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Enantioselective 1,6-Michael addition of anthrone to 3-methyl-4-nitro-5-alkenyl-isoxazoles catalyzed by bifunctional thiourea-tertiary amines

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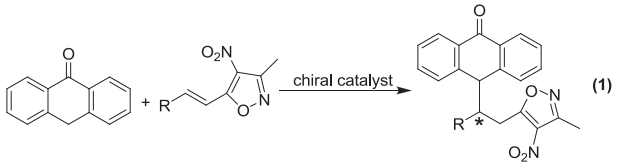
ABSTRACT

A simple and efficient method for the enantioselective 1,6-Michael addition reaction of anthrone to a series of 3-methyl-4-nitro-5-alkenyl-isoxazoles with a bifunctional thiourea-tertiary amine as catalyst is described. This transformation proceeds smoothly with 10 mol % catalyst and provides a series of Michael adducts bearing 3-methyl-4-nitro-isoxazole and anthrone units with good to high enantioselectivities (up to 96% ee) and in very high yields (up to 99%).

1. Introduction

Michael addition reaction of carbon-centered nucleophiles to various Michael acceptors represents a direct and powerful method for the C–C bond formation and has found widespread application in organic synthesis. Consequently, considerable effort has been devoted to the development of enantioselective versions of this transformation.[1] Despite the fact that remarkable advances have been made in the catalytic asymmetric Michael reaction,[1] the development of new Michael reaction for efficient construction of various new compounds is an important goal of research carried out in both academic and industrial laboratories. In this area, as for the Michael donor, various carbon-centered nucleophiles including aldehydes and ketones,[2] malonate esters,[3] ketoesters,[4] and 1,3-diketones[5] have been extensively reported, by comparison, little progress has been made in the development of using anthrone as a nucleophile for the Michael addition reaction.[6,7] In parallel, as for the Michael acceptor, in contrast to often-used electrophiles, such as nitro olefins, α,β-unsaturated aldehydes, α,β-unsaturated ketones, and maleimides,[1,8] the number of methods that involved 3-methyl-4-nitro-5-alkenyl-isoxazoles as Michael acceptor is rather limited.[9] Therefore, it is easy to understand why there is no report about the Michael reaction of anthrone with 3-methyl-4-nitro-5-alkenyl-isoxazoles leading to chiral products bearing 3-methyl-4-nitro-isoxazole units so far. This fact encouraged us to develop the protocol for the enantioselective conjugated addition of anthrone to 3-methyl-4-nitro-5-alkenyl-isoxazoles [Eq. 1].



(1)

Anthrones are important compounds in natural products and in medicinal chemistry.[10] From the chemical standpoint, anthrones and their enol tautomers, the 9-anthrols, play a central role in the chemistry of anthracenes, because by oxidation of the central ring they afford 9,10-anthraquinones, extremely valuable compounds as pigments or anticancer agents.[11] On the other hand, the reduction of anthrones provide anthracenes, useful in the preparation of dyestuffs and of optoelectronic materials.[12] And it also has been found that some anthrone derivatives may display various interesting biological properties[13] and possess some potent and

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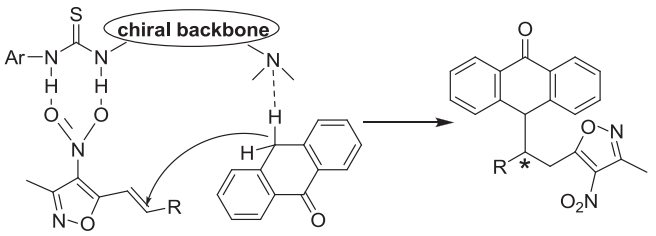
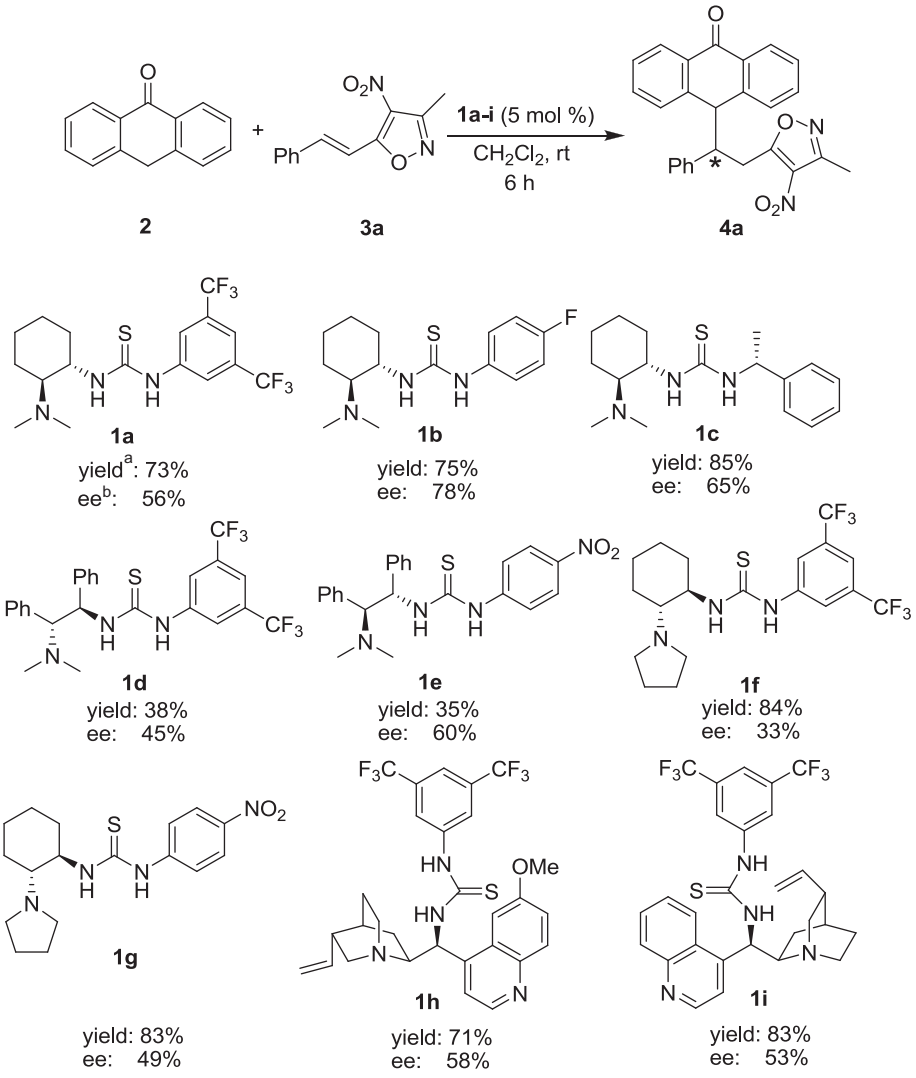
selective antitumor activity.[14] We also noted that 3-methyl-4-nitro-5-alkenyl-isoxazoles were able to be accepted as cinnamate equivalents that show high reactivity toward stabilized nucleophiles. However, only a few reports by Adamo and co-workers have addressed the Michael addition reaction with 3-methyl-4-nitro-5-alkenyl-isoxazoles as electrophiles.[9] Furthermore, over the past several years, numerous reports on the application of related tertiary amine thiourea frameworks as bifunctional catalysts in a wide variety of enantioselective catalytic reactions have been published.[15] Therefore, as a continuation of our efforts on the asymmetric organocatalysis,[7a,16] we became interested in the possible use of chiral bifunctional thiourea-tertiary amine catalysts for the enantioselective Michael addition of anthrone to various 3-methyl-4-nitro-5-alkenyl-isoxazoles. On the basis of our previous study, we thought that the tertiary amine group of the catalyst would function as a general base catalyst and activate the nucleophile (anthrone) while the thiourea group would simultaneously enable to activate the electrophile (3-methyl-4-nitro-5-alkenyl-isoxazoles) by double hydrogen bonding (Scheme 1), resulting in the Michael addition of nucleophile to electrophile. Herein, we hope to report the first example of a bifunctional thiourea-tertiary amine-catalyzed enantioselective 1,6-Michael addition of anthrone to various 3-methyl-4-nitro-5-alkenyl-isoxazoles, providing the corresponding adducts with good to high enantioselectivities (up to 96% ee) and in very high yields (up to 99%).



Scheme 1. Designation of the conjugated addition reaction catalyzed by chiral bifunctional thiourea-tertiary amine catalysts.

2. Results and discussion

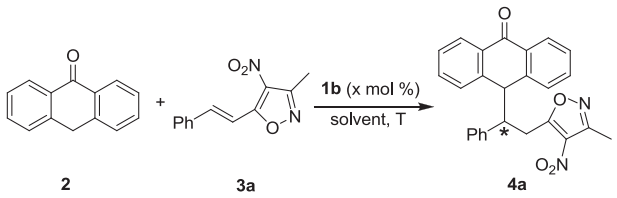
The reaction between anthrone (**2**) and (*E*)-3-methyl-4-nitro-5-styrylisoxazole (**3a**)[17] was chosen as a model reaction for the catalysts study (Scheme 2). Takemoto's thiourea catalyst **1a**[3a,3c] and some other analogous bifunctional thiourea-tertiary amine catalysts **1b**–**i** with various chiral scaffolds, which have been previously reported by some chemists,[18] were screened in the model reaction with CH_2Cl_2 as solvent at room temperature for 6 h. All of the results were summarized in Scheme 2, and we found that the desired Michael adduct **4a** could be obtained in poor to good yields with acceptable enantioselectivities with 5 mol% catalyst. By comparison, bifunctional thiourea-tertiary amine catalyst **1b** proved to be the most effective catalyst in view of the reactivity (75% yield) and enantioselectivity (78% ee).



Scheme 2. Model reaction and catalysts study. Reaction conditions: **2** (0.20 mmol), **3a** (0.24 mmol), and chiral catalysts **1** (5 mol%) were stirred in CH_2Cl_2 (1.0 mL) at rt for 6 h. [a]Isolated yield. [b]Determined by chiral HPLC analysis.

Having identified the best catalyst (**1b**), optimization of reaction conditions was further investigated to further improve the Michael reaction efficiency (Table 1). Screening of solvents revealed that the reaction proceeded well in various solvents (Table 1, entries 1–9). Using CH_3CN as solvent, compound **4a** was obtained smoothly in high to 94% yield but was racemic (Table 1, entry 3). Among the solvent surveyed, the best result was achieved in CH_2Cl_2 in view of the yield and ee value (Table 1, entry 6). We then turned our attention to the survey of catalyst loading (Table 1, entries 10 and 11). The product **4a** could be obtained in 83% yield and the ee value without significant variation with 10 mol % **1b** (Table 1, entry 10 vs 6). However, with catalyst loading increased to 20 mol %, the product **4a** also was achieved in 84% yield but the enantioselectivity decreased to 69% (Table 1, entry 11). Afterward, optimization of the ratio of two substrates with 5 mol % catalyst in CH_2Cl_2 was carried out (Table 1, entries 12 and 13). It was observed that product **4a** was able to be achieved with 78% ee in 99% yield using only a twofold excess of anthrone relative to reagent **3a** (Table 1, entry 13). In addition, it was noted that lowering the reaction temperature resulted in a further improvement of the enantioselectivity (87%) without sacrificing the yield although with an extension of the reaction time (12 h, Table 1, entry 14). Moreover, when the same reaction was performed at −20 °C with 10 mol % **1b** as catalyst, the desired adduct **4a** was obtained with high to 96% ee in quantitative yield with further extension of the reaction time (24 h, Table 1, entry 15). However, there were significant effects on the yield (29%) and enantioselectivity (57%) when the reaction temperature was further lowered to −40 °C (Table 1, entry 16). Thus, the above studies provided the optimal reaction conditions: addition of anthrone (**2**) 0.4 mmol to a solution of 3-methyl-4-nitro-5-styrylisoxazole (**3a**) 0.2 mmol in CH_2Cl_2 in the presence of 10 mol % **1b** at −20 °C for 24 h.

Table 1
Optimization of the reaction conditions[a]

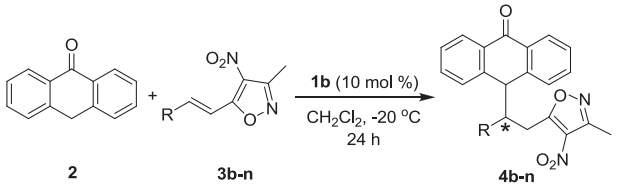


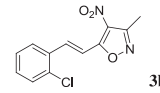
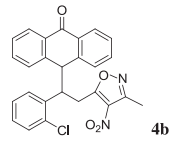
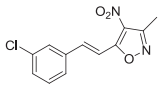
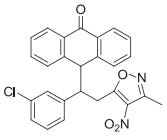
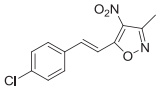
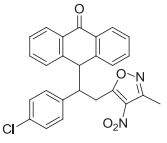
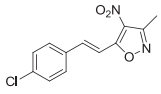
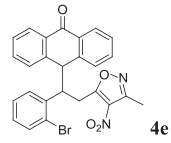
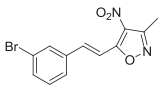
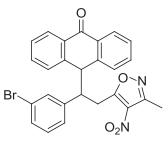
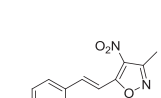
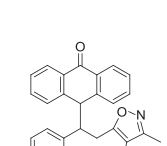
Entry	Solvent	*x*	*T* (°C)	Yield[b] (%)	ee[c] (%)
1	THF	5	rt	53	65
2	Toluene	5	rt	54	65
3	CH_3CN	5	rt	94	1
4	$CHCl_3$	5	rt	73	49
5	DCE	5	rt	78	63
6	CH_2Cl_2	5	rt	75	78
7	CCl_4	5	rt	75	73
8	Et_2O	5	rt	48	48
9	EtOAc	5	rt	59	75
10	CH_2Cl_2	10	rt	83	76
11	CH_2Cl_2	20	rt	84	69
12	CH_2Cl_2	5	rt	86	77[d]
13	CH_2Cl_2	5	rt	99	78[e]
14	CH_2Cl_2	5	0	99	87[e,f]
15	CH_2Cl_2	10	−20	99	96[e,g]
16	CH_2Cl_2	10	−40	29	57[e,g]

[a] Reaction conditions: unless otherwise noted, **2** (0.20 mmol), **3a** (0.24 mmol), and catalyst **1b** (5 mol %) were stirred in the specified solvent (1.0 mL) at rt for 6 h.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] Compounds **2** (0.20 mmol) and **3a** (0.40 mmol) were used.
[e] Compounds **2** (0.40 mmol) and **3a** (0.20 mmol) were used.
[f] Run for 12 h.
[g] Run for 24 h.

With these reaction parameters defined, a wide range of 3-methyl-4-nitro-5-alkenyl-isoxazoles were prepared[17] and surveyed to determine the scope and limitations of the methodology. As shown in Table 2, the reaction scope generally proved to be broad with respect to Michael acceptor 3-methyl-4-nitro-5-styrylisoxazoles **3b**–**m**. We found that various electron-rich and -poor reagents **3** with different substitution patterns on the phenyl ring were equally good substrates (Table 2, entries 1–9). However, there was an obvious drop in yield when electron-donating groups were attached on the Michael acceptor, contrasting with electron-withdrawing groups were attached on the Michael acceptor (Table 2, entries 7–9 vs entries 1–6). In addition, compounds **3k**–**l** containing heterocyclic ring were also excellent substrates and gave their corresponding products **4k**–**l** in very high yield with enantioselectivity (Table 2, entries 10 and 11). Particularly, we also verified that the more sterically demanding substrate **3m** was viable substrate for this asymmetric transformation, just with good enantioselectivity in moderate yield (Table 2, entry 12). More interestingly, the method is compatible with isoxazole derivative **3n**,

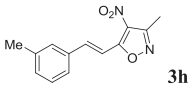
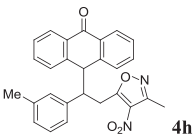
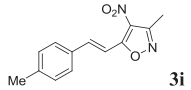
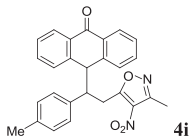
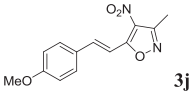
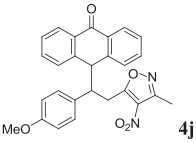
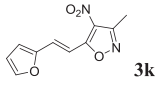
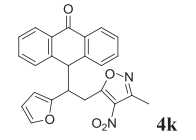
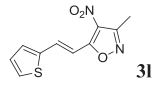
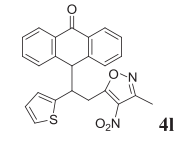
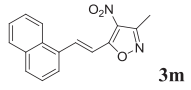
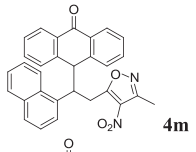
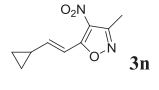
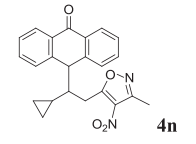
Table 2
Asymmetric Michael addition of anthrone to various 3-methyl-4-nitro-5-alkenyl-isoxazoles[a]



Entry	3	4	Yield[b] (%)	ee[c] (%)
1	 3b	 4b	87	(−)84
2	 3c	 4c	99	(+)89
3	 3d	 4d	99	(+)89
4	 3e	 4e	99	(−)94
5	 3f	 4f	99	(+)94
6	 3g	 4g	82	(+)92

(*continued on next page*)

Table 2 (*continued*)

Entry	3	4	Yield[b] (%)	ee[c] (%)
7	 **3h**	 **4h**	73	(+)95
8	 **3i**	 **4i**	73	(+)93
9	 **3j**	 **4j**	69	(+)92
10	 **3k**	 **4k**	99	(+)96
11	 **3l**	 **4l**	93	(+)94
12	 **3m**	 **4m**	57	(−)72
13	 **3n**	 **4n**	85	(+)93

[a] Reaction conditions: **2** (0.40 mmol), **3a** (0.20 mmol), and catalyst **1b** (10 mol %) were stirred in the CH_2Cl_2 (1.0 mL) at −20 °C for 24 h.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.

in which R is represented by a cyclopropyl, affording the corresponding product **4n** in 85% yield with 93% ee (Table 2, entry 13).

3. Conclusion

In conclusion, we have developed an organocatalytic methodology for the enantioselective 1,6-Michael addition of anthrone to various 3-methyl-4-nitro-5-alkenyl-isoxazoles in the presence of a chiral bifunctional thiourea-tertiary amine. This highly enantioselective protocol gives a family of Michael adducts bearing an anthrone as well as a 3-methyl-4-nitro-isoxazole ring units in very high yields with good to high enantioselectivites, but a harsh temperature (−20 °C) is needed. These studies carried out in this report further demonstrate that anthrone is a highly reactive carbon nucleophile[6,7] as well as 3-methyl-4-nitro-5-alkenyl-isoxazole is a kind of promising Michael acceptor in organic synthesis.[9] This methodology provides useful procedure for the synthesis of chiral anthrone derivatives. Certainly the possibility of employing this type of Michael acceptor for some other enantioselective addition is under investigation in our laboratory.

4. Experimental section

4.1. General information

Reagents and starting materials obtained from commercial suppliers were used without further purification unless otherwise stated. All reactions were conducted in a closed system with an atmosphere of air and were monitored by TLC. ^{1}H NMR and ^{13}C NMR spectra were performed on a Brucker-300 MHz spectrometer for products dissolved by $CDCl_3$ with tetramethylsilane (TMS) as an internal standard. Data for ^{1}H are reported as follows: chemical shift (in ppm) and multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet). Splitting patterns that could not be clearly distinguished are designated as multiplets (m). Data for ^{13}C NMR are reported in parts per million. High-resolution mass spectral analyses (HRMS) were measured using ESI ionization. High performance liquid chromatography (HPLC) analysis was performed on chiral columns. Optical rotations were measured in the solvent indicated. Melting points were recorded on a Buchi Melting Point B-545 unit.

4.2. General procedure for the enantioselective addition of anthrone to 3-methyl-4-nitro-5-alkenyl-isoxazoles

A solution of 3-methyl-4-nitro-5-alkenyl-isoxazoles **3** (0.2 mmol) and bifunctional thiourea catalyst **1b** (0.02 mmol) in CH_2Cl_2 (1.0 mL) was cooled to −20 °C, and then anthrone **2** (0.4 mmol) was added. After being stirred for 24 h at the same temperature, the reaction mixture was subjected to flash column chromatography on silica gel (petroleum ether/ethyl acetate=10:1) to furnish the corresponding products **4**.

*4.2.1. (+)-10-(2-(3-Methyl-4-nitroisoxazol-5-yl)-1-phenylethyl)anthracen-9(10H)-one (**4a**).* White solid, yield 99%; 96% ee, $[\alpha]_D^{20}$ +21.5 (*c* 1.0, $CHCl_3$); mp: 127–132 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.43 (s, 3H), 3.55–3.59 (m, 2H), 3.83–3.88 (m, 1H), 4.55 (d, *J*=3.9 Hz, 1H), 6.31 (d, *J*=7.2 Hz, 2H), 6.98 (t, *J*=7.5 Hz, 2H), 7.13 (t, *J*=7.5 Hz, 1H), 7.22 (d, *J*=7.5 Hz, 1H), 7.40–7.47 (m, 1H), 7.49–7.56 (m, 3H), 7.60–7.65 (m, 1H), 8.05 (d, *J*=7.8 Hz, 1H), 8.10 (d, *J*=7.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.5, 30.1, 49.6, 52.8, 126.9, 127.2, 127.7, 127.8, 127.9, 128.0, 128.4, 128.5, 128.6, 132.2, 132.3, 133.4, 133.9, 136.2, 140.6, 142.0, 155.5, 172.9, 183.7. HRMS (ESI) calcd for $C_{26}H_{20}N_2NaO_4$ $[M+Na]^+$: 447.1315; found: 447.1306. HPLC conditions: Chiralcel OD-H column, *i*-PrOH/hexane 20:80, flow rate 1.0 mL/min, UV detection at 254 nm, t_R (major)=11.91 min, t_R (minor)=13.18 min.

*4.2.2. (−)-10-(1-(2-Chlorophenyl)-2-(3-methyl-4-nitroisoxazol-5-yl) ethyl)anthracen-9(10H)-one (**4b**).* White solid, yield 87%; 84% ee, $[\alpha]_D^{20}$ −12.5 (*c* 1.0, $CHCl_3$); mp: 127–133 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.36 (s, 3H), 3.10–3.22 (m, 2H), 4.55–4.60 (m, 1H), 4.70 (d, *J*=3.9 Hz, 1H), 6.50 (d, *J*=7.8 Hz, 1H), 6.60 (d, *J*=6.9 Hz, 1H), 7.04 (t, *J*=7.5 Hz, 1H), 7.20 (t, *J*=7.5 Hz, 1H), 7.33–7.38 (m, 2H), 7.44–7.54 (m, 2H), 7.65–7.70 (m, 1H), 7.77 (d, *J*=6.9 Hz, 1H), 8.23 (t, *J*=7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.4, 27.0, 46.9, 47.4, 126.3, 127.2, 127.4, 127.9, 128.0, 128.3, 129.0, 129.5, 129.9, 130.0, 131.7, 133.1, 133.4, 133.5, 134.9, 135.4, 139.3, 142.0, 155.4, 172.3, 184.3. HRMS (ESI) calcd for $C_{26}H_{19}ClN_2NaO_4$ $[M+Na]^+$: 481.0926; found: 481.0920. HPLC conditions: Chiralcel OD-H column, *i*-PrOH/hexane 20:80, flow rate 1.0 mL/min, UV detection at 254 nm, t_R (major)=19.37 min, t_R (minor)=11.97 min.

*4.2.3. (+)-10-(1-(3-Chlorophenyl)-2-(3-methyl-4-nitroisoxazol-5-yl) ethyl)anthracen-9(10H)-one (**4c**).* Yellow solid, yield 99%; 89% ee, $[\alpha]_D^{20}$ +22.4 (*c* 1.0, $CHCl_3$); mp: 122–131 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.44 (s, 3H), 3.47–3.56 (m, 2H), 3.78–3.83 (m, 1H), 4.52

(d, *J*=3.9 Hz, 1H), 6.16 (d, *J*=7.8 Hz, 1H), 6.25 (t, *J*=1.5 Hz, 1H), 6.90 (t, *J*=7.8 Hz, 1H), 7.10 (d, *J*=7.5 Hz, 1H), 7.23 (d, *J*=7.5 Hz, 1H), 7.42–7.58 (m, 4H), 7.61–7.66 (m, 1H), 8.07 (d, *J*=7.8 Hz, 1H), 8.12 (d, *J*=7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.5, 30.0, 49.3, 52.4, 126.6, 127.0, 127.3, 127.8, 127.9, 128.1, 128.4, 129.0, 129.1, 132.4, 132.5, 133.2, 133.8, 133.9, 138.1, 140.0, 141.6, 155.6, 172.4, 183.4. HRMS (ESI) calcd for $C_{26}H_{19}ClN_2NaO_4$ $[M+Na]^+$: 481.0926; found: 481.0919. HPLC conditions: Chiralcel OD-H column, *i*-PrOH/hexane 20:80, flow rate 1.0 mL/min, UV detection at 254 nm, t_R (major)=15.09 min, t_R (minor)=17.99 min.

*4.2.4. (+)-10-(1-(4-Chlorophenyl)-2-(3-methyl-4-nitroisoxazol-5-yl) ethyl)anthracen-9(10H)-one (**4d**).* Yellow solid, yield 99%, 89% ee, $[\alpha]_D^{20}$ +34.2 (*c* 1.0, $CHCl_3$); mp: 147–154 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.43 (s, 3H), 3.53–3.56 (m, 2H), 3.80–3.87 (m, 1H), 4.52 (d, *J*=3.9 Hz, 1H), 6.24 (d, *J*=8.4 Hz, 2H), 6.96 (d, *J*=8.4 Hz, 2H), 7.24 (d, *J*=7.5 Hz, 1H), 7.42–7.58 (m, 4H), 7.61–7.66 (m, 1H), 8.07 (d, *J*=7.8 Hz, 1H), 8.13 (d, *J*=7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.5, 30.1, 49.3, 52.2, 127.1, 127.3, 127.8, 128.0, 128.1, 128.4, 128.5, 129.8, 132.3, 132.5, 133.2, 133.7, 133.8, 134.7, 140.2, 141.6, 155.5, 172.5, 183.5. HRMS (ESI) calcd for $C_{26}H_{19}ClN_2NaO_4$ $[M+Na]^+$: 481.0926; found: 481.0912. HPLC conditions: Chiralcel OD-H column, *i*-PrOH/hexane 20:80, flow rate 1.0 mL/min, UV detection at 254 nm, t_R (major)=13.78 min, t_R (minor)=19.56 min.

*4.2.5. (−)-10-(1-(2-Bromophenyl)-2-(3-methyl-4-nitroisoxazol-5-yl) ethyl)anthracen-9(10H)-one (**4e**).* Yellow solid, yield 99%, 94% ee, $[\alpha]_D^{20}$ −22.5 (*c* 1.0, $CHCl_3$); mp: 131–137 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.35 (s, 3H), 3.08–3.20 (m, 2H), 4.55–4.59 (m, 1H), 4.73 (d, *J*=3.9 Hz, 1H), 6.47–6.50 (m, 1H), 6.54–6.56 (d, *J*=7.5 Hz, 1H), 7.06–7.15 (m, 2H), 7.34 (t, *J*=7.5 Hz, 1H), 7.45–7.58 (m, 3H), 7.66–7.71 (t, *J*=7.5 Hz, 1H), 7.84 (d, *J*=7.2, 1H), 8.24 (t, *J*=8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.5, 27.1, 46.9, 50.0, 126.9, 127.2, 127.4, 127.9, 128.0, 128.2, 129.3, 129.7, 130.1, 131.6, 133.2, 133.4, 133.5, 136.9, 139.0, 142.1, 155.4, 172.3, 184.3. HRMS (ESI) calcd for $C_{26}H_{19}BrN_2NaO_4$ $[M+Na]^+$: 525.0420; found: 525.0412. HPLC conditions: Chiralcel OD-H column, *i*-PrOH/hexane 20:80, flow rate 1.0 mL/min, UV detection at 254 nm, t_R (major)=16.10 min, t_R (minor)=10.33 min.

*4.2.6. (+)-10-(1-(3-Bromophenyl)-2-(3-methyl-4-nitroisoxazol-5-yl) ethyl)anthracen-9(10H)-one (**4f**).* Yellow solid, yield 99%, 94% ee, $[\alpha]_D^{20}$ +23.2 (*c* 1.0, $CHCl_3$); mp: 121–126 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.45 (s, 3H), 3.52–3.56 (m, 2H), 3.78–3.83 (m, 1H), 4.53 (d, *J*=3.9 Hz, 1H), 6.21 (d, *J*=7.5 Hz, 1H), 6.40 (s, 1H), 6.85–6.87 (m, 1H), 7.22–7.28 (m, 2H), 7.46–7.57 (m, 4H), 7.64–7.65 (m, 1H), 8.07–8.15 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.5, 29.9, 49.3, 52.4, 122.0, 127.0, 127.2, 127.9, 128.1, 128.3, 128.4, 129.3, 130.8, 131.9, 132.3, 132.5, 133.2, 133.9, 138.4, 140.0, 141.5, 155.6, 172.4, 183.4. HRMS (ESI) calcd for $C_{26}H_{19}BrN_2NaO_4$ $[M+Na]^+$: 525.0420; found: 525.0418. HPLC conditions: Chiralcel OD-H column, *i*-PrOH/hexane 20:80, flow rate 1.0 mL/min, UV detection at 254 nm, t_R (major)=11.69 min, t_R (minor)=13.54 min.

*4.2.7. (+)-10-(1-(4-Bromophenyl)-2-(3-methyl-4-nitroisoxazol-5-yl) ethyl)anthracen-9(10H)-one (**4g**).* Yellow solid, yield 82%, 92% ee, $[\alpha]_D^{20}$ +32.5 (*c* 1.0, $CHCl_3$); mp: 152–158 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.43 (s, 3H), 3.51–3.55 (m, 2H), 3.79–3.86 (m, 1H), 4.52 (d, *J*=3.9 Hz, 1H), 6.21 (d, *J*=8.4 Hz, 2H), 7.12 (d, *J*=8.4 Hz, 2H), 7.22 (d, *J*=7.5 Hz, 1H), 7.43–7.58 (m, 4H), 7.61–7.66 (m, 1H), 8.09 (d, *J*=7.5 Hz, 1H), 8.14 (d, *J*=7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.5 30.0, 49.3, 52.3, 121.9, 127.1, 127.4, 127.9, 128.0, 128.3, 128.5, 130.2, 131.1, 132.4, 132.5, 133.2, 133.8, 135.3, 140.3, 141.6, 155.6, 172.5, 183.6. HRMS (ESI) calcd for $C_{26}H_{19}BrN_2NaO_4$ $[M+Na]^+$: 525.0420; found: 525.0414. HPLC conditions: Chiralcel OD-H column, *i*-PrOH/hexane 20:80, flow rate 1.0 mL/min, UV detection at 254 nm, t_R (major)=10.51 min, t_R (minor)=13.41 min.

*4.2.8. (+)-10-(2-(3-Methyl-4-nitroisoxazol-5-yl)-1-m-tolylethyl)anthracen-9(10H)-one (**4h**).* Yellow solid, yield 73%, 95% ee, $[\alpha]_D^{20}$ +19.8 (*c* 1.0, $CHCl_3$); mp: 158–161 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.07 (s, 3H), 3.43 (s, 3H), 3.51–3.55 (m, 2H), 3.79–3.84 (m, 1H), 4.52 (d, *J*=3.9 Hz, 1H), 6.07 (s, 1H), 6.11 (d, *J*=7.5 Hz, 1H), 6.83–6.92 (m, 2H), 7.20 (d, *J*=7.5 Hz, 1H), 7.42–7.53 (m, 4H), 7.58–7.65(m, 1H), 8.05 (d, *J*=7.8 Hz, 1H), 8.11 (d, *J*=7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.5, 21.1, 29.9, 49.5, 52.6, 125.5, 126.8, 127.0, 127.6, 127.7, 127.8, 128.3, 128.4, 128.6, 129.5, 132.1, 132.2, 133.4, 133.9, 135.9, 137.4, 140.7, 142.0, 155.5, 173.0, 183.6. HRMS (ESI) calcd for $C_{27}H_{22}N_2NaO_4$ $[M+Na]^+$: 461.1472; found: 461.1466. HPLC conditions: Chiralcel OD-H column, *i*-PrOH/hexane 20:80, flow rate 1.0 mL/min, UV detection at 254 nm, t_R (major)=7.96 min, t_R (minor)=9.09 min.

*4.2.9. (+)-10-(2-(3-Methyl-4-nitroisoxazol-5-yl)-1-p-tolylethyl)anthracen-9(10H)-one (**4i**).* Yellow solid, yield 73%, 93% ee, $[\alpha]_D^{20}$ +32.2 (*c* 1.0, $CHCl_3$); mp: 143–149 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.22 (s, 3H), 2.41 (s, 3H), 3.45–3.58 (m, 2H), 3.80–3.86 (m, 1H), 4.52 (d, *J*=3.9 Hz, 1H), 6.23 (d, *J*=8.1 Hz, 2H), 6.80 (d, *J*=7.8 Hz, 2H), 7.18 (d, *J*=7.2 Hz, 1H), 7.42–7.54 (m, 4H), 7.60–7.65 (m, 1H), 8.07 (d, *J*=7.8 Hz, 1H), 8.11 (d, *J*=7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.5, 21.0, 29.9, 49.6, 52.4, 126.9, 127.1, 127.6, 127.7, 128.4, 128.5, 128.6, 128.7, 132.2, 133.1, 133.2, 133.8, 137.4, 140.8, 141.9, 155.5, 173.1, 183.7. HRMS (ESI) calcd for $C_{27}H_{22}N_2NaO_4$ $[M+Na]^+$: 461.1472; found: 461.1459. HPLC conditions: Chiralcel OD-H column, *i*-PrOH/hexane 20:80, flow rate 1.0 mL/min, UV detection at 254 nm, t_R (major)=8.13 min, t_R (minor)=9.37 min.

*4.2.10. (+)-10-(1-(4-Methoxyphenyl)-2-(3-methyl-4-nitroisoxazol-5-yl)ethyl)anthracen-9(10H)-one (**4j**).* Yellow solid, yield 69%, 92% ee, $[\alpha]_D^{20}$ +25.2 (*c* 1.0, $CHCl_3$); mp: 125–131 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.42 (s, 3H), 3.48–3.58 (m, 2H), 3.69 (s, 3H), 3.78–3.82 (m, 1H), 4.51 (d, *J*=3.9 Hz, 1H), 6.21 (d, *J*=8.7 Hz, 2H), 6.50 (d, *J*=8.7 Hz, 2H), 7.21 (d, *J*=7.5 Hz, 1H), 7.40–7.55 (m, 4H), 7.60–7.65 (m, 1H), 8.06 (d, *J*=7.8 Hz, 1H), 8.12 (d, *J*=7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.6, 30.2, 49.7, 52.1, 55.1, 113.2, 126.6, 126.9, 127.1, 127.6, 127.8, 127.9, 128.5, 128.6, 129.6, 132.1, 132.2, 132.3, 133.2, 133.8, 140.7, 142.0, 155.5, 159.0, 173.1, 183.7. HRMS (ESI) calcd for $C_{27}H_{22}N_2NaO_5$ $[M+Na]^+$: 477.1421; found: 477.1408. HPLC conditions: Chiralcel OD-H column, *i*-PrOH/hexane 20:80, flow rate 1.0 mL/min, UV detection at 254 nm, t_R (major)=9.05 min, t_R (minor)=13.4 min.

*4.2.11. (+)-10-(1-(Furan-2-yl)-2-(3-methyl-4-nitroisoxazol-5-yl) ethyl)anthracen-9(10H)-one (**4k**).* Yellow solid, yield 99%, 96% ee, $[\alpha]_D^{20}$ +26.2 (*c* 1.0, $CHCl_3$); mp: 125–128 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.41 (s, 3H), 3.11–3.14 (m, 2H), 3.98–4.04 (m, 1H), 4.75 (d, *J*=3.9 Hz, 1H), 5.68 (d, *J*=3.0 Hz, 1H), 6.20–6.22 (m, 1H), 6.74–6.77 (m, 1H), 7.32 (d, *J*=1.2 Hz, 1H), 7.4–7.59 (m, 4H), 7.63–7.69 (m, 1H), 8.20–8.25 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.5, 26.9, 46.0, 47.1, 108.8, 110.5, 127.2, 127.3, 127.8, 128.5, 128.6, 132.4, 132.9, 133.0, 133.1, 140.1, 141.3, 142.1, 151.6, 155.5, 172.3, 184.1. HRMS (ESI) calcd for $C_{24}H_{18}N_2NaO_5$ $[M+Na]^+$: 437.1108; found: 437.1103. HPLC conditions: Chiralcel OD-H column, *i*-PrOH/hexane 20:80, flow rate 1.0 mL/min, UV detection at 254 nm, t_R (major)=12.77 min, t_R (minor)=9.80 min.

*4.2.12. (+)-10-(2-(3-Methyl-4-nitroisoxazol-5-yl)-1-(thiophen-2-yl) ethyl)anthracen-9(10H)-one (**4l**).* Yellow solid, yield 93%, 94% ee, $[\alpha]_D^{20}$ +22.4 (*c* 1.0, $CHCl_3$); mp: 120–126 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.45 (s, 3H), 3.48–3.54 (m, 2H), 4.13–4.18 (m, 1H), 4.61 (d, *J*=3.6 Hz, 1H), 6.01 (d, *J*=3.3 Hz, 1H), 6.70 (t, *J*=4.2 Hz, 1H), 7.05 (d,

J=4.8 Hz, 1H), 7.21 (d, *J*=7.5 Hz, 1H), 7.40–7.58 (m, 4H), 7.63–7.68 (m, 1H), 8.12 (d, *J*=7.8 Hz, 1H), 8.16 (d, *J*=7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.6, 31.5, 47.9, 49.8, 125.1, 126.6, 127.0, 127.3, 127.8, 127.9, 128.0, 128.3, 128.4, 128.5, 132.1, 132.4, 132.6, 133.3, 133.8, 139.2, 140.1, 141.5, 155.6, 172.4, 183.8. HRMS (ESI) calcd for $C_{24}H_{18}N_2NaO_4S$ $[M+Na]^+$: 453.0879; found: 453.0881. HPLC conditions: Chiralcel AS-H column, *i*-PrOH/hexane 20:80, flow rate 1.0 mL/min, UV detection at 254 nm, t_R (major)=12.72 min, t_R (minor)=10.58 min.

*4.2.13. (−)-10-(2-(3-Methyl-4-nitroisoxazol-5-yl)-1-(naphthalen-1-yl)ethyl)anthracen-9(10H)-one (**4m**).* Yellow solid, yield 57%, 72% ee, $[\alpha]_D^{20}$ −26.6 (*c* 1.0, $CHCl_3$); mp: 122–129 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.31 (s, 3H), 3.30–3.44 (m, 2H), 4.71 (d, *J*=3.9 Hz, 1H), 4.92–4.96 (m, 1H), 6.46 (d, *J*=7.5 Hz, 1H), 6.61 (d, *J*=7.2 Hz, 1H), 7.22–7.51 (m, 6H), 7.69–7.77 (m, 5H), 8.07 (d, *J*=7.2 Hz, 1H), 8.21 (d, *J*=7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.5, 28.0, 45.8, 48.3, 121.8, 124.5, 125.6, 126.0, 126.6, 127.0, 127.2, 127.8, 127.9, 128.1, 128.5, 129.2, 129.8, 131.5, 131.6, 133.0, 133.7, 140.0, 142.0, 155.4, 172.8, 184.1. HRMS (ESI) calcd for $C_{30}H_{22}N_2NaO_4$ $[M+Na]^+$: 497.1472; found: 497.1463. HPLC conditions: Chiralcel OD-H column, *i*-PrOH/hexane 30:70, flow rate 1.0 mL/min, UV detection at 254 nm, t_R (major)=14.16 min, t_R (minor)=11.38 min.

*4.2.14. (+)-10-(1-Cyclopropyl-2-(3-methyl-4-nitroisoxazol-5-yl) ethyl)anthracen-9(10H)-one (**4n**).* White solid, yield 85%, 93% ee, $[\alpha]_D^{20}$ +36.5 (*c* 1.0, $CHCl_3$); mp: 172–173 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ −0.35 to 0.32 (m, 1H), −0.15 to 0.14 (m, 1H), 0.28–0.29 (m, 1H), 0.45–0.50 (m, 2H), 1.70–1.75 (m, 1H), 2.50 (s, 3H), 2.79–2.87 (m, 1H), 3.01–3.07 (m, 1H), 4.46 (d, *J*=3.0 Hz, 1H), 7.44–7.64 (m, 6H), 8.28 (t, *J*=7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 4.9, 5.3, 11.6, 13.3, 29.9, 47.3, 53.0, 127.2, 127.3, 127.6, 127.7, 128.3, 128.6, 132.5, 132.9, 133.2, 133.6, 141.7, 142.1, 155.5, 174.1, 184.8. HRMS (ESI) calcd for $C_{23}H_{20}N_2NaO_4$ $[M+Na]^+$: 411.1315; found: 411.1301. HPLC conditions: Chiralcel OD-H column, *i*-PrOH/hexane 30:70, flow rate 1.0 mL/min, UV detection at 254 nm, t_R (major)=7.58 min, t_R (minor)=8.77 min.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.04.032.

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