Catalytic Asymmetric Direct Vinylogous Michael Addition of γ-Aryl-Substituted Deconjugated Butenolides to Nitroolefins and *N*-Phenylmaleimide

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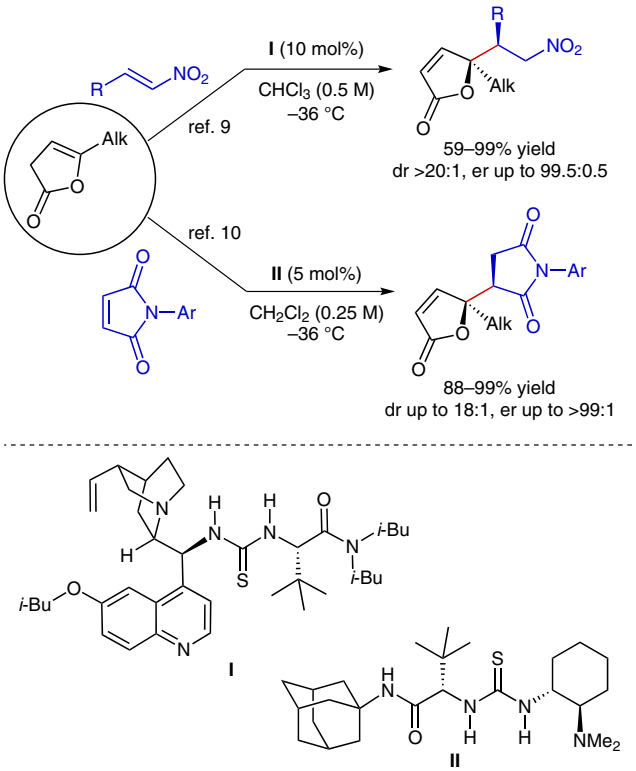
Received: 08.03.2013; Accepted after revision: 15.04.2013

Abstract: Direct asymmetric vinylogous Michael reactions of γ-aryl-substituted deconjugated butenolides with nitroolefins and *N*-phenylmaleimide are described using bifunctional thiourea derivatives as the catalyst. The resulting butenolide derivatives containing adjacent quaternary and tertiary stereocenters are obtained in good yields (54–90%) and with excellent enantioselectivities (er up to 99:1) and high diastereoselectivities (dr up to >20:1).

Key words: Michael reaction, butenolide, quaternary stereocenter, nitroolefin, maleimide

Owing to their widespread occurrence as substructures in various natural products, butenolides bearing a γ-quaternary stereocenter[1] have been a target of general interest among synthetic chemists.[2] In recent years, a number of reports concerning the stereoselective synthesis of butenolides containing the γ-quaternary stereocenter have appeared in the literature.[3–10] Because of their potential for the direct construction of γ,γ-disubstituted butenolides, γ-substituted deconjugated butenolides have garnered significant attention. However, most of these reports entail either alkyl- or aryl-substituted deconjugated butenolides as a pronucleophile. For example, Alexakis reported the Michael addition reaction of γ-alkyl-substituted deconjugated butenolides to enals using iminium catalysis.[4] Similarly, the catalytic asymmetric vinylogous Mannich-type reaction of α-angelica lactone with aldimines was reported by Feng using a chiral *N*,*N*′-dioxide–Sc(III) complex.[5] In the case of the reaction with isatin-derived Morita–Baylis–Hillman carbonates, disclosed by Chen, γ-aryl-substituted deconjugated butenolides were found to be unreactive.[6] To date, the number of reports where both γ-alkyl- and γ-aryl-substituted butenolides have been utilized successfully for the same transformation are very limited.[7,8] Recently, we disclosed the enantioselective vinylogous Michael addition of γ-alkyl-substituted deconjugated butenolide to nitroolefins[9] and N-substituted maleimides[10] with the help of bifunctional organocatalysts **I** and **II**, respectively (Scheme 1): Michael adducts containing contiguous quaternary and tertiary stereocenters were obtained with good to outstanding diastereoselectivity and excellent enantioselectivity.



Scheme 1 Bifunctional thiourea-catalyzed direct asymmetric vinylogous Michael addition of γ-alkyl-substituted deconjugated butenolides to nitroolefins and maleimides

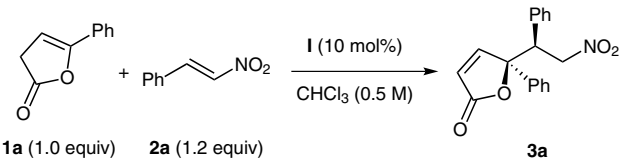
Inspired by these results and with our continued interest in developing new methods for the construction of quaternary stereocenters in a catalytic enantioselective fashion, we explored the compatibility of our protocols with γ-aryl-substituted deconjugated butenolides. Herein we disclose our findings on the asymmetric vinylogous Michael addition of such arylated deconjugated butenolides to nitroolefins and *N*-phenylmalemide using our previously reported catalysts **I** and **II**, respectively.

We commenced our studies with the vinylogous Michael addition to nitroolefins (Table 1). When the reaction between γ-phenyl-substituted deconjugated butenolide **1a** and β-nitrostyrene (**2a**) was conducted under our previously optimized reaction conditions (10 mol% catalyst **I**, $CHCl_3$, –36 °C),[9] the expected Michael adduct **3a** was obtained as a single diastereomer with reasonably high enantioselectivity (er 93:7) in 88% yield within 1.5 hours (entry 1). Moreover, the reaction was once again found to be highly regioselective as no α-Michael adduct was ob-

SYNTHESIS 2013, 45, 1641–1646
Advanced online publication: 08.05.2013
DOI: 10.1055/s-0033-1338705; Art ID: SS-2013-C0191-ST

served. Higher reactivity of γ-phenyl-substituted butenolide **1a** compared to its alkyl counterparts presumably stems from the enhanced acidity of the α-proton. Lowering the temperature to –45 °C slightly improved the enantioselectivity (er 94.5:5.5) without affecting the yield (entry 2). However, further decreasing the temperature to –60 °C resulted in diminished enantioselectivity (entry 3). The catalyst loading could be reduced to 5 mol% without affecting the stereochemical outcome of the reaction, however the reaction rate decreased considerably (entry 4).

Table 1 Optimization of the Reaction Temperature for Vinylogous Michael Addition of γ-Phenyl-Substituted Butenolide **1a** to β-Nitrostyrene (**2a**)



1a (1.0 equiv) **2a** (1.2 equiv) **3a**

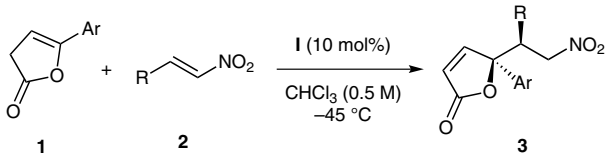
Entry	Temp (°C)	Time (h)	Yield[a] (%)	dr[b]	er[c]
1	–36	1.5	88	>20:1	93:7
2	–45	5	88	>20:1	94.5:5.5
3	–60	12	86	>20:1	91:9
4[d]	–45	60	72	>20:1	94.5:5.5

[a] Isolated yield after column chromatography.
[b] Determined by ^{1}H NMR analysis of the crude reaction mixture.
[c] Determined by HPLC analysis using a stationary phase chiral column.
[d] Using 5 mol% catalyst.

We then turned our attention towards investigating the scope of various γ-aryl-substituted butenolides in this reaction under our optimized reaction conditions (Table 1, entry 2). The results are presented in Table 2. In all the cases, the Michael adducts **3a**–**i** were obtained as single diastereomers in moderate to good yields. Both electron-rich as well as electron-deficient aryl-substituted butenolides can be used as the nucleophile. Heteroaryl-substituted butenolides are also efficient nucleophiles as evident from 2-furyl-substituted butenolide (entry 6). As expected, both electron-rich and electron-deficient nitroolefins worked equally well, and the products were obtained in very good yields with excellent enantioselectivities (entry 7 and 8). Particularly noteworthy is the less reactive and more challenging aliphatic nitroolefin **2d**, where a prolonged reaction time ensured that the product **3i** was obtained in good yield and high enantioselectivity (entry 9).

After successfully demonstrating the compatibility of our previously reported protocol for the vinylogous Michael reaction of γ-aryl-substituted butenolides to nitroolefins, we focused on maleimide as the Michael acceptor. Initial studies were carried out using the reaction between **1a** and *N*-phenylmaleimide (**4**) using catalyst **II** at –41 °C (Table 3).[10] The Michael adduct **5a** was formed with excellent enantioselectivity (er 98:2) and high diastereoselectivity (dr 12:1) in 86% yield (entry 1). Lowering the catalyst loading from 5 to 2 mol% provided better enantioselectivity, despite slight erosion of both the diastereoselectivity and reaction rate (entry 2). We were excited to find that the catalyst loading could be further reduced to 1 mol% while still maintaining a high level of enantioselectivity (entry 3). However, a longer reaction time was required in this case to achieve a reasonable chemical yield.

Table 2 Substrate Scope for the Asymmetric Vinylogous Michael Addition of γ-Aryl-Substituted Butenolides **1** to Nitroolefins **2**[a]

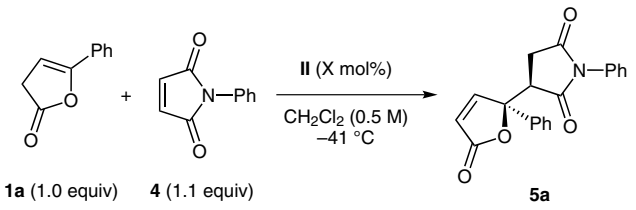


1 **2** **3**

Entry	Ar	R	Time (h)	Product	Yield[b] (%)	er[c]
1	Ph (**1a**)	Ph (**2a**)	5	**3a**	88	94.5:5.5
2	4-MeC_6H_4 (**1b**)	Ph (**2a**)	6	**3b**	83	96:4
3	3,4-$Me_2C_6H_3$ (**1c**)	Ph (**2a**)	7	**3c**	75	92:8
4	2-naphthyl (**1d**)	Ph (**2a**)	4.5	**3d**	68	92.5:7.5
5	4-ClC_6H_4 (**1e**)	Ph (**2a**)	2.5	**3e**	85	91:9
6	2-furyl (**1f**)	Ph (**2a**)	2.5	**3f**	67	90.5:9.5
7	4-MeC_6H_4 (**1b**)	4-MeOC_6H_4 (**2b**)	6	**3g**	90	97:3
8	4-MeC_6H_4 (**1b**)	4-ClC_6H_4 (**2c**)	4	**3h**	86	96:4
9	4-MeC_6H_4 (**1b**)	*i*-Bu (**2d**)	84	**3i**	79	96:4

[a] Reaction conditions: **1** (1.0 equiv), **2** (1.2 equiv), argon atmosphere.
[b] Isolated yield of the products after column chromatography. In all cases, products were obtained with dr >20:1.
[c] Determined by HPLC analysis using a stationary phase chiral column.

Table 3 Catalyst Loading Optimization for Vinylogous Michael Addition of γ-Phenyl-Substituted Butenolide **1a** to *N*-Phenylmaleimide (**4**)



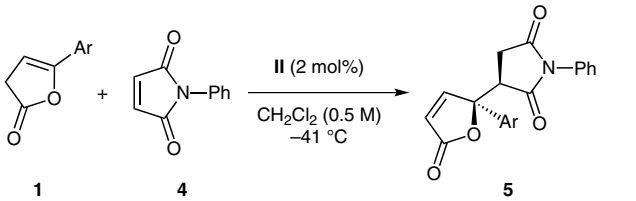
1a (1.0 equiv) **4** (1.1 equiv) **5a**

Entry	X	Time (h)	Yield[a] (%)	dr[b]	er[c]
1	5	1.5	86	12:1	98:2
2	2	6	84	10:1	99:1
3	1	12	62	10:1	98:2

[a] Isolated yield after column chromatography.
[b] Determined by ^{1}H NMR analysis of the crude reaction mixture.
[c] Determined by HPLC analysis using a stationary phase chiral column.

With practicality in mind, we decided to use 2 mol% of catalyst **II** in experiments to demonstrate the scope of γ-aryl-substitution of the butenolide in its addition reaction to *N*-phenylmaleimide (**4**). As can be seen in Table 4, in all cases, the Michael adducts **5a**–**e** were obtained with good to excellent levels of enantioselectivity. Even though the electrophile scope was restricted only to *N*-phenylmaleimide (**4**) for this study, similar level of diastereo- and enantioselectivity may be expected for Michael addition of these arylated butenolides to other N-substituted maleimides.

Table 4 Substrate Scope for the Asymmetric Vinylogous Michael Addition of γ-Aryl-Substituted Butenolides to *N*-Phenylmaleimide (**4**)[a]



1 **4** **5**

Entry	Ar	Time (h)	**5**	Yield[b] (%)	dr[c]	er[d]
1	Ph (**1a**)	6	**5a**	84	10:1	99:1
2	4-MeC_6H_4 (**1b**)	4.5	**5b**	83	10:1	99:1
3	3,4-$Me_2C_6H_3$ (**1c**)	10	**5c**	54	7:1	98:2
4	2-naphthyl (**1d**)	5	**5d**	60	7:1	98:2
5	4-FC_6H_4 (**1g**)	10	**5e**	68	6:1	96:4

[a] Reaction conditions: **1** (1.0 equiv), **4** (1.1 equiv).
[b] Isolated yield of the products after column chromatography.
[c] Determined by ^{1}H NMR analysis of the crude reaction mixture.
[d] Determined by HPLC analysis using a stationary phase chiral column.

In conclusion, we were able to broaden the scope of our previously reported catalyst systems to γ-aryl-substituted deconjugated butenolides. The same catalysts were found to be at least equally efficient both for the direct vinylogous Michael addition to nitroolefins as well as to maleimides under the reaction conditions, which were nearly identical to those used for γ-alkyl-substituted butenolides. Higher reactivity of arylated butenolides allowed us to reduce the catalyst loading to 1 mol% for the addition to *N*-phenylmaleimide. Therefore, our protocols are among the few catalytic asymmetric transformations,[7,8] where both γ-alkyl- and γ-aryl-substituted deconjugated butenolides can be used with equal efficiency.

Unless stated otherwise, all reactions were carried out with distilled and dried solvents under an atmosphere of argon. Oven (120 °C) dried glassware with standard vacuum line techniques were used. Organic solvents used for reactions were dried using standard methods. γ-Arylbutenolides were prepared according to literature procedures.[11,12] All workups and purifications were carried out with reagent grade solvents in air. TLC was performed using Merck silica gel 60 F_{254} pre-coated plates (0.25 mm). Column chromatography was performed using silica gel (230–400 or 100–200 mesh); PE = petroleum ether. FT-IR spectra were recorded on a Perkin Elmer Spectrum BX spectrophotometer. NMR spectra were recorded on Bruker Ultrashield spectrometer at 400 MHz (^{1}H) and 100 MHz (^{13}C). Reference: TMS with the solvent resonance as internal standard [$CDCl_3$: δ = 7.26 (^{1}H); $CDCl_3$: δ = 77.16 (^{13}C)]. HRMS was performed on Micromass Q-TOF Micro instrument. Optical rotations were measured on JASCO P-1020 polarimeter. Melting points were measured using ANALAB μ-Thermocal 10 melting point apparatus. All melting points were measured in open glass capillary and values are uncorrected. Enantiomeric ratios were determined by HPLC analysis using chiral columns in comparison with authentic racemic materials.

(*S*)-5-[(*S*)-2-Nitro-1-phenylethyl]-5-phenylfuran-2(5*H*)-one (3a); Typical Procedure

An oven-dried Schlenk tube was charged with β-nitrostyrene (**2a**, 28.6 mg, 0.19 mmol, 1.2 equiv) and catalyst **I** (10.4 mg, 0.016 mmol, 0.1 equiv) under argon flow. $CHCl_3$ (0.10 mL) was added to the mixture and it was cooled to –45 °C under positive argon pressure. A solution of butenolide **1a** (25 mg, 0.16 mmol, 1.0 equiv) in $CHCl_3$ (0.22 mL) was added, and the resulting soln was stirred at –45 °C until TLC (20% EtOAc–PE) revealed complete consumption of **1a** (5 h). The mixture was brought up to r.t., the solvent was removed in vacuo, and the residue was purified by column chromatography (silica gel, 100–200 mesh, EtOAc–PE, 1:3) to afford **3a** (42.5 mg, 0.14 mmol, 88%) as an off-white solid; mp 168–170 °C; $[\alpha]_D^{21}$ –84.5 (*c* 2.0, $CHCl_3$).

HPLC (Chiralpak AD-H column, *n*-hexane–EtOH, 75:25, 1.0 mL/min, 20 °C, 210 nm): t_R = 13.2 (minor), 17.7 min (major).

FT-IR (KBr): 3100 (m), 2930 (w), 1747 (s), 1541 (s), 1434 (w), 1381 (m), 1202 (w), 1127 (w), 1118 cm^{-1} (m).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.39 (m, 6 H), 7.34–7.22 (m, 5 H), 5.68 (d, *J* = 5.6 Hz, 1 H), 4.98 (dd, *J* = 11.3, 13.6 Hz, 1 H), 4.50 (dd, *J* = 3.8, 13.7 Hz, 1 H), 4.31 (dd, *J* = 3.8, 11.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4, 158.0, 136.7, 133.3, 129.7, 129.34, 129.26, 129.0, 128.7, 124.9, 120.1, 90.9, 75.6, 52.2.

HRMS (ESI+): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{15}NNaO_4$: 332.0899; found: 332.0898.

(*S*)-5-[(*S*)-2-Nitro-1-phenylethyl]-5-*p*-tolylfuran-2(5*H*)-one (3b)
Column chromatography (EtOAc–PE, 1:4); white solid; yield: 42 mg (0.13 mmol, 83%); mp 174–176 °C; $[\alpha]_D^{21}$ –120.5 (*c* 1.0, $CHCl_3$).

HPLC (Chiralpak AD-H column, *n*-hexane–EtOH, 75:25, 1.0 mL/min, 20 °C, 210 nm): t_R =12.7 (minor), 14.9 min (major).

FT-IR (KBr): 3109 (w), 2921 (w), 1748 (s), 1557 (m), 1543 (m), 1435 (w), 1381 (m), 1193 (m), 1101 cm^{-1} (m).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.39 (m, 3 H), 7.33–7.27 (m, 7 H), 5.65 (d, *J* = 5.6 Hz, 1 H), 4.97 (dd, *J* = 11.4, 13.5 Hz, 1 H), 4.52 (dd, *J* = 3.7, 13.6 Hz, 1 H), 4.28 (dd, *J* = 3.8, 11.3 Hz, 1 H), 2.38 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5, 158.2, 139.4, 133.7, 133.4, 130.4, 129.2, 128.9, 128.7, 124.7, 119.8, 90.9, 75.6, 52.2, 21.1.

HRMS (ESI+): *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{17}NNaO_4$: 346.1055; found: 346.1053.

(*S*)-5-(3,4-Dimethylphenyl)-5-[(*S*)-2-nitro-1-phenylethyl]furan-2(5*H*)-one (3c)
Column chromatography (EtOAc–PE, 1:4); off-white solid; yield: 39.6 mg (0.117 mmol, 75%); mp 204–206 °C; $[\alpha]_D^{21}$ –123.9 (*c* 1.0, $CHCl_3$).

HPLC (Chiralpak AD-H column, *n*-hexane–EtOH, 75:25, 1.0 mL/min, 20 °C, 254 nm): t_R = 6.7 (major), 9.8 min (minor).

FT-IR (KBr): 3031 (w), 2922 (w), 2854 (w), 1746 (s), 1549 (m), 1454 (w), 1381 (m), 1198 (w), 1104 cm^{-1} (m).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.41 (d, *J* = 5.6 Hz, 1 H), 7.34–7.22 (m, 8 H), 5.64 (d, *J* = 5.6 Hz, 1 H), 4.98 (dd, *J* = 11.4, 13.6 Hz, 1 H), 4.53 (dd, *J* = 3.7, 13.7 Hz, 1 H), 4.27 (dd, *J* = 3.7, 11.3 Hz, 1 H), 2.32 (s, 3 H), 2.29 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7, 158.4, 138.3, 138.0, 134.0, 133.5, 130.8, 129.2, 128.9, 128.7, 125.8, 122.2, 119.7, 90.9, 75.7, 52.2, 20.2, 19.6.

HRMS (ESI+): *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{19}NNaO_4$: 360.1212; found: 360.1209.

(*S*)-5-(Naphthalen-2-yl)-5-[(*S*)-2-nitro-1-phenylethyl]furan-2(5*H*)-one (3d)
Column chromatography (EtOAc–PE, 1:4); off-white solid; yield: 38 mg (0.106 mmol, 68%); mp 195 °C (dec); $[\alpha]_D^{21}$ –117.7 (*c* 1.0, $CHCl_3$).

HPLC (Chiralpak AD-H column, *n*-hexane–EtOH, 75:25, 1.0 mL/min, 20 °C, 254 nm): t_R = 16.7 (minor), 20.1 min (major).

FT-IR (KBr): 3089 (w), 2925 (m), 1773 (m), 1752 (s), 1551 (m), 1376 (w), 1194 (w), 1100 cm^{-1} (m).

^1H NMR (400 MHz, $CDCl_3$): δ = 8.02 (br s, 1 H), 7.98 (d, *J* = 8.6 Hz, 1 H), 7.91–7.87 (m, 2 H), 7.60–7.54 (m, 4 H), 7.37–7.30 (m, 5 H), 5.71 (d, *J* = 5.6 Hz, 1 H), 5.03 (dd, *J* = 11.5, 13.4 Hz, 1 H), 4.52 (dd, *J* = 3.7, 13.6 Hz, 1 H), 4.44 (dd, *J* = 3.6, 11.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5, 158.0, 133.9, 133.33, 133.27, 129.9, 129.3, 129.1, 128.7, 128.4, 127.9, 127.4, 124.4, 121.9, 120.2, 91.1, 75.6, 52.0.

HRMS (ESI+): *m*/*z* $[M + Na]^+$ calcd for $C_{22}H_{17}NNaO_4$: 382.1055; found: 382.1053.

(*S*)-5-(4-Chlorophenyl)-5-[(*S*)-2-nitro-1-phenylethyl]furan-2(5*H*)-one (3e)
Column chromatography (EtOAc–PE, 9:41); off-white solid; yield: 45 mg (0.131 mmol, 85%); mp 158–160 °C; $[\alpha]_D^{25}$ –94.7 (*c* 1.0, $CHCl_3$).

HPLC (Chiralpak ID column, *n*-hexane–EtOH, 95:5, 1.5 mL/min, 20 °C, 254 nm): t_R = 12.4 (minor), 14.1 min (major).

FT-IR (KBr): 3112 (w), 2922 (w), 1771 (s), 1557 (s), 1494 (w), 1379 (m), 1228 (w), 1194 (m), 1095 cm^{-1} (m).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.40 (m, 5 H), 7.33–7.31 (m, 3 H), 7.26–7.23 (m, 2 H), 5.71 (d, *J* = 5.6 Hz, 1 H), 4.95 (dd, *J* = 11.1, 13.4 Hz, 1 H), 4.50 (dd, *J* = 3.8, 13.5 Hz, 1 H), 4.27 (dd, *J* = 3.8, 10.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 157.5, 135.5, 135.3, 133.1, 129.9, 129.3, 129.1, 128.6, 126.4, 120.4, 90.4, 75.4, 52.1.

HRMS (ESI+): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{14}ClNNaO_4$: 366.0509; found: 366.0509.

(*S*)-5-(Furan-2-yl)-5-[(*S*)-2-nitro-1-phenylethyl]furan-2(5*H*)-one (3f)
Column chromatography (EtOAc–PE, 1:3); off-white solid; yield: 31.3 mg (0.105 mmol, 67%); mp 105–107 °C; $[\alpha]_D^{21}$ –45.1 (*c* 1, $CHCl_3$).

HPLC (Chiralpak AD-H column, *n*-hexane–EtOH, 75:25, 1.0 mL/min, 20 °C, 254 nm): t_R = 9.9 (minor), 27.6 min (major).

FT-IR (thin film): 2923 (w), 1774 (s), 1555 (s), 1432 (w), 1378 (w), 1183 (w), 1098 cm^{-1} (w).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.51 (br s, 1 H), 7.42 (d, *J* = 5.6 Hz, 1 H), 7.33–7.20 (m, 5 H), 6.44–6.40 (m, 2 H), 5.79 (d, *J* = 5.6 Hz, 1 H), 4.95 (dd, *J* = 10.6, 13.7 Hz, 1 H), 4.72 (dd, *J* = 4.2, 13.7 Hz, 1 H), 4.48 (dd, *J* = 4.2, 10.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 155.7, 148.5, 144.0, 133.1, 129.3, 129.1, 128.5, 121.0, 111.1, 108.5, 87.5, 75.8, 49.2.

HRMS (ESI+): *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{13}NNaO_5$: 322.0691; found: 322.0692.

(*S*)-5-[(*S*)-1-(4-Methoxyphenyl)-2-nitroethyl]-5-*p*-tolylfuran-2(5*H*)-one (3g)
Column chromatography (EtOAc–PE, 1:3); white solid; yield: 49.6 mg (0.140 mmol, 90%); mp 175–177 °C; $[\alpha]_D^{23}$ –81.3 (*c* 1.5, $CHCl_3$).

HPLC (Chiralpak AD-H column, *n*-hexane–EtOH, 75:25, 1.0 mL/min, 20 °C, 210 nm): t_R =14.2 min (major), 24.1 min (minor).

FT-IR (thin film): 3086 (w), 2924 (s), 1775 (s), 1760 (s), 1554 (m), 1515 (m), 1440 (w), 1252 (m), 1183 (m), 1034 cm^{-1} (m).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.38 (m, 3 H), 7.27 (d, *J* = 7.7 Hz, 2 H), 7.18 (d, *J* = 8.5 Hz, 2 H), 6.83 (d, *J* = 8.5 Hz, 2 H), 5.67 (d, *J* = 5.6 Hz, 1 H), 4.91 (dd, *J* = 11.7, 13.1 Hz, 1 H), 4.48 (dd, *J* = 3.7, 13.4 Hz, 1 H), 4.24 (dd, *J* = 3.6, 11.2 Hz, 1 H), 3.77 (s, 3 H), 2.38 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.6, 159.9, 158.4, 139.3, 133.8, 130.3, 129.8, 125.2, 124.7, 119.8, 114.5, 91.2, 75.8, 55.3, 51.5, 21.2.

HRMS (ESI+): *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{19}NNaO_5$: 376.1161; found: 376.1162.

(*S*)-5-[(*S*)-1-(4-Chlorophenyl)-2-nitroethyl]-5-*p*-tolylfuran-2(5*H*)-one (3h)
Column chromatography (EtOAc–PE, 1:4); white solid; yield: 48.2 mg (0.135 mmol, 86%); mp 181–183 °C; $[\alpha]_D^{23}$ –86.3 (*c* 2.0, $CHCl_3$).

HPLC (Chiralpak IE column, *n*-hexane–EtOH, 90:10, 1.0 mL/min, 20 °C, 210 nm): t_R =11.8 min (major), 14.7 min (minor).

FT-IR (thin film): 3093 (w), 2923 (w), 1778 (s), 1760 (s), 1556 (s), 1436 (w), 1378 (m), 1182 (m), 1093 cm^{-1} (m).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.37 (m, 3 H), 7.31–7.20 (m, 6 H), 5.70 (d, *J* = 5.6 Hz, 1 H), 4.91 (dd, *J* = 11.7, 13.3 Hz, 1 H), 4.50 (dd, *J* = 3.7, 13.7 Hz, 1 H), 4.26 (dd, *J* = 3.6, 11.3 Hz, 1 H), 2.38 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.3, 158.0, 139.5, 135.0, 133.3, 131.9, 130.5, 130.0, 129.5, 124.7, 120.2, 90.7, 75.5, 51.6, 21.2.

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{16}ClNNaO_4$: 380.0666; found: 380.0667.

(*S*)-5-[(*S*)-4-Methyl-1-nitropentan-2-yl]-5-*p*-tolylfuran-2(5*H*)-one (3i)

Column chromatography (EtOAc–PE, 1:3); white solid; yield: 37 mg (0.123 mmol, 79%); mp 118–120 °C; $[\alpha]_D^{21}$ –239.7 (*c* 1, $CHCl_3$).

HPLC (Chiralpak AD-H column, *n*-hexane–EtOH, 75:25, 1.0 mL/min, 20 °C, 254 nm): t_R = 6.2 min (major), 7.2 min (minor).

FT-IR (KBr): 3122 (w), 2924 (w), 1756 (s), 1552 (s), 1434 (w), 1383 (w), 1199 (w), 1109 cm^{-1} (w).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 5.6 Hz, 1 H), 7.30–7.21 (m, 4 H), 6.09 (d, *J* = 5.6 Hz, 1 H), 4.35 (dd, *J* = 4.5, 13.5 Hz, 1 H), 4.26 (dd, *J* = 7.5, 13.6 Hz, 1 H), 3.21–3.15 (m, 1 H), 2.35 (s, 3 H), 1.53–1.43 (m, 1 H), 1.29–1.19 (m, 2 H), 0.91 (d, *J* = 6.5 Hz, 3 H), 0.87 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7, 158.1, 139.2, 134.0, 130.2, 125.0, 120.3, 92.3, 76.7, 43.2, 36.9, 26.5, 22.9, 22.1, 21.2.

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{21}NNaO_4$: 326.1368; found: 326.1366.

(*R*)-3-[(*S*)-5-Oxo-2-phenyl-2,5-dihydrofuran-2-yl]-1-phenylpyrrolidine-2,5-dione (5a); Typical Procedure

An oven-dried Schlenk tube was charged, under argon, with catalyst **II** (1.4 mg, 0.0032 mmol, 0.02 equiv) and *N*-phenylmaleimide (**4**; 30.5 mg, 0.176 mmol, 1.1 equiv), followed by the addition of CH_2Cl_2 (0.1 mL). The resulting soln was cooled to –41 °C under positive argon pressure. A soln of **1a** (25 mg, 0.16 mmol, 1.0 equiv) in CH_2Cl_2 (0.22 mL) was added at –41 °C over 5 min. The resulting mixture was allowed to stir at this temperature until completion of the reaction (TLC monitoring, 6 h). The mixture was allowed to warm up to r.t. and concentrated to a residue that was purified by column chromatography (silica gel, 230–400 mesh, EtOAc–toluene, 1:3) to afford **5a** (44.8 mg, 0.134 mmol, 84%) as an off-white foam.

HPLC (Daicel Chiralpak ID column, *n*-hexane–EtOH, 70:30, 1.0 mL/min, 20 °C, 210 nm): t_R = 10.8 (minor), 12.4 min (major).

FT-IR (KBr): 3100 (w), 2926 (w), 1772 (s), 1714 (s), 1500 (m), 1387 (m), 1202 (m), 1104 cm^{-1} (w).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.43 (d, *J* = 5.7 Hz, 1 H), 7.46–7.40 (m, 8 H), 7.02–6.99 (m, 2 H), 6.22 (d, *J* = 5.7 Hz, 1 H), 3.41 (dd, *J* = 4.6, 9.0 Hz, 1 H), 3.06 (dd, *J* = 9.0, 19.0 Hz, 1 H), 2.96 (dd, *J* = 4.6, 19.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.3, 174.0, 170.7, 158.3, 136.9, 133.9, 131.3, 129.7, 129.4, 129.2, 126.4, 126.0, 120.4, 89.3, 50.7, 31.1.

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{15}NNaO_4$: 356.0899; found: 356.0894.

(*R*)-3-[(*S*)-5-Oxo-2-(*p*-tolyl)-2,5-dihydrofuran-2-yl]-1-phenylpyrrolidine-2,5-dione (5b)

Column chromatography (EtOAc–toluene, 1:3); sticky gel; yield: 40.4 mg (0.116 mmol, 83%).

HPLC (Daicel Chiralpak AD-H column, *n*-hexane–EtOH, 50:50, 1.0 mL/min, 20 °C, 254 nm): t_R= 13.2 (minor), 15.1 min (major).

FT-IR (KBr): 3100 (w), 2926 (m), 1771 (s), 1714 (s), 1500 (m), 1387 (s), 1190 (m), 1095 cm^{-1} (m).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.41 (d, *J* = 5.6 Hz, 1 H), 7.47–7.40 (m, 3 H), 7.33 (d, *J* = 7.7 Hz, 2 H), 7.21 (d, *J* = 7.6 Hz, 2 H), 7.03 (d, *J* = 7.3 Hz, 2 H), 6.20 (d, *J* = 5.5 Hz, 1 H), 3.39 (dd, *J* = 4.4, 8.4 Hz, 1 H), 3.05 (dd, *J* = 9.0, 19.1 Hz, 1 H), 2.95 (dd, *J* = 4.2, 18.9 Hz, 1 H), 2.36 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.3, 174.1, 170.8, 158.5, 139.8, 131.3, 130.9, 130.4, 130.1, 129.4, 129.2, 126.5, 125.8, 120.2, 89.4, 50.7, 31.1, 21.2.

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{17}NNaO_4$: 370.1055; found: 370.1060.

(*R*)-3-[(*S*)-2-(3,4-Dimethylphenyl)-5-oxo-2,5-dihydrofuran-2-yl]-1-phenylpyrrolidine-2,5-dione (5c)

Column chromatography (EtOAc–toluene, 1:3); brownish sticky gel; yield: 25.2 mg (0.070 mmol, 54%).

HPLC (Daicel Chiralpak AD-H column *n*-hexane–EtOH, 50:50, 1.0 mL/min, 20 °C, 254 nm): t_R= 11.6 (minor), 14.1 min (major).

FT-IR (KBr): 3102 (w), 2924 (w), 1768 (m), 1715 (s), 1503 (w), 1386 (m), 1194 (m), 1100 cm^{-1} (w).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.40 (d, *J* = 5.7 Hz, 1 H), 7.44 (d, *J* = 7.8 Hz, 2 H), 7.22–7.15 (m, 4 H), 7.03 (d, *J* = 7.8 Hz, 2 H), 6.18 (d, *J* = 5.6 Hz, 1 H), 3.37 (dd, *J* = 4.7, 8.6 Hz, 1 H), 3.04 (dd, *J* = 8.6, 18.9 Hz, 1 H), 2.96 (dd, *J* = 4.8, 19.1 Hz, 1 H), 2.25 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.4, 174.3, 158.7, 138.4, 138.0, 131.2, 130.6, 129.4, 129.2, 126.9, 126.7, 126.5, 123.3, 120.0, 89.4, 50.7, 31.1, 20.1, 19.6.

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{19}NNaO_4$: 384.1212; found: 384.1210.

(*R*)-3-[(*S*)-2-(Naphthalen-2-yl)-5-oxo-2,5-dihydrofuran-2-yl]-1-phenylpyrrolidine-2,5-dione (5d)

Column chromatography (EtOAc–toluene, 1:3); off-white foam; yield: 22.0 mg (0.072 mmol, 60%).

HPLC (Daicel Chiralpak AD-H column, *n*-hexane–EtOH, 50:50, 1.0 mL/min, 20 °C, 254 nm): t_R = 23.6 (minor), 29.0 min (major).

FT-IR (KBr): 3059 (w), 2926 (m), 1773 (m), 1713 (s), 1499 (w), 1388 (m), 1193 (m), 1098 cm^{-1} (w).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.53 (d, *J* = 5.7 Hz, 1 H), 7.97–7.96 (m, 1 H), 7.87–7.84 (m, 2 H), 7.58–7.55 (m, 2 H), 7.52–7.45 (m, 2 H), 7.41–7.38 (m, 3 H), 6.98–6.95 (m, 2 H), 6.24 (d, *J* = 5.7 Hz, 1 H), 3.49 (dd, *J* = 4.8, 8.9 Hz, 1 H), 3.08 (dd, *J* = 8.9, 19.0 Hz, 1 H), 2.99 (dd, *J* = 4.9, 19.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.4, 173.9, 170.8, 158.4, 133.3, 133.1, 131.3, 131.2, 129.41, 129.39, 129.2, 128.5, 127.8, 127.5, 127.4, 126.7, 126.4, 125.8, 122.6, 120.5, 89.6, 50.7, 31.1.

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{17}NNaO_4$: 406.1055; found: 406.1054.

(*R*)-3-[(*S*)-2-(4-Fluorophenyl)-5-oxo-2,5-dihydrofuran-2-yl]-1-phenylpyrrolidine-2,5-dione (5e)

Column chromatography (EtOAc–toluene, 1:3); sticky gel; yield: 33.6 mg (0.096 mmol, 68%).

HPLC (Daicel Chiralpak AD-H column, *n*-hexane–EtOH, 50:50, 1.0 mL/min, 20 °C, 254 nm): t_R = 11.8 (minor), 23.1 min (major).

FT-IR (KBr): 3080 (w), 2926 (w), 1772 (m), 1714 (s), 1512 (m), 1387 (m), 1201 (m), 1114 (w), 1090 cm^{-1} (w).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.38 (d, *J* = 5.7 Hz, 1 H), 7.46–7.42 (m, 5 H), 7.13–7.09 (m, 2 H), 7.02 (d, *J* = 7.6 Hz, 2 H), 6.21 (d, *J* = 5.7 Hz, 1 H), 3.41 (dd, *J* = 4.5, 9.1 Hz, 1 H), 3.05 (dd, *J* = 9.2, 18.9 Hz, 1 H), 2.89 (dd, *J* = 4.5, 18.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.2, 173.8, 170.4, 164.4, 158.1, 131.2, 129.9, 129.4, 129.2, 128.1, 128.0, 126.6, 126.3, 120.5, 116.6, 116.4, 88.8, 50.5, 30.9.

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{14}FNNaO_4$: 374.0805; found: 374.0804.

Acknowledgment

Generous financial support from Indian Institute of Science, Bangalore in the form of a start-up grant is gratefully acknowledged. This research program is funded by the Department of Science and Technology (DST), New Delhi (Grant No. SR/FT/CS-90/2010) and the

Council of Scientific and Industrial Research (CSIR), New Delhi (Grant No.01 (2505)/11/EMR-II). V.K. thanks IISc for a postdoctoral fellowship. We wish to thank Mr. Madhu Sudan Manna for sharing the catalysts used in this study.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

References

(1) For selected reviews on the generation of quaternary stereogenic centers, see: (a) Das, J. P.; Marek, I. *Chem. Commun.* **2011**, *47*, 4593. (b) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369. (c) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473. (d) Christoffers, J.; Mann, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 4591.

(2) For selected examples on butenolide as substructure in natural products, see: (a) Igarashi, Y.; Ogura, H.; Furihata, K.; Oku, N.; Indananda, C.; Thamchaipenet, A. *J. Nat. Prod.* **2011**, *74*, 670. (b) Montagnon, T.; Tofi, M.; Vassilikogiannakis, G. *Acc. Chem. Res.* **2008**, *41*, 1001. (c) Shiomi, K.; Ui, H.; Suzuki, H.; Hatano, H.; Nagamitsu, T.; Takano, D.; Miyadera, H.; Yamashita, T.; Kita, K.; Miyoshi, H.; Harder, A.; Tomoda, H.; Ōmura, S. *J. Antibiot.* **2005**, *58*, 50.

(3) For a non-asymmetric γ-arylation of butenolides, see: Hyde, A. M.; Buchwald, S. L. *Org. Lett.* **2009**, *11*, 2663.

(4) Quintard, A.; Lefranc, A.; Alexakis, A. *Org. Lett.* **2011**, *13*, 1540.

(5) Zhou, L.; Lin, L.; Ji, J.; Xie, M.; Liu, X.; Feng, X. *Org. Lett.* **2011**, *13*, 3056.

(6) Huang, X.; Peng, J.; Dong, L.; Chen, Y.-C. *Chem. Commun.* **2012**, *48*, 2439.

(7) Cui, H.-L.; Huang, J.-R.; Lei, J.; Wang, Z.-F.; Chen, S.; Wu, L.; Chen, Y.-C. *Org. Lett.* **2010**, *12*, 720.

(8) Zhang, W.; Tan, D.; Lee, R.; Tong, G.; Chen, W.; Qi, B.; Huang, K.-W.; Tan, C.-H.; Jiang, Z. *Angew. Chem. Int. Ed.* **2012**, *51*, 10069.

(9) Manna, M. S.; Kumar, V.; Mukherjee, S. *Chem. Commun.* **2012**, *48*, 5193.

(10) Manna, M. S.; Mukherjee, S. *Chem. Eur. J.* **2012**, *18*, 15277.

(11) Sonpatki, V. M.; Herbert, M. R.; Sandvoss, L. M.; Seed, A. J. *J. Org. Chem.* **2001**, *66*, 7283.

(12) Osman, N. A.; Mahmoud, A. H.; Allarà, M.; Niess, R.; Abouzid, K. A.; Marzo, V. D.; Abadi, A. H. *Bioorg. Med. Chem.* **2010**, *18*, 8463.

