Organocatalytic enantioselective Michael addition of β-diketones to β-nitrostyrene: The first Michael addition of dipivaloylmethane to an activated olefin

Declan P. Gavin and John C. Stephens*

Department of Chemistry, National Univeristy of Ireland Maynooth, Co. Kildare, Ireland
E-mail: john.stephens@nuim.ie

Abstract
The addition of a family of β-diketones to β-nitrostyrene was explored using a library of cinchona organocatalysts. A thiourea organocatalyst, under improved reaction conditions, is shown to be much more efficient at catalyzing this reaction than previously reported giving excellent yields and enantioselectivites (up to 95% yield and 97% *ee*). The same thiourea organocatalyst was employed in the first successful Michael addition of the sterically challenging dipivaloylmethane to β-nitrostyrene (99% *ee*).

Keywords: Organocatalysis, nitrostyrene, β-diketones, Michael addition, bifunctional thiourea catalysts, cinchona alkaloids

Introduction

The synthesis of enantiopure molecules in a simple and environmentally friendly manner is a major challenge for synthetic chemistry and the chemical industry. Organocatalysis has emerged as an exciting method of choice for the generation of such efficient asymmetric reactions. In this field, the asymmetric Michael addition of carbon-centred nucleophiles to electron deficient nitroolefins is an important and powerful tool.[1,2] The resulting optically active nitroalkanes are versatile synthetic building blocks by virtue of the reactive nitro functional group, which can be easily transformed into a variety of groups.[1,2] In recent times impressive progress has been made using metal free organocatalysts in the asymmetric addition of aldehydes, ketones, ketoesters and malonate esters to nitroolefins.[1-5] There have been fewer reports of successful additions of β-diketones to nitroolefins. To the best of our knowledge, Brunner *et al.* described the first enantioselective addition of a β-diketone to a nitroolefin in 1996 (*ee* < 30%)[6] with the first report of a highly enantioselective addition only appearing in 2005.[7] Subsequent publications by Wang[8] and others,[9,10] have also described the selective addition of a β-diketone to β–nitrostyrene using bifunctional organocatalysts.

Bifunctional organocatalysts consisting of urea/thiourea hydrogen-bond donors and a basic amine function has emerged as a viable organocatalyst design for many asymmetric transformations.[11] In 2003 Takemoto and co-workers[12] reported the first bifunctional amine-thiourea organocatalyst **1** and applied it in a highly enantioselective Michael addition of dimethyl malonate to nitroolefins. Takemoto's catalyst represented a logical extension of earlier work on thiourea H-bonding catalysts by Curran, Jacobsen and Schreiner.[13] Since then significant advances have been made in catalyst design with Chen, Soós, Connon and Dixon independently reporting the design and application of new cinchona urea/thiourea catalysts in 2005.[5,11,14]

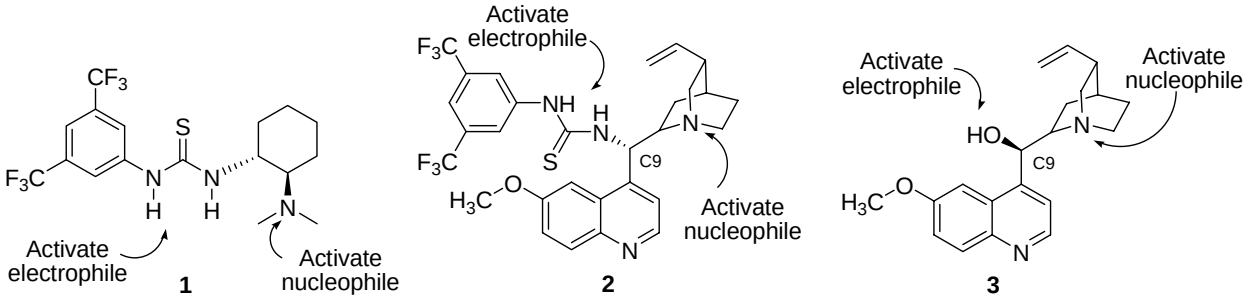


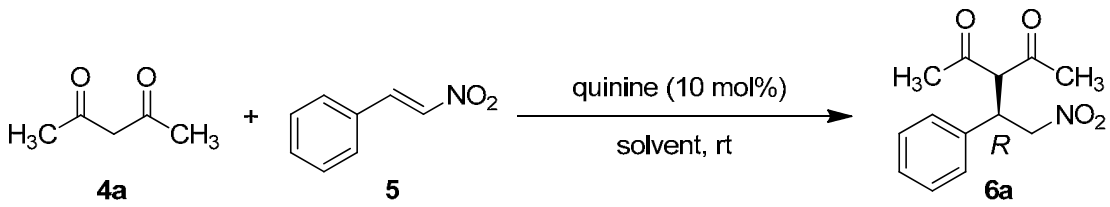
Figure 1. Examples of bifunctional organocatalysts.

In this present study we have screened nine cinchona catalysts in the addition of β-diketones to β-nitrostyrene. Our study indicates that (a) under improved reaction conditions the cinchona thiourea catalyst **2** is much more effective (95% yield after only 1 hour) at catalyzing this reaction than previously reported (47% yield after 48 hours),[8](b) the first Michael addition of the sterically challenging dipivaloylmethane to an activated olefin, β-nitrostyrene (99% *ee*), was achieved using catalyst **2** and (c) both a H-bonding motif and steric bulk is required at C9 to generate a high yielding and enantioselective reaction.

Results and Discussion

We anticipated that solvent choice would have a large effect on the catalytic activity of a bifunctional catalyst[4a] and began our study by performing a solvent screen for the organocatalyzed Michael addition of 2,4-pentanedione to β-nitrostyrene. Quinine **3** was chosen as the model catalyst for the solvent screen as it is a bifunctional catalyst, inexpensive and commercially available (Figure 1). The results for the solvent screen are shown in Table 1. The stereochemistry of the major product was confirmed as (*R*) by comparing the specific rotation of **6a** with literature values.[9]

Table 1. Solvent screen



Entry	Solvent	Aprotic protic	Time (h)	Yield (%)[a]	*ee* (%)[b]	E_T30[15]	α[15]	β[15]
1	Toluene	Aprotic	24	89	16	33.9	0	0.11
2	MeCN	Aprotic	24	96	2	45.6	0.19	0.40
3	Dioxane	Aprotic	24	72	14	36	0	0.37
4	EtOAc	Aprotic	24	35	9	38.1	0	0.45
5	Acetone	Aprotic	24	82[c]	3	42.2	0.08	0.43
6	THF	Aprotic	24	12	12	37.4	0	0.55
7	DMF	Aprotic	24	49	2	43.8	0	0.69
8	Ethylene glycol	Protic	24	90	0	56.3[d]	0.9[e]	0.52[e]
9	MeOH	Protic	24	80[c]	2	55.4	0.98	0.66
10	1,4-Butanediol	Protic	24	78	4	53.5[d]	0.63[f]	0.68[f]
11	1-Butanol	Protic	24	89	8	48.6	0.79	0.84

Reaction conditions:75 mg (0.5 mmol) of trans-β-nitrostyrene, 0.1 ml (1 mmol) of 2,4-pentanedione, 10 mol% quinine, 2 ml of solvent, rt. [a]Isolated yields. [b]Enantiomeric excess (*ee*) determined by chiral HPLC analysis (Chiralpak IA). [c]Determined by 1H NMR. [d]See ref. 16. [e]See ref. 17. [f]See ref 18.

Results were examined for any correlation between yield or enantioselectivity with polarity (E_T30), H-bond donor ability (α values) and H-bond acceptor ability (β values). A good correlation was observed when enantioselectivity was plotted as a function of solvent polarity, E_T30, (Table 1, Figure 2). The enantioselectivity directly depends on the solvent polarity with the less polar solvents giving superior enantioselectivity. A similar trend was observed in both aprotic solvents (Figure 2) and protic solvents (Figure 2, insert). No direct correlation was observed between enantioselectivity and H-bond donor, α, or H-bond acceptor, β, ability (Table 1), although the protic solvents did give poorer enantioselectivity when compared to the aprotic solvents. This was as expected as the achiral protic solvents and chiral catalyst were anticipated to competitively activate the reaction.[4a,12] No direct correlation was observed in terms of reaction yield. Acetonitrile generated the highest yielding reaction, albeit with poor selectivity, with

toluene emerging as the highest yielding of the selective non-polar solvents. All of the protic solvents gave high yields due to their ability to activate the Michael acceptor.

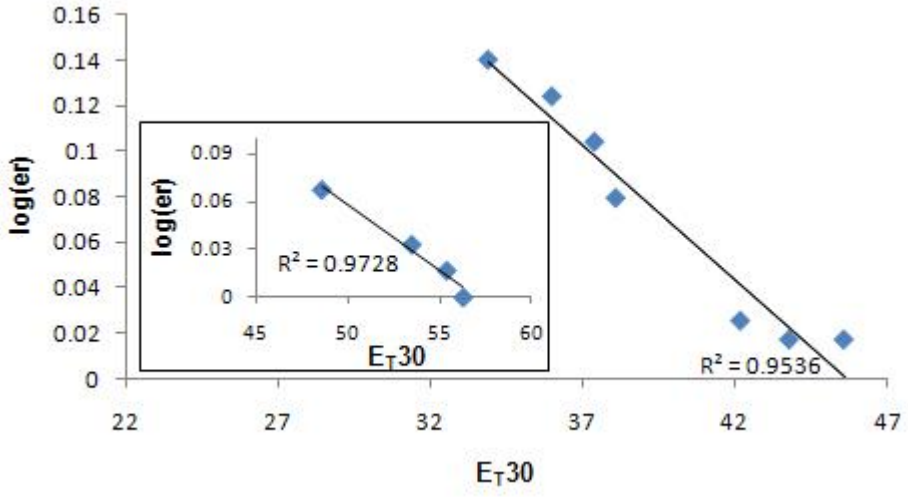


Figure 2. Plot of enantiomeric ratio (er) against polarity (E_T30) for aprotic solvents. Insert: Plot for protic solvents.

Although acetonitrile generated a high yielding reaction it was not chosen for the subsequent catalyst screen due to its propensity to disrupt the hydrogen bonding action of bifunctional catalysts and hence lower the enantioselectivity (2% *ee* with quinine). The less polar solvent, toluene, gave a similar yield and an improved *ee* and was clearly more effective at promoting a selective reaction than the polar solvents. As such toluene was selected as the solvent of choice for the subsequent catalyst screen. The role and choice of catalyst was explored in a catalyst screen involving nine cinchona type organocatalysts **2, 3, 7-13** (Figure 3). The Michael addition of 2,4-pentanedione to β-nitrostyrene was employed as the model reaction, with toluene as the solvent of choice, (Table 2).

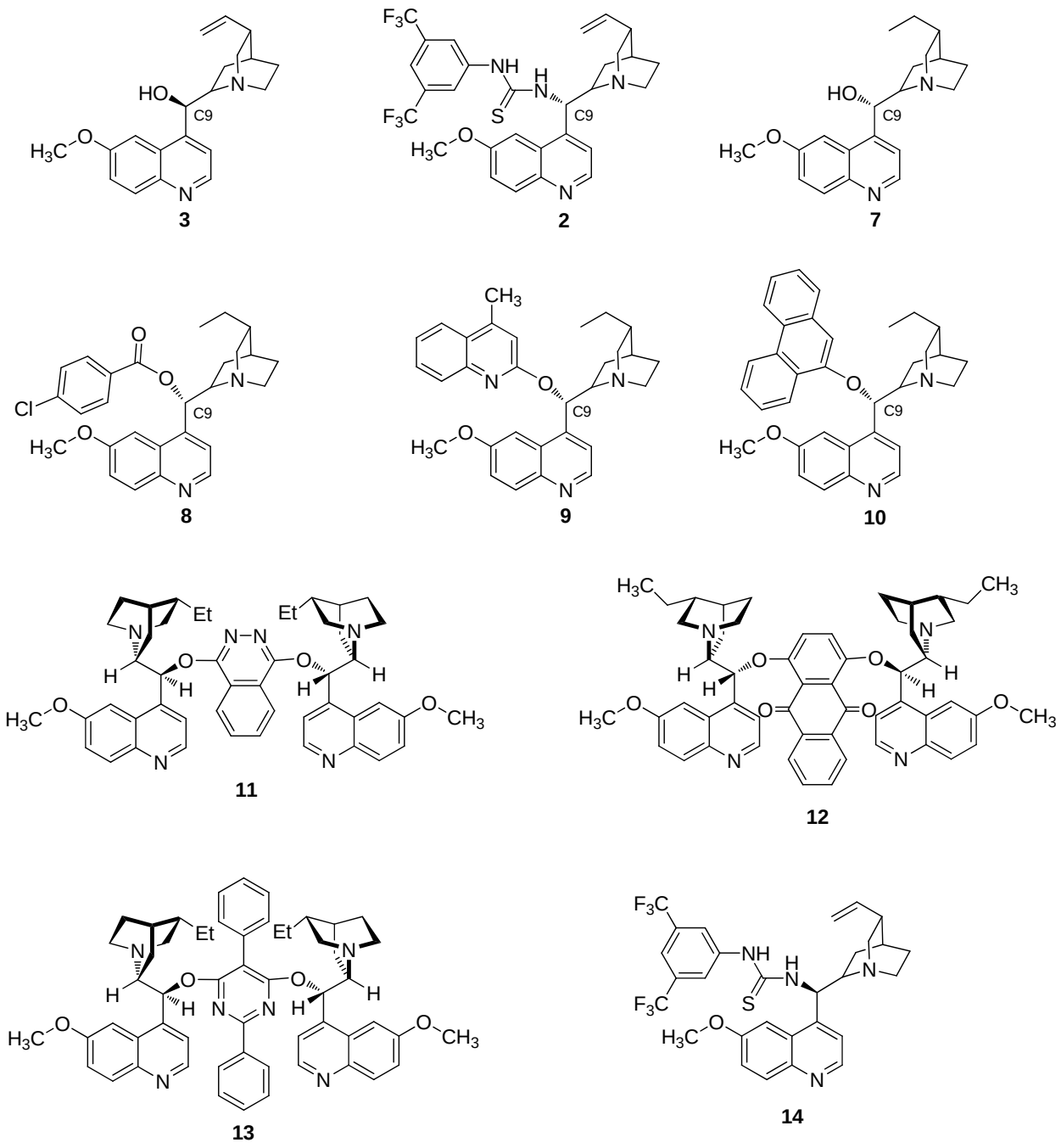
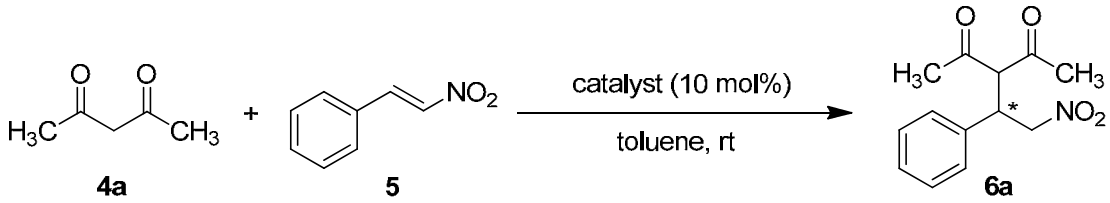


Figure 3. Screened organocatalysts.

There have been several reports of asymmetric C-C bond forming reactions employing the dimeric catalysts $(DHQD)_2PHAL$ **11**, $(DHQ)_2AQN$ **12** and $(DHQD)_2PYR$ **13**.[11a] In our hands the dimeric catalysts proved ineffective giving either a poor yield or poor *ee* in each case. The reactions with $(DHQ)_2AQN$ **12** and $(DHQD)_2PYR$ **13**, entries 9 and 10, were sluggish and gave only 6% and 7% of the Michael adduct respectively after 144 hours. On the other hand,

$(DHQD)_2PHAL$ **11** proved more reactive giving a 77% yield after 144 hours but with no enantiocontrol. The monomeric C9-OR modified catalysts **8**, **9** and **10** showed a slight improvement with yields of 32-52% and *ee* of 11-35% in 144 hours, entries 5, 6 and 7. The catalytic activity increased greatly with the monodentate hydrogen bond donor catalysts quinine **3** and DHQD **7**, 89% and 87% yield respectively in just 24 hours. This is likely due to their ability to activate the nitroolefin through the C9-OH hydrogen bonding functionality.[4] This increase in catalytic activity was not mirrored by a corresponding increase in enantiocontrol and instead the enantioselectivity dropped to only 16% *ee* for quinine and 7% *ee* for DHQD. This reduction in selectivity may be due to the reduced steric bulk at C9 in quinine and DHQD when compared with the more selective C9-OR catalysts **8**, **9** and **10**.

Table 2. Catalyst screen



Entry	Catalyst	Time (h)	Yield (%)[a]	*ee* (%)[b]
1	Triethylamine	36	68	racemic
2	**2**	1	95	97 (+)
3	Quinine **3**	24	89	16 (-)
4	DHQD **7**	24	87	7 (-)
5	**8**	144	42	21 (+)
6	**9**	144	32	11 (+)
7	**10**	144	52	35 (+)
8	$(DHQD)_2PHAL$ **11**	144	77	Racemic
9	$(DHQ)_2AQN$ **12**	144	6	55 (-)
10	$(DHQD)_2PYR$ **13**	144	7	5 (-)

Reaction conditions: 60 mg (0.4 mmol) of trans-β-nitrostyrene, 0.8 ml (0.8 mmol) of 2,4-pentanedione, 10 mol% catalyst, 2 ml of toluene, rt. [a]Isolated yields. [b]Enantiomeric excess (*ee*) determined by chiral HPLC analysis (Chiralpak IA). [c]As reported by W. Wang and coworkers using 10 mol% catalyst in THF.[8]

The thiourea catalyst **2** showed an even larger and more dramatic enhancement in catalytic activity generating the Michael adduct in 95% yield and 97% *ee* (*S* = major product) after only 1 hour. Catalyst **2** has both a thiourea and a tertiary amino functionality on a chiral cinchona scaffold and introduces both a bidentate hydrogen bonding functionality and steric bulk at C9.

The bifunctional nature of catalyst **2** allows it to activate both β-nitrostyrene and 2,4-pentanedione simultaneously, Figure 3.[7] The excellent result in toluene is a marked improvement from that reported by Wang[8] in THF (95% yield, 97% *ee* in 1 hour versus 47% yield, 96% *ee* in 48 hours) and emphasizes the importance of solvent choice in bifunctional organocatalysis. The catalytic activity of the thiourea catalyst **2** is greatly enhanced in the less polar solvent toluene, generating a significantly higher yielding and faster reaction. This effect is most likely due to increased hydrogen bonding activation of β-nitrostyrene by **2** in the less polar solvent.

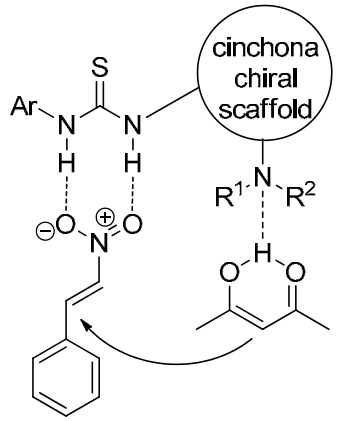


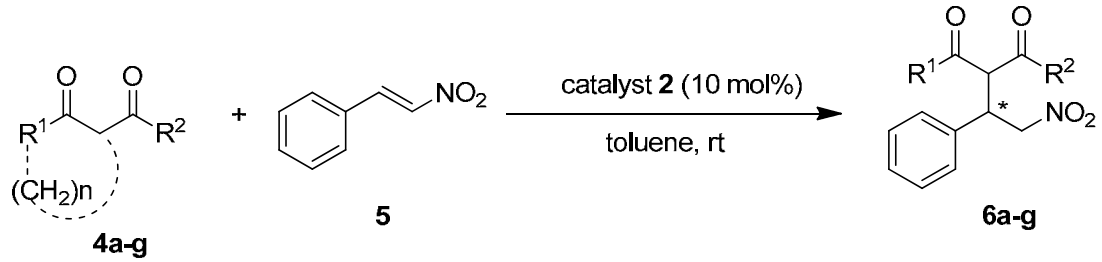
Figure 4. Simultaneous activation of both the nitroolefin and nucleophile.

The size of the R group on the β-diketones **4a-g** had a significant effect on the yield of the reaction. The yield was similar for β-diketones with similarly sized R groups, e.g. R = Et or Ph, entries 3 and 7, (Table 3). In contrast, the more sterically bulky R groups, *i*Pr and *t*Bu, resulted in a substantial reduction in reactivity, entries 4 and 5, (Table 3). A plot comparing yield and Charton steric value clearly demonstrates the effect the R group has on reaction yield (Figure 5). The size of the R group had no real effect on the enantiomeric ratios with all reactions giving high enantioselectivities (92-99% *ee*), with the exception of **6f** (70% *ee*).

The *t*Bu substituted β-diketone, dipivaloylmethane, was expected to be too sterically hindered to undergo a Michael addition. To our delight catalyst **2** successfully generated a Michael addition of dipivaloylmethane to β-nitrostyrene, (99% *ee*), entry 5, (Table 3). To the best of our knowledge, the chiral or achiral Michael addition of dipivaloylmethane to an activated olefin has never been reported. Attempts to generate a racemic addition of dipivaloylmethane to β-nitrostyrene proved unsuccessful and indicate how challenging this transformation is. KO*t*Bu, DABCO and NEt_3 were employed as base but all returned unreacted β-nitrostyrene. NaOMe resulted in polymerization of the β-nitrostyrene with no sign of the desired Michael adduct. The fact that the addition only occurred when the cinchona thiourea catalysts were used demonstrates the exceptional activating ability of the thiourea motif and that a highly activating bifunctional catalyst is essential for this challenging Michael addition. The

quinidine bifunctional catalyst **14** was used to obtained the opposite enantiomer of the dipivaloylmethane product **6d** and hence allow accurate determination of the enantioselectivity.

Table 3. Substrate screen



Entry		R^1	R^2	Time (h)	Yield (%)[a]	*ee* (%)[b]	Charton value (v)[19]
1	**4a**	Me, n=0	Me	1	95	97 (+)	0.52
2	**4a**	Me, n=0	Me	1[c]	92[c]	92[c] (-)	0.52
3	**4b**	Et, n=0	Et	1	92	96 (+)	0.56
4	**4c**	*i*Pr, n=0	*i*Pr	6	84	93 (+)	0.76
5	**4d**	*t*Bu, n=0	*t*Bu	96	30	99 (+)	1.24
6	**4d**	*t*Bu, n=0	*t*Bu	96[c]	45[c]	92[c] (-)	1.24
7	**4e**	Ph, n=0	Ph	4	93	94 (+)	0.57
9	**4f**	CH_2, n=2	Me	12	89	70[d,e]	-
10	**4g**	CH_2, n=3	Me	-	0	-	-

Reaction conditions: 37.5 mg (0.25 mmol) of trans-β-nitrostyrene, (0.5 mmol) of β-diketone, catalyst **2** (10 mol%), 1 ml toluene, rt. [a]Isolated yields. [b]Enantiomeric excess (*ee*) determined by chiral HPLC analysis (Chiralpak IA) [c]Reaction performed with catalyst **14 (**10 mol%). [d]*ee* determined by chiral HPLC analysis (Chiralpak IB). [e]Diastereomeric ratio = 1:1.2 (determined by ^{1}H NMR), *ee* of major isomer = 70%.

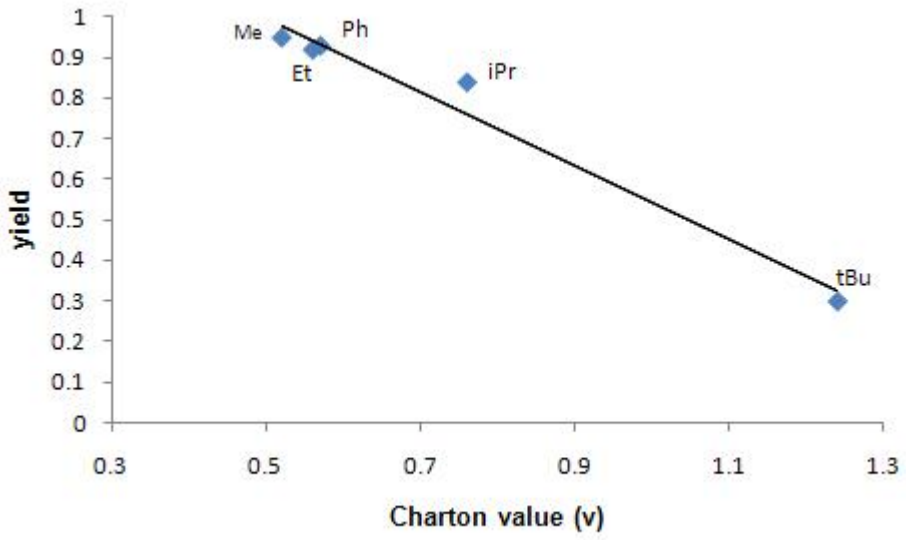


Figure 5. Charton plot of yield against Charton value.

The cyclohexyl derivative **4g** proved to be completely unreactive in our hands, entry 6, Table 3. Toma and coworkers reported the same result for **4g** in their ionic liquid-proline catalyzed addition to β-nitrostyrene. They suggested that the reduced reactivity was due to the geometry of **4f** allowing the formation of a hydrogen bond-stabilized enol.[20] Decreasing the ring size to the cyclopentyl derivative **4f** resulted in a change in geometry and a high yielding Michael addition, entry 9, (Table 3).

Conclusion

In conclusion, we have demonstrated that solvent polarity has a significant effect on enantioselectivity in the quinine catalyzed Michael addition of acetylacetone to β-nitrostyrene, with less polar solvents giving a superior enantiomeric ratio. Furthermore, it was necessary to have both a good H-bonding motif and steric bulk at C9 of the cinchona catalyst to generate both a high yielding and enantioselective reaction. The thiourea bifunctional organocatalyst **2** was the most powerful catalyst tested and was shown to be much more effective at catalyzing the Michael addition of β-diketones to β-nitrostyrene than previously reported with a dramatic improvement in yield and reaction time (47% → 95%, 48 h → 1 h). The thiourea bifunctional organocatalyst **2** is such an effective catalyst for this transformation that it was able to promote the challenging Michael addition of dipivaloylmethane to β-nitrostyrene (99% *ee*), which is reported herein for the first time.

Supporting Information

NMR spectra and HPLC chromatograms are available free of charge via the Internet at http://www.arkat-usa.org.

Experimental Section

General. Reagents were used as purchased from suppliers, unless otherwise indicated. Solvents were distilled and dried before use. Toluene and anhydrous DMF were used as purchased. Reactions requiring inert conditions were performed in dried glassware under a positive pressure of argon. Compounds **4a-g**, **5** and catalysts **3**,**7-13** were purchased and used without further purification. Reactions were monitored by thin layer chromatography using SiO_2 (silica gel 60 F254, Merck, coated aluminum plates), and visualizing by UV light or by aqueous $KMnO_4$ or solutions. Flash chromatography was carried out on SiO_2 (silica gel 60 F254, 230-400 mesh ASTM, Merck). ^1H and ^{13}C NMR spectra were recorded with a Bruker Avance 300 NMR spectrometer. Chemical shifts are reported in ppm relative to TMS internal standard ($\delta = 0.00$) in $CDCl_3$ for ^1H NMR spectra. For ^{13}C NMR spectra, solvent residual peaks ($\delta = 77.0$ ppm for $CDCl_3$ were used as internal reference. Abbreviation of multiplicities is as follows: s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet), app s (apparent singlet), br s (broad singlet). High-resolution mass spectrometric data was recorded with an Agilent Technologies 6410 Time of Flight LC/MS at NUI Maynooth. IR spectra were recorded with Perkin Elmer System 2000 FT-IR instrument. Optical rotations were obtained with a Perkin-Elmer 343 polarimeter ($\lambda = 589$ nm) using a 0.5 dm cell. Chiral HPLC analysis was performed with a Perkin Elmer Series 200 HPLC. The exact conditions are reported in connection with each analyzed substance. HPLC analyses were performed before crystallization steps to exclude possible additional enantioenrichment. Melting points were recorded with Stuart SMP11 melting point apparatus in open capillary tubes.

General procedure for conjugate addition reactions

To a stirred solution of trans-β-nitrostyrene (37.5 mg, 0.25 mmol) and 1,3-dicarbonyl compound (2 equiv., 0.5 mmol) in solvent (1 mL) was added the chiral organocatalyst (10 mol%). Upon consumption of the nitrostyrene (monitored by TLC), the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography to afford the conjugate addition product. The corresponding racemic products were synthesized using KOtBu (5 mol%) in toluene.

3-(2-Nitro-1-phenylethyl)pentane-2,4-dione (6a). Reaction solvent = toluene. Flash column chromatography (3:2 Et_2O:hexane) afforded **6a** (59 mg, 95%) as a white solid, mp 110-112 ºC. ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.95 (s, 3H), 2.30 (s, 3H), 4.2-4.28 (m, 1H), 4.38 (d, $^3J_{HH} = 10.5$ Hz, 1H), 4.60-4.68 (m, 2H), 7.17-7.20 (m, 2H). 7.27-7.35 (m, 3H). ^{13}C NMR (300 MHz, $CDCl_3$)

δ_C 29.7, 30.5, 42.8, 70.6, 128.0, 128.3, 128.5, 129.3, 136.0, 201.0, 201.8. HPLC (IA, 15% isopropyl alcohol in hexane, 1 mL/min, 238 nm): t (major) = 8.43 min, t (minor) = 10.45 min, catalyst **2** 98% *ee*. Catalyst **14**-92% *ee*.

4-(2-Nitro-1-phenylethyl)heptane-3,5-dione (6b). Reaction solvent = toluene. Flash column chromatography (3:2 Et_2O:hexane) afforded **6b** (60 mg, 92%) as a white solid, mp 95-97 ^oC. ^1H NMR (300 MHz, $CDCl_3$): δ_H 0.77 (t, $^3J_{HH}$ = 7.2 Hz, 3H), 1.06 (t, $^3J_{HH}$ = 7.2 Hz, 3H), 2.03-2.21 (m, 1H), 2.23-2.40 (m, 1H), 2.42-2.64 (m, 2H), 4.23-4.38 (m, 2H), 4.62-4.69 (m, 2H), 7.12-7.22 (m, 2H), 7.24-7.42 (m, 3H). ^{13}C NMR ($CDCl_3$): δ_C 7.31, 7.5, 36.4, 36.8, 43.0, 69.2, 78.0, 127.9, 128.4, 129.2, 136.3, 203.3, 204.5. HPLC (IA, 15% isopropyl alcohol in hexane, 1 mL/min, 238 nm): t (major) = 6.8 min, t (minor) = 8.4 min, 96% *ee*.

2,6-Dimethyl-4-(2-nitro-1-phenylethyl)heptane-3,5-dione (6c). Reaction solvent = toluene. Flash column chromatography (2:1 hexane:Et_2O) afforded **6c** (76 mg, 84%) as a white solid. ^1H NMR (300 MHz, $CDCl_3$): δ_H 0.72 (d, $^3J_{HH}$ = 6.7 Hz, 3H), 0.84 (d, $^3J_{HH}$ = 6.7 Hz, 3H), 1.07 (dd, $^3J_{HH}$ = 6.7 Hz, 6H), 2.48 (m, 1H), 2.72 (sept, 1H), 4.3 (ddd, $^3J_{HH}$ = 9.8 Hz, 1H), 4.53 (d, $^3J_{HH}$ = 9 .8 Hz, 1H), 4.62 (dd, $^3J_{HH}$ = 12.8 Hz, 1H), 4.74 (dd, $^3J_{HH}$ = 12.8 Hz. 1H), 7.07-7.5 (m, 5H). ^{13}C NMR (300 MHz, $CDCl_3$): δ_C 17.8, 18.0, 18.2, 18.7, 41.0, 41.1, 43.3, 67.3, 128.2, 128.4, 129.1, 136.5, 207.4, 207.8. mp 127-128 ^oC. HPLC (IA, 15% isopropyl alcohol in hexane, 1 mL/min, 238 nm): t (major) = 5.2 min, t (minor) = 6 min, 93% *ee*.

2,2,6,6-Tetramethyl-4-(2-nitro-1-phenylethyl)heptane-3,5-dione (6d). Reaction solvent = toluene. Flash column chromatography (6:1 hexane:Et_2O) afforded **6d** (25 mg, 30%) as a white solid, mp 156-158 ^oC, IR (ν_{max}, cm^{-1}): 1677 and 1713 (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ_H 0.82 (s, 9H, $C(CH_3)_3$), 1.34 (s, 9H, $C(CH_3)_3$), 4.14-4.2 (m, 1H, NO_2-CH_2CH), 4.69 (dd, $^3J_{HH}$ = 14Hz, 1H, NO_2-CH_2), 4.96 (d, $^3J_{HH}$ = 4.1Hz, 1H, HC(CO $C(CH_3)_3)_2$), 5.58 (dd, $^3J_{HH}$ = 10.8Hz, 1H, NO_2-CH_2), 7.22-7.33 (m, $5H_{arom}$). ^{13}C NMR (300 MHz, $CDCl_3$): δ_C 25.8 ($(CH_3)_3$), 28.2 ($(CH_3)_3$), 44.0 ($C(CH_3)_3$), 44.7 ($C(CH_3)_3$), 45.4 (NO_2-CH_2CH), 59.4 (NO_2-CH_2), 75.6 (HC(CO $C(CH_3)_3)_2$), 127.8, 128.3, 129.1 and 134.5 ($4C_{arom}$), 208.9 (C=O), 209.5 (C=O). $[\alpha]_D^{25}$: + 120.7 (c 0.0007, CH_2Cl_2). LC/TCOF-MS: $(M + Na)^+$ required 356.1832, found 356.1831. HPLC (IA, 30% isopropyl alcohol in hexane, 1 mL/min, 238 nm): t (major) = 8.4 min, t (minor) = 9.3 min, catalyst **2**: 99% *ee*. Catalyst **14**:-92% ee.

2-(2-Nitro-1-phenylethyl)-1,3-diphenylpropane-1,3-dione (6e). Reaction solvent = toluene. Flash column chromatography (3:1 hexane:Et_2O) afforded **6e** (76 mg, 84%) as a white solid, mp 127-128 ^oC. ^1H NMR (300 MHz, $CDCl_3$): δ_H 4.62 (m, 1H), 4.99 (dd, $^3J_{HH}$ = 6.8Hz, 2H), 5.86 (d, $^3J_{HH}$ = 8.1 Hz, 1H), 7.14-7.26 (m, 5H), 7.31-7.41 (m, 4H), 7.48-7.56 (m, 2H), 7.76-7.87 (m, 4H). ^{13}C NMR (300 MHz, $CDCl_3$): δ_C 44.0, 59.9, 77.3, 128.2, 128.3, 128.6, 128.8, 128.9, 129.0, 133.8, 134.1, 135.8, 136.2, 136.8, 193.6, 194.2. HPLC (IA, 30% isopropyl alcohol in hexane, 1 mL/min, 238 nm): t (major) = 8.2 min, t (minor) = 15 min, 94% *ee*.

2-Acetyl-2-(2-nitro-1-phenylethyl)cyclopentanone (6f). Reaction solvent = toluene. Flash column chromatography (3:1 hexane: Et_2O) afforded **6f** (124 mg, 89%) as a white solid, mp 114-116 ^oC.

Major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.33-1.47 (m, 1H), 1.64-1.79 (m, 1H), 1.93-2.02 (m, 1H), 2.04-2.17 (m, 1H), 2.19 (s, 3H), 2.32-2.50 (m, 2H), 4.28 (dd, $^3J_{HH}$ = 3.8 Hz, 1H), 4.60 (dd, $^3J_{HH}$ = 3.8 Hz, 1H), 5.02 (dd, $^3J_{HH}$ = 11 Hz, 1H), 7.16-7.22 (m, 2H), 7.29-7.35 (m, 3H). ^{13}C NMR (300 MHz, $CDCl_3$): δ_C 19.4, 26.7, 31.1, 39.4, 36.2, 70.2, 76.9, 128.6, 128.8, 129.1, 135.2, 203.2, 217.0. HPLC (IB, 20% isopropyl alcohol in hexane, 1 mL/min, 238 nm): t (major) = 11.4 min, t (minor) = 16.7 min, 70% *ee*.

Minor diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.67-1.80 (m, 3H), 1.92-2.02 (m, 1H), 2.12-2.28 (m, 1H), 2.34 (s, 3H), 2.54-2.61 (m, 1H), 4.39 (dd, $^3J_{HH}$ = 3.9 Hz, 1H), 4.50 (dd, $^3J_{HH}$ = 3.9 Hz, 1H), 4.87 (dd, $^3J_{HH}$ = 11.6 Hz, 1H), 7.24-7.35 (m, 5H). ^{13}C NMR (300 MHz, $CDCl_3$): δ_C 19.5, 26.6, 27.2, 38.7, 46.3, 71.2, 76.6, 128.5, 128.9, 129.5, 134.2, 202.8, 213.1. HPLC (IB, 20% isopropyl alcohol in hexane, 1 mL/min, 238 nm): t (major) = 10.1 min, t (minor) = 28.6 min, 17% *ee*.

9-Amino-(9-deoxy)-*epi*-quinine.[21] A solution of hydrazoic acid in toluene (5.18 mL, 0.449M, 2.33 mmol) was added to a stirred solution of quinine (0.496 g, 1.53 mmol) and triphenylphosphine (0.483 g, 1.84 mmol) in dry THF (15 mL) via syringe under argon. The solution was cooled to 0 ^{o}C and after 5 minutes at this temperature diiospropyl azodicarboxylate (0.36 mL, 1.84 mmol) in THF (2 mLs) was added dropwise via syringe. The solution was allowed to warm to room temperature and was stirred for 4 hours, after which triphenylphosphine (0.401 g, 1.53 mmol) in THF (2 mL) was added in one portion. The mixture was stirred until gas evolution ceased (approx. 4 hours). Water (1 mL) was then added and the solution was stirred for a further 4 hours. The reaction was then concentrated *in vacuo* and the residue partitioned between DCM and 2M HCl (1:1, 20 mL). After the mixture was vigorously shaken the aqueous layer was separated and washed with DCM (2 x 10 mL portions). The aqueous layer was then concentrated under reduced pressure and the residue partitioned between 0.5M NaOH and DCM (1:1, 100 mL). The organic layer was separated and the aqueous layer was re-extracted with DCM (2 x 10 mL portions). The combined organic extracts were dried over Na_2SO_4 and concentrated to yield a brown oil (0.418 g, 84%) which was used without further purification.

Organocatalyst (2).[21] A solution of 9-amino-(9-deoxy)-*epi*-quinine (0.418 g, 1.78 mmol) in dry DCM (5 mL) was cooled to 0 ^{o}C. After 10 minutes at this temperature 3,5-(bis-trifluoromethyl)phenyl isothiocyanate (0.52 mL, 2.85 mmol) was added via syringe with stirring. The resulting solution was allowed to warm to room temperature and stirred for 12 hours and then concentrated under reduced pressure. The residue was purified by flash chromatography (elution gradient: 1:1 hexane ethyl acetate to 85:10:5 EtOAc:MeOH:Et_3N). This yielded an off-white solid which was recrystallized by dissolving it in a minimal amount of DCM and adding hexane dropwise at 0 ^{o}C to afford the desired product **2** (0.34 g, 32%) as a white amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.00-1.10 (m, 1H), 1.26-1.35 (m, 1H), 1.50-1.68 (m, 2H), 1.73 (app s, 1H), 2.36-2.44 (m, 1H), 2.82-3.12 (m, 4H), 3.23-3.41 (m, 2H), 3.97 (s, 3H), 5.21 (dd, $^3J_{HH}$ = 11.2 Hz, 2H), 5.81-5.92 (m, 1H), 6.0 (br s, 1H), 7.29 (d, J = 4.5 Hz, 1H), 7.39 (dd, $^3J_{HH}$ = 9.1 Hz, 1H), 7.65 (app s, 2H), 7.93 (app s, 2H), 7.99 (d, $^3J_{HH}$ = 9.1 Hz, 1H), 8.63 (d, $^3J_{HH}$

= 4.5 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ_C 25.9, 27.6, 39.1, 41.5, 54.8, 55.8, 60.8, 102.2, 115.0, 118.7 (q, J = 3.6 Hz), 121, 122.1, 123.6, 124.7, 128.0, 128.3, 128.8, 131.3 (q, J = 33.5 Hz), 131.9, 149.1, 140.8, 144.5, 147.2, 158.1, 180.6. LC/TCOF-MS: $(M + H)^+$ required 595.1961, found 595.1940.

Hydrazoic acid solution. Water (2 mL) and NaN_3 (2.8g, 24.6 mmol) were stirred together to form a slurry. Toluene (20 mL) was added and the biphasic mixture was cooled to 0 ^{o}C. Sulphuric acid (3.2 mL, 1.5 eq.) was added dropwise while the solution was still in ice. The suspension was stirred for 10 minutes and the toluene layer was decanted off. The remaining salts were washed with toluene (2 x 10 mLs) and the combined organic washings were dried over sodium sulphate and filtered. The molar concentration of the solution was calculated by titrating it against a standardized NaOH solution.

9-Amino-(9-deoxy)-*epi*-quinidine.[21] Diisopropyl azodicarboxylate (DIAD, 0.73 mLs, 3.7 mmol) was added to a solution of quinidine (1 g, 3.1 mmol) and triphenylphosphine (0.97 g, 3.7 mmol) in dry THF (10 mL) at 0 ^{o}C all at once. After 5 minutes, a solution of diphenylphosphoryl azide (DPPA, 0.8 mL, 3.7 mmol) in dry THF (5 mL) was added dropwise at 0 ^{o}C. The mixture was warmed to room temperature. After being stirred overnight, the solution was heated at 50 ^{o}C for 2 hours. Triphenylphosphine (1 g) was then added and the heating was maintained until gas evolution had ceased (approx. 3 hours). The solution was cooled to room temp. And water (1 mL) was added. After stirring for 4 hours, the solvents were removed and the residue was partitioned between DCM and 2M HCl (1:1, 20 mL). The aqueous phase was extracted with DCM (3 x 10 mL), made alkaline with a saturated solution of Na_2CO_3 and extracted with DCM. Concentration of the dried extracts afforded a yellow residue (0.91 g, 90%) which was used without further purification.

Organocatalyst (14).[21] A solution of 9-amino-(9-deoxy)-*epi*-quinidine (0.91 g, 2.8 mmol) in dry THF (10 mL) was cooled to ^{o}C. After 10 minutes at this temperature 3,5-(bis-trifluoromethyl)phenyl isothiocyanate (0.52 mL, 2.85 mmol) was added via syringe with stirring. The resulting solution was allowed to warm to room temperature and stirred for 12 hours and then concentrated under reduced pressure. The residue was purified by flash chromatography (elution gradient: 100% DCM to 93:6:1 DCM:MeOH:Et_3N). This yielded the desired product **14** (0.43 g, 52%) as a white amorphous solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.00-1.10 (m, 1H), 1.26-1.35 (m, 1H), 1.50-1.68 (m, 2H), 1.73 (app s, 1H), 2.36-2.44 (m, 1H), 3.82-2.12 (m, 4H), 3.23-3.41 (m, 2H), 3.97 (s, 3H), 5.21 (dd, $^3J_{HH}$ = 11.2 Hz, 2H), 5.81-5.92 (m, 1H), 6.0 (br s, 1H), 7.29 (d, $^3J_{HH}$ = 4.5 Hz, 1H), 7.39 (dd, $^3J_{HH}$ = 9.1 Hz, 1H), 7.65 (app s, 2H), 7.93 (app s, 2H), 7.99 (d, $^3J_{HH}$ = 9.1 Hz, 1H), 8.63 (d, $^3J_{HH}$ = 4.5 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ_C 24.8, 25.5, 26.9, 38.2, 46.9, 48.7, 55.7, 61.4, 101.8, 115.8, 118.5, 119.4 (q, J = 3.6 Hz), 121.2, 123.4, 123.4, 124.8, 127.9, 128.4, 131.7, 132.3 (q, J = 33.5 Hz), 138.9, 140.2, 144.8, 147.4, 158.3, 181.0. LC/TCOF-MS: $(M + H)^+$ required 595.1961, found 595.1940.

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