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Organocatalytic asymmetric aza-Michael addition of pyrazole to chalcone

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ABSTRACT

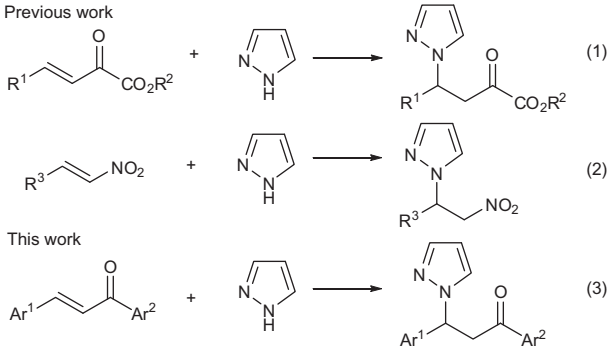
An efficient enantioselective aza-Michael addition of pyrazole to chalcone was established. In the presence of the primary amine derived from cinchona alkaloid and acidic additive, the reactions afforded 1,4-adducts in high yields (up to 98%) with 68–88% ee.

1. Introduction

The stereocontrolled construction of carbon–nitrogen bonds is an important topic in modern organic synthesis, driven by the significance of the biologically and synthetically interesting products formed.[1] Among a number of methods for this stereoselective transformation, the Michael addition of nitrogen nucleophiles, also known as aza-Michael addition, offers a straightforward C–N bond-formation and has been successfully employed in the synthesis of diversified bioactive natural products.[2] In particular, organocatalytic asymmetric aza-Michael addition reactions have received widespread attention because of the advantages of easy availability and of carrying out asymmetric transformations in a metal-free environment and under mild and non-inert reaction conditions.[3]

The search for new *N*-heterocyclic nucleophiles, as suitable acceptors as well as more efficient catalyst systems for the synthesis of compounds containing azole groups is of current interest. Until now, various types of nitrogen nucleophiles have been explored in asymmetric aza-Michael addition such as N-protected carbamates, triazoles, tetrazoles, benzotriazoles, imidazoles, amines, imines, amides, indoles, tryptamines, hydrazones, ureas etc.[4] However, the organocatalytic enantioselective aza-Michael additions of azole with impressive results are rarely reported. Notably, poor yields (21% and 29%,[5e] 43%[5g]) with no more than 83% ee were obtained in the organocatalytic aza-Michael additions of azole to chalcone even with a catalyst loading of 20 mol %.[5]

Recently, we have successfully developed catalyst-free aza-Michael addition of an azole to β,γ-unsaturated α-keto esters[6] and nitroalkenes[7] (Scheme 1, Eqs. 1 and 2). Moreover, it was found that no reaction took place between pyrazole and chalcone without a catalyst. That is to say, the transformation would be less affected by the background reaction between the nitrogen nucleophile and chalcone and the asymmetric induction could be realized with a suitable organocatalyst in the aza-Michael addition. Herein we report an efficient organocatalytic asymmetric aza-Michael addition of pyrazole to chalcone in the presence of a primary amine combined with an acidic additive (Scheme 1, Eq. 3).



Scheme 1. Aza-Michael addition of pyrazole.

2. Results and discussion

Initially we focused our attention on the primary amine[8] and thiourea[9] catalytic aza-Michael additions between chalcone **1a** and pyrazole **2a**, and the results are displayed in Table 1. The initial results indicated that both primary amine **I** and thiourea **II** failed to give asymmetric induction (Table 1, entries 1–3). A remarkable enhancement was achieved when an acidic additive, 4-nitrobenzoic acid **A1**, was introduced into the primary amine catalyzed reaction system (Table 1, entry 4).[10] Employing 3-hydroxy-2-naphthoic acid **A2** as an acidic additive resulted in a higher enantioselectivity

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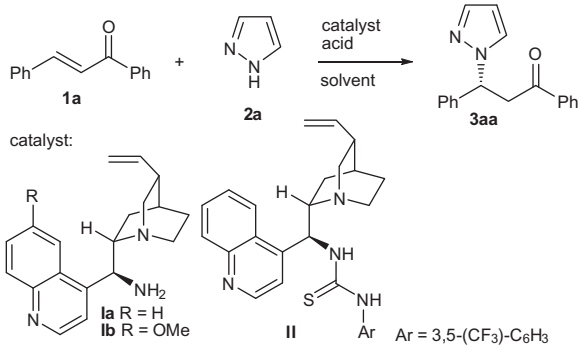
(Table 1, entry 5). When the reaction was carried out in Et_2O as the solvent, the combination of **Ia** and **A2** furnished a 1,4-adduct in 85% yield with 84% ee (Table 1, entry 6). Furthermore, good results could be obtained when **Ib** was used as the chiral organocatalyst (Table 1, entries 8 and 9). With these encouraging results in hand, further optimization of the reaction conditions was carried out. After careful screening of acidic additives, 1-hydroxy-2-naphthoic acid **A3**, $PhCO_2H$ **A4**, *N*-Boc phenylglycine **A5**, and *N*-Boc glycine **A6**, it was found that 1-hydroxy-2-naphthoic acid **A3** afforded better results (Table 1, entries 10–13). Investigation of the reaction media indicated that ether was more suitable for the system (Table 1, entries 14–19). Increasing or reducing the loading of **A3** led to similar yields and slightly lower ee values (Table 1, entries 20 and 21). Doubling the loadings of **Ib** and **A3** afforded 1,4-adduct **3aa** in 80% isolated yield with 80% ee (Table 1, entry 22). If the reaction was performed in Et_2O, **Ib** with a loading of 10 mol %, it enabled the formation of **3aa** in 93% isolated yield with 76% ee (Table 1, entry 23). Using 1,4-dioxane as the solvent furnished **3aa** with 86% ee, the best enantioselectivity, and 62% isolated yield (Table 1, entry 24).

Table 1
Optimization of reaction conditions[a]

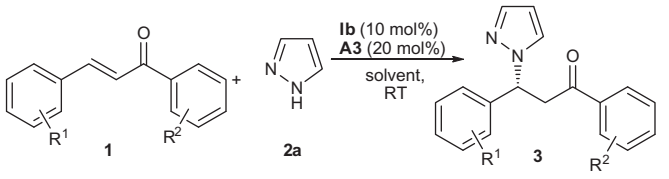


Entry	Cat.	Acid	Solvent	*t* (h)	Yield[b] (%)	ee[c] (%)
1	**Ia**	—	CH_2Cl_2	24	12	0
2	**Ib**	—	CH_2Cl_2	24	14	0
3	**II**	—	CH_2Cl_2	24	12	0
4	**Ia**	**A1**	CH_2Cl_2	24	43	56
5	**Ia**	**A2**	CH_2Cl_2	24	48	72
6	**Ia**	**A2**	Et_2O	42	85	84
7[d]	**Ia**	**A2**	Et_2O	20	80	80
8[d]	**Ib**	**A1**	Et_2O	20	69	70
9	**Ib**	**A2**	Et_2O	48	90	82
10[d]	**Ib**	**A3**	Et_2O	20	83	83
11[d]	**Ib**	**A4**	Et_2O	20	37	44
12[d]	**Ib**	**A5**	Et_2O	20	75	80
13[d]	**Ib**	**A6**	Et_2O	20	51	73
14[d]	**Ib**	**A3**	1,4-dioxane	20	52	72
15[d]	**Ib**	**A3**	$MeOCH_2OMe$	20	73	78
16[d]	**Ib**	**A3**	$(MeOCH_2)_2$	20	49	68
17[d]	**Ib**	**A3**	*t*-BuOMe	20	79	82
18[d]	**Ib**	**A3**	EtOAc	20	51	68
19[d]	**Ib**	**A3**	Toluene	20	79	74
20[e]	**Ib**	**A3**	Et_2O	20	85	75
21[f]	**Ib**	**A3**	Et_2O	20	82	78
22[d]	**Ib**	**A3**	Et_2O	48	80 (Isolated)	80
23	**Ib**	**A3**	Et_2O (0.15 mL)	96	93 (Isolated)	76
24	**Ib**	**A3**	1,4-Dioxane	112	62 (Isolated)	86

[a] Unless noted, reaction was carried out: chalcone (0.10 mmol), pyrazole (0.2 mmol), catalyst (10 mol %), and acidic additive (20 mol %) in the solvent (0.3 mL) were stirred at room temperature for the time given.
[b] HPLC yield.
[c] Determined by chiral HPLC with Chiralpak AD-H.
[d] Catalyst (20 mol %) and acid (40 mol %) were employed.
[e] Catalyst (20 mol %) and acid (30 mol %) were employed.
[f] Catalyst (20 mol %) and acid (60 mol %) were employed.

Under the optimized reaction conditions, **Ib**/**A3**-catalyzed aza-Michael additions between a series of chalcones **1** and pyrazole **2a** were surveyed (Table 2). In the presence of **Ib** combined with **A3**, 1,4-adducts **3aa**–**la** were isolated in 50–96% yields with 68–84% ee. Increasing Et_2O solvents ranging from 0.15 mL to 0.30 mL led to an increase of the asymmetric induction from 72% to 77% (Table 2, entry 5). Replacing Et_2O with 1,4-dioxane as the reaction medium resulted in a higher enantioselectivity (Table 2, entry 6). Various substituents, either electron-withdrawing (Table 2, entries 2, 4–10, 14) or electron-donating groups (Table 2, entries 1, 3, 11–13), could be introduced into both aromatic rings of chalcone. 4-Methoxychalcone **1k** was found to form 1,4-adduct **3ka** with inferior results, 68% yield with 46% ee, in Et_2O while the ee value could be increased to 72% when the reaction was performed in 1,4-dioxane (Table 2, entries 12 and 13).

Table 2
Substrate scope of the aza-Michael addition[a]

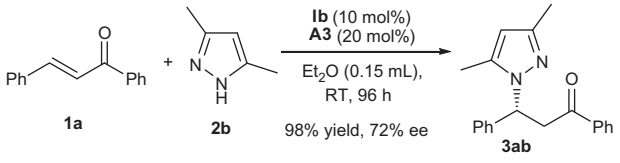


Entry	R^1	R^2	Solvent	*t* (h)	Yield[b] (%)	ee[c] (%)
1	4-Me	H	Et_2O (0.15 mL)	96	**3ba**, 93	68
2	3-Br	H	Et_2O (0.15 mL)	96	**3ca**, 95	82
3	H	3-MeO	Et_2O (0.15 mL)	96	**3da**, 85	77
4	4-F	H	Et_2O (0.15 mL)	96	**3ea**, 96	72
5	4-F	H	Et_2O	112	**3ea**, 88	77
6	4-F	H	1,4-Dioxane	112	**3ea**, 68	84
7	4-CF_3	H	Et_2O	96	**3fa**, 81	84
8	4-Br	H	Et_2O	96	**3ga**, 89	83
9	3-NO_2	H	Et_2O	96	**3ha**, 50	80
10	4-Br	3-Cl	Et_2O	96	**3ia**, 51	76
11	4-Me	4-MeO	Et_2O	96	**3ja**, 66	83
12	4-MeO	H	Et_2O	112	**3ka**, 68	46
13	4-MeO	H	1,4-Dioxane	112	**3ka**, 50	72
14	H	3-Cl	Et_2O	112	**3la**, 70	71
15[d]	3-NO_2	H	1,4-Dioxane	90	**3ha**, 40	88
16[d]	4-Me	4-MeO	1,4-Dioxane	90	**3ja**, 53	86

[a] Unless noted, the reaction was carried out with **1** (0.10 mmol), **2a** (0.20 mmol), **Ib** (10 mol %), and **A3** (20 mol %) in a solvent (0.30 mL) at room temperature for the time given.
[b] Isolated yield.
[c] Determined by chiral HPLC.
[d] Instead of **Ib** and **A3**, **Ia** (10 mol %) and **A2** (20 mol %) were employed.

The **Ia**/**A2**-catalyzed aza-Michael additions of pyrazole to chalcone were also revisited. Higher asymmetric induction with medium yields was obtained when the conjugate reactions were catalyzed by the **Ia**/**A2** system in 1,4-dioxane (Table 2, entries 15 and 16)

In addition to pyrazole **1a**, we also expanded our catalytic system to other azoles. Preliminary studies showed that up to 98% yield with 72% ee could be obtained from the aza-Michael addition of 3,5-dimethylpyrazole **2b** to chalcone **1a** when the **Ib**/**A3** system was employed as the chiral catalyst in a solution of Et_2O (Scheme 2).



Scheme 2. Aza-Michael addition of 3,5-dimethylpyrazole.

3. Conclusion

Herein we have developed an organocatalytic aza-Michael addition of pyrazole to chalcone to afford products in 40–98% yields with 68–88% ee. Compared with the reported results,[5e,g] higher ee values and yields were obtained with this methodology. A wide range of chalcones reacted smoothly with pyrazole to afford good yields and ee values. These results represent the first systematic and general report on the organocatalytic enantioselective aza-Michael addition of pyrazole to chalcone. The development of a new type of organocatalyst and further applications of these reactions are currently under investigation.

4. Experimental

4.1. General procedure for aza-Michael addition

Unless noted otherwise, the reaction was carried out as follows: to a solution of Et_2O or 1,4-dioxane (0.3 mL) were added chalcone **1** (0.1 mmol) and pyrazole **2** (0.2 mmol) in the presence of catalyst **Ib** (10 mol %) combined with **A3** (20 mol %). The reaction mixture was stirred at room temperature for the time given. Then the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel to yield the desired Michael adducts **3**.

4.2. 1,3-Diphenyl-3-(1*H*-pyrazol-1-yl)propan-1-one 3aa

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.98 (d, J = 7.2 Hz, 2H), 7.58–7.50 (m, 3H), 7.46–7.43 (m, 2H), 7.34–7.26 (m, 5H), 6.24 (t, J = 1.8 Hz, 1H), 6.12 (dd, J = 5.2, 8.4 Hz, 1H), 4.50 (dd, J = 4.6, 17.8 Hz, 1H), 3.64 (dd, J = 5.2, 18.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 196.7, 140.9, 139.4, 136.7, 133.5, 129.9, 128.9, 128.7, 128.3, 128.1, 126.8, 105.7, 60.9, 44.3. $[\alpha]_D^{20} = +64.3$ (c 1.00, $CHCl_3$) 76% ee. IR ν_{max}: 3063, 3031, 2914, 1684, 1556, 1508, 1449, 1261, 1207, 1043, 751, 689 cm^{-1}. HRMS: exact mass calculated for $[M+Na]^+$ ($C_{18}H_{16}N_2ONa$) requires m/z 299.1160, found m/z 299.1161.

4.3. 1-Phenyl-3-(1*H*-pyrazol-1-yl)-3-*p*-tolylpropan-1-one 3ba

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.98 (d, J = 7.2 Hz, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.50 (s, 1H), 7.47–7.42 (m, 3H), 7.24 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 6.22 (t, J = 2.0 Hz, 1H), 6.10–6.06 (m, 1H), 4.46 (dd, J = 8.4, 17.6 Hz, 1H), 3.64 (dd, J = 5.2, 17.6 Hz, 1H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 196.8, 139.3, 137.9, 137.8, 136.8, 133.4, 129.7, 129.6, 128.7, 128.3, 126.8, 105.6, 60.8, 44.3, 21.2. $[\alpha]_D^{20} = +34.2$ (c 1.00, $CHCl_3$) 68% ee. IR ν_{max}: 3060, 3022, 2920, 1686, 1596, 1513, 1448, 1283, 1204, 1043, 749, 688 cm^{-1}. HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{19}N_2O$) requires m/z 291.1497, found m/z 291.1499.

4.4. 3-(3-Bromophenyl)-1-phenyl-3-(1*H*-pyrazol-1-yl)propan-1-one 3ca

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.98–7.96 (m, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.52–7.50 (m, 3H), 7.45 (t, J = 7.6 Hz, 2H), 7.41 (d, J = 8.0 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.19 (t, J = 7.8 Hz, 1H), 6.25 (t, J = 2.0 Hz, 1H), 6.07 (dd, J = 5.2, 8.4 Hz, 1H), 4.47 (dd, J = 8.4, 17.6 Hz, 1H), 3.61 (dd, J = 5.2, 17.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 196.3, 143.1, 139.7, 136.5, 133.6, 131.3, 130.5, 130.0, 128.8, 128.3, 125.5, 123.0, 106.0, 60.3, 44.2. $[\alpha]_D^{20} = +56.9$ (c 1.00, $CHCl_3$) 82% ee. IR ν_{max}: 3110, 3059, 2914, 1685, 1596, 1509, 1448, 1395, 1207, 1090, 756, 690 cm^{-1}. HRMS: exact mass calculated for $[M+H]^+$ ($C_{18}H_{16}N_2OBr$) requires m/z 355.0446, found m/z 355.0445.

4.5. 1-(3-Methoxyphenyl)-3-phenyl-3-(1*H*-pyrazol-1-yl)propan-1-one 3da

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.96 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 9.6, Hz, 2H), 7.33–7.24 (m, 5H), 6.91 (d, J = 8.8 Hz, 2H), 6.22 (s, 1H), 6.11 (dd, J = 5.4, 8.6 Hz, 1H), 4.42 (dd, J = 8.4, 17.2 Hz, 1H), 3.84 (s, 3H), 3.60 (dd, J = 5.2, 17.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 195.2, 163.8, 141.0, 139.4, 130.7, 129.9, 129.8, 128.9, 128.0, 126.8, 113.9, 105.6, 61.1, 55.6, 43.9. $[\alpha]_D^{20} = +66.5$ (c 1.00, $CHCl_3$) 77% ee. IR ν_{max}: 3063, 3031, 2930, 1675, 1600, 1510, 1455, 1259, 1212, 1170, 1028, 835, 754, 694 cm^{-1}. HRMS: exact mass calculated for $[M+Na]^+$ ($C_{19}H_{18}N_2O_2Na$) requires m/z 329.1266, found m/z 329.1257.

4.6. 3-(4-Fluorophenyl)-1-phenyl-3-(1*H*-pyrazol-1-yl)propan-1-one 3ea

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.98-7.96 (m, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.52–7.48 (m, 2H), 7.44 (d, J = 7.8 Hz, 2H), 7.35–7.32 (m, 2H), 7.01 (t, J = 8.8 Hz, 2H), 6.23 (t, J = 2.0 Hz, 1H), 6.09 (dd, J = 5.6, 8.0 Hz, 1H), 4.43 (dd, J = 8.0, 17.6 Hz, 1H), 3.65 (dd, J = 5.6, 17.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 196.6, 162.5 (d, $^1J_{C-F}$ = 245.4 Hz), 139.6, 136.6 (d, $^4J_{C-F}$ = 3.3 Hz), 136.58, 133.6, 129.8, 128.8, 128.6 (d, $^3J_{C-F}$ = 8.1 Hz), 128.3, 115.8 (d, $^2J_{C-F}$ = 21.4 Hz), 105.8, 60.3, 44.4. $[\alpha]_D^{20} = +58.2$ (c 1.00, $CHCl_3$) 72% ee. IR ν_{max}: 3117, 3063, 2914, 1685, 1597, 1510, 1449, 1396, 1224, 1045, 752, 689 cm^{-1}. HRMS: exact mass calculated for $[M+Na]^+$ ($C_{18}H_{15}N_2OFNa$) requires m/z 317.1066, found m/z 317.1065.

4.7. 3-(4-(Trifluoromethyl)phenyl)-1-phenyl-3-(1*H*-pyrazol-1-yl) propan-1-one 3fa

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.97 (d, J = 7.2 Hz, 2H), 7.60–7.51 (m, 5H), 7.47–7.43 (m, 4H), 6.26 (t, J = 2.0 Hz, 1H), 6.19–6.16 (m, 1H), 4.48 (dd, J = 8.0, 17.6 Hz, 1H), 3.68 (dd, J = 5.4, 17.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 196.3, 144.9, 139.9, 136.5, 133.7, 130.0, 128.8, 128.3, 127.3, 125.9 (q, J_{C-F} = 3.6 Hz), 106.1, 60.5, 44.3. $[\alpha]_D^{20} = +60.2$ (c 1.00, in $CHCl_3$) 84% ee. IR ν_{max}: 3060, 2917, 1686, 1621, 1505, 1449, 1326, 1167, 1124, 1069, 753, 688 cm^{-1}. HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{16}N_2OF_3$) requires m/z 345.1215, found m/z 345.1199.

4.8. 3-(4-Bromophenyl)-1-phenyl-3-(1*H*-pyrazol-1-yl)propan-1-one 3ga

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.96 (d, J = 7.2 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.51–7.48 (m, 2H), 7.46–7.44 (m, 4H), 7.22 (d, J = 8.4 Hz, 2H), 6.24 (t, J = 2.0 Hz, 1H), 6.08–6.05 (m, 1H), 4.43 (dd, J = 8.0, 17.6 Hz, 1H), 3.64 (dd, J = 5.4, 17.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 196.4, 139.9, 139.7, 136.5, 133.6, 132.0, 129.9, 128.8, 128.6, 128.3, 122.1, 105.9, 60.4, 44.2. $[\alpha]_D^{20} = +36.0$ (c 1.00, $CHCl_3$) 83% ee. IR ν_{max}: 3060, 2920, 1685, 1596, 1488, 1448, 1396, 1207, 1011, 754, 689 cm^{-1}. HRMS: exact mass calculated for $[M+H]^+$ ($C_{18}H_{16}N_2OBr$) requires m/z 355.0446, found m/z 355.0445.

4.9. 3-(3-Nitrophenyl)-1-phenyl-3-(1*H*-pyrazol-1-yl)propan-1-one 3ha

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.25 (s, 1H), 8.14 (d, J = 8.0 Hz, 1H), 7.97 (d, J = 8.8 Hz, 2H), 7.70 (d, J = 8.0 Hz, 1H), 7.59–7.55 (m, 3H), 7.51 (t, J = 8.8 Hz, 1H), 7.46 (t, J = 7.6 Hz, 2H), 6.27 (t, J = 2.0 Hz, 1H), 6.23-6.19 (m, 1H), 4.47 (dd, J = 7.8, 17.8 Hz, 1H), 3.74 (dd, J = 5.6, 18.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 196.0, 142.9, 140.2, 136.3, 133.8, 133.2, 130.1,

129.9, 128.9, 128.3, 123.2, 122.1, 106.2, 60.2, 44.2. $[\alpha]_D^{20} = +27.9$ (*c* 0.80, $CHCl_3$) 80% ee. IR ν_{max}: 3079, 2914, 1684, 1597, 1529, 1448, 1351, 1210, 1092, 758, 688 cm^{-1}. HRMS: exact mass calculated for $[M+H]^+$ ($C_{18}H_{16}N_3O_3$) requires *m*/*z* 322.1192, found *m*/*z* 322.1180.

4.10. 3-(4-Bromophenyl)-1-(3-chlorophenyl)-3-(1*H*-pyrazol-1-yl) propan-1-one 3ia

^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.93 (t, *J* = 1.8 Hz, 1H), 7.85-7.82 (m, 1H), 7.54–7.51 (m, 2H), 7.46 (d, *J* = 2.4 Hz, 2H), 7.44 (s, 1H), 7.41-7.37 (m, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 6.24 (t, *J* = 2.2 Hz, 1H), 6.03 (dd, *J* = 5.4, 8.2 Hz, 1H), 4.43 (dd, *J* = 8.4, 17.6 Hz, 1H), 3.57 (dd, *J* = 5.4, 17.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 195.3, 139.7, 138.0, 135.2, 133.6, 132.1, 130.1, 129.9, 128.6, 128.5, 126.4, 122.3, 106.1, 60.3, 44.3. $[\alpha]_D^{20} = +27.8$ (*c* 1.00, $CHCl_3$) 76% ee. IR ν_{max}: 3066, 2961, 2923, 1690, 1603, 1488, 1394, 1280, 1207, 1074, 1011, 793, 679 cm^{-1}. HRMS: exact mass calculated for $[M+H]^+$ ($C_{18}H_{15}N_2OClBr$) requires *m*/*z* 389.0056, found *m*/*z* 389.0068.

4.11. 1-(4-Methoxyphenyl)-3-(1*H*-pyrazol-1-yl)-3-*p*-tolylpropan-1-one 3ja

^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.96 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 2.0 Hz, 1H), 7.47 (d, *J* = 2.4 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 7.6 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.21 (t, *J* = 2.0 Hz, 1H), 6.09–6.05 (m, 1H), 4.39 (dd, *J* = 8.4, 17.2 Hz, 1H), 3.85 (s, 3H), 3.60 (dd, *J* = 5.4, 17.4 Hz, 1H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 195.3, 163.8, 139.3, 137.9, 137.8, 130.6, 129.8, 129.7, 129.5, 126.8, 113.9, 105.5, 60.9, 55.6, 43.9, 21.2. $[\alpha]_D^{20} = +32.1$ (*c* 1.00, $CHCl_3$) 83% ee. IR ν_{max}: 3006, 2920, 2832, 1675, 1601, 1510, 1420, 1259, 1170, 1025, 809, 753 cm^{-1}. HRMS: exact mass calculated for $[M+H]^+$ ($C_{20}H_{21}N_2O_2$) requires *m*/*z* 321.1603, found *m*/*z* 321.1608.

4.12. 3-(4-Methoxyphenyl)-1-phenyl-3-(1*H*-pyrazol-1-yl)propan-1-one 3ka

^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.97 (d, *J* = 7.2 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.50 (s, 1H), 7.47–7.42 (m, 3H), 7.29 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 6.21 (t, *J* = 2.0 Hz, 1H), 6.07–6.04 (m, 1H), 4.43 (dd, *J* = 8.0, 17.6 Hz, 1H), 3.77 (s, 3H), 3.65 (dd, *J* = 5.6, 17.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 196.9, 159.5, 139.4, 136.8, 133.4, 132.9, 129.6, 128.7, 128.3, 128.2, 114.3, 105.6, 60.6, 55.4, 44.4. $[\alpha]_D^{20} = +12.5$ (*c* 1.00, $CHCl_3$) 30% ee. IR ν_{max}: 2958, 2930, 2832, 1684, 1610, 1514, 1448, 1250, 1176, 1030, 748, 688 cm^{-1}. HRMS: exact mass calculated for $[M+Na]^+$ ($C_{19}H_{18}N_2O_2Na$) requires *m*/*z* 329.1266, found *m*/*z* 329.1252.

4.13. 1-(3-Chlorophenyl)-3-phenyl-3-(1*H*-pyrazol-1-yl)propan-1-one 3la

^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.94 (t, *J* = 1.8 Hz, 1H), 7.86–7.84 (m, 1H), 7.54–7.50 (m, 2H), 7.47 (d, *J* = 2.4 Hz, 1H), 7.40–7.34 (m, 2H), 7.32–7.28 (m, 4H), 6.24 (t, *J* = 2.0 Hz, 1H), 6.08 (dd, *J* = 5.0, 8.2 Hz, 1H), 4.48 (dd, *J* = 8.6, 17.8 Hz, 1H), 3.58 (dd, *J* = 5.2, 17.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 195.6, 140.7, 139.4, 138.2, 135.1, 133.4, 130.1, 129.9, 129.0, 128.5, 128.2, 126.8, 126.4, 105.9, 60.9, 44.4. $[\alpha]_D^{20} = +49.0$ (*c* 1.00, $CHCl_3$) 66% ee. IR ν_{max}: 3065, 3031, 2918, 1690, 1572, 1496, 1424, 1396, 1285, 1259, 1204, 1091, 1045, 753, 703 cm^{-1}. HRMS: exact mass calculated for $[M+H]^+$ ($C_{18}H_{16}N_2OCl$) requires *m*/*z* 311.0951, found *m*/*z* 311.0948.

4.14. 3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-1,3-diphenylpropan-1-one 3ab

^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.01–7.99 (m, 2H), 7.57–7.53 (m, 1H), 7.46–7.42 (m, 2H), 7.33–7.29 (m, 2H), 7.26–7.22 (m, 3H), 5.98 (dd, *J* = 4.8, 8.8 Hz, 1H), 5.78 (s, 1H), 4.58 (q, *J* = 8.8 Hz, 1H), 3.54 (dd, *J* = 4.6, 17.8 Hz, 1H), 2.26 (s, 3H), 2.19 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 197.4, 147.2, 141.5, 139.7, 136.9, 133.3, 128.8, 128.6, 128.4, 127.6, 126.6, 105.4, 56.8, 44.9, 13.8, 11.2. $[\alpha]_D^{20} = +124.4$ (*c* 1.00, $CHCl_3$, 72% ee). IR ν_{max}: 3062, 3025, 2917, 1685, 1555, 1449, 1361, 1206, 1024, 750, 690 cm^{-1}. HRMS: exact mass calculated for $[M+H]^+$ ($C_{20}H_{21}N_2O$) requires *m*/*z* 305.1654, found *m*/*z* 305.1644.

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