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N-tert-Butanesulfinyl imine and aromatic tertiary amide derived non-biaryl atropisomers as chiral ligands for silver-catalyzed *endo*-selective [3+2] cycloaddition of azomethine ylides with maleimides

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ABSTRACT

Simple modifications of our novel ligand (Xing-Phos) were presented in this work, and a series of aromatic tertiary amide derived non-biaryl atropisomers were successfully synthesized in good yields. In addition, it was found that the multifunctional aromatic tertiary amide derived non-biaryl atropisomers exhibited an excellent *endo*-selectivity in the silver-catalyzed [3+2]-cycloaddition of azomethine ylides with *N*-aromatic maleimide. And especially, good to high levels of enantioselectivity (up to 98% *ee*) was obtained with a wide range of substrates in the presence of *syn*-(R, R_S)-**2a** (Xing-Phos). Furthermore, on the basis of the experimental data, it was demonstrated that a trace amount of water play an important role in the enhancement of enantioselectivity.

1. Introduction

During the past decades, intense research efforts have been devoted to develop highly effective silver-based catalyst systems with functional chiral ligands, including S-ligands and P-ligands.[1] Especially, the chiral silver complexes have been attracted much attention from organic chemists because of its privileged catalytic activity in many organic reactions, which provided versatile and powerful potential for the synthesis of synthetically useful and optically active molecules.[2] Despite numerous elegant methods have been established for the construction of the highly efficient silver-based catalyst system, the development of novel silver complex with new chiral ligands as an effective catalyst is highly desired in comparison to that of other transition metals, such as palladium, rhodium, etc. In addition, the crucial role of chiral ligand promoted the chemists to design functional ligands to control the catalytic activity of silver complex.[1–3] However, the synthesis of chiral ligands, including chiral phosphine ligands, with good catalytic activity is not an easy task and still be recognized as a great challenge in asymmetric catalysis. In this context, we became interested in the synthesis of chiral phosphine ligands with sulfinyl groups and its potential application as a controlled element in the catalytic asymmetric [3+2] cycloaddition of azomethine ylides with maleimides, for the preparation of functional pyrrolidines.

Functionalized pyrrolidines are key units in medicinal chemistry and also a type of highly valuable synthetic building blocks for nature products.[4] In addition, chiral proline derivatives, similarly to the basic structure of pyrrolidines, also proved to be useful organic catalysts in many catalytic asymmetric transformations.[5] The great synthetic potential of this five-membered ring heterocycles inspired the huge development of diastereoselective [3+2] cycloadditions of azomethine ylide with activated alkenes, which is an extremely powerful and atom-economical strategy for the enantioselective construction of pyrrolidine ring.[6] Since the pioneering work of Grigg[7] and Zhang,[8] much more efficient high diastereo- and enantioselective catalytic system have been reported with the efforts of Jørgensen,[9] Schreiber,[10] Zhou,[11] Carrerero,[12] Hou,[13] Wang,[14] Fukuzawa[15] and other groups.[16] Organocatalyzed 1,3-dipolar [3+2] cycloadditions also made progress in MacMillan[17] and other chemist's efforts.[18]

Very recently, we have reported the design and synthesis of a kind of novel multifunctional ligand, aromatic tertiary amide

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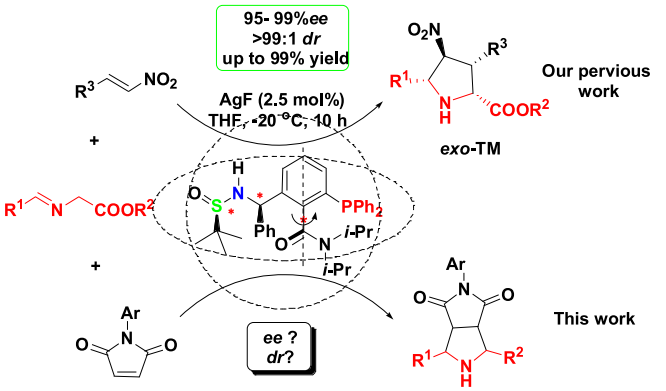
0040-4020/

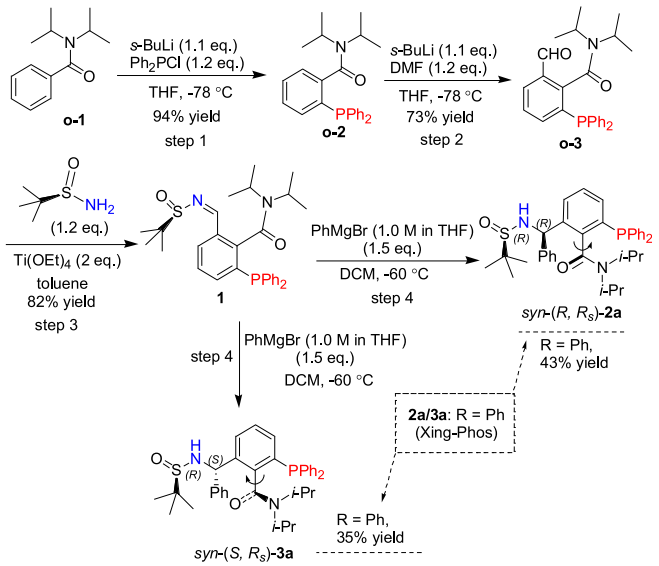
derived non-biaryl atropisomer as phosphine ligand (also called as Xing-Phos).[19] We have also found that the Xing-Phos was a highly efficient ligand in the Ag^{I}-catalyzed *exo*-selective [3+2] cycloaddition of azomethine ylides with *trans*-β-nitrostyrene (Scheme 1).[19a] Although this protocol has made great success in this field, the variety of aromatic amide-derived non-biaryl atropisomer derivatives still too limited and the application of aromatic amide-derived non-biaryl atropisomer with both phosphine and sulfinyl groups in silver-catalyzed [3+2] cycloaddition remained to be widened. It is necessary to synthesis versatile aromatic amide-derived non-biaryl atropisomer derivatives and figure out whether high diastereo- and enantioselectivity cloud be obtained when other dipolarophilic olefins used instead of *trans*-β-nitrostyrene. Interesting, previously reported silver-catalyzed [3+2] cycloadditions of azomethine ylide are almost *endo*-selective in most cases, especially with substituted maleimides.[11,16,20] Thus previous works inspired our curiosity about whether it is possible to get higher *endo*-selectivity and high *ee* value under suitable conditions in the presence of Xing-Phos and other aromatic tertiary amide derived non-biaryl atropisomers. We speculated that the geometrical configuration of olefins might change the mutual effect of [3+2] cycloaddition procedure in this Ag/Xing-Phos catalysis system, and accordingly, we considered that maleimide derivatives could be used as Z-alkene. Herein, we report the enantioselective synthesis of aromatic amide-derived non-biaryl atropisomer derivatives, the analogues of Xing-Phos, and investigate their application in silver-catalyzed cycloaddition of azomethine ylide with *N*-aromatic maleimide. This work reveals that the silver-catalyzed asymmetric [3+2] cycloaddition reaction of glycine imino esters with maleimide can proceed smoothly to give the corresponding pyrrolidine derivatives in good to excellent enantioselectivity in the presence of the Xing-Phos under mild conditions.



Scheme 1. Silver-catalyzed [3+2] cycloaddition of azomethine in the presence of Xing-Phos: *exo*-selectivity or *endo*-selectivity for the silver-catalyzed cycloaddition of maleimide?

2. Results and discussion

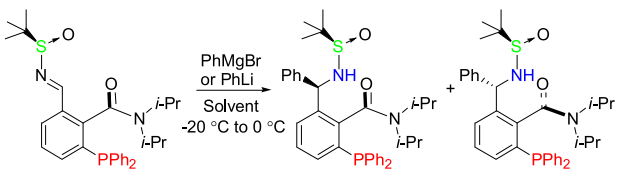
We initiated our studies by synthesizing a series of novel aromatic amide-derived non-atropisomer derivatives bearing both axial and sp^3 central chirality. We had prepared a special aromatic amide-derived non-biaryl atropisomer, also called as Xing-Phos, started with *N*,*N*-diisopropylbenzamide in four steps (Scheme 2).[19] All the first three steps were simple and classic transformations with high yield, while the fourth step was frustrating, in which 43% yield of *syn*-(*R*, R_S)-**2a** and 35% yield of *syn*-(*S*, R_S)-**3a** was achieved in this 1,2-addition reaction. Not only the stereocontrol of diastereoselectivity but also the epimerization should be cautious in this 1,2-addition reaction of Grignard reagents or organometallic reagents to aromatic amide-derived sulfinyl imine **1**. Actually, we observed that the addition of Grignard reagent to sulfinyl imino **1** almost was not occurred until the temperature rose to about −20 °C, and the epimerization was quenched when temperature was below 0 °C. If keep the reaction mixture at room temperature (20 °C), new isomers produced by epimerization of Ar−CO bond would grow as time goes on. Hence, we decreased the reaction temperature to −20 °C because of the possible epimerization at room temperature.



Scheme 2. Stereodivergent preparation of aromatic amide-derived non-biaryl atropisomers with both phosphine and sulfinyl groups.[19].

As shown in Table 1, the diastereoselectivities were varied under different reaction conditions, for example, the desired aromatic amide-derived non-biaryl atropisomer could be obtained in a diastereoisomer ratio of 67/33 when phenyl Grignard reagent as

Table 1
Optimization of the 1,2-addition of aromatic amide derivative **1** with phenyl metal reagents[a]



Entry	Solvent	Additive	PhMgBr or PhLi	**2**/**3**[b]
1	DCM	—	PhMgBr in THF (1.0M)	67/33
2	DCM	—	PhLi in THF (1.7M)	56/44
3	THF	—	PhLi in THF (1.7M)	69/31
4	Toluene	—	PhLi in THF (1.7M)	56/44
5	Toluene	—	PhLi in ether (1.5M)	54/46
6	Toluene	—	PhMgBr in THF (1.0M)	71/29
7	Toluene	Me_3Al	PhLi in THF (1.7M)	53/47
8	Toluene	HMPA	PhMgBr in THF (1.0M)	56/43
9	Toluene	TMEDA	PhMgBr in THF (1.0M)	49/51

[a] The reaction was carried out under N_2 atmosphere and solvents were dried before use in all cases.

[b] The ratio of *syn*-(*R*, R_S)-**2a**/*syn*-(*S*, R_S)-**3a** was determined by chiral HPLC with chiarlpark AD-H column (Hexane:*i*-PrOH=96:4, 1 mL/min).

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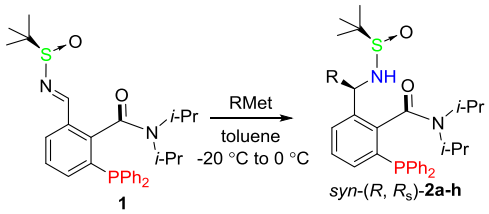
organometallic substrate (Table 1, entry 1). The effects of different phenyl-metallic reagents, solvent and Lewis acid auxiliaries also carried out in this work.[21] The diastereoselectivity of this 1, 2-addition was almost reached at a moderate level no matter the phenyl-metallic reagent changed or the auxiliaries added. So far, the best result in term of diastereoselectivity we got in this work was carried out in toluene with PhMgBr (**2**/**3**=71/29, entry 6).

Then we used different organometallic reagent to expand the diversity of this aromatic amide derived non-biaryl atropisomers. As shown in Fig. 1, both aromatic and aliphatic Grignard reagents were investigated in the 1,2-addition of organometallic reagents to aromatic amide-derived sulfinyl imide **1**. In all cases, two isolable isomers were detected by TLC and the small polar ones could be isolated as pure atropisomers successively. Although the isolated yields (varied from 28 to 55%) were not good enough, the type of present multifunctional aromatic amide derived non-biaryl atropiosmers enlarged the scope of optically pure atropisomers, and accordingly, the high level of enantioselective inductivity of these aromatic amide-derived atropisomers could be desired in various organic transformations.

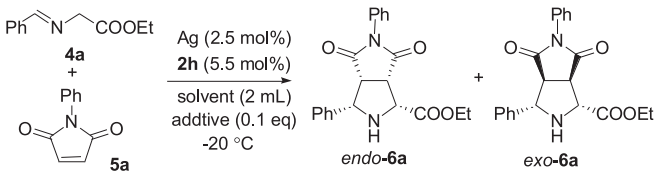


R	product	yield (%)
Ph	*syn*-(*R*, R_S)-**2a**	55
4-MeO-C_6H_4	*syn*-(*R*, R_S)-**2b**	44
3-MeO-C_6H_4	*syn*-(*R*, R_S)-**2c**	35
benzyl	*syn*-(*R*, R_S)-**2d**	41
vinyl	*syn*-(*R*, R_S)-**2e**	40
isopropenyl	*syn*-(*R*, R_S)-**2f**	37
i-Pr	*syn*-(*R*, R_S)-**2g**	28
Me	*syn*-(*R*, R_S)-**2h**	47

Fig. 1. The synthesis of aromatic amide-derived non-biaryl atropisomers **2a**–**h**.

Subsequently, we began to evaluate the catalytic activity and enantioselectivity of the aromatic amide-derived non-biaryl atropisomers **2a**–**h** in silver-catalyzed [3+2] cycloaddition of azomethine ylides with *N*-aromatic maleimide. Initially, the cycloaddition of *N*-benzylideneglycine ethyl ester **4a** with *N*-phenyl maleimide **5a** was selected as the model reaction. We first examined the reaction at −20 °C in THF for 5 h with 2.5 mol % AgF and 5.5 mol % *syn*-(*R*, R_S)-**2h**[19], which was the optimized reaction condition for the cycloaddition of *N*- benzyl-ideneglycine methyl ester with *trans*-β-nitrostyrene (*exo*: *endo*=>99: <1, up to 97% *ee*). To our delight, the diastereoselectivity successfully reversed to *endo*-selectivity (*endo*:*exo*=>95:<5), however, the enantioseclectivity dropped obviously (70% *ee*, Table 2, entry 1) in comparison to that of nitrostyrene. Then we investigate the solvent effect because of the possibly significant impacts of solvent on 1,3-dipolar cycloaddition.[22] As the data summarized in Table 1 illustrated, when DCM was used as solvent, the *ee* of *endo*-**6aa** decreased to 62% (Entry 2). Fortunately, the *endo*-selectivity kept in a high level and the *endo*-**6aa** was obtained in 82% *ee* in toluene (Entry 4). Similarly, the same diastereoselectivity was obtained in xylene but this solvent was not in favour of enantiselectivity (60% *ee*, entry 8). Despite the cycloaddition processed smoothly when protic solvent EtOH was employed, the diastereo- and enantioselectivity were unsatisfying (80% *ee*, entry 3). However, the enantioselectivity was not improved when the reaction temperature was decreased to −40 °C (77% *ee*, entry 5). We also evaluated the effect of both organic and inorganic bases on the silver-catalyzed cycloaddition (Entries 9–13). It tuned out that inorganic bases work against the enantioselectivity (<53% *ee* when HCOONa or K_2CO_3 was used in this case), while most of organic bases slightly result in decreased enantioselectivity of *endo*-**6a**. And unexpectedly, the *ee* of *endo*-**6a** decreased dramatically to 22% when DBU was added. The negative effect of these bases might be aroused from the disturbing intermolecular interaction of catalyst-substrate in the catalytic asymmetric [3+2] cycloaddition.

Table 2
Ag(I)-catalyzed [3+2] cycloaddition of **4a** with **5a** in presence of aromatic amide-derived non-biaryl atropisomer **2h**[a]



Entry	Ag	Additive	Solvent	*endo*/*exo*[b]	Yield (%)[b]	*Ee* (%)[c]
1	AgF	—	THF	95:5	70	70
2	AgF	—	DCM	80:20	75	62
3	AgF	—	EtOH	88:12	80	80
4	AgF	—	Toluene	>98:2	90	82
5[d]	AgF	—	Toluene	>98:2	91	77
6[d,e]	AgF	—	Toluene	>98:2	74	71
7[f]	AgF	—	Toluene	94:6	85	74
8	AgF	—	Xylene	95:5	82	60
9	AgF	HCOONa	Toluene	>98:2	83	47
10	AgF	K_2CO_3	Toluene	>98:2	90	53
11	AgF	Et_3N	Toluene	>98:2	95	79
12	AgF	DBU	Toluene	>98:2	75	22
13	AgF	i-Pr_2NEt	Toluene	>98:2	88	78
14	AgF	Urea	Toluene	>98:2	91	81
15	AgF	TFE	Toluene	>98:2	92	81
16[g]	AgF	H_2O	Toluene	>98:2	92	83
17	$AgClO_4$	NEt_3	Toluene	>98:2	93	76
18	AgOAc	NEt_3	Toluene	>98:2	89	77
19	AgOTf	NEt_3	Toluene	>98:2	90	75
20	$Cu(OAc)_2$	NEt_3	Toluene	—	Trace	—
21	CuF_2	NEt_3	Toluene	—	Trace	—
22	CuCl	NEt_3	Toluene	—	Trace	—

[a] The metal salt (2.5 mol %) was dissolved in corresponding solvent (2 mL), then the ligand was added. The mixture was stirred at −20 °C for 15 min before **1a** (0.4 mmol) was added. Then base (10 mol %) and **2a** (0.2 mmol) was added successively and stirred for 5 h.
[b] Measured by ^{1}H NMR spectroscopy of the crude reaction mixture with 4-dimethylaminopyridine as internal standard.
[c] Enantiomeric excesses were determined by chiral HPLC.
[d] The reaction was carried out at −40 °C.
[e] The reaction was carried out under N_2 atmosphere in this case.
[f] The reaction was carried out at −5 °C.
[g] The AgF was dissolved with a trace amount of H_2O (0.1 mL), then the reaction was carried out in 2 mL of toluene.

The finding that there is no improvement in enantioselectivity in anhydrous toluene (Entry 6 of Table 1, 71% *ee*) promoted us to evaluate the possible activation by the hydrogen-bonding interaction. Notably, the addition of trace amount of water to the solvent, *endo*-**6a** was obtained in higher enantioselectivity (83% *ee*, Entry 16). However, urea and trifluoroethanol (TFE) were not necessary for this reaction in term of catalytic activity and enantioselectivity (Entries 14–15). In addition, as shown in Table 1, other silver Lewis acid, such as AgOAc, $AgClO_4$ and AgOTf, gave a slight lower *ee* (Entries 17–19). To support the powerful of silver-based catalyst system with **2h**, the copper salts was used as a catalyst in

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this reaction (Entries 20–22). Unfortunately, the Cu/**2h** exhibited almost no activity in this reaction (below 10% even extension the reaction time to 24 h).

Next, we evaluated the catalytic or enantioselective activity of the aromatic amide-derived non-biaryl atropisomers (Fig. 1) and ligand **2i**[19] in this AgF-catalyzed [3+2] cycloaddition under the optimized condition. The catalytic activity of silver-Xing-Phos (**2a**) was compared to those of aromatic amide-derived phosphines bearing analogous groups (**2b**–**i**), and the results are shown in Fig. 2. As expected, the enantioselectivity of Xing-Phos (**2a**) remained the best level in this reaction (84% *ee*), while other aromatic amide-derived non-biaryl atropisomers **2b**–**i** only gave lower enantioselectvities (46–80% *ee*) albeit the diastereoselectivities were high for every cases under the optimized reaction conditions (*endo*:*exo*>95:5). Notably, on the basis of characterization or experimental data, the stability of ligands **2b**–**g** was not as good as that of ligand **2a** and **2h** in solution, which supported the partial oxidation of phosphine center on the aromatic amide-derived atropisomers. Thus accordingly, these ligands **2b**–**g** exhibited the decreased enantioselectivity in comparison to that of **2a** in this reaction. Furthermore, two major finding can be drawn from the experiment data: 1) the phosphine contained multifunctional non-biaryl atropisomers performed an excellent *endo*-selectivity in the silver-catalyzed [3+2] cycloaddition of azomethine ylide with *N*-phenyl maleimide; 2) the *R*-group exerted a not obvious effect on the enantioselectivity (from 74% to 83% *ee* when under nitrogen atmosphere) in the silver-catalyzed cycloaddition, but really effected the air-stability of these aromatic tertiary amide derived non-biaryl atropisomers. In general, a bulky and rigid aromatic group (e.g., phenyl) was beneficial to improve the stability and then keep the enantioselectivity under air-atmosphere. We also evaluated ligands **2a**–**h** in the silver-catalyzed [3+2] cycloaddition under nitrogen atmosphere (see Fig. S1 of Supplementary data), and we found that the diastereoselectivities of all the desired products were also obtained in quite high level (*endo*:*exo*>98:2). And as shown in Fig. S1, the same level of enantioselectivities (74–83%*ee*) was achieved with these aromatic amide-derived atropisomers (**2a**–**h**). Although the enantioselectivity of present [3+2] cycloaddition remained to be improved, this *endo*-selective AgF/Xing-Phos catalyst system proved to a valuable find because of the paradoxical diastereoselectivity compared with the *exo*-selectivity in the cycloaddition of azomethine ylide with nitroolefins, chalcones, or methyl cinnamates.[19]

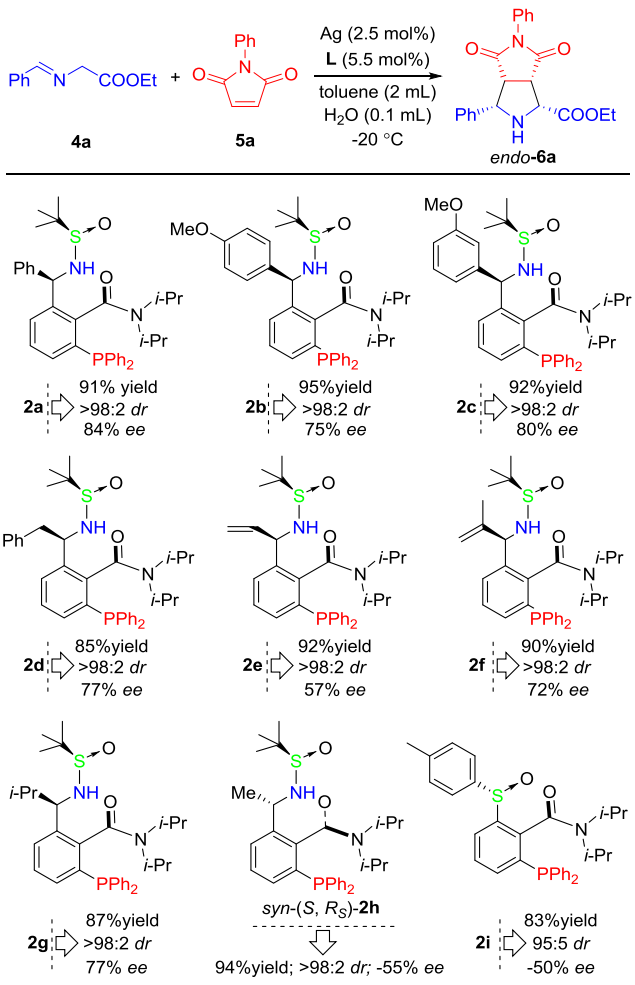

Fig. 2. Comparison of enantioselective activity of aromatic amide-derived non-biaryl atropisomers under the optimized reaction condition.

Next, under the optimized experimental conditions with Xing-Phos, we explored the catalytic asymmetric 1,3-dipolar [3+2] cycloaddition of a series of representative imino esters with *N*-substituted maleimides. As seen from the results listed in Table 3, a wide variety of sterically and electronically different aromatic α-imino esters on aryl rings, reacted smoothly with *N*-arylmaleimides, affording the desired products in good enantioselectivities and excellent yields. In most cases, the moisture solvent was beneficial to the silver-Xing-Phos promoted [3+2] cycloaddition of imino esters with maleimides because most of corresponding products **6a**–**z** were obtained with a high level of *endo*-selectivity (>98:<2 *dr*) and good enantioselectivity (up to 98% *ee*) within 10 h. However, the diastereoselectivities of products **6k** (92:8 *dr*, entry 11) and **6r** (95:5 *dr*, entry 18) were not enough good, which would be probably arose from the steric repulsion of *ortho*-substituted group of aryl imino esters (e.g., **4c**). It was also observed that the level of enantioselectivity obtained from moderate to excellent with different substituent group. As expected, the change of substituent group on the phenyl of *N*-phenyl maleimide has little influence on the *ee* of corresponding product *endo*-**6c**–**j** (Entries 3–7, 80–85% *ee*). When α-imino methyl ester was used instead of ethyl ester, the enantioselectivity was slightly rose to 86–88% *ee* (Entries 6 and 9). Then we extended the study of the cycloaddition to various substituted aromatic α-imino methyl ester. 2-methoxyl-phenyl substituted imino ester gave *endo*-**6k** in only a moderate diastereoselectivity, and accordingly the *ee* was decreased to 80% (Entry 11). When methoxyl substituted at *meta*-position, high level of diastereoselectivity was achieved, but enantioselectivity remained at a moderate level (81% *ee*, entry 12). It seemed that steric effect was generally disfavorable for the achievement of high diastereoselectivity in this reaction. A series of electronically different aromatic α-imino esters and it was found that the electronic effect of substituted group on the aryl rings influenced the enantioselectivity obviously. For example, 4-Me-phenyl substituted imino ester afforded the corresponding *endo*-**6n** with only 65% *ee* (Entry 14), and in contrast, the *para*-halogen substituted phenyl substituted imino ester gave a single *endo*-selectivity with 90–91% *ee* (Entries 15–17). The electron-withdrawing substituent group also resulted in good enantioselectivity (88% *ee*, Entries 18 and 19), especially the use of *para*-phenyl substituted aromatic α-imino methyl ester led to the formation of the desired product in excellent enantioselectivity and diastereoselectivity (98% *ee* and >98:<2 *dr*, entry 20). In addition, we found that different *N*-aromatic maleimides could smoothly react with 4-Ph substituted *N*-benzylideneglycine methyl ester to give corresponding pyrrolidines in excellent enantioselectivities (89–90% *ee*).

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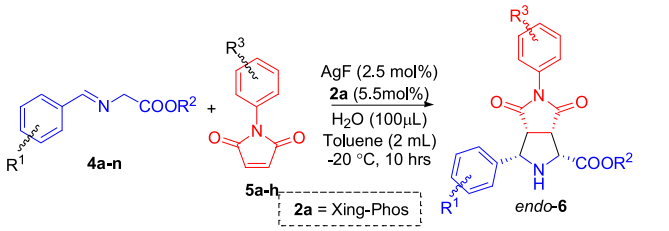
Table 3
Catalytic asymmetric [3+2] cycloaddition of various imino esters with *N*-aromatic maleimides



4a: R^1 = H, R^2 = Et
4b: R^1 = Ph, R^2 = Me
4c: R^1 =2-MeO, R^2 = Me
4d: R^1 = 3-MeO, R^2 = Me
4e: R^1 = 3-Br, R^2 = Me
4f: R^1 = 4-Me, R^2 = Me
4g: R^1 = 4-F, R^2 = Me
4h: R^1 = 4-Cl, R^2 = Me
4i: R^1 = 4-Br, R^2 = Me
4j: R^1 = C_4H_4, R^2 = Me
4k: R^1 = 4-CF_3, R^2 = Me
4l: R^1 = 4-Ph, R^2 = Me
4m: R^1 = 4-MeS C_6H_4, R^2 = Me
4n: R^1 = 3,5-DiCF$_3$ C_6H_4, R^2 = Me
5a: R^3 = H
5b: R^3 = 3-Cl
5c: R^3 = 3-Me
5d: R^3 = 3-Br
5e: R^3 = 4-EtO
5f: R^3 = 4-MeO
5g: R^3 = 4-Br
5h: R^3 = 3,5-DiMethyl

Entry	**4**/imine	**5**/maleimide	TM	*endo*:*exo*	Yield (%)[a]	*ee* (%)[b]
1	**4a**	**5a**	**6a**	>98:<2	91	84
2	**4b**	**5a**	**6b**	>98:<2	93	84
3	**4a**	**5b**	**6c**	>98:<2	90	84
4	**4a**	**5c**	**6d**	>98:<2	91	85
5	**4a**	**5d**	**6e**	>98:<2	85	85
6	**4a**	**5e**	**6f**	>98:<2	85	80
7	**4a**	**5f**	**6g**	>98:<2	88	85
8	**4b**	**5d**	**6h**	>98:<2	93	88
9	**4b**	**5g**	**6i**	>98:<2	92	86
10	**4b**	**5h**	**6j**	>98:<2	90	84
11[c]	**4c**	**5a**	**6k**	92:8	89	80
12	**4d**	**5a**	**6l**	>98:<2	90	81
13	**4e**	**5a**	**6m**	>98:<2	93	85
14	**4f**	**5a**	**6n**	>98:<2	87	65
15	**4g**	**5a**	**6o**	>98:<2	85	91
16	**4h**	**5a**	**6p**	>98:<2	91	90
17	**4i**	**5a**	**6q**	>98:<2	86	91
18[d]	**4j**	**5a**	**6r**	95:5	83	88
19	**4k**	**5a**	**6s**	>98:<2	89	88
20	**4l**	**5a**	**6t**	>98:<2	99	98
21	**4l**	**5g**	**6u**	>98:<2	93	90
22	**4l**	**5h**	**6v**	>98:<2	99	90
23	**4l**	**5e**	**6w**	>98:<2	83	89
24	**4l**	**5c**	**6x**	>98:<2	98	92
25	**4m**	**5a**	**6y**	>98:<2	96	90
26	**4n**	**5a**	**6z**	>98:<2	99	93

[a] Isolated yield.
[b] The *ee* values were determined by chiral HPLC.
[c] The reaction time was 40 h in this case.
[d] The reaction temperature was 0 °C in this case and reacted for 36 h.

3. Conclusions

In summary, we have reported an improved procedure for the synthesis of a new family of axially chiral aromatic amide derived non-biaryl atropisomers (AAAs) with the aid of chiral *N*-*tert*-butanesulfinamide (Ellman reagent).[23] The novel and air-stable multifunctional phosphines (AAAs) featured with phosphine and oxygen-based binding site (*P*,*O*-ligands) and an additional axially aromatic amide and sulfinyl group. And notably, such aromatic amide-derived chiral phosphine ligands could be synthesized in gram scale. In this work, we determined the enantioselective activity of these axially chiral aromatic amide derived non-biaryl atropisomers in catalytic asymmetric AgF-catalyzed [3+2] cycloaddition of azomethine ylide with substituted maleimides. The enantioselective Ag-catalyzed [3+2] cycloaddition reaction of imino esters with maleimides was proved to a practical and efficient procedure for the synthesis of imide-containing pyrrolidines in the presence of Xing-Phos, one of these AAAs ligands. The [3+2] cycloaddition reaction proceed with excellent yields (up to 99% isolated yields) and excellent diastereoselectivity (>98:2 *dr*) with *endo*-selectivity. And the enantiomeric excesses of desired pyrrolidines derivatives were also promising and could reach at good level (up to 98% *ee*), which offered a simple and unprecedented example that axially chiral aromatic amide-derived phosphine bearing both axial and sp^3 central chirality exhibited enough good enantiocontrol and high catalytic performances in enantioselective silver-catalyzed [3+2] cycloaddition-type reaction. Furthermore, we believed that the moisture- and oxygen-resistant Xing-Phos would exhibit significant application value in various asymmetric organic transformations. Besides, further development of the new axially chiral AAAs ligands for catalytic asymmetric reactions to the synthesis of useful molecules will be the focus of our ongoing studies in the near future.

4. Experimental section

4.1. General

Unless specifically stated, all the solvents such as dichloromethane (DCM), trifluoroethanol (TFE), toluene, THF and EtOH was used directly without dried or distilled. Reactions were monitored by thin layer chromatography (TLC) using silica gel plates. Thin layer chromatography was performed using silica gel; F254 TLC plates and visualized with ultraviolet light. Flash column chromatography was performed over silica (200–300 mesh). ^{1}H NMR, and ^{13}C NMR were recorded at 400 (or 500) and 100 (or 125) MHz, respectively on Advance (Brucker) 400 MHz Nuclear Magnetic Resonance Spectrometer, and were referenced to the internal solvent signals. HPLC was carried out with a Waters 2695 Millennium system equipped with a photodiode array detector. EI and CI mass spectra were performed on a Trace DSQ GC/MS spectrometer. Data are reported in the form of (*m*/*z*).

4.2. General procedure for the synthesis of ligands 2b–h

*4.2.1. Typical procedure for the synthesis of **2** through the 1,2-addition of organometallic reagents to sulfinyl imine **1** (Fig. 1).* The synthesis of sulfinyl imine **1** and **2a** have been reported in our previous work and was completed respectively according to the reported procedure.[19] Grignard reagent was added (2.0 equiv) to a −20 °C solution of sulfinyl imine **1** (1.0 equiv) in dried toluene (distilled fresh from CaH_2). The mixture was stirred at −20 °C for 1 h until the reaction was completed. Then the reaction mixture was quenched with plenty of NH_4Cl aqueous solution and extract with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, concentrated, and purified by flash chromatography immediately.

*4.2.2. 2-((1R)-((tert-Butylsulfinyl)amino) (phenyl)methyl)-6-(diphenylphosphanyl)-N,N-diisopropylbenzamide (**2a**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J*=7.8 Hz, 1H), 7.56 (d, *J*=7.5 Hz, 2H), 7.26 (dd, *J*=19.9, 13.3 Hz, 15H), 7.08 (dd, *J*=7.4, 2.9 Hz, 1H), 5.73 (s, 1H), 3.89–3.70 (m, 1H), 3.64–3.59 (m, 2H), 1.71 (dd, *J*=30.1, 6.7 Hz, 6H), 1.39–1.23 (m, 15H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.81 (d, *J*=4.7 Hz), 143.48 (d, *J*=37.7 Hz), 140.62, 138.82 (d, *J*=8.9 Hz), 137.89 (d, *J*=11.7 Hz), 136.45 (d, *J*=11.4 Hz), 134.84 (d, *J*=16.8 Hz), 134.53 (d, *J*=2.0 Hz), 133.44 (d, *J*=20.3 Hz), 133.02 (d, *J*=18.1 Hz), 128.63, 128.51, 128.45, 128.43, 128.38 (d, *J*=1.9 Hz), 128.30, 128.17, 127.89, 127.52, 57.76, 55.70, 51.17, 46.39, 22.67, 21.61, 20.97 (d, *J*=7.3 Hz), 20.75, 19.94 (d, *J*=1.6 Hz). ^{31}P NMR (202 MHz, $CDCl_3$) δ=−13.94. HRMS (APCI): *m*/*z*: $[M+H]^+$ calculated for $C_{36}H_{44}N_2O_2PS$: 599.2856, found: 599.2857. IR (KBr) ν_{max}: 3447, 3297, 3058, 2963, 2927, 2869,

1629, 1475, 1446, 1433, 1368, 1339, 1319, 1063, 1037, 763, 743, 695. $[\alpha]_D^{30}$ −68.2 (*c* 0.61, $CHCl_3$).

*4.2.3. 2-((1R)-((tert-Butylsulfinyl)amino) (4-methoxyphenyl)methyl)-6-(diphenylphosphanyl)-N,N-diisopropylbenzamide (**2b**).* ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J*=7.8 Hz, 1H), 7.47 (d, *J*=8.2 Hz, 2H), 7.37−7.15 (m, 11H), 7.11 (d, *J*=7.3 Hz, 1H), 6.82 (d, *J*=8.1 Hz, 2H), 5.69 (s, 1H), 3.89−3.76 (m, 1H), 3.75 (s, 3H), 3.71−3.58 (m, 2H), 1.76 (d, *J*=6.6 Hz, 3H), 1.69 (d, *J*=6.6 Hz, 3H), 1.35 (d, *J*=6.5 Hz, 4H), 1.30 (s, 9H), 1.26 (d, *J*=6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.86 (d, *J*=4.7 Hz), 158.94, 143.39 (d, *J*=38.0 Hz), 139.03 (d, *J*=6.6 Hz), 137.88 (d, *J*=11.7 Hz), 136.46 (d, *J*=11.4 Hz), 134.74 (d, *J*=16.7 Hz), 134.52 (d, *J*=1.9 Hz), 133.47 (d, *J*=20.3 Hz), 132.99 (d, *J*=18.1 Hz), 132.50 (d, *J*=5.3 Hz), 129.07, 128.64, 128.53, 128.43 (d, *J*=5.7 Hz), 128.35 (d, *J*=7.3 Hz), 128.20, 128.16, 113.84, 57.22 (d, *J*=17.5 Hz), 55.60 (d, *J*=2.6 Hz), 55.12, 51.19, 46.37, 22.67, 21.56, 20.92 (d, *J*=7.0 Hz), 20.76, 19.94. ^{31}P NMR (202 MHz, $CDCl_3$) δ=−14.13. HRMS (ESI): *m*/*z*: $[M+H]^+$ calculated for $C_{37}H_{46}N_2O_3PS$: 629.2961, found: 629.2956.

*4.2.4. 2-((1R)-((tert-Butylsulfinyl)amino)(3-methoxyphenyl)methyl)-6-(diphenylphosphanyl)-N,N-diisopropylbenzamide (**2c**).* ^1H NMR (400 MHz, $CDCl_3$) δ=7.67 (d, *J*=7.8 Hz, 1H), 7.33−7.12 (m, 14H), 7.10−7.06 (m, 1H), 6.80−6.69 (m, 1H), 5.70 (s, 1H), 3.81−3.76 (m, 1H), 3.74 (s, 3H), 3.64 (s, 1H), 3.63−3.55 (m, 1H), 1.74 (d, *J*=6.8 Hz, 3H), 1.66 (d, *J*=6.8 Hz, 3H), 1.33 (d, *J*=6.7 Hz, 3H), 1.30 (s, 9H), 1.25 (d, *J*=6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.81 (d, *J*=4.7 Hz), 159.57, 143.53 (d, *J*=37.9 Hz), 142.29, 138.72 (d, *J*=8.9 Hz), 137.89 (d, *J*=11.8 Hz), 136.57 (d, *J*=11.4 Hz), 134.84 (d, *J*=16.9 Hz), 134.62 (d, *J*=2.1 Hz), 133.55, 133.35, 133.18, 133.00, 129.41, 128.57, 128.51, 128.47, 128.42, 128.34, 128.27, 128.22, 120.40, 113.22 (d, *J*=13.8 Hz), 57.70, 55.77, 55.19, 51.14, 46.37, 22.70, 21.61, 21.02 (d, *J*=7.2 Hz), 20.76, 20.01 (d, *J*=1.8 Hz). ^{31}P NMR (202 MHz, $CDCl_3$) δ=−13.90. HRMS (ESI): *m*/*z*: $[M+H]^+$ calculated for $C_{37}H_{46}N_2O_3PS$: 629.2961, found: 629.2968.

*4.2.5. 2-((1R)-1-((tert-Butylsulfinyl)amino)-2-phenylethyl)-6-(diphenylphosphanyl)-N,N-diisopropylbenzamide (**2d**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J*=7.8 Hz, 1H), 7.35−7.27 (m, 8H), 7.24−7.17 (m, 6H), 7.09 (dd, *J*=6.6, 5.0 Hz, 3H), 4.69−4.65 (m, 1H), 3.96−3.85 (m, 1H), 3.73 (d, *J*=6.1 Hz, 1H), 3.64−3.58 (m, 1H), 3.42 (dd, *J*=13.8, 3.3 Hz, 1H), 2.73 (dd, *J*=13.8, 9.0 Hz, 1H), 1.69 (dd, *J*=6.8, 3.2 Hz, 6H), 1.24 (dd, *J*=16.1, 6.6 Hz, 6H), 1.02 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.47 (d, *J*=4.8 Hz), 143.02 (d, *J*=37.3 Hz), 138.71 (d, *J*=8.6 Hz), 137.85, 137.74, 136.88 (d, *J*=11.5 Hz), 134.32, 134.16, 133.61, 133.41, 133.13, 132.95, 129.84, 128.67, 128.45 (d, *J*=5.7 Hz), 128.37 (d, *J*=7.4 Hz), 128.25, 128.18, 128.05, 126.60, 58.96, 56.61, 51.05, 46.27, 44.43, 22.26, 21.91, 21.30, 20.73 (d, *J*=7.6 Hz), 19.85 (d, *J*=2.6 Hz). ^{31}P NMR (202 MHz, $CDCl_3$) δ −14.46. HRMS (ESI): *m*/*z*: $[M+H]^+$ calculated for $C_{37}H_{46}N_2O_2PS$: 613.3012, found: 613.3019.

*4.2.6. 2-((1R)-1-((tert-Butylsulfinyl)amino)allyl)-6-(diphenylphosphanyl)-N,N-diisopropylbenzamide (**2e**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J*=7.3 Hz, 1H), 7.34−7.19 (m, 12H), 7.16−7.10 (m, 1H), 5.83−5.76 (m, 1H), 5.34 (d, *J*=17.1 Hz, 1H), 5.18 (d, *J*=10.1 Hz, 1H), 5.08 (d, *J*=6.8 Hz, 1H), 3.83−3.72 (m, 1H), 3.60−3.53 (m, 1H), 3.43 (d, *J*=1.6 Hz, 1H), 1.64 (dd, *J*=6.8, 2.9 Hz, 6H), 1.27−1.25 (m, 12H), 1.20 (d, *J*=6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.54 (d, *J*=4.7 Hz), 143.78 (d, *J*=38.1 Hz), 137.87 (d, *J*=3.3 Hz), 137.77, 137.36, 136.63 (d, *J*=11.5 Hz), 134.89 (d, *J*=16.6 Hz), 134.67 (d, *J*=2.2 Hz), 133.63, 133.43, 133.12, 132.94, 128.63, 128.48, 128.46, 128.42, 128.40, 128.33, 127.89, 118.37, 57.66, 57.64, 55.51, 51.12, 46.29, 22.63, 21.43, 20.90 (d, *J*=6.7 Hz), 20.50, 19.99 (d, *J*=1.6 Hz). ^{31}P NMR (202 MHz, $CDCl_3$) δ −14.31. HRMS (ESI): *m*/*z*: $[M+H]^+$ calculated for $C_{32}H_{42}N_2O_2PS$: 549.2699, found: 549.2693.

*4.2.7. 2-((1R)-1-((tert-Butylsulfinyl)amino)-2-methylallyl)-6-(diphenylphosphanyl)-N,N-diisopropylbenzamide (**2f**).* ^1H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J*=7.7 Hz, 1H), 7.32−7.16 (m, 12H), 5.17 (s, 1H), 5.10 (s, 1H), 5.02 (s, 1H), 3.80−3.69 (m, 1H), 3.59−3.55 (m, 1H), 3.40 (s, 1H), 1.70 (s, 3H), 1.66 (d, *J*=6.6 Hz, 3H), 1.29−1.27 (m, 12H), 1.23 (d, *J*=6.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.43 (d, *J*=4.7 Hz), 144.29 (d, *J*=37.8 Hz), 142.60, 137.99 (d, *J*=11.8 Hz), 136.69 (d, *J*=3.5 Hz), 136.61, 134.89 (d, *J*=16.7 Hz), 134.76 (d, *J*=2.0 Hz), 133.54, 133.38, 133.07, 132.93, 128.60, 128.45, 128.40, 128.33, 128.14, 127.90, 116.33, 59.82, 55.50, 51.03, 46.27, 22.67, 21.43, 20.98 (d, *J*=6.9 Hz), 20.73, 19.91 (d, *J*=1.9 Hz), 18.80. ^{31}P NMR (202 MHz, $CDCl_3$) δ −14.23. HRMS (ESI): *m*/*z*: $[M+H]^+$ calculated for $C_{33}H_{44}N_2O_2PS$: 563.2856, found: 563.2861.

*4.2.8. 2-((1R)-1-((tert-Butylsulfinyl)amino)-2-methylpropyl)-6-(diphenylphosphanyl)-N,N-diisopropylbenzamide (**2g**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J*=7.7 Hz, 1H), 7.32−7.20 (m, 11H), 7.10−7.07 (m, 1H), 4.49 (s, 1H), 3.85−3.80 (m, 1H), 3.64−3.53 (m, 1H), 3.46 (s, 1H), 2.52−2.34 (m, 1H), 1.65 (d, *J*=6.8 Hz, 3H), 1.57 (d, *J*=6.8 Hz, 3H), 1.34−1.25 (m, 15H), 1.04 (d, *J*=7.0 Hz, 3H), 0.70 (d, *J*=7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.11 (d, *J*=4.7 Hz), 143.81 (d, *J*=37.3 Hz), 138.35 (d, *J*=8.6 Hz), 138.11 (d, *J*=11.8 Hz), 136.80 (d, *J*=11.4 Hz), 134.78 (d, *J*=16.2 Hz), 133.49 (d, *J*=2.0 Hz), 133.09 (d, *J*=18.1 Hz), 131.99 (d, *J*=35.6 Hz), 128.62, 128.57, 128.39, 128.33, 128.26, 128.09, 127.08, 56.12, 51.10, 46.13, 33.33, 22.78, 21.55, 21.12 (d, *J*=8.0 Hz), 20.76, 20.60, 19.91 (d, *J*=2.3 Hz), 14.62.^{31}P NMR (202 MHz, $CDCl_3$) δ −13.94. HRMS (ESI): *m*/*z*: $[M+H]^+$ calculated for $C_{33}H_{46}N_2O_2PS$: 565.3012, found: 565.3018.

*4.2.9. 2-((1R)-1-((tert-Butylsulfinyl)amino)ethyl)-6-(diphenylphosphanyl)-N,N-diisopropylbenzamide (**2h**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J*=7.5 Hz, 1H), 7.34−7.20 (m, 11H), 7.11 (ddd, *J*=7.6, 3.4, 1.0 Hz, 1H), 4.64 (qd, *J*=6.3, 2.2 Hz, 1H), 3.77 (dt, *J*=13.2, 6.6 Hz, 1H), 3.55 (dt, *J*=13.6, 6.8 Hz, 1H), 3.36 (d, *J*=2.1 Hz, 1H), 1.61 (dd, *J*=12.5, 6.8 Hz, 6H), 1.47 (d, *J*=6.3 Hz, 3H), 1.26 (s, 9H), 1.20 (dd, *J*=9.5, 6.7 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.89 (d, *J*=4.7 Hz), 142.51 (d, *J*=37.8 Hz), 139.87 (d, *J*=9.0 Hz), 136.78 (d, *J*=11.7 Hz), 135.79 (d, *J*=11.5 Hz), 133.48 (d, *J*=16.3 Hz), 133.24 (d, *J*=2.0 Hz), 132.58 (d, *J*=20.2 Hz), 132.12 (d, *J*=18.3 Hz), 127.66, 127.52, 127.47, 127.42, 127.35, 127.25, 126.03, 54.46, 50.16, 50.06 (d, *J*=2.0 Hz), 45.24, 22.82, 21.72, 21.58, 20.32, 19.87 (d, *J*=6.7 Hz), 19.43, 19.07 (d, *J*=1.5 Hz). ^{31}P NMR (202 MHz, $CDCl_3$) δ −14.40. HRMS (APCI): *m*/*z*: $[M+H]^+$ calculated for $C_{31}H_{42}N_2O_2PS$: 537.2699, found: 537.2681. IR (KBr)ν_{max}: 3434, 3054, 2971, 2931, 1627, 1476, 1435, 1369, 1327, 1302, 1091, 1072, 751, 700. $[\alpha]_D^{30}$ −63.8 (*c* 0.32, $CHCl_3$).

4.3. Typical procedure for the synthesis of 6 through the silver-catalyzed [3+2] cycloaddtion of azomethine ylides 4a−n with *N*-aromatic maleimides 5a−h

To the AgF (0. 8 mg, 0.0063 mmol, 2.5 mmol%) catalysis in reaction tube, 100 μL H_2O was added to dissolve the AgF. Toluene (2 mL) was added and the resulting mixture was stirred for 5 min. Then *sys*-(*R*, *Rs*)-**2a** (0.0082 g, 0.0138 mmol, 5.5 mmol %) was added. The mixture was stirred at −20 °C for 15 min, then iminoester (0.6 mmol, 1.2 equiv) and maleimide (0.5 mmol, 1.0 equiv) were added successively. The reaction was allowed to proceed for 10 h at −20 °C, after which 5 mL H_2O was added to quench the reaction. The organic layer was diluted with 10 mL EtOAc and water layer was extracted with EtOAc (5mL×2).

The combined organic layer was dried with Na_2SO_4 and concentrated. A portion of the cured was analysed with ^1H NMR to determine the diastereomeric ratio and recovered. The structures of some products were known[16] and confirmed by NMR, IR and MS. The enantiomeric excesses of the products were determined by chiral stationary phase HPLC using a chiral column after purification.

*4.3.1. Ethyl (1S,3R,3aS,6aR)-4,6-dioxo-3,5-diphenyloctahydropyrrolo [3,4-c] pyrrole-1-carboxylate (**6a**).*[16a] ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J=7.6 Hz, 2H), 7.32–7.22 (m, 6H), 7.07 (d, J=7.6 Hz, 2H), 4.53 (d, J=8.7 Hz, 1H), 4.31–4.21 (m, 2H), 4.05 (d, J=6.6 Hz, 1H), 3.68–3.63 (m, 1H), 3.52–3.46 (m, 1H), 1.29 (t, J=7.2 Hz, 3H). Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexanes: 2-propanol=50:50, 0.7 mL/min, 210 nm); minor enantiomer t_r=12.5 min, major enantiomer t_r=27.8 min.

*4.3.2. Methyl (1S,3R,3aS,6aR)-4,6-dioxo-3,5-diphenyloctahydro-pyrrolo [3,4-c]pyrrole-1-carboxylate (**6b**).*[16b] ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J=7.1 Hz, 2H), 7.42–7.28 (m, 6H), 7.14 (dd, J=5.4, 3.5 Hz, 2H), 4.62 (d, J=8.6 Hz, 1H), 4.15 (d, J=6.6 Hz, 1H), 3.87 (s, 3H), 3.73 (t, J=7.2 Hz, 1H), 3.57 (t, J=8.3 Hz, 1H), 2.35 (s, 1H). Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexanes: 2-propanol=50:50, 0.7 mL/min, 210 nm); minor enantiomer t_r=12.2 min, major enantiomer t_r=20.9 min.

*4.3.3. Ethyl(1S,3R,3aS,6aR)-5-(3-chlorophenyl)-4,6-dioxo-3-phenyl-octahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**6c**).* $[\alpha]_D^{25}$ −69.9 (*c* 3.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 7.49–7.44 (m, 2H), 7.42–7.31 (m, 5H), 7.21 (t, J=1.9 Hz, 1H), 7.12–7.07 (m, 1H), 4.63 (d, J=8.8 Hz, 1H), 4.43–4.32 (m, 2H), 4.14 (d, J=6.7 Hz, 1H), 3.74 (t, J=7.2 Hz, 1H), 3.58 (t, J=8.3 Hz, 1H), 2.38 (s, 1H), 1.40 (t, J=7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.55, 173.25, 169.47, 136.57, 134.52, 132.69, 129.95, 128.66, 128.54, 127.08, 126.44, 124.36, 64.27, 62.12, 61.60, 49.53, 48.31, 14.17. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexanes: 2-propanol=50:50, 0.7 mL/min, 210 nm); minor enantiomer t_r=11.9 min, major enantiomer t_r=25.5 min.

*4.3.4. Ethyl (1S,3R,3aS,6aR)-4,6-dioxo-3-phenyl-5-(m-tolyl)-ctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**6d**).* $[\alpha]_D^{25}$ −78.1 (*c* 2.6, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, J=7.3 Hz, 2H), 7.42–7.26 (m, 4H), 7.15 (d, J=7.7 Hz, 1H), 6.96 (d, J=6.3 Hz, 2H), 4.63 (d, J=8.8 Hz, 1H), 4.47–4.29 (m, 2H), 4.15 (d, J=6.7 Hz, 1H), 3.74 (dd, J=7.6, 6.9 Hz, 1H), 3.58 (dd, J=8.6, 8.0 Hz, 1H), 2.35 (s, 3H), 2.33 (br s, 1H), 1.40 (t, J=7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.97, 173.68, 169.58, 139.01, 136.68, 131.58, 129.35, 128.84, 128.47, 128.42, 127.15, 126.81, 123.32, 77.29, 77.03, 76.78, 64.34, 62.14, 61.53, 49.61, 48.41, 21.29, 14.16. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexanes: 2-propanol=50:50, 0.7 mL/min, 210 nm); minor enantiomer t_r=11.4 min, major enantiomer t_r=26.3 min.

*4.3.5. Ethyl(1S,3R,3aS,6aR)-5-(3-bromophenyl)-4,6-dioxo-3-phenyl-octahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**6e**).* $[\alpha]_D^{25}$ −68.8 (*c* 2.8, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 7.50–7.44 (m, 3H), 7.42–7.37 (m, 2H), 7.37–7.33 (m, 2H), 7.27 (t, J=8.1 Hz, 1H), 7.14 (ddd, J=8.0, 1.9, 0.9 Hz, 1H), 4.63 (d, J=8.8 Hz, 1H), 4.43–4.31 (m, 2H), 4.15 (d, J=6.7 Hz, 1H), 3.74 (dd, J=7.7, 6.8 Hz, 1H), 3.58 (dd, J=8.7, 7.9 Hz, 1H), 2.25 (br s, 1H), 1.40 (t, J=7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.52, 173.23, 169.45, 136.56, 132.79, 131.56, 130.19, 129.24, 128.55, 128.53, 127.06, 124.83, 122.26, 64.26, 62.12, 61.59, 49.53, 48.31, 14.17. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexanes: 2-propanol=50:50, 0.7 mL/min, 210 nm); minor enantiomer t_r=12.7 min, major enantiomer t_r=27.6 min.

*4.3.6. Ethyl(1S,3R,3aS,6aR)-5-(4-ethoxyphenyl)-4,6-dioxo-3-phenyl-octahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**6f**).* $[\alpha]_D^{25}$ −78.2 (*c* 2.8, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, J=7.2 Hz, 2H), 7.38 (dd, J=10.1, 4.7 Hz, 2H), 7.35–7.30 (m, 1H), 7.11–7.04 (m, 2H), 6.94–6.85 (m, 2H), 4.62 (d, J=8.7 Hz, 1H), 4.45–4.29 (m, 2H), 4.14 (d, J=6.7 Hz, 1H), 4.02 (q, J=7.0 Hz, 2H), 3.73 (t, J=7.2 Hz, 1H), 3.57 (t, J=8.3 Hz, 1H), 1.41 (t, J=7.0 Hz, 3H), 1.39 (t, J=7.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.13, 173.83, 169.62, 158.76, 136.72, 128.47, 128.39, 127.33, 127.12, 124.22, 114.89, 64.35, 63.68, 62.15, 61.52, 49.57, 48.35, 14.72, 14.16. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexanes: 2-propanol=50:50, 0.7 mL/min, 210 nm); minor enantiomer t_r=18.7 min, major enantiomer t_r=28.2 min.

*4.3.7. Ethyl(1S,3R,3aS,6aR)-5-(4-methoxyphenyl)-4,6-dioxo-3-phenyl -octahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**6g**).* $[\alpha]_D^{25}$ −79.2 (*c* 1.9, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, J=7.2 Hz, 2H), 7.38 (dd, J=8.1, 6.7 Hz, 2H), 7.34 (dd, J=4.8, 3.6 Hz, 1H), 7.14–7.04 (m, 2H), 6.94–6.86 (m, 2H), 4.62 (d, J=8.8 Hz, 1H), 4.44–4.29 (m, 2H), 4.14 (d, J=6.7 Hz, 1H), 3.80 (s, 3H), 3.77–3.68 (m, 1H), 3.66–3.53 (m, 1H), 2.53 (s, 1H), 1.39 (t, J=7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.13, 173.83, 169.62, 159.38, 136.74, 128.47, 128.39, 127.39, 127.12, 124.41, 114.36, 64.33, 62.14, 61.52, 55.45, 49.56, 48.35, 14.17. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexanes: 2-propanol=50:50, 0.7 mL/min, 210 nm); minor enantiomer t_r=18.6 min, major enantiomer t_r=31.9 min.

*4.3.8. Methyl(1S,3R,3aS,6aR)-5-(3-bromophenyl)-4,6-dioxo-3-phenyl-octahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**6h**).* ^1H NMR (500 MHz, $CDCl_3$) δ 7.48 (m, 2H), 7.43–7.34 (m, 4H), 7.31–7.26 (m, 2H), 7.14 (d, J=8.0 Hz, 1H), 4.66 (d, J=8.8 Hz, 1H), 4.18 (d, J=6.6 Hz, 1H), 3.91 (s, 3H), 3.76 (dd, J=7.7, 6.7 Hz, 1H), 3.60 (dd, J=8.7, 7.9 Hz, 1H), 2.56 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.16, 169.91, 132.74, 131.59, 130.19, 129.21, 128.62, 128.57, 127.07, 124.78, 77.26, 77.00, 76.75, 64.28, 61.96, 52.38, 49.44, 48.31. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexanes: 2-propanol=50:50, 0.7 mL/min, 210 nm); minor enantiomer t_r=15.5 min, major enantiomer t_r=35.8 min.

*4.3.9. Methyl(1S,3R,3aS,6aR)-5-(4-bromophenyl)-4,6-dioxo-3-phenyl-octahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**6i**).* $[\alpha]_D^{25}$ −91.9 (*c* 3.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.54–7.47 (m, 2H), 7.46–7.39 (m, 2H), 7.34 (dt, J=8.5, 6.8 Hz, 3H), 7.08–6.99 (m, 2H), 4.60 (d, J=8.8 Hz, 1H), 4.13 (d, J=6.6 Hz, 1H), 3.87 (s, 3H), 3.76–3.65 (m, 1H), 3.56 (d, J=8.6 Hz, 1H), 2.35 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.73, 173.25, 169.98, 136.58, 132.19, 130.62, 128.54, 127.60, 127.07, 122.28, 64.25, 61.93, 52.37, 49.42, 48.30. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexanes: 2-propanol=50:50, 0.7 mL/min, 210 nm); minor enantiomer t_r=15.3 min, major enantiomer t_r=26.6 min.

*4.3.10. Methyl (1S,3R,3aS,6aR)-5-(3,5-dimethylphenyl)-4,6-dioxo-3-phenyl-octahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**6j**).* $[\alpha]_D^{25}$ −93.2 (*c* 1.9, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J=7.2 Hz, 2H), 7.40–7.27 (m, 3H), 6.94 (s, 1H), 6.71 (s, 2H), 4.60 (d, J=8.5 Hz, 1H), 4.16–4.08 (m, 1H), 3.87 (s, 3H), 3.70 (t, J=6.5 Hz, 1H), 3.54 (t, J=7.6 Hz, 1H), 2.35 (br s, 1H), 2.27 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.17, 173.74, 170.08, 138.79, 136.69, 131.42, 130.38, 128.46, 127.19, 123.94, 64.30, 61.93, 52.32, 49.51, 48.42, 21.19. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexanes:

2-propanol=50:50, 0.7 mL/min, 210 nm); minor enantiomer t_r=11.1 min, major enantiomer t_r=24.7 min.

*4.3.11. Methyl (1S,3R,3aS,6aR)-3-(2-methoxyphenyl)-4,6-dioxo-5-phenyl-octahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**6k**).*[16c] $[\alpha]_D^{25}$ −120.2 (*c* 1.9, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (dd, *J*=7.5, 1.1 Hz, 1H), 7.35 (dd, *J*=8.2, 6.9 Hz, 2H), 7.31–7.26 (m, 2H), 7.11 (dd, *J*=5.3, 3.3 Hz, 2H), 6.95 (td, *J*=7.5, 0.7 Hz, 1H), 6.88 (d, *J*=8.2 Hz, 1H), 4.73 (d, *J*=7.9 Hz, 1H), 4.15 (d, *J*=6.6 Hz, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.77–3.67 (m, 2H), 2.84 (br s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.27, 173.72, 170.38, 157.31, 131.81, 129.23, 128.91, 128.31, 126.87, 126.13, 124.76, 120.67, 110.34, 62.48, 60.78, 55.45, 52.37, 48.96, 48.30. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexanes: 2-propanol=50:50, 0.7 mL/min, 210 nm); minor enantiomer t_r=15.8 min, major enantiomer t_r=33.5 min.

*4.3.12. Methyl (1S,3R,3aS,6aR)-3-(3-methoxyphenyl)-4,6-dioxo-5-phenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**6l**).* $[\alpha]_D^{25}$ −71.7 (*c* 2.3, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.38 (m, 2H), 7.37–7.29 (m, 2H), 7.20–7.16 (m, 2H), 7.04 (dd, *J*=14.3, 4.9 Hz, 2H), 6.89–6.84 (m, 1H), 4.62 (d, *J*=8.9 Hz, 1H), 4.17 (d, *J*=6.7 Hz, 1H), 3.90 (s, 3H), 3.79 (s, 3H), 3.75 (dd, *J*=7.8, 6.6 Hz, 1H), 3.59 (dd, *J*=8.7, 7.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.96, 173.44, 169.96, 159.79, 138.24, 131.68, 129.54, 129.01, 128.48, 126.12, 119.47, 113.78, 112.94, 64.24, 61.90, 55.21, 52.34, 49.44, 48.33. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexanes: 2-propanol=50:50, 0.7 mL/min, 210 nm); minor enantiomer t_r=18.1 min, major enantiomer t_r=44.0 min.

*4.3.13. Methyl (1S,3R,3aS,6aR)-3-(3-bromophenyl)-4,6-dioxo-5-phenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**6m**).*[16c] $[\alpha]_D^{25}$ −73.4 (*c* 3.1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.46–7.29 (m, 5H), 7.22 (t, *J*=7.8 Hz, 1H), 7.17–7.11 (m, 2H), 4.55 (d, *J*=8.9 Hz, 1H), 4.12 (d, *J*=6.6 Hz, 1H), 3.86 (s, 3H), 3.71 (t, *J*=7.2 Hz, 1H), 3.54 (t, *J*=8.3 Hz, 1H), 2.35 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.84, 173.41, 169.78, 139.21, 131.61, 131.53, 130.11, 130.05, 129.12, 128.62, 126.19, 126.06, 122.79, 63.39, 61.74, 52.37, 49.17, 48.01. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexanes: 2-propanol=50:50, 0.7 mL/min, 210 nm); minor enantiomer t_r=16.7 min, major enantiomer t_r=43.9 min.

*4.3.14. Methyl (1S,3R,3aS,6aR)-4,6-dioxo-5-phenyl-3-(p-tolyl)-octahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**6n**).*[16d] $[\alpha]_D^{25}$ −106.8 (*c* 2.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.36 (m, 2H), 7.32 (d, *J*=7.8 Hz, 3H), 7.18–7.13 (m, 4H), 4.57 (d, *J*=8.8 Hz, 1H), 4.16–4.07 (m, 1H), 3.86 (s, 3H), 3.76–3.66 (m, 1H), 3.53 (t, *J*=8.3 Hz, 1H), 2.64–2.52 (br s, 1H), 2.33 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.10, 173.68, 170.09, 138.12, 133.55, 131.70, 129.23, 129.02, 128.46, 127.00, 126.17, 64.28, 61.98, 52.32, 49.53, 48.46, 21.23. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexanes: 2-propanol=50:50, 0.7 mL/min, 210 nm); minor enantiomer t_r=14.7 min, major enantiomer t_r=37.8 min.

*4.3.15. Methyl(1S,3R,3aS,6aR)-3-(4-fluorophenyl)-4,6-dioxo-5-phenyl-octahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**6o**).*[16e] $[\alpha]_D^{25}$ −100.3 (*c* 2.4, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48–7.39 (m, 4H), 7.38–7.32 (m, 1H), 7.16 (d, *J*=7.4 Hz, 2H), 7.07 (dd, *J*=12.2, 4.9 Hz, 2H), 4.62–4.58 (m, 1H), 4.19–4.09 (m, 1H), 3.93–3.82 (m, 3H), 3.77–3.65 (m, 1H), 3.57–3.52 (m, 1H), 2.38 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.95, 173.53, 169.94, 162.64 (d, *J*=246.8 Hz), 132.50, 131.60, 129.08, 128.79 (d, *J*=8.1 Hz), 128.57, 126.08, 115.46 (d, *J*=21.6 Hz), 63.48, 61.80, 52.34, 49.24, 48.10. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexanes: 2-propanol=50:50, 0.7 mL/min, 210 nm); minor enantiomer t_r=16.2 min, major enantiomer t_r=36.2 min.

*4.3.16. Methyl(1S,3R,3aS,6aR)-3-(4-chlorophenyl)-4,6-dioxo-5-phenyl-octahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**6p**).*[16d] $[\alpha]_D^{25}$ −127.9 (*c* 2.5, $CHCl_3$).^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42–7.37 (m, 4H), 7.33 (t, *J*=7.5 Hz, 3H), 7.15–7.11 (m, 2H), 4.57 (d, *J*=8.8 Hz, 1H), 4.13 (d, *J*=6.8 Hz, 1H), 3.86 (s, 3H), 3.76–3.67 (m, 1H), 3.60–3.49 (m, 1H), 2.35 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.85, 173.41, 169.87, 135.21, 134.17, 131.55, 129.10, 128.71, 128.61, 128.52, 126.08, 63.53, 61.83, 52.37, 49.18, 48.04. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexanes: 2-propanol=50:50, 0.7 mL/min, 210 nm); minor enantiomer t_r=15.9 min, major enantiomer t_r=47.5 min.

*4.3.17. Methyl(1S,3R,3aS,6aR)-3-(4-bromophenyl)-4,6-dioxo-5-phenyl-octahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**6q**).*[16d] $[\alpha]_D^{25}$ −129.9 (*c* 2.7, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49–7.45 (m, 2H), 7.42–7.36 (m, 2H), 7.33 (dt, *J*=7.5, 1.9 Hz, 3H), 7.15–7.11 (m, 2H), 4.54 (d, *J*=8.7 Hz, 1H), 4.12 (dd, *J*=6.9, 2.1 Hz, 1H), 3.86 (s, 3H), 3.71 (dd, *J*=7.6, 6.9 Hz, 1H), 3.59–3.48 (m, 1H), 2.47 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.86, 173.41, 169.89, 135.79, 131.64, 131.55, 129.11, 128.84, 128.61, 126.08, 122.33, 63.58, 61.85, 52.36, 49.13, 48.03. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexanes: 2-propanol=50:50, 0.7 mL/min, 210 nm); minor enantiomer t_r=13.4 min, major enantiomer t_r=30.9 min.

*4.3.18. Methyl (1S,3R,3aS,6aR)-3-(naphthalen-2-yl)-4,6-dioxo-5-phenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**6r**).*[16e] $[\alpha]_D^{25}$ −130.1 (*c* 2.9, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.84–7.78 (m, 3H), 7.50 (dd, *J*=8.5, 1.6 Hz, 1H), 7.48–7.43 (m, 2H), 7.35–7.25 (m, 3H), 7.12–7.07 (m, 2H), 4.69 (d, *J*=8.8 Hz, 1H), 4.12 (d, *J*=6.6 Hz, 1H), 3.88 (s, 3H), 3.71 (dd, *J*=7.6, 6.8 Hz, 1H), 3.59 (dd, *J*=8.6, 7.9 Hz, 1H), 2.35 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.08, 173.58, 170.10, 134.35, 133.40, 133.31, 131.64, 129.00, 128.44, 128.13, 127.96, 127.86, 126.30, 126.12, 126.06, 125.65, 125.38, 64.29, 61.93, 52.36, 49.38, 48.40. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexanes: 2-propanol=50:50, 0.7 mL/min, 210 nm); minor enantiomer t_r=19.5 min, major enantiomer t_r=65.8 min.

*4.3.19. Methyl (1S,3R,3aS,6aR)-4,6-dioxo-5-phenyl-3-(4-(trifluoromethyl)phenyl)octahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**6s**).* $[\alpha]_D^{25}$ −94.9 (*c* 1.9, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (q, *J*=8.5 Hz, 4H), 7.42–7.38 (m, 2H), 7.36–7.31 (m, 1H), 7.14–7.10 (m, 2H), 4.65 (d, *J*=8.6 Hz, 1H), 4.17 (d, *J*=6.9 Hz, 1H), 3.87 (s, 3H), 3.78–3.70 (m, 1H), 3.67–3.56 (m, 1H), 2.35 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.72, 173.26, 169.81, 131.48, 130.56 (d, *J*=32.4 Hz), 129.14, 129.03, 128.69, 127.61, 126.07, 125.44 (q, *J*=3.7 Hz), 125.08, 63.68, 61.93, 52.41, 49.18, 47.95. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexanes: 2-propanol=50:50, 0.7 mL/min, 210 nm); minor enantiomer t_r=11.4 min, major enantiomer t_r=29.4 min.

*4.3.20. Methyl (1S,3R,3aS,6aR)-3-([1,1′-biphenyl]-4-yl)-4,6-dioxo-5-phenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**6t**).* $[\alpha]_D^{25}$ −163.3 (*c* 2.5, $CHCl_3$). ^{1}H NMR (400 MHz, DMSO) δ 7.67 (dd, *J*=13.5, 7.8 Hz, 4H), 7.47 (ddd, *J*=11.9, 9.6, 6.2 Hz, 6H), 7.37 (dd, *J*=14.0, 7.3 Hz, 2H), 7.16–7.08 (m, 2H), 4.53 (dd, *J*=8.7, 3.5 Hz, 1H), 4.08 (dd, *J*=6.7, 3.6 Hz, 1H), 3.79 (t, *J*=7.3 Hz, 1H), 3.71 (s, 3H), 3.66–3.56 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ 175.74, 174.30, 170.35, 139.88, 139.03, 138.07, 132.24, 128.88, 128.80, 128.15, 127.97, 127.29, 126.55 (d, *J*=13.0 Hz), 126.04, 62.79, 61.21, 51.37, 49.10, 48.20. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column

(hexanes: 2-propanol=50:50, 0.7 mL/min, 210 nm); minor enantiomer t_r=14.4 min, major enantiomer t_r=35.1 min.

*4.3.21. Methyl (1S,3R,3aS,6aR)-3-([1,1′-biphenyl]-4-yl)-5-(4-bromophenyl)-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**6u**).* $[\alpha]_D^{25}$ −149.7 (*c* 3.8, $CHCl_3$). ^1H NMR (400 MHz, DMSO) δ 7.72–7.60 (m, 6H), 7.53–7.44 (m, 4H), 7.36 (t, *J*=7.3 Hz, 1H), 7.10 (dd, *J*=9.1, 2.3 Hz, 2H), 4.52 (dd, *J*=8.7, 4.4 Hz, 1H), 4.08 (dd, *J*=6.9, 4.3 Hz, 1H), 3.78 (t, *J*=7.3 Hz, 1H), 3.71 (s, 3H), 3.65–3.57 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ 175.54, 174.08, 170.32, 139.88, 139.07, 138.00, 131.88, 131.45, 128.88, 128.58, 127.94, 127.30, 126.50, 126.07, 121.07, 62.79, 61.22, 51.40, 49.19, 48.29. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexanes: 2-propanol=50:50, 0.7 mL/min, 210 nm); minor enantiomer t_r=18.0 min, major enantiomer t_r=43.9 min.

*4.3.22. Methyl(1S,3R,3aS,6aR)-3-([1,1′-biphenyl]-4-yl)-5-(3,5-dimethyl-phenyl)-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**6v**).* $[\alpha]_D^{25}$ −146.6 (*c* 3.2, $CHCl_3$). ^1H NMR (400 MHz, DMSO) δ 7.67 (dd, *J*=11.5, 7.9 Hz, 4H), 7.54–7.44 (m, 4H), 7.36 (s, 1H), 7.01 (s, 1H), 6.71 (s, 2H), 4.52 (dd, *J*=8.7, 4.0 Hz, 1H), 4.07 (dd, *J*=6.8, 4.0 Hz, 1H), 3.77 (t, *J*=7.2 Hz, 1H), 3.71 (s, 3H), 3.62–3.55 (m, 2H), 2.27 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 175.74, 174.34, 170.36, 139.89, 139.04, 138.12, 137.98, 132.13, 129.52, 128.89, 128.02, 127.29, 126.46, 126.00, 124.21, 62.74, 61.18, 51.36, 49.05, 48.17, 20.68. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexanes: 2-propanol=50:50, 0.7 mL/min, 210 nm); minor enantiomer t_r=12.9 min, major enantiomer t_r=50.6 min.

*4.3.23. Methyl (1S,3R,3aS,6aR)-3-([1,1′-biphenyl]-4-yl)-5-(4-ethoxyphenyl)-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**6w**).* $[\alpha]_D^{25}$ −148.2 (*c* 2.0, $CHCl_3$). ^1H NMR (400 MHz, DMSO) δ 7.65 (dd, *J*=16.4, 7.8 Hz, 4H), 7.55–7.42 (m, 4H), 7.35 (t, *J*=7.3 Hz, 1H), 6.99 (q, *J*=9.1 Hz, 4H), 4.50 (dd, *J*=8.7, 4.4 Hz, 1H), 4.06–3.99 (m, 3H), 3.74 (t, *J*=7.2 Hz, 1H), 3.69 (s, 3H), 3.57 (dd, *J*=10.3, 6.3 Hz, 2H), 1.31 (t, *J*=7.0 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 175.90, 174.48, 170.37, 158.02, 139.89, 139.01, 138.13, 128.88, 127.97, 127.79, 127.28, 126.49, 126.02, 124.70, 114.52, 63.29, 62.77, 61.18, 51.36, 49.01, 48.09, 14.51. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexanes: 2-propanol=50:50, 0.7 mL/min, 210 nm); minor enantiomer t_r=36.2 min, major enantiomer t_r=51.7 min.

*4.3.24. Methyl (1S,3R,3aS,6aR)-3-([1,1′-biphenyl]-4-yl)-4,6-dioxo-5-(m-tolyl)octahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**6x**).* $[\alpha]_D^{25}$ −152.0 (*c* 3.9, $CHCl_3$). ^1H NMR (400 MHz, DMSO) δ 7.65 (dd, *J*=12.5, 7.8 Hz, 4H), 7.53–7.42 (m, 4H), 7.38–7.29 (m, 2H), 7.18 (d, *J*=7.6 Hz, 1H), 6.90 (s, 2H), 4.51 (d, *J*=8.8 Hz, 1H), 4.05 (d, *J*=6.9 Hz, 1H), 3.76 (t, *J*=7.3 Hz, 1H), 3.70 (s, 3H), 3.64–3.55 (m, 1H), 3.34 (s, 1H), 2.30 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 175.75, 174.33, 170.37, 139.88, 139.03, 138.23, 138.10, 132.18, 128.89, 128.79, 128.62, 128.00, 127.29, 127.04, 126.47, 126.02, 123.73, 62.67, 61.11, 51.37, 49.05, 48.16, 20.75. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexanes: 2-propanol=50:50, 0.7 mL/min, 210 nm); minor enantiomer t_r=15.1 min, major enantiomer t_r=54.4 min.

*4.3.25. Methyl (1S,3R,3aS,6aR)-3-(4′-(methylthio)-[1,1′-biphenyl]-4-yl)-4,6-dioxo-5-(m-tolyl)octahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**6y**).* $[\alpha]_D^{25}$ −180.6 (*c* 2.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (dt, *J*=8.0, 6.3 Hz, 6H), 7.39 (t, *J*=7.6 Hz, 2H), 7.32 (t, *J*=7.4 Hz, 3H), 7.16 (d, *J*=7.8 Hz, 2H), 4.65 (d, *J*=8.7 Hz, 1H), 4.17 (d, *J*=6.7 Hz, 1H), 3.88 (s, 3H), 3.75 (t, *J*=7.2 Hz, 1H), 3.61 (t, *J*=8.2 Hz, 1H), 2.51 (s, 3H), 2.35 (br s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.96, 173.55, 170.01, 140.57, 137.76, 137.47, 135.54, 131.67, 129.08, 128.55, 127.70, 127.46, 126.97, 126.87, 126.15, 64.20, 62.00, 52.39, 49.49, 48.39, 15.92. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexanes: 2-propanol=50:50, 0.7 mL/min, 210 nm); minor enantiomer t_r=32.7 min, major enantiomer t_r=89.4 min.

*4.3.26. Methyl (1S,3R,3aS,6aR)-3-(3′,5′-bis(trifluoromethyl)-[1,1′-biphenyl]-4-yl)-4,6-dioxo-5-(m-tolyl)octahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**6z**).* $[\alpha]_D^{25}$ −131.2 (*c* 4.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 2H), 7.84 (s, 1H), 7.59 (s, 4H), 7.40 (t, *J*=7.5 Hz, 2H), 7.33 (t, *J*=7.3 Hz, 1H), 7.16 (d, *J*=7.5 Hz, 2H), 4.67 (d, *J*=8.6 Hz, 1H), 4.18 (d, *J*=6.8 Hz, 1H), 3.89 (s, 3H), 3.76 (t, *J*=7.3 Hz, 1H), 3.63 (t, *J*=8.2 Hz, 1H), 2.30 (br s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.90, 173.51, 169.97, 142.78, 138.20, 137.64, 132.14 (d, *J*=33.2 Hz), 131.63, 129.15, 128.67, 128.18, 127.31, 127.26, 126.18, 124.75, 122.04, 121.00, 63.94, 62.04, 52.43, 49.43, 48.17. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexanes: 2-propanol=50:50, 0.7 mL/min, 210 nm); minor enantiomer t_r=9.2 min, major enantiomer t_r=19.4 min.

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Supplementary data

Supplementary data (General remarks and the procedure of the synthetic reaction, NMR data diagrams for all the products **2**–**6**) related to this article can be found at http://dx.doi.org/10.1016/j.tet.2015.09.068.

References and notes

1. Selected reviews: (a) Li, Z. G.; He, C. *Eur. J. Org. Chem.* **2006**, 4313–4322; (b) Yamamoto, H.; Wadamoto, M. *Chem.—Asian. J.* **2007**, *2*, 692–698; (c) Yanagisawa, A.; Arai, T. *Chem. Commun.* **2008**, 1165–1172; (d) Naodovic, M.; Yamamoto, H. *Chem. Rev.* **2008**, *108*, 3132–3148; (e) Mejiboom, R.; Bowen, R. J.; Berners-Price, S. J. *Coord. Chem. Rev.* **2009**, *253*, 325–342; (f) Teichert, J. F.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2010**, *49*, 2486–2528 For recent examples: (g) McNulty, J.; Keskar, K.; Vemula, R. *Chem.—Eur. J.* **2011**, *17*, 14727–14730; (h) Zhao, Y.; Zhou, X.; Okamura, T.; Chen, M.; Lu, Y.; Sun, W. Y.; Yu, J. Q. *Dalton Trans.* **2012**, *41*, 5889–5896; (i) Iglesias, M. J.; Nicasio, M. C.; Caballero, A.; Perez, P. J. *Dalton Trans.* **2013**, *42*, 1191–1195; (j) Valderas, C.; De la Torre, M. C.; Fernandz, I.; Munoz, M. P.; Sierra, M. A. *Organometallics* **2013**, *32*, 951–956; (k) Zheng, L. S.; Li, L.; Yang, K. F.; Zheng, Z. J.; Xiao, X. X.; Xu, L. W. *Tetrahedron* **2013**, *69*, 8777–8784; (l) Ye, F.; Zheng, Z. J.; Deng, W. H.; Zheng, L. S.; Deng, Y.; Xia, C. G.; Xu, L. W. *Chem.—Asian. J.* **2013**, *8*, 2242–2253; (m) Ye, F.; Zheng, Z. J.; Li, L.; Yang, K. F.; Xia, C. G.; Xu, L. W. *Chem.—Eur. J.* **2013**, *19*, 15452–15457.
2. For selected and recent examples: (a) Sawamura, M.; Hamashima, H.; Ito, Y. *J. Org. Chem.* **1990**, *55*, 5935–5936; (b) Yanagisawa, A.; Matsumoto, Y.; Nakashima, H.; Asakawa, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1997**, *119*, 9319–9320; (c) Wadamoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, *127*, 14556–14557; (d) Sladojevich, F.; Trabocchi, A.; Guarna, A.; Dixon, D. J. *J. Am. Chem. Soc.* **2011**, *133*, 1710–1713; (e) Wang, Y.; Zheng, K.; Hong, R. *J. Am. Chem. Soc.* **2012**, *134*, 4096–4099; (f) Kohn, B. L.; Ichiishi, N.; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2013**, *52*, 4414–4417; (g) Terada, M.; Li, F.; Toda, Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 235–239; (h) Shao, P. L.; Liao, J. Y.; Ho, Y. A.; Zhao, Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 5435–5439.
3. For recent reviews and books: (a) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029–3069; (b) *Privileged Chiral Ligands and Catalysts*; Zhou, Q. L., Ed.; Wiley-VCH: Singapore, 2011.
4. For representative reviews, see: (a) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209–2219; (b) Moonen, K.; Laureyn, I.; Stevens, C. V. *Chem. Rev.* **2004**, *104*, 6177–6216; (c) Bellina, F.; Renzo, R. *Tetrahedron* **2006**, *62*, 7213–7256; (d) Pandey, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484–4517; (e) Álvarez-Corral, M.; Muñoz-Dorado, M.; Rodriguez-García, I. *Chem. Rev.* **2008**, *108*, 3174–3198; (f) Najera, C.; Sansano, J. M. *Org. Biomol. Chem.* **2009**, *7*, 4567–4581; (g) Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev.* **2009**, *38*, 3051–3060; (h) Narayan, R.; Potowski, M.; Jia, Z. J.; Antonchick, A. P.; Waldmann, H. *Acc. Chem. Res.* **2014**, *47*, 1296–1310; (i) Kumar, I. *RSC Adv.* **2014**, *4*, 16397–16408; (j) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2015**, *115*, 5366–5412 and references cited there in.

5. (a) Pandey, J.; Anand, N.; Tripathi, R. P. *Tetrahedron* **2009**, *65*, 9350–9356; (b) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569; (c) Kotsuki, H.; Ikishima, H.; Okuyama, A. *Heterocycles* **2008**, *75*, 493–529; (d) Gruttadauria, M.; Giacalone, F.; Noto, R. *Chem. Soc. Rev.* **2008**, *37*, 1666–1688; (e) Chen, F.; Huang, S.; Zhang, H.; Liu, F.; Peng, Y. *Tetrahedron* **2008**, *64*, 9585–9591.
6. (a) Stocker, B. L.; Dangerfield, E. M.; Win-Mason, A. L.; Haslett, G. W.; Timmer, M. S. M. *Eur. J. Org. Chem.* **2010**, 1615–1637; (b) Najera, C.; Sansano, J. M. *J. Organomet. Chem.* **2014**, *771*, 78–92; (c) Najera, C.; Sansano, J. M. *Monatsh. Chem.* **2011**, *142*, 659–680 For recent examples, see: (d) Albrecht, Ł.; Jiang, H.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 8492–8509; (e) González, A. Z.; Benitez, D.; Tkatchouk, E.; Goddard, W. A.; Toste, F. D. *J. Am. Chem. Soc.* **2011**, *133*, 5500–5507; (f) Jui, N. T.; Garber, J. A.; Finelli, F. G.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2012**, *134*, 11400–11403; (g) Jing, X.; He, C.; Dong, D.; Yang, L.; Duan, C. *Angew. Chem., Int. Ed.* **2012**, *51*, 10127–10131; (h) Wang, Z.; Luo, S.; Zhang, S.; Yang, W. L.; Liu, Y. Z.; Li, H.; Luo, X.; Deng, W. P. *Chem.—Eur. J.* **2013**, *19*, 6739–6745; (i) Hut'ka, M.; Tsubogo, T.; Kobayashi, S. *Adv. Synth. Catal.* **2013**, *355*, 1561–1569; (j) Hernández-Toribio, J.; Padilla, S.; Adrio, J.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2012**, *51*, 8854–8858; (k) Trost, B. M.; Lam, T. M.; Herbage, M. A. *J. Am. Chem. Soc.* **2013**, *135*, 2459–2461; (l) Sunsdahl, B.; Smith, A. R.; Livinghouse, T. *Angew. Chem., Int. Ed.* **2014**, *53*, 14352–14356; (m) Maroto, E. E.; Filippone, S.; Suárez, M.; Martinez-Álvarez, R.; de Cózar, A.; Cossío, F. P.; Martin, N. *J. Am. Chem. Soc.* **2014**, *136*, 705–712.
7. Allway, P.; Grigg, R. *Tetrahedron Lett.* **1991**, *32*, 5817–5820.
8. Longmire, J. M.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 13400–13401.
9. Gothelf, A. S.; Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4236–4238.
10. Chen, C.; Li, X.; Schreiber, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 10174–10175.
11. Zeng, W.; Zhou, Y.-G. *Org. Lett.* **2005**, *7*, 5055–5058.
12. (a) Cabrera, S.; Arrayás, R. G.; Carretero, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 16394–16395; (b) López-Pérez, A.; Adrio, J.; Carretero, J. C. *J. Am. Chem. Soc.* **2008**, *130*, 10084–10085.
13. Yan, X.-X.; Peng, Q.; Zhang, Y.; Zhang, K.; Hong, W.; Hou, X.-L.; Wu, Y.-D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1979–1983.
14. (a) Wang, C.-J.; Liang, G.; Xue, Z.-Y.; Gao, F. *J. Am. Chem. Soc.* **2008**, *130*, 17250–17251; (b) Xue, Z.-Y.; Li, Q.-H.; Tao, H.-Y.; Wang, C.-J. *J. Am. Chem. Soc.* **2011**, *133*, 11757–11765.
15. (a) Fukuzawa, S.-i.; Oki, H. *Org. Lett.* **2008**, *10*, 1747–1750; (b) Imae, K.; Konno, T.; Ogata, K.; Fukuzawa, S.-i. *Org. Lett.* **2012**, *14*, 4410–4413.
16. (a) Yan, S.; Zhang, C.; Wang, Y.-H.; Cao, Z.; Zheng, Z.; Hu, X.-P. *Tetrahedron Lett.* **2013**, *54*, 3669–3672; (b) Gu, X.; Xu, Z.-J.; Lo, Vanessa K.-Y.; Che, C.-M. *Synthesis* **2012**, *44*, 3307–3314; (c) Bai, J.-F.; Wang, L.-L.; Peng, L.; Guo, Y.-L.; Ming, J.-N.; Wang, F.-Y.; Xu, X.-Y.; Wang, L.-X. *Eur. J. Org. Chem.* **2011**, 4472–4478; (d) Wang, C.-J.; Xue, Z.-Y.; Liang, G.; Lu, Z. *Chem. Commun.* **2009**, 2905–2907; (e) Zeng, W.; Zhou, Y.-G. *Tetrahedron Lett.* **2007**, *48*, 4619–4622.
17. Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874–9875.
18. (a) Najera, C.; Sansano, J. M.; Yus, M. *J. Braz. Chem. Soc.* **2010**, *21*, 377–412; (b) Randjelovic, J.; Simic, M.; Tasic, G.; Husinec, S.; Savic, V. *Curr. Org. Chem.* **2014**, *18*, 1073–1096.
19. (a) Bai, X.-F.; Song, T.; Xu, Z.; Xia, C.-G.; Huang, W.-S.; Xu, L.-W. *Angew. Chem., Int. Ed.* **2015**, *54*, 5255–5259 The compound *syn*-(*R*, R_S)-**2h** and it's epimer *syn*-(*S*, R_S)-2h had also been reported in this reference; (b) Bai, X. F.; Xu, Z.; Xia, C. G.; Zheng, Z. J.; Xu, L. W. *ACS Catal.* **2015**, *5*, 6016–6020.
20. (a) Shimizu, K.; Ogata, K.; Fukuzawa, S.-i. *Tetrahedron Lett.* **2010**, *51*, 5068–5070; (b) López-Pérez, A.; Segler, M.; Adrio, J.; Carretero, J. C. *J. Org. Chem.* **2011**, *76*, 1945–1948; (c) Nájera, C.; de Gracia Retamosa, M.; Martín-Rodríguez, M.; Sansano, J. M.; de Cózar, A.; Cossío, F. P. *Eur. J. Org. Chem.* **2009**, 5622–5634.
21. (a) Cogan, D. A.; Liu, G. C.; Ellman, J. *Tetrahedron* **1999**, *55*, 8883–8904; (b) Zhang, Z. M.; Chen, P.; Li, W.; Niu, Y.; Zhao, X. L.; Zhang, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 4350–4354; (c) Clayden, J.; McCarthy, C.; Westlund, N.; Frampton, C. S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1363–1378.
22. Cabrera, S.; Arrayás, R. G.; Martín-Matute, B.; Cossío, F. P.; Carretero, J. C. *Tetrahedron* **2007**, *63*, 6587–6602.
23. (a) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 1984–1995; (b) Ellman, J. A. *Pure Appl. Chem.* **2003**, *75*, 39–46; (c) Senanayake, C. H.; Krishnamurthy, D.; Lu, Z.-H.; Han, Z.; Gallon, E. *Aldrichimica Acta* **2005**, *38*, 93–103; (d) Daniel, M.; Stockman, R. A. *Tetrahedron* **2006**, *62*, 8868–8905; (e) Lin, G. Q.; Xu, M. H.; Zhong, Y. W.; Sun, X. W. *Acc. Chem. Res.* **2007**, *41*, 831–840.

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