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SHORT COMMUNICATION

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Organocatalyzed Enantioselective Allylation of Isatins by Using a Chiral Amino Alcohol Derived Squaramide as Catalyst[‡]

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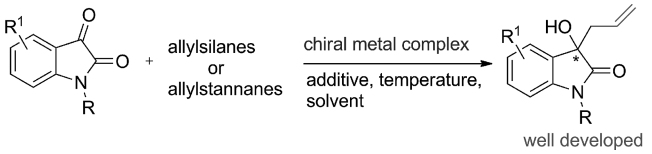
Keywords: Organocatalysis / Enantioselectivity / Allylation / Isatins / Squaramides

A series of new squaramide-based organocatalysts were synthesized from commercially available 3,4-dimethoxycyclobut-3-ene-1,2-dione in two steps. A 2.5 mol-% loading of the organocatalyst successfully catalyzed the asymmetric allylation of isatins with allyltributyltin to give the corresponding 3-allyl-3-hydroxyoxindoles in high yields and enantioselectivities (up to 98 % *ee*).

Introduction

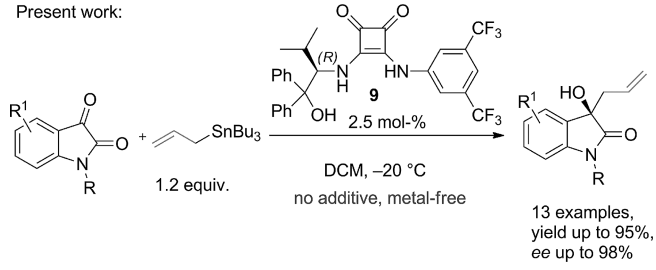
Optically active oxindole derivatives, which have found widespread uses in natural product, agricultural and pharmaceutical chemistry,[1] are important building blocks for various biologically active compounds.[2] In addition, the alkene functionality in 3-allyl-3-hydroxyoxindole can be utilized to synthesize desired organic molecules.[3,4] In the last few years, various metal-based efficient catalytic systems were reported[5] [Equation (1)] for enantioselective allylation of isatins; however, an organocatalyst version had remained unexplored for this type of substrates, although very recently an organocatalytic asymmetric allylation of isatins has been reported by Hoveyda et al.[6] In our quest to develop a new and efficient metal-free catalytic system for the asymmetric allylation reaction of isatins with allyltin or allylsilane compounds, we are now reporting for the first time a chiral squaramide as organocatalyst for the enantioselective allylation of isatins [Equation (2)].

Previous works for asymmetric allylation of isatins using chiral metal complexes



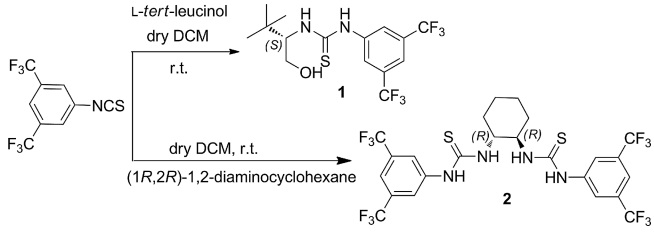
(1)

Present work:



(2)

Prior works on organocatalysts for different organic transformations had revealed that the presence of key features such as the ability to act as hydrogen-bond donor or the presence of one or more chiral centres with critical and desired electronic environments are necessary to affect high reaction rate and stereoinduction. Organic molecules having a squaramide[7] or thiourea[8] skeleton have these desired features; therefore, for the present study we have synthesized a series of thiourea- (Scheme 1) as well as squaramide-based (Scheme 2) organocatalysts (Figure 1) and



Scheme 1. Synthesis of thiourea-based organocatalysts **1**–**2**.

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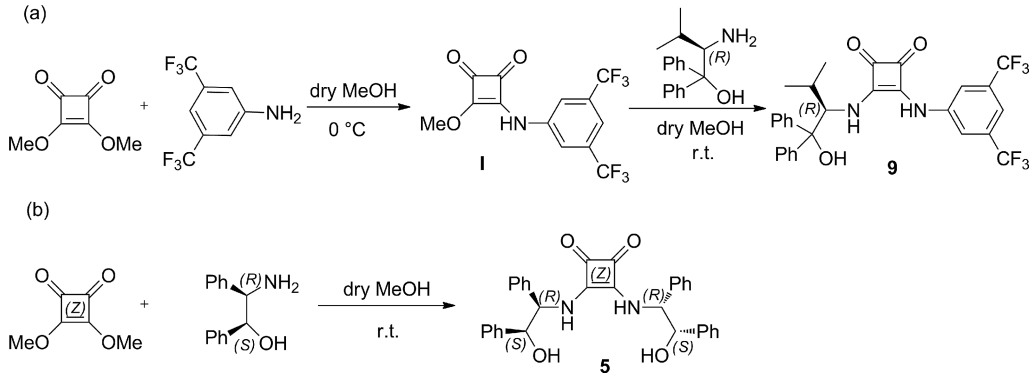


Scheme 2. (a) Synthesis of squaramide-based organocatalyst **9**. Other organocatalysts **3**, **4**, **6**–**11** were synthesized according to the same procedure. (b) Synthesis of C_2-symmetric organocatalyst **5**.

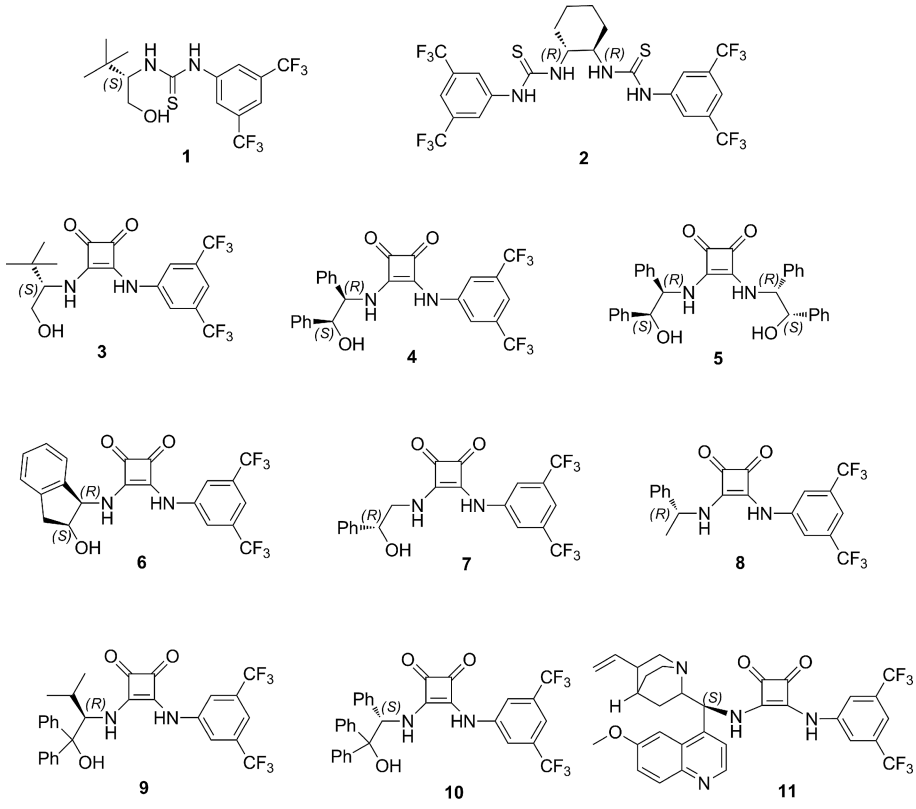


Figure 1. Various organocatalysts used in the present study.

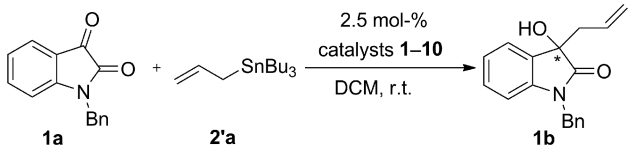
tested their efficacies for asymmetric allylation of isatins with allyltributyltin in dichloromethane (DCM) as solvent at room temperature (r.t.).

Results and Discussion

Our present investigation started with the synthesis of chiral thiourea **1** and bis(thiourea) **2** from L-*tert*-leucinol and (1*R*,2*R*)-1,2-diaminocyclohexane, respectively, and we used them as catalysts for the enantioselective allylation reaction of *N*-benzylisatin with allyltributyltin in DCM at room temperature Although allylation product was obtained with moderate yield (Table 1, Entries 1–2), no enantioselectivity (*ee*) was observed. As a result we synthesized chiral squaramide **3** (containing the L-*tert*-leucinol moiety) and **4** [containing the (1*S*,2*R*)-2-amino-1,2-diphenylethanol moiety] to use them as catalysts for this reaction.

This met with some degree of success (Entries 3–4), particularly in the case of catalyst **4** (Entry 4; 80% yield, 35% *ee*). Although the product *ee*s were low, we visualized an improvement in the results by varying the steric and electronic features in the squaramide-based catalyst. Noticeably, on replacing the 3,5-bis(trifluoromethyl)aniline moiety of catalyst **4** by the (1*S*,2*R*)-2-amino-1,2-diphenylethanol moiety of C_2-symmetric catalyst **5**, both product yield (50%) and *ee* (20%) decreased significantly (Entry 5).

Table 1. Screening of the catalysts.[a]



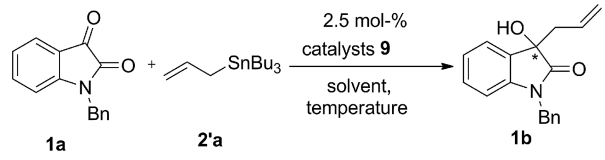
Entry	Catalyst	Time [h]	Yield[b] [%]	*ee*[c] [%]
1	**1**	24	25	0
2	**2**	24	50	0
3	**3**	24	45	20 (*S*)[d]
4	**4**	14	80	35 (*R*)[d]
5	**5**	24	50	15 (*R*)[d]
6	**6**	24	70	18 (*R*)[d]
7	**7**	24	60	0
8	**8**	24	30	12 (*R*)[d]
9	**9**	12	87	65 (*R*)[d]
10	**10**	12	82	50 (*S*)[d]
11	**11**	36	25	10 (*S*)[d]

[a] All the reactions were carried out by using substrate **1a** (0.5 mmol), allyltributyltin (0.6 mmol), and catalyst (2.5 mol-%) in DCM at room temp. [b] Isolated yields after column chromatography. [c] *ee* determined by chiral HPLC using a Daicel Chiralcel OD-H column. [d] Absolute configurations were assigned by comparing both retention time and optical rotation with reported reliable data.

Therefore, for subsequent changes in the catalyst we kept the 3,5-bis(trifluoromethyl)aniline moiety intact and replaced the amino alcohol part of the organocatalyst **4** by (1*R*,2*S*)-1-amino-2-indanol, (*R*)-2-amino-1-phenylethanol and (*R*)-α-methylbenzylamine to obtain organocatalysts **6**, **7** and **8**, respectively, with variable steric features; but even these could not match the performance of catalyst **4** (Entries 4, 6–8). To our pleasant surprise, sterically more demanding organocatalysts **9** and **10** derived from (*R*)-2-amino-3-methyl-1,1-diphenylbutanol and (*S*)-2-amino-1,1,2-triphenylethanol, respectively, showed a dramatic improvement in the product enantioselectivity (Entries 9–10). It is also worth noticing that the organocatalyst **9** (Entry 9; 87% yield, 65% *ee*) gave a higher *ee* in the product with opposite configuration as compared to the organocatalyst **10**. We also synthesized the quinine-based squaramide catalyst **11**, but it gave the allylation product with significantly lower yield (25%) and *ee* (10%) (Entry 11). When comparing the catalytic efficacy of the organocatalysts **3**–**11**, it can be concluded that the presence of a chiral centre near the amine moiety and a high steric crowding around the alcohol carbon atom of the amino alcohol side of the catalyst possibly help in increasing the stereoinduction in the product.

Having identified catalyst **9** as the best among many, the optimization of other reaction conditions such as temperature and solvents were investigated for the model reaction as these parameters are known to influence the yield and enantioselectivity of the products. First, we screened various solvents frequently used for this type of reaction by using allyltributyltin as an allylating agent and keeping other parameters constant (Table 2, Entries 1–5); we found thatDCM was the most suitable solvent among the those studied (Table 3, Entry 5). The temperature ranged from –40 °C to room temperature (Table 2, Entries 6–9); it was revealed that –20 °C is the best temperature as a product *ee* (90%) with a 85% yield was obtained within 24 h (Entry 8).

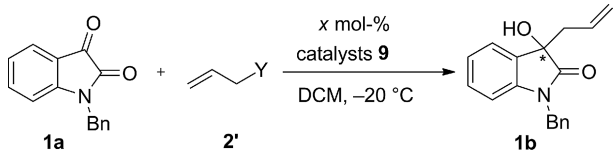
Table 2. Optimization of solvents and reaction temperature.[a]



Entry	Solvent	Temp. [°C]	Time [h]	Yield[b] [%]	*ee*[c] [%]
1	toluene	r.t.	36	35	25
2	THF	r.t.	36	50	33
3	$CHCl_3$	r.t.	36	62	52
4	DCE	r.t.	24	65	49
5	DCM	r.t.	12	87	65
6	DCM	0	24	85	70
7	DCM	–10	24	85	80
8	DCM	–20	24	85	90
9	DCM	–40	36	60	89

[a] Reaction conditions as per Table 1. [b] Isolated yields after column chromatography. [c] *ee* determined by chiral HPLC using a Daicel Chiralcel OD-H column.

Table 3. Optimization of catalyst loading and allylating agents.[a]

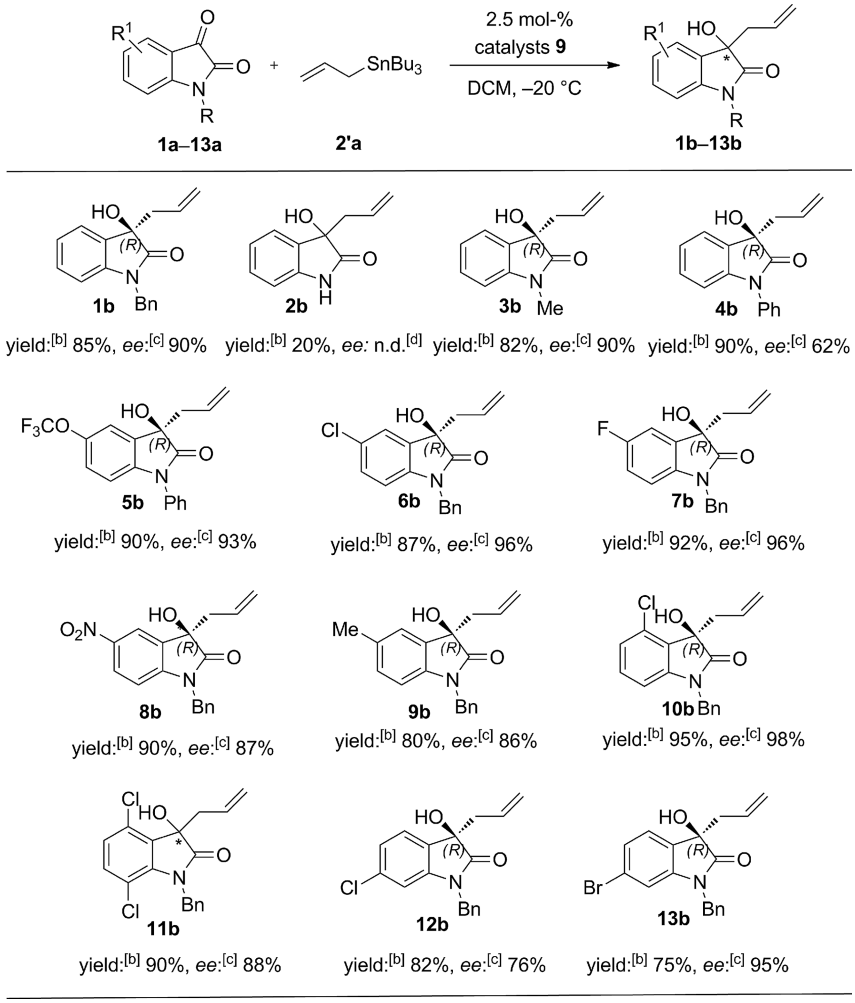


Entry	Catalyst loading (*x* [mol-%])	Allylating agent **2′**	Time [h]	Yield[b] [%]	*ee*[c] [%]
1	1	allyltributyltin	36	75	90
2	2.5	allyltributyltin	24	85	90
3	5	allyltributyltin	24	85	90
4	2.5	tetraallyltin	48	70	35
5	2.5	pinacol allylboronate	48	60	15
6	2.5	allyltrimethylsilane	48	30	25
7	2.5	allyltrichlorosilane	48	n.d.[d]	n.d.[d]

[a] All the reactions were carried out by using substrate **1a** (0.5 mmol), allyltributyltin (0.6 mmol), and catalyst (1–5 mol-%) in DCM at –20 °C. [b] Isolated yields after column chromatography. [c] *ee* determined by chiral HPLC using a Daicel Chiralcel OD-H column. [d] Not determined.

Further, the catalyst loading of 2.5 mol-%, which was used in the preceding experiments, was found to be optimal (Table 3, Entry 2) as it was observed that by decreasing the catalyst loading (1 mol-%) the product yield (75%) dropped significantly (Entry 1). On the other hand, there was no added advantage by increasing the catalyst loading (5 mol-%) (Entry 3). To know the effect of allylating agents we have used various other allylating agents e.g. allyltrimethylsilane, allyltrichlorosilane, pinacol allylboronate and tetraallyltin, but the results showed that allyltributytin was the most suitable one (Entries 2, 4–7).

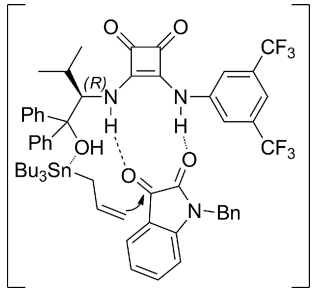
Table 4. Substrate scope.[a]



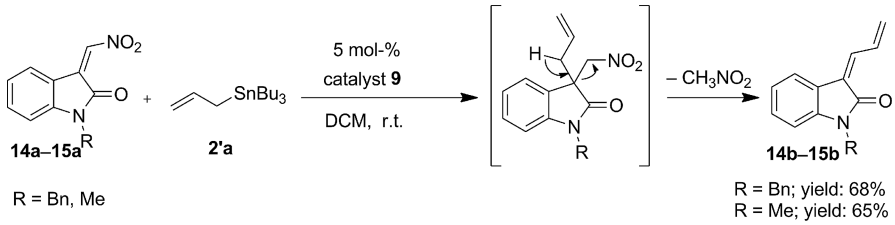
[a] Conditions: Isatins **1a**–**13a** (0.5 mmol), allyltributyltin **2′a** (0.6 mmol), chiral organocatalyst (0.0125 mmol) in DCM, reaction temperature –20 °C, reaction time 24 h. [b] Isolated yields after column chromatography. [c] *ee* determined by chiral HPLC using a Daicel Chiralcel OD-H/IA column. [d] Not determined.

With the optimal reaction conditions (Table 3, Entry 2), the scope of the organocatalyst **9** was extended to the asymmetric allylation reaction of various substituted isatins (Table 4). The results showed that the present catalytic system is highly efficient for most of the *N*-protected isatins, whereas it fails for unprotected isatin. For most of the *N*-protected isatins, product yields were very good (75–95%) and *ee*s were good to excellent (62–98%), irrespective of the position of the substituents, although for electron-donating substituents (e.g. 5-methyl) the product yield and *ee* were comparatively lower than those obtained with electron-withdrawing substituents (e.g. 5-nitro, 5-fluoro).

Based on the results obtained from the catalyst variation study, we propose a possible transition state for this reaction (Scheme 3). Firstly, by comparing the catalytic activity of the catalysts **4** and **5** (Table 1, Entries 4, 5) we can say that the 3,5-bis(trifluoromethyl)aniline moiety in the active catalyst **9** is essential to obtain good yields as well as *ee*s of the allylation product. This happens probably due to the substrate activation by two –NH protons of the squaramide-based catalyst.[7] Secondly, by comparing the catalytic activity of the catalysts **7**, **8** and **9** (Table 1, Entries 7, 8 and 9) we can say that the presence of an –OH group in the active catalyst is necessary to achieve good yields of the allylation product. Thus, the –OH group in active catalyst **9** probably helps in activating the allyltributyltin reagent as given in the proposed transition-state model. Thus, a preferential *Re*-face attack of the allyltributyltin nucleophile on



Scheme 3. Proposed transition state.



Scheme 4. Allylation of *N*-protected isatins derived from nitro olefins.

the isatins results in the observed major (*R*) enantiomer (Scheme 3).

We have also tested the efficacy of the organocatalyst **9** for nitro olefin derived isatins. However, instead of obtaining allylation products, we detected structurally interesting 1-substituted 3-allylideneindolin-2-one compounds; but at this point of time we do not know if these compounds have any practical use (Scheme 4).

Conclusions

We have developed a series of new squaramide-based organocatalysts among which catalyst **9** showed very good catalytic efficiency in the asymmetric allylation reaction of various isatins with allyltributyltin as allyl source. A 2.5 mol-% loading of the organocatalyst is sufficient to give the corresponding 3-allyl-3-hydroxyoxindoles in high yields with enantioselectivities of up to 98% *ee*. An attempt for the allylation of *N*-protected isatins derived from nitro olefins was also made, which gave substituted allylideneindolin-2-ones instead of the expected allylated products. Further work in this direction is currently in progress in our laboratory to further expand the scope of the organocatalyst thus developed.

Experimental Section

General Procedure for the Catalytic Asymmetric Allylation of Isatins with Allyltributyltin by Using 9 as Organocatalyst: In an oven-dried 5 mL glass flask were placed catalyst **9** (7 mg, 0.0125 mmol) and isatin (0.5 mmol), and DCM (2 mL) was added. The reaction mixture was then cooled to –20 °C. Allyltributyltin (1.2 equiv. with respect to isatin) was added dropwise. The resulting mixture was stirred at this temperature until the reaction was complete as indicated by TLC. The reaction was quenched with distilled H_2O and the mixture extracted with EtOAc. The combined organic layers were washed with H_2O, saturated aqueous NaCl solution, dried with anhydrous Na_2SO_4 and concentrated under vacuum. The products were purified by flash chromatography on silica gel. Products were identified by NMR spectroscopic data corresponding to those published.

Supporting Information (see footnote on the first page of this article): Experimental details, characterization data of both catalysts and substrates, HPLC profile of the products and copies of the ^1H and ^{13}C NMR spectra of all new catalysts and products.

Acknowledgments

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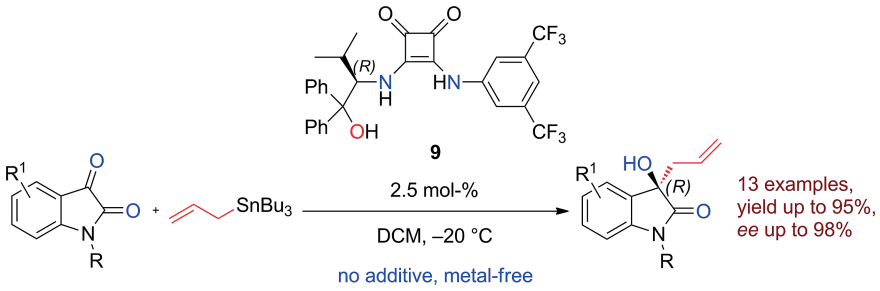
Squaramide Catalysis



A new series of squaramide-based organocatalysts were developed and successfully applied for the asymmetric allylation reaction of isatins with allyltributltin. The present catalytic system was highly efficient for the allylation of *N*-protected isatins giving very good yields (75–95%) and excellent enantioselectivities (62–98%) of the allylation products.

Keywords: Organocatalysis / Enantioselectivity / Allylation / Isatins / Squaramides

