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Organocatalyzed Formal [4+2] Cycloaddition of *in situ* Generated Azoalkenes with Arylacetic Acids: An Efficient Approach to the Synthesis of 4,5-Dihydropyridazin-3(2*H*)-ones

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Abstract: An unprecedented [4+2] cycloaddition of *in situ* generated azoalkenes with arylacetic acids has been developed under the catalysis of isothiourea. The reaction provided an efficient approach to the synthesis of 4,5-dihydropyridazin-3(2*H*)-one derivatives in moderate to good yields (up to 95%).

Keywords: 1,2-diaza-1,3-dienes; 4,5-dihydropyridazin-3(2*H*)-ones; isothiourea catalysis

Dihydropyridazinones and pyridazinones are important six-membered aza-heterocycles, and are present in a wide range of bioactive compounds with anti-inflammatory,[1] anti-platelet aggregation[2] and anti-congestive heart failure activities (Figure 1). To the best of our knowledge, the reported synthetic strategies for the synthesis of dihydropyridazinones are normally limited to the condensation of costly substrate γ-oxo acids and hydrazine.[3] Therefore, the development of a new strategy that allows rapid access to dihydropyridazinones from readily accessible starting materials using a practical method is still highly desirable and an enduring goal of organic chemistry.

Organocatalysis is now a well established instrument in the organic chemists' tool box due to the generally stability, high quality, inexpensive price, and lower toxicity compared to transition metals. Isothioureas,[4] one kind of frequently used organocatalyst, initially introduced by Birman[5] and Okamoto,[6] could promote the *in situ* generation of ammonium enolates from a carboxylic acid, introducing functionalization to the carboxylic acid through a Michael–lactonization sequence.[7]

1,2-Diaza-1,3-dienes, generated from the corresponding α-halo hydrazones, have recently been identified as a robust and versatile synthetic building blocks with wide applications in the assembly of various five-, six-, and seven-membered heterocyclic ring systems.[8] In 2014, the Glorius group reported the first example of NHC-catalyzed formal [4+3] and [4+1] annulations of 1,2-diaza-1,3-dienes with enals, providing a highly enantioselective access to the chiral dihydrodiazepinones[9] (Scheme 1a). The Xiao group[10] and the Luo group[11] achieved the [4+3] and [4+2] annulations of the *in situ* generated 1,2-diaza-1,3-dienes with 1,3-dipoles and olefins employing an inorganic base, leading to the important building blocks of the tetrazepine and tetrahydropyridazine types (Scheme 1b, c). Inspired by these works, we envisaged that the possible [4+2] cycloaddition between α-halo hydrazones and arylacetic acids under the cat-

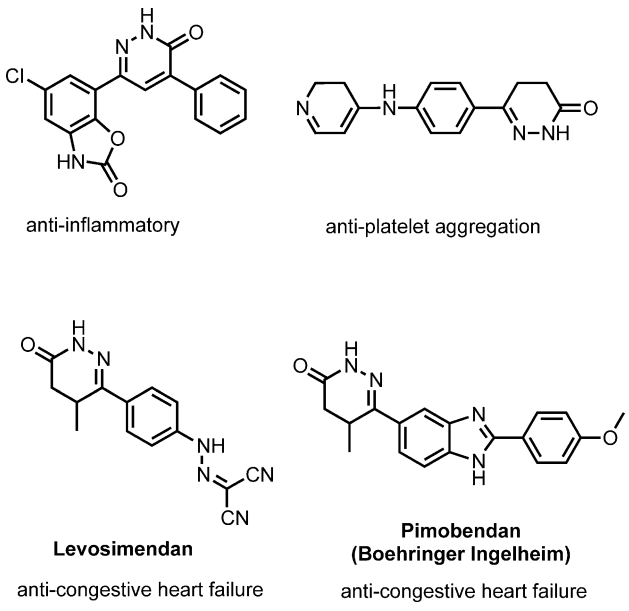
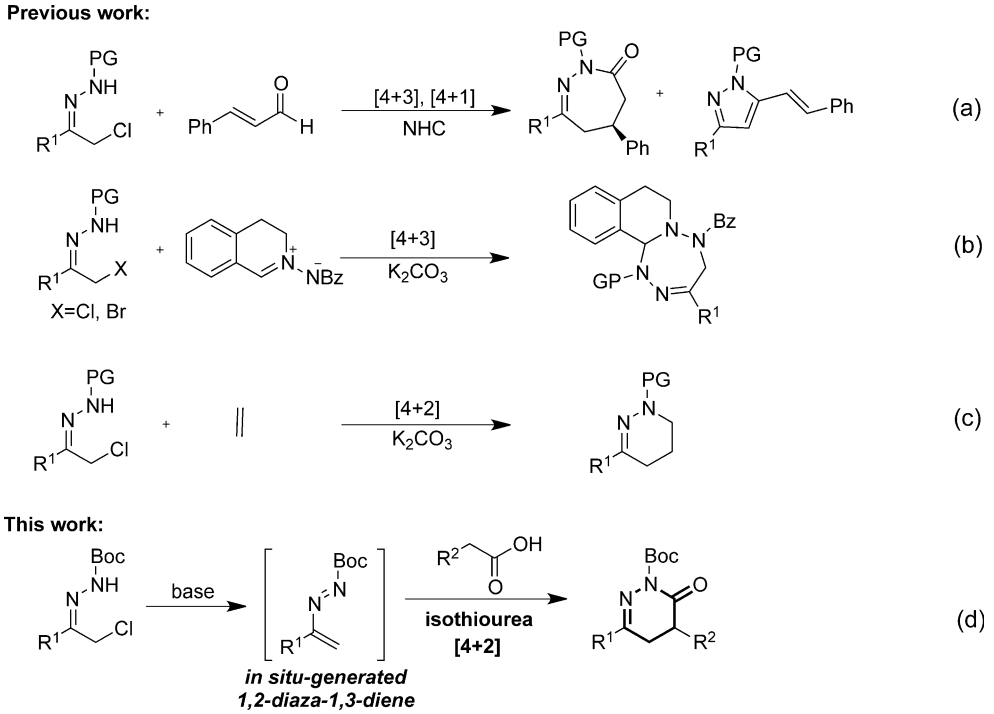


Figure 1. Examples of dihydropyridazinone derivatives in bioactive compounds.



Scheme 1. Non-metal-catalyzed cycloaddition reactions of azoalkenes.

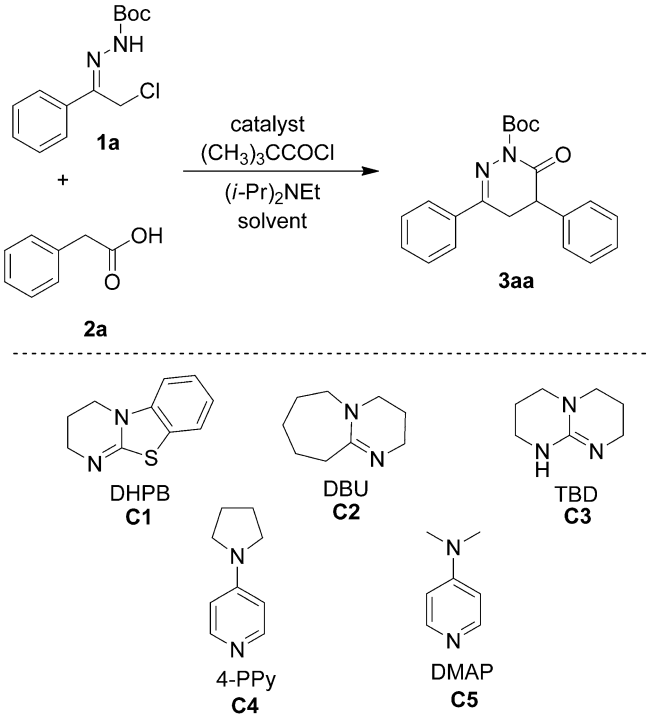
alysis of isothiourea would provide an efficient access to dihydropyridazinone derivatives. Herein, we report the first example of isothiourea-catalyzed formal [4+2] annulation reactions of *in situ* generated azoalkenes with arylacetic acids, constructing 4,5-dihydropyridazin-3(2*H*)-one derivatives in moderate to excellent yields (Scheme 1d).

We started our investigation with the reaction between readily available α-chloro *N*-Boc-hydrazone **1a** and phenylacetic acid **2a**. When the reaction was performed in DCE at ambient temperature, compound **1a** could indeed react with compound **2a** under the catalysis of **C1**,[12–13] giving 4,5-dihydropyridazin-3(2*H*)-one **3aa** in 58% yield (Table 1, entry 1). Encouraged by this result, various solvents and catalysts were then evaluated to optimize the reaction conditions. Screening of solvents revealed that the yield of **3aa** was increased to 84% when DME was employed as a solvent (Table 1, entries 2–5). Screening of catalysts showed that DBU, TBD, 4-PPy and DMAP failed to offer the desired product (Table 1, entries 6–9). A control experiment indicated that **C1** was necessary to promote the reaction (Table 1, entry 10). Finally, we were delighted to find that the yield of **3aa** could be further improved to 91% by increasing the ratio of **2a** to 1.5 (Table 1, entry 11).

With the optimized conditions in hand, we next probed the substrate scope and the generality of this reaction. We first examined the substituent effect on the benzene ring of the aromatic acetic acid. As shown in Table 2, a variety of functional groups at the 4-position, such as electron-donating and electron-withdrawing groups, and halogen atoms were all compatible under the optimized conditions, providing the desired products in moderate to excellent yields. The substrates bearing methyl or methoxy groups afforded the corresponding products **3ab** and **3ac** in 89% and 71% yield, respectively. The substrate with an electron-withdrawing group (CF_3) gave **3ad** in 45% yield. In addition, the halogen-substituted substrates could also be converted into the desired products **3ae–3ag** in moderate to good yields. Also, the reaction was compatible with the sterically hindered C-2 bromo, methyl and C-3 methoxy groups on the phenyl ring of the aromatic acetic acid, giving rise to the corresponding products **3ah–3ak** in 63–95% yields. 2-Naphthyl-, 1-naphthyl-, 2-thienyl- and biphenylacetic acids could also participate in this transformation, resulting in the coupling products **3al–3ao** in 50–73% yields. Investigations on the substituent effect on the aromatic ring in the hydrazone part revealed that a range of substituted aromatic hydrazones could also generate the functionalised 4,5-dihydropyridazin-3(2*H*)-ones **3ba–3ja** in 40–94% yields. When R^1 or R^2 was an alkyl group, the reaction failed to offer the desired product.

According to the literature,[14] we proposed the reaction mechanism as shown in Figure 2. *N*-Acylation of DHPB (**C1**) with anhydride **I**, which was formed

Table 1. Optimization of the reaction conditions.[a,b]



Entry	Catalyst	Solvent	1a:2a	Yield
1	**C1**	DCE	1:1	58%
2	**C1**	CH_3CN	1:1	32%
3	**C1**	THF	1:1	62%
4	**C1**	1,4-dioxane	1:1	81%
5	**C1**	DME	1:1	84%
6	**C2**	DME	1:1	NR
7	**C3**	DME	1:1	NR
8	**C4**	DME	1:1	NR
9	**C5**	DME	1:1	NR
10	–	DME	1:1	NR
11	**C1**[c]	DME	1:1.5	93% (91%[d])

[a] *Reaction conditions:* **1a** (0.2 mmol), **2a** (0.2 mmol), catalyst (0.04 mmol, 20 mol%), $(CH_3)_3CCOCl$ (0.3 mmol, 1.5 equiv.), $(i\text{-Pr})_2NEt$ (0.8 mmol, 4 equiv.) in solvent (2.5 mL) at ambient temperature under an argon atmosphere.

[b] Yield was determined by ^1H NMR using dibromomethane as the internal standard.

[c] The catalyst **C1** amount is 0.06 mmol (30 mmol%).

[d] Isolated yield.

from pivaloyl chloride and phenylacetic acid **2a**, afforded acylisothiouronium **II**. Deprotonation generated isothiouronium enolate **III**, which underwent Michael addition of the *in situ* generated azoalkene **V** from compound **1a** and subsequent intramolecular lactamization to generate the corresponding 4,5-dihydropyridazin-3(2*H*)-one **3aa** and regenerated DHPB to complete this catalytic cycle.

To gain insight into the utility of the reaction, the dihydropyridazinones were further functionalized. As shown in Scheme 2, the *tert*-butyloxycarbonyl group in compound **3aa** could be removed easily by CF_3COOH in 68% yield (Scheme 2a). Subsequently, the compound **4** could be further functionalized to afford compound **5** and **6** in 51% and 61% yield, respectively (Scheme 2b, c). It was noteworthy that compound **5** is the core skelecton of a fungicide.[15] Besides, the dihydropyridazinone could also be converted into pyrdazinone **7** through a Br_2 and AcOH-mediated deprotection and oxidation step in 60% yield (Scheme 2d). Furthermore, product **3ag** could be transformed to **3ao** through a Suzuki coupling reaction in 75% yield (Scheme 2e).

Encouragingly, preliminary studies showed that the asymmetric version of this reaction was also feasible. For example, when chiral catalyst **C6**[16] was employed, dihydropyridazinone **3aa** could be obtained in 91% yield with 92% *ee* (Scheme 3).

In conclusion, we have developed the first organocatalyzed formal [4+2] cycloaddition between the *in situ* generated 1,2-diaza-1,3-dienes and aromatic acetic acids. This protocol provided a facile access to the 4,5-dihydropyridazin-3(2*H*)-ones in moderate to excellent yields with good functional group tolerance. Studies have shown that asymmetric version was also accessible with a chiral catalyst. Further efforts will be devoted to understanding the reaction mechanism, expanding the substrate scope, and developing a more effective asymmetric process.

Experimental Section

General Procedure for the Formal [4+2] Cycloaddition

A sealed tube was charged with phenylacetic acid 2 (0.3 mmol, 1.5 equiv.) in dry DME at 0 °C under an argon atmosphere. $(i\text{-Pr})_2NEt$ (0.45 mmol, 2.25 equiv.) and pivaloyl chloride (0.45 mmol, 2.25 equiv.) were then added at 0 °C. After 30 min, the corresponding catalyst (0.06 mmol, 30 mol%), α-chloro *N*-Boc-hydrazone 1 (0.2 mmol, 1.0 equiv.) and $(i\text{-Pr})_2NEt$ (0.5 mmol, 2.5 equiv.) were added and the reaction was warmed up to ambient temperature and monitored by TLC until completion. The solvent was then evaporated and the residue was purified by column chromatography to afford the dihydropyridazinone as a white solid.

Acknowledgements

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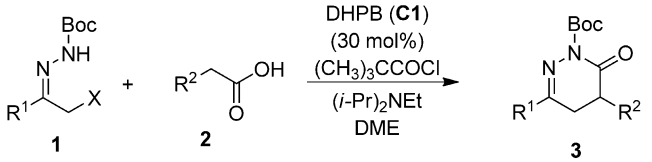
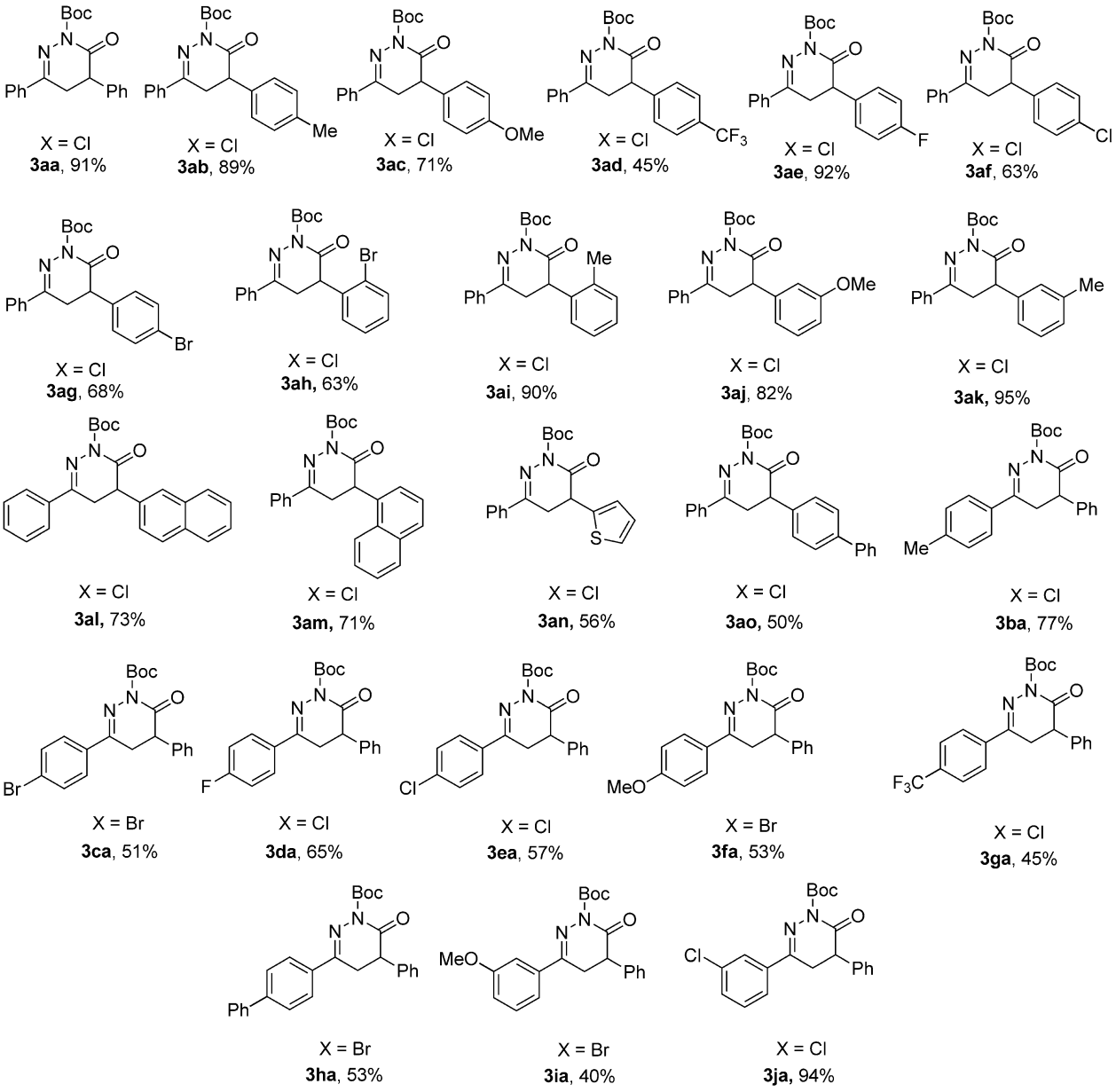
Table 2. Substrate scope of the reaction.[a,b]





[a] *Reaction conditions:* **1** (0.2 mmol), **2** (0.3 mmol), **C1** (0.06 mmol, 30 mol%), $(CH_3)_3CCOCl$ (0.45 mmol, 2.25 equiv.), $(i\text{-Pr})_2NEt$ (0.95 mmol, 4.75 equiv.), in DME (2.5 mL) at ambient temperature under an argon atmosphere.

[b] Isolated yield.

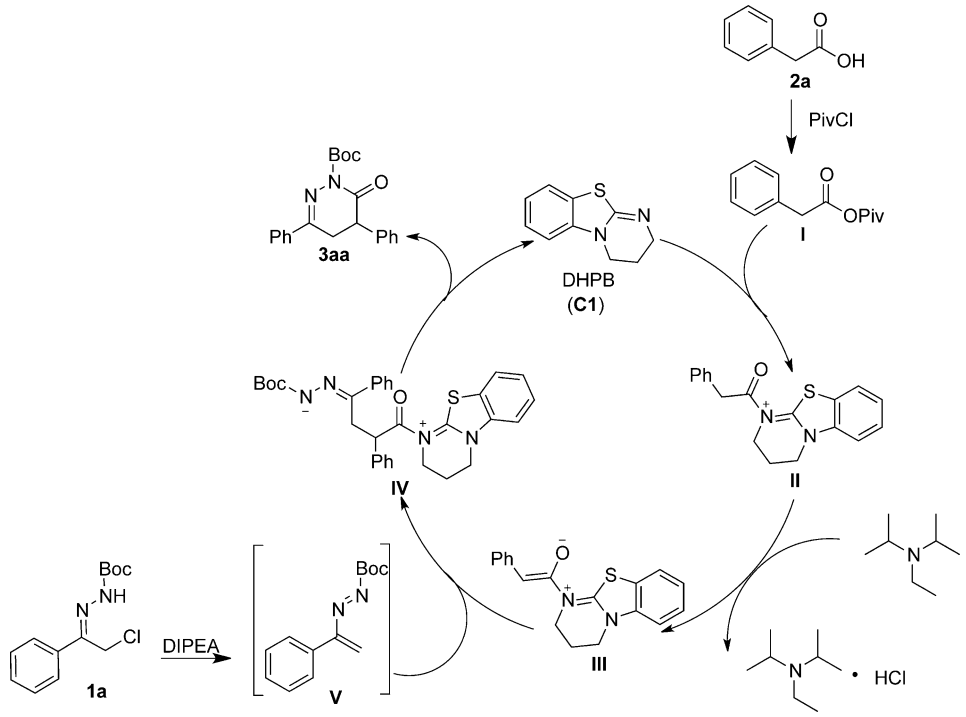
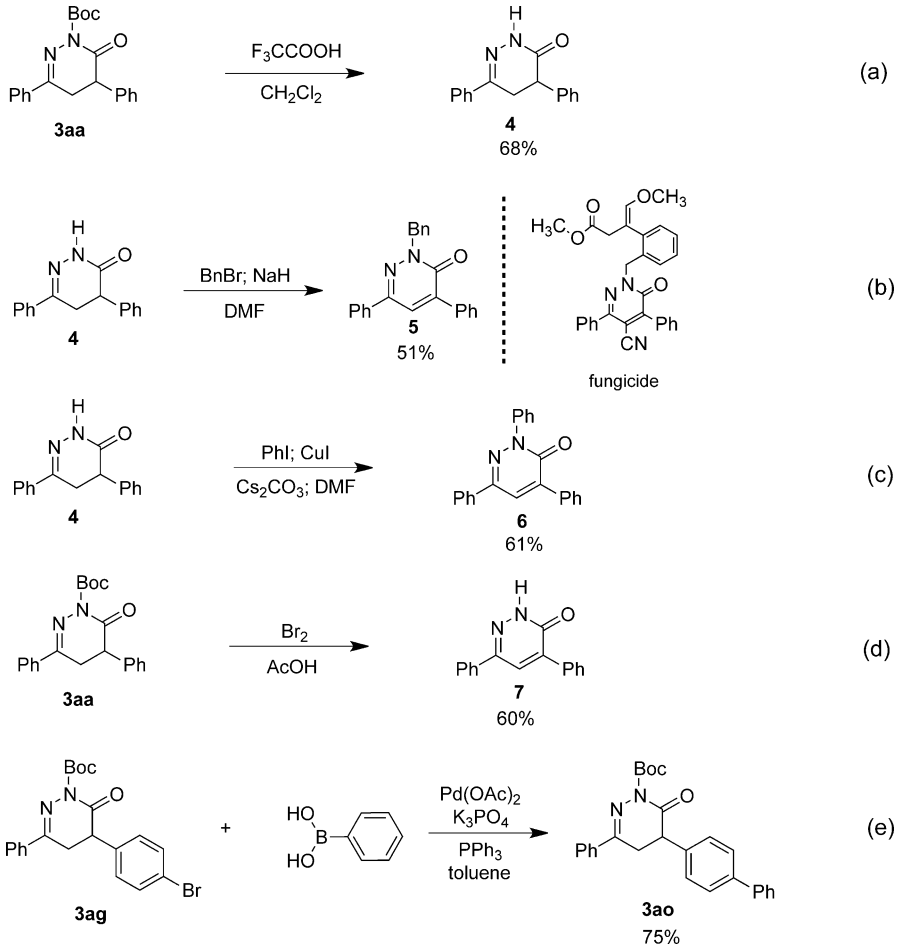
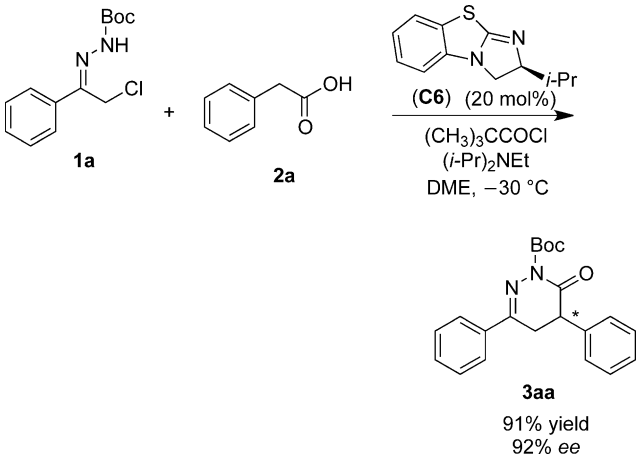


Figure 2. Proposed reaction mechanism.



Scheme 2. Synthetic transformation of the products.



Scheme 3. Preliminary asymmetric studies.

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