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Lewis Base Assisted Brønsted Base Catalysis: Direct Asymmetric Allylic Alkylation of Indenes

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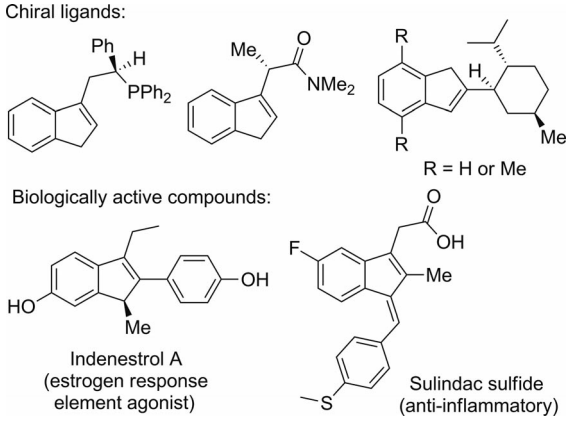
Keywords: Asymmetric catalysis / Alkaloids / Enantioselectivity / Allylation / Alkylation / Lewis bases

A direct, asymmetric allylic alkylation of indenes with Morita–Baylis–Hillman (MBH) carbonates has been developed based on a Lewis base assisted Brønsted base catalysis strategy. This process is promoted by a modified cinchona alkaloid hydroquinidine (anthraquinone-1,4-diyl) diether [$(DHQD)_2AQN$] and gives rise to multifunctional chiral indene derivatives with moderate to excellent enantioselectivities (53–95 % *ee*), albeit in low to modest yields (27–71 %).

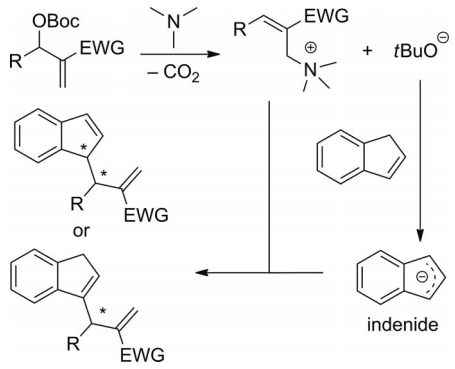
Introduction

As a privileged scaffold, indene systems are frequently found in an array of functional compounds, including biologically active molecules,[1] ligand precursors for transition metal complexes[2] (Scheme 1), and material science.[3] Although elegant constructions of diverse indene derivatives have been presented,[4] the asymmetric synthesis of chiral indenes is still rare. The limited number of available examples have focused on the use of chiral sources[5] or chiral transition metal catalysis in an indirect pathway.[6] On the other hand, it is well established that simple indene bears a relatively acidic C–H group [pK_a = 20.1 in dimethyl sulfoxide (DMSO)],[7] and undergoes facile C–C bond-forming reactions with indenides generated in situ.[8] However, the direct catalytic asymmetric modification of indenes is still an unexplored field despite the convenience of such a strategy, probably due to the requirement for stoichiometric amounts of strong base and the formation of unstabilized carbanions.[9,10]

Recently, we reported that a Lewis base assisted Brønsted base catalysis (LBABBC) strategy was quite successful in the direct asymmetric vinylogous alkylation of allyl phenyl sulfone (pK_a = 22.5 in DMSO).[11,12] We envisioned that the same catalytic pattern might be also applicable to the direct asymmetric C–C bond-forming reaction of indene compounds with comparably acidic C–H groups, as outlined in Scheme 2; thus, multifunctional chiral indene derivatives could be efficiently constructed.



Scheme 1. Some chiral ligands and drug candidates containing the indene structure.



Scheme 2. Lewis base-assisted Brønsted base catalysis strategy for direct asymmetric allylic alkylation of indene.

Results and Discussion

Based on the above considerations, simple indene **1a** was initially investigated with Morita–Baylis–Hillman (MBH) carbonate **2a** under the catalysis of 1,4-diazabicyclo[2.2.2]-

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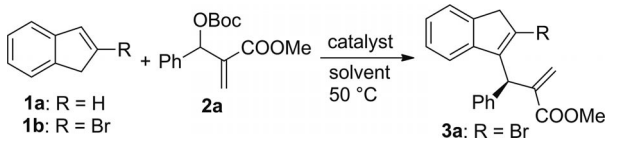
octane (DABCO) at ambient temperature. Unfortunately, although both starting materials were consumed, a mixture of complex products was obtained (Table 1, Entry 1). Nevertheless, it was pleasing to observe that a cleaner reaction occured when 2-bromoindene[13] (**1b**) was applied. The desired allylic alkylation product **3a** was isolated in moderate yield, although a few unidentified minor products were also detectable (Table 1, Entry 2). Subsequently, chiral tertiary amines were employed to induce chirality in the product. A modified cinchona alkaloid hydroquinidine (anthraquinone-1,4-diyl) diether [$(DHQD)_2AQN$] exhibited lower catalytic activity,[14] but good enantioselectivity, and a higher yield was afforded (Table 1, Entry 3). Solvent screenings were not beneficial, and poorer data were generally attained with alternative solvents (Table 1, Entries 4–6). In addition, other modified cinchona alkaloids, such as hydroquinidine 1,4-phthalazinediyl diether and hydroquinidine 2,5-diphenyl-4,6-pyrimidinediyl diether [$(DHQD)_2PHAL$ and $(DHQD)_2PYR$], also delivered inferior results (Table 1, Entries 7 and 8). More reaction parameters were then examined with $(DHQD)_2AQN$ in 1,2-dichloroethane (DCE) to improve the enantioselectivity and yield. Lowering of the reaction temperature resulted in a dramatically decreased yield (Table 1, Entry 9). Substrate concentration was explored, and it was found that better yields could be attained with higher concentrations (Table 1, Entry 10 vs. 11). The results could not be improved by using *S*-BINOL as a co-catalyst (Table 1, Entry 12). Further studies on substrate ratios were also unproductive (Table 1, Entries 13 and 14). Finally, it was found that neither yield nor enantioselectivity were affected when $(DHQD)_2AQN$ was applied at a 5 mol-% loading, although a longer reaction time was required (Table 1, Entry 15). In comparison, $(DHQ)_2AQN$ gave the product with opposite configuration but with only a moderate *ee* value (Table 1, Entry 16).

With the optimal reaction conditions in hand, we explored the substrate scope and limitations of the catalytic allylic alkylation of indenes. For 2-bromoindene (**1b**), a spectrum of MBH carbonates bearing a diverse range of aryl substituents could be well tolerated, and high enantioselectivities were generally obtained, although only low to moderate yields could be isolated due to the occurrence of side reactions (Table 2, Entries 1–7).[15] The indene product **3h** was attained with a dramatically diminished *ee* value when 2-furyl-substituted MBH carbonate was applied (Table 2, Entry 8). MBH carbonates derived from methyl vinyl ketone (MVK) showed better reactivity under the same conditions, and similar enantiocontrol was attained (Table 2, Entries 9 and 10). An MBH carbonate derived from alkanecarbaldehyde and acrylonitrile could be utilized, but only modest enantioselectivity with low yield was delivered even after prolonged reaction time (Table 2, Entry 11). On the other hand, a few substituted indene derivatives were investigated, and it was found that indene **1c**,

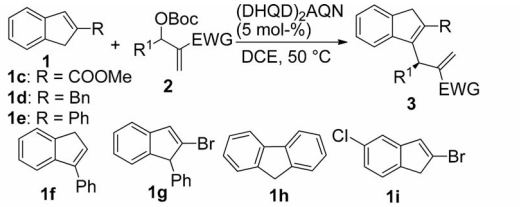
Table 1. Asymmetric allylic alkylation of indenes **1** with MBH carbonate **2a**.[a]

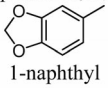
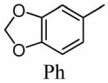


Entry	Catalyst[b]	Solvent	*t* [h]	Yield[c] [%]	*ee*[d] [%]
1[e,f]	DABCO	DCE	24	–	–
2[e]	DABCO	DCE	6	40	–
3	$(DHQD)_2AQN$	DCE	15	50	90
4	$(DHQD)_2AQN$	toluene	12	23	75
5	$(DHQD)_2AQN$	$PhCF_3$	12	43	89
6	$(DHQD)_2AQN$	CCl_4	13	trace	–
7	$(DHQD)_2PHAL$	DCE	15	38	65
8	$(DHQD)_2PYR$	DCE	15	44	72
9	$(DHQD)_2AQN$	DCE	62	36[g]	91
10	$(DHQD)_2AQN$	DCE	62	44[h]	89
11	$(DHQD)_2AQN$	DCE	24	56[i]	90
12	$(DHQD)_2AQN$	DCE	44	56[i,j]	90
13	$(DHQD)_2AQN$	DCE	12	62[i,k]	81
14	$(DHQD)_2AQN$	DCE	14	50[i,l]	88
15	$(DHQD)_2AQN$	DCE	35	58[i,m]	90
16	$(DHQ)_2AQN$	DCE	48	55[i,m]	–60

[a] Reagents and conditions: **1b** (0.1 mmol), **2a** (0.2 mmol), catalyst (0.02 mmol), solvent (0.5 mL), 50 °C. [b] DABCO: 1,4-diazabicyclo[2.2.2]octane; $(DHQD)_2AQN$: hydroquinidine (anthraquinone-1,4-diyl) diether; $(DHQD)_2PHAL$: hydroquinidine 1,4-phthalazinediyl diether; $(DHQD)_2PYR$: hydroquinidine 2,5-diphenyl-4,6-pyrimidinediyl diether; $(DHQ)_2AQN$: hydroquinine anthraquinone-1,4-diyl diether. [c] Isolated yield. [d] Determined by chiral HPLC analysis. [e] At room temp. [f] **1a** was used. [g] At 35 °C. [h] 0.1 M. [i] 0.4 M. [j] *S*-BINOL (10 mol-%) was added. [k] **1a** (2 equiv.) was used. [l] **2a** (3 equiv.) was used. [m] Catalyst (5 mol-%) was applied.

Table 2. Asymmetric allylic alkylation of indenes **1** with MBH carbonates **2**.[a]

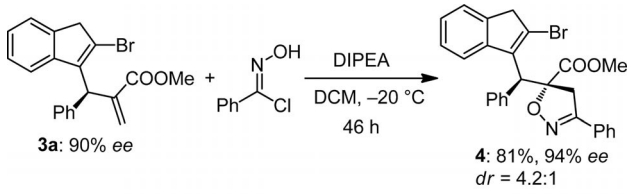


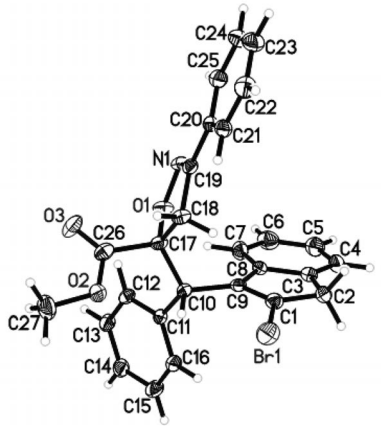
Entry	**1**	R^1	EWG	*t* [h]	**3**, yield[b] [%]	*ee*[c] [%]
1	**1b**	Ph	CO_2Me	58	**3a**, 58	90
2	**1b**	*o*-BrC_6H_4	CO_2Me	48	**3b**, 46	91
3	**1b**	*p*-ClC_6H_4	CO_2Me	84	**3c**, 43	95
4	**1b**	*m*-MeC_6H_4	CO_2Me	42	**3d**, 60	94
5	**1b**	*p*-$MeOC_6H_4$	CO_2Me	45	**3e**, 65	89
6	**1b**		CO_2Me	48	**3f**, 54	94
7	**1b**	1-naphthyl	CO_2Me	46	**3g**, 71	92
8	**1b**	2-furyl	CO_2Me	72	**3h**, 52	53
9	**1b**	Ph	COMe	12	**3i**, 62	90
10	**1b**	*m*-MeC_6H_4	COMe	19	**3j**, 56	92
11	**1b**	Et	CN	168	**3k**, 27	56
12	**1c**	Ph	CO_2Me	17	**3l**, 64	88
13	**1c**		CO_2Me	22	**3m**, 60	92
14	**1d**	Ph	CO_2Me	24	n.d.[d]	–

[a] Reagents and conditions: **1** (0.2 mmol), **2** (0.4 mmol), $(DHQD)_2AQN$ (5 mol-%), DCE (0.5 mL), 50 °C. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] The desired product was not isolated. Similar results were observed when indenes **1e**–**i** were applied.

containing a methoxycarbonyl group at the C2 position, reacted smoothly to provide the expected alkylation product with good data (Table 2, Entries 12 and 13). Unfortunately, either no reaction took place or complex mixtures of products were observed when other indenes **1d**–**i** were applied under the current catalytic conditions (Table 2, Entry 14). We propose that an electron-withdrawing group at the C2 position is necessary for the generation and stabilization of the corresponding indenides.

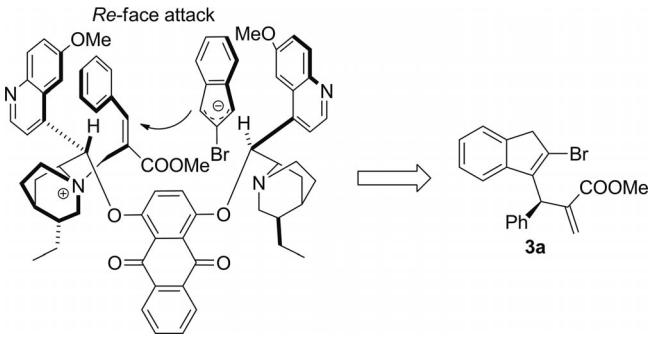
To determine the stereochemistry of the allylic alkylation products, a diastereoselective dipolar [3+2] cycloaddition was carried out between **3a** and nitrile *N*-oxide generated in situ. Crystals of the major diastereomer of cycloadduct **4** that were suitable for X-ray crystallographic analysis could be obtained from a solution of petroleum ether and ethyl acetate,[16] which facilitated the determination of the absolute configuration of **3a** (Scheme 3).[17]





Scheme 3. The [3+2] dipolar cycloaddition of indene derivative **3a**.

As shown in Scheme 4, a plausible transition state is proposed that can rationalize the observed stereocontrol.[11] The Lewis base promoted Michael addition/elimination cascade enables the formation of a quaternary ammonium cation and the generation of a strong Brønsted base that facilitates the deprotonation of indene. The *Si* face of this complex is blocked in the generated chiral environment, thus favoring attack from the *Re* face. A subsequent Michael addition, elimination, and isomerization cascade would deliver the observed chiral product.



Scheme 4. Proposed transition state for the formation of **3a**.

Conclusions

We have demonstrated that a Lewis base assisted Brønsted base catalysis strategy could be applied for the direct asymmetric C–C bond-forming reaction of indene compounds, as exemplified with the first allylic alkylation by using MBH carbonates. A variety of multifunctional chiral indene derivatives were obtained in moderate to excellent enantioselectivities (up to 95% *ee*), albeit with low to modest yields due to some side reactions. An expansion of the synthetic applications of the chiral indene products is underway in our laboratory.

Experimental Section

General: Cinchona alkaloid catalysts $(DHQD)_2PHAL$, $(DHQD)_2PYR$, $(DHQD)_2AQN$, and $(DHQ)_2AQN$ were purchased from Aldrich Chemical Company. MBH carbonates[18] and substituted indenes were prepared according to literature procedures.[19] Dicholoroethane was distilled from CaH_2. All other chemicals were used without purification as commercially available.

General Procedure for Asymmetric Allylic Alkylation Reaction: To a solution of indene **1b** or **1c** (0.2 mmol) and $(DHQD)_2AQN$ (8.6 mg, 5 mol-%) in dry DCE (0.5 mL), was added MBH carbonate **2** (0.4 mmol). The reaction mixture was stirred at 50 °C and monitored by TLC analysis. After completion, purification by silica gel flash chromatography (EtOAc/petroleum ether) gave the chiral indene product **3**.

Methyl (*R*)-2-[(2-Bromo-1*H*-inden-3-yl)(phenyl)methyl]acrylate (3a): 58% yield. $[\alpha]_D^{20}$ = –25.5 (*c* = 0.70 in CH_2Cl_2); 90% *ee*, determined by HPLC analysis [Daicel Chiralcel OD, *n*-hexane/*i*PrOH = 99:1, 1.0 mL/min, λ = 254 nm]: t_R = 14.19 (major), 16.53 (minor) min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.34 (m, 1 H), 7.31–7.22 (m, 5 H), 7.16–7.09 (m, 3 H), 6.48 (s, 1 H), 5.61 (s, 1 H), 5.52 (s, 1 H), 3.72 (s, 3 H), 3.67 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.1, 143.2, 142.3, 140.9, 140.4, 139.1, 128.6, 128.4, 128.0, 126.8, 126.3, 124.6, 123.9, 123.1, 120.5, 52.1, 46.2, 45.0 ppm. HRMS (ESI): calcd. for $C_{20}H_{17}BrO_2Na$ 391.0310; found 391.0324.

Methyl (*S*)-2-[(2-Bromo-1*H*-inden-3-yl)(2-bromophenyl)methyl]-acrylate (3b): 46% yield. $[\alpha]_D^{20}$ = +70.5 (*c* = 0.80 in $CHCl_3$); 91% *ee*, determined by HPLC analysis [Daicel Chiralcel OD, *n*-hexane/*i*PrOH = 80:20, 1.0 mL/min, λ = 220 nm]: t_R = 10.11 (major), 6.11 (minor) min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 7.6 Hz, 1 H), 7.38–7.34 (m, 2 H), 7.24–7.12 (m, 2 H), 7.16–7.09 (m, 3 H), 6.51 (s, 1 H), 5.79 (s, 1 H), 5.41 (s, 1 H), 3.73 (s, 3 H), 3.68 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.7, 143.7, 142.1, 139.2, 139.1, 138.4, 133.3, 130.3, 128.7, 128.3, 127.3, 126.5, 125.3, 124.8, 124.6, 123.1, 119.8, 52.2, 46.4, 45.4 ppm. HRMS (ESI): calcd. for $C_{20}H_{16}Br_2O_2Na$ 468.9415; found 468.9427.

Methyl (*R*)-2-[(2-Bromo-1*H*-inden-3-yl)(4-chlorophenyl)methyl]acrylate (3c): 43% yield. $[\alpha]_D^{20}$ = –53.9 (*c* = 1.30 in $CHCl_3$); 95% *ee*, determined by HPLC analysis [Daicel Chiralcel OD, *n*-hexane/*i*PrOH = 90:10, 1.0 mL/min, λ = 254 nm]: t_R = 5.06 (major), 6.36 (minor) min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.32 (m, 1 H), 7.27–7.19 (m, 4 H), 7.14–7.11 (m, 3 H), 6.49 (s, 1 H), 5.58 (s, 1 H), 5.54 (s, 1 H), 3.73 (s, 3 H), 3.67 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.0, 142.9, 142.3, 140.5, 139.8, 137.7, 132.6, 130.0, 128.7, 128.3, 126.4, 124.8, 124.3, 123.3, 120.4, 52.2, 45.6, 45.1 ppm. HRMS (ESI): calcd. for $C_{20}H_{16}BrClO_2Na$ 424.9920; found 424.9912.

Methyl (*R*)-2-[(2-Bromo-1*H*-inden-3-yl)(*m*-tolyl)methyl]acrylate (3d): 60% yield. $[\alpha]_D^{20}$ = –12.7 (*c* = 0.88 in $CHCl_3$); 94% *ee*, determined by HPLC analysis [Daicel Chiralcel OD, *n*-hexane/*i*PrOH = 90:10, 1.0 mL/min, λ = 254 nm]: t_R = 4.55 (major), 5.64 (minor) min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.34 (m, 1 H), 7.20–7.03 (m, 7 H), 6.47 (s, 1 H), 5.58 (s, 1 H), 5.52 (s, 1 H), 3.72 (s, 3 H), 3.67 (s, 2 H), 2.30 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.7.2, 143.3, 142.3, 141.0, 140.4, 139.0, 138.0, 129.4, 128.3, 127.9, 127.6, 126.3, 125.8, 124.6, 123.9, 123.1, 120.6, 52.1, 46.1, 45.0, 21.5 ppm. HRMS (ESI): calcd. for $C_{20}H_{19}BrO_2Na$ 405.0466; found 405.0475.

Methyl (*R*)-2-[(2-Bromo-1*H*-inden-3-yl)(4-methoxyphenyl)methyl]-acrylate (3e): 65% yield. $[\alpha]_D^{20}$ = –18.1 (*c* = 1.04 in CH_2Cl_2); 89% *ee*, determined by HPLC analysis [Daicel Chiralcel OD, *n*-hexane/*i*PrOH = 90:10, 1.0 mL/min, λ = 254 nm]: t_R = 6.81 (major), 7.89 (minor) min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.33 (m, 1 H), 7.19–7.10 (m, 5 H), 6.82 (d, *J* = 8.8 Hz, 1 H), 6.45 (s, 1 H), 5.53 (s, 1 H), 5.51 (s, 1 H), 3.76 (s, 3 H), 3.70 (s, 3 H), 3.65 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.2, 158.3, 143.3, 142.3, 141.0, 140.7, 131.1, 129.6, 127.8, 126.3, 124.6, 123.7, 123.1, 120.6, 113.8, 55.1, 52.1, 45.5, 45.0 ppm. HRMS (ESI): calcd. for $C_{21}H_{19}BrO_3Na$ 421.0415; found 421.0419.

Methyl (*R*)-2-[Benzo[*d*][1,3]dioxol-5-yl(2-bromo-1*H*-inden-3-yl)-methyl]acrylate (3f): 54% yield. $[\alpha]_D^{20}$ = –42.5 (*c* = 0.86 in $CHCl_3$); 94% *ee*, determined by HPLC analysis [Daicel Chiralcel OD, *n*-hexane/*i*PrOH = 90:10, 1.0 mL/min, λ = 254 nm]: t_R = 7.25 (major), 8.75 (minor) min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.13 (m, 4 H), 6.76 (s, 1 H), 6.74 (s, 2 H), 6.46 (s, 1 H), 5.92 (s, 2 H), 5.55 (s, 1 H), 5.51 (s, 1 H), 3.72 (s, 3 H), 3.66 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.1, 147.7, 146.4, 143.2, 142.3, 140.9, 140.4, 132.9, 127.9, 126.3, 124.7, 123.8, 123.2, 121.6, 120.5, 109.2, 108.2, 101.0, 52.2, 50.7, 45.9 ppm. HRMS (ESI): calcd. for $C_{21}H_{17}BrO_4Na$ 435.0208; found 435.0213.

Methyl (*R*)-2-[(2-Bromo-1*H*-inden-3-yl)(naphthalen-1-yl)methyl]acrylate (3g): 71% yield. $[\alpha]_D^{20}$ = –37.9 (*c* = 0.78 in CH_2Cl_2); 92% *ee*, determined by HPLC analysis [Daicel Chiralcel OD, *n*-hexane/*i*PrOH = 95:5, 1.0 mL/min, λ = 254 nm]: t_R = 9.11 (major), 10.92 (minor) min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00–7.98 (m, 1 H), 7.88–7.85 (m, 1 H), 7.80 (d, *J* = 8.0 Hz, 1 H), 7.51–7.40 (m, 4 H), 7.36 (d, *J* = 6.0 Hz, 1 H), 7.18 (d, *J* = 7.6 Hz, 1 H), 7.14–7.09 (m, 2 H), 6.52 (s, 1 H), 6.28 (s, 1 H), 5.47 (s, 1 H), 3.74 (s, 3 H), 3.70 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.2, 143.7, 142.2, 139.9, 134.9, 134.0, 131.8, 128.8, 128.5, 128.0, 126.4, 126.3, 126.2, 125.7, 125.1, 124.7, 124.5, 123.8, 123.2, 122.8, 119.2, 52.2, 45.2, 43.0 ppm. HRMS (ESI): calcd. for $C_{24}H_{19}BrO_2Na$ 441.0466; found 441.0469.

Methyl (R)-2-[(2-Bromo-1*H*-inden-3-yl)(furan-2-yl)methyl]acrylate (3h): 52% yield. $[\alpha]_D^{20}$ = +9.8 (*c* = 1.66 in $CHCl_3$); 53% *ee*, determined by HPLC analysis [Daicel Chiralpak IB, *n*-hexane/*i*PrOH = 95:5, 1.0 mL/min, λ = 254 nm]: t_R = 5.15 (major), 5.47 (minor) min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.14 (m, 5 H), 6.45 (s, 1 H), 6.32 (s, 1 H), 6.14 (d, *J* = 2.4 Hz, 1 H), 5.63 (s, 2 H), 3.74 (s, 3 H), 3.66 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.7, 152.1, 142.8, 142.2, 141.9, 138.8, 138.0, 127.8, 126.4, 124.8, 124.5, 123.1, 120.3, 110.3, 108.0, 52.2, 45.0, 40.4 ppm. HRMS (ESI): calcd. for $C_{18}H_{15}BrO_3Na$ 381.0102; found 381.0104.

(*R*)-3-[(2-Bromo-1*H*-inden-3-yl)(phenyl)methyl]but-3-en-2-one (3i): 62% yield. $[\alpha]_D^{20}$ = +18.2 (*c* = 1.70 in $CHCl_3$); 90% *ee*, determined by HPLC analysis [Daicel Chiralpak IC, *n*-hexane/*i*PrOH = 95:5, 1.0 mL/min, λ = 254 nm]: t_R = 7.12 (major), 8.29 (minor) min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.21 (m, 5 H), 7.14–7.10 (m, 3 H), 6.31 (d, *J* = 1.8 Hz, 1 H), 5.67 (d, *J* = 1.8 Hz, 1 H), 5.64 (s, 1 H), 3.64 (s, 2 H), 2.41 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 198.6, 149.2, 143.7, 142.3, 141.1, 139.3, 128.9, 128.5, 127.7, 126.8, 126.3, 124.7, 123.6, 123.2, 120.3, 45.3, 45.1, 26.2 ppm. HRMS (ESI): calcd. for $C_{20}H_{17}BrONa$ 375.0360; found 375.0354.

(*R*)-3-[(2-Bromo-1*H*-inden-3-yl)(*p*-tolyl)methyl]but-3-en-2-one (3j): 56% yield. $[\alpha]_D^{20}$ = +12.2 (*c* = 0.41 in $CHCl_3$); 92% *ee*, determined by HPLC analysis [Daicel Chiralpak AD, *n*-hexane/*i*PrOH = 90:10, 1.0 mL/min, λ = 254 nm]: t_R = 4.54 (major), 5.00 (minor) min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.32 (m, 1 H), 7.18–7.07 (m, 7 H), 6.30 (d, *J* = 1.8 Hz, 1 H), 5.67 (d, *J* = 1.8 Hz, 1 H), 5.59 (s, 1 H), 3.64 (s, 2 H), 2.41 (s, 3 H), 2.30 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.7, 149.3, 143.6, 142.3, 141.1, 136.3, 136.1, 129.8, 129.2, 128.6, 127.6, 126.3, 124.6, 123.3, 120.3, 45.1, 44.7, 26.3, 21.0 ppm. HRMS (ESI): calcd. for $C_{21}H_{19}BrONa$ 389.0517; found 389.0522.

(*R*)-3-(2-Bromo-1*H*-inden-3-yl)-2-methylenepentanenitrile (3k): 27% yield. $[\alpha]_D^{20}$ = –26.0 (*c* = 0.96 in $CHCl_3$); 56% *ee*, determined by HPLC analysis [Daicel Chiralcel OD, *n*-hexane/*i*PrOH = 95:5, 1.0 mL/min, λ = 254 nm]: t_R = 6.04 (major), 5.57 (minor) min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 7.2 Hz, 1 H),7.36–7.34 (m, 1 H), 7.25–7.17 (m, 2 H), 6.00 (d, *J* = 2.2 Hz, 1 H), 5.83 (d, *J* = 2.2 Hz, 1 H), 3.86–3.81 (m, 1 H), 3.69 (s, 2 H), 2.19–2.06 (m, 3 H), 0.92 (t, *J* = 7.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.4, 141.2, 139.1, 131.1, 126.4, 125.8, 125.1, 123.8, 123.6, 120.1, 118.3, 45.0, 44.3, 23.4, 12.0 ppm. HRMS (ESI): calcd. for $C_{15}H_{14}BrNNa$ 310.0207; found 310.0205.

Methyl (*S*)-3-[2-(Methoxycarbonyl)-1-phenylallyl]-1*H*-indene-2-carboxylate (3l): 64% yield. $[\alpha]_D^{20}$ = –14.0 (*c* = 1.12 in $CHCl_3$); 88% *ee*, determined by HPLC analysis [Daicel Chiralcel OD, *n*-hexane/*i*PrOH = 95:5, 1.0 mL/min, λ = 254 nm]: t_R = 9.98 (major), 7.85 (minor) min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 7.6 Hz, 1 H), 7.36 (d, *J* = 8.0 Hz, 1 H), 7.30–7.14 (m, 7 H), 6.62 (s, 1 H), 6.45 (s, 1 H), 5.44 (s, 1 H), 3.81 (s, 3 H), 3.73 (d, *J* = 5.6 Hz, 2 H), 3.67 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 167.3, 165.7, 153.9, 144.0, 141.8, 140.1, 131.3, 128.8, 128.05, 127.5, 127.2, 126.7, 126.4, 124.2, 124.1, 52.1, 51.4, 45.0, 39.0, 29.7 ppm. HRMS (ESI): calcd. for $C_{22}H_{20}O_4Na$ 371.1259; found 371.1247.

Methyl (*S*)-3-[1-(Benzo[*d*][1,3]dioxol-5-yl)-2-(methoxycarbonyl)allyl]-1*H*-indene-2-carboxylate (3m): 60% yield. $[\alpha]_D^{20}$ = –35.5 (*c* = 1.2 in $CHCl_3$); 92% *ee*, determined by HPLC analysis [Daicel Chiralcel OD, *n*-hexane/*i*PrOH = 90:10, 1.0 mL/min, λ = 254 nm]: t_R = 12.40 (major), 9.83 (minor) min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 7.2 Hz, 1 H), 7.40 (d, *J* = 7.6 Hz, 1 H), 7.28 (t, *J* = 7.6 Hz, 1 H), 7.18 (t, *J* = 7.6 Hz, 1 H), 6.78–6.71 (m, 3 H), 6.53 (s, 1 H), 6.43 (s, 1 H), 5.90 (d, *J* = 2.4 Hz, 2 H), 5.48 (s, 1 H), 3.82 (s, 3 H), 3.70 (d, *J* = 4.0 Hz, 2 H), 3.67 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.2, 165.7, 153.9, 147.7, 146.2, 143.9, 143.7, 141.8, 133.8, 131.0, 127.4, 127.3, 126.4, 124.2, 124.1, 121.8, 109.4, 108.2,

101.0, 52.1, 51.4, 44.6, 38.9 ppm. HRMS (ESI): calcd. for $C_{23}H_{20}O_6Na$ 415.1158; found 415.1152.

Procedure for Dipolar [3 + 2] Cycloaddition: A solution of chorobenzaldoxime (67.5 mg, 0.43 mmol) in anhydrous CH_2Cl_2 (1.5 mL) was cooled to –40 °C, and DIPEA (59.5 μL, 0.36 mmol) was added. After stirring for 10 min, a solution of **3a** (133.0 mg, 0.36 mmol) in CH_2Cl_2 (1.0 mL) was added dropwise. The reaction mixture was slowly warmed to –20 °C and stirred for 46 h. The solution was poured into saturated aqueous NH_4Cl (5 mL), and extracted with CH_2Cl_2 (2 × 5 mL). The combined organic phases were washed with water (2 × 5 mL) and brine (2 × 5 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated. Purification by silica gel flash chromatography (EtOAc/petroleum ether = 1:20) gave **4** (mixture of diastereomers, 4.2:1) as a white semi-solid (143.3 mg, 81%); $[\alpha]_D^{20}$ = –147.5 (*c* = 1.11 in $CHCl_3$).

Methyl (*R*)-5-[(*S*)-(2-Bromo-1*H*-inden-3-yl)(phenyl)methyl]-3-phenyl-4,5-dihydroisoxazole-5-carboxylate (Major Isomer of 4): 94% *ee*, determined by HPLC analysis [Daicel Chiralpak AD, *n*-hexane/*i*PrOH = 90:10, 1.0 mL/min, λ = 254 nm]: t_R = 31.80 (major), 31.14 (minor) min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 7.6 Hz, 2 H), 7.48 (d, *J* = 7.2 Hz, 2 H), 7.36–7.02 (m, 8 H), 7.11–7.02 (m, 2 H), 5.42 (s, 1 H), 3.70 (d, *J* = 4.0 Hz, 2 H), 3.67 (s, 3 H), 3.61 (d, *J* = 3.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.0, 141.9, 140.2, 136.9, 130.3, 129.6, 128.8, 128.7, 128.6, 128.5, 128.4, 127.1, 126.8, 126.3, 124.8, 123.1, 122.6, 90.7, 53.1, 49.8, 44.8, 44.3, 43.3 ppm. HRMS (ESI): calcd. for $C_{27}H_{22}BrNO_3Na$ 510.0681; found 510.0684.

Supporting Information (see footnote on the first page of this article): General methods, attempted synthetic transformations of indene products, crystal data of [3 + 2] cycloadduct **4** (major diastereomer), NMR spectra and HPLC chromatograms.

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