effects of molecular structure and functional groups of the catalyst. For example, when utilizing *Cinchona*-derived thiourea **4a** or BINOL-derived cyclohexane-diamine thiourea **4b** as catalyst, very low diastereoselectivity and enantioselectivity were observed (entries 1–2). In addition to the above amine-thioureas, the squaramide catalysts having

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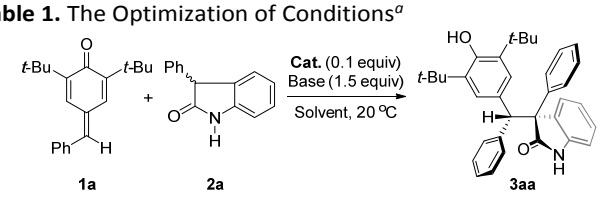
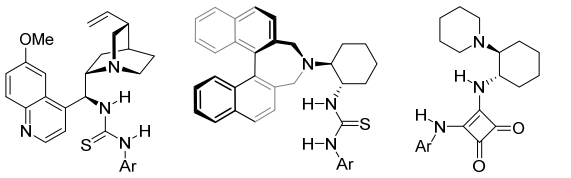
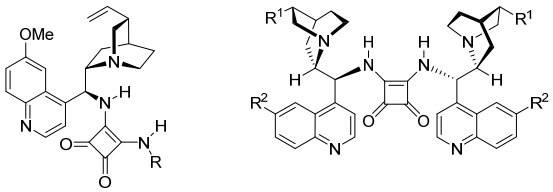
Table 1. The Optimization of Conditions[a]







Entry	Cat.	Solvent	Base	*t* (h)	Yield (%)[b]	dr[c]	*ee* (%)[d,e]
1	**4a**	CH_2Cl_2	K_2CO_3	18	93	5:3	19 (0)
2	**4b**	CH_2Cl_2	K_2CO_3	23	91	5:3	0 (0)
3	**4c**	CH_2Cl_2	K_2CO_3	24	97	8:3	-11 (0)
4	**4d**	CH_2Cl_2	K_2CO_3	23	93	4:1	37 (21)
5	**4e**	CH_2Cl_2	K_2CO_3	13	94	4:1	64 (24)
6	**4f**	CH_2Cl_2	K_2CO_3	12	95	4:1	64 (21)
7	**4g**	CH_2Cl_2	K_2CO_3	28	87	3:1	51 (13)
8	**4h**	CH_2Cl_2	K_2CO_3	12	95	4:1	79 (17)
9	**4i**	**CH_2Cl_2**	**K_2CO_3**	**9**	**94**	**5:1**	**80 (9)**
10	**4j**	CH_2Cl_2	K_2CO_3	8	93	7:2	74 (12)
11	**4i**	THF	K_2CO_3	1	98	13:1	90 (73)
12	**4i**	THF	/	72	36	13:1	93 (65)
13	**4i**	THF	Cs_2CO_3	1.2	76	5:2	0 (6)
14	**4i**	**THF**	**Na_2CO_3**	**6**	**97**	**17:1**	**94 (79)**
15	**4i**	THF	Li_2CO_3	36	90	11:1	91 (73)
16	**4i**	THF	$NaHCO_3$	12	94	13:1	94 (77)
17	**4i**	THF	Et_3N	48	88	14:1	93 (75)
18	**4i**	THF	DABCO	33	91	12:1	95 (83)
19	**4i**	THF	DMAP	10	93	17:1	92 (71)
20[f]	**4i**	THF	Na_2CO_3	12	96	15:1	96 (85)
21[g]	**4i**	THF	Na_2CO_3	14	94	34:1	98 (83)
22[h]	**4i**	**THF**	**Na_2CO_3**	**18**	**96**	**51:1**	**99 (90)**

[a]Unless otherwise noted, all reactions were performed with **1a** (0.05 mmol) and **2a** (0.05 mmol) in the presence of catalyst **4** (0.005 mmol) and base (0.075 mmol) in the indicated solvent (1.0 mL) at 20 °C. [b]Yield of isolated product. [c]Determined by HPLC. [d]Determined by HPLC analysis using a chiral stationary phase. [e]The ee's in the parentheses referred to the minor diastereoisomer. [f]Performed at 0 °C. [g]Performed at –20 °C. [h]Performed at –40 °C.

cyclic diamine framework (**4c**) and acyclic diamine skeleton (**4d**–**4g**) were also investigated (entries 3–7), and the improvement of stereoselectivity (up to 4:1 *dr* and 64% *ee*) was primarily seen in the cases using the *Cinchona*-based squaramides. Inspired by such positive results, the dimeric *Cinchona*-derived squaramides **4h**–**4j** were then evaluated (entries 8–10),[8] in which the C_2-symmetric squaramide **4i**[9] gave the superior result (9 h, 94% yield, 5:1 *dr*, 80% *ee*). Interestingly, the subsequent investigation on the influences of reaction medium revealed that THF as a suitable solvent (entry 11) could give the further improved result (1 h, 98% yield, 13:1 *dr*, 90% *ee*).[10] It should be noted this model reaction using **4i** as catalyst and THF as solvent at 20 °C proceeded very slowly in the absence of K_2CO_3 (entry 12; 72 h, 36% yield), albeit without the erosion of stereoselectivity. To identify the influences of the base, various inorganic and organic bases were examined (entries 13–19), and Na_2CO_3 was found compatible with the improvement of stereoselectivity (entry 14; 17:1 *dr*, 94% *ee*). Significantly, the further improvement of reaction stereoselectivity could be achieved by varying the temperature (entries 20–22), leading to an optimal result of 96% yield, 51:1 *dr* and 99% *ee* for **3aa** (entry 22).

With the above optimized conditions in hand for the asymmetric catalytic 1,6-addition reaction of *p*-QMs, as tabulated in Table 2, the scope of 3-substituted oxindoles **2a**–**2y** as donors was preliminarily explored in the presence of *p*-QM **1a**, and generally the desired addition products (**3aa**–**3ay**)[11] containing highly congested vicinal tertiary and quaternary centers could be obtained in good to high yields (85–97%) with good to excellent stereoselectivities (10:1 to 20:1 *dr*, up to 99% *ee*). For example, a series of substituted oxindoles **2b**–**2e** bearing different *N*-protecting groups (*e.g.*, R^a = allyl, Bn, Me, CO_2Et) were examined firstly. Compared with the case using *N*-protecting-group-free oxindole **2a** (R^a = H, Ar = Ph, X = H), the varied influences of *N*-substituents in oxindoles **2b**–**2e** have been observed. The oxindoles bearing *N*-allyl (**2b**) and *N*-methyl (**2d**) could give the products **3ab** and **3ad** with almost analogous reactivity and stereoselectivity, in which the absolute configuration of **3ab** was established on the basis of X-ray crystallographic analysis.[12] However, while using *N*-ethoxycarbonyl-substituted oxindole **2e** as donor, only a modest enantioselectivity of 11% *ee* was observed for **3ae**, partially showing the unfavorable electron withdrawing effect of *N*-substituent of the oxindole donor. It should be noted that a gram scale experiment for the formation of **3aa** was performed, and an analogous positive result was achieved (98% yield, >20:1 *dr*, 96% *ee*).

In addition, a variety of electronically and sterically different aryl and heteroaryl groups at C3 position of oxindoles **2f**–**2s** were extensively investigated under the standard conditions. Various diarylmethine-substituted oxindole products having two vicinal stereocenters, **3af**–**3as**, could be readily afforded in good to high yields (85–97%) with high diastereoselectivities (12:1 to >20:1 *dr*) and good to excellent enantioselectivities (89–99% *ee*). Notably, one example using **2s** (R^a = X = H, Ar = 1-pyrrolyl) as donor led to a structurally interesting oxindole derivative (**3as**) bearing vicinal tertiary and aza-quaternary stereocenters (97% yield, >20:1 *dr*, 99% *ee*). The influence of substituents at C5, C6 or C7 position of

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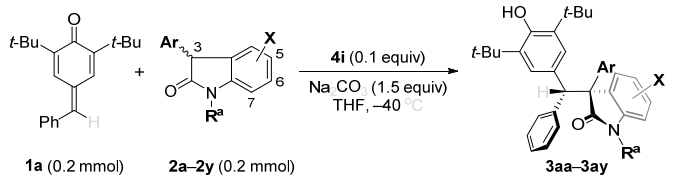
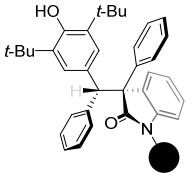
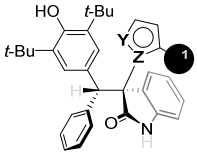
Table 2. The Scope of 3-Substituted Oxindoles as Donors[a,b]

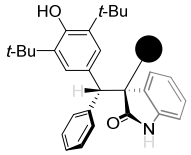




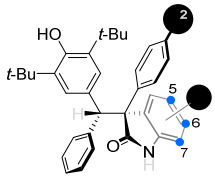
3aa: R^a = H (18 h, 96% yield, >20:1 dr, 99% *ee*) (gram scale: 18 h, 98% yield, >20:1 dr, 96% ee)
3ab: R^a = allyl (19 h, 96% yield, >20:1 dr, 96% *ee*)[b]
3ac: R^a = Bn (19 h, 94% yield, 10:1 dr, 79% *ee*)
3ad: R^a = Me (22 h, 93% yield, >20:1 dr, 90% *ee*)
3ae: R^a = CO$_2$Et (13 h, 96% yield, 10:1 dr, 11% *ee*)



3aq: Y = S, Z = C, R^1 = H (13 h, 97% yield, 16:1 dr, 98% *ee*)
3ar: Y = S, Z = C, R^1 = Me (96 h, 85% yield, >20:1 dr, 99% *ee*)
3as: Y = CH, Z = N, R^1 = H (12 h, 97% yield, >20:1 dr, 99% *ee*)



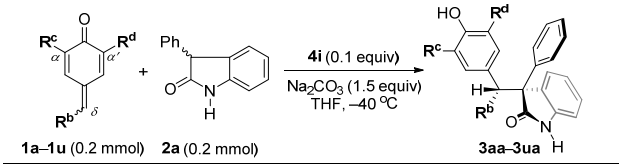
3af: Ar = 4-C$_6$H$_4$Me (15 h, 97% yield, >20:1 dr, 99% *ee*)
3ag: Ar = 4-C$_6$H$_4$OMe (24 h, 97% yield, >20:1 dr, 99% *ee*)
3ah: Ar = 4-C$_6$H$_4$NMe$_2$ (21 h, 90% yield, 12:1 dr, >99% *ee*)
3ai: Ar = 4-C$_6$H$_4$F (13 h, 94% yield, >20:1 dr, 98% *ee*)
3aj: Ar = 4-C$_6$H$_4$Cl (20 h, 97% yield, >20:1 dr, 97% *ee*)
3ak: Ar = 3-C$_6$H$_4$Me (20 h, 96% yield, >20:1 dr, 99% *ee*)
3al: Ar = 3-C$_6$H$_4$OMe (20 h, 96% yield, >20:1 dr, 99% *ee*)
3am: Ar = 2-C$_6$H$_4$OMe (33 h, 89% yield, >20:1 dr, 95% *ee*)[c]
3an: Ar = 3,5-(OMe)$_2$C$_6$H$_3$ (20 h, 94% yield, >20:1 dr, 99% *ee*)
3ao: Ar = 3,5-F$_2$C$_6$H$_3$ (30 h, 95% yield, >20:1 dr, 89% *ee*)
3ap: Ar = 2-naphthyl (18 h, 97% yield, >20:1 dr, 99% *ee*)

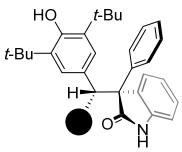


3at: R^2 = H, X = 5-OMe (21 h, 94% yield, >20:1 dr, >99% *ee*)
3au: R^2 = H, X = 5-Br (26 h, 96% yield, >20:1 dr, 96% *ee*)
3av: R^2 = OMe, X = 5-Br (20 h, 96% yield, >20:1 dr, 97% *ee*)
3aw: R^2 = OMe, X = 5-F (18 h, 96% yield, >20:1 dr, 99% *ee*)
3ax: R^2 = OMe, X = 6-Br (20 h, 96% yield, >20:1 dr, 97% *ee*)
3ay: R^2 = OMe, X = 7-F (18 h, 94% yield, 16:1 dr, 95% *ee*)

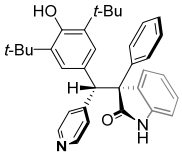
[a]For experimental details, see ESI. [b]The absolute configuration of **3ab** was established by X-ray analysis, and accordingly the reaction enantioselectivity in other cases was assigned by analogy. [c]K_2CO_3 instead of Na_2CO_3 at –20 °C.

Table 3. The Scope of *p*-QMs as Acceptors[a]

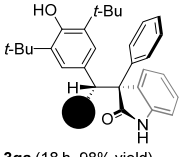




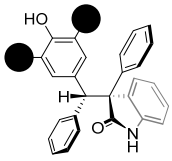
3aa–3na (>20:1 dr)
3aa: Ar = Ph (18 h, 96% yield, 99% *ee*)
3ba: Ar = 4-C$_6$H$_4$Me (18 h, 95% yield, 98% *ee*)
3ca: Ar = 4-C$_6$H$_4$OMe (72 h, 98% yield, 99% *ee*)
3da: Ar = 4-C$_6$H$_4$F (13 h, 96% yield, 98% *ee*)
3ea: Ar = 4-C$_6$H$_4$Cl (18 h, 98% yield, 98% *ee*)
3fa: Ar = 4-C$_6$H$_4$Br (13 h, 98% yield, 98% *ee*)
3ga: Ar = 3-C$_6$H$_4$Br (12 h, 98% yield, 97% *ee*)
3ha: Ar = 2-C$_6$H$_4$Br (14 h, 98% yield, 99% *ee*)
3ia: Ar = 2-C$_6$H$_4$Cl (20 h, 98% yield, 99% *ee*)
3ja: Ar = 2-C$_6$H$_4$CO$_2$Me (7 d, 88% yield, 98% *ee*)
3ka: Ar = 2-C$_6$H$_4$OAc (72 h, 93% yield, 98% *ee*)
3la: Ar = 3,4-(OCH$_2$O)C$_6$H$_3$ (48 h, 94% yield, 98% *ee*)
3ma: Ar = 3,5-(OMe)$_2$C$_6$H$_3$ (14 h, 96% yield, 99% *ee*)
3na: Ar = 1-naphthyl (5 d, 88% yield, 99% ee)
3oa: Ar = 2-naphthyl (18 h, 98% yield, 97% *ee*)



3pa: (9 h, 98% yield, >20:1 dr, 98% *ee*)



3qa (18 h, 98% yield) (5.7:1 dr, 93% *ee*)[b]



3ra: R^o = R^d = Me (10 h, 98% yield, >20:1 dr, 98% *ee*)
3sa: R^o = R^d = Ph (18 h, 98% yield, 9:1 dr, 96% *ee*)[b]
3ta: R^o = R^d = TMS (18 h, 98% yield, 13:1 dr, 99% *ee*)[b]
3ua: R^o = Me, R^d = *t*-Bu (16 h, 98% yield, 18:1 dr, 98% *ee*)[c]

[a]For experimental details, see ESI. [b]Performed at –60 °C. [c]The stereoisomeric ratio of about 1:1 for *p*-QM **1u**.

oxindoles **2t–2y** was also probed, and the similar positive results (94–96% yield, 16:1 to >20:1 *dr*, 95–99% *ee*) for **3at–3ay** were achieved, demonstrating the good tolerance of substituents on the aromatic ring of oxindoles.

To expand the reaction scope, as shown in Table 3, the subsequent exploration of structurally diverse *p*-QMs as acceptors was then conducted in asymmetric catalytic 1,6-conjugate addition. Compared with the model acceptor **1a** (R^b = Ph, R^c = R^d = *t*-Bu), *p*-QMs (**1b–1o**) incorporating a series of aryl groups at δ position (R^b = Ar) underwent smoothly the asymmetric 1,6-addition, giving the products **3ba–3oa** in good to high yields (88–98%) with excellent diastereoselectivity and enantioselectivity (>20:1 *dr*, 97–99% *ee*). Notably, most of reactions using *p*-QMs with the electron withdrawing δ-aryl groups accomplished within 20 h, due to the enhanced electrophilicity of the acceptor dienone system. In contrast, the employment of *p*-QMs (**1c**, **1j–1l** and **1n**) with the electron donating *para*-substituted or sterically bulky *ortho*-substituted δ-aryl groups generally led to the prolonged time required for the formation of the related products (**3ca**, **3ja–3la** and **3na**). Meanwhile, one example involving the use of *p*-QM **1p** containing the heteroaryl group (R^b = 4-pyridinyl) at δ position was also considered, and analogously the functionalized oxindole product **3pa** was accessed effectively (98% yield, >20:1 *dr*, 98% *ee*). In addition to the above cases using δ-aryl substituted *p*-QMs, the reaction generality was further probed by employing *p*-QM **1q** with δ-alkyl group (R^b = Me), and the product **3qa** could be afforded in high level of efficiency and enantiocontrol (98% yield, 93% *ee*), albeit with moderate diastereoselectivity (5.7:1 *dr*). Furthermore, the

investigation on the influence of different α- and α'-substituents in *p*-QMs **1r–1t** was pursued in the current reaction. Despite somewhat decreased diastereocontrol (9:1 to >20:1 *dr*) in these cases, the excellent efficiency and enantioselectivity (98% yield, 96–99% *ee*) were similarly achieved for the formation of **3ra–3ta**. Importantly, the controlled experiment using a stereoisomeric mixture of *p*-QM **1u** (≈1:1 *dr*) disclosed that both diastereo- and enantiodiscrimination for the formation of **3ua** (18:1 *dr*, 98% *ee*) during 1,6-addition were mostly independent of the stereochemistry of the exocyclic methylene substituent of *p*-QM.

In conclusion, a novel tertiary amine-squaramide catalyzed asymmetric 1,6-conjugate addition of prochiral *p*-QMs with racemic oxindoles has been developed, in which a new mode based on the bifunctional organocatalysis was explored in the design of asymmetric catalytic methodology related to *para*-quinone methide chemistry. This methodology provides an effective, diastereoselective and enantioselective approach to the stereocontrolled synthesis of various diarylmethine-substituted oxindoles bearing vicinal tertiary and quaternary stereocenters. The present reaction not only explores the potential of the dimeric *Cinchona*-derived squaramides in asymmetric organocatalysis, but also enriches the development of methodologies based on unique bisvinylogous enone system of *p*-QMs in asymmetric synthesis.

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