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The first catalytic enantioselective Diels–Alder reactions of 1,2-dihydropyridine: efficient syntheses of optically active 2-azabicyclo[2.2.2]octanes with chiral BINAM derived Cr(III) salen complexes

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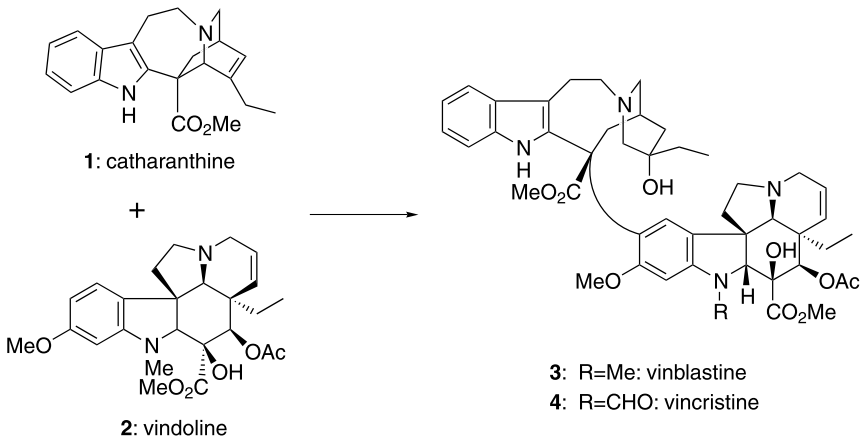
Abstract—We have synthesized a new family of enantiomerically enriched BINAM-derived Schiff base Cr(III) complexes and evaluated them as catalysts for Diels–Alder reactions. These complexes effectively catalyze, for the first time, the enantioselective Diels–Alder reactions between 1,2-dihydropyridine and *N*-acryloyloxazolidinone to afford 2-azabicyclo[2.2.2]octanes in high yields (89–99%) and with moderate to good enantioselectivities (79–85%). © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

The 2-azabicyclo[2.2.2]octane skeleton is found widely in natural products, particularly among the *Iboga* family of alkaloids, members of which have varied and interesting biological properties.[1–3] Of particular interest to us are the pharmacologically important *Vinca* alkaloids, such as vinblastine and vincristine (**3**, **4**).[2,3] These alkaloids arise from coupling of catharanthine (**1**), which possesses the 2-azabicyclo[2.2.2]octane skeleton, with the *Aspidosperma* portion (Scheme 1).[2,4]

A well-established route to the 2-azabicyclo[2.2.2]octane skeleton is through the Diels–Alder reaction of a suitably protected dihydropyridine with a dienophile (Eq. (1)).[1,5,6] Although such cycloadditions provide the most direct and efficient access to the desired isoquinuclidine system, there has been little work on the asymmetric variants of this process.[5] All reported examples of asymmetric Diels–Alder reactions of dihydropyridines are diastereoselective processes: stoichiometric chirality, whether in the diene or the dienophile, induces asymmetry in the cycloaddition step. The variations that have been investigated are those in



Scheme 1.

Keywords: Diels–Alder reaction; enantioselective; alkaloids; asymmetric catalysis; 2-azabicyclo[2.2.2]octane.

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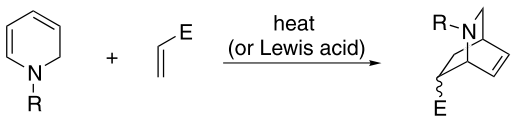
which (a) the 1,2-dihydropyridine possesses a chiral centre,[5a] (b) the dihydropyridine nitrogen is attached to a chiral auxiliary,[5b,c] or (c) the dienophile has a chiral auxiliary.[5d,e] Despite its obvious advantages, to the best of our knowledge, there are no reports of asymmetric Diels–Alder reactions of dihydropyridines catalysed by a sub-stoichiometric amount of a Lewis acid. Indeed, because 1,2-dihydropyridines are unstable to many Lewis acids, the reported cycloadditions of this diene are generally carried out under thermal (uncatalysed) conditions, often with poor *endo*–*exo* selectivity. A further problem with the use of Lewis acids is its expected complexation with the Diels–Alder products, which would impede catalyst turnover.[7]

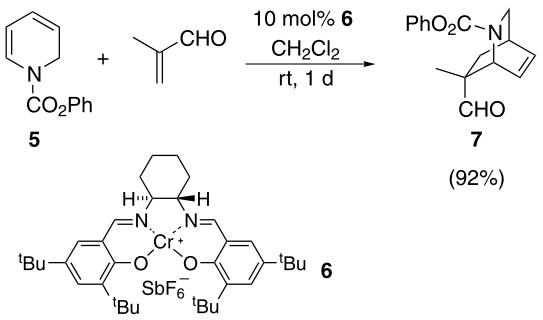


(1)

In connection with our interest in the development of an efficient asymmetric synthesis of *Vinca* alkaloids, we had previously investigated the catalysed enantioselective Diels–Alder reactions of amino dienes with dienophiles. Our studies had revealed that weakly Lewis acidic Cr(III) salen complexes, of the type used by Jacobsen, promoted the Diels–Alder reactions through an efficient catalytic cycle, and afforded cycloadducts in high yields, and excellent ee's.[8] Given the success of these asymmetric Diels–Alder reactions, we decided to utilise similar catalysis for the cycloadditions with 1,2-dihydropyridines.

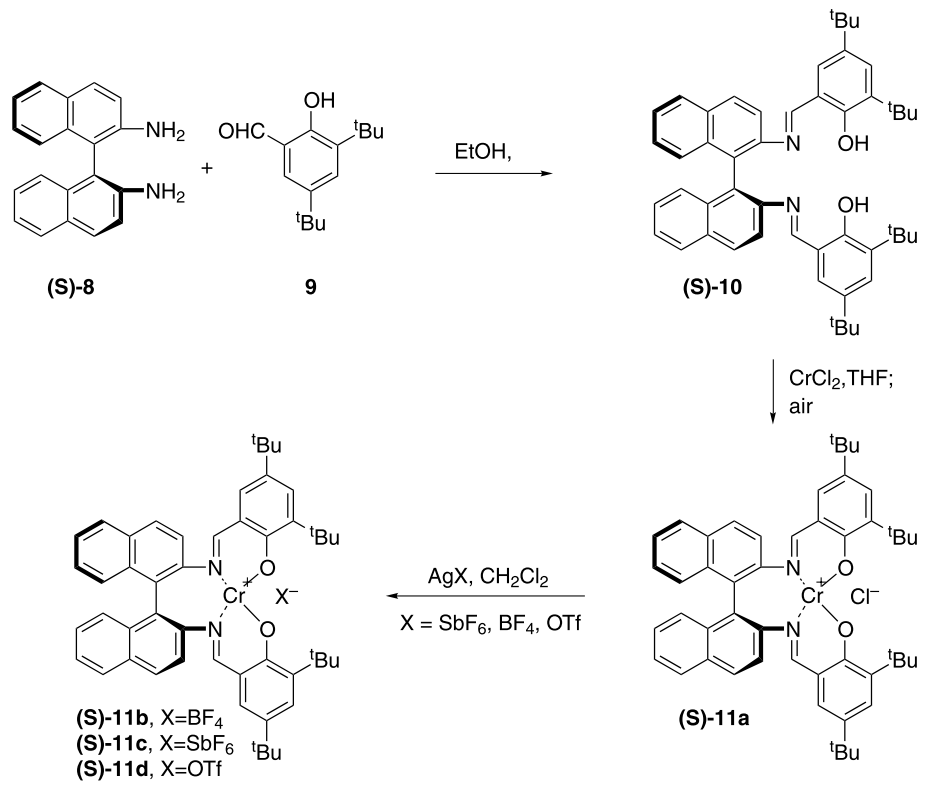
2. Results and discussion

The initial investigations focused on the use of Jacobsen-type salen complexes for the Diels–Alder reaction between 1,2-dihydropyridines and common dienophiles. The reaction between diene **5** and methacrolein was carried out in the presence of 10 mol% of Cr(III) salen complex **6** (Eq. (2)). We were delighted to find that the catalyst not only greatly accelerated the reaction, ultimately giving the product (**7**) in 92% yield, but that it promoted the exclusive formation of the *endo*-cycloadduct (by NMR). Importantly, the catalytic cycle (turnover) was efficient, despite the potential for the catalyst to coordinate strongly to the Lewis basic carbamate carbonyl in the product.



(2)

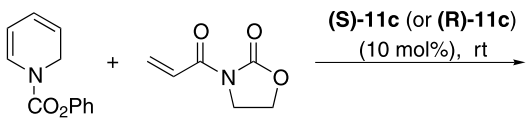
The determination of the cycloadduct enantioselectivity proved challenging. The aldehyde group was reduced using $NaBH_4$ and the resulting alcohol was converted to its Mosher ester. Although accurate determination of the diastereomeric ratio by NMR was difficult, due to the presence of carbamate rotomers, it was immediately clear that the cycloaddition had proceeded with poor enantioselectivity (ca. 10% ee). The poor enantioselectivity obtained with **6** prompted us to consider the use of salens that were structurally quite dissimilar.



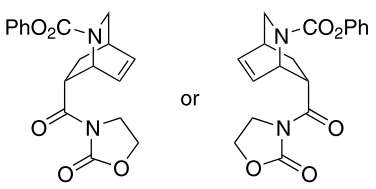
Scheme 2.

After considering several different chiral diamines, we decided to examine salens prepared from 1,1′-bi-2-naphthylamine (BINAM) **8**, which has received considerably less attention than *trans*-1,2-cyclohexanediamine. Schiff bases of BINAM have, however, been prepared, as have some metal complexes thereof.[9] The Cr(III) complex required for Diels–Alder catalysis was prepared as shown in Scheme 2. An ethanolic solution of BINAM and 3,5-di-*tert*-butylsalicylaldehyde, both available commercially, was heated to reflux overnight and then diluted with water.[9] The resulting precipitate was isolated in good yield by simple filtration of the reaction mixture. The BINAM Schiff base (**10**) was mixed with $CrCl_2$ in THF and stirred under N_2 overnight and then under an air atmosphere for another 12 h to produce the Cr(III) complex, **11**.[10] The chloride ion was exchanged using silver salts of the desired counter ion. The catalyst preparation method employed here is operationally simple and does not require the use of a dry box.

BINAM–salen complex **11c** effectively catalysed the cycloaddition between 1,2-dihydropyridine (**5**) and methacrolein. Although the desired product was obtained in good yield and with moderately good enantioselectivity (60% ee), determination of the product's ee was difficult, as mentioned previously. On the other hand, *N*-acryloyloxazolidinone (**12**) proved to be a very effective dienophile for these cycloadditions, and it was used for most of the subsequent investigations (Eq. (3)). The cycloadducts were not only formed in higher ee, but the enantioselectivity determination was also simpler, since the two enantiomers were nicely separated by HPLC using a chiral stationary phase.[11]



5 **12**



13 **ent-13**

(3)

We examined the above Diels–Alder reaction in several different solvents in order to see how the coordinating properties of the solvent would affect yield and enantioselectivity (Table 1). The reaction of diene **5** (1.0 equiv.) and dienophile **12** (2.0 equiv.) was carried out at ambient temperature in CH_2Cl_2 in the presence of 10 mol% of Cr(III) catalyst (*R*)-**11** and 4 Å molecular sieves. A clean reaction ensued, affording exclusively (by NMR) the *endo*-cycloadduct (**13**) in 86% yield with 74% ee. An interesting and somewhat surprising trend can be gleaned from the solvent survey, shown in Table 1. The preferred solvents for this cycloaddition—in term of rate, yield, and enantioselectivity—were the more Lewis basic ones. Cyclic ether solvents, THF and THP, gave similar yields but higher ee's than did CH_2Cl_2. The best results were obtained in solvents having a carbonyl group, especially acetone and EtOAc.[12] Practically no reaction occurred in dimethylacetamide (DMA), presumably because the highly polarised carbonyl group of DMA coordinates strongly with Cr(III) and prohibits it from catalysing the cycloaddition. Although THF and acetone were equally effective in terms of enantioselectivity, the reaction was faster in acetone, as reflected in the yield.[13,14] The role of Lewis basic solvents in increasing both yield and ee remains unclear.

Table 1. Effect of solvent on yield and enantioselectivity of **13**

Entry[a]	Solvent	Yield (%)[b]	Cat (*S*)-**11b** %ee of **13**	Cat (*R*)-**11b** %ee of ent-**13**
1	CH_2Cl_2	86		74
2	THF	90		84
3	THP	83	73	
4	Et_2O	63	53	
5	Acetone	99	74	85
6	EtOAc	97		79
7	2-Butanone	85		75
8	DMA	ND[c]		ND

[a] All reactions were carried out for 24 h, except for entry 8, which was a 3 day reaction.
[b] The yields refer to isolated, purified products.
[c] The yield was not determined (ND), since very little of the cycloadduct was present.

Table 2. Effects of counter ion (X^-) of **11** on yield and ee

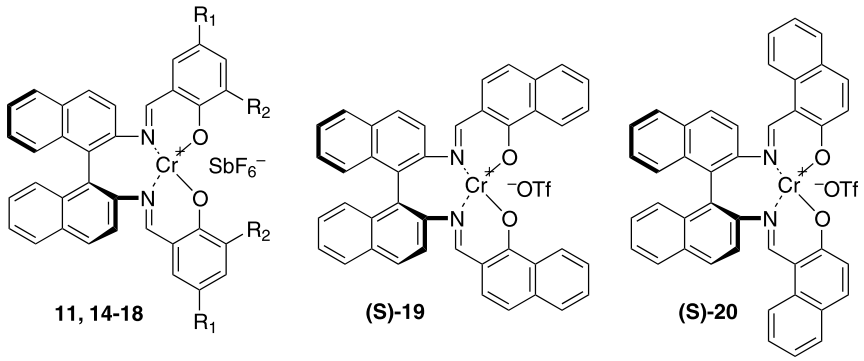
Entry[a]	Counter ion (X)	Yield (%)[b]	%ee of **13**	Rxn time (h)
1	Cl	ND	0	72
2	BF_4	99	70	24
3	SbF_6	99	74	24
4	PF_6	ND	ND[c]	72
5	OTf	93	79	24

[a] All reactions were carried out in acetone at room temperature.
[b] The yields refer to isolated, purified products.
[c] Not determined (ND).

Our work on the Diels–Alder reaction of amino dienes had shown that highly dissociated counter ions yielded products with the highest ee's. The same trend was observed for the cycloaddition with 1,2-dihydropyridine, shown in Eq. (3) (Table 2). The reactions were performed at room temperature in acetone, since this solvent gave the best results for the cycloaddition. The complex with the chloride counter ion (**11a**) was an ineffective catalyst (entry 1). Only a small amount of the product had formed after 3 days at room temperature, and, even then, the product was racemic. For reasons that are not clear, the complex having PF_6^- as the counter ion was also a poor catalyst for this cycloaddition. Among the fluorinated counter ions, the complex having SbF_6^- (**11c**) was the best catalyst for the reaction, albeit by only a small margin over BF_4^- (entries 2 and 3). The superior enantioselectivity observed for the antimonate counter ion parallels the reactivity profile observed for different salens for the Diels–Alder reactions of acyclic amino dienes.[8a] The complex having trifluoromethanesulfonate counter ion afforded the highest enantioselectivity.

In order to assess the influence of the salen scaffold structure on enantioselectivity, we prepared and evaluated the effectiveness of BINAM derived Cr(III) complexes in

Table 3. Effectiveness of other salen complexes



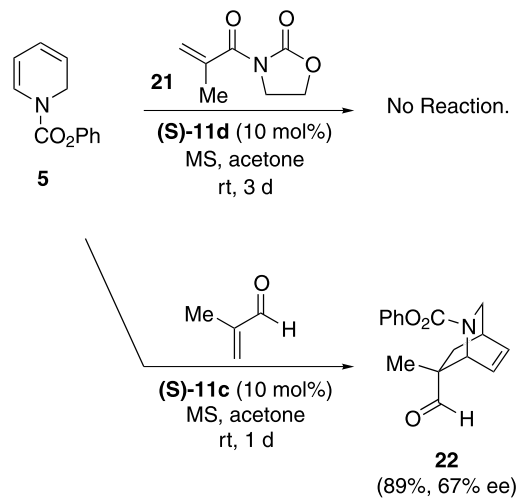
Entry	Cr(III)[a]	R_1	R_2	Yield (%)[b]	Product	ee (%)	Rxn time (h)
1	(*R*-**11**	*t*Bu	*t*Bu	99	ent-**13**	85	24
2	(*R*)-**14**	Me	*t*Bu	99	ent-**13**	70	24
3	(*R*)-**15**	OMe	*t*Bu	93	ent-**13**	81	48
4	(*R*)-**16**	Cl	Cl	54	ND[c]	ND[c]	72
5	(*S*)-**17**[d]	Me	ad[e]	86	**13**	65	24
6	(*S*)-**18**[d]	*t*Bu	SPh	61	ent-**13**	23	72
7	(*S*)-**19**			96	**13**	28	24
8	(*S*)-**20**			78	**13**	9	48

[a] All reactions were carried out in acetone at room temperature.
[b] The yields refer to isolated, purified products.
[c] Not determined (ND).
[d] The counter ion for entries 5–8 was TfO^-.
[e] ad=adamantyl.

which the salicylaldehyde component, especially substituents R_1 and R_2, are varied (Table 3). Complex **14**, with the sterically less demanding methyl group instead of the *tert*-butyl group for position R_1, gave lower enantioselectivity in the Diels–Alder reaction (entries 1 and 2). On the other hand, the analogous complex in which the *tert*-butyl group is replaced with a methoxy, gave only slightly lower enantioselectivity than the *tert*-butyl complex (entry 3). The observed decrease in reaction rate with complex **15** can be understood if the electron donating property of the methoxy substituent reduces the Lewis acidity of the metal. Curiously, rather than being more reactive, dichloro-substituted complex **16** was a poor catalyst for the cycloaddition. The reaction was quite slow, and even after 3 days considerable starting material remained. The slow turnover for this catalyst may be attributable to a strong interaction between the metal and the reaction product, which would diminish the reaction rate as product concentration increased. The complex having methyl/adamantly substituents (**17**, entry 5) was comparable in efficacy to the methyl/*tert*-butyl complex (**14**). The phenyl sulfide containing complex, **18**, provided a surprise. Although a poor catalyst, in terms of product yield and ee, complex **18** favoured the formation of ent-**13** as the major product, opposite of what one might have expected based on entries 1–5. The lower reactivity of **18** can be attributed to the presence of the thiophenyl group, but further studies are needed to understand the factors responsible for enantioselectivity reversal.

In addition to the salicylaldehyde derived BINAM complexes, two isomeric hydroxynaphthaldehyde (i.e. benzosalicylaldehyde) derived complexes, **19** and **20**, were also prepared. Both of these complexes catalysed the desired cycloaddition, but with poor enantioselectivity. The results in Table 3 highlight the importance of large aliphatic substituents on the effectiveness of the BINAM salen catalysts for the Diels–Alder reaction with dihydropyridine.

In order to broaden the utility of this enantioselective Diels–Alder reaction, we examined the cycloaddition reactions with two other dienophiles, methacrolyloxazolidinone (**21**) and methacrolein, both possessing substituent at the α-position (Scheme 3). Unfortunately, dienophile **21** was completely unreactive, even under the optimised conditions. On the other hand, the cycloaddition with methacrolein proceeded well and afforded the cycloadduct (**22**) with higher ee than under the conditions



Scheme 3.

originally used (vide supra). The poor reactivity of **21**, while disappointing, is not surprising given the combined steric effects of the methyl group and oxazolidinone unit.

In summary, we have described the first catalysed enantioselective Diels–Alder reactions of 1,2-dihydropyridine. A family of BINAM based Cr(III) salen complexes were developed specifically for these cycloadditions. Under optimised reaction conditions, the cycloaddition between the dihydropyridine and *N*-acryloyloxazolidinone (**12**) proceeded in excellent yield (99%) and good ee (up to 85%). The BINAM catalysts described here should prove useful not only for other Diels–Alder reactions but also for other asymmetric processes.[15]

3. Experimental

3.1. General information

All reactions were carried out under a nitrogen atmosphere unless otherwise indicated. All commercial reagents were used as received from commercial suppliers unless otherwise indicated. All known compounds were prepared according to the literature. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium-benzophenone ketyl prior to use. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride. 2-Butanone was distilled from and stored over $CaSO_4$. *N*,*N*-Dimethylacetamide (DMA), tetrahydropyran (THP), and ethyl acetate (EtOAc) were stored over activated 4 Å molecular sieve and used without distillation. Acetone was stored over $CaSO_4$ and used without distillation. Reactions were monitored by thin layer chromatography (TLC) using 250 μm Whatman precoated silica gel plates. Flash column chromatography was performed over EM Science Laboratories silica gel (230–400 mesh). Proton and carbon NMR spectra were recorded on Brüker DRX-500 and 400 spectrometers. ^{1}H NMR chemical shifts are reported as δ values (ppm) relative to internal tetramethylsilane in chloroform-d or the residual proton solvent signals. Splitting patterns are designated as: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. ^{13}C NMR chemical shifts are reported as δ values (ppm) relative to $CDCl_3$ or DMSO-d. High performance liquid chromatography (HPLC) was performed using the CHIRALPAK® AD (25 cm).

3.2. General procedure for binaphthyl Schiff base[9,12a,16]

To an oven-dried round-bottom flask fitted with a magnetic stir bar and a water-jacketed condenser were added (*S*)-1,1′-binaphthyl-2,2′-diamine (1.00 g, 3.52 mmol) and 3,5-di-*tert*-butyl-salicylaldehyde (1.65 g, 7.04 mmol). The flask was charged with absolute ethanol (117 mL) and brought to reflux for 24 h. Enough water was added to the refluxing reaction mixture to ensure some precipitation, and the reaction mixture was cooled down to ambient temperature. The yellow precipitate was collected by filtration and dried in vacuo to give 1.84 g (2.57 mmol, 73%) of (*S*)-2,2′-bis(3,5-di-*tert*-butyl-2-hydroxybenzylideneamino)-1,1′-binaphthyl which was used without further purification. Spectral data matched literature values.[9n]

3.2.1. (*R*)-2,2′-Bis(3-*tert*-butyl-5-methyl-2-hydroxybenzylideneamino)-1,1′-binaphthyl. ^{1}H NMR (400 MHz, chloroform-d) δ 12.70 (br s, 2H), 8.50 (s, 2H), 8.04 (d, *J*=8.0 Hz, 2H), 7.95 (d, *J*=8.0 Hz, 2H), 7.53 (d, *J*=8.0 Hz, 2H), 7.44 (t, *J*=8.0 Hz, 2H), 7.33 (d, *J*=8.0 Hz, 2H), 7.28 (t, *J*=4.0 Hz, 2H), 6.99 (d, *J*=2 Hz, 2H), 6.77 (d, *J*=2 Hz, 2H), 2.18 (s, 6H), 1.20 (s, 18H).

3.2.2. (*R*)-2,2′-Bis(3-*tert*-butyl-5-methoxy-2-hydroxybenzylideneamino)-1,1′-binaphthyl. ^{1}H NMR (400 MHz, chloroform-d) δ 12.50 (br s, 2H), 8.52 (s, 2H), 8.05 (d, *J*=8.0 Hz, 2H), 7.96 (d, *J*=8.0 Hz, 2H), 7.55 (d, *J*=8.0 Hz, 2H), 7.45 (t, *J*=8.0 Hz, 2H), 7.34 (d, *J*=8.0 Hz, 2H), 7.30 (t, *J*=4.0 Hz, 2H), 6.85 (d, *J*=3.2 Hz, 2H), 6.45 (d, *J*=3.2 Hz, 2H), 3.68 (s, 6H), 1.20 (s, 18H).

3.2.3. (*S*)-2,2′-Bis(3-adamantyl-5-methyl-2-hydroxybenzylideneamino)-1,1′-binaphthyl. ^{1}H NMR (400 MHz, chloroform-d) δ 8.57 (s, 2H), 8.04 (d, *J*=8.8 Hz, 2H), 7.94 (d, *J*=8.0 Hz, 2H), 7.57 (d, *J*=8.0 Hz, 2H), 7.39–7.44 (m, 4H), 7.32 (t, *J*=1.2 Hz, 2H), 6.91 (d, *J*=2 Hz, 2H), 6.77 (d, *J*=1.4 Hz, 2H), 2.17 (s, 6H), 2.02 (br s, 6H), 1.88 (br s, 12H), 1.75 (br s, 12H).

3.3. General procedure for Cr(III) chloride complex

To an oven-dried round-bottom flask containing a magnetic stir bar and anhydrous $CrCl_2$ (235.97 mg, 1.92 mmol) was added a solution of (*S*)-2,2′-bis(3,5-di-*tert*-butyl-2-hydroxybenzylideneamino)-1,1′-binaphthyl (1.25 g, 1.74 mmol) in THF (50 mL). The reaction mixture was stirred for 12 h under a nitrogen atmosphere and another 12 h under air at ambient temperature (the reaction mixture was brought to reflux for 12 h in the cases of (*S*)-**5**, and (*S*)-**6**). The reaction mixture was then diluted with reagent grade diethyl ether (50 mL) and washed with saturated, aqueous NH_4Cl, brine, dried (Na_2SO_4) and concentrated in vacuo to afford 1.38 g (1.72 mmol, 99%) of (*S*)-2,2′-bis(3,5-di-*tert*-butyl-2-hydroxybenzylideneamino)-1,1′-binaphthyl chromium(III) chloride as a dark green solid which was used without further purification.

3.4. General procedure for Cr(III) trifluoromethanesulfonate complex

To an oven-dried round-bottom flask containing a magnetic stir bar and (*S*)-2,2′-bis(3,5-di-*tert*-butyl-2-hydroxybenzylideneamino)-1,1′-binaphthyl chromium(III) chloride (95.5 mg, 0.12 mmol) was added AgOTf (62.0 mg, 0.24 mmol). The flask was charged with CH_2Cl_2 (4 mL) and stirred for 12 h in the dark. The reaction mixture was filtered through a short pad of Celite® and concentrated in vacuo to afford 108.8 mg (0.12 mmol, quant.) of (*S*)-2,2′-bis(3,5-di-tert-butyl-2-hydroxybenzylideneamino)-1,1′-binaphthyl chromium(III) trifluoromethanesulfonate as a dark brown solid which was used without further purification.

3.4.1. General procedure for 7-(2-oxo-oxazolidine-3-carbonyl)-2-aza-bicyclo[2.2.2]oct-5-ene-2-carboxylic acid phenyl ester. An oven-dried round-bottom flask containing a stir bar was charged with 1,2-dihydropyridine[17] (46.5 mg, 0.23 mmol), *N*-acryloyloxazolidinone[18]

(65.0 mg, 0.46 mmol), dry powdered 4 Å molecular sieve (138.0 mg), and (*S*)-2,2′-bis(3,5-di-*tert*-butyl-2-hydroxybenzylideneamino)-1,1′-binaphthyl chromium(III) trifluoromethanesulfonate (21.0 mg, 0.023 mmol). Acetone (0.5 mL) was added to the flask and the reaction mixture was stirred for 24 h at ambient temperature. The reaction mixture was filtered through a short pad of silica gel and the pad was rinsed with ethyl acetate. The crude reaction mixture was concentrated in vacuo and then purified by flash chromatography on silica gel (50% ethyl acetate in hexanes) to give 77.9 mg (quant.) of the title compound, a light yellow foam. ^{1}H NMR (400 MHz, DMSO-d_6, 120°C) δ (7.35, J=16.0, 8.0 Hz, 2H), 7.18 (t, J=8.0 Hz, 1H), 7.13 (d, J=8.0 Hz, 2H), 6.49 (dd, J=16.0, 8.0 Hz, 1H), 6.41 (dd, J=12.0, 8.0 Hz, 1H), 5.03 (br s, 1H), 4.39 (m, 2H), 4.14 (m, 1H), 3.88 (m, 2H), 3.42 (br d, J=8.0 Hz, 1H), 3.06 (br d, J=8.0 Hz, 1H), 2.91 (br s, 1H), 2.12 (t, J=8 Hz, 1H), 1.68 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, 120°C) δ 171.3, 152.3, 151.7, 150.9, 133.6, 130.2, 128.2, 124.0, 120.7, 61.7, 46.8, 46.4, 43.1, 42.0, 29.7, 26.6; HPLC analysis (CHIRALPAK® AD, 75% *i*PrOH/hexanes, 1.0 mL/min, 254 nm; t_r (minor)=8.29, t_r (major)=12.51, 79% ee).

3.4.2. General procedure for 7-formyl-7-methyl-2-azabicyclo[2.2.2]oct-5-ene-2-carboxylic acid phenyl ester. An oven-dried round-bottom flask containing a stir bar was charged with 1,2-dihydropyridine (46.5 mg, 0.23 mmol), dry powdered 4 Å molecular sieve (138.0 mg), (*S*)-2,2′-bis(3,5-di-*tert*-butyl-2-hydroxybenzylideneamino)-1,1′-binaphthyl chromium(III) SbF_6 (23.0 mg, 0.023 mmol), and acetone (0.5 mL). Methacrolein (38 μL, 0.46 mmol) was added to the flask and the reaction mixture was stirred for 24 h at ambient temperature. The reaction mixture was filtered through a short pad of silica gel and the pad was rinsed with ethyl acetate. The crude reaction mixture was concentrated in vacuo and then purified by flash chromatography on silica gel (20% ethyl acetate in hexanes) to give 55.5 mg (0.20 mmol, 89%) of the product as a light yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6, 120°C) δ (???, J=16.0, 8.0 Hz, 2H), 7.19 (t, J=8.0 Hz, 1H), 7.12 (d, J=8.0 Hz, 2H), 6.47 (m, 2H), 4.76 (br d, J=4 Hz, 1H), 3.45 (br d, J=8.0 Hz, 1H), 3.06 (br d, J=8.0 Hz, 1H), 2.92 (m, 1H), 2.09 (dt, J=12.0, 2.8 Hz, 1H), 1.38 (dd, J=12.0, 4.0 Hz, 1H), 1.25 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, 120°C) δ 202.3, 150.9, 134.8, 130.7, 128.3, 124.1, 120.6, 52.1, 50.7, 46.9, 31.3, 30.1, 20.1; enantiomeric excess of the title compound was determined to be 67% by the Mosher ester analysis of the corresponding alcohol prepared by $NaBH_4$ reduction.

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