Organocatalytic Enantioselective Michael Reaction of Aminomaleimides with Nitroolefins Catalyzed by Takemoto’s Catalyst

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Abstract: Known as electrophiles, maleimides are often used as acceptors in Michael additions to produce succinimides. However, reactions with maleimides as nucleophiles for enantioselective functionalization are only rarely performed. In this paper, a series of bifunctional Takemoto’s catalysts were used to organocatalyze the enantioselective Michael reaction of aminomaleimides with nitroolefins. The resulting products were obtained in good yields (76–86%) with up to 94% enantiomer excess (ee). The catalyst type and the substrate scope were broadened using this methodology.

Keywords: Takemoto’s catalyst; enantioselective; Michael addition; aminomaleimides; nitroolefins

1. Introduction

Maleimide scaffolds are promising skeletons, which have been widely found in many natural alkaloids and bioactive pharmaceuticals [1–8]. Additionally, maleimide could be transformed into many important heterocyclic frameworks such as succinimides, pyrrolidines, and 2-pyrrolidones. Thus, intensive attention has been focused on the synthesis and modification of maleimide derivatives. In general, functionalization of maleimides mainly takes place on the double bond of maleimide through Michael addition, oxidative coupling, cycloaddition reaction, etc. [9–24]. Accordingly, enantioselective Michael addition of maleimides has been well established with maleimides as Michael acceptors [25–27]. Although maleimides are often used as electrophiles, their application as nucleophiles or Michael donors for the construction of maleimide-containing compounds is limited [28–30].

In 2021, Mori’s group first reported asymmetric Michael addition of α-aminomaleimides as Michael donors to β-nitroolefins using Cinchona alkaloid as the organocatalyst [31]. Furthermore, density functional theory (DFT) was employed in research to improve the enantioselectivity of the adduct and to reveal the mechanism of stereochemistry. Through DFT calculation, the author predicted that increasing the size of the N substituent of the maleimide could be favorable for stereo control. As expected, the ee value was significantly increased by 16% when N-Me was substituted with an N-iBu group of the α-aminomaleimide in this asymmetric reaction.

To the best of our knowledge, only the above one item of literature involves asymmetric Michael addition using α-aminomaleimides as nucleophiles. Therefore, it is important to develop this reaction by using new types of catalysts. Takemoto’s catalyst is the commercially available chiral organocatalyst, which was first synthesized by Takemoto in 2003 [32]. Subsequently, they were widely used in various diastereoselective and enantioselective reactions [33–40]. In this paper, we offer the first reports on the enantioselective Michael addition of α-aminomaleimides and nitroolefins by employing Takemoto-type catalysts 1a–1h bearing (thio)urea or squareamide moiety (Figure 1).
2. Results and Discussion

We first applied the Takemoto-type catalysts 1a–1h in the Michael reaction of \(\alpha\)-aminomaleimide (2a) and \(\beta\)-nitrostyrene (3a) to screen the optimal catalyst. According to the optimized condition reported [31], the reaction was carried out with Et\(_2\)O as a solvent in the presence of 10 mol\% of catalysts at r.t. (Table 1). All catalysts proceeded the reaction smoothly to give the desired product 4a in 69–78\% yields with moderate to high enantioselectivities. Among of them, (R,R)-thiourea catalyst 1c was optimal in terms of the yield and enantioselectivity (entry 3). When the thiourea moiety in catalyst 1c was substituted with squareamide moiety in catalyst 1d, the similar stereoselectivity was afforded (entry 4 vs. entry 3). Additionally, \(N,N\)-dimethyl tertiary amine of 1c was changed to the steric bulk moieties in catalysts 1e–1h, led to reduction both in the yields and ees (entries 5–8 vs. entry 3). Therefore, \(N,N\)-dimethyl tertiary amine proved to be crucial. Although the optical rotation values of the products were not reported in the literature, it indicated that quinine catalyzed the reaction to obtain S configuration of the major product [31]. Therefore, we repeated a quinine-catalyzed Michael reaction of \(\alpha\)-aminomaleimide 2a and \(\beta\)-nitrostyrene 3a to obtain the S-adduct 4a (entry 9). Then, the optical rotation data of two products from quinine- or 1c-induced reaction were determined with MeOH as solvent to afford two negative values (entries 3 and 9). Accordingly, the configuration of the major product catalyzed by 1c was proved to be S.

Table 1. Asymmetric Michael reaction of \(\alpha\)-aminomaleimide with \(\beta\)-nitrostyrene catalyzed by 1a–h.

| Entry | Catalyst | Yield (%) | %ee | Configuration \(\alpha\) \(\beta\) | %ee | Configuration \(\alpha\) \(\beta\) |
|-------|----------|-----------|-----|--------------------------------|-----|--------------------------------|
| 1     | 1a       | 78        | 90  | R                             |     | R                             |
| 2     | 1b       | 76        | 89  | R                             |     | R                             |
| 3     | 1c       | 80        | 91  | S \((-6.70)\)                 |     | S \((-3.82)\)                 |
| 4     | 1d       | 73        | 90  | S                             |     | S                             |
| 5     | 1e       | 74        | 87  | S                             |     | S                             |
| 6     | 1f       | 69        | 76  | S                             |     | S                             |
| 7     | 1g       | 72        | 82  | S                             |     | S                             |
| 8     | 1h       | 70        | 74  | S                             |     | S                             |
| 9     | quinine  | 80        | 53  | S                             |     | S                             |

\(\alpha\)-aminomaleimide (0.10 mmol), \(\beta\)-nitrostyrene (0.10 mmol), and catalysts (0.01 mmol) in Et\(_2\)O (1 mL). Isolated yield. Determined by HPLC analysis (Chiralpak IA). The configuration was determined by comparison with the known result catalyzed by quinine according to the literature [31]. The optical rotation values were determined using an automatic polarimeter.
To further improve the enantioselectivity of the transformation, a screened catalyst 1c was applied to the Michael reaction of α-aminomaleimide 2a and β-nitrostyrene 3a under the different conditions (Table 2).

Table 2. Screening of reaction condition for the asymmetric Michael reaction catalyzed by 1c.

| Entry | Solvent     | Temperature | Catalyst Amount (% mmol) | Yield (%) b | %ee c |
|-------|-------------|-------------|--------------------------|-------------|-------|
| 1     | CH₂Cl₂      | rt          | 10                       | 82          | 90    |
| 2     | CHCl₃       | rt          | 10                       | 80          | 91    |
| 3     | THF         | rt          | 10                       | 76          | 88    |
| 4     | Et₂O        | rt          | 10                       | 78          | 91    |
| 5     | MTBE        | rt          | 10                       | 80          | 90    |
| 6     | 1,4-dioxane | rt          | 10                       | 82          | 85    |
| 7     | PhMe        | rt          | 10                       | 84          | 92    |
| 8     | xylene      | rt          | 10                       | 76          | 91    |
| 9     | MeOH        | rt          | 10                       | 70          | 23    |
| 10    | PhMe        | 0           | 10                       | 83          | 93    |
| 11    | PhMe        | −10         | 10                       | 68          | 94    |
| 12    | PhMe        | −20         | 10                       | 55          | 94    |
| 13    | PhMe        | 0           | 5                        | 74          | 93    |
| 14    | PhMe        | 0           | 20                       | 86          | 93    |
| 15 d  | PhMe        | 0           | 10                       | 56          | 91    |
| 16 e  | PhMe        | 0           | 10                       | 85          | 94    |

a Reaction condition: α-aminomaleimides (0.10 mmol), β-nitrostyrene (0.10 mmol), and 1c (0.01 mmol) in solvent (1 mL). b Isolated yield. c Determined by HPLC analysis (Chiralpak IA). d 2 mL of solvent. e 4Å MS (about 200 mg).

First, a variety of solvents were investigated. All the reactions proceeded smoothly in the screened solvent. It is noteworthy that aprotic solvents were suitable for the reaction to give 85–93% ees (entries 1–8), while protic MeOH was unfavorable for asymmetric induction (entry 9). Among them, toluene was optimal in terms of the yield and enantioselectivity (entry 7). When the reaction temperature was lowered from r.t. to 0 °C, an improved ee of 93% was afforded (entry 10 vs. entry 7). With further temperature decreases to −10 °C and −20 °C, both enantioselectivities were increased by 1%, but showed significantly lower yields (entries 11, 12 vs. entry 10). Therefore, 0 °C was regarded to be the most suitable reaction temperature. When reducing the catalyst loading to 5 mol%, the enantioselectivity was maintained at an excellent level, but with a relatively low yield (entry 13 vs. entry 10), and 20 mol% loading offered no improvement in the asymmetric induction, albeit with a slightly improved yield (entry 14 vs. entry 10). Furthermore, diluting the reaction concentration by half was detrimental for yield and enantiocontrol (entry 15 vs. entry 10). Adding 4 Å molecular sieves (MS) led to a slightly higher ee value of 94% and increased yield (entry 16 vs. entry 10). Based on these experiments, the optimized conditions were determined to be toluene as the solvent with a 10 mol% loading of catalyst 1c in the presence of 4Å MS (200 mg) at 0 °C.

With the optimized conditions in hand, we explored the scope and general applicability of the protocol. A wide range of substituted α-aminomaleimides and β-nitroolefins were evaluated as shown in Table 3.

All of the substrates reacted smoothly to give the corresponding products in high yields (76–86%) with good ees (81–94%). Therefore, the stereoselectivities were barely affected by the type and position of the substituents on α-aminomaleimide. However, the substituent and position on the β-nitrostyrene was found to have influence on the enantioselectivity. It can be seen that the 2-Br substituent on phenyl of nitrostyrene led to slightly decreased ee values (entries 4, 18). Compared with the data of the reported literature listed in parentheses (Table 3) [31], our screened catalyst system showed similar enantioselectivities in most reactions. Exceptionally, in the reaction with N-Bn substituted maleimide as Michael donor, a markedly increased ee value was obtained (entry 17), while in the reaction with β-nitro-1-naphthalene ethylene as Michael acceptor, 10% reduction...
in enantioselectivity was observed (entry 12) in this paper. To extend the type of Michael acceptor in the reaction of α-aminomaleimide as donor, we tried unsaturated carbonyl compounds such as methyl cinnamate 5 and chalcone 6 to substitute the β-nitroolefin. Surprisingly, neither reaction occurred under the screened condition (Scheme 1).

Table 3. Generality of the enantioselective Michael reaction of α-aminomaleimides with β-nitroolefins.

| Entry | R₁, R₂, R₃ | Product | Yield (%) | %ee c |
|-------|------------|---------|-----------|-------|
| 1     | iBu, H, H  | 4a      | 85        | 94 (90) d |
| 2     | iBu, H, 2-F| 4b      | 83        | 92    |
| 3     | iBu, H, 2-Cl| 4c     | 86        | 88    |
| 4     | iBu, H, 2-Br| 4d     | 86        | 86 (88) d |
| 5     | iBu, H, 3-Br| 4e     | 81        | 92 (92) d |
| 6     | iBu, H, 3-F| 4f     | 82        | 93    |
| 7     | iBu, H, 4-F| 4g     | 85        | 93    |
| 8     | iBu, H, 4-Cl| 4h     | 84        | 93    |
| 9     | iBu, H, 4-Br| 4i     | 86        | 90 (90) d |
| 10    | iBu, H, 4-Me| 4j     | 78        | 93 (90) d |
| 11    | iBu, H, 4-OMe| 4k    | 76        | 93 (90) d |
| 12    | iBu, H, 1-Nap| 4l    | 78        | 81 (91) d |
| 13    | iBu, H, 2-thienyl| 4m | 83        | 92 (89) d |
| 14    | iBu, 4-Cl, H| 4n     | 81        | 92 (92) d |
| 15    | iBu, 4-Cl, 2-Cl| 4o | 80        | 89    |
| 16    | iBu, 3-Cl, H| 4p     | 85        | 93    |
| 17    | Bn, H, H   | 4q     | 83        | 90 (80) d |
| 18    | Bn, H, 2-Br| 4r     | 80        | 84    |
| 19    | Bn, H, 3-Br| 4s     | 82        | 90    |
| 20    | Bn, H, 4-Br| 4t     | 84        | 90    |

*Reaction condition: α-aminomaleimides (0.01 mmol), β-nitroolefins (0.10 mmol), and 1c (0.01 mmol) in (1 mL) at 0 °C. d Isolated yield. d Determined by HPLC analysis (Chiralpak IA). d The data in parentheses are the ee values in reference [31].

Scheme 1. Michael reaction of α-aminomaleimide 2a with unsaturated carbonyl compounds.

Based on the obtained absolute configuration described above and the previously reported enantioselective Michael addition of α-aminomaleimide 2a and β-nitrostyrene.
3a [31], a proposed transition-state model is depicted in Scheme 2. β-nitrostyrene 3a is oriented and activated by the thiourea moiety through hydrogen bonding and the NH group in 2a is deprotoned and oriented by the tertiary amine of catalyst 1c through another hydrogen bonding. Then, the reaction proceeds with a Sc-face addition of α-aminomaleimide to β-nitrostyrene, affording the desired product S-4a.

Scheme 2. Proposed stereochemical model.

3. Experimental

3.1. Chemistry

The \(^1\)H NMR spectra were recorded on a 500 MHz for \(^1\)H and at 125 MHz for \(^13\)C NMR, using CDCl\(_3\) as a solvent. The chemical shifts were reported in ppm, and the residual nondeuterated solvent (CHCl\(_3\)) as internal standard (7.26 and 77.0 ppm, respectively). The splitting patterns of the signals were reported as s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; m, multiplet. High-resolution mass spectra (HRMS) were measured on a triple TOF 5600+ mass spectrometer equipped with an electrospray ionization (ESI) source in the negative-ion mode. The enantiomeric excess (ee) values of the products were determined through chiral HPLC, using Daicel Chiralpak IA columns (4.6 mm × 250 mm). The optical rotation values were determined using an automatic polarimeter. The reactions were monitored by thin layer chromatography (TLC). Purifications by column chromatography were conducted over silica gel (200–300 mesh). The organocatalysts 1a–1h were purchased from Daicel Chiral Technologies (China) Co.

3.2. General Procedure for the Enantioselective Michael Reaction of α-Aminomaleimides and β-Nitrostyrenes

To a mixture of nitrostyrenes (0.1 mmol), maleimides (0.1 mmol) and organocatalyst 1c (0.01 mmol), toluene (1.0 mL) was added. The resulting mixture was stirred at 0 °C for 24 h (TLC). After the reaction was finished, it was directly poured into a column chromatography on silica gel with hexane/EtOAc (5:1) as eluent to afford the products 4a–t. Among them, 4b, 4c, 4f–h, 4o, 4p, and 4r–t were the new compounds. Experimental data can be found in the Supplementary Materials.

3.2.1. (S)-1-Isobutyl-3-(2-nitro-1-phenylethyl)-4-(phenylamino)-1H-pyrrole-2,5-dione (4a)

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.44–7.39 (m, 2H), 7.38–7.34 (m, 1H), 7.21–7.18 (m, 3H), 7.15 (d, \(J = 7.5\) Hz, 2H), 6.97 (s, 1H), 6.91–6.80 (m, 2H), 5.47 (dd, \(J = 10.0\), 6.0 Hz, 1H), 4.60 (dd, \(J = 12.5\), 6.0 Hz, 1H), 4.29 (dd, \(J = 10.0\), 6.0 Hz, 1H), 3.34 (d, \(J = 7.5\) Hz, 2H), 2.04 (hept, \(J = 7.0\) Hz, 1H), 0.91 (d, \(J = 7.0\) Hz, 6H); \([\alpha]_D^{25} = -6.70\) (c 0.52, MeOH) (94% ee); HPLC (Chiralpak IA, hexane/EtOAc = 90:10, 1.0 mL/min, 254 nm), \(t_{R}\) = 10.2 min (minor), 20.0 min (major).

3.2.2. (S)-3-(1-(2-Fluorophenyl)-2-nitroethyl)-1-isobutyl-4-(phenylamino)-1H-pyrrole-2,5-dione (4b)

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.35–7.27 (m, 3H), 7.25–7.17 (m, 2H), 7.09–6.98 (m, 4H), 6.94–6.88 (m, 1H), 5.39 (dd, \(J = 14.0\), 11.5 Hz, 1H), 4.65–4.52 (m, 2H), 3.35 (d, \(J = 7.5\) Hz, 2H), 2.05 (hept, 7.0 Hz, 1H), 0.93 (d, \(J = 6.5\) Hz, 6H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 173.2,
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167.5, 141.1, 136.6, 129.5, 127.2, 124.5, 124.3 (d, J = 14.1 Hz), 115.5, 115.3, 95.7, 75.3, 45.4, 32.9, 27.9, 20.1. HRMS (ESI) m/z: [M + Na]+ calcld for C_{22}H_{22}FN_{3}O_{4}Na 434.1492; found 434.1497; [α]_{D}^{25} = 6.15 (c 0.72, MeOH)(92% ee); HPLC (Chiralpak IA, hexane:PrOH = 97:3, 0.5 mL/min, 254 nm), t_R = 48.6 min (minor), 51.4 min (major).

3.2.3. (S)-3-(1-(2-Chlorophenyl)-2-nitroethyl)-1-isobutyl-4-(phenylamino)-1H-pyrrole-2,5-dione (4c)

1H NMR (500 MHz, CDCl_3) δ 7.35 (dd, J = 7.0, 2.0 Hz, 1H), 7.27–7.25 (m, 3H), 7.25–7.18 (m, 3H), 7.02 (s, 1H), 6.99–6.91 (m, 2H), 5.39 (dd, J = 13.0, 10.5 Hz, 1H), 4.69 (dd, J = 10.5, 4.5 Hz, 1H), 4.57 (dd, J = 13.0, 4.5 Hz, 1H), 3.38 (d, J = 7.5 Hz, 2H), 2.07 (hept, J = 7.0, 1H), 0.94 (dd, J = 6.5, 3.5 Hz, 6H); 13C NMR (125 MHz, CDCl_3) δ 173.5, 167.4, 141.4, 136.6, 134.3, 133.6, 129.9, 129.7, 129.6, 129.1, 127.4, 127.0, 124.1, 95.6, 74.5, 45.4, 36.8, 27.9, 20.0; HRMS (ESI) m/z: [M + Na]+ calcld for C_{22}H_{22}CNN_{3}O_{4}Na 450.1917; found 450.1914; [α]_{D}^{25} = 7.41 (c 0.58, MeOH) (87% ee); HPLC (Chiralpak IA, hexane:PrOH = 90:10, 1.0 mL/min, 254 nm), t_R = 9.8 min (minor), 11.3 min (major).

3.2.4. (S)-3-(1-(2-Bromophenyl)-2-nitroethyl)-1-isobutyl-4-(phenylamino)-1H-pyrrole-2,5-dione (4d)

1H NMR (500 MHz, CDCl_3) δ 7.44 (dd, J = 8.0, 1.0 Hz, 1H), 7.38 (dd, J = 8.0, 1.5 Hz, 1H), 7.28 (dd, J = 7.5, 1.0 Hz, 1H), 7.25 (d, J = 3.5 Hz, 3H), 7.12 (td, J = 7.5, 1.6 Hz, 1H), 7.00 (s, 1H), 6.97–6.91 (m, 2H), 5.40 (dd, J = 13.0, 10.5 Hz, 1H), 4.65 (dd, J = 10.5, 4.5 Hz, 1H), 4.59 (dd, J = 13.0, 4.5 Hz, 1H), 3.39 (d, J = 7.5 Hz, 2H), 2.08 (hept, J = 13.9, 7.0 Hz, 1H), 0.95 (dd, J = 6.5, 4.5 Hz, 6H); [α]_{D}^{25} = 5.36 (c 0.60, MeOH) (86% ee); HPLC (Chiralpak IA, hexane:PrOH = 95:5, 0.8 mL/min, 254 nm), t_R = 19.1 min (minor), 24.0 min (major).

3.2.5. (S)-3-(1-(3-Bromophenyl)-2-nitroethyl)-1-isobutyl-4-(phenylamino)-1H-pyrrole-2,5-dione (4e)

1H NMR (500 MHz, CDCl_3) δ 7.50–7.38 (m, 3H), 7.33 (ddd, J = 8.0, 2.0, 1.0 Hz, 1H), 7.17 (d, J = 7.5 Hz, 2H), 7.08 (t, J = 8.0 Hz, 1H), 7.00 (s, 1H), 6.89 (d, J = 8.0 Hz, 1H), 6.82 (t, J = 2.0 Hz, 1H), 5.42 (dd, J = 13.0, 10.0 Hz, 1H), 4.59 (dd, J = 13.0, 6.0 Hz, 1H), 4.22 (dd, J = 10.0, 6.0 Hz, 1H), 3.34 (d, J = 7.5 Hz, 2H), 2.03 (hept, J = 7.0 Hz, 1H), 0.92 (d, J = 6.5 Hz, 6H); [α]_{D}^{25} = –24.42 (c 0.65, MeOH) (92% ee); HPLC (Chiralpak AS, hexane:PrOH = 90:10, 1.0 mL/min, 254 nm), t_R = 12.6 min (minor), 15.9 min (major).

3.2.6. (S)-3-(1-(3-Fluorophenyl)-2-nitroethyl)-1-isobutyl-4-(phenylamino)-1H-pyrrole-2,5-dione (4f)

1H NMR (500 MHz, CDCl_3) δ 7.47–7.41 (m, 2H), 7.41–7.37 (m, 1H), 7.21–7.13 (m, 3H), 7.00 (s, 1H), 6.89 (dd, J = 8.5, 2.5, 1.0 Hz, 1H), 6.64 (d, J = 8.0 Hz, 1H), 6.60–6.51 (m, 1H), 5.41 (dd, J = 13.0, 10.0 Hz, 1H), 4.62 (dd, J = 13.0, 6.0 Hz, 1H), 4.26 (dd, J = 10.0, 6.0 Hz, 1H), 3.34 (d, J = 7.5 Hz, 2H), 2.03 (hept, J = 7.0 Hz, 1H), 0.92 (d, J = 6.5 Hz, 6H); 13C NMR (125 MHz, CDCl_3) δ 173.1, 167.5, 141.0, 140.1 (d, J = 6.9 Hz), 136.6, 130.3 (d, J = 8.1 Hz), 129.6, 127.6, 125.6, 123.5, 115.2, 115.0, 114.6 (d, J = 21.0 Hz), 96.6, 76.8, 45.4, 39.2, 27.9, 20.0. HRMS (ESI) m/z: [M + Na]+ calcld for C_{22}H_{22}FN_{3}O_{4}Na 434.1492; found 434.1497; [α]_{D}^{25} = –28.98 (c 0.75, MeOH) (93% ee); HPLC (Chiralpak IA, hexane:PrOH = 90:10, 1.0 mL/min, 254 nm), t_R = 10.3 min (minor), 12.4 min (major).

3.2.7. (S)-3-(1-(4-Fluorophenyl)-2-nitroethyl)-1-isobutyl-4-(phenylamino)-1H-pyrrole-2,5-dione (4g)

1H NMR (500 MHz, CDCl_3) δ 7.45–7.41 (m, 2H), 7.40–7.36 (m, 1H), 7.16 (d, J = 7.5 Hz, 2H), 6.96 (s, 1H), 6.88 (dd, J = 12.0, 5.5 Hz, 2H), 6.86–6.80 (m, 2H), 5.39 (dd, J = 12.5, 10.0 Hz, 1H), 4.60 (dd, J = 12.5, 6.0 Hz, 1H), 4.26 (dd, J = 10.0, 6.0 Hz, 1H), 3.34 (d, J = 7.5 Hz, 2H), 2.03 (hept, J = 7.0 Hz, 1H), 0.92 (d, J = 6.5 Hz, 6H); 13C NMR (125 MHz, CDCl_3) δ 167.6, 140.7, 136.7, 133.5, 129.7(d, J = 8.1 Hz), 129.6, 127.5, 125.5, 115.8, 115.6, 97.2, 77.1, 45.4, 38.8, 27.9, 20.0. HRMS (ESI) m/z: [M + Na]+ calcld for C_{22}H_{22}FN_{3}O_{4}Na 434.1492; found 434.1499;
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[α]_D^25 = −16.12 (c 0.55, MeOH) (93% ee); HPLC (Chiralpak IA, hexane:PrOH = 90:10, 1.0 mL/min, 254 nm), t_R = 10.3 min (minor), 17.2 min (major).

3.2.8. (S)-3-(1-(4-Chlorophenyl)-2-nitroethyl)-1-isobutyl-4-(phenylamino)-1H-pyrrole-2,5-dione (4h)

^1^H NMR (500 MHz, CDCl_3) δ 7.45–7.41 (m, 2H), 7.40–7.36 (m, 1H), 7.19–7.13 (m, 4H), 7.00 (s, 1H), 6.82–6.75 (m, 2H), 5.38 (dd, J = 12.5, 10.0 Hz, 1H), 4.60 (dd, J = 12.5, 6.0 Hz, 1H), 4.25 (dd, J = 10.0, 6.0 Hz, 1H), 3.33 (d, J = 7.5 Hz, 2H), 2.03 (hept, J = 7.0 Hz, 1H), 0.91 (d, J = 6.5 Hz, 6H); ^13^C NMR (125 MHz, CDCl_3) δ 173.2, 167.5, 140.8, 136.6, 136.2, 133.5, 129.6, 129.4, 129.0, 127.6, 96.8, 76.9, 45.4, 38.9, 31.6, 27.9, 22.6, 20.04 (d, J = 12.5, 6.0 Hz, 1H), 4.23 (dd, J = 9.5, 6.0 Hz, 1H), 3.33 (d, J = 7.5 Hz, 2H), 2.03 (hept, J = 7.0 Hz, 1H), 0.91 (d, J = 6.5 Hz, 6H); [α]_D^25 = −12.33 (c 0.49, MeOH) (90% ee); HPLC (Chiralpak IA, hexane:PrOH = 90:10, 1.0 mL/min, 254 nm), t_R = 11.4 min (minor), 16.6 min (major).

3.2.9. (S)-3-(1-(4-Bromophenyl)-2-nitroethyl)-1-isobutyl-4-(phenylamino)-1H-pyrrole-2,5-dione (4i)

^1^H NMR (500 MHz, CDCl_3) δ 7.46–7.36 (m, 3H), 7.35–7.29 (m, 2H), 7.16 (d, J = 7.5 Hz, 2H), 6.99 (s, 1H), 6.76–6.70 (m, 2H), 5.38 (dd, J = 13.0, 9.5 Hz, 1H), 4.60 (dd, J = 13.0, 6.0 Hz, 1H), 4.23 (dd, J = 9.5, 6.0 Hz, 1H), 3.33 (d, J = 7.5 Hz, 2H), 2.28 (hept, J = 7.0 Hz, 1H), 0.91 (d, J = 6.5 Hz, 6H); [α]_D^25 = −8.89 (c 0.51, MeOH) (93% ee); HPLC (Chiralpak IA, hexane:PrOH = 90:10, 1.0 mL/min, 254 nm), t_R = 14.9 min (major).

3.2.10. (S)-1-Isobutyl-3-(2-nitro-1-(p-tolyl)ethyl)-4-(phenylamino)-1H-pyrrole-2,5-dione (4j)

^1^H NMR (500 MHz, CDCl_3) δ 7.45–7.39 (m, 2H), 7.38–7.33 (m, 1H), 7.16 (d, J = 7.5 Hz, 2H), 7.01 (d, J = 8.0 Hz, 2H), 6.92 (s, 1H), 6.76 (d, J = 8.0 Hz, 2H), 5.44 (dd, J = 12.5, 10.0 Hz, 1H), 4.58 (dd, J = 12.5, 6.0 Hz, 1H), 4.25 (dd, J = 10.0, 6.0 Hz, 1H), 3.33 (d, J = 7.5 Hz, 2H), 2.28 (hept, J = 7.0 Hz, 1H), 0.92 (d, J = 6.5 Hz, 6H); [α]_D^25 = −30.50 (c 0.59, MeOH) (92% ee); HPLC (Chiralpak IA, hexane:PrOH = 90:10, 1.0 mL/min, 254 nm), t_R = 13.2 min (minor), 27.6 min (major).

3.2.11. (S)-1-Isobutyl-3-(1-(4-methoxyphenyl)-2-nitroethyl)-4-(phenylamino)-1H-pyrrole-2,5-dione (4k)

^1^H NMR (500 MHz, CDCl_3) δ 7.42 (dd, J = 10.0, 5.0 Hz, 2H), 7.35 (dd, J = 8.5, 6.5 Hz, 1H), 7.15 (d, J = 7.5 Hz, 2H), 6.93 (s, 1H), 6.83–6.77 (m, 2H), 6.76–6.70 (m, 2H), 5.41 (dd, J = 12.5, 10.0 Hz, 1H), 4.57 (dd, J = 12.5, 6.0 Hz, 1H), 4.23 (dd, J = 10.0, 6.0 Hz, 1H), 3.75 (s, 3H), 3.33 (d, J = 7.5 Hz, 2H), 2.04 (hept, J = 7.0 Hz, 1H), 0.92 (d, J = 6.5 Hz, 6H); [α]_D^25 = −14.13 (c 0.66, MeOH) (92% ee); HPLC (Chiralpak IA, hexane:PrOH = 90:10, 1.0 mL/min, 254 nm), t_R = 12.2 min (minor), 28.2 min (major).

3.2.12. (S)-1-Isobutyl-3-(1-(naphthalen-2-yl)-2-nitroethyl)-4-(phenylamino)-1H-pyrrole-2,5-dione (4l)

^1^H NMR (500 MHz, CDCl_3) δ 7.84 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 6.5 Hz, 1H), 7.45 (dd, J = 8.0, 7.0, 1.0 Hz, 1H), 7.41 (t, J = 8.0 Hz, 1H), 7.28 (dd, J = 8.5, 7.0, 1.5 Hz, 1H), 7.11 (d, J = 8.5 Hz, 1H), 7.06 (t, J = 7.5 Hz, 1H), 7.01–6.94 (m, 3H), 6.91 (d, J = 7.5 Hz, 2H), 5.60 (dd, J = 13.0, 11.0 Hz, 1H), 5.11 (dd, J = 11.0, 4.0 Hz, 1H), 4.56 (dd, J = 13.0, 4.0 Hz, 1H), 3.42 (d, J = 7.5 Hz, 2H), 2.11 (hept, J = 6.5 Hz, 2H), 0.97 (d, J = 6.5, 4.5 Hz, 6H); [α]_D^25 = −14.13 (c 0.66, MeOH) (92% ee); HPLC (Chiralpak IA, hexane:PrOH = 90:10, 1.0 mL/min, 254 nm), t_R = 12.2 min (minor), 28.2 min (major).

3.2.13. (S)-1-Isobutyl-3-(2-nitro-1-(thiophen-2-yl)ethyl)-4-(phenylamino)-1H-pyrrole-2,5-dione (4m)

^1^H NMR (500 MHz, CDCl_3) δ 7.44 (dd, J = 10.5, 5.0 Hz, 2H), 7.37 (t, J = 7.5 Hz, 1H), 7.23 (d, J = 7.5 Hz, 2H), 7.16 (dd, J = 5.0, 1.0 Hz, 1H), 7.00 (s, 1H), 6.87 (dd, J = 5.0, 3.5 Hz, 1H), 6.65 (d, J = 3.5 Hz, 1H), 5.33 (dd, J = 12.5, 10.0 Hz, 1H), 4.63 (dd, J = 12.5, 5.5 Hz, 1H), 4.52 (dd, J = 10.0, 5.5 Hz, 1H), 3.34 (d, J = 7.5 Hz, 2H), 2.04 (hept, J = 7.0 Hz, 1H),
0.92 (d, J = 6.5 Hz, 6H); [α]D25 = −14.13 (c 0.53, MeOH) (92% ee); HPLC (Chiralpak IA, hexane:iPrOH = 90:10, 1.0 mL/min, 254 nm), tR = 12.2 min (minor), 28.2 min (major).

3.2.14. (S)-3-(((4-Chlorophenyl)amino)-1-isobutyl-4-(2-nitro-1-phenylethyl)-1H-pyrrole-2,5-dione (4n)

1H NMR (500 MHz, CDCl3) δ 7.38 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 9.0 Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 6.96–6.92 (m, 3H), 5.62–5.48 (m, 1H), 4.61 (dd, J = 13.0, 5.5 Hz, 1H), 4.30 (dd, J = 10.5, 5.5 Hz, 1H), 3.36 (d, J = 7.5 Hz, 2H), 2.06 (hept, J = 7.0 Hz, 1H), 0.94 (d, J = 6.5 Hz, 6H); [α]D25 = −19.26 (c 0.65, MeOH) (92% ee); HPLC (Chiralpak IA, hexane:iPrOH = 95:5, 0.8 mL/min, 254 nm), tR = 26.7 min (minor), 49.6 min (major).

3.2.15. (S)-3-(((4-Chlorophenyl)amino)-1-isobutyl-4-(1-(2-chlorophenyl)-2-nitroethyl)-1H-pyrrole-2,5-dione (4o)

1H NMR (500 MHz, CDCl3) δ 7.76–7.69 (m, 1H), 7.68–7.64 (m, 1H), 7.59 (t, J = 6.0 Hz, 4H), 7.34 (s, 1H), 7.26 (d, J = 8.5 Hz, 2H), 5.86–5.69 (m, 1H), 5.02 (dd, J = 11.0, 4.5 Hz, 1H), 4.91 (dd, J = 13.0, 4.5 Hz, 1H), 3.74 (d, J = 7.5 Hz, 2H), 2.43 (hept, J = 7.0 Hz, 1H), 1.30 (dd, J = 6.5, 4.5 Hz, 6H); 13C NMR (125 MHz, CDCl3) δ 173.4, 167.3, 141.3, 135.2, 134.1, 133.6, 132.7, 129.8, 129.2, 129.3, 127.5, 125.5, 96.4, 74.4, 45.4, 36.8, 27.9, 20.0; HRMS (ESI) m/z: [M + Na]+ calcd for C27H21Cl2N3O4Na 528.0535; found 528.0541; [α]D25 = 3.64 (c 0.50, MeOH) (89% ee); HPLC (Chiralpak IA, hexane:iPrOH = 90:10, 1.0 mL/min, 254 nm), tR = 10.9 min (minor), 14.2 min (major).

3.2.16. (S)-3-(((3-Chlorophenyl)amino)-1-isobutyl-4-(2-nitro-1-phenylethyl)-1H-pyrrole-2,5-dione (4p)

1H NMR (500 MHz, CDCl3) δ 7.35 (d, J = 7.0 Hz, 2H), 7.28 (m, 3H), 7.13 (s, 1H), 7.06 (d, J = 6.5 Hz, 1H), 6.99–6.89 (m, 3H), 5.58–5.48 (m, 1H), 4.62 (dd, J = 13.0, 5.5 Hz, 1H), 4.31 (dd, J = 9.5, 5.5 Hz, 1H), 3.36 (d, J = 7.5 Hz, 2H), 2.06 (hept, J = 7.0 Hz, 1H), 0.94 (d, J = 6.5 Hz, 6H); 13C NMR (126 MHz, CDCl3) δ 173.0, 167.5, 140.1, 138.2, 137.0, 135.2, 130.5, 129.1, 128.0, 127.8, 127.3, 125.2, 123.2, 98.9, 45.4, 39.9, 27.9, 20.0; HRMS (ESI) m/z: [M + Na]+ calcd for C27H22ClN3O4Na 497.0212; found 497.0212; [α]D25 = −30.83 (c 0.71, MeOH) (93% ee); HPLC (Chiralpak IA, hexane:iPrOH = 90:10, 1.0 mL/min, 254 nm), tR = 10.2 min (minor), 16.0 min (major).

3.2.17. (S)-1-Benzyl-3-(2-nitro-1-phenylethyl)-(4-phenylamino)-1H-pyrrole-2,5-dione (4q)

1H NMR (500 MHz, CDCl3) δ 7.43–7.38 (m, 2H), 7.39–7.32 (m, 5H), 7.31–7.27 (m, 1H), 7.21–7.17 (m, 3H), 7.14 (d, J = 7.5 Hz, 2H), 6.94 (s, 1H), 6.88–6.82 (m, 2H), 5.44 (dd, J = 12.5, 9.5 Hz, 1H), 4.69 (s, 2H), 4.64 (dd, J = 12.5, 6.0 Hz, 1H), 4.28 (dd, J = 9.5, 6.0 Hz, 1H); [α]D25 = −16.15 (c 0.62, MeOH) (90% ee); HPLC (Chiralpak IA, hexane:iPrOH = 90:10, 1.0 mL/min, 254 nm), tR = 19.6 min (minor), 24.2 min (major).

3.2.18. (S)-1-Benzyl-3-((1-2-bromophenyl)-2-nitroethyl)-(4-phenylamino)-1H-pyrrole-2,5-dione (4r)

1H NMR (500 MHz, CDCl3) δ 7.43 (dd, J = 8.0, 1.5 Hz, 1H), 7.40–7.29 (m, 6H), 7.26–7.23 (m, 4H), 7.11 (td, J = 7.5, 1.5 Hz, 1H), 7.00 (s, 1H), 6.95–6.90 (m, 2H), 5.40 (dd, J = 13.0, 10.5 Hz, 1H), 4.74 (dd, J = 21.0, 13.5 Hz, 2H), 4.66 (dd, J = 10.5, 4.5 Hz, 1H), 4.61 (dd, J = 13.0, 4.5 Hz, 1H); 13C NMR (125 MHz, CDCl3) δ 172.9, 166.9, 141.8, 136.6, 136.3, 135.8, 133.2, 130.0, 129.8, 129.3, 128.8, 128.2, 127.8, 127.1, 124.3, 124.1, 96.4, 74.5, 41.7, 39.4, 29.7; HRMS (ESI) m/z: [M + Na]+ calcd for C29H20BrN3O4Na 582.0535; found 582.0541; [α]D25 = 36.0 (c 0.69, MeOH) (84% ee); HPLC (Chiralpak IA, hexane:iPrOH = 90:10, 1.0 mL/min, 254 nm), tR = 18.9 min (minor), 23.1 min (major).

3.2.19. (S)-1-Benzyl-3-((3-bromophenyl)-2-nitroethyl)-(4-phenylamino)-1H-pyrrole-2,5-dione (4s)

1H NMR (500 MHz, CDCl3) δ 7.50–7.38 (m, 3H), 7.38–7.27 (m, 6H), 7.15 (d, J = 7.5 Hz, 2H), 7.07 (t, J = 8.0 Hz, 1H), 6.98 (s, 1H), 6.87 (d, J = 8.0 Hz, 1H), 6.81 (t, J = 2.0 Hz, 1H), 5.39
(dd, \( J = 13.0, 9.5 \) Hz, 1H), 4.69 (s, 2H), 4.63 (dd, \( J = 13.0, 6.0 \) Hz, 1H), 4.22 (dd, \( J = 9.5, 6.0 \) Hz, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 172.5, 166.9, 141.4, 140.0, 136.5, 136.2, 131.2, 130.8, 130.4, 129.7, 128.7, 128.2, 127.9, 126.4, 125.9, 122.7, 97.0, 41.6, 39.2, 29.7; HRMS (ESI) m/z: [M + Na]\(^+\) calcld for C\(_{25}\)H\(_{20}\)BrN\(_3\)O\(_4\)Na 528.0535; found 528.0543; \([\alpha]\)\(_D\)\(_{25}\) = −11.22 (c 0.63, MeOH) (90% ee); HPLC (Chiralpak IA, hexane:iPrOH = 90:10, 1.0 mL/min, 254 nm), \( t_R \) = 18.7 min (minor), 21.6 min (major).

3.2.20. (S)-1-Benzyl-3-(1-(4-bromophenyl)-2-nitroethyl)-4-(phenylamino)-1H-pyrrole-2,5-dione (4t)

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.40 (dd, \( J = 17.0, 7.0 \) Hz, 3H), 7.36–7.27 (m, 7H), 7.15 (d, \( J = 6.5 \) Hz, 2H), 7.02 (s, 1H), 5.34 (t, \( J = 11.0 \) Hz, 1H), 4.76–4.57 (m, 3H), 4.23 (d, \( J = 5.0 \) Hz, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 172.5, 167.0, 141.2, 136.7, 136.5, 136.1, 132.0, 129.7, 129.6, 128.7, 128.2, 127.8, 127.7, 125.7, 121.7, 97.1, 41.6, 39.0, 29.7; HRMS (ESI) m/z: [M + Na]\(^+\) calcld for C\(_{25}\)H\(_{20}\)BrN\(_3\)O\(_4\)Na 528.0535; found 528.0546; \([\alpha]\)\(_D\)\(_{25}\) = −27.63 (c 0.72, MeOH) (90% ee); HPLC (Chiralpak IA, hexane:iPrOH = 90:10, 0.5 mL/min, 254 nm), \( t_R \) = 42.9 min (minor), 45.5 min (major).

4. Conclusions

In summary, we described the first Takemoto-type catalyst to promote the enantioselective Michael addition of \( \alpha \)-aminomaleimides and \( \beta \)-nitroolefins. The \( \alpha \)-aminomaleimides were used as nucleophiles rather than electrophiles in this transformation to create the desired maleimide-containing adducts with high enantioselectivity (up to 94% ee). Moreover, we used our optimized conditions to expand upon the substrate scope of this reaction. Further study of \( \alpha \)-aminomaleimides as donors in Michael additions with other acceptors is under way.

Supplementary Materials: Copies of \(^1\)H and \(^{13}\)C-NMR spectra and HPLC trace of products are available online at https://www.mdpi.com/article/10.3390/molecules27227787/s1. Figures S1–S30: NMR spectra of compounds 4a–t; Figures S31–S70: HPLC trace of compounds 4a–4t.

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References

1. Kim, K.J.; Choi, M.J.; Shin, J.-S.; Kim, M.J.; Choi, H.-E.; Kang, S.M.; Jin, J.H.; Lee, K.-T.; Lee, J.Y. Synthesis, biological evaluation, and docking analysis of a novel family of 1-methyl-1H-pyrrole-2,5-diones as highly potent and selective cyclooxygenase-2 (COX-2) inhibitors. Bioorg. Med. Chem. Lett. 2014, 24, 1958–1962. [CrossRef] [PubMed]
2. Guo, X.; Wang, L.; Wang, S.; Li, Y.; Zhang, F.; Song, B.; Zhao, W. Syntheses of new chlorin derivatives containing maleimide functional group and their photodynamic activity evaluation. Bioorg. Med. Chem. Lett. 2015, 25, 4078–4081. [CrossRef]
3. Eloah, K.; Demurtas, M.; Mura, M.G.; Deplano, A.; Onnis, V.; Sasanelli, N.; Maxia, A.; Caboni, P. Potent Nematicidal Activity of Maleimide Derivatives on Meloidogyne incognita. J. Agric. Food Chem. 2016, 64, 4876–4881. [CrossRef]
4. Eis, M.J.; Evenou, J.P.; Schuler, W.; Zenke, G.; Vangrevelinghe, E.; Wagner, J.; Matt, P. Indolyl-naphthyl-maleimides as potent and selective inhibitors of protein kinase C-\( \alpha \)/\( \beta \). Bioorg. Med. Chem. Lett. 2017, 27, 781–786. [CrossRef] [PubMed]
5. Ho, S.-Y.; Alam, J.; Jayaraj, D.-A.; Wang, W.; Lin, G.-R.; Ang, S.-H.; Tan, E.-S.-W.; Lee, M.-A.; Ke, Z.; Madan, B.; et al. Scaffold Hopping and Optimization of Maleimide Based Porcupine Inhibitors. J. Med. Chem. 2017, 60, 6678–6692. [CrossRef]
6. Serafim, R.A.M.; Sorrell, F.J.; Berger, B.-T.; Collins, R.J.; Vasconcelos, S.N.S.; Massirer, K.B.; Knapp, S.; Bennett, J.; Fedorov, O.; Patel, H.; et al. Discovery of a Potent Dual SLK/STK10 Inhibitor Based on a Maleimide Scaffold. J. Med. Chem. 2021, 64, 13259–13278. [CrossRef] [PubMed]

7. Kjærsgaard, N.L.; Hansen, R.A.; Gothelf, K.V. Preparation of Maleimide-Modified Oligonucleotides from the Corresponding Amines Using N-Methoxycarbonyl maleimide. Bioconjug. Chem. 2022, 33, 1254–1260. [CrossRef] [PubMed]

8. Giglio, J.; Fernandez, S.; Martinez, A.; Zeni, M.; Reyes, L.; Rey, A.; Cerretto, H. Glycogen Synthase Kinase-3 Maleimide Inhibitors As Potential PET-Trackers for Imaging Alzheimer’s Disease and In Vivo Proof of Concept. J. Med. Chem. 2022, 65, 1342–1351. [CrossRef]

9. Mandal, R.; Emayavaramban, B.; Sundararaju, B. Cp*Co(III)-Catalyzed C–H Alkylation with Maleimides Using Weakly Coordinating Carbonyl Directing Groups. Org. Lett. 2018, 20, 2835–2838. [CrossRef]

10. Li, F.; Zhou, Y.; Yang, H.; Liu, D.; Sun, B.; Zhang, F.-L. Assembly of Diverse Spirocyclic Pyrrolidines via Transient Directing Group Enabled Ortho-C(sp2)-H Alkylation of Benzaldehydes. Org. Lett. 2018, 20, 146–149. [CrossRef]

11. Yu, J.T.; Chen, R.; Jia, H.; Pan, C. Rhodium-Catalyzed Site-Selective ortho-C–H Activation: Enone Carbonyl Directed Hydroarylation of Maleimides. J. Org. Chem. 2018, 83, 12086–12093. [CrossRef] [PubMed]

12. Lin, C.; Zhen, L.; Cheng, Y.; Du, H.-J.; Zhao, H.; Wen, X.; Kong, L.-Y.; Xu, Q.-L.; Sun, H. Visible-Light Induced Isoindoles Towards the Synthesis of Chiral Succinimide Derivatives. Chem. Asian J. 2019, 14, 6048–6051. [CrossRef] [PubMed]

13. Uno, B.-E.; Dicken, R.-D.; Redfern, L.-R.; Stern, C.-M.; Krzywicki, G.-G.; Scheidt, K.-A. Calcium(II)—Catalyzed enantioselective conjugate additions of amines. Chem. Sci. 2018, 9, 1634–1639. [CrossRef] [PubMed]

14. Jafarpour, F.; Shamsianpour, M.; Issazadeh, S.; Dorrani, M.; Hazrati, H. Palladium-catalyzed direct arylation of maleimides: A simple route to bisaryl-substituted maleimides. Tetrahedron 2017, 73, 1668–1672. [CrossRef]

15. Jafarpour, F.; Shamsianpour, M. Palladium-catalyzed cross-dehydrogenative coupling of maleimides with simple amines: A fast track to highly substituted maleimides. RSC Adv. 2016, 6, 103567–103570. [CrossRef]

16. Yang, Z.-H.; An, Y.-L.; Chen, Y.; Shao, Z.-Y.; Zhao, S.-Y. Copper(I) Iodide-Catalyzed Silylenylation of Maleimides and Related 3-Indolylmaleimides with Thiols. Adv. Synth. Catal. 2018, 360, 3869–3875. [CrossRef]

17. Dana, S.; Mandal, A.; Sahoo, H.; Baidyana, M. Ru(II)-Catalyzed C–H Activation with Electrophiles: A Demonstration of Umpolung Strategy. Org. Lett. 2017, 19, 1902–1905. [CrossRef]

18. An, Y.-L.; Zhang, H.-H.; Yang, Z.-H.; Lin, L.; Zhao, S.-Y. Cu/Ag-Cocatalyzed Aerobic Oxidative Amination and CuCl2-Mediated Aerobic Oxidative Chloroamination of Maleimides. Eur. J. Org. Chem. 2016, 2016, 5405–5414. [CrossRef]

19. Yang, Z.-H.; Tan, H.-R.; An, Y.-L.; Zhao, Y.-W.; Lin, H.-P.; Zhao, S.-Y. Three-Component Coupling Reactions of Maleimides, Thiols, and Amines: One-Step Construction of 3,4-Heteroatom-functionalized Maleimides by Copper-Catalyzed C(sp2)–H Thioamination. Adv. Synth. Catal. 2018, 360, 173–179. [CrossRef]

20. Yang, Z.-H.; Tan, H.-R.; Zhu, J.-N.; Zheng, J.; Zhao, S.-Y. Regioselective Silver-Catalyzed Carbon-Phosphorus Disfunctionalization of Maleimides: One-Step Construction of Phosphonated Indolylmaleimides and Pyrrolylmal maleimides. Adv. Synth. Catal. 2018, 360, 1523–1529. [CrossRef]

21. Baker, J.-R.; Tedaldi, L.-M.; Aliev, A.-E. [2 + 2] Photocycloadditions of thiomaleimides. Chem. Commun. 2012, 48, 4725–4727. [CrossRef]

22. Lin, C.; Zhen, L.; Cheng, Y.; Du, H.-J.; Zhao, H.; Wen, X.; Kong, L.-Y.; Xu, Q.-L.; Sun, H. Visible-Light Induced Isoindoles Formation To Trigger Intermolecular Diels–Alder Reactions in the Presence of Air. Org. Lett. 2015, 17, 2684–2687. [CrossRef] [PubMed]

23. Ding, G.; Wu, X.; Jiang, L.; Zhang, Z.; Xie, X. Reduction of Benzolactams to Isoindoles via an Alkoxide-Catalyzed Hydroisilylation. Org. Lett. 2017, 19, 6048–6051. [CrossRef] [PubMed]

24. Qiu, S.; Lee, R.; Zhu, B.; Coote, M.-L.; Zhao, X.; Jiang, Z. Highly Enantio- and Diastereoselective [4 + 2] Cycloaddition of 5H-oxa-4-ones with N-Maleimides. J. Org. Chem. 2016, 81, 8061–8069. [CrossRef] [PubMed]

25. Chauhan, P.; Kaur, J.; Chimni, S.S. Asymmetric Organocatalytic Addition Reactions of Maleimides: A Promising Approach Towards the Synthesis of Chiral Succinimide Derivatives. Chem. Asian J. 2013, 8, 328–346. [CrossRef] [PubMed]

26. Ravasco, J.M.J.M.; Faustino, H.; Trindade, A.; Gois, P.M.P. Bioconjugation with Maleimides: A Useful Tool for Chemical Biology. Chem. Eur. J. 2019, 25, 43–59. [CrossRef]

27. Gómez-Torres, E.; Alonso, D.A.; Gómez-Bengoa, E.; Nájera, C. Enantioselective synthesis of succinimides by Michael addition of 1,3-dicarbonyl compounds to maleimides catalyzed by a chiral bis(2-aminobenzimidazole) organocatalyst. Eur. J. Org. Chem. 2013, 2013, 1434–1440. [CrossRef]

28. Yuan, F.; Duan, W.; Li, Z.; Luo, X.; Zhang, M.; Deng, H.; Song, L. One-Pot Synthesis of Trifluoromethylated Pyrazol-4-Ylpyrrole-2,5-Dione Derivatives. Synthesis 2019, 51, 3345–3355. [CrossRef]

29. Khan, M.M.; Shareef, S.; Khan, S.; Saigal; Sahoo, S.C. Organocatalyzed Highly Efficient Synthesis of Densely Functionalized Pyrrole-Fused 1,4-Dihydropyridine Derivatives. Synth. Commun. 2019, 49, 2884–2894. [CrossRef]

30. Xie, D.-H.; Niu, C.; Du, D.-M. Enantioselective Michael/ Hemiketalization Cascade Reactions between Hydroxymaleimides and 2-Hydroxynitrostyrenes for the Construction of Chiral ChromanFused PyrrolineDiones. Molecules 2022, 27, 5081. [CrossRef]

31. Sakai, N.; Kawashima, K.; Kajitani, M.; Mori, S.; Oriyama, T. Combined Computational and Experimental Studies on the Asymmetric Michael Addition of α-Aminomaleimides to β-Nitrostyrenes Using an Organocatalyst Derived from Cinchona Alkaloid. Org. Lett. 2021, 23, 5714–5718. [CrossRef]
32. Okino, T.; Hoashi, Y.; Takemoto, Y. Enantioselective Michael Reaction of Malonates to Nitroolefins Catalyzed by Bifunctional Organocatalysts. *J. Am. Chem. Soc.* 2003, 125, 12672–12673. [CrossRef]

33. Hoashi, Y.; Okino, T.; Takemoto, Y. Enantioselective Michael Addition to α, β-unsaturated Imides Catalyzed by a Bifunctional Organocatalyst. *Angew. Chem. Int. Ed. Engl.* 2005, 44, 4032–4035. [CrossRef] [PubMed]

34. Zea, A.; Valero, G.; Alba, A.R.; Moyano, A.; Rios, R. Development of Diphenylamine-linked Bis(imidazoline) Ligands and Their Application in Asymmetric Friedel-Crafts Alkylation of Indole Derivatives with Nitroalkenes. *Adv. Synth. Catal.* 2010, 352, 1102–1106. [CrossRef]

35. Raimondi, W.; Baslé, O.; Constantieux, T.; Bonne, D.; Rodriguez, J. Activation of 1, 2-Ketoesters with Takemoto’s Catalyst toward Michael Addition to Nitroalkenes. *Adv. Synth. Catal.* 2012, 354, 563–568. [CrossRef]

36. Ansari, S.; Raabe, G.; Enders, D. Asymmetric Michael Addition of 1, 3-Bis(phenylthio)propan-2-one to Nitroalkenes Employing Takemoto’s Thiourea Catalyst. *Monatsh. Chem.* 2013, 144, 641–646. [CrossRef]

37. Wang, Y.; Mo, M.; Zhu, K.; Zheng, C.; Zhang, H.; Wang, W.; Shao, Z. Asymmetric Synthesis of Syn-propargylamines and Unsaturated β-amino Acids under Brønsted Base Catalysis. *Nat. Commun.* 2015, 6, 8544–8582. [CrossRef] [PubMed]

38. Wang, P.; Li, H.-F.; Zhao, J.-Z.; Du, Z.-H.; Da, C.-S. Organocatalytic Enantioselective Cross-aldol Reaction of o-Hydroxyarylketones and Trifluoromethyl Ketones. *Org. Lett.* 2017, 19, 2634–2637. [CrossRef]

39. Wu, H.; Wang, L.-M.; Zhang, J.-W.; Jin, Y. Urea Derivative Catalyzed Enantioselective Hydroxyalkylation of Hydroxyindoles with Isatins. *Molecules* 2019, 24, 3944. [CrossRef] [PubMed]

40. Chen, Z.; Zhang, T.-Y.; Sun, Y.-H.; Wang, L.-M.; Jin, Y. Organocatalytic enantioselective aza-Friedel–Crafts alkylation of β-naphthols and isatin-derived ketimines via a Takemoto-type catalyst. *New J. Chem.* 2021, 45, 10481–10487. [CrossRef]