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**COMMUNICATION** Jian Zhou *et al.* A facile method for the synthesis of oxindole based quaternary α-aminonitriles *via* the Strecker reaction

**EMERGING AREA** Maurizio Benaglia and Sergio Rossi Chiral phosphine oxides in present-day organocatalysis



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## A facile method for the synthesis of oxindole based quaternary $\alpha$ -aminonitriles *via* the Strecker reaction<sup>†</sup>

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The direct  $\alpha$ -cyanoamination of isatins using TMSCN has been developed, which is carried out in methanol without any catalyst. A new bifunctional cinchona alkaloid-based phosphinamide catalyst 7 could promote the Strecker reaction of isatins derived ketimine with TMSCN in up to 74% ee.

The 3,3-disubstituted oxindole structure motif is a privileged heterocyclic subunit in a large number of bioactive natural products and drugs.<sup>1</sup> Much attention has been devoted to the development of catalytic asymmetric method for the synthesis of sufficient amount of these compounds and their analogues for biological evaluation and studies on the structure-activity relationship, aiming at the development of new therapeutic agents or important biological tools.<sup>2</sup> Among these structures, 3-substituted-3aminooxindole is very useful because of its presence in natural products and several pharmaceutical candidates,<sup>3</sup> including the potent gastrin/CCK-B receptor antagonist AG-041R<sup>3a</sup> and the vasopressin VIb receptor antagonist SSR-149415.3b-c Although several methods have already been developed to prepare this important structure motif, including imine addition reaction,<sup>4</sup> intramolecular arylation,<sup>5</sup> alkylation of 3-aminooxindole,<sup>6</sup> Mannich reaction<sup>7</sup> and direct amination of 3-substituted oxindoles,<sup>8</sup> catalytic asymmetric methods are very limited.<sup>5a,8</sup> Surprisingly, the catalytic asymmetric addition of nucleophiles to ketimines derived from isatins has not been reported yet, despite it is a very straightforward method for the synthesis of this subunit.

As part of a program directed at the synthesis of 3,3disubstituted oxindole derivatives for biological evaluation, we have already developed a highly enantioselective amination of unprotected 3-substituted oxindoles<sup>8b</sup> and the Michael addition of unprotected 3-substituted oxindoles to nitroolefins.<sup>2r</sup> We are also interested in the synthesis of 3-substituted-3-aminooxindoles *via* the Strecker reaction<sup>9</sup> which is largely unexplored. Only one example was reported using isatin, KCN and methylamine hydrochloride or aniline in large excess of acetic acid.<sup>10</sup> In this communication, we wish to report a catalyst-free direct  $\alpha$ -cyanoamination<sup>11</sup> of isatins using TMSCN, and the initial results in the catalytic asymmetric Strecker reaction of isatins derived ketimines with TMSCN using a new bifunctional cinchona alkaloid-based chiral phosphinic amide catalyst.

For convenience and safety, other cyanating agents were introduced to avoid the use of toxic HCN, and trimethyl silyl cyanide (TMSCN) turned out to be a widely used cyanide source, less harmful and easily manageable.<sup>9</sup> Since several reactions involving silicon based nucleophiles could be promoted by the reaction solvent without any catalyst,<sup>12</sup> we first evaluated if the reaction of ketimine **1a** with TMSCN could be accelerated by the reaction solvent. The solvent effects were summarized in Table 1.

To be strict, all the reactions shown in Table 1 were carried out at 50 °C under an atmosphere of nitrogen. In 1,2-dichloroethane (DCE) or toluene, no reaction took place after 48 h, partly because the ketimine **1a** dissolved poorly in the two solvents. In THF, DMSO or DMF, the ketimine **1a** dissolved well, but still only trace amount of the desired product was detected. It was unexpected that almost no reaction took place in CH<sub>3</sub>CN or DMF, because it was reported that CH<sub>3</sub>CN as the solvent could accelerate the three component Strecker reaction of aldehydes,<sup>12d</sup> and DMF as the solvent could promote the cyanosilylation of aldehydes.<sup>12e</sup>

All these solvents that might serve as neutral coordinateorganocatalysts<sup>12h</sup> failed to promote the desired reaction, suggesting that ketimine **1a** was not reactive enough. Recently, Rueping *et al.* found that chiral diols such as TADDOL were effective catalysts for the enantioselective Strecker reaction of aldimines and HCN.<sup>13</sup> Although the use of alcohol for the hydrogen-bond activation of ketimines was not reported in their work, we tried the alcohol as the solvent,<sup>14,15</sup> with the anticipation that the alcohol solvent might serve as both a hydrogen-bonding donor promoter to activate the ketimine and a Lewis base to facilitate the cyanide transfer.<sup>16</sup> To our delight, the use of MeOH as solvent greatly accelerated the reaction, and almost full conversion could be achieved within 15 h at 50 °C, affording product **3a** in 84% yield (entry 2). In EtOH and *i*-PrOH (entries 3–4), the reaction still worked well but were obviously slower than that in methanol.

To investigate the role of alcoholic solvent in this reaction, several control experiments were conducted using DCE as the solvent (entries 5-12), since no reaction took place in DCE. First, to check if the HCN produced from methanol and TMSCN<sup>16</sup> served as a Brønsted acid<sup>15b-f</sup> to promote the reaction, MeOH was used as an additive for the reaction. Although the ketimine 1a dissolved poorly in DCE, the use of one equiv. of MeOH relative to TMSCN afforded product 3a in 13% yield, suggesting that HCN alone was inefficient to promote the reaction (entry 5). With the increase of the usage of MeOH additive, the yield of product 3a was improved (entries 5–10). Obvious improvement in the yield of product 3a was observed when six equiv. of MeOH relative to TMSCN was added (entry 8), and the use of ten equivs of MeOH improved the yield to 79% (entry 10). Based on these results, the role of MeOH to promote this reaction was believed to activate ketimine 1a through hydrogen-bonding and to facilitate the cyanide transfer. The efficiency of the MeOH as the solvent to promote the reaction was further demonstrated by the control

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experiment using 10 mol% of Schreiner's thiourea  $4^{15e}$  with MeOH as additive, which afforded product 3a in only 36% yield (entry 11)

On the basis of the aforementioned optimization, we further tried to develop a one-pot sequential reaction of isatins **5**, anilines **6** and TMSCN, since the direct  $\alpha$ -cyanoamination of ketones<sup>11</sup> still remained a big challenge and only one example of catalyst-free version was reported,<sup>17</sup> using solvent-free condition at 100 °C, but limited to several cyclic ketones.

It was found that acceptable yields could be obtained if TMSCN was added after the isatins 5 reacted with anilines 6 in methanol for one hour, in the presence of MS 5 Å at 50 °C. This reaction was carried out in air, operationally very simple. Under the optimal reaction condition, we next examined the substrate scope, and a variety of different substituted isatins and anilines were subjected to the standard condition (Table 2). Generally, the reaction worked well whatever the substituents on the isatins. In the case of isatins with electron-withdrawing groups, longer reaction time would lead to the formation of side products, so the reactions were stopped after 15 h, affording the desired product in good to high yield (entries 1-5). While in the case of other isatins, the reaction time was prolonged to 24 h and the desired product was obtained in slightly higher yield (entries 6–9). The substituents of anilines 6 also influenced the reactivity, and electron-donating substituents on the 4-position had a beneficial effect on the reaction outcome. In the case of *m*-methoxyaniline and *p*-chloroaniline, the yields were obvious lower (entries 10-12).

Based on our analysis of the role of alcohol in this reaction, we next tried to develop an asymmetrical version of the Strecker reaction of ketimines 1 with TMSCN,<sup>18</sup> especially focusing on the use of bifunctional catalyst. Of all the catalysts we screened, our newly developed bifunctional cinchona alkaloid-based phosphinamide catalyst 7 turned out to be the most enantioselective one (see

Table 2 Substrate scope of direct  $\alpha$ -cyanoamination of isatins

R <sup>1</sup> R <sup>2</sup> 5 (1	0 N H	+ TMSCN 2 (2.0 eq)	+ R <sup>3</sup> + NH <sub>2</sub> 6 (1.1 eq)	MeOH, MS 5	R <sup>3</sup>	NH CN NH CN R <sup>2</sup> 3
Entry <sup>a</sup>	Isatin 5		<b>R</b> <sup>3</sup>	3	Time/h	Yield <sup>b</sup> (%)
1 2 3 4 5 6 6 7 8 9 10 11 12	$R^{1} = Cl, R^{2} = NC R^{2} = NC R^{2} = R, R^{1} = Br, R^{1} = Br, R^{1} = Br, R^{1} = Me R^{1} = H, R^{1}$	$R^{2} = H$	p-OMe p-OMe p-OMe p-OMe p-OMe p-OMe p-OMe p-OMe p-OMe p-OMe p-OMe p-Cl	3a 3b 3c 3d 3e 3f 3g 3h 3i 3j 3k 3l	15 15 15 15 15 24 24 24 24 24 24 24 24	69 81 84 63 58 85 83 73 76 68 83 55
" Reaction	on scale: (	).5 mmol, <sup><i>b</i></sup>	Isolated vie	ld.		

ESI<sup>†</sup>).<sup>19</sup> With catalyst **7**, we further examined the solvent effects, and 1,1,2,2-tetrachloroethane (TTCE) as the solvent resulted in acceptable yield and enantioselectivity (see ESI<sup>†</sup>). Under this condition, a variety of ketimines were examined, and the results were summarized in Table 3. Since some of the ketimines dissolves poorly in TTCE, the conversion was not high even the reaction time was nearly five days, and the corresponding products were obtained in only moderate yield (entries 1–3 and 9) and up to 74% ee. In the case of ketimines with a better solubility in TTCE, the yield was higher, but the enantioselectivity was lower. Although the yield and the enantioselectivity of this reaction had much

#### Table 3 Substrate scope of catalytic asymmetric Strecker reaction



<sup>*a*</sup> Reaction scale: 0.25 mmol; <sup>*b*</sup> Isolated yield, <sup>*c*</sup> Determined by chiral HPLC analysis, <sup>*d*</sup> At 0  $^{\circ}$ C for 90 h and 20  $^{\circ}$ C for 22 h.

room for further improvement, this represented the first example of catalytic asymmetric addition of nucleophiles to isatin derived ketimines to construct the desired quaternary 3-aminooxindoles.

In conclusion, we have developed the first example of catalyst free α-cyanoamination of isatins to construct useful 3-substituted-3-aminooxindole 3. This is also the first example of alcohol solvent promoted one-pot sequential Strecker reaction of ketones using TMSCN as a cyanide source. We also reported the first example of catalytic asymmetric nucleophilic addition to isatin derived ketimines using TMSCN. The new bifunctional cinchona alkaloid-based phosphinamide catalyst 7 could promote the Strecker reaction of ketimine 1 with TMSCN in moderate to good yield and enantioselectivity. The simple and mild reaction conditions including air-tolerance, together with the usefulness of the product, make our method very useful. The development of new bifunctional Brønsted acid-Lewis base catalyst is now underway in our lab, aiming to develop a highly enantioselective Strecker reaction of ketimines derived from isatins to prepare chiral 3-substituted aminooxindoles.

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