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Polymer-Supported Highly Enantioselective Catalyst for Nitro-Michael Addition: Tuning through Variation of the Number of H-Bond Donors and Spacer Length

Lital Tuchman-Shukron[a] and Moshe Portnoy[a,*]

[a] School of Chemistry, Raymond and Beverly Sackler Faculty of Exact Sciences, Tel Aviv University, Tel Aviv, 69978, Israel
Fax: (+972)-3-640-9293; e-mail: portnoy@post.tau.ac.il

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Abstract: Two series of polymer-bound bifunctional organocatalysts, based on chiral diamine scaffolds, were prepared by solid-phase synthesis. The series, incorporating a single hydrogen bond donor carbamate functionality, was notably more enantioselective in the Michael reaction of acetone and nitrostyrene than the series that includes a double hydrogen bond donor urea moiety, or the polymer-bound diamine that lacks sufficiently acidic protons. The best aminocarbamate catalyst promoted the addition of acetone to nitroolefins with enantioselectivity unmatched by known heterogeneous catalysts. Introduction of a short linear spacer between the support and the scaffold improves the activity but reduces the selectivity of the catalyst. Alternatively, an increase in the reaction yield could be induced by the benzoic acid additive.

Keywords: asymmetric catalysis; dendrimers; Michael addition; organocatalysis; supported catalysis

The preparation of easily removable and recoverable catalysts remains a subject of high priority in synthetic organic chemistry due to the economic and environmental benefits of such systems.[1] Moreover, immobilization of organocatalysts can, at least partially, ease the problem of the low turnover numbers and, consequently, the requirement for high catalyst loading, usually associated with organocatalysts.[2] Particularly extensive efforts were devoted to the immobilization of chiral organocatalysts, due to the constantly growing impact of asymmetric catalysis on modern synthetic chemistry.[3] One of the modes of action of homogeneous, as well as heterogeneous, organocatalysts is bifunctional activation, particularly that based on H-bond formation. Many types of bifunctional organocatalysts which posses both acidic (H-bond donating) and basic (nucleophilic) moieties, were introduced during the past few years.[4] Several urea- and thiourea-based bifunctional organocatalysts have been established as efficient catalysts for promoting asymmetric transformations such as Strecker synthesis, nitro-Mannich reaction, Baylis–Hillman reaction and Michael addition.[5–8]

In the context of our interest in the development of supported catalytic systems, we turned our attention to the catalytic enantioselective Michael addition reaction of ketones to nitroolefins.[9,10] Among the numerous asymmetric carbon-carbon bond forming reactions, this addition constitutes an important and powerful tool for the introduction of chirality. Employing nitroolefins as Michael acceptors in a reaction with ketone nucleophiles represents a convenient access to γ-nitro ketones, which are masked synthons of several valuable building blocks in organic synthesis (e.g., γ-amino ketones).[9,11] It is essential to point out that the most common substrate, which has been used as Michael donor, is cyclohexanone. There are notably less studies that have explored acetone as Michael donor, and only in a few of them was high enantioselectivity (70% to 99% *ee*) achieved.[12] The overwhelming majority of the reports dealt with homogeneous organocatalytic systems, while the efforts toward the development of recyclable catalysts for this transformation were scarce and have only recently been published.[13,14] Surprisingly, there are only four examples demonstrating a heterogeneous organocatalysis of the reaction with acetone, with low to moderate *ee*s being reached in this reaction.[13,14b] Accordingly, the reaction between *trans*-β-nitrostyrene and acetone was selected as the model reaction for our research efforts.

In this paper, we report the preparation of polymer-supported recyclable bifunctional organocatalysts, based on chiral diamines, with a particular emphasis on simultaneous activation of the nucleophile and electrophile by two moieties in the catalyst: one that acts as a Lewis base (primary amine) and the other as an H-bond donor. For this purpose, we used commercial as well as dendronized hydroxy- or amine-terminated resins. These types of resins enable the immobilization of chiral diamines *via* carbamate or urea connectors that can act as single or double H-bond donors, respectively. Remarkably, we discovered that the number of H-bond donors in the proximity of the amine and the length of the tether to the support are crucial parameters, determining the activity and selectivity of the catalyst.

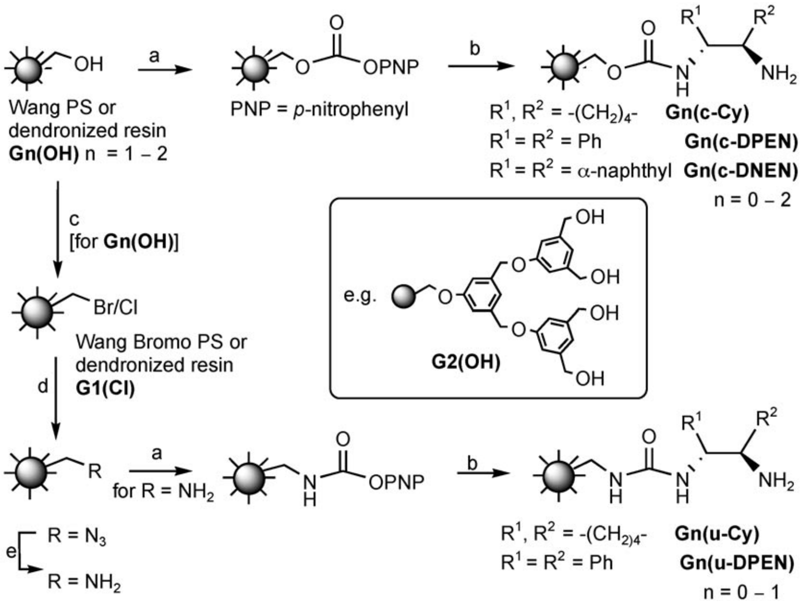
The catalytic systems, which included the carbamate moiety, were synthesized up to the second-generation dendrons. The polymer-bound benzylic alcohols were used to immobilize the catalytic units: Wang polystyrene resin for **G0**; **G1(OH)** and **G2(OH)** for first and second generation catalysts, respectively (Scheme 1).[15] The starting resins were treated with *p*-nitrophenyl chloroformate and DIPEA (Hünig's base) in order to form the mixed carbonate. This was followed by the reaction with the appropriate chiral diamine to yield the desired catalysts. In this way, new by design, polymer-supported bifunctional catalysts were prepared. These compounds possess a chiral core and can provide *one a mildly acidic proton* (single H-bond donor of the carbamate moiety) and a primary basic amine that can act as a Lewis base.

An additional series of bifunctional catalysts that were based on the urea connecting unit, which can act as a double hydrogen bond donor, was prepared as described in Scheme 1.[5a–c,6,7] The starting compounds for the synthesis of this series were Wang bromo polystyrene for **G0** and **G1(Cl)** for the first generation catalyst. These resins were converted to benzyl azide resins **Gn(N$_3$)**, $n=0,1$,[16] which underwent reduction with LiBH$_4$ to form **Gn(NH$_2$)** resins. The latter were treated with *p*-nitrophenyl chloroformate and DIPEA forming activated carbamates. This step was followed by the reaction of the carbamate intermediates with the appropriate chiral diamine to yield the set of the urea-incorporating catalysts (Scheme 1).

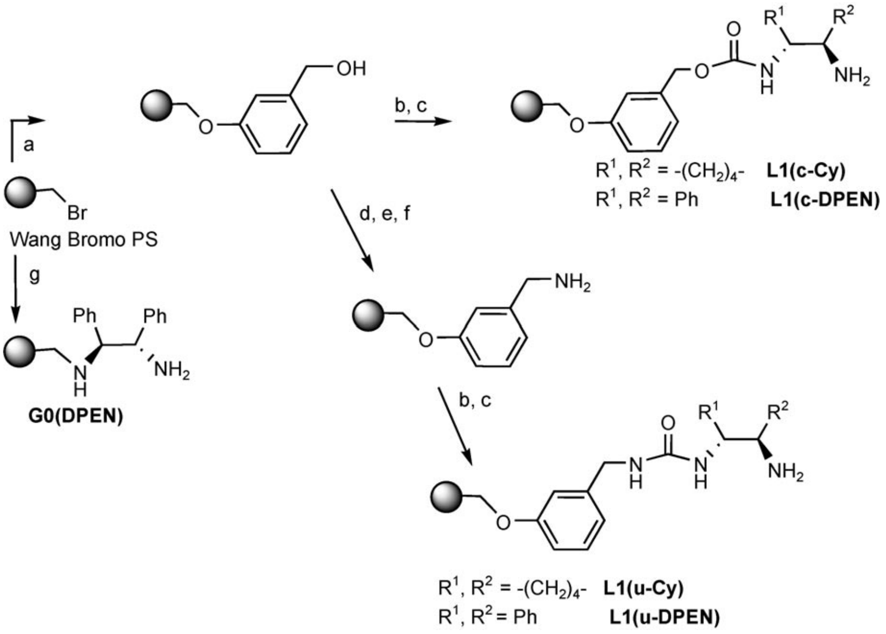
For comparison with catalysts including the single and double hydrogen bond donors, we prepared a derivative **G0(DPEN)** in which we eliminated the acidic protons entirely, *via* immobilization of the chiral diamine directly to the halide-terminated Wang bromo polystyrene (Scheme 2).

In order to further examine the influence of the spacer length and architecture on the catalytic performance, an additional broadening of the sets of catalysts under investigation was undertaken, when a linear spacer derived from 3-hydroxybenzyl alcohol was introduced into the amino-carbamate or amino-urea catalyst design (Scheme 2).

The catalytic efficiency of the prepared systems was evaluated in the reaction between *trans*-β-nitrostyrene and acetone. The results, summarized in Table 1, reveal that in both carbamate- and urea-including catalysts the diphenylethylenediamine (entries 5–8, 13–15) is favoured as a chiral scaffold over the cyclohexanediamine (entries 1–4, 10–12) for achieving higher enantioselectivity. An opposite influence of the diamine scaffold is observed on the activity of the cata-

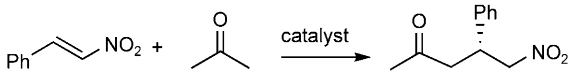


Scheme 1. *Reagents and conditions:* (a) *p*-nitrophenyl chloroformate, DIPEA, THF, room temperature, 2 h; (b) (1*R*,2*R*)-(−)-1,2-cyclohexanediamine/(1*R*,2*R*)-(+)-1,2-diphenylethylenediamine/(1*S*,2*S*)-(+)-1,2-dinaphthylethylenediamine, DMF, 50 °C, 24 h; (c) PPh$_3$, C$_2$Cl$_6$, THF, room temperature, overnight; (d) NaN$_3$, TBAI, DMF, 60 °C, overnight; (e) LiBH$_4$, B(OMe)$_3$, THF, 60 °C, overnight.



Scheme 2. *Reagents and conditions:* (a) 3-hydroxybenzyl alcohol, LiH, TBAI, DMF, 60 °C, overnight; (b) *p*-nitrophenyl chloroformate, DIPEA, THF, room temperatue, 2 h; (c) (1*R*,2*R*)-(−)-1,2-cyclohexanediamine/(1*R*,2*R*)-(+)-1,2-diphenylethylenediamine, DMF, 50 °C, 24 h; (d) PPh_3, C_2Cl_6, THF, room temperature, overnight; (e) NaN_3, TBAI, DMF, 60 °C, overnight; (f) $LiBH_4$, $B(OMe)_3$, THF, 60 °C, overnight; (g) (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine, DIPEA, TBAI, DMF, 60 °C, overnight.

Table 1. The asymmetric nitro-Michael addition of acetone to *trans*-*β*-nitrostyrene.[a]



Entry	Catalyst	Conversion [%][b]	Yield [%][b]	*ee* [%][c]
1	G0(c-Cy)	44	33	54
2	L1(c-Cy)	70	59	52
3	G1(c-Cy)	92	65	42
4	G2(c-Cy)	41	28	38
5	**G0(c-DPEN)**	**23**	**23**	**82**
6	L1(c-DPEN)	37	26	76
7	G1(c-DPEN)	72	56	67
8	G2(c-DPEN)	64	51	69
9	G0(c-DNEN)	10	10	82[d]
10	G0(u-Cy)	88	63	46
11	L1(u-Cy)	94	71	42
12	G1(u-Cy)	41	31	45
13	G0(u-DPEN)	58	58	63
14	L1(u-DPEN)	72	72	58
15	G1(u-DPEN)	35	35	61
16	G0(DPEN)	18	18	66

[a] *Reaction conditions:* 0.25 mmol of *trans*-β-nitrostyrene, 1.25 mmol of acetone and 30 mol% of immobilized catalytic units, 2 mL toluene, 4 d, room temperature.

[b] Determined by NMR.

[c] The *ee* was determined by HPLC, using a Chiralcel OJ column.

[d] The opposite enantiomer is predominantly formed.

lysts. Similar trends were reported by Tsogoyeva for homogeneous thiourea-including catalysts.[12b] Increasing the steric size of the aryl groups on ethylenediamine from phenyl to 1-naphthyl (entries 5 *vs.* 9) does not improve the enantioselectivity but lowers the yield.

Remarkably, a comparison of the **G0** catalysts reveals that the optimal number of H-bond donors for achieving the highest enantioselectivity is one, while the optimal number for highest activity is two. Increase in the number of acidic protons in the **G0** catalyst from zero to two [**G0(DPEN)** through **G0(c-DPEN)** to **G0(u-DPEN)**] results in more than threefold increase in the reaction yield (entries 16, 5 and 13, respectively). Likewise, comparison of **L1(c-DPEN)** to **L1(u-DPEN)** (one acidic proton *vs.* two, entry 6 *vs.* 14) reveals more than a two-fold increase in yield. On the other hand, the enantioselectivity is highest for the catalyst with one acidic proton (i.e., carbamate derivatives). With **G0(c-DPEN)** the highest 82% *ee* was reached, while for the **G0(DPEN)** or **G0(u-DPEN)** the enantiomeric excess was substantially lower (entry 5 *vs.* 16 and 13, respectively). A comparison of **L1(c-DPEN)** and **L1(u-DPEN)** also supports this conclusion (entry 6 *vs.* 14). A similar dependence is observed for the cyclohexanediamine derivatives (entries 1 *vs.*10 and 2 *vs.* 11).

Interestingly, the first-generation dendritic carbamate-including catalysts [**G1(c-Cy)** and **G1(c-DPEN)**] are higher-yielding but less enantioselective than their non-dendritic **G0** analogues. Noteworthy, these first generation catalysts have two acidic protons per dendron. Thus, the trends observed for the **G0** catalysts are also preserved for **G1** carbamate-type ones.

Proceeding to the higher generation catalysts that include four potential H-bond donors in a single dendron (second generation carbamate-including catalysts and first generation urea-including, entries 4, 8, 12, 15) leads to a moderate to strong decrease in the reaction yield and a slight additional deterioration in the enantioselectivity, as compared to their lower generation two H-bond donor analogues. Thus, also for the activity parameter there is an optimum number of the potential acidic protons on a single attachment site. Steric hindrance in the higher generation dendrons can also add some negative contribution.

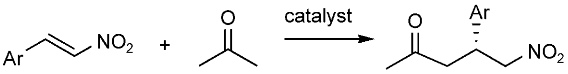
Noteworthy, the catalysts based on the linear spacer (**L1**, entries 2, 6, 11, 14) are slightly less selective than their spacer-less (**G0**) analogues, but usually exhibit much higher reactivity. Yet, since in the most enantioselective c-DPEN series only a slight increase in yield (from 23% to 26%, entry 6 *vs.* 5) could be achieved due to the introduction of the linear spacer, and worse, it is concurrent with a 6% loss in *ee*, it was decided to use the most enantioselective catalyst **G0-(c-DPEN)**, rather than **L1(c-DPEN)**, for further optimization of the reaction conditions.

For further optimization of the reaction conditions, a range of solvents and additives was screened and changes in the reaction temperature were examined (Table 2). The use of CH_3CN, $CHCl_3$ and $CHCl_3$:*i*-PrOH (1:1) as solvents led to a decrease in the reaction yield and selectivity with respect to toluene (Table 2, entries 4–6 *vs.* 1). The use of DMF led to an increase in the reaction yield, but also to a sharp decrease in the enantioselectivity compared to toluene (entry 2 *vs.* 1). Improvement in the *ee* to 88% was observed only in THF, albeit that it was accompanied by a notable decrease in reactivity (entry 3 *vs.* 1).

Gratifyingly, screening several additives allowed the improvement of the yield of the reaction. The use of $PhCO_2H$ (0.1 equiv.) as an additive led to a dramatic increase in reactivity in toluene, yielding 60% of the product without detrimental effects on the enantioselectivity (Table 2, entry 7 *vs.* 1).[12a,17] Increase in the additive amount (entry 8) did not lead to any further improvement. Acetic acid was less successful in boosting the yield (entry 13). Whereas in THF an even more dramatic increase in reactivity upon addition of benzoic acid was observed (66% yield), it was accompanied, unfortunately, by a decrease in enantioselectivity to 70% *ee* (Table 2, entry 14 *vs.* 2).

Noteworthy, changing the reaction temperature (4°C or 50°C, entries 9 and 10, respectively) only affected the yield, but not the enantioselectivity of the reaction. Two additional Michael acceptors, *p*-methoxynitrostyrene and 2-(2-nitrovinyl)furan, reacted with acetone under these condition with lower yields, but even greater enantioselectivity (up to 92% *ee*, entries 11 and 12).

Table 2. The influence of solvents, additives, temperature and substituents on the nitro-Michael addition reaction with **G0(c-DPEN)**.[a]



Entry	Ar	Additive (equiv.)	Solvent	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	Ph	–	Toluene	r.t.	23	82
2	Ph	–	DMF	r.t.	38	14
3	Ph	–	THF	r.t.	10	88
4	Ph	–	CH_3CN	r.t.	10	64
5	Ph	–	$CHCl_3$	r.t.	10	66
6	Ph	–	$CHCl_3$:*i*-PrOH (1:1)	r.t.	10	63
7	Ph	$PhCO_2H$ (0.1)	Toluene	r.t.	60	83
8	Ph	$PhCO_2H$ (0.2)	Toluene	r.t.	60	82
9	Ph	$PhCO_2H$ (0.1)	Toluene	4	33	83
10	Ph	$PhCO_2H$ (0.1)	Toluene	50	65	82
11	*p*-$MeOC_6H_4$	$PhCO_2H$ (0.1)	Toluene	r.t.	28	86
12	2-Furanyl	$PhCO_2H$ (0.1)	Toluene	r.t.	30	92[d]
13	Ph	AcOH (0.3)	Toluene	r.t.	43	81
14	Ph	$PhCO_2H$ (0.1)	THF	r.t.	66	70
15	Ph	$PhCO_2H$ (0.1)	THF	4	19	70

[a] *Reaction conditions:* 0.25 mmol of nitroolefins, 1.25 mmol of acetone and 30 mol% of catalyst, 2 mL of solvent, 4 d, room temperature.

[b] Determined by NMR.

[c] The *ee* was determined by HPLC, using a Chiralcel OJ column.

[d] The *ee* was determined by HPLC, using a Chiralpak AD column.

It is currently not clear how carboxylic acids speed up the reaction. While there is a similarity to the activation exerted by the H-bond donors of the catalyst, the magnitude of the effect and the unchanged enantioselectivity in toluene may point to a different mode of action. Noteworthy, there are many orders of magnitude difference in the acidity of the carbamate and carboxyl protons.

The recycling experiments (Table 3) demonstrated that the enantioselectivity is unaffected for three reaction cycles (with or without the acid additive), while there is only a slight decrease in the yield, most probably because of the inevitable loss of the catalytic beads during filtration, wash and resuspension.

Table 3. The recycling of catalyst **G0(c-DPEN)** in the asymmetric nitro-Michael addition of acetone to *trans*-β-nitrostyrene.[a]

Cycle	Conversion/Yield [%][b]	*ee* [%][c]
1	23	82
2	23	81
3	17	82
1[d]	60	82
2[d]	58	84
3[d]	56	84

[a] *Reaction conditions:* 0.25 mmol of *trans*-β-nitrostyrene, 1.25 mmol of acetone and 30 mol% of catalyst, 2 mL toluene, 4 d, room temperature.

[b] Determined by NMR.

[c] The *ee* was determined by HPLC, using Chiralcel OJ column.

[d] In the presence of 0.2 equiv. of $PhCO_2H$.

In conclusion, we have prepared a range of new polystyrene-supported bifunctional organocatalysts for the asymmetric nitro-Michael addition of acetone to nitroolefins. The best of these catalysts induces high enantioselectivity that approaches the best results obtained in solution and is significantly better than that of the previously reported polymer-bound catalysts.[12,13] We have demonstrated an important strong dependence of the reactivity and enantioselectivity of such catalysts on the number of H-bond donors in the catalyst and a milder connection between these catalytic parameters and the length of the tether between the polymer and the catalytic module. Moreover, we have demonstrated that the addition of an external carboxylic acid leads to a dramatic increase in reactivity without affecting enantioselectivity, and that the properties of the catalyst are preserved upon recycling. Additional optimization of these catalytic systems for the nitro-Michael reaction and extending their application to other asymmetric C–C bond forming processes, utilizing the principles elucidated in this study, are underway.

Experimental Section

General Procedure for the Preparation of Carbamate-Including Catalysts

p-Nitrophenyl chloroformate (10 equiv. per hydroxybenzyl unit), DIPEA (20 equiv. per hydroxybenzyl unit) and a catalytic amount of pyridine (0.1 equiv.) were added to a suspension of hydroxybenzyl-terminated resin (1 equiv.) in THF (10 mL per 1 g resin). The suspension was stirred at room temperature for 2 h. The resin was washed with water, THF/water, THF, DCM and then dried under vacuum. The resin was stirred in DMF (10 mL per 1 g resin) and the appropriate chiral diamine (7 equiv. per carbonate unit) was added. The suspension was heated to 50 °C overnight. The resin was washed with DMF/water, DMF, THF/water, THF, DCM and then dried under vacuum.

G0(c-DPEN): Starting materials – Wang polystyrene (0.93 mmol g^{-1}) and (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine. Yield: 100%, loading 0.75 mmol g^{-1}. Following TFA-induced cleavage: ^{1}H NMR (400 MHz, $CDCl_3$/TFA, 1:1): $\delta = 8.50$ (br s, 6H); 7.37–7.39 (m, 2H); 7.28–7.34 (m, 4H); 7.19–7.20 (m, 4H); 5.25 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$/TFA, 1:1): $\delta = 131.6$, 131.4, 130.3, 127.9, 59.3.

General Procedure for the Azide Reduction

$LiBH_4$ (10 equiv. per azide unit, 2 M solution in THF) and $B(OMe)_3$ (0.5 equiv. per azide unit) were added to a suspension of azide-terminated resin (1 equiv.) in THF (10 mL per 1 g resin). The mixture was refluxed overnight. The resin was washed with water, an aqueous solution of ammonium chloride/THF, ethanolamine/THF, THF, DCM and then dried under vacuum.

G1(NH$_2$): Starting material – G1(N_3) (0.69 mmol g)$^{-1}$.[16] Yield: 59%, loading 0.42 mmol g^{-1}. Following TFA-induced cleavage: ^{1}H NMR (200 MHz, $CDCl_3$/TFA, 1:1): $\delta = 7.15$–7.19 (br s, 6H); 7.12 (s, 2H); 7.08 (s, 1H); 4.28–4.31 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$/TFA 1:1): $\delta = 156.7$, 134.6, 123.3, 118.7, 41.8.

General Procedure for the Preparation of Urea-Including Catalysts

p-Nitrophenyl chloroformate (10 equiv. per aminobenzyl unit), DIPEA (20 equiv. per aminobenzyl unit) and a catalytic amount of pyridine (0.1 equiv.) were added to a suspension of aminobenzyl-terminated resin (1 equiv.) in THF (10 mL per 1 g resin). The suspension was stirred at room temperature for 2 h. The resin was washed with water, THF/water, THF, DCM and then dried under vacuum. The resin was stirred in DMF (10 mL per 1 g resin) and the appropriate chiral diamine (7 equiv. per carbamate unit) was added. The suspension was heated to 50 °C overnight. The resin was washed with DMF/water, DMF, THF/water, THF, DCM and then dried under vacuum.

G1(u-DPEN): Starting materials – **G1(NH$_2$)** (0.42 mmol g^{-1}) and (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine. Yield: 72%, loading 0.38 mmol g^{-1} .Following TFA-induced cleavage: ^{1}H NMR (400 MHz, $CDCl_3$/TFA 1:1): $\delta =$ 8.27 (s, 4H); 7.54 (br s, 6H); 7.12–7.33 (m, 20H); 6.78–7.12 (m, 3H); 5.36 (m, 2H), 4.74 (m, 2H); 4.30–4.33 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$/TFA 1:1): $\delta = 161.9$, 156.5, 136.5, 133.2, 132.0, 131.0, 130.9, 130.8, 130.4, 129.8, 128.5, 120.6, 115.0, 69.2, 63.2, 60.4.

General Procedure for the Catalytic Asymmetric Nitro-Michael Addition

To a mixture of catalyst (0.075 mmol of the catalytic unit) and nitroolefin (0.25 mmol) in toluene (2 mL), were added acetone (1.25 mmol) and, in some experiments, benzoic acid (0.025 mmol). The suspension was stirred at room temperature for 4 days. After the reaction, the mixture was filtered and the catalyst was washed with AcOEt (3×10 mL), and dried for reuse. The organic layer was evaporated and the residue was purified by flash column chromatography on silica gel (hexane/AcOEt, 80:20) to afford the Michael adduct. The enantiomeric excess of the product was determined by chiral HPLC analysis using Chiralcel-OJ or Chiralpak-AD columns.

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