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# Combining *in situ* Generated Chiral Silicon Lewis Acid and Chiral Brønsted Acid Catalysts for [3+2]Cycloadditions: Cooperative Catalysis as a Convenient Enantioselective Route to Pyrazolidines

Olga V. Serdyuk,[a] Alexandru Zamfir,[a] Frank Hampel,[a] and Svetlana B. Tsogoeva[a,*]

[a] Department of Chemistry and Pharmacy, Chair of Organic Chemistry I, University of Erlangen-Nuremberg, Henkestrasse 42, 91054 Erlangen, Germany
Fax: (+49)-(0)9131-85-26865; phone: (+49)-(0)9131-85-22541; e-mail: tsogoeva@chemie.uni-erlangen.de

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**Abstract:** A facile enantioselective synthesis of chiral pyrazolidines *via* a [3+2]cycloaddition reaction, involving a BINOL-derived phosphoric acid and an *in situ* generated BINOL phosphate-derived silicon Lewis acid, which may act cooperatively, has been developed.

**Keywords:** [3+2]cycloaddition; enantioselective synthesis; organocatalysis; pyrazolidines; silicon catalysts

## Introduction

Pyrazolidine and pyrazoline heterocycles are ubiquitous in pharmaceutical compounds. They are widely used as antidepressants,[1] acyltransferase inhibitors,[2] analgesic[3] and antimicrobial agents.[4] Some of them show antitumor,[5] or anticonvulsant[6] activities and are used in agriculture as arthropodicidal agents[7] (Figure 1). Representing attractive synthetic targets, these heterocycles are of particular interest for organic chemists.

[3+2]Cycloadditions of hydrazones to olefins provide a direct access to pyrazolidines and pyrazolines.[8,9] Much effort has been devoted to the development of catalytic versions of this reaction. In 2002, it was reported by Kobayashi et al. that Lewis acids effectively promote this transformation.[10] For example, in the presence of a stoichiometric amount of $BF_3{\cdot}OEt_2$ or a catalytic amount of $Zr(OTf)_4$ and $Hf(OTf)_4$, the corresponding pyrazolidine derivatives can be obtained in good yields. Later, an asymmetric version of the [3+2]cycloaddition has been developed using $Zr(OTf)_4$/BINOL derivatives as chiral

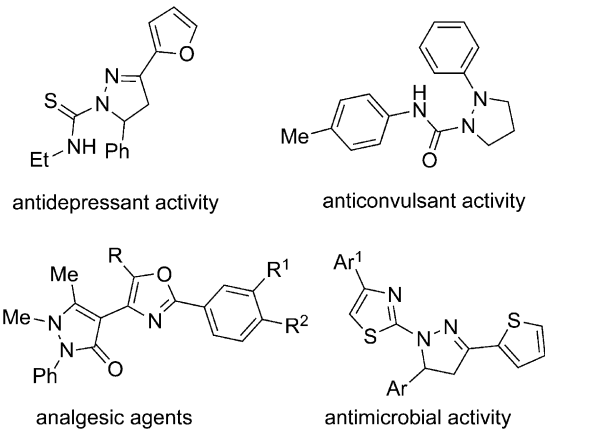


**Figure 1.** Pyrazolines and pyrazolidines as subunits of bioactive compounds and drugs.

Lewis acid catalysts.[11] Recently, it was reported that $Cu(OTf)_2$ can catalyze the cycloaddition of fluorinated hydrazones with ethynyl ketones.[12] Leighton and co-workers described an asymmetric intermolecular [3+2] acylhydrazone-enol ether cycloaddition using 1.5 equiv. of a chiral pseudoephedrine-derived silane Lewis acid.[13] In 2009 Müller and List showed[14] that chiral Brønsted acids efficiently catalyze the cycloisomerization of α,β-unsaturated hydrazones to give pyrazolines in high yields and enantioselectivities.

Recently, we have demonstrated for the first time that the [3+2]cycloaddition reaction between *N*-acylhydrazones and cyclopentadiene can be successfully performed in high yields (up to 99%), with a diastereoselectivity of up to 98:2 *dr* by using catalytic amounts of TMSOTf (trimethylsilyl triflate) as a readily available achiral silicon Lewis acid catalyst.[15] Nonetheless, identification of enantioselective metal-free catalyst systems for this useful intermolecular reaction remains an important challenge.

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Inspired by the proven ability of silicon Lewis acids to serve as effective catalysts in this reaction,[15] and by the fact that BINOL phosphates[16] can enantioselectively catalyze the cycloisomerization of α,β-unsaturated hydrazones[14] we envisioned to achieve an enantioselective intermolecular [3+2] cycloaddition of hydrazones to olefins through combining an achiral silicon Lewis acid catalyst with chiral BINOL phosphates **1a–f** (Figure 2 and Figure 3).

Herein, we wish to report our studies, aimed at the development of a new and easily accessible silicon Lewis acid catalytic system for the enantioselective [3+2] cycloaddition reaction between *N*-benzoylhydrazones and cyclopentadiene, providing a convenient and facile process for the synthesis of pyrazolidines under metal-free conditions in good yields, high enantioselectivities and diastereoselectivities.

Compared with those advancements achieved with chiral Brønsted acid organocatalysts,[16] silicon-based Lewis acid enantioselective catalysis finds itself still in the early stages.[17–19] Undoubtedly, however, chiral silicon Lewis acids as enantioselective catalysts hold significant potential in the broad area of Lewis acid catalysis. Very recently, Schreiner and co-workers have reported a new and interesting class of Lewis acid catalysts based on the combination of achiral thiourea and $SiCl_4$ for the stereospecific rearrangement of epoxides to quaternary carbaldehydes.[20] Thus, our new catalytic system, generated *in situ* from chiral BINOL-derived phosphoric acid and achiral halosilane, might contribute to the rare examples of asymmetric catalysis by *in situ* formed chiral silane species.

## Results and Discussion

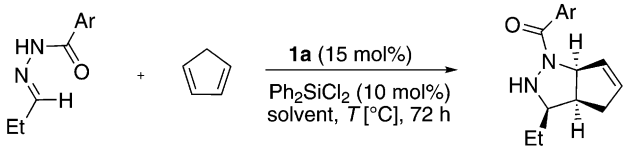
First, we undertook a systematic investigation of solvents and reaction temperature for the model reaction of *N*-benzoylhydrazone **2a** with cyclopentadiene using the combination of chiral BINOL phosphate **1a** and $Ph_2SiCl_2$ as a catalytic system.

Our screening experiments demonstrated that toluene was the most suitable among the studied solvents in terms of the observed stereoselectivities (entry 3, Table 1). Decreasing the temperature from room temperature to −20 °C led to an improvement in the enantioselectivity from 40% to 80% *ee*, but resulted in lower yield (entry 3 *vs.* entry 2).

Next, we tested an assumed synergism between the BINOL phosphate **1a** and $Ph_2SiCl_2$. While **1a** itself showed low reactivity and moderate enantioselectivity (47% *ee*, 99:1 *dr*, entry 1, Table 2) and the weak Lewis acid additive $Ph_2SiCl_2$ alone was inactive in the catalysis under these reaction conditions (entry 2), the combination of both components resulted in the product with low yield, but fairly good enantioselectivity and diastereoselectivity (80% *ee*, 96:4 *dr*, entry 3, Table 2). Most likely this might be explained by the fact, that weak silicon Lewis acids can be activated, besides using Lewis bases,[21] also by connection to a strongly electron-withdrawing group,[22] which is represented by the BINOL-derived phosphoric acid moiety in our system (Figure 2).

To further improve the outcome of the reaction, we screened several other commercially available Lewis acid additives in combination with **1a**. While $BBr_3$, $PhSiCl_3$, and TMSOTf provided good yields of 56–64%, low enantioselectivities were observed (3–32% *ee*, entries 4–6). Thus, the originally applied combination of $Ph_2SiCl_2$ and **1a** was confirmed as the most op-

**Table 1.** [3+2] Cycloaddition reaction of hydrazone **2a** with cyclopentadiene using **1a**/$Ph_2SiCl_2$ as a catalytic system.




**2a**
Ar = 4-$NO_2C_6H_4$

**3a**-*syn*

| Entry | Solvent | *T* [°C] | Yield [%][a] | *syn/anti*[b] | *ee* [%][c] *syn* |
|---|---|---|---|---|---|
| 1 | DCM | −10 | 46[d] | n.d. | 30 |
| 2 | toluene | r.t. | 37 | 95:5 | 40 |
| 3 | toluene | −20 | 18 | 96:4 | 80 |
| 4 | chlorobenzene | −20 | 33 | 98:2 | 72 |
| 5 | *m*-xylene | −20 | 36 | 97:3 | 69 |

[a] Yield of the isolated product.
[b] The *dr* was determined by HPLC (Daicel Chiralpak IA).
[c] Enantiomeric excess was determined by HPLC (Daicel Chiralpak IA).
[d] 11 mol% of **1a** was used.

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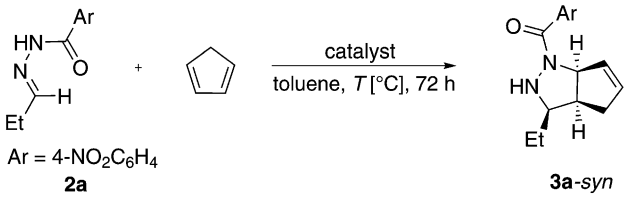
**Table 2.** Optimization of the catalytic system.




| Entry | Catalyst [mol%] | Additive [mol%] | $T$ [°C] | Yield [%][a] | *syn/anti*[b] | *ee* [%][c] *syn* |
|---|---|---|---|---|---|---|
| 1 | **1a** (15) | – | −20 | 13 | 99:1 | 47 |
| 2 | **–** | $Ph_2SiCl_2$ (10) | −20 | n.r. | – | – |
| 3 | **1a** (15) | $Ph_2SiCl_2$ (10) | −20 | 18 | 96:4 | 80 |
| 4 | **1b** (12) | $BBr_3$ (10) | −20 | 56[d] | 97:3 | 3 |
| 5 | **1a** (30) | $PhSiCl_3$ (15) | −15 | 64 | 84:16 | 32 |
| 6 | **1a** (30) | TMSOTf (15) | −15 | 59 | 89:11 | 24 |
| 7 | **1a** (15) | $Ph_2SiCl_2$ (30) | −15 | 64 | 96:4 | 43 |
| 8 | **1a** (30) | $Ph_2SiCl_2$ (30) | −15 | 69 | 92:8 | 57 |
| 9 | **1a** (30) | $Ph_2SiCl_2$ (20) | −15 | 62 | 99:1 | 70 |
| 10 | **1a (30)** | **$Ph_2SiCl_2$ (15)** | **−15** | **62** | **98:2** | **82** |
| 11 | **1a** (30) | $Ph_2SiCl_2$ (10) | −15 | 47 | 93:7 | 59 |
| 12 | **1a** (20) | $Ph_2SiCl_2$ (15) | −15 | 56 | 93:7 | 43 |
| 13 | **1a** (30) | $Ph_2SiCl_2$(15) | −15 | 41[e] | 92:8 | 82 |
| 14 | **1a** (30) | $Ph_2SiCl_2$(15) | −15 | 64[f] | 91:9 | 62 |

[a] Yield of the isolated product.
[b] The *dr* was determined by HPLC (Daicel Chiralpak IA).
[c] Enantiomeric excess was determined by HPLC (Daicel Chiralpak IA).
[d] The reaction was performed for 18 h.
[e] MS 4 Å were added to the reaction mixture.
[f] 50 mol% of $H_2O$ was added to the reaction mixture.

timal and was used for further studies concerning the influence of co-catalysts ratio on the reaction outcome. We noticed an improvement of the enantioselectivity upon lowering the amount of $Ph_2SiCl_2$ with respect to the amount of **1a** (entry 10 *vs.* 7–9). The reaction in toluene at −15 °C, in the presence of 30 mol% of **1a** and 15 mol% of $Ph_2SiCl_2$ resulted in 62% yield, 82% *ee* and 98:2 *dr* (entry 10). Interestingly, while addition of 4 Å MS to the reaction mixture has not influenced the enantioselectivity (entry 13 *vs.* entry 10), a significant decrease in the enantioselectivity (from 82% to 62%, entry 14 *vs.* entry 10) was noted upon addition of water to the reaction mixture.

Our further studies were commenced with the screening of different BINOL phosphates **1a–1g** (Figure 3) readily available in our group.[16f,19] The results obtained (Table 3), demonstrate that BINOL

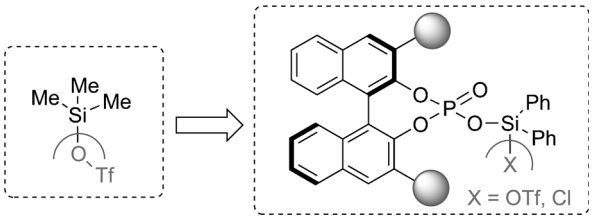
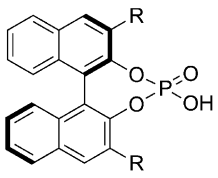



**Figure 2.** Design of new chiral silicon-derived catalysts.




**1a**: R = 4-(β-Naph)-$C_6H_4$
**1b**: R = 4-$NO_2$-$C_6H_4$
**1c**: R = 4-$CF_3$-$C_6H_4$
**1d**: R = 2,4-$(NO_2)_2$-$C_6H_3$
**1e**: R = $SiPh_3$
**1f**: R = 4-*t*-Bu-$C_6H_4$
**1g**: R = 9-anthracenyl

**Figure 3.** Screened BINOL phosphates.

phosphate **1a** was the best choice and gave the product in 62% yield and 82% *ee* (entry 1). The catalyst **1d** (entry 4) provided the product with slightly higher yield (64%), however, in much lower enantioselectivity (30% *ee*).

With the selected catalyst system **1a**/$Ph_2SiCl_2$ and reaction conditions established, a variety of hydrazones were then evaluated as substrates and the results are summarized in Table 4. To our delight, most of the reactions can be performed in good yields (53–80%), high enantioselectivities and excellent diastereoselectivities (82–95% *ee*, up to 98:2 *dr*, entries 1–6, Table 4). The exception was the experiment using hydrazone with $R^1 = CO_2Et$, $R^2 = 4\text{-}NO_2C_6H_4$, where the product was isolated with 60% yield and in only 48% *ee* (entry 7). Notably, while [3+2]cycloaddition reactions of *N*-benzoylhydrazones bearing different alkyl

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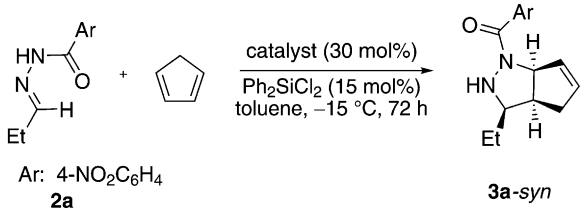
**Table 3.** Screening of BINOL phosphates **1a**–**1g**.




Ar: 4-$NO_2C_6H_4$ **2a**

**3a**-*syn*

| Entry | Catalyst | Yield [%][a] | *syn*/*anti*[b] | *ee* [%][c] *syn* |
|---|---|---|---|---|
| 1 | **1a** | 62 | 98:2 | 82 |
| 2 | **1b** | <1 | 95:5 | 15 |
| 3 | **1c** | 44 | 97:3 | 5 |
| 4 | **1d** | 64 | 92:8 | 30 |
| 5 | **1e** | 34 | 70:30 | 12 |
| 6 | **1f** | 30 | 96:4 | 2 |
| 7 | **1g** | n.r. | – | – |

[a] Yield of the isolated product.
[b] The *dr* was determined by HPLC (Daicel Chiralpak IA).
[c] Enantiomeric excess was determined by HPLC (Daicel Chiralpak IA).

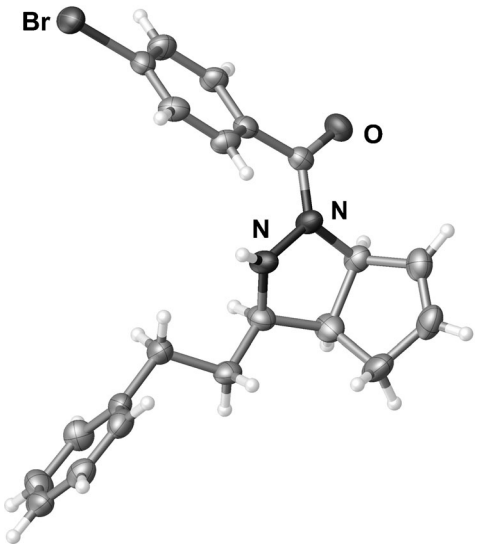



**Figure 4.** Determination of the absolute configuration by X-ray crystal structure analysis of **3f**-*syn*.

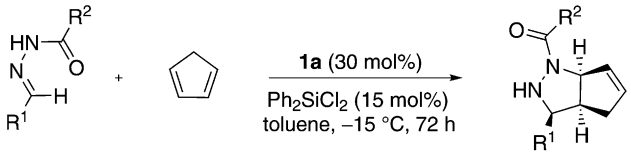
rests ($R^1$ = Et, *i*-Bu, $CH_2CH_2Ph$) resulted in the formation of the product in good to high yields and enantioselectivities (entries 1–6), in the case of the substrate with $R^1$ = Ph the reaction did not proceed (entry 8), most probably due to steric reasons.

The absolute configuration (*SSS*) of the major diastereomer of the [3+2]cycloaddition products has been determined by X-ray crystal structure analysis of the pyrazolidine **3f**-*syn* (Figure 4).[24]

Additional attempts to promote the cycloaddition between *N*-benzoylhydrazone **2a** and selected vinyl ethers (*tert*-butyl vinyl ether and propyl vinyl ether) using BINOL phosphate/$Ph_2SiCl_2$ as a catalytic system revealed that the reaction was slow and proceeded sluggishly under the standard reaction conditions. Further studies with vinyl ethers are, therefore, required to elaborate suitable reaction conditions and to develop a silicon-based catalytic system providing the desired chiral cycloaddition products.

Obviously, the catalytic system is generated from BINOL phosphate and $Ph_2SiCl_2$ *in situ* by exchanging one of the two chlorine atoms: the second one remains as a leaving group (Figure 2), which might eliminate upon catalyst interaction with hydrazone. The assumption that the presence of the leaving

**Table 4.** Scope of hydrazones.




**2** **3a**–**g**-*syn*

| Entry | Product | $R^1$ | $R^2$ | Yield [%][a] | *syn*/*anti*[b] | *ee* [%][c] *syn* |
|---|---|---|---|---|---|---|
| 1 | **3a** | Et | 4-$NO_2C_6H_4$ | 62 | 98:2 | 82 |
| 2 | **3b** | Et | 4-$BrC_6H_4$ | 53 | 96:4 | 84 |
| 3 | **3c** | *i*-Bu | 4-$NO_2C_6H_4$ | 80 | 96:4 | 88 |
| 4 | **3d** | $CH_2CH_2Ph$ | Ph | 72 | 96:4 | 95 |
| 5 | **3e** | $CH_2CH_2Ph$ | 4-$NO_2C_6H_4$ | 61 | 97:3 | 86 |
| 6 | **3f** | $CH_2CH_2Ph$ | 4-$BrC_6H_4$ | 54 | 98:2 | 95 |
| 7 | **3g** | $CO_2Et$ | 4-$NO_2C_6H_4$ | 60 | 91:9 | 48 |
| 8 | – | Ph | 4-$NO_2C_6H_4$ | – | – | – |

[a] Yield of the isolated product.
[b] The *dr* was determined by HPLC (Daicel Chiralpak IA, IB, AS).
[c] Enantiomeric excess was determined by HPLC (Daicel Chiralpak IA, IB, AS).

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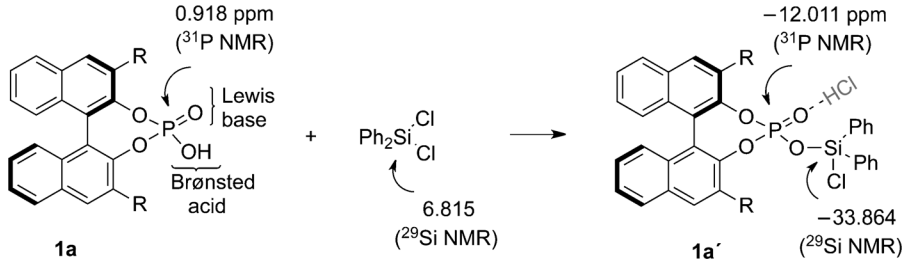



**Scheme 1.** $^{31}$P NMR and $^{29}$Si NMR studies of the reaction of **1a** with $Ph_2SiCl_2$.

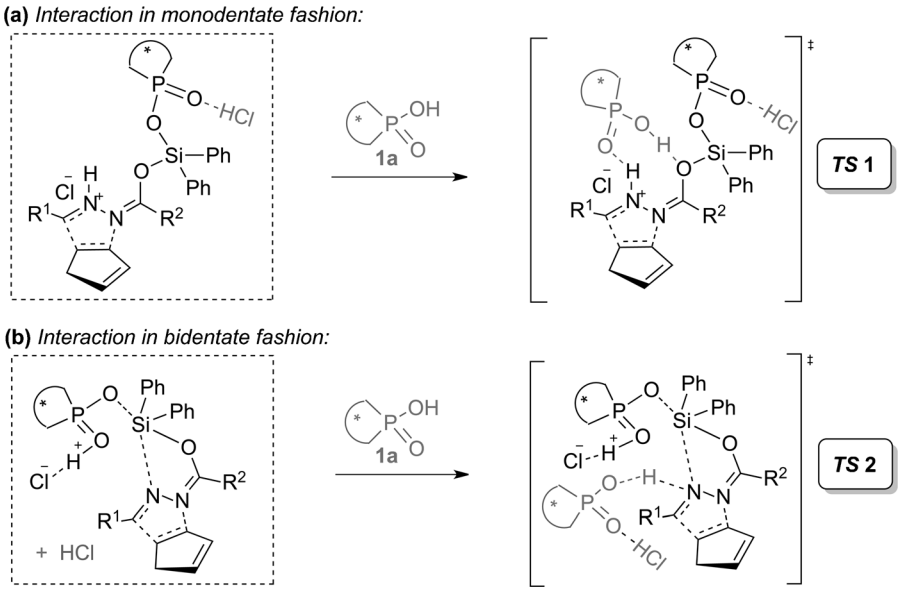
group in the *in situ* generated catalyst is required for the formation of the cycloaddition product, is supported by the observation that no reaction occurs using the combination of **1a** with $Ph_3SiCl$ as a catalytic system.

The *in situ* formation of *O*-silylated BINOL phosphate species is indicated by $^{31}$P NMR studies of both the BINOL phosphate **1a** and the 2:1 mixture of **1a** with $Ph_2SiCl_2$ stirred for 1 hour at room temperature before NMR measurement (Scheme 1). The major signal corresponds to free BINOL phosphate **1a** and the new signal that appeared at −12.011 ppm might be assigned the structure **1a′**.

We also performed $^{29}$Si NMR experiments under conditions similar to those used in the synthetic procedure. Upon mixing BINOL phosphate **1a** and $Ph_2SiCl_2$ in a 2:1 ratio in $CDCl_3$ we observed only one signal at −33.864 ppm. The $^{29}$Si NMR signal shifted upfield by nearly 40 ppm from +6.815 ppm in free $Ph_2SiCl_2$[23] to −33.864 ppm in the *in situ* formed silicon compound **1a′** (Scheme 1). The observed signal at −33.864 ppm lies in the region for a four-coordinate silicon species.[25]

Based on $^{31}$P and $^{29}$Si NMR experiments, X-ray studies and our previous DFT computations of TMSOTf catalyzed [3+2]cycloaddition reactions[15a] we propose a plausible transition state structure (***TS* 1**) for this reaction, demonstrating the interaction of the *in situ* formed catalyst **1a′** with hydrazone in a monodentate fashion (Scheme 2a). However, the interaction of catalyst **1a′** with hydrazone in a bidentate fashion (in analogy to the report of Leighton[13a]) is also reasonable (Scheme 2b). Both transition state structures might provide the products with the same stereochemistry.

Because of the bifunctional character of the phosphoric acid group in BINOL phosphate (*Lewis base*/*Brønsted acid*), the dual role of the additional BINOL phosphate molecule could be imagined: while the P=O moiety acts as a Lewis base and might coordinate to the HCl generated in the reaction system (preventing non-enantioselective catalysis by HCl), the Brønsted acidic part is supposed to coordinate to the hydrazone and to additionally stabilize the proposed transition state structure (***TS* 1** and ***TS* 2**, Scheme 2).




**Scheme 2.** Proposed transition state structures demonstrating the possible role of an additional molecule **1a**.

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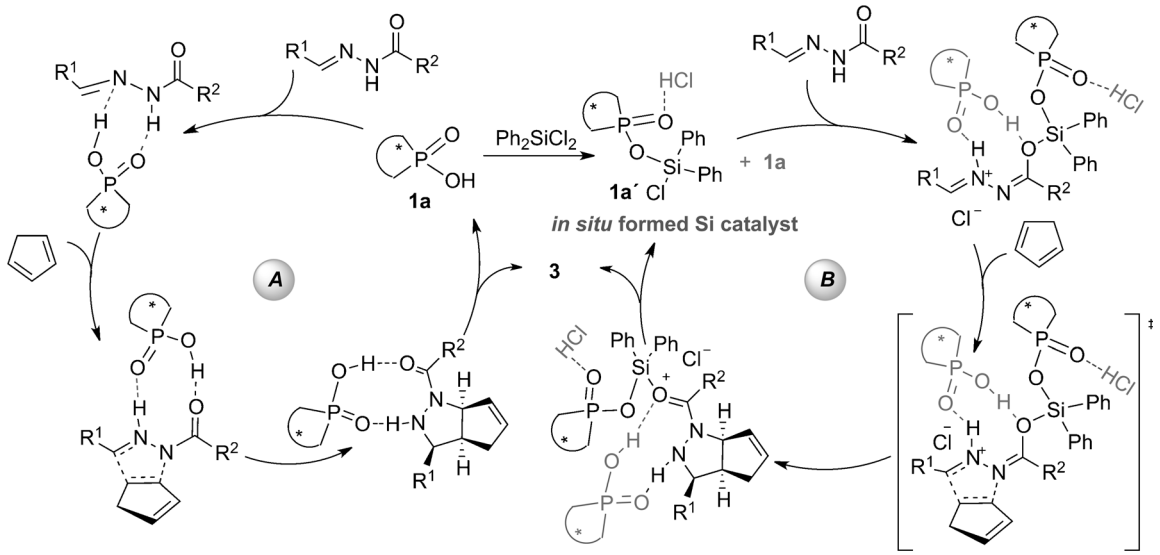


**Scheme 3.** Postulated mechanisms for the [3+2]cycloaddition reaction by using BINOL phosphate alone (catalytic cycle ***A***) and applying BINOL phosphate/$Ph_2SiCl_2$ (2:1) as a catalytic system (catalytic cycle ***B***).

While in principle, two reaction pathways are possible in the [3+2]cycloaddition of the hydrazones to olefins,[11b] one – a stepwise pathway, and the second – a [3+2] concerted pathway, we suggest here a concerted mechanism based on our previous DFT computations of a related system using an achiral silicon catalyst (Scheme 2).[15a] Notably, the concerted pathway reported by Kobayashi and co-workers in their zirconium-catalyzed enantioselective [3+2]cycloaddition of hydrazones to external olefins[11b] further supports our suggested concerted mechanism.

Since BINOL phosphate **1a** itself can also give the product (and with the same absolute configuration as that obtained with **1a**/$Ph_2SiCl_2$ system), albeit with modest results (13% yield, 47% *ee*, 99:1 *dr*, entry 1, Table 2), we propose here two catalytic cycles for both BINOL phosphate catalysis (cycle A, Scheme 3) and a more efficient cooperative silicon-Lewis acid/Brønsted acid catalysis (cycle B, Scheme 3), demonstrating the advantages of **1a**/$Ph_2SiCl_2$ catalytic system over BINOL phosphate **1a** itself.

## Conclusions

In conclusion, we have successfully developed the enantioselective [3+2]cycloaddition reaction between different *N*-benzoylhydrazones and cyclopentadiene, catalyzed by a combination of Brønsted acid with chiral silicon Lewis acid, easily generated *in situ* from Brønsted acid and $Ph_2SiCl_2$. This metal-free transformation provides a simple access to pyrazolidines in up to 80% yields, up to 95% *ee* and 98:2 *dr*. We believe that the cooperative catalysis system involving silicon-Lewis acid catalysis and Brønsted acid catalysis will find applications for other important asymmetric transformations and might become a powerful tool in organic synthesis.

Further studies focusing on the full scope of this and related pericyclic reactions and other organic transformations using this new facile approach are currently underway.

## Experimental Section

### General Procedure for the [3+2] Cyloaddition between Hydrazones and Cyclopentadiene

To a solution of BINOL phosphate **1a** (60 mg, 0.0798 mmol, 30 mol%) in toluene (2 mL) was added $SiCl_2Ph_2$ (8.4 μL, 0.00398 mmol, 15 mol%) and the mixture was stirred for 1 h at room temperature. The reaction mixture was then cooled to −15 °C, and hydrazone **2a** (60 mg, 0.2715 mmol) and freshly distilled cyclopentadiene (400 μL) were added. After stirring for 72 h at −15 °C, the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL) and extracted with $CH_2Cl_2$ (3×20 mL). The combined organic layers were dried ($MgSO_4$), the solvent was removed under reduced pressure, and the residue purified by silica gel column chromatography (EtOAc-PE, 1:4) to afford the product **3a**; yield: 48 mg (0.1673 mmol, 62%).

### Supporting Information

General remarks, characterization data, determination of the absolute configuration, copies of the NMR spectra and HPLC chromatograms are available in the Supporting Information.

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