Towards a Catalytic Asymmetric Version of the [3+2] Cycloaddition between Hydrazones and Cyclopentadiene

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Received 12 April 2011

Abstract: A novel and easily accessible metal-free catalytic system, an in situ generated BINOL-phosphate-derived silicon Lewis acid, has been described for the [3+2] cycloaddition of *N*-benzoylhydrazone to cyclopentadiene to afford a cycloadduct in high diastereomeric ratio of 95:5 (*syn*/*anti*) and enantiomeric excess of 89%. These results provide insights in the future design and development of highly active and enantioselective silicon Lewis acids for this and other cycloaddition types.

Key words: cycloaddition, silicon, hydrazones, Lewis acids, nitrogen heterocycles

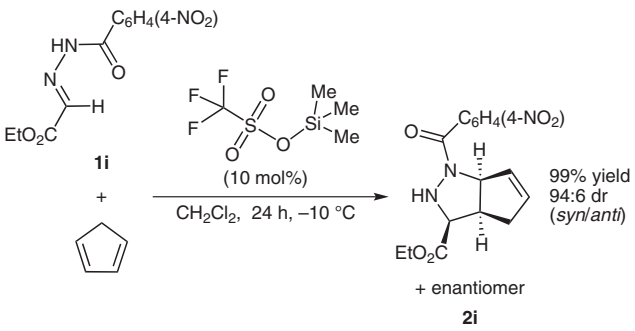
[3+2] Cycloaddition of hydrazones to olefins is a straightforward synthetic route providing direct access to pyrazolidines and pyrazolines. These types of heterocyclic subunits are found in natural products and bioactive compounds,[1] presenting therefore attractive targets for synthetic chemists. The pioneering work in this field was reported from the groups of Hesse, Hamelin, and Grigg. Hesse[2a] obtained pyrazolidines under strong acidic conditions[2] (acetic acid in the presence of a stoichiometric amount of sulfuric acid) out of a three-component reaction between an aldehyde, an *N*-acetylhydrazine, and an olefin. The addition reaction of acetaldehyde hydrazone with *E*- and *Z*-alkenes in acidic media was reported by Hamelin and co-wokers[2b,c] in 1979. In their study, the results were compatible with a concerted process of the polar [3+2] cycloaddition type. Thermal conditions[3] (150 °C) were also found to activate the reaction between a hydrazone and an activated olefin by Grigg and co-workers.[3a,b] Recently Kobayashi found that Lewis acids also promote this transformation. Pyrazolidine derivatives were isolated, by using a stoichiometric amount of $BF_3{\cdot}OEt_2$ (1.1 equiv) or a catalytic amount of $Zr(OTf)_4$ and $Hf(OTf)_4$.[4a]

Regarding an asymmetric version for this kind of reactions, some examples are found in literature, but these are restricted to intermolecular cyclizations,[4b,5] or reactions with activated olefins.[4c,6] Thus, there is still a lot of space for development and improvement especially for the [3+2] cycloaddition of hydrazones with nonfunctionalized olefins, which lacks a catalytic asymmetric method. Furthermore, a factor that has gained importance for different organic transformations in recent years is the use of metal-free catalysis because of its operational simplicity, mild reaction conditions, and environmental advantages.[7]

Inspired by the work of Kobayashi, which showed that Lewis acids are potent catalysts for this reaction, our attention was set on silicon compounds,[8] as catalytic species. The use of silicon-based Lewis acids[8e] as well as hydrazones are accompanied by practical advantages, which motivated our current and previous work.[9] Our intention was, first to find a proper achiral silicon-based catalyst that would efficiently promote the reaction, and then extend the results to the asymmetric reaction, by modifying the catalyst structure to a chiral compound.

The model reaction between ethyl glyoxylate-derived hydrazone **1i** and freshly distilled cyclopentadiene was investigated first. Cyclopentadiene was used in excess due to its tendency to form dimers. By studying different tetravalent silicon compounds[10] we found that the cycloaddition proceeded smoothly in the presence of TMSOTf (trimethylsilyl triflate) at 10 mol% loading. Adducts of cyclopentadiene were observed as side products, which showed no problems of separation from the pyrazolidines. The suitable solvent for the reaction was dichloromethane. The acidic conditions were found to favor the isomerization of the *E*-configured hydrazone to the *Z*-form, which showed to be less reactive. Lowering the temperature from room temperature to –10 °C reduced the isomerization, so that the product of the cycloaddition could be obtained in 99% yield and with a diastereoselectivity of 94:6 (Scheme 1).

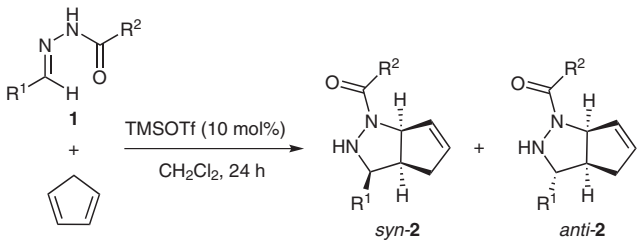
Next different hydrazones as substrates were investigated (Table 1) and generally excellent yields and selectivities were obtained (up to 99% yield, 98:2 dr). Using the 4-nitro or 4-bromo derivatives of the benzoyl protecting group



Scheme 1 TMSOTf-catalyzed [3+2] cycloaddition of hydrazone **1i** to cyclopentadiene

SYNTHESIS 2011, No. 12, pp 1988–1992
Advanced online publication: 17.05.2011
DOI: 10.1055/s-0030-1260467; Art ID: C01111SS

Table 1 Substrate Scope for the Catalytic [3+2] Cycloaddition of Hydrazones and Cyclopentadiene



Entry	1	R^1	R^2	Temp (°C)	Yield (%)[a]	dr (*syn*/*anti*)
1	**1a**	Ph	C_6H_4(4-NO_2)	r.t.	–	–
2	**1b**	$PhCH_2$	C_6H_4(4-NO_2)	r.t.	58	95:5[b]
3	**1c**	$PhCH_2CH_2$	C_6H_4(4-NO_2)	r.t.	99	89:11[c]
4	**1d**	$PhCH_2CH_2$	C_6H_4(4-Br)	r.t.	88	97:3[c]
5	**1e**	$PhCH_2CH_2$	Ph	r.t.	90	97:3[c]
6	**1f**	Et	C_6H_4(4-NO_2)	r.t.	98	96:4[c]
7	**1g**	Et	C_6H_4(4-Br)	r.t.	99	96:4[c]
8	**1h**	*i*-Bu	C_6H_4(4-NO_2)	r.t.	99	98:2[c]
9	**1i**	EtO_2C	C_6H_4(4-NO_2)	–10	99	94:6[b,d]
10	**1j**	EtO_2C	Ph	r.t.	88	89:11[b,d]

[a] Yield of the isolated product.
[b] The dr was determined by HPLC.
[c] The dr was determined by NMR spectroscopy.
[d] Both isomers were isolated.

a slight improvement of selectivity and yield was found (Table 1, compare entries 9 and 10).

Generally, aliphatic aldehyde-derived *N*-benzoylhydrazones performed well in this cycloaddition reaction (entries 3–8). Phenylacetaldehyde-derived hydrazone gives a product with 58% yield (entry 2) while the benzaldehyde-derived hydrazone did not react (entry 1), showing that the reaction is drastically influenced by the steric demand of the substituent on the aldehyde unit of hydrazone ($PhCH_2$ → Ph). For the 3-phenylpropionaldehyde-derived hydrazones, the presence of 4-bromobenzoyl- (entry 4) and benzoyl-protecting groups (entry 5), shows better selectivities but lower yields than their 4-nitrobenzoyl derivative (entry 3).[11] With TMSOTf, as a suitable catalyst for this system, an analogue chiral silicon-based catalyst was envisioned that would share the following feature: it should contain a tetravalent silicon center, with a leaving group similar to TfO^-.

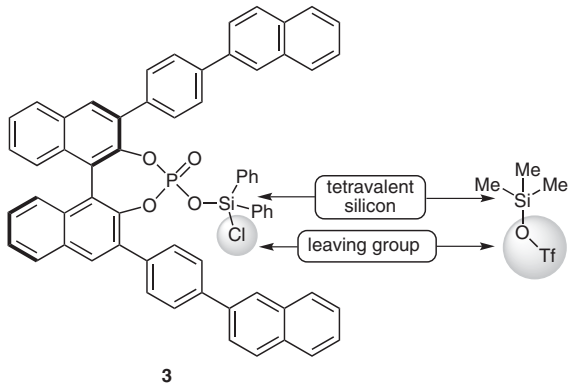


Figure 1 Rationalizing a chiral catalyst

Structure **3** (Figure 1) was proposed as a candidate. As a chirality source a BINOL phosphate derivative was considered, because of the rigid qualities of the BINOL-scaffold. The use of phosphates is also practical from a synthetic point of view: due to their higher acidity (pK_a = ~1) compared to BINOL's (pK_a = ~17)[12] they react directly with silicon compounds that contain leaving groups. This is an advantage, because such silicon-based catalysts could be obtained in situ from the corresponding BINOL phosphates.

Based on our recent DFT studies of the reaction mechanism, considering TMSOTf as a catalyst and **1i** as a substrate,[10] two plausible TS structures of a closely related reaction of hydrazone **1f** and cyclopentadiene with both achiral and chiral catalysts are proposed (**TS 1** and **TS 2**, respectively, Figure 2). In accordance with the proposed **TS 2**, the use of newly designed catalyst **3** is expected to induce enantioselectivity.

The system of BINOL phosphate **3′** and $SiCl_2Ph_2$ that would bind by exchanging one of its chlorine groups was used to give the catalyst **3** in situ by stirring for one hour

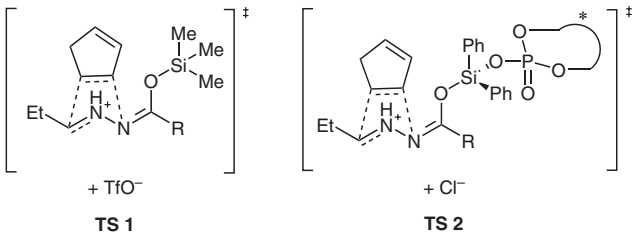
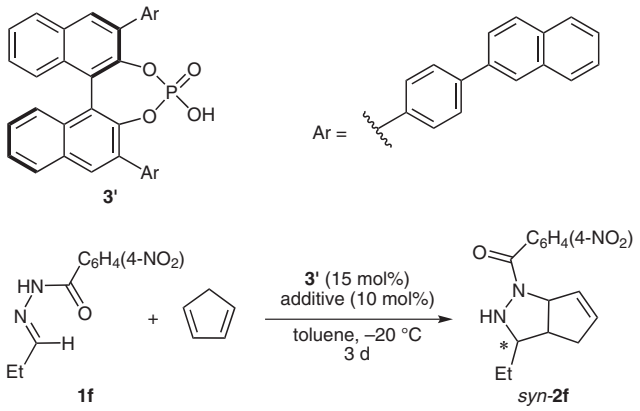


Figure 2 Proposed transition state structures for [3+2] cycloadditions catalyzed by TMSOTf (**TS 1**) and chiral BINOL-phosphate-derived silicon Lewis acid (**TS 2**); R = $C_6H_4(4\text{-}NO_2)$

at room temperature; 15 mol% of BINOL phosphate was used to ensure the full complexation of silicon. The reaction was first carried out with BINOL phosphate **3′** without the use of silicon additives as a reference. The *syn* (dr = 99:1) product was obtained in 13% yield and 47% ee (Table 2, entry 1). Running the reaction for three days at –20 °C, and using $SiCl_2Ph_2$ as an additive (entry 2), the *syn* product (dr = 96:4) was obtained in 18% yield, but in higher enantioselectivity (80% ee). Addition of 4 Å MS to the reaction mixture raised the selectivity of the reaction to 89% ee (entry 3).

Table 2 Asymmetric [3+2] Cycloaddition of Hydrazones and Cyclopentadiene



Entry	Additive	Yield (%)[a]	dr[b]	ee (%) (*syn*)[b]
1	–	13	99:1	47
2	$SiPh_2Cl_2$	18	96:4	80
3[c]	$SiPh_2Cl_2$	13	95:5	89
4	$SiPh_3Cl$	–	–	–

[a] Yield of the isolated product.
[b] Determined by HPLC.
[c] MS 4 Å were added to the reaction mixture.

Lastly, $SiPh_3Cl$ was used as an additive (entry 4). In this case the reaction did not take place, suggesting that the proposed **TS 2** is plausible: however, the lack of a leaving group hinders the binding with the hydrazone. The low yields may suggest that there is a problem with the regeneration of the catalyst after the product is formed.

In summary, we have developed a novel and practical cycloaddition of aliphatic aldehyde-derived *N*-acylhydrazones with cyclopentadiene using catalytic amounts of readily available TMSOTf (trimethylsilyl triflate) as a Lewis acid. This method has been expanded to the asymmetric reaction, delivering the product with high enantioselectivity, but in low yield. With these novel insights in the development of enantioselective silicon-based Lewis acidic catalysts, further investigations are currently in progress in our laboratory.

Commercial products were used without further purification. Hydrazones were synthesized from commercial available hydrazines and aldehydes, purchased from Sigma-Aldrich Co. or Acros Organics. Cyclopentadiene was obtained from commercially available dicyclopentadiene (Merck KGaA) through heating and distillation at 205 °C at atmospheric pressure. All solvents used were previously dried using appropriate methods. Petroleum ether (PE) used refers to the fraction boiling in the range 40–65 °C. Column chromatography was performed on Acros silica gel 60A and TLC on Macherey-Nagel ALUGram® SIL G/UV_{254} plates. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance 400 (400 MHz; 2001) or Bruker Avance 300 (300 MHz; 2001) using the solvent as internal standard. Mass spectra [*m*/*z*, relative intensity (%)] were obtained with a Shimadzu AXIMA Confidence - MALDI Time of Flight (TOF) or Micromass ZabSpec FAB mass spectrometer; DCTB = 2-[(2*E*)-3-(4-*tert*-butylphenyl)-2-methylprop-2-enylidene]malonitrile; DHB = 2,5-dihydroxybenzoic acid; w/o m = without matrix. HPLC measurements were recorded on Agilent 1200 Series system.

TMSOTf-Catalyzed [3+2] Cyloaddition of Cyclopentadiene to Hydrazones; Typical Procedure

To a solution of TMSOTf (1.9 μL, 0.0113 mmol, 10 mol%) in CH_2Cl_2 (2 mL) were added hydrazone **1i** (30 mg, 0.113 mmol) and freshly distilled cyclopentadiene (200–300 μL). After stirring for 24 h at r.t., the reaction mixture was quenched by the addition of sat. aq $NaHCO_3$ (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, 1:1) to afford product **2i**.

2b

^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.89, 33.88, 43.90, 64.62, 69.55, 122.15, 126.17, 127.63, 128.10, 128.36, 128.43, 129.61, 134.92, 137.53, 140.86, 147.95, 165.61.

MALDI-MS (DCTB): *m*/*z* = 350 $[M + H]^+$, 390 $[M + K]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.34 (m, 1 H), 2.54 (d, *J* = 16 Hz, 1 H), 2.66 (m, 1 H), 2.84 (m, 1 H), 3.09 (m, 1 H), 3.40 (m, 1 H), 4.01 (d, *J* = 13 Hz, 1 H), 5.50 (d, *J* = 7 Hz, 1 H), 5.82 (m, 1 H), 5.95 (m, 1 H), 7.10–7.29 (m, 5 H), 7.79 (d, *J* = 9 Hz, 2 H), 8.10 (d, *J* = 9 Hz, 2 H).

2c

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.75 (m, 2 H), 2.40 (m, 2 H), 2.63 (m, 2 H), 3.10 (m, 2 H), 3.73 (d, *J* = 12 Hz, 1 H), 5.57 (m, 1 H), 5.80 (m, 1 H), 5.96 (m, 1 H), 7.0–7.4 (m, 5 H), 7.81 (d, *J* = 9 Hz, 2 H), 8.19 (d, *J* = 9 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.65, 21.49, 30.46, 31.45, 33.66, 44.58, 60.82, 63.54, 70.22, 123.09, 126.64, 128.71, 128.91, 130.39, 135.76, 141.32, 142.00, 148.84, 166.82.

MALDI-MS (DHB): *m*/*z* = 364 $[M]^+$.

2d

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.67–1.82 (m, 2 H), 2.37 (m, 2 H), 2.65 (m, 2 H), 3.06 (m, 2 H), 3.73 (d, *J* = 12 Hz, 1 H), 5.72 (br s, 1 H), 5.79 (br s, 1 H), 5.93 (m, 1 H), 7.00–7.30 (m, 5 H), 7.48 (d, *J* = 9 Hz, 2 H), 7.62 (d, *J* = 9 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.71, 30.57, 32.84, 43.54, 62.56, 69.28, 124.20, 125.73, 127.89, 127.92, 127.98, 128.04, 130.19, 130.50, 133.65, 134.46, 134.46, 140.57, 166.88.

MALDI-MS (DCTB): *m*/*z* = 397 $[M]^+$, 398 $[M + H]^+$.

2e

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.76 (m, 2 H), 2.38 (m, 2 H), 2.68 (m, 2 H), 3.07 (m, 2 H), 3.70 (m, 1 H), 5.61 (br s, 1 H), 5.82 (br s, 1 H), 5.94 (m, 1 H), 7.00–7.30 (m, 5 H), 7.30–7.48 (m, 3 H), 7.60–7.75 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.50, 33.72, 44.47, 70.09, 126.55, 127.79, 128.89, 135.81, 141.55.

MALDI-MS (DCTB): *m*/*z* = 319 $[M + H]^+$, 341 $[M + Na]^+$.

2f

HPLC: Chiralpak IA, *n*-hexane: propan-2-ol (95:5), flow rate = 1 mL/min, λ = 254 nm, t_{syn1} = 31.8 min, t_{syn2} = 35.9 min, t_{anti} = 19.01 min (unseparated).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 8 Hz, 3 H), 1.35 (m, 1 H), 1.54 (m, 1 H), 2.38 (m, 2 H), 3.02 (m, 1 H), 3.12 (m, 1 H), 3.68 (d, *J* = 13 Hz, 1 H), 5.56 (d, *J* = 8 Hz, 1 H), 5.79 (m, 1 H), 5.94 (m, 1 H), 7.83 (d, *J* = 9 Hz, 2 H), 8.18 (d, *J* = 9 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.83, 21.81, 31.11, 44.20, 65.99, 70.19, 123.09, 128.47, 130.33, 135.70, 141.94, 148.82, 166.59.

MALDI-MS (DCTB): *m*/*z* = 288 $[M + H]^+$, 310 $[M + Na]^+$.

2g

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7 Hz, 3 H), 1.32 (m, 1 H), 1.54 (m, 1 H), 2.33 (m, 2 H), 3.04 (m, 1 H), 3.67 (d, *J* = 12 Hz, 1 H), 5.52 (br s, 1 H), 5.76 (br s, 1 H), 5.89 (m, 1 H), 7.42 (d, *J* = 8 Hz, 2 H), 7.60 (d, *J* = 8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.89, 21.86, 31.15, 44.11, 65.90, 125.01, 128.78, 131.02, 131.34, 134.52, 135.26, 135.29, 135.31, 167.33.

MALDI-MS (DCTB): *m*/*z* = 322 $[M + H]^+$.

2h

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.80–0.90 (m, 6 H), 1.28 (t, *J* = 7 Hz, 2 H), 1.59 (m, 1 H), 2.35 (m, 2 H), 3.11 (m, 2 H), 3.66 (d, *J* = 12 Hz, 1 H), 5.54 (d, *J* = 6 Hz, 1 H), 5.79 (m, 1 H), 5.93 (m, 1 H), 7.82 (d, *J* = 9 Hz, 2 H), 8.16 (d, *J* = 9 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.99, 23.45, 26.69, 31.49, 37.77, 44.84, 62.64, 70.07, 123.06, 128.48, 130.32, 135.71, 141.95, 148.81, 166.65.

MALDI-MS (w/o m): *m*/*z* = 316 $[M + H]^+$.

2i

syn-Diastereomer

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.1 Hz, 3 H), 2.1–2.24 (m, 1 H), 2.48–2.6 (m, 1 H), 3.42 (m, 1 H), 3.84 (m, 1 H), 4.21 (q, *J* = 7.1 Hz, 2 H), 4.53 (d, *J* = 13.2 Hz, 1 H), 5.67 (m, 3 H), 5.95 (m, 1 H), 7.84 (d, *J* = 8.9 Hz, 2 H), 8.20 (d, *J* = 9 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.12, 33.96, 43.98, 61.55, 65.28, 68.98, 122.77, 127.47, 129.89, 135.06, 140.81, 148.57, 167.09, 169.18.

FAB-MS: *m*/*z* = 332 $[M + H]^+$.

anti-Diastereomer

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18 (t, *J* = 7.1 Hz, 3 H), 2.41 (d, *J* = 18 Hz, 1 H), 2.82 (m, 1 H), 3.27 (m, 1 H), 3.58 (m, 1 H), 4.08 (q, *J* = 7 Hz, 2 H), 4.59 (d, *J* = 6.6 Hz, 1 H), 5.64 (d, *J* = 7.6 Hz, 1 H), 5.8 (s, 1 H), 5.96 (m, 1 H), 7.92 (d, *J* = 8.7 Hz, 2 H), 8.19 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.00, 38.35, 46.15, 60.31, 68.11, 68.57, 122.64, 128.07, 129.89, 134.19, 141.62, 148.36, 167.44, 170.75.

FAB-MS: *m*/*z* = 332 $[M + H]^+$.

2j

syn-Diastereomer

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7 Hz, 3 H), 2.13–2.19 (m, 1 H), 2.45–2.52 (m, 1 H), 3.34–3.41 (m, 1 H), 3.83 (dd, *J* = 12, 8 Hz, 1 H), 4.18 (q, *J* = 7 Hz, 2 H), 4.63 (d, *J* = 12 Hz, 1 H), 5.75 (m, 2 H), 5.90 (m, 1 H), 7.31–7.40 (m, 3 H), 7.68 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.64, 31.35, 34.49, 44.50, 61.80, 65.81, 128.02, 128.52, 129.43, 130.88, 135.25, 169.97.

MALDI-MS (DCTB): *m*/*z* = 286 $[M]^+$, 287 $[M + H]^+$.

anti-Diastereomer

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11 (t, *J* = 6 Hz, 3 H), 2.35 (d, *J* = 17 Hz, 1 H), 2.70 (dd, *J* = 8, 17 Hz, 1 H), 3.15–3.23 (m, 1 H), 3.52 (s, 1 H), 4.03 (q, *J* = 6 Hz, 2 H), 4.70 (br s, 1 H), 5.58 (br s, 1 H), 5.85–5.87 (m, 1 H), 7.23–7.34 (m, 3 H), 7.63–7.71 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.59, 37.66, 45.52, 60.88, 68.26, 127.09, 128.26, 129.72, 133.14, 135.00, 170.60.

MALDI-MS (DCTB): *m*/*z* = 286 $[M]^+$, 287 $[M + H]^+$.

Asymmetric [3+2] Cyloaddition of Cyclopentadiene to Hydrazones; Typical Procedure

To solution of BINOL-phosphate **3′** (15 mg, 0.0199 mmol, 15 mol%) in toluene (1 mL) was added $SiCl_2Ph_2$ (2.8 μL, 0.00136 mmol, 10 mol%) and the mixture was stirred for 1 h at r.t. The mixture was then cooled to –20 °C, and hydrazone **1f** (30 mg, 0.1356 mmol) and freshly distilled cyclopentadiene (200 μL) were added. After stirring for 3 d at –20 °C, the reaction mixture was quenched by the addition of sat. aq $NaHCO_3$ (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, 1:1) to afford product **2f**.

Acknowledgment

The authors gratefully acknowledge generous financial support from the Deutsche Forschungsgemeinschaft (Schwerpunktprogramm 1179 ‘Organokatalyse’) and the Bundesministerium für Bildung und Forschung (DLR, Project MDA 08/010).

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