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Organocatalytic asymmetric cyanation of isatin derived *N*-Boc ketoimines†‡

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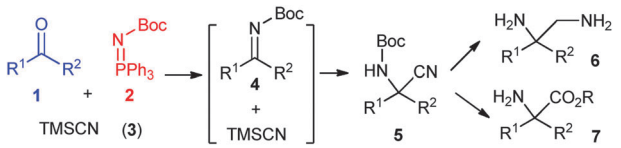
We report the first catalytic asymmetric cyanation of *N*-Boc ketoimines, which enables highly enantioselective synthesis of oxindole based α-amino nitriles. An unprecedented tandem aza-Wittig/Strecker reaction is also developed, emerging as a promising strategy for the catalytic asymmetric cyanation of ketoimines formed *in situ* from achiral ketones.

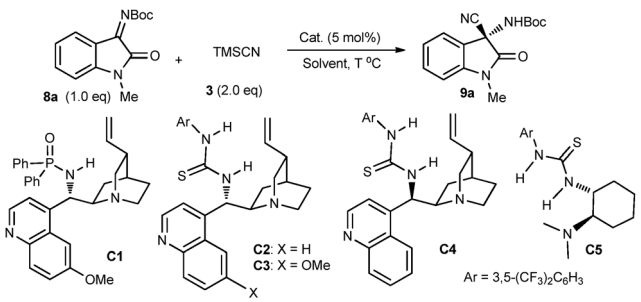
Despite the great achievements in the catalytic asymmetric Strecker reaction of aldimines,[1] the corresponding processes using ketoimine substrates proved to be more difficult.[2] As enantioenriched C^{α}-tetrasubstituted α-amino acid derivatives and diamines are very useful,[3] much effort has gone into catalytic asymmetric cyanation of ketoimines. While Jacobsen, Shibasaki, Feng and Yamamoto have made significant contributions in this field,[2] there is still much to be done to improve synthetic efficiency and enlarge the scope of ketoimine substrates. For example, the use of *N*-Boc protected ketoimines for reaction development is unknown, despite the easy removal of Boc group from products. In addition, the catalytic asymmetric Strecker reaction of ketoimines formed *in situ* from achiral ketones was unsuccessful,[4] possibly due to two reasons. (1) To improve the reactivity, activated *N*-tosyl[2g] or *N*-phosphinyl ketoimines[2e] were mostly used, but their synthetic procedures made it difficult to develop the one-pot three component process. (2) The water produced in imine formation might have a negative effect on the enantiofacial control.[4c]



With our efforts in the cyanation of ketoimines[5a–c] and Wittig chemistry,[6a] we considered using *N*-Boc iminophosphorane **2**[6b] as an amine source to react with ketone **1** to enable a catalyst-free synthesis of *N*-Boc ketoimine **4** without water generation, which might be used to develop one-pot three-component protocols. In addition, the resulting imines **4** might be substantially reactive due to the electron-withdrawing Boc group. To testify this idea, isatin derived *N*-Boc ketoimines **8**[7] were first prepared for the Strecker reaction, as the highly enantioselective synthesis of oxindole based α-amino nitriles is unprecedented, despite the need for privileged scaffolds in drug discovery to promote the catalytic asymmetric synthesis of 3-aminooxindoles, which widely occur in natural products and drugs.[8] Previously, we had pioneered the catalytic asymmetric cyanation of *p*-methoxyaniline derived isatin ketoimines, which were not reactive enough and afforded the desired products in only moderate yield and ee.[5c] In addition, we tried in vain to remove the *p*-methoxyphenyl group of products by all the known methods, which greatly decreased the value of this method. Here, we wish to report that the use of *N*-Boc ketoimines **8** is a good solution to the aforementioned problems.

The reaction of *N*-Boc ketoimine **8a** and TMSCN was undertaken for condition optimization (Table 1). The ketoimine

Table 1 Reaction optimization



Entry[a]	Cat.	Solvent	Temp (°C)	Additive	Time (h)	Yield[b] (%)	ee[c] (%)
1	**C1**	CH_2Cl_2	−30	—	36	77	32
2	**C2**	CH_2Cl_2	−30	—	36	97	92
3	**C3**	CH_2Cl_2	−30	—	36	94	91
4	**C4**	CH_2Cl_2	−30	—	36	86	92[d]
5	**C5**	CH_2Cl_2	−30	—	36	91	83[d]
6	**C2**	Toluene	−30	—	36	92	92
7	**C2**	EtOAc	−30	—	36	67	90
8	**C2**	CH_2Cl_2	−70	—	96	56	98
9	**C2**	CH_2Cl_2	−70	HFIP (1.0 equiv.)	96	93	98
10	**C2**	CH_2Cl_2	−70	HFIP (2.0 equiv.)	96	94	96
11[e]	**C2**	CH_2Cl_2	−70	HFIP (1.0 equiv.)	144	61	96

[a] Run on a 0.10 mmol scale. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Opposite enantiomer. [e] 1.0 mol% of catalyst loading.

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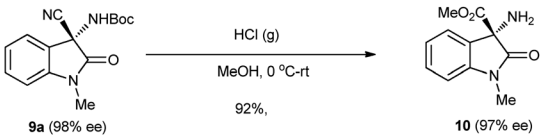
8a was indeed very reactive, so the evaluation of catalysts was carried out at −30 °C using CH_2Cl_2 as the solvent, in the presence of 5.0 mol% of the catalyst. Based on our previous studies,[5b,c] bifunctional tertiary amine–hydrogen bond donor catalysts were tried.[9,10] Phosphinamide **C1**[5c] proved to be ineffective (entry 1). To our delight, cinchonidine derived thiourea catalyst **C2**[9e–h] could promote the reaction to finish within 36 h, giving product **9a** in 97% yield with 92% ee (entry 2). No improvement was observed when using quinidine derived catalyst **C3** (entry 3). The cinchonine derived thiourea catalyst **C4** afforded the opposite enantiomer of **9a** in 91% ee (entry 4). Takemoto's catalyst **C5**[10e] provided **9a** in 83% ee (entry 5). The toluene and ethyl acetate were also good reaction media when using catalyst **C2** (entries 6 and 7), but CH_2Cl_2 was the best. Further lowering the temperature to −70 °C improved the ee to 98%, but the reaction was very slow (entry 8). Helpfully, the addition of 1.0 equiv. of $(CF_3)_2CHOH$ (HFIP)[5b] could improve the reactivity without the erosion of ee (entry 9 *vs.* 10). Even using only 1.0 mol% of catalyst **C2**, product **9a** could be obtained in 61% yield and 96% ee (entry 11).

Based on the above screenings, the substrate scope was investigated under the optimal conditions to run the reaction in CH_2Cl_2 at −70 °C, using 5 mol% of catalyst **C2** and 1.0 equiv. of HFIP. This protocol was able to tolerate a variety of different substituted *N*-Boc ketoimines **8** (Table 2). The position of substituents had no obvious effect on the enantiofacial control, as evidenced by the excellent ee for all the products **9a–r**. It should be noted that both enantiomers of product **9** could be readily obtained in excellent ee by using catalyst **C2** or **C4**. For instance, both (*R*)-**9r** and (*S*)-**9r** were obtained in excellent ee, but catalyst **C4** was not as reactive as **C2**, which gave (*S*)-**9r** in obviously lower yield (also see entries 2 and 4 in Table 1).

The α-amino nitrile **9a** could be readily converted to the C^{α}-tetrasubstituted α-amino acid ester **10**, without loss of ee. Such conformationally constrained α-amino acid esters are potentially useful in peptidomimetic chemistry.[3]



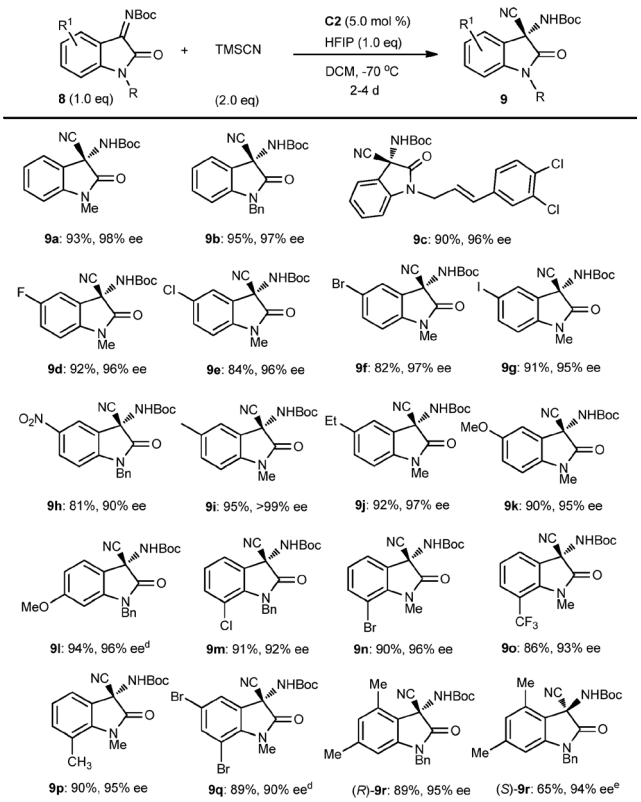
9a (98% ee) **10** (97% ee)

The synthetic utility of this method was further demonstrated in the first catalytic asymmetric synthesis of spirohydantoin **I**, which was developed by AstraZeneca for the potential use in the treatment of pain. (Scheme 1).[11] The *N*-Boc ketoimine **8c** was prepared in 84% yield from **14b** *via* an aza-Wittig reaction. To demonstrate the practicability of our method, the Strecker reaction of **8c** and TMSCN was carried out on a 2.5 mmol scale. The use of 5.0 mol% of chiral catalyst **C4** readily gave (*S*)-**9c** in 82% yield and 94% ee. The removal of the Boc group by HCl gave the corresponding nitrile **15**, which was not stable and was directly converted to the desired spirohydantoin **I** in 46% yield in two steps, with a diminished 79% ee. Fortunately, the ee could be easily improved to 99% by a single recrystallization.

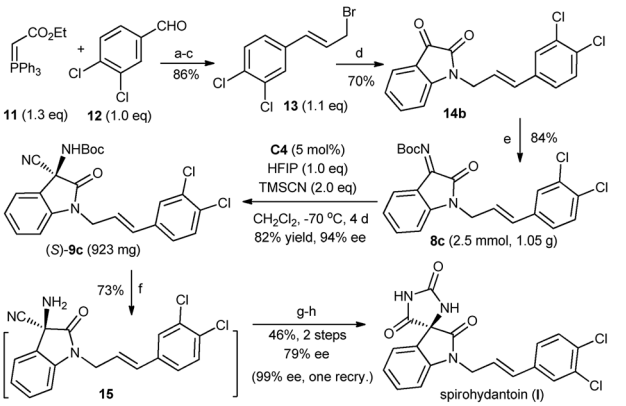
By studying control experiments, it was believed that bifunctional catalysis played an important role in this reaction, with the tertiary amine moiety of catalyst **C2** activating the *in situ* generated HCN[12] and the activation of *N*-Boc ketoimines **8** by the thiourea part through H-bonding interaction (for details and the stereochemical model, see ESI‡).

To improve the synthetic efficiency, we further tried the combination of the aza-Wittig and Strecker reaction in a one-pot sequential protocol. The presence of Ph_3PO and remaining reagents had a negative effect on the reactivity, so the Strecker reaction step of this one-pot procedure was run at −30 °C to secure reasonable yield of product **9**. By this novel sequence,

Table 2 Substrate scope[a,b,c]



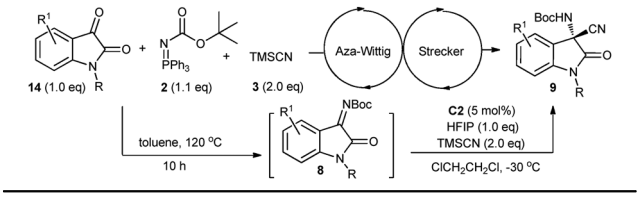
[a] On a 0.25 mmol scale. [b] Isolated yield. [c] Determined by HPLC analysis. [d] $ClCH_2CH_2Cl$ was used at −30 °C. [e] 5.0 mol% of catalyst **C4** was used.

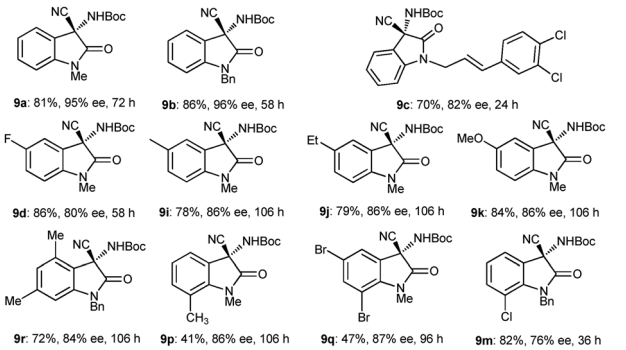


Reagent and condition: a) toluene, 120 °C. b) DIBAL-H, THF, 0 °C. c) PBr_3 (4.0 eq), Et_2O, 0 °C. d) isatin **14a** (1.0 eq), NaH, DMF. e) **3** (1.0 eq), Toluene/dioxane = 3:1, 120 °C. f) HCl (g), EtOAc, rt. g) chlorosulfonyl isocyanate (1.0 eq), CH_2Cl_2. h) 2N HCl, reflux.

Scheme 1 Total synthesis of spirohydantoin **I**.

Table 3 One-pot tandem aza-Wittig/Strecker reaction[a,b,c]





[a] On a 0.25 mmol scale. [b] Isolated yield. [c] Determined by HPLC analysis.

products **9** were obtained in good to excellent ee (Table 3). Despite the ample room for improvement, these results clearly demonstrated that the novel aza-Wittig/Strecker sequence is a promising approach for the development of the catalytic asymmetric Strecker reaction of ketoimines formed *in situ* from achiral ketones.

In conclusion, we have developed a highly enantioselective synthesis of oxindole based α-amino nitriles, and applied it to the total synthesis of spirohydantoin **I**. This is the first time that *N*-Boc ketoimines have been used for the catalytic asymmetric Strecker reaction. A tandem aza-Wittig/Strecker reaction has also been developed, which offers the premise to develop catalytic asymmetric Strecker reaction of ketoimines generated *in situ* from achiral ketones. The development of catalytic asymmetric Strecker reactions of other types of *N*-Boc ketoimines is now in progress.

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