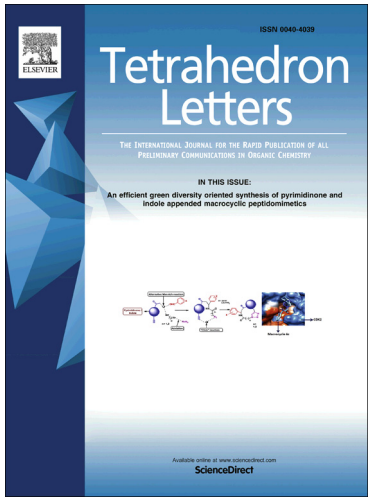

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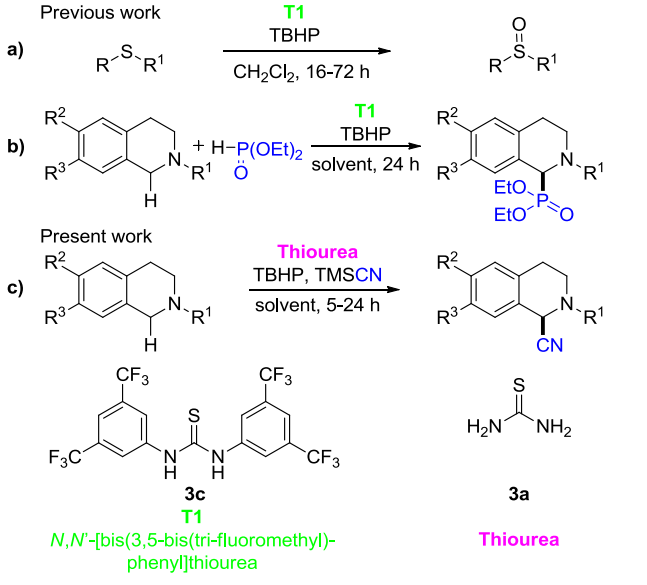
ABSTRACT

Thiourea itself has been introduced as a mild and efficient organocatalyst for the oxidative α-cyanation of *N*-aryltetrahydroisoquinolines (THIQs) with TMSCN, giving the corresponding products in good to excellent yields. Experimental investigations demonstrated that thiourea acts as a radical initiator by abstracting hydroxyl radical (·OH) from *tert*-butyl hydroperoxide (TBHP) directly instead of non-covalent H-bonding activation. The use of thiourea as a radical initiator offers a new avenue for innovative chemical transformations in organocatalyzed radical chemistry.

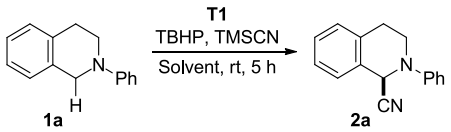
Thiourea and its derivatives have been frequently employed as organocatalysts for the acceleration of a wide range of chemical transformations.[1-7] The ready availability of structure-diverse thiourea derivatives greatly facilitates their development to be the main pillar of noncovalent organocatalysts.[1-3,8-10] A great deal of mechanistic investigations has further intensified the notion that thioureas activate electrophiles through hydrogen bonding (H-bonding).[11,12] Therefore, several strategies are often employed to adjust the catalytic effect of thioureas, i.e. introduction of electron-withdrawing groups to enhance H-bonding action, incorporation of additional functionalities to generate multifunctional H-bond donor catalysts, etc.[1-3,13-17] In this context, *N,N'*-bis[3,5-bis(trifluoromethyl)phenyl]thiourea, introduced by Schreiner's group (abbreviated here as **T1**), represents a privileged organocatalyst and its applications have been extended to a wide range of useful chemical transformations.[1-3,18] **T1** is reported to promote the oxidation of sulfides by TBHP through double hydrogen-bonding interaction (Scheme 1a).[12] We recently reported **T1**-catalyzed cross-dehydrogenative coupling (CDC) of C(sp^3)-H with phosphites and nitroalkanes by using *tert*-butyl hydroperoxide (TBHP) as a terminal oxidant (Scheme 1b).[19,20] Experimental investigation into the mechanism showed that the reaction proceeds through the hydrogen bonding interaction of **T1** with TBHP and radical chain process.[19,20] On the other hand, thiourea itself or its derivatives work as radical initiators have also been reported in chemical transformations.[21,22] Inspired by these works, we envisioned that thiourea might also be a suitable catalyst for the oxidative cyanation of THIQs with a nucleophilic cyanide. Herein, we present a novel catalytic mode of thiourea as a radical initiator in the oxidative α-cyanation of THIQs using TBHP as a terminal oxidant (Scheme 1c).



Scheme 1. Thiourea and its derivatives catalyzed oxidative reactions with TBHP.

We commenced our investigation with the oxidative α-cyanation of *N*-phenyltetrahydroisoquinoline **1a** with TMSCN as a model reaction in the presence of 20 mol% of **T1** and 2.0 equiv. of THBP (Table 1). We were pleased to find that the reaction gave the desired product **2a** in 47% yield at room temperature (rt) in 5 hours using CH_3CN as the solvent (Table 1, entry 2). The reaction performed in toluene, $CHCl_3$ or under solvent-free conditions afforded similar amount of α-cyanation product (Table 1, entries 3–5). Notably, the yield was dramatically

Table 1. Optimization of reaction conditions for the oxidative α-cyanation of *N*-phenyltetrahydroisoquinoline with TMSCN.[a]



Entry	T1 (mol %)	Solvent	Yield (%)[b]
1	20	MeOH	81
2	20	CH_3CN	47
3	20	Toluene	40
4	20	$CHCl_3$	35
5	20	Neat	45
6	15	MeOH	70
7	20	MeOH	60[c]
8	–	MeOH	14[d]
9	20	MeOH	21[e]

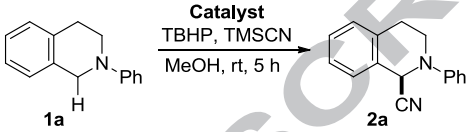
[a]Reaction conditions: **1a** (0.2 mmol), TMSCN (2.0 equiv.), TBHP (2.0 equiv., 5.5 M in decane), 15–20 mol % of **T1**, solvent (0.6 mL), rt, 5 h. [b]Isolated yield. [c]Malononitrile as a cyanide source. [d]Without a catalyst. [e]Adding 2.0 equiv. of a radical inhibitor (BHT).

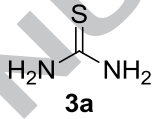
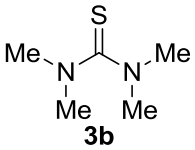
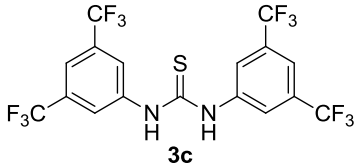
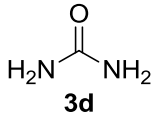
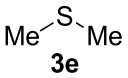
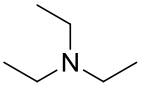
improved to 81% when the solvent was switched to methanol, probably due to the formation of HCN, which works as cyanide source instead of TMSCN (Table 1, entry 1).[23-25] The control experiment showed that only 14% yield of product can be obtained in the absence of T1. Interestingly, malononitrile can also be employed as a cyanide source, giving the product in 60% yield (Table 1, entry 7). Only 21% yield of the corresponding α-aminonitriles was obtained in the presence of a radical inhibitor 2,6-di-*tert*-butyl-4-methylphenol (BHT), suggesting that a radical pathway was likely involved in this reaction (Table 1, entry 9).

To determine the catalytic role of T1 in the oxidative cyanation of THIQ, we screened a series of thiourea derivatives (Table 2). Much to our surprise, thiourea itself demonstrated superior catalytic efficiency to T1 (Table 2, entry 1), which are contradictory to common sense that the ability of H-bond donor is decisive for reaction acceleration. This observation was further highlighted when an 84% yield was obtained using tetramethylthiourea as the catalyst (Table 2, entry 2), suggesting that an alternative reaction pathway may be involved instead of H-bonding activation. The essential effect of thiourea functionality was demonstrated by the significantly lower yield obtained when the reaction was performed in the presence of urea as the catalyst (Table 2, entry 4). The use of methanol as the solvent was also found to be crucial for this oxidative cyanation of THIQ. No acceleration effect was observed with dimethyl sulfide and triethylamine as catalysts (Table 2, entries 5 and 6).

With the optimum conditions in hand, the scope of the oxidative α-cyanation reaction was explored. A number of *N*-

Table 2. Catalysts screening for the oxidative α-cyanation of *N*-phenyltetrahydroisoquinoline with TMSCN.[a]



Entry	Catalyst	Yield (%)[b]
1	 **3a**	90
2	 **3b**	84
3	 **3c**	81
4	 **3d**	15
5	 **3e**	17
6	 **3f**	8

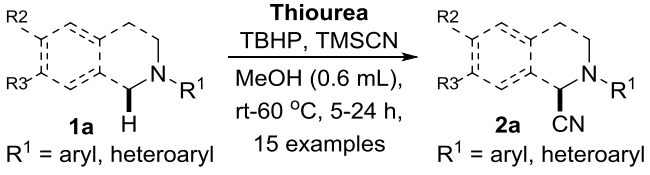
[a]Reaction conditions: **1a** (0.2 mmol), TMSCN (2.0 equiv.), TBHP (2.0 equiv., 5.5 M in decane), 20 mol % of catalyst, MeOH (0.6 mL), rt, 5 h. [b]Determined by ^{1}H NMR using mesitylene as an internal standard.

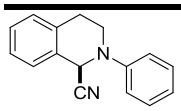
aryltetrahydroisoquinolines were tested for this protocol (Table 3). All the substrates containing electron-withdrawing groups (EWGs) and electron-donating groups (EDGs) on *N*-aryl ring tolerated well with this catalytic protocol. THIQs substituted with halogens (Br, Cl, and F) at the para-position

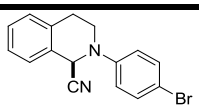
were all efficiently transformed into corresponding products in 80-81% yield (**2b-d**).

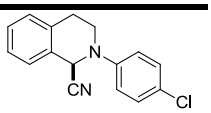
THIQs with the *para*-substituted nitro group gave moderate yield (52%) after 24 hours which may be due to the inhibitory effect of nitro group in the formation of active iminium intermediate. The *p*-methyl and *p*-methoxy substituted substrates also provided excellent yields of 84% and 87% respectively. The di-substituted substrate with methoxy groups on the main skeleton of THIQ gave 58% yield of the product **2h** after 24 hours. It is worthy of pointing out that inert *N*,*N*-dimethylanilines were also viable substrates for this protocol, giving 80% yield after 24 hours when the reaction temperature increases from rt to

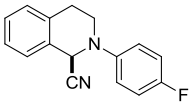
Table 3. The substrate scope of thiourea catalyzed oxidative α-cyanation of tertiary amines.[a, b]

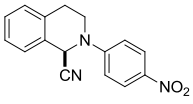


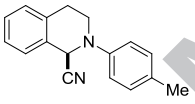

2a: 86%
rt, 5 h

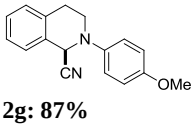

2b: 80%
rt, 5 h

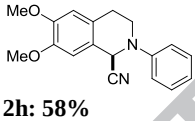

2c: 80%
rt, 5 h

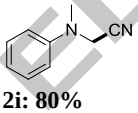

2d: 81%
rt, 5 h

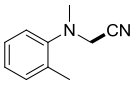

2e: 52%
rt, 24 h

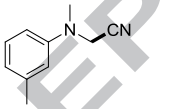

2f: 84%
rt, 5 h

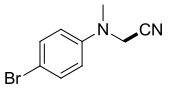

2g: 87%
rt, 5 h

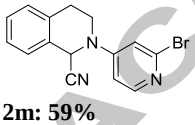

2h: 58%
rt, 24 h

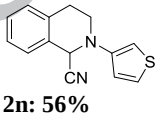

2i: 80%
60 °C, 24 h

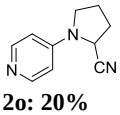

2j: 76%
60 °C, 24 h


2k: 78%
60 °C, 24 h


2l: 78%
60 °C, 24 h


2m: 59%
60 °C, 24 h


2n: 56%
60 °C, 5 h

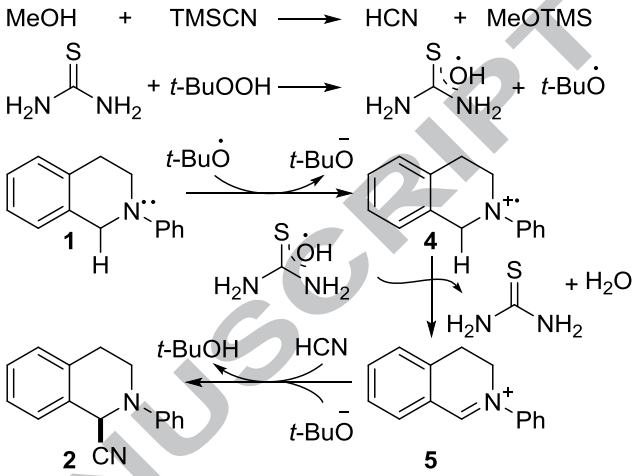

2o: 20%
60 °C, 24 h

[a]The reaction was carried out with tertiary amines (0.2 mmol), TMSCN (2.0 equiv.), TBHP (2.0 equiv., 5.5 M in decane) in the presence of 20 mol % of thiourea for 5-24 h using MeOH (0.6 mL) as a solvent system at room temperature (**2a-h**) and at 60 °C (**2i-l**). [b]Isolated yield.

60 °C. Furthermore, substituted *N*,*N*-dimethylanilines derivatives with a methyl group at *o*-, *m*-positions and bromo at *p*-position were all tolerant with this protocol, affording the corresponding products in yield of 76%, 78% and 78% respectively (**2j-l**).

We further extended substrates scope to THIQ substituted with heteroaromatic groups. The THIQ substrate bearing *N*-2-bromo-4-pyridinyl group gave the corresponding product (**2m**) in 59% yield. THIQ substrate substituted with an *N*-thiophen-3-yl group produced the target compound (**2n**) in 56% yield. The relatively inert heteroaromatic tertiary amine **1o** was also tolerated with this protocol, albeit only 20% yield of the corresponding product was isolated.

Presently the exact mechanism of thiourea itself catalyzed oxidative cyanation of THIQs is not clear. Keeping in view that tetramethylthiourea can also promote the



Scheme 2. A plausible mechanism of thiourea itself catalyzed oxidative cyanation of *N*-aryltetrahydroisoquinolines.

oxidative cyanation of THIQs, a plausible mechanism is proposed as illustrated in Scheme 2. In comparison to the previous mechanistic proposal that thiourea derivatives facilitate the formation of active iminium intermediate through hydrogen-bonding interaction with TBHP.[19,20] However, in this case, thiourea itself presumably operates as a radical initiator by accepting hydroxyl radical (·OH) from TBHP to generate a *tert*-butoxyl radical (*t*-BuO·).[21,22,26-29] This *tert*-butoxyl radical trigger a SET from **1** to form a radical ion pair composed of an *N*-aryltetrahydroisoquinoline radical cation **4** and a *tert*-butoxyl anion. Subsequently, radical cation **4** goes through hydrogen radical (·H) transfer to thiourea-hydroxyl radical, giving iminium ion **5** as an intermediate, while thiourea is regenerated with production of water (H_2O). The iminium ion **5** undergoes a nucleophilic attack of HCN to form the desired product **2**.

Conclusions

In conclusion, we have developed the thiourea itself catalyzed oxidative cyanation of *N*-aryltetrahydroisoquinolines. This method provides mild, efficient, and environmentally friendly access to C-C coupling product in good to excellent yields, while avoiding the use of metal catalysts. Experimental investigation reveals that the reaction proceeds via the function of thiourea as a radical initiator instead of hydrogen bonding activation. Given the widespread applications of radical chemistry and the ready availability of thioureas, this mode of action may serve as a stimulus for exploratory research of thiourea derivatives in synthetic chemistry.

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Authors Contributions

The manuscript was written through the contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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Graphical Abstract

New catalytic effect of thiourea on the oxidative cyanation of *N*-aryltetrahydroisoquinolines

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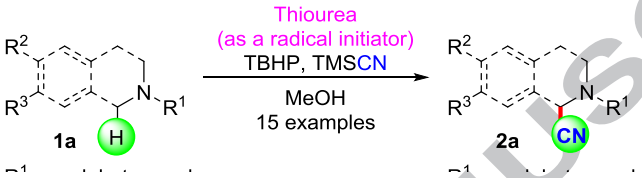
Bakhtar Ullah, Yuli Zhou, Jingwen Chen, Zongbi Bao, Yiwen Yang, Qiwei Yang, Qilong Ren and Zhiguo Zhang*



Highlights

- Thiourea itself was used as an organocatalyst for C(sp^3)−H bond activation.
- α-Aminonitriles were obtained in good to excellent yields.
- Thiourea acts as a radical initiator instead of non-covalent H-bond donor.