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Catalytic enantioselective synthesis of 2-pyrazolines *via* one-pot condensation/6π-electrocyclization: 3,5-bis(pentafluorosulfanyl)-phenylthioureas as powerful hydrogen bond donors†

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A new conjugate-base-stabilized carboxylic acid (CBSCA) containing a 3,5-bis(pentafluorosulfanyl) phenylthiourea functionality catalyses challenging one-pot condensations/6π-electrocyclizations of hydrazines and α,β-unsaturated ketones under mild conditions. Structurally diverse *N*-aryl 2-pyrazolines are obtained in good yields and enantioselectivities. The superior performance of 3,5-bis(SF_5) phenylthioureas over the widely used 3,5-bis(CF_3)phenylthioureas is further demonstrated in the Michael addition of dimethyl malonate to nitrostyrene, using a new Takemoto-type catalyst.

Introduction

2-Pyrazolines are valuable structural motifs, exhibiting a range of biological activities including anticancer, anti-inflammatory, antimicrobial, antiviral, and antidiabetic.[1] While 2-pyrazolines are most commonly prepared as racemates,[2] several mechanistically distinct catalytic enantioselective approaches have emerged. Kanemasa and Kanai reported the first catalytic enantioselective synthesis of 2-pyrazolines: a chiral Lewis acid catalysed 1,3-dipolar cycloaddition of trimethylsilyldiazomethane with chelating dipolarophiles such as 3-crotonoyl-2-oxazolidinone (Scheme 1a(a)).[3] Subsequent reports disclosed related catalytic enantioselective 1,3-dipolar cycloadditions of various diazo compounds and dipolarophiles.[4,5] Sibi *et al.* utilized hydrazonyl bromides as precursors to nitrile imines in asymmetric Lewis acid catalysed cycloadditions with 3-crotonoyl-2-oxazolidinone and related substrates (Scheme 1a(b)).[6] Brière and coworkers reported an asymmetric phase transfer approach to the synthesis of 2-pyrazolines, involving the conjugate addition of *N*-Boc hydrazine to α,β-unsaturated ketones, followed by condensation (Scheme 1a(c)).[7] Employing related substrates, an iminium catalysis strategy was reported by Deng and coworkers where the initial conjugate addition is facilitated by a 9-*epi*-amino cinchona alkaloid catalyst (Scheme 1a(d)).[8] Dixon *et al.* used monoalkyl-substituted hydrazine-derived hydrazones, which, in the presence of a cinchona alkaloid derived bifunctional organocatalyst, undergo enantioselective conjugate addition to α,β-unsaturated ketones (Scheme 1a(e)).[9,10] Subsequent hydrolysis followed by intramolecular condensation provides the corresponding 2-pyrazolines. *N*-Sulfonyl hydrazones with pendent alkenes have been shown to undergo enantioselective formation of 2-pyrazolines *via* organocatalytic iodoaminocyclization[11] or *via* palladium-catalysed aza-Wacker-type cyclization (Scheme 1a(f)).[12] Hu and coworkers reported a method for the synthesis of 2-pyrazolines from propargylic acetates and hydrazines, involving a (3 + 2) cycloaddition facilitated by a chiral copper catalyst (Scheme 1a(g)).[13] A unique approach to the catalytic enantioselective synthesis of medicinally relevant *N*-aryl 2-pyrazolines was reported by List and coworkers (Scheme 1b).[14] In this transformation, which was first described in its racemic form by Fischer and Knoevenagel,[15] hydrazones derived from α,β-unsaturated ketones undergo cyclization in the presence of a BINOL-derived phosphoric acid catalyst to provide *N*-aryl 2-pyrazolines in good to high enantioselectivity. This represents the first catalytic enantioselective 6π-electrocyclization, a challenging type of reaction for which there are still only a limited number of examples.[16,17] Here we report a one-pot condensation/6π-electrocyclization approach to access highly enantioenriched *N*-aryl 2-pyrazolines directly from hydrazines and α,β-unsaturated ketones (Scheme 1c).[18] Reactions are catalysed by a new conjugate-base-stabilized carboxylic acid (CBSCA) containing a 3,5-bis(pentafluorosulfanyl)-phenylthiourea functionality which has not yet been successfully utilized in

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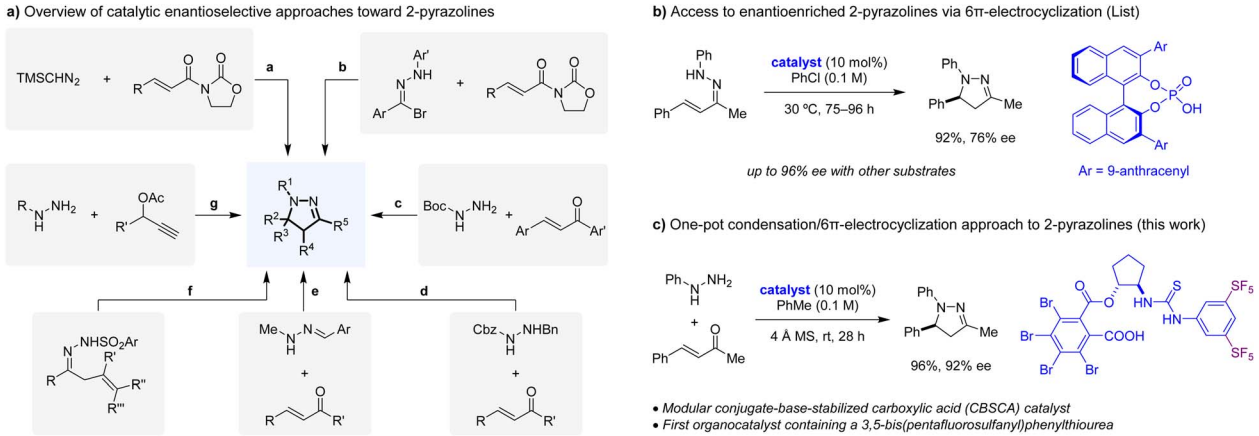


Scheme 1 Relevant precedent on the catalytic enantioselective synthesis of 2-pyrazolines and current work.

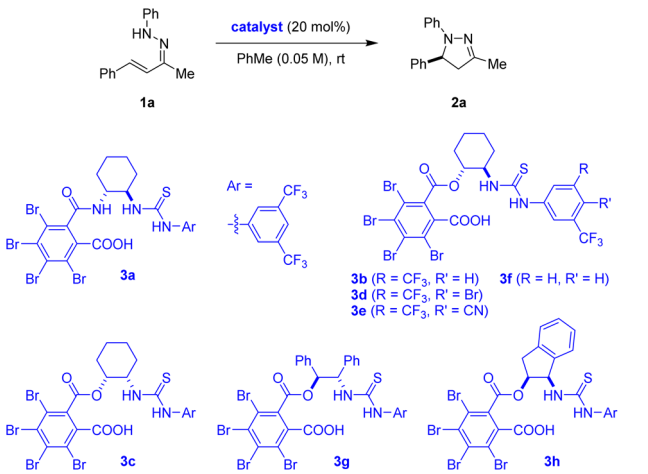
asymmetric organocatalysis. We further demonstrate the significant potential of 3,5-bis(pentafluorosulfanyl)phenylthioureas in the context of bifunctional catalysis.

Results and discussion

Asymmetric Brønsted acid catalysis continues to be dominated by BINOL-derived phosphoric acids and structurally related species.[19] With few exceptions, simple carboxylic acids typically lack sufficient acidity to promote a diverse array of reactions.[19g,l,20] Driven in large part by the desire to enhance the structural diversity of chiral Brønsted acid catalysts and the reactions they facilitate, our group previously introduced CBSCAs.[21] These catalysts contain both a (thio)urea and a carboxylic acid functionality and efficiently facilitate reactions involving iminium and oxocarbenium ions.[21] The acidity of CBSCAs, which can exceed that of typical BINOL-derived phosphoric acids,[21f,g,22] is largely derived from conjugate base stabilization *via* anion binding.[23] In an effort to further expand the utility of these versatile catalysts, we decided to evaluate CBSCAs in the challenging asymmetric 6π-electrocyclization first reported by List and coworkers.[14a,b] Preformed hydrazone **1a** was selected as the model substrate (Table 1). In the presence of 20 mol% of (1*R*,2*R*)-cyclohexane-1,2-diamine-derived carboxylic acid **3a**, **1a** underwent transformation into the desired 2-pyrazoline **2a** at room temperature (Table 1, entry 1). Product **2a** was obtained with an encouraging level of enantioselectivity. Remarkably, the closely related (1*R*,2*R*)-2-aminocyclohexan-1-ol-derived carboxylic acid catalyst **3b** provided a significant boost to both reactivity and enantioselectivity (Table 1, entry 2). Further modifications to the catalyst backbone and aryl substituents on the thiourea functionality did not result in any further improvements (Table 1, entries 3–8).

We next sought to develop a one-pot approach to 2-pyrazolines starting from arylhydrazines and α,β-unsaturated ketones, with the additional goals of lowering the catalyst loading and further increasing catalyst efficiency. While the List group also reported a streamlined synthesis of enantioenriched *N*-aryl pyrazolines from arylhydrazines and α,β-unsaturated ketones, their protocol required initial heating of these starting materials at 50 °C in the presence of molecular sieves but, importantly, in the absence of catalyst. For reasons that remain unclear, the hydrazone formation step (a commonly acid-catalysed process) was found to be incompatible with the phosphoric acid catalyst, and the spent dehydrating agent had

Table 1 Reaction development with preformed hydrazone[a]



Entry	Catalyst	Time [h]	Yield (%)	ee (%)
1	**3a**	96	68	75
2	**3b**	24	91	90
3	**3c**	24	69	5
4	**3d**	24	78	87
5	**3e**	24	44	39
6	**3f**	96	94	84
7	**3g**	24	90	61[b]
8	**3h**	48	53	31

[a] Reactions were performed with 0.1 mmol of **1a**. Yields correspond to isolated yields of chromatographically purified products. The ee values were determined by supercritical fluid chromatography analysis. [b] The opposite enantiomer was obtained.

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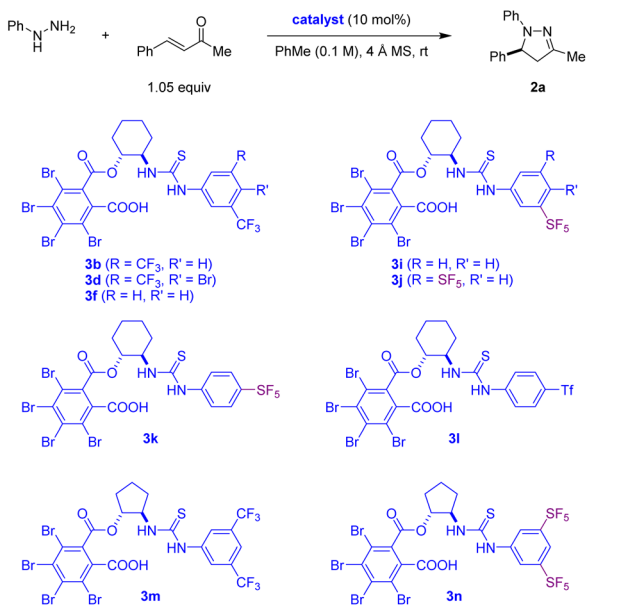
to be removed by filtration prior to the addition of the chiral Brønsted acid.[14a,b] We were pleased to observe that CBSCA **3b** efficiently promotes the condensation/6π-electrocyclization of phenylhydrazine with 4-phenyl-3-buten-2-one at room temperature in the presence of 4 Å molecular sieves, providing **2a** in excellent yield and enantioselectivity (Table 2, entry 1). Not surprisingly, considering the reduced catalyst loading, the reaction time required doubled compared to the synthesis of **2a** from the preformed hydrazone (*cf.* Table 1, entry 2). Consistent with the results shown in Table 1, catalysts **3d** and **3f** proved less effective than **3b**.

To potentially generate more active catalysts, we explored the replacement of trifluoromethyl substituents with pentafluorosulfanyl (SF_5) groups. Compared to a CF_3 substituent, the SF_5 group offers several potential advantages, including increased bulk, electronegativity, and lipophilicity, properties which may lead to favourable characteristics of the corresponding catalysts.[24] While CF_3 groups are ubiquitous substituents in chiral organocatalysts, and the 3,5-bis(CF_3)phenyl substituent in particular is well-recognized as a privileged group,[25] the occurrence of SF_5 groups in chiral organocatalysts remains rare.[26–28] For example, successful applications were reported in the context of asymmetric Brønsted acid catalysis with BINOL-derived catalysts in which 3,5-bis(SF_5)phenyl substituents are placed in the 3,3′ positions of the BINOL backbone.[26] In the reported cases, these catalysts generally outperform the corresponding catalysts containing 3,5-bis(CF_3) phenyl groups. A 3,5-bis(SF_5)phenyl group was also incorporated into an axially chiral bifunctional catalyst containing both phosphite and 3,5-bis(CF_3)phenylurea functionalities.[27] We are aware of only one catalyst containing a 3,5-bis(SF_5)phenylthiourea group.[28] However, in this case, this substituent offered no advantages over the most effective aryl group. In our case, catalyst **3i** containing one SF_5 group in the 3-position significantly outperformed the corresponding catalyst **3f** containing a single CF_3 group (Table 2, entry 4). The performance improved even more dramatically with catalyst **3j** containing a 3,5-bis(SF_5) phenyl substituent (Table 2, entry 5). Catalysts **3k** and **3l** containing a SF_5 or a triflyl (Tf) group in the 4-position offered no advantages over **3j** (Table 2, entries 6 and 7). Finally, a change of the (1*R*,2*R*)-2-aminocyclohexan-1-ol backbone to (1*R*,2*R*)-2-aminocyclopentan-1-ol provided a boost in enantioselectivity. While this improvement was seen for both 3,5-bis(CF_3)phenylthiourea catalyst **3m** and 3,5-bis(SF_5)phenylthiourea catalyst **3n**, the latter outperformed the former in regard to both reactivity and enantioselectivity (Table 2, entries 8 and 9).

Table 2 Development of the one-pot approach[a]



Entry	Catalyst	Time [h]	Yield (%)	ee (%)
1	**3b**	48	90	89
2	**3d**	48	82	87
3	**3f**	96	74	83
4	**3i**	40	90	85
5	**3j**	28	93	90
6	**3k**	48	92	63
7	**3l**	48	89	71
8	**3m**	48	93	91
9	**3n**	28	96	92

[a] Reactions were performed with 0.1 mmol of phenylhydrazine. Yields correspond to isolated yields of chromatographically purified products. The ee values were determined by supercritical fluid chromatography analysis.

With the optimal reaction conditions in hand, the scope of the transformation was evaluated with regard to arylhydrazines and α,β-unsaturated ketones (Scheme 2). Various electronically diverse substituents on the aromatic ring of the enones were well tolerated (products **2a–2i**). A furan substituent was also successfully accommodated (product **2j**). Similarly, electron-rich and electron-poor hydrazines engaged in the title reaction, providing the corresponding *N*-aryl 2-pyrazolines in good to high yields and enantioselectivities (products **2l–2n**). Addressing a previous limitation,[14a,b] hydrazones formed *in situ* from arylhydrazines and enones bearing alkyl groups other than methyl also engaged in enantioselective 6π-electrocyclization reactions. Good enantioselectivities were obtained for non-branched aliphatic substituents (products **2o** and **2p**) while the introduction of an isopropyl substituent led to a small drop in ee (product **2q**). A further drop in enantioselectivity was noted in *N*-aryl 2-pyrazolines containing a *tert*-butyl group (products **2r–2t**). The synthesis of these materials in enantioenriched form is nevertheless significant. For example, 2-pyrazoline **2t** has been identified as a potent and selective allosteric inhibitor of PKCζ, a therapeutic target in pulmonary and hepatic inflammatory diseases.[29]

To further explore the potential of 3,5-bis(SF_5)phenylthioureas as hydrogen bond donor motifs in asymmetric catalysis, we decided to prepare an analogue of the eponymous Takemoto catalyst, replacing the 3,5-bis(CF_3)phenylthiourea (Scheme 3). The Takemoto catalyst (**5a**) and related bifunctional catalysts have been shown to catalyse a broad range of transformations. Catalyst **5a** was first utilized in a catalytic enantioselective Michael addition of 1,3-dicarbonyl compounds to

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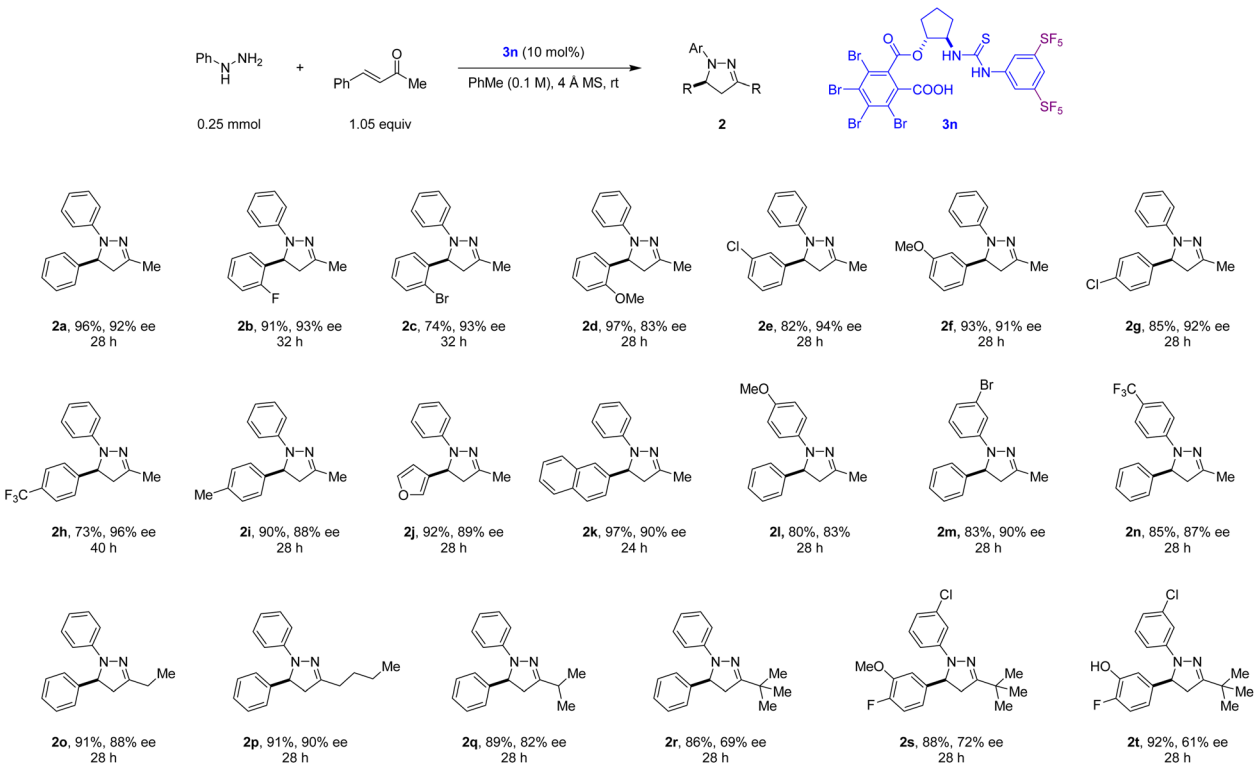
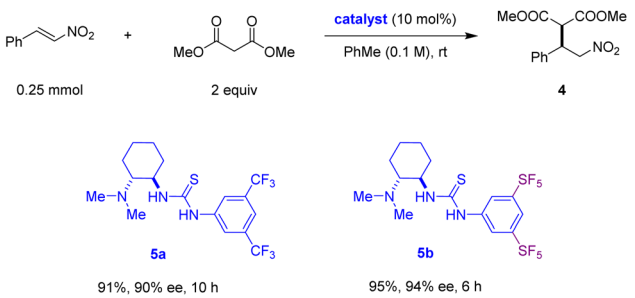


Scheme 2 Reaction scope.



Scheme 3 Enantioselective Michael addition with a new Takemoto-type catalyst.

nitroalkenes.[30,31] In our hands, using catalyst **5a**, the reaction of dimethyl malonate to nitrostyrene provided product **4** in 91% yield and 90% ee, following a reaction time of 10 h. The new 3,5-bis(SF_5)phenylthiourea containing catalyst **5b** furnished **4** in 95% yield and 94% ee within 6 h. The superior performance of **5b** in regard to both reactivity and enantioselectivity suggests that the further exploration of bis(SF_5)phenylthioureas in asymmetric organocatalysis is warranted.

Conclusions

In summary, we have achieved a practical and efficient one-step asymmetric synthesis of 1,3,5-trisubstituted 2-pyrazolines. This method allows for the incorporation of diverse substitution patterns into the 2-pyrazoline scaffold, thereby providing a valuable platform for the synthesis of enantioenriched *N*-aryl 2-pyrazolines exhibiting promising biological activities. As part of this investigation, we have introduced a new conjugate-base-stabilized carboxylic acid (CBSCA) containing a 3,5-bis(pentafluorosulfanyl)phenylthiourea functionality, a catalyst that was shown to significantly outperform the corresponding catalyst containing a 3,5-bis(trifluoromethyl)phenylthiourea group. The superiority of the 3,5-bis(pentafluorosulfanyl)-phenylthiourea as a hydrogen bond donor was further demonstrated in the context of a catalytic enantioselective Michael addition of dimethyl malonate to nitrostyrene, using a new Takemoto-type catalyst.

Data availability

All supplementary data are available in the ESI.†

Author contributions

M. A. R. R. performed experiments and wrote the original drafts of the manuscript and ESI.† S. D. performed experiments and edited the ESI.† M. O. and C. M. also performed experiments. D. S. conceived of and directed the project and edited the manuscript.

Conflicts of interest

There are no conflicts to declare.

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