

Substrate-Controlled Michael Additions of Titanium Enolates from Chiral α -Benzyloxy Ketones to Conjugated Nitroalkenes

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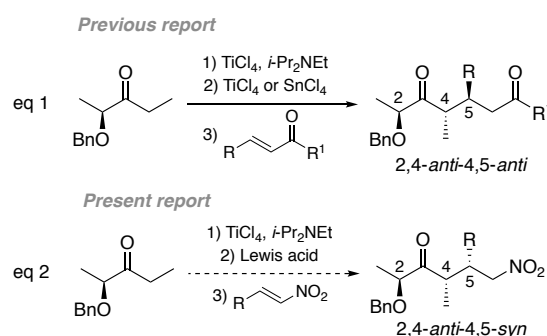
Abstract: Lewis acid-mediated substrate-controlled reactions of the titanium(IV) enolates of chiral α -benzyloxy ketones with conjugated nitroalkenes give the 2,4-*anti*-4,5-*syn* Michael adducts in good yields and diastereomeric ratios. The supplementary Lewis acid plays a key role in the outcome of these transformations, probably as a consequence of the formation of bimetallic enolates that increase the reactivity of the enolate and direct the approach of the nitroalkene. Importantly, the most appropriate Lewis acid depends on the electrophilic partner: TiCl₄ is the most suitable Lewis acid for β -aryl nitroalkenes while the best results for β -alkyl nitroalkenes are obtained with SnCl₄. Finally, the nitro group of the resultant compounds can be converted into the corresponding amino, oxime, and nitrile groups under mild conditions, which permits the synthesis of a variety of enantiomerically pure derivatives with excellent yields.

Introduction

The venerable Michael reaction, which refers to additions of stable carbon nucleophiles to conjugated olefins bearing an electron-withdrawing group, is beyond doubt one of the most powerful carbon-carbon bond forming reactions.^[1] Indeed, the wide range of structural motifs it gives access to and the possibility of installing up to three new stereocenters sustain a great and lingering interest in the Michael reaction within synthetic chemistry. Thus, tremendous effort has been dedicated to developing asymmetric procedures that permit control of the configuration of as many stereocenters as possible,^[2,3] and a variety of recently reported enantioselective and catalytic Michael additions have already been employed in the synthesis of a plethora of natural products.^[4,5] Unfortunately, and despite such achievements, most of these methods hinge on the use of metal enolates from 1,3-dicarbonyl compounds,^[6] and other activated substrates,^[7] as the nucleophilic partner, which restricts their scope.^[8] Meanwhile, more classic stoichiometric and chiral auxiliary-based approaches take advantage of the high reactivity of lithium and titanium(IV)

enolates to tackle more challenging additions.^[9] Surprisingly, parallel substrate-controlled Michael reactions from chiral ketones that might achieve similar levels of stereocontrol are almost unknown, and only a few examples have been reported to date.^[10,11]

Therefore, considering that titanium(IV) enolates from chiral α -benzyloxy ketones take part in highly stereocontrolled aldol reactions,^[12] we envisaged that they might also participate in diastereoselective Michael reactions. We were pleased to discover that enones are excellent acceptors and afforded the corresponding 1,5-dicarbonyl compounds in high yields and diastereomeric ratios (see eq 1 in Scheme 1).^[13] Then, bearing in mind that α,β -unsaturated nitro derivatives are more active Michael acceptors than enones, and also the various transformations available for the nitro group,^[14] we hypothesized that substrate-controlled Michael additions of the aforementioned chiral ketones to conjugated nitroalkenes might afford the corresponding adducts, which could in turn be easily converted into a range of enantiomerically pure intermediates. Herein, we report that the Lewis acid-mediated addition of titanium(IV) enolates from chiral α -benzyloxy ketones to a wide range of nitroalkenes affords 2,4-*anti*-4,5-*syn* adducts with good yields and diastereoselectivities (see eq 2 in Scheme 1).



Scheme 1. Substrate-controlled Michael additions from α -benzyloxy ketones.

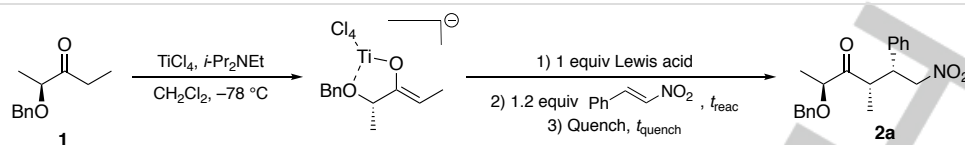
Results and Discussion

Taking advantage of our experience with substrate-controlled Michael additions to enones,^[13] we initially assessed the Lewis acid-mediated reaction of lactate-derived ketone **1**^[15] to β -nitrostyrene (**a**). Surprisingly, and in spite of the strong character of β -nitrostyrene (**a**) as a Michael acceptor, the simple reaction with the titanium(IV) enolate from **1** did not produce any Michael adduct, and the starting materials were recovered unchanged (entry 1 in Table 1). In contrast, full conversion was achieved by

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Table 1. Lewis acid-mediated Michael additions of titanium(IV) enolates from **1** to β -nitrostyrene.

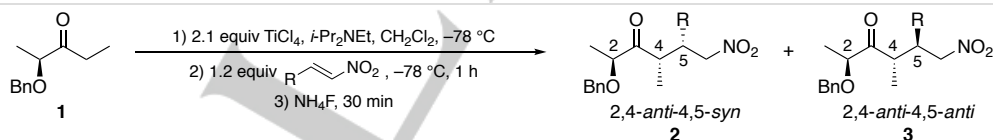
Entry	Lewis acid	t_{reac} [h]	Quench	t_{quench} [min]	dr ^[a]	Yield 2a [%] ^[b]
1	–	1.5	NH ₄ Cl	10	–	–
2	TiCl ₄	1.5	NH ₄ Cl	10	nd	41
3	TiCl ₄	1.5	HCl	10	nd	47
4	TiCl ₄	1.5	NH ₄ F	90	87:13	79
5	TiCl ₄	1	NH ₄ F	30	87:13	80
6	AlEt ₂ Cl	1.5	NH ₄ F	30	75:25	(60) ^[c]
7	SnCl ₄	1.5	NH ₄ F	30	50:50	(82) ^[c]

[a] Diastereomeric ratio established by ¹H NMR (400 MHz). [b] Isolated yield of **2a**. [c] Overall yield of all the diastereomers.

adding a second equivalent of TiCl₄ to the enolate and quenching the reaction mixture with saturated NH₄Cl; however, unexpectedly, the diastereomerically pure adduct **2a** was isolated with only a moderate yield after chromatographic purification (entry 2 in Table 1). The use of a stronger Brønsted acid to quench the reaction failed to increase the yield (entry 3 in Table 1). Careful analysis of the literature revealed that Seebach had faced a similar problem. Indeed, he found that the addition of titanium(IV) enolates from chiral imides to conjugate nitroalkenes gave stable nitronates that were not satisfactorily released using standard acid treatments.^[16] Instead, it was necessary to quench the reaction with NH₄F. By subjecting our reaction to such conditions we obtained an 87:13 diastereomeric

mixture, from which adduct **2a** was isolated with an 80% yield (entries 4 and 5 in Table 1). Finally, other Lewis acids such as AlEt₂Cl and SnCl₄ were also tested, but both the diastereoselectivity and the yield were poorer than those obtained with TiCl₄ (compare entries 5–7 in Table 1).

Having established the key role of a second equivalent of TiCl₄ and the importance of quenching the reaction mixture with NH₄F, we then assessed reactions with a variety of β -aryl nitroalkenes (see Table 2).^[17] With the exception of the 4-nitrophenyl derivative **f**, all the substrates examined reacted smoothly to afford mixtures from which 2,4-*anti*-4,5-*syn* **2** diastereomers were isolated in high yields (entries 1–6 in Table 2). Remarkably,

Table 2. TiCl₄-Mediated Michael additions of titanium(IV) enolates from **1** to β -aryl nitroalkenes.

Entry	β -Aryl nitroalkene	R	Major diastereomer	dr [2:3] ^[a]	Yield of 2 [%] ^[b]
1	a	Ph	2a	87:13	80
2	b	4-MePh	2b	88:12	80
3	c	4-MeOPh	2c	93:7	80
4	d	3,4-(OCH ₂ O)Ph	2d	90:10	82
5	e	4-ClPh	2e	87:13	70
6	f	4-NO ₂ Ph	2f	nd	traces
7	g	2-Furyl	2g	93:7	64

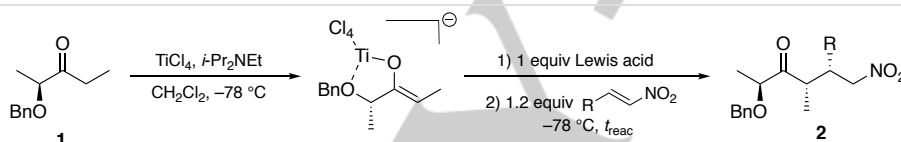
[a] Diastereomeric ratio established by ¹H NMR (400 MHz). [b] Isolated yield.

even the addition of **1** to a Lewis acid-sensitive acceptor such as furyl nitroalkene **g** proceeded, and led to a good yield (entry 7 in Table 2). Interestingly, the diastereoselectivity of the reaction was observed to be dependent in some way on the electronic character of the aromatic ring: it was slightly higher for those substrates containing electron-donating groups on the aromatic ring, such as **c** (entry 3 in Table 2).

With the aim of expanding the scope of the process, we next examined parallel conjugate additions to β -alkyl nitroalkenes. To our surprise, the reaction of **1** with (*E*)-1-nitro-4-phenyl-1-butene (**h**) gave the expected product **2h** but only with moderate stereocontrol and yield (dr 60:40, 60% overall yield, see entry 1 in Table 3). Then, considering the crucial impact of the second equivalent of Lewis acid on the outcome of these additions, we evaluated the influence of this component on the addition to β -alkyl nitroalkenes. After careful analysis, we observed that other titanium(IV) as well as zirconium(IV) or aluminum Lewis acids produced similar or even worse results; but SnCl₄ provided much better diastereoselectivity with a comparable yield (compare entries 1–6 in Table 3). Indeed, treatment of the titanium(IV) enolate from **1** with one equivalent of SnCl₄ before

the addition of the nitroalkene **h** yielded a mixture of three diastereomers (dr 84:10:6) from which adduct **2h** was isolated with a 46% yield (entry 6 in Table 3). An increase of the temperature to –40 °C improved the yield, but a higher temperature had a negative impact on the yield (compare entries 6–8 in Table 3). Finally, a longer reaction time also improved the yield (compare entries 6–9 in Table 3), so diastereomerically pure **2h** was finally isolated with a 54% yield after 3 h at –78 °C (entry 9 in Table 3). These optimized experimental conditions were further applied to other β -alkyl nitroalkenes (**i–m**)^[18] to afford 2,4-*anti*-4,5-*syn* adducts **2i–m** with high stereocontrol. Interestingly, the addition proved to be very sensitive to the steric bulk and the presence of potential chelating functional groups on R. Indeed, the addition of the titanium enolate from **1** to (*E*)-3-methyl-1-nitro-1-butene (**k**) in which an isopropyl group is attached to the electrophilic center gave the 2,4-*anti*-4,5-*syn* adduct **2k** with a low diastereoselectivity and yield (entry 12 in Table 3). In turn, the reaction with benzyl-protected 4-hydroxy-1-nitro-1-butene (**l**) gave **2l** with an excellent diastereoselectivity but in a low yield (entry 13 in Table 3); whereas the use of a

Table 3. Lewis acid-mediated Michael additions of titanium(IV) enolates from **1** to β -alkyl nitroalkenes.



Entry	Lewis acid	β -Alkyl nitroalkene	R	t_{reac} [h]	Major diastereomer	dr ^[a,b]	Yield of 2 [%] ^[c]
1	TiCl ₄	h	PhCH ₂ CH ₂	1	2h	60:40	(60)
2	TiBr ₄	h	PhCH ₂ CH ₂	1	2h	–	–
3	TiCl ₃ (<i>i</i> -PrO)	h	PhCH ₂ CH ₂	1	2h	65:35	17
4	ZrCl ₄	h	PhCH ₂ CH ₂	1	2h	70:30	27
5	AlEt ₂ Cl	h	PhCH ₂ CH ₂	1	2h	62:38	30
6	SnCl ₄	h	PhCH ₂ CH ₂	1	2h	84:16	46
7 ^[d]	SnCl ₄	h	PhCH ₂ CH ₂	2	2h	83:17	56
8 ^[e]	SnCl ₄	h	PhCH ₂ CH ₂	2	2h	nd	(33)
9	SnCl ₄	h	PhCH ₂ CH ₂	3	2h	84:16	54
10	SnCl ₄	i	CH ₃ CH ₂ CH ₂	3	2i	89:11	68
11	SnCl ₄	j	(CH ₃) ₂ CHCH ₂	3	2j	88:12	80
12	SnCl ₄	k	(CH ₃) ₂ CH	3	2k	72:28	28
13	SnCl ₄	l	BnOCH ₂ CH ₂	3	2l	94:6	25
14	SnCl ₄	m	TIPSOCH ₂ CH ₂	3	2m	97:3	64

[a] Ratio of major/sum of minor diastereomers. [b] Diastereomeric ratio established by ¹H NMR (400 MHz). [c] Isolated yield. [d] The reaction was carried out at –78 °C for 1 h and at –40 °C for 1 h. [e] The reaction was carried out at –78 °C for 1 h and at –20 °C for 1 h.

bulky and non-chelating TIPS protecting group in **m** provided the desired adduct **2m** as a single diastereomer with a good yield (entry 14 in Table 3).

The configurations of major and minor diastereomer, **2** and **3** respectively, were established through X-ray analyses of crystalline adducts **2g** and **3a** shown in Figure 1.^[19]

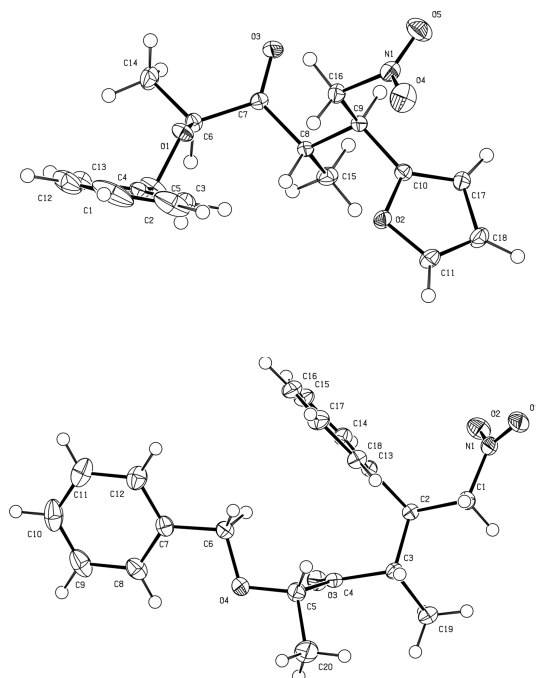
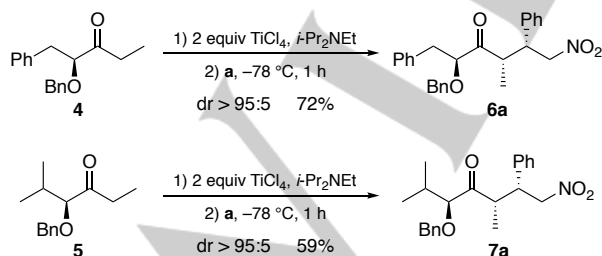


Figure 1. ORTEP X-ray structures of compounds **2g** and **3a** [ellipsoid contour probability: 50%]

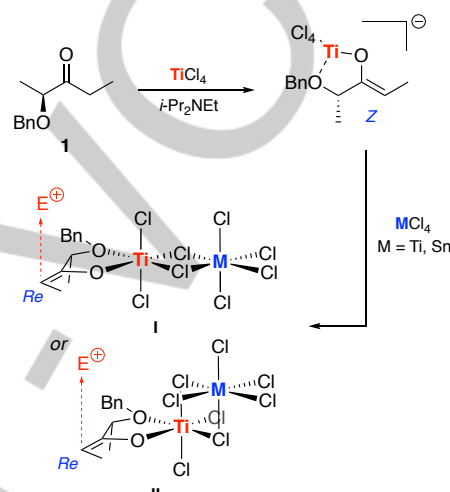
The broad scope of the abovementioned Lewis acid-mediated Michael additions of **1** to conjugated nitroalkenes encouraged us to explore similar substrate-controlled reactions with other chiral α -hydroxy ketones. Thus, we were pleased to observe that the titanium(IV) enolates from α -benzyloxy ketones **4** and **5**^[20] smoothly added to β -nitrostyrene (**a**) to afford basically a single diastereomer **6a–7a** in yields of up to 72% (Scheme 2).



Scheme 2. Substrate-controlled Michael additions from α -benzyloxy ketones.

All together, these results prove that chiral α -benzyloxy ketones are excellent platforms from which to carry out highly

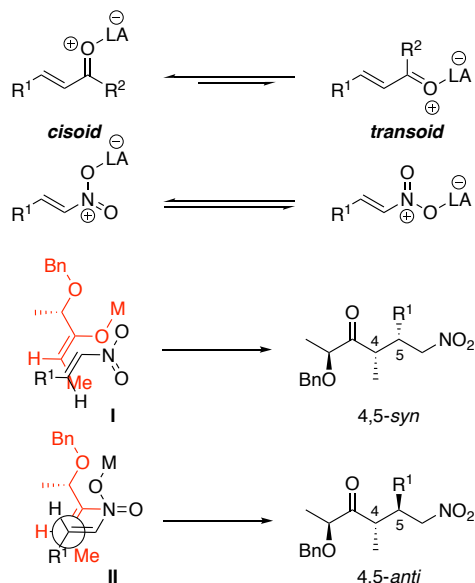
stereoselective Lewis acid-mediated Michael reactions with a wide range of nitroalkenes. As for enones, the supplementary Lewis acid plays a crucial role in these additions. Indeed, TiCl_4 and SnCl_4 turned out to be the most suitable Lewis acids, depending on the acceptor, β -aryl or β -alkyl nitroalkenes respectively. This indicates that the second Lewis acid must interact with the enolate, producing the real nucleophilic species (see Scheme 3), which must also be responsible for the activation of the nitroalkene.



Scheme 3. Potential bimetallic enolates from **1**.

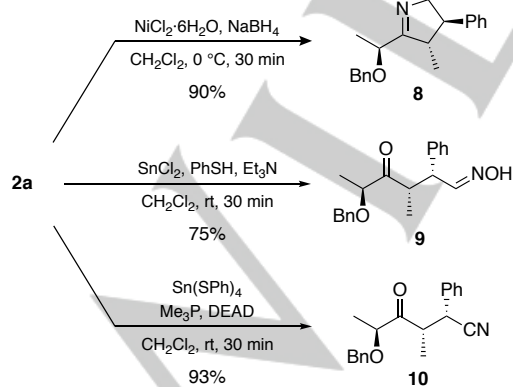
Irrespective of the precise structure of such an intermediate and according to the structure both of the major and minor diastereomers shown in Figure 1, the electrophile would attack the *Re* face of the enolate, thus controlling the configuration of the α -stereocenter. In turn, that of the β -stereocenter relies on the approach of the electrophile to the *Re* face of the enolate. Enones produce the relative configuration *anti*; nitroalkenes the *syn* configuration (see Scheme 1). The reasons for such a discrepancy may be conformational differences operating on the activation of the double bond. Indeed, the equilibrium for enones is shifted towards the *cisoid* conformation which avoids $A(1,3)$ interactions, whereas the lack of an R^2 group in nitroalkenes makes the *transoid* conformation more accessible.^[21] Actually, both conformers of nitroalkenes may be considered as tautomers in which the metal atom is bound to different oxygen atoms of the nitro group. Moreover, the key role played by the additional Lewis acid suggests that the reaction might proceed through a cyclic transition state involving a bimetallic enolate;^[22] then, the essentially flat nitroalkene does not contain an R^2 group that would prevent it from evolving through an eclipsed approach (**I** in Scheme 4), which looks like an eight-membered cycle.^[23] Our working hypothesis precisely predicted such an approach as being responsible for the 4,5-*syn* diastereomer, whereas the 4,5-*anti* counterpart may arise from a staggered approach (**II** in Scheme 4). So, slight differences in the electronic character of nitroalkenes (aryl or alkyl) and the steric bulk of R^1

can have a dramatic impact on the stereochemical outcome of these additions.



Scheme 4. Mechanistic hypothesis.

Finally, we explored the conversion of the nitro group into other functional groups, to confirm their synthetic potential. Thus, the reduction of the nitro group of adduct **2a** catalyzed by NiCl_2 led to enantiomerically pure cyclic imine **8** in 90% yield (Scheme 5).^[24,6c] Moreover, **2a** was easily converted into oxime **9** using a tin-based reducing agent (Scheme 5).^[25] Finally, a reductive dehydration of **2a** catalyzed by $\text{Sn}(\text{SPh})_4$ allowed us to isolate β -cyano ketone **10** with an excellent yield (Scheme 5).^[26] All these reactions were carried out under mild conditions and the resulting densely functionalized compounds **8–10** were easily isolated in high yields and without any loss of the steric integrity of the starting material.



Scheme 5. Further transformations from adduct **2a**.

Conclusions

In summary, Lewis acid-mediated substrate-controlled Michael additions of α -benzyloxy ketones to a wide range of β -aryl- as well as β -alkyl-conjugated nitroalkenes afford the corresponding 2,4-*anti*-4,5-*syn* diastereomers with good yields and high stereocontrol. It is probable that a bimetallic enolate arising from the interaction of the titanium(IV) enolate with the supplementary Lewis acid (TiCl_4 or SnCl_4) is responsible for the *syn* trend observed for these additions. Furthermore, simple transformations of the nitro group offer access to other nitrogen-based functional groups in a straightforward manner.

Experimental Section

General: Unless otherwise noted, reactions were conducted in oven-dried glassware under inert atmosphere of N_2 with anhydrous solvents. The solvents and reagents were dried and purified when necessary according to standard procedures. Commercially available reagents were used as received. Analytical thin-layer chromatography (TLC) was carried out on Merck silica gel 60 F₂₅₄ plates and analyzed by UV (254 nm) and stained with phosphomolybdic acid and *p*-anisaldehyde; R_f values are approximate. Column chromatographies were carried out under low pressure (flash) conditions and performed on SDS silica gel 60 (35–70 μm). Specific rotations ($[\alpha]_D$) were determined at 20 °C on a Perkin-Elmer 241 MC polarimeter. IR spectra (Attenuated Total Reflectance, ATR) were recorded on a Nicolet 6700 FT-IR Thermo Scientific spectrometer and only the more representative frequencies (ν) are reported in cm^{-1} . ^1H NMR (400 MHz) and ^{13}C NMR (100.6 MHz) spectra were recorded on a Varian Mercury 400. Chemical shifts (δ) are quoted in ppm and referenced to internal TMS (δ 0.00 for ^1H NMR) or CDCl_3 (δ 77.0 for ^{13}C NMR); coupling constants (J) are quoted in Hz; data are reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet (and their corresponding combinations); where necessary, 2D techniques (NOESY, COSY, HSQC) were also used to assist on structure elucidation. High resolution mass spectra (HRMS) were obtained with an Agilent 1100 spectrometer by the Unitat d'Espectrometria de Masses (CCiTUB), Universitat de Barcelona.

General Experimental Procedure for the TiCl_4 -Mediated Michael Additions from Ketone **1:** Neat TiCl_4 (235 μL , 2.1 mmol) was carefully added to a solution of **1** (192 mg, 1.0 mmol) in CH_2Cl_2 (4 mL) at -78 °C under N_2 . The resultant yellow suspension was stirred for 5 min and *i*-Pr₂NEt (195 μL , 1.1 mmol) was added dropwise. The ensuing dark red solution was stirred for 30 min at -78 °C. Then, the corresponding nitroalkene (1.2 mmol) was added and the reaction mixture was stirred at -78 °C for 1 h. The reaction was quenched at -78 °C with 25% NH_4F (6 mL) and stirred for 30 min at room temperature. The mixture was partitioned with CH_2Cl_2 (20 mL) and H_2O (20 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 \times 10 mL). The combined organic layers were dried (MgSO_4) and concentrated. The residue was analyzed by ^1H NMR and purified by flash column chromatography to afford the corresponding Michael adduct **2**.

(2*S*,4*S*,5*R*)-2-Benzyloxy-4-methyl-6-nitro-5-phenyl-3-hexanone (2a): Purple oil. Yield: 276 mg (0.8 mmol), 80%; R_f (hexanes/EtOAc 90:10) 0.20. $[\alpha]_D^{20} +99.0$ (c 1.0, CHCl_3). IR (ATR): $\nu = 3014, 3082, 3060, 3028, 2974, 2930, 2870, 1708, 1549, 1451, 1369$ cm^{-1} . ^1H NMR (400 MHz, CDCl_3): $\delta = 7.41\text{--}7.14$ (m, 10 H), 4.64 (d, $J = 11.7$ Hz, 1 H), 4.62 (dd, $J = 12.6, 10.0$ Hz, 1 H), 4.54 (d, $J = 11.7$ Hz, 1 H), 4.52 (dd, $J = 12.6, 4.6$ Hz, 1 H), 4.01 (q, $J = 6.7$ Hz, 1 H), 3.72 (td, $J = 9.9, 4.6$ Hz, 1 H), 3.41 (dq, J

= 9.9, 7.0 Hz, 1 H), 1.32 (d, $J = 6.7$ Hz, 3 H), 0.92 (d, $J = 7.0$ Hz, 3 H) ppm. ^{13}C NMR (100.6 MHz, CDCl_3): $\delta = 213.5, 137.6, 137.3, 128.9, 128.6, 128.1, 128.0, 127.9, 127.8, 79.1, 78.2, 71.9, 46.2, 43.8, 16.3, 15.8$ ppm. HRMS (ESI): calcd. for $\text{C}_{20}\text{H}_{23}\text{NNaO}_4$ [$\text{M} + \text{Na}$] $^+$: 364.1519; found: 364.1522.

(2S,4S,5S)-2-Benzoyloxy-4-methyl-6-nitro-5-phenyl-3-hexanone (3a): White needles; m.p. 93–95 °C; R_f (hexanes/EtOAc 90:10) 0.15. $[\alpha]_D^{25} +14.9$ (c 1.0, CHCl_3). IR (ATR): $\nu = 3025, 2976, 2918, 2874, 1708, 1548, 1454, 1370, 1107$ cm^{-1} . ^1H NMR (400 MHz, CDCl_3): $\delta = 7.35\text{--}7.17$ (m, 10 H), 4.76 (dd, $J = 12.7, 5.1$ Hz, 1 H), 4.69 (dd, $J = 12.7, 9.8$ Hz, 1 H), 4.28 (d, $J = 11.7$ Hz, 1 H), 4.10 (d, $J = 11.7$ Hz, 1 H), 3.84 (td, $J = 9.8, 5.1$ Hz, 1 H), 3.73 (q, $J = 6.9$ Hz, 1 H), 3.42 (dq, $J = 9.8, 6.9$ Hz, 1 H), 1.17 (d, $J = 6.9$ Hz, 3 H), 1.04 (d, $J = 6.9$ Hz, 3 H) ppm. ^{13}C NMR (100.6 MHz, CDCl_3): $\delta = 212.9, 138.3, 137.7, 129.0, 128.6, 128.3, 128.1, 128.0, 127.8, 80.6, 77.7, 71.5, 45.9, 44.5, 16.4, 14.6$ ppm. HRMS (ESI): calcd. for $\text{C}_{20}\text{H}_{23}\text{NNaO}_4$ [$\text{M} + \text{Na}$] $^+$: 364.1519; found: 364.1516.

(2S,4S,5R)-2-Benzoyloxy-4-methyl-5-(4-methylphenyl)-6-nitro-3-hexanone (2b): Purple oil. Yield: 141 mg (0.4 mmol, 0.5 mmol scale), 80%; R_f (hexanes/EtOAc 90:10) 0.20. $[\alpha]_D^{25} +12.1$ (c 1.0, CHCl_3). IR (ATR): $\nu = 3025, 2976, 2918, 2874, 1708, 1548, 1454, 1370, 1107$ cm^{-1} . ^1H NMR (400 MHz, CDCl_3): $\delta = 7.39\text{--}7.31$ (m, 5 H), 7.13–7.09 (m, 2 H), 7.06–7.02 (m, 2 H), 4.63 (d, $J = 11.7$ Hz, 1 H), 4.58 (dd, $J = 12.5, 10.2$ Hz, 1 H), 4.54 (d, $J = 11.7$ Hz, 1 H), 4.50 (dd, $J = 12.5, 4.6$ Hz, 1 H), 4.00 (q, $J = 6.8$ Hz, 1 H), 3.70–3.64 (m, 1 H), 3.42–3.34 (m, 1 H), 2.31 (s, 3 H), 1.32 (d, $J = 6.8$ Hz, 3 H), 0.92 (d, $J = 7.0$ Hz, 3 H) ppm. ^{13}C NMR (100.6 MHz, CDCl_3): $\delta = 213.7, 137.7, 137.5, 134.6, 129.7, 128.7, 128.2, 128.0, 128.0, 79.3, 78.5, 72.0, 46.0, 43.9, 21.2, 16.5, 15.9$ ppm. HRMS (ESI): calcd. for $\text{C}_{21}\text{H}_{29}\text{N}_2\text{O}_4$ [$\text{M} + \text{NH}_4$] $^+$: 373.2122; found: 373.2130.

(2S,4S,5R)-2-Benzoyloxy-5-(4-methoxyphenyl)-4-methyl-6-nitro-3-hexanone (2c): Brownish oil. Yield: 215 mg (0.8 mmol), 80%; R_f (hexanes/EtOAc 85:15) 0.25. $[\alpha]_D^{25} +146.0$ (c 1.0, CHCl_3). IR (ATR): $\nu = 3085, 3057, 3030, 2981, 2933, 2870, 2834, 1708, 1549, 1450, 1375$ cm^{-1} . ^1H NMR (400 MHz, CDCl_3): $\delta = 7.41\text{--}7.33$ (m, 5 H), 7.10–7.05 (m, 2 H), 6.86–6.82 (m, 2 H), 4.64 (d, $J = 11.7$ Hz, 1 H), 4.56 (dd, $J = 12.4, 4.6$ Hz, 1 H), 4.54 (d, $J = 11.7$ Hz, 1 H), 4.49 (dd, $J = 12.4, 4.6$ Hz, 1 H), 4.01 (q, $J = 6.7$ Hz, 1 H), 3.78 (s, 3 H), 3.67 (dt, $J = 9.8, 4.6$ Hz, 1 H), 3.37 (dq, $J = 9.8, 7.0$ Hz, 1 H), 1.32 (d, $J = 6.7$ Hz, 3 H), 0.92 (d, $J = 7.0$ Hz, 3 H) ppm. ^{13}C NMR (100.6 MHz, CDCl_3): $\delta = 213.7, 159.1, 137.3, 129.4, 129.1, 128.6, 128.1, 127.9, 79.2, 78.4, 71.8, 55.2, 45.5, 43.9, 16.3, 15.8$ ppm. HRMS (ESI): calcd. for $\text{C}_{21}\text{H}_{25}\text{NNaO}_5$ [$\text{M} + \text{Na}$] $^+$: 394.1625; found: 394.1636.

(2S,4S,5R)-2-Benzoyloxy-4-methyl-5-(3,4-methylenedioxyphenyl)-6-nitro-3-hexanone (2d): Yellowish oil. Yield: 157 mg (0.41 mmol, 0.5 mmol scale), 82%; R_f (hexanes/EtOAc 90:10) 0.20. $[\alpha]_D^{25} +16.5$ (c 1.0, CHCl_3). IR (ATR): $\nu = 3025, 2985, 2927, 2900, 2869, 1712, 1543, 1499, 1485, 1441, 1370, 1241, 1031$ cm^{-1} . ^1H NMR (400 MHz, CDCl_3): $\delta = 7.41\text{--}7.31$ (m, 5 H), 6.75–6.73 (m, 1 H), 6.63–6.60 (m, 2 H), 5.95 (s, 2 H), 4.66 (d, $J = 11.7$ Hz, 1 H), 4.54 (d, $J = 11.7$ Hz, 1 H), 4.51 (dd, $J = 12.5, 9.9$ Hz, 1 H), 4.46 (dd, $J = 12.5, 4.9$ Hz, 1 H), 4.02 (q, $J = 6.7$ Hz, 1 H), 3.63 (td, $J = 9.9, 4.9$ Hz, 1 H), 3.33 (dq, $J = 9.9, 7.0$ Hz, 1 H), 1.33 (d, $J = 6.7$ Hz, 3 H), 0.92 (d, $J = 7.0$ Hz, 3 H) ppm. ^{13}C NMR (100.6 MHz, CDCl_3): $\delta = 213.6, 148.2, 147.3, 137.4, 131.3, 128.8, 128.3, 128.1, 121.8, 108.7, 108.1, 101.3, 79.2, 78.6, 72.0, 46.1, 44.0, 16.4, 15.9$ ppm. HRMS (ESI): calcd. for $\text{C}_{21}\text{H}_{27}\text{N}_2\text{O}_8$ [$\text{M} + \text{NH}_4$] $^+$: 403.1864; found: 403.1873.

(2S,4S,5R)-2-Benzoyloxy-5-(4-chlorophenyl)-4-methyl-6-nitro-3-hexanone (2e): Yellowish oil. Yield: 262 mg (0.7 mmol), 70%; R_f (hexanes/EtOAc 85:15) 0.30. $[\alpha]_D^{25} +42.0$ (c 1.0, CHCl_3). IR (ATR): $\nu = 3083, 3063, 3030, 2977, 2928, 2874, 1708, 1549, 1490, 1370$ cm^{-1} . ^1H NMR (400 MHz, CDCl_3): $\delta = 7.44\text{--}7.27$ (m, 7 H), 7.12–7.08 (m, 2 H), 4.67 (d, $J =$

$J = 11.6$ Hz, 1 H), 4.56 (dd, $J = 12.7, 10.0$ Hz, 1 H), 4.54 (d, $J = 11.6$ Hz, 1 H), 4.50 (dd, $J = 12.7, 4.7$ Hz, 1 H), 4.02 (q, $J = 6.7$ Hz, 1 H), 3.70 (td, $J = 10.0, 4.7$ Hz, 1 H), 3.38 (dq, $J = 10.0, 7.0$ Hz, 1 H), 1.32 (d, $J = 6.7$ Hz, 3 H), 0.90 (d, $J = 7.0$ Hz, 3 H) ppm. ^{13}C NMR (100.6 MHz, CDCl_3): $\delta = 213.2, 137.2, 136.1, 133.7, 129.4, 128.1, 128.6, 128.2, 128.0, 78.9, 78.1, 71.9, 45.6, 43.6, 16.2, 15.7$ ppm. HRMS (ESI): calcd. for $\text{C}_{20}\text{H}_{22}\text{ClNNaO}_4$ [$\text{M} + \text{Na}$] $^+$: 398.113; found: 398.1133.

(2S,4S,5S)-2-Benzoyloxy-5-furyl-4-methyl-6-nitro-3-hexanone (2g): Brown needles. Yield: 104 mg (0.32 mmol, 0.5 mmol scale), 64%; m.p. 47–49 °C; R_f (hexanes/EtOAc 90:10) 0.20. $[\alpha]_D^{25} +19.1$ (c 1.0, CHCl_3). IR (ATR): $\nu = 2980, 2936, 2860, 1717, 1548, 1508, 1450, 1365, 1094$ cm^{-1} . ^1H NMR (400 MHz, CDCl_3): $\delta = 7.39\text{--}7.30$ (m, 6 H), 6.28 (dd, $J = 3.2, 1.9$ Hz, 1 H), 6.18–6.16 (m, 1 H), 4.66 (dd, $J = 12.7, 9.9$ Hz, 1 H), 4.62 (d, $J = 11.7$ Hz, 1 H), 4.54 (d, $J = 11.8$ Hz, 1 H), 4.49 (dd, $J = 12.7, 4.4$ Hz, 1 H), 4.01 (q, $J = 6.8$ Hz, 1 H), 3.95–3.89 (m, 1 H), 3.54–3.47 (m, 1 H), 1.33 (d, $J = 6.8$ Hz, 3 H), 1.01 (d, $J = 7.1$ Hz, 3 H) ppm. ^{13}C NMR (100.6 MHz, CDCl_3): $\delta = 213.0, 150.9, 142.6, 137.5, 128.7, 128.2, 128.0, 110.5, 108.9$ (CH), 79.3, 76.3, 71.9, 42.4, 40.0, 16.1, 15.6 ppm. HRMS (ESI): calcd. for $\text{C}_{18}\text{H}_{25}\text{N}_2\text{O}_5$ [$\text{M} + \text{NH}_4$] $^+$: 349.1758; found: 349.1760.

General Experimental Procedure for the SnCl_4 -Mediated Michael Additions from Ketone 1: Neat TiCl_4 (61 μL , 0.55 mmol) was carefully added to a solution of **1** (96 mg, 0.5 mmol) in CH_2Cl_2 (2 mL) at -78 °C. The resultant yellow suspension was stirred for 5 min and $i\text{-Pr}_2\text{NEt}$ (96 μL , 0.55 mmol) was added dropwise. The ensuing dark red solution was stirred for 30 min at -78 °C. Then, 1 M SnCl_4 in CH_2Cl_2 (0.55 mL μL , 0.55 mmol) was added, followed 5 min later by the corresponding nitroalkene (0.6 mmol) and the resultant mixture was stirred at -78 °C for 3 h. The reaction was quenched at -78 °C with 25% NH_4F (3 mL) and stirred for 30 min at room temperature with vigorous stirring. The mixture was partitioned with CH_2Cl_2 (10 mL) and H_2O (10 mL), the aqueous layer was extracted with CH_2Cl_2 (3 \times 10 mL). The combined organic layers were dried (MgSO_4) and concentrated. The residue was analyzed by ^1H NMR and purified by flash column chromatography to afford the corresponding Michael adduct **2**.

(2S,4S,5S)-2-Benzoyloxy-4-methyl-5-nitromethyl-7-phenyl-3-heptanone (2h): Yellowish oil. Yield: 99 mg (0.27 mmol), 54%; R_f (hexanes/EtOAc 90:10) 0.10. $[\alpha]_D^{25} +164.0$ (c 1.0, CHCl_3). IR (ATR): $\nu = 3083, 3057, 3025, 2976, 2927, 2860, 1708, 1544, 1450, 1375, 1112$ cm^{-1} . ^1H NMR (400 MHz, CDCl_3): $\delta = 7.39\text{--}7.09$ (m, 10 H), 4.57 (d, $J = 11.7$ Hz, 1 H), 4.53 (d, $J = 11.7$ Hz, 1 H), 4.52 (dd, $J = 12.7, 4.4$ Hz, 1 H), 4.29 (dd, $J = 12.7, 8.0$ Hz, 1 H), 3.99 (q, $J = 6.8$ Hz, 1 H), 3.28 (qd, $J = 7.1, 5.1$ Hz, 1 H), 2.65–2.55 (m, 2 H), 2.63 (t, $J = 8.1$ Hz, 2 H), 1.36 (d, $J = 6.8$ Hz, 3 H), 1.03 (d, $J = 7.1$ Hz, 3 H) ppm. ^{13}C NMR (100.6 MHz, CDCl_3): $\delta = 213.6, 140.7, 137.3, 128.5, 128.5, 128.2, 128.0, 127.8, 126.2, 79.4, 76.4, 71.7, 41.2, 38.1, 33.1, 32.0, 16.7, 11.7$ ppm. HRMS (ESI): calcd. for $\text{C}_{22}\text{H}_{27}\text{NNaO}_4$ [$\text{M} + \text{Na}$] $^+$: 392.1832; found: 392.1839.

(2S,4S,5S)-2-Benzoyloxy-4-methyl-5-nitromethyl-3-octanone (2i): Yellowish oil. Yield: 105 mg (0.34 mmol), 68%; R_f (hexanes/EtOAc 85:15) 0.10. $[\alpha]_D^{25} +22.9$ (c 1.0, CHCl_3). IR (ATR): $\nu = 2963, 2932, 2869, 1708, 1552, 1450, 1370, 1111$ cm^{-1} . ^1H NMR (400 MHz, CDCl_3): $\delta = 7.38\text{--}7.29$ (m, 5 H), 4.60 (d, $J = 11.8$ Hz, 1 H), 4.56 (d, $J = 11.8$ Hz, 1 H), 4.49 (dd, $J = 12.6, 4.3$ Hz, 1 H), 4.24 (dd, $J = 12.6, 8.2$ Hz, 1 H), 4.04 (q, $J = 6.8$ Hz, 1 H), 3.28–3.23 (m, 1 H), 2.61–2.54 (m, 1 H), 1.39 (d, $J = 6.8$ Hz, 3 H), 1.38–1.31 (m, 4 H), 1.01 (d, $J = 7.1$ Hz, 3 H), 0.89–0.85 (m, 3 H) ppm. ^{13}C NMR (100.6 MHz, CDCl_3): $\delta = 214.1, 137.5, 128.7, 128.1, 128.0, 79.7, 76.8, 71.9, 41.3, 38.3, 32.7, 20.1, 17.0, 13.9, 11.7$ ppm. HRMS (ESI): calcd. for $\text{C}_{17}\text{H}_{29}\text{N}_2\text{O}_4$ [$\text{M} + \text{NH}_4$] $^+$: 325.2122; found: 325.2118.

(2S,4S,5S)-2-Benzoyloxy-4,7-dimethyl-5-nitromethyl-3-octanone (2j): Yellowish oil. Yield: 128 mg (0.40 mmol), 80%; R_f (hexanes/EtOAc 90:10)

0.25. $[\alpha]_D^{25} +21.4$ (c 1.0, CHCl₃). IR (ATR): $\nu = 3029, 2954, 2932, 2865, 1708, 1552, 1450, 1378, 1111$ cm⁻¹. ¹H NMR (400 MHz, CDCl₃): $\delta = 7.38\text{--}7.28$ (m, 5 H), 4.59 (d, $J = 11.8$ Hz, 1 H), 4.56 (d, $J = 11.8$ Hz, 1 H), 4.47 (dd, $J = 12.6, 4.3$ Hz, 1 H), 4.21 (dd, $J = 12.6, 8.1$ Hz, 1 H), 4.03 (q, $J = 6.8$ Hz, 1 H), 3.26–3.19 (m, 1 H), 2.67–2.60 (m, 1 H), 1.65–1.55 (m, 1 H), 1.40 (d, $J = 6.8$ Hz, 3 H), 1.30–1.17 (m, 2 H), 1.00 (d, $J = 7.0$ Hz, 3 H), 0.88 (d, $J = 6.6$ Hz, 3 H), 0.82 (d, $J = 6.6$ Hz, 3 H) ppm. ¹³C NMR (100.6 MHz, CDCl₃): $\delta = 214.2, 137.5, 128.7, 128.2, 128.1, 79.7, 77.0, 71.9, 41.4, 39.7, 36.2, 25.2, 22.8, 22.2, 17.1, 11.4$ ppm. HRMS (ESI): calcd. for C₁₈H₃₁N₂O₄ [M + NH₄]⁺: 339.2278; found: 339.2276.

(2S,4S,5S)-2-Benzoyloxy-4,6-dimethyl-5-nitromethyl-3-heptanone

(2k): Yellowish oil. Yield: 44 mg (0.14 mmol), 28%; *R_f* (hexanes/EtOAc 90:10) 0.30. $[\alpha]_D^{25} +15.9$ (c 1.0, CHCl₃). IR (ATR): $\nu = 3025, 2963, 2932, 2883, 1708, 1543, 1454, 1374, 1107$ cm⁻¹. ¹H NMR (400 MHz, CDCl₃): $\delta = 7.39\text{--}7.29$ (m, 5 H), 4.61 (d, $J = 11.8$ Hz, 1 H), 4.56 (d, $J = 11.8$ Hz, 1 H), 4.45 (dd, $J = 13.8, 4.4$ Hz, 1 H), 4.29 (dd, $J = 13.8, 7.1$ Hz, 1 H), 4.06 (q, $J = 6.8$ Hz, 1 H), 3.39–3.33 (m, 1 H), 2.61–2.55 (m, 1 H), 1.74–1.66 (m, 1 H), 1.41 (d, $J = 6.8$ Hz, 3 H), 0.97 (d, $J = 7.0$ Hz, 3 H), 0.96 (d, $J = 6.8$ Hz, 3 H), 0.87 (d, $J = 6.8$ Hz, 3 H) ppm. ¹³C NMR (100.6 MHz, CDCl₃): $\delta = 214.2, 137.6, 128.7, 128.1, 128.0, 79.5, 75.1, 71.8, 43.5, 40.5, 30.1, 20.6, 19.2, 17.1, 12.1$ ppm. HRMS (ESI): calcd. for C₁₇H₂₉N₂O₄ [M + NH₄]⁺: 325.2122; found: 325.2125.

(2S,4S,5S)-2,7-Dibenzoyloxy-4-methyl-5-nitromethyl-3-heptanone (2l):

Colorless oil. Yield: 51 mg (0.13 mmol), 25%; *R_f* (hexanes/EtOAc 80:20) 0.20. $[\alpha]_D^{25} +10.2$ (c 1.0, CHCl₃). IR (ATR): $\nu = 3025, 2972, 2927, 2856, 1717, 1548, 1459, 1378, 1094$ cm⁻¹. ¹H NMR (400 MHz, CDCl₃): $\delta = 7.38\text{--}7.26$ (m, 5 H), 4.55 (s, 2 H), 4.52 (dd, $J = 13.0, 4.6$ Hz, 1 H), 4.42 (d, $J = 11.8$ Hz, 1 H), 4.38 (d, $J = 11.8$ Hz, 1 H), 4.36 (dd, $J = 13.0, 7.7$ Hz, 1 H), 4.04 (q, $J = 6.8$ Hz, 1 H), 3.49 (t, $J = 6.0$ Hz, 2 H), 3.30–3.24 (m, 1 H), 2.77–2.69 (m, 1 H), 1.71 (ddd, $J = 12.5, 6.1, 2.4$ Hz, 2 H), 1.34 (d, $J = 6.8$ Hz, 3 H), 1.03 (d, $J = 7.0$ Hz, 3 H) ppm. ¹³C NMR (100.6 MHz, CDCl₃): $\delta = 213.8, 138.1, 137.6, 128.6, 128.5, 128.1, 128.0, 127.8, 79.4, 76.6, 73.1, 71.8, 67.9, 41.8, 36.6, 30.3, 16.8, 12.2$ ppm. HRMS (ESI): calcd. for C₂₃H₃₃N₂O₅ [M + NH₄]⁺: 417.2384; found: 417.2393.

(2S,4S,5S)-2-Benzoyloxy-4-methyl-5-nitromethyl-7-triisopropylsilyloxy-3-heptanone (2m):

Colorless oil. Yield: 133 mg (0.29 mmol, 0.45 mmol scale), 64%; *R_f* (hexanes/EtOAc 90:10) 0.30. $[\alpha]_D^{25} +11.6$ (c 1.0, CHCl₃). IR (ATR): $\nu = 2942, 2860, 1710, 1546, 1457, 1372, 1096$ cm⁻¹. ¹H NMR (400 MHz, CDCl₃): $\delta = 7.40\text{--}7.20$ (m, 5 H), 4.56 (dd, $J = 12.9, 5.0$ Hz, 1 H), 4.56 (s, 2 H), 4.40 (dd, $J = 12.9, 7.3$ Hz, 1 H), 4.07 (q, $J = 6.8$ Hz, 1 H), 3.75 (t, $J = 5.9$ Hz, 2 H), 3.30 (dq, $J = 7.0, 5.2$ Hz, 1 H), 2.79–2.70 (m, 1 H), 1.67–1.50 (m, 2 H), 1.37 (d, $J = 6.8$ Hz, 3 H), 1.05 (d, $J = 7.0$ Hz, 3 H), 1.10–1.00 (m, 21 H) ppm. ¹³C NMR (100.6 MHz, CDCl₃): $\delta = 213.6, 137.5, 128.5, 127.9, 79.3, 76.6, 71.6, 61.1, 41.5, 36.3, 32.9, 17.9, 16.7, 12.3, 11.8$ ppm. HRMS (ESI): calcd. for C₂₅H₄₃NNaO₅Si [M + Na]⁺: 488.2803; found: 488.2806.

(2S,4S,5R)-2-Benzoyloxy-4-methyl-6-nitro-1,5-diphenyl-3-hexanone

(6a): Neat TiCl₄ (61 μ L, 0.55 mmol) was carefully added to a solution of chiral ketone **4** (134 mg, 0.5 mmol) in CH₂Cl₂ (2 mL) at –78 °C under N₂ and the resultant yellow suspension was stirred for 5 min. *i*-Pr₂NEt (96 μ L, 0.55 mmol) was added dropwise and the ensuing dark solution was stirred for 30 min at –78 °C. Then, TiCl₄ (61 μ L, 0.55 mmol) was added dropwise, followed 10 min later by the addition of (*E*)- β -nitrostyrene (**a**) (89 mg, 0.6 mmol). The resultant mixture was stirred at –78 °C for 1 h. The reaction was quenched at –78 °C with a 25% NH₄F (2 mL) and stirred for 30 min at room temperature with vigorous stirring. The mixture was diluted with CH₂Cl₂ (10 mL) and H₂O (10 mL). The aqueous layer was extracted with CH₂Cl₂ (3 \times 20 mL) and the organic extracts were dried over MgSO₄, filtered, and concentrated. The resulting crude product was purified by column chromatography (hexanes/EtOAc 90:10) to afford

151 mg (0.36 mmol, 72% yield) of (2S,4S,5R)-2-benzoyloxy-4-methyl-6-nitro-1,5-diphenyl-3-hexanone (**6a**) as a purple oil. *R_f* (hexanes/EtOAc 90:10) 0.20. $[\alpha]_D^{25} -8.4$ (c 1.0, CHCl₃). IR (ATR): $\nu = 3081, 3062, 3024, 2926, 2872, 1707, 1549, 1492, 1454, 1372, 1087, 732, 697$ cm⁻¹. ¹H NMR (400 MHz, CDCl₃): $\delta = 7.35\text{--}7.05$ (m, 15 H), 4.56 (d, $J = 11.4$ Hz, 1 H), 4.46 (d, $J = 11.4$ Hz, 1 H), 4.17 (dd, $J = 6.8, 4.5$ Hz, 1 H), 4.14 (d, $J = 10.7$ Hz, 1 H), 4.07 (dd, $J = 10.7, 4.5$ Hz, 1 H), 3.64 (td, $J = 10.3, 4.5$ Hz, 1 H), 3.22 (dq, $J = 10.3, 7.0$ Hz, 1 H), 3.15 (dd, $J = 14.1, 4.5$ Hz, 1 H), 2.94 (dd, $J = 14.1, 6.8$ Hz, 1 H), 0.78 (d, $J = 7.0$ Hz, 3 H) ppm. ¹³C NMR (100.6 MHz, CDCl₃): $\delta = 212.9, 137.5, 136.9, 136.8, 129.9, 128.8, 128.6, 128.5, 128.2, 128.2, 128.0, 127.8, 126.9, 83.9, 77.8, 73.1, 45.8, 44.3, 36.4, 15.9$ ppm. HRMS (ESI): calcd. for C₂₆H₃₁N₂O₄ [M + NH₄]⁺: 435.2278; found: 435.2279.

(2R,3S,5S)-5-Benzoyloxy-3,6-dimethyl-1-nitro-2-phenyl-4-heptanone

(7a): Neat TiCl₄ (97 μ L, 0.88 mmol) was carefully added to a solution of chiral ketone **5** (176 mg, 0.8 mmol) in CH₂Cl₂ (3.2 mL) at –78 °C under N₂ and the resultant yellow suspension was stirred for 5 min. *i*-Pr₂NEt (153 μ L, 0.88 mmol) was added dropwise and the ensuing dark solution was stirred for 30 min at –78 °C. Then, TiCl₄ (97 μ L, 0.88 mmol) was added dropwise, followed 10 min later by the addition of (*E*)- β -nitrostyrene (**a**) (143 mg, 0.96 mmol). The resultant mixture was stirred at –78 °C for 1 h. The reaction was quenched at –78 °C with a 25% NH₄F (4 mL) and stirred for 30 min at room temperature with vigorous stirring. The mixture was diluted with CH₂Cl₂ (20 mL) and H₂O (20 mL). The aqueous layer was extracted with CH₂Cl₂ (3 \times 20 mL) and the organic extracts were dried over MgSO₄, filtered, and concentrated. The resulting crude product was purified by column chromatography (from hexanes/EtOAc 95:5 to 90:10) to afford 173 mg (0.47 mmol, 59% yield) of (2R,3S,5S)-5-benzoyloxy-3,6-dimethyl-1-nitro-2-phenyl-4-heptanone (**7a**) as a brownish oil. *R_f* (hexanes/EtOAc 90:10) 0.25. $[\alpha]_D^{25} +11.5$ (c 1.0, CHCl₃). IR (ATR): $\nu = 3024, 2961, 2936, 2869, 1707, 1564, 1451, 1378, 1064, 729, 697$ cm⁻¹. ¹H NMR (400 MHz, CDCl₃): $\delta = 7.40\text{--}7.22$ (m, 8H), 7.17–7.10 (m, 2H), 4.60 (d, $J = 11.5$ Hz, 1H), 4.56 (dd, $J = 12.6, 10.3$ Hz, 1H), 4.49 (d, $J = 11.5$ Hz, 1H), 4.48 (dd, $J = 12.6, 4.5$ Hz, 1H), 3.70 (td, $J = 9.4, 5.4$ Hz, 1H), 3.66 (d, $J = 4.8$ Hz, 1H), 3.19 (dq, $J = 9.4, 6.9$ Hz, 1H), 2.22–2.10 (m, 1H), 0.98 (d, $J = 6.8$ Hz, 3H), 0.95 (d, $J = 6.9$ Hz, 3H), 0.93 (d, $J = 6.9$ Hz, 3H) ppm. ¹³C NMR (100.6 MHz, CDCl₃): $\delta = 213.0, 137.5, 137.4, 128.9, 128.5, 128.1, 128.0, 127.9, 127.9, 89.0, 77.7, 73.9, 46.6, 44.8, 30.0, 19.6, 17.2, 16.4$ ppm. HRMS (ESI): calcd. for C₂₂H₃₁N₂O₄ [M + NH₄]⁺: 387.2278; found: 387.2281.

(3R,4S)-5-[(S)-1-Benzoyloxyethyl]-4-methyl-3-phenyl-3,4-dihydro-2H-pyrrole (8):

Solid NaBH₄ (6 mg, 0.15 mmol) was added in one portion to a mixture of NiCl₂·6H₂O (12 mg, 50 μ mol) in MeOH (2 mL) at room temperature, which produced the formation of black clumps and heavy frothing. The mixture was sonicated for 30 min and the resultant black dispersion was cooled to 0 °C. The subsequent addition of a solution of Michael adduct **2a** (34 mg, 0.1 mmol) in MeOH (2 mL) followed by solid NaBH₄ (19 mg, 0.5 mmol) in one portion caused more frothing. The reaction mixture was stirred at 0 °C for 30 min. Then, this was quenched by the addition of a saturated solution of NH₄Cl (5 mL) with vigorous stirring. It was partitioned in CH₂Cl₂ and H₂O. The aqueous layer was extracted with CH₂Cl₂ (3 \times 10 mL) and the combined organic extracts were dried (MgSO₄), filtered, and concentrated. Eventually, the residue was purified by flash column chromatography (CH₂Cl₂/MeOH 96:4) to afford 26 mg (90 μ mol, 90% yield) of (3R,4S)-5-[(S)-1-benzoyloxyethyl]-4-methyl-3-phenyl-3,4-dihydro-2H-pyrrole (**8**) as a colorless oil. *R_f* (CH₂Cl₂/MeOH 96:4) 0.5. $[\alpha]_D^{25} +4.3$ (c 1.1, CHCl₃). IR (ATR): $\nu = 3083, 3061, 3034, 2976, 2923, 2865, 1574, 1499, 1454, 1365, 1205, 1067$ cm⁻¹. ¹H NMR (400 MHz, CDCl₃): $\delta = 7.38\text{--}7.19$ (m, 10 H), 5.15 (q, $J = 6.7$ Hz, 1 H), 4.63 (d, $J = 11.7$ Hz, 1 H), 4.57 (d, $J = 11.7$ Hz, 1 H), 4.43 (ddd, $J = 14.1, 8.7, 2.3$ Hz, 1 H), 4.09 (dd, $J = 14.1, 7.0, 2.0$ Hz, 1 H), 3.16–3.06 (m, 2 H), 1.42 (d, $J = 6.7$ Hz, 3 H), 1.07 (d, $J = 6.7$ Hz, 3 H) ppm. ¹³C NMR

(100.6 MHz, CDCl₃): δ = 149.9, 141.1, 138.2, 129.2, 128.5, 127.8, 127.8, 127.6, 127.0, 72.0, 69.0, 68.6, 46.4, 46.4, 18.3, 17.3 ppm. HRMS (ESI): calcd. for C₂₀H₂₄NO₂ [M + H]⁺: 294.1852; found: 294.1861.

(2R,3S,5S)-5-Benzyloxy-3-methyl-4-oxo-2-phenylhexanal oxime (9): Thiophenol (140 μ L, 1.35 mmol) and triethylamine (210 μ L, 1.5 mmol) were added to a suspension of SnCl₂ (86 mg, 0.45 mmol) in CH₃CN (0.6 mL) at room temperature. Then, a solution of nitroalkane **2a** (103 mg, 0.3 mmol) in CH₃CN (1.2 mL) was added carefully and the resultant mixture was stirred for 30 min. The mixture was concentrated under vacuum and the residue was purified by flash column chromatography (hexanes/EtOAc 80:20) to afford 73 mg (0.23 mmol, 75% yield) of (2R,3S,5S)-5-benzyloxy-3-methyl-4-oxo-2-phenylhexanal oxime (**9**) as a yellow oil. *R*_f(hexanes/EtOAc) 0.20. [α]_D²⁰ -104.2 (c 1.3, CHCl₃). IR (ATR): ν = 3278 (br), 3084, 3062, 3024, 2974, 2932, 2875, 1495, 1451, 1368, 1096 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 7.38–7.18 (m, 11 H), 4.72 (d, *J* = 11.8 Hz, 1 H), 4.48 (d, *J* = 11.8 Hz, 1 H), 3.79 (q, *J* = 6.4 Hz, 1 H), 3.27 (dd, *J* = 11.7, 1.5 Hz, 1 H), 2.28 (dq, *J* = 11.7, 6.6 Hz, 1 H), 1.40 (d, *J* = 6.4 Hz, 3 H), 0.83 (d, *J* = 6.6 Hz, 3 H) ppm. ¹³C NMR (100.6 MHz, CDCl₃): δ = 152.1, 139.2, 138.0, 129.1, 129.0, 128.5, 128.0, 127.9, 127.6, 98.9, 76.6, 71.4, 43.4, 34.7, 13.0, 12.6 ppm. HRMS (ESI): calcd. for C₂₀H₂₄NO₃ [M + H]⁺: 326.1751; found: 326.1750.

(2R,3S,5S)-5-Benzyloxy-3-methyl-4-oxo-2-phenylhexanenitrile (10): A solution of nitroalkane **2a** (34 mg, 0.1 mmol) in CH₂Cl₂ (0.5 mL) was added to a stirred suspension of Sn(SPh)₄ (11 mg, 20 μ mol), DMAP (13 mg, 0.11 mmol), 1 M Me₃P in THF (220 μ L, 0.22 mmol), and 40% DEAD in toluene (50 μ L, 0.11 mmol) in CH₂Cl₂ (0.5 mL) at 0 °C and the resulting mixture was stirred for 30 min at 0 °C. The reaction mixture was concentrated under vacuum and the residue was purified by flash column chromatography (hexanes/EtOAc 90:10) to afford 28 mg (90 μ mol, 93% yield) of (2R,3S,5S)-5-benzyloxy-3-methyl-4-oxo-2-phenylhexanenitrile (**10**) as a colorless oil. *R*_f(hexanes/EtOAc) 0.2. [α]_D²⁰ -104.2 (c 1.3, CHCl₃). IR (ATR): ν = 3084, 3059, 3031, 2974, 2929, 2869 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 7.40–7.28 (m, 10 H), 4.56 (s, 2H), 4.10 (q, *J* = 6.9 Hz, 1 H), 3.94 (d, *J* = 9.5 Hz, 1 H), 3.57 (dq, *J* = 9.5, 7.0 Hz, 1 H), 1.35 (d, *J* = 6.9 Hz, 3 H), 1.01 (d, *J* = 7.0 Hz, 3 H) ppm. ¹³C NMR (100.6 MHz, CDCl₃): δ = 212.0, 137.5, 133.5, 129.2, 128.7, 128.7, 128.6, 128.1, 127.9, 120.2, 80.0, 71.7, 46.0, 39.4, 16.4, 15.6 ppm. HRMS (ESI): calcd. for C₂₀H₂₅N₂O₂ [M + NH₄]⁺: 325.1913; found: 325.1913.

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Keywords: Michael addition • Diastereoselectivity • Substrate control • Chiral ketone • Titanium

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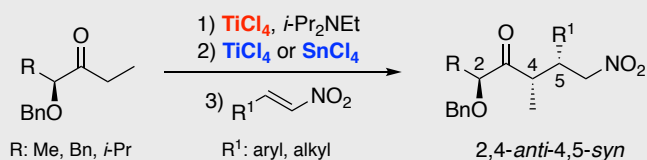
obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Lewis acid-mediated Michael additions of titanium enolates of chiral α -benzyloxy ketones to conjugated nitroalkenes proceed with high diastereoselectivity in good yields

Stereoselective Michael additions

Alejandro Gómez-Palomino, Adrián Barrios, Pedro García-Lorente, Pedro Romea, Fèlix Urpi* and Mercè Font-Bardia*

Page No. – Page No.

Substrate-Controlled Michael Additions of Titanium Enolates from Chiral α -Benzyloxy Ketones to Conjugated Nitroalkenes