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Enantiodivergent Brucine Diol-Catalyzed 1,3-Dipolar Cycloaddition of Azomethine Ylides with α,β-Unsaturated Ketones

Jian-Yuan Li,[a] Hun Young Kim,[b] and Kyungsoo Oh[b,*]

[a] Department of Chemistry and Chemical Biology, Indiana University Purdue University Indianapolis, Indianapolis, Indiana 46202, USA

[b] Center for Metareceptome Research, College of Pharmacy, Chung-Ang University, 84 Heukseok-ro, Dongjak, Seoul 156-756, Republic of Korea
Fax: (+82)-2-816-7338; e-mail: kyungsoooh@cau.ac.kr

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Abstract: Enantiodivergent catalyst systems were developed using metals with different ionic radii and a multifunctional brucine diol (BD) ligand. The catalytic use of purported 1:1 Cu-BD complexes in the 1,3-dipolar cycloaddition of azomethine ylides with chalcones resulted in the selective formation of *endo*-pyrrolidines in 87–96% *ee*s with an absolute stereochemical outcome of (2*R*,3*S*,4*R*,5*S*). In contrast, an opposite absolute stereochemical outcome was observed by using the catalysts derived from Ag(I) salts and BD. The demonstration of enantiodivergent approaches to a broad class of substrates/reaction types underlines their synthetic value in asymmetric synthesis.

Keywords: asymmetric catalysis; copper; enantiodivergence; pyrrolidines; silver

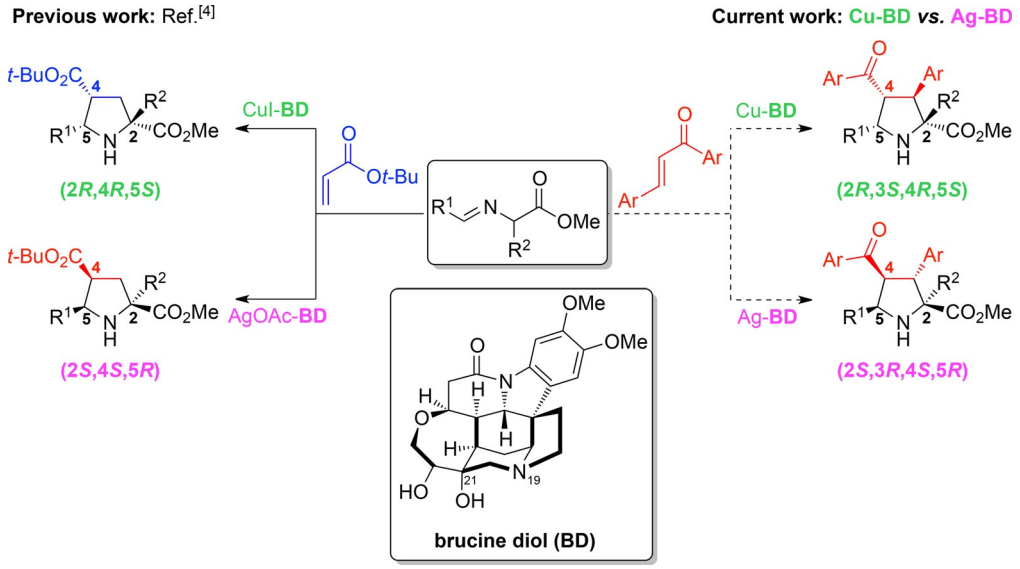
Introduction

Transition metal-catalyzed asymmetric reactions are one of the most powerful and practical synthetic methods in organic synthesis.[1] The unique advantages of such chiral metal complex catalysts lie in the fact that the reactivity as well as the selectivity of catalysts can be readily modulated by using (i) the modifications of the ligand, (ii) the different natures of the metals, and (iii) other reaction parameters such as solvent, reaction temperature, and additives. Collectively, the combination of one or more experimental parameters leads to a drastic change in the reactivity and selectivity of a given asymmetric reaction. The recent development of enantiodivergent asymmetric catalysis essentially captures the concept of stereocontrol using multiple reaction parameters to induce the respective enantiomeric products *on demand* using a single chiral source.[2] While recent years have witnessed the emergence of several successful enantiodivergent catalyst systems, most of these catalyst systems lack the generality to be applied to new asymmetric reactions due to the specific chemotypes associated with given asymmetric reactions.[3] Consequently, the application of enantiodivergent reactions to a broad class of substrates is a much-needed step toward their entry into the mainstream of asymmetric catalysis.

Previously, we reported an enantiodivergent 1,3-dipolar cycloaddition reaction of imino esters with acrylates using Cu(I)-BD and Ag(I)-BD complexes derived from a single chiral source, brucine diol (BD) (Scheme 1).[4] The underlying concept of our earlier approach was based on the possible formation of different metal-BD complexes in the presence of metals with different ionic radii. With the aim of broadening the enantiodivergent approaches in asymmetric catalysis,[5] we investigated the substrate generality in the 1,3-dipolar cycloaddition reactions of imino esters with chalcone derivatives. Herein, we report the use of Cu(I)-BD and Ag(I)-BD complexes as orthogonal enantioselective catalysts for the 1,3-dipolar cycloaddition of imino esters with chalcones, demonstrating the generality of enantiodivergent asymmetric catalysis.

Results and Discussion

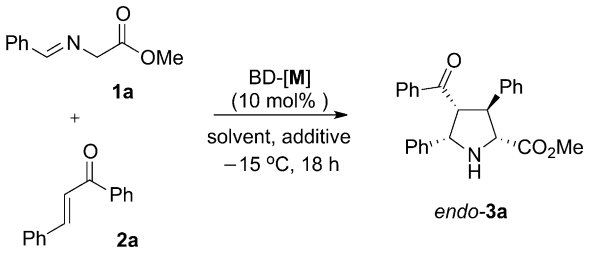
The catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides with α,β-unsaturated ketones was first pioneered by the group of Carretero using Cu(I)-Fesulphos complexes,[6] where the preferential formation of *exo*-pyrrolidines was observed. Subsequent studies by the groups of Zheng,[7] Wang,[8] and Waldmann[9] established the Cu(I)-catalyzed *endo*-selective 1,3-dipolar cycloaddition reactions of various α,β-un-



Scheme 1. Enantiodivergent Cu-BD and Ag-BD catalyst systems.

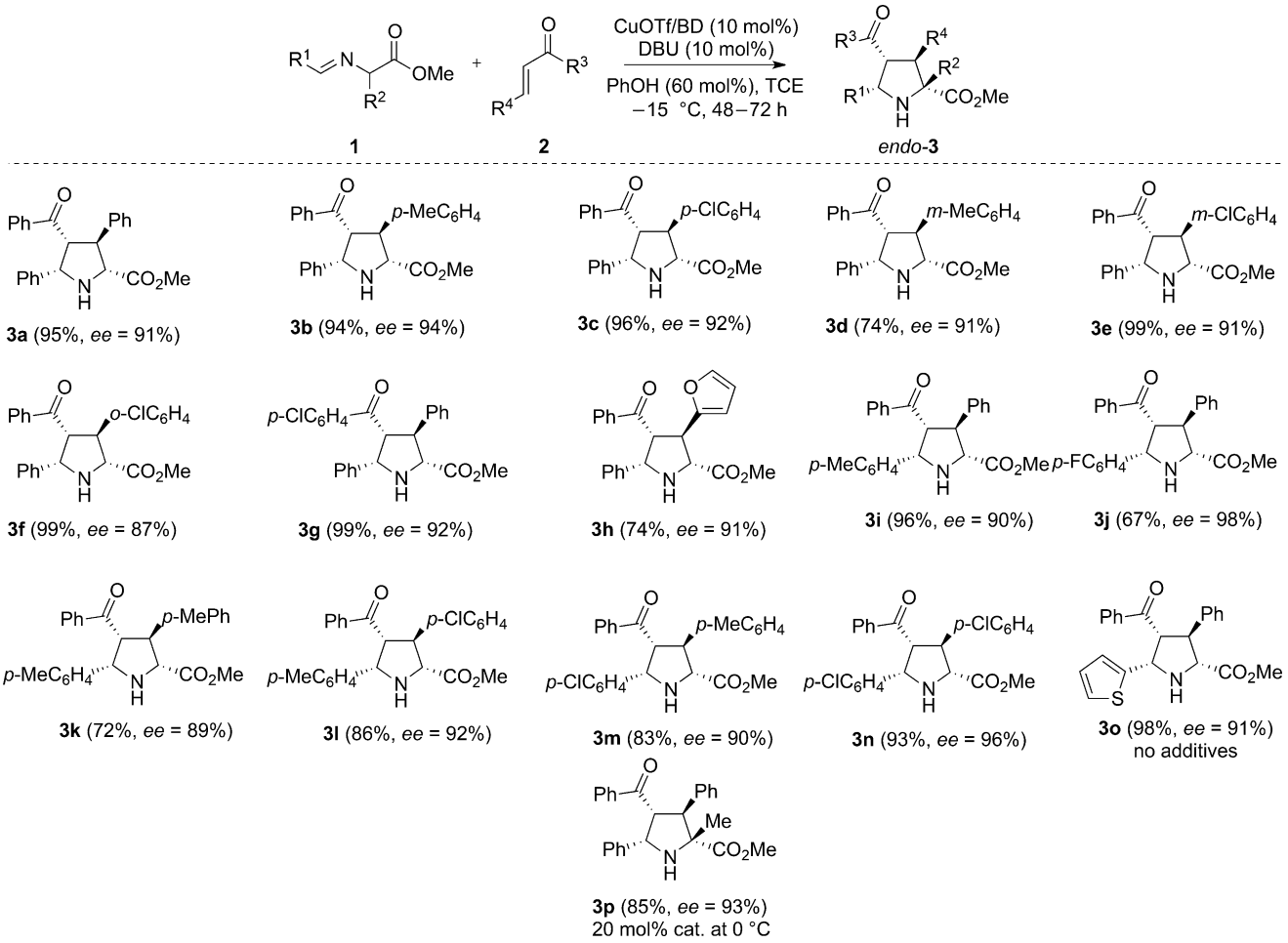
saturated ketones. In related studies, the groups of Cossío,[10] Fukuzawa,[11] Wang,[12] and Singh[13] reported the use of chiral Ag(I) complexes in the *endo*-selective 1,3-dipolar cycloaddition of azomethine ylides with cyclic and acyclic enones. While it is abundantly clear that both chiral Cu(I) and Ag(I) complexes are effective catalysts for the 1,3-dipolar cycloaddition of azomethine ylides with enones,[14] the possibility of developing enantiodivergent Cu(I) and Ag(I) catalysts has not been explored in spite of extensive screenings using various Cu(I) and Ag(I) salts during the optimization processes. To explore the effect of different metal-BD molecularities to the stereochemical outcome of 1,3-dipolar cycloaddition of azomethine ylides and enones, we first examined various Cu-BD catalysts in the reaction between methyl imino ester **1a** and chalcone **2a** (Table 1). The use of Cu-BD catalysts derived from CuOAc led to the exclusive formation of *endo*-pyrrolidine **3a** with 75% *ee* (Table 1, entry 1). Next, we opted for the use of other Cu-BD catalysts to improve the enantioselectivity as well as the reaction conversion. The change of copper salts marginally improved the enantioselectivity to 80–83% *ee* (Table 1, entries 2–5). However, the reaction conversion remained <30%. The examination of solvent effects revealed that the use of chlorinated solvents such as $CHCl_3$ and 1,1,2-trichloroethane was better suited for consistent results (Table 1, entry 6). The beneficial effect of alcohol additives has been noted in the previous metal-BD-catalyzed asymmetric reactions.[5] While such additive effects are not a common optimization parameter in the asymmetric 1,3-dipolar cycloaddition reaction, the use of achiral and meso ligands in enantioselective catalysis has been widely reported.[15] Our efforts to improve the reaction conversion using protic additives were quite

Table 1. Optimization of Cu(I)-BD-catalyzed 1,3-dipolar cycloaddition reaction.



Entry	Metal/ Base	Solvent	Additive[a]	Yield [%][b]	*ee* [%][c]
1	CuOAc/–	CH_2Cl_2	–	9	75
2	CuCl/Et_3N	CH_2Cl_2	–	20	83
3	CuI/DBU	CH_2Cl_2	–	22	80
4	CuOTf/DBN	CH_2Cl_2	–	26	82
5	CuOTf/DBU	CH_2Cl_2	–	30	83
6	CuOTf/DBU	TCE	–	28	83
7	CuOTf/DBU	TCE	EtOH	47	80
8	CuOTf/DBU	TCE	*t*-BuOH	25	82
9	CuOTf/DBU	TCE	TFE	54	83
10	CuOTf/DBU	TCE	PhOH	79	88
11[d]	CuOTf/DBU	TCE	PhOH	80	91
12[d,e]	CuOTf/DBU	TCE	PhOH	95	91
13[f]	CuOTf/DBU	TCE	PhOH	99	82
14[g]	CuOTf/DBU	TCE	PhOH	70	87

[a] Unless otherwise stated, 20 mol% of additive were added.
[b] Isolated yields of products after column chromatography (unreacted chalcones were recovered).
[c] Determined by HPLC using a chiral column.
[d] 60 mol% of PhOH additive.
[e] Reaction for 48 h.
[f] Reaction at 0 °C.
[g] Use of 5 mol% catalyst for 120 h.



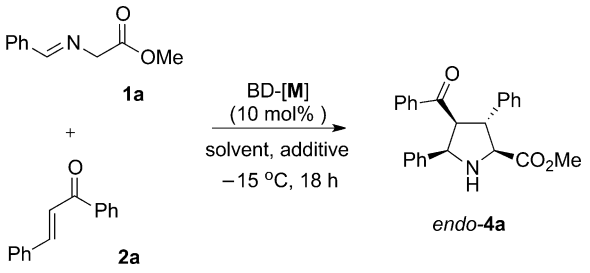
Scheme 2. Scope of Cu(I)-BD-catalyzed 1,3-dipolar cycloaddition reaction.

rewarding (Table 1, entries 7–11), leading to 80% conversion in the presence of 20 mol% of PhOH. Ultimately, the use of 60 mol% of PhOH in conjunction with a longer reaction time of 48 h led to the formation of *endo*-**3a** in 95% yield with 91% *ee* (Table 1, entry 12). Control experiments either under elevated reaction temperature (0 °C) or with less catalyst loading (5 mol%) confirmed the optimal reaction temperature of −15 °C and the catalyst loading of 10 mol% for the observed reactivity and enantioselectivity (Table 1, entries 13 and 14).

The optimized CuOTf-BD-catalyzed 1,3-dipolar cycloaddition conditions were further investigated using other imino esters and chalcone derivatives (Scheme 2). A wide range of imino esters and chalcones with different electronic and steric effect provided the desired *endo*-**3a–p** in high yields with excellent enantioselectivities (87–98% *ee*s). In particular, the imino ester with a coordinating heteroarene moiety, thiophene, did not need the protic additives, providing *endo*-pyrrolidine (**3o**) in 98% yield with 91% *ee*. In addition, the imino ester derived from alanine smoothly underwent the cycloaddition at 0 °C to give *endo*-pyrrolidine (**3p**) in 85% yield with 93% *ee*. The absolute stereochemistry of *endo*-**3** was confirmed to be (2*R*,3*S*,4*R*,5*S*) by comparison of its HPLC retention times with that of authentic samples (see the Supporting Information for details).

To investigate the scope of enantiodivergent approaches in the 1,3-dipolar cycloaddition of azomethine ylides and enones, we next examined various Ag-BD catalysts. The screening of silver salts swiftly resulted in the identification of AgF as an optimal silver source (Table 2, entries 1–7), leading to the exclusive formation of *endo*-**4a**, the mirror image form of *endo*-**3a**, in 74% *ee* (Table 2, entry 7). It is worth noting that the use of silver salts provides *endo*-**4a** as a major enantiomer regardless of the nature of the counter anions, clearly demonstrating the viability of our enantiodivergent approaches based on metals with different ionic radii. An examination of the solvent effect was next conducted (Table 2, entries 8–11), where a coordinating solvent, THF, emerged as an optimal solvent to provide *endo*-**4a** in 91% yield with 79% *ee* (Table 2, entry 11). While the use of an additional amount of BD could improve the observed

Table 2. Optimization of Ag(I)-BD-catalyzed 1,3-dipolar cycloaddition reaction.



Entry	Metal	Solvent	Additive[a]	Yield [%][b]	*ee* [%][c]
1	AgOAc	CH_2Cl_2	–	60	38
2	AgOTf	CH_2Cl_2	–	76	71
3	AgTFA	CH_2Cl_2	–	46	60
4	Ag(2-EHA)	CH_2Cl_2	–	93	64
5	$AgPF_6$	CH_2Cl_2	–	88	59
6	AgI	CH_2Cl_2	–	11	30
7	AgF	CH_2Cl_2	–	85	74
8	AgF	DCE	–	3	35
9	AgF	TCE	–	16	56
10	AgF	$CHCl_3$	–	46	58
11	AgF	THF	–	91	79
12	AgF	THF	BD	82	84
13[d]	AgF	THF	BD	50	64
14	AgF	THF	PhOH	91	79
15	AgF	THF	*t*-BuOH	89	87

[a] Unless otherwise stated, 10 mol% of additive were added.
[b] Isolated yields of products after column chromatography (unreacted chalcones were recovered).
[c] Determined by HPLC using a chiral column.
[d] Use of 50 mol% BD. 2-EHA = 2-ethylhexanoic acid.

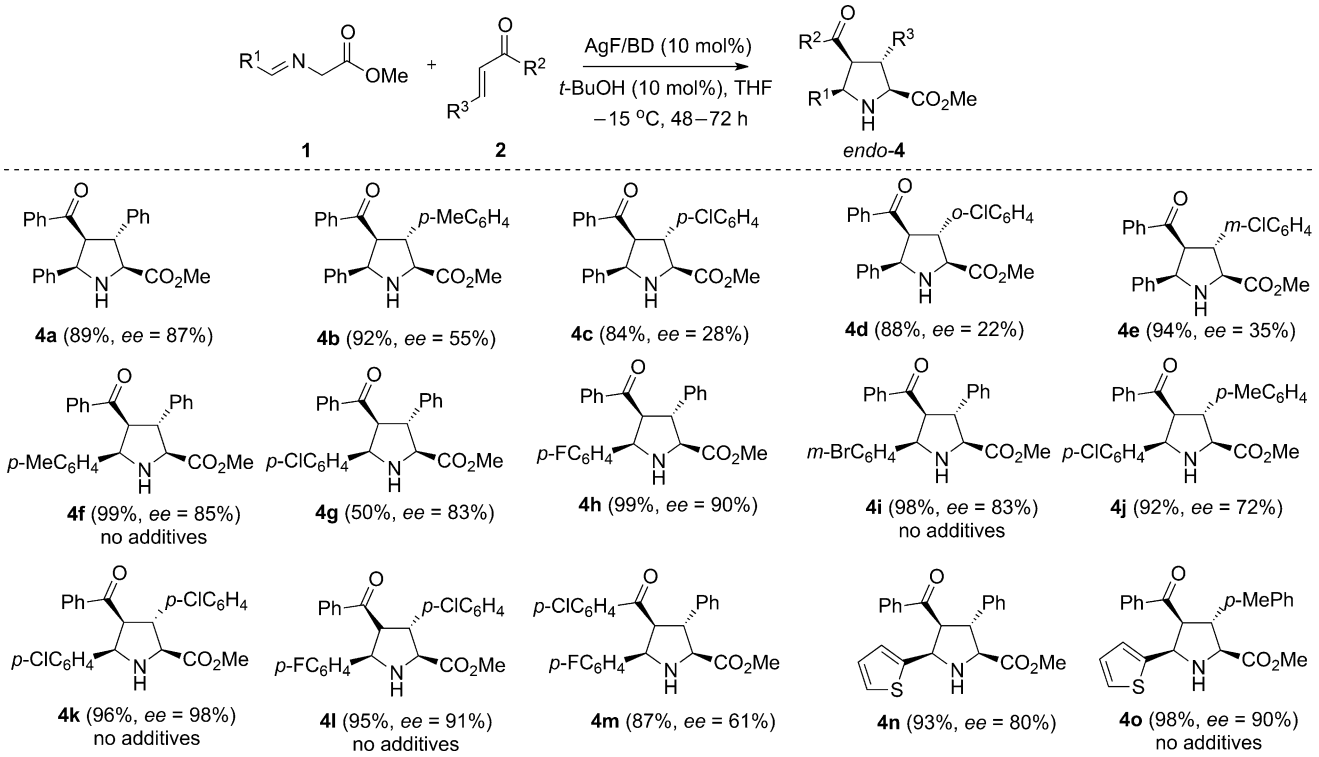
enantioselectivity to 84% (Table 2, entries 12 and 13), the subsequent protic additive screening revealed that the use of 10 mol% of *t*-BuOH could also provide *endo*-**4a** in 89% yield with 87% *ee* (Table 2, entry 15).

The scope of the AgF-BD-catalyzed 1,3-dipolar cycloaddition was examined using a series of imino esters and chalcone derivatives (Scheme 3). Thus, under the two different sets of optimal conditions (with or without protic additives, *t*-BuOH), the facile formation of *endo*-**4** was observed albeit with slightly varying the scope of substrates. For instance, the electronic nature of the chalcone's β-aryl substituent detrimentally influenced the observed enantioselectivities of *endo*-pyrrolidine to 22–55% *ee*s (**4b–4e**). However, the aryl substituent on the imino esters did not exert a significant effect on the observed enantioselectivities, providing *endo*-**4f–i** in 83–90% *ee*s. In addition, the effect of the chalcone's β-aryl substituent could be minimized with the introduction of electron-withdrawing groups to the imino esters and chalcones, whereby *endo*-pyrrolidines (**4j–o**) were obtained in 61–98% *ee*s. An additional limitation of the current AgF-BD-catalyzed 1,3-dipolar cycloaddition was evident upon using the imino ester derived from alanine; the reaction was sluggish and low yielding.[16] While there exists room for improvement in the enantioselectivity of the AgF-BD-catalyzed reactions, the goal of developing the enantiodivergent catalyst systems is within reach with different metal-BD complexes in the presence of metals with different ionic radii, resulting *endo*-**4** with the opposite absolute stereochemical outcome to the CuOTf-BD-catalyzed reactions.

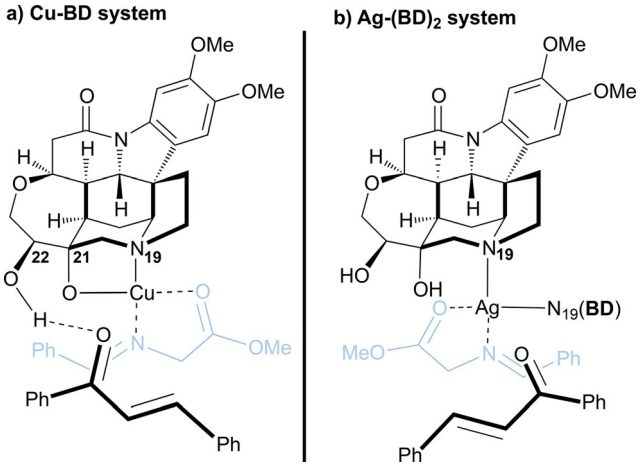
The absolute stereochemical outcomes of both Cu-BD-catalyzed and Ag-BD-catalyzed reactions of chalcones are identical to those of our previous enantiodivergent approaches in the 1,3-dipolar cycloaddition using acrylates.[4] Previously, we proposed that a different stoichiometry between metals and ligand was responsible for the enantiodivergent catalyst behaviours. Thus, since the reported ionic radius of Cu(I) metal with a coordination number four is about 0.60 Å, and the corresponding Ag(I) metal is around 1.00 Å, the formations of 1:1 Cu-BD complexes and 1:2 Ag-BD complexes were proposed.[17] Likewise, the current enantiodivergent 1,3-dipolar cycloaddition of enones could be explained using the different molecularity of the catalysts (Scheme 4). Thus, a smaller metal, Cu(I), forms a five-membered metallocycle with the tertiary amine moiety (N-19) and the tertiary alcohol (C-21) of BD, whereas a metal with relatively large ionic radius, Ag(I), complexes with two BD ligands through the highly Lewis basic tertiary amine moiety (N-19). While more detailed mechanistic work is needed, our preliminary data were consistent with the proposed molecularity of the catalysts. Thus, while the optimal ratio between Cu(I) salts and BD ligand in the Cu-BD catalysts was 1:1, the Ag-BD catalysts well tolerated the ratio between Ag(I) salts and BD ligand upto 1:3 without a significant decrease in enantioselectivity. In particular, the addition of *t*-BuOH in place of BD provided the products with consistent enantioselectivities, suggesting an intricate H-bonding network in the multiple ligands binding to the Ag(I) metal center. Nevertheless, the possible involvement of a metallo-azomethine ylide-chiral base ion pair, originally proposed by Jørgensen in the AgF-hydrocinchonine catalyst system,[18] cannot be completely ruled out. At present time, we postulate that the protic additive in the Cu-BD catalyst system takes on the role of proton shuttle to improve catalyst turnover as their effect on the observed enantioselectivity was insignificant in the Cu-BD catalyst system.

Conclusions

In summary, we have developed enantiodivergent catalyst systems for the 1,3-dipolar cycloaddition of azomethine ylides with chalcone derivatives. The differ-



Scheme 3. Scope of Ag(I)-BD-catalyzed 1,3-dipolar cycloaddition reaction.



Scheme 4. Stereomodels of enantiodivergent catalyst systems.

ent stoichiometry of catalysts derived from metals with different ionic radii and ligands is believed to effect enantiodivergent pathways, demonstrating the generality of enantiodivergent approaches to a broad class of dipolarophile substrates. We are currently investigating the origin of enantioselectivity in our catalyst systems, and our results will be reported in due course. Meanwhile, we are eager to encounter the implementation of enantiodivergent approaches to other synthetic transformations.

Experimental Section

General Procedure for Racemic *endo*-Selective Cycloaddition Products

To a stirred solution of methyl (*E*)-2-(benzylideneamino)acetate derivative (**1**, 0.5 mmol), (*E*)-chalcone derivative (**2**, 0.5 mmol) and silver(I) acetate (0.5 mmol) in dry DCM (1.0 mL), was added Et_3N (0.5 mmol) at ambient temperature. The resulting solution was stirred for 18 h. After which, the solution was concentrated under the reduced pressure and the desired *endo*-cycloaddition product was isolated from crude mixture *via* column chromatograph in 20–35% yield.

General Procedure A for the Cu-BD Complex-Catalyzed *endo*-Selective [3+2] Cycloaddition Reactions

A 10-mL Schlenk flask was charged with $(CuOTf)_2{\cdot}C_6H_6$ (10 mol%, 25 mg) and brucine diol (10 mol%, 21 mg). Dry 1,1,2-trichloroethane (2.2 mL) was then added to the flask at 0 °C, followed by addition of DBU (10 mol%, 8 μL). The solution was stirred for 4 h at this temperature. The resulting solution was cooled to −15 °C, and methyl (*E*)-2-(benzylideneamino)acetate derivative (**1**, 0.5 mmol) was added and stirring continued for 10 min. After which, (*E*)-chalcone derivative (**2**, 0.5 mmol) and phenol additive (60 mol%, 28 mg) were added. The solution was allowed to stir at −15 °C until the reaction was complete by TLC (48–72 h). The reaction mixture was loaded and chromatographed on a short silica column (10–20% ethyl acetate in hexanes).

Methyl (2*R*,3*S*,4*R*,5*S*)-4-benzoyl-3,5-diphenylpyrrolidine-2-carboxylate (3a): light yellow solid; yield: 183 mg (95%); mp 150–154 °C; ^{1}H NMR and ^{13}C NMR spectra for this compound are consistent with previously reported literature data.[10] ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.52–7.51 (m, 2H), 7.38–7.30 (m, 5H), 7.23–7.20 (m, 3H), 7.12–7.03 (m, 5H), 4.98 (d, J = 8.5 Hz, 1H), 4.52–4.49 (m, 1H), 4.19–4.11 (m, 2H), 3.72 (s, 3H), 3.04 (brs, NH); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 198.8, 173.4, 140.9, 139.2, 137.5, 132.9, 128.9, 128.3, 128.2, 128.1, 127.8, 127.7, 127.5, 127.2, 67.8, 66.7, 60.7, 52.8, 52.3; IR (neat): ν = 3345, 3091, 3064, 3032, 3002, 2977, 2953, 1734, 1603, 1553, 1498, 1455, 1435, 1370, 1255, 1221, 1141, 1030, 984, 873, 809, 750, 700, 667 cm^{-1}; HR-MS (CI): m/z = 386.1761 $(M+H)^+$, calcd. for $C_{25}H_{24}NO_3$: 386.1751

Methyl (2*R*,3*S*,4*R*,5*S*)-4-benzoyl-5-phenyl-3-(*p*-tolyl)pyrrolidine-2-carboxylate (3b): light yellow solid; yield: 188 mg (94%); mp 117–119 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.52–7.50 (m, 2H), 7.36–7.34 (m, 1H), 7.27–7.19 (m, 4H), 7.13–7.10 (m, 4H), 7.07–7.00 (m, 3H), 4.97 (d, J = 9.0 Hz, 1H), 4.48 (t, J = 8.0 Hz, 1H), 4.15 (d, J = 9.0 Hz, 1H), 4.08 (t, J = 8.0 Hz, 1H), 3.71 (s, 3H), 3.07 (brs, NH), 2.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 198.8, 173.5, 139.2, 137.8, 137.6, 136.8, 132.8, 129.5, 128.3, 128.1, 128.1, 127.7, 127.6, 127.5, 67.8, 66.7, 60.7, 52.5, 52.3, 21.1; IR (neat): ν = 3354, 3063, 3027, 2951, 2920, 1736, 1679, 1515, 1448, 1434, 1384, 1334, 1262, 1217, 1178, 1128, 1017, 813, 754, 699 cm^{-1}; HR-MS (CI): m/z = 400.1907 $(M+H)^+$, calcd. for $C_{26}H_{26}NO_3$: 400.1913.

Methyl (2*R*,3*S*,4*R*,5*S*)-4-benzoyl-3-(4-chlorophenyl)-5-phenylpyrrolidine-2-carboxylate (3c): yellow solid; yield: 202 mg (96%); mp 115–117 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.52–7.50 (m, 2H), 7.38–7.35 (m, 1H), 7.31–7.25 (m, 4H), 7.23–7.20 (m, 2H), 7.09–7.02 (m, 5H), 4.97 (d, J = 9.0 Hz, 1H), 4.47–4.44 (m, 1H), 4.14–4.08 (m, 2H), 3.70 (s, 3H), 3.00 (brs, NH); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 198.1, 173.2, 139.2, 139.0, 137.3, 132.9, 132.9, 129.2, 128.9, 128.3, 128.1, 128.0, 127.7, 127.5, 67.4, 66.4, 60.7, 52.3, 51.6; IR (neat): ν = 3354, 3088, 3056, 3018, 2952, 2927, 1737, 1679, 1597, 1493, 1448, 1434, 1373, 1333, 1261, 1217, 1178, 1129, 1092, 1014, 825, 755, 719, 698 cm^{-1}; HR-MS (CI): m/z = 420.1362 $(M+H)^+$, calcd. for $C_{25}H_{23}ClNO_3$: 420.1366.

Methyl (2*R*,3*S*,4*R*,5*S*)-4-benzoyl-5-phenyl-3-(*m*-tolyl)pyrrolidine-2-carboxylate (3d): light yellow solid; yield: 148 mg (74%); mp 125–128 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.53–7.51 (m, 2H), 7.37–7.34 (m, 1H), 7.23–7.16 (m, 5H), 7.12–7.10 (m, 2H), 7.07–7.01 (m, 4H), 4.98 (d, J = 9.0 Hz, 1H), 4.50–4.47 (m, 1H), 4.17 (d, J = 9.0 Hz, 1H), 4.10–4.07 (m, 1H), 3.73 (s, 3H), 3.07 (brs, NH), 2.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 198.9, 173.5, 140.9, 139.1, 138.4, 137.5, 132.8, 128.7, 128.6, 128.2, 128.2, 128.1, 128.0, 127.6, 127.5, 124.8, 67.8, 66.8, 60.6, 52.8, 52.3, 21.6; IR (neat): ν = 3345, 3063, 3028, 2917, 1736, 1680, 1596, 1492, 1448, 1434, 1384, 1331, 1263, 1216, 1178, 1128, 784, 754, 700, 668 cm^{-1}; HR-MS (CI): m/z = 400.1906 $(M+H)^+$, calcd. for $C_{26}H_{26}NO_3$: 400.1913.

Methyl (2*R*,3*S*,4*R*,5*S*)-4-benzoyl-3-(3-chlorophenyl)-5-phenylpyrrolidine-2-carboxylate (3e): yellow solid; yield: 208 mg (99%); mp 117–120 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.52–7.51 (m, 2H), 7.38–7.35 (m, 2H), 7.26–7.17 (m, 5H), 7.09–7.02 (m, 5H), 4.97 (d, J = 9.0 Hz, 1H), 4.48–4.45 (m, 1H), 4.15–4.08 (m, 2H), 3.71 (s, 3H), 3.02 (brs, NH); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 198.1, 173.1, 142.8, 139.1, 137.3, 134.5, 132.9, 130.1, 128.3, 128.2, 128.1, 127.9, 127.7, 127.5, 127.4, 126.3, 67.4, 66.5, 60.6, 52.4, 51.9; IR (neat): ν = 3354, 3060, 3031, 2942, 2914, 1737, 1679, 1597, 1573, 1479, 1448, 1435, 1384, 1331, 1259, 1217, 1179, 1129, 1083, 755, 725, 696 cm^{-1}; HR-MS (CI): m/z = 420.1343 $(M+H)^+$, calcd. for $C_{25}H_{23}ClNO_3$: 420.1366.

Methyl (2*R*,3*S*,4*R*,5*S*)-4-benzoyl-3-(2-chlorophenyl)-5-phenylpyrrolidine-2-carboxylate (3f): light yellow solid; yield: 208 mg (99%); mp 99–102 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.52–7.49 (m, 3H), 7.40–7.38 (m, 1H), 7.37–7.34 (m, 1H), 7.31–7.28 (m, 1H), 7.22–7.18 (m, 3H), 7.13–7.11 (m, 2H), 7.07–7.00 (m, 3H), 4.96 (d, J = 8.5 Hz, 1H), 4.62 (dd, J = 8.0, 7.0 Hz, 1H), 4.53 (dd, J = 8.5, 7.0 Hz, 1H), 4.22 (d, J = 8.0 Hz, 1H), 3.78 (s, 3H), 3.17 (brs, NH); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 199.3, 173.4, 138.5, 138.5, 137.5, 134.6, 132.8, 130.2, 128.5, 128.4, 128.3, 128.2, 128.2, 127.8, 127.4, 127.4, 66.7, 66.3, 59.2, 52.6, 50.0; IR (neat): ν = 3348, 3066, 3028, 2952, 2923, 1737, 1679, 1596, 1478, 1448, 1435, 1384, 1332, 1262, 1218, 1180, 1128, 1036, 755, 699 cm^{-1}; HR-MS (CI): m/z = 420.1348 $(M+H)^+$, calcd. for $C_{25}H_{23}ClNO_3$: 420.1366.

Methyl (2*R*,3*S*,4*R*,5*S*)-4-(4-chlorobenzoyl)-3,5-diphenylpyrrolidine-2-carboxylate (3g): light yellow solid; yield: 207 mg (99%); mp 115–119 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.44–7.42 (m, 2H), 7.37–7.30 (m, 4H), 7.24–7.21 (m, 1H), 7.18–7.16 (m, 2H), 7.11–7.03 (m, 5H), 4.96 (d, J = 9.0 Hz, 1H), 4.41 (dd, J = 8.5, 7.5 Hz, 1H), 4.17–4.10 (m, 2H), 3.72 (s, 3H), 3.04 (brs, NH); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 197.7, 173.3, 140.8, 139.2, 138.9, 135.9, 129.5, 128.9, 128.6, 128.3, 127.8, 127.8, 127.4, 127.3, 67.7, 66.7, 60.7, 52.8, 52.4; IR (neat): ν = 3360, 3091, 3060, 3025, 2949, 2914, 1736, 1681, 1588, 1495, 1455, 1434, 1401, 1384, 1261, 1216, 1176, 1092, 1011, 757, 700 cm^{-1}; HR-MS (CI): m/z = 420.1346 $(M+H)^+$, calcd. for $C_{25}H_{23}ClNO_3$: 420.1366.

Methyl (2*R*,3*R*,4*R*,5*S*)-4-benzoyl-3-(furan-2-yl)-5-phenylpyrrolidine-2-carboxylate (3h): light yellow solid; yield: 139 mg (74%); mp: 139–143 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.58–7.56 (m, 2H), 7.42–7.38 (m, 2H), 7.27–7.23 (m, 2H), 7.12–7.02 (m, 5H), 6.32 (dd, J = 3.0, 2.0 Hz, 1H), 6.24 (d, J = 3.0 Hz, 1H), 4.93 (d, J = 8.0 Hz, 1H), 4.58 (dd, J = 8.0, 6.0 Hz, 1H), 4.26 (d, J = 8.0 Hz, 1H), 4.20 (dd, J = 8.0, 6.0 Hz, 1H), 3.83 (s, 3H), 3.52 (brs, NH); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 199.3, 172.8, 153.7, 142.2, 138.1, 137.4, 133.0, 128.4, 128.3, 128.3, 127.8, 127.4, 110.6, 107.0, 66.6, 65.1, 57.1, 52.7, 46.5; IR (neat): ν = 3338, 3060, 3031, 3006, 2958, 2920, 1740, 1682, 1596, 1448, 1435, 1384, 1328, 1217, 1180, 1148, 1013, 754, 699 cm^{-1}; HR-MS (CI): m/z = 376.1530 $(M+H)^+$, calcd. for $C_{23}H_{22}NO_4$: 376.1549.

Methyl (2*R*,3*S*,4*R*,5*S*)-4-benzoyl-3-phenyl-5-(*p*-tolyl)pyrrolidine-2-carboxylate (3i): light yellow solid; yield: 192 mg (96%); mp 167–169 °C; ^{1}H NMR and ^{13}C NMR spectra for this compound are consistent with previously reported literature data;[10] ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.55–7.53 (m, 2H), 7.39–7.36 (m, 3H), 7.33–7.30 (m, 2H), 7.25–7.20 (m, 3H), 6.99 (d, J = 8.0 Hz, 2H), 6.87 (d, J = 8.0 Hz, 2H), 4.96 (d, J = 9.0 Hz, 1H), 4.51–4.48 (m, 1H), 4.16 (d, J = 9.0 Hz, 1H), 4.12–4.09 (m, 1H), 3.72 (s, 3H), 2.96 (brs, NH), 2.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 198.8, 173.5, 140.9, 137.6, 137.3, 136.2, 132.8, 128.9. 128.9, 128.3, 128.2, 127.9, 127.4, 127.2, 67.8, 66.6, 60.8, 52.8, 52.3, 21.1; IR (neat): ν = 3351, 3066, 3015, 3009, 2942, 2911, 1737, 1676, 1448, 1433, 1384, 1261, 1212, 1177, 820, 760, 734, 701, 686, 528 cm^{-1};

HR-MS (CI): m/z = 400.1903 $(M+H)^+$, calcd. for $C_{26}H_{26}NO_3$: 400.1913.

Methyl (2*R*,3*S*,4*R*,5*S*)-4-benzoyl-5-(4-fluorophenyl)-3-phenylpyrrolidine-2-carboxylate (3j): yellow solid; yield: 135 mg (67%); mp 164–167 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.54–7.53 (m, 2H), 7.41–7.30 (m, 5H), 7.27–7.21 (m, 3H), 7.10–7.08 (m, 2H), 6.78–6.74 (m, 2H), 4.98 (d, J = 9.0 Hz, 1H), 4.51–4.48 (m, 1H), 4.18–4.11 (m, 2H), 3.72 (s, 3H), 2.95 (brs, NH); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 198.5, 173.5, 162.2 (d, J = 245.0 Hz), 140.6, 137.5, 135.2 (d, J = 2.5 Hz), 133.1, 129.2 (d, J = 7.5 Hz), 128.9, 128.4, 128.1, 127.9, 127.3, 115.1 (d, J = 21.3 Hz), 67.6, 65.9, 60.5, 52.4, 52.4; IR (neat): ν = 3351, 3060, 3022, 2952, 2917, 1735, 1674, 1600, 1509, 1447, 1435, 1384, 1353, 1326, 1262, 1219, 1180, 1158, 1130, 1077, 1013, 986, 836, 823, 760, 699, 687, 605, 533, 512 cm^{-1}; HR-MS (CI): m/z = 404.1625 $(M+H)^+$, calcd. for $C_{25}H_{23}FNO_3$: 404.1662.

Methyl (2*R*,3*S*,4*R*,5*S*)-4-benzoyl-3,5-di-(*p*-tolyl)pyrrolidine-2-carboxylate (3k): light yellow solid; yield: 149 mg (72%); mp 153–156 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.54–7.52 (m, 2H), 7.37–7.34 (m, 1H), 7.26–7.20 (m, 4H), 7.11 (d, J = 7.5 Hz, 2H), 6.99 (d, J = 8.0 Hz, 2H), 6.86 (d, J = 8.0 Hz, 2H), 4.95 (d, J = 9.0 Hz, 1H), 4.49–4.45 (m, 1H), 4.13 (d, J = 9.0 Hz, 1H), 4.09–4.05 (m, 1H), 3.71 (s, 3H), 3.04 (brs, NH), 2.28 (s, 3H), 2.15 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 198.8, 173.5, 137.8, 137.6, 137.2, 136.7, 136.3, 132.7, 129.5, 128.8, 128.2, 128.1, 127.7, 127.3, 67.8, 66.5, 60.8, 52.5, 52.3, 21.1, 21.0; IR (neat): ν = 3351, 3056, 3023, 2951, 2922, 2863, 1736, 1680, 1596, 1580, 1515, 1448, 1434, 1384, 1329, 1261, 1217, 1178, 1128, 1022, 814, 757, 704, 689, 527 cm^{-1}; HR-MS (CI): m/z = 414.2049 $(M+H)^+$, calcd. for $C_{27}H_{28}NO_3$: 414.2069.

Methyl (2*R*,3*S*,4*R*,5*S*)-4-benzoyl-3-(4-chlorophenyl)-5-(*p*-tolyl)pyrrolidine-2-carboxylate (3l): yellow solid; yield: 187 mg (86%); mp 140–143 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.55–7.53 (m, 2H), 7.41–7.38 (m, 1H), 7.31–7.23 (m, 6H), 6.97 (d, J = 8.0 Hz, 2H), 6.87 (d, J = 8.0 Hz, 2H), 4.95 (d, J = 8.5 Hz, 1H), 4.45 (t, J = 8.5 Hz, 1H), 4.13–4.07 (m, 2H), 3.71 (s, 3H), 2.96 (brs, NH), 2.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 198.1, 173.3, 139.1, 137.5, 137.4, 136.3, 132.9, 129.3, 129.0, 129.0, 128.9, 128.4, 128.2, 127.4, 67.4, 66.3, 60.9, 52.4, 51.8, 21.1; IR (neat): ν = 3357, 3053, 3022, 2946, 2920, 1736, 1679, 1596, 1493, 1448, 1434, 1384, 1329, 1260, 1216, 1179, 1129, 1092, 1014, 819, 758, 691 cm^{-1}; HR-MS (CI): m/z = 434.1498 $(M+H)^+$, calcd. for $C_{26}H_{25}ClNO_3$: 434.1523.

Methyl (2*R*,3*S*,4*R*,5*S*)-4-benzoyl-5-(4-chlorophenyl)-3-(*p*-tolyl)pyrrolidine-2-carboxylate (3m): light yellow solid; yield: 180 mg (83%); mp 155–157 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.55–7.53 (m, 2H), 7.41–7.38 (m, 1H), 7.27–7.23 (m, 4H), 7.12–7.11 (m, 2H), 7.06–7.02 (m, 4H), 4.94 (d, J = 8.5 Hz, 1H), 4.50 −4.47 (m, 1H), 4.15–4.05 (m, 2H), 3.71 (s, 3H), 3.00 (brs, NH), 2.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 198.5, 173.5, 138.2, 137.5, 137.4, 136.9, 133.3, 133.1, 129.6, 128.9, 128.5, 128.3, 128.1, 127.7, 67.6, 65.8, 60.4, 52.3, 52.1, 21.1; IR (neat): ν = 3364, 3060, 3018, 2952, 2927, 2860, 1736, 1679, 1596, 1515, 1491, 1448, 1435, 1384, 1259, 1217, 1178, 1114, 1092, 1014, 816, 757, 690 cm^{-1}; HR-MS (CI): m/z = 434.1504 $(M+H)^+$, calcd. for $C_{26}H_{25}ClNO_3$: 434.1523.

Methyl (2*R*,3*S*,4*R*,5*S*)-4-benzoyl-3,5-bis(4-chlorophenyl)-pyrrolidine-2-carboxylate (3n): yellow solid; yield: 211 mg (93%); mp 123–126 °C; ^{1}H NMR and ^{13}C NMR spectra for this compound are consistent with previously reported literature data;[7,11] ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.56–7.54 (m, 2H), 7.45–7.41 (m, 1H), 7.31–7.27 (m, 6H), 7.05–7.02 (m, 4H), 4.95 (d, J = 8.5 Hz, 1H), 4.61 (t, J = 8.5 Hz, 1H), 4.14–4.07 (m, 2H), 3.72 (s, 3H), 2.95 (brs, NH); ^{13}C NMR ($CDCl_3$, 125 MHz): δ =)197.8, 173.2, 138.7, 138.1, 137.3, 133.5, 133.3, 133.1, 129.3, 129.1, 128.9, 128.6, 128.3, 128.1, 67.3, 65.5, 60.5, 52.5, 51.3; IR (neat): ν = 3345, 3066, 3022, 2946, 2917, 1736, 1678, 1596, 1492, 1448, 1435, 1412, 1384, 1258, 1218, 1179, 1129, 1092, 1014, 824, 771, 693 cm^{-1}; HR-MS (CI): m/z = 454.0942 $(M+H)^+$, calcd. for $C_{25}H_{22}Cl_2NO_3$: 454.0977.

Methyl (2*R*,3*S*,4*R*,5*S*)-4-benzoyl-3-phenyl-5-(thiophen-2-yl)pyrrolidine-2-carboxylate (3o): yellow solid; yield: 192 mg (98%); mp 165–167 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.69–7.67 (m, 2H), 7.46–7.42 (m, 1H), 7.38–7.37 (m, 2H), 7.33–7.29 (m, 4H), 7.24–7.20 (m, 1H), 7.01 (dd, J = 5.0, 1.5 Hz, 1H), 6.72–6.69 (m, 2H), 5.26 (d, J = 8.5 Hz, 1H), 4.53–4.50 (m, 1H), 4.19–4.14 (m, 2H), 3.71 (s, 3H), 3.10 (brs, NH); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 197.6, 173.3, 143.2, 140.4, 137.4, 133.1, 128.9, 128.5, 128.2, 127.9, 127.2, 126.6, 125.5, 124.8, 67.3, 61.8, 60.3, 52.4, 51.6; IR (neat): ν = 3367, 3066, 3018, 2952, 2920, 1736, 1679, 1448, 1435, 1384, 1272, 1234, 1215, 1179, 760, 699 cm^{-1}; HR-MS (CI): m/z = 392.1302 $(M+H)^+$, calcd. for $C_{23}H_{22}NO_3S$: 392.1320.

Methyl (2*R*,3*S*,4*R*,5*S*)-4-benzoyl-2-methyl-3,5-diphenyl-pyrrolidine-2-carboxylate (3p): light yellow solid; yield: 170 mg (85%); mp 168–172 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.57–7.55 (m, 2H), 7.37–7.34 (m, 1H), 7.28–7.16 (m, 7H), 7.13–7.09 (m, 2H), 7.06–7.01 (m, 3H), 5.02 (d, J = 9.5 Hz, 1H), 4.88 (dd, J = 10.0, 9.5 Hz, 1H), 4.46 (d, J = 10.0 Hz, 1H), 3.77 (s, 3H), 3.20 (brs, NH), 1.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 197.9, 175.8, 139.8, 137.8, 137.7, 132.7, 128.6, 128.3, 128.3, 128.1, 128.0, 127.8, 127.6, 127.2, 68.7, 64.2, 56.7, 55.1, 52.5; IR (neat): ν = 3345, 3066, 3029, 2990, 2942, 1728, 1677, 1597, 1496, 1448, 1434, 1384, 1256, 1218, 1177, 1135, 1004, 756, 699 cm^{-1}; HR-MS (CI): m/z = 400.1895 $(M+H)^+$, calcd. for $C_{26}H_{26}NO_3$: 400.1913.

General Procedure B for the Ag-BD Complex-Catalyzed *endo*-Selective [3+2] Cycloaddition Reactions

To a stirred suspension of AgF (10 mol%, 6 mg) and brucine diol (10 mol%, 21 mg), was added dry THF (2.2 mL) at 0 °C under argon. The solution was stirred for 4 h at this temperature. The resulting solution was cooled to −15 °C, and methyl (*E*)-2-(benzylideneamino)acetate derivative (**1**, 0.5 mmol) was added and stirring continued for 10 min. After which, (*E*)-chalcone derivative (**2**, 0.5 mmol) was added with *t*-BuOH as additive (10 mol%, 5 μL). The solution was stirred at −15 °C until the reaction was complete by TLC (48–72 h). The reaction mixture was loaded and chromatographed on a short silica column (10–20% ethyl acetate in hexanes).

Methyl (2*S*,3*R*,4*S*,5*R*)-4-benzoyl-3,5-diphenylpyrrolidine-2-carboxylate (4a): light yellow solid; yield: 172 mg (89%); mp 150–154 °C; ^{1}H NMR and ^{13}C NMR spectra for this compound are consistent with previously reported literature data;[10] ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.52–7.51 (m, 2H), 7.38–7.30 (m, 5H), 7.23–7.20 (m, 3H), 7.12–7.03 (m, 5H),

4.98 (d, $J=8.5$ Hz, 1H), 4.52–4.49 (m, 1H), 4.19–4.11 (m, 2H), 3.72 (s, 3H), 3.04 (brs, NH); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta=198.8$, 173.4, 140.9, 139.2, 137.5, 132.9, 128.9, 128.3, 128.2, 128.1, 127.8, 127.7, 127.5, 127.2, 67.8, 66.7, 60.7, 52.8, 52.3; IR (neat): $\nu=3345$, 3091, 3064, 3032, 3002, 2977, 2953, 1734, 1603, 1553, 1498, 1455, 1435, 1370, 1255, 1221, 1141, 1030, 984, 873, 809, 750, 700, 667 cm^{-1}; HR-MS (CI): $m/z=386.1761$ $(M+H)^+$, calcd. for $C_{25}H_{24}NO_3$: 386.1751.

Methyl (2*S*,3*R*,4*S*,5*R*)-4-benzoyl-5-phenyl-3-(*p*-tolyl)pyrrolidine-2-carboxylate (4b): light yellow solid; yield: 184 mg (92%); mp: 139–142 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta=$ 7.52–7.50 (m, 2H), 7.36–7.34 (m, 1H), 7.27–7.19 (m, 4H), 7.13–7.10 (m, 4H), 7.07–7.00 (m, 3H), 4.97 (d, $J=9.0$ Hz, 1H), 4.48 (t, $J=8.0$ Hz, 1H), 4.15 (d, $J=9.0$ Hz, 1H), 4.08 (t, $J=8.0$ Hz, 1H), 3.71 (s, 3H), 3.07 (brs, NH), 2.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta=198.8$, 173.5, 139.2, 137.8, 137.6, 136.8, 132.8, 129.5, 128.3, 128.1, 128.1, 127.7, 127.6, 127.5, 67.8, 66.7, 60.7, 52.5, 52.3, 21.1; IR (neat): $\nu=3364$, 3062, 3030, 2952, 2920, 1736, 1676, 1606, 1455, 1434, 1409, 1373, 1336, 1264, 1219, 1179, 1128, 1033, 1016, 824, 756, 700 cm^{-1}; HR-MS (CI): $m/z=400.1891$ $(M+H)^+$, calcd. for $C_{26}H_{26}NO_3$: 400.1907.

Methyl (2*S*,3*R*,4*S*,5*R*)-4-benzoyl-3-(4-chlorophenyl)-5-phenylpyrrolidine-2-carboxylate (4c): yellow solid; yield: 176 mg (84%); mp: 115–117 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta=7.52$–7.50 (m, 2H), 7.38–7.35 (m, 1H), 7.31–7.25 (m, 4H), 7.23–7.20 (m, 2H), 7.09–7.02 (m, 5H), 4.97 (d, $J=9.0$ Hz, 1H), 4.47–4.44 (m, 1H), 4.14–4.08 (m, 2H), 3.70 (s, 3H), 3.00 (brs, NH); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta=$ 198.1, 173.2, 139.2, 139.0, 137.3, 132.9, 132.9, 129.2, 128.9, 128.3, 128.1, 128.0, 127.7, 127.5, 67.4, 66.4, 60.7, 52.3, 51.6; IR (neat): $\nu=3354$, 3088, 3056, 3018, 2952, 2927, 1737, 1679, 1597, 1493, 1448, 1434, 1373, 1333, 1261, 1217, 1178, 1129, 1092, 1014, 825, 755, 719, 698 cm^{-1}; HR-MS (CI): $m/z=$ 420.1362 $(M+H)^+$, calcd. for $C_{25}H_{23}ClNO_3$: 420.1366.

Methyl (2*S*,3*R*,4*S*,5*R*)-4-benzoyl-3-(3-chlorophenyl)-5-phenylpyrrolidine-2-carboxylate (4d): yellow solid; yield: 185 mg (99%); mp 117–120 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta=7.52$–7.51 (m, 2H), 7.38–7.35 (m, 2H), 7.26–7.17 (m, 5H), 7.09–7.02 (m, 5H), 4.97 (d, $J=9.0$ Hz, 1H), 4.48–4.45 (m, 1H), 4.15–4.08 (m, 2H), 3.71 (s, 3H), 3.02 (brs, NH); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta=198.1$, 173.1, 142.8, 139.1, 137.3, 134.5, 132.9, 130.1, 128.3, 128.2, 128.1, 127.9, 127.7, 127.5, 127.4, 126.3, 67.4, 66.5, 60.6, 52.4, 51.9; IR (neat): $\nu=$ 3354, 3060, 3031, 2942, 2914, 1737, 1679, 1597, 1573, 1479, 1448, 1435, 1384, 1331, 1259, 1217, 1179, 1129, 1083, 755, 725, 696 cm^{-1}; HR-MS (CI): $m/z=420.1343$ $(M+H)^+$, calcd. for $C_{25}H_{23}ClNO_3$: 420.1366.

Methyl (2*S*,3*R*,4*S*,5*R*)-4-benzoyl-3-(2-chlorophenyl)-5-phenylpyrrolidine-2-carboxylate (4e): light yellow solid; 198 mg (99%); mp: 99–102 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta=7.52$–7.49 (m, 3H), 7.40–7.38 (m, 1H), 7.37–7.34 (m, 1H), 7.31–7.28 (m, 1H), 7.22–7.18 (m, 3H), 7.13–7.11 (m, 2H), 7.07–7.00 (m, 3H), 4.96 (d, $J=8.5$ Hz, 1H), 4.62 (dd, $J=8.0$, 7.0 Hz, 1H), 4.53 (dd, $J=8.5$, 7.0 Hz, 1H), 4.22 (d, $J=8.0$ Hz, 1H), 3.78 (s, 3H), 3.17 (brs, NH); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta=199.3$, 173.4, 138.5, 138.5, 137.5, 134.6, 132.8, 130.2, 128.5, 128.4, 128.3, 128.2, 128.2, 127.8, 127.4, 127.4, 66.7, 66.3, 59.2, 52.6, 50.0; IR (neat): $\nu=3348$, 3066, 3028, 2952, 2923, 1737, 1679, 1596, 1478, 1448, 1435, 1384, 1332, 1262, 1218, 1180, 1128, 1036, 755, 699 cm^{-1}; HR-MS (CI): $m/z=420.1348$ $(M+H)^+$, calcd. for $C_{25}H_{23}ClNO_3$: 420.1366.

Methyl (2*S*,3*R*,4*S*,5*R*)-4-benzoyl-3-phenyl-5-(*p*-tolyl)pyrrolidine-2-carboxylate (4f): light yellow solid; yield: 197 mg (99%); mp 167–169 °C; ^{1}H NMR and ^{13}C NMR spectra for this compound are consistent with previously reported literature data;[10] ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta=7.55$–7.53 (m, 2H), 7.39–7.36 (m, 3H), 7.33–7.30 (m, 2H), 7.25–7.20 (m, 3H), 6.99 (d, $J=8.0$ Hz, 2H), 6.87 (d, $J=8.0$ Hz, 2H), 4.96 (d, $J=9.0$ Hz, 1H), 4.51–4.48 (m, 1H), 4.16 (d, $J=9.0$ Hz, 1H), 4.12–4.09 (m, 1H), 3.72 (s, 3H), 2.96 (brs, NH), 2.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta=198.8$, 173.5, 140.9, 137.6, 137.3, 136.2, 132.8, 128.9. 128.9, 128.3, 128.2, 127.9, 127.4, 127.2, 67.8, 66.6, 60.8, 52.8, 52.3, 21.1; IR (neat): $\nu=$ 3351, 3066, 3015, 3009, 2942, 2911, 1737, 1676, 1448, 1433, 1384, 1261, 1212, 1177, 820, 760, 734, 701, 686, 528 cm^{-1}; HR-MS (CI): $m/z=400.1903$ $(M+H)^+$, calcd. for $C_{26}H_{26}NO_3$: 400.1913.

Methyl (2*S*,3*R*,4*S*,5*R*)-4-benzoyl-5-(4-chlorophenyl)-3-phenylpyrrolidine-2-carboxylate (4g): light yellow solid; yield: 105 mg (50%); mp: 155–158 °C; ^{1}H NMR and ^{13}C NMR spectra for this compound are consistent with previously reported literature data;[7,11] ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta=7.55$–7.54 (m, 2H), 7.43–7.40 (m, 1H), 7.37–7.31 (m, 4H), 7.28–7.22 (m, 3H), 7.07–7.03 (m, 4H), 4.96 (d, $J=8.5$ Hz, 1H), 4.51 (t, $J=8.5$ Hz, 1H), 4.17 (d, $J=9.0$ Hz, 1H), 4.12–4.09 (m, 1H), 3.73 (s, 3H), 2.98 (brs, NH); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta=198.4$, 173.4, 140.5, 138.1, 137.5, 133.4, 133.1, 128.9, 128.9, 128.5, 128.3, 128.1, 127.8, 127.3, 67.6, 65.9, 60.4, 52.4 (2C); IR (neat): $\nu=3370$, 3060, 3025, 2955, 2914, 1737, 1678, 1596, 1492, 1448, 1435, 1384, 1260, 1217, 1179, 1129, 1091, 1014, 828, 770, 699 cm^{-1}; HR-MS (CI): $m/z=420.1356$ $(M+H)^+$, calcd. for $C_{25}H_{23}ClNO_3$: 420.1366.

Methyl (2*S*,3*R*,4*S*,5*R*)-4-benzoyl-5-(4-fluorophenyl)-3-phenylpyrrolidine-2-carboxylate (4h): yellow solid; yield: 200 mg (99%); mp 164–167 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta=7.54$–7.53 (m, 2H), 7.41–7.30 (m, 5H), 7.27–7.21 (m, 3H), 7.10–7.08 (m, 2H), 6.78–6.74 (m, 2H), 4.98 (d, $J=$ 9.0 Hz, 1H), 4.51–4.48 (m, 1H), 4.18–4.11 (m, 2H), 3.72 (s, 3H), 2.95 (brs, NH); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta=198.5$, 173.5, 162.2 (d, $J=245.0$ Hz), 140.6, 137.5, 135.2 (d, $J=$ 2.5 Hz), 133.1, 129.2 (d, $J=7.5$ Hz), 128.9, 128.4, 128.1, 127.9, 127.3, 115.1 (d, $J=21.3$ Hz), 67.6, 65.9, 60.5, 52.4, 52.4; IR (neat): $\nu=3351$, 3060, 3022, 2952, 2917, 1735, 1674, 1600, 1509, 1447, 1435, 1384, 1353, 1326, 1262, 1219, 1180, 1158, 1130, 1077, 1013, 986, 836, 823, 760, 699, 687, 605, 533, 512 cm^{-1}; HR-MS (CI): $m/z=404.1625$ $(M+H)^+$, calcd. for $C_{25}H_{23}FNO_3$: 404.1662.

Methyl (2*S*,3*R*,4*S*,5*R*)-4-benzoyl-5-(3-bromophenyl)-3-phenylpyrrolidine-2-carboxylate (4i): yellow solid; yield: 227 mg (98%); mp 126–130 °C: ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta=7.54$–7.52 (m, 2H), 7.42–7.15 (m, 10H), 7.1–7.09 (m, 1H), 6.96–6.93 (m, 1H), 4.92 (d, $J=9.0$ Hz, 1H), 4.51–4.48 (m, 1H), 4.17 (d, $J=9.0$ Hz, 1H), 4.12–4.09 (m, 1H), 3.72 (s, 3H), 3.09 (brs, NH); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta=198.4$, 173.2, 141.7, 140.6, 137.5, 133.1, 130.8, 130.7, 129.8, 128.9, 128.5, 128.1, 127.8, 127.3, 125.9, 122.2, 67.6, 65.8, 60.2, 52.4, 52.2; IR (neat): $\nu=3373$, 3066, 3028, 2946, 1738, 1679, 1596, 1448, 1435, 1384, 1256, 1216, 1178, 757, 692 cm^{-1}; HR-MS (CI): $m/z=464.0853$ $(M+H)^+$, calcd. for $C_{25}H_{23}BrNO_3$: 464.0861.

Methyl (2*S*,3*R*,4*S*,5*R*)-4-benzoyl-5-(4-chlorophenyl)-3-(*p*-tolyl)pyrrolidine-2-carboxylate (4j): light yellow solid; yield: 199 mg (92%); mp 155–157 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.55–7.53 (m, 2H), 7.41–7.38 (m, 1H), 7.27–7.23 (m, 4H), 7.12–7.11 (m, 2H), 7.06–7.02 (m, 4H), 4.94 (d, J = 8.5 Hz, 1H), 4.50–4.47 (m, 1H), 4.15–4.05 (m, 2H), 3.71 (s, 3H), 3.00 (brs, NH), 2.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 198.5, 173.5, 138.2, 137.5, 137.4, 136.9, 133.3, 133.1, 129.6, 128.9, 128.5, 128.3, 128.1, 127.7, 67.6, 65.8, 60.4, 52.3, 52.1, 21.1; IR (neat): ν = 3364, 3060, 3018, 2952, 2927, 2860, 1736, 1679, 1596, 1515, 1491, 1448, 1435, 1384, 1259, 1217, 1178, 1114, 1092, 1014, 816, 757, 690 cm^{-1}; HR-MS (CI): m/z = 434.1504 $(M+H)^+$, calcd. for $C_{26}H_{25}ClNO_3$: 434.1523.

Methyl (2*S*,3*R*,4*S*,5*R*)-4-benzoyl-3,5-bis(4-chlorophenyl)-pyrrolidine-2-carboxylate (4k): light yellow solid; yield: 218 mg (96%); mp 123–126 °C; ^{1}H NMR and ^{13}C NMR spectra for this compound are consistent with previously reported literature data;[7,11] ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.56–7.54 (m, 2H), 7.45–7.41 (m, 1H), 7.31–7.27 (m, 6H), 7.05–7.02 (m, 4H), 4.95 (d, J = 8.5 Hz, 1H), 4.61 (t, J = 8.5 Hz, 1H), 4.14–4.07 (m, 2H), 3.72 (s, 3H), 2.95 (brs, NH); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 197.8, 173.2, 138.7, 138.1, 137.3, 133.5, 133.3, 133.1, 129.3, 129.1, 128.9, 128.6, 128.3, 128.1, 67.3, 65.5, 60.5, 52.5, 51.3; IR (neat): ν = 3345, 3066, 3022, 2946, 2917, 1736, 1678, 1596, 1492, 1448, 1435, 1412, 1384, 1258, 1218, 1179, 1129, 1092, 1014, 824, 771, 693 cm^{-1}; HR-MS (CI): m/z = 454.0942 $(M+H)^+$, calcd. for $C_{25}H_{22}Cl_2NO_3$: 454.0977.

Methyl (2*S*,3*R*,4*S*,5*R*)-4-benzoyl-3-(4-chlorophenyl)-5-(4-fluorophenyl)pyrollidine-2-carboxylate (4l): yellow solid; yield: 208 mg (95%); mp 154–158 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.54–7.53 (m, 2H), 7.43–7.40 (m, 1H), 7.31–7.25 (m, 6H), 7.08–7.05 (m, 2H), 6.77–6.74 (m, 2H), 4.97 (d, J = 4.0 Hz, 1H), 4.46–4.43 (m, 1H), 4.14–4.09 (m, 2H), 3.72 (s, 3H), 2.75 (brs, NH); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 198.0, 173.3, 162.2 (d, J = 246.3 Hz), 138.9, 137.4, 135.3 (d, J = 2.5 Hz), 133.2, 133.1, 129.3, 129.2 (d, J = 6.3 Hz), 129.1, 128.5, 128.1, 115.1 (d, J = 21.3 Hz), 67.3, 65.6, 60.6, 52.4, 51.4; IR (neat): ν = 3352, 3059, 3022, 3018, 2951, 2926, 1736, 1674, 1508, 1492, 1448, 1434, 1219, 1179, 1092, 1014, 759, 699 cm^{-1}; HR-MS (CI): m/z = 438.1282 $(M+H)^+$, calcd. for $C_{25}H_{22}ClFNO_3$:438.1272.

Methyl (2*S*,3*R*,4*S*,5*R*)-4-(4-chlorobenzoyl)-5-(4-fluorophenyl)-3-phenylpyrrolidine-2-carboxylate (4m): yellow solid; yield: 190 mg (87%); mp 152–156 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.42–7.52 (m, 2H), 7.28–7.41 (m, 4H), 7.18–7.27 (m, 3H), 7.02–7.17 (m, 2H), 6.79–6.82 (m, 2H), 4.96 (d, 1H, J = 8.7 Hz), 4.42 (dd, 1H, J = 8.7, 7.5 Hz), 4.01–4.22 (m, 2H), 3.73 (s, 3H), 2.42 (brs, NH); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 197.4, 173.3, 163.1, 161.2, 140.4, 139.5, 135.7, 134.9, 129.4, 129.2, 129.1, 128.9, 128.7, 127.8, 127.3, 115.2, 115.1, 67.5, 65.8, 60.5, 52.4 (2C); IR (neat): ν = 3356, 3060, 3023, 2950, 2916, 1736, 1677, 1595, 1502, 1450, 1434, 1384, 1261, 1218, 1177, 1157, 1130, 1080, 1012, 836, 760, 699, 687 cm^{-1}; HR-MS (CI): m/z = 438.1275 $(M+H)^+$, calcd. for $C_{25}H_{22}ClFNO_3$: 438.1272.

Methyl (2*S*,3*R*,4*S*,5*R*)-4-benzoyl-3-phenyl-5-(thiophen-2-yl)pyrrolidine-2-carboxylate (4n): yellow solid; yield: 176 mg (93%); mp 165–167 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.69–7.67 (m, 2H), 7.46–7.42 (m, 1H), 7.38–7.37 (m, 2H), 7.33–7.29 (m, 4H), 7.24–7.20 (m, 1H), 7.01 (dd, J = 5.0, 1.5 Hz, 1H), 6.72–6.69 (m, 2H), 5.26 (d, J = 8.5 Hz, 1H), 4.53–4.50 (m, 1H), 4.19–4.14 (m, 2H), 3.71 (s, 3H), 3.10 (brs, NH); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 197.6, 173.3, 143.2, 140.4, 137.4, 133.1, 128.9, 128.5, 128.2, 127.9, 127.2, 126.6, 125.5, 124.8, 67.3, 61.8, 60.3, 52.4, 51.6; IR (neat): ν = 3367, 3066, 3018, 2952, 2920, 1736, 1679, 1448, 1435, 1384, 1272, 1234, 1215, 1179, 760, 699 cm^{-1}; HR-MS (CI): m/z = 392.1302 $(M+H)^+$, calcd. for $C_{23}H_{22}NO_3S$: 392.1320.

Methyl (2*S*,3*R*,4*S*,5*R*)-4-benzoyl-5-(thiophen-2-yl)-3-(*p*-tolyl)pyrrolidine-2-carboxylate (4o): yellow solid; yield: 198 mg (98%); mp: 151–154 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.67–7.65 (m, 2H), 7.43–7.40 (m, 1H), 7.30–7.22 (m, 4H), 7.11–7.09 (m, 2H), 6.99–6.98 (m, 1H), 6.70–6.68 (m, 2H), 5.23 (d, J = 8.5 Hz, 1H), 4.50–4.47 (m, 1H), 4.15–4.10 (m, 2H), 3.69 (s, 3H), 2.99 (brs, NH), 2.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 197.7, 173.3, 143.3, 137.4, 137.3, 136.7, 133.0, 129.5, 128.4, 128.2, 127.7, 126.6, 125.4, 124.7, 67.2, 61.7, 60.3, 52.3, 51.3, 21.1; IR (neat): ν = 3366, 3065, 3019, 2951, 2920, 1736, 1678, 1447, 1434, 1384, 1261, 1216, 1177, 1017, 760, 699 cm^{-1}; HR-MS (CI): m/z = 406,1487 $(M+H)^+$, calcd. for $C_{24}H_{24}NO_3S$: 406.1477.

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